Egypt. J. Chem. **Vol. 68**, No. 5 pp. 207 - 219 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Gene Downregulation by Natural Products for Alleviating Dyslipidemia

Miral O. Sabry [a,] *, Mohamed S. Sedeek [a], Marwa Y. Issa [a], Soheir M. El Zalabani [a]

[a]*Pharmacognosy Department, Faculty of Pharmacy, Cairo University, Kasr El-Ainy Street, Cairo 11562, Egypt*

Abstract

The levels of lipids in our bodies are regulated through regulatory proteins known as sterol regulatory element binding proteins (SREBPs). Dietary triglycerides are transported from the liver and intestine to body tissues by the microsomal triglyceride transfer protein (MTP). The role of the dysregulation of lipid components in metabolic diseases and cancer is reviewed herein. The current survey provides a comprehensive overview of published data spanning from 1997 to 2023, sourced from Scopus, Google Scholar, PubMed, Web of Science, and ScienceDirect, concerning dyslipidemia and the downregulation of SREBP-1, SREBP-2, and MTP gene expression by natural products. Natural products, mainly phenolic compounds such as hesperidin, luteolin, xanthohumol, silymarin, curcumin, and quercetin, triterpenes such as betulin, in addition to alkaloids as berberine, and fatty acids like oleic acid and α-linolenic acid were found to downregulate SREBP-1 and SERBP-2. Taxifolin, piperine, and ellagic acid inhibited MTP gene expression. Natural products regulating triglycerides and cholesterol-related gene expression could be key lead drugs to new medicines used to treat hyperlipidemia, hypercholesteremia, liver cancer, breast cancer, and metabolic disorders.

Keywords: cytotoxicity; gene expression; herbal medicines; hyperlipidemia; MTP; SREBP.

Introduction

Dyslipidemia is a collective term used to describe abnormal levels of triglycerides, cholesterol, and/or high-density lipoproteins. It is characterized by a complex interplay of various lipid components, including elevated triglycerides (TG) and TG-rich lipoproteins, along with increased postprandial TG levels [1]. The imbalance is made worse by lower levels of Apolipoprotein A-I (Apo A-I) and high-density lipoprotein cholesterol (HDL-C) [2]. Dyslipidemia is marked by an increase in Apolipoprotein B (Apo B), reflecting higher levels of atherogenic lipoproteins [3]. Notably, there is an elevation in low-density lipoprotein cholesterol (LDL-C) particles number, especially the small dense LDL particles, which raises the risk of cardiovascular disease [4]. It was found that individuals with type 2 diabetes and metabolic syndrome commonly have dyslipidemia [5].

Dyslipidemia can be mediated by genetic factors, diet (such as unhealthy and ultraprocessed foods), lifestyle (such as sedentary lifestyle and smoking), and certain types of drugs [6]. Dyslipidemia can be a primary disease condition, or it can be secondary to certain disease conditions such as diabetes mellitus. Dyslipidemia contributes as a risk factor in fatal cardiovascular complications leading to the increase in risk of mortality [6–9].

Moreover, dyslipidemia in diabetic individuals is characterized by an increase in oxidized and glycated lipids, emphasizing the role of oxidative stress and glycation in lipid metabolism abnormalities associated with type 2 diabetes and metabolic syndrome [10].

Excessive accumulation of liver lipids contributes to inflammation and lipid metabolism disorders, causing non-alcoholic fatty liver disease (NAFLD). This condition is considered as a major cause of hepatic cancer [11]. Therefore, controlling lipid levels would be a promising strategy for combating NAFLD and liver cancer.

Currently, achieving an effective control of dyslipidemia is usually carried out with multi-drug treatment, preferably accompanied with lifestyle and dietary adjustments and restrictions. However, patients may have low compliance in following lifestyle changes [12]. In addition, long-term use of lipid-lowering medications can cause serious side effects. Therefore, finding alternatives from natural source and thus fewer side effects can be of great merit [7, 9, 13].

Nature serves as a significant and ongoing source of inspiration for researchers and scientists due to its abundance of bioactive compounds [14]. Natural products have long been utilized in traditional and modern medicine due to their diverse pharmacological properties, which include antimicrobial, anti-inflammatory, antioxidant, antidiabetic, and anticancer,

*Corresponding author e-mail: miral.om.mohamed@std.pharma.cu.edu.eg.; (Miral O. Sabry).
Received date 23 May 2024; Revised date 26 June 2024; Accepted date 07 July 2024
DOI: 10.21608/ejchem.2024.292003.9756

antihypertensive, activities, where the therapeutic efficacy of natural products is attributed to their complex structures and the specific mechanisms through which they interact with biological targets [15–22].

