Review Article

Hepatic Lipid Metabolism and Herbal Impacts on Non-Alcoholic Fatty Liver Disease

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Abstract

Dysregulation of hepatic lipid metabolism is one of the most important causal events of non-alcoholic fatty liver disease (NAFLD). The balance between lipogenesis and lipolysis achieved through pharmacological intervention is proven to effectively ameliorate NAFLD induced liver injury in both pre-clinical studies and clinical trials. In recent years, treatment of NAFLD using herbal derivatives receives wide attention because they effectively restore normal functions on several key pathological events during NAFLD progression with minimal adverse effects when taken in a suggested reasonable dose. The objectives of this review are 1) to summarize literature findings regarding the metabolic processes that regulate hepatic lipid metabolism, particularly under NAFLD conditions and 2) to review recent advances in the ameliorative effect studies of herbal derivatives, including wolfberry, garlic, green tea, grape and others, on the dysfunction of lipid metabolism. These herbal derivatives are shown to reduce steatosis and inflammation/oxidative stress/fibrosis in animal studies and, for some of them, in clinical trials. Their impacts on hepatic lipid metabolism are mainly on modulating key regulatory genes for both lipogenesis and lipolysis, such as SREBP-1c and PPARy. However, future studies are warranted to deeply investigate the influence of herbal derivatives the kinetic changes of the lipid metabolic balance in the liver during the development of NAFLD.

Introduction

Up to date, non-alcoholic fatty liver disease (NAFLD) is a significant global problem which influences one third of the adult population in affluent countries and obese people [1-3]. It is a kind of hepatic- and metabolic-disorder disease not attributed to the abuse of alcohol (< 30 g/day for men, < 20 g/day for women) [4]. NAFLD is considered as an independent predictor of insulin resistance [5], the metabolic syndrome [6], and cardiovascular diseases [7]. Moreover, a certain percentage of NAFLD patients may progress to late-stage liver diseases, including cirrhosis and hepatocellular carcinoma [8]. Therefore, elucidating the pathogenic mechanisms of NAFLD is crucial for the clinical control and therapy of this liver disease. The most updated pathological model for NAFLD is the “multiple parallel hit” model in which the dysregulation of lipid metabolism and insulin resistance are considered as the “first-hits” to the liver. Then other typical features of clinical NAFLD, such as oxidative stress, inflammation, chemoattraction, necrosis, fibrosis, and apoptosis, are “parallel multiple hits” subsequently [9]. Recent studies also pointed out that the “downstream” events may regulate or influence the “upstream” event lipid metabolism, forming a positive or negative feedback loop during the development of NAFLD. For example, hepatic autophagy is found to regulate the lipid metabolism and mitochondrial conformation, demonstrating two novel physiological activities namely “lipophagy” and “mitophagy”, respectively [10,11]. As the direct cause of steatosis, lipoperoxidative stress and inflammation, lipid accumulation results from an imbalance between lipid availability (hepatic lipogenic pathways) and lipid disposal (hepatic lipolytic pathways) in a dynamic process [12]. Besides conventional diagnostic means, there are several novel biomarkers which have been identified based on the unbalance between apoptosis/anti-apoptosis process [13,14], low grade chronic inflammation [15,16], contribution of adipose tissue [17], and the key role of the liver-spleen axis [18]. For example, it is found that anti-apoptotic serum marker Bcl-2 [13] and apoptosis-related cytochrome c [14] can be used as diagnostic indicators in overweight/obese patients with NAFLD. In addition, interleukin-6 (IL-6) is highly specific in confirming the absence of NASC at normal values, which can also be used as a novel biomarker [19]. Until now, there is no direct and effective therapy for NAFLD. Current therapeutic strategies include two major categories: (1) lifestyle interventions (include weight reduction, dietary modification and physical exercise) and (2) pharmaceutical therapies [20]. Besides regular pharmaceutical intervention (e.g. insulin sensitizer and lipid lowering agent), applying herbal derivatives as antioxidant and lipid-balancing agents received massive attention in recent years. Although the underlying mechanisms of the beneficial effects warrant further investigation, herbal derivatives hold several advantages in the daily prevention or treatment of NAFLD. They are widely available around the world and with low or minimal side-effects. Some of them have been extensively studied in modern basic and clinical studies [21]. Therefore, in the present review, the lipid accumulation pathways during NAFLD is described firstly, followed by the current advances in the beneficial impacts of herbal derivatives on the lipid regulation pathways. Several derivatives, which have been extensively investigated for their lipid-regulating and anti-NAFLD mechanisms in recent years, will also be highlighted in this review.

