Nutrition 126 (2024) 112517

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Emerging role of natural lipophagy modulators in metabolic dysfunction–associated steatotic liver disease

Nahla E. El-Ashmawy [a,b], Eman G. Khedr [a], Ghada M. Al-Ashmawy [a,c], Asmaa A. Kamel [a,*]

[a] Department of Biochemistry, Faculty of Pharmacy, Tanta University, Tanta, Egypt
[b] Department of Pharmacology & Biochemistry, Faculty of Pharmacy, The British University in Egypt, El Sherouk, Cairo, Egypt
[c] Department of Biochemistry, Faculty of Pharmacy, Al Salam University in Egypt, Kafr Az Zayat, Egypt

ARTICLE INFO

Article History:
Received 10 April 2024
Received in revised form 2 June 2024
Accepted 8 June 2024

Keywords:
MASLD
NAFLD
Autophagy
Lipophagy
Natural products
Lipid droplets

ABSTRACT

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is a seriously increasing liver disorder affecting nearly 32% of adults globally. Hepatic triglycerides (TG) accumulation is the hallmark of MASLD, which results from dysregulated lipid and fatty acid uptake, increased de novo lipogenesis (DNL), and decreased lipid removal. More recently, selective autophagy of lipid droplets (LDs), termed lipophagy, has emerged to be closely associated with disrupted hepatic lipid homeostasis. Recent studies have indicated that a series of natural products have shown promise as an alternative approach in attenuating MASLD via regulating lipophagy in vivo and in vitro. Therefore, lipophagy could be a new approach for natural products to be used to improve MASLD. This article aims to provide a comprehensive overview on the interrelationship between dysregulated lipid metabolism, lipophagy, and MASLD pathogenesis. In addition, the role of some natural products as lipophagy modulators and their impact on MASLD will be discussed.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is assumed to be the most common form of chronic hepatic diseases worldwide, affecting nearly 32% of adults with wide variation among countries and ethnicities [1]. It is characterized by an excessive accumulation of triglycerides (TG) in more than 5% of hepatocytes resulting from causes other than alcohol consumption, use of steatosis-inducing drugs such as amiodarone, and other chronic hepatic disorders such as hemochromatosis, viral hepatitis, autoimmune hepatitis, Wilson's disease, and so on [2]. MASLD covers a wide spectrum of hepatic diseases including simple hepatic steatosis (intrahepatic lipid buildup), steatohepatitis (hepatic fat accumulation associated with inflammation), progression to fibrosis and cirrhosis (irreversible replacement of normal liver tissue with scarring fibrous tissue), and ultimately hepatocellular carcinoma [3].

Autophagy (self-eating) is a conservative process responsible for disposal of and recycling abnormal, damaged, or dysfunctional cellular organelles and macromolecules [4]. It is therefore vital for maintaining cellular physiology and homeostasis, and plays an essential role during growth and development, inflammatory responses, as well as metabolic and immune processes. The effect of autophagy has been well known in different organelles since the early 1960s. However, autophagic degradation of lipid droplets (LDs) was relatively more recently identified. The term "lipophagy" originated from a pioneering work by Singh et al., which clearly proved that autophagy is involved in the degradation of LDs in hepatocytes [5].

Defective lipophagy in hepatocytes has been linked to the pathogenesis of MASLD and lipid dysregulation. It is widely acknowledged that acute increase in lipid availability during the early stages of MASLD triggers lipophagy activation, which attenuates hepatic lipid deposition. However, hepatic lipophagy is impaired upon sustained lipid availability, as occurs with a prolonged high-fat diet (HFD) [6]. These results suggest that a promising strategy to support the resolution of fatty liver would be to specifically stimulate lipophagy. Current research is looking into a number of therapies that have been demonstrated to increase conventional autophagy as a means of treating MASLD [7].

Natural products have been utilized as an alternative therapy for liver diseases and dyslipidemia due to their good efficacy and low adverse effects [8]. Numerous regulatory mechanisms, such as

*Corresponding author: Tel.: 0020-106-670-2638.
E-mail address: asmaa.kamel@pharm.tanta.edu.eg (A.A. Kamel).

https://doi.org/10.1016/j.nut.2024.112517
0899-9007/

lowering lipogenesis, enhancing β-oxidation, improving insulin sensitivity, and suppressing inflammatory and cellular stress pathways, have been shown to be involved in preventing hepatic steatosis by natural products. According to recent research, certain natural compounds have demonstrated their benefits in alleviating MASLD through the activation of lipophagy [2]. This review aims to provide a comprehensive overview about the interrelationship between dysregulated lipid metabolism, lipophagy, and MASLD pathogenesis. In addition, the role of some natural products as lipophagy modulators and their impact on MASLD will be discussed.

Theories of MASLD

The "2-hit hypothesis" was the early theory to characterize the pathophysiology of MASLD [9]. The first hit is represented by hepatic lipid buildup in hepatocytes, which is directly linked to obesity, HFD, sedentary lifestyle, and insulin resistance (IR). This strike makes the liver more susceptible to other elements that make up the second hit, such as oxidative stress, inflammatory cytokines, adipokines, and mitochondrial dysfunction. Consequently, fibrosis and necroinflammation may occur, leading to cirrhosis [10]. But it quickly became apparent that this theory is too simplistic to adequately represent the complexity of the human MASLD, in which several concurrent factors work synergistically in genetically predisposed individuals [11]. Thus, the most widely recognized theory is the "multiple parallel hits theory," which postulates a greater degree of metabolic dysfunction due to a combination of environmental and genetic factors, as well as alterations in the crosstalk between various organs and tissues, such as the liver, adipose tissue (AT), pancreas, gut, and other organs [12]. These multiple factors include obesity and AT dysfunction, IR, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, gut microbiota, dietary and environmental factors, and genetic determinants [13].

Dysregulated lipid metabolism in MASLD

Lipids in the forms of TG, cholesteryl esters, and retinyl esters are stored in LDs, which are eukaryotic spherical organelles encircled by a single layer of phospholipids [10]. The surface of the LDs is coated with several proteins including the 5 perilipin family members (PLIN1−PLIN5). These proteins are necessary for LD packing, interactions with other organelles, droplet size management, and accessibility to lipolytic processes. Lipolytic proteins are also associated with LD surface, including hormone-sensitive lipase (HSL), adipose triglyceride lipase (ATGL), and monoglyceride lipase. Other lipases that are also present on the surface of LDs include the patatin-like phospholipase domain−containing protein (PNPLA) family, including PNPLA2, which shares significant sequence identity with ATGL [14]. LDs are generally synthesized at the ER and they can vary greatly in size, from 1 μm in most cell types to 100 μm in white adipocytes. In addition to being the primary storage site of lipids in cells, LDs are crucial to lipid metabolism [8].

The liver controls the production of new fatty acids, their export and subsequent redistribution to other tissues, and their use as energy substrates. It is a key player in maintaining lipid homeostasis. The hallmark of MASLD is the intracellular accumulation of LDs in the cytoplasm of hepatocytes as a result of an imbalance between lipid input and output [15]. Under normal intracellular nutrition, fatty acids are typically transformed into TG and stored in LDs in adipocytes, but when there is a need for energy, the lipids stored in LDs are hydrolyzed into free fatty acids (FFAs) by the process of β-oxidation in mitochondria. When fatty acids are either supplied in excess or their disposal is impaired, a large number of LDs tends to accumulate, not only within the AT, but also in other tissues, particularly in the liver, which is called ectopic lipid [16].

The accumulated fatty acids can also act as a substrate for the synthesis of lipotoxic compounds such as ceramides, diacylglycerols, and lysophosphatidylcholine. These metabolites provoke fibrogenesis and genomic instability that predispose to cirrhosis and hepatocellular cancer by inducing hepatocellular stress and damage [17]. There are 5 major lipid metabolic pathways that have been found to be associated with TG accumulation in hepatocytes: 1) uptake of circulating fatty acids from the diet or AT; 2) hepatic fatty acid synthesis, also referred to as de novo lipogenesis (DNL); 3) TG secretion in the form of very-low-density lipoprotein (VLDL) particles; 4) fatty acid oxidation; and 5) turnover of LDs by lipophagy. Normal versus dysregulated lipid metabolism in liver is presented in Figure 1.

Increased uptake of fatty acids derived from the diet or the AT

After being absorbed from the small intestine, dietary lipids are condensed into chylomicrons and released into the bloodstream. Most of the fatty acids produced from the chylomicrons after TG breakdown by lipoprotein lipase are retained in the AT, while the liver uptakes the remainder [18]. Normally, circulating insulin prevents lipolysis in the AT after feeding. In contrast, during the fasting state, catecholamine promotes lipolysis where TG stored in the AT will be liberated as FFAs under the control of ATGL, HSL, and monoglyceride lipase. The released FFAs are subsequently transported in the bloodstream bound to albumin before being redistributed to other organs in order to meet energy needs. One of the primary causes of MASLD is thought to be the continuously high flux of fatty acids to the liver that results from AT lipolysis, which is increased with IR [19].

According to estimates, diet accounts for 15% of the liver fatty acids in patients with MASLD, circulation for 59%, and DNL for 26%. Fatty acids in the bloodstream are taken up by the liver by both passive diffusion and active transport with the aid of several proteins, such as fatty acid translocase CD36, fatty acid transport proteins, and fatty acid binding proteins. One important component of the pathogenesis of MASLD may be the overexpression of any of these proteins [20]. Lipolysis is not only restricted to the AT, but it also occurs in hepatocytes. ATGL is abundantly expressed in the liver and AT, and is involved in the initial stage of lipolysis, which hydrolyzes TG into diacylglycerols. A mutation in the PNPLA2 gene, a paralog of ATGL, may increase the risk of developing hepatic steatosis. The isoleucine to methionine substitution at amino acid position 148 causes PNPLA2 to sequester abhydrolase domain containing 5, the common cofactor of ATGL and PNPLA2, more strongly resulting in decreased hepatic lipolysis and buildup of LDs in the liver [17].

Increased de novo lipogenesis

Hepatic DNL is the metabolic process by which excess carbohydrates, usually glucose, are converted into fatty acids in the liver. In this process, acetyl-CoA is first converted to malonyl-CoA by acetyl-CoA carboxylase, and then fatty acid synthase converts the malonyl-CoA to palmitate [21]. This is how the liver typically synthesizes new fatty acids from acetyl-CoA. FFAs derived from DNL are converted to TG and either released as VLDL from the liver or stored inside LDs in hepatocytes. Normally, insulin increases the storage of hepatic glucose as glycogen and enhances distribution of carbohydrates to the peripheral tissues (such as muscle and AT).

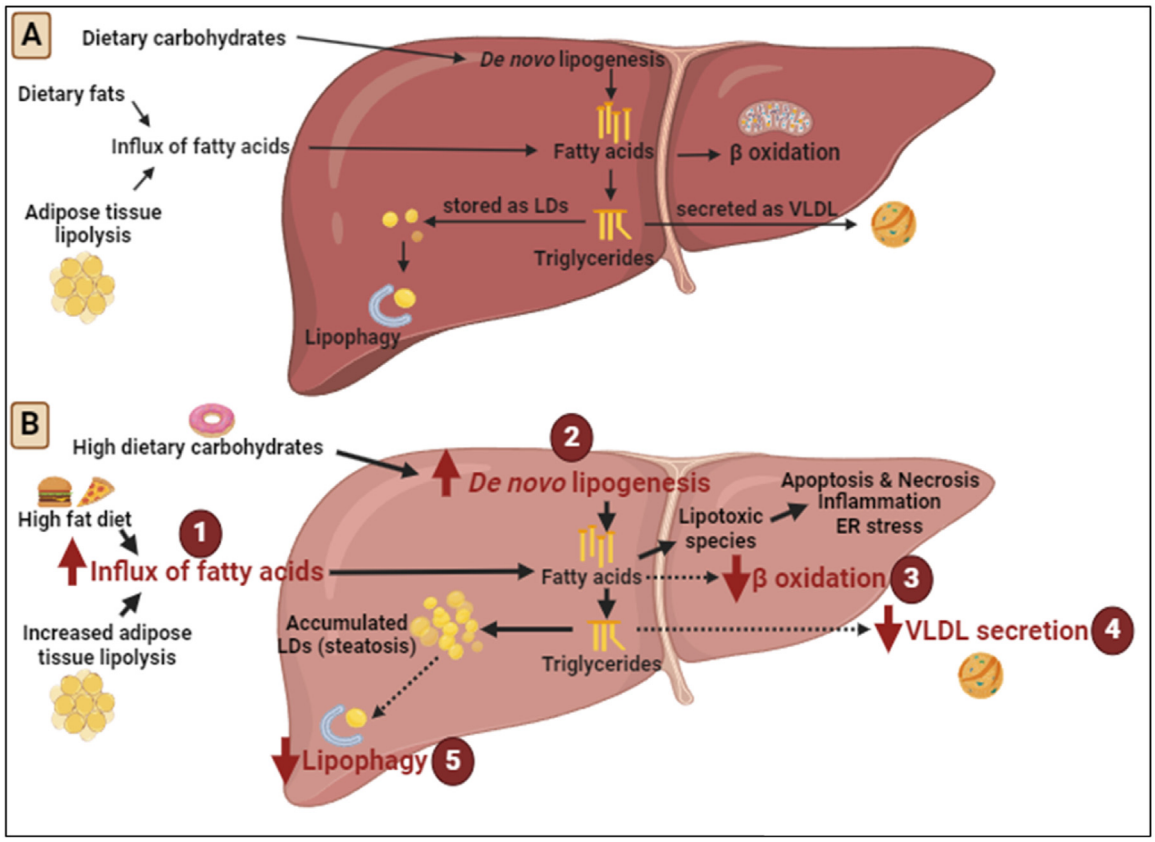

Fig. 1. (A) Normal lipid metabolism in the liver. (B) Dysregulated lipid metabolism in MASLD. Five main pathways have been established to be contributing to hepatic steatosis, including: 1) increased influx of fatty acids; 2) increased de novo lipogenesis; 3) decreased fatty acid oxidation; 4) decreased triglycerides secretion; and 5) dysregulated lipophagy. ER, endoplasmic reticulum; LD, lipid droplets; MASLD, metabolic dysfunction-associated steatotic liver disease; VLDL, very-low-density lipoprotein.