Transcription factors are proteins involved in the process of converting, or transcribing, DNA into RNA [23]. Those concerned with lipid metabolism are the Sterol Regulatory Element-Binding Proteins (SREBPs) and the Microsomal Triglyceride Transfer Proteins (MTP) [24, 25]**.** Several phenolic compounds were found to be effective in regulating lipid metabolism. For example flavonoids can target lipid metabolism by inhibiting sterol regulatory element-binding protein-1 (SREBP-1), leading to inhibition of fatty acid synthase and associated enzymes [11]**,** specially rutin, which was found to downregulate the transcription of SREBP-1c in hepatic cell line, thus decreasing the levels of triglycerides and cholesterol. Taxifolin, as well, downregulated the transcription of SREBP-1c in mice fed with high fat-diet [11].

SREBPs are a class of proteins that were initially identified by Brown and Goldstein nearly thirty years ago. These proteins regulate the transcriptional level of body lipids, including triglycerides and cholesterol . According to Wen et al., (2018), SREBPs are the transcription factors that control the expression of the genes that govern the synthesis of fatty acids, cholesterol, and triglycerides [30]. Three isoforms of SREBPs—SREBP-1a, SREBP-1c, and SREBP-2—are recognized and have been found to regulate different pathways that slightly overlap [24, 30, 31].

The regulatory protein involved in the synthesis of cholesterol and fatty acids is SREBP-1a, and that involved in the synthesis of fatty acids is SREBP-1c. The gene encoding SREBP-1 is located on chromosome 17 [30]. The SREBP-1 gene uses a different transcription start site to encode each of SREBP-1a and SREBP-1c [30]. Following gene transcription, their mRNA is translated into the inactive SREBP-1 protein, which *via* regulated cellular transport, is activated at the Golgi apparatus through proteolysis. The active SREBP-1 protein finally moves into the cell nucleus, where it activates the fatty acid biosynthesis by upregulating the genetic expression of the involved enzymes, such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). When the blood levels of fatty acids and triglycerides reach normal healthy levels, SREBP-1 is suppressed through end-product feedback inhibition. At the same time, the SREBP transcriptional activity is depressed. However, this step fails to occur in hyperlipidemic individuals [29, 32].

A similar process takes place in regulating cholesterol biosynthesis in the body. The involved protein is SREBP-2, which is carried on chromosome 22. SREBP-2 controls cholesterol synthesis in insulin-responsive tissues such as the liver. In case of cellular demand for cholesterol, or when the blood levels of glucose or insulin increase, SREBP-2 is activated through proteolysis at the Golgi apparatus, resulting in activation of the cholesterol biosynthesis pathway including all its enzymes. When cholesterol blood levels reach normal healthy levels, SREBP-2 is suppressed through end-product feedback inhibition, and at the same time, the SREBP transcriptional activity is depressed. However, this step fails to occur in hypercholesterolemic individuals [29, 32, 33].

On the other hand, MTP protein is responsible for activation of the assembly of VLDL (Very Low-Density Lipoprotein) and synthesis of chylomicrons in the liver and intestine [34]. In addition, VLDL is the lipoprotein responsible for the transport of lipids from the liver to body tissues, thus raising lipid levels in the body, while chylomicrons are responsible for the absorption of dietary lipids in the small intestine. Therefore, downregulating the gene expression of MTP protein is expected to decrease the lipid levels in blood [35–37].

MTP is mainly produced in hepatocytes and enterocytes, and inhibition of its production was found to decrease the secretion and synthesis of VLDL in the liver and to reduce the plasma levels of triglycerides by decreasing the fat absorbed through chylomicrons [36, 38].

The term hyperlipidemia designates a group of medical conditions in which blood levels of triglycerides and cholesterol are increased above normal levels. This condition was found to be directly linked to fatal heart and blood vessel diseases [28]. In addition, high blood levels of triglycerides and cholesterol were recorded in certain types of cancer, such as hepatic and breast cancers. Besides, its pathogenesis was found to be associated with upregulated SREBP-1, SREBP-2, and MTP genetic expression [30, 35, 39, 40].