Hepatic Lipid Metabolism During NAFLD Pathogenesis

Hepatic lipolytic pathways

In the pathogenesis of NAFLD, several hepatic fatty acids (FA) pathways are involved. The mitochondrial and peroxisomal β-oxidations are the major processes that metabolize FA [22,23]. The third pathway is the ω-oxidation which occurs in the endoplasmic reticulum (microsomes) through the actions of cytochrome P450 4A (CYP4A) [24,25]. Mitochondrial β-oxidation is the primary pathway that metabolizes short-chain (< C12), medium-chain (C12-C16), and long-chain (C16-C20) FA, in order to provide energy to other cellular activities. During this process, electrons are transferred from fatty acyl-CoA to flavin adenine dinucleotide and is oxidized to nicotinamide adenine dinucleotide (NAD+), resulting in...
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Hepatic lipidic pathways

Hepatic non-esterified fatty acid (NEFA) uptake: Non-esterified fatty acids (NEFA) are taken by the liver from the blood in proportion to their circulating concentration. They can be metabolized from the hydrolysis of complex lipids by lipases either from dietary or endogenous sources, or from the hydrolysis of fatty acid-CoA by thioesterases. In the liver, fatty acid transport protein (FATP) or fatty acid translocase (FAT) and CD36 are important cellular transporters that facilitate the entry of NEFA into the cells. After that, lipids are covalently bound by fatty acid binding protein (FABP) or acyl-CoA synthetases (ACS) expressed in the outer mitochondrial membrane and the microsomes for further metabolism or transcription factor activation in the nucleus [41]. These metabolic pathways are responsible for the maintenance of low intracellular NEFA and FA levels.

A recent study exhibits that the structural integrity of lipid rafts in cell membrane is vital for its lipid uptake [42]. Caveolin proteins (caveolin-1, -2 and -3) are cytoplasmically-oriented integral membrane proteins. They are proven to mediate the uptake of lipids into the cells. Mice with caveolin-1 deficiency are resistant to diet-induced obesity and reduced lipid accumulation in hepatocytes [43,44]. Over-expression of caveolin-3 in diabetic mice is found to improve glucose metabolism and insulin signaling [45].

De novo lipogenesis of FA: The process of de novo synthesis of FA is vital for the hepatic lipid homeostasis. It is tightly controlled and regulated at both hormonal and nutritional levels, because high carbohydrate diet induces while starvation inhibits the de novo synthesis of FA. Furthermore, the degree of de novo synthesis of FA is closely associated with the level of insulin and tissue insulin sensitivity. In healthy human, de novo lipogenesis is only elevated postprandially. However, in NAFLD patients, this process is elevated in fasting conditions without further enhancement after meal [46,47]. At the molecular level, a complicated network including a spectrum of transcription factors and receptors is responsible for the precise regulation of de novo lipogenesis. As a result of hyperinsulinemia and endocannabinoid activation, sterol-regulatory element binding protein-1c (SREBP-1c) is over-expressed during the development of NAFLD. SREBP-1c is an important transcription factor regulating de novo lipogenesis. It has high expressions in the liver, white adipose tissue, adrenal gland and brain. SREBP-1c expression is suppressed during fasting but significantly elevated after the meal (particularly high-fat or high carbohydrate food) by insulin signaling through the phosphoinositide 3-kinase (PI3K)-dependent pathways [48-50]. Glucagon, forkhead box protein O1 (FoxO1) and AMP-activated kinase (AMPK)-dependent pathways are shown to inhibit the activity of SREBP-1c [51-53]. Interestingly, SREBP-1c alone is not enough to induce gene expression in response to carbohydrate since SREBP-1c gene deletion in mice only results in a 50% reduction in FA synthesis [54]. A recently identified transcription factor known as carbohydrate responsive element binding protein (ChREBP) partly fills this gap. In the liver, this factor is activated by glucose and translocated into the nucleus, then it induces the transcription of lipogenic gene through binding to their carbohydrate responsive element in the promoter region [55,56]. Recently, it is found that liver X receptors (LXRs) can directly regulate the activity of ChREBP [57]. When ChREBP is knockdown in ob/ob mice, hepatic lipogenic rates, fat accumulation,
plasma TG and NEFA concentrations are significantly declined, leading to the improvement of hyperglycemia and hyperinsulinemia [58]. In response to mitochondrial and peroxisomal β-oxidation, peroxisome proliferator-activated receptors (PPARs) are induced to prevent hepatic triacylglycerol infiltration and to increase the rate of fatty acid catabolism [59,60]. In a methionine- and choline-deficient (MCD) diet-induced NAFLD mouse model, treatment with the PPARα agonist Wy-14643 reduced fibrotic steatohepatitis by the reduction of stimuli (e.g. lipid peroxides) and the activation of cells responsible for promotion of hepatic fibrosis [61]. This result is consistent with other reports indicating the anti-inflammatory properties of PPARα, probably through inhibiting IL-6 and cyclooxygenase-2 (COX-2) mediated by nuclear factor-kappa B (NF-kB) [59,62]. PPARγ is also important for the regulation of lipid metabolism, with highest expression in adipose tissue and relatively low level in hepatocytes, stellate cells and macrophages. It promotes FA uptake and insulin sensitivity when there is an increased lipid “influx” in hepatocytes and adipocytes. Liver-specific deletion of PPARγ in db/db mice improves fatty liver but aggravates diabetic phenotypes [63]. In addition, it also increases the plasma level of adiponectin and adiponectin receptor expression in the liver [64,65]. Overall, developing novel PPARγ agonists is promising since PPARγ may reverse a variety of NAFLD features including steatosis, inflammation and fibrosis.

