The Impacts of Herbal Medicines and Natural Products on Regulating the Hepatic Lipid Metabolism

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The dysregulation of hepatic lipid metabolism is one of the hallmarks in many liver diseases including alcoholic liver diseases (ALD) and non-alcoholic fatty liver diseases (NAFLD). Hepatic inflammation, lipoperoxidative stress as well as the imbalance between lipid availability and lipid disposal, are direct causes of liver steatosis. The application of herbal medicines with anti-oxidative stress and lipid-balancing properties has been extensively attempted as pharmaceutical intervention for liver disorders in experimental and clinical studies. Although the molecular mechanisms underlying their hepatoprotective effects warrant further exploration, increasing evidence demonstrated that many herbal medicines are involved in regulating lipid accumulation processes including hepatic lipolytic and lipogenic pathways, such as mitochondrial and peroxisomal β-oxidation, the secretion of very low density lipoprotein (VLDL), the non-esterified fatty acid (NEFA) uptake, and some vital hepatic lipogenic enzymes. Therefore, in this review, the pathways or crucial mediators participated in the dysregulation of hepatic lipid metabolism are systematically summarized, followed by the current evidences and advances in the positive impacts of herbal medicines and natural products on the lipid metabolism pathways are detailed. Furthermore, several herbal formulas, herbs or herbal derivatives, such as Erchen Dection, Danshen, resveratrol, and berberine, which have been extensively studied for their promising potential in mediating lipid metabolism, are particularly highlighted in this review.

Keywords: herbal medicines, natural products, lipid metabolism, fatty liver, lipolysis, lipogenesis

INTRODUCTION

Generally, liver regulates lipid metabolism by three major processes: (1) uptake free fatty acids from circulation, and de novo fatty acid synthesis (FAS); (2) lipid storage, including converting fatty acids into triglyceride (TG) and other lipid droplets, which are subsequently exported to adipose tissue or stored in liver; and (3) lipid consumption, including lipolysis, β-oxidation, and the generation of lipoproteins (Reddy and Rao, 2006; Musso et al., 2009; Ponziani et al., 2015; Mato et al., 2019). These processes are presented in Figure 1. Correct control of lipid level is critical for cellular and organismal homeostasis, while interferences with the lipogenic pathways are accompanied with a variety of metabolic syndromes. The disorders of lipid metabolism, such as decreased β-oxidation,
enhanced lipolysis, and secretion of very low-density lipoprotein (VLDL), as well as altered pathways involved in the FAS, drive the accumulation of lipid droplets into the hepatocytes, eventually leading to the development of hepatic steatosis, which is a common pathological feature in various liver diseases (Reddy and Rao, 2006; Nguyen et al., 2008; Tessari et al., 2009; Perla et al., 2017).

The most prevalent liver diseases resulting from lipid metabolism disorder are alcoholic and non-alcoholic fatty liver diseases. Except difference in alcohol consumption, alcoholic and non-alcoholic fatty liver diseases show similar pathological process, which is characterized by long-term excessive fat accumulation in the liver (Younossi, 2019). They represent a wide range of liver injury, from simple fatty liver through steatosis with necrosis and inflammation to fibrosis and cirrhosis (Lomonaco et al., 2013; Heeboll et al., 2018). In particular, non-alcoholic fatty liver diseases (NAFLD), as the metabolic diseases induced by obesity and type 2 diabetes mellitus, are the second leading causes of death globally, becoming a heavy economic burden in many countries due to the high prevalence (Albhaisi and Sanyal, 2018; Al-Dayyat et al., 2018). Since inordinate lipid metabolism is intensively involved in fatty liver diseases progression, reducing lipid accumulation is a major target of development of pharmaceutical agents for various liver diseases (Ipsen et al., 2018). Simvastatin has been used as lipid-lowering drug in patients with hyperlipidemia (Aronow, 2006). However, it shows side effects, such as constipation headaches, nausea, myopathy, elevated blood sugar, and even liver damage. As a matter of fact, there is currently no satisfying therapeutic drug for fatty liver diseases (Issa et al., 2018; Moctezuma-Velazquez, 2018).

Over the past decades, due to the positive efficacy and minimal side effects, herbal medicines, and natural products have obtained increasing attention as alternative therapeutic agents for liver disorders and dyslipidemia (Xiao et al., 2013; Yao et al., 2016; Liu Q. et al., 2017). Growing evidence from preclinical studies suggests that many herbs and isolated compounds could inhibit the progression of hepatic steatosis (Dong et al., 2012; Liu Z. L. et al., 2013). A variety of mechanisms have been demonstrated to be implicated in preventing hepatic steatosis, including reducing lipogenesis, enhancing β-oxidation, increasing insulin sensitivity, suppressing oxidative stress, and inhibiting activation of inflammatory pathways (Dong et al., 2012; Yao et al., 2016). In recent studies, sterol regulatory element-binding protein 1c (SREBP-1c), peroxisome proliferator activated receptor α (PPARα), AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) signaling pathways have been highlighted as crucial molecular targets of action mechanisms by which herbal medicines regulate hepatic lipid metabolism (Liu Z. L. et al., 2013). In this review, herbal medicines involved in regulating hepatic lipolytic and lipogenic pathways, such as mitochondrial and peroxisomal β-oxidation, the secretion of very low-density lipoprotein (VLDL), the non-esterified fatty acid (NEFA) uptake, and some vital hepatic lipogenic enzymes are summarized. Current clinical evidences and meta-analysis in the positive impacts of herbal medicines on the hepatic lipid metabolism pathways have also been reviewed. Furthermore, several herbal formulae, herbs or herbal derivatives, such as Erchen Dection, Danshen, resveratrol, and berberine which have been extensively studied for their promising potential in mediating lipid metabolism, are particularly highlighted in this review. This review aims to update and summarize current evidence from laboratory and clinic studies to provide alternative and complementary medical therapies with the regulatory property of hepatic lipid metabolism to current pharmaceuticals for the treatment of liver diseases.
HERBAL MEDICINES AND NATURAL PRODUCTS REGULATE ON THE HEPATIC LIPID METABOLISM PATHWAYS

Increasing evidence indicated that many herbs, natural products, and their derived compounds could inhibit the progression of hepatic steatosis. A variety of mechanisms have been demonstrated to be implicated in preventing hepatic steatosis and modulating lipid metabolism by herbs, including anti-oxidative stress, anti-inflammation, reducing hepatocyte fatty acid uptake and trafficking, reducing hepatic de novo lipogenesis, increasing lipolysis, induction of lipophagy, enhancing fatty acid β-oxidation. In particular, SREBP-1c, PPARγ, AMPK, and SIRT1 signaling pathways have been highlighted as crucial molecular targets of action mechanisms by which herbal medicines regulate hepatic lipid metabolism. In Table 1, we reviewed the effects and mechanisms of herbs and some natural products on fatty liver diseases from recent studies. In the following section, we will discuss herbs that attenuate hepatic steatosis via reducing hepatocyte fatty acid uptake and trafficking, reducing hepatic de novo lipogenesis, increasing lipolysis, induction of lipophagy, and enhancing fatty acid β-oxidation in detail.

Reducing Hepatocyte Fatty Acid Uptake and Trafficking

Nonesterified fatty acids (NEFAs) and glycerol are generated and released from adipose tissue via lipolysis (Kawano and Cohen, 2013). Then NEFAs enter into hepatocytes principally through CD36, and fatty acid transports (FATPs) (Kawano and Cohen, 2013). Several mediators have been demonstrated to play a role in regulating CD36 and FATPs, such as pregnane X receptor (PXR), and several mediators have been demonstrated to play a role in regulating CD36 and FATPs, such as pregnane X receptor (PXR), which impact the hepatocyte fatty acid uptake. Increasing evidence has shown that a variety of herbs and natural compounds attenuate hepatic steatosis via modulating genes for fatty acid uptake.

Scutellaria, one of the Traditional Chinese Medicines (TCM) used for liver diseases and diabetes, was found to reduce insulin-dependent lipid accumulation and the mRNA expression of CD36 in HepG2 cells treated with palmitic acid (Luan et al., 2019). Several other TCM and isolated compounds, babaodan, licorice extract, polyphenol-enriched fraction from Herba Erigerontis, and magnesiuim lisosphemate B, reduced hepatic CD36 expression in mice fed with High Fat Diet (HFD) (Wu and Wang, 2012; Wang et al., 2016; Sheng et al., 2019). Dansameum reduced the expression level of CD36 in liver of apolipoprotein E-Knockout mice with NAFLD (Ahn et al., 2019). In another mice model of NAFLD induced by high-fat and high-cholesterol diet, gypenosides which are a type of TCM extracted from plants downregulated CD36 level in the liver, alleviating the progression of hepatic steatosis (Huang et al., 2019). Berberine attenuated fat accumulation in the liver partially via suppressing the expression of FATP gene in HFD-fed mice (Zhou et al., 2019).

Reducing Hepatic De Novo Lipogenesis

De novo lipogenesis in the liver is tightly controlled by metabolic hormones such as insulin, and glucose level (Wang Y. et al., 2015). In the normal physiological status, high level of glucose promotes the secretion of insulin, activates carbohydrate-responsive element-binding protein (ChREBP), and meanwhile, provides substrate to facilitate lipogenesis in the liver (Wang Y. et al., 2015). In terms of insulin, it activates sterol regulatory element-binding protein 1c (SREBP-1c) to up-regulate lipogenic enzymes, and then promotes de novo lipogenesis (Eissing et al., 2013; Chao et al., 2019). Figure 2 shows the overview of lipogenesis in hepatocytes. Herbs and isolated natural compounds have been demonstrated by animal studies and in vitro studies to alleviate hepatic steatosis by ChREBP pathway and insulin-SREBP-1c pathway, as well as other factors, such as AMPK, PPARγ, SIRT1, inflammatory cytokines, immuno-modulation, and microRNAs. We summarized medicinal herbs and isolated natural compounds from recent literatures with the effects of reducing hepatic lipogenesis in Table 2 and discussed some representative studies in detail as following.

Magnolia officinalis Rehder & E.H.Wilson, Houptuyinia cordata Thunb., 3-Caffeoyl, 4-dihydrocaffeoylquinic acid from Salicornia europaea L., puerarin and four kinds metabolites of berberine attenuated lipid accumulation in HepG2 cells in vitro via down-regulation of lipogenesis gene expressions through activation of the AMPK signaling pathway (Cao et al., 2013) (Pil Hwang et al., 2013; Kang and Koppula, 2014). Gyeongshingangjeewhan 18 (an herbal drug composed of Laminaria japonica, Rheum palmatum, and Ephedra sinica), Herbal Formula HT048 (Citrus unshiu and Crataegus pinnatifida), Fructus Xanthii (Xanthium sibiricum Patr.), Lycium barbarum polysaccharide, Jatrorrhizine hydrochloride, oxyresveratrol, and alisol A isolated from Rhizoma alismatis (Oriental Waterplantain Tuber., decreased hepatic steatosis and inflammation effect of Gambigyeongsinhwan in Otsuka Long-Evans Tokushima fatty rats and HepG2 cells (Yoon et al., 2017).