Conversely, IR leads to decreased glycogenesis and glycolysis, thereby increasing hepatic DNL and TG storage [22].

The process of DNL is regulated by 2 key transcription factors: sterol regulatory element-binding protein-1c (SREBP-1c), which is activated by both insulin and liver X receptor α, and carbohydrate regulatory element-binding protein (ChREBP), which is activated by carbohydrates. Growing evidence indicates that altered expression of these transcription factors contributes to MASLD via increasing the expression of DNL-related enzymes such fatty acid synthase and acetyl-CoA carboxylase. The ablation of SREBP-1c can also enhance the compensatory overexpression of SREBP-2, which increases hepatic cholesterol production and accumulation, linking both DNL and cholesterol metabolism [23].

Disturbances in hepatic triglyceride secretion

The liver secretes TG in the form of VLDL particles. These lipoprotein particles, which are made up of lipidated apolipoprotein B (ApoB), transport TG to peripheral tissues such as the heart, muscle, and AT. The lipoprotein lipase then hydrolyzes the TG, releasing fatty acids to satisfy the energy demand [24]. Although decreased VLDL secretion may be a factor in the excessive buildup of TG in the liver, this occurs rarely in patients who are genetically afflicted. Genetic defects in the gene encoding ApoB (hypobetalipoproteinemia) and alterations in the microsomal TG transport protein gene, which lipidates ApoB (abetalipoproteinemia), were found to reduce VLDL secretion and aggravate hepatic steatosis [25]. Additionally, a recent study reported that the liver-specific deletion of the transmembrane 6 superfamily 2, which is involved in the transport of VLDL from the ER to the Golgi, decreased the secretion of VLDL and increased the risk of developing hepatic steatosis, fibrosis, and hepatic cancer [26].

MASLD is more frequently linked to the secretion of larger and more TG-rich VLDL particles due to increased TG availability for the intrahepatic ApoB lipidation process. This results in mixed hyperlipidemia, which is characterized by increased levels of both low-density lipoprotein and VLDL that often occurs in IR patients with MASLD [23]. It has been demonstrated that insulin decreases hepatic VLDL secretion via inducing apoB100 degradation and suppressing microsomal triglyceride transfer protein synthesis. IR increases VLDL secretion and boosts hepatic DNL in MASLD. However, if the diameter of these TG-enriched VLDL particles becomes greater than that of the sinusoidal endothelial pores of hepatocytes, they cannot be secreted [3]. Lipid export in MASLD typically exhibits a biphasic pattern, with an initial increase and then a plateau or even decline. Reduced export causes intracellular lipid accumulation and hepatic lipid overload resulting in steatosis, lipotoxicity, liver damage, and fibrosis [27].

Disturbances in hepatic fatty acid oxidation

Hepatic fatty acid oxidation is the process by which fatty acids are broken down into shorter chains by a number of dehydrogenases in the mitochondria and, in the case of very long-chain fatty acids, the peroxisomes. This process produces ATP, particularly in conditions associated with low levels of circulating glucose. To do this, the enzymes carnitine palmitoyltransferase-1 (CPT1) and CPT2, which are found in the outer and inner mitochondrial

membranes, respectively, help the fatty acids cross the mitochondrial membrane. Carnitine is added to the fatty acyl-CoA molecule by CPT1 to aid in mitochondrial transport, whereas CPT2 eliminates carnitine [22]. However, ω-oxidation in the cytochromes also plays a role in cases of lipid overload, such as MASLD, producing significant levels of reactive oxygen species and toxic dicarboxylic acids, which may promote inflammation as well as disease development and progression [28].

It has been demonstrated that steatosis can be caused by disorders of fatty acid oxidation. For instance, fasting mice with pharmacological inhibition of CPT1 developed significant hepatic steatosis. Furthermore, animals lacking the nuclear receptor known as peroxisome proliferator-activated receptor α (PPARα), which regulates the expression of nearly all fatty acid oxidation genes, exhibit hepatic steatosis and elevated plasma FFA concentrations after fasting [29]. Some steatohepatitis patients have altered β-oxidation and mitochondrial dysfunction in the liver, and potentially also in other organs throughout the body. Fatty acid oxidation in dysfunctional mitochondria produces excessive reactive oxygen species, and this process may also increase the use of cytochromes and peroxisomes for fatty acid oxidation. This ultimately aids disease progression by increasing oxidative stress and inflammation [25]. Results of the studies of fatty acid oxidation in patients with steatosis or steatohepatitis were found to be conflicting, reporting increased, unchanged or decreased fatty acid oxidation. This variation may be attributed to the wide spectrum of hepatic conditions that fall under the umbrella of MASLD and the varying degrees of severity of the disease observed in different patients. Nevertheless, even in research indicating increased fatty acid oxidation, this enhanced oxidation does not appear to be sufficient in removing the lipids from the liver [30].

Defective hepatic lipophagy

Besides lipolysis, lipid degradation can also be accessible by lipophagy, a unique type of autophagy that breaks down LDs deposited in cells. In order to degrade the excess LDs generated in cells, the autophagosomal double membrane wraps the LDs and then fuses with lysosomes to form autolysosomes. It is essential for preserving the steady state of the cell [4]. Acute increases in lipid availability during the early stages of MASLD trigger lipophagy, which helps lower lipid accumulation. However, when lipids are sustained in excess during prolonged high-fat dieting, hepatic lipophagy is compromised. The altered kinase pathways functioning upstream of autophagy, such as mitogen-activated protein kinase (MAPK), may be indirectly responsible for the defective autophagy brought on by an excess of nutritional supply [31].

Recent studies have indicated that lipophagy is largely reduced in MASLD patients and animal models, while stimulating lipophagy can prevent disease progression [32]. The degree of MASLD severity was also found to be correlated with autophagy dysregulation. Higher MASLD activity scores were associated with elevated numbers of autophagosomes and lipid-laden lysosomes, or lipolysosomes, in the liver. Sequestosome-1 (SQSTM1/p62) was also correlated with steatosis and fibrosis grade. According to recent studies, autophagy loss or suppression results in higher levels of TG and LDs both in vivo and in vitro, as well as reduced TG breakdown [33].

Depending on the LD size and how it is transported into lysosomes/vacuoles, LDs can be targeted either by macrolipophagy, in which LDs are sequestered by autophagosomes and delivered to lysosomes, or microlipophagy, which involves a direct engulfment of LDs by lysosome/vacuole membrane. Either way, lysosomal acid lipases break down the contents of the LDs including TG, diacylglycerides, cholesteryl esters, and retinyl esters following lysosomal engulfment [34]. The capacity of these lipases to function in an acidic (pH = 4.5–5.0) as opposed to neutral (pH = ~7) environment sets them apart from their cytosolic counterparts. The third type of autophagy involved in LD metabolism is called chaperone-mediated autophagy (CMA), in which adenosine monophosphate-activated protein kinase (AMPK) signaling controls the removal of PLINs, the LD coat proteins, prior to LD degradation by either autophagy or cytosolic lipolysis (Fig. 2).

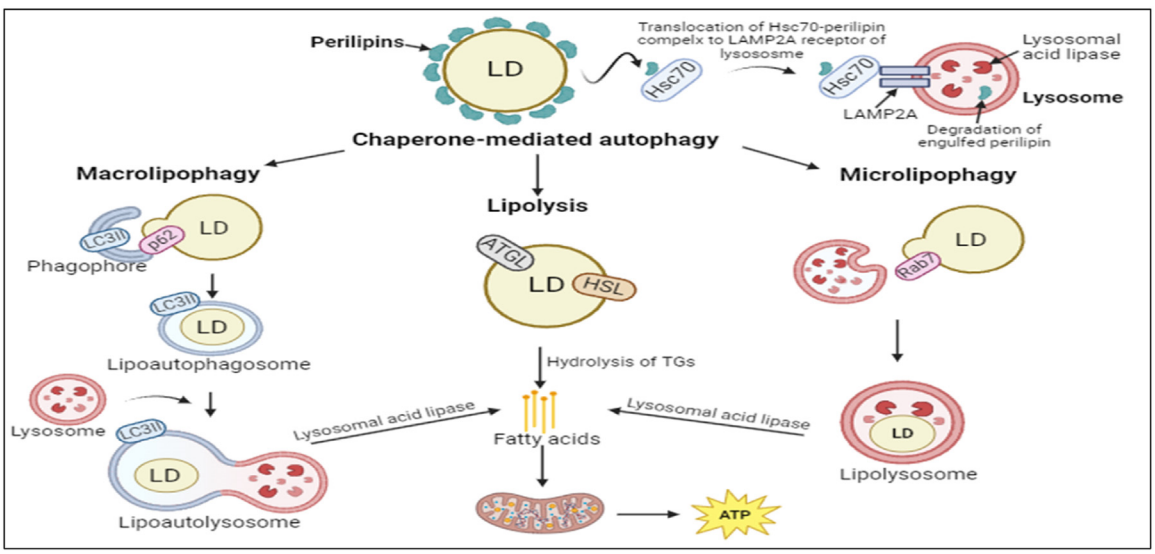

Fig. 2. Types of lipophagy and lipophagy–lipolysis crosstalk. Macrolipophagy involves LC3-II–positive membranes engulfing portions of large LDs to form lipoautophagosomes, which then fuse with lysosomes, wherein lysosomal acid lipase degrades the lipid cargo, generating FFAs that undergo β-oxidation for energy production. Microlipophagy involves direct binding of lysosomes to LDs in a Rab7-dependent manner. Chaperone-mediated autophagy degrades the LD coat proteins (perilipins 2 and 3) through the coordinated action of HSC70 and LAMP2A, thereby increasing the accessibility of the 'naked' LDs to both cytosolic lipolysis and lipophagy. ATGL, adipose triglyceride lipase; FFA, free fatty acids; HSC70, heat-shock cognate 71 kDa protein; HSL, hormone-sensitive lipase; LAMP2A, lysosome-associated membrane glycoprotein 2A; LC3-II, microtubule-associated protein light chain 3; LD, lipid droplet, p62, sequestosome-1; Rab7, Ras-related protein 7.

Macrolipophagy

Macrolipophagy is the main type of autophagic degradation of LDs that involves microtubule-associated protein 1A/1B-light chain 3-II (MAP1LC3-II/LC3-II)-positive phagophores engulfing small LDs or sequestering portions of large LDs. The formed lipoautophagosomes deliver the LD cargo to lysosomes, where the internal lysosomal acid lipases attack and degrade the TG packed in LDs, generating FFAs that are released into the cytosol [35]. The selective recognition of LDs could occur by either an Ub-dependent or Ub-independent manner. The Ub-dependent pathway involves, in brief, polyubiquitinatation of some LD-associated proteins such as PLIN2, leading to binding of autophagy cargo receptor p62 and macrolipophagy initiation [36]. On the other hand, during Ub-independent macrolipophagy both ATGL and HSL, the 2 lipolytic enzymes distributed on the surface of LDs, interact with LC3 through their LC3-II interaction motifs. This results in the local, in situ, development of a phagophore in a process triggered by sirtuin 1 (SIRT1). Other lipases such as PNPLA3, PNPLA5, and PNPLA8 have shown a potential role in LD recognition and initiation of lipophagy by enhancing the formation of autophagosomes through the mobilization of TG and steryl esters [33].

Members of the Rab guanosine triphosphatases (GTPases) family of proteins, which are necessary for the regulation of membrane dynamics and trafficking, have also been connected to macrolipophagy. Thus far, the surface of LDs has been discovered to harbor almost 30 Rab GTPases [37]. Rab7 is a highly prevalent Rab that is found on the surface of the LD. It is essential for the regulation of autophagosomal maturation events and late endocytic membrane trafficking, which in turn controls macrolipophagy in mammalian cells [38]. The stimulation of lipolysis mediated by β-adrenergic receptor activation enhances Rab7 recruitment to both LDs and autophagosomal membranes. Conversely, Rab7 knockdown or inactivation could inhibit macrolipophagy, leading to aberrant accumulation of LDs in liver cells [39]. Rab10, a different Rab protein, has similarly been shown to localize to LDs and autophagosomal membranes in a Rab7-dependent way. After that, it binds its effector proteins, which includes the endocytic adaptor Eps15 homology (EH) domain-binding protein 1 and the EH domain−containing protein 2. This trimeric complex helps extend the phagophore membrane around the LD, which ultimately causes the LD to be engulfed, forming a complete autophagosome [40].

Microlipophagy

Unlike macrolipophagy, which involves autophagosome formation prior to fusion with the lysosomes, microlipophagy involves a direct and transient engulfment of the LDs by the lysosomes via a “kiss and run” mechanism in a process that requires Rab7. The sterol-transporting Niemann-Pick type C proteins (Ncr1 and Npc2) were found to be involved in the formation of these vacuolar microdomains and ensuing LD engulfment, which may happen in ways that are Atg-dependent or Atg-independent [41]. While *Saccharomyces cerevisiae* is the yeast in which microlipophagy has been extensively studied, current research suggests that microlipophagic mechanisms also exist in mammalian cells [42]. A recent study used live-cell microscopy of primary hepatocytes or hepatocyte-derived cell lines to explore whether lysosomes alone could be adequate to promote LD turnover in the absence of an autophagosomal intermediary. Interactions between mammalian lysosomes and LDs have been observed, wherein the lipid contents of the LD can be extruded straight into the lysosomal lumen in the absence of double membrane lipoautophagosomes [43].

