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Review paper

Targeting AMPK related signaling pathways: A feasible approach for natural herbal medicines to intervene non-alcoholic fatty liver disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a metabolic disease characterized by abnormal deposition of lipid in hepatocytes. If not intervened in time, NAFLD may develop into liver fibrosis or liver cancer, and ultimately threatening life. NAFLD has complicated etiology and pathogenesis, and there are no effective therapeutic means and specific drugs. Currently, insulin sensitizers, lipid-lowering agents and hepatoprotective agents are often used for clinical intervention, but these drugs have obvious side effects, and their effectiveness and safety need to be further confirmed. Adenosine monophosphate (AMP)-activated protein kinase (AMPK) plays a central role in maintaining energy homeostasis. Activated AMPK can enhance lipid degradation, alleviate insulin resistance (IR), suppress oxidative stress and inflammatory response, and regulate autophagy, thereby alleviating NAFLD. Natural herbal medicines have received extensive attention recently because of their regulatory effects on AMPK and low side effects. In this article, we reviewed the biologically active natural herbal medicines (such as natural herbal medicine formulas, extracts, polysaccharides, and monomers) that reported in recent years to treat NAFLD via regulating AMPK, which can serve as a foundation for subsequent development of candidate drugs for NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is an acquired chronic metabolic stress induced liver injury, characterized by abnormal deposition of lipid in hepatocytes, including liver steatosis, steatohepatitis, cirrhosis and hepatocellular cancer [1–3]. NAFLD is not only an important cause of disability and death of liver disease, but also affects the progress of other chronic metabolic diseases and participates in the onset of type 2 diabetes (T2DM) [4], arteriosclerotic cardio cerebrovascular diseases [5,6], and extrahepatic cancers [7].

Recent researches have found that the prevalence of NAFLD in adults worldwide is about 25% [8], while this data reaches 40%–60% in overweight and obese people [9,10]. Notably, patients with diabetes have the highest prevalence (between 55% and 70%) [11,12]. Due to the complicated pathophysiology of NAFLD and the absence of adequate models for target discovery and chemical screening [13], there are currently no authorized pharmaceutical treatments for any of the stages of the disease [2,14–16]. Currently, the only available treatment for NAFLD is diet and exercise management, with the aim of reducing body weight by 7% [17–19]. Since patients are usually difficult to achieve and maintain such weight loss levels, finding safe, efficient, and economical drugs has become an important strategy for the treatment of NAFLD [15,19].

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In recent decades, an increasing number of researches have confirmed that natural herbal medicines have the potential to attenuate NAFLD while having few negative side effects, such as *Coptis chinensis* Franch. [20], *Cnidium monnieri* (L.) Cuss [21] and *Astragalus membranaceus* (Fisch.) Bge [22]. Furthermore, some monomers from natural herbs also exhibit anti-NAFLD properties, such as stilbenoids, flavonoids, terpenoids and quinones. Natural herbal medicines treatments for NAFLD can reduce inflammatory pathways, inhibit oxidative stress, control lipid synthesis, promote autophagy, and improve insulin resistance (IR). This information properly illustrates the promising future of natural herbal medicines.

Adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) consists of one catalytic subunit (α) and two regulatory subunits (β and γ). It is a kinase that balances the body's nutritional supply and the energy needs of various tissues and organs. The β-subunit of AMPK contains a carbohydrate binding domain that is associated with glycogen binding, while the function of the γ-subunit involves the monitoring and regulation of adenosine triphosphate (ATP)/AMP levels [23]. Meanwhile, under the action of upstream kinases such as liver kinase B1 (LKB1), the α-subunit can be phosphorylated at Thr172 site, which directly leads to the phosphorylation of AMPK. The phosphorylation (p)-AMPK improves hepatic lipid deposition by regulating catabolic processes (including glucose metabolism, autophagy and lipid oxidation) and anabolic processes (including lipid synthesis and glycogen storage) [24,25]. At present, more than 190 natural herbal medicines (including natural herbal medicine formulas, extracts, polysaccharides, and monomers, etc.) have been reported to treat NAFLD through activating AMPK. Therefore, this article reviews the biologically active natural herbal medicines that have been demonstrated in recent years to treat NAFLD by activating AMPK, which can provide a foundation for subsequent screening of new drugs for NAFLD.

2. AMPK related pathways and NAFLD

The 'two-hit' hypothesis is a classical theory of the pathogenesis of NAFLD [26,27]. Under insulin resistance (IR), insulin loses its inhibitory effect on lipids and causes the production of free fatty acids (FFA), eventually leading to triglyceride (TG) accumulation in hepatocytes and increased sensitivity of hepatocytes to damage factors, which is called the first hit. In addition, the accumulation of TG also causes the inhibition of autophagy. The second hit refers to the occurrence of oxidative stress reaction on the basis of the first hit, and the aggregation of oxidation products causes inflammatory reaction of hepatocytes, resulting in hepatocyte degeneration and necrosis [28]. The pathogenesis of NAFLD is shown in Fig. 1.

The role of AMPK in the development of NAFLD has been gradually clarified. Highly phosphorylated AMPK indicated a lower grade of NAFLD. AMPK can improve NAFLD by regulating lipid metabolism, autophagy, oxidative stress, inflammation, and IR-related signaling pathways. After activation, AMPK can inhibit hepatic fat synthesis and lipid deposition via suppressing acetyl-CoA carboxylase 1 (ACC1), sterol regulatory element binding protein 1 (SREBP-1) and fatty acid synthase (FAS) and upregulating peroxisome proliferators-activated receptor α (PPARα) [29]. Activated AMPK can also enhance autophagy through phosphorylating Beclin1 at Thr388 site and promoting mammalian target of rapamycin (mTOR) and unc-51-like kinase 1 (ULK1) phosphorylation, thereby promoting lipid degradation [30]. Studies have shown that IR is the main factor that aggravates liver lipid deposition and is regulated by AMPK. Activated AMPK can improve IR through increasing insulin sensitivity, enhancing glucose uptake and fatty acid oxidation (FAO) [31,32]. In addition, oxidative stress and inflammation are also regulated by AMPK, and the activation of AMPK is beneficial to reduce reactive oxygen species and inflammatory markers production in liver tissue [33–35]. Therefore, maintaining AMPK activation as a key strategy for treating NAFLD has attracted widespread attention [36].

3. Natural herbal medicines treat NAFLD through AMPK related pathways

NAFLD has a complex pathogenesis, and there is a lack of effective therapeutic drugs in clinical practice, but natural herbal medicines have shown advantages in NAFLD treatment with their overall concept and syndrome differentiation and treatment. In this review, we summarized the biologically active natural herbal medicines that have been confirmed in recent years to treat NAFLD by activating AMPK (Tables 1–5 and Fig. 2) [37–173].

3.1. AMPK-mediated lipid metabolism pathway

First, we observed that some natural herbal medicines increase PPARα, and inhibit SREBP-1 and FAS through regulating AMPK-managed silent information regulator factor 1 (SIRT1), mTOR and ACC signaling pathways, ultimately inhibiting FAA and TG production and improving NAFLD (Figs. 3 and 4).

3.1.1. Herbal medicine monomers

Betulinic acid is a triterpenoid compound which could relieve NAFLD in HepG2 cells with IR, primary rat hepatocytes and high fat diet (HFD)-fed Institute of Cancer Research (ICR) mice through suppressing SREBP-1 nuclear expression, and downregulating mTOR and ribosome S6 protein kinase (S6K) by promoting AMPK phosphorylation [37]. In 2014, Sun et al. [38] proposed that Radix Hedysari polysaccharides (RHP) obviously increased p-AMPK, p-ACC and PPARα, inhibited SREBP-1c, and improved hepatic lipid metabolism disorder in HFD rats. In the same year, isoquercitrin was revealed to upregulate adiponectin receptor agonist 1 (AdipoR1), downregulate SREBP-1 and FAS, and inhibit lipid accumulation in rat hepatoma H4IIE cells by activating AMPK. Moreover, Compound C markedly reversed the increase of p-AMPK and FAS induced by isoquercitrin [39]. Caffeine is a methyl purine alkaloid extracted from coffee beans, which can attenuate liver steatosis induced by high-energy diet (HED). Caffeine dose-dependently reduced alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by upregulating sirtuin 3 (SIRT3)/AMPK/ACC pathway. Moreover, SIRT3 knockout inhibited AMPK and ACC phosphorylation induced by caffeine in oleic acid (OA)-treated HepG2 cells [40].

In 2016, a study reported that treatment with Lycium barbarum polysaccharide (LBP) significantly improved lipid accumulation in palmitic acid (PA)-stimulated HepG2 cells and HFD-fed mice liver. Further studies revealed that LBP enhanced LKB1 deacetylation and AMPK phosphorylation through increasing SIRT1 [41]. β-Caryophyllene is an essential oil component extracted from Artemisia annua Linn., Artemisia argyi Levl.et Vant., Aquilaria Lam., and other plants. Based on PA-induced HepG2 cells lipid accumulation model, reserchers demonstrated that β-caryophyllene could improve lipid metabolism disorder by preventing SREBP-1c nuclear translocation and increasing forkhead box O1 (FOXO1) cytoplasmic translocation via activating AMPK and ACC1 [43]. In 2017, Wang et al. [44] reported that emodin could inhibit mTOR and S6K phosphorylation to block SREBP-1 nuclear translocation, thereby improving HFD-stimulated liver fat accumulation in mice. In 2018, Lin et al. [45] reported that ursolic acid could activate AMPK and ACC, and reduce the binding of SRC-1 to the SREBP-1c promoter region by targeting liver X receptor alpha (LXRα), thereby inhibiting the transcription

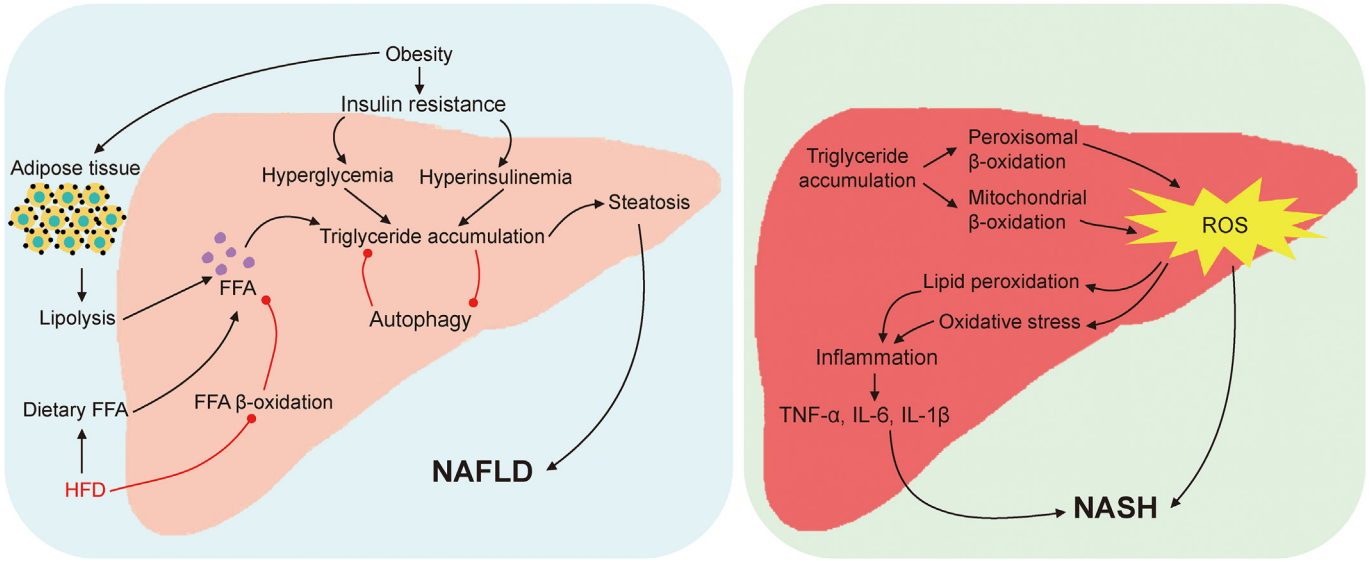


Fig. 1. The pathogenesis of non-alcoholic fatty liver disease (NAFLD). FFA: free fatty acids; HFD: high fat diet; IL-1β: interleukin-1β; IL-6: interleukin-6; NASH: non-alcoholic steatohepatitis; ROS: reactive oxygen species; TNF-α: tumor necrosis factor-α.

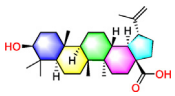
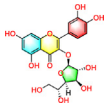
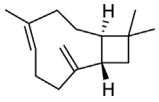
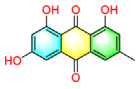
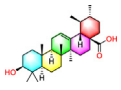
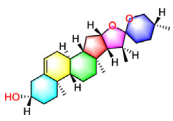
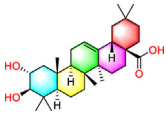
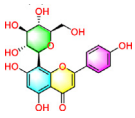
of SREBP-1c and improving T0901317-induced steatosis in HepG2 cells. Diosgenin (DSG) is mainly derived from the rhizome of Dioscoreaceae, and is currently used to synthesize various steroid drugs such as hydrocortisone, prednisone, norethisterone, relaxant and dexamethasone. In the same study, Cheng et al. [46] demonstrated that DSG could relieve NAFLD in HG-induced HepG2 cells through regulating AMPK and LXR.

Maslinic acid is a pentacyclic triterpene with anti-inflammatory and antioxidant activity. In 2019, a study reported that maslinic acid significantly inhibited FAS, upregulated SIRT1 and adipose triglyceride lipase (ATGL), and activated AMPK and ACC to ameliorate lipid accumulation and steatosis in NAFLD model [47]. In the same year, vitexin was revealed to relieve hepatic lipid deposition in HFD mice via activating AMPK to downregulate recombinant human CCAAT/enhancer binding protein-α (C/EBPα), SREBP-1c, PPARγ, FAS, and ACC, and upregulate PPARα and ATGL [48]. Later, berberine (BBR) was revealed to exert anti-NAFLD effects by upregulating AMPK/SREBP-1c/stearoyl-CoA desaturase-1 (SCD1) axis. BBR treatment activated AMPK and SREBP-1c, inhibited SREBP-1c and SCD1, and reduced TG release [49]. Another study found that BBR attenuated NAFLD via activating AMPK and its downstream PR domain-containing 16 (PRDM16) to enhance the overall energy consumption of diet-induced obese mice [50]. In addition, BBR also could increase p-ACC and SIRT3 in HFD rats' liver by upregulating p-AMPK, eventually improving NAFLD [51]. Tomatidine is a steroid alkaloid from green tomato. Tomatidine could enhance the conversion of TG and reduce adipogenesis in PA-simulated HepG2 cells by upregulating AMPK signaling to upregulate ATGL expression and downregulate FAS expression [52]. Acanthoic acid could exert hepatoprotective effects by activating AMPK/LKB1 and SIRT1 signaling pathways in an FXR/LXR-dependent manner in HFD mice. Moreover, Acanthoic acid also reduced α-smooth muscle actin (α-SMA), collagen I and tissue inhibitor of metalloproteinase-1 (TIMP1), improving HFD-induced liver fibrosis [53]. Guo et al. [54] proposed that s-petasin could decrease SREBP-1 and increase FOXO1 by activating AMPK, thus downregulating FAS and SCD-1, upregulating ATGL and hormone-sensitive triglyceride lipase (HSL), enhancing TG turnover, and inhibiting OA-induced adipogenesis in HepG2 cells.

In 2020, Sun et al. [55] showed that baicalein could reduce the transcriptional activity of SREBP-1 through upregulating AMPK signaling to inhibit SREBP-1 cleavage, eventually improve NAFLD. Antrodan is a β-glucan derived from A. cinnamomea. Under the stimulation of HFD, malondialdehyde (MDA), TG, TC, glucose, and insulin in plasma of mice were abnormally upregulated. However, antrodan could improve these effects by regulating AMPK/SIRT1/PPARγ/SREBP-1c signaling pathway [56]. Later, Cha et al. [57] found that diphlorethohydroxycarmalol (DPHC) had a therapeutic effect on NAFLD. DPHC treatment inhibited SREBP-1, C/EBPα, carbohydrate response element binding protein (ChREBP) and FAS in PA-treated HepG2 cells by enhancing AMPK and SIRT activities. In addition, DPHC also reversed the decrease of AMPK and SIRT activity in PA-induced zebrafish liver. Theaflavin-3,3′-digallate (TF3) is an active ingredient derived from black tea. The study has shown that TF3 plays an anti-NAFLD role by upregulating the AMPK axis to suppress lipid deposition in hepatocytes [58]. Kim et al. [59] confirmed that cyndione A could activate AMPK by enhancing LKB1 phosphorylation, thus reversing the increased mRNA expression of ACC, SREBP-1c and FAS caused by GW3954 and T0901317, and reducing lipid synthesis in HepG2 cells. In 2021, Chen et al. [60] reported that betaine attenuated NAFLD in ApoE$^{-/-}$ mice caused by HFD by upregulating AMPK, fibroblast growth factor 10 (FGF10) and ATGL. Moreover, FGF10 overexpression increased AMPK and reduced lipid deposition in HepG2 cells exposed to OA. Based on PA- and OA-caused HepG2 cells and HFD-stimulated mice NAFLD models, Sun et al. [61] showed that curcumin suppressed solute carrier family 13 member 5 (SLC13A5)/ATP citrate lyase (ACLY)-regulated citrate transport and metabolism through the AMPK/mTOR axis, thus inhibiting abnormal liver lipid deposition. Importantly, transfection of SLC13A5 and ACLY reversed the above effects. Acacetin is a bioactive compound contained in Acacia farnesiana (Linn.) Willd.

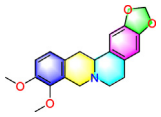
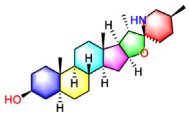
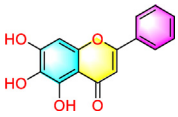
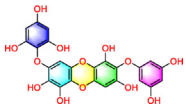
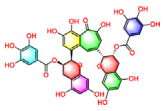
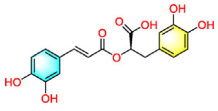
In 2022, Liou et al. [62] proposed that acacetin could improve HFD-induced hepatic lipid deposition in mice through activating AMPK to inhibit SREBP-1C, C/EBPα, C/EBPβ, and FAS mRNA expression. Acacetin also improved OA-induced lipid metabolism disorders in mouse FL83B hepatocytes. In the same year, Quercetin was found to reduce lipid accumulation in HepG2 cells exposed to FFA via regulating ACC1/AMPK/protein phosphatase 2A (PP2A) axis [63]. Subsequently, Wang et al. [64] revealed that limonin treatment could inhibit hepatic lipid deposition and FAS in HFD mice by AMPK-mediated SREBP-1/2 inhibition. Abietic acid is the main component of Pinus L. resin. Currently, another study by Jung et al. [65] revealed abietic acid treatment could reverse the enhanced expression of

Table 1
Adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)-mediated lipid metabolism pathway.

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/ Concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Monomers							
Betulinic acid		HFD -induced male SD rats HepG2 cells	5, 10 mg/kg for 14 days 10, 20, 40 μM	Betulinic acid relieved NAFLD by suppressing SREBP-1 through AMPK/ mTOR/SREBP axis.	PPARα, CD36, p-AMPK, p-ACC, CAMKK	SREBP-1, FAS, SCD1, p-mTOR, pS6K	[37]
RHP	–	HFD-induced SD rats	50, 150 mg/kg for 8 weeks	RHP suppressed lipid deposition in NAFLD model through upregulating AMPK/PPARα pathway.	p-AMPK, PPARα, p-ACC, CPT1, ATGL	SREBP-1c, FAS, SCD1	[38]
Isoquercitrin		FFA (0.1 mM)-induced H4IIE cells	50, 100, 200 μM	Isoquercetin improved fatty acid metabolism by promoting AMPK activation, upregulating AdipoR1, and inhibiting SREBP-1 and FAS.	p-AMPKα, p-ACC, AdipoR1	SREBP-1, FAS	[39]
Caffeine		HFD -induced C57BL/6 mice OA (1mM)-induced HepG2 cells	10, 20 mg/kg for 10 weeks 2 mM	Caffeine relieved HED-stimulated hepatic lipid deposition through cAMP/CREB/SIRT3/ AMPK/ACC axis.	p-CREB, SIRT3, p-AMPK, p-ACC		[40]
LBP	–	HFD -induced C57BL/6 mice PA (250 μM)-induced HepG2 cells	100, 200 mg/kg for 12 weeks 30, 100, 300, 600, 900 μg/mL	LBP attenuated NAFLD by activating SIRT1/ LKB1/AMPK axis.	p-AMPK, p-ACC, SIRT1, ATGL, CPT1	FAS, ELOVL6, DGAT, LKB1	[41]
β-Caryophyllene		PA-induced HepG2 cells	0.1, 0.5, 1, 5 μM	β-Caryophyllene relieved hepatic lipid deposition by upregulating AMPK signaling by activating CB2 receptor.	p-AMPKα, p-ACC, FOXO1, p-SREBP-1c, ATGL	FAS	[43]
Emodin		HFD -induced SD rats FFA (1 mM)-induced HepG2 cells	40, 80, 160 mg/kg for 8 weeks 20, 40, 80 μM	Emodin attenuated lipid deposition by upregulaing CaMKK/AMPK/ mTOR/ p70S6K/ SREBP-1 axis.	CPT1, PPARα, p-AMPK, p-ACC, p-CaMKK	SREBP-1, SCD1, FAS, CD36, p- mTOR, p-p70S6K	[44]
Ursolic acid		T0901317-induced male C57BL/6J mice HepG2 cells with IR	100, 250 mg/kg/day UA for 7 days 10 or 20 μM UA	Ursolic acid attenuated hepatic lipid deposition by regulating LXRα-mediated SREBP-1c and AMPK pathways.	p-AMPK, SMILE	SREBP-1c, FAS, SCD, SRC-1, ACC, ACLY, FAE, LXRα	[45]
Diosgenin (DSG)		HFD -induced SD rats High glucose-induced HepG2 cells	HFD mixed with 0.5%, 1% diosgenin 1, 10, 25, 50 μM	Diosgenin prevented NAFLD via the AMPK and LXRα pathways.	p-AMPK and p-ACC	LXRα, SREBP-1c	[46]
Maslinic acid		HFD -induced C57BL/6 mice OA (0.5 mM)-induced HepG2 cells	10, 20 mg/kg twice a week for 12 weeks 6.25–50 μM	Maslinic acid attenuated hepatic lipid deposition and decreased adipose tissue weight through activating SIRT1/AMPK signaling.	ATGL, SIRT1, p-AMPK, CPT1, HSL, CPT-2	C/EBPβ, PPARγ, SREBP-1c, FAS	[47]
Vitexin		HFD-induced C57BL/6J mice	1, 10, 20 mg/kg for 8 weeks	Vitexin relieved NAFLD through upregulating AMPK signaling via binding and activating LepR.	PPARα, ATGL, PGC-1a, CPT1α, p-AMPK, p-AKT	PPARγ, CEBPa, SREBP-1c, FAS, ACC, p-IRS1	[48]

