



OPEN ACCESS

EDITED BY
Dong-Hua Yang,
St. John's University, United States

REVIEWED BY
Hongyan Li,
Qingdao University of Science and
Technology, China
Hanan Farouk Aly,
National Research Centre, Egypt

*CORRESPONDENCE
Shou-Dong Guo,
SD-GUO@hotmail.com

[†]These authors have contributed equally
to this work

SPECIALTY SECTION
This article was submitted to
Experimental Pharmacology and Drug
Discovery,
a section of the journal
Frontiers in Pharmacology

RECEIVED 22 July 2022
ACCEPTED 29 August 2022
PUBLISHED 14 September 2022

CITATION
Lin P, Shen N, Yin F and Guo S-D (2022),
Sea cucumber-derived compounds for
treatment of dyslipidemia: A review.
Front. Pharmacol. 13:1000315.
doi: 10.3389/fphar.2022.1000315

COPYRIGHT
© 2022 Lin, Shen, Yin and Guo. This is an
open-access article distributed under
the terms of the [Creative Commons
Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use,
distribution or reproduction in other
forums is permitted, provided the
original author(s) and the copyright
owner(s) are credited and that the
original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution
or reproduction is permitted which does
not comply with these terms.

Sea cucumber-derived compounds for treatment of dyslipidemia: A review

Ping Lin[†], Nuo Shen[†], Fan Yin and Shou-Dong Guo*

Institute of Lipid Metabolism and Atherosclerosis, Innovative Drug Research Centre, School of
Pharmacy, Weifang Medical University, Weifang, China

Dyslipidemias are disorders of plasma levels of lipids, such as elevated levels of total cholesterol and triglyceride, that are associated with various human diseases including cardiovascular disease (CVD) and non-alcoholic fatty liver disease (NAFLD). Statins are the first-line drugs for treatment of dyslipidemia. However, a substantial proportion of patients cannot reach the recommended LDL-c level even with the highest tolerated doses of statins, and there is no available drug specifically for NAFLD therapy. Sea cucumbers are one of the widely distributed invertebrates, and are an important resource of food and medicine. Sea cucumbers have many valuable nutrients including saponins, fatty acids, phospholipids, cerebrosides, sulfated polysaccharides, as well as proteins and peptides. In recent years, these natural products derived from sea cucumbers have attracted attentions for treatment of CVD and NAFLD because of their lipid-lowering effect and low toxicity. However, the hypolipidemic mechanisms of action and the structure-activity relationship of these bioactive components have not been well-documented in literature. This review article summarizes the signaling pathways and the potential structure-activity relationship of sea cucumber-derived bioactive compounds including saponins, lipids, carbohydrates as well as peptides and proteins. This article will provide information useful for the development of sea cucumber-derived lipid-lowering compounds as well as for investigation of hypolipidemic compounds that are derived from other natural resources.

KEYWORDS

sea cucumber, bioactive component, lipid-lowering, mechanisms of action, NAFLD, cardiovascular disease

Introduction

Lipid homeostasis is finely tuned by multiple systems and organs, which interact with each other through cross-talks via cellular signaling upon molecular stimulation. Peroxisome proliferator-activated receptors (PPARs) are lipid sensors and play key roles in lipid homeostasis. PPAR α is primarily expressed in liver, brown adipose tissue, heart, and muscle tissue. It is the master regulator of lipid metabolism via modulating fatty acid (FA) transport and β -oxidation. PPAR γ is expressed mainly in adipose tissue, where it regulates adipogenesis (Tian et al., 2020). The wingless-type MMTV integration site (WNT)/ β -Catenin pathway plays a key role in regulating

adipogenesis. Glycogen synthase kinase-3 β can phosphorylate β -Catenin, thereby causing degradation of β -Catenin. Furthermore, the frizzled receptor (Fz) and lipoprotein receptor-related protein (LRP)5/6 coreceptors located at the cell membrane can bind to WNT10b, destructing the activated degradation of β -Catenin, thereby promoting the accumulation of β -Catenin in cytoplasm and the subsequent nuclear translocation. In the nucleus, β -Catenin binds to T cell factor lymphoid enhancer factor family to activate downstream genes, such as cyclin D1 and C-myc, leading to inhibition of the expression of PPAR γ and CCAAT/enhancer binding protein- α (C/EBP α) (Christodoulides et al., 2009; Lee et al., 2010; Xu et al., 2014; Xu et al., 2015a). Additionally, accumulating evidence have demonstrated that gut microbiota consisted of trillions of bacteria affect host lipid homeostasis (Aron-Wisniewsky et al., 2021; de Vos et al., 2022).

Dyslipidemias are disorders of plasma levels of lipids, such as elevated levels of total cholesterol (TC) and triglyceride (TG), that are associated with various human diseases including cardiovascular disease (CVD) and fatty liver diseases (Pirillo et al., 2021). Accumulating evidence have demonstrated that hypercholesteremia, especially elevated level of low-density lipoprotein (LDL) cholesterol (LDL-c), is the major risk factor for CVD (Atar et al., 2021). Furthermore, hypertriglyceridemia is a key risk factor of the residual CVD and non-alcoholic fatty liver disease (NAFLD) (Heeren and Scheja, 2021; Zhang B. H. et al., 2022). According to the World Health Organization report in 2021, CVD remains the leading cause of human death and accounts for approximately 32% of the total deaths in 2019 (World Health Organization, 2021). NAFLD is characterized by the accumulation of TG and cholesterol in the liver and has a global prevalence of 25% (Powell et al., 2021). Lipid-lowering therapy is an effective strategy for prevention and/or treatment of CVD as well as NAFLD that are induced by dyslipidemia (Beshir et al., 2021; Ferraro et al., 2022). Statins are the first-line drugs for treatment of dyslipidemia. However, a substantial proportion of patients cannot reach the recommended LDL-c level even with the maximum tolerated doses of statins (De Backer et al., 2019). Furthermore, the overall efficacy of non-statin drugs on CVD outcomes is much less robust than that of statins (Visseren et al., 2021), and there is no available drug specifically for NAFLD therapy. In recent years, natural products have attracted attentions for treatment of CVD and NAFLD due to their powerful hypolipidemic effects and low toxicity (Singh and Sashidhara, 2017; Li et al., 2022).

Sea cucumbers are one of the widely distributed invertebrates, and are an important resource for food and medicine. The idea of “medicine and food are homologous (药食同源)” has been widely accepted in Asia, especially in China, and this idea is spreading all over the world. As reviewed previously, sea cucumbers have many valuable nutrients including vitamins, minerals, triterpene glycosides (saponins), sulfated polysaccharides, sterols, phenolics, cerebrosides, peptides, FA, and others. These components

show various bioactivities such as anti-angiogenic, anti-tumor, anticoagulant, anti-hypertension, anti-inflammatory, anti-oxidant, antithrombotic, antimicrobial, immunomodulatory, and wound healing functions (Bordbar et al., 2011; Khotimchenko, 2018). Diets containing sea cucumber (*Isostichopus badionotus*) meals can reduce serum levels of TC and TG in young rats via modulating the expression of multiple genes including sterol regulatory element-binding transcription factor (SREBP), 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR), and liver X receptor (LXR) that are associated with lipogenesis (Olivera-Castillo et al., 2013). In the past decades, the lipid-modulatory mechanisms of action of the compounds derived from sea cucumbers have been understood. Additionally, novel technologies, such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), are applied for the detection of metabolites of sea cucumbers (Wang et al., 2020; Zhao et al., 2020; Savarino et al., 2021). These advances make it possible to discuss the structure-activity relationship of these compounds obtained from sea cucumber. In this article, we summarize the lipid-lowering mechanisms of action and the potential structure-activity relationship of sea cucumber-derived bioactive components including saponin, lipid, long chain base, carbohydrate, peptide and protein. The related literature used in this article were mainly obtained as search results from PubMed using “sea cucumber and lipid” as keywords.

The lipid-modulatory mechanisms of sea cucumber-derived compounds

Saponin

Saponin is one of the most important secondary metabolites and bioactive constituents of sea cucumbers (Meng et al., 2018). In a comparative study, saponins derived from *Cucumaria frondosa* show better lipid-lowering activity compared to other components of sea cucumber including polysaccharides, collagen peptides, dregs, or non-saponin residues in rats. The underlying mechanism of action is associated with inhibition of the activity of pancreatic lipase, which is responsible for hydrolysis of dietary fat in the small intestine (Hu X. et al., 2012; Hu X. Q. et al., 2012). The crude saponins of sea cucumbers are generally extracted with 60% ethanol, and the obtained mixture can be further extracted with water-saturated *n*-butanol to obtain the final crude extracts that are consisted approximately 66% of saponins. These extracts obtained from sea cucumbers, such as *Thelenota ananas*, *Pearsonothuria graeffei* Semper (Holothuriidae), and *Holothuria fuscoglivia*, significantly downregulate the activity of pancreatic lipase *in vitro*. Of note, the major bioactive component of saponin, echinoside A (Figure 1) accounts for 35.6% of the above water-saturated *n*-butanol dissolved components and has a 50% inhibitory