Chaperone-mediated autophagic degradation of LD surface proteins

PLINs, a family of proteins that coat the surface of LDs, physically prevent access to the TG and cholesteryl ester-rich core, thereby controlling both lipophagy and lipolysis. PLIN2 plays a regulatory role in hepatic steatosis, as observed when mice lacking PLIN2 did not develop fatty liver upon being fed an HFD [36]. Briefly, the 71-kDa cytosolic chaperone heat-shock cognate protein and its co-chaperones identify proteins with a KFERQ motif, such as PLIN2, PLIN3, and PLIN5. This cargo-chaperone complex is subsequently translocated to the lysosomal-associated membrane protein 2A (LAMP2A) receptors of the lysosome, to be imported into the lumen of the lysosome and degraded by proteases enzymes [37]. CMA functions as an upstream regulator of both neutral lipolysis and macrolipophagy. This is because degradation of the LD-anchored PLINs facilitates recruitment of cytosolic lipases such as ATGL and docking of protein effectors of macrolipophagy such as LC3-II [44].

Regulatory mechanisms of lipophagy

Lipophagy can be controlled by several pathways that detect and respond to the cellular nutritional state such as mammalian target of rapamycin complex 1 (mTORC1) and AMPK [34]. In general, lipophagy is stimulated by food scarcity and inhibited by plenty. Apart from insulin and glucagon, other hormones that can control lipophagy include thyroidine, fibroblast growth factor 21 (FGF21), and adrenaline [45]. Consistent with its role in promoting hepatic mitochondrial β-oxidation, thyroidine was found to be required for the mobilization of lipids via autophagy. The liver secretes FGF21, which in turn stimulates autocrine/paracrine-dependent macrolipophagy in hepatocytes. β-adrenergic stimulation in the liver and AT can induce lipophagy in a Rab7-dependent manner [32]. The major mechanisms regulating hepatic lipophagy are presented in Figure 3.

Many transcription factors and co-activators, including PPARα, PPAR-activated receptor gamma coactivator 1-alpha (PPARGC1A), transcription factor E3 (TFE3), transcription factor EB (TFEB), cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), and forkhead box O (FOXO1, FOXO3, and FOXO4) are primarily responsible for controlling the expression of lipophagy-associated genes. Other nutrient-induced transcription factors include farnesoid X receptor (FXR), which can suppress lipophagy [46].

The members of the microphthalmia-associated/TFE subfamily of basic/helix-loop-helix/leucine zipper transcription factors, which includes TFEB and TFE3, are the most common transcriptional regulators of autophagy/lipophagy. TFEB and TFE3 are both master regulators of lysosomal activity and macroautophagy [47]. Macrolipophagy is necessary for the effect of TFEB on lipid metabolism. This was observed when TFEB overexpression did not reverse the rise in liver lipid content in HFD-fed mice in which hepatic autophagy was particularly repressed by autophagy-associated protein (Atg7) deletion. TFE3 can mitigate the hepatocellular steatosis caused by FFA exposure by means of macrolipophagy and PPARGC1A-mediated FFA β-oxidation. Blocking these pathways with small interfering RNA against Atg5 and PPARGC1A, respectively, significantly decreased the TFE3-mediated mitigation of hepatic steatosis [48].

The FOXO family is another transcription factor family that is involved in the control of macrolipophagy. FOXO1 affects lipid metabolism in different ways via upregulating lysosomal acid lipase, triggering macrolipophagy in response to nutrient deprivation, and promoting the production of ATGL in adipocytes. Along with FOXO3 and FOXO4, FOXO1 is also required for mediating lipophagy in hepatocytes [49]. It has also been demonstrated that CREB1/CREB can stimulate macrolipophagy in conditions of

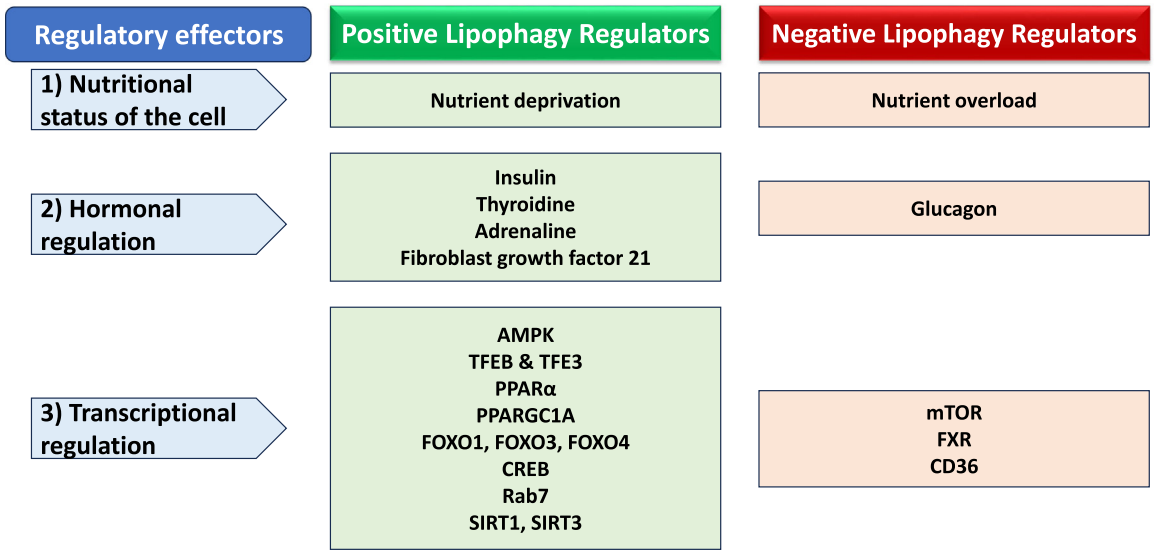

Fig. 3. Regulatory mechanisms of hepatic lipophagy. AMPK, adenosine monophosphate-activated protein kinase; CREB, cyclic adenosine monophosphate response element-binding protein; FOXO, forkhead box O; FXR, farnesoid X receptor; mTOR, mammalian target of rapamycin; PPARGC1A, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARα, peroxisome proliferator-activated receptor α; SIRT, sirtuin; TFE3, transcription factor E3; TFEB, transcription factor EB.

nutritional deficiency, but fed-state sensing FXR inhibits this response [31].

The fatty acid transporter CD36 was demonstrated to act as a negative regulator of lipophagy in hepatocytes. In hepatoma-derived cell lines (HepG2 and Huh7), overexpression of CD36 results in decreased autophagy and higher LD content; conversely, CD36 knockdown has the opposite effect. Mice with CD36 deletion had elevated autophagy, an effect that was diminished upon CD36 rescue [50]. Tumor-associated gene microRNA-425 is implicated in the development of hepatocellular carcinoma and can promote drug resistance and cell proliferation. Inhibiting the expression of microRNA-425 led to a rise in SIRT1 expression, which in turn promoted lipophagy and inhibited the proliferation of liver cancer cells [51]. The small GTPase Rab7 plays a central role in regulating lipophagy in hepatocytes. Hepatocellular lipophagy is attenuated when Rab7 is depleted because it causes dramatic morphological alterations to lysosomes, autophagosomes, and multivesicular bodies [38].

The 7 members of the sirtuin family (SIRT1−7) have distinct cellular localizations and are involved in a variety of cellular functions. Exercise, calorie restriction, fasting, and polyphenols all upregulate SIRT1, while it is downregulated by nutritional excess. Recent research using liver-specific SIRT1 knockout mice indicated that SIRT1 is required for ATGL-mediated induction of lipophagy [52]. A recent study indicated that lipotoxicity reduced SIRT3 expression along with lipophagic flux and increased LD accumulation in primary hepatocytes from HFD-fed mice and palmitate/oleate-treated mouse hepatocytes, ultimately leading to severe steatosis and hepatotoxicity [44]. However, the increased expression of SIRT3 enhanced macroautophagy in LDs via AMPK activation [53].

Targeting lipophagy as a therapeutic strategy against MASLD

As previously mentioned, LDs can be degraded via lipophagy for either energy supply or removal of excess fat from tissues to restore the normal cellular function. Hence, recent research focused on the reduction of ectopic fat deposition in liver, β-cells, and skeletal muscle by regulating lipophagy in order to improve many metabolic disorders including fatty liver [54]. In previous studies, MASLD was established using diets such as HFD in animal models or palmitic acid and/or oleic acid in vitro to efficiently induce the lipid accumulation [55].

Various techniques and biological parameters can be used to evaluate whether or not lipophagy is functioning properly. These include oil red O staining, biochemically determining the TG of cells or tissues, serum total cholesterol, high- and low-density lipoprotein cholesterol, as well as liver enzymes. Furthermore, measurements of autophagy flux and lipophagy-related proteins are crucial markers for assessing the turnover of fats packed in LDs [56]. More importantly, the co-localization of LDs and autophagic vacuoles, which can be visualized by transmission electron microscopy or double immunofluorescent staining, is considered more direct evidence for this pathway. Lipophagy inducers such as rapamycin and/or inhibitors such as chloroquine can also be used to confirm that some synthetic or natural products could reduce the fat accumulation through lipophagy modulation [36].

Many natural compounds have been shown to have regulatory effects on MASLD through various mechanisms, such as regulating lipid metabolism, repairing mitochondrial dysfunction, reducing inflammation, as well as improving IR, oxidative stress, and ER stress [8]. Here, we focus on the natural products targeting lipophagy for the treatment or prevention of MASLD. Natural products acting as lipophagy inducers in MASLD are summarized in Table 1.

Flavonoids

Quercetin

Quercetin is one of the most prevalent flavonoids in fruits and vegetables. It has a wide range of biological activities, including immunomodulatory, anti-inflammatory, and antioxidant properties [57]. Liu et al. reported that treatment of ApoE-knockout C57BL/6J mice with 100 mg/kg of quercetin for 6 mo significantly ameliorated HFD-induced liver damage through reducing the levels of hepatic cholesterol and oxidized low-density lipoprotein (ox-LDL) [58]. Quercetin treatment could also enhance autophagy via increasing the expression of LC3-II while decreasing the expression of both p62 and mTOR. Thus, quercetin's hepatoprotective effects may be related to its enhanced autophagy-lysosomal breakdown of ox-LDL [58]. According to Zhu et al., in FFA-treated HepG2

Table 1
Natural products acting as lipophagy inducers in treating or preventing metabolic dysfunction-associated steatotic liver disease

Active compound	Natural source	Experimental model	Targeted pathway	References
FLAVONOIDS				
Quercetin	*Capparis spinosa L.; Piper Nigrum L.*	HFD-fed ApoE-knockout C57BL/6J mice	mTOR	[58]
		HFD-fed Sprague-Dawley rats and FFA-exposed HepG2 cells	IRE1a/XBP1	[59]
		Fatty acid–induced AML12 hepatocytes	AMPK	[60]
		Rats	SIRT1/AMPK	[61]
		Palmitic acid–treated HepG2 cells	cAMP/AMPK/SIRT1	[62]
Apigenin	*Petroselinum cripspum; Matricaria chamomilla*	Palmitic acid–treated HepG2 cells	mTOR	[63]
		Oleic acid–induced Huh7 cells	Autophagy-mitochondrial pathway	[64]
Nobiletin	*Citrus* fruits	HFD-fed ApoE$^{-/-}$ mice and FFA-treated HepG2 cells	TFEB	[66]
Luteolin	*Lonicera japonica; Nepeta cateria L.; Chrysanthemum morifolium; Ajuga decumbens* Thunb.	Palmitate-induced lipotoxicity in AML12 liver cells and mouse primary hepatocytes	AMPK	[68]
Phloretin	*Malus* spp.	Fatty acid–exposed Huh7 cells and Western diet-fed C57BL/6J mice	AMPK	[70]
Galangin	*Alpinia galanga*	HFD-fed C57BL/6J mice and fatty acid–exposed HepG2 cells	AMPK/mTOR	[72]
Pueraria	*Pueraria lobata*	HFD-fed C57BL/6 J mice and fatty acid–-treated HepG2 cells	PI3K/Akt/mTOR	[74]
Bergamot polyphenol fraction	*Citrus bergamia*	HepaRG cells and palmitic acid–treated GR-LC3-HepG2	—	[76]
ALKALOIDS				
Nuciferine	*Nelumbo nucifera*	HFD-fed C57BL/6N mice and palmitic acid-challenged primary hepatocytes isolated from TFEB knockout mice as well as AML12 cells	mTORC1-TFEB-autophagy-lysosomal pathway	[78]
Ajugol	*Rehmannia glutinosa*	HFD-fed C57BL/6 mice and palmitate-treated AML12 mouse hepatocytes and isolated primary hepatocytes from mice liver	TFEB-mediated lysosome biogenesis	[80]
Trigonelline	*Trigonella foenum-graecum*	High-cholesterol and HFD-fed C57BL/6J mice and palmitic acid–exposed AML12 cells and HepG2 cells	–	[82]
POLYPHENOLS				
Resveratrol	*Veratrum grandiflorum*	HFD-fed wild-type and autophagic mediator ULK1 heterozygous knockout mice	ULK1	[83]
		HFD-fed rats	SIRT1	[85]
		HFD-fed mice and palmitate-treated HepG2 cells	cAMP-PRKA-AMPK-SIRT1	[86]
		Palmitate-treated HepG2 cells	cAMP/AMPK/SIRT1	[87]
Polydatin	*Polygonum cuspidatum* Sieb. et Zucc.	Methionine–choline–deficient diet-fed C57Bl/KsJ–*db*–/*db* (*db*/*db*) mice and palmitic acid–treated human hepatocyte LO2 cells	TFEB	[89]
Olive leaf extract	*Olea europaea* L.	Palmitate/oleate-treated HuH7 cell	–	[91]
Magnolol	*Magnolia officinalis*	Tyloxapol-induced hyperlipidemia in rats and palmitic acid–stimulated HepG2 cells	mTOR	[95]
Honokiol	*Magnolia officinalis*	Choline-deficient HFD-fed C57BL/6J mice and palmitate/oleate-treated AML12 cells	SIRT3/AMPK	[97]
Epigallocatechin-3-gallate	*Camellia sinensis* (L.) O. Ktze.	HFD-fed mice and oleic acid–treated L02 and QSG-7701 liver cells	Reactive oxygen species-mediated MAPK	[99]
		High-fat/Western-style diet-fed C57BL/6 mice and HepG2 as well as Huh7 cells	AMPK	[100]
Apple polyphenol extract	*Malus* spp.	Palmitate/oleate-treated HepG2 cells	SIRT1/AMPK	[102]
		HFD-fed 12-mo-old C57BL/6 mice	SIRT1	[103]
Lotus seedpod extract	*Nelumbo nucifera* Gaertn.	Oleic acid–treated HepG2 cells	–	[105]
MISCELLANEOUS				
Iridoids of *Valeriana fauriei*	*Valeriana fauriei*	HFD-fed C57BL/6 J mice and oleic acid–-treated Huh7 and MEF cells	mTORC1	[107]
Steviosides of *Stevia rebaudiana* Bertoni	*Stevia rebaudiana* Bertoni	C57BL/6J *db*/*db* mouse (BKS.Cg-Dock7m +/+ Leprdb/J, homozygote) and FFA-exposed HepG2 cells	PPARα	[109]
Phillygenin	Forsythiae Fructus	HFD-fed C57BL/6 J mice and palmitate-stimulated AML12 cells and primary hepatocytes	Ca^{2+}/calcineurin/TFEB	[111]

