Fatty liver diseases, mechanisms, and potential therapeutic plant medicines

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Available online 20 Mar., 2020

[Introduction] The liver is an important metabolic organ and controls lipid, glucose and energy metabolism. Dysruption of hepatic lipid metabolism is often associated with fatty liver diseases, including nonalcoholic fatty liver disease (NAFLD), alcoholic fatty liver disease (AFLD) and hyperlipidemia. Recent studies have uncovered the contribution of hormones, transcription factors, and inflammatory cytokines to the pathogenesis of dyslipidemia and fatty liver diseases. Moreover, a significant amount of effort has been put to examine the mechanisms underlying the potential therapeutic effects of many natural plant products on fatty liver diseases and metabolic diseases. We review the current understanding of insulin, thyroid hormone and inflammatory cytokines in regulating hepatic lipid metabolism, focusing on several essential transcription regulators, such as Sirtuins (SIRTs), Forkhead box O (FoxO), Sterol-regulatory element-binding proteins (SREBPs). We also discuss a few representative natural products with promising thereapeutic effects on fatty liver disease and dyslipidemia.

[KEY WORDS] Fatty liver disease; Lipid metabolism; Hormones; Transcription factors; Inflammatory cytokines; Natural products

[Introduction] The liver is a pivot organ of lipid metabolism and plays an essential role in the synthesis, metabolism, and transportation of lipids. Disruption of hepatic lipid metabolism often leads to dyslipidemia and fat accumulation in the liver. Based on the etiology, fatty liver disease is clinically classified into nonalcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD) [1]. Recently, experts reached the consensus that NAFLD does not reflect current knowledge, and metabolic (dysfunction) associated fatty liver disease (MAFLD) is a more appropriate overarching term [2]. While, we continue to use NAFLD, not MAFLD, in this review, considering that it was quoted as NAFLD in many cited references.

During the past two decades, the prevalence of NAFLD in China has climbed from 18% (2008) to 29.2% (2018) [3] substantially with modifications in lifestyle, which was comparable with that in the US (24.13%) and Europe (23.71%) [4]. Also, China now has a notable prevalence of AFLD (4.5%), which is similar to that of the US (6.2%) and European countries (6%) and dwarfs that of Japan (1.56%–2.34%) [7]. Whereas AFLD occurs in many people, NAFLD represents the most common chronic liver disease and is the most common cause of liver enzyme abnormalities globally. Both diseases encompass the clinical spectrum of steatosis, steatohepatitis, and cirrhosis. Although they are histologically indistinct, AFLD and NAFLD follow the similar pathological mechanisms to a large extent [8].

Importantly, hepatic lipid metabolism is regulated by various hormones. For example, insulin, which is an important synthetic signal in the body, can act on hepatocytes and generally increase the synthesis of lipids [9,10]. Thyroid hor-
Hormones

Hormone regulation network is complex but crucial for hepatic lipid metabolism. Conversely, the liver also plays an essential role in regulating hormone activation, transport, and metabolism. Here we will focus on insulin and thyroid hormone in fatty liver diseases (Table 1).

Insulin and lipid synthesis

Insulin is considered as the paramount anabolic hormone, which plays a key role in the control of both carbohydrate and lipid metabolism. It also has a significant impact on protein and mineral metabolism. Insulin exerts its function through the activation of its cell surface receptor, insulin receptor (IR). The IR is a tyrosine kinase, and it autophosphorylates through the activation of its cell surface receptor, insulin [9]. Insulin exerts its functional effects on dyslipidemia and lipid metabolism. It also has a significant impact, insulin and thyroid hormones and lipogenesis in fatty liver diseases (Table 1).

Insulin binds to insulin receptor then activates PI3K-Akt pathway, consequently activates transcription factors such as FoxO family to promote lipogenic genes. TH interacts with its receptor and influence fatty uptake proteins to increase hepatic lipotoxicity. At the same time, many studies have provided promising evidence that flavonoids, alkaloids, and saponins from many natural products have therapeutic effects on dyslipidemia and fatty liver disease.

