Ceramides as Potential Therapeutic Targets

Subjects: Allergy

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Ceramides are bioactive lipid intermediates and members of the sphingolipid family that take part in the formation of the lipid bilayer of the cell membrane. Although ceramide synthesis occurs in actually all organs in the body, the principal site for ceramide production is the liver. In cultured cells and isolated tissues, ceramides perturb mitochondrial function, block fuel usage, disrupt vasodilatation and promote apoptosis.

Keywords: non-alcoholic fatty liver disease ; NAFLD ; ceramide ; sphingolipids ; SL ; atherosclerosis ; ATS ; biomarkers ; therapeutic targets

1. Ceramides as Potential Therapeutic Targets

A myriad of research, including some clinical trials such as NCT02133144 [1], or NCT02211612 [2], have displayed the impact of high saturated fat consumption on human organism. For that reason, lipid excess leads to increased intrahepatic TG accumulation, lipolysis, and harmful plasma ceramides formation. Given their common role in the onset and progression of both metabolic diseases NAFLD and ATS, ceramides continue to be researched as potential therapeutic targets. By this novel approach inhibition of ceramide pathway could alleviate hepatic inflammation precursors, oxidative cell secretion, circulating LDL aggregation and foam cell formation, benefiting both disease [3].

1.1. Myriocin

Thermozymocidin also known as Myriocin is an irreversible and high affinity inhibitor of SPT, an enzyme involved in up-regulation in de novo synthesis of ceramide that has therapeutic potential against diabetes, ATS and hepatic steatosis by decresing ceramide levels [4]. In humans treatment with Myriocin did not changed the amount of LDL particles or TG, but rather it changed the composition of LDL particles, especially the concentration of SM [5]. Additionally, Yang et al. [6] demonstrated the efficacy of Myriocin in NAFLD severity by decreasing the levels of plasma ceramides. They examined three groups of mice: control group, rats fed with standard diet for 16 weeks, and the third group formed by rats with high-fat diet (HFD) + Myriocin 0.3 mg/kg on alternate days from the 8 week to 16 week by gavage. Rats fed with HFD increased in body weight, while those with Myriocin decreased in body weight, and their hepatic levels of LC-3II and p62 were inverted to normal levels. They observed decreasing of LC-3 II/I ratio and increasing of p62 at 12, 24 and 48 h post FFAs incubation, while in Myriocin cells the level of LC-3 II/I was restored to normal at 12 and 24 h, at 48 h for p62 [6].

Another study analyzed the effect of Myriocin on 4–6 weeks rats and the importance of lowering ceramides in development of NAFLD. By dividing also, into same three groups, they noted that the serum ceramide content were remarkable higher in those with high-fat diet, and that Myriocin treatment reduced ceramide content, liver TG and improved the level of inflammation, the expression of TNF-α, and significantly attenuated hepatic fibrosis, the expression of p-JNK/JNK (p-Jun N-terminal kinase/Jun N-terminal kinase), cytochrome c, and Bax, a multitude of markers involved in apoptotic processes. Hence therapy with Myriocin may help reduce the risk of developing NAFLD and later NASH [7].

1.2. CerS Inhibitors

With inflammation as a main link, additional therapies such as methotrexate, PCSK9 inhibitors or interleukin-1b inhibition, may be new strategies for treating cardiovascular diseases [8]. Moreover, several enzymes of the sphingolipid synthesis have already been tested as potential drug targets as their inhibition has been shown to decrease ATS [9]. There are six mammalian CerS (CerS1-6) known, each being codified on a different chromosome [10]. Each CerS are distributed differently in tissue. A model of CerS2-null mice, generates disruption of different cellular pathways and biochemical processes with decrease of C22–C24 ceramides [10]. Since ceramides, are implicated in a lot of diseases, CerS might potentially be targets for therapeutic direction in various pathologies [3].

Subsequent research identified that not only deficiency in CerS can modulate ceramide levels, inhibition of several CerS also affect the serum levels of ceramides, one of them is Fumonisin B1 (FB1), a CerS inhibitor produced by *Fusarium moniliforme* which contains an aminopentol backbone with two hydroxyl groups esterified with tricarballylic acids [11]. CerS inhibition by FB1 triggers a “perfect storm” of alterations in structural and signaling sphingolipids such as: reduced formation of dihydroceramides and ceramides. Practically, this compound inhibits sphinganine and acyl-CoA [12]. Because of the potential hepato-renal toxicity, the clinical use of fumonisin B1 is limited [13]. The affection caused by FB1 can be called “sphingolipidoses”, and the authors attention users about the consequences of CerS inhibition with future precautions when investigating other naturally occurring and synthetic compounds [14].

