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Molecular mechanisms of cholesterol-lowering peptides derived from food proteins

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Some food proteins exhibit hypocholesteromic activity, which is largely associated with peptide fragments released after their enzymatic hydrolysis. This review provides a highlight of the recent progress on the hypocholesterolemic mechanisms of food protein-derived peptides, which include bile acid binding, inhibition of cholesterol micellar solubility and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (statin-like activity), and targeting of proprotein convertase subtilisin/kexin type 9 interaction with low-density lipoprotein receptor, and sterol regulatory element-binding protein and hepatocyte nuclear factor 1α pathways.

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Introduction

The role of food proteins in health outcome extends beyond nutritional value of supplying amino acids. For instance, peptides derived from protein hydrolysis have several biological effects, including the lowering of lipid levels during dyslipidemia, as demonstrated in both animal and human studies [1,2]. Available evidence shows that hypocholesteromic peptides act either by targeting exogenous cholesterol, or by modulating endogenous cholesterol level via cholesterol metabolism pathways [2,3]. The mechanism behind the effect on exogenous cholesterol mostly involves hindering initial intestinal absorption of dietary cholesterol. On the other hand, endogenous cholesterol is thought to be reduced if the active peptides can cross the intestinal barrier and are bioavailable in the liver and adipose tissues. Some peptides hinder enterohepatic circulation of bile acids, while others directly target endogenous cholesterol metabolism in tissues [2,3], which makes it necessary to establish the absorption, distribution, metabolism, excretion and toxicity (ADMET) of the peptides and their derivatives. Recent studies have reported particular hypocholesteromic mechanisms of food-derived peptides, including inhibition of 3-hydroxy-3-methylglutaryl CoA reductase (HMGCoAR) activity, and targeting of the expression of proteins involved in cholesterol metabolism including sterol regulatory element binding protein 2 (SREBP2), proprotein convertase subtilisin/kexin type 9 (PCSK9), hepatocyte nuclear factor (HNF)-1α, and low density lipoprotein receptor (LDLR). The cholesterol-reducing mechanisms discussed in this review, summarized in Table 1, are from recent reports (2014–2017) involving only peptides, proteins, or protein hydrolysates derived from lupin, soybean, royal jelly (RJ), cowpea, rice bran, and hempseed.

Physical interaction of peptides with bile acids and micelles

The gastrointestinal tract, especially the intestines, plays an important role in the packaging and transport of dietary cholesterol, and in recirculation of cholesterol metabolites via the enterohepatic route. This provides an opportunity for food peptides to modulate cholesterol metabolism in the gut. The widely proposed mechanism for gut-active hypocholesterolemic peptides involves hydrophobic interaction, at least partially, for bile acid binding and inhibition of cholesterol micellar solubility [1,3]. This mechanism was recently demonstrated with peptides derived from silk sericin, a non-dietary protein [4], and rice bran proteins [5]. In the studies, serum total and non-HDL cholesterol levels decreased in rats that consumed high-cholesterol diets with the rice bran protein or sericin peptides, indicating hypocholesterolemic effects. The rice bran proteins also increased fecal excretion of sterols [5]. Application of the sericin-derived oligopeptides to cultured Caco-2 cells inhibited cholesterol uptake into the cells, which was proposed to be due to inhibition of micellar cholesterol solubility by the peptides [4]. It is worth investigating whether the peptides also block the functioning of intestinal cholesterol transport protein.

The *in vivo* hypocholesterolemic mechanism could also be due to bile acid binding capacity because the protein or peptides bound taurocholate, taurodeoxycholate, and

Table 1

Mechanisms underlying the hypocholesterolemic activity of peptides.