 Thyroid hormones and lipid metabolism

THs are critical for hepatic lipid metabolism. In the classic mechanism, THs interact with TH receptors (THRs), which act as ligand-dependent transcription factors, to modulate lipid metabolism. There are two isoforms of THR: THRα and THRβ, whereas THRβ is the major isoform expressed in the liver. Circulating free fatty acids (FFAs), which are the major lipid source for liver, can take advantage of protein transporters as fatty acid translocase (also known as CD36), liver fatty acid-binding proteins and the family of fatty acid transport proteins. These fatty acid uptake proteins can be positively induced by peroxisome proliferator-activated receptors (PPARs) in transcription level, which has crosstalk with THRs. Recent studies suggest that THR may also regulate fatty acid transporters. It has been reported that the hepatic uptake of triglyceride-derived FFAs was decreased in hypothyroid rats, but increased in hyperthyroid rats. THs are proved to promote lipogenesis by directly regulating two key enzymes, acetyl-CoA carboxylase (ACC) and increase PPARα, meanwhile up-regulates AMPK to exert lipolytic activity.

**Table 1 Typical Mechanisms of lipid metabolism in fatty liver diseases.**

<table>
<thead>
<tr>
<th>Type</th>
<th>Mode</th>
<th>Consequence</th>
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<tbody>
<tr>
<td>Hormone</td>
<td>Insulin</td>
<td>Lipid synthesis</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>TH interacts with its receptor and influence fatty uptake proteins to increase hepatic lipotoxicity</td>
<td>Lipid synthesis/ Lipid breakdown</td>
</tr>
<tr>
<td>Transcription factor</td>
<td>SIRT1,3,6</td>
<td>Lipid breakdown</td>
</tr>
<tr>
<td>FoxO</td>
<td>FOX protein stimulates triacylglycerol lipase and activates autophagy to promote lipid breakdown</td>
<td></td>
</tr>
<tr>
<td>SREBPα, SREBPβ</td>
<td>Hepatic SREBPα, SREBPβ mRNA elevates when given a high carbohydrate diet. SREBPα, SREBPβ activities associate with ubiquitin-dependent proteasomal degradation.</td>
<td>Promote lipogenesis</td>
</tr>
<tr>
<td>Inflammatory cytokine</td>
<td>IL-6 downregulates TNF-α and increase PPARαs meanwhile up-regulates AMPK to exert lipolytic activity.</td>
<td>Promote lipid breakdown and ameliorate hepatic steatosis exacerbate liver deposition</td>
</tr>
<tr>
<td>TNF-α</td>
<td>TNF-α Presents together with nonalcoholic steatohepatitis</td>
<td></td>
</tr>
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</table>
and fatty acid synthase (FASN) [24]. Additionally, THs are able to promote SREBP-1 protein level via MAPK/ERK and PI3K/Akt pathways, leading to the influence in various lipogenic genes at transcriptional level [37]. Furthermore, THs can induce the gene expression of ChREBP and liver X receptor, both of which have vital functions in hepatic lipogenesis.

While THs can promote lipogenesis, prolonged treatment results in mounting fatty acid oxidation. The exact mechanism for this on-off point is currently unclear [28]. There are two major hepatic cytosolic lipases, hepatic lipase and adipose triglyceride lipase, which can result in the utilization of stored triglyceride and β-oxidation. These lipases are modulated by THs status [39]. Ferrandino G and his colleagues reported that the hepatic THs signaling was significantly down-regulated in hypothyroid mice, which was accompanied by suppression of adipose tissue lipolysis [40]. A recent study has shown a link between THs and lipolysis, a process in which neutral lipid droplets are digested by autolysosomes to release FFAs for mitochondrial fatty oxidation [51]. It is also found that lipophagy requires THs-mediated ketogenesis in hepatic cells [37].

Overall, THs actively participate in the process of hepatic lipogenesis, lipolysis and lipophagy [39].

**Transcription factors**

The hepatic lipid metabolism is tightly regulated at both transcriptional and post-transcriptional levels. Numerous transcription factors have identified. As lists in Table 1, we focus on three key transcription factors.

**SIRTs**

SIRTs, including seven homologs of SIRT1-7 in mammalian, are a group of highly conserved NAD-dependent deacetylases, or ADP-ribosyl transferases. Increasing evidence indicates that SIRTs play a pivotal function in various biological processes such as energy metabolism, tumor progression, DNA repair and Inflammation [11-14]. SIRT1, as the most extensively studied member of SIRT family, plays a beneficial role in modulating hepatic lipid metabolism. Liver-specific deletion of SIRT1 using Alb-Cre (SIRT1 LKO) results in the hepatic lipid accumulation and fatty liver even with the control diet [40]. In contrast, mice with moderate SIRT1 overexpression were protected from lipid-induced inflammation and hepatic steatosis [35].