(*continued*)

Table 1 (*Continued*)

Active compound	Natural source	Experimental model	Targeted pathway	References
Sulforaphane	Broccoli sprouts	Hepatocytes	Nrf2	[113]
		HFD-fed mice and 3T3-L1 adipocytes	AMPK/mTOR/ULK1	[114]
Rhodiola crenulata	*Rhodiola crenulate*	Fructose-fed Sprague-Dawley rats	–	[116]
Veronica ciliata Fisch.	*Veronica ciliata* Fisch.	*tert*-Butyl hydroperoxide–induced Institute of Cancer Research mice and ethanol-induced rat hepatocyte cell line BRL-3A	AMPK/p62/Nrf2	[118]
Oleic acid	*Olea europaea* L.	HFD-fed C57/BL6 mice and palmitic acid/tunicamycin-treated human hepatoma cell line HepG2 cells, mouse normal liver cells AML12 cells, and human normal liver cells L-02 cells	TFEB	[121]
Shenling Baizhu powder	10 Chinese medicinal herbs [122]	HFD-fed Wistar rats	SIRT1	[123]

AML12, alpha mouse liver 12; AMPK, adenosine monophosphate-activated protein kinase; HFD, high-fat diet; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor erythropoietin-2-related factor 2; SIRT1, sirtuin 1; TFEB, transcription factor EB; ULK1, Unc-51-like autophagy activating kinase 1.

cells and HFD-fed Sprague-Dawley rats, quercetin alleviated MASLD by stimulating hepatic VLDL assembly and lipophagy through the inositol-requiring transmembrane kinase/endoribonuclease 1α/ spiced X-box binding protein 1 (IRE1a/XBP1) pathway [59]. Quercetin consumption increased the co-localization of LDs with lysosomes and suppressed p62 level, while thapsigargin or STF-083010, an IRE1α endonuclease inhibitor, partially eliminated the lipophagy-inducing effect of quercetin in an mTOR-independent manner [59]. Another study by Fukaya et al. showed that treating FFA-exposed alpha mouse liver 12 (AML12) hepatocytes with 10 μM quercetin for 12 h promoted lipophagy, as represented by increased co-localization of LDs with lysosomes [60]. The enhancement of fatty acid β-oxidation induced by quercetin was eliminated by pharmacological inhibition of the autophagy-lysosomal pathway using 3-methyladenine. This indicates that quercetin's enhancement of lipophagy contributed to increased oxidation of fatty acids in an AMPK-dependent manner [60]. A recent study showed that thymoquinone (10 mg/kg/d) and quercetin (50 mg/kg/d) co-treatment protected rats against hepatic steatosis via SIRT1/AMPK stimulation. This combination suppressed proinflammatory and oxidative markers and reduced the levels of PLIN2 and hepatic lipogenic enzymes, while it activated autophagy protein Atg7 and cytosolic ATGL [61]. In another experimental study, the involvement of autophagy in the lipid-lowering actions of quercetin, either alone or in conjunction with metformin, was investigated using a palmitic acid-induced hepatic steatosis model in HepG2 cells [62]. In addition to decreasing TG levels and lipogenic gene expression, co-treatment of cells with both quercetin and metformin induced autophagy via increasing the levels of LC3-I and LC3-II proteins and decreasing the expression of p62 more remarkably than monotherapy. Quercetin and metformin co-treatment reduced the production of proinflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and IL-1B in HepG2 cells. However, levels of cAMP, phosphorylated AMPK, and Beclin-1 were increased. This effect was countered by the addition of 10 μM of sirtinol, an inhibitor of SIRT1, suggesting that the quercetin-metformin combination diminished hepatic steatosis by activating autophagy via the cAMP/AMPK/SIRT1 signaling pathway [62].

Apigenin

Apigenin is a prominent, naturally occurring flavonoid found in a wide range of fruits and vegetables, particularly onions, celery, parsley, oranges, thyme, chamomile, and tea. The potential effect of apigenin in enhancing autophagy and alleviating lipid accumulation in HepG2 cells treated with palmitic acid has been studied by Lu et al. [63], where it was postulated that apigenin reduced the intracellular lipid content by inducing the autophagic lipid breakdown demonstrated by LDs co-localizing with LC3; this effect was blocked by the addition of chloroquine. Additionally, it was shown that apigenin reduced expression of the p62 protein and p-mTOR/mTOR ratio while inducing autophagosome formation and increasing the LC3-II/I ratio [63]. Another research group examined the molecular mechanisms underlying the protective effect of apigenin against the dysregulation of hepatic lipid metabolism using oleic acid–induced steatosis in Huh7 cells as an in vitro model [64]. After apigenin treatment (20 μM), there was an increase in intracellular fatty acid levels due to the enhanced production of autophagy-related proteins such as Beclin1, Atg5, Atg7, and LC3-II, as well as induced autophagolysosome formation. The protective properties of apigenin against oleic acid–induced lipid buildup were eliminated when bafilomycin A1 or chloroquine were used to inhibit autophagy [64].

Nobiletin

Nobiletin is a citrus flavonoid that is notable for having a variety of pharmacological properties, such as neuroprotective, anti-inflammatory, anti-IR, antitumor, and antioxidant properties [65]. A recent study investigated the preventive effect of nobiletin on MASLD using HFD-fed ApoE$^{-/-}$ mice and FFA-treated HepG2 cells [66]. Different doses of nobiletin (50, 100, and 200 mg/kg/d) could significantly ameliorate MASLD mainly via TFEB-mediated lysosomal biogenesis and lipophagy. Nobiletin treatment increased levels of positive regulators of hepatic lipophagy including TFEB, Rab7, and LAMP1, as well as autophagy biomarkers such as Beclin1 and LC3 [66].

Luteolin

Numerous fruits, vegetables, and herbs such as celery, broccoli, green pepper, peppermint, and thyme contain this tetrahydroxyflavone. Luteolin has neuroprotective, antitumorigenic, and antidiabetic activities. These effects are linked to luteolin's capacity to reduce oxidative stress and inflammation, as well as to regulate autophagy and ER stress [67]. Luteolin was demonstrated to mitigate palmitate-induced lipotoxicity in AML12 liver cells and mouse primary hepatocytes by enhancing antioxidant defense, boosting AMPK-mediated autophagy, attenuating ER stress, and reversing the damage caused to autophagic flux [68].

Phloretin

Strawberries and apples are rich sources of this common dihydrochalcone flavonoid. Phloretin has strong antioxidant, anticancer, anti-inflammatory, and antidiabetic properties [69]. Chhimwal et al. reported that phloretin upregulated autophagy-mediated lipid breakdown to mitigate the evolution of MASLD in both palmitate- and oleate-exposed Huh7 cells and Western diet-fed C57BL/6J mice via reducing mitochondrial dysfunction and oxidative stress [70]. Phloretin significantly enhanced autophagy through

increasing the protein expression of Atg5, Atg7, LC3-II/I, and Beclin1, while decreasing the expression of p62 protein [70].

Galangin

Galangin is a flavonol compound and curcumin derivative with anti-inflammatory, antiviral, anticancer, antibacterial, antidiabetic, and anticlastogenic properties [71]. Through the activation of hepatic autophagy, galangin (100 mg/kg/d) was observed to diminish the fatty degeneration of liver tissue generated by an HFD diet in C57BL/6J mice, both at preventive and therapeutic levels [72]. The protective impact of galangin on hepatic steatosis was hindered by 3-methyladenine, the autophagy inhibitor, which resulted in a large accumulation of TG and cholesterol in the hepatocytes of mice. The reported data also showed that galangin enhanced the levels of CPT1 and PPARα mRNA in the livers of HFD-fed mice, while it downregulated levels of ChREBP, CD36, and SREBP-1c. In FFA-treated HepG2 cells, galangin decreased lipid buildup and augmented hepatocyte autophagy at the cellular level [72].

***Pueraria* flavonoids**

Pueraria flavonoids provide numerous health benefits for the kidney, liver, heart, brain, stomach, muscle, skin, bone, and reproductive system, in addition to their anti-inflammatory and antioxidant properties [73]. It has been shown that the flavonoids found in *Pueraria* promote autophagy through blocking activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mTOR signaling pathway, which in turn decreases intracellular lipid accumulation and inflammation. *Pueraria* flavonoids at doses of 50, 100, and 200 mg/kg/d administered intragastrically for 4 wk were shown to dramatically increase autophagy levels and the amount of autophagosomes in C57BL/6 J mice fed on an HFD. Autophagy blockage by siRNA transfection increased the accumulation of lipids and the release of inflammatory cytokines. At a cellular level, *Pueraria* flavonoids (12.5, 25, and 50 μg/mL) reduced lipid deposition and cellular inflammation by increasing the autophagy flux in palmitate- and oleate-exposed HepG2 cells [74].

Bergamot polyphenol fraction (BPF)

Bergamot is a citrus fruit belonging to the *Rutaceae* family and to the genus *Citrus*, which grows in southern Italy [75]. BPF was analyzed for its proautophagic compounds using liquid chromatography-high resolution mass spectrometry (LC-HRMS) [76]. This screening revealed that the hydrophobic fraction of acid-hydrolyzed BPF (A-BPF), which contained 6 flavanone and flavone aglycones, promoted autophagy in palmitic acid–treated GR-LC3-HepG2 cells. The weakest inducers of autophagy among them were diosmetin, hesperitin, eriodictyol, and naringenin, whereas apigenin and luteolin showed more potent autophagic activation. At an early time interval (6 h), apigenin exhibited the strongest and most dose-dependent proautophagic action. Luteolin elicited a significant autophagic induction at low dosages, but at greater concentrations it became inhibitory, thereby exhibiting a biphasic autophagy response. Upon examining the cytotoxicity of these flavonoids, it was found that both apigenin and luteolin were harmful to HepG2 cells and to differentiated human liver progenitors, HepaRG cells, after prolonged treatment (24 h). On the other hand, BPF and A-BPF caused a sustained increase in autophagic flow without exhibiting any toxicity. This indicates that using isolated flavonoids to treat MASLD may not be as safe or beneficial as using a natural polyphenol phytocomplex such as BPF [76].

Alkaloids

Nuciferine

Nuciferine is an aromatic ring-containing alkaloid that has been demonstrated to have a wide range of pharmacological effects on the metabolic syndrome, including anti-inflammatory, antiobesity, and antioxidant properties [77]. Du et al. reported that nuciferine was able to alleviate MASLD via controlling the mTORC1–TFEB–autophagy-lysosomal pathway in mice and AML12 cells [78]. It was revealed that nuciferine interacts with the Ragulator subunit hepatitis B X-interacting protein and inhibits the Ragulator complex's ability to interact with Rag GTPases. This suppresses mTORC1 activity and lysosomal localization, which in turn activates the TFEB-mediated autophagy-lysosomal pathway, thereby mitigating hepatic steatosis and IR [78].

Ajugol

In traditional Chinese and Korean medicine ajugol is an active alkaloid with anti-inflammatory and antioxidant activities that is frequently used to treat a variety of disorders such as lipid metabolic diseases and diabetes [79]. Ajugol was shown to improve TFEB-mediated lysosome formation and lipophagy, hence mitigating palmitate-induced lipid accumulation in hepatocytes and HFD-induced hepatic steatosis in C57BL/6 mice [80]. By inactivating mTOR and inducing the nuclear translocation of TFEB, a crucial regulator of lysosomal biogenesis, ajugol was able to alleviate defective autophagic flux and steatosis by promoting the fusion of autophagosomes and lysosome. These protective effects were considerably eliminated by TFEB knockdown induced by siRNA [80].