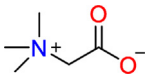
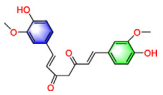
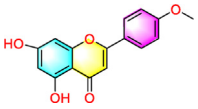
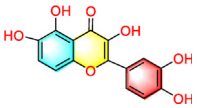
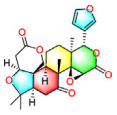
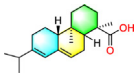
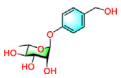
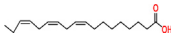
(continued on next page)

Table 1 (*continued*)

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/ Concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Berberine (BBR)		HFD-induced C57BL/6 mice PA (200 μM)-induced HepG2 and AML12 cells	300 mg/kg for 4 weeks 20 μM	BBR relieved hepatic lipid deposition by activating AMPK/ SREBP-1c/SCD1 pathway.	p-AMPK, p-SREBP-1c	SCD1, SREBP-1P, SREBP-1c	[49]
		HFD-induced male C57BL/6J mice; Adipose-specific AMPKα1/α2 KO mice	1.5 mg/kg/day daily for 6 weeks; 1.5 mg/kg/day for 8 weeks	BBR attenuated NAFLD via AMPK/ PRDM16 signaling.	UCP1, PRDM16, PPARγ, C/EBPa Cidea, PPARgc1a, PPARgc1b, ELOVL3, Cox7a1, Cox8b, PPARα, CPT1β, ACOX1, LCAD, PPARg, CEBPa, aP2		[50]
		HFD-induced SD rats	100 mg/kg BBR once a day for 8 and 16 weeks	BBR attenuated HFD-caused hepatic lipid deposition through SIRT3/AMPK/ ACC axis.	SIRT3, p-AMPK, p-ACC and CPT1α		[51]
Tomatidine		PA (0.5 mM)-induced HepG2 cells	0.1−10 μM for 24 h	Tomatidine reduced palmitate-caused lipid deposition by activating AMPK through VDR-regulated signaling.	p-AMPKa, p-ACC1, p-SREBP-1c, FOXO1, ATGL	SREBP-1, FAS	[52]
Acanthoic acid		HFD-induced male C57BL/6 mice	20, 40 mg/kg for 12 weeks	Acanthoic acid attenuated hepatic lipid deposition and fibrosis in NAFLD through upregulating FXR-LXRs -regulated AMPK/SIRT1 signaling.	PPARα, LXRα, LXRβ, FXR, p-AMPK, SIRT1	SREBP-1, FASN, SCD, ACLY, PPARγ, α-SMA, collagen I, TIMP1, p-LKB1	[53]
S-petasin		OA (0.4 mM)-induced HepG2 cells	0.2, 0.5, 1 μM	S-petasin inhibited lipid deposition by upregulating AMPK/ACC signaling.	p-AMPK, p-ACC, ATGL, HSL, FKHR	SREBP-1, FAS, SCD1	[54]
Baicalein		HFD-induced male Kunming mice OA (1 mM)-induced HepG2 cells	50, 200 mg/kg/day for 3 months 1, 5 μM	Baicalein suppressed hepatic lipid deposition by activating AMPK.	phospho-SREBP-1, p-SREBP-1, p-AMPK, p-ACC	FASN, ACC, mSREBP-1	[55]
Antrodan	–	HFD-induced C57BL/6 mice	20, 40 mg/kg for 45 days	Antrodan relieved NAFLD by activating AMPK/ SIRT1/SREBP-1c/ PPARγ pathway.	p-AMPK, SIRT1	SREBP-1c, PPARγ	[56]
DPHC		PA-induced HepG2 cells and zebrafiffish embryos	20, 40, 80 μM	DPHC inhibited hepatic lipid deposition and inflammation to improve NAFLD by activating SIRT1/ AMPK.	p-AMPK, SIRT1	SREBP-1c, C/EBPβ, ChREBP, FAS	[57]
TF3		OA-induced HepG2 and HEK 293T cells	1, 5, 10 μM	TF3 suppressed lipid deposition through targeting PK/AMPK axis.	p-AMPKα, p-ACC, CPT1	FAS, SREBP-1c	[58]
Rosmarinic acid		MCD diet-fed db/db mice PA (0.5 mM)-induced HepG2 cells	10 or 30 mg/kg for 2 weeks 20 or 40 μM	Rosmarinic acid attenuated hepatic steatosis and inflammation via AMPK and Nrf2 signaling.	p-AMPK, p-ACC, p-LKB1	FAS, SREBP-1c, ACC, SCD1	[59]

(*continued on next page*)

Table 1 (*continued*)

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/ Concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Betaine		HFD-induced male ApoE$^{-/-}$ mice OA (0.2 mM)-induced HepG2 cells	2% in drinking water for 8 weeks 20, 40, 80, 160 mM for 48 h	Betain attenuated HFD-stimulated NAFLD through upregulating FGF10/AMPK signaling.	p-AMPKa, LCAT, ATGL, Rxra	p-SREBF1, p-ACC, SIRT1, CPT1α, FASN, PPARγ, ACC2, HMGCR, NR1H3	[60]
Curcumin		HFD-induced C57BL/6J mice FFA (PA/OA, 1:4, 300 μM)-induced HepG2 cells	50, 150 mg/kg for 6 weeks 0.1, 1, 10, 100 μM	Curcumin improved SLC13A5/ ACLY dysregulation through AMPK/ mTOR signaling.	p-AMPK	SLC13A5, ACLY, p-mTOR	[61]
Acacetin		HFD-induced male C57BL/6 mice	5, 10 mg/kg i.p. twice per week for 12 weeks	Acacetin activated AMPK to promote fatty acid β-oxidation and inhibit hepatic inflammatory response.	ATGL, HSL, CPT1, CPT-2, PPARα, SIRT-1, p-AMPK	SREBP-1c, C/EBPα, C/EBPβ, FAS	[62]
Quercetin		FFA (0.75 mM) -induced HepG2 cells	5 μM	Quercetin exerted anti-NAFLD effect through suppressing DNL via ACACA/AMPK/ PP2A pathway.	p-ACC, p-AMPK	XBP-1, p-eIF2α, SREBP-1, ACACA, CiC, DGAT2, PP2A	[63]
Limonin		HFD-induced male C57BL/6 mice PA (0.4 mM)-induced AML12 cells	50 mg/kg/day for 9 weeks 50, 100 μM	Limonin attenuated NAFLD through activating AMPK-mediated inhibit of SREBP-1/2 transcriptional activity.	p-AMPKα, p-ACC	FASN, SCD1, ACC1, HMGCR, HMGCS, SREBP-1, SREBP2	[64]
Abietic acid		PA (250 or 400 μM)-induced human primary hepatocytes	20, 50 and 100 mM	Abietic acid attenuated ERS and lipid deposition via the AMPK/ORP150 pathway.	p-AMPK, ORP150	SREBP-1, SCD1, peIF2α, CHOP	[65]
GR		FFA (0.4 mM)-induced L02 cells	50, 200, 500 μg/mL	GR suppressed lipid deposition through activating AMPK/ mTOR/ SREBP-1 axis.	PPARα, p-AMPK	p-mTOR, SREBP-1	[66]
α-linolenic acid		HFD -induced C57BL/6J mice/OA (0.9 mM)-induced HepG2 cells	2.2, 3.3, 5.5 g/ kg·bw /0.1 mM	α-linolenic acid attenuated NAFLD by activating AMPK to inhibit apoptosis.	Bcl-2, p-AMPK,	GRP78, CHOP, p-IRE1α, TRAF2, p-JNK, Bax, FAS, SREBP-1c	[67]
Herbal formulas							
QHD	*Artemisia capillaris* Thunb., *Polygonum cuspidatum* Sieb. et Zucc., *Hypericum japonicum* Thunb., *Urcuma Longa* L., and *Gardenia jasminoides* Ellis	HFD-induced SD rats FFA-induced L02 cells	0.1 mL/kg/day for 4 weeks 5%, 10%, 15% QHD serum for 48 h	QHD suppressed hepatic lipid deposition via upregulating p-AMPK *in vivo* and *in vitro*.	p-AMPK, p-ACCα	ACCα, SREBP-1, ChREBP	[68]
BHJRST	Anemarrhena asphodeloides Bge., Gypsum Fibrosum, root of Glycyrrhiza uralensis Fisch., seed of Oryza sativa, and root of Panax ginseng C. A. Mey.	male db/db mice PA (0.1 mM)-induced HuS-E/2 cells	900 mg/kg twice daily for 6 weeks 100 or 250 μg/mL	BHJRST exerted lipid-lowering effect by regulating AMPK/ACC signaling.	p-AMPK, p-ACC, ATGL		[69]
SC	Silybin accounts for 50%−70% of the seed extract of *Silybum marianum* (L.) Gaertn.	HFD-induced hamsters	50, 100 mg/kg for 8 weeks	SC relieved NAFLD by modifying de novo lipogenesis and FAO via AMPK.	CPT1α, p-AMPK	PPARγ, ACC, FAS, FABP, p-caveolin 1	[70]
HQT	Alisma plantago-aquatica Linn., *Fructus Crataegus* pinnatifida Bge., *Typha angustifolia* and *Nelumbo nucifera* Gaertn. leaves	FFA (1 mM) induced L02 and HepG2 cells	HQT-medicated serum of SD rats with 2.7, 5.4, 10.8 g/ kg/day for 7 days	HQT prevented lipid deposition through activating AMPK/PPARα axis.	p-AMPK, PPARα, CPT1, ACOX1	SREBP-1	[71]

(*continued on next page*)

Table 1 (*continued*)

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/ Concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
CHLZT	*Bupleurum chinense* DC, *Scutellaria baicalensis* Georgi, *Pinellia ternate* (Thunb.) Breit., *Codonopsis pilosula* (Franch.) Nannf., *Curcuma Longa* L., Glycyrrhizae radix et rhizome praeparata cum melle, *Zingiber officinale* Rosc., and *Ziziphus jujuba* Mill. var. spinosa (Bunge) Hu ex H. F. Chou.	HFD-induced male SD rats 1% long chain fat emulsion-induced HepG2 cells	3.5 mL/day for 4 weeks CHLZT-containing serum	CHLZT relieved NAFLD via upregulating p-AMPKα to suppress ACC, SREBP2 and HMGR.	p-AMPKα, PPARγ	ACCα, p-ACCα, SREBP-2, HMGR	[72]
LXT	Radix ET Rhizoma Gentiana scabra Bge., Radix Scutellaria baicalensis Georgi, Fructus Gardenia jasminoides Ellis, *Alisma plantago-aquatica* Linn., *Plantago asiatica* L., *Angelica sinensis* (Oliv.) Diels, *Rehmannia glutinos*a Libosch., *Bupleurum chinense* DC., *Taraxacum mongolicum* Hand. -Mazz., *Lophatherum gracile* Brongn., *Glycyrrhiza uralensis* Fisch.	Olanzapine (5 mg/kg)-induced male SD rats	50 and 500 mg/kg for 8 weeks	LXT ameliorated NAFLD through regulating AMPK/PPARα/SREBP-1c signaling.	PPARα, CPT1, ACO, p-AMPK-α	SREBP-1c, ACC-1, FAS, SCD1, AMPK-α	[73]
YQ	*Astragalus membranaceus* (Fisch.) *Bge.var.mongholicus* (Bge.) Hsiao, *Dioscorea opposita* Thunb., *Panax ginseng* C. A. Mey., *Polygonatum sibiricum* Red., *Cornus officinalis* Sieb. et Zucc., *Pueraria lobata* (Willd.) Ohwi, *Crataegus pinnatifida* Bge. fructus, and fermented soya beans.	T2DM rats	3.5, 7, 14 g/kg for 3 weeks	YQ attenuated T2DM by regulating IRS-2/AKT/GLUT4 axis and relieved hepatic lipid deposition through activating AMPK/PPARα/SREBP-1/ACC1 pathway.	p-AMPK, p-ACC, CPT1, IRS-2, p-PI3K, p-AKT, GLUT4, PPARα	SREBP-1c, ACC, FAS, SCD	[74]
FTZ	*Fructus Ligustri* Lucidi, *Coptis chinensis* Franch., *Rubia cordifolia* L., *Salvia miltiorrhiza* Bge., *Eucommia ulmoides* Oliv., *Panax notoginseng* (Burk.) F. H. Chen, *Atractylodes lancea* (Thunb.) DC. and *Fructus Citrus* medica L. var. sarcodactylis Swingle	HFD-induced castrated minipigs FFA-induced HepG2 cells	1.2 g/kg/day for 22 weeks 25, 50, 100 μg	FTZ alleviated hepatic steatosis and fibrosis via activating AMPK.	Bcl-2/Bax, p-AMPK	Cleaved Caspase-3, Bax, α-SMA	[75]
QSHY	*Artemisia capillaris* Thunb., *Polygonum cuspidatum* Sieb. et Zucc., Curcuma Longa L., *Gardenia jasminoides* Ellis fructus, and *Hypericum japonicum* Thunb.	HFD-induced C57BL/6J mice	0.21g of crude drug/kg for 6 weeks	QSHY attenuated hepatic lipid deposition in NAFLD mice through activating AMPK/SIRT1/UCP1 pathway.	p-AMPK, SIRT1, UCP1		[76]
ZXD	*Atractylodes lancea* (Thunb.) DC. and *Alisma orientale* (Sam.) Juzep.	HFD-induced C57BL/6J mice PA (0.1 mM)-induced HepG2	1.3, 2.6, 5.2 mg/kg for 10 weeks 250, 500, 1000 μg/mL	ZXD relieved NAFLD through upregulating LKB1/AMPK/PGC-1α axis.	PGC-1α, ACADS, CPT1α, CPT1β, UCP1, ACSL-1, NRF-1, LKB1, p-AMPK, p-ACC		[77]
ZXBZ	*Alisma orientale* (Sam.) Juzep. and *Atractylodes lancea* (Thunb.) DC.	HFD-induced C57/BL6 mice	750 and 1500 mg/kg for 12 weeks	ZXBZ exerted lipid-lowering via activating AMPK to regulated the energy sensing network.	SIRT1, PPARα, PGC-1α, p-AMPK, p-ACC, CYP7a1, CYP27a1, LXRα, LPL, CPT1α	SREBP-1c, p-mTOR, ChREBP, HMGCR	[78]

(*continued on next page*)

Table 1 (*continued*)

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/ Concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Extracts							
CJE	–	FFA (1 mM)-induced HepG2 cells	0.5, 1 mg/mL	CJE relieved hepatic lipid deposition by activating AMPK.	PPARα, CPT1, p-AMPK, p-ACC	FAS, ACC	[79]
MO	–	FFA (0.5 mM)-induced HepG2 and FL83B cells	50, 100 μg/mL	MO inhibited TG synthesis and lipid deposition through promoting AMPK phosphorylation.	p-AMPK	SCD1, FAS, CD36, SREBP-1c	[80]
DLL-Ex	–	FFA (1 mM)-induced HepG2 cells	1, 10, 50, 100, 250 μg/mL	DLL-Ex exerted anti-NAFLD effects by activating AMPK to inhibit FFA uptake and improve mitochondrial dysfunction.	p-AMPK, PGC-1a	Adrp, Cidec, Fit2, CD36, VLDLR, pERK, p-JNK, p-p38	[81]
BHe	–	HFD-induced ICR mice	100, 200, 400 mg/kg for 84 days	BHe showed anti-NAFLD activities via activating AMPK to enhance hepatic glucose intake and lipid metabolism, and improve oxidative stress	AMPKα, UCP2	ACC1, C/EBP, SREBP-1c	[82]
TQPE	–	HFD-induced ICR mice	15, 30 mg/kg for 8 weeks	TQPE attenuated hepatic steatosis through improving lipid metabolism and insulin resistance -mediated by AMPK.	p-AMPK, p-ACC, p-IRS-1, p-AKT	SREBP	[83]
TSB and TSF	–	FFA (1 mM)-induced HepG2 cells	100, 200, 500 μg/mL	TSB and TSF showed lipid-lowering effects by activating AMPK, PPAR, and LC3.	p-AMPK, p-ACC, PPARα, LC3II, p-ULK1	LXR, SREBP-1c, ACC, FASN, SCD	[84]
RO	–	1% OA-induced SD rats OA-induced HepG2 cells	100, 200, 400 mg/kg/day for 21 days 1, 10, 60, 100 μg/mL	RO showed lipid-lowering effect via AMPK/SREBP-1c axis.	p-AMPK, p-CaMKK, p-ACC	SREBP-1c, p-LKB1, FAS	[85]
HLF	–	HFD-induced SD rats	50, 100 mg/kg/day for 12 weeks	HLF relieved NAFLD by regulating adiponectin/AMPK pathway- related molecules expression.	AdipoR2, PPARα, CPT1, ACO, ACOX1, p-AMPKa	CHREBP, SREBP-1c, LXRα, CD36, FAS, SCD1	[86]
CAE	–	HFD-induced C57BL/6J mice	100, 200 mg/kg/day for 6 weeks	CAE attenuated NAFLD through balancing lipogenesis and FAO via activating AMPK.	p-AMPK, PPARα, CPT1, PGC-1a, SIRT1	p-NF-κB, p-IκB, TLR4, GPAM, SREBP-1, FAS	[87]
MCA	–	HFD-induced male C57BL/6 J mice OA (0.1 mM) -induced HuS-E/2 cells	1% or 3% lyophilized MCA for 10 weeks 10, 50, 100 μg/mL	MCA enhanced insulin sensitivity and relieved HFD-caused NAFLD through activating AMPK.	p-AMPK, p-ACC		[88]
AP	–	HFD-induced C57BL/6J mice FFA (1 mM)-induced HepG2 cells	20 mg/kg 2.5, 5, 10 μg/mL	AP improved hepatic glucose and lipid metabolism to relieve NAFLD by regulating intestinal flora through AMPK/ACC pathway.	PPARγ, p-AMPK, p-ACC	SREBP-1c, FAS, p-NF-κB	[89]

(*continued on next page*)

Table 1 (*continued*)

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/ Concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
BME	–	HFD-induced C57BL/6J mice	6 g/500 g diet for 12 weeks	BME enhanced insulin sensitivity and attenuated hepatic lipid deposition through upregulating FGF21 and AMPK/SIRT1 signaling.	FGFR1, FGFR3, FGFR4, PGC-1a, p-AMPK, SIRT1		[90]
DI-HET	–	OA (0.1 mM)-induced HepG2 cells	5, 10 μg/mL	DI-HET relieved OA -caused lipid deposition through regulating SIRT-1/ LKB-1/AMPK signaling.	SIRT-1, p-LKB1, p-AMPK, p-ACC, PPARα, CPT1,	FAS, LXR-α, SREBP-1c, SREBP-2, HMGCR, CD36, ACOX-1	[91]

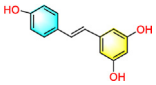
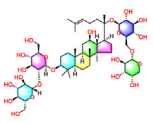
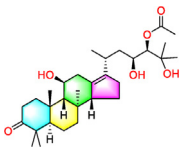
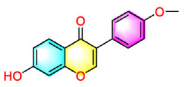
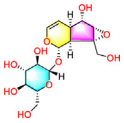
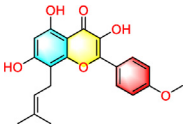
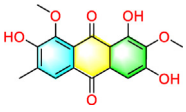
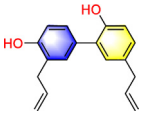
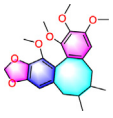
ACADS: acyl-CoA dehydrogenase short chain gene; ACC: acetyl-CoA carboxylase; ACLY: ATP citrate lyase; ACSL-1: acyl-CoA synthetase long chain family member 1; ACOX1: acyl-CoA oxidase 1; Adrp: adipose differentiation-related protein; AdipoR: adiponectin receptor; AKT: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; AP: Adlay (*Coix lacryma-jobi* L.) polyphenol; aP2: adipocyte protein 2; ATGL: adipose triglyceride lipase; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; BHe: *Lonicera caerulea* L. extract; BHJRST: Bai-Hu-Jia-Ren-Shen-Tang; BME: *Momordica charantia* L. extract; CA: corosolic acid; CAE: *Cynanchum atratum* Bge. ethanol extract; CaMKK: calmodulin dependent protein kinase kinase; CD36: platelet glycoprotein 4; CEBP or C/EBP: CCAAT/enhancer-binding protein; CHLZT: ChaiHu Li Zhong Tang; CHOP: C/EBP homologous protein; ChREBP: carbohydrate response element binding protein; Cide: cell death-inducing DFFA-like effector; CJE: *Cirsium japonicum* DC. ethanol extract; COL1A1: collagen type I alpha 1; Cox7a1: cytochrome c oxidase subunit 7a1; Cox8b: cytochrome c oxidase subunit 8b; CPT1: carnitine palmitoyltransferase 1; DGAT: diacylglycerol O-acyltransferase; DI-HET: *Dillenia indica* L. hydroethanolic extract; DLL-Ex: *Dolichos lablab* Linne water extract; DPHC: diphlorethohydroxycarmalol; ELOVL: elongase of very long chain fatty acids family member; FABP: fatty acid binding protein; FAE: fatty acid elongase; FAS or FASN: fatty acid synthase; FFA: free fatty acids; FGFR: fibroblast growth factor receptor; Fit2: fat storage-inducing transmembrane protein 2; FOXO1: forkhead box O1; FTZ: Fufang Zhenzhu Tiaozhi capsule; FXR: farnesoid X receptor; GPAM: glycerol-3-phosphate acyltransferase: mitochondrial; GLUT4: glucose transporter type 4; GRP78: glucose-regulated protein 78; GR: gastrodigenin rhamnopyranoside; HED: high-energy diet; HFD: high fat diet; HLF: *Crataegus pinnatifida* Bge. leaf flavonoids; HMGCR or HMGR: 3-hydroxy-3-methylglutaryl-coA reductase; HMGCS: 3-hydroxy-3-methylglutaryl-coA synthase; HO-1: heme oxygenase-1; HQT: Hugan Qingzhi tablet; HSL: hormone-sensitive lipase; LBP: *Lycium barbarum* polysaccharide; LCAD: long-chain acyl-CoA dehydrogenase; LCAT: lecithin-cholesterol acyltransferase; LC3: microtubule-associated proteins 1A/1B light chain 3; LKB1: liver kinase B1; LXR: liver X receptors; LXT: Longdan Xiegan Tang; MCA: *Momordica cochinchinensis* Arill; MCD: methionine/choline-deficient; MO: *Magnolia officinalis* Rehd.et Wils. extract; mTOR: mammalian target of rapamycin; Nrf2: nuclear factor erythroid 2-related factor 2; NR1H3: nuclear receptor subfamily 1 group H member 3; OA: oleic acid; ORP150: oxygen-regulated protein 150 kd; PA: palmitic acid; p-ACC: phospho-acetyl-CoA carboxylase; p-AKT: phosphorylated protein kinase B; p-AMPK: phosphorylated AMP-activated protein kinase; p-eIF2α: phosphorylated eukaryotic translation initiation factor 2 alpha; PGC1: peroxisome proliferator-activated receptor gamma coactivator-1; p-IκB: phospho-IκBα; p-IRE1: phosphorylated inositol-requiring enzyme 1; p-IRS1: phosphorylated insulin receptor substrate 1; PI3K: phosphoinositide 3-kinase; p-JNK: phosphorylated JNK; p-LKB1: PPAR: peroxisome proliferator-activated receptor; PP2A: protein phosphatase 2A; PRDM16: PR domain containing 16; p-ULK1: phosphorylated unc-51 like kinase 1; QHD: QushiHuayu Decoction; QSHY: Qushi Huayu granules; RHP: Radix Hedysari polysaccharide; RO: *Rosmarinus officinalis* L. ethanol extract; SC: Silibinin Capsules; SCD1: stearoyl-coA desaturase 1; SIRT1: sirtuin1; SLC13A5: solute carrier family 13 member 5; SMA: smooth muscle actin; SMILE: small heterodimer partner-interacting leucine zipper protein; SRC-1: steroid receptor coactivator 1; SREBP: sterol regulatory element binding protein; TF3: theaflavin-3:3'-digallate; TIMP1: tissue inhibitor of metalloproteinases 1; TLR4: toll-like receptor 4; TQPE: *Trapa quadrispinosa* pericarp extract; TRAF2: tumor necrosis factor receptor-associated factor 2; TSB: *Toona sinensis* bark extract; TSF: *Toona sinensis* fruit extract; UA: ursolic acid; UCP: uncoupling protein; VLDLR: very low density lipoprotein receptor; XBP-1: X-box binding protein 1; YQ: YiQi YangYin Decoction; ZXBZ: ZexieBaizhu Decoction; ZXD: Zexie Decoction.

endoplasmic reticulum stress (ERS) markers phosphorylation of eukaryotic initiation factor-2α (eIF2α) and C/EBP homologous protein (CHOP), improving lipid accumulation and reducing apoptosis in PA-stimulated human primary hepatocytes. Importantly, siRNA-mediated AMPK knockdown reversed the effect of abietic acid on adipogenesis and promoted apoptosis. Gastrodigenin rhamnopyranoside (GR) is an antioxidant component extracted from M. oleifera seeds, which has significant hypolipidemic and hepatoprotective effects. Another study by Liao et al. [66] reported that GR treatment suppressed lipid deposition in L02 cells exposed to FFA by activating AMPK/mTOR/SREBP-1 and PPARα pathways. Under the stimulation of OA and HFD, phospho-inositol-requiring enzyme 1α (p-IRE1α) and Bcl2-associated X (Bax) were abnormally increased, while Bcl-2 was significantly downregulated in HepG2 cells and mice liver. However, α-linolenic acid intervention could improve these changes by activating AMPK [67].