Recent studies have expounded on the role of SIRT1 in lipid metabolism. It is well-known that SREBP-1c and ChREBP are two major transcription factors involved in regulating triglyceride (TG) synthesis in hepatocytes. SREBP-1c and ChREBP are critical regulators of many lipogenic genes, including ACC1, FASN, and so on [34, 36]. It has been reported that SIRT1 reduces the transcriptional activity of SREBP-1c and decreases its binding ability to its target genes through deacetylating the DNA binding domain of SREBP-1c, and subsequently resulting in ubiquitination and proteasomal degradation [17-38]. The ChREBP is up-regulated in hepatocyteconditional SIRT1 knockout mice, which is correlated to the increased acetylation of histone H3K9 and histone H4K16 in ChREBP promoter due to the loss of deacetylase activity of SIRT1 [34]. In addition to decrease lipogenesis, SIRT1 increases fatty acid β-oxidation through activating PPARα/peroxisome proliferative activated receptor, gamma, coactivator 1α (PGC-1α) signaling pathway. PGC-1α is a transcription co-activator that interacts with PPARα to promote PPAR-α gene transcription. Consequently, PPAR-α induces the expression of fatty acid catabolic genes [39-40]. Collectively, these studies indicate that SIRT1 acts as a significant regulator in hepatic lipid metabolism via modulating SREBP-1c/ChREBP-dependent lipogenesis and PPARα/PGC-1α-dependent fatty acid β-oxidation.

Besides SIRT1, SIRT3, which is mainly localized in the mitochondrial matrix, has also been identified as a regulator hepatic lipid metabolism. In the absence of SIRT3, mice fed a high-fat diet had increased acetylation status of hepatic proteins and reduced activity of respiratory complexes III and IV [43]. In vitro studies showed that overexpression of SIRT3 significantly reduced oleate-induced lipid accumulation in HepG2 cells [42]. These studies indicate that SIRT3 represents another potential therapeutic target for fatty liver disease.

Similar to SIRT1 and SIRT3, SIRT6 is also reported to promote lipid metabolism in the liver [43]. SIRT6 deficiency leads to the upregulation of the key genes involved in hepatic long-chain fatty acid uptaking and the down-regulation of the genes involved in fatty acid β-oxidation. Consistently, the expression level of SIRT6 is significantly reduced in the liver of human patients with fatty liver disease [44].

**FoxO**

FoxO transcription factors have been identified as critical regulators for hepatic liver metabolism [17]. In mammals, FoxO family consists of FoxO1, FoxO3, FoxO4 and FoxO6, which are expressed ubiquitously and extensively in the body.

FoxO transcription factors are major targets of insulin. In general, insulin promotes Akt-mediated phosphorylation of FoxO proteins, stimulates their translocation from the nucleus to the cytoplasm, and thereby suppresses their effects in gene expression [45]. Recent studies show that in liver, FoxO proteins stimulate adipose triacylglycerol lipase (ATGL) expression, which mediates the first step in lipolysis, and meanwhile, suppress the G9/G1 switch-2 protein (G9/S2), which interacts with ATGL to inhibit its activity [46-47]. In in vivo experiment, liver-specific FoxO1/3/4 triple knockout mice (LTKO) show severe hepatic steatosis comparing with WT controls when treated with very high-fat diet or moderately high-fat plus cholesterol diet [48]. Additionally, FoxOs can activate the autophagy pathway to promote lipid breakdown as autophagy-related 14 (ATG14) has been verified to be a direct target of FoxOs [49].

As to FoxO6, it has the lowest degree of homology (about 30%) in amino acid sequence compared with other FoxO isoforms [50], which implies its divergent function from the FoxO subfamily. To elucidate the role of FoxO6 in...
hepatic lipid metabolism, Kim and co-workers have observed that hepatic FoxO6-transgenic mice develop hyperlipidemia, characterizing as elevated TG levels in plasma [53]. Besides, they have manifested that Foxo6 promotes TG-rich very low-density lipoprotein (VLDL) secretion. Consistent with previous findings, Foxo6 promotes production the lipid transfer protein such as microsomal triglyceride transfer protein (MTP) in the liver. MTP can heterodimerize with its small subunit protein disulfide isomerase in the endoplasmic reticulum, consequently catalyzes lipid transportation to nascent apolipoprotein B, a pivotal process to mediate secretion of VLDL and chylomicrons [54].