Dysregulation of the sphingolipid pathway has been described in several inflammatory and immune-mediated diseases such as systemic lupus erythematosus (SLE) [15]. Data shows that SLE patients have higher plasma levels of total ceramides, including C16:0, C18:1, C18:0, C20:1, C:20:0, C24:1, and 26:1 Cer species [16]. As ceramides are associated with apoptosis and inflammation which are pathways to ATS and CAD, SLE patients have a raised risk of disease development [17]. Thus, it is essential to find a treatment that would decrease the concentration of ceramides and somewhat all phenomena triggered by them, in order to decrease this risk. Evidence describes the role of S1P in NAFLD, IR and obesity development. There are two sphingosine kinase isoforms, SPHK1 and SPHK2, which synthesize S1P by phosphorylating sphingosine [18]. With this in mind, another inhibitor of CerS is Australia fungin FTY720 (Fingolimod), an FDA-approved drug for treatment of multiple sclerosis and an agonist of S1P receptors (S1PR) that inhibits CerS by noncompetitive inhibition of acyl-CoA [19][20]. He is also researched as a potent immunosuppressive agent currently in Phase III clinical trials for kidney transplantation [12]. In a recent article, oral administration of FTY720 in diet-induced animal model of NAFLD (DIAMOND), improved glucose tolerance, reduced steatosis and TG levels [21]. Aditionally, treatment with FTY720 reduced liver sphingolipid levels, including ceramides, monohexosylceramides, and sphingomyelins, especially the C16:0 and C24:1 species, as well as dihydro-S1P and S1P [20][21]. After 20 weeks of high-cholesterol diet to apolipoprotein E deficient mice, FTY720 drastically reduced atherosclerotic lesion volume (62.5%), most probably by uppressing the machinery involved in monocyte/macrophage emigration to atherosclerotic lesions. Given the fact that vascular S1P receptors stayed functional under Fingolimod, S1P agonists that selectively target the vasculature and not the immune system, may be promising new therapy against ATS [22].

On this note, a small part of the HDL population contains apolipoprotein M (ApoM), which is the main plasma carrier of the bioactive lipid mediator S1P. The majority of S1P is linked to ApoM and have an impact on the atherosclerotic process by regulation of adhesion molecule abundance, leukocyte-endothelial adhesion, and endothelial barrier. This axis also has proposed in recent years for ATS treatment [23][24]. A detailed scientometric research study which analyzed the use of S1P in age-related diseases, recommend evaluating the interconnection and unintended side effects of S1P, with the future possibility of discovering novel avenues for research and broaden the clinical value of S1P [25]. Interestingly, genetic deficiency of SphK2 but not SphK1, aggravates the formation of atherosclerotic lesions in mice with ApoE deficiency. Their results indicate that SphK2 may be a novel target for treating ATS, as it is required for autophagosome- and lysosome-mediated catabolism of intracellular lipid droplets to interfere with the development of ATS [26].

1.3. Des1 Inhibitors

Another caching therapeutic target is Des1, an enzyme that catalyzes the final step in the de novo synthesis of ceramide: the insertion of a C4 double bond into the precursor dihydroceramide to form ceramide [27]. The study reported by Chaurasia et al. [28] revealed that inducible genetic ablation of DES1, which prevents the conversion of dihydroceramides to ceramides during de novo sphingolipid synthesis, has substantial improvement in insulin sensitivity, prevention of pancreatic b-cell dysfunction, and resolution of liver fat, hepatocyte inflammation and fibrosis [28]. Likewise, animal studies pointed out that with the decline of DEGS1 (the gene encoding for Des1), de novo biosynthesis of ceramide is disturbed [29]. Development of inhibitors of Des1 in the ceramide pathway [30] offers exciting opportunities to reduce the cardiometabolic disease for a large number of suffering individuals, therefore, further research is needed in order to decipher the complex role of dihydroceramides in cell biology and reveal new therapeutic approaches.