3.1.2. Herbal medicine formulas

In 2013, Feng et al. [68] found that QushiHuayu Decoction (QHD) reduced lipid production in FFA-stimulated L02 cells and HFD-fed rats, and the potential molecular mechanism is related to the reduction of SREBP-1 and ChREBP, and increase p-AMPK and p-ACC. In 2015, Bai-Hu-Jia-Ren-Shen-Tang (BHJRST) was reported to reduce PA-caused lipid deposition in HuS-E/2 cells and hepatic steatosis in db/db mice liver through upregulating AMPK/ACC signaling axis [69]. In 2017, Cui et al. [70] reported that Silibinin Capsules (SC) could improve liver lipid deposition in male hamsters exposed to HFD by increasing p-AMPKα and decreasing SIRT1. Later, Yin et al. [71] studied the effect of Hugan Qingzhi Tablets (HQT) on NAFLD; HQT enhanced adiponectin expression, upregulated p-AMPK and PPARα, downregulated SREBP-1, and reduced lipid accumulation in FFA-induced HepG2 and L02 cells. In 2018, Zhang et al. [72] demonstrated that Chaihu Lizhong Tang (CHLZT) could attenuate NAFLD in HFD rats via upregulating p-AMPKα and PPARγ and downregulating SREBP2, 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) and p-ACC. Similar results were observed with the application of AMPK agonist acadesine (AICAR). Using olanzapine-induced NAFLD model in male rats, Ren et al. [73] found that Longdan Xiegan Tang/Decoction (LXT) improved liver adipogenesis by increasing p-AMPKα and reducing SREBP-1c. In 2021, Li et al. [74] found that Yiqi Yangyin Decoction (YQ) could improve hepatic lipid accumulation in T2DM rat with NAFLD via upregulating AMPK/PPARα/SREBP-1/ACC1 pathway. Later, Wang et al. [75] researched the effects of Fufang Zhenzhu Tiaozhi capsule (FTZ) on NAFLD and found that FTZ could increase p-AMPK and reduce lipid deposition in FFA-simulated HepG2 cells, and these effects were reversed by AMPK inhibitor compound C. In addition, Zhang et al. [76] demonstrated that TG and ALT were abnormally increased in C57BL/6J mice liver after HFD feeding. However, Qushi Huayu Granules (QSHY) intervention could improve these effects through upregulating AMPK/SIRT1/uncoupling protein 1 (UCP1) axis. In 2022, Wang et al. [77] showed that Zexie Decoction (ZXD) could

Table 2
Adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK)-mediated autophagy pathway.

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Monomers							
Resveratrol		HFD-fed mice PA (0.2 mM)-induced HepG2 cells	0.4% in the diet for 4 weeks 20, 40, and 80 μM	RSV improved hepatic lipid deposition by activating autophagy through enhanced cAMP/PRKA/AMPK/SIRT1 signaling.	LC3II, CPT1α, p-ACC, SIRT1, p-AMPK	p62, SREBP-1c	[92]
Ginsenoside Rb2		C57BL/KsJ-Lepdb (db/db) mice OA (1 mM)-induced HepG2	10 mg/kg for 4 weeks 50 μM	Ginsenoside Rb2 attenuated hepatic lipid deposition through promoting autophagy via SIRT1 and AMPK pathways.	p-AMPK, SIRT1, LC3II	p-mTOR, p62	[93]
AA		MCD-induced C57BL/6 mice MCD-induced WRL-68 and LX-2	15, 30, 60 mg/kg for 4 weeks 1, 2, 4, 8, 16 μM	AA attenuated NAFLD through suppressing oxidative stress and activating autophagy via regulating AMPK/mTOR signaling.	LC3II, p-ULK1, p-AMPK	TGF-β, α-SMA, IL-1β, MCP1, p62, TIMP, IL-6, p-mTOR	[94]
Formononetin		HFD-induced C57BL/6 J mice FFA (1 mM)-induced HepG2 cells	100 mg/kg per day for 14 weeks 20 μM	Formononetin enhanced TFEB nuclear expression to promote autophagy and attenuate lipid deposition through activating AMPK.	p-AMPK, TFEB, Beclin1, LAMP1, ATP6V1A, PGC-1α, LC3II	p-S6K1, p62	[95]
Catalpol		Male ob/ob mice HFD-induced C57BL/6 mice PA (0.3 mM)-induced HepG2 cells	100 mg/kg for 4 weeks 50 mg/kg/day for 4 weeks 10 μg/mL	Catalpol relieved hepatic lipid deposition and lipotoxicity through activating autophagy by upregulating AMPK-mediated TFEB translocation.	p-AMPK, LC3II, PPARα, CPT1, nu-TFEB	p62, ACC1α, FAS	[96]
Icaritin		sodium oleate at 100 μM-induced L02 cells, 3T3-L1 preadipocytes, and C2C12 myoblasts	0.7, 2.2, 6.7, or 20 μM	Icaritin relieved lipid deposition by enhanced autophagy via LKB1/AMPK/ACC axis.	CaMKKβ, p-LKB1, p-AMPK, p-ACC, LC3II	p62	[97]
Aurantio-obtusin		HFD-induced C57BL/6J mice FFA (0.75 mM)-induced HepG2 cells	5, 10 and 15 mg/kg for 4 weeks 12.5, 25 and 50 μM	Aurantio-obtusin enhanced autophagy and relieved hepatic steatosis through activating AMPK and TFEB.	PPARα, ACOX1, p-AMPK, ATG5, LC3II/LC3I, TFEB	SREBP-1, Ccl2, TGF-β1, Cyp7a1, Col1a1, FASN, p62	[98]
Honokiol		HFD-induced C57BL/6J mice FFA (0.75 mM)-induced AML12 cells	2.5, 10 mg/kg for 4 weeks 2.5, 5, 10 μM	Honokiol protected hepatocytes from lipotoxic stress by upregulating SIRT3-AMPK signaling.	SIRT3, p-AMPK, LCAD, LC3	p62	[99]
Schisandrin B		HFD-induced Male C57BL/6J mice FFA (0.5 mM)-induced HepG2 cells and MPHs	50 mg/kg for 5 weeks 12.5, 25, 50 μM	Schisandrin B attenuated hepatic lipid deposition and enhanced FAO through activating autophagy via AMPK/mTOR signaling.	p-AMPK, p-ULK1 (Ser555), PI3KC3, Beclin-1, ATG7, ATG5, LAMP1, LC3II, CYP7A1, CPT1α, ACOX1, ACADL, ACADM, HMGCS2	p62, p-mTOR, p-ULK1 (Ser757), p-p70	[100]
Formulas							
TSF	*Astragalus membranaceus* (Fisch.) Bge.var.mongholicus (Bge.) Hsiao, *Euonymus*	HFD-induced C57BL/6J mice PA (0.3 mM)-	2.4 g/kg/day for 16 weeks 25, 50, 100 μg/mL	TSF attenuated hepatic lipid deposition through activating AMPK/	p-AMPK, SIRT1, LC3II	p62	[101]

(*continued on next page*)

Table 2 (*continued*)

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
	alatus (Thunb.) Sieb, *Rehmannia glutinosa* Libosch., *Citrus aurantium* Engl., *Cornus officinalis* Sieb. et Zucc., *Rheum palmatum* L., and *Panax notoginseng* (Burk.) F. H. Chen.	induced HepG2 cells		SIRT1 pathway -regulated autophagy.			
Extracts							
APE	–	FFA (0.3 mM)-induced HepG2 cells	10, 20 μg/mL	APE relieved lipid deposition in FFA-simulated HepG2 cells by upregulating SIRT1/ AMPK-mediated autophagy.	p-ACC, SCD1, PPARα, PGC-1α, LC3II, p62, ATG7, RAB7, Beclin1, LAMP2, SIRT1, LKB1, p-AMPK, ULK1	SREBP-1c, ACC, FASN	[102]

AA: alisol A 24-acetate; ACC: acetyl-CoA carboxylase; ACOX1: acyl-CoA oxidase 1; AMPK: adenosine monophosphate-activated protein kinase; APE: apple polyphenol extract; CaMKK: calmodulin dependent protein kinase kinase; CPT1: carnitine palmitoyltransferase 1; COL1A1: collagen type I alpha 1; FAS or FASN: fatty acid synthase; FFA: free fatty acids; HFD: high fat diet; LAMP: lysosome-associated membrane protein; LCAD: long-chain acyl-CoA dehydrogenase; LC3: microtubule-associated proteins 1A/1B light chain 3; HMGCS: 3-hydroxy-3-methylglutaryl-coA synthase; LKB1: liver kinase B1; MCD: methionine/choline-deficient; OA: oleic acid; PA: palmitic acid; p-ACC: phospho-acetyl-CoA carboxylase; p-AMPK: phosphorylated AMP-activated protein kinase; PGC1: peroxisome proliferator-activated receptor gamma coactivator-1; PI3K: phosphoinositide 3-kinase; PPAR: peroxisome proliferator-activated receptor; p-ULK1: phosphorylated unc-51 like kinase 1; p62: sequestosome 1; mTOR: mammalian target of rapamycin; SCD1: stearoyl-coA desaturase 1; SIRT1: sirtuin1; SMA: smooth muscle actin; SREBP: sterol regulatory element binding protein; TGF: transforming growth factor; TIMP1: tissue inhibitor of metalloproteinases 1; TSF: Tangshen formula; ULK1: unc-51 like kinase 1.

suppress lipid deposition in PA-stimulated HepG2 cells and HFD mice liver. Further research confirmed that ZXD activated peroxisome proliferators-activated receptor γ coactivator l alpha (PGC-1α), and upregulated p-AMPK, LKB1, PGC-1α, and p-ACC. A recent study demonstrated that ZexieBaizhu Decoction (ZXBZ) attenuated HFD-caused hepatic steatosis in mice, and the mechanism was related to upregulate SIRT1, p-ACC, p-AMPK, and PPARα [78].

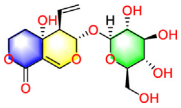
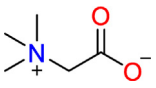
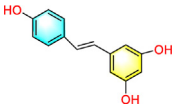
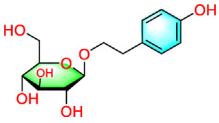
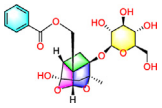
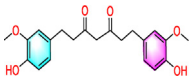
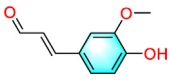
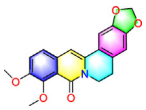
3.1.3. Herbal medicine extracts

Cirsium japonicum DC. (CJ) is an Asteraceae plant with antioxidant and hepatoprotective effects. CJ ethanol extract (CJE) could activate AMPK and downregulate FAS and ACC expression, thus decreasing TC and TG contents and lipid deposition in high free fatty acidemia (HFFA)-stimulated HepG2 cells [79]. *Magnolia officinalis* Rehd.et Wils. has been used to treat hepatic diseases. In 2014, a study reported that *Magnolia officinalis* Rehd.et Wils. extract (MO) pretreatment reduced lipid deposition in FFA-simulated HepG2 cells by inhibiting SCD-1, FAS, and SREBP-1. Notably, these effects are reversed by compound C [80]. Later, Im et al. [81] demonstrated that *Dolichos lablab* linne water extract (DLL-Ex) suppressed FFA-stimulated lipid deposition in HepG2 cells. Mechanistically, DLL-Ex reduced platelet glycoprotein 4 (CD36) expression and BODIPY-labeled fatty acid uptake, and inhibited FFA-induced cellular energy expenditure. Importantly, DLL-Ex activated AMPK. In 2018, Kim et al. [82] found that berries of Lonicera caerulea L. extract (BHe) had an anti-NAFLD effect, and the mechanism was related to the upregulation of AMPKα and UCP2, and downregulation of ACC1, C/EBP, and SREBP-1c. In 2019, Jian et al. [83] proposed that *Trapa quadrispinosa* pericarp extract (TQPE) could alleviate NAFLD in HFD-fed mice through activating AMPK/SREBP/ACC and insulin receptor substrate 1 (IRS-1)/protein kinase B (AKT) axis. Similarly, Toona sinensis bark and fruit extracts (TSB and TSF) also had a protective effect on FFA-stimulated HepG2 cells. Mechanistically, TSB and TSF increased p-AMPK, p-ACC, and PPARα, and decreased LXR, FAS, and SREBP-1. Furthermore, compound C partially rescued the lipid-lowering effects of TSB and TSF [84]. Then, Wang et al. [85] reported that *Rosmarinus officinalis* L. ethanol extract (RO) could attenuate OA-induced NAFLD in rats. RO therapy inhibited SREBP-1c by activating AMPK, thereby reducing liver TC and TG levels. Notably, the metabolites of *Rosmarinus officinalis* L. ethanol, rosmarinic acid, and carnosic acid showed similar effects to RO. *Crataegus pinnatifida* Bge. leaf flavonoids (HLF) also had a liver protective effect on HFD-fed rats via upregulation of p-AMPK and PPARα, and downregulation of SREBP-1c. In addition, HLF treatment significantly increased circulating adiponectin levels and AdipoR2 [86]. In 2021, Wang et al. [87] studied the effect of *Cynanchum atratum* Bge. ethanol extract (CAE) on NAFLD in HFD mice and demonstrated that CAE suppressed glycerol-3-phosphate acyltransferase, Mitochondrial (GPAM), FAS, and SREBP-1, increased PPARα, promoted the phosphorylation of AMPKα, and eventually improved NAFLD. *Momordica cochinchinensis* (Lour.) Spreng is a cucurbitaceous herb. Huang et al. [88] reported that *Momordica cochinchinensis* (Lour.) Spreng. aril (MCA) protected mice from weight gain, hyperlipidemia, and hyperglycemia caused by HFD. Moreover, in OA-stimulated HuS-E/2 cells, MCA reduced lipid deposition through promoting AMPK/PPARα signaling. In 2022, Ma et al. [89] showed that Adlay (*Coix lacryma-jobi* L.) Polyphenol (AP) could attenuated NAFLD in mice stimulated by HFD. Moreover, AP significantly reduced accumulation of HepG2 cells exposed to FFA treatment, and the mechanism was related to upregulate AMPK/ACC pathway. Then, Yu et al. [90] reported that *Momordica charantia* L. extract (BME) improved HFD-stimulated NAFLD in mice via increasing AMPKp, AMPKα1, AMPKα2, and SIRT1. In addition, BME treatment also suppressed FGF21 and increased fibroblast growth factor receptor (FGFR)1, FGFR3, and FGFR4. *Dillenia indica* L. is a traditional herbal medicine with anti-diabetes, anti-indigestion, and anti-asthma effects. Recently, *Dillenia indica* L. hydroethanolic extract (DI-HET) was reported to protect HepG2 cells from OA-induced NAFLD by regulating AMPK and PPARα pathways [91].

3.2. AMPK-mediated autophagy pathway

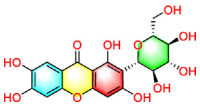
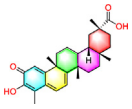
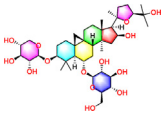
The improvement of NAFLD by natural products could also be achieved through upregulating AMPK-managed autophagy. Activated AMPK promoted the formation and phosphorylation of ULK complex, enhanced the phosphorylation of beclin1, and alleviated the inhibition of mTOR-regulated transcription factor EB (TFEB) nuclear translocation and MAP1LC3 I (LC3I) to LC3II conversion, thereby initiating autophagy (Figs. 5 and 6).

Table 3
Adenosine 50-monophosphate (AMP)-activated protein kinase (AMPK)-mediated insulin resistance (IR) pathway.

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Monomers							
Swertiamarin		OA (1 mM)-induced HepG2 cells	25 μg/mL	Swertiamarin attenuated NAFLD through relieving hepatic glycemic burden, lipid deposition, insulin resistance and ROS production via activating AMPK and PPARα.	IR-β, p-AKT, PI3K, p-AMPKa	PPARα, p-IRS-1, PPARγ, SREBP-1c, ACC-1, FAS, CPT1, PCK	[42]
Betaine		10% fructose fed male SD rats	62.5, 125, and 250 mg/kg for 4 weeks	Betaine attenuated hepatic steatosis, gluconeogenesis, and inflammatory response through activating AMPK.	LXRα, PPARα, CPT1α, GPIHBP1, apolipoprotein B, ApoB	SREBP-1c, ATF6, p-PERK, p-eIF2α, XBP-1, SCD1, FAS, CPTII, p-FOXO1, p-AKT, p-p38, ASC, p-mTOR, p-NF-κB, NLRP3, Caspase-1	[103]
Resveratrol		HFD-induced Male C57BL/6J mice	200 mg/kg, once every two days, i.v. for 6 weeks	Resveratrol inhibited hepatic steatosis, relieved IR and reduced TG production through upregulating AMPK/SIRT/ FAS/ SREBP-1c axis.	p-AMPK, SIRT1	SREBP-1c, FAS, p-IRS	[104]
Daphnetin		OA (0.5 mM)-induced HepG2 cells	5, 20, and 50 μM for 24 h	Daphnetin exerted against NAFLD effect through enhancing insulin sensitivity and suppressing oxidative stress via AMPK.	p-AMPK, PPARα, 2-NBDG, PI3K, p-AKT, Nrf2	SREBP-1c, PNPLA3, CYP2E1, CYP4A	[105]
Salidroside		HFD-induced C57BL/6 mice	100 mg/kg for 8 weeks	Salidroside attenuated NAFLD by regulating AMPK-mediated TXNIP/NLRP3 pathway.	p-AMPK, p-ACC, p-AKT, p-GSK3β	FAS, TNFα, NLRP3, Caspase1, IL-1β, IL-18, TXNIP	[106]
Paeoniflorin		20% Fructose SD rats	10, 20, 40 mg/kg for 8 weeks	Paeoniflorin improved insulin resistance and hepatic lipid deposition through upregulating LKB1/ AMPK and AKT pathways.	CPT1, p-AKT, p-AMPK, p-ACC1, LKB1	SREBP-1c, SCD1, FAS	[107]
THC		OA (0.2 mM)-induced HepG2 cells	10, 25, 50, 100 μM	THC relieved insulin resistance and hepatic steatosis through regulating AMPK -dependent pathway.	p-AMPK, p-ACC, CPT1α, PPARα, p-PI3K, p-AKT, p-FOXO1, p-GSK3β	PPARγ, SREBP-1c, FAS, FABP4, p-IRS1, PEPCK	[108]
Coniferaldehyde		PA (0.2 mM)-induced HepG2 cells	20, 50, 100 μM	Coniferaldehyde attenuated NAFLD through suppressing lipid deposition and insulin resistance via LKB1/AMPK signaling.	CPT1α, GLUT2, p-GSK3β, p-AMPKa, p-ACC, p-LKB1	SREBP-1, FAS, SCD1, p-GS	[109]
Oxyberberine		HFD-induced male SD rats	25, 50, 100 mg/kg for 8 weeks	OBB improved NAFLD and hepatic lipid metabolism by activating AMPK.	p-AMPK, PI3K, p-AKT, p-GSK-3β, Arg1, Acaca, UCP1	p-IRS, MCP1, Cd68, Nos2, Cd11c	[110]

(*continued on next page*)

Table 3 (*continued*)