Although statins are currently considered a cornerstone in treating dyslipidemia because they inhibit the essential enzyme HMG-CoA reductase which is involved in the cholesterol biosynthesis pathway, their reputed drawbacks would preferably be avoided [36]. In addition to causing myopathy, rhabdomyolysis, and liver damage [28, 41, 42], statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway, leading to a decrease in intracellular cholesterol levels. As a compensatory response, this inhibition triggers upregulation of the entire cholesterol biosynthetic pathway, including an increase in the expression of HMG-CoA reductase and other enzymes involved in the pathway [43]. Optimal treatment with statins still leaves a 60-80% residual cardiovascular risk [36, 44]. This residual risk is attributed to various factors, including persistent LDL cholesterol levels, elevated triglycerides, low HDL cholesterol, and other non-lipid-related risk factors, requiring further strategies such as combination therapies and lifestyle modifications to address this residual risk [44, 45]. Therefore, searching for natural products that can treat dyslipidemia by downregulating the gene expression of SREBPs and MTP, and thus suppressing the biosynthesis and absorption of lipids in the body from the very beginning, would be preferable.

Other than just hyperlipidemia, SREBPs were found to contribute to the pathogenesis of several diseases and disorders. These include obesity, cancer, non-alcoholic fatty liver, diabetes mellitus, atherosclerosis, chronic kidney, and neurodegenerative diseases [40, 46, 47]. SREBPs contribute to these diseases through several pathways that generate reactive oxygen species (ROS), increase endoplasmic reticulum stress, and cause inflammation, autophagy, and apoptosis [29, 48]. Among natural products, polyphenols have been extensively studied for their antioxidant properties [49, 50]. For instance, the polyphenol resveratrol is known to specifically reduce ROS generation by upregulating antioxidant enzymes such as superoxide dismutase and catalase, and by directly scavenging free radicals [51–53]. This action helps to mitigate oxidative stress and inflammation, which are critical factors in the pathogenesis of cardiovascular and metabolic diseases [54, 55].

Targeting SREBPs and MTP gene expression might be a promising approach in treating liver and breast cancers [56]. Cancer

cells satisfy their high lipid and cholesterol needs by increasing the uptake of dietary lipids as well as their endogenous synthesis [57]. Increased de-novo lipid biosynthesis is a necessary hallmark of cancer progression and metastasis. Part of this effect was found to be due to the increased expression of SREBP-1 [58].

Targeting De-novo lipid biosynthesis could be considered as a promising strategy in combating cancer since normal tissues depend on circulating lipids; meanwhile, cancer cells depend on de-novo synthesized lipids [58]. Blood levels of lipids are directly associated with hepatic and breast cancers. Several studies have proved that increased SREPBs activation is associated with cancer development [39, 40], tumor metastasis, as well as poor prognosis in breast cancer [30]. Moreover, in various types of cancers, it was found that the expression of SREBPs target genes are elevated above normal levels [59, 60].

Likewise, it was observed that down-regulating the gene expression of SREBPs altered the metabolic pathways in cancer cells *in-vitro* [30]. In fact, downregulating the expression of MTP protein in obese mice was found to treat dyslipidemia and to shrink tumor volume by 50% *via* alteration of circulating lipids [61]. The mevalonate pathway, through which lipids are synthesized and controlled by SREBPs, was upregulated in hepatic and breast cancers. A possible explanation was the mutations in sterol-regulatory related genes such as SREBPs [29].

AMPK (AMP-activated protein kinase) is a cellular energy sensor that becomes activated in response to low energy conditions [62]. Once activated, AMPK exerts profound effects on lipid and cholesterol metabolism [63]. AMPK activation inhibits SREBPs, particularly SREBP-1c, which reduces the production of fatty acids and cholesterol precursors in the liver and other tissues [64]. Many natural products, such as glabridin from licorice root, polyphenols from black nightshade, and components from okra, have been shown to activate AMPK [65–67].

The mechanism of action of natural products downregulating SREBP-1, SREBP-2, and MTP gene expression is represented in **figure 1**.