1.4. MTP Inhibitors

Accretion microsomal triglyceride transfer proteins are important in regulating the secretion, synthesis of ceramides and are directly involved in the sphingolipid transport to the plasma by setting release of beta-lipoproteins [31]. Apo-B-containing lipoproteins (B-lps) are a type of lipoproteins involved in transport of different types of lipids inclusive ceramides [32]. The loss of this protein in humans is called abetalipoproteinemia (ABL), an autosomal recessive disorder with an estimated frequency of <1 in 1,000,000 [31][33]. In an experimental animal study, authors objected that MTP is involved in ceramide and sphingomyelin secretion, but not in their synthesis, also MTP might regulate plasma ceramide and

sphingomyelin levels by transferring these lipids to B-lps in the liver and intestine, and facilitate their secretion [31][33]. They compared a mouse model of ABL, with deleted MTP gene in the liver and small intestine and controls group. Mice plasma concentrations of TG, phospholipid, cholesterol, and ceramide were reduced by >90% compared with control mice. Plasma sphingomyelin levels were reduced by ~73% in the MTP-deficient mice, and all levels of ceramides decreased [34]. The selective inhibition of MTP triglyceride transfer activity may reduce hyperlipidemia while protecting the hepatic parenchyma from excess lipid accumulation [35]. Disrupting the formation of ceramides by ABL in patients or MTP-deficient mice leads to a decrease in plasma ceramides concentrations and implicitly to a decrease in the formation of atheroma plaque [18]. Additionally, treatment with the MTP inhibitor led to reversal of hyperlipidemia in atherosclerotic mice, and beneficial changes in the composition and the inflammatory state of the plaque [36]. MTP inhibitor may serve as a therapeutic target especially in those with less therapeutic effect with current treatments, such as statins.

1.5. ASMase Inhibitors

Enzyme such as acid sphingomyelinase (aSMase) catalyzes the hydrolysis of sphingomyelin (ASMase) to ceramide, mediates redox signaling in coronary arterial endothelial cells [37].

Palmitic acid (PA) and lipopolysaccaharide (LPS) play a major role in this processes by stimulating ASM and up-regulates pro-inflammatory cytokines [38][39]. High sphingolipid levels are linked with plaque instability through contribution of SMases in different inflamatory pathways [40]. The aSMase and neutral SMase (nSMase), especially the type 2-neutral SMase (nSMase2—a cloned N-SMase isoform), are activated in vascular cells by inflammatory agents and may contribute to endothelial activation and inflammation [41].

To elucidate the role of nSMase2 in atherogenesis, researchers explored a genetic double mutant mouse model deficient in both nSMase2 activity and ApoE deficient and a pharmacological model of long-term inhibition of nSMase2 by GW4869 in ApoE deficient mice [42]. The results show that the genetic deficiency of nSMase2 or its pharmacological inhibition by GW4869, significantly reduced the size of atherosclerotic areas, and the accumulation of macrophages, by 68% in mice treated with GW4869 compared to 49% control mice [43] Additionally, the deficiency or inhibition of nSMase2 activity resulted in a significant decrease in plasma ceramide levels, particularly in 24:1, 22:0, and 24:0 ceramide levels [43][44]. The inhibition of nSMase2 suppress inflammation by two mechanisms: a short time process implicating Nrf2 (nuclear factor [erythroid-derived 2]-like 2 or) that plays as an anti-inflammatory response, and long-term action, by decreasing the production of pro-inflammatory ceramides [45]. The pharmacological or genetic inhibition of nSMase2 was not associated with plasma lipoprotein changes, but with the direct effect on the arterial wall [43].

Lu et al. [43] noticed in their metabolic study that both amitriptyline and GW4869 reduced glucose, lipids, and IR. Amitriptyline inhibits ATS through modulation of sphingolipid metabolism [46]. Given to mice with LDL receptor-deficient that contain high amounts of SFFA, such as PA, a high-fat diet, they observed an increased development of systemic inflammation, activation of Toll-like receptors in macrophages and cytokines, with subsequently ATS [43]. Collectively, this research pointed that amitriptyline inhibited NASH and ATS through modulation of sphingolipid metabolism in rodents, indicating that sphingolipid metabolism in macrophages plays a crucial role in the linkage of NASH and ATS [42][43].

Imipramine, another tricyclic antidepressant, significantly decreased the total ceramide concentrations, phospho-p38, phospho-JNK and steatosis levels in ethanol-fed mice [47]. ASMase inhibitors may be considered to be a therapeutic target for alcohol-induced hepatic steatosis and stress kinases activation.