In summary, FoxOs play important roles in hepatic lipid homeostasis by inhibiting lipogenesis and increasing triglyceride breakdown and triglyceride export from hepatocytes.

**SREBPs**

SREBPs, are highly conserved across the different species and regulate the expression of genes involved in lipid metabolism. There are three SREBP isoforms including SREBP-1a, SREBP-1c, and SREBP-2, while SREBP-1c is the major isoform expressed in the liver [55]. It has been identified that SREBP-1c preferentially controls the gene expression of fatty acid synthesis, whereas SREBP-2 regulates the transcription of genes involved in cholesterol metabolism [56].

SREBPs are synthesized in the ER as a membrane-bound premature form and have to go through ER/Golgi process to form an active mature form via two proteolytical cleavage processes. SREBPs anchor in the ER membrane by two transmembrane helices, which associate with the SREBP cleavage activating protein (SCAP) and ER retention protein Insig. Then the SREBP-SCAP complex separate from Insig and move to Golgi apparatus by COPII-coated vesicles. In the Golgi, SREBPs are cleaved by site 1 (S1P) and site 2 (S2P) proteases, leaving the N-terminal cytosolic portion of the protein entering the nucleus to exert its function [59].

SREBP-1c mRNA level can be regulated by the nutritional condition in the body. When given a high carbohydrate diet, hepatic SREBP-1c mRNA expression can be highly induced, whereas, in the fasted state, its expression is suppressed. This process is regulated by hormones, including insulin [21], THs [51], and glucagon [58]. Studies have identified the critical role of mTORC1 in regulating SREBP-1c transcription. The protein level of mature SREBP-1c and the expression levels of the lipogenic genes are suppressed by a mTORC1 inhibitor rapamycin [57]. Besides, mTORC1 can phosphorylate two major downstream targets, initiation factor 4E-binding protein (4E-BP) and p70 ribosomal S6 kinase (p70S6K). In return, p70S6K promotes the proteolytical processing of SREBP-1c protein [55]. It has also been reported that clusterin, an 80-kDa disulfide-linked heterodimeric protein, negatively regulates hepatic lipogenesis by inhibiting SREBP-1c expression. More detailed, clusterin inhibits SREBP-1c expression by directly inhibiting SREBP1c promote activity and/or via the suppression of liver X receptor (LXR) and specificity protein 1 activity [58]. Recently, a study identified a new regulator of SREBPs, transforming growth factor-β-activated kinase 1 (TAK1). TAK1 is a crucial mediator of inflammatory response. Extensive studies have been done to identify the mechanism of TAK1 activation. Under the inflammatory conditions, TAK1 can be activated by IL-1, TNF-α, or Toll-like receptor ligands, and inhibit the activation of SREBPs [59].

The activated nuclear forms of SREBPs are rapidly degraded by the ubiquitin-dependent proteasomal pathway [60]. F-box and WD repeat domain-containing 7 (Fbw7) is a cullin-RING type E3 ubiquitin ligase which functions as the major ubiquitin ligase for SREBPs. Fbw7-mediated degradation is dependent on the phosphorylation of SREBPs by protein kinases such as GSK-3 and cyclin-dependent kinase 8 (CDK8) [61]. Therefore, inactivation of Fbw7 will result in the stabilization of SREBPs and subsequently enhance the cholesterol and fatty acid synthesis as well as hepatic lipid uptake. However, the expression of CDK8 is suppressed by insulin. In the presence of insulin, SREBP-1c promotes lipogenesis by increasing the expression of its target genes, including FASN, ACS, and SCD1 [62].

**Inflammatory cytokines**

Inflammation contributes to the pathogenesis of various liver diseases, especially fatty liver diseases. Cytokines are important signaling molecules involved in the regulation of various physiological and pathological pathways. Here we will discuss the two most studied proinflammatory cytokines in hepatic metabolism, IL-6 and TNF-α, as illustrated in Table 1.