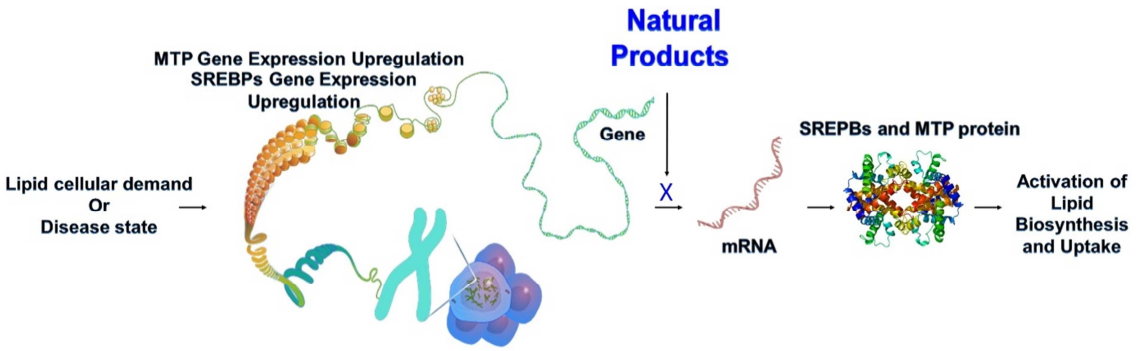

Figure 1: Mechanism of action of natural products downregulating SREBP-1, SREBP-2, and MTP gene expression.

The following survey intends to shed light on the nature of plant metabolites downregulating SREBP-1, SREBP-2, and MTP gene expression, their respective sources, and mechanisms of action to facilitate further incorporation in pharmaceutical formulations. Structural formulae of natural products isolated and/or identified in plants and proved to exert anti-hyperlipidemic and/or anti-hypercholesteremic activities are represented in **figure 2**. Recently, these compounds were found to act through downregulating SREBPs and/or MTP gene expression. It can be observed that the majority of the mentioned examples are mainly of phenolic or terpenoid nature.

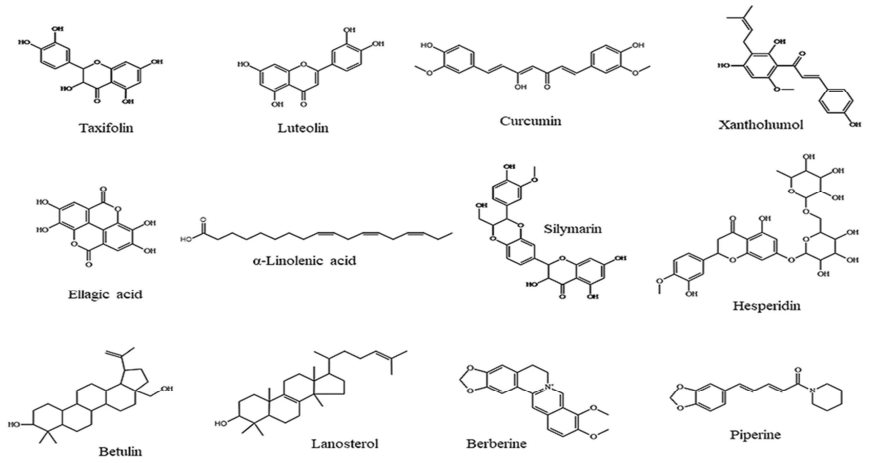

Figure 2: Representative examples of natural products downregulating SREBP-1, SREBP-2 and MTP gene expression.

1. Phenolic Compounds and Flavonoids

1.1. Quercetin flavonoid

Quercetin is a flavonoid widely distributed in plants. It belongs to the flavonols subfamily and acts as a pigment and is present in black tea, onions, citrus fruits, grapes, berries, cherries, apples, buckwheat, kale, tomatoes, and broccoli [68–71]. It is well recognized to possess anti-inflammatory, antioxidant, and neuroprotective potentials and is capable of protecting against aging-related diseases [71–74]. Quercetin reduces plasma LDL levels and prevents LDL oxidation, contributing to a decreased risk of cardiovascular diseases [71]. According to recent studies, quercetin quickly reduced the synthesis of fatty acids and cholesterol. Additionally, these investigations indicated that quercetin lowered the expression of the SREBP-1 and SREBP-2 genes [75–77].