1.6. Lip-C6

Ceramide have also a negative impact on the balance of energy homeostasis, including the inhibition of the energy-sensor adenosine monophosphate activated kinase (AMPK) phosphorylation and different transcription agents such as Nrf2 [48]. The general effects of ceramides depends on specific chain lengths, a few years ago started the preclinical development of the Ceramide NanoLiposome (CNL), as an anticancer drug for the initial indication of hepatocellular carcinoma (HCC). The CNL short-chain C6-ceramide (Lip-C6), can actually exercise anti-inflammatory and anti-lipogenesis effects [49]. Zanleri et al. [50] studied the effects of non-apoptotic systemic doses of the cell permeable ceramide Lip-C6 on AMPK-and Nrf2-dependent oxidative stress [50]. The results showed that Lip-C6 is not as metabolically active, treatment induced a strong phosphorylation of AMPK in methionine-choline deficient (MCD)-fed mice, but overall reversed the imbalance in hepatic phosphatidylcholines and diacylglycerides species, energy/metabolic depletion and raised protective anti-oxidant signaling pathways, most likely by restoring homeostatic lipid function [50].

1.7. Glucagon-like Peptide-1 (GLP-1)

Liraglutide a GLP-1 receptor agonist, (GLP-1R), beyond its action on T2DM it has directly effects on hepatocytes, limit ER stress and has anti-steatotic effects [51][52]. Methionine-choline deficient (MCD) diet rodents have a higher development of steatosis and inflammation, with elevated concentration of ceramides especially CER16, CER24, compared to the MCD-liraglutide-treated mice, who showed decreased levels of plasma lipids [53]. Different gene expression of Sptlc2, cerS4, and cerS6 were down-regulated by liraglutide, emphasizing the effect of liraglutide on sphingolipid metabolism and mainly on evolution of NAFLD [54]. Another role of GLP-1R is to prevent accumulation of ceramide in the cardiac progenitor cells, and the subsequently development of various cardiovascular pathologies, such as ATS [55][56]. GLP-1-based therapies appear to provide beneficial effects against ATS and NAFLD; however, additional randomized data will be required to arrive at conclusive evidence.

1.8. Intestinal FXR/SMPD3 Axis

Another therapeutic target that should be considered is the intestinal farnesoid X receptor (FXR), which is a ligand-activated nuclear receptor significantly activated in patients with hypercholesteremia and mice fed a high-cholesterol diet (HCD) [57]. Recent studies performed on HCD-rodents showed that intestinal FXR deficiency or direct FXR inhibition (via treatment with the FXR antagonist glycoursodeoxycholic acid [GUDCA]), decreased ATS and reduced the levels of circulating ceramides and cholesterol, all these results suggesting that intestinal FXR modulates intestinal ceramide production [58]. Furthermore, in this study they identified sphingomyelin phosphodiesterase 3 (SMPD3), as an FXR target gene which can regulate cholesterol catabolism by modulating the hepatic CYP7A1 activity [58]. Hepatic CYP7A1 represents the rate-limiting enzyme in the classical bile acid synthesis pathway, and, also, the key enzyme involved in cholesterol catabolism, which can potentiate ATS [59]. Additionally, they reported that fibroblast growth factor 15/19 (FGF15/19) binds to FGF receptor 4 (FGFR4) to suppress hepatic expression of CYP7A1 [59]. This study showed that intestinal FXR/SMPD3 inhibition could be considered to be a therapeutic target for ATS treatment by lowering the circulating ceramide level and by protecting against metabolic diseases including obesity, IR, and fatty liver [59].

1.9. Other Therapeutic Approaches

Velázquez et al. [60] revealed that administration of high-fat-high-fructose (HF-HFr) diet causes hypertriglyceridemia and hepatic lipid deposition, but not inflammation, ER stress or oxidative stress. Moreover, liver ceramides were reported to be increased in NASH, but not in simple steatosis in humans [60]. They compared four groups: first the control group, second HF-HFr, third high-fat diet containing caffeine (CAF), fourth high-fat diet containing a green coffee extract providing 0.18 g of caffeine/kg of diet, and 10% fructose in the drinking water. The HF-HFr diet significantly reduced the levels of Cer 14:0 and Cer 16:0 and fat liver accumulation [57]. It is known by now that regular coffee consumption is significantly associated with a reduced risk of NAFLD and of liver fibrosis [61]. More epidemiological studies are needed to validate coffee consumption as an essential preventive measure in hepatic steatosis [62]. Besides coffee consumption, a dietary change based on increasing intake of fruit and vegetables in parallel with decreasing consumption of refined carbohydrates or fat, may reduce serum concentration of ceramides. Targeting dietary patterns, showed the importance of healthy diet in lowering the concentration of plasma ceramides and decrease in cardiovascular risk [63].