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Mangiferin		HFD-induced male C57BL/6J mice PA (0.3 mM)-induced HepG2 cells	25, 50, 100 mg/kg/d for 12 weeks 25, 50, and 100 μM	Mangiferin improved NAFLD by regulating AMPK and NLRP3 pathways.	p-AMPKa, p-ACC	NLRP3, Caspase-1, IL-1β, GSDMD	[111]
Celastrol		HFD-induced C57BL/6 N mice	0.3 mg/kg for 16 days	Celastrol could activate AMPK and SIRT1 to improve NAFLD.	p-AMPK, SIRT1	FASN, SREBP-1c, CD36, ACC	[112]
Astragalosides IV		HepG2 cells with IR	50 μg/mL	Astragaloside IV suppressed lipid deposition by regulating AMPK -mediated SREBP-1c phosphorylation.	AMPKα1, AMPKα2	SREBP-1c, FAS, ACC1, SCD1	[113]
Formulas							
BBD	Bovis calculus, Snake gall, Saiga tatarica Linnaeus, Pteria martensii, Panax notoginseng (Burk.) F. H. Chen, and Moschus berezovskii Flerov.	HFD-stimulated Male C57BL/6 mice	25 mg/kg every 3 days for 8 weeks	BBD protected against HFD -sitimulated hepatic steatosis through activating AMPK.	p-AMPK, CPT1 and PPARα	SREBP-1-c, ACC, SCD1, LXR-1α, CD36	[114]
JKW	The roots of Scutellaria baicalensis Georgi and fruits of Euodia rutaecarpa (Juss.) Benth.	HFD -induced C57BL/6J mice HepG2 cells	100, 200 mg/kg for 15 weeks 10, 25 μg/mL for 48 h	Jwa alleviated NAFLD via activating AMPK to improve insulin resistance.	p-IRS-1, p-PI3K, p-AKT, p-AMPK, CPT1	C/EBPα, PPARγ	[115]
SGD	ShengMai-Yin composed of Panax ginseng C. A. Mey., Ophiopogon japonicus (L. f.) Ker-Gawl. and Fructus Schisandra chinensis (Turcz.) Baill., and Ganmaidazao decoction composed of Glycyrrhiza uralensis Fisch., Fructus Tritici levis, and Fructus Ziziphus jujuba Mill.	HFD-induced C57BL/6J and KKAy mice	5, 10, 15 g/kg for 4 weeks	SGD attenuated hepatic lipid deposition and insulin resistance through upregulating AMPK/PPARα and PI3K/AKT pathways.	p-PI3K, p-AKT, PPARα, HSL	GSK3β, SREBP-1, FASN	[116]
DST	Angelica sinensis (Oliv.) Diels, Prunus persica (L.) Batsch, Rehmannia glutinosa Libosch., Paeonia lactiflora Pall., Carthamus tinctorius L., and Cnidium monnieri (L.) Cuss.	HFD-induced C57BL/6J mice	50, 100 mg/kg/day for 10 weeks	DST improved hepatic steatosis by activating AMPK/ IRS-1 and AKT pathways.	p-AMPK, IRS-1, p-AKT	C/EBPα, PPARγ, Bax/Bcl-2	[117]
KTZG	Pueraria lobata (Willd.) Ohwi, Dioscoreae Rhizoma., Sophora flavescens Ait., Morus alba L. leaves, Polygonatum odoratum (Mill.) Druce, Fructus Morus alba L., and Fructus Chaenomeles speciosa (Sweet) Nakai Fructus.	HFD-induced SD rats FFA (1 mM)-induced HepG2 cells	0.75, 1.5, 3 mg/kg/day, i.g. for 6 weeks Serum samples were obtained from the KTZG 0.75, 1.5, 3 mg/kg SD rats	KTZG effectively ameliorated NAFLD via AMPK/mTOR pathway.	PPAR-γ, p-AMPK, GLUT2, SIRT1	SREBP-1, p-AKT, p-mTOR, FAS	[118]
Extracts							
LRE	–	HFD-induced male C57BL/6J mice	2, 5 g/kg/day for 12 weeks	LRE inhibited hepatic lipid deposition via upregulating AMPK/PPARα signaling.	PPARα, PGC-1α, p-AMPK	SREBP-1C, FAS	[119]
SCO	–	HFD-induced male C57BL/6J mice	250 mg/kg for 4 weeks	SCO relieved NAFLD in HFD-caused obesity mice through upregulating hepatic insulin and AMPK signaling.	IRS-2, p-IRS-1, p-IRβ, p-AKT, p-AMPK, p-ACC	PTP1B, FAS, SREBP	[120]

(*continued on next page*)

Table 3 (*continued*)

Monomers/ formulas/extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
RP	–	HFD-induced Male SD rats	690, 1300 mg/kg for 6 weeks	RP activated AMPK/ ACC signaling to attenuated NAFLD.	p-AMPK, p-ACC	SREBP-1c, ChREBP, ACC1, FAS, PPARα	[121]
HZ	–	HFD-induced male C57BL/6 J mice PA (0.1mM)-induced HuS-E/2 cells	578 mg/kg/day for 12 weeks 10, 20 μg/mL	HZ suppressed lipid accumulation and improved NAFLD through promoting AMPK/ACC signaling.	p-AMPK, p-ACC, PPARα	SREBP-1c	[122]

ACC: acetyl-CoA carboxylase; AKT: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; ATF6: activating transcription factor 6; Bax: Bcl-2-associated X protein; BBD: Babaodan; CA: Coniferaldehyde; CD36: platelet glycoprotein 4; CEBP or C/EBP: CCAAT/enhancer-binding protein; ChREBP: carbohydrate response element binding protein; CPT1: carnitine palmitoyltransferase 1; DST: Dohongsamul-tang; FABP: fatty acid binding protein; FABP4: fatty acid binding protein 4; FAS or FASN: fatty acid synthase; FFA: free fatty acids; FOXO1: forkhead box O1; GLUT2: glucose transporter type 2; GSDMD: gasdermin-D; HFD: high fat diet; HSL: hormone-sensitive lipase; HZ: *Helminthostachys zeylanica* (L.) Hook.; IRS: insulin receptor substrate; JKW: Jwa Kum Whan; KTZG: Kangtaizhi granule; LKB1: liver kinase B1; LRE: *Lycium ruthenicum* extract; LXR: liver X receptors; MCP1: monocyte chemoattractant protein 1; NLRP3: NOD-like receptor thermal protein domain associated protein 3; Nos2: nitric oxide synthase 2; Nrf2: nuclear factor erythroid 2-related factor 2; OA: oleic acid; PA: palmitic acid; p-ACC: phospho-acetyl-CoA carboxylase; p-AKT: phosphorylated protein kinase B; p-AMPK: phosphorylated AMP-activated protein kinase; PCK: phosphoenolpyruvate carboxykinase; p-eIF2α: phosphorylated eukaryotic translation initiation factor 2 alpha; PEPCK: phosphoenolpyruvate carboxykinase; PGC: peroxisome proliferator-activated receptor gamma coactivator; p-IRS1: phosphorylated insulin receptor substrate 1; p-GS: phosphorylated glycogen synthetase; PI3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; PPAR: peroxisome proliferator-activated receptor; PTP1B: protein tyrosine phosphatase-1B; RP: *Rheum palmatum* L. extract; SCD1: stearoyl-CoA desaturase-1; SCO: *Artemisia scoparia* Waldst. et Kit. extract; SGD: ShengMai-Yin and Ganmaidazao decoction; SREBP: sterol regulatory element binding protein; THC: tetrahydrocurcumin; TXNIP: thioredoxin interacting protein; XBP-1: X-box binding protein 1; 2-NBDG: 2-deoxy-2- [(7-nitro-2,1,3-benzoxadiazol-4-yl)amino]-D-glucose.

3.2.1. Herbal medicine monomers

In 2015, Zhang et al. [92] revealed that resveratrol promoted autophagy in HepG2 cells exposed to PA via the AMPK/SIRT1 pathway, thus attenuating lipid deposition. In addition, AMPK inhibition significantly eliminated resveratrol-mediated hepatic lipid metabolism and autophagy. In 2017, ginsenoside Rb2 was reported to improve NAFLD by activating AMPK. Ginsenoside Rb2 treatment obviously suppressed IR and reduced hepatic lipid deposition in male db/db mice. Moreover, ginsenoside Rb2 increased the autophagy flux, and reduced OA- and HG-caused lipid deposition in HepG2 cells by downregulating SQSTM1 (p62), which was restored by blocking AMPK pathway [93]. Alisol A 24-acetate (AA) is a natural triterpenoid isolated from Alismatis Rhizoma. In 2018, Wu et al. [94] revealed that AA improved methionine and choline deficiency-stimulated non-alcoholic steatohepatitis (NASH) in mice via upregulating AMPK/mTOR/ULK1 axis-mediated autophagy. Notably, inhibition of AMPK by dorsomorphin partially prevented AA-induced autophagy *in vitro*. In 2019, formononetin was reported to attenuate NAFLD *in vivo* and *in vitro*. Formononetin treatment promoted lysosomal biogenesis and autophagosome-lysosomal fusion, alleviated the blockage of autophagy flux, and further induced phagocytosis through activating AMPK signaling and promoting TFEB translocation from cytoplasm to nucleus [95]. Catalpol is a triterpenoid compound extracted from *Rehmannia glutinosa* (Gaertn.) Libosch. ex Fisch. & C. A. Mey. roots. Ren et al. [96] found that catalpol has a protective effect on NAFLD, and the specific mechanism was associated with the activation of autophagy. In brief, catalpol promoted TFEB nuclear translocation in ob/ob mice liver and PA-stimulated HepG2 cells in an AMPK-dependent manner, thereby increasing LC3II levels and reducing p62 levels. Using sodium oleate-stimulated NAFLD model in L02 cells, 3T3-L1 preadipocytes, and C2C12 myoblasts, Wu et al. [97] confirmed that icaritin improved NAFLD through promoting AMPK-mediated autophagy.

Aurantio-obtusin is a quinone compound extracted from *Cinnamomum tamala* (Bauch.-Ham.) Nees et Eberm, which has the effect of improving obesity and IR, and also has a certain therapeutic effect on NAFLD. In 2021, Zhou et al. [98] found that aurantio-obtusin significantly improved HFD and glucose-fructose water-caused lipid deposition in mice and OA- and PA-induced lipid accumulation in hepatocytes. Mechanically, aurantio-obtusin significantly promoted autophagy flux and promoted lipid droplet degradation by activating AMPK, activated AMPK activated TFEB and promoted FAO by triggering PPARα and acyl-CoA oxidase 1 (ACOX1) activation. In the same year, Liu et al. [99] revealed that honokiol improved lipid deposition in AML12 cells induced by PA and OA through activating SIRT3-AMPK pathway-mediated autophagy. Additionally, honokiol prevented hepatic steatosis in HFD-fed mice. Compound C almost eliminated the above effects. In 2022, Yan et al. [100] found that schisandrin B (Sch B) could relieve lipid deposition in FFA-stimulated HepG2 cells and mononeuclear phagocyte system (MPS) by enhancing autophagy and reducing lipid accumulationin through upregulating AMPK/mTOR signaling. Notably, autophagy-related 5 (ATG5) and TFEB inhibition or 3-MA treatment alleviated autophagy and FAO production caused by Sch B.

3.2.2. Herbal medicine formulas

Tangshen formula (TSF) was reported to attenuate HFD-caused hepatic steatosis in mice via upregulating SIRT1 and inducing autophagy in an AMPK-dependent manner. Importantly, TSF also alleviated PA-induced SIRT1 downregulation and autophagy inhibition in HepG2 cells [101].

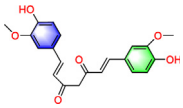
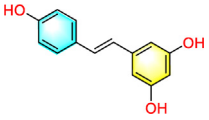
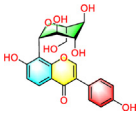
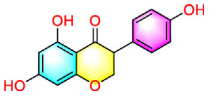
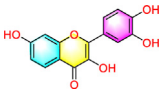
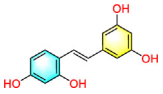
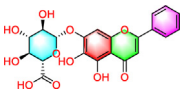
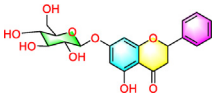
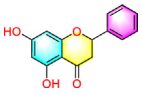
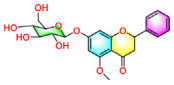
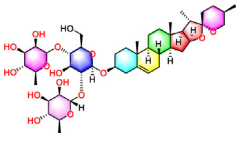
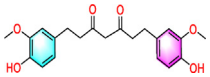
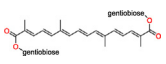
3.2.3. Herbal medicine extracts

Lipid accumulation was increased and fatty acid oxidation, autophagy, and lysosomal acidification were inhibited in the cells exposed to OA and PA. However, apple polyphenol extract (APE) treatment could reverse these effects through activating the SIRT1/AMPK pathway. Moreover, SIRT1 and ATG7 inhibition attenuated the lipid-lowering effect of APE and increased intracellular TG content [102].

3.3. AMPK-mediated IR pathway

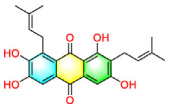
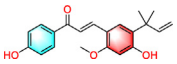
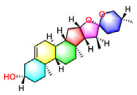
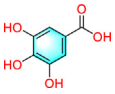
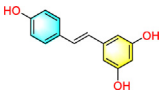
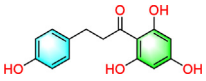
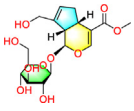
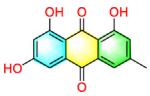
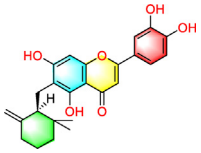
During the progression of NAFLD, insulin receptor/PI3K/AKT pathway inhibition reduced the plasma membrane localization of glucose transporter type 4 (GLUT4) and promoted the phosphorylation of glycogen synthase kinase 3β (GSK3β), thereby reducing glucose absorption and leading to IR. However, natural products can improve these effects by activating AMPK. Meanwhile,

Table 4
Adenosine 50-monophosphate (AMP)-activated protein kinase (AMPK)-mediated oxidative stress pathway.

Monomers/ formulas/ extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Monomers							
Curcumin		OA (0.5 mM)-induced HepG2 cells	1, 5, and 10 μM	Curcumin attenuated NAFLD by promoting AMPK/ACC signaling.	PPARα, p-AMPK	SREBP-1c, FAS	[123]
Resveratrol		HFD –induced KKAy and C57BL/6J mice	2 to 4 g/kg in diet for12 weeks	RSV relieved lipid deposition and oxidative stress by regulating SIRT1/ AMPK pathway.	p-HSL and ATGL, SIRT1, p-AMPK, p-FOXO1, FOXO1	p47phox, gp91phox	[124]
Puerarin		OA (0.5 mM)-induced HepG2 cells	25, 50 and 100 μM	Puerarin suppress lipid deposition and increased FAO by promoting AMPK phosphorylation and PPARα expression.	PPARα, p-AMPK	SREBP-1, FAS	[125]
Genistein		HFD –induced male SD rats	4, 8 mg/kg for 12 weeks	Genistein suppressed hepatic lipid synthesis and enhanced FAO via activating AMPK.	p-AMPK, p-ACC, PPARα, CPT1, ACOX	SREBP-1, FAS, GPAT	[126]
Fisetin		HFD -induced male C57BL/6 mice OA (0.5 mM)-induced FL83B cells	20 mg/kg by intraperitoneal injection twice a week for 10 weeks 3, 10, 30, 100 μM	Fisetin inhibited hepatic lipid deposition by upregulating SIRT1/ AMPK signaling and increasing β-oxidation.	SIRT1, p-AMPKα, p-ACC, CPT1, ATGL, p-HSL, PPARα	SREBP-1c, C/EBPα, C/EBPβ, PPARγ, FAS	[127]
Oxyresveratrol		HepG2 cells stimulated by T090	10−100 μM	OXY suppressed hepatic lipid deposition via AMPK/ SREBP-1c signaling.	p-AMPK	SREBP-1c	[128]
Baicalin		OA-induced SD rats	125, 250, 500 mg/ kg for 8 weeks 12.5, 25, 50 mg/kg for 18 days	Baicalin relieved hepatic FFA lipotoxicity by regulating AMPK-mediated SREBP signaling.	p-AMPK, CPT1α, Nrf 2, p-CaMKK	SREBP-1c, FAS, SCD, HSL, ATGL, ACC	[129]
PCBG		HepG2 cells stimulated by FFA (0.8 mM)	0.1, 1, 10 μM	PCBG exerted anti-hepatic steatosis effect through upregulating SIRT1/ AMPK signaling.	p-AMPK, SIRT-1, PPARα	SREBP-1c, SCD1, FAS, ACC	[130]
PCB							
MPG							
Dioscin		PA-induced ML-12, HepG-2 and Primary cultured hepatocytes	125, 150, 200, 250, 300, 400, 500, 600, 800 ng/mL	Dioscin attenuated hepatic lipid deposition, and via the SIRT1/AMPK signaling.	SIRT1, p-AMPKα, CPT, FOXO1, ATGL	SREBP-1c, FAS, SCD	[131]
THC		HFD-induced C57BL/6J mice	20, 100 mg/kg per day for 10 weeks	THC relieved hepatic lipid deposition via activating AMPK to increase FAO.	Dlk1/Pref-1, p-AMPK, p-ACC, CPT1, p-PI3K, p-AKT, p-FOXO1, p-GSK3β, Glut2	PPARγ, C/EBPα, FAS, MCP-1, SREBP-1c, FABP4, p-IRS1, PEPCK1	[132]
Crocin		C57BL/KsJ-Lepdb (db/db) mice	20 mg/kg crocin for 8 weeks	Crocin attenuated hepatic steatosis through upregulating AMPK signaling/ PPARα.	p-AMPK, PPARα, ACOX1, CPT1, HMGCS2	p-mTOR, SREBP-1c, FAS, SCD1, PPARγ, DGAT1	[133]

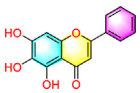
(*continued on next page*)

Table 4 (*continued*)

Monomers/ formulas/ extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
γ-mangostin		FFA (0.3 mM)-induced L02 and HepG2		γ-Mangostin attenuated hepatic lipid deposition through the SIRT1/LKB1/AMPK signaling.	SIRT1, p-ACC, p-LKB1, p-AMPK, CPT1α	HMGCR	[134]
Licochalcone A		HFD -induced male C57BL/6 mice OA (0.5 mM) -induced HepG2	5, 10 mg/kg twice a week for 12 weeks 1.5, 3, 6, 12 μM	Licochalcone A relieved NAFLD through upregulating SIRT1/AMPK signaling.	p-HSL, ATGL, CPT1, SIRT1, p-ACC, p-AMPK	SREBP-1c, PPARγ, FAS	[135]
Diosgenin (DSG)		PA (0.25 mM)-induced L02 cells	0.1, 1 μM	Diosgenin relieved NAFLD through regulating the AMPK/ACC/CPT1α axis.	p-AMPK, p-ACC, CPT1α	FAS, SREBP-1	[136]
FYGL	—	PA (0.2 mM)-induced HepG2 cells	100, 200, 300 μg/mL	FYGL suppressed hepatic lipid deposition via regulating AMPK/ACC pathway.	p-AMPK, p-ACC, CPT1, Bcl-2	ACC, SREBP-1 and FASN, Cleaved Caspase-3, Bax	[137]
Gallic acid		PA-induced HepG2 cells	50, 100, 200 μM	Gallic acid exerted anti-NAFLD effect by activating AMPK -mediated HO-1 pathway.	p-AMPK, HO-1,	CD36, SLC27A2, ACACA, SREBF1, NR1H3	[138]
Resveratrol		HFD-induced male SD rats PA (0.2 mM)-induced HepG2 cells	100 mg/kg for 8 weeks 40 μM	RSV attenuated NAFLD through inhibiting lipid deposition and oxidative stress by activating PKA/AMPK/PPARα signaling.	PPARα, CPT1, SOD, CAT, p-AMPK, p-ACC, p-PKA	SREBP-1c, FAS	[139]
Phloretin		HFD-induced C57BL/6 mice OA (0.5 mM)-induced HepG2 cells	10, 20 mg/kg twice a week for 12 weeks 10, 30 μM	Phloretin attenuated hepatic lipid deposition through regulating lipogenesis and promoting SIRT1/AMPK signaling.	ATGL, p-HSL, CPT1, CPT-2, PPARα, p-AMPK, p-ACC, SIRT1	SREBP-1c, C/EBPβ, FAS	[140]
Geniposide		Wild-type and Nrf2$^{-/-}$ C57BL/6 mice FFA (1 mM)-induced HepG2 cells	50, 75, 100 mg/kg Gen for 18 h 65, 130, 260 μmol/L	Geniposide suppress oxidative stress and inflammation to attenuate NAFLD through activating Nrf2 and AMPK/PI3K/mTOR signaling.	Nrf2, PPARα, PPARγ, Nrf2, HO-1, p-AKT, p-GSK3β, p-AMPKα, AMPKβ, p-ACC, p-AKT	p-mTORC1, P-S6, PI3K, HMGB1, SREBP-1c	[142]
		HFD-induced male wistar rats	0. 01 mL/g for 4 weeks	Geniposide attenuated NAFLD by AMPK/ACC/Malonyl-CoA-FFA signaling.	AMPK	FAS, ACCase, Malony1-CoA	[141]
Hypericin		FFA (1 mM)-induced L02, HepG2 and mouse primary hepatocytes	20 nM, 200 nM, and 2 μM	Hypericin improved NAFLD and abnormal lipid metabolism through activating PKA -regulated AMPK signaling.	p-AMPK, p-ACC, PPARα, CPT1α, PKACα, PKACβ, p-HSL	Cleaved Caspase-3, Cleaved Caspase-9, Bax/Bcl-2, FAS, CD36, LDLR, SCD1, SREBP-1	
Emodin		Egg yolk-induced Zebrafish	0.5, 0.25 μg/mL for 72 h	Emodin treated NAFLD by activating AMPK to inhibit IR and increase FAO.	AMPKα and p-AMPKα, PI3K, AKT, PPARα, CPT1α, ACOX1, AdipoR2		[144]
Ugonin J		HFD-induced C57BL/6 J mice PA (0.1 mM)-induced HuS-E/2 cells	15 or 30 mg/kg per day for 12 weeks 2.5, 5, 10, 20 μM	Ugonin J relieved NAFLD by upregulating AMPK/ACC signaling.	p-AMPK, p-ACC, CPT1	SREBP-1c	[145]

(*continued on next page*)

Table 4 (*continued*)

Monomers/ formulas/ extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Baicalein		10% fructose Male SD rats	25, 100 mg/kg i.g. for 5 weeks	Baicalein enhanced FAO through upregulating AMPK and PPARα signaling.	p-SREBP-1c, p-AMPK, PGC-1a, PPARα, CPT1α, ACOX1	ChREBP, SCD1, FASN, ACC, SREBP-1c, LPK	[146]
Formulas							
PTR	Alisma plantago-aquatica Linn., Atractylodes lancea (Thunb.) DC., Rheum palmatum L. and Crataegus pinnatifida Bge.	Male SD rats	0.42, 0.84 g/kg per day daily for 8 weeks	PTR attenuated hepatic steatosis and enhanced FAO by upregulating AMPK pathway.	p-AMPK, PPARα, PPARγ, p-ACC, PGC-1α	SREBP-1c, FAS, L-FABP	[147]
AZB	Hydroxy-α-Sanshool, Hydroxy-β-Sanshool, Hydroxy-γ-Sanshool and Hydroxy- -Sanshool	HFD-induced C57BL/6 J mice	5, 10 and 20 mg/kg per day daily for 12 weeks	AZB relieved NAFLD by activating AMPK/ Nrf2 signaling	p-AMPK, Nrf2, HO-1, SOD, CAT, GSH-Px	MDA	[148]
Extracts							
CLW	–	HFD-induced male C57BL/6 J mice FFA (1 mM)-induced HepG2 cells	300, 900 mg/kg/day for 8 weeks 50 and 100 μg/mL	CLW suppressed hepatic steatosis and oxidative stress via promoting fatty acid uptake via AMPK pathway.	p-AMPK, PPARα, CPT1, p-ACC	CD36, FATP5, FATP2, SREBP-1c, FAS, ACC	[149]
AM and LE	–	HFD-induced C57BL/6J mice	50, 100, 200 mg/kg for 6 weeks	AM and LE suppressed HFD -caused hepatic lipid deposition through regulating AMPK and ACC pathways.	p-AMPK, p-ACC, CPT1	SREBP-1c, FAS	[150]
CPEs	–	HFD-induced SD rats PA (0.25 mM)-induced AML 12 cells	50, 100 mg/kg/d for 21 days 25, 50, 100 μg/mL	CPEs relieved hepatotoxicity and NAFLD development, and prevents lipid deposition by activating AMPK and alleviating mTORC1-ER stress.	p-AMPK	p-mTOR, p-p70S6K, p-4EBP-1, GRP78, CHOP, p-PERK, p-eIF2α, SCD1, GPAT, ACC-1, FAS, SREBP-1	[151]
QW and QA	–	HFD-induced SD rats	200, 600 mg/kg for 14 weeks	QW and QA attenuated NAFLD by upregulating AMPK/ PPARα axis to reduce lipid deposition and activate Nrf2.	AdipoR2, Nrf2, HO-1, NQO1, p-AMPK, CPT1, PPARα	FAS, SREBP-1	[152]