1.2. Citrus fruits flavonoids

For instance, hesperidin (hesperitin-7-rutinoside), a flavanone glycoside commonly present in citrus fruits (*Citrus* L. species, family Rutaceae) [78], successfully prevented the buildup of fat in mice receiving a high-fat diet, and in HepG2 cell lines exposed to oleic acid, besides exerting several pharmacological activities including anti-inflammatory and antioxidant [79–81]. In a clinical study [80], hesperidin treatment improved lipid and glucose metabolisms in non-alcoholic fatty liver patients besides reducing inflammation and liver steatosis. Furthermore, Chen et al. (2022) discovered that hesperidin reduced the accumulation of lipids in the liver through a number of mechanisms, including downregulation of SREBP-1C expression [80].

Naringenin, another citrus fruits flavanone, was found to inhibit the secretion of Apolipoprotein B100 by downregulating the gene expression of microsomal triglyceride transfer protein (MTP) in HepG2 cells *via* a mechanism similar to that of insulin [82].

1.3. Celery and parsley flavonoids

Luteolin (3',4',5,7-tetrahydroxyflavone), a flavonoid present in celery and parsley (*Petroselinum crispum* Mill. and *Apium graveolens* L., family Apiaceae), was found effective against many types of tumors. These include stomach, prostate, and lung cancers [83]. Luteolin significantly downregulated SREBP-2 and SREBP-1 expression and subsequently lowered fatty acid and cholesterol levels in the blood [83, 84].

1.4. Hops prenylated flavonoids

Hops (*Humulus lupulus* L., family Cannabinaceae) is a renowned anti-hyperlipidemic. The major constituent of its fruit is the prenylated flavonoid xanthohumol that exerts anti-oxidative, chemopreventive, and anti-inflammatory actions. A recent study [85] revealed that xanthohumol reduced the gene expression of SREBP-1 in mice liver, besides suppressing the development of obesity. Moreover, xanthohumol prevented the activation of SREBP by blocking its endoplasmic reticulum to Golgi apparatus transportation. Likewise, it was found to reduce cholesterol and triglyceride levels, thus preventing obesity, hepatic steatosis, and atherosclerotic plaque development [29, 85, 86].

1.5. Tamarind and pine flavonoids

The flavonoid taxifolin present in tamarind (*Tamarindus indica* L, family Fabaceae) and Pine (*Pinus* species Lindl., family Pinaceae) was found to downregulate the gene expression of MTP protein [87, 88]. Furthermore, tamarind fruit pulp reduced total cholesterol and LDL-C levels in human subjects to a significant extent [89] while pine bark extract reduced LDL-C and increased HDL-C in human subjects [90].

1.6. Licorice root flavonoids

Glabridin is one of the prenylated isoflavanes extracted from the roots of licorice (*Glycyrrhiza glabra* L., family Fabaceae). Glabridin was claimed to exert numerous bioactivities, including antitumor, cardiovascular and hepatic protection, anti-obesity, and anti-diabetes [91]. In fact, the glabridin-rich acetone extract of licorice inhibited adipogenesis in 3T3-L1 adipocytes *in-vitro*, in addition to downregulating the expression of the lipogenic genes, stearoyl-CoA desaturase, fatty acid synthase, and SREBP-1 [92]. Moreover, in obese mice receiving a high-fat diet, AMPK (AMP-activated protein kinase) was activated by glabridin, and thus suppressing the expression of SREBP-1c [65].

1.7. Milk thistle fruit flavonolignans

Silymarin, the active component of dried milk thistle (*Silybum marianum* L., family Asteraceae) fruits extract consisting of a mixture of flavonolignans is reputed for its well-established hepatoprotective, antioxidant, antifibrotic, and anti-inflammatory properties besides being safe and clinically well tolerated. Recently, silymarin was found to suppress the expression of SREBP-1c mRNA [93–95].

1.8. Red soybeans isoflavones and amino acids

Several studies demonstrated the efficacy of soy beans protein in decreasing serum lipid levels [96]. The consumption of red soybean (*Glycine* species Willd., family Fabaceae) by mice fed a high-fat diet was found to decrease the expression of SREBP-1, this was referred to its isoflavone and amino acid contents [97].

1.9. Lizard's tail lignans

Sauchinone, a lignan present in lizard's tail (*Saururus chinensis* (Lour.) Baill., family Saururaceae), is well-known for its antioxidant, hepatoprotective, anti-inflammatory, and anti-steatosis properties [98, 99]. Both *in-vivo* and *in-vitro*, it was found to inhibit SREBP-1c through activation of AMPK (AMP-activated protein kinase) and inhibition of liver-X-receptor-α [100]. Another study prooved that sauchinone is capable of downregulating both SREBP-1 and SREBP-2 in HepG2 cells [99].