Trigonelline

Trigonelline is one of the plant alkaloids that is found in many palatable natural products. It is characterized by having antidiabetic, antihypercholesterolemic, and anticarcinogenic properties [81]. Through the restoration of hepatic autophagy, it has been shown that trigonelline prevents the development of MASLD by inhibiting high-cholesterol HFD-induced hepatic steatosis in C57BL/6J mice and lipotoxicity in palmitate-exposed AML12 cells and HepG2 cells [82]. Restoration of cellular autophagy by trigonelline was demonstrated by enhanced phosphorylation of AMPK and preventing mTOR upregulation, which is linked to the upregulation of Beclin-1 and Atg7, and degradation of p62. These beneficial effects were abrogated in Atg7$^{-/-}$HepG2 cells exposed to chloroquine [82].

Polyphenols

Resveratrol

Resveratrol is a dietary polyphenol (3,4′,5-trihydroxystilbene) that is present in red wine and grapes. Resveratrol has been shown to prevent a number of metabolic disorders, including MASLD [83]. Several studies have investigated the role of autophagic degradation of LDs by resveratrol, either alone or in combination, in protection against various metabolic disorders. Wild-type and autophagic mediator Unc-51–like autophagy activating kinase 1 (ULK1) heterozygous knockout mice were administered 50 mg/kg of resveratrol daily for 4 wk after being fed an HFD for 8 wk [84], where it was found to ameliorate MASLD and its associated metabolic dysregulation via enhancing autophagy and reducing the activity of nuclear factor-κB (NF-κB). However, partial suppression of ULK1 expression impaired resveratrol's ability to mitigate MASLD-induced hepatic injury, suggesting a significant role of autophagy in resveratrol-mediated hepatic protection [84]. By analyzing the molecular interactions between SIRT1 and autophagy, Ding et al. aimed to clarify the mechanism by which resveratrol supplementation and caloric restriction mitigate HFD-induced hepatic steatosis in rats and to compare the effects of resveratrol and caloric restriction on hepatic lipid metabolism [85]. Resveratrol (200 mg/kg) and 30% caloric restriction enhanced the expression of SIRT1 and autophagy markers, decreased markers of ER stress in the liver, and partially averted hepatic steatosis and hepatocellular

ballooning, all of which helped to alleviate lipid metabolic disorder [85]. According to their findings, there was no significant change in the hepatic protein expression of LC3-II between rat groups treated with either resveratrol or caloric restriction. However, caloric restriction provided a better net protection against HFD-induced steatosis than did resveratrol [85]. In another study by Zhang et al., it was found that resveratrol significantly prevented palmitate-induced lipid deposition in HepG2 cells by triggering autophagy through the cAMP-protein kinase A (PRKA)–AMPK–SIRT1 pathway [86]. The improvement of hepatic steatosis mediated by resveratrol was significantly eliminated by autophagy inhibitors. In HepG2 cells, resveratrol increased the amounts of cAMP, SIRT1, phosphorylated PRKA, and pAMPK. The addition of inhibitors or siRNA of adenylyl cyclase, PRKA, AMPK, and SIRT1 diminished resveratrol-mediated autophagy induction. Similar results were obtained using 0.4% resveratrol in HFD-fed mice with hepatic steatosis [86]. Using the palmitic acid–induced hepatic steatosis model in HepG2 cells, the role of autophagy in the lipid-lowering actions of resveratrol, both alone and in combination with metformin, was recently studied [87]. The combination of resveratrol and metformin increased the levels of LC3-I and LC3-II proteins and decreased the expression of p62 to activate autophagy. This combination also increased the levels of Beclin-1, pAMPK, and cAMP. Furthermore, autophagy induced by resveratrol and metformin co-treatment was suppressed by SIRT1 inhibitor, suggesting that SIRT1 is required for autophagy activation [87].

Polydatin

Polydatin is a natural monocrystalline precursor of resveratrol that is commonly found in grapes, peanuts, hop cones, and red wine. Polydatin has been shown to protect against liver damage induced by alcohol, carbon tetrachloride, and galactose/fructose overload [88]. Oral administration of 100 mg/kg/d of polydatin for 4 wk protected against hepatic fatty deposition and alleviated hepatocellular inflammation and damage in *db/db* mice fed on a methionine–choline–deficient diet [89]. Additionally, polydatin ameliorated palmitic acid–induced lipid buildup in human hepatocyte LO2 cells. The hepatoprotective effects of polydatin were mediated via restoring autophagic flux through inhibition of mTOR signaling and upregulation of the expression and activity of TFEB, a master regulator of lysosomal function [89].

Olive leaf extract

Olive leaf extract is rich in polyphenols with hypolipidemic and antioxidant activities that have been successfully applied in pharmaceutical, cosmetic, and medical products [90]. According to a recent in vitro study, lipophagy activation and modulation of the protein expression of enzymes involved in LD metabolism reduced hepatic steatosis and improved oxidative stress parameters when an aqueous olive leaf extract was added to an FFA-treated HuH7 cell line. Additionally, the results showed that the lysosome component, autophagosome formation, and LC3-II/LC3-I ratio were enhanced when olive leaf extract and FFA-treated cells were co-cultured, suggesting that the degradative pathway had been activated [91].

Oleuropein

Oleuropein is a phenolic glycosylated seco-iridoid with strong anti-inflammatory and antioxidant qualities, and is the most abundant bioactive substance in olive leaves [92]. Porcu et al. investigated whether or not oleuropein's protective properties against liver steatosis could be related to autophagy [93]. Their results indicated that treatment of HFD-fed C57BL/6J mice with 3% of oleuropein dissolved in drinking water induced autophagy by stimulating the AMPK/ULK1 pathway in both sexes. Oleuropein modulated autophagy-related proteins by upregulating the expression of LC3-II/I and downregulating p62 and Beclin-1 expression levels [93].

Magnolol

Magnolol has a broad spectrum of biological effects, such as anti-inflammatory, antimicrobial, antioxidant, anticancer, neuroprotective, cardiovascular protection, and lipolytic properties [94]. Kuo et al. employed a tyloxapol-induced hyperlipidemia model in rats and palmitic acid–exposed HepG2 cells to examine the effects of magnolol against hepatic steatosis [95]. By decreasing NLR family pyrin domain containing 3 (NLRP3) inflammasome activation and raising cellular nuclear factor erythropoietin-2–related factor 2/heme oxygenase 1 (Nrf2/HO-1) antioxidant capabilities, magnolol successfully modulated lipid accumulation and improved hepatic steatosis. The administration of magnolol additionally induced autophagic flux via phosphorylating mTOR, lowering p62, and raising Beclin1, Atg7, Atg5-12, and LC3-II/LC3-I ratios. Magnolol-mediated decreases in inflammation and lipid metabolism were significantly abolished in HepG2 cells upon autophagy inhibition with 3-methyladenine, suggesting that lipophagy activation may contribute to the protective effects of magnolol [95].

Honokiol

Various biological properties, such as anti-arrhythmic, anti-inflammatory, anti-oxidative, anti-depressant, anti-thrombotic, and anxiolytic effects, have been demonstrated by this natural lignan [96]. By using FFA-induced lipotoxic AML12 cells and choline-deficient HFD-induced liver steatosis in C57BL/6J mice, Liu et al. demonstrated that honokiol (2.5 and 10 mg/kg) could protect hepatocytes against lipotoxicity through enhancing SIRT3-AMPK–mediated lipophagy and maintaining mitochondrial morphology and integrity in mice [97]. Honokiol (5 and 10 μM) showed a similar result in AML12 cells treated with palmitate/oleate mixture. The honokiol-induced protective effect was significantly diminished by the administration of compound C, an AMPK inhibitor [97].

Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is a polyphenol in green tea that has been demonstrated to contribute to the various biological and pharmacological characteristics of the tea, including its antiviral, anticancer, antiaging, chemopreventive, renoprotective, and antiamyloidogenic effects [98]. Wu et al. conducted a new investigation to determine the mechanism underlying the protective effect of EGCG on the progression of MASLD [99]. A total of 50 mg/kg of EGCG was administered daily to HFD-induced MASLD in mice, while 50 μM of EGCG was added for 24 h to oleic acid––treated L02 and QSG-7701 liver cells. It was found that EGCG improved autophagy, which was implicated in the improvement of MASLD via the reactive oxygen species-mediated MAPK pathway. This was demonstrated by increased expression levels of Beclin-1 and LC3 and decreased expression levels of p62 [99]. Zhou et al. also reported that EGCG showed beneficial effects in reducing hepatic steatosis via induction of AMPK-mediated hepatic autophagy in HepG2 and Huh7 hepatic cells and in C57BL/6 mice fed a high-fat, Western-style diet [100]. EGCG enhanced hepatic autophagy in various ways by increasing autophagosome formation and the LD engulfment within autophagosomes and autolysosomes, raising lysosomal acidity, and boosting autophagic flux. However, EGCG's induction of autophagy was reversed by AMPK siRNA knockdown [100].

Apple polyphenol extract

Apple polyphenol extract (APE), a type of polyphenol that is isolated from fresh whole apples, has been demonstrated to have strong anti-inflammatory and antioxidant properties. Procyanidins, phloretin, chlorogenic acid, quercetin, catechin, and epicatechin are the major components of APE [101]. APE administration reduces intracellular lipid deposition induced by oleate/palmitate mixture through stimulating autophagy, restoring lysosomal

acidity, inhibiting lipogenesis, and promoting fatty acid oxidation [102]. Mechanistically, APE blocks mTOR signaling, activates the liver kinase B1 (LKB1)/AMPK pathway, and elevates SIRT1 expression. The lowering effect of APE on lipid accumulation is compromised by SIRT1 and Atg7 knockdown, which results in a rise in intracellular TG levels. Therefore, SIRT1/AMPK signaling pathway mediates APE's induction of autophagy to mitigate FFA-induced lipid accumulation [102]. In another study by Yin et al., APE intervention has been shown to mitigate metabolic abnormalities as well as hepatic steatosis and injury in HFD-fed 12-mo-old C57BL/6 mice [103]. Autophagy induction was significantly involved in regulating hepatic lipid metabolism observed with APE intervention through increasing the gene expression of SIRT1, HSL, Atg5, ULK1, and Beclin-1 and decreasing the gene expression of HMG-CoA reductase and FOXO1 [103].

Lotus seedpod extract

Polyphenol-rich lotus seedpod, a traditional Chinese herbal medicine, has been shown to possess antioxidant, antiaging, antimemory impairment, radioprotective, and anti-inflammatory activities [104]. Liu et al. investigated the hepatoprotective properties of lotus seedpod extract at different concentrations of 2.5, 5, and 10 μg/mL, as well as its major bioactive component epigallocatechin at 4 μM, using an oleic acid–induced hepatic steatosis model in HepG2 cells [105]. Lotus seedpod extract mitigated hepatic lipotoxicity via reducing intracellular lipid accumulation and reactive oxygen species production that was majorly mediated through inhibiting apoptotic pathways. Their findings revealed that lotus seedpod extract or epigallocatechin treatments slightly downregulated autophagy-related proteins (LC3-II/LC3-I ratio and Atg5/12 conjugation). This indicates that the autophagy mechanism is not primarily responsible for lotus seedpod extract's ability to reduce hepatic lipotoxicity in HpG2 cells [105].

Miscellaneous

Iridoids of *Valeriana fauriei*

Valeriana fauriei is extensively distributed in Northeast China, South Korea, and Japan. It is used to treat cardiovascular problems, sleep disorders, anxiety, epilepsy, and insomnia. Numerous substances, including alkaloids, iridoids, monoterpenes, and sesquiterpenes, are found in *V. fauriei* [106]. Among other natural compounds, *V. fauriei* was selected by Lee et al. as a possible inducer of autophagy. *V. fauriei* 70% ethanol extract decreased oleic acid–induced lipid accumulation and downregulated genes linked to lipogenesis in Huh7 and MEF cells through inducing autophagy [107]. This was demonstrated by higher LC3-II levels and an increase in autophagosome count in a way that was reliant on mTORC1. It has been demonstrated that ethanolic extract–containing iridoids, which include didrovaltrate, valeriotriate B, valeriotetrate C, valtrate, and valechlorine, can promote autophagy [107].

Steviosides of *Stevia rebaudiana* Bertoni

Stevia rebaudiana is a naturally occurring sweetener with a number of biological benefits for health. The plant leaf extract, which includes secondary metabolites including polyphenols and steviol glycosides such as stevioside, rebaudioside A, and rebaudioside C, is responsible for these biological actions. Stevioside exhibits anti-inflammatory, antitumor, antidiabetic, antihyperlipidemic, antidiarrheal, and antihypertensive properties [108]. A recent study indicated that the induction of PPARα-dependent lipophagy by *S. rebaudiana* Bertoni and stevioside could ameliorate hepatic steatosis in the C57BL/6J *db/db* mouse model [109]. The administration of *Stevia* (200 and 500 mg/kg/d) and stevioside (40 mg/kg/d) resulted in increased levels of PPARα and LC3-II, enhanced expression of Beclin-1, LAMP1, and pAMPK, but decreased p62 in the liver of *db/db* mice. The administration of *Stevia* and stevioside decreased the liver concentration of LDs and TG in *db/db* mice due to the enhanced activity of the lysosomal acid lipase. Additionally, PPARα and CPT-1 were upregulated and the expression of SREBP-1c, fatty acid synthase, PPARγ, and CCAAT/enhancer-binding protein alpha was downregulated, suggesting that *Stevia* and stevioside improved the oxidation of fatty acids. Nevertheless, the stevioside-induced restoration of lipophagy in HepG2 cells was inhibited by PPARα knockdown [109].

Phillygenin

Phillygenin is a lignan with various biological and pharmacological effects including hepatoprotective effects [110]. According to the findings of a recent study by Zhou et al., phillygenin can regulate the Ca^{2+}/calcineurin/TFEB axis in palmitate-treated AML12 cells, primary hepatocytes, and C57BL/6 J mice [111]. This can lead to the restoration of lipophagy and the suppression of lipid buildup and inflammation. Phillygenin also activates calcineurin by enhancing ER Ca^{2+} release, leading to promotion of lysosomal biogenesis and regulation of TFEB dephosphorylation and nuclear translocation. Nevertheless, these beneficial effects were strongly diminished in hepatocyte-specific TFEB knockout mice [111].