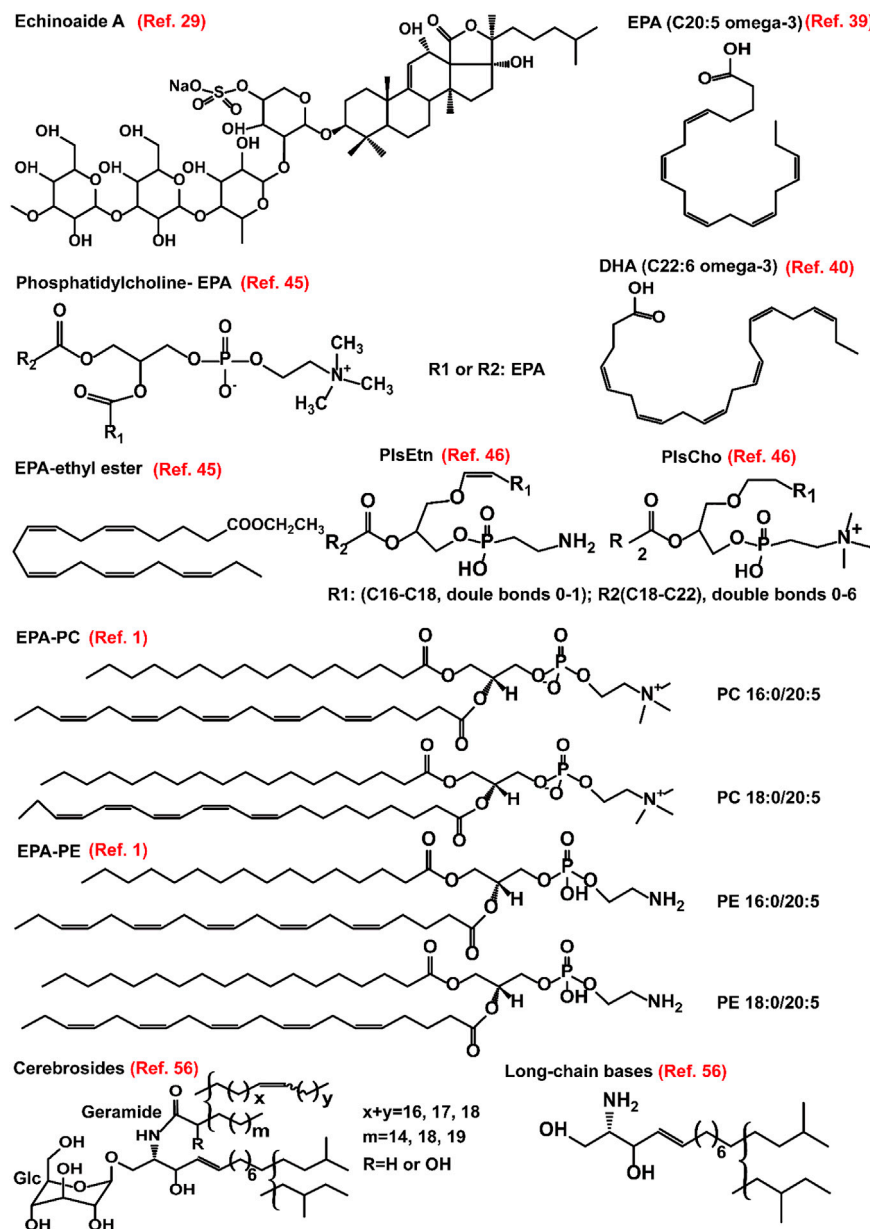


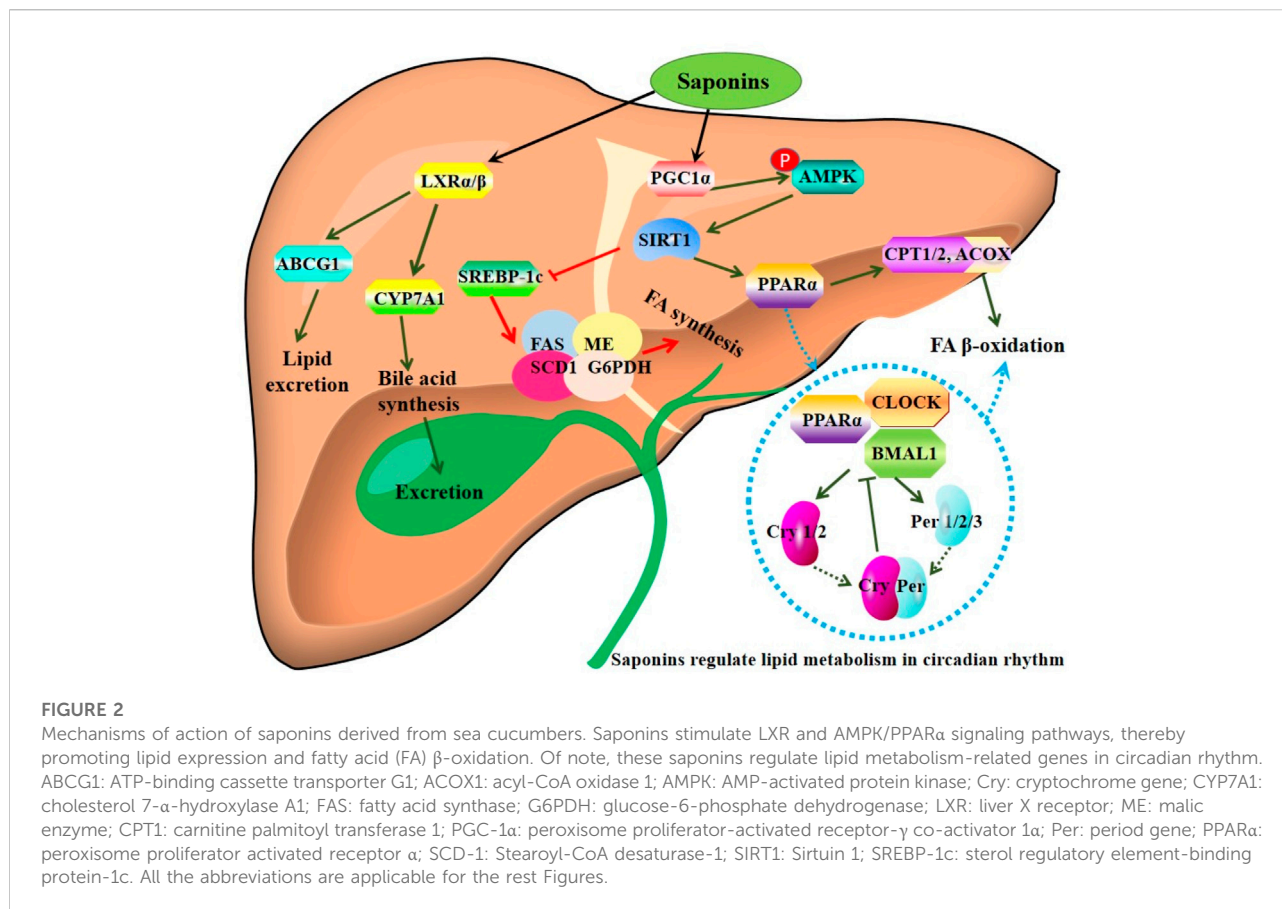
FIGURE 1

Structure of representative small molecules that are derived from sea cucumbers. These small molecules are found to modulate hyperlipidemia in different models including non-alcoholic fatty acid disease and atherosclerosis. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PC, phosphatidylcholine; PE, phosphatidylethanoamine; PlsCho, plasmanyl phosphatidylcholine; PlsEtn, plasmeryl phosphatidylethanoamine.

concentration of 0.76 μM for pancreatic lipase *in vitro* (Guo et al., 2016). The 60% ethanol extract of *P. graeffei* reduces the body weight, serum levels of TC, TG, and LDL-c, and hepatic TC and TG in C57BL/6 mice fed with a high-fat diet. Mechanistically, this extract upregulates the LXR- β signaling molecules including LXR- β , ATP-binding cassette transporter (ABC) G1, and cholesterol 7- α hydroxylase (CYP7A1). Importantly, the bioactive component echinoside A acts not only by

upregulating the expression of LXR- β but also via enhancing the expression of LXR- α , ABCG1, apolipoprotein (apo) E, and CYP7A1 in HepG2 cells at the dose of 2.5 μM (Guo et al., 2016). These data suggest that saponins, such as echinoside A, may alleviate hyperlipidemia via promoting the conversion of cholesterol to bile acid as well as lipid excretion.

Furthermore, sea cucumber saponins reduce lipogenesis and promote FA β -oxidation via inhibiting SREBP-1c and enhancing



the expression of PPAR α and acyl-CoA oxidase 1 (ACOX1), respectively, thereby improving lipid deposition in Sprague-Dawley (SD) rats and C57BL/6 mice (Hu et al., 2010; Guo et al., 2018; Meng et al., 2018). Saponins inhibit the activity and mRNA expression of lipogenic enzymes including fatty acid synthase (FAS), malic enzyme, and glucose-6-phosphate dehydrogenase (G6PDH) in the liver of mice fed with the diet containing 1% OA and 0.05% saponins (Hu et al., 2010). In combination with eicosapentaenoic acid (EPA)-enriched phospholipids, sea cucumber saponins further reduce hepatic TG partially by enhancing the expression of PPAR α . Furthermore, this combination shows better effect on improving glucose intolerance and systematic insulin sensitivity than monotherapy (Han et al., 2019). Interestingly, sea cucumber saponin treatment induces changes of lipid metabolism-related genes such as PPAR α , SREBP-1c, carnitine palmitoyl transferase (CPT), and FAS in rhythm, suggesting saponin may modulate lipid metabolism by regulating the clock genes such as CLOCK and BMAL1 in the ICR male mice fed with 0.03% sea cucumber saponin in regular chow (Wen et al., 2014). The major bioactive component of saponin, echinoside A, also regulates the expression of some key genes involved in lipid metabolism in a diurnal manner (Wen et al.,

2016). The mechanisms of action of saponins are summarized in Figure 2.

FA and phospholipid

Exogenous molecules can modulate lipid homeostasis by different signaling pathways. Exogenous lipids are recycled and/or degraded and participate in the formation of lipid raft, thereby affecting raft-related signaling pathways (Abumrad et al., 2012; Duan et al., 2012). Sea cucumber is a valuable food of FAs as well as other nutritional phospholipids (Roggatz et al., 2016; Roggatz et al., 2018). In the sea cucumber *Athyonidium chilensis*, saturated FAs are predominant in the tubule phospholipids (40.7%), while monounsaturated FAs account for approximately 42.0% and 38.0% of the phospholipids in the internal organs and body wall, respectively. The major polyunsaturated FAs are C20: 2 ω -6 FA, arachidonic acid (C20: 4 ω -6), and EPA (C20-5 ω -3) (Figure 1) (Careaga et al., 2013). Furthermore, the presence of the odd carbon saturated FAs may be originated from the detritus, which is a part of the diet of sea cucumber (Careaga et al., 2013). Different solvents have distinct ability for extraction of FAs, and water is found to

have a higher efficiency for extraction of docosahexaenoic acid (C22:6, Figure 1) compared to phosphate buffer saline, methanol, or ethanol (Fredalina et al., 1999). Accumulating evidence have demonstrated the health-beneficial effects of polyunsaturated FAs for treatment of lipid disorders (Djuricic and Calder, 2021; Mitrovic et al., 2022). Therefore, FAs, especially the n-3 polyunsaturated FAs that are enriched in sea cucumbers have potential application in pharmaceutical industries for intervention of dyslipidemias.

Some EPA-enriched phospholipids are shown in Figure 1. EPA-enriched phospholipids reduce hepatic TG and TC in orotic acid-induced SD rats with NAFLD via enhancing PPAR α -mediated FA β -oxidation. Furthermore, these 1% EPA-enriched phospholipids promote the expression of ACOX1 but not CPT-1 and CPT-2 (Guo et al., 2018). In rats, EPA-enriched phosphatidylcholine (EPA-PC) (80 mg/kg) attenuates NAFLD induced by 1% orotic acid via suppressing the mRNA expression of *HMGCR* and increasing the expression of sterol carrying protein 2, thereby inhibiting cholesterol synthesis and improving fecal cholesterol excretion, respectively. The underlying mechanisms are associated with the upregulation of PPAR α and adenosine monophosphate activated protein kinase (AMPK) as well as its upstream modulators including liver kinase B1 and Ca²⁺-dependent kinase (Liu et al., 2017). A recent study demonstrated that PC contained in EPA-PC and PE contained in EPA-enriched phosphatidylethanoamine (EPA-PE) directly bind to and activate PPAR α and PPAR γ . In mouse hepatocytes and liver, 0.3% EPA-PC and 0.3% EPA-PE reduce lipid accumulation via enhancing PPAR α -mediated FA β -oxidation. Although EPA-PC and EPA-PE (200 μ g/ml) promote the conversion of preadipocyte to mature adipocyte in a 3T3-L1 cell model, they reduce phosphorylation of PPAR γ at Ser273 *in vivo*, which may partially explain the reductions in the weight of adipose and the size of adipocyte (Tian et al., 2020). Furthermore, EPA-enriched phospholipids isolated from sea cucumber *C. frondosa* suppress lipid accumulation in mouse liver and white adipose via inhibiting the expression of lipiddroplet associated protein FSP27 and enhancing the expression of lipolysis genes including hormone-sensitive lipase (*HSL*), adipose triglyceride lipase (*ATGL*) as well as the lipogenesis gene *PPAR γ* in the white adipose of male C57BL/6J mice fed with high-sucrose diet (Zhang et al., 2020). However, EPA-PC has no effect on FA profiles in the brain (Wen et al., 2018). Sea cucumbers are rich in ether-linked phospholipids including plasmeyl phosphatidylethanoamine (PlsEtn) and plasmeyl phosphatidylcholine (PlsCho) (Figure 1). PlsEtn accounts for >83% of the total PE, and PlsCho accounts for >59% of the total PC in sea cucumber. Both 0.3% PlsEtn and 0.3% PlsCho, especially PlsEtn, significantly reduce hepatic TC and TG in C57BL/6N mice with alcoholic liver disease induced by ethanol gavage. Mechanistically, PlsEtn and PlsCho inhibit FA uptake and TG synthesis via downregulation of the mRNA expression of

hepatic cluster of differentiation 36 (*CD36*) and diacylglycerol acyltransferase 1, respectively. Additionally, PlsCho enhances FA oxidation via increasing the mRNA expression of *CPT-1 α* in the liver of mice (Wang et al., 2022). The mechanisms of action of FAs and phospholipids derived from sea cucumbers are summarized in Figure 3.

Cerebroside

The structure of some glucocerebroside molecular species has been characterized by different groups (Figure 1) (Yamada et al., 2002; Kisa et al., 2005; Yamada et al., 2005). Except for the classical column separation in combination with high-performance liquid chromatography, cerebrosides can be isolated using high speed counter-current chromatography (Xu et al., 2013). Sea cucumber cerebrosides isolated from *C. frondosa* contain approximately 48.0% of EPA. These lipids in liposome forms have particle sizes ranging from 169 to 189 nm and can efficiently penetrate the cell membrane in an M cell monolayer model as well as in a Caco-2 cell monolayer model (Du et al., 2016). The cerebrosides isolated from *Stichopus japonicus* can be absorbed *in vivo*, and then they are incorporated into ceramides, thereby improving the skin barrier function and increasing the cecal content of short-chain FA (SCFA) (Duan et al., 2016). A recent study indicates that liposomes derived from sea cucumbers is safe even at the concentration of 0.1 mg/ml (Mecheta et al., 2020). These data suggest that sea cucumber-derived cerebrosides can be explored as drug-loading nanoparticles.