Important hepatic lipogenic enzymes: Some lipogenic enzymes are also thought to be crucial for the induction of steatosis during NAFLD initiation and progression. The first example is acetyl-CoA carboxylases (ACCs, include ACC-1 and ACC-2). In general, ACCs control the rate of de novo lipid synthesis and FA oxidation (e.g. malonyl-CoA) [66]. The tissue distribution of ACC-1 and ACC-2 is different. ACC-1 is mainly expressed in the cytosol of hepatocytes and adipocytes, where ACC-2 is expressed in the heart and skeletal muscle, with relatively lower expression in the liver [67]. In a high-fat diet induced insulin resistance and steatohepatitis rat model with inhibition of ACC-1 and ACC-2 expression using antisense oligonucleotides, the inhibition of ACCs improves insulin sensitivity and reduces the contents of hepatic triacylglycerol, long chain acyl-coenzymes A and diacylglycerol partially through Akt- and FoxO1-dependent pathways. ACC-1 inhibition also reduces hepatic lipogenesis while deficiency of ACC-2 has no such effect [68]. Drugs that can inhibit the activity of ACCs have been used in several pre-clinical studies and offered improved metabolic-controlling outcomes. However, due to their non-specific effect on hypothalamus and pancreas, these drugs may also increase food intake and reduce insulin secretion, respectively [69]. Stearoyl-CoA desaturase 1 (SCD1) is another important lipogenic enzyme that mediates the synthesis of monounsaturated long-chain FAs from saturated fatty acyl-CoAs. Since it is predominantly expressed in the liver, SCD1 has become a potential target for treating NAFLD. In mice NAFLD models fed with a high-fat diet or a high carbohydrate diet, knockout of SCD1 improves insulin sensitivity and decreases hepatic liver accumulation via reduced lipogenic activity and increased β-oxidation [70-72]. Recent study also indicates that SCD1 expression is required for carbohydrate-induced adiposity. Its expression in extrahepatic tissues is closely related to the occurrence of obesity and insulin resistance induced by high-fat diet [73]. The role of SCD-1 in cellular pro-inflammatory responses and carcinogenesis are demonstrated in some other recent reports [74,75]. The third lipogenic enzymes that arises emerging attention in NAFLD study is fatty acid synthase (FAS). Its main function is to catalyze the synthesis of palmitate from acetyl-CoA and malonyl-CoA into long-chain saturated fatty acids. In the liver, FAS is regulated by hormones and nutritional state. It is also reversely regulated by the intracellular FA concentration [76]. Very interestingly, knockout of FAS in mice fed with a low fat/high carbohydrate diet for 4 weeks does not protect the mice liver from NAFLD, but exacerbate it due to a reduction of β-oxidation. Such effects are mediated through the activity of a pool of nuclear receptors (e.g., PPARα) which lead to the enhancement of cellular β-oxidation [77].