Peptide source	Peptide sequence	Hypocholesterolemic mechanism	Reference
Cowpea	Peptide mixtures	Binding to bile acids/salts or lipids, and inhibition of micellar cholesterol solubility	[4–6,8,13]
Sericin	Peptide mixtures		
Royal jelly	Peptide mixtures		
Chemical synthesis	KRES		
Rice bran	Not applicable		
Cowpea	Peptide mixtures	Inhibition of HMGCoAR activity — inhibits the mevalonate pathway and cholesterol biosynthesis	[6,15,16•,17,22,23]
Lupin	Peptide mixtures		
Hempseed	Peptide mixtures		
Amaranth	GGV, IVG, VGVL		
Soy β-conglycinin	YVVNPDNDEN		
Soy β-conglycinin	YVVNPDNNEN		
Soy glycinin	IAVPGEVA		
Soy glycinin	IAVPTGVA		
Soy glycinin	LPYP		
Lupin β-conglutin	LILPKHSDAD		
Lupin β-conglutin	LTFPGSAED		
Chemical synthesis	PMAS		
Lupin	Peptide mixtures	Increasing of SREBP2 and LDLR protein levels — increases LDL uptake and cholesterol degradation	[14•,15,16•]
Hempseed	Peptide mixtures		
Soy glycinin	IAVPGEVA		
Soy glycinin	IAVPTGVA		
Soy glycinin	LPYP		
Soy β-conglycinin	YVVNPDNDEN		
Soy β-conglycinin	YVVNPDNNEN		
Lupin proteins	Peptide mixtures	Decreasing of PCSK9 production (via effect on HNF1α protein) and secretion — increases LDLR level and LDL uptake by hepatocytes	[18••,26]
Lupin β-conglutin	LILPKHSDAD	Inhibition of PCSK9–LDLR interaction — increases LDL uptake	[21••]

HMGCoAR, 3-hydroxy-3-methylglutaryl CoA reductase; LDL, low-density lipoprotein; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SREBP2, sterol regulatory element binding protein 2; HNF1α, hepatocyte nuclear factor 1α.

glycodeoxycholate *in vitro* [4,5]. Such direct interaction with lipids was observed for a <3 kDa peptide fraction from cooked cowpea, which inhibited micellar cholesterol solubility *in vitro* [6]. Interestingly, this effect was absent for a similar amount of the peptide fraction from raw cowpea [6]. This finding demonstrates that the food matrix and pretreatment steps influence the release and bioaccessibility of bioactive peptides [7]. In a study with royal jelly, a cholesterol-lowering food, a bile acid-binding protein named MRJP1 (major RJ protein 1) was obtained by cholic acid affinity purification [8]. The isolated protein bound taurocholate *in vitro* and decreased cholesterol uptake in Caco-2 intestinal cells. Further hypocholesterolemic effects, such as decrease in total/LDL/VLDL cholesterol and atherogenic index, and increase in hepatic bile acid biogenesis, were observed in rats after consuming MRJP1 proteins, which is likely due to direct interaction between MRJP1 peptide fragments and cholesterol/bile acids in the gut leading to increase in fecal excretion of sterols [8].

The presence of hydrophobic cores in peptides is important for cholesterol and bile acid binding. This structural mechanism was demonstrated with plastein peptide aggregates, which had higher binding capacity to primary, secondary and conjugated bile acids because of their higher surface hydrophobicity when compared to the original peptides [9•,10], even when amino acid compositions of the hydrolysates and peptide aggregates were similar [11]. Similarly, due to its physiological role that involves hydrophobic interaction with lipids, non-specific lipid-transfer protein 1, as well as lectin, was purified as the major component of rice bran protein that inhibited cholesterol micellar solubility [12•], and possibly responsible for its hypocholesterolemic effect in rats [5]. Amphipathicity of peptides is also thought to enhance their ability to interact with free and micellar bile acids [2], which can decrease the emulsification, solubility and total amount of dietary cholesterol absorbed in the small intestine. Although not directly related to bile acids/salts or micelles, one study found that amphipath-like tetrapeptides KRES and FREL, but not KERS, exhibited anti-atherogenic properties *in vivo* by interacting with HDL, due to their ability of form organized peptide-lipid structures, even without forming amphipathic helices [13]. This property was thought to have facilitated the removal of lipoprotein lipid hydroperoxides in mice that consumed the peptides. However, there is limited information on the structure–function relationship of bile acid/lipid interactions with food protein-derived peptides. Studies on bile acid binding and micelle disruption have mostly focused on peptide mixtures. Therefore, studies