1.10. Turmeric herb polyphenolics

Curcumin, the main active polyphenolic compound of turmeric (*Curcuma longa* L., family Zingiberaceae), has demonstrated a wide range of biological and pharmacological activities, including antimicrobial, anti-inflammatory, anticancer, anti-diabetic, anti-malarial, antiprotozoal, and antioxidant effects, making it a promising scaffold for drug design and development despite its low bioavailability challenges [101]. It was also found to promote weight loss in clinical trials and to reduce the incidence of obesity-related metabolic disorders [102]. Published data supported that, among natural products, curcumin is reported to significantly inhibit SREBPs signaling, and, consequently to manage dyslipidemia and decrease lipid accumulation through downregulation of SREBPs [103].

1.11. Mulberry leaf phenolics

Mulberry (*Morus* species L., family Moraceae) leaf aqueous extract, a traditional Chinese remedy for treatment of obesity, is rich in phenolics and flavonoids. A dose-dependent decrease was observed in the level of triglycerides, preventing aggregation of lipid globules and downregulating the gene expression of SREBP-1c [104].

1.12. Black nightshade whole plant polyphenols

Black nightshade (*Solanum nigrum* L., family Solanaceae) is known to be rich in polyphenols [66]. The aqueous extract of the whole plant was reported to exhibit lipid-lowering activity, reducing blood triglycerides and cholesterol levels in mice *via* downregulation of SREBP gene expression through AMPK-dependent phosphorylation of SREBP [66, 105, 106].

1.13. Oak bark and Pomegranate rind polyphenols

Ellagic acid, a polyphenolic constituent of oak bark (*Quercus* species L., family Fagaceae) and pomegranate (*Punica granatum* L., family Lythraceae), was found to regulate the metabolism of cholesterol in hepatocytes through down-regulation of MTP mRNA [107]. Ellagic acid supplementation in mice enhances hepatic lipid metabolism and antioxidant capacity, improving cholesterol profiles and increasing specific enzyme abundances to promote liver health [108].

1.14. Red grapes polyphenolic stilbenoids

Resveratrol is a polyphenolic stilbene present in peanuts (*Arachis hypogaea* L., family Fabaceae) and red grapes (genus *Vitis* L., family Vitaceae) [109]. Studies revealed that resveratrol prevents fat accumulation *in-vivo* in the liver of mice receiving a high-fat diet and *in-vitro* in HepG2 cells [109]. In addition, it exerts anti-neoplastic effects against different types of cancers [110]. Besides resveratrol was claimed to downregulate the gene expression of SREBP-1 and to inhibit its activity in HepG2 cells. This was suggested to be mediated by the Sirt1–FOXO1 (Sirtuin 1-Forkhead box protein O1) signaling pathway [109].

Besides, resveratrol was found effective against xenograft oral cancer by significantly reducing lipogenesis, mediated through downregulation of the gene expression of SREBP-1 and epidermal fatty acid-binding protein (E-FABP). In addition, it initiated autophagy in oral cancer cells, and this was suggested to be through inhibition of SREBP-1-mediated cell survival signaling [110]. Moreover, resveratrol was found to sensitize pancreatic cancer cells to the anticancer drug gemcitabine through inhibition of SREBP [111].

Many strategies have been studied to enhance the bioavaliabilty of resveratrol. For instance, resveratrol-based coumarins, synthesized and characterized for their enhanced biomedical effects, showed improvements in pharmacokinetic properties and various therapeutic activities compared to resveratrol alone [112].

2. ***Triterpenoids***

2.1. Birch bark lupane triterpenoids

Betulin is a lupane triterpenoid found in Birch bark (*Betula* species L., family Betulaceae). It downregulates cholesterol and fatty acid synthesis and reduces blood lipid levels while increasing insulin sensitivity and inhibiting SREBP maturation [29, 113].