Sulforaphane

The chemotherapeutic isothiocyanate sulforaphane has been reported to possess a wide range of activity and remarkable potential as an anti-inflammatory, antioxidant, anticancer, and antiangiogenic substance [112]. Sulforaphane was found to reduce hepatic fat buildup by regulating lipophagy both in vivo and in vitro [113]. The enhancement of hepatic lipophagy by sulforaphane was confirmed by: 1) increased mRNA levels of LC3, Atg4, ULK1, Atg7, and Atg5 genes; 2) enhanced localization of LC3, LAMP1, Atg7, and Atg5 with LDs; and 3) visualization of LDs in autophagosomes. Lipophagy was induced by sulforaphane in an Nrf2-dependent manner, as evidenced by the increase in TG contents and the decrease in Atg7 and Atg5 protein expression observed upon Nrf2 gene silencing [113]. In addition to its ability to induce lipophagy in the liver, another study showed that sulforaphane could also enhance autophagic degradation of LDs in adipocytes through the AMPK-mTOR-ULK1 signaling pathway [114]. The researchers found that LC3 induced by sulforaphane was co-localized with LDs in 3T3-L1 adipocytes, while it was co-localized with PLIN in the adipocytes of HFD-fed mice [114].

Rhodiola crenulata

Due to its many health benefits, including antioxidation, anti-inflammation, antifatigue, antimountain sickness, and immunological boosting, *Rhodiola crenulata* has been utilized traditionally in both Asia and Europe [115]. Hepatic steatosis caused by fructose was alleviated by *R. crenulata* root extract in Sprague-Dawley rats [116]. Mechanistically, injection of 50 mg/kg of *R. crenulata* root extract led to enhanced expression of SIRT1, Atg4B, and Beclin1, but reduced expression of the B-cell lymphoma 2 (Bcl2)-Beclin1 complex. Furthermore, in the livers of rats given fructose, this root extract reduced the expression of autophagolysosome marker p62 and elevated the expression of autophagosome markers such as LC3-II and Atg5-Atg12-Atg16L1 [116].

***Veronica ciliata* Fisch.**

Veronica ciliata Fisch. is one of the traditional Chinese medicines that has been used for the treatment of liver disease, cholecystitis, urticaria, and rheumatism [117]. Lu et al. investigated the preventive activity of an ethyl acetate extract of *V. ciliata* (EAFVC) against oxidative stress-induced liver injury in Institute of Cancer Research mice and rat hepatocyte cell line BRL-3A [118]. Treatment of mice with EAFVC at different doses of 350, 700, and 1400 mg/kg for 14 consecutive days relieved *tert*-butyl hydroperoxide–induced liver

impairment in a dose-dependent manner in mice. The components of EAFVC were chromatographically separated and characterized into 2 fractions: a polyphenol-enriched fraction and an iridoid glycoside–enriched fraction. The polyphenol-enriched fraction of EAFVC and its major bioactive component, luteolin, were found to exhibit the strongest hepatoprotective activity in BRL-3A cells. Mechanistically, the polyphenol-enriched fraction of EAFVC and luteolin-activated AMPK phosphorylation induced autophagy, upregulated the expression of p62, phosphorylated-p62 and Beclin-1, and finally stimulated the Nrf2 pathway to exert its hepatoprotective effect [118].

Oleic acid

Oleic acid, the predominant component of olive oil, is a type of monounsaturated fat that has been studied in the context of MASLD [119]. High concentrations of FFAs, including oleic acid, can cause a buildup of lipids in liver cells, which is a characteristic of MASLD. However, some studies have shown that oleic acid can also have protective effects against lipotoxicity induced by other fatty acids such as palmitic acid [120]. The hepatoprotective effects of oleic acid were examined by Liu et al. in vivo using HFD-fed C57/BL6 mice and in vitro using HepG2, AML12, and L-02 cells treated with 2 μg/mL of tunicamycin (a chemical ER stress agonist) and 0.5 mM of oleic acid, either individually or in combination [121]. In vivo, replacement of HFD with 30% olive oil beneficially ameliorated steatosis via reducing autophagy impairment, ER stress, and apoptosis in the liver of mice. In vitro, oleic acid could attenuate autolysosomes dysfunction by: 1) regulation of the expression of both LC3-II and p62; 2) improvement of lysosomal swelling; 3) recovery of lysosomal acidity; 4) increasing the expression of TFEB and cathepsin B, a key lysosomal protease; and 5) increasing the nuclear translocation of TFEB [121].

Shenling Baizhu powder

Shenling Baizhu powder is comprised of 10 Chinese medicinal herbs that have been used to prevent and treat MASLD in Chinese clinical practice [122]. A comprehensive study by Pan et al. identified quercetin, kaempferol, ellagic acid, formononetin, isorhamnetin, stigmasterol, and luteolin as the major bioactive components in Shenling Baizhu powder [123]. According to their findings, intragastric administration of Shenling Baizhu powder (30 g/kg/d) showed anti-MASLD protective effects through regulating autophagy in HFD-induced Wistar rats. Shenling Baizhu powder enhanced the autophagic flux via SIRT1 activation, thereby alleviating ER and oxidative stress, as well as mitochondrial dysfunction [123].

Conclusion

This article summarizes natural compounds in the recent literature that have demonstrated regulatory effects on in vitro and in vivo models of MASLD, and presents an overview of the current state of knowledge about the role of lipophagy in MASLD development and progression. Interestingly, these active substances improved MASLD by regulating lipophagy through multitargeted actions, such as modulating AMPK, PPAR, mTOR, SIRT1, TFEB, and other proteins. These lipophagy-targeting natural products could be a promising avenue for the study and development of novel medications aimed at treating or preventing MASLD. Nevertheless, it is important to note that the current research focuses on the positive effect of natural products in animal or cellular models of MASLD, which does not completely reflect the complexity of the entire spectrum of MASLD in humans. Therefore, future studies should assess the therapeutic efficacy and safety of natural products or active compounds that target hepatic lipophagy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Nahla E. El-Ashmawy: Writing – review & editing, Supervision. **Eman G. Khedr:** Writing – review & editing, Supervision. **Ghada M. Al-Ashmawy:** Writing – review & editing, Supervision. **Asmaa A. Kamel:** Writing – original draft.

Funding

No funding organizations supported our work financially.

References

[1] Teng ML, Ng CH, Huang DQ, Chan KE, Tan DJ, Lim WH, et al. Global incidence and prevalence of nonalcoholic fatty liver disease. Clin Mol Hepatol 2022;29:S32–42. https://doi.org/10.3350/CMH.2022.0365.
[2] Grefhorst A, van de Peppel IP, Larsen LE, Jonker JW, Holleboom AG. The role of lipophagy in the development and treatment of non-alcoholic fatty liver disease. Front Endocrinol (Lausanne) 2021;11:1–12. https://doi.org/10.3389/fendo.2020.601627.
[3] Salah HM, Pandey A, Soloveva A, Abdelmalek MF, Diehl AM, Moylan CA, et al. Relationship of nonalcoholic fatty liver disease and heart failure with preserved ejection fraction. JACC Basic Transl Sci 2021;6:918–32. https://doi.org/10.1016/j.jacbts.2021.07.010.
[4] Carotti S, Aquilano K, Zalfa F, Ruggiero S, Valentini F, Zingariello M, et al. Lipophagy impairment is associated with disease progression in MASLD. Front Physiol 2020;11:850. https://doi.org/10.3389/FPHYS.2020.00850/BIBTEX.
[5] Singh R, Xiang Y, Wang Y, Baikati K, Cuervo AM, Luu YK, et al. Autophagy regulates adipose mass and differentiation in mice. J Clin Invest 2009;119:3329–39. https://doi.org/10.1172/JCI39228.
[6] Schulze RJ, Sathyanarayan A, Mashek DG. Breaking fat: The regulation and mechanisms of lipophagy. Biochim Biophys Acta - Mol Cell Biol Lipids 2017;1862:1178–87. https://doi.org/10.1016/J.BBALIP.2017.06.008.
[7] Zechner R, Madeo F, Kratky D. Cytosolic lipolysis and lipophagy: Two sides of the same coin. Nat Rev Mol Cell Biol 2017;18:671–84. https://doi.org/10.1038/nrm.2017.76.
[8] Tarantino G, Balsano C, Santini SJ, Brienza G, Clemente I, Cosimini B, et al. It is high time physicians thought of natural products for alleviating MASLD. Is there sufficient evidence to use them? Int J Mol Sci 2021;22. https://doi.org/10.3390/ijms222413424.
[9] Day CP, James OFW. Steatohepatitis: A tale of two "Hits"? Gastroenterology 1998;114:842–5. https://doi.org/10.1016/S0016-5085(98)70599-2.
[10] Rikhi R, Singh T, Modaresi Esfeh J. Work up of fatty liver by primary care physicians, review. Ann Med Surg 2020;50:41–8. https://doi.org/10.1016/j.amsu.2020.01.001.
[11] Wei W, Liu L, Liu X, Tao Y, Zhao X, Gong J, et al. Exploring the therapeutic effects of black ginseng on non-alcoholic fatty liver disease by using network pharmacology and molecular docking. Chem Biodivers 2022;19. https://doi.org/10.1002/cbdv.202200719.
[12] Xu H, Wang L. The role of Notch signaling pathway in non-alcoholic fatty liver disease. Front Mol Biosci 2021;8:1119. https://doi.org/10.3389/FMOLB.2021.792667/BIBTEX.
[13] Gariani K, Jornayvaz FR. Pathophysiology of NASH in endocrine diseases. Endocr Connect 2021;10:R52–65. https://doi.org/10.1530/EC-20-0490.
[14] Scorletti E, Carr RM. A new perspective on MASLD: Focusing on lipid droplets. J Hepatol 2022;76:934–45. https://doi.org/10.1016/j.jhep.2021.11.009.
[15] Pino-de la Fuente F, Bórquez JC, Díaz-Castro F, Espinosa A, Chiong M, Troncoso R. Exercise regulation of hepatic lipid droplet metabolism. Life Sci 2022;298. https://doi.org/10.1016/j.lfs.2022.120522.
[16] Sharma A. Lipid droplets associated perilipins protein insights into finding a therapeutic target approach to cure non-alcoholic fatty liver disease (MASLD). Futur J Pharm Sci 2022;8:1–11. https://doi.org/10.1186/s43094-021-00395-0.
[17] Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of MASLD development and therapeutic strategies. Nat Med 2018;24:908–22. https://doi.org/10.1038/s41591-018-0104-9.
[18] Rasineni K, Jordan CW, Thomes PG, Kubik JL, Staab EM, Sweeney SA, et al. Contrasting effects of fasting on liver-adipose axis in alcohol-associated and non-alcoholic fatty liver. Front Physiol 2021;12:1–16. https://doi.org/10.3389/fphys.2021.625352.