In an orotic acid-induced NAFLD model, cerebrosides obtained from *Acaudina molpadioides* increase serum TG, but reduce liver index and hepatic TG. Mechanistically, these cerebrosides reduce the activities and expression of lipogenic enzymes including FAS, malic enzyme, and G6PDH, that are the target genes of SREBP-1c. Furthermore, the mRNA expression of *SREBP-1c* and the activity of microsomal triglyceride transfer protein are inhibited by cerebrosides at 0.006% in the liver of rats (Zhang et al., 2012). As a diet supplement, the cerebroside isolated from sea cucumber *A. molpadioides*, designated as AMC-2, can reduce hepatic TC and TG via down-regulating the activity and mRNA expression of stearoyl-CoA desaturase (*SCD*) in rats with NAFLD (Xu et al., 2011). In apolipoprotein E-deficient mouse, an atherosclerosis model, cerebrosides isolated from sea cucumber *A. molpadioides* reduce the formation of atherosclerotic plaques, serum levels of TC and LDL-c, and hepatic TC and TG when they are added to food at the dose of 0.06%. Mechanistically, cerebroside treatment promotes the expression of LDL receptor, CYP7A1 and ABCG5/G8, thereby promoting reverse cholesterol transport. Furthermore, these compounds improve FA oxidation via enhancing the expression of PPAR α , CPT-1 α , and ACOX1, and suppress lipogenesis by inhibiting the expression of

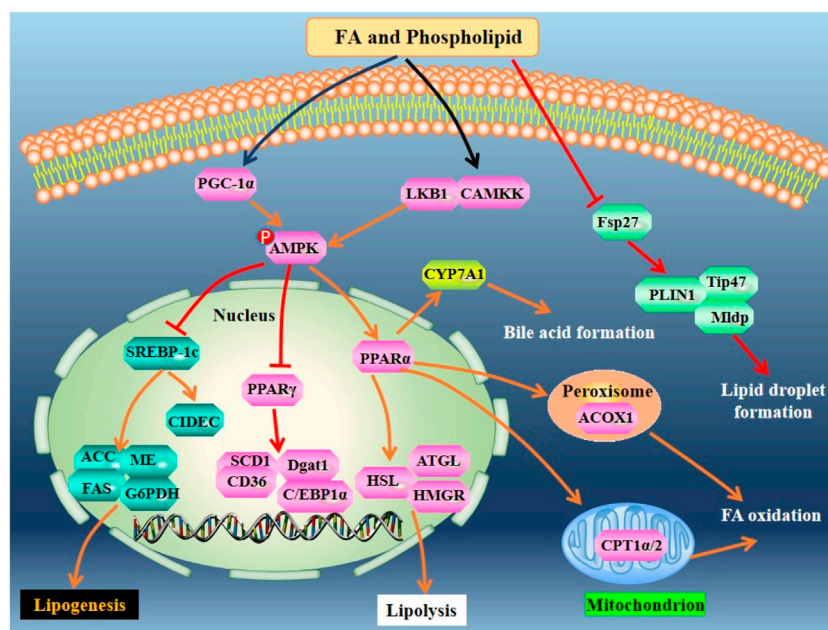


FIGURE 3
 Mechanisms of action of FA and phospholipid derived from sea cucumbers. CAMKK, Ca²⁺-dependent kinase; C/EBPs: CCAAT/enhancer binding proteins; CIDEC: cell-death-inducing DFFA-like effector c; Dgat1, diacylglycerol acyltransferase 1; Fsp27, fat-specific protein 27; HMGR: hydroxymethyl glutaric acid acyl; LKB1, liver kinase B1; Mldp, perilipin5; PLIN1, perilipin1; Tip47, perilipin 3. All the abbreviations are applicable for the rest Figures.

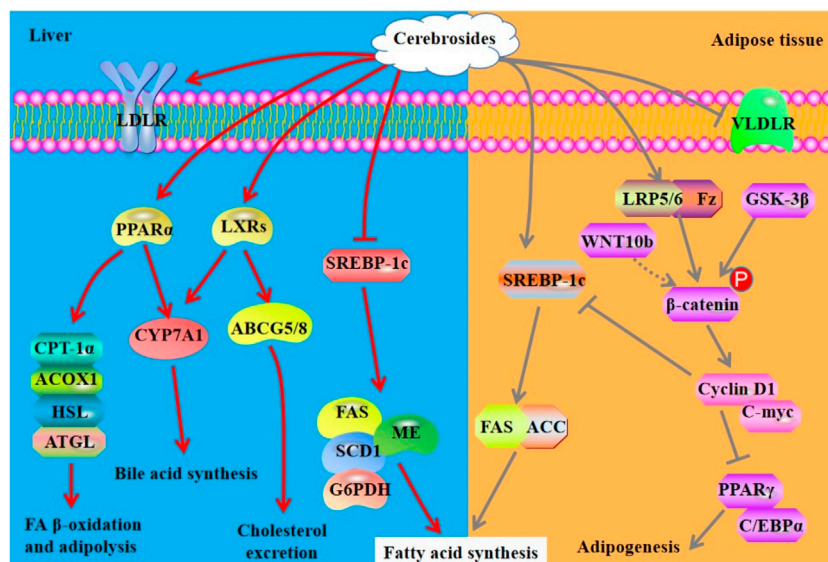


FIGURE 4
 Mechanisms of action of cerebroside derived from sea cucumbers. ACC, acetyl-CoA carboxylase; ATGL: adipose triglyceride lipase; GSK-3β, glycogen synthase kinase-3β; HSL, hormone sensitive lipase; LRP, lipoprotein receptor related protein; VLDLR, very low-density lipoprotein receptor; WNT10b, wingless-type MMTV integration site10b. All the abbreviations are applicable for the rest Figures.

SREBP-1c and its target genes including *FAS* and *SCD1* (Zhang et al., 2018). The cerebroside obtained from sea cucumber *A. molpadioides* also exhibit powerful effects on reduction of fat weight and serum and hepatic levels of TG via inhibiting the enzymatic activity of FAS and malic enzyme, the content of CPT, and the mRNA expression of *SREBP-1c* and *FAS*, in the liver of C57BL/6J mice fed with a diet containing 0.025% of cerebroside. Furthermore, these cerebroside significantly decrease the mRNA expression of very low-density lipoprotein receptor and lipoprotein lipase (*LPL*) and increase the expression of *SREBP-1c*, *FAS*, *ATGL*, and acetyl CoA carboxylase (*ACC*) in the white adipose tissue (Liu et al., 2015). In 3T3-L1 cells, 250 µg/ml cerebroside isolated from sea cucumber *C. frondosa* promote the nuclear translocation of β -Catenin and the expression of its target genes such as cyclin D1 and C-myc, and the expression of Fz and LRP5, thereby suppressing the expression of PPAR γ and C/EBP α (Xu et al., 2015a). Cerebroside have different effects on modulation of adipocyte differentiation both *in vitro* and *in vivo* via regulation of related signaling pathways in a different manner. The mechanisms of action of cerebroside derived from sea cucumber are summarized in Figure 4.

Long-chain base

Long-chain bases can be obtained by acid hydrolysis of cerebroside (using 10% HCl) (Figure 1), which are the main active structural units of cerebroside for intervention of hyperlipidemia (Liu et al., 2015). Long-chain bases are found to ameliorate obesity by multiple pathways. The long-chain bases isolated from *A. molpadioides* significantly reduce the body weight, fat weight, plasma levels of TG, TC, LDL-c, glucose, leptin, and insulin, and increase the levels of plasma high density lipoprotein cholesterol (HDL-c), fecal SCFAs including acetate, propionate, and butyrate, as well as the expression of SCFAs-mediated G-protein-coupled receptors in mice. In the gut, long-chain bases induce reductions in *Firmicutes* and *Actinobacteria* phylum, and obesity-associated bacteria including *Desulfovibrio*, *Bifidobacterium*, and *Romboutsia* at the genus level. They increase the abundance of *Bacteroidetes*, *Proteobacteria*, and *Verrucomicrobia* phylum, and the SCFAs-producing bacteria including *Bacteroides*, *Lactobacillus*, and *Lachnospiraceae_NK4A136_group* at the genus level (Hu et al., 2019). Phosphorylation of AMPK stimulates the phosphorylation of ACC, causing down-regulation of the activity of ACC and the expression of lipogenesis related enzymes including FAS. Furthermore, activation of AMPK through phosphorylation un-regulates lipidolysis via enhancing the expression of HSL and CPT-1 (Tian et al., 2016; Aslam and Ladilov, 2022). Of note, 50 µg/ml and 100 µg/ml of long-chain bases obtained from *C. frondosa* inhibit adipogenesis in 3T3-L1 pre-adipocytes via enhancing the phosphorylation of AMPK and ACC. Furthermore, they

inhibit the transcriptional factors, such as C/EBPs and PPAR γ , and activate WNT/ β -catenin and its target genes including cyclin D1 and C-myc, thereby inhibiting adipocyte differentiation (Tian et al., 2016). The mechanisms of action of long chain bases derived from sea cucumber are summarized in Figure 5.

Carbohydrate

Polysaccharides of sea cucumber reduce serum levels of TG, TC, and LDL-c, and increase the level of HDL-c in rats (Hu X.Q. et al., 2012; Liu et al., 2012). The health-beneficial activities including the hypolipidemic effect of fucosylated chondroitin sulfate (FCS) isolated from sea cucumbers have been reviewed recently by Xu et al. (2022). Here, we summarize the mechanisms of action and the structure-activity relationship of FCS as lipid-lowering agents (Figure 6). The structure of these FCSs extracted from different sea cucumbers are shown in Figure 7. FCS isolated from *A. molpadioides* elevates the expression of Wnt/ β -Catenin signaling molecules, such as Wnt10b, β -Catenin, Fz, and LRP5, leading to down-regulation of the transcriptional factors including SREBP-1c, PPAR γ , and C/EBP α , thereby exhibiting anti-adipogenic effects in 3T3-L1 cells and mice (Xu et al., 2015b). Of note, the FCS isolated from *P. graeffei* with 3,4-O-disulfated fucose branches exhibits a more powerful effect in lipid-lowering than the FCS obtained from *I. badionotus* with 2,4-O-disulfated fucose branches (Chen et al., 2012; Wu et al., 2016). These data suggest that the substitution position of the sulfate group at the branched fucosyls plays a key role in the hypolipidemic effect of FCS. Furthermore, the FCS (40 mg/kg) with a molecular weight (Mw) of 4.3 kDa obtained via degradation of FCS of *I. badionotus* shows hypolipidemic effect in C57BL/6 mice fed with a high-fat diet by down-regulating the mRNA expression of *FAS* and *PPAR γ* in adipose tissues (Li et al., 2018a). These data suggest that depolymerized FCS with low Mw maintains the lipid-lowering effect of its native FCS. However, the influence of Mw on the hypolipidemic effect of FCS need to be further investigated by comparative studies.