Mathews et al. [64] discovered that 8 week of free-living fruit and vegetables diet can lower ceramide concentration. All 36 subject were divided into three groups: fruit and vegetables, low refined carbohydrates and low fat. They discovered that majority of ceramides, especially C24:0 a known insulin signaling modulator and the most abundant ceramide in circulation, diminished by week 5, up to 48% in the fruit and vegetables plus low fat group. Additionally, C24:0 was correlated with pro-inflammatory cytokines such as IFN-γ (Interferon-γ) or interleukin-10 (IL-10). In addition to the decrease in ceramide levels, a decrease in waist circumference, systolic boold presure and circulating cholesterol was, also, noticed [64]. All data collected from the study, point out the importance of a health diet concerning the diminishing of ceramide content and augment clinical biomarkers in metabolic and cardiovascular disorders.

The traditional Mediterranean diet (MedDiet) may have the potential to lessen the injurios effect associated with elevated baseline plasma ceramide concentrations on CVD risk [65]. The effect of MedDiet was studied in a PREDIMED trial consisted of 980 participants including 230 incident cases of CVD and 787 randomly selected participants at baseline (including 37 overlapping cases), tracked up to 7.4 years. They observed how MedDiet intervention modified the damaging effect of higher ceramide concentrations on CVD risk. Consumption of MedDiet may directly influence ceramide biosynthesis by changing circulating FFAs composition through modifying dietary fat intake, decreasing saturated fat entrance, by improving monounsaturated and polyunsaturated fat intakes, and by modulating de novo lipogenesis upon improvement in dietary carbohydrate quality [66].

Alpha-mangostin and aSMase/ceramide pathway may modulate NO production by regulating reactive oxyge species (ROS) production and improve endothelial dysfunction [67]. Hence, another pharmacological approach described by Jiang et al. [68] involves alpha-mangostin, a naturally compound detached from various parts of the mangosteen tree that inhibits elevated aSMase/ceramide pathway. They figured out that treatment with alpha-mangostin ameliorates endothelial dysfunction in vivo and in vitro, through inhibition of the aSMase/ceramide course. The vascular dysfunction in the diabetic group was partly regained by the alpha-mangostin treatment, accompanied by lowered aSMase activity and ceramide content in normal mice [68].

Nutrition takes a central role in NAFLD development, micronutrients such as electrolytes, minerals, vitamins, and carotenoids, are needed to sustain physiologic functions. The lock micronutrients have been reported as crucial in NAFLD progression [69]. Sangineto et al. [70] explored the probable beneficial effects of dietary supplementation with FLINAX, an innovative composition of nutraceuticals (vitamin E, vitamin D3, olive dry-extract, cinnamon dry-extract and fish oil) in a NAFLD model characterized by oxidative stress and mitochondrial function damaged. The Flinax group significantly presented lower hepatic fat accumulation compared to non-supplemented. The administration of Flinax protected the liver, reducing important lipoperoxidation markers, crucial enzymes in fatty acids oxidation (FAO), tangled in acyl-CoA formation such as carnitine palmitoyltransferase 1A (CPT1A) and carnitine palmitoyltransferase 2A (CPT2) [71].

Despite the therapeutic potential of sphingolipids (**Table 1**), the ability to develop this class of compounds as active pharmaceutical ingredients has been hampered by issues of solubility and delivery. Beyond these technical hurdles, significant challenges in completing the necessary preclinical studies to support regulatory review are necessary for commercialization.

Table 1. Deletion of specific genes, enzymes or supplementation with a specific diet helps to decrease the concentration of ceramides. sphingomyelin (SM); sphingosine kinase 1 (SPHK1); sphingosine kinase 2 (SPHK2); ceramide synthase 2 (CerS2); ceramide synthase 5 (CerS5); ceramide synthase 6 (CerS6); fruit and vegetables (FRUVED); low refined carbohydrates (LRC); ceramide (Cer); triglycerides (TG); alanine-aminotransferase (ALT); aspartate transaminase (AST); dihydroceramide desaturase (DES); Adenosine 5'-triphosphate (ATP); control group (Ctrl); fatty acid elongase 6 (Elovl6); ceramide synthase 1 (CERS1); carnitine palmitoyltransferase 1A (CPT1A); carnitine palmitoyltransferase (CPT2); serine palmitoyltransferase long chain base subunit 2 (Sptlc2).