[19] Grabner GF, Xie H, Schweiger M, Zechner R. Lipolysis: Cellular mechanisms for lipid mobilization from fat stores. Nat Metab 2021;3:1445–65. https://doi.org/10.1038/s42255-021-00493-6.
[20] Khandelwal R, Dassanayake AS, Conjeevaram HS, Singh SP. Non-alcoholic fatty liver disease in diabetes: When to refer to the hepatologist? World J Diabetes 2021;12:1479–93. https://doi.org/10.4239/wjd.v12.i9.1479.
[21] Kang H, You HJ, Lee G, Lee SH, Yoo T, Choi M, et al. Interaction effect between NAFLD severity and high carbohydrate diet on gut microbiome alteration and hepatic de novo lipogenesis. Gut Microbes 2022;14(1):2078612. https://doi.org/10.1080/19490976.2022.2078612.
[22] Smith GI, Shankaran M, Yoshino M, Schweitzer GG, Chondronikola M, Beals JW, et al. Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. J Clin Invest 2020;130:1453–60. https://doi.org/10.1172/JCI134165.
[23] Heeren J, Scheja L. Metabolic-associated fatty liver disease and lipoprotein metabolism. Mol Metab 2021;50:101238. https://doi.org/10.1016/j.molmet.2021.101238.
[24] Lytle KA, Bush NC, Triay JM, Kellogg TA, Kendrick ML, Swain JM, et al. Hepatic fatty acid balance and hepatic fat content in humans with severe obesity. J Clin Endocrinol Metab 2019;104:6171–81. https://doi.org/10.1210/jc.2019-00875.
[25] Bessone F, Razori MV, Roma MG. Molecular pathways of nonalcoholic fatty liver disease development and progression. Cell Mol Life Sci 2019;76:99–128. https://doi.org/10.1007/s00018-018-2947-0.
[26] Luo F, Oldoni F, Das A. TM6SF2: A novel genetic player in nonalcoholic fatty liver and cardiovascular disease. Hepatol Commun 2022;6:448–60. https://doi.org/10.1002/hep4.1822.
[27] Lucero D, Miksztowicz V, Gualano G, Longo C, Landeira G, Álvarez E, et al. Non-alcoholic fatty liver disease associated with metabolic syndrome: Influence of liver fibrosis stages on characteristics of very low-density lipoproteins. Clin Chim Acta 2017;473:1–8. https://doi.org/10.1016/j.cca.2017.08.006.
[28] Qiu YY, Zhang J, Zeng FY, Zhu YZ. Roles of the peroxisome proliferator-activated receptors (PPARs) in the pathogenesis of nonalcoholic fatty liver disease (MASLD). Pharmacol Res 2023;192:106786. https://doi.org/10.1016/j.phrs.2023.106786.
[29] Schlaepfer IR, Joshi M. CPT1A-mediated fat oxidation, mechanisms, and therapeutic potential. Endocrinol (United States) 2020;161:1–14. https://doi.org/10.1210/endocr/bqz046.
[30] Ipsen DH, Lykkesfeldt J, Tveden-Nyborg P. Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease. Cell Mol Life Sci 2018;75:3313–27. https://doi.org/10.1007/s00018-018-2860-6.
[31] Zhang Z, Yao Z, Chen Y, Qian L, Jiang S, Zhou J, et al. Lipophagy and liver disease: New perspectives to better understanding and therapy. Biomed Pharmacother 2018;97:339–48. https://doi.org/10.1016/j.biopha.2017.07.168.
[32] Li HY, Peng ZG. Targeting lipophagy as a potential therapeutic strategy for nonalcoholic fatty liver disease. Biochem Pharmacol 2022;197:114933. https://doi.org/10.1016/j.bcp.2022.114933.
[33] Filali-Mouncef Y, Hunter C, Roccio F, Zagkou S, Dupont N, Primard C, et al. The ménage à trois of autophagy, lipid droplets and liver disease. Autophagy 2022;18:50–72. https://doi.org/10.1080/15548627.2021.1895658.
[34] Kounakis K, Chaniotakis M, Markaki M, Tavernarakis N. Emerging roles of lipophagy in health and disease. Front Cell Dev Biol 2019;7:1–8. https://doi.org/10.3389/fcell.2019.00185.
[35] Wu K, Fan S, Zou L, Zhao F, Ma S, Fan J, et al. Molecular events occurring in lipophagy and its regulation in flaviviridae infection. Front Microbiol 2021;12:1191. https://doi.org/10.3389/FMICB.2021.651952/BIBTEX.
[36] Zhang S, Peng X, Yang S, Li X, Huang M, Wei S, et al. The regulation, function, and role of lipophagy, a form of selective autophagy, in metabolic disorders. Cell Death Dis 2022;13:1–11. https://doi.org/10.1038/s41419-022-04593-3.
[37] Schulze RJ, Drižytė K, Casey CA, McNiven MA. Hepatic lipophagy: New insights into autophagic catabolism of lipid droplets in the liver. Hepatol Commun 2017;1:359–69. https://doi.org/10.1002/hep4.1056.
[38] Schroeder B, Schulze RJ, Weller SG, Sletten AC, Casey CA, McNiven MA. The small GTPase Rab7 as a central regulator of hepatocellular lipophagy. Hepatology 2015;61:1896–907. https://doi.org/10.1002/hep.27667.
[39] Proikas-Cezanne T, Simos G, Liu X, Kounakis K, Chaniotakis M, Markaki M, et al. Emerging roles of lipophagy in health and disease. Front Cell Dev Biol 2019:7:185. https://doi.org/10.3389/fcell.2019.00185.
[40] Li Z, Schulze RJ, Weller SG, Krueger EW, Schott MB, Zhang X, et al. A novel rab10-EHBP1-EHD2 complex essential for the autophagic engulfment of lipid droplets. Sci Adv 2016;2. https://doi.org/10.1126/sciadv.1601470.
[41] Oku M, Sakai Y. Three distinct types of microautophagy based on membrane dynamics and molecular machineries. BioEssays 2018;40:1–6. https://doi.org/10.1002/bies.201800008.
[42] Schott MB, Weller SG, Schulze RJ, Krueger EW, Drizyte-Miller K, Casey CA, et al. Lipid droplet size directs lipolysis and lipophagy catabolism in hepatocytes. J Cell Biol 2019;218:3320–35. https://doi.org/10.1083/JCB.201803153.
[43] Schulze RJ, Krueger EW, Weller SG, Johnson KM, Casey CA, Schott MB, et al. Direct lysosome-based autophagy of lipid droplets in hepatocytes. Proc Natl Acad Sci U S A 2020;117:32443–52. https://doi.org/10.1073/pnas.2011442117.
[44] Zhang T, Liu J, Shen S, Tong Q, Ma X, Lin L. SIRT3 promotes lipophagy and chaperon-mediated autophagy to protect hepatocytes against lipotoxicity. Cell Death Differ 2020;27:329–44. https://doi.org/10.1038/s41418-019-0356-z.
[45] Mashek DG. Hepatic lipid droplets: A balancing act between energy storage and metabolic dysfunction in MASLD. Mol Metab 2021;50:101115. https://doi.org/10.1016/j.molmet.2020.101115.
[46] Khawar MB, Abbasi MH, Rafiq M, Naz N, Mehmood R, Sheikh N. A decade of mighty lipophagy: What we know and what facts we need to know? Oxid Med Cell Longev 2021;2021. https://doi.org/10.1155/2021/5539161.
[47] Schulze RJ, Sathyanarayan A, Mashek DG. Breaking fat: The regulation and mechanisms of lipophagy. Biochim Biophys Acta - Mol Cell Biol Lipids 2017;1862:1178–87. https://doi.org/10.1016/j.bbalip.2017.06.008.
[48] Xiong J, Wang K, He J, Zhang G, Zhang D, Chen F. TFE3 alleviates hepatic steatosis through autophagy-induced lipophagy and PGC1α-mediated fatty acid β-oxidation. Int J Mol Sci 2016;17. https://doi.org/10.3390/ijms17030387.
[49] Dong XC. FOXO transcription factors in non-alcoholic fatty liver disease. Liver Res 2017;1:168–73. https://doi.org/10.1016/j.livres.2017.11.004.
[50] Samovski D, Abumrad NA. Regulation of lipophagy in MASLD by cellular metabolism and CD36. J Lipid Res 2019;60:755–7. https://doi.org/10.1194/jlr.C093674.
[51] SUN G, YANG L, WEI S, JIN H, LI B, LI H. miR-425 regulates lipophagy via SIRT1 to promote sorafenib resistance in liver cancer. Oncol Lett 2021;22:1–10. https://doi.org/10.3892/ol.2021.12956.
[52] Wu LX, Tan XY, Xu YC, Zheng H, Wei XL, Lv WH, et al. SIRT1-NRF2-TFEB axis-mediated hepatic lipophagy alleviates the lipid deposition induced by high glucose in yellow catfish *Pelteobagrus fulvidraco*. Comp Biochem Physiol Part - B Biochem Mol Biol 2024;269:110894. https://doi.org/10.1016/j.cbpb.2023.110894.
[53] Zhang T, Liu J, Tong Q, Lin L. SIRT3 acts as a positive autophagy regulator to promote lipid mobilization in adipocytes via activating AMPK. Int J Mol Sci 2020;21. https://doi.org/10.3390/ijms21020372.
[54] Huang M, Yang X, Wang Z, Long J, Wang A, Zhang Y, et al. Lipophagy: A new perspective of natural products in type 2 diabetes mellitus treatment. Diabetes, Metab Syndr Obes 2021;14:2985–99. https://doi.org/10.2147/DMSO.S310166.
[55] Zhang L, Yao Z, Ji G. Herbal extracts and natural products in alleviating non-alcoholic fatty liver disease via activating autophagy. Front Pharmacol 2018;9:1–7. https://doi.org/10.3389/fphar.2018.01459.
[56] Fairman G, Ouimet M. Lipophagy pathways in yeast are controlled by their distinct modes of induction. Yeast 2022;39:429–39. https://doi.org/10.1002/yea.3705.
[57] Hosseini A, Razavi BM, Banach M, Hosseinzadeh H. Quercetin and metabolic syndrome: A review. Phyther Res 2021;35:5352–64. https://doi.org/10.1002/ptr.7144.
[58] Liu L, Gao C, Yao P, Gong Z. Quercetin alleviates high-fat diet-induced oxidized low-density lipoprotein accumulation in the liver: Implication for autophagy regulation. Biomed Res Int 2015;2015. https://doi.org/10.1155/2015/607531.
[59] Zhu X, Xiong T, Liu P, Guo X, Xiao L, Zhou F, et al. Quercetin ameliorates HFD-induced MASLD by promoting hepatic VLDL assembly and lipophagy via the IRE1a/XBP1s pathway. Food Chem Toxicol 2018;114:52–60. https://doi.org/10.1016/j.fct.2018.02.019.
[60] Fukaya M, Sato Y, Kondo S, I Adachi S, Yoshizawa F, Sato Y. Quercetin enhances fatty acid β-oxidation by inducing lipophagy in AML12 hepatocytes. Heliyon 2021;7:e07324. https://doi.org/10.1016/j.heliyon.2021.e07324.
[61] Ashour H, Rashed L A, Hassanein R T, Aboulhoda BE, Ebrahim HA, Elsayed MH, et al. Thymoquinone and quercetin protect against hepatic steatosis in association with SIRT1/AMPK stimulation and regulation of autophagy, perilipin-2, and cytosolic lipases. Arch Physiol Biochem 2023;129:268–81. https://doi.org/10.1080/13813455.2022.2134423.
[62] Afshari H, Noori S, Zarghi A. Hepatic steatosis alleviated by a novel metformin and quercetin combination activating autophagy through the cAMP /AMPK / SIRT1. Pathway 2023;22:1–14. https://doi.org/10.5812/ijpr-136952.
[63] Lu J, Meng Z, Chen Y, Yu L, Gao B, Zheng Y, et al. Apigenin induced autophagy and stimulated autophagic lipid degradation. Food Funct 2020;11:9208–15. https://doi.org/10.1039/d0fo00949k.
[64] Chen Hsu M, Chia Guo B, Hu P-A, Hui Chen C, Lee T-S. Apigenin ameliorates hepatic lipid accumulation by activating the autophagy-mitochondria pathway. J Food Drug Anal 2021;29(2):240–54. https://doi.org/10.38212/2224-6614.3269.
[65] Singh AP, Kandpal JB, Sharma RK, Chitme H. Nobiletin a biologically active phytoconstituent: Systematic review. J Biol Act Prod from Nat 2021;11:204–11. https://doi.org/10.1080/22311866.2021.1920461.
[66] Yang X, Deng Y, Tu Y, Feng D, Liao W. Nobiletin mitigates MASLD via lipophagy and inflammation. Food Funct 2022:10186–99. https://doi.org/10.1039/d2fo01682f.
[67] Caporali S, De Stefano A, Calabrese C, Giovannelli A, Pieri M, Savini I, et al. Anti-inflammatory and active biological properties of the plant-derived bioactive compounds luteolin and luteolin 7-glucoside. Nutrients 2022;14:1–19. https://doi.org/10.3390/nu14061155.
[68] Huang CY, Chen HW, Lo CW, Wang YR, Li CC, Liu KL, et al. Luteolin ameliorates palmitate-induced lipotoxicity in hepatocytes by mediating endoplasmic reticulum stress and autophagy. Food Chem Toxicol 2023;171:113554. https://doi.org/10.1016/j.fct.2022.113554.