2.2. Chaga lanostane triterpenoids

Chaga (*Inonotus obliquus* Pilát, family Hymenochaetaceae), a mushroom traditionally used in Chinese Medicine to treat various gastrointestinal diseases, was found to possess significant anticancer, anti-inflammatory and hypoglycemic activities [114]. Its active constituents *viz*. the lanostane triterpenoids inotodiol, lanosterol, and trametenolic acid, significantly decreased hepatic lipid accumulation through the downregulation of SREBP-1c [114].

2.3 Okra fruits triterpenoids

The alcohol extract of okra (*Abelmoschus esculentus* L., family Malvaceae) fruit, rich in quercetin glucosides and pentacyclic triterpene ester, was found to be effective in stimulating AMP-activated protein kinase (AMPK) leading to phosphorylation of SREBP-1c and consecutively its downregulation [67, 106]. Its water extract, rich in polysaccharides, was relatively more stable in decreasing the expression of SREBP-1c [115].

3. *Miscellaneous Compounds*

3.1. Chinese goldthread alkaloids

Berberine is an isoquinoline alkaloid isolated from several plants of family Berberidaceae, especially *Coptis* species. Among these, *Coptis chinensis* F. (Chinese goldthread) rhizome is considered one of the main sources of berberine [116]. Berberine was found to be effective in treating a variety of cancers, including liver, colon, breast, and lung cancers. Moreover, its lipid-lowering, immunomodulatory, antioxidative, cardioprotective, hepatoprotective, and renoprotective activities were reported [116, 117]. Besides, a clinical trial demonstrated that berberine can be used in the treatment of dyslipidemia alone or together with simvastatin [116]. Recently, berberine was proven to inhibit SREBP-1 activation and expression of its transporting protein SREBP and cleavage-activating protein (SCAP) [118, 119].

3.2. Black and white pepper alkaloids

Piperine is the major pungent alkaloid in *Piper nigrum* L., family Piperaceae. It occurs in both black and white pepper and was found to lower plasma cholesterol levels through several mechanisms, including downregulation of the gene expression of intestinal MTP [120].

3.3. Unsaturated fatty acids

Unsaturated fatty acids such as α-Linolenic acid (ALA) were found to downregulate SREBP-2, SREBP-1a, and SREBP-1c expression [121–124]. Moreover, PUFAs and oleic acid were reported to inhibit the proteolysis of SREBP-1 and to downregulate its expression. Thus, they could help in the treatment of hyperlipidemia and other metabolic diseases, taking into consideration that SREBP-1 activation was found to produce lipotoxicity, which contributes to several lipidemic disorders [29, 122, 123, 125].

3.4. Citrus pectin

Pectin is a complex and soluble polysaccharide found in the cell walls of citrus fruits [126]. Pectin has long been recognized for its impact on lipid metabolism, proven by a clinical trial conducted in 1977 which involved administering 40-50 g/day of pectin for two weeks to nine normolipidemic and hyperlipidemic patients. The results demonstrated that while pectin supplementation significantly decreased serum total and unesterified cholesterol levels in hypercholesterolemic subjects [127]. Recently, Wang *et al*. (2022) reported that citrus pectin lowered cholesterol and triglyceride levels in HepG2 cells through downregulation of fatty acid synthetase and SREBP-1c [128].

3.5. Garlic bulbs

Garlic (*Allium sativum* L., family Amyrallidaceae) is known to possess cardiovascular benefits and anti-hyperlipidemic activity [129]. Many human studies have proven that garlic can reduce the blood levels of total cholesterol and LDL-C in patients with hypercholesterolemia [130–132]. Garlic extract was recently reported to reduce the gene expression of SREBP-1c, leading to a decrease in its target genes [105].

3.6. Chinese toad bufadienolides

Cinobufotalin is one of the bufadienolides extracted from the venomous skin secretions of Chinese toads (*Bufo bufo gargarizans* Cantor, family Bufonidae). The dried skin secretion of *Bufo bufo gargarizans* has been used in Traditional Chinese Medicine in treatment of several types of cancers [133]. Many studies reported the powerful anticancer activity of cinobufotalin against hepatocellular carcinoma, human lymphoma, lung cancer, and colon adenocarcinoma through numerous mechanisms [134–138]. Among the various mechanisms cinobufotalin targeted cancer through inhibiting lipogenesis in hepatocellular carcinoma specifically by inhibiting SREBP-1 expression [136].