Glycycoumarin, a representative of coumarin compounds isolated from licorice, and Alisol B 23-acetate exert ability of reducing hepatic lipogenesis in methionine-choline-deficient (MCD) diet-fed mice (Meng et al., 2017; Zhang E. et al., 2019). MCD diet is a classical dietary model of non-alcoholic steatohepatitis. With the lack of methionine and choline and high sucrose (40%) and fat (10%), impaired hepatic mitochondrial β-oxidation and very low-density lipoprotein (VLDL) synthesis are observed in mice (Ibrahim et al., 2016). Glycycoumarin activated AMPK signaling pathway to reduce lipogenesis. Alisol B 23-acetate, a natural triterpenoid derived from TCM Rhizoma alismatis (Oriental Waterplantain Tuber.), decreased hepatic
TABLE 1 | The effects and mechanisms of herbs and some natural products on fatty liver diseases.

| Herbs or Natural products | Model | Effects | Mechanisms | References |
|---------------------------|-------|---------|------------|------------|
| Rosmarinus officinalis Linn. | Orotic acid induced NAFLD model in rats | Reduced the levels of hepatic TG, TC, FFA and improved cell hypertrophy, vacuolation, and cell necrosis in the liver | ↑ Phosphorylation of AMPK and ↓ SREBP-1c cracking into the nucleus, following ↓ FAS | (Wang et al., 2019) |
| Chinese Herbal Formula (CHFG3, composition confidentiality) | HFD induced NAFLD model in mice; AML12 cells treated with palmitic acid in vitro | Reduced hepatic steatosis | ↓ lipogenesis via down-regulating the expression of SREBF1, Fasn, and Acaca, ↓ lipid accumulation | (Cui et al., 2019) |
| Dachahu Decoction (Bupleuri Radix, Scutellaria baicalensis Georgi, Pinellia ternata, Paonia lactiflora, Citrus trifoliata, Rheum rhabarbarum, Zingiber officinale, Ziziphus jujuba Mill) | High-fat high-fructose diet induced NAFLD model in rats | Reduced the levels of elevated liver coefficient, serum TG, TC, LDL, AST, and ALT, blood glucose, plasma endotoxin, reduced TG, TGF-β, NF-κB, and TLR4 in nucleus, following ↓ FAS | ↓ lipogenesis, down-regulating the expression of SREBF1, Fasn, and Acaca, ↓ lipid accumulation | (Cui et al., 2019) |
| Leaves of Aloysia citrodora Paláu (syn. Lippia triphylla) | KK-Ay mice | Improved hepatic lipid metabolism via activating AMPK | mRNA expression of carnitine palmitoyl transferase-1 and uncoupling protein-2 respectively, ↓ expression of caspase 9, caspase 3 and Bax in hepatocytes, ↑ expression of Bcl-2 in hepatocytes and cytochrome c in mitochondria | (Zhang Y., et al., 2019) |
| Polygonatum kingianum | HFD induced NAFLD model in rats | ↓ ALT, AST, TC, LDL in serum, and hepatic TC and TG | ↓ body weight gain | (Yang J.M. et al., 2019) |
| Bangouingtongsieng-san (Bofutsushosan) | HFD induced NAFLD model in C57BL/6J mice | Ameliorated dyslipidemia and hepatic steatosis, reduced body weight gain | Altered transcriptional changes in the liver, ↓ mitochondrial oxidative phosphorylation-related genes in the liver, ↓ hepatic fibrosis-related transcriptome | (Choi et al., 2019) |
| Thymbra spicata L. extracts | fructose-fed mice | Ameliorated lipid accumulation, oxidative stress and inflammation, reduced hepatic steatosis | Preventing endothelium dysfunction | (Khall et al., 2019) |
| Swertiamarin | fructose-fed mice | Lowed levels of serum glucose, TG, uric acid, ALT, AST, alleviation of hepatic ballooning degeneration and steatosis | ↓ SREBP-1, FAS and acetyl-CoA carboxylase 1 (ACC1) in liver | (Yang Y., et al., 2019) |
| Si He Decoction (Zingiber officinale., Cyperus rotundus L., Lilium, Lindera aggregate, Salvia miltiorrhiza, Santalum album, Amomum villosum, Typha angustifolia L., Troglotopotes xanthipes Miene) | HFD induced NAFLD model in rats | Improved liver pathological conditions | ↓ expression level of TNF-alpha and IL-6, ↓ visfatin, adiponectin, leptin and resistin, targeting adipokines | (Sun et al., 2019) |
| Modified Longdan Xiegan Tang (composed of Scutellaria baicalensis Gepri, Gardenia jasminoides, Adenophora capillaris, Akebia quinata, Plantago asiatica, Angelica sinesis, Rehmannia glutinosa, Alisma plantago-aquatica, Bupleurum gabritamum, and Glycyrrhiza uralensis) | Olanzapine- and Oil Red O-stained area | ↓ TG, cell vacuolar degeneration and Oxidized LDL | Regulating hepatic de novo lipogenesis and fatty acid β-oxidation-associated Gene expression mediated by SREBP-1c, PPARα and AMPKα | (Fen et al., 2019) |
| LongShengZhi Capsule | apoE-Deficient Mice | Reduced atherosclerosis | ↓ lipogenic and cholesterol synthetic genes while activating expression of triglyceride catabolism genes | (Ma et al., 2019) |
| Thymoquinone | Hypothyroidism with NAFLD rats | Reduced steatosis and lobular inflammation | ↓ antioxidant CAT gene | (Ayub et al., 2019) |
| Monomer Hairy Calycosin | NAFLD rats | Control the lipid peroxidation, and reduce the levels of serum TNF-alpha, IL-6, MDA and FFA, improve the steatosis and inflammation of liver tissue | ↓ CYP2E1, ↓ apoptosis of hepatocytes | (Liu X. et al., 2019) |

(Continued)
| Herbs or Natural products | Model | Effects | Mechanisms | References |
|--------------------------|-------|---------|------------|------------|
| **TABLE 1** | | | | Continued |
| Hongqi Jiangzhi Formula (Astragali Radix, Red yeast rice, Nelumbinis Foliun, Curcumae Longae Rhizoma, Lych Fructus, Magnolae Officinalis Cortex, Artemisiae Scopariae Herba) | HFD induced NAFLD model in rats | Reduced lipid accumulation | The expression of NF-kappa B through TLR4 downstream signaling pathways | Liang et al., 2019 |
| | NAFLD in animal and PA-treated hepatocytes in vitro | Showed anti-steatotic effects | Droplet degradation via autophagy through the mTOR signaling | Zheng et al., 2018 |
| Jiang Zhi Granule (Herba Gynostemmatis, Folium Nelumbinis, Radix Salviae, Rhizoma Polygoni Cuspidati, and Herba Artemisiae Scopariae) | NAFLD in rats | Improved lipid accumulation | Reversed the DNA methylation at the PPAR-alpha gene | Li Y. Y. et al., 2018 |
| Curcumin | Steatotic hepatocyte model in vitro and NAFLD rat models | Improved lipid accumulation | | |
| Samjunghwan Herbal Formula (Morus Fructus, Lycium chinensis Miller, Atractylodis Rhizoma) | HepG2 Cells and OLETF Rats | ↓Body weights, and visceral adipose tissue (VAT) weights, AST and ALT levels, | ↓MGGOR, SREBP, and ACC, and ↓AMPK and LDLR gene expressions levels. | (Ansari et al., 2018) |
| Oxyresveratrol | NAFLD in mice | Altered NAFLD | ↓LXR alpha agonists-mediated SREBP-1c induction and expression of the lipogenic genes, ↑mRNA of fatty acid beta-oxidation-related genes in hepatocytes; induced AMPK activation, helped inhibit SREBP-1c using compound C. | Lee et al., 2018 |
| Sedum sarmentosum Bunge extract | Tilapia fatty liver model | Restored the changes to feed coefficient, immune capacity, and pathological characters | Altered expression of genes in the lipid metabolic process, metabolic process, and oxidation-reduction process. Our results suggest that disorders of the PPAR and pS3 signaling pathways | Huang et al., 2018 |
| Berberine and curcumin | HFD induced NAFLD model in rats | | | |
| Gegen Qinlian decoction (Pueraria laci Crab, Scutellaria baicalensis Georgi, Coptis chinensis Franch., and Glycyrrhiza uralensis Fisch.) and resveratrol | Rat model of HFD-induced NAFLD | Restored lipid metabolism and inflammatory and histological abnormalities | Triggering the Sirt1 pathway | Guo et al., 2017 |
| Gegengnajin Decoction | Rat model of HFD-induced NAFLD and HepG2 | Supress inflammation and regulate lipid | Improving PPAR-γ | Wang Y. L. et al., 2015 |
| Lingguizhugan Decoction (Poria, Ramulus Cinnamomi, Rhizoma Atractylodis Macrocephalae, and Radix Glycyrrhizae) | Rat model of HFD-induced NAFLD | Attenuated phenotypic characteristics of NAFLD | By affecting insulin resistance and lipid metabolism related pathways (e.g., PkdK-Act, AMPK); activating cholesterol secreto; increasing serum thyroid hormone levels, improving beta-oxidation (via modulation of TR beta 1 and CPT1A expression), metabolism and transport (through modulation of SREBP-1c, ACSL and ApoB100 expression) of fatty acid. | Liu X. et al., 2017; Yang et al., 2017; Zhu et al., 2017 |
| Chinese herb extract, QSH-X (Bupleurum falcatum, Salvia miltiorrhiza, rhubarb, lotus leaf, capillary Artemisia, rhizome polygoni cuspidate and gynostemma pentaphyllum) | High-fat and high-sugar diet-induced NAFLD in rat | ↓Body weight, liver index, and serum levels of AST, ALT and TG; and increased the serum level of adiponectin | Promoting the expression of HMW APN and DsbA-L, which may have been induced by inhibiting the activation and expression of FOXO1 in adipocytes | Liu X. et al., 2017 |
| Quashi Huayu Decoction (Herba Artemisiae capillaris, Polygonum cuspidatum, Hypericum japonicum Thumb, Gardenia, and Rhizoma Curcumae Longae) | NAFLD rats | Attenuated phenotypic characteristics of NAFLD | ↑Hepatic anti-oxidative mechanism, ↑Hepatic lipid synthesis, and promoted the regulatory T cell inducing microbiota in the gut. | Feng et al., 2017 |

(Continued)
| Herbs or Natural products                                      | Model                              | Effects                                      | Mechanisms                                                                                           | References      |
|---------------------------------------------------------------|------------------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------|
| Rhododendron oldhamii Maxim. leaf extract                     | HepG2 cells and HFD-fed mice       | Improves fatty liver syndrome                | Increasing lipid oxidation and decreasing the lipogenesis pathway                                    | (Liu Y. L. et al., 2017) |
| Herbal Formula HT048 (Crataegus pinnatifida leaf and Citrus unshiu peel extracts.) | HFD-fed rats                        | Attenuates Diet-Induced Obesity              | Genes involved in lipogenesis, gluconeogenesis, and adipogenesis, β-oxidation genes, CAT and sterol carrier protein2 (SCP2), the expression of lipid metabolism related genes-Isopase member C (LIPC) and PPAR-γ | (Lee Y. H. et al., 2016) |
| Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. | HFD-induced hyperlipidemic mice    | ↓TC and TG in the livers                     | ↓CAT and sterol carrier protein2 (SCP2), ↑the expression of lipid metabolism related genes-Isopase member C (LIPC) and PPAR-γ | (Lu et al., 2016) |
| Daisaikoto (Supleuri Radix, Scutellaria baicalensis Georgii, Pinellia ternate, Paeonia lactiflora, Citrus trifoliata, Rheum rhabarbarum, Zingiber officinalis, Ziziphus jujuba Mill) | Diabetic fatty liver rats induced by a high-fat diet and streptozotocin (STZ) | Reversing dyslipidemia and insulin resistance | Regulating expressions of SIRT1 and NF-κB | (Qian et al., 2016) |
| Herbal Formula HT048 (Crataegus pinnatifida leaf and Citrus unshiu peel extracts.) | HFD-fed rats                        | Inhibited lipid accumulation                | Gene expressions involved in lipogenesis and related regulators                                   | (Park et al., 2015) |
| Hawthorn (Crataegus) leaf flavonoids                          | HFD-fed mice                        | Alleviated NAFLD                            | Enhancing the adiponectin/AMPK pathway                                                            | (Li et al., 2015) |
| Herbal SGR Formula (Semen Hoveniae extract, Ginkgo biloba extract, and Rosa roxburghii Tratt extract) | Acute ethanol-induced liver steatosis in mice | Inhibited acute ethanol-induced liver steatosis, ↓serum and hepatic TG level, and improved classic histopathological changes | ↓Gene expression related to lipid homeostasis in liver, modulating the lipolysis-lipogenesis balance, ↑AMPK, ↑SREBP-1c, ACC, and FAS, ↑sirtuin I and deletion of malonyl-CoA, ↑fatty acid oxidation | (Li Y. et al., 2014) |
| Nitraria retusa (Forsk.) Asch. ethanolic extract               | db/db mice model                    | Increases in body and fat mass weight, ↓TG and LDL-C levels | ↑Expression of FAS, ACC, ↑carnitine palmitoyltransferase (CPT)                                   | (Li W. et al., 2014) |
| 14-Deoxyandrographolide                                       | Ethanol-induced hepatosteatosis in rats | ↑TG, TC, and LDL-C levels and ↓HDL-C level | ↓Expression of FAS, ACC, ↑carnitine palmitoyltransferase (CPT)                                   | (Li Y. et al., 2014) |
| Total Alkaloids in Rubus aiaefolius Poir                      | Modified HFD-fed rats               | Improved body compositions and lipid metabolic profiles, ↓hepatic triglyceride level | ↓SREBP-1c, ↑AMPK activation                                                                      | (Liu L. et al., 2013) |
| Lycium barbarum L. polysaccharide                             | HFD-fed mice                        | Diminished fructose-induced fatty liver      | ↓SREBP-1/1c mRNA and nuclear protein                                                              | (Liu L. et al., 2013) |
| Salacia oblonga Wall. ex Wight & Arn. root                    | fructose-induced fatty liver in rats| ↓TG, AST, ALT, ALP, and total bilirubin      | Anti-oxidative stress                                                                             | (Park et al., 2015) |
| Chunggong extract (Artemisia capillaries Thunberg. Trionyx sinensis | methionine- and choline-deficient (MCD) diet | ↓TG, free cholesterol (FC), cholesterol ester (CE) and TG in liver | ↑mRNA abundance of cholesterol 7 alpha-hydroxylase A1 (CYP7A1) and 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR). | (Zhang et al., 2013) |
| Celastrus orbiculatus Thunb.                                  | HFD-induced NAFLD in guinea pigs   | ↓TC, free cholesterol (FC), cholesterol ester (CE) and TG in liver | ↓SREBF1 and ↑PPAR-α                                                                            | (Shi et al., 2013) |
| Oxytetrine                                                    | NAFLD rats fed with high fructose diet | ↓Body weight gain, liver weight, liver index, dyslipidemia, and TG, ↓ liver lipid accumulation. | ↑ mRNA abundance of cholesterol 7 alpha-hydroxylase A1 (CYP7A1) and 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR). | (Shi et al., 2013) |
lipogenesis via FXR-dependent pathway. It decreased hepatic levels of SREBP-1c, FAS, ACC1 and SCD1, and promoted lipid metabolism via inducing PPAR α, CPT1 α, ACADS, and LPL (Meng et al., 2017). In an apolipoprotein E-knockout mice model, Dansameum (Salvia miltiorrhiza root), a kind of Korean polyherbal medicine, reduced hepatic lipogenesis, and inflammation via regulating PPAR-γ, SREBP-1c, FAS, ACC1, and CD36 (Ahn et al., 2019).