**IL-6**

IL-6 is a multifunctional cytokine that has broad biological activities in various organs. It can exert simultaneously as a pro-inflammatory or an anti-inflammatory mediator. In the setting of metabolic disorders, IL-6 has been identified as a key contributor to hyperinsulinemia, insulin resistance, dyslipidemia and so on [16-20]. It is found that IL-6 concentration is higher in adipose tissue of obese patients compared with the healthy group. Moreover, IL-6, generated by adipose tissue, can induce hepatic VLDL secretion to influence hepatic lipid metabolism [63]. It is also reported that hepatic oxidative stress is positively correlated with increased serum IL-6 level and interrelated with the dysregulation of lipid homeostasis [64].

On the contrary, IL-6 exhibits a hepatoprotective effect on various forms of liver injury by modulating the immune response. IL-6-deficient mice tend to aggragate alcohol-induced lipid accumulation, which can be ameliorated by supplemental injection with IL-6 [65]. Another report indicates that IL-6 treatment decreases hepatic steatosis, which is accompanied by down-regulation of TNF-α, activation of PPAR-α, and promotion of fatty acid β-oxidation [66]. Meanwhile, studies in an in vitro hepatoma cell line showed that IL-6 reduced the SREBP-1c mRNA level, which is accompanied by decreased fatty acid synthesis [67]. The previous
studies also reported that IL-6 was able to up-regulate AMP-activated protein kinase (AMPK) in muscle, liver, and adipocytes and increase the lipolytic activities \cite{80}. However, more studies are needed to clarify the impact of IL-6 on hepatic lipid metabolism. \n
**TNF-α**

TNF-α is another important proinflammatory cytokine involved in metabolic syndromes. It has been found that plasma TNF-α is increased in the transgenic mice of the adipocyte-specific nuclear form of SREBP-1c (nSREBP-1c). Meanwhile, these mice develop hepatic lesions that resemble human nonalcoholic steatohepatitis (NASH) \cite{21}. In contrast, the TNF-α receptor knockout mice show a reduced prevalence of hepatic steatosis. Furthermore, TNF-α induced the expression of Mcp1, Tgfβ1, and Timp1 in primary hepatocytes which may represent a critical driving force of NAFLD/NASH progression \cite{69}.

**Therapeutic Natural products for liver disease**

Numerous natural products have been identified with beneficial effects on modulating hepatic lipid metabolism and improving fatty liver diseases. Here we review several most studied candidates (Table 2).

**Flavonoids**

Flavonoids are a diverse group of polyphenols present in almost all fruits and vegetables with anti-oxidation, anti-inflammatory, and lipid modulating activities \cite{70}. Herbacetin, a dietary flavonoid, shows anti-hyperglycaemic and anti-hyperlipidemic properties in high-fat diet-induced mice. It also been reported the herbacetin administration can ameliorate obesity-associated insulin resistance, hyperlipidemia, and hepatic lipid accumulation by regulating lipid metabolizing enzymes \cite{71}. Besides, there are a lot of Citrus flavonoids, including naringenin, hesperetin, nobiletin, and tangeretin, showing properties of modulating hepatic steatosis and dyslipidemia via increasing fatty acid oxidation and inhibiting hepatic fatty acid synthesis \cite{72}. Fisetin, a natural flavonoid that is rich in various fruits and vegetables, has a significant impact on alleviating hepatic lipid metabolism through promoting SIRT1/AMPK and β-oxidation pathway \cite{73}. Baicalin (BA), originating from the herb of Scutellaria baicalensis Georgi, is an active flavonoid. Recently, studies have shown that BA attenuates MCD diet-induced hepatic steatosis at least in part through the inhibition of lipogenesis and activation of fatty acid β-oxidation by modulating SREBP-1c, PPARα, FASN, SCD1, and ACC1 \cite{74}. Flavonoid from the hydroalcoholic extract of Cyperus scariosus L. root (HCS) has hypolipidemic and antioxidant activities. Besides, HSC-treated animals showed decreased lipid accumulation and improvement of hepatocytes function \cite{75}.

**Alkaloids**

Alkaloids are a class of organic nitrogen-containing bases present in many plants. Alkaloids have diverse beneficial physiological effects, such as anti-pathogenic microorganisms, anti-inflammatory, anti-tumor, cardioprotection, hypoglycemia, regulation of lipid metabolism, and immune regulation.