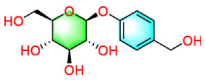
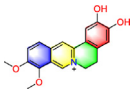
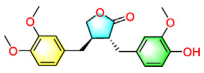
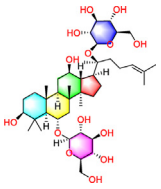
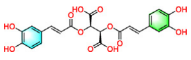
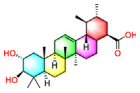
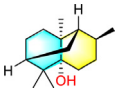
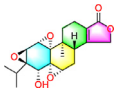
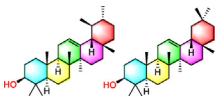
ACC: acetyl-CoA carboxylase; ACOX1: acyl-CoA oxidase 1; AdipoR: adiponectin receptor; AKT: protein kinase B; AM: *Astragalus membranaceus* (Fisch.) Bge. extract; AMPK: adenosine monophosphate-activated protein kinase; ATGL: adipose triglyceride lipase; AZB: amides in *Z. bungeanum*; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; CaMKK: Calmodulin-dependent protein kinase kinase; p-CaMKK: Phosphorylated calmodulin-dependent protein kinase kinase; CD36: Platelet glycoprotein 4; CHOP: C/EBP homologous protein; ChREBP: carbohydrate response element binding protein; CLW: hot water extract of *Curcuma Longa* L.; CPT1: carnitine palmitoyltransferase 1; DGAT: diacylglycerol O-acyltransferase; FABP: fatty acid binding protein; FAS or FASN: fatty acid synthase; FFA: free fatty acids; FOXO1: forkhead box O1; FYGL: *Ganoderma lucidum* Polysaccharide; GRP78: glucose-regulated protein 78; HFD: high fat diet; HMGCS: 3-hydroxy-3-methylglutaryl-coA synthase; HO-1: heme oxygenase-1; HSL: hormone-sensitive lipase; LE: *Arnebia euchroma* (Royle) Johnst. extract; LKB1: liver kinase B1; MPG: 5-methoxy-pinocembrin-7-O-β-d-glucoside; mTOR: mammalian target of rapamycin; Nrf2: nuclear factor erythroid 2-related factor 2; NR1H3: nuclear receptor subfamily 1 group H member 3; OA: oleic acid; PA: palmitic acid; p-ACC: phospho-acetyl-CoA carboxylase; p-AKT: phosphorylated protein kinase B; p-AMPK: phosphorylated AMP-activated protein kinase; PCB: pinocembrin; PCBG: pinocembrin-7-O-β-d-glucoside; PTR: Ping-tang Recipe; p-eIF2α: phosphorylated eukaryotic translation initiation factor 2 alpha; p-IRS1: phosphorylated insulin receptor substrate 1; PI3K: phosphoinositide 3-kinase; PPAR: peroxisome proliferator-activated receptor; QA: Queous-ethanol extract; QW: Que Zui tea hot water extract; SC: Silibinin Capsules; SCD: stearoyl-coA desaturase; SIRT1: sirtuin1; SOD: superoxide dismutase; SREBP: sterol regulatory element binding protein; THC: tetrahydrocurcumin.

activated AMPK could also upregulate PGC-1α and downregulate phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) to reduce IR (Figs. 7 and 8).

3.3.1. Herbal medicine monomers

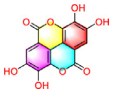
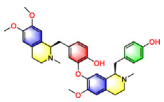
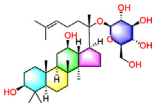
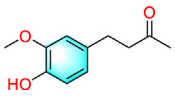
Swertiamarin is a bicyclic iridoid glycoside also with lipid-lowering activity and anti-diabetic effect. In 2016, Patel et al. [42] reported that swertiamarin decreased TC level and prevented apoptosis in OA-induced HepG2 cells by reducing LDH release, and relieving hepatic glycemic burden and IR via the activation of AMPK. In the same year, Ge et al. [103] proposed that betaine alleviated hepatic steatosis and gluconeogenesis in fructose-fed rats through upregulating AMPK downstream targets PPARα and LXRα. Liver-targeted nanocarriers containing bioactive compounds may provide new strategies for improving NAFLD. Recently, nanocarrier Gal-OSL was shown to deliver resveratrol to liver to amplify its therapeutic efficiency. Gal-OSL/resveratrol effectively improved lipid deposition and IR through activating AMPK and inhibiting IRS-1 phosphorylation at Ser307 [104]. Daphnetin, an active ingredient with significant antioxidant and anti-inflammatory effects that is isolated from Daphne Koreana Nakai, could suppress lipid deposition in HepG2 cells exposed to OA. Mechanically, daphnetin inhibited SREBP-1c and patatin like phospholipase domain containing 3 (PNPLA3), and increased PPARα through activating AMPK

Table 5
Adenosine 50-monophosphate (AMP)-activated protein kinase (AMPK)-mediated inflammation pathway.

Monomers/ formulas/ extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Monomers							
Gastrodin		HFD-induced C57BL/6 mice OA (0.6 mM)-induced HL-7702 cells	10, 20, 50 mg/kg for 10 weeks 25, 50, 100, 200 μg/mL	Gastrodin improved NAFLD via oxidative stress and inflammatory response through regulating AMPK/Nrf2 signaling.	HO-1, Nrf2, p-AMPK, p-LKB1	SREBP-1c, FAS, ACC1, ACOX1	[153]
DMB		MCD-induced male ICR mice and male db/db mice	20, 40 mg/kg/d for 4 weeks	DMB attenuated NAFLD and preventing NASH by activating AMPK to suppress the oxidative stress and inflammatory response.	p-AMPK, p-ACC, PGC-1a, CPT1α, SIRT4, MCAD, ACOX, MTTP	PPARγ, CD36, SREBP2, LXRa, ACC, SREBP-1c	[154]
Arctigenin		OA (0.1 mM)-induced WRL-68 cells	20, 50, 100 μM	Arctigenin exerted anti-NAFLD effect via PI3K/AKT and AMPK signaling.	PPARγ, CPT1, PPARα, p-PI3K, p-AKT, p-AMPK	ACC1, SREBP-1, TBARS, ICAM-1	[155]
Ginsenoside Rg1		PA (0.5 mM)-induced HepG2 cells	40, 80 μg/mL	Ginsenoside Rg1 attenuated NAFLD and inflammation by regulating AMPK/NF-κB pathway.	p-AMPK, p-ACCα	p-NF-κB, p-IκBα, FAS, SREBP-1c	[156]
Chicoric acid		HFD-induced C57BL/6 mice PA (250 μM)-induced HepG2 cells	15, 30 mg/kg for 9 weeks 10, 20 μM	Chicoric acid attenuated NAFLD through the AMPK/Nrf2/NF-κB axis.	Nrf2, HO-1, SOD1, SOD2, p-AMPK	IL-2, IL-6, IL-1β, TNF-α, p-IKKα/β, p-IκBα, p-NF-κB, Keap1	[157]
Cordycepin		HFD-induced male C57BL/6J mice	50 mg/kg for 8 weeks	Cordycepin improved NAFLD by activating AMPK/PPARα signaling.	p-AMPK, CPT1, PPARα	SREBP-1-c, ACC, SCD1, LXRα, CD36	[158]
Corosolic acid		HFD-induced C57BL/6J mice FFA (0.5 mM)-induced HepG2 cells	10, 20 mg/kg for 9 weeks 5, 10, 20 μM	Corosolic acid attenuated hepatic fibrosis and lipid deposition via TGF-β1/Smad2, NF-κB and AMPK pathways.	p-AMPK, p-ACC, p-IκBα	α-SMA, Collagen I, TIMP1, TGF-β1, p-Smad2, NF-κB, SREBP-1, FAS	[159]
Patchouli alcohol		male C57BL/6J mice PA (0.2 mM) induced C2C12 and HepG2	20 mg/kg, once every 2 days i.p. for 6 weeks 10, 30 μg/mL	Patchouli alcohol attenuated inflammation and ameliorated skeletal muscle insulin resistance and hepatic steatosis through the LKB1/AMPK/SIRT1 -dependent pathway.	p-AMPK, SIRT1, p-LKB1	SREBP-1, SCD1, p-NF-κB, p-IκB	[160]
Triptolide		MCS or MCD diet-induced male C57BL/6J mice	50, 100 μg/kg twice a week for 10 weeks	Triptolide activated AMPK to relieve hepatic lipid deposition inflammation, fibrosis, and NAFLD	p-ACC1, p-AMPK, PPARα, IDH2, CPT1α	FN, MCP1, α-SMA, Col-1, Col-4, TGF-β, FAS, SREBP-1, SCD1, TGF-β, UCP2, ACC1	[161]
α, β-Amyrin		HFD-induced male Swiss mice	10, 20 mg/kg for 15 weeks	α, β-Amyrin improved hepatic lipid deposition through the MPK/mTORC1/SREBP-1 pathways.	p-AMPK, PPARα	ACC1, FAS, CD36, SREBP-1, p-mTORC	[162]

(*continued on next page*)

Table 5 (*continued*)

Monomers/ formulas/ extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
Ellagic acid		Male Wistar rats with T1DM	50 mg/kg for 12 weeks	Ellagic acid treated NAFLD by activating AMPK -mediated Nrf2 and NF-κB pathways.	Nrf2, PPARα, CPT1α, CPT1β, p-AMPK	NF-κB, SREBP-1, FAS, ACC-1	[163]
Liensinine		HF -induced male C57BL/6 mice PA (0.5 mM)-induced AML12 and L02 cells	15, 30 and 60 mg/kg for 16 weeks 10, 20, 30 μM	Liensinine attenuated HFD -caused NAFLD by improving anti-oxidant capacity and suppressing inflammatory response through regulating TAK1/AMPK axis.	p-AMPK, p- ACC, PPARα, CPT1α, UCP2, HO-1, NQO1, GCLM, GCLC, Nrf2	FAS, SCD, PPARγ, NOX2, NOX4, Keap1, p-TAK1, p-IκBα, IκBα, p-NF-κB	[164]
Ginsenoside CK		FFA (1 mM)-induced HepG2 cells	5, 10, 20 μM	Ginsenoside CK attenuated hepatic lipid deposition by promoting LKB1/AMPK pathway.	p-AMPK, p-ACC1, ATGL, SIRT1, PPARα, CPT1α, p-LKB1	FASN, SREBP-1c, ACC1	[165]
Zingerone		HFD-induced male Wistar rats	100 mg/kg for 12 weeks	Zingerone attenuated NAFLD by activating AMPK -mediated Nrf2 signaling.	Nrf2, Bcl-2, p-AMPK	Bax, Cleaved Caspase-3, SREBP-1c, SREBP2	[166]
mAPS	–	HFD-induced SD rats	200 mg/kg for 6 weeks	mAPS attenuated NAFLD through regulating gut microbiota, suppressing TLR4/NF-κB/NLRP3 signaling, downregulating GPR41 and GPR43, and activating AMPK/PPARα signaling.	p-AMPK, PPARα, ZO-1	SREBP-1, TLR4, NLRP3, p-NF-κB, GPR41, GPR43	[167]
Extracts							
GTP	–	HFD-induced Male SD rats	200 mg/kg daily for 8 weeks	GTP relieved hepatic steatosis by improving hepatic steatosis, insulin sensitivity and inflammatory response through AMPK pathway.	p-AMPK		[168]
		HFD-induced Male Zucker fatty (fa/fa) rats (ZF)	200 mg/kg daily for 8 weeks	GTP protected hepatic steatosis in genetically obese ZF rats by activating AMPK/ACC pathway.	p-AMPK, p-ACC	SREBP-1c	[169]
RCMFP	–	HFD-induced Male SD rats	200, 600 mg of extract per kg for 12 weeks	RCMFP activated AMPK to relieved hepatic lipid deposition, inflammatory response, apoptosis.	p-AMPK, PPARα, CPT1, Bcl-2	FAS, PPARγ, CYP2E1, p-p38, iNOS, p-NF-κB, COX2, Caspase-3	[170]
VTE	–	HFD-induced C57BL/6J mice	1% diet for 6 weeks	VTE enhanced AMPK activity and inhibit AMPK -regulated LXRα activation to attenuated NAFLD.	CPT1α, CPT1β, p-AMPK	Cleaved Caspase-3, CHOP, LXRα, ABCA1, ABCG1, CYP7A1, SCD1, FAS, SREBP-1c	[171]
PNS	–	Obese ob/ob and HFD-induced C57BL/6J mice PA-induced AML12 cells	800 mg/kg per day for 8 weeks 50 μg/mL for 24 h	PNS regulated gut-liver axis in NAFLD by inhibiting TLR4 pathway and activating AMPKα.	PPARα, PPARγ, CPT1, ACOX1, ECH1, p-AMPK, p-ACC	ACC, FAS, SREBP-1c, CD36, ACAT1, ACAT2, collagen I, collagen IV, α-SMA, TLR4, p-p38, AMPKα	[172]

(*continued on next page*)

Table 5 (*continued*)

Monomers/ formulas/ extracts	Chemical structure/ compositions	Animal/cells	Dose/concentration	Detail effects	Related molecular targets		Refs.
					Up-regulated	Down-regulated	
POF	–	FFA (1 mM)-induced L02 cells	5, 10 and 20 μg/mL	POF suppressed lipid deposition and inflammation by regulating AMPK/ NF-κB signaling.	p-AMPK, PPARγ, SOD2	p-NF-κB/NF-κB	[173]

ACAT: acetyl-CoA acetyltransferase; ACC: acetyl-CoA carboxylase; ACOX1: acyl-CoA oxidase 1; AKT: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; ATGL: adipose triglyceride lipase; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; CD36: platelet glycoprotein 4; CHOP: C/EBP homologous protein; Col-1: collagen I: Col-4: collagen IV; COX2: cyclooxygenase-2; CPT1: carnitine palmitoyltransferase 1; DMB: demethyleneberberine; ECH1: enoyl-CoA hydratase; FAS or FASN: fatty acid synthase; FFA: free fatty acids; FN: fibronectin; GCLC: glutamate-cysteine ligase catalytic subunit; GCLM: glutamate-cysteine ligase modifier subunit; GPR: G-protein coupled receptor; GTP: green tea polyphenols; HFD: high fat diet; HO-1: heme oxygenase-1; ICAM-1: intercellular cell adhesion molecule-1; LKB1: liver kinase B1; LXR: liver X receptors; mAPS: *Astragalus mongholicus* polysaccharides; MCAD: medium-chain acyl-CoA dehydrogenase; MCD: methionine/choline-deficient; MCP1: monocyte chemo-attractant protein 1; MTTP: microsomal triglyceride transfer protein; mTOR: mammalian target of rapamycin; NLRP3: NOD-like receptor thermal protein domain associated protein 3; NOX: NADPH oxidase; NQO1: NAD(P)H: quinone oxidoreductase 1; Nrf2: nuclear factor erythroid 2-related factor 2; OA: oleic acid; PA: palmitic acid; p-AKT: phosphorylated protein kinase B; p-AMPK: phosphorylated AMP-activated protein kinase; PGC: peroxisome proliferator-activated receptor gamma coactivator; p-IκB: phospho-IκBα; PI3K: phosphoinositide 3-kinase; PNS: *Panax notoginseng* (Burk.) F. H. Chen saponins; POF: *Polygonum orientale* L. Fructus; PPAR: peroxisome proliferator-activated receptor; p-TAK1: phospho-TAK1; RCMFP: *R. chinensis* Mill. fruits phenolic extracts; SCD: stearoyl-coA desaturase; SMA: smooth muscle actin; SOD: superoxide dismutase; SREBP: sterol regulatory element binding protein; TAK1: TGF beta-Activated Kinase 1; TBARS: thiobarbituric acid reactive substances; TIMP1: tissue inhibitor of metalloproteinases 1; TLR4: toll-like receptor 4; UCP: uncoupling protein; VTE: *Ampelopsis grossedentata* (Hand-Mazz) W. T. Wang extract; ZO-1: zonula occludens-1.

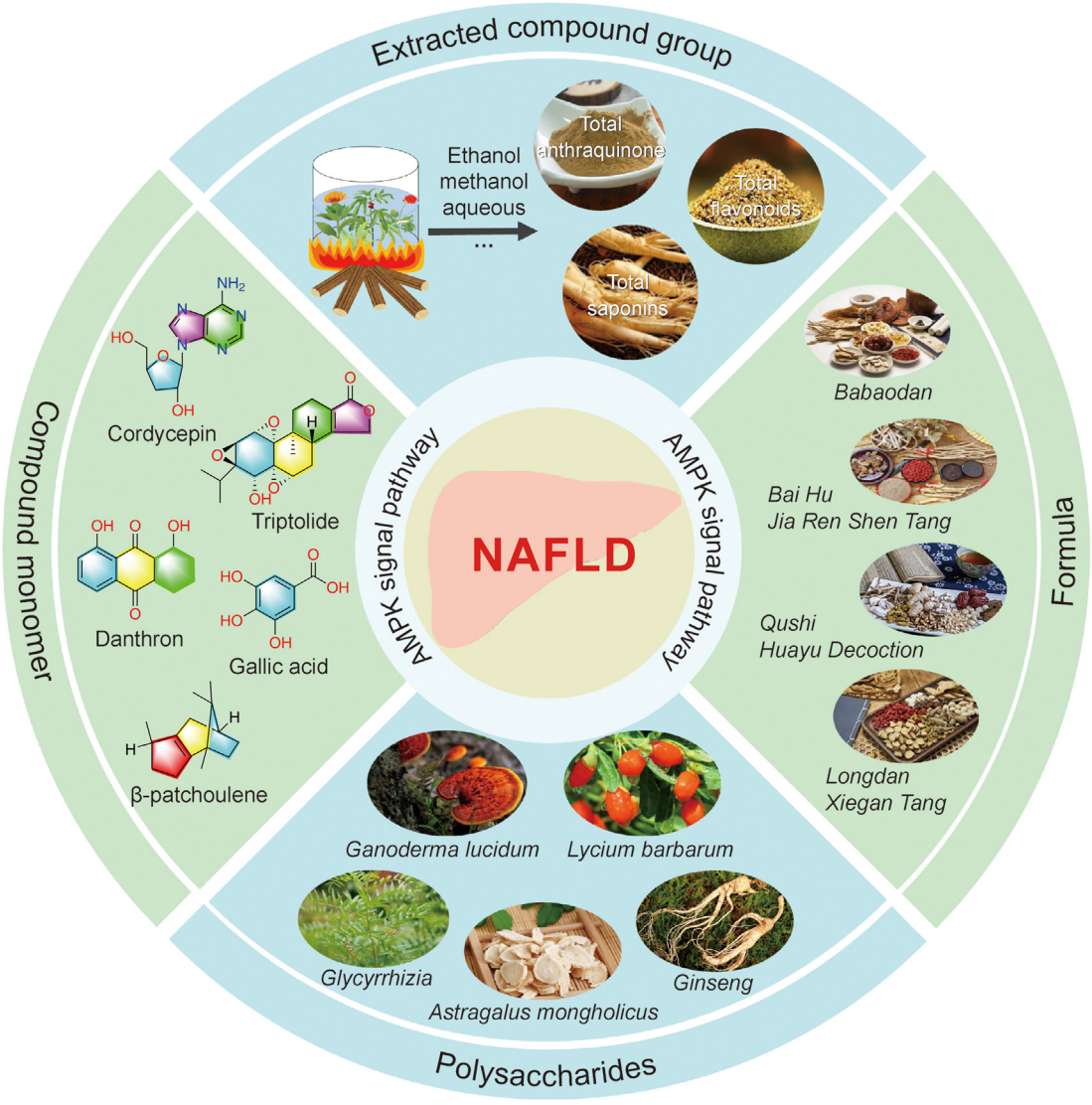


Fig. 2. Herbal medicines improve non-alcoholic fatty liver disease (NAFLD) by regulating adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) signal pathway.

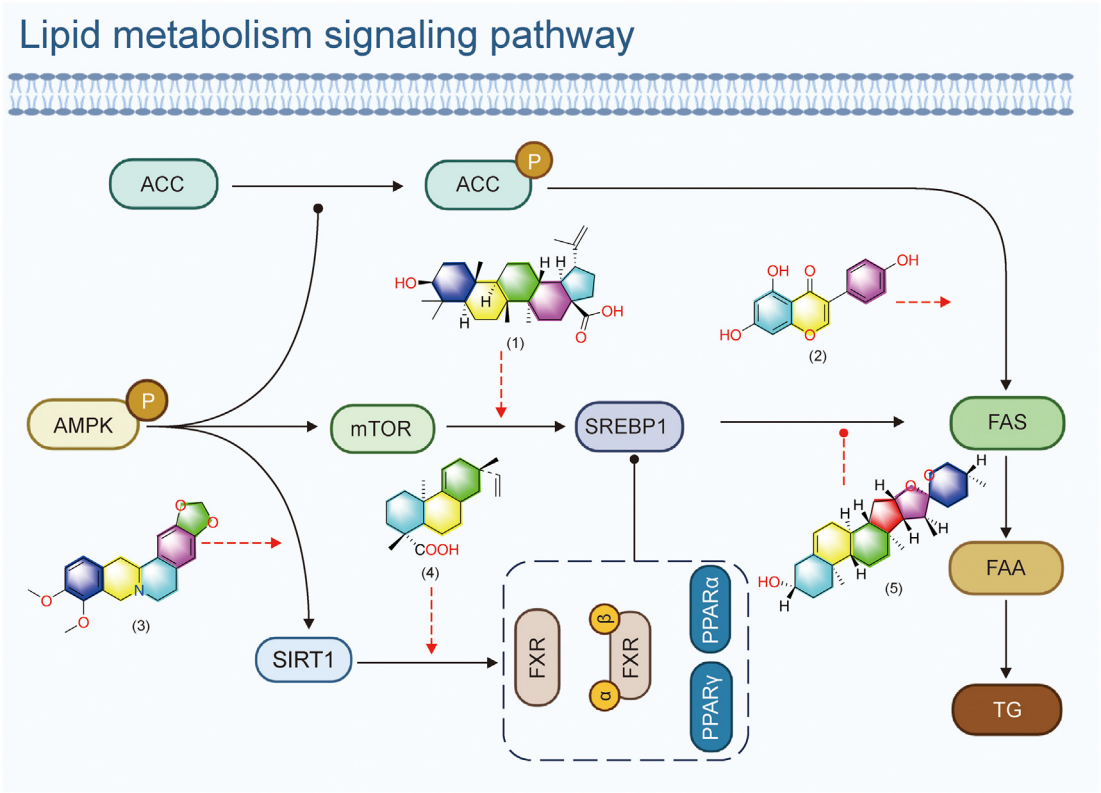


Fig. 3. Herbal medicines improve non-alcoholic fatty liver disease (NAFLD) by regulating adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated lipid metabolism signal pathway. (1) betulinic acid, (2) genistein, (3) berberine, (4) acanthoic acid, (5) diosgenin. ACC: acetyl-CoA carboxylase; FAA: free fatty acids; FAS: fatty acid synthase; FXR: farnesoid X receptor; mTOR: mammalian target of rapamycin; PPAR: peroxisome proliferators-activated receptor; SREBP1: sterol regulatory element binding protein 1; SIRT1: silent information regulator factor 1; TG: triglycerides.

signaling. In addition, daphnetin reduced IR and promoted glucose uptake in hepatocytes [105].