Dangguiliuhuang Decoction, a TCM formula composed of radix rehmanniae (root of Rehmannia Glutinosa), angelica (Angelica acutiloba Siebold et Zucc.), Coptis chinensis Franch., Radix Rehmanniae Praeparata (Rehmannia root), Astragalus propinquus (the root of astragalus membranaceus), Chinese skullcap (Scutellaria baicalensis) and Phellodendron amurense (Phellodendron chinense Schneid.), is used for the treatment of autoimmune diseases and diabetes (Cao et al., 2017; Cao et al., 2018). In a study of ob/ob mice model, it normalized glucose and insulin level, diminished fat accumulation and lipogenesis, increased the expression of adiponectin, and promoted glucose uptake (Cao et al., 2017). It showed modulation abilities on inflammation and immune response. Dangguiliuhuang Decoction (composition as listed above) promoted the shift of pro-inflammatory to anti-inflammatory cytokines. Furthermore, it decreased T cells proliferation while increased regulatory T cells (Tregs) differentiation, reduced dendritic cells (DCs) maturation and secretion of IL-12p70 cytokine, decreased DCs-stimulated T cells proliferation, and promoted the interaction of DCs with Tregs. In adipocytes and hepatocytes as well as DCs and T cells, Dangguiliuhuang Decoction treatment altered PI3K/Akt signaling pathway and increased PPAR-γ expression, indicating the ameliorated glucose and lipid metabolism (Cao et al., 2017).

MicroRNA (miR), a small non-coding RNA molecule, has been recently demonstrated to play a role in mediating the anti-hepatic steatosis effects of natural compounds derived from herbs. Berberine reduced steatosis in MIHA and HepG2 cells by mechanism associating with up-regulation of miR-373, which decreased its mRNA level target gene AKT serine/threonine kinase 1 (AKT1), resulting in the suppression of AKT-mTOR-S6K signaling pathway in hepatocytes (Cao et al., 2018). Genipin reduced HFD-induced hyperlipidemia and hepatic lipid accumulation in mice via increasing the expression levels of miR-142a-5p, which bound to 3’-untranslated region of SREBP-1c, thus leading to the inhibition of lipogenesis (Zhong et al., 2018).

**Increasing Lipolysis**

Lipolysis is the catabolic process of hydrolytic cleavage of ester bonds in TG, leading to the production of fatty acids and glycerol, which could be further utilized for β-oxidation and subsequent ATP generation (Lass et al., 2011). It predominantly occurs in adipose tissues, but also in the liver, with different physiological functions. Dietary fat is digested into the gut lymphatic system as chylomicrons, which arrives at the liver through the circulation and release NEFAs through lipolysis which mediated mainly by lipoprotein lipase (LPL) (Rui, 2014). Other lipolytic enzymes contributing to hepatic TG metabolism include adiponutrin/
patatin-like phospholipase domain containing 3 (PNPLA3) (Kumashiro et al., 2013), lysosomal acid lipase (LAL) (Quiroga and Lehner, 2018), arylacetamide deacetylase (Lo et al., 2010), hepatic lipase (HL) (Chatterjee and Sparks, 2011) and some members of the carboxylesterase family. In adipose tissue, inhibition of lipolysis improves glucose metabolism and insulin sensitivity, whereas in liver tissue, increasing lipolysis facilitates the attenuation of hepatic steatosis.

As far as now, limited herbs were found to show regulatory effect on hepatic lipolysis. 

Lavatera critica (Cornish mallow), a green leafy vegetable, attenuated hepatic lipid accumulation induced by HFD via reversing lipolysis genes acetyl-CoA carboxylase (Veeramani et al., 2017). 

Nitraria retusa (Forssk.) Asch. ethanolic extract modulated the lipolysis-lipogenesis balance in the liver of db/db mice (Veeramani et al., 2017). 

Caffeic acid upregulated the phosphorylation of AMPK and its primary downstream targeting enzyme, acetyl-CoA carboxylase, to promote the lipolysis in HepG2 cells with oleic acid administration (Liao et al., 2014). 

Polygonatum stenophyllum (PS) Maxim. rhizome showed efficacy on menopausal obesity by activating lipolysis-related genes including hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) (Lee J. E. et al., 2016). 

Mulberry (Fructus Mori) water extracts promoted hepatic lipolysis and protected liver from steatosis in obesity (Peng et al., 2011). More herbs or natural compounds exerted effects on lipolysis in adipose tissues and attenuated hepatic steatosis via liver-adipose tissue crosstalk, which are not going to be discussed in detail here.

**Induction of Lipophagy**

In addition to lipolysis, lipid breakdown can also be accessed via lipophagy, a special kind of autophagy to degrade lipid droplets (Singh and Cuervo, 2012; Kounakis et al., 2019). It is a process that the double membrane wraps lipid droplets and sends them to lysosomes to form autolysosomes for degradation of excessive lipid droplets deposited in cells (Liu and Czaja, 2016; Ward et al., 2016). It plays a vital role in maintaining the cellular steady state.

During the early stage of NAFLD, lipophagy is activated in response to acute increase in lipid availability, thus reduce lipid deposition (Czaja, 2016; Ipsen et al., 2018). However, in the condition of such as long-lasting high fat dieting, hepatic lipophagy is impaired when lipids are sustained overwhelmed (Kwanten et al., 2014; Czaja, 2016; Ipsen et al., 2018). Growing evidence raised from recent studies indicate that lipophagy is partially suppressed in patients and animal models of NAFLD and restoring lipophagy may slow the progression of hepatic steatosis. Lipophagy could be activated by various approaches, such as mTOR and AMPK-targeting agents. Glycycoumarin, a representative of coumarin compounds isolated from licorice, mitigated hepatic steatosis partially through AMPK-mediated lipophagy in a murine model of NAFLD induced by MCD diet (Zhang et al., 2016). Dioscin is a saponin extracted and isolated from Polygonatum zanlanscianense Pamp. It has been proposed as a healthcare product against hepatic fibrosis with remarkable ability to inhibit the expression of p-mTOR/mTOR level and sequentially promote autophagy (Xu et al., 2017). In another study, Bergamot polyphenol fraction prevents NAFLD via stimulation of lipophagy in cafeteria diet induced rat model of metabolic syndrome. The increased levels of LC3 and Beclin 1, and concomitant reduction of SQSTM1/p62 proved the promoted lipophagy with the treatment of Bergamot polyphenol fraction (Parafati et al., 2015). Increasing number of herbs or natural products have been demonstrated to exert significant effects on regulating lipophagy in the liver. Current understanding of mechanisms associated with autophagy/lipophagy of herbal medicines and natural products in preventing and treating NAFLD has been well reviewed in Zhang et al. (2018), which could be referred for further reading.

In alcoholic liver diseases (ALD), upon acute consumption of alcohol, lipophagy is activated in hepatocytes, serving as a defensive mechanism against injury to steatosis (Yan et al., 2019). However, it is impaired by chronic alcohol exposure, which is likely due to the activation of mTOR signaling and decreased lysosomal biogenesis in hepatocytes (Kounakis et al., 2019; Yang L. et al., 2019). There are...
| Herbs or compounds                                                                 | Model                        | Effect                                | Mechanism                                                                 | References                                      |
|----------------------------------------------------------------------------------|------------------------------|---------------------------------------|---------------------------------------------------------------------------|------------------------------------------------|
| Dansaumeum (Salvia miltiorrhiza root)                                             | Apolipoprotein E-Knockout mice | Reduced hepatic lipogenesis and inflammation | Regulating LXR-α, PPAR-γ, SREBP-1, FAS, ACC1, and CD36                | (Ahn et al., 2019)                              |
| Alisol A                                                                         | HFD-induced obese mice       | Reduced hepatic steatosis and improved liver function | AMPK/ACC/SREBP-1c pathway                                                | (Ho et al., 2019)                               |
| Ling-gui-zhu-gan decoction (Poria cocos, Ramulus cinnamom, Atractylidis macrocephalae Rhizoma, and Radix glycyrrhiza) | HFD-fed rats                 | Reduced hepatic glycogen              | Inhibited the activity of ACC, SREBP-1c and HMGCR, via inhibiting PPP1R3C targeting pathways | (Dang et al., 2019)                             |
| Salvianolic acids                                                                | Ovariectomized rats          | Reduced body weight gain and attenuated | Blocking STAT-3/SREBP1 signaling                                         | (Dang et al., 2019)                             |
| Gyeongshingangjeewhan 18 (Laminaria japonica, Rheum palmatum, and Ephedra sina)   | HFD-induced obese mice       | Attenuated visceral obesity and NAFLD | Down-regulated lipogenesis-related genes                                 | (Lim et al., 2018)                              |
| Cordycepin                                                                       | Oleic acid-induced mouse FL808 hepatocytes | Attenuated lipid accumulation | Activating AMPK and regulating mitochondrial function                     | (Lee et al., 2018)                              |
| Oxyresveratrol                                                                   | HFD-fed mice                 | Ameliorated NAFLD                     | AMPK/SREBP-1c pathway                                                    | (Lee et al., 2018)                              |
| Berberine                                                                        | MIHA and HepG2 cells         | Reduced hepatosteatosis               | Up-regulation of mR-373 reduced mRNA level target gene AKT1, leading to inhibition of AKT-mTOR-S6K signaling pathway in hepatocytes | (Li C. H. et al., 2018)                         |
| Genipin                                                                          | HFD-fed mice                 | Increased expression of mR-142a-5p, which bound to 3 untranslated region of SREBP-1c | Modulation of lipogenic transcription factors SREBP-1c, PPAR-γ and ChREBP-α | (Zhang et al., 2018)                            |
| Gangjihwan (Ephedra intermedia Schrenk & C.A.Mey., Lithospermum erythrorhizon Siebold & Zucc., and Rheum palmatum L.) | HFD-induced obese mice | Inhibited fat accumulation | Increased mRNA levels of fatty acid oxidation genes and decreased mRNA levels of genes for lipogenesis | (Roh et al., 2017)                              |
| Gangjihwan (Ephedra intermedia Schrenk & C.A.Mey., Lithospermum erythrorhizon Siebold & Zucc., and Rheum palmatum L.) | HFD-fed CS7BL/6 J mice and HepG2 cells | Anti-obesity and anti-nonalcoholic steatohepatitis |Increased the expression levels of fatty acid oxidation and lipogenesis genes and decreased mRNA levels of genes for lipogenesis | (Yoon et al., 2017)                             |
| Dangguilihuang Decoction (root of Rehmannia glutinosa, Angelica acutiloba Siebold et Zucc., Coptis chinensis Franch., Radix Rehmanniae Praeparata, Astragalus propinquus, Scutellaria baicalensis, and Phellodendron chinense Schneid.) | ob/ob mice                   | Normalized glucose and insulin level, increased the expression of adiponectin, diminished fat accumulation and lipogenesis, and promoted glucose uptake | ↓ T cells, ↑ Tregs differentiation, ↓ DCs maturation, ↓ DCs-stimulated T cells proliferation and secretion of IL-12p70 cytokine, promoted the interaction of DCs with Tregs, changed P38/Akt signaling pathway and ↓ PPAR-γ | (Cao et al., 2017)                              |
| Glycyrruzarin                                                                     | MCD diet mice                | Prevented hepatic steatosis           | Activation of AMPK signaling pathway                                      | (Zhang et al., 2016)                            |
| Gambigyeongsinhwang (Curcuma longa, Alnus japonica, and Massa Medicata Fermentata) | Otsuka Long-Evans Tokushima fatty rats and HepG2 cells | Suppressed hepatic steatosis and obesity-related hepatic inflammation | ↓ mRNA levels of FAS, ACC1, ChREBP alpha, and SREBP-1c | (Lee et al., 2016)                              |
| Alisol B 23-acetate                                                              | MCD diet-fed mice            | ↓ ALT, AST, TG                        | FXR-dependent, ↓ hepatic lipogenesis through decreasing hepatic levels of SREBP-1c, FAS, ACC1 and SCD1 and ↓ lipid metabolism via inducing PPAR-α, CPT1 α, ACADS and LPL | (Meng et al., 2017)                             |
| Herbal Formula HT048 (Crataegus pinnatifida leaf and Citrus unshiu peel extracts) | HFD-fed obese rats           | Decreased obesity and insulin resistance | ↓ Genes involved in lipogenesis                                         | (Lee Y. H. et al., 2016)                        |
| Jatrohzhine hydrochloride                                                         | HFD-induced obesity mouse model | Attenuated hyperlipidemia              | ↓ SREBP-1c and FAS, and induced PPAR- and CPT1A | (Yang et al., 2016)                             |
| Puerarin                                                                         | Oleic acid (OAT)-treated HepG2 cells | Ameliorated hepatic steatosis         | ↑ PPAR-α and AMPK signaling pathways, ↓ SREBP-1c and FAS expression      | (Kang et al., 2015)                             |
| Protopanaxatriol                                                                 | HFD-induced obesity (DIO) mice | Alleviated steatosis                  | Inhibition of PPAR-γ activity                                            | (Zhang et al., 2014)                            |
| Magnolia officinalis Rehder & E.H.Wilson                                         | HepG2 cells and mouse        | Attenuated TG biosynthesis            | Inhibition of SREBP-1c via AMPK phosphorylation                           | (Seo et al., 2014)                              |