Main Focus	Species	Outcomes	Year	Ref.
Fumonisine B1	Mice	60% reduction of hepatic SM levels ($p < 0.05$), increase expression of hepatic SPT ($p < 0.01$); SPHK 1 maximal at the lowest dose of 0.75 mg/kg ($p < 0.05$), expression of SPHK2 not affected;	2006	[11]
Elovl6	Mice	Reduced: Ceramide(d18:1/18:0)(0.63, $p < 0.001$); ceramide (d18:2/18:0) (1.68, $p < 0.05$), oleate (C18:1n-9) and stearate (C18:0);	2020	[72]
CerS2	Mice	Reduced lipid accumulation, sphingomyelin levels ~50%, uptake in the liver, reduction in very long chain acyl ceramides, enzymatic activity-decreased;	2015	[73]
CerS6	Mice	Reduce C16:0 ceramides, serum insulin concentrations, protects from macrophage infiltration, activation of pro-inflammatory gene expression; improve glucose tolerance and insulin sensitivity; reduced adiposity and increased energy expenditure, ($p < 0.05$);	2014	[74]
Diet	Human	Ceramides C22:0, C24:1; C26:0 reduced-29%, ($p < 0.05$), C24:0 50%, ($p < 0.01$); at week 8 increase of C16:0 ($p < 0.05$);	2017	[66]
P053	Mice	5 mg/kg/day reduced C18 ceramide by 31%, ($p < 0.01$); Reduces whole-body fat mass and the weight of white adipose depots;	2018	[75]
GW4869	Mice	Decrease of: the atherosclerotic area, accumulation of macrophages by 68%; atherosclerotic lesions by 69% ($p < 0.001$), in plasma Cer24:1, Cer22:0, and Cer24:0, ($p < 0.05$), lipid accumulation by 68% ($p < 0.01$);	2018	[42]
CerS1	Mice	The sphingolipid content in heart, liver, and white adipose tissue—not affect, imprivement of liver glucose metabolism, 95% reduction in C18:0 ceramide;	2019	[76]
CerS5	Mice	Improves glucose tolerance, insulin sensitivity, reduces white adipose inflammation, In skeletal muscle without obvious decrease;	2019	[76]
Bortezomib	Mice	Increase hepatic CerS2 expression, protects from development of NAFLD, decreases weight gain, TG levels lower ($p < 0.01$);	2019	[77]
Exendin-4	Mice	Decrease lobular inflammation ($p = 0.18$), fibrosis stages ($p = 0.24$)	2019	[78]

Main Focus	Species	Outcomes	Year	Ref.
DEGS1 gene	Mice	Decreased: Cer16:0–0.09, Cer18:0–0.1 ($p < 0.001$), whole-body insulin sensitivity-restored, selective insulin resistance-reversed in the liver ($p < 0.001$);	2019	[35]
Myriocin	Rats	Reduced: serum ceramide content reduced, ($p < 0.05$), hepatic triglyceride, ALT, AST, hepatic inflammation, amount of inflammatory cell; Bcl-2 expression restored, ($p < 0.05$);	2019	[5]
Fenretinide	Mice	Lowered: plaque area 50.8% ($p < 0.05$), plasma lipid levels by 20.1%, ($p < 0.05$), and plasma ceramides;	2020	[79]
Diet	Mice	Flinax reduced lipoperoxidation markers, hepatic fat accumulation restores complex I, III, V (ATP-synthase), lower peroxides levels, ($p < 0.05$), no difference in complex IV, and higher production of CPT1A and CPT2;	2021	[70]
Alpha-mangostin	Mice	Inhibits: ceramide content, and, Inhibites aSMase activity,	2021	[68]
Farnesoid X receptor	Mice	Lower: ceramide content, hepatic cholesterol levels, mRNA levels of Smpd3 elevates hepatic Cyp7a1 mRNA levels Repressed lesion areas in aortas and smaller atherosclerotic lesions;	2021	[40]
Liraglutide	Mice	Gene expression Sptlc2, cerS4, and cerS6 decreased; C16 and C24 accumulation was limited ($p < 0.05$); Unchanged: saturated fatty acid, phospholipids with long chains-reduced, phospholipids with very long chains		

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