Impacts of Some Herbal Derivatives on Lipid Metabolism During NAFLD

*Lycium barbarum* polysaccharide (LBP)

LBP is the polysaccharide portion of the fruit (wolfberry or goji berry) of *Lycium barbarum* in the family Solanaceae. The usage of wolfberry as a medicinal herb is over 1,000 years in China. Modern biological studies indicate that LBP is the most important part of wolfberry, in terms of beneficial properties against oxidative stress, inflammation, glucose metabolism dysfunction and tumor [78]. In traditional Chinese medicine, the primary protective function of LBP is in the liver and eyes. Therefore, it is interesting to investigate the possible beneficial effects of LBP on the abnormalities or pathological processes in these organs [79]. With alcoholic administration, co-treatment with LBP significantly ameliorated lipid peroxidation and steatosis in the liver [80]. In a carbon tetrachloride (CCL4)-induced acute liver injury model, oral pre-treatment with 1 mg/kg or 10 mg/kg LBP prevents hepatic necrosis, oxidative stress and inflammation, as well as promotes liver regeneration partly through the modulation of NF-kB [81]. In our rat NAFLD model, 8-week feeding with a high-fat diet produces clinical NAFLD symptoms at different levels, including steatosis, fibrosis, inflammation, oxidative stress, apoptosis and autophagy [82,83]. Daily oral feeding with 1 mg/kg LBP significantly improves these NAFLD features without showing obvious influence on healthy rats. For lipid metabolism, in NAFLD rat, the expression of lipogenic genes (SREBP1c and PPARγ2) is up-regulated while the expression of lipolytic genes adipose triglyceride lipase (ATGL) is down-regulated, leading to an increase in the circulating level of free fatty acid (FFA) and occurrence of steatosis [84]. LBP treatment re-balances the expression of both lipogenic and lipolytic genes to correct the FFA level and ameliorate steatosis [85]. However, we are still investigating the effective monomer(s) of LBP that is responsible for its anti-NAFLD properties.

Garlic

Garlic is a species in the onion genus, *Allium*. It has a history of medicinal use in human for over 7,000 years. Modern science focuses on its therapeutic mechanisms in infection and several diseases, including atherosclerosis, high cholesterol, hypertension, diabetes and cancer [86]. In the liver, it is found that in CCl4- and acetaminophen-induced acute liver injury models, treatment with S-allymercaptocteysteine (SAMC) derived from aged garlic significantly improves typical acute injury features, such as hepatocytes necrosis, oxidative stress, and inflammation [87,88]. Similar to LBP, co-treatment with SAMC alleviated a variety of NAFLD symptoms, from histological changes to apoptosis and autophagy [82]. Increased expression of lipogenic gene (SREBP1c) is observed in the NAFLD rats, whereas the expression of lipolytic gene (adiponectin) is reduced, suggesting an on-going process of hepatic lipid accumulation. Administration of SAMC reverses this process by correcting the expression of these two genes [82]. It is interesting that SAMC treatment also enhances the hepatic autophagy during NAFLD
Green tea

It is reported that consumption of green tea improves human health due to its cholesterol reduction and antioxidant properties [90]. In the liver, numerous studies reveal the protective or therapeutic effects of green tea on hepatic disorders. For the treatment of NAFLD, several reports demonstrated that administration of whole green tea extract (GTE) or monomer from green tea alleviates hepatocyte necrosis, fibrosis and other features of NAFLD, particularly hepatic lipid accumulation. In obese mice, 6-week oral GTE administration reduces the body weight of mice. It also ameliorates steatosis through adiponectin-mediated lipid metabolism [91] and the decrease of the release of FA from adipose tissue [92]. GTE down-regulates the expression of SREBP-1c, FAS and SCD-1 in adipose tissue but not in the liver. In addition, the mRNA level of hormone-sensitive lipase and NEFA is also reduced [92]. When co-administered with grape extract and l-carnitine, GTE dramatically reduces high-fat diet induced obesity, with suppressed hyperlipidemia via decreasing the plasma levels of LDL, cholesterol and TG [93]. An 11-month study in mice fed with a high-fat diet containing 0.5% of highly concentrated GTE (92% total polyphenols, 73% total catechins) showed that GTE reduces adipose mass and hepatic TG accumulation due to enhanced β-oxidation [94]. In a human study, acute administration of GTE increases energy expenditure while it decreases the respiratory quotient when compared with the placebo group treated with equivalent caffeine content [95]. Overall, green tea is a promising herbal supplement against NAFLD with a potent ability in regulating hepatic lipid metabolism [96]. Up to date, epigallocatechin-3-gallate (EGCG) is considered as the main effective monomer that plays major roles in modulating NAFLD-induced hepatic abnormalities [83,97].