(Continued)
TABLE 2 | Continued

| Herbs or compounds | Model | Effect | Mechanism | References |
|--------------------|-------|--------|-----------|------------|
| Lycium barbarum polysaccharide | normal FL83B hepatocytes, HFD-fed mice | Attenuate liver steatosis | ↓SREBP-1c expression via AMPK activation | (Li W. et al., 2014) |
| Houttuynia cordata Thunb. | HepG2 | Attenuates Lipid Accumulation | AMPK signaling | (Kang and Koppula, 2014) |
| Berberine metabolites | HepG2 | TG-lowering effects | ↓Lipopogenesis gene expressions through activation of the AMPK signaling pathway | (Cao et al., 2013) |
| 3-Caffeoyl, 4-dihydrocaffeoylquinic acid from Salicornia herbacea | HepG2 | Attenuated high glucose-induced hepatic lipogenesis | Prevented lipid accumulation by blocking the expression of SREBP-1c and FAS through LKB1/SIRT1 and AMPK activation | (Pil Hwang et al., 2013) |
| Fructus Xanthii (Xanthium strumarium) | HFD-fed rats | Attenuated hepatic steatosis | ↓The expression of lipogenic genes | (Li et al., 2013) |

† means increase and up-regulate and ↓ means decrease and down-regulate.

Growing number of herbs and natural products have been found to protect liver from injury induced by alcohol by mechanism of lipophagy stimulation. Corosolic acid, a compound derived from the leaves of *Langertiaemia speciosa* L. Pers., protected the liver from alcoholic-induced liver injury partially via restoring hepatic lipophagy due to mTORC1 suppression after AMPK activation (Guo et al., 2016). Another natural compound, quercitin, which is extensively found in many fruits and herbal plants, remarkably reversed the alcohol-induced blockade of TFEB nuclear localization, via restoring lysosome function and autophagic flux in livers of ethanol-fed C57BL6 mice (Li et al., 2019). Salvianolic acid A, a phenolic carboxylic acid extracted from *Salvia miltiorrhiza Bunge*, reduced hepatic steatosis induced by alcohol administration in rats. The action mechanism is attributed to enhanced autophagosome-lysosome fusion after restoring lysosomal cathepsin activities (Shi et al., 2018).

As a matter of fact, the field of lipophagy in liver diseases has yet to be fully developed. Its pathological role in different stages and circumstances of various liver disorders still needs to be revealed. Nevertheless, current studies concerning lipophagy have already provided new insights on lipid metabolism and energy homeostasis in the liver. It represents a promising path forward to the therapeutic of hepatic steatosis. Pharmacutic agents including herbs, natural products or compounds targeting lipophagy in the liver deserve to be further investigated in future basic and clinic researches.

**Enhancing Fatty Acid β-Oxidation**

Fatty acid could be oxidized by β-oxidation, α-oxidation, omega-oxidation, and peroxisomal oxidation, among which β-oxidation is the major type occurring in the mitochondria matrix (Wanders et al., 2015). In β-oxidation, two carbon subunits from fatty acids are removed repeatedly until the fatty acid carbon chain is fully degraded to form acetyl-CoA, which is further oxidized to carbon dioxide and H₂O in the tricarboxylic acid cycle (TCA) (Canbay et al., 2007). β-oxidation plays a vital role in hepatic lipid consumption. A variety of proteins and enzymes are involved in the process of mitochondrial fatty acid β-oxidation, such as plasma membrane fatty acid binding protein (FABPpm) (Furuhashi and Hotamisligil, 2008), fatty acid transport protein (FATP) (Ouali et al., 2000), carnitine acylcarnitine translocase (CACT) (Pierre et al., 2007), carnitine palmitoyltransferases 1 and 2 (CPT1/2), etc. (Bonnefont et al., 2004; Houten and Wanders, 2010). More importantly, mitochondrial fatty acid β-oxidation is regulated by both transcriptional and posttranscriptional mechanisms. Peroxisome proliferator-activated receptors (PPARs) are activated by fatty acids, having specific roles in physiology of different tissues (Yu et al., 2003; Lamichane et al., 2018). In liver, PPARα controls many genes involved in mitochondrial fatty acid β-oxidation (Lamichane et al., 2018). In terms of posttranscriptional mechanism, the inhibition of CPT1 by malonyl-CoA is a vital regulatory step. The levels of malonyl-CoA in hepatocytes are regulated via degradation induced by malonyl-CoA decarboxylase and via production by acetyl-CoA carboxylase (ACC) (Park et al., 2002). PPARs-mediated activation persuades transcription of malonyl-CoA decarboxylase, and phosphorylated AMPK inactivated ACC (Saha and Ruderman, 2003). They stimulate mitochondrial fatty acid β-oxidation by reducing malonyl-CoA levels. Additionally, peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC-1α) has also been regarded as a factor of posttranscriptional regulation of β-oxidation (Fernandez-Marcos and Auwerx, 2011). The activation of PGC-1α is mediated by AMPK via SIRT1-mediated deacetylation (Canto and Auwerx, 2009).

Many herbs and active compounds protect liver from steatosis via regulation of fatty acid β-oxidation. Herbacetin is a dietary flavonoid with plenty of pharmacological activities. Its anti-hyperglycemic and anti-hyperlipidemic properties was associated with up-regulation of CPT to enhanced β-oxidation and hepatic lipid metabolism (Veeramani et al., 2018). Acteoside, a major compound isolated from leaves of *Aloysia citriodora* Palau (syn. *Lippia triphylla*), promoted lipolysis and fatty acid oxidation by enhancing mRNA expression level of adipose triglyceride lipase (ATGL) and CPT-1, and thus improved hepatic lipid metabolism (Zhang Y. et al., 2019). Cordycepin enhanced β-oxidation and suppressed lipid accumulation via regulating AMPK pathway and mitochondrial fusion in hepatocytes (Uen et al., 2018).

In China, the modified Longdan Xiegan Tang (mLXT), composed of Scutellaria baicalnsis Geprgi, Gardenia jasminoides, Adenophora capillaris, Akebia quinata, Plantago asiatica, Angelica sinensis, Rehmannia glutinosa, Alisma plantago-aquatica, Bupleurum gibraltaricum, and Glycyrrhiza uralensis) has been used clinically for various liver diseases such as NAFLD. It was...
found to activate hepatic expression of PPAR α and its target genes associated with fatty acid β-oxidation (Ren et al., 2019). Babaodan, a TCM, up-regulated the expression of CPT-1 and PPAR α in liver of HFD-fed mice with NAFLD, leading to the enhanced β-oxidation (Sheng et al., 2019). Rosa rugosa Thunb., another TCM, is used for treatment of cardiovascular diseases and diabetes, hypertension, hyperlipidemia, and inflammation. R. rugosa flavonoids, the major components in R. rugosa Thunb., were observed to up-regulate the mRNA expression of PPAR α and its downstream gene of acyl-coenzyme A oxidase X (ACOX) in a mouse model of hypertriglyceridemia (Balyisaiti et al., 2019). Thereby, R. rugosa flavonoids could reduce TG in hepatocytes via rising β-oxidation. *Gynura procumbens* Merr., one of precious medicinal herbs of Asteraceae, up-regulated the mRNA expression of genes involved in β-oxidation, including PPAR α, CPT1 α, ACOX, fatty acid-binding proteins 5 (FABP5), stearoyl-coenzyme A desaturase-1 (SCD-1), glycerol-3-phosphate acyltransferase (mGPAT), microsomal triglyceride transfer protein (MTPP), to increase β-oxidation and efflux of fatty acids in liver of mice fed with MCD diet, and consequently decreased hepatic lipid accumulation (Liu Y. Y. et al., 2019). An herbal formula Gyeongshingangjeewhan 18 (GGEx18), composed of Laminaria japonica Aresch (Laminariaceae), Rheum palmatum L. (Polygonaceae) and Ephedra sinica Stapf (Ephedraceae), has traditionally been described to against obesity and related metabolic disease such as dyslipidemia. In HFD-fed mice receiving GGEx18, genes related to hepatic fatty acid β-oxidation was higher compared to mice fed with only HFD (Lim et al., 2018).

Evidence from recent studies has also indicated that some natural compounds promoted fatty acid oxidation by regulating the AMPK/PGC-1α signaling pathway. Yellow pigments, monascin, and ankaflavin, as secondary metabolites derived from monascus-fermented products, could reduce fatty acid accumulation partly mediated by the AMPK signaling activation and enhancement of β-oxidation by PGC-1α (Hsu et al., 2014). Myricetin, a natural flavonol with many biological activities, decreased PGC-1α acetylation through SIRT1 activation, and thus enhanced mitochondrial activity, suggesting its potential role in regulating hepatic lipid metabolism (Jung et al., 2017).

**CLINICAL TRIALS**

Given to the encouraging effects of herbal medicines on liver diseases, plenty of clinical trials have been extensively performed. The potential therapeutic benefits of herbal medicines in patients with NAFLD have been reviewed in several papers in recent years (Xiao et al., 2013; Bedi et al., 2016; Perumpail et al., 2018). In present review, we focused on the efficacy of herbal medicines to mediate lipid metabolism and attenuate hepatic steatosis. Dava Al-Balgham, as one of the traditional medicine products composed of *Nigella sativa* L., *Pistacia lentiscus* L., *Zataria multiflora* Boiss. (ZM), and *Trachyspermum ammi* L., was tested for its effect on NAFLD by a randomized, double-blinded, placebo-controlled trial with 76 NAFLD patients. Placebo or Dava Al-Balgham were consumed with each meal for three months. The results showed that Dava Al-Balgham could cause weight loss and have anti-hyperlipidemic effect (Hormati et al., 2019).

The effect of *Z. multiflora* supplementation on NAFLD was studied by a randomized double-blind placebo-controlled clinical trial. Total 85 patients with NAFLD were treated with ZM powder (700 mg) or placebo twice daily for 3 months. However, no significant difference between two ZM-treated groups and placebo groups regarding ALT, TNF-α, grade of fatty liver in ultrasonography, lipid profiles, and high sensitive C-reactive protein (hs-CRP), while it could improve insulin resistance in patients with NAFLD. Further studies with larger sample size and longer duration are recommended (Zamani et al., 2018).

A 12-weeks randomized, controlled, double-blind trial included with was 44 NAFLD patients, was performed to evaluate the efficacy of *Capparis spinosa* L. on disease regression of NAFLD. Patients are randomly divided into control (n=22) or caper (n=22) group. The caper group was treated with 40-50 g caper fruit pickles with meals every day. Results obtained after treatment of 12 weeks indicated that the grade of fatty liver and serum lipoproteins were improved by *C. spinosa* administration (Khavasi et al., 2017).

We further checked the registered clinical trials about testing effects of the herbs and natural products on fatty liver via the website of www.clinicaltrial.gov. The intensively studied herbs and derived compounds are resveratrol, ginseng, and ginger, which were discussed in detail in following. Other herbs and some natural products that are undergoing or were performed clinical trials on fatty liver diseases are listed in Table 3.

Resveratrol is a stilbenoid and a phytoalexin generated by several plants, such as red grapes in response to stimuli (Hasan and Bae, 2017). It is an activator of AMPK and SIRT1, and thus has a critical role in promoting fat breakdown and removal from the liver, preventing liver damage and inhibiting the progression of NAFLD (Shang et al., 2008; Charytoniuk et al., 2017; Theodotou et al., 2019). Resveratrol has been involved in three trials (NCT01446276; NCT01464801; NCT02030977) included patients of fatty liver, NAFLD, and obesity.