[69] Nakhate KT, Badwaik H, Choudhary R, Sakure K, Agrawal YO, Sharma C, et al. therapeutic potential and pharmaceutical development of a multitargeted flavonoid phloretin. Nutrients 2022;14:3638. https://doi.org/10.3390/nu14173638.
[70] Chhimwal J, Goel A, Sukapaka M, Patial V, Padwad Y. Phloretin mitigates oxidative injury, inflammation, and fibrogenic responses via restoration of autophagic flux in in vitro and preclinical models of MASLD. J Nutr Biochem 2022;107:109062. https://doi.org/10.1016/j.jnutbio.2022.109062.
[71] Alfwuaires MA. Galangin mitigates oxidative stress, inflammation, and apoptosis in a rat model of methotrexate hepatotoxicity. Environ Sci Pollut Res 2022;29:20279–88. https://doi.org/10.1007/s11356-021-16804-z.
[72] Zhang X, Deng Y, Xiang J, Liu H, Zhang J, Liao J, et al. Galangin improved nonalcoholic fatty liver disease in mice by promoting autophagy. Drug Des Devel Ther 2020;14:3393–405. https://doi.org/10.2147/DDDT.S258187.
[73] Wang S, Zhang S, Wang S, Gao P, Dai L. A comprehensive review on *Pueraria*: Insights on its chemistry and medicinal value. Biomed Pharmacother 2020;131. https://doi.org/10.1016/j.biopha.2020.110734.
[74] Sun C, Zhang J, Hou J, Hui M, Qi H, Lei T, et al. Induction of autophagy via the PI3K/Akt/mTOR signaling pathway by *Pueraria* flavonoids improves nonalcoholic fatty liver disease in obese mice. Biomed Pharmacother 2023;157:114005. https://doi.org/10.1016/j.biopha.2022.114005.
[75] Addi M, Elbouzidi A, Abid M, Tungmunnithum D, Elamrani A, Hano C. An overview of bioactive flavonoids from citrus fruits. Appl Sci 2022;12:1–15. https://doi.org/10.3390/app12010029.
[76] Lascala A, Martino C, Parafati M, Salerno R, Oliverio M, Pellegrino D, et al. Analysis of proautophagic activities of citrus flavonoids in liver cells reveals the superiority of a natural polyphenol mixture over pure flavones. J Nutr Biochem 2018;58:119–30. https://doi.org/10.1016/j.jnutbio.2018.04.005.
[77] Ning Q, Wang Y, Zhang Y, Shen G, Xie Z, Pang J. Nuciferine prevents hepatic steatosis by regulating lipid metabolism in diabetic rat model. Open Life Sci 2020;14:699–706. https://doi.org/10.1515/biol-2019-0079.
[78] Du X, Di Malta C, Fang Z, Shen T, Niu X, Chen M, et al. Nuciferine protects against high-fat diet-induced hepatic steatosis and insulin resistance via activating TFEB-mediated autophagy−lysosomal pathway. Acta Pharm Sin B 2022;12:2869–86. https://doi.org/10.1016/j.apsb.2021.12.012.
[79] Xu R, Tian F, Zhao X, Peng Q, Zhou J, Wang W. Ajugol attenuates renal injury in multiple myeloma by blocking LILRB4 signaling pathway to reduce PFKFB3 expression. Mater Express 2023;13:815–22. https://doi.org/10.1166/mex.2023.2420.
[80] Zhang H, Lu J, Liu H, Guan L, Xu S, Wang Z, et al. Ajugol enhances TFEB-mediated lysosome biogenesis and lipophagy to alleviate non-alcoholic fatty liver disease. Pharmacol Res 2021;174:105964. https://doi.org/10.1016/j.phrs.2021.105964.
[81] Mohamadi N, Sharififar F, Pournamdari M, Ansari M. A Review on biosynthesis, analytical techniques, and pharmacological activities of trigonelline as a plant alkaloid. J Diet Suppl 2018;15:207–22. https://doi.org/10.1080/19390211.2017.1329244.
[82] Sharma L, Lone NA, Knott RM, Hassan A, Abdullah T. Trigonelline prevents high cholesterol and high fat diet induced hepatic lipid accumulation and lipo-toxicity in C57BL/6J mice, via restoration of hepatic autophagy. Food Chem Toxicol 2018;121:283–96. https://doi.org/10.1016/j.fct.2018.09.011.
[83] Tian B, Liu J. Resveratrol: A review of plant sources, synthesis, stability, modification and food application. J Sci Food Agric 2020;100:1392–404. https://doi.org/10.1002/jsfa.10152.
[84] Li L, Hai J, Li Z, Zhang Y, Peng H, Li K, et al. Resveratrol modulates autophagy and NF-κB activity in a murine model for treating non-alcoholic fatty liver disease. Food Chem Toxicol 2014;63:166–73. https://doi.org/10.1016/j.fct.2013.08.036.
[85] Ding S, Jiang J, Zhang G, Bu Y, Zhang G, Zhao X. Resveratrol and caloric restriction prevent hepatic steatosis by regulating SIRT1-autophagy pathway and alleviating endoplasmic reticulum stress in high-fat diet-fed rats. PLoS One 2017;12. https://doi.org/10.1371/journal.pone.0183541.
[86] Zhang Y, liang Chen M, Zhou Y, Yi L, xiang Gao Y, Ran L, et al. Resveratrol improves hepatic steatosis by inducing autophagy through the cAMP signaling pathway. Mol Nutr Food Res 2015;59:1443–57. https://doi.org/10.1002/mnfr.201500016.
[87] Afshari H, Noori S, Zarghi A. A novel combination of metformin and resveratrol alleviates hepatic steatosis by activating autophagy through the cAMP/AMPK/SIRT1 signaling pathway. Naunyn Schmiedebergs Arch Pharmacol 2023;3. https://doi.org/10.1007/s00210-023-02520-7.
[88] Baran MF, Keskin C, Baran A, Eftekhari A, Omarova S, Khalilov R, et al. The investigation of the chemical composition and applicability of gold nanoparticles synthesized with *Amygdalus communis* (Almond) leaf aqueous extract as antimicrobial and anticancer agents. Molecules 2023;28. https://doi.org/10.3390/molecules28062428.
[89] Chen X, Chan H, Zhang L, Liu X, Ho IHT, Zhang X, et al. The phytochemical polydatin ameliorates non-alcoholic steatohepatitis by restoring lysosomal function and autophagic flux. J Cell Mol Med 2019;23:4290–300. https://doi.org/10.1111/jcmm.14320.
[90] Acar-Tek N, Ağagündüz D. Olive leaf (*Olea europaea* L. folium): Potential effects on glycemia and lipidemia. Ann Nutr Metab 2020;76:10–5. https://doi.org/10.1159/000505508.
[91] Tacconi S, Longo S, Guerra F, Moliteni C, Friuli M, Romano A, et al. An aqueous olive leaf extract (OLE) ameliorates parameters of oxidative stress associated with lipid accumulation and induces lipophagy in human hepatic cells. Food Funct 2023;14:5805–19. https://doi.org/10.1039/d3fo00817g.
[92] Topuz S, Bayram M. Oleuropein extraction from leaves of three olive varieties (*Olea europaea* L.): Antioxidant and antimicrobial properties of purified oleuropein and oleuropein extracts. J Food Process Preserv 2022;46:1–12. https://doi.org/10.1111/jfpp.15697.
[93] Porcu C, Sideri S, Martini M, Cocomazzi A, Galli A, Tarantino G, et al. Oleuropein induces AMPK-dependent autophagy in NAFLD mice, regardless of the gender. Int J Mol Sci 2018;19. https://doi.org/10.3390/ijms19123948.
[94] Zhang J, Chen Z, Huang X, Shi W, Zhang R, Chen M, et al. Insights on the multifunctional activities of magnolol. Biomed Res Int 2019;2019:1847130. https://doi.org/10.1155/2019/1847130.
[95] Kuo NC, Huang SY, Yang CY, Shen HH, Lee YM. Involvement of HO-1 and autophagy in the protective effect of magnolol in hepatic steatosis-induced nlrp3 inflammasome activation in vivo and in vitro. Antioxidants 2020;9:1–19. https://doi.org/10.3390/antiox9100924.
[96] Rauf A, Olatunde A, Imran M, Alhumaydhi FA, Aljohani ASM, Khan SA, et al. Honokiol: A review of its pharmacological potential and therapeutic insights. Phytomedicine 2021;90:153647. https://doi.org/10.1016/j.phymed.2021.153647.
[97] Liu J, Zhang T, Zhu J, Ruan S, Li R, Guo B, et al. Honokiol attenuates lipotoxicity in hepatocytes via activating SIRT3-AMPK mediated lipophagy. Chinese Med (United Kingdom) 2021;16:1–13. https://doi.org/10.1186/s13020-021-00528-w.
[98] Ouyang J, Zhu K, Liu Z, Huang J. Prooxidant effects of epigallocatechin-3-gallate in health benefits and potential adverse effect. Oxid Med Cell Longev 2020;2020:9723686. https://doi.org/10.1155/2020/9723686.
[99] Wu D, Liu Z, Wang Y, Zhang Q, Li J, Zhong P, et al. Epigallocatechin-3-gallate alleviates high-fat diet-induced nonalcoholic fatty liver disease via inhibition of apoptosis and promotion of autophagy through the ROS/MAPK signaling pathway. Oxid Med Cell Longev 2021;2021:1–16. https://doi.org/10.1155/2021/5599997.
[100] Zhou J, Farah BL, Sinha RA, Wu Y, Singh BK, Bay BH, et al. Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, stimulates hepatic autophagy and lipid clearance. PLoS One 2014;9:e87161. https://doi.org/10.1371/journal.pone.0087161.
[101] Li D, Liu F, Wang X, Li X. Apple polyphenol extract alleviates high-fat-diet-induced hepatic steatosis in male C57BL/6 mice by targeting LKB1/AMPK pathway. J Agric Food Chem 2019;67:12208–18. https://doi.org/10.1021/acs.jafc.9b05495.
[102] Li D, Cui Y, Wang X, Liu F, Li X. Apple polyphenol extract alleviates lipid accumulation in free-fatty-acid-exposed HepG2 cells via activating autophagy mediated by SIRT1/AMPK signaling. Phytother Res 2021;35:1416–31. https://doi.org/10.1002/ptr.6902.
[103] Yin Y, Xie Y, Wu Z, Qian Q, Yang H, Li S, et al. Preventive effects of apple polyphenol extract on high-fat-diet-induced hepatic steatosis are related to the regulation of hepatic lipid metabolism, autophagy, and gut microbiota in aged mice. J Agric Food Chem 2023;71:20011–33.
[104] Shen Y, Guan Y, Song X, He J, Xie Z, Zhang Y, et al. Polyphenols extract from lotus seedpod (*Nelumbo nucifera* Gaertn.): Phenolic compositions, antioxidant, and antiproliferative activities. Food Sci Nutr 2019;7:3062–70. https://doi.org/10.1002/fsn3.1165.
[105] Liu YT, Lai YH, Lin HH, Chen JH. Lotus seedpod extracts reduced lipid accumulation and lipotoxicity in hepatocytes. Nutrients 2019;11:1–15. https://doi.org/10.3390/nu11122895.
[106] Li J, Li X, Wang C, Zhang M, Ye M, Wang Q. The potential of *Valeriana* as a traditional Chinese medicine: traditional clinical applications, bioactivities, and phytochemistry. Front Pharmacol 2022;13:1–23. https://doi.org/10.3389/fphar.2022.973138.
[107] Lee DH, Park SH, Huh YH, Jung Kim M, Seo HD, Ha TY, et al. Iridoids of *Valeriana fauriei* contribute to alleviating hepatic steatosis in obese mice by lipophagy. Biomed Pharmacother 2020;125:109950. https://doi.org/10.1016/j.biopha.2020.109950.
[108] Peteliuk V, Rybchuk L, Bayliak M, Storey KB, Lushchak O. Natural sweetener *Stevia rebaudiana*: Functionalities, health benefits and potential risks. EXCLI J 2021;20:1412–30. https://doi.org/10.17179/excli2021-4211.
[109] Park M, Sharma A, Baek H, Han JY, Yu J, Lee HJ. *Stevia* and stevioside attenuate liver steatosis through PPARα-mediated lipophagy in db/db mice hepatocytes. Antioxidants 2022;11:1–12. https://doi.org/10.3390/antiox11122496.
[110] Wang C, Wu R, Zhang S, Gong L, Fu K, Yao C, et al. A comprehensive review on pharmacological, toxicity, and pharmacokinetic properties of phillygenin: Current landscape and future perspectives. Biomed Pharmacother 2023;166:115410. https://doi.org/10.1016/j.biopha.2023.115410.
[111] Zhou W, Yan X, Zhai Y, Liu H, Guan L, Qiao Y, et al. Phillygenin ameliorates nonalcoholic fatty liver disease via TFEB-mediated lysosome biogenesis and lipophagy. Phytomedicine 2022;103:154235.
[112] Mangla B, Javed S, Sultan MH, Kumar P, Kohli K, Najmi A, et al. Sulforaphane: A review of its therapeutic potentials, advances in its nanodelivery, recent patents, and clinical trials. Phyther Res 2021;35:5440–58. https://doi.org/10.1002/ptr.7176.
[113] Lei P, HuY Gao P, Ding Q, Yan J, Zhao J, et al. Sulforaphane ameliorates hepatic lipid metabolism via modulating lipophagy in vivo and in vitro. J Agric Food Chem 2022;70:15126–33.

[114] Masuda M, Yoshida-Shimizu R, Mori Y, Ohnishi K, Adachi Y, Sakai M, et al. Sulforaphane induces lipophagy through the activation of AMPK-mTOR-ULK1 pathway signaling in adipocytes. J Nutr Biochem 2022;106:109017. https://doi.org/10.1016/j.jnutbio.2022.109017.

[115] Tao H, Wu X, Cao J, Peng Y, Wang A, Pei J, et al. *Rhodiola* species: A comprehensive review of traditional use, phytochemistry, pharmacology, toxicity, and clinical study. Med Res Rev 2019;39:1779–850. https://doi.org/10.1002/med.21564.

[116] Yuan C, Jin Y, Yao L, Liu L, Li J, Li H, et al. *Rhodiola crenulata* root extract ameliorates fructose-induced hepatic steatosis in rats: Association with activating autophagy. Biomed Pharmacother 2020;125:109836. https://doi.org/10.1016/j.biopha.2020.109836.

[117] Yin L, Wei L, Fu R, Ding L, Guo Y, Tang L, et al. Antioxidant and hepatoprotective activity of *Veronica ciliata* Fisch. Extracts against carbon tetrachloride-induced liver injury in mice. Molecules 2014;19:7223–36. https://doi.org/10.3390/molecules19067223.

[118] Lu Q, Shu Y, Wang L, Li G, Zhang S, Gu W, et al. The protective effect of *Veronica ciliata* Fisch. Extracts on relieving oxidative stress-induced liver injury via activating AMPK/p62/Nrf2 pathway. J Ethnopharmacol 2021;270:113775. https://doi.org/10.1016/j.jep.2021.113775.

[119] Tutunchi H, Ostadrahimi A, Saghafi-Asl M. The effects of diets enriched in monounsaturated oleic acid on the management and prevention of obesity: A systematic review of human intervention studies. Adv Nutr 2020;11:864–77. https://doi.org/10.1093/ADVANCES/NMAA013.

[120] Zeng X, Zhu M, Liu X, Chen X, Yuan Y, Li L, et al. Erratum: Oleic acid ameliorates palmitic acid induced hepatocellular lipotoxicity by inhibition of ER stress and pyroptosis (Nutrition and Metabolism (2020) 17 (11). Nutr Metab 2020;17:1–14. https://doi.org/10.1186/s12986-020-00438-y.

[121] Liu X, Li X, Su S, Yuan Y, Liu W, Zhu M, et al. Oleic acid improves hepatic lipotoxicity injury by alleviating autophagy dysfunction. Exp Cell Res 2023;429:113655. https://doi.org/10.1016/j.yexcr.2023.113655.

[122] Ji HJ, Kang N, Chen T, Lv L, Ma XX, Wang FY, et al. Shen-ling-bai-zhu-san, a spleen-tonifying Chinese herbal formula, alleviates lactose-induced chronic diarrhea in rats. J Ethnopharmacol 2019;231:355–62. https://doi.org/10.1016/j.jep.2018.07.031.

[123] Pan M, Deng Y, Qiu Y, Pi D, Zheng C, Liang Z, et al. Shenling Baizhu powder alleviates non-alcoholic fatty liver disease by modulating autophagy and energy metabolism in high-fat diet-induced rats. Phytomedicine 2024;130:155712. https://doi.org/10.1016/j.phymed.2024.155712.