Most of the fucoidans extracted from sea cucumbers have \rightarrow 3)Fuc (1 \rightarrow linked linear structure as shown in Figure 8. These fucoidans exhibit powerful lipid-modulatory effects. Fucoidan obtained from *I. badionotus* ameliorates serum levels of TC and TG in C57BL/6J mice fed with a high-fat high-sucrose diet at the dosage of 80 mg/kg/d (Wang et al., 2016). Of note, the fucoidan isolated from *P. graeffei* shows a better hypolipidemic effect than that from *I. badionotus* by increasing the expression of CYP7A1 in SD rats fed with a high-fat diet at the dosage of 40 mg/kg. The structure-activity relationship analysis suggests that 4-O-sulfation of the fucoidan obtained from *P. graeffei* benefits its lipid-lowering effect (Chen et al., 2012; Hu et al., 2015; Li et al., 2017). Furthermore, this fucoidan obtained from *P.*

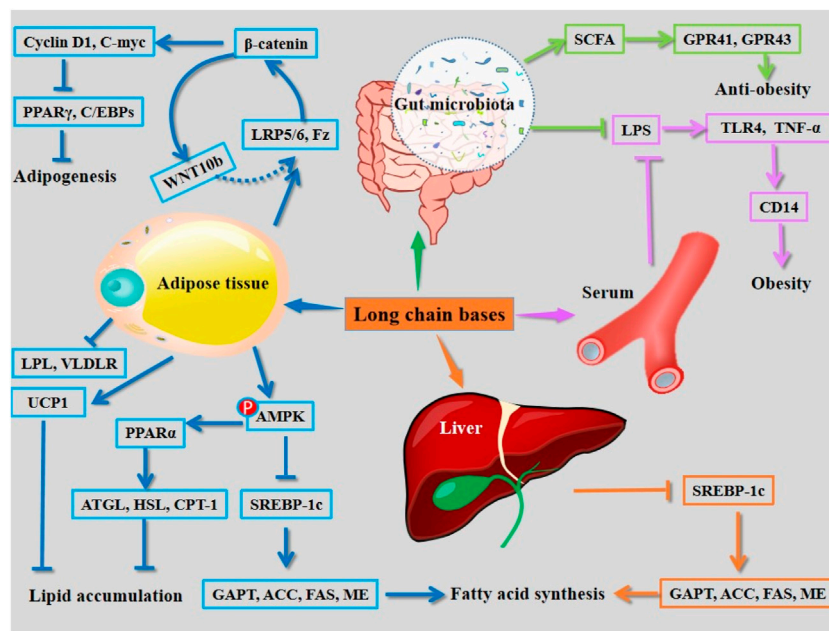


FIGURE 5

Mechanisms of action of long chain bases derived from sea cucumbers. CD14, cluster of differentiation 14; GPAT, glycerol-3-phosphate acyl-transferase; GPR, G protein-coupled receptor; LPL, lipoprotein lipase; LPS, lipopolysaccharide; SCFA, short chain fatty acid; TLR4, Toll-like receptor 4; TNF- α , tumor necrosis factor α ; UCP1, uncoupling protein 1. All the abbreviations are applicable for the rest Figures.

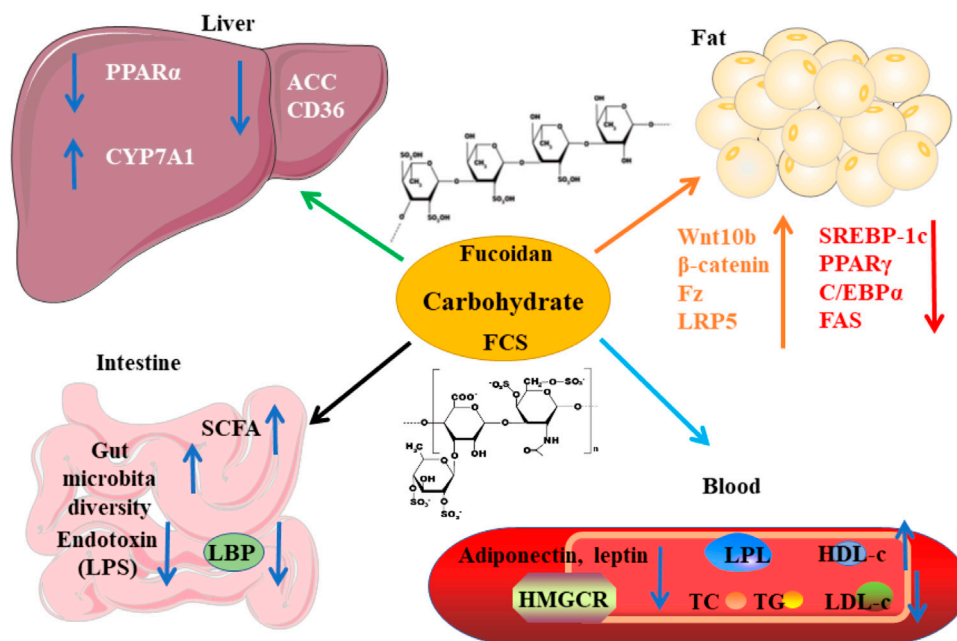


FIGURE 6

The mechanisms of action of carbohydrates derived from sea cucumbers. These polysaccharides include fucoidan and fucosylated chondroitin sulfate (FCS). HDL-c, high-density lipoprotein cholesterol; LBP, lipopolysaccharide binding protein; LDL-c, low-density lipoprotein cholesterol; LPS, lipopolysaccharide; TC, total cholesterol; TG, triglyceride. All the abbreviations are applicable for the rest Figures.

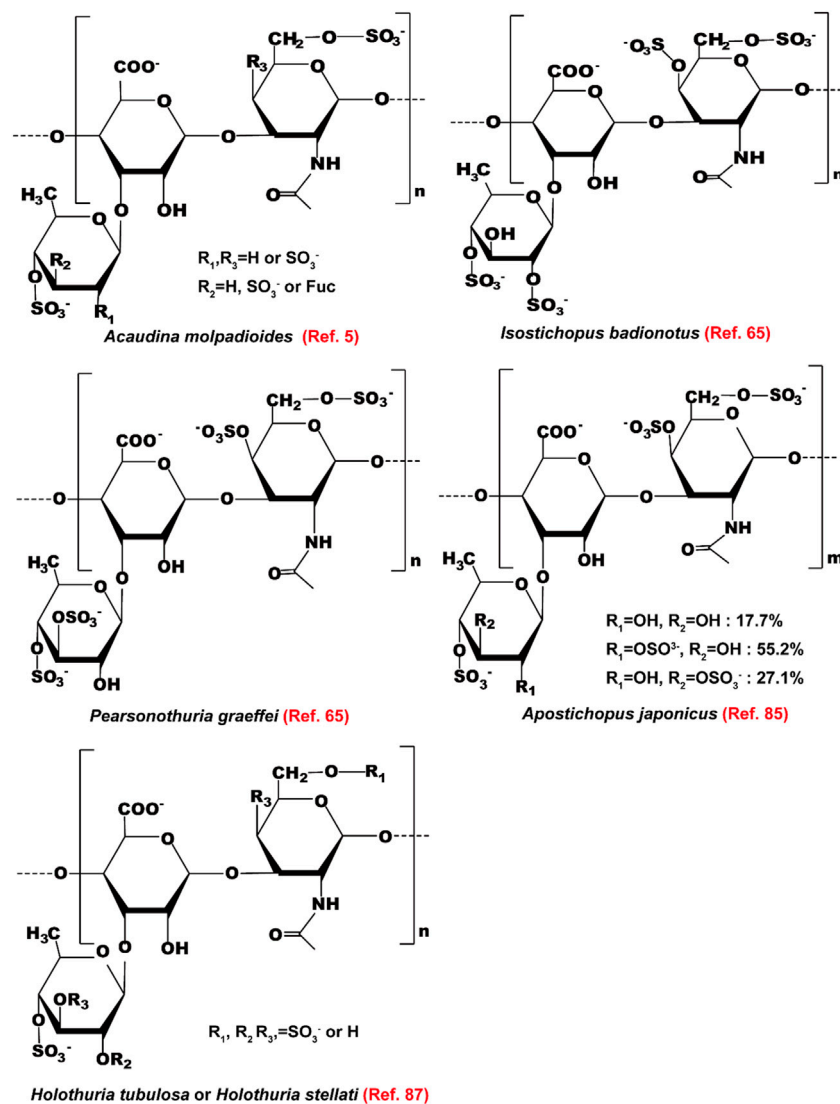


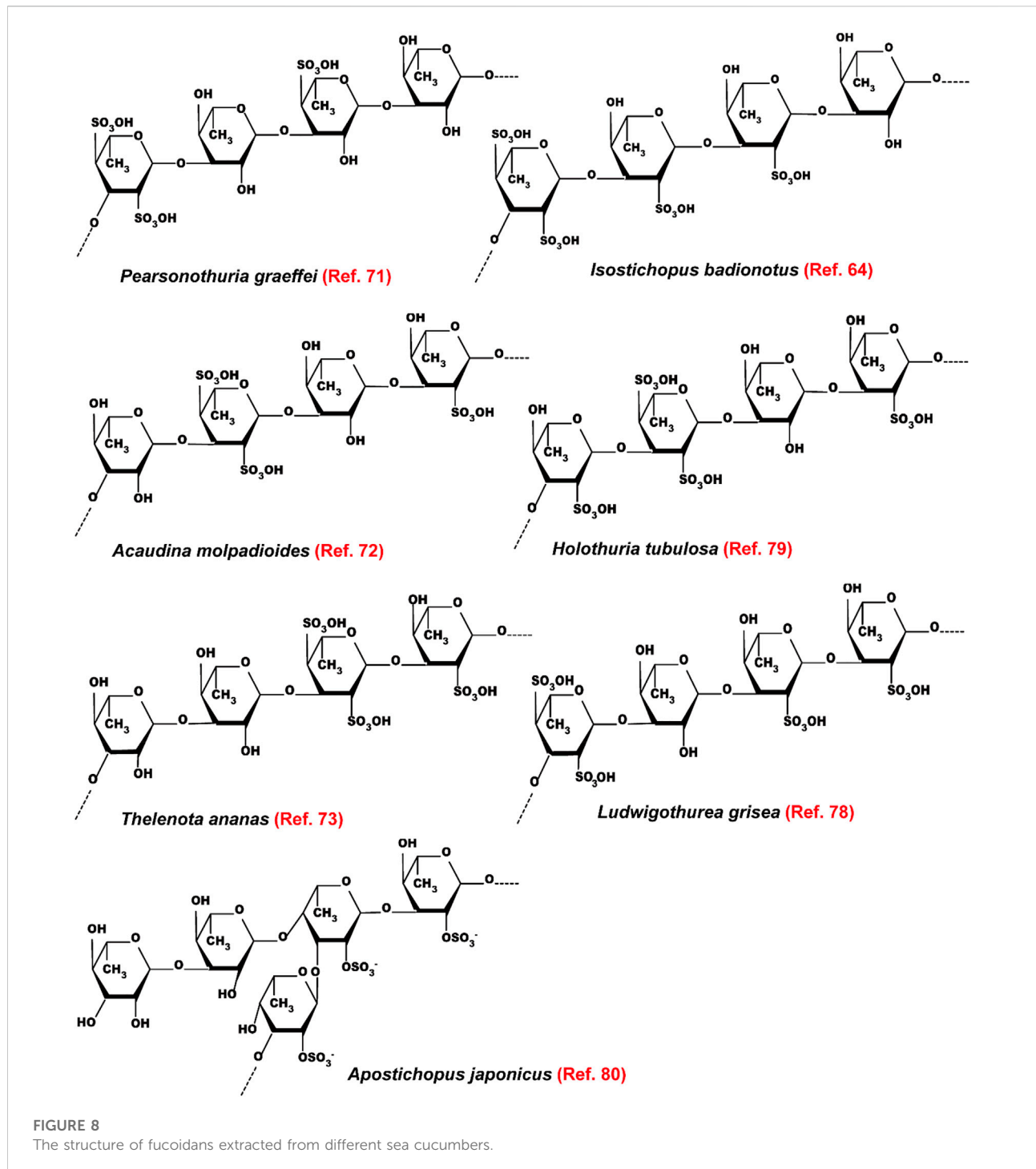
FIGURE 7

The structure of fucosylated chondroitin sulfates extracted from different sea cucumbers.

graeffei mainly act in the colon by increasing the abundance of *Bacteroidetes* and *Actinobacteria* and reducing the abundance of *Firmicutes* and *Proteobacteria* (Li et al., 2018b). Similar to FCS, fucoidan from the sea cucumber *A. molpadioides* inhibits adipocyte proliferation and differentiation as evaluated in 3T3-L1 cells and mice at the dose of 200 $\mu\text{g/ml}$ and 80 mg/kg/d , respectively, via enhancing the expression of Wnt/ β -Catenin signaling molecules, such as Wnt10b, β -Catenin, Fz, and LRP5, which suppress the expression of transcriptional factors including SREBP-1c, PPAR γ , and C/EBP α , and their downstream genes such as FAS and glycerol-3-phosphate acyl-transferase (Yu et al., 2014a; Xu et al., 2014).