Another herb, ginseng, has been traditionally used for more than 2,000 years with various biological effects. A great deal of preclinical studies have demonstrated the protective effects of ginseng on liver diseases, including ALD and NAFLD. Korean Red Ginseng (Panax ginseng) (Park et al., 2017) enhanced the decreased phosphorylation of AMPK induced by ethanol consumption. Notably, it reduced the accumulation of fat in hepatocytes caused by ethanol via regulation of SREBP-1, SIRT-1 and PPAR-α (Huu Tung et al., 2012; Park et al., 2017). Clinical trial (NCT0394512) has been performed to study the effect of red ginseng on liver dysfunction. Fermented ginseng powder has also been tested to study its efficacy on NAFLD (NCT03260543).

Ginger is the root of *Zingiber officinale* Roscoe and is one of the most used spices in many countries (Hu Tung et al., 2012). It contains active compounds, such as shogaol, gingerol, zingerone, and β-bisabolene. It has been shown that ginger can reduce insulin resistance and serum TG level in patients with Type II diabetes and hyperlipidemia (Arabliou et al., 2014). In a randomized, double-blind, placebo-controlled clinical trial with 44 patients of NAFLD, ginger supplementation significantly...
| NCT number | Status          | Conditions                  | Interventions | Outcome Measures                                                                 | Population                                      | Dates                  |
|------------|-----------------|-----------------------------|---------------|----------------------------------------------------------------------------------|-------------------------------------------------|------------------------|
| NCT02030977 | Completed       | NAFLD                       | Resveratrol   | ALT                                                                              | Enrollment: 50 Age: 18 Years to 80 Years (Adult, Older Adult) Sex: All | Study Start: June 2012 Study Completion: March 2013 |
| NCT01464801 | Completed       | Fatty liver                 | Resveratrol   | • Change in hepatic steatosis and inflammation                              | Enrollment: 28 Age: 18 Years to 70 Years (Adult, Older Adult) Sex: All | Study Start: September 2011 Study Completion: June 2015 |
| NCT01446276 | Completed       | Obesity                     | Resveratrol   | • Hepatic VLDL-TG secretion and peripheral VLDL-TG clearance                     | Enrollment: 26 Age: 25 Years to 65 Years (Adult, Older Adult) Sex: All | Study Start: November 2011 Study Completion: April 2014 |
| NCT04130321 | Not yet recruiting | Overweight                  | Camu camu (Myrciaria dubia) | • Change in Gut Microbiota Composition and Diversity                           | Enrollment: 32 Age: 18 Years to 75 Years (Adult, Older Adult) Sex: All | Study Start: January 6, 2020 Study Completion: June 30, 2022 |
| NCT0394512  | Completed       | Liver Dysfunction           | Red ginseng   | Liver enzyme                                                                     | Enrollment: 94 Age: 37 Years to 63 Years (Adult) Sex: All | Study Start: January 1, 2018 Study Completion: December 31, 2018 |
| NCT03260543 | Completed       | NAFLD                       | Fermented ginseng powder | Changes of ALT                                          | Enrollment: 90 Age: 19 Years to 70 Years (Adult, Older Adult) Sex: All | Study Start: July 2016 Study Completion: August 2017 |
| NCT04049396 | Completed       | NAFLD                       | Berberine     | ALT; AST; ALP; fasting blood sugar; total cholesterol; LDL-Cholesterol; HDL - Cholesterol; TG | Enrollment: 50 Age: 18 Years to 65 Years (Adult, Older Adult) Sex: All | Study Start: October 1, 2018 Study Completion: June 15, 2019 |
| NCT02535195 | Completed       | NAFLD                       | Ginger        | • Serum levels of the ALT liver enzyme                                       | Enrollment: 60 Age: 18 Years to 70 Years (Adult, Older Adult) Sex: All | Study Start: March 2013 Study Completion: August 2015 |

(Continued)
| NCT number       | Status                        | Conditions                                      | Interventions          | Outcome Measures                                                                 | Population                                      | Dates                          |
|------------------|-------------------------------|------------------------------------------------|------------------------|----------------------------------------------------------------------------------|------------------------------------------------|--------------------------------|
| NCT02289235      | Enrolling by invitation       | Fatty Liver, Diabetes Mellitus, Type 2          | Ginger                 | Change in ALT level                                                              | Enrollment: 90                                  | Study Start: November 1, 2018  |
|                  |                               |                                                 |                        | Change in AST level                                                              | Age: 20 Years to 65 Years (Adult, Older Adult) | Study Completion: December 1, 2019 |
|                  |                               |                                                 |                        | Change in score of fatty liver in fibroscan                                      | Sex: All                                        |                                |
|                  |                               |                                                 |                        | Change in Gama GT (#- glutamyl transpeptidase) levels                           |                                                |                                |
|                  |                               |                                                 |                        | Number of patients with adverse events                                           |                                                |                                |
| NCT03864783      | Recruiting                    | NAFLD, Insulin Resistance, Glucose Tolerance, Impaired Obesity, Abdominal | Curcumin (Meriva®)     | Curcumin’s effect on steatosis                                                   | Enrollment: 40                                  | Study Start: March 5, 2019     |
|                  |                               |                                                 |                        | Total amino acids in plasma                                                      | Age: 20 Years and older (Adult, Older Adult)   | Study Completion: October 2020 |
|                  |                               |                                                 |                        | Curcumin’s effect on plasma concentration of urea                              | Sex: Male                                       |                                |
|                  |                               |                                                 |                        | Curcumin’s effect on urine concentration of urea                                |                                                |                                |
|                  |                               |                                                 |                        | Curcumin’s effect on serum concentration of inflammatory marker interleukin (IL)-1b |                                                |                                |
|                  |                               |                                                 |                        | Curcumin’s effect on serum concentration of inflammatory marker IL-2            |                                                |                                |
|                  |                               |                                                 |                        | Curcumin’s effect on serum concentration of inflammatory marker IL-6            |                                                |                                |
|                  |                               |                                                 |                        | Curcumin’s effect on serum concentration of inflammatory marker IL-10           |                                                |                                |
|                  |                               |                                                 |                        | Curcumin’s effect on serum concentration of inflammatory marker tumor necrosis factor (TNF)- alpha |                                                |                                |
|                  |                               |                                                 |                        | and 34 more                                                                      |                                                |                                |
|                  |                               |                                                 |                        | ALT                                                                              |                                                |                                |
| NCT03073343      | Recruiting                    | Non-Alcoholic Fatty Liver Disease               | Betaine                | Change (Reduction) of parameters of liver steatosis defined by CAP (Controlled Attenuation Parameter) and liver fibrosis defined by LSM ( liver stiffness measurements) during the 6 months period | Enrollment: 48                                  | Study Start: November 12, 2013|
|                  |                               |                                                 |                        | Change in liver enzymes in period of 6 months                                   | Age: 18 Years to 75 Years (Adult, Older Adult) | Study Completion: June 30, 2020|
|                  |                               |                                                 |                        | Change in insulin resistance in period of 6 months                              | Sex: All                                        |                                |
|                  |                               |                                                 |                        | Change in lipodogram in period of 6 months                                       |                                                |                                |
| NCT02973295      | Recruiting                    | NAFLD                                           | Silymarin              | Hepatic steatosis                                                               | Enrollment: 400                                 | Study Start: September 20, 2019|
|                  |                               |                                                 |                        | Glucose                                                                          | Age: 18 Years to 70 Years (Adult, Older Adult) | Study Completion: June 30, 2021|
|                  |                               |                                                 |                        | Glycated hemoglobin (HBA1C)                                                     | Sex: All                                        |                                |
|                  |                               |                                                 |                        | ALT                                                                              |                                                |                                |
|                  |                               |                                                 |                        | hs- CRP                                                                          |                                                |                                |
|                  |                               |                                                 |                        | gut microbiota                                                                   |                                                |                                |
| NCT02929901      | Completed                     | Type 2 Diabetes Nonalcoholic Fatty Liver         | Caffeine and chlorogenic acid        | Hepatic steatosis                                                               | Enrollment: 200                                 | Study Start: December 2016   |
|                  |                               |                                                 |                        | Glucose                                                                          | Age: 30 Years to 65 Years (Adult, Older Adult) | Study Completion: March 2019  |
|                  |                               |                                                 |                        | Glycated hemoglobin (HBA1C)                                                     | Sex: All                                        |                                |
|                  |                               |                                                 |                        | ALT                                                                              |                                                |                                |
|                  |                               |                                                 |                        | AST                                                                              |                                                |                                |
|                  |                               |                                                 |                        | hs- CRP                                                                          |                                                |                                |
| NCT02908152      | Unknown status                | Type 2 Diabetes Nonalcoholic Fatty Liver         | Curcumin                | Hepatic steatosis                                                               | Enrollment: 50                                  | Study Start: February 2017   |
|                  |                               |                                                 |                        | Glucose                                                                          | Age: 30 Years to 65 Years (Adult, Older Adult) | Study Completion: October 2017|
|                  |                               |                                                 |                        | HBA1C                                                                            | Sex: All                                        |                                |
|                  |                               |                                                 |                        | ALT                                                                              |                                                |                                |
|                  |                               |                                                 |                        | AST                                                                              |                                                |                                |
| NCT0206498       | Completed                     | NAFLD                                           | Silymarin                | To assess the efficacy                                                          | Enrollment: 99                                  | Study Start: June 2012       |
|                  |                               |                                                 |                        | of Silymarin as defined by an improvement in non-alcoholic steatosis (NAS) activity score by at least 30% from baseline compared to placebo | Age: 18 Years and older (Adult, Older Adult)   | Study Completion: December 2015|
|                  |                               |                                                 |                        | To assess the safety and adverse event profile of Silymarin compared to placebo | Sex: All                                        |                                |

(Continued)
| NCT number | Status      | Conditions     | Interventions                          | Outcome Measures                                                                 | Population                                      | Dates               |
|------------|-------------|----------------|----------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------|---------------------|
| NCT01940263 | Completed   | NAFLD          | Anthocyanin                           | • Biomarkers related to oxidative stress  
• Biomarkers related to inflammation | Enrollment: 63  
Age: 18 Years to 65 Years (Adult, Older Adult)  
Sex: All | Study Start: June 2013  
Study Completion: June 2014 |
| NCT02307344 | Unknown status  | Nonalcoholic Steatohepatitis  
Liver Steatosis | Nigella sativa L.  
Effect of Nigella Sativa on Liver Triglyceride Concentration  
Effect of Nigella Sativa on Improvement in NASH Activity Index  
Effect of Nigella Sativa on Fibrosis Staging | | Enrollment: 100  
Age: 18 Years and older (Adult, Older Adult)  
Sex: All | Study Start: January 2015  
Study Completion: January 2017 |
| NCT02303314 | Completed   | NAFLD          | Trigonella foenum-graecum Seed extract | Liver stiffness change | Enrollment: 35  
Age: 18 Years to 70 Years (Adult, Older Adult)  
Sex: All | Study Start: November 2014  
Study Completion: September 2017 |
| NCT01707914 | Completed   | NAFLD          | Chinese bayberry juice (Myrica rubra)  
Drug: Chinese herb (YiqiSanJu) (Angelica sinensis, Rehmannia, Cinnamomum cassia, Glycyrrhiza uralensis, Eucommia ulmoides, Achyranthes bidentate, Lycium chinense) | Plasma lipids profile  
The CT ratio of liver/spleen  
BMI (Body Mass Index)  
liver function  
lipid profile  
NEFA  
HOMA index  
adiponectin  
IL-6  
hs-CRP (C-reactive protein)  
TNF-a  
leptin | Enrollment: 44  
Age: 18 Years to 25 Years (Adult)  
Sex: All | Study Start: June 2012 |
| NCT01677325 | Completed   | NAFLD          | Phyllanthus urinaria L.  
Drug: Chinese herb (YiqiSanJu) (Angelica sinensis, Rehmannia, Cinnamomum cassia, Glycyrrhiza uralensis, Eucommia ulmoides, Achyranthes bidentate, Lycium chinense) | Histologic NAFLD activity score  
ALT normalization  
Metabolic endpoints  
Changes in magnetic resonance spectroscopy  
Liver stiffness measurement  
Biomarkers of NASH and liver fibrosis  
Histologic NAFLD activity score  
ALT normalization  
Metabolic endpoints  
Changes in magnetic resonance spectroscopy  
Liver stiffness measurement  
Biomarkers of NASH and liver fibrosis | Enrollment: 60  
Age: 18 Years to 70 Years (Adult, Older Adult)  
Sex: All | Study Start: May 2010  
Study Completion: May 2012 |
| NCT00816465 | Completed   | NAFLD          | Hoodia gordonii (Masson) Sweet ex Decne.  
Effect of Hoodia Gordonii on Liver Steatosis | Decreased insulin resistance  
Safety  
Reduced hepatic injury  
Reduced weight/BMI/abdominal circumference | Enrollment: 20  
Age: 18 Years to 65 Years (Adult, Older Adult)  
Sex: All | Study Start: May 2009  
Study Completion: August 2010 |
Due to the positive efficacy, and minimal side effects, herbal medicines have obtained increasing attention as alternative therapeutic agents for liver disorders and dyslipidemia. Increasing evidence from laboratory studies suggests that many herbs, natural products, and derived compounds could inhibit the progression of hepatic steatosis. A variety of mechanisms have been demonstrated to be implicated in preventing hepatic steatosis and modulating lipid metabolism by herbs, including reducing hepatocyte fatty acid uptake and trafficking, reducing hepatic de novo lipogenesis, increasing lipolysis, inducing lipophagy, enhancing fatty acid β-oxidation. In particular, SREBP-1c, PPARα, AMPK, and SIRT1 signaling pathways have been highlighted as crucial molecular targets of action mechanisms by which herbal medicines regulate hepatic lipid metabolism. Current clinical evidences and meta-analysis showing the positive impacts of herbal medicines on the hepatic lipid metabolism pathways are still not strong enough. Further multicenter large-sample randomized clinical trials are still required to confirm the efficacy and safety of herbal medicines on hepatic lipid metabolism. Herbs mix and single medical plants as well as their components have been widely applied in the treatment of NAFLD. We consider the main actor should be the active components. For both herbs mix and single medical plants, they are containing many compounds, which may act synergistically in ways to enhance the therapeutic effects. Identifying the active components in herbs is a crucial and significant subject for the development of TCM. Currently, network pharmacology-based strategy has been extensively used for the prediction of the active components from herbs. Network pharmacology is an approach based on systems biology, poly-pharmacology, and molecular networks, to analyze relationships between drugs and diseases in recent decade, which has attracted considerable attention among Chinese medicine researchers for its ability in predicting and illustrating interactive relationships between numerous components and targets of herbal medicines. Network-based pharmacological analysis is a desirable approach as well as a good tool of in silico prediction for investigating the mechanisms of action for herbs and formulae and their potential bioactive components at molecular and systemic levels, which renders more effective subsequent exploration with experimental approaches. With the promising and effective prediction, subsequently validation experiments in laboratory and bench would be performed to confirm their pivotal role. In conclusion, herbal medicines have the potency to be alternative and complementary medical therapies to current pharmaceuticals for the treatment of liver diseases with lipid metabolism disorder.