In 2018, Zheng et al. [106] found that Salidroside alleviated HFD-induced obesity, IR and hepatic lipid deposition by inhibiting ROS production, thioredoxin interacting protein (TXNIP) expression and NOD-like receptor thermal protein domain associated protein 3 (NLRP3) activation in db/db mice. However, Compound C treatment or AMPK knockdown reversed these beneficial effects. Later, Li et al. [107] reported that Paeoniflorin improved NAFLD in fructose-fed rats through upregulating LKB1 and activating AMPK and ACC. Moreover, Paeoniflorin treatment also reduced serum glucagon and insulin contents. Tetrahydrocurcumin (THC) is a naturally occurring metabolite of curcumin with a therapeutic effect on OA-stimulated lipid deposition in HepG2 cells. Mechanistically, THC inhibited IRS-1 and PEPCK, and upregulated carnitine palmitoyltransferase 1α (CPT1α) and PPARα. Meanwhile, THC relieved OA-stimulated adipogenesis in an AMPK-dependent manner [108]. In 2020, Gai et al. [109] found that coniferaldehyde (CA) downregulated SREBP-1, FAS, and SCD1, and upregulated CPT1α to alleviate lipid accumulation. Moreover, CA also upregulated GLUT2 expression and GSK-3β phosphorylation, and downregulated glycogen synthase phosphorylation. Importantly, AMPK inhibitor and siRNA knockdown of LKB1 reversed most of the CA effects. In 2021, Li et al. [110] compared the anti-NAFLD effects of oxyberberine and BBR and found that oxyberberine had a stronger affinity with AMPK and a stronger inhibiting effect of IRS. In the same year, Yong et al. [111] showed mangiferin significantly promoted AMPKα phosphorylation to attenuate hepatic lipid deposition and IR in HFD-induced mice. In addition, mangiferin also promoted glucose consumption and suppressed lipid deposition in HepG2 cells exposed to FFA by activating AMPKα. In 2022, Fan et al. [112] embedded celastrol into the Lac-BSA carrier to form a nanoparticle celastrol-Lac-BSA that could be targeted to the liver, and found that celastrol-Lac-BSA had a better effect on HFD-induced hepatic steatosis and IR in mice compared with celastrol. Further mechanism studies showed that celastrol-Lac-BSA more efficiently inhibited FAS and SREBP-1c by activating AMPK. Under the stimulation of glucose and insulin, HepG2 cells showed significant IR and lipid deposition. However, astragalosides IV treatment could improve these responses by activating AMPKα-mediated SREBP-1c phosphorylation at Ser372 [113].

3.3.2. *Herbal medicine formulas*

In 2019, Sheng et al. [114] reported that babaodan (BBD) could reduce serum glucose level and improve NAFLD. Mechanistically, BBD downregulated SREBP-1c, SCD-1, ACC, CD36, and LXRα, and upregulated CPT1 and PPARα through activating AMPK signaling pathway. In the same year, Lim et al. [115] proposed that Jwa Kum Whan (Jwa) significantly reduced lipid deposition *in vitro* and *in vivo*. Jwa treatment stimulated AMPK, PI3K and IRS-1 phosphorylation, thereby upregulaing CPT1 and downregulating C/EBPα and PPARγ. Then, Li et al. [116] found that ShengMai-Yin and Ganmaidazao Decoction (SGD) could reduce serum glucose, TG and TC contents, and alleviate hepatic steatosis in T2DM KKAy mice with NAFLD through activating AMPK. In 2020, Park et al. [117]

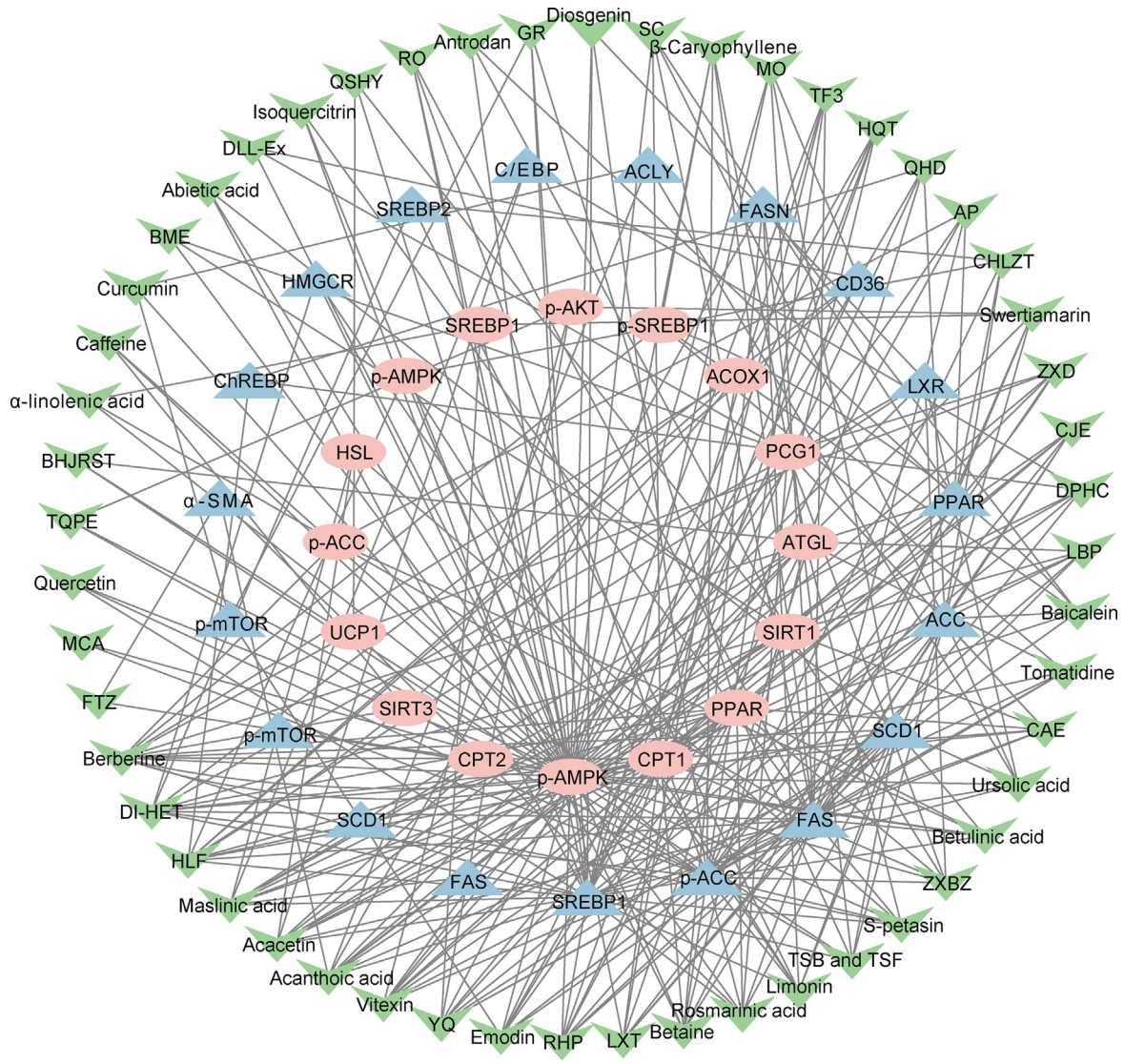


Fig. 4. Herbal medicines-targets network map based on adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) -mediated lipid metabolism signal pathway. ACC: acetyl-CoA carboxylase; ACLY: ATP citrate lyase; ACOX1: acyl-CoA oxidase 1; AP: Adlay (*Coix lacrymajobi* L.) Polyphenol; ATGL: adipose triglyceride lipase; BHJRST: Baihu-Jia-Renshen-Tang; BME: *Momordica charantia* L. extract; CAE: *Cynanchum atratum* Bge. ethanol extract; C/EBP: CCAAT/enhancer-binding protein; ChREBP: carbohydrate response element binding protein; CHLZT: Chaihu Lizhong Tang; CJE: *Cirsium japonicum* DC. ethanol extract; CPT: carnitine palmitoyltransferase; DI-HET: *Dillenia indica* L. hydroethanolic extract; DLL-Ex: *Dolichos lablab* Linne water extract; DPHC: diphlorethohydroxycarmalol; FAS or FASN: fatty acid synthase; FTZ: Fufang-Zhenzhu-Tiaozhi capsule; GR: gastrodigenin rhamno-pyranoside; HLF: *Crataegus pinnatifida* Bge. leaf flavonoids; HMGCR: 3-hydroxy-3-methylglutaryl-coA reductase; HQT: Hugan Qingzhi tablet; HSL: hormone-sensitive lipase; LBP: *Lycium barbarum* polysaccharide; LXR: liver X receptors; LXT: Longdan Xiegan Tang; MCA: *Momordica cochinchinensis* Arill; MO: *Magnolia officinalis* Rehd. et Wils. extract; p-ACC: phospho-acetyl-CoA carboxylase; p-AKT: phosphorylated AKT; p-AMPK: phosphorylated AMP-activated protein kinase; PGC1: peroxisome proliferator-activated receptor gamma coactivator 1; p-mTOR: phosphorylated mammalian target of rapamycin; PPAR: peroxisome proliferator-activated receptor; p-SREBP1: phosphorylated sterol regulatory element-binding protein 1; QHD: QushiHuayu Decoction; QSHY: Qushi Huayu granules; RHP: Radix Hedysari polysaccharide; RO: *Rosmarinus officinalis* L. ethanol extract; SC: Silibinin Capsules; SCD: stearoyl-coA desaturase; SIRT: sirtuin; SMA: smooth muscle actin; SREBP: sterol regulatory element-binding protein; TF3: theaflavin-3:3'-digallate; TQPE: *Trapa quadrispinosa* pericarp extract; TSB: *Toona sinensis* bark extract; TSF: *Toona sinensis* fruit extract; UCP1: uncoupling protein 1; YQ: YiQi YangYin Decoction; ZXBZ: ZexieBaizhu Decoction; ZXD: Zexie Decoction.

reported that Dohongsamul-tang (DST) could reduce AST and ALT release and improve lipid deposition in HCD rats by down-regulating C/EBPα, PPARγ and p-AMPK. In addition, DST treatment reduced Bax/Bcl-2 ratio and upregulated IRS-1 and p-AKT. In the same year, Zhang et al. [118] found that Kangtaizhi Granule (KTZG) could improve NAFLD in HFD rats. Mechanistically, KTZG activate AMPK/mTOR signaling pathway to increase PPAR-γ, GLUT2, and SIRT1, and decrease SREBP-1, p-AKT, and FAS.

3.3.3. Herbal medicine extracts

In 2015, Lin et al. [119] found that *Lycium ruthenicum* extract (LRE) could protect mice form HFD-stimulated NAFLD. LRE markly upregulated AMPK/PPARα axis, which reduced serum TG and TC contents and improved IR. Using diet-induced obesity mice NAFLD model, Artemisia scoparia Waldst. et Kit. extract (SCO) was reported to attenuate hepatic lipid deposition via upregulating p-AMPKα1, insulin receptor β, IRS-1, AKT1, and AKT2, increasing

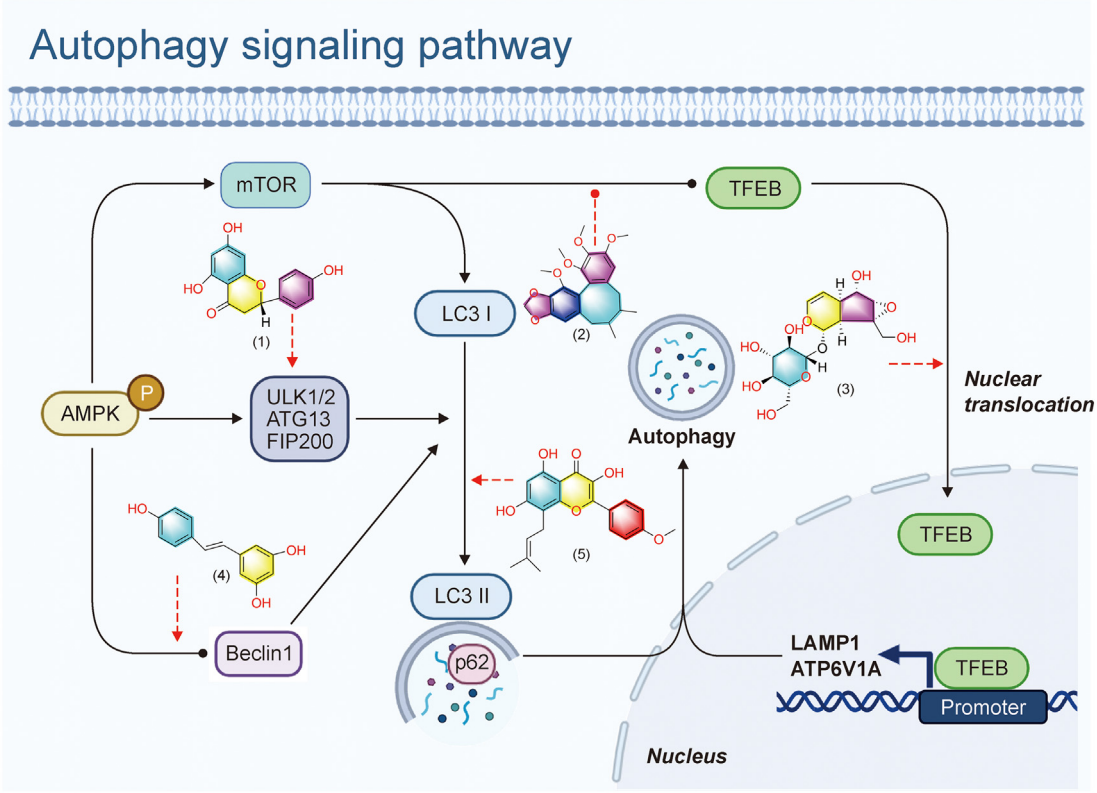


Fig. 5. Herbal medicines improve non-alcoholic fatty liver disease (NAFLD) by regulating adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated autophagy signal pathway. (1) naringenin, (2) schisandrin B, (3) catalpol, (4) resveratrol, (5) icaritin. ATG: autophagy-related proteins; LC3: microtubule-associated proteins 1A/1B light chain 3; mTOR: mammalian target of rapamycin; p62: sequestosome 1; TFEB: transcription factor EB; ULK1/2: unc-51-like kinase 1/2.

hepatic IRS-2 content, and inhibiting FAS, HMG-CoA, HMGR, and SREBP-1c expression [120]. In 2016, Yang et al. [121] reported that aqueous Rheum palmatum L. extraction (RP) could improve HFD-induced liver weight increase, glucose tolerance and TG content, and the mechanism is related to the upregulation of AMPK/ACC axis. In 2018, Kin et al. [82] reported that Berries of *Lonicera caerulea* L. extract (BHe) could improve HFD-induced NAFLD in mice by increasing AMPKα1 and AMPKα2, inhibiting the activity of phosphoenolpyruvate carboxykinase and G6P, and down-regulating SREBP-1c, ACC1, C/EBPα, and C/EBPβ. *Helminthostachys zeylanica* (L.) Hook. (HZ) is an herb with significant anti-pyretic and anti-inflammatory activities. Recent studies showed that HZ extract attenuated hepatic steatosis and IR in HFD mice by promoting AMPK and ACC phosphorylation. Additionally, they identified two main components (ugonins J and K) from the HZ extract [122].

3.4. AMPK-mediated oxidative stress pathway

The improvement of AMPK/oxidative stress also helps to alleviate NAFLD. AMPK, activated by natural herbal medicines, participated in the regulation of PPARα-dependent activation of ACOX1 and CPT1α, thereby enhancing fatty acid β-oxidation and achieving lipid-lowering effects. In addition, activated AMPK promoted the activation of CPT1α by increasing ACC phosphorylation to inhibit malonyl-CoA. Moreover, the activation of AMPK could also increase the transcription of heme oxygenase-1 (HO-1) and NADH quinone oxidoreductase 1 (NQO1) by promoting nuclear factor erythroid2-related factor 2 (Nrf2) nuclear translocation, ultimately reducing reactive oxygen species (ROS) production and improving oxidative (Figs. 9 and 10).

3.4.1. Herbal medicine monomers

In 2013, a study reported that curcumin increased PPARα expression and decreased SREBP-1 and FAS expression through upregulating AMPK signaling, thereby suppressing lipid deposition and increasing antioxidant capacity in OA-stimulated HepG2 cells [123]. In 2014, Zhu et al. [124] reported that resveratrol could decrease TG and MDA, and increase high density lipid-cholesterol (HDL-C) and superoxide dismutase (SOD) in KKAy mice serum. Moreover, resveratrol increased glutathione (GSH) and glutathione peroxidase (GPx) contents and suppressed ROS production in KKAy mice liver. Mechanistically, resveratrol activated AMPK and promoted FOXO1 release from the nucleus to the cytoplasm. Puerarin is considered to improve NAFLD recently. Kang et al. [125] showed that puerarin inhibited lipid accumulation and improved antioxidant capacity through activating AMPK to increase its downstream protein PPARα and reduce FAS and SREBPs *in vitro*. In 2017, Liu et al. [126] proposed that genistein could attenuate HFD-stimulated hepatic steatosis HFD rats. Genistein treatment activated AMPK and ACC, and decreased SREBP-1. Furthermore, genistein also increased PPARα, CPT1 and ACO mRNA expression. Using HFD-induced obese mice and FL83B hepatocytes, researchers found that fisetin could improve lipid metabolism through upregulating CPT1 and SIRT1,

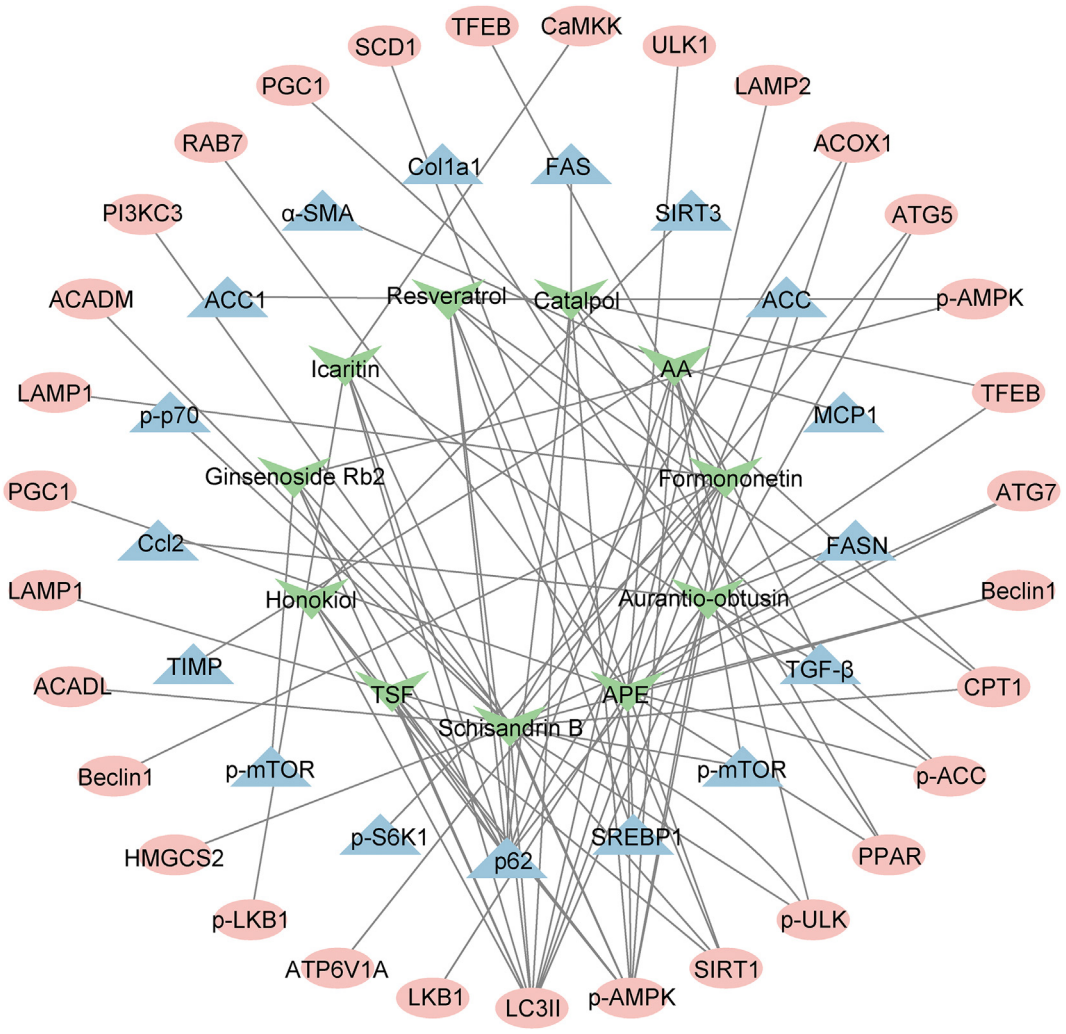


Fig. 6. Herbal medicines-targets network map based on adenosine 5'-monophosphate-activated protein kinase (AMPK)-mediated autophagy signal pathway. AA: alisol A 24-acetate; ACC: acetyl-CoA carboxylase; ACADL: acyl-CoA dehydrogenase long chain; ACADM: acyl-CoA dehydrogenase medium chain; ACOX1: acyl-CoA oxidase 1; APE: apple polyphenol extract; ATG: autophagy related protein; ATP6V1A: V-type proton ATPase catalytic subunit A; CaMKK: calmodulin dependent protein kinase kinase; Ccl2: C-C motif chemokine ligand 2; Col1a1: collagen type I alpha 1 chain; CPT1: carnitine palmitoyl transferase 1; FAS or FASN: fatty acid synthase; HMGCS2: 3-hydroxy-3-methylglutaryl-CoA synthase 2; LAMP: lysosomal associated membrane protein; LC3: autophagy marker light chain 3; LKB1: liver kinase B1; MCP1: monocyte chemotactic protein 1; p62: sequestosome 1; p-AMPK: phosphorylated AMP-activated protein kinase; PGC1: peroxisome proliferator-activated receptor gamma coactivator 1; PI3KC3: phosphoinositide 3-kinase class 3; p-LKB1: phosphorylated liver kinase B1; p-mTOR: phospho-mammalian target of rapamycin; PPAR: peroxisome proliferator-activated receptor; p-S6K1: phospho-protein S6 Kinase1; p-ULK: phospho-unc-51-like kinase 1; RAB7: Ras-related protein 7; SCD1: stearoyl-CoA desaturase 1; SIRT: sirtuin; α-SMA: alpha-smooth muscle actin; SREBP1: sterol regulatory element binding protein 1; TFEB: transcription factor EB; TGF-β: transforming growth factor beta; TIMP: tissue inhibitor of metalloproteinase; TSF: Tangshen formula; ULK1: unc-51 like autophagy activating kinase 1.

downregulating SREBP-1c, C/EBPα, PPAR-γ, and FAS, and promoting ACC-1, AMPKα, ATGL, and HSL phosphorylation [127].