A recent study indicates that fucoidans extracted from *T. ananas* with low Mw and a random coil conformation have better

effect than those with large Mw on attenuating hyperlipidemia and fat accumulation (Yu et al., 2014b; Xu et al., 2018; Zhu et al., 2021). Another study also demonstrates that the sulfated polysaccharides containing FCS and fucoidan that are isolated from sea cucumber *Stichopus japonicus* as well as its depolymerized derivatives decrease serum levels of TC and TG and fat accumulation in BALB/c mice fed with a high-fat diet by modulating gut microbiota at the dosage of 300 mg/kg/d . In addition to increasing the ratio of *Bacteroidetes/Firmicutes*, these polysaccharides enhance the abundance of the genus *Akkermansia* in the phylum Verrucomicrobia, which is associated with weight reduction. Furthermore, these polysaccharides increase the SCFAs-producing microbiota including *Bacteroides* and *Alloprevotella* as well as the content



of SCFAs, which benefit glucose tolerance and insulin resistance. Of note, the depolymerized derivatives with similar structural characteristics as its native polysaccharides show better effect on preventing fat accumulation. These derivatives improve the enrichment of health-beneficial bacteria including *Akkermansia muciniphila* and *Parabacteroides goldsteinii*, suggesting that fucoidans with low Mw are superior to the

growth of beneficial microbiota (Zhu et al., 2018a). These polysaccharides extracted from sea cucumber *S. japonicus* and its depolymerized derivatives also exhibit similar effects in mice fed with a normal chow diet (Zhu et al., 2018b). Presently, the hypolipidemic bioactivity of the \rightarrow 3)Fuc (1 \rightarrow linked linear fucoidan isolated from *Ludwigothurea grisea* and *Holothuria tubulosa* as well as the \rightarrow 3,4)Fuc (1 \rightarrow branched fucoidan

extracted from sea cucumber *Apostichopus japonicus* has been reported (Figure 8) (Mulloy et al., 1994; Yu et al., 2015; Chang et al., 2016). The mechanisms of action of fucoidans are shown in Figure 6.

Glycosaminoglycans (GAGs) extracted from sea cucumber *Metriatyla scabra* also reduce serum levels of TC and LDL-c as well as atherosclerosis index and enhance HDL-c level via inhibiting HMGCR and improving the activity of LPL. These GAGs show dose-dependent effects when the dosages are lower than 20 mg/kg (Liu et al., 2002). The polysaccharides isolated from sea cucumber *Holothuria leucospilota* (HLP) are rich in sulfated GAGs. These polysaccharides with an oral dosage of 300 mg/kg/d reduce plasma levels of TC, TG, and LDL-c, and enhance the levels of HDL-c and SCFAs in male BALB/c mice. Mechanistically, HLP improves the expression of PPAR α and CD36 as well as the abundance of gut microbiota. Accumulating studies have demonstrated that the reduced ratio of *Bacteroidetes/Firmicutes* promotes the development of obesity in different models (Zhu et al., 2018c). At the phylum level, HLP elevates the amount of *Bacteroidetes*, *TM7*, *Cyanobacteria* and *Tenericutes* and reduces the abundance of *Firmicutes*, *Proteobacteria*, *Spirochaetes*, and *Actinobacteria*. Of note, HLP intervention increases the abundance of SCFAs-producing bacterial genera including *Clostridium*, *Turicibacter*, *Allobaculum*, and *Ruminococcus* (Zhao et al., 2020). In line with these findings, gastrointestinal digestion reduces the Mw and changes the microstructure of polysaccharides that are extracted from *H. leucospilota* *in vitro* (Yuan et al., 2019a). Furthermore, these polysaccharides (200 mg/kg BW) are found to ameliorate hyperlipidemia in rats via reducing the expression of ACC and CD36 and potentially by enhancing the production of SCFAs (Yuan et al., 2019b). Although the structural characteristics of GAGs isolated from *A. japonicus* and *H. tubulosa* have been elucidated, their hypolipidemic effects have not been investigated (Yang et al., 2015; Ustyuzhanina et al., 2018; Chen et al., 2019). The mechanisms of action of carbohydrates derived from sea cucumbers are summarized in Figure 6.

Protein and peptide

A recent literature demonstrates that the sea cucumber ovum powder, which mainly composed of protein (62.08%) as well as other components such as polyunsaturated FAs (6.74%) can significantly reduce plasma TG and hepatic TG and TC, thereby improving NAFLD in rats fed with a high-fat diet at the dosage of 450 mg/kg (Han et al., 2020). Mechanistically, this powder modulates the relative expression of 767 proteins as revealed by LC-MS/MS. Some of these differentially expressed proteins are associated with FA oxidation and lipogenesis (Han et al., 2020). However, the contribution of other lipid-lowering components contained in this sea cucumber powder cannot be

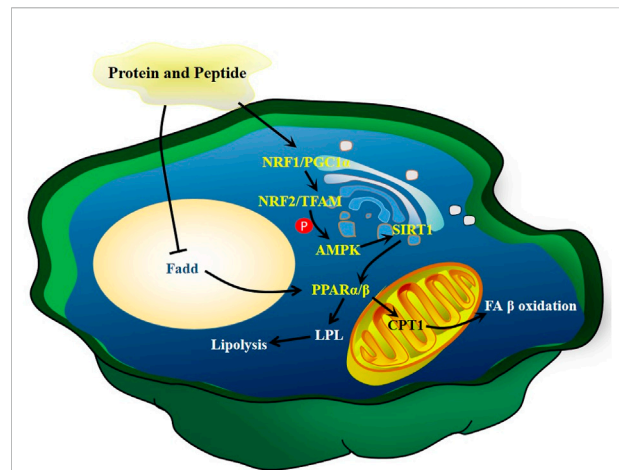


FIGURE 9

The mechanisms of action of peptides and proteins of sea cucumbers. Fadd, FAS associated death domain protein; NRF, nuclear respiratory factor; TFAM, mitochondrial transcription factor A.

ruled out. Therefore, the actual hypolipidemic effects of sea cucumber proteins need to be further investigated in future.

Diet supplementation of collagen peptides (2.4 g/kg) isolated from *C. frondosa* reduces serum TG in rats (Hu X. Q. et al., 2012). The peptides obtained from sea cucumber *S. japonicus* enhance gluconeogenesis and maintain lipid homeostasis via increasing the mRNA expression of AMPK, PPAR γ coactivator 1- α and its downstream genes PPAR α and PPAR β in a dose-dependent manner in the liver, skeletal muscle, and heart. Furthermore, these peptides enhance the expression of LPL and CPT1, which are key rate-limiting enzyme genes for lipoprotein hydrolysis and FA β -oxidation, respectively (Yu et al., 2020). The peptides isolated from sea cucumber *Stichopus japonicus* can increase the content of unsaturated lipids in mouse and rat hippocampus (Lu et al., 2022a). As unsaturated lipids can modulate lipid metabolism (Djuricic and Calder, 2021; Mitrovic et al., 2022), the above results suggest that peptides alleviate hyperlipidemia by regulating the metabolism of unsaturated lipids. The potential mechanisms of action of peptides and proteins of sea cucumbers are summarized in Figure 9.

The sea cucumber-derived compounds for treatment of cardiac complications

In addition to lipid-lowering, sea cucumber-derived compounds have other attractive bioactivities for treatment of cardiac complications. Studies on system pharmacology predict that sea cucumber-derived compounds have potential application for treatment of cardiac complications (Guo et al.,

2015). These activities include anti-hypertensive, anti-angiogenic, anti-inflammatory, anti-diabetic, anti-coagulation, and antioxidation activities. As these activities have been reviewed by different groups, we make a brief review of these aspects in the following (Bordbar 2011; Khotimchenko, 2018; Hossain et al., 2020).

The cerebrosides and long-chain bases from *A. molpadioides* can reduce serum glucose level in addition to improving the lipid profiles in high fat diet-fed mice (Liu et al., 2015). A study demonstrates that sea cucumber-derived ceramides and glucosylceramides attenuate insulin resistance in high-fructose-diet-induced rats via upregulation of the insulin receptor substrate-phosphatidylinositol 3 kinase-serine/threonine kinase signalling pathway (Yang et al., 2021). As reviewed recently, the anti-diabetic effects of sea cucumber-derived peptides and carbohydrates are related to their modulation of angiogenesis (Khosravifar et al., 2022).

The sea cucumber-derived carbohydrates and other components are able to inhibit clot and thrombus formation as reviewed previously (Pomin, 2014; Dashi and Naiwal, 2021). The mechanisms of action of these components have also been documented (Dashi and Naiwal, 2021). For instance, a clinical study has demonstrated that the Kang-Shuan Capsule, which consisted of *Holothuria ldeucospilota* acid mucopolysaccharide, improves lipid profiles, reduces blood viscosity, and exhibits good anticoagulant effect in patients with ischemic heart disease (Wang et al., 1997).

CVD is closely associated with nuclear factor kappa B (NF- κ B)-mediate inflammatory response (Zhang Q. et al., 2022). Many sea cucumber-derived bioactive compounds including Ds-echinoside A, Fronodoside A, Holothurin A1, and Psolusodie are found to inhibit NF- κ B. As reviewed recently, sea cucumber compounds can target the NF- κ B signalling pathway, which is involved in inflammation, immunity, cellular differentiation, cell adhesion, and survival (Wargasetia 2022). The extracts of *Holothuria forskali* and *Parastichopus tremulus* are reported to inhibit inflammation in endothelial cells (Mena-Bueno et al., 2016). In a triple-blinded randomized controlled trial, the *Stichopus horrens* extract toothpaste can alleviate plaque-induced gingivitis, suggesting the anti-inflammatory effect of the sea cucumber compounds in human (Bakar et al., 2020). The oligopeptides obtained from *A. japonicus* and *A. leucoprocata* may suppress inflammatory response via inhibiting Toll-like receptor 4/myeloid differentiation factor 88/NF- κ B signalling pathway (Wan et al., 2020). The fucoidan from *A. japonicus* reduces lipopolysaccharide-induced inflammation via inhibiting the phosphorylation of p38 mitogen-activated protein kinase/extracellular regulated protein kinase1/2 and the downstream NF- κ B in mice (Yin et al., 2019). The anti-inflammatory effects of the carbohydrates obtained from sea cucumbers have been documented by various groups of researchers (Kapoor et al., 2019; Xu et al., 2022).

The anti-oxidant compounds, such as peptides, from sea cucumbers may also benefit CVD because the initiation and development of CVD are tightly associated with oxidative stress (Lu et al., 2022b; Qiao et al., 2022). The Reinhartdt and Sea Cucumber Capsule improves agitation in moderate to severe Alzheimer disease partly due to its effect on attenuating oxidative stress (Yu et al., 2017). The aqueous extract of sea cucumber *Holothuria atra* exhibits anti-oxidation activity *in vitro* and in doxorubicin-induced rats (Ibrahim et al., 2017). The saponins from *Holothuria lessona* contribute to the anti-oxidant activity of this sea cucumber extracts (Bahrami et al., 2018). The health-beneficial effects including antioxidant, anti-diabetes, and immunomodulatory activities of sea cucumber peptides have been recently reviewed (Lu et al., 2022a).

Additionally, sea cucumber is an important constituent of food therapy for treatment of hypertension in Traditional Chinese Medicine (Zou, 2016). The peptides obtained from *Acaudina molpadioides* and *Actinopyga lecanora* show angiotensin I-converting enzyme inhibitor effect and exhibits antihypertensive activity in rats at 3 μ M/kg and 800 mg/kg, respectively (Zhao et al., 2009; Vishkaei et al., 2016; Festa et al., 2020).

Conclusion and future perspective

The components of sea cucumbers exhibit powerful lipid-lowering activity and have great potential applications for intervention of CVD and NALFD via modulating multiple signaling pathways involved in lipid homeostasis as well as gut microbiota. Saponins are one of the most important hypolipidemic components of sea cucumbers. Saponins of sea cucumbers enhance the LXR, SREBP-1c, and PPAR α signaling pathways. Among saponins isolated from sea cucumbers, only the lipid-lowering effects and mechanisms of action of echinoside A have been well-documented. Other bioactive compounds derived from these saponins need to be evaluated in the future to understand their potential structure-activity relationship. FAs and phospholipids are well-documented lipid-lowering components of sea cucumbers. EPA, PC, and PE exhibit powerful hypolipidemic effects, and the combination of EPA-PC or EPA-PE shows attractive applications for treatment of NALFD. Long-chain bases are the main active structural units of cerebrosides for intervention of hyperlipidemia. These long-chain bases modulate multiple signaling pathways involved in lipid homeostasis as well as gut microbiota. However, the studies of the lipid-lowering activity of these lipids are mostly carried out in NALFD models. The activity of these compounds needs to be investigated in CVD models in the future. Carbohydrates derived from sea cucumbers also have a potential application for treatment of hyperlipidemia. Structure-activity relationship analysis demonstrates that 4-O-sulfation of the glycosyls as well as low Mw polysaccharides benefit their hypolipidemic

activities. However, comparative studies need to be performed to investigate the relationship between Mw and the lipid-lowering effect of these carbohydrates.