Resveratrol

Resveratrol (3,5,40-trihydroxystilbene) is a natural compound present in grapes and other food products [98]. Previous studies have proven its surprising antioxidant, anti-aging, anti-inflammatory and anti-cancer properties [99-103]. In animal studies, resveratrol is shown to improve insulin sensitivity and lower body weight through regulating AMPK [104], sirtuin-1 (SIRT1) and peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) [105], indicating its potential anti-diabetic property. In a palmitate-induced steatosis cell model using hepatoma cell line HepG2, administration of resveratrol significantly reduces the accumulation of cellular TG via up-regulation of FoxO1 and down-regulation of SREBP-1c, and further explores the anti-NAFLD mechanism of resveratrol [106]. These findings are then expanded in a fa/fa Zucker rat model. When resveratrol is orally taken for 6 weeks, it reduces liver weight, NEFA and triacylglycerol contents without influencing the activities of CPT-1a and acyl-coenzyme A oxidase (ACO) [107]. Another report points out that in a high fat/sucrose diet (HFS)-induced Wistar rat NAFLD model, resveratrol treatment alleviates steatosis. This effect is mediated by the restoration of LDLR and scavenger receptor class B type 1 (SR-BI) at both transcriptional and translational levels [108]. In clinical studies, as early as 2008, Sirtris Pharmaceuticals announces that their patent formulation of resveratrol, SRT501, could improve glucose tolerance in type 2 diabetes in a Phase 1b clinical trial [109], followed by a recent study showing the molecular anti-aging target and mechanisms of resveratrol in the Science Magazine [102]. Overall, the report regarding to the effect of resveratrol on human lipid metabolism is rather limited. If its efficacy can be more thoroughly demonstrated, resveratrol is an attractive choice for the clinical therapeutic application on NAFLD.

Other derivatives

In the past decade, there is a large number of studies investigated the ameliorative effects of herbal derivatives on lipid metabolism during NAFLD progression. For example, silymarin and silibinin are derivatives of plant milk thistle (Silybum marianum). Clinical trials indicate that hepatic steatosis (histological analysis and expression of gamma-glutamyl transpeptidase) and general injury are ameliorated by the treatment of silymarin [110] or the combination of silymarin and vitamin E [111]. In experimental non-alcoholic steatohepatitis mice model, when db/db mice are fed with MCD diet, co-treatment with silibinin improves lipid metabolism in the liver by restoring the expression and activity of SCD-1 [112].

Curcumin is another important herbal derivative extracted from popular Indian spice turmeric, a member of the ginger family (Zingiberaceae). It is found to be effective against the liver injury and lipid accumulation in experimental NAFLD animal models. In obese mice with steatosis, apart from the ameliorative effects on hepatic inflammation and oxidative stress, curcumin administration obviously reduces lipid deposition in the liver through the down-regulation of SREBP-1c gene expression [113]. In a hepatic stellate cells (HSCs) activation model, curcumin is shown to reduce the abundance of LDLR in activated HSCs and to differentially regulate the expression of SREBP-1 and SREBP-2, leading to the reduced level of cholesterol [114]. This study provides a novel mechanism for the regulatory role of curcumin in hepatic lipid metabolism, making it a good candidate for the prevention hypercholesterolemia-associated hepatic fibrogenesis.