Oxyresveratrol is a type of stilbenoids extracted from *Morus alba* L. with a hepatoprotective effect in HFD-fed mice. Further research found that oxyresveratrol activated AMPK, inhibited LXRα and SREBP-1c, and upregulated SCD-1, CPT1, FAS, and PPARα. In addition, treatment with compound C reversed the above effects [128]. Based on the OA-induced rat hepatic steatosis model, Chen et al. [129] revealed that baicalin significantly relieved NAFLD via activating AMPK and reducing SREBP-1c *in vivo*. In addition, baicalin markedly reduced FAS, HSL, ATGL, ACC, and SCD1, but promoted ACC phosphorylation and CPT1 and Nrf2 expression *in vitro*. Pinocembrin-7-O-β-*d*-glucoside (PCBG), pinocembrin (PCB), and 5-methoxy-pinocembrin-7-O-β-*d*-glucoside (MPG) are three natural flavonoids extracted from Penthorum chinense Pursh. These three flavonoids could alleviate FFA-stimulated lipid deposition in HepG2 cells by reducing MDA, AST, and ALT levels and inhibiting SOD and GSH-Px activities through increasing p-AMPK, PPARα and SIRT1, and inhibiting FAS, SREBP-1c, ACC and SCD1 [130]. Using PA-induced HepG-2 cells, AML-12 cells and primary hepatocytes and HFD-fed mice and rat NAFLD models, dioscin was reported to relieve lipid deposition via activating the SIRT1/AMPK signaling to upregulate CPT, FOXO1 and ATGL, and downregulate SREBP-1c, FAS, and SCD [131]. In addition, THC also could attenuate hepatic lipid deposition in HFD mice via activating AMPK, enhancing fatty acid oxidation and regulating IR [132]. In 2019, Luo et al. [133] found that crocin reduced AST, ALT, and TG levels and liver morphological damage in db/db mice. Mechanistically, crocin downregulated FAS, SREBP-1c, and SCD1 mRNA, and increased PPARα, ACOX1, and CPT1 mRNA. Furthermore, lentivirus-mediated AMPK downregulation could reverse these effects. In the same year,

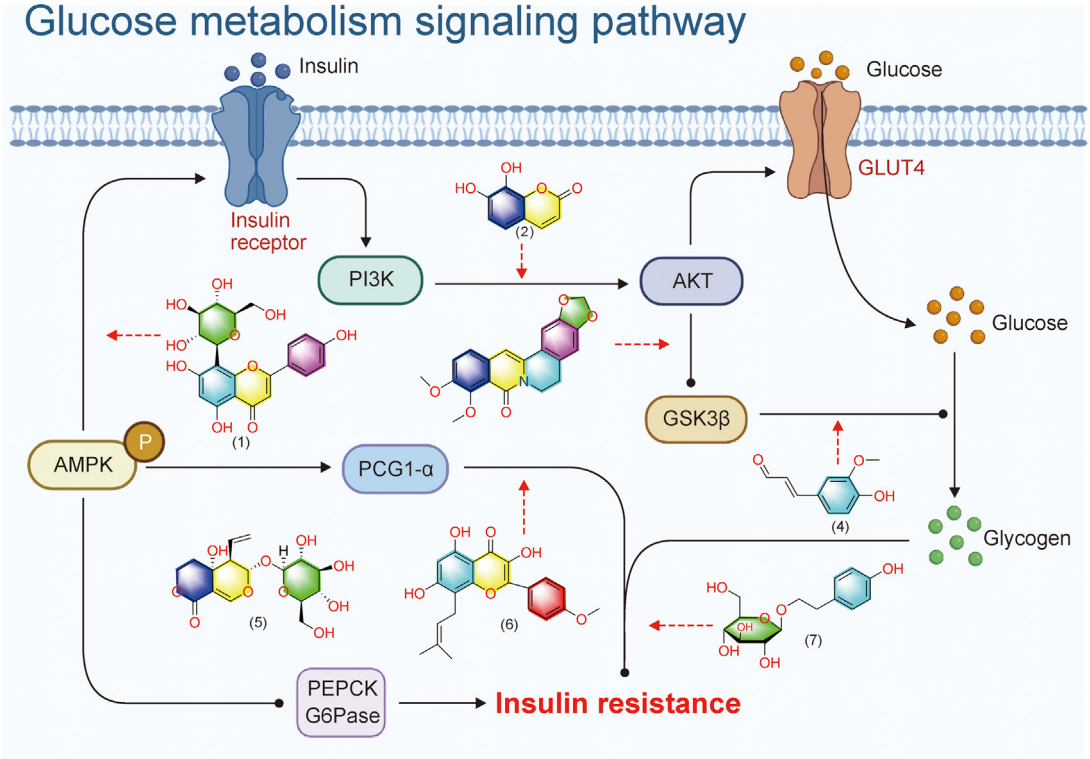


Fig. 7. Herbal medicines improve non-alcoholic fatty liver disease (NAFLD) by regulating adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated glucose metabolism signal pathway. (1) vitexin, (2) daphnetin, (3) oxyberberine, (4) coniferaldehyde, (5) swertiamarin, (6) icaritin, (7) salidroside. PI3K: phosphatidylinositide 3-kinases; AKT: protein kinase B; GLUT4: glucose transporter type 4; GSK3β: glycogen synthase kinase 3β; G6Pase: glucose-6-phosphatase; PEPCK: phosphoenolpyruvate carboxykinase.

γ-mangostin was revealed to attenuate FFA-stimulated lipid deposition in L02 and HepG2 cells. γ-Mangostin treatment upregulated SIRT1/LKB1/AMPK signaling to increase CPT1 and reduce TC, TG, ALT, and AST. Importantly, compound C attenuated the lipid-lowering effect of γ-mangostin [134]. Then, Liou et al. [135] found that licochalcone A also could improve HFD-induced hepatic steatosis *in vivo*. Mechanistically, licochalcone A upregulated SIRT1, CPT1, and ATGL, downregulated SREBP-1c, PPAR-γ, and FAS, and increased p-AMPK and ACC. Notably, licochalcone A could restore the downregulation of p-ACC and p-AMPK levels induced by compound C. Another research reported that DSG treatment also could activate AMPK to upregulate CPT1α and p-ACC and inhibit FAS and SREBP-1c, thus improving lipid accumulation in PA-simulated L02 cells [136].

In 2020, Yuan et al. [137] extracted a hyperbranched proteoglycan from Ganoderma lucidum, namely FYGL, and found that FYGL could significantly relieved PA-stimulated lipid deposition in HepG2 cells. FYGL treatment decreased TC and TG content, suppressed MDA and ROS production, and increased total antioxidant capacity (T-AOC) and SOD, which were related to the inhibition of SREBP-1 and FAS and increase of CPT1 via activating AMPK and ACC. Tanaka et al. [138] reported that gallic acid inhibited PA-caused HepG2 cells lipid deposition by activating AMPK-mediated HO-1 pathway. Moreover, GA also restored cells viability and inhibited cell apoptosis in HepG2 cells exposed to PA and H_2O_2. Later, Huang et al. [139] demonstrated that resveratrol reduced SREBP-1c and FAS through upregulating PPARα and CPT1, thereby relieving oxidative stress and lipid accumulation. siRNA-mediated PPARα or PPARα knockdown and AMPK inhibitor treatment eliminated the protective effect of resveratrol on NAFLD. Liou et al. [140] reported phloretin activated ACC, AMPK, and HSL, increased PPARα, SIRT1, CPT1, and ATGL, and inhibited FAS, SREBP-1c, and C/EBPβ, thus improving NAFLD *in vivo* and *in vitro*. Geniposide is extracted from Gardenia jasminoides Ellis, which have anti-diabetes, lipid-lowering and anti-oxidation activities. There are some reports that geniposide improved NAFLD by activating AMPK and promoting the nuclear expression of Nrf2 [141,142]. Hypericin is a main active ingredient of *Hypericum perforatum* L., which may be used to treat NAFLD. A study reported that hypericin inhibited lipid deposition in FFA-stimulated L02 and HepG2 cells and HFHS-stimulated mice liver by reducing oxidative stress, suppressing adipogenesis and upregulating lipid oxidation. The potential molecular mechanism was related to the activation of AMPK signaling via direct binding of hypericin to PKACαco [143]. Oxyberberine is an oxidative metabolite of BBR mediated by intestinal flora. Based on egg yolk-induced zebrafish NAFLD model, Yu et al. [144] confirmed that Radix Polygoni Multiflori Preparata (RPMP) and its main component emodin inhibited lipid accumulation in zebrafish liver. RPMP obviously decreased TG, while emodin significantly reduced TC and TG. Remarkably, both emodin and RPMP could promote the phosphorylation of AMPKα by activating PI3K/AKT2 signaling, thus upregulating PPARα, CPT1α, and ACOX1 mRNA, and enhancing FAO. In 2021, Chang et al. [145] found that ugonin J treatment improved HFD-induced hyperlipidemia, liver inflammation, glucose tolerance and IR in mice. Further research found that Ugonin J increased p-AMPK, p-ACC, and CPT1 and reduced SREBP-1c in PA-stimulated HuS-E/2 cells. In 2022, Li et al. [146] proposed that oral baicalein significantly reduced TG, LDL-C, and AST contents in fructose-fed rats liver. Mechanically, baicalein upregulated CPT1α through activating AMPK/PGC-1α signaling axis, thereby enhancing fatty acid oxidation.

3.4.2. *Herbal medicine formulas*

Yang et al. [147] reported that the lipolysis regulatory genes PPAR-α and PPAR-γ decreased, and the adipogenic genes FAS,

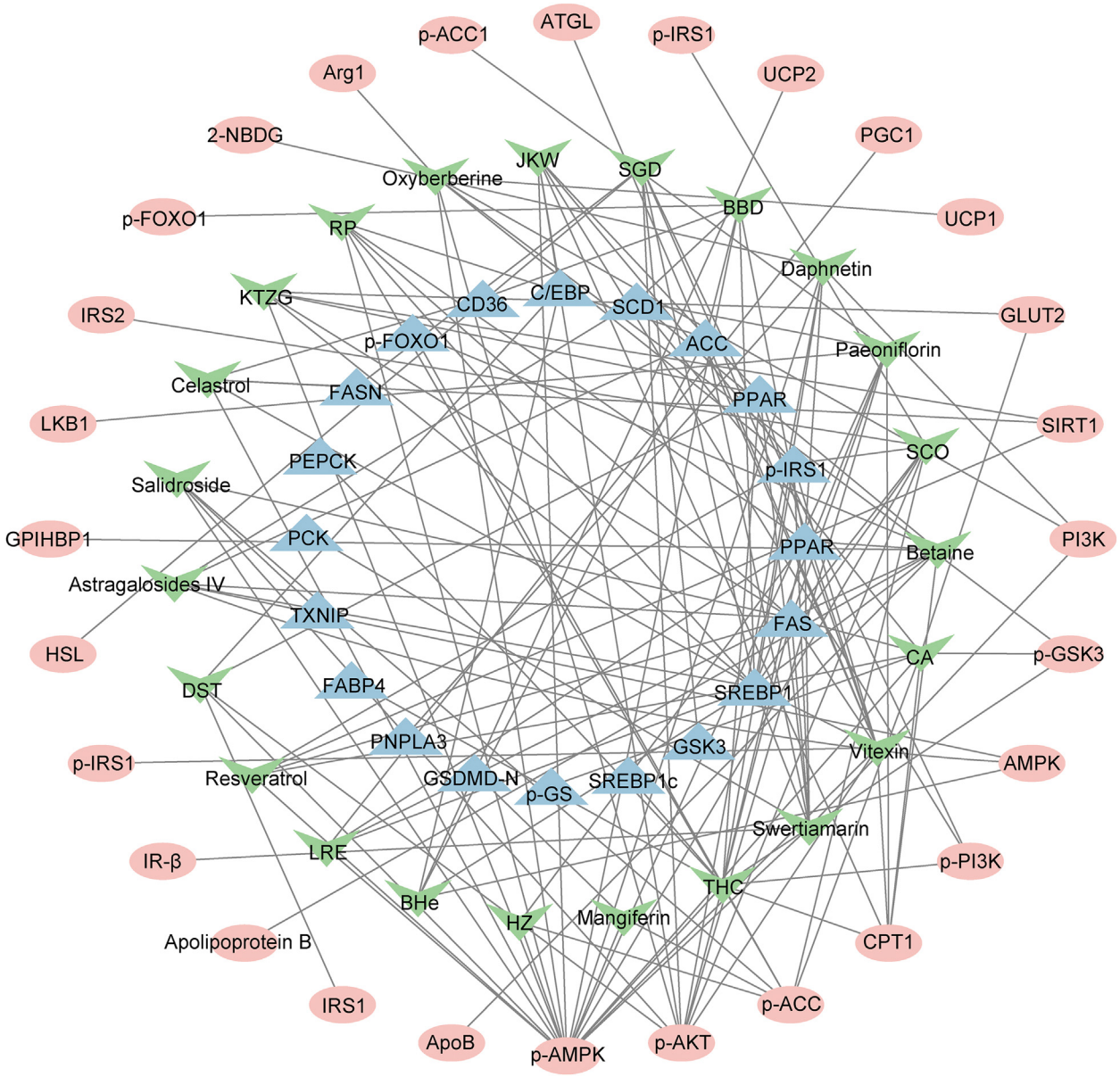


Fig. 8. Herbal medicines-targets network map based on adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated autophagy signal pathway. AA: alisol A 24-acetate; ACC: acetyl-CoA carboxylase; ACADL: acyl-CoA dehydrogenase long chain; ACADM: acyl-CoA dehydrogenase medium chain; ACOX1: acyl-CoA oxidase 1; APE: apple polyphenol extract; ATG: autophagy related protein; ATP6V1A: V-type proton ATPase catalytic subunit A; CaMKK: calmodulin dependent protein kinase kinase; Ccl2: C-C motif chemokine ligand 2; Col1a1: collagen type I alpha 1; CPT1: carnitine palmitoyl transferase 1; FAS or FASN: fatty acid synthase; LAMP: lysosome-associated membrane protein; LC3: autophagy marker light chain 3; LKB1: liver kinase B1; MCP1: monocyte chemotactic protein 1; p62: sequestosome 1; p-AMPK: phosphorylated AMPK; PGC1: peroxisome proliferator-activated receptor gamma coactivator-1; PI3KC3: phosphatidylinositol 3-kinase catalytic subunit type 3; p-mTOR: phospho-mammalian target of rapamycin; p-S6K1: phospho-protein S6 kinase1; p-ULK1: phospho-unc-51-like kinase 1; SCD1: stearoyl-CoA desaturase-1; SIRT: sirtuin; SMA: smooth muscle actin; SREBP1: sterol regulatory element binding protein 1; TFEB: transcription factor EB; TGF: transforming growth factor; TIMP: tissue inhibitor of metalloproteinase; TSF: Tangshen formula. ULK1: unc-51-like kinase 1.

SREBP-1c, and L-FABP upregulated in the liver of HFD-fed rat. However, *Ping-tang* Recipe (PTR) intervention could improve these changes by activating AMPK and promoting acetyl-CoA carboxylase phosphorylation. *Zanthoxylum bungeanum* Maxim. (Rutaceae) is a Chinese herbal medicine with biological activities such as anti-obesity, lipid-lowering, and anti-diabetes, and amides in *Z. bungeanum* (AZB) are considered to be the main active agent. In 2024, Peng et al. [148] found that AZB could alleviate oxidative stress, liver damage and fat accumulation in liver tissue by upregulating AMPK/Nrf2 signaling, thereby improving HFD-induced NAFLD in mice.

3.4.3. Herbal medicine extracts

In 2019, Mun et al. [149] showed that hot water extract of Curcuma longa L. (CLW) inhibited ROS and MDA production, downregulated SREBP-1, FAS, and ACC, upregulated PPARα, AMPK, and CPT1, and improved NAFLD in FFA-stimulated HepG2 cells and HFD mice. In 2020, a study found that Astragalus membranaceus (Fisch.) Bge. and Arnebia euchroma (Royle) Johnst. extracts (AM and LE) protected mice from HFD-induced NAFLD by activating AMPK and ACC to upregulate CPT1 and downregulate FAS and SREBP-1c [150]. Kim et al. showed that Lemon balm extract (LBE) could attenuate NASH in PA-stimulated HepG2 cells and methionine-choline

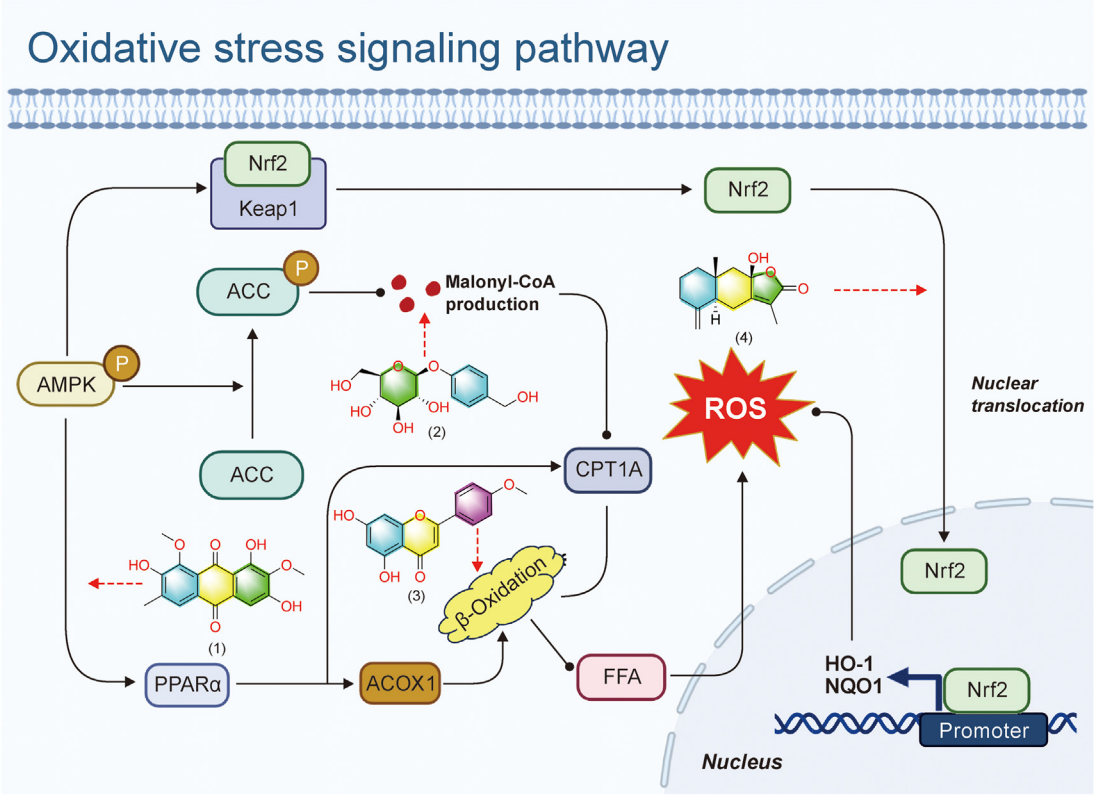


Fig. 9. Herbal medicines improve non-alcoholic fatty liver disease (NAFLD) by regulating adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated oxidative stress signal pathway. (1) aurantio-obtusin, (2) gastrodin, (3) acacetin, (4) atractylenolide III. ACC: acetyl-CoA carboxylase; ACOX1: acyl-CoA oxidase 1; CPT1α: carnitine palmitoyltransferase 1A; FFA: free fatty acids; HO-1: heme oxygenase-1; NQO1: NADH quinone oxidoreductase 1; Nrf2: nuclear factor erythroid 2-related factor 2; PPARα: peroxisome proliferators-activated receptor α; ROS: reactive oxygen species.

deficient diet (MCDD) db/db mice. LBE treatment activated AMPK, and in turn increased Nrf2 and HO-1 and reduced SREBP-1 and SCD1. In 2020, Lee et al. [151] proposed that Citrus peel extracts (CPEs) could protect rats from HFD-induced hepatic steatosis. Further research found that CPEs activated AMPK and reduced ROS production. Furthermore, CPEs treatment also inhibited the phosphorylation of mTOR. Que Zui tea hot water extract and aqueous-ethanol extract (QW and QA) were reported to reduce TG, TC, AST, and ALT contents in HFD-induced SD rats' liver via AMPK/PPARα pathway by increasing AdipoR2. In addition, QW and QA improved lipid peroxidation-induced liver injury by regulating Nrf2 to activate GSH, SOD, and catalase (CAT) [152].

3.5. AMPK-mediated inflammation pathway

Some natural products could inhibit tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β production by activating AMPK to increase macrophages transformation from M1 to M2 and nuclear factor kappa-B (NF-κB) nuclear level, and ultimately improve NAFLD (Figs. 11 and 12).

3.5.1. Herbal medicine monomers

In 2016, Qu et al. [153] reported that gastrodin increased SOD level, reduced ROS and MDA release, downregulated IL-6, TNF-α, cyclooxygenase-2 (COX2), and SOD1 mRNA expression, and improved OA-stimulated lipid deposition in HL-7702 cells and HFD-caused hepatic steatosis in mice and rats through promoting Nrf2 phosphorylation at serine 40. Interestingly, the activation of Nrf2 pathway by gastrodin and its anti-inflammatory activity were blocked by compound C in OA-induced HL-7702 cells. In the same year, Qiang et al. [154] confirmed that demethyleneberberine (DMB) restored fatty acid β-oxidation via activating AMPK, thus maintaining the stability of lipid metabolism in HFD mice. In addition, DMB treatment also inhibited the production of TNFα and IL-1β. Arctigenin was shown to suppress OA-induced lipid deposition *in vitro*. Indepth mechanism studies found that arctigenin could inhibit ACC and SREBP-1 and increase CPT1 and PPARα via upregulating PI3K/AKT and AMPK signaling. Furthermore, arctigenin treatment also inhibited ICAM-1, IL-1β, IL-6, IL-6sR, IL-7, and IL-8 release [155]. Ginsenoside is an active saponin extracted from ginseng, which has the activity of improving lipid metabolism disorder. In 2019, Xiao et al. [156] reported that ginsenoside Rg1 could downregulate ALT and AST levels and inhibit inflammatory cytokines release, thus improving PA-stimulated hepatic lipid deposition and inflammation in HepG2 cells. Further mechanism studies showed that ginsenoside Rg1 promoted AMPK phosphorylation and inhibited NF-κB translocation, which were blocked by AMPK inhibitors. In 2020, chicoric acid was found to alleviate lipid accumulation and oxidative stress in PA-stimulated HepG2 cells. Mechanistically, chicoric acid promoted AMPK phosphorylation, upregulated Nrf2 nuclear protein levels, and inhibited NF-κB phosphorylation *in vitro* and *in vivo*. Notably, compound C reversed chicoric acid-mediated inhibition of ROS release, while AMPK activator AICAR showed a similar effect as chicoric acid [157].