Author contributions

PL, NS, and FY performed reference collection, drew the figures, and wrote the manuscript; S-DG re-edited the manuscript.

Funding

This research was funded by the National Natural Science Foundation of China (82070469 and 81770463).

References

- Abumrad, N. A., Piomelli, D., Yurko-Mauro, K., Merrill, A., Clandinin, M. T., and Serhan, C. N. (2012). Moving beyond “good fat, bad fat”: The complex roles of dietary lipids in cellular function and health: Session abstracts. *Adv. Nutr.* 3, 60–68. doi:10.3945/an.111.000802
- Aron-Wisniewsky, J., Warmbrunn, M. V., Nieuwdorp, M., and Clément, K. (2021). Metabolism and metabolic disorders and the microbiome: The intestinal microbiota associated with obesity, lipid metabolism, and metabolic health-physiology and therapeutic strategies. *Gastroenterology* 160, 573–599. doi:10.1053/j.gastro.2020.10.057
- Aslam, M., and Ladilov, Y. (2022). Emerging role of cAMP/AMPK signaling. *Cells* 11, 308. doi:10.3390/cells11020308
- Atar, D., Jukema, J. W., Molemans, B., Taub, P. R., Goto, S., Mach, F., et al. (2021). New cardiovascular prevention guidelines: How to optimally manage dyslipidaemia and cardiovascular risk in 2021 in patients needing secondary prevention? *Atherosclerosis* 319, 51–61. doi:10.1016/j.atherosclerosis.2020.12.013
- Bahrami, Y., Zhang, W., and M M Franco, C. (2018). Distribution of saponins in the sea cucumber *Holothuria lessona*; the body wall versus the viscera, and their biological activities. *Mar. Drugs* 16, 423. doi:10.3390/md16110423
- Bakar, N. A., Jayah, N. I., Mohamed, N. R., Ali, S. M., Nasir, S. H., Hashim, R., et al. (2020). The effectiveness of pure *Stichopus horrens* extract toothpaste in reducing plaque-induced gingivitis following orthodontic bonding: A triple-blinded randomized controlled trial. *J. World Fed. Orthod.* 9, 3–8. doi:10.1016/j.jewf.2019.11.004
- Beshir, S. A., Hussain, N., Elnor, A. A., and Said, A. S. A. (2021). Umbrella review on non-statin lipid-lowering therapy. *J. Cardiovasc. Pharmacol. Ther.* 26, 437–452. doi:10.1177/10742484211002943
- Bordbar, S., Anwar, F., and Saari, N. (2011). High-value components and bioactives from sea cucumbers for functional foods--a review. *Mar. Drugs* 9, 1761–1805. doi:10.3390/md9101761
- Careaga, V. P., Muniain, C., and Maier, M. S. (2013). Fatty acid composition of the edible sea cucumber *Athyonidium chilensis*. *Nat. Prod. Res.* 27, 638–646. doi:10.1080/14786419.2012.686909
- Chang, Y., Hu, Y., Yu, L., McClements, D. J., Xu, X., Liu, G., et al. (2016). Primary structure and chain conformation of fucoidan extracted from sea cucumber *Holothuria tubulosa*. *Carbohydr. Polym.* 136, 1091–1097. doi:10.1016/j.carbpol.2015.10.016
- Chen, S., Hu, Y., Ye, X., Li, G., Yu, G., Xue, C., et al. (2012). Sequence determination and anticoagulant and antithrombotic activities of a novel sulfated fucan isolated from the sea cucumber *Isostichopus badiionotus*. *Biochim. Biophys. Acta* 1820, 989–1000. doi:10.1016/j.bbagen.2012.03.002
- Chen, Y., Wang, Y., Yang, S., Yu, M., Jiang, T., and Lv, Z. (2019). Glycosaminoglycan from *Apostichopus japonicus* improves glucose metabolism in the liver of insulin resistant mice. *Mar. Drugs* 18, 1. doi:10.3390/md18010001
- Christodoulides, C., Lagathu, C., Sethi, J. K., and Vidal-Puig, A. (2009). Adipogenesis and WNT signalling. *Trends Endocrinol. Metab.* 20, 16–24. doi:10.1016/j.tem.2008.09.002
- Dashi, G., and Naiwal, N. (2021). A review on molecular mechanisms and patents of marine-derived anti-thrombotic agents. *Curr. Drug Targets* 22 (3), 318–335. doi:10.2174/1389450121666201020151927
- De Backer, G., Jankowski, P., Kotseva, K., Mirraikhimov, E., Reiner, Ž., Rydén, L., et al. (2019). Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis* 285, 135–146. doi:10.1016/j.atherosclerosis.2019.03.014
- De Vos, W. M., Tilg, H., Van Hul, M., and Cani, P. D. (2022). Gut microbiome and health: Mechanistic insights. *Gut* 71, 1020–1032. doi:10.1136/gutjnl-2021-326789
- Djuricic, I., and Calder, P. C. (2021). Beneficial outcomes of omega-6 and omega-3 polyunsaturated fatty acids on human health: An update for 2021. *Nutrients* 13, 2421. doi:10.3390/nu13072421
- Du, L., Yang, Y. H., Xu, J., Wang, Y. M., Xue, C. H., Kurihara, H., et al. (2016). Transport and uptake effects of marine complex lipid liposomes in small intestinal epithelial cell models. *Food Funct.* 7, 1904–1914. doi:10.1039/c6fo00066e
- Duan, J., Ishida, M., Aida, K., Tsuduki, T., Zhang, J., Manabe, Y., et al. (2016). Dietary cerebroside from sea cucumber (*Stichopus japonicus*): Absorption and effects on skin barrier and cecal short-chain fatty acids. *J. Agric. Food Chem.* 64, 7014–7021. doi:10.1021/acs.jafc.6b02564
- Ferraro, R. A., Leucker, T., Martin, S. S., Banach, M., Jones, S. R., and Toth, P. P. (2022). Contemporary management of dyslipidemia. *Drugs* 82, 559–576. doi:10.1007/s40265-022-01691-6
- Festa, M., Sansone, C., Brunet, C., Crocetta, F., Di Paola, L., Lombardo, M., et al. (2020). Cardiovascular active peptides of marine origin with ACE inhibitory activities: Potential role as anti-hypertensive drugs and in prevention of SARS-CoV-2 infection. *Int. J. Mol. Sci.* 21, 8364. doi:10.3390/ijms21218364
- Fredalina, B. D., Ridzwan, B. H., Abidin, A. A., Kaswandi, M. A., Zaiton, H., Zali, I., et al. (1999). Fatty acid compositions in local sea cucumber, *Stichopus chloronotus*, for wound healing. *Gen. Pharmacol.* 33, 337–340. doi:10.1016/s0306-3623(98)00253-5
- Guo, L., Gao, Z., Zhang, L., Guo, F., Chen, Y., Li, Y., et al. (2016). Saponin-enriched sea cucumber extracts exhibit an anti-obesity effect through inhibition of pancreatic lipase activity and up-regulation of LXR- β signaling. *Pharm. Biol.* 54, 1312–1325. doi:10.3109/13880209.2015.1075047
- Guo, Y., Ding, Y., Xu, F., Liu, B., Kou, Z., Xiao, W., et al. (2015). Systems pharmacology-based drug discovery for marine resources: An example using Sea cucumber (*holothurians*). *J. Ethnopharmacol.* 165, 61–72. doi:10.1016/j.jep.2015.02.029
- Guo, Y., Han, X., Che, H., Li, Z., Dong, P., Xue, C., et al. (2018). Synergistic effect of eicosapentaenoic acid-enriched phospholipids and sea cucumber saponin on orotic acid-induced non-alcoholic fatty liver disease in rats. *R. Soc. Open Sci.* 5, 172182. doi:10.1098/rsos.172182
- Han, B., Jian, Y., Xia, X., Hu, W., Zhang, L., and Zhou, P. (2020). Studying the effects of sea cucumber ovum powder on nonalcoholic fatty liver disease by