**META-ANALYSIS STUDIES**

HuoXueHuaYu (HXHY), a TCM formula, has been widely used in clinic for patients with NAFLD. Cai et al. performed a meta-analysis of randomized controlled trial of HXHY in NAFLD. There are 13 studies involving 1429 patients which 654 patients receiving conventional treatment group and 775 patients belonged to HXHY group. HXHY showed better ability on lowing TC and TG levels than that of conversational treatment. HXHY might be an effective and safe therapy for NAFLD, and trials with rigorous design, multicenter, large-scale, and high-quality worldwide are still expected (Cai et al., 2019).

Erchen Decoction (ECD), a TCM formula, is often used in the therapy of various diseases. A meta-analysis of the efficacy of ECD for the treatment of NAFLD by PRISMA systematic review standard has been performed. Seven randomized controlled trial with a total of 1951 participants were included in this study. The analysis results showed that patients with ECD treatment showed an improved status compared to the conventional treatment. Longer follow-up periods and larger-scale randomized controlled trial are still required to evaluate the efficacy of ECD in NAFLD (Li et al., 2017).

The efficiency and safety of a famous TCM Danshen in the treatment of NAFLD has also been analyzed by a meta-analysis study. Eight randomized controlled trials with 800 patients of NAFLD were identified. The results indicated that Danshen had improved total effectiveness rate, lower level of TC, TG, LDL, ALT, and AST, suggesting that Danshen may have potential effects on NAFLD, while multicenter large-sample randomized clinical trials are still expected to confirm the efficacy and safety of Danshen (Peng et al., 2016).

Another study performed by Narjes et al. on 2017 has evaluated the efficiency of all kinds of TCM on the treatment of NAFLD. Literature were searched on China National Knowledge and PubMed from 1995 to 2010. Total 5904 patients from 62 randomized controlled trials were included for meta-analysis. Results showed that TCM had a better effect on the normalization of ALT level and disappearance of radiological steatosis for the patients of NAFLD. Finally, authors concluded that TCM is of modest benefit to the therapy of NAFLD (Shi et al., 2012).

**CONCLUSIONS AND PERSPECTIVES**

Due to the positive efficacy and minimal side effects, herbal medicines have obtained increasing attention as alternative therapeutic agents for liver disorders and dyslipidemia. Increasing evidence from laboratory studies suggests that many herbs, natural products, and derived compounds could inhibit the progression of hepatic steatosis. A variety of mechanisms have been demonstrated to be implicated in preventing hepatic steatosis and modulating lipid metabolism by herbs, including reducing hepatocyte fatty acid uptake and trafficking, reducing hepatic de novo lipogenesis, increasing lipolysis, inducing lipophagy, enhancing fatty acid β-oxidation. In particular, SREBP-1c, PPARα, AMPK, and SIRT1 signaling pathways have been highlighted as crucial molecular targets of action mechanisms by which herbal medicines regulate hepatic lipid metabolism. Current clinical evidences and meta-analysis showing the positive impacts of herbal medicines on the hepatic lipid metabolism pathways are still not strong enough. Further multicenter large-sample randomized clinical trials are still required to confirm the efficacy and safety of herbal medicines on hepatic lipid metabolism. Herbs mix and single medical plants as well as their components have been widely applied in the treatment of NAFLD. We consider the main actor should be the active components. For both herbs mix and single medical plants, they are containing many compounds, which may act synergistically in ways to enhance the therapeutic effects. Identifying the active components in herbs is a crucial and significant subject for the development of TCM. Currently, network pharmacology-based strategy has been extensively used for the prediction of the active components from herbs. Network pharmacology is an approach based on systems biology, poly-pharmacology, and molecular networks, to analyze relationships between drugs and diseases in recent decade, which has attracted considerable attention among Chinese medicine researchers for its ability in predicting and illustrating interactive relationships between numerous components and targets of herbal medicines. Network-based pharmacological analysis is a desirable approach as well as a good tool of in silico prediction for investigating the mechanisms of action for herbs and formulae and their potential bioactive components at molecular and systemic levels, which renders more effective subsequent exploration with experimental approaches. With the promising and effective prediction, subsequently validation experiments in laboratory and bench would be performed to confirm their pivotal role. In conclusion, herbal medicines have the potency to be alternative and complementary medical therapies to current pharmaceuticals for the treatment of liver diseases with lipid metabolism disorder.

**AUTHOR CONTRIBUTIONS**

YF designed and conceived the study. SL and YF retrieved and analyzed the data, and drafted the manuscript. SL, YX, WG, FC, CZ, HT, and NW discussed and revised the manuscript. All authors confirmed final version of the manuscript.

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REFERENCES

Ahn, S. H., Lee, K. P., Kim, K., Choi, J. Y., Park, S. Y., and Cheon, J. H. (2019). Dansaenum regulates hepatic lipogenesis and inflammation in vitro and in vivo. Food Sci. Biotechnol. 28 (5), 1543–1551. doi: 10.1007/s10068-019-00579-8

Albhaisi, S., and Sanyal, A. (2018). Recent advances in understanding and managing non-alcoholic fatty liver disease. F1000Res 7. doi: 10.12688/ f1000research.14421.1

Al-Dayyat, H. M., Rayyan, M. Y., and Tafseem, R. F. (2018). Non-alcoholic fatty liver disease and associated dietary and lifestyle risk factors. Diabetes Metab. Syndr. 12 (4), 569–575. doi: 10.1016/j.dsx.2018.03.016

Ansari, A., Bose, S., Patra, J. K., Shin, N. R., Lim, D. W., Kim, K. W., et al. (2018). A Controlled Fermented Samjungwhal Herbal Formula Ameliorates Non-alcoholic Hepatosteatosis in HepG2 Cells and OLETF Rats. Front. Pharmacol. 9, 596. doi: 10.3389/fphar.2018.00596

Arablou, T., Aryaeian, N., Valizadeh, M., Shari

Ansari, A., Bose, S., Patra, J. K., Shin, N. R., Lim, D. W., Kim, K. W., et al. (2018). A Controlled Fermented Samjungwhal Herbal Formula Ameliorates Non-alcoholic Hepatosteatosis in HepG2 Cells and OLETF Rats. Front. Pharmacol. 9, 596. doi: 10.3389/fphar.2018.00596

Arablou, T., Aryaeian, N., Valizadeh, M., Shari

Ash, A., Ghaedi, A., Keyvan, S., and Khodadadi, G. (2017). Effect of an Herbal Product on the Serum Level of Liver Enzymes in Patients with Non-Alcoholic Fatty Liver Disease. Herbal Formula (CHF03) Attenuates Non-Alcoholic Fatty Liver Disease (NAFLD) Through Inhibiting Lipogenesis and Anti-Oxidation Mechanisms. Front. Pharmacol. 10, 1196. doi: 10.3389/fphar.2019.01190

Aziz, M. J. (2016). Function of Autophagy in Nonalcoholic Fatty Liver Disease. Dig. Dis. Sci. 61 (5), 1304–1313. doi: 10.1007/s10602-015-4025-x

Dang, Y., Hao, S., Zhou, W., Zhang, L., and Ji, G. (2019). The traditional Chinese formulation Ling-gui-zhu-gan decoction alleviated non-alcoholic fatty liver disease via inhibiting PPP1R3C mediated molecules. BMC Complement Altern. Med. 19 (1), 8. doi: 10.1186/s12906-018-2424-1

Dong, H., Lu, F. E., and Zhao, L. (2012). Chinese herbal medicine in the treatment of nonalcoholic fatty liver disease. Chin. J. Integr. Med. 18 (2), 152–160. doi: 10.1007/s11655-012-0993-2

Eissing, L., Scherer, T., Todler, K., Knipschild, U., Greve, J. W., Buurman, W. A., et al. (2013). De novo lipogenesis in human fat and liver is linked to ChREBP-beta and metabolic health. Nat. Commun. 4, 1528. doi: 10.1038/ncomms2537

Feng, Q., Liu, W., Baker, S. S., Li, H., Chen, C., Liu, Q., et al. (2017). Multi-targeting therapeutic mechanisms of the Chinese herbal medicine QHD in the treatment of non-alcoholic fatty liver disease. Oncotarget 8 (17), 27820–27838. doi: 10.18632/oncotarget.15482

Feng, W. W., Kung, S. Y., Tu, C., Ma, Z. J., Pang, J. Y., Wang, Y. H., et al. (2018). Natural products berberine and curcumin exhibited better ameliorative effects on rats with non-alcoholic fatty liver disease than lovastatin. BioMed. Pharmacother. 99, 325–333. doi: 10.1016/j.biopha.2018.01.071

Fernandez-Marcos, P. J., and Auwertz, J. (2011). Regulation of PGC-1alpha, a nodal regulator of mitochondrial biogenesis. Am. J. Clin. Nutr. 93 (4), 8845–8890.

Furuhashi, M., and Hotamisligil, G. S. (2008). Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. Nat. Rev. Drug Discovery 7 (6), 489–503. doi: 10.1038/nrd2589

Guo, X., Cui, R., Zhao, J., Mo, R., Peng, L., and Yan, M. (2016). Corosolic acid protects hepatocytes against ethanol-induced damage by modulating mitogen-activated protein kinases and activating autophagy. Eur. J. Pharmacol. 791, 578–588. doi: 10.1016/j.ejphar.2016.09.031

Guo, Y., Li, J. X., Mao, T. Y., Zhao, W. H., Liu, L. J., and Wang, Y. L. (2017). Targeting Sirt1 in a rat model of high-fat-diet-induced non-alcoholic fatty liver disease: Comparison of Gegen Qinlian decoction and resveratrol. Exp. Ther. Med. 14 (4), 4277–4287. doi: 10.3892/etm.2017.5076

Hasan, M., and Bae, H. (2017). “An Overview of Stress-Induced Resveratrol Synthesis in Grapes: Perspectives for Resveratrol-Enriched Grape Products.” Molecules 22 (2). doi: 10.3390/molecules22020294

Heeboll, S., Vilstorp, H., and Gronbaek, H. (2018). “Treatment of non-alcoholic fatty liver disease.” Ugeskr Laeger 180 (31). 