In recent years, the link between coffee consumption and NAFLD receives mass attention since coffee is one of the three major drinks all over the world. In a clinical study, scientists found that high coffee intake is associated with a decrease grade of NAFLD. There is no significant difference in the antioxidant factors measured in this study [115]. In addition, another clinical trial points out that coffee caffeine consumption significantly reduces the risk of fibrosis among NAFLD/NASH patients [116]. To investigate the underlying mechanism, NASH is firstly established in rats fed with a high-fat/calorie solid diet for 4 weeks. After that, certain amount of decaffeinated coffee or its polyphenols or melatonin which correspond to approximately 2 cups of filtered coffee or 6 cups of espresso coffee for a 70-kg person is treated for another 8 weeks. It is shown that coffee and its polyphenols and melatonin improves NASH through (1) a reduction in hepatic fat accumulation by increasing β-oxidation; (2) amelioration of hepatic oxidative stress; and (3) reduction in hepatic inflammation via suppressing the expression of pro-inflammatory cytokines [117].

Goshajinkigan (GJ) is an extract from traditional Japanese herbal medicine (Kampo). GJ has been demonstrated to treat patients with numbness, melosalgia, and back pain [118,119]. Furthermore, GJ is capable to reduce the homeostasis model assessment ratio (HOMA-R) of diabetic patients [120]. In a streptozotocin-induced diabetic rat model, GJ is found to reduce hyperinsulinemia via the NO pathway [119]. Recently, in a study using rat NAFLD model fed...
with high-fat diet, GJ treatment significantly reduced the weight of liver and the level of serum AST that elevated by high-fat diet [120]. However, the main effective component (monomer) of GJ for NAFLD therapy needs further investigation.

Rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid) is the major monomer component of Rheum palmatum L., which has been widely used in traditional Chinese medicine for more than 2,000 years. Modern studies pointed out the anti-osteoarthritic properties of rhein in both human and animal models [121,122]. In a high-fat diet-induced obese and NAFLD mice model, administration of rhein ameliorated NAFLD-associated steatosis, recovered hepatic functions and corrected the T helper (Th)1/Th2 cytokine imbalance. In addition, rhein re-balanced the lipid metabolism through SREBP-1c and LXR-related pathways [123].

There are numbers of herbal derivatives which exhibit beneficial effects against the development of NAFLD in animal studies, such as sinae san from Chai Hu (Radix Bupleuri) [124], lotus root from Nelumbo nucifera [125], Gymnostemma pentaphyllum extract [126], and total alkaloids from Rubus aleaefolius Poir. [127]. However, the detailed mechanism for the re-balance of the lipid metabolism by those derivatives is not clear and needs further investigation.