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

- proteomics techniques in a rat model. *Food Funct.* 11, 6139–6147. doi:10.1039/d0fo00741b
- Han, X. Q., Zhang, L. Y., Ding, L., Shi, H. H., Xue, C. H., Zhang, T. T., et al. (2019). Synergistic effect of sea cucumber saponins and EPA-enriched phospholipids on insulin resistance in high-fat diet-induced obese mice. *Food Funct.* 10, 3955–3964. doi:10.1039/c9fo01147a
- Heeren, J., and Scheja, L. (2021). Metabolic-associated fatty liver disease and lipoprotein metabolism. *Mol. Metab.* 50, 101238. doi:10.1016/j.molmet.2021.101238
- Hossain, A., Dave, D., and Shahidi, F. (2020). Northern Sea cucumber (*Cucumaria frondosa*): A potential candidate for functional food, nutraceutical, and pharmaceutical sector. *Mar. Drugs* 18, 274. doi:10.3390/md18050274
- Hu, S., Xu, Y., Gao, X., Li, S., Jiang, W., Liu, Y., et al. (2019). Long-chain bases from sea cucumber alleviate obesity by modulating gut microbiota. *Mar. Drugs* 17, 455. doi:10.3390/md17080455
- Hu, X., Li, Z., Xue, Y., Xu, J., Xue, C., Wang, J., et al. (2012). Dietary saponins of sea cucumber ameliorate obesity, hepatic steatosis, and glucose intolerance in high-fat diet-fed mice. *J. Med. Food* 15, 909–916. doi:10.1089/jmf.2011.2042
- Hu, X. Q., Wang, Y. M., Wang, J. F., Xue, Y., Li, Z. J., Nagao, K., et al. (2010). Dietary saponins of sea cucumber alleviate orotic acid-induced fatty liver in rats via PPAR α and SREBP-1c signaling. *Lipids Health Dis.* 9, 25. doi:10.1186/1476-511X-9-25
- Hu, X. Q., Xu, J., Xue, Y., Li, Z. J., Wang, J. F., Wang, J. H., et al. (2012). Effects of bioactive components of sea cucumber on the serum, liver lipid profile and lipid absorption. *Biosci. Biotechnol. Biochem.* 76, 2214–2218. doi:10.1271/bbb.120495
- Hu, Y., Li, S., Li, J., Ye, X., Ding, T., Liu, D., et al. (2015). Identification of a highly sulfated fucoidan from sea cucumber *pearsonothuria graeffei* with well-repeated tetrasaccharides units. *Carbohydr. Polym.* 134, 808–816. doi:10.1016/j.carbpol.2015.06.088
- Ibrahim, D. M., Radwan, R. R., and Abdel Fattah, S. M. (2017). Antioxidant and antiapoptotic effects of sea cucumber and valsartan against doxorubicin-induced cardiotoxicity in rats: The role of low dose gamma irradiation. *J. Photochem. Photobiol. B* 170, 70–78. doi:10.1016/j.jphotobiol.2017.03.022
- Kapoor, S., Nailwal, N., Kumar, M., and Barve, K. (2019). Recent patents and discovery of anti-inflammatory agents from marine source. *Recent Pat. Inflamm. Allergy Drug Discov.* 13 (2), 105–114. doi:10.2174/1872213X13666190426164717
- Khosravifar, M., Sajadimajid, S., and Bahramic, G. (2022). Anti-diabetic effects of macronutrients via modulation of angiogenesis: A comprehensive review on carbohydrates and proteins. *Curr. Mol. Med.* 22. doi:10.2174/1566524022666220321125548
- Khotimchenko, Y. (2018). Pharmacological potential of sea cucumbers. *Int. J. Mol. Sci.* 19, 1342. doi:10.3390/ijms19051342
- Kisa, F., Yamada, K., Kaneko, M., Inagaki, M., and Higuchi, R. (2005). Constituents of *Holothuroidea*, 14. Isolation and structure of new glucocerebroside molecular species from the sea cucumber *Stichopus japonicus*. *Chem. Pharm. Bull. (Tokyo)* 53, 382–386. doi:10.1248/cpb.53.382
- Lee, H., Bae, S., Kim, K., Kim, W., Chung, S. I., and Yoon, Y. (2010). Beta-Catenin mediates the anti-adipogenic effect of baicalin. *Biochem. Biophys. Res. Commun.* 398, 741–746. doi:10.1016/j.bbrc.2010.07.015
- Li, S., Li, J., Mao, G., Hu, Y., Ye, X., Tian, D., et al. (2018a). Fucosylated chondroitin sulfate oligosaccharides from *Isochopous badionotus* regulates lipid disorder in C57BL/6 mice fed a high-fat diet. *Carbohydr. Polym.* 201, 634–642. doi:10.1016/j.carbpol.2018.08.020
- Li, S., Li, J., Mao, G., Wu, T., Hu, Y., Ye, X., et al. (2018b). A fucoidan from sea cucumber *Pearsonothuria graeffei* with well-repeated structure alleviates gut microbiota dysbiosis and metabolic syndromes in HFD-fed mice. *Food Funct.* 9, 5371–5380. doi:10.1039/c8fo01174e
- Li, S., Li, J., Zhi, Z., Hu, Y., Ge, J., Ye, X., et al. (2017). 4-O-Sulfation in sea cucumber fucodians contribute to reversing dyslipidaemia caused by HFD. *Int. J. Biol. Macromol.* 99, 96–104. doi:10.1016/j.ijbiomac.2017.01.145
- Li, X., Zhang, Y., Wang, S., Shi, C., Wang, S., Wang, X., et al. (2022). A review on the potential use of natural products in overweight and obesity. *Phytother. Res.* 36, 1990–2015. doi:10.1002/ptr.7426
- Liu, H. H., Ko, W. C., and Hu, M. L. (2002). Hypolipidemic effect of glycosaminoglycans from the sea cucumber *Metriatyla scabra* in rats fed a cholesterol-supplemented diet. *J. Agric. Food Chem.* 50, 3602–3606. doi:10.1021/jf020070k
- Liu, X., Sun, Z., Zhang, M., Meng, X., Xia, X., Yuan, W., et al. (2012). Anti-oxidant and anti-hyperlipidemic activities of polysaccharides from sea cucumber *Apostichopus japonicus*. *Carbohydr. Polym.* 90, 1664–1670. doi:10.1016/j.carbpol.2012.07.047
- Liu, X., Xu, J., Xue, Y., Gao, Z., Li, Z., Leng, K., et al. (2015). Sea cucumber cerebrosides and long-chain bases from *Acadina maldopioides* protect against high fat diet-induced metabolic disorders in mice. *Food Funct.* 6, 3428–3436. doi:10.1039/c5fo00602c
- Liu, Y., Shi, D., Tian, Y., Liu, Y., Zhan, Q., Xu, J., et al. (2017). Eicosapentaenoic acid-enriched phosphatidylcholine attenuated hepatic steatosis through regulation of cholesterol metabolism in rats with nonalcoholic fatty liver disease. *Lipids* 52, 119–127. doi:10.1007/s11745-016-4222-1
- Lu, Z., Sun, N., Dong, L., Gao, Y., and Lin, S. (2022a). Production of bioactive peptides from sea cucumber and its potential health benefits: A comprehensive review. *J. Agric. Food Chem.* 70 (25), 7607–7625. doi:10.1021/acs.jafc.2c02696
- Lu, Z., Xu, X., Li, D., Sun, N., and Lin, S. (2022b). Sea cucumber peptides attenuated the scopolamine-induced memory impairment in mice and rats and the underlying mechanism. *J. Agric. Food Chem.* 70, 157–170. doi:10.1021/acs.jafc.1c06475
- Mecheta, A., Hanachi, A., Jeandel, C., Arab-Tehrany, E., Bianchi, A., Velot, E., et al. (2020). Physicochemical properties and liposomal formulations of hydrolysate fractions of four sea cucumbers (*Holothuroidea: Echinodermata*) from the northwestern Algerian coast. *Molecules* 25, 2972. doi:10.3390/molecules25132972
- Mena-Bueno, S., Atanasova, M., Fernández-Trasancos, Á., Paradelo-Dobarro, B., Bravo, S. B., Álvarez, E., et al. (2016). Sea cucumbers with an anti-inflammatory effect on endothelial cells and subcutaneous but not on epicardial adipose tissue. *Food Funct.* 7, 953–963. doi:10.1039/c5fo01246e
- Meng, J., Hu, X., Zhang, T., Dong, P., Li, Z., Xue, C., et al. (2018). Saponin from sea cucumber exhibited more significant effects than ginsenoside on ameliorating high fat diet-induced obesity in C57BL/6 mice. *Medchemcomm* 9, 725–734. doi:10.1039/c7md000653e
- Mitrovic, M., Sistilli, G., Horakova, O., and Rossmesl, M. (2022). Omega-3 phospholipids and obesity-associated NAFLD: Potential mechanisms and therapeutic perspectives. *Eur. J. Clin. Invest.* 52, e13650. doi:10.1111/eci.13650
- Mulloy, B., Ribeiro, A. C., Alves, A. P., Vieira, R. P., and Mourão, P. A. (1994). Sulfated fucans from echinoderms have a regular tetrasaccharide repeating unit defined by specific patterns of sulfation at the 0-2 and 0-4 positions. *J. Biol. Chem.* 269, 22113–22123. doi:10.1016/s0021-9258(17)31763-5
- Olivera-Castillo, L., Davalos, A., Grant, G., Valadez-Gonzalez, N., Montero, J., Barrera-Perez, H. A. M., et al. (2013). Diets containing sea cucumber (*Isochopous badionotus*) meals are hypocholesterolemic in young rats. *PLoS One* 8, e79446. doi:10.1371/journal.pone.0079446
- Pirillo, A., Casula, M., Olmastroni, E., Norata, G. D., and Catapano, A. L. (2021). Global epidemiology of dyslipidaemias. *Nat. Rev. Cardiol.* 18, 689–700. doi:10.1038/s41569-021-00541-4
- Pomin, V. H. (2014). Sea, carbohydrates and clotting: A triad on the road of drug discovery. *Mini Rev. Med. Chem.* 14 (9), 717–724. doi:10.2174/1389557514666140820121048
- Powell, E. E., Wong, V. W., and Rinella, M. (2021). Non-alcoholic fatty liver disease. *Lancet* 397, 2212–2224. doi:10.1016/S0140-6736(20)32511-3
- Qiao, Y. N., Zou, Y. L., and Guo, S. D. (2022). Low-density lipoprotein particles in atherosclerosis. *Front. Physiol.* 13, 931931. doi:10.3389/fphys.2022.931931
- Roggatz, C. C., González-Wangüemert, M., Pereira, H., Rodrigues, M. J., da Silva, M. M., Barreira, L., et al. (2016). First report of the nutritional profile and antioxidant potential of *Holothuria arguinensis*, a new resource for aquaculture in Europe. *Nat. Prod. Res.* 30, 2034–2040. doi:10.1080/14786419.2015.1107555
- Roggatz, C. C., González-Wangüemert, M., Pereira, H., Vizetto-Duarte, C., Rodrigues, M. J., Barreira, L., et al. (2018). A first glance into the nutritional properties of the sea cucumber *Parastichopus regalis* from the Mediterranean Sea (SE Spain). *Nat. Prod. Res.* 32, 116–120. doi:10.1080/14786419.2017.1331224
- Savarino, P., Demeyer, M., Decroo, C., Colson, E., and Gerbaux, P. (2021). Mass spectrometry analysis of saponins. *Mass Spectrom. Rev.* doi:10.1002/mas.21728
- Singh, S. P., and Sashidhara, K. V. (2017). Lipid lowering agents of natural origin: An account of some promising chemotypes. *Eur. J. Med. Chem.* 140, 331–348. doi:10.1016/j.ejmech.2017.09.020
- Tian, Y., Hu, S., Xu, H., Wang, J., Xue, C., and Wang, Y. (2016). Long-chain bases from *Cucumaria frondosa* inhibit adipogenesis and regulate lipid metabolism in 3T3-L1 adipocytes. *Food Sci. Biotechnol.* 25, 1753–1760. doi:10.1007/s10068-016-0267-4
- Tian, Y., Liu, Y., Xue, C., Wang, J., Wang, Y., Xu, J., et al. (2020). Exogenous natural EPA-enriched phosphatidylcholine and phosphatidylethanolamine ameliorate lipid accumulation and insulin resistance via activation of PPAR α / γ in mice. *Food Funct.* 11, 8248–8258. doi:10.1039/d0fo01219j
- Ustyuzhanina, N. E., Bilan, M. I., Dmitrenok, A. S., Nifantiev, N. E., and Usov, A. I. (2018). Fucosylated chondroitin sulfates from the sea cucumbers *Holothuria*