Ho, C., Gao, Y., Zheng, D., Liu, Y., Shan, S., Fang, B., et al. (2019). Alisol A attenuates high-fat-diet-induced obesity and metabolic disorders via the AMPK/ACC/REBP-1c pathway. J. Cell Mol. Med. 23 (8), 5108–5118. doi: 10.1111/jcmm.14380

Hormati, A., Toosikerany, F., Mohammadbeigi, A., Aliasl, F., and Dehnavi, H. M. (2019). Effect of an Herbal Product on the Serum Level of Liver Enzymes in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized, Double-Blinded, Placebo-Controlled Trial. Iranian Red Crescent Med. J. 21 (7), 7. doi: 10.5812/rcrmj.91024

Houten, S. M., and Wanders, R. J. (2010). A general introduction to the biochemistry of mitochondrial fatty acid beta-oxidation. J. Inherit. Metab. Dis. 33 (5), 469–477. doi: 10.1007/s10545-010-9061-2

Hsu, W. H., Chen, T. H., Lee, B. H., Hsu, Y. W., and Pan, T. M. (2014). Monascin and ankaflavin act as natural AMPK activators with PPARalpha agonist activity to down-regulate nonalcoholic steatohepatitis in high-fat diet-fed C57BL/6 mice. Food Chem. Toxicol. 64, 94–103. doi: 10.1016/j.fct.2013.11.015
Huang, L., Cheng, Y., Huang, K., Zhou, Y., Ma, Y., and Zhang, M. (2018). Ameliorative effect of Sedum sarmentosum Bunge extract on T2D fatty liver via the PPAR and P38 signaling pathway. Sci. Rep. 8 (1), 8456.

Hu et al. (2019). Gypsogenic improves the intestinal microbiota of non-alcoholic fatty liver in mice and alleviates its progression. BioMed. Pharmacother. 118, 109258. doi: 10.1016/j.biopharm.2019.109258

Huang, L., Cheng, Y., Huang, K., Zhou, Y., Ma, Y., and Zhang, M. (2018). Herbs on Hepatic Lipid Metabolism.

Li et al. (2016). Polygonatum sibiricum, a Chinese herb formula HT048 attenuates diet-induced obesity by improving Hepatic Lipid Metabolism and Insulin Resistance in Obese Rats. Molecules 21 (11). doi: 10.3390/molecules21111424

Lee, J. H., Baek, S. Y., Jung, Y. J., Xu, S. K., Kim, K. M., Ki, S. H., et al. (2018). Oxyrevorotol ameliorates nonalcoholic fatty liver disease by regulating hepatic lipogenesis and fatty acid oxidation through liver kinase B1 and AMP-activated protein kinase. Chem. Biol. Interact. 289, 68–74. doi: 10.1016/j.cbi.2018.04.023

Li, X., Li, Z., Xue, M., Ou, Z., Liu, M., Yang, M., et al. (2013). Fructus Xanthii attenuates hepatic steatosis in rats fed on high-fat diet. PLoS One 8 (4), e61499. doi: 10.1371/journal.pone.0061499

Li, W., Li, Y., Wang, Q., and Yang, Y. (2014). Crude extracts from Lycium barbarum suppress SREBP-1c expression and prevent diet-induced fatty liver through AMPK activation. BioMed. Res. Int. 2014, 196196.

Li, Y., Zhao, J., Zheng, H., Zhong, X., Zhou, J., and Hong, Z. (2014). Treatment of Nonalcoholic Fatty Liver Disease with Total Alkaloids from Rubus alceifolius Por through Regulation of Fat Metabolism. Evid. Based Complement Alternat. Med. 2014, 768540. doi: 10.1155/2014/768540

Li, Z., Xu, J., Zheng, P., Xing, L., Shen, H., Yang, L., et al. (2015). Hawthorn leaf flavonoids alleviate nonalcoholic fatty liver disease by enhancing the adiponectin/AMPK pathway. J. Clin. Exp. Med. 8 (10), 17295–17307.

Li, W. S., Wu, Y., Ge, W. Z., Fan, L., and Sun, W. (2017). A herbal formula Erchen decoction for non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. Int. J. Clin. Exp. Med. 10 (6), 9110–9116.

Li, C. H., Tang, S. C., Wong, C. H., Wang, Y., Jiang, J. D., and Chen, Y. (2018). Puerarin induces miR-373 expression in hepatocytes to inactive hepatic steatosis associated AKT-S6 kinase pathway. Eur. J. Pharmacol. 825, 107–118. doi: 10.1016/j.ejphar.2018.02.035

Li, Y. Y., Tang, D., Du, Y. L., Cao, C. Y., Nie, Y. Q., Cao, J., et al. (2018). Fatty liver mediated by pereoxisome proliferator-activated receptor-alpha DNA methylation can be reversed by a methylation inhibitor and curcumin. J. Investig. Med. 19 (7), 421–430. doi: 10.1111/jm.13676

Lim, J., Lee, H., Ahn, J., Kim, J., Jang, J., Park, Y., et al. (2018). Quercetin ameliorates autophagy in alcohol liver disease associated with lysosome through miTOR-TFEB pathway. J. Pathol. 252, 177–185. doi: 10.1002/path.4810

Liang, Z. E., Zhang, Y. P., Tang, K. R., Deng, Y. J., Liang, Y. Q., Liang, S., et al. (2019). Anti-inflammation effect via TLR4-mediated MyD88-dependent and -independent signalling pathways in non-alcoholic fatty liver disease rats. Chinese herb formula. Int. J. Clin. Exp. Med. 12 (3), 2265–2277.

Liao, C. C., Ou, T. T., Huang, H. P., and Wang, C. J. (2014). The inhibition of oleic acid induced hepatic lipogenesis and the promotion of lipolysis by caffeic acid via up-regulation of AMP-activated kinase. J. Sci. Food Agric. 94 (6), 1154–1162. doi: 10.1002/jsfa.6386

Liu, J. E., Lee, H., Ahn, J., Kim, J., Jang, J., Park, Y., et al. (2018). The polyherbal drug Erchen decoction for non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. Int. J. Clin. Exp. Med. 10 (6), 9110–9116.

Mimaki, K., Chaniotakis, M., Markaki, M., and Tavernarakis, N. (2019). Emerging Roles of Lipophagy in Health and Disease. Front. Cell Dev. Biol. 7 (1), 6237.

Nishino, N., Sori, M. H., Khadem, E., Faramarzi, E., Ayati, M. H., Fazljooy, M. S. B., et al. (2017). Effect of Daily Caper Fruit Pickle Consumption on Disease Regression in Patients with Non-Alcoholic Fatty Liver Disease: a Double-Blinded Randomized Trial. Adv. Food. Nutr. Res. 77 (4), 645–650. doi: 10.1515/advfnr-2017-0077

Sanchez, S., Lahmichan, B., and Kwon, S. M. (2018). Pivotal Roles of Peroxisome Proliferator-Activated Receptors (PPARs) and Their Signal Cascade for Cellular and Whole-Body Energy Homeostasis. Int. J. Mol. Sci. 19 (4). doi: 10.3390/ijms19040949

Sano, H., Shimizu, H., and Uchida, A. (2018). Toei-ya, K., and Zaima, T. (2020). Regulation of AMP-activated protein kinase. J. Ethnopharmacol. 239, 111919.

Kavadias, N., Michail, V., Michielsen, P. P., and Francque, S. M. (2014). Role of autophagy in the pathophysiology of nonalcoholic fatty liver disease: a controversial issue. World J. Gastroenterol. 20 (23), 7325–7338. doi: 10.3748/wjg.v20.i23.7325

Lamichanhe, S., Dahal Lamichanhe, B., and Kwon, S. M. (2018). Pivotal Roles of Peroxisome Proliferator-Activated Receptors (PPARs) and Their Signal Cascade for Cellular and Whole-Body Energy Homeostasis. Int. J. Mol. Sci. 19 (4). doi: 10.3390/ijms19040949

Lass, A., Zimmermann, R., Oberer, M., and Zeichner, R. (2011). Lipolysis - a highly regulated multi-enzyme complex mediates the catabolism of cellular fat stores. Prog. Lipid Res. 50 (1), 14–27. doi: 10.1016/j.plipres.2010.01.004

Lee, J. E., Kim, E. J., Kim, M. H., Hong, J., and Yang, W. M. (2016). Polygonatum sibiricum improves menopausal obesity via regulation of lipolysis-related enzymes. J. Nat. Med. 70 (4), 789–796. doi: 10.1007/s11418-016-1018-9

Lee, Y. H., Jinn, B., Lee, S. H., Song, M., Bae, H., Min, B. J., et al. (2016). Herbal Formula HT048 Attenuates Diet-Induced Obesity by Improving Hepatic Lipid Metabolism.
Liu, X., Xie, Z. H., Liu, C. Y., and Zhang, Y. (2019). Effect of Chinese Herbal Monomer Harry Calycosin on Nonalcoholic Fatty Liver and its Mechanism. Combi. Chem. High Througput Screen 22 (3), 194–200. doi: 10.2174/138620732266619041112814

Liu, Y. Y., You, J. J., Xu, W., Zhai, T., Du, C. Y., Chen, Y., et al. (2019). Gynura procumbens aqueous extract alleviates nonalcoholic steatohepatitis through CFEAR-JNK pathway in vivo and in vitro. Chin. Herb. Medicines 11 (4), 369–378. doi: 10.1016/j.chmed.2019.09.005

Lo, V., Erickson, B., Thomason-Hughes, M., Ko, K. W., Dolinsky, V. W., Nelson, R., et al. (2010). Arachidamide decataylase attenuates fatty-acid-induced triacylglycerol accumulation in rat hepatoma cells. J. Lipid Res. 51 (2), 368–377. doi: 10.1194/jlr.M000396

Lomonaco, R., Sunny, N. E., Bril, F., and Cusi, K. (2013). Nonalcoholic fatty liver disease: current issues and novel treatment approaches. Drugs 73 (1), 1–14. doi: 10.1007/s40265-012-0004-0

Liu, X., Yuan, Z. Y., Yan, X. J., Lei, F., Jiang, J. F., Yu, X., et al. (2016). Effects of Angelica dahurica on obesity and fatty liver in mice. Chin. J. Nat. Med. 14 (9), 641–652. doi: 10.1016/S1875-5364(16)30076-0

Luan, H., Huo, Z., Zhao, Z., Zhang, S., Huang, Y., Shen, Y., et al. (2019). Scutellaria, a modulator of mTOR, attenuates hepatic insulin resistance by regulating hepatocyte lipid metabolism via SREBP-1c suppression. Phytother. Res. doi: 10.1002/ptr.6582

Ma, J., Zhoa, D., Wang, X., Ma, C., Feng, K., Zhang, S., et al. (2019). LongShengZhi Capsule Reduces Established Atherosclerotic Lesions in apoe-Deficient Mice by Ameliorating Hepatic Lipid Metabolism and Inhibiting Inflammation. J. Cardiovasc. Pharmacol. 73 (2), 105–117. doi: 10.1097/FCC.0000000000000642

Mandal, S., Mukhopadhyay, S., Bandhopadhyay, S., Sen, G., and Biswas, T. (2014). 14-Deoxyandrographolide alleviates ethanol-induced hepatosteatosis through stimulation of AMP-activated protein kinase activity in rats. Alcohol 48 (2), 123–132. doi: 10.1016/j.alcohol.2013.11.005

Mato, J. M., Alonso, C., Noureddin, M., and Lu, S. C. (2019). Biomarkers and disease. Cell Mol. Biol. (Noisy-le-grand) 65 (3), 652. doi: 10.1016/j.cmb.2019.07.004

Perumpail, B. J., Li, A. A., Iqbal, U., Sallam, S., Shah, N. D., Kwong, W., et al. (2018). Potential Therapeutic Benefits of Herbs and Supplements in Patients with NAFLD. Diseases 6 (3), 579. doi: 10.3390/diseases6030080

Pierre, G., Macdonald, A., Gray, G., Hendrikz, C., Preece, M. A., and Chakrapani, A. (2007). Prospective treatment in carnitine-acylcarnitine translocase deficiency. J. Inher. Metab. Dis. 30 (5), 815. doi: 10.1016/S0390-9538(07)60052-0

Qi, P., Li, X., Kong, D. S., Li, H. Z., Niu, C. C., and Pan, S. H. (2015). Herbal SGR Formula Prevents Acute Ethanol-Induced Liver Steatosis via Inhibition of Lipogenesis and Enhancement Fatty Acid Oxidation in Mice. Evid. Based Complement Alternat. Med. 2015, 613584. doi: 10.1155/2015/613584

Quiroga, A. D., and Lehner, R. (2018). Pharmacological intervention of liver triacylglycerol lipolysis: The good, the bad and the ugly. Biochem. Pharmacol. 155, 233–241. doi: 10.1016/j.bcp.2018.07.005

Reddy, J. K., and Rao, M. S. (2006). Lipid metabolism and liver inflammation. Am. J. Physiol. Gastrointest Liver Physiol. 290 (5), G852–G858.