### Table 1: Summary of impacts of herbal derivative treatment on hepatic lipid metabolism from recent studies.

<table>
<thead>
<tr>
<th>Herbal derivative</th>
<th>Model</th>
<th>Treatment and dosage</th>
<th>Lipid regulation mechanism(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lycium barbarum</strong> (wolfberry, goji berry)</td>
<td>Eight-week induction of NAFLD using a voluntary high-fat diet model (30% fat) in SD rats</td>
<td>Daily oral feeding with 1 mg/kg LBP</td>
<td>Rebalance the expression of lipogenic genes (SREBP1c and PPARy2) and lipolytic genes (ATGL and adiponectin); Reduce circulating FFAs</td>
<td>[85]</td>
</tr>
<tr>
<td><strong>Garlic</strong></td>
<td>Eight-week induction of NAFLD using a voluntary high-fat diet model (30% fat) in SD rats</td>
<td>Intraperitoneal injection of 200 mg/kg garlic-derived SAMG 3 times a week</td>
<td>Rebalance the expression of lipogenic gene (SREBP1c) and lipolytic gene (adiponectin); Reduce circulating FFAs</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td>High-fat diet induction for 10 weeks to form NAFLD in SD rats</td>
<td>Oral feeding with 2.86 g/kg aged garlic extract 5 times a week.</td>
<td>Reduce visceral fat; Attenuate total cholesterol, low-density lipoprotein-cholesterol and triglycerides</td>
<td>[128]</td>
</tr>
<tr>
<td></td>
<td>Five-week induction of NAFLD using high-fat diet in SD rats</td>
<td>Dietary supplementation of 2% (w/w) high hydrostatic pressure extract of garlic</td>
<td>Reduce the plasma levels of triglyceride and low-density lipoprotein cholesterol; Decrease the hepatic triglyceride and total cholesterol levels; Up-regulate the expression of apolipoprotein A-I, ABCA1 and LCAT</td>
<td>[129]</td>
</tr>
<tr>
<td><strong>Green tea</strong></td>
<td>Obese ob/ob mouse model</td>
<td>Six-week feeding of green tea extract at 0.5, 1 or 2% (w/w)</td>
<td>Reduce the hepatic lipid content and alpha-tocopherol level; Restore the adiponectin level; Alter the expression of SREBP1c, FAS, SCD-1 and HSL with decreased serum NEFA content</td>
<td>[81,92]</td>
</tr>
<tr>
<td></td>
<td>Three-week NAFLD induction by high-fat diet in C57BL/6 mice</td>
<td>Eight-week oral feeding with 300 mg/kg or 1200 mg/kg RGTC (grape extract-green tea catechin-L-carnitine combination mixture)</td>
<td>Reduce the plasma level of low-density lipoprotein cholesterol and triglycerides; Down-regulate the plasma level of glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase</td>
<td>[93]</td>
</tr>
<tr>
<td></td>
<td>Eleven-month NAFLD induction using high-fat diet in C57BL/6 mice</td>
<td>Co-treatment with 0.1-0.5% (w/w) tea catechins</td>
<td>Decrease visceral and hepatic fat accumulation; Increase the expression of acyl-CoA oxidase and medium chain acyl-CoA dehydrogenase</td>
<td>[84]</td>
</tr>
<tr>
<td><strong>Resveratrol</strong></td>
<td>Ten-week induction for NAFLD using high-fat diet in Wistar rats (in vivo); HepG2 incubated with high concentration of glucose (25 mM) and insulin (100 nM) to induce steatosis (in vitro)</td>
<td>Oral administration with 100 mg/kg resveratrol (in vivo); HepG2 cells were exposed to 10, 25, and 50 μM resveratrol for 6 or 24 h (in vitro).</td>
<td>Improve insulin resistance and triacylglycerol accumulation; Promote the activity of AMPK; Suppress the expression of SREBP-1c and FAS</td>
<td>[104]</td>
</tr>
<tr>
<td></td>
<td>Fifteen-week NAFLD induction with high-fat diet in C57BL/6 mice</td>
<td>Dietary form of 200 or 400 mg/kg/day resveratrol</td>
<td>Increase aerobic capacity; Decrease PGC-1α acetylation but increase PGC-1α activity; Activate SIRT1</td>
<td>[105]</td>
</tr>
<tr>
<td></td>
<td>HepG2 cell was exposed to 0.05-0.3 mM palmitate for 24 h to induce steatosis</td>
<td>Co-treatment with 0.4 μM resveratrol</td>
<td>Up-regulate the expression of SIRT1 and FoxO1; Reduce the expression and activity of SREBP1</td>
<td>[106]</td>
</tr>
<tr>
<td></td>
<td>Obese fa/fa Zucker rats</td>
<td>Six-week oral feeding with 15 mg/kg or 45 mg/kg resveratrol</td>
<td>Reduce hepatic triacylglycerol; Increase the activity of CPT-1α and ACC; Reduce the content of NEFA and ALP</td>
<td>[107]</td>
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</table>

### Concluding Remarks

Dysregulation of hepatic lipid metabolism is one of the earliest events during the initiation of NAFLD. It is directly linked to the occurrence of insulin resistance and glucose metabolism impairment, although the exact causal and mechanistic relationship remains poorly understood. Theoretically, the dynamic imbalance between lipogenesis and lipolysis in the liver causes the deposition of lipid in hepatocytes. Therapeutic strategy that retard or reverses the NAFLD progression should at least ameliorate the fat accumulation, through either the reduction of lipogenesis or the enhancement of lipolysis, or both at the same time. Treatment or dietary supplementation with herbal derivatives against NAFLD receives increasing attention recently because these natural compounds have protective properties with minimal adverse effects, when administered in a reasonable dose. The proposed lipid-rebalancing mechanisms of key derivatives in recent studies have been summarized in Table 1. However, the lack of long-term clinical evaluation and mechanistic investigation (particularly at the molecular level) hinder the wide application of herbal derivatives in the daily prevention of fatty liver diseases. Future studies should focus on these aspects to further expand the therapeutic application against NAFLD.
References


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