- tubulosa and *Holothuria stellati*. *Carbohydr. Polym.* 200, 1–5. doi:10.1016/j.carbpol.2018.07.035
- Vishkaei, M. S., Ebrahimpour, A., Abdul-Hamid, A., Ismail, A., and Saari, N. (2016). Angiotensin-I converting enzyme (ACE) inhibitory and anti-hypertensive effect of protein hydrolysate from *Actinopyga lecanora* (sea cucumber) in rats. *Mar. Drugs* 14 (10), 176. doi:10.3390/md14100176
- Visseren, F. L. J., Mach, F., Smulders, Y. M., Carballo, D., Koskinas, K. C., Bäck, M., et al. (2021). 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* 42, 3227–3337. doi:10.1093/eurheartj/ehab484
- Wan, H., Han, J., Tang, S., Bao, W., Lu, C., Zhou, J., et al. (2020). Comparisons of protective effects between two sea cucumber hydrolysates against diet induced hyperuricemia and renal inflammation in mice. *Food Funct.* 11, 1074–1086. doi:10.1039/c9fo02425e
- Wang, J., Hu, S., Jiang, W., Song, W., Cai, L., and Wang, J. (2016). Fucoidan from sea cucumber may improve hepatic inflammatory response and insulin resistance in mice. *Int. Immunopharmacol.* 31, 15–23. doi:10.1016/j.intimp.2015.12.009
- Wang, X., Cong, P., Chen, Q., Li, Z., Xu, J., and Xue, C. (2020). Characterizing the phospholipid composition of six edible sea cucumbers by NPLC-Triple TOF-MS/MS. *J. Food Compos. Anal.* 94, 103626. doi:10.1016/j.jfca.2020.103626
- Wang, X., Wang, H., Hu, D., Guo, X., Jin, C., Lu, N., et al. (1997). Clinical study on the antithrombotic effects of *Holothuria Ldeucospilota* acidic mucopolysaccharide. *Chin. J. Hematol.* 18, 457–459.
- Wang, X., Wang, Y., Liu, Y., Cong, P., Xu, J., and Xue, C. (2022). Hepatoprotective effects of sea cucumber ether-phospholipids against alcohol-induced lipid metabolic dysregulation and oxidative stress in mice. *Food Funct.* 13, 2791–2804. doi:10.1039/d1fo03833h
- Wargasetia, T. L., Ratnawati, H., and Widodo, N. (2022). sea cucumber compounds targeting NF- κ B in cancer treatment. *Bioinform. Biol. Insights* 16, 1177932221091740. doi:10.1177/1177932221091740
- Wen, M., Cui, J., Xu, J., Xue, Y., Wang, J., Xue, C., et al. (2014). Effects of dietary sea cucumber saponin on the gene expression rhythm involved in circadian clock and lipid metabolism in mice during nighttime-feeding. *J. Physiol. Biochem.* 70, 801–808. doi:10.1007/s13105-014-0349-9
- Wen, M., Ding, L., Zhang, L., Cong, P., Zhang, T., Xu, J., et al. (2018). A comparative study of eicosapentaenoic acid enriched phosphatidylcholine and ethyl ester in improving cognitive deficiency in Alzheimer's disease model rats. *Food Funct.* 9, 2184–2192. doi:10.1039/c7fo01815k
- Wen, M., Fu, X., Han, X., Hu, X., Dong, P., Xu, J., et al. (2016). Sea cucumber saponin *Echinoidside A* (EA) stimulates hepatic fatty acid β -oxidation and suppresses fatty acid biosynthesis coupling in a diurnal pattern. *J. Nutr. Sci. Vitaminol. (Tokyo)* 62, 170–177. doi:10.3177/jnsv.62.170
- World Health Organization (2021). *Cardiovascular diseases (CVDs)*. [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) (accessed sept 20, 2021).
- Wu, N., Zhang, Y., Ye, X., Hu, Y., Ding, T., and Chen, S. (2016). Sulfation pattern of fucose branches affects the anti-hyperlipidemic activities of fucosylated chondroitin sulfate. *Carbohydr. Polym.* 147, 1–7. doi:10.1016/j.carbpol.2016.03.013
- Xu, H., Wang, F., Wang, J., Xu, J., Wang, Y., and Xue, C. (2015b). The WNT/ β -catenin pathway is involved in the anti-adipogenic activity of cerebrosides from the sea cucumber *Cucumaria frondosa*. *Food Funct.* 6, 2396–2404. doi:10.1039/c5fo00273g
- Xu, H., Wang, J., Chang, Y., Xu, J., Wang, Y., Long, T., et al. (2014). Fucoidan from the sea cucumber *Acaudina molpadioides* exhibits anti-adipogenic activity by modulating the Wnt/ β -catenin pathway and down-regulating the SREBP-1c expression. *Food Funct.* 5, 1547–1555. doi:10.1039/c3fo60716j
- Xu, H., Wang, J., Zhang, X., Li, Z., Wang, Y., and Xue, C. (2015a). Inhibitory effect of fucosylated chondroitin sulfate from the sea cucumber *Acaudina molpadioides* on adipogenesis is dependent on Wnt/ β -catenin pathway. *J. Biosci. Bioeng.* 119, 85–91. doi:10.1016/j.jbiosc.2014.05.026
- Xu, H., Zhou, Q., Liu, B., Chen, F., and Wang, M. (2022). Holothurian fucosylated chondroitin sulfates and their potential benefits for human health: Structures and biological activities. *Carbohydr. Polym.* 275, 118691. doi:10.1016/j.carbpol.2021.118691
- Xu, J., Guo, S., Du, L., Wang, Y. M., Sugawara, T., Hirata, T., et al. (2013). Isolation of cytotoxic glucocerosides and long-chain bases from sea cucumber *Cucumaria frondosa* using high speed counter-current chromatography. *J. Oleo Sci.* 62, 133–142. doi:10.5650/jos.62.133
- Xu, J., Wang, Y. M., Feng, T. Y., Zhang, B., Sugawara, T., and Xue, C. H. (2011). Isolation and anti-fatty liver activity of a novel cerebroside from sea cucumber *Acaudina molpadioides*. *Biosci. Biotechnol. Biochem.* 75, 1466–1471. doi:10.1271/bbb.110126
- Xu, X., Chang, Y., Xue, C., Wang, J., and Shen, J. (2018). Gastric protective activities of sea cucumber fucoidans with different molecular weight and chain conformations: A structure-activity relationship investigation. *J. Agric. Food Chem.* 66, 8615–8622. doi:10.1021/acs.jafc.8b01497
- Yamada, K., Sasaki, K., Harada, Y., Isobe, R., and Higuchi, R. (2002). Constituents of *Holothuroidea*, 12. Isolation and structure of glucocerosides from the sea cucumber *Holothuria pervicax*. *Chem. Pharm. Bull. (Tokyo)* 50, 1467–1470. doi:10.1248/cpb.50.1467
- Yamada, K., Wada, N., Onaka, H., Matsubara, R., Isobe, R., Inagaki, M., et al. (2005). Constituents of *Holothuroidea*, 15. Isolation of ante-iso type regioisomer on long chain base moiety of glucoceroside from the sea cucumber *Holothuria leucospilota*. *Chem. Pharm. Bull. (Tokyo)* 53, 788–791. doi:10.1248/cpb.53.788
- Yang, J., Wang, Y., Jiang, T., and Lv, Z. (2015). Novel branch patterns and anticoagulant activity of glycosaminoglycan from sea cucumber *Apostichopus japonicus*. *Int. J. Biol. Macromol.* 72, 911–918. doi:10.1016/j.ijbiomac.2014.10.010
- Yang, J. Y., Zhang, T. T., Dong, Z., Shi, H. H., Xu, J., Mao, X. Z., et al. (2021). Dietary supplementation with exogenous sea-cucumber-derived ceramides and glucosylceramides alleviates insulin resistance in high-fructose-diet-fed rats by upregulating the IRS/PI3K/Akt signaling pathway. *J. Agric. Food Chem.* 69, 9178–9187. doi:10.1021/acs.jafc.0c06831
- Yin, J., Yang, X., Xia, B., Yang, Z., Wang, Z., Wang, J., et al. (2019). The fucoidan from sea cucumber *Apostichopus japonicus* attenuates lipopolysaccharide-challenged liver injury in C57BL/6J mice. *J. Funct. Foods* 61, 103493. doi:10.1016/j.jff.2019.103493
- Yu, E., Liao, Z., Tan, Y., Chou, Y., Zhu, J., Chen, Y., et al. (2017). [Efficacy and tolerance of Memantine monotherapy and combination therapy with Reinhartdt and Sea Cucumber Capsule on agitation in moderate to severe Alzheimer disease]. *Zhonghua Yi Xue Za Zhi* 97, 2091–2094. doi:10.3760/cma.j.issn.0376-2491.2017.27.003
- Yu, L., Ge, L., Xue, C., Chang, Y., Zhang, C., Xu, X., et al. (2014a). Structural study of fucoidan from sea cucumber *Acaudina molpadioides*: A fucoidan containing novel tetra-fucose repeating unit. *Food Chem.* 142, 197–200. doi:10.1016/j.foodchem.2013.06.079
- Yu, L., Xue, C., Chang, Y., Hu, Y., Xu, X., Ge, L., et al. (2015). Structure and rheological characteristics of fucoidan from sea cucumber *Apostichopus japonicus*. *Food Chem.* 180, 71–76. doi:10.1016/j.foodchem.2015.02.034
- Yu, L., Xue, C., Chang, Y., Xu, X., Ge, L., Liu, G., et al. (2014b). Structure elucidation of fucoidan composed of a novel tetra-fucose repeating unit from sea cucumber *Thelenota ananas*. *Food Chem.* 146, 113–119. doi:10.1016/j.foodchem.2013.09.033
- Yu, Y., Wu, G., Jiang, Y., Li, B., Feng, C., Ge, Y., et al. (2020). sea Cucumber peptides improved the mitochondrial capacity of mice: A potential mechanism to enhance gluconeogenesis and fat catabolism during exercise for improved antifatigue property. *Oxid. Med. Cell. Longev.* 2020, 4604387. doi:10.1155/2020/4604387
- Yuan, Y., Li, C., Zheng, Q., Wu, J., Zhu, K., Shen, X., et al. (2019a). Effect of simulated gastrointestinal digestion *in vitro* on the antioxidant activity, molecular weight and microstructure of polysaccharides from a tropical sea cucumber (*Holothuria leucospilota*). *Food Hydrocol.* 89, 735–741. doi:10.1016/j.foodhyd.2018.11.040
- Yuan, Y., Liu, Q., Zhao, F., Cao, J., Shen, X., and Li, C. (2019b). *Holothuria leucospilota* polysaccharides ameliorate hyperlipidemia in high-fat diet-induced rats via short-chain fatty acids production and lipid metabolism regulation. *Int. J. Mol. Sci.* 20, 4738. doi:10.3390/ijms20194738
- Zhang, B. H., Yin, F., Qiao, Y. N., and Guo, S. D. (2022a). Triglyceride and triglyceride-rich lipoproteins in atherosclerosis. *Front. Mol. Biosci.* 9, 909151. doi:10.3389/fmolb.2022.909151
- Zhang, B., Xue, C., Hu, X., Xu, J., Li, Z., Wang, J., et al. (2012). Dietary sea cucumber cerebroside alleviates orotic acid-induced excess hepatic adipogenesis in rats. *Lipids Health Dis.* 11, 48. doi:10.1186/1476-511X-11-48
- Zhang, L., Ding, L., Shi, H., Wang, C., Xue, C., Zhang, T., et al. (2020). Eicosapentaenoic acid-enriched phospholipids suppressed lipid accumulation by specific inhibition of lipid droplet-associated protein FSP27 in mice. *J. Sci. Food Agric.* 100, 2244–2251. doi:10.1002/jsfa.10250
- Zhang, L., Zhang, T., Ding, L., Xu, J., Xue, C., Yanagita, T., et al. (2018). The protective activities of dietary sea cucumber cerebroside against atherosclerosis through regulating inflammation and cholesterol metabolism in male mice. *Mol. Nutr. Food Res.* 62, e1800315. doi:10.1002/mnfr.201800315
- Zhang, Q., Wang, L., Wang, S., Cheng, H., Xu, L., Pei, G., et al. (2022b). Signaling pathways and targeted therapy for myocardial infarction. *Signal Transduct. Target. Ther.* 7 (1), 78. doi:10.1038/s41392-022-00925-z

- Zhao, G., Zhao, W., Han, L., Ding, J., and Chang, Y. (2020). Metabolomics analysis of sea cucumber (*Apostichopus japonicus*) in different geographical origins using UPLC-Q-TOF/MS. *Food Chem.* 333, 127453. doi:10.1016/j.foodchem.2020.127453
- Zhao, Y., Li, B., Dong, S., Liu, Z., Zhao, X., Wang, J., et al. (2009). A novel ACE inhibitory peptide isolated from *Acaudina molpadioides* hydrolysate. *Peptides* 30, 1028–1033. doi:10.1016/j.peptides.2009.03.002
- Zhu, Y., Tian, Y., Wang, N., Chang, Y., Xue, C., and Wang, J. (2021). Structure-function relationship analysis of fucoidan from sea cucumber (*Holothuria tubulosa*) on ameliorating metabolic inflammation. *J. Food Biochem.* 45, e13500. doi:10.1111/jfbc.13500
- Zhu, Z., Zhu, B., Ai, C., Lu, J., Wu, S., Liu, Y., et al. (2018b). Development and application of a HPLC-MS/MS method for quantitation of fucosylated chondroitin sulfate and fucoidan in sea cucumbers. *Carbohydr. Res.* 466, 11–17. doi:10.1016/j.carres.2018.07.001
- Zhu, Z., Zhu, B., Sun, Y., Ai, C., Wang, L., Wen, C., et al. (2018c). Sulfated polysaccharide from sea cucumber and its depolymerized derivative prevent obesity in association with modification of gut microbiota in high-fat diet-fed mice. *Mol. Nutr. Food Res.* 62, e1800446. doi:10.1002/mnfr.201800446
- Zhu, Z., Zhu, B., Sun, Y., Ai, C., Wu, S., Wang, L., et al. (2018a). Sulfated polysaccharide from sea cucumber modulates the gut microbiota and its metabolites in normal mice. *Int. J. Biol. Macromol.* 120, 502–512. doi:10.1016/j.ijbiomac.2018.08.098
- Zou, P. (2016). Traditional Chinese medicine, food therapy, and hypertension control: A narrative review of Chinese literature. *Am. J. Chin. Med.* 44, 1579–1594. doi:10.1142/S0192415X16500889

Glossary

- ABC** ATP binding cassette
- ACC** acetyl CoA carboxylase
- ACOX1** acyl-CoA oxidase 1
- AMPK** adenosine monophosphate activated protein kinase
- Apo** apolipoprotein
- ATGL** adipose triglyceride lipase
- CD36** cluster of differentiation 36
- C/EBP α** CCAAT/enhancer binding protein- α
- CPT** carnitine palmitoyl transferase
- CVD** cardiovascular disease
- CYP7A1** cholesterol 7- α -hydroxylase A1
- EPA** eicosapentaenoic acid
- EPA-PC** EPA-enriched phosphatidylcholine
- EPA-PE** EPA-enriched phosphatidylethanoamine
- FA** fatty acid
- FAS** fatty acid synthase
- FCS** fucosylated chondroitin sulfate
- Fz** frizzled receptor
- GAGs** glycosaminoglycans
- G6PDH** glucose-6-phosphate dehydrogenase
- HDL-c** high-density lipoprotein cholesterol
- HLP** polysaccharides isolated from sea cucumber *Holothuria leucospilota*
- HMGCR** 3-hydroxy-3-methyl-glutaryl-CoA reductase
- HSL, hormone-sensitive lipase;**
- LC-MS/MS** liquid chromatography-tandem mass spectrometry
- LDL** low-density lipoprotein
- LDL-c** low-density lipoprotein cholesterol
- LPL** lipoprotein lipase
- LRP** lipoprotein receptor-related protein
- LXR** liver X receptor
- Mw** molecular weight
- NAFLD** non-alcoholic fatty liver disease;
- PlsCho** plasmalyl phosphatidylcholine
- PlsEtn** plasmalyl phosphatidylethanoamine
- PPAR** peroxisome proliferator-activated receptor
- SCD** stearoyl-CoA desaturase
- SCFA** short-chain fatty acid
- SD** Sprague-Dawley
- SREBP** sterol regulatory element-binding protein
- TC** total cholesterol
- TG** triglyceride