Ren, L., Sun, D., Zhou, X., Yang, Y., Huang, X., Li, Y., et al. (2019). Chronic treatment with the modified Longdan Xiangan Tang attenuates carnitine-adequate fatty liver in rats by regulating hepatic de novo lipogenesis and fatty acid beta-oxidation-associated gene expression mediated by SREBP-1c, PPAR-alpha and AMPK-alpha. J. Ethnopharmacol. 232, 176–187. doi: 10.1016/j.jep.2018.12.034

Roh, J. S., Lee, H., Lim, J., Kim, J., Yang, H., Yoon, Y., et al. (2017). Effect of Ganjihwan on hepatic steatosis and inflammation in high fat diet-fed mice. J. Ethnopharmacol. 206, 315–326. doi: 10.1016/j.jep.2017.06.008

Rui, L. (2014). Energy metabolism in the liver. Compr. Physiol. 4 (1), 177–197. doi: 10.1002/cphy.c130024

Saha, A. K., and Rudnerman, N. B. (2003). Malonyl-CoA and AMP-activated protein kinase: an expanding partnership. Mol. Cell Biochem. 253 (1–2), 65–70. doi: 10.1023/A:1020053308203

Seo, M. S., Hong, S. W., Yeon, S. H., Kim, Y. M., Um, K. A., Kim, J. H., et al. (2014). Magnolia officinalis attenuates free fatty acid-induced lipogenesis via AMPK phosphorylation in hepatocytes. J. Ethnopharmacol. 157, 140–148. doi: 10.1016/j.jep.2014.09.031

Shang, J., Chen, L. L., Xiao, F. X., Sun, H., Ding, H. C., and Xiao, X. (2008). Resveratrol improves non-alcoholic fatty liver disease by activating AMPK-activated protein kinase. Acta Pharmacol. Sin. 29 (6), 698–706. doi: 10.1111/j.1745-750x.2008.00807.x

Xing, H., Wang, Y. N., Liu, X. B., Sheng, H., and Zang, Y. Q. (2011). Rhein ameliorates fatty liver disease through negative energy balance, hepatic...
lipogenic regulation, and immunomodulation in diet-induced obese mice. Am. J. Physiol. Endocrinol. Metab. 305 (5), E886–E893. doi: 10.1152/ajpendo.00333.2010

Sheng, D., Zhao, S., Gao, L., Zheng, H., Liu, W., Hou, J., et al. (2019). BabaoDan attenuates high-fat diet-induced non-alcoholic fatty liver disease via activation of AMPK signaling. Cell Biosci. 9, 77. doi: 10.1186/s13578-019-0339-2

Shi, K. Q., Fan, Y. C., Liu, W. Y., Li, L. F., Chen, Y. P., and Zheng, M. H. (2012). Traditional Chinese medicines benefit to nonalcoholic fatty liver disease: a systematic review and meta-analysis. Mol. Biol. Rep. 39 (10), 9715–9722. doi: 10.1007/s11033-012-1836-0

Shi, L. J., Shi, L., Song, G. Y., Zhang, H. F., Hu, Z. J., Wang, C., et al. (2013). Oxymatrine attenuates hepatic steatosis in non-alcoholic fatty liver disease rats fed with high fructose diet through inhibition of sterol regulatory element binding transcription factor 1 (Srebf1) and activation of peroxisome proliferator activated receptor alpha (PPARalpha). Eur. J. Pharmacol. 714 (1–3), 89–95. doi: 10.1016/j.ejphar.2013.06.015

Sun, X. H., Zhao, L. D., and Wei, W. (2019). A study on the mechanism of adipokine in non-alcoholic fatty liver in rats treated by four herbs decoction. Eur. J. Inflammation 17, 8. doi: 10.1177/2058739218853970

Tessari, P., Coracina, A., Cosma, A., and Tiengo, A. (2009). Hepatic lipid metabolism and non-alcoholic fatty liver disease. Nutr. Metab. Cardiovasc. Dis. 19 (4), 291–302. doi: 10.1016/j.numecd.2008.12.015

Theodoutou, M., Fokianos, K., Moniatis, D., Kadlenc, R., Chrysikou, A., Aristotelous, A., et al. (2019). Effect of resveratrol on non-alcoholic fatty liver disease. Exp. Ther. Med. 18 (1), 559–565. doi: 10.3892/etm.2019.7607

Uen, W. C., Shi, Y. C., Choong, C. Y., and Tai, C. J. (2018). Cordycepin suppressed lipid accumulation via regulating AMPK activity and mitochondrial fusion in hepatocytes. J. Food Biochem. 42 (5), 7. doi: 10.1111/jfb.12569

Veeramani, C., Alsaif, M. A., and Al-Numair, K. S. (2017). Lavatera critica, a green Uen, W. C., Shi, Y. C., Choong, C. Y., and Tai, C. J. (2018). Pharmacological characterization and applications of Sarax confusa mesophyll chlorophyll and its active components. Acta Pharmacol. Sin. 33 (9), 1119–1130. doi: 10.1038/aps.2012.126

Xiao, J., Fai, S. K., Liovig, E. C., and Tiope, G. L. (2013). Recent advances in hyperlipidemia treatment of non-alcoholic fatty liver disease. J. Tradit. Complement Med. 3 (2), 88–94. doi: 10.4103/2222-4110.110411

Xu, L., Yin, L., Tao, X., Qi, Y., Han, X., Xu, Y., et al. (2017). Dionocin, a potent ITGAI5 inhibitor, reduces the synthesis of collagen against liver fibrosis: Insights from SILAC-based proteomics analysis. Food Chem. Toxicol. 107 (Pt A), 318–328. doi: 10.1016/j.fct.2017.07.014

Yan, S., Kambhu, B., Hong, H., Liu, G., Huda, N., and Yin, X. M. (2019). Autophagy, Metabolism, and Alcohol-Related Liver Disease: Novel Modulators and Functions. Int. J. Mol. Sci. 20 (20), doi: 10.3390/ijms20205029

Yang, W., She, L., Yu, K., Yan, S., Zhang, X., Tian, X., et al. (2016). Jatrohorrizine hydrochloride attenuates hyperlipidemia in a high-fat diet-induced obesity mouse model. Mol. Med. Rep. 14 (4), 3277–3284. doi: 10.3892/mmr.2016.5634

Yang, L., Lin, W., Nigent, C. A., Hao, S., Song, H., Liu, T., et al. (2017). Linguiniughan Decoction Protects against High-Fat-Diet-Induced Nonalcoholic Fatty Liver Disease by Alleviating Oxidative Stress and Activating Cholesterol Secretion. Int. J. Genomics 2017, 2790864. doi: 10.1155/2017/2790864

Yang, J. M., Sun, Y., Wang, M., Zhang, X. L., Zhang, S. J., Gao, Y. S., et al. (2017). Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J. Gastroenterol. 25 (34), 5105–5119. doi: 10.3748/wjg.v25.i34.5105

You, Y., Yang, C., Thomas, P. G., Kharbanda, K. K., Casey, C. A., McNiven, M. A., et al. (2019). Lipophagy and Alcohol-Induced Fatty Liver. Front. Pharmacol. 10, 495. doi: 10.3389/fphar.2019.00495

Yao, Y. X., Wang, X., Shi, T. T., Dong, J. C., Li, F. J., Zeng, L. X., et al. (2019). Mitochondrial dysfunction in high-fat diet-induced nonalcoholic fatty liver disease: The alleviating effect and its mechanism of Polygonatum kingianum. J. Ethnopharmacol. 176, 1109083. doi: 10.1016/j.biopharma.2019.1109083

Yao, Y. X., Li, Y., Wei, C., He, Y., Cao, Y., Zhang, Y., et al. (2019). Amelioration of nonalcoholic fatty liver disease by swertiamarin in fructose-fed mice. Phytomedicine 59, 152782. doi: 10.1016/j.phymed.2018.12.005

Yao, H., Qiao, Y. J., Zhao, Y. L., Tao, X. F., Xu, L. N., Yin, L. H., et al. (2017). Herbal medicines and nonalcoholic fatty liver disease. World J. Gastroenterol. 22 (30), 6890–6905. doi: 10.3748/wjg.v22.i30.6890

Yoon, S., Kim, J., Lee, H., Lee, H., Lim, J., Yang, H., et al. (2017). The effects of herbal composition Gambigyeongsinhwang (4) on hepatic steatosis and inflammation in Otsuka Long-Evans Tokushima fatty rats and HepG2 cells. J. Ethnopharmacol. 195, 204–213. doi: 10.1016/j.jep.2016.11.020

Younossi, Z. M. (2019). Non-alcoholic fatty liver disease - A global public health perspective. J. Hepatol. 70 (3), 531–544. doi: 10.1016/j.jhep.2018.10.033

Yu, S., Rao, S., and Reddy, J. K. (2003). Peroxisome proliferator-activated receptors, fatty acid oxidation, steatohepatitis and hepatocarcinogenesis. Curr. Mol. Med. 3 (6), 561–572. doi: 10.2174/1566524033479537

Zamani, N., Shams, M., Nimrouzi, M., Zarshenas, M. M., Abbolhasani Foroughi, A., Fallahzadeh Aburghoei, E., et al. (2018). The effects of Zataria multiflora Boiss. (Shirazi thyme) on nonalcoholic fatty liver disease and insulin resistance: A randomized double-blind placebo-controlled clinical trial. Complement Ther. Med. 41, 118–123. doi: 10.1016/j.ctim.2018.09.010

Zar Kalai, F., Han, J., Ksouri, R., Abelldy, C., and Isoda, H. (2014). Oral administration of Nitraria retusa ethanolic extract enhances hepatic lipid metabolism in db/db mice model. BKS.Cg-Dock7(m)+/+ Lepr(db/)) through the modulation of lipogenesis-lipolysis balance. Food Chem. Toxicol. 72, 247–256. doi: 10.1016/j.fct.2014.07.029

Zhang, Y., Si, Z., Zhai, L., Yang, N., Yao, S., Sang, H., et al. (2013). Celastrus orbiculatus Thumb. ameliorates high-fat diet-induced non-alcoholic fatty liver disease in guinea pigs. Pharmazie 68 (10), 850–854.

Zhang, Y., Yu, L., Cai, W., Fan, S., Feng, L., Ji, G., et al. (2014). Protepanaxatriol, a novel PPARgamma antagonist from Panax ginseng, alleviates steatosis in mice. Sci. Rep. 4, 7375. doi: 10.1038/​srep07375

Zhang, E., Yin, S., Song, X., Fan, L., and Hu, H. (2016). Glycyrrhizin inhibits hepatocyte lipoprotein lipase through activation of autophagy and inhibition of ER stress/GSK-3-mediated mitochondrial pathway. Sci. Rep. 6, 38138. doi: 10.1038/srep38138
Zhang, L., Yao, Z., and Ji, G. (2018). Herbal Extracts and Natural Products in Alleviating Non-alcoholic Fatty Liver Disease via Activating Autophagy. *Front. Pharmacol.* 9, 1459. doi: 10.3389/fphar.2018.01459

Zhang, E., Yin, S., Zhao, S., Zhao, C., Yan, M., Fan, L., et al. (2019). Protective effects of glycyrrhizin on liver diseases. *Phytother. Res.* doi: 10.1002/ptr.6598

Zhang, Y., Liu, M., Chen, Q., Wang, T., Yu, H., Xu, J., et al. (2019). Leaves of Lippia triphylla improve hepatic lipid metabolism via activating AMPK to regulate lipid synthesis and degradation. *J. Nat. Med.* 73 (4), 707–716. doi: 10.1007/s11418-019-01316-5

Zheng, Y., Wang, M., Zheng, P., Tang, X., and Ji, G. (2018). Systems pharmacology-based exploration reveals mechanisms of anti-steatotic effects of Jiang Zhi Granule on non-alcoholic fatty liver disease. *Sci. Rep.* 8 (1), 13681.

Zhong, H., Chen, K., Feng, M., Shao, W., Wu, J., Chen, K., et al. (2018). Genipin alleviates high-fat diet-induced hyperlipidemia and hepatic lipid accumulation in mice via miR-142a-3p/SREBP-1c axis. *FEBS J.* 285 (3), 501–517. doi: 10.1111/febs.14349

Zhou, W., Rahimejad, S., Lu, K., Wang, L., and Liu, W. (2019). Effects of berberine on growth, liver histology, and expression of lipid-related genes in blunt snout bream (Megalobrama amblycephala) fed high-fat diets. *Fish Physiol. Biochem.* 45 (1), 83–91. doi: 10.1007/s10695-018-0536-7

Zhu, M., Hao, S., Liu, T., Yang, L., Zheng, P., Zhang, L., et al. (2017). Lingguizhugan decoction improves non-alcoholic fatty liver disease by altering insulin resistance and lipid metabolism related genes: a whole transcriptome study by RNA-Seq. *Oncotarget* 8 (47), 82621–82631. doi: 10.18632/oncotarget.19734

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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