Cordycepin is an adenosine analogue extracted from Cordyceps. In 2021, Gong et al. [158] found that cordycepin improved HFD-

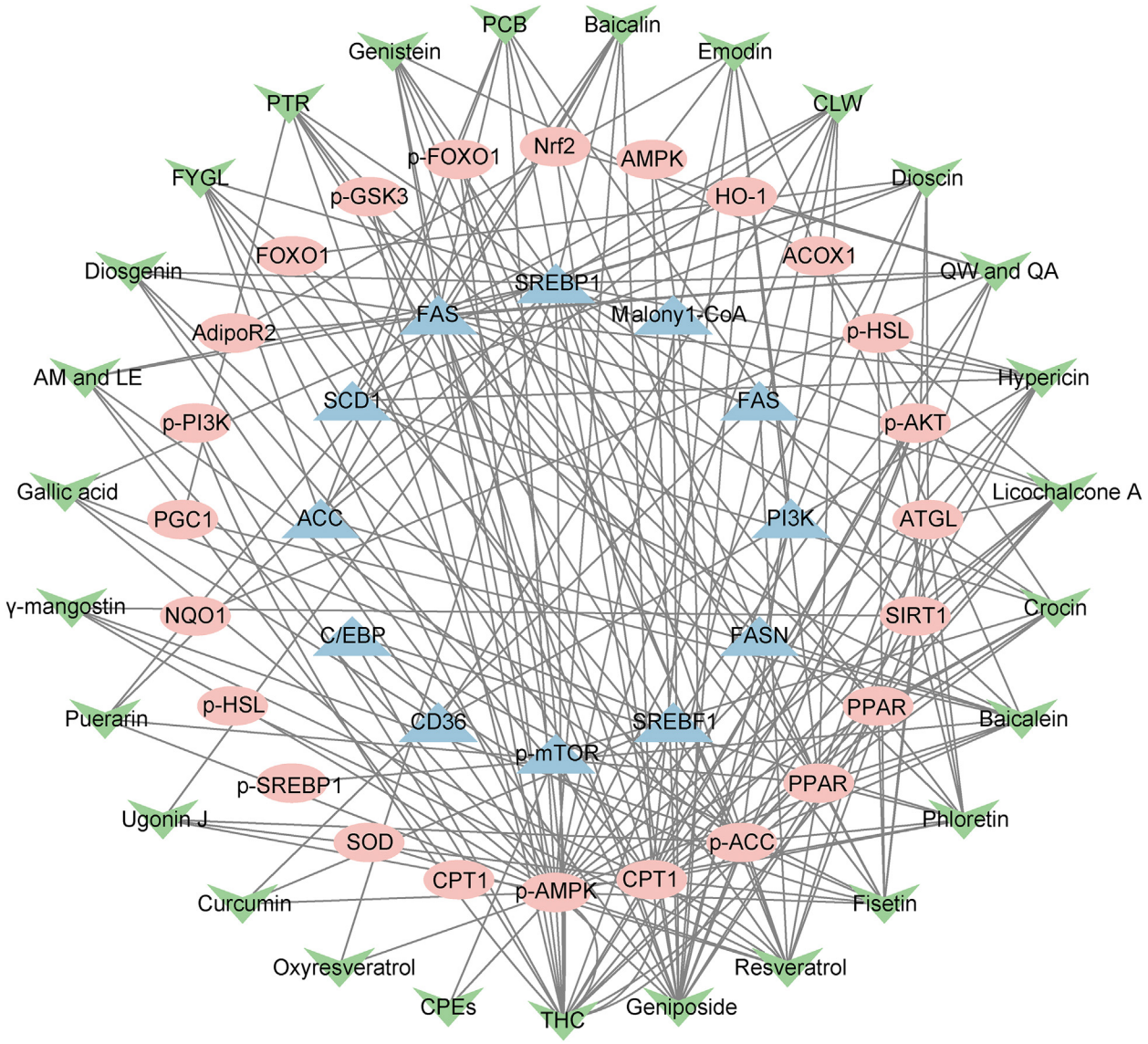


Fig. 10. Herbal medicines-targets network map based on adenosine 5'-monophosphate-activated protein kinase (AMPK)-mediated oxidative stress signal pathway. ACC: acetyl-CoA carboxylase; ACOX1: acyl-CoA oxidase 1; AdipoR2: adiponectin receptor 2; AM: *Astragalus membranaceus* (Fisch.) Bge. extract; AMPK: AMP-activated protein kinase; ATGL: adipose triglyceride lipase; AZB: Amides in *Z. bungeanum*; CLW: water extract of *Curcuma Longa* L.; CPT1: carnitine palmitoyltransferase 1; FAS or FASN: fatty acid synthase; FOXO1: forkhead box O1; FYGL: *Ganoderma lucidum* polysaccharide; HO-1: heme oxygenase-1; LE: *Arnebia euchroma* (Royle) Johnst. extract; MPG: 5-methoxy-pinocembrin-7-O-β-d-glucoside; NQO1: NAD(P)H: quinone oxidoreductase 1; Nrf2: nuclear Factor erythroid 2-related factor 2; p-ACC: phosphorylated acetyl-CoA carboxylase; p-AKT: phosphorylated protein kinase B; p-AMPK: phosphorylated AMP-activated protein kinase; PCB: pinocembrin; PCBG: pinocembrin-7-O-β-d-glucoside; PGC1a: PPARγ coactivator-1α; p-FOXO1: phosphorylated forkhead box O1; p-GSK3: phosphorylated glycogen synthase kinase 3; p-HSL: phosphorylated hormone-sensitive lipase; PI3K: phosphoinositide 3-kinase; p-mTOR: phosphorylated mammalian target of rapamycin; PPAR: peroxisome proliferator-activated receptor; PTR: Ping-tang Recipe; QA: Queous-ethanol extract; QW: Que Zui tea hot water extract; SC: Silibinin Capsules; SCD1: stearoyl-CoA desaturase 1; SIRT1: sirtuin 1; SOD: superoxide dismutase; SREBP1: sterol regulatory element-binding transcription factor 1; THC: Tetrahydrocurcumin.

stimulated NAFLD in mice. Cordycepin treatment decreased serum AST, ALT, TG, TC, and LDL-C contents and increased HDL-C contents. Meanwhile, cordycepin also suppressed TNF-α, IL-1β, IL-6, and MCP1 production. These effects were related to the activation of AMPK. In the same year, Liu et al. [159] reported that corosolic acid reduced AST, ALT, TG, and TC contents and inhibited IL-6, TNF-α, IL-1β, and caspase-1 production via activating AMPK and inhibiting NF-κB, thereby improving FFA-stimulated lipid deposition in HepG2 cells and HFD- and CCl_4-caused hepatic steatosis and inflammation in mice. Patchouli alcohol has significant lipid-lowering and anti-inflammatory effects. Pyun et al. [160] demonstrated that patchouli alcohol improved PA-induced lipid accumulation and HFD-induced hepatic steatosis by promoting AMPK phosphorylation, increasing SIRT1 expression, and reducing p-NF-κB levels. Huang et al. [161] reported that triptolide improved hepatic adipogenesis, FAO, and NAFLD in obese db/db mice by regulating AMPK/ACC signaling. In addition, triptolide treatment inhibited fibrosis and inflammation in MCD-fed mice liver. Using HFD-stimulated NAFLD model in male Swiss mice, Lima et al. [162] reported that α, β-amyrin significantly activated AMPK, thus inhibiting mTORC1 activity and SREBP-1 expression, and ultimately inhibiting adipogenesis and inflammatory response. In 2022, ALTamimi et al. [163] reported that ellagic

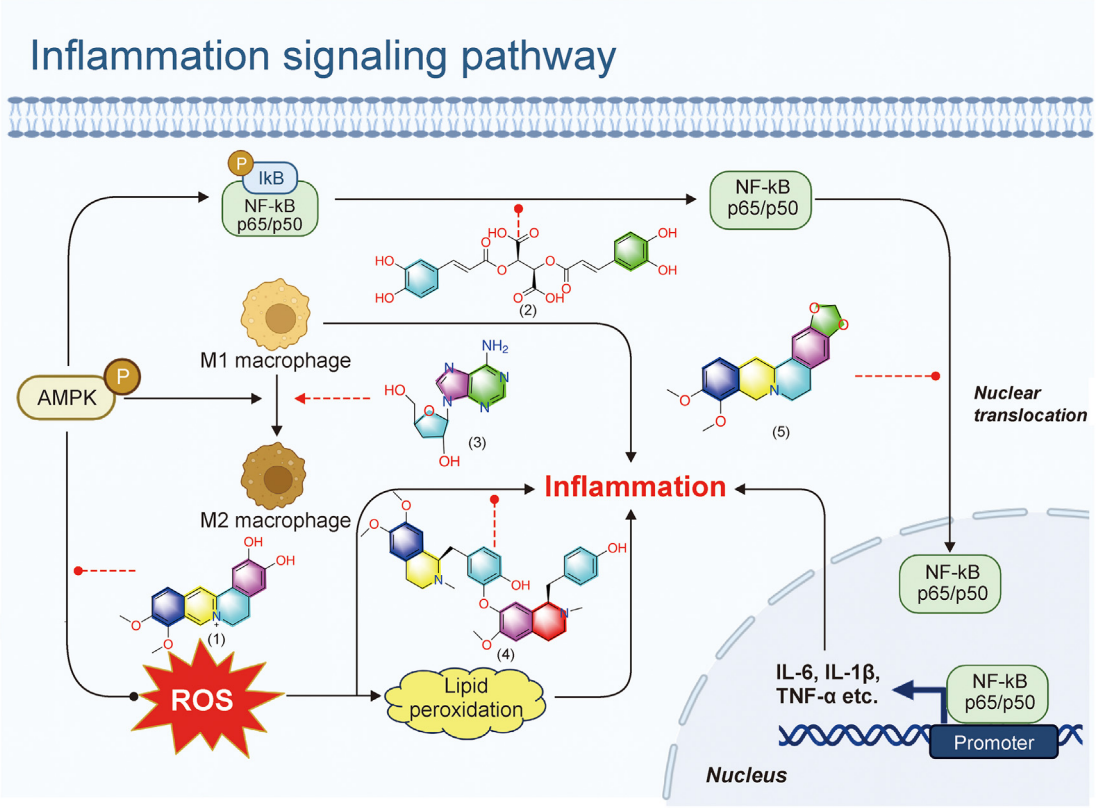


Fig. 11. Herbal medicines improve non-alcoholic fatty liver disease (NAFLD) by regulating adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated inflammation signal pathway. (1) demethyleneberberine, (2) chicoric aci, (3) cordycepin, (4) liensinine, (5) berberine. IL-1β: interleukin-1β; IL-6: interleukin-6; ROS: reactive oxygen species; TNF-α: tumor necrosis factor-α.

acid relieved hepatic steatosis in type I diabetes rats caused by streptozotocin through suppressing NF-κB, and increasing Nrf2 nuclear translocation to eliminate streptozotocin-induced down-regulation of SOD and GSH, and prevent ROS, MDA, IL-6, and TNF-α production. All of the above effects were reversed by compound C, indicating that EA regulates NAFLD by activating AMPK. Liensinine is an isoquinoline alkaloid and has a significant NAFLD improving effect. Liang et al. [164] reported that liensinine could enhance Nrf2 nuclear translocation and reduced ROS production, and inhibit PA-stimulated lipid deposition in L02 and AML12 cells. Moreover, liensinine improved PA-induced inflammation by suppressing TGF beta-activated kinase 1 (TAK1)/NF-κB axis. Importantly, liensinine treatment inhibited lipid synthesis and restored insulin uptake in HFD mice via activating AMPK. Later, ginsenoside CK was found to reduce PA- and OA-stimulated lipid deposition in HepG2 cells and fructose-caused inflammation and injury in mice liver. Ginsenoside CK treatment upregulated lipid synthesis and metabolism related factors (SIRT1, p-ACC, PPARα, and CPT1α) by activating LKB1 and AMPK. Notably, Compound C partially eliminated these effects *in vitro* [165]. Based on HFD-induced rats lipid metabolism disorder model. Mohammed et al. [166] found that zingerone could promote Nrf2 nuclear expression, inhibit SREBP-1, SREBP2, and NF-κB, and improve hepatic lipid deposition, steatosis and inflammation through activating AMPK. A recent study found that *Astragalus mongholicus* polysaccharides (mAPS) (a type of polysaccharide widely present in Astragalus) could interfere with the AMPK/PPARα/SREBP-1 pathway to reduce serum TG and TC contents, inhibit liver AST and ALT production, and improve IR and hepatic steatosis in HFD rats. Additionally, mAPS pretreatment reduced HFD-induced toll-like receptor 4 (TLR4) and p-NF-κB increase and TNF-α release [167].

3.5.2. Herbal medicine extracts

Green tea polyphenols (GTP) have the activity of improving metabolic syndrome. GTP treatment obviously reduced serum ALT, AST, IL-6, and TNF-α contents, and inhibited liver MDA and SOD production in HFD-stimulated lipid metabolism disorder model in rats and mice via increasing AMPK phosphorylation. Meanwhile, GTP significantly attenuated IR [168,169]. Using HFD-induced rats liver lipid accumulation model, Wu et al. [170] studied the effects of *R. chinensis* Mill. fruits phenolic extracts (RCMFP) on NAFLD and found that RCMFP could upregulate CPT1 and PPARα, downregulate PPAR-γ, and attenuate hepatic lipid deposition by activating AMPK. In addition. RCMFP also attenuated liver inflammation and apoptosis through increasing Bcl-2 and decreasing p-NF-κB, COX2 and caspase-3. In 2021, Chen et al. [171] reported that *Ampelopsis grossedentata* (Hand-Mazz) W.T. Wang extract (VTE) could improve hepatic steatosis and inflammation in HFD-caused NAFLD and MCDD-induced NASH models. Further mechanistic studies confirmed that VTE activated AMPK and suppressed LXRα. In addition, AMPK knockdown attenuated the antagonistic effect of VTE on LXRα. Panax notoginseng (Burk.) F.H. Chen Saponins (PNS) had significant anti-inflammatory and hepatoprotective effects. Mechanistically, PNS treatment alleviated HFD- and ob/ob-induced liver steatosis and liver fibrosis in mice by activating AMPKα, which was restored by LPS supplementation [172]. Based on network pharmacology analyze, Chen et al. [173] found that Polygonum orientale L. Fructus (POF) could improve NAFLD. Further mechanistic studies demonstrated that POF treatment promoted AMPK phosphorylation, inhibited NF-κB phosphorylation, increased PPARγ and SOD2 expression, and reduced steatosis, oxidative stress, mitochondrial dysfunction, and inflammation in FFA-stimulated L02 cell.

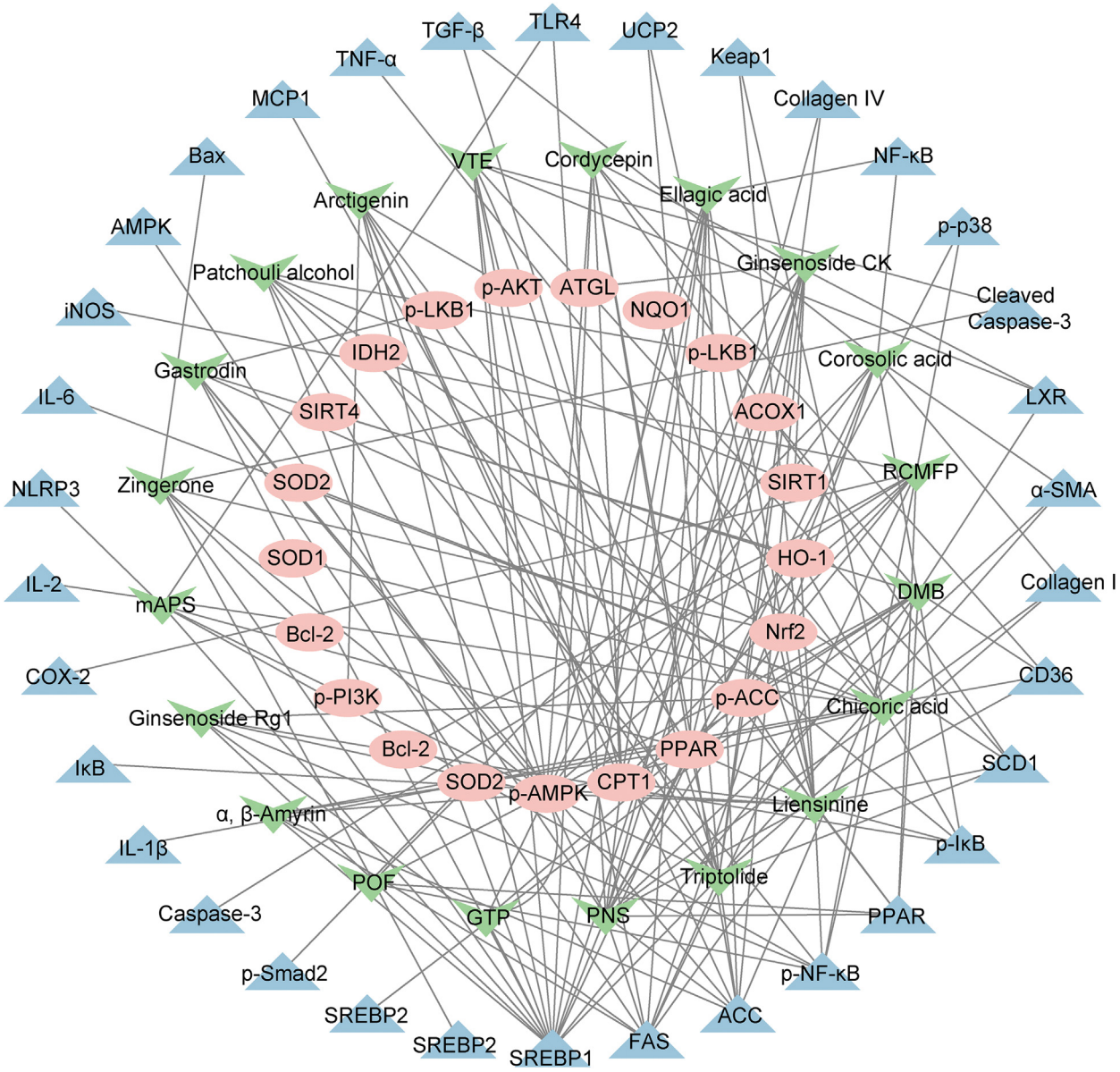


Fig. 12. Herbal medicines-targets network map based on adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated inflammation signal pathway. ACC: acetyl-CoA carboxylase; ACOX1: acyl-CoA oxidase 1; ATGL: adipose triglyceride lipase; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; COX2: cyclooxygenase-2; CPT1: Ccarnitine palmitoyltransferase 1; DMB: demethyleneberberine; FAS: fatty acid synthase; GTP: green tea polyphenols; HO-1: heme oxygenase 1; IL-1: interleukin-1; IL-2: interleukin-2; IL-6: interleukin-6; iNOS: inducible nitric oxide synthase; LXR: liver X receptor; mAPS: *Astragalus mongholicus* polysaccharides; MCP1: monocyte chemoattractant protein 1; NLRP3: NOD-like receptor family pyrin domain containing 3; NQO1: NAD(P)H quinone dehydrogenase 1; Nrf2: nuclear factor erythroid 2-related factor 2; p-AKT: phosphorylated protein kinase B; p-AMPK: phosphorylated AMP-activated protein kinase; p-LKB1: phosphorylated liver kinase B1; PNS: *Panax notoginseng* (Burk.) F.H. Chen saponins; POF: *Polygonum orientale* L. Fructus; PPAR: peroxisome proliferator-activated receptor; p-PI3K: phospho-phosphatidylinositol 3-kinase; RCMFP: *R. chinensis* Mill. fruits phenolic extracts; SIRT: sirtuin; SMA: smooth muscle actin; SOD2: superoxide dismutase 2; SREBP: sterol regulatory element-binding protein; TGF: transforming growth factor; TNF-α: tumor necrosis factor alpha; TLR4: toll-like receptor 4; UCP2: uncoupling protein 2; VTE: *Ampelopsis grossedentata* (Hand-Mazz) W.T. Wang extract.

4. Conclusions

In this article, we summarized traditional Chinese medicine formulas that have protective effects on NAFLD, as well as natural monomers and herbal extracts with potential therapeutic effects. These natural products include alkaloids, flavonoids, glycosides, terpenoids, quinones, phenylpropanoids, coumarins, and lignin. Most of these agents improve lipid accumulation by reducing inflammatory pathways, inhibiting oxidative stress, controlling lipid synthesis, promoting autophagy, and improving IR, and the main mechanisms are closely related to the activation of AMPK signaling pathway. Although continued progress has been made in various aspects of developing natural preparations that have protective effects on NAFLD by activating AMPK signals, the related new drugs are still few, and more in-depth researches are needed in preclinical and clinical settings from discovery of these agents to the application of new drugs for treating NAFLD.

Firstly, most of the natural herbal medicines mentioned in this review only involve preliminary pharmacological studies, and their molecular mechanisms require further research. Therefore, in-depth exploration should be conducted on the molecular mechanisms of targeting AMPK signaling to treat NAFLD by these natural agents. Secondly, these reported natural monomers and herbal extracts lack relevant pharmacokinetic and clinical research data,

and there are also few reports on their toxicity and target organs. Therefore, more work should be made in the future to study the pharmacokinetic characteristics and toxic side effects of these candidate drugs. In addition, in-depth clinical studies are needed to confirm the true efficacy of candidate natural herbal medicines. And more importantly, the treatment of NAFLD usually requires a longer course, so oral medication is the preferred choice. However, the bioavailability of most of the aforementioned drugs (such as Celastrol and Curcumin) is low, and traditional oral administration cannot effectively exert their therapeutic effects. So relevant drugs should undergo structurally modifications or develop new drug delivery systems (DDS). The researches on DDS or structural modification based on AMPK targeting molecular docking will revolve around how to better reach and deliver drugs and therapies to the lesion, while also producing better drug targeting effects and reducing side effects on the human body.

In conclusion, AMPK is one of the core molecules that regulate bioenergy metabolism, and some AMPK activators are considered beneficial in the treatment of NAFLD. So, activating AMPK is an important potential strategy for the treatment of metabolic disease, NAFLD. In summary, this article presents the latest information on natural preparations with protective activity against NAFLD by activating AMPK. We hope that this review can provide a foundation for subsequent screening of new drugs for NAFLD.

CRediT authorship contribution statement

Yongqing Cai: Writing – original draft, Validation, Resources, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Lu Fang:** Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Fei Chen:** Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Peiling Zhong:** Investigation, Data curation. **Xiangru Zheng:** Investigation, Data curation. **Haiyan Xing:** Investigation, Data curation. **Rongrong Fan:** Supervision, Investigation. **Lie Yuan:** Writing – review & editing, Investigation, Formal analysis. **Wei Peng:** Writing – review & editing, Investigation, Formal analysis. **Xiaoli Li:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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