Berberine (BBR), a bioactive alkaloid isolated originally from Berberis, is an ancient medicinal plant. It has more than a thousand years of history of use in traditional Chinese medicine. It has anti-microbial, anti-tumoral, anti-inflammatory, cholesterol-lowering effects, and so on \cite{76-77}. Recent studies reported that BBR upregulated hepatic low-density lipoprotein receptor (LDLR) expression via activation of signaling cascade AMPK/Raf-1/MEK/ERK, leading to a higher LDL uptake into the cell \cite{78}. BBR is also able to regulate microRNAs to impact hepatic lipid metabolism. MiR-122, a predominant miRNA in the liver, has been shown to promote lipogenesis by regulating the expression of lipogenic genes, such as SREBP-1c. BBR treatment significantly inhibits the expression level of miR122, sequentially, attenuates lipogenesis \cite{79}. Trigonelline, a plant alkaloid, recently was found its effect on attenuating NAFLD by modulating autophagy, showing autophagy restoration, and reduced lipotoxicity \cite{80}. Nuciferine, which is isolated from Nelumbo nucifera leaves, can activate PPARα/PGC1α pathway to promote fatty acid oxidation and attenuate hepatic steatosis \cite{81}.

**Saponins**

Saponins are common sterol glycosides and triterpene glycosides found in many plants, especially high in legumes. Saponins have a variety of health benefits, including the cholesterol lowering effect, anti-inflammation, immune-boosting effect, antibacterial effect, and anti-oxidative stress effect \cite{82}.

Ginsenoside Rb2 is one of the major ginsenosides in Panax ginseng. A recent study found Rb2 can restore autophagy via the induction of SIRT1 and activation of AMPK in the hepatocyte, consequently, alleviate hepatic lipid accumulation and attenuate NAFLD \cite{83}. Akebia Saponin D (ASD), abundant in the rhizome of Dipsacus asper Wall, has multiple pharmacological activities, including alleviation of hepatic steatosis through increased autophagy and cardioprotective effect. A recent study identified a potential mechanism underlying ASD-mediated protective effect against hepatic inflammation, activating mitophagy.

**Table 2** Representative natural products in lipid metabolism

<table>
<thead>
<tr>
<th>Natural products</th>
<th>Mode</th>
<th>Consequence</th>
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<tbody>
<tr>
<td><strong>Flavonoids</strong></td>
<td></td>
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<tr>
<td>Herbacetin, argenin, hesperetin, nobiletin, tangeretin, fisetin, baicalin</td>
<td>Anti-hyperglycaemic and anti-hyperlipidemic properties, ameliorating obesity, inducing fatty acid β-oxidation</td>
<td></td>
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<tr>
<td><strong>Alkaloids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berberine, trigonelline, nuciferine</td>
<td>Cholesterol-lowering regulation</td>
<td></td>
</tr>
<tr>
<td><strong>Saponins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginsenoside Rb2, Akebia Saponin</td>
<td>Improving hepatic lipid accumulation, attenuating hepatic inflammation, activating mitophagy</td>
<td></td>
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<tr>
<td>D, Sea Cucumber Saponin</td>
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steatosis. This study reported that ASD treatment activated mitochondrion and alleviated hepatic steatosis by increasing the expression of BNip3, a critical mitochondrial outer membrane protein responsible for maintaining mitochondrial integrity and controlling mitochondrial mass [46]. Sea Cucumber Saponin Echinoid A (EA) is another bioactive member of Saponin family and also has various bioactivities, including immune-stimulating activity, hypolipidemic activity, and inhibition of hepatic lipid accumulation [66].

**Conclusion**

The liver has a complex lipid metabolism regulation system. It is tightly regulated by various hormones and inflammatory cytokines. At the same time, the hepatic lipid metabolism is also closely linked to the regulatory network of multiple transcription factors in hepatocytes. During the past decades, plant medicines are getting significant attention in developing effective therapies for metabolic diseases and fatty liver diseases. Although several cellular and molecular mechanisms have been identified, there are still many challenges that need to be addressed before these plant medicines can be translated to the clinic.

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seed flavonoid, ameliorates high percent dietary fat induced insulin resistance and lipid accumulation through the regulation of hepatic lipid metabolizing and lipid-regulating enzymes [J]. Chem Biol Interact, 2018, 288: 49–56.


Cite this article as: ZHU Jia-Zhen, YI Hong-Wei, HUANG Wei, PANG Tao, ZHOU Hui-Ping, WU Xu-Dong. Fatty liver diseases, mechanisms, and potential therapeutic plant medicines [J]. Chin J Nat Med, 2020, 18(3): 161-168.

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