3.7. Fenugreek steroidal saponin

Fenugreek (*Trigonella foenum-graecum* L., family Fabaceae) is known to decrease serum triglycerides and cholesterol, as well as hepatic lipids [139–141]. Diosgenin is a saponin phytosterol effective against lipid metabolism disorders and is extracted from fenugreek [142–144]. When mice on a high-fat diet were given diosgenin, their weight gain was considerably reduced and their lipid profile was improved. Furthermore, diosgenin suppressed their two-fold increase in the gene expression of SREBP-1c and its downstream gene, fatty acid synthase [142]. *In-vitro*, diosgenin inhibited the accumulation of triglycerides and downregulated the lipogenic genes' expression, including SREBP-1c, in HepG2 cells. This activity was through inhibiting the transactivation of liver-X-receptor-α, which is the transcription factor responsible for stimulating the gene expression of SREBP-1c [140, 145].

Applications and Prospects

Microsomal triglyceride transfer protein (MTP) regulates the absorption and transportation of lipids by playing a role in the assembly and secretion of Apolipoproteins as chylomicrons and VLDL in the intestine and liver [146]. A few MTP inhibitors have been identified, and they were proven to reduce the levels of plasma lipids. However, inhibiting MTP resulted in accumulation of lipids in the liver, a significant drawback that stopped previously identified MTP inhibitors from reaching clinical use [88]. For instance, Lomitapide is known to inhibit MTP activity and reduce lipid levels. However, its use is limited due to hepatotoxicity [147, 148]. Therefore, it appears essential to search for intestine-specific MTP inhibitors or to find lead drugs capable of regulating the expression of MTP instead of inhibiting it, to serve as starting points for further

optimization and development into potential therapeutic agents [146]. This mechanism offers a safer and potentially more effective strategy for managing hyperlipidemia. Therefore, natural products that downregulate the gene expression of MTP instead of inhibiting its activity can be considered as a better approach to lower plasma lipids.

Using SREBP inhibitors in combination with fatty acid synthase (FAS) inhibitors in the treatment of cancer might be considered as a promising strategy in the treatment of primary cutaneous T-cell lymphomas (CTCL) [149]. FAS, the enzyme that catalyzes the biosynthesis of fatty acids, is highly expressed in CTCL and contributes to oncogenicity in other malignancies. However, inhibition of FAS was found to increase FAS expression due to feedback inhibition. Adding an SREBP inhibitor partially reduced the upregulation of FAS caused by FAS inhibitors. This is explained by the role of SREBP in upregulating FAS gene expression [149].

Recently, a novel stilbene resveratrol derivative (BF175) containing boron and two chlorine groups was synthesized. Adding boron to small molecules enhanced their binding to target molecules, such as proteins, DNA or RNA. BF175 inhibited the target gene expression of SREBP, while its non-chlorine-containing analogue showed no effects. BF175 repressed the expression of SREBP-1c only in HepG2 cells while decreasing the transcripion of both SREBP-1 and SREBP-2 genes *in-vivo* in mice liver [150]. Since Natural polyphenolics, such as resveratrol, are hindered by their relatively low bioavailability, using a similar strategy for chemical modifications can be developed for the improvement of their bioavailability.

2. Conclusions

In conclusion, sterol regulatory element-binding proteins (SREBPs) and microsomal triglyceride transfer protein (MTP) are responsible for regulating the process of endogenous lipids synthesis and the uptake of exogenous lipids. However, this process is disrupted in many metabolic diseases such as dyslipidemia, obesity, cancer, non-alcoholic fatty liver, diabetes mellitus, atherosclerosis, chronic kidney diseases, and neurodegenerative diseases. Targeting the gene expression of these proteins is a promising strategy for the treatment of many metabolic diseases. Strikingly, a large number of natural products downregulate the gene expression of SREBPs and MTP proteins, and thus could be considered as potential therapeutic agents in the treatment of hyperlipidemic conditions.

Natural products reported to downregulate SREBPs are mainly of polyphenolic and terpenoid nature, including hesperidin, luteolin, quercetin, xanthohumol, curcumin, silymarin, and ellagic acid. Besides, the alkaloids berberine and piperine, citrus pectin, chaga, mulberry, black nightshade, garlic, red soya bean, and okra extracts were also active. Meanwhile, gene expression of MTP protein was reported to be downregulated by taxifolin, piperine, and ellagic acid.

3. Conflicts of interest

There are no conflicts to declare.

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