Flavonoids and Related Compounds in Non-Alcoholic Fatty Liver Disease Therapy

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Abstract: Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome, is one of the most common chronic liver diseases, which may progress to fibrosis, cirrhosis and hepatocellular carcinoma. NAFLD is characterized by the accumulation of lipids in the liver arising from multiple factors: increased fatty acid uptake, increased *de novo* lipogenesis, reduced fatty acid oxidation and very low density lipoproteins (VLDL) secretion. Most therapeutic approaches for this disease are often directed at reducing body mass index and improving insulin resistance through lifestyle modifications, bariatric surgery and pharmacological treatments. Nevertheless, there is increasing evidence that the use of natural compounds, as polyphenols, exert multiple benefits on the disorders associated with NAFLD. These molecules seem to be able to regulate the expression of genes mainly involved in *de novo* lipogenesis and fatty acid oxidation, which contributes to their lipid-lowering effect in the liver. Their antioxidant, anti-inflammatory, antifibrogenic and antilipogenic properties seem to confer on them a great potential as strategy for preventing NAFLD progression. In this review, we summarized the effects of these compounds, especially flavonoids, and their mechanisms of action, that have been reported in several studies carried out in *in vitro* and *in vivo* models of NAFLD.

Keywords: antioxidant, flavonoids, insulin resistance, lipid accumulation, NAFLD, quercetin.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases in Western countries and its worldwide prevalence rate ranges from 6% to 35%, with a median of 20% [1]. It is considered the hepatic manifestation of the metabolic syndrome [2], ranging from simple steatosis to non-alcoholic steatohepatitis, liver fibrosis, cirrhosis and hepatocellular carcinoma [3]. About 10-20% of patients who have fatty liver develop inflammation and fibrosis, probably as consequence of a failure of antilipotoxic protection; nevertheless, inflammation may precede steatosis. In both situations, many parallel hits derived from extrahepatic tissues may promote liver inflammation and contribute to its progression to fibrosis and tumor development [4]. The best known risk factors for NAFLD are obesity, hyperglycemia, insulin resistance and hypertriglyceridemia [5].

NAFLD is characterized by the accumulation of lipids in the liver that stems from multiple factors. Thus, the increased fatty acid uptake as a result of the enhancement of the lipolysis from the adipocytes or the increased intake of dietary fat could contribute to this phenomenon. Additionally, increased *de novo* lipogenesis as well as reduced fatty acid oxidation and very low density lipoproteins (VLDL) secretion contribute to triglyceride accumulation in the liver [6]. However, this accumulation of triglycerides in the form of droplets within the hepatocytes may be protective whereas free fatty acids can serve as substrates for the formation of nontriglyceride lipotoxic metabolites that could cause actually the liver injury [7].

As it is represented in Fig. **1**, the main proteins implicated in fatty acid uptake and trafficking are caveolins, fatty acid transport proteins (FATPs), fatty acid translocase (FAT) CD36 and fatty acid binding proteins (FABPs) [6, 8]. A complex network of nuclear receptors regulates enzymes, such as fatty acid synthase (FAS), involved in different steps of hepatic *de novo* lipogenesis [9]. It is worth mentioning liver X receptor (LXR), sterol regulatory element binding protein (SREBP)-1c, peroxisome proliferator activated receptor (PPAR)γ or carbohydrate responsive element binding protein (ChREBP) [10, 11]. PPARα plays a central role in promoting the expression of key enzymes of fatty acid oxidation such as carnitine palmitoyltransferase 1 (CPT1), medium-chain acyl-CoA dehydrogenase (MCAD) or acyl-CoA oxidase (ACO) [12]. Finally, the microsomal triglyceride transfer protein (MTP) regulates triglyceride secretion through VLDL formation [13].
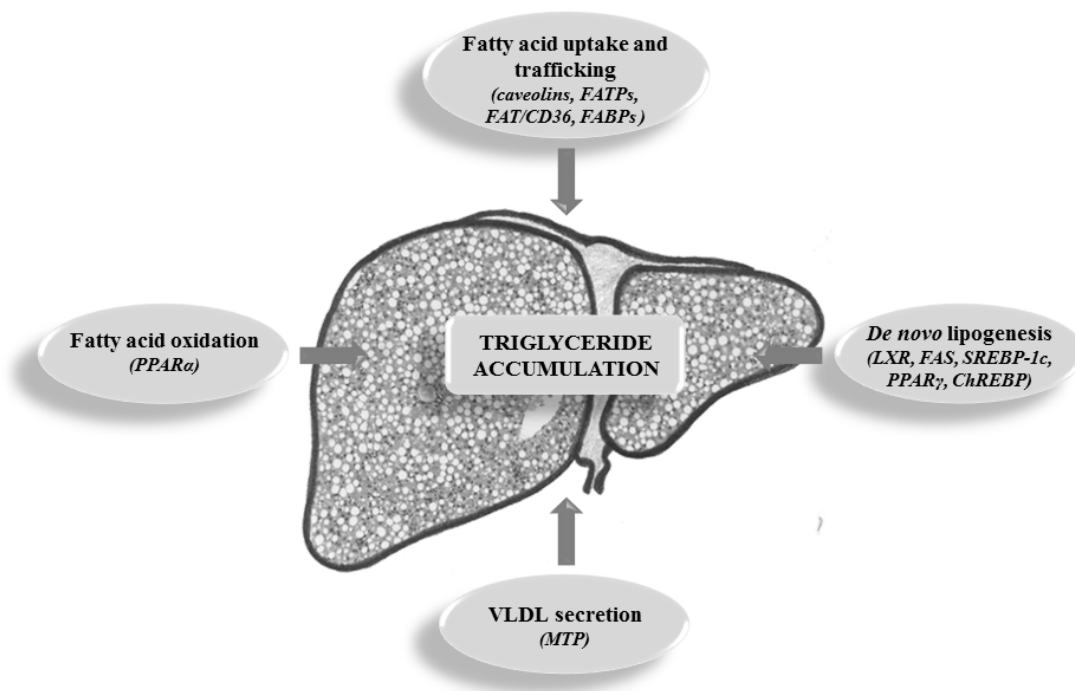
Fig (1). Principal genes that regulate the different processes controlling hepatic triglyceride accumulation.

Most therapies for NAFLD target the major pathways that seem to be essential in the pathogenesis of this disease and are usually directed at reducing body mass index and improving insulin resistance through physical exercise, dietary modification, bariatric surgery and pharmacological treatments [14]. As oxidative stress and inflammation play central roles in NAFLD progression, the use of flavonoids and related compounds with antioxidant and anti-inflammatory properties results in beneficial effects on this and other chronic diseases [15-17]. Moreover, polyphenols can target specific miRNAs that regulate several metabolic pathways including lipid metabolism, which suggests an alternative mechanism by which these compounds could protect from NAFLD [18]. Moreover, development and progression of NAFLD is linked to small intestinal bacterial overgrowth, so supplementation with probiotics seems to improve liver damage, reducing oxidative stress and inflammation by making stronger the intestinal wall, thereby reducing its permeability, bacterial translocation and endotoxemia [19]. In this regard, it has been reported that several flavonoids display prebiotic actions [20], which contribute to their beneficial effects on NAFLD.

These evidences place the use of polyphenolic compounds as an attractive and potential therapeutic strategy for preventing the progression of NAFLD. Their multiple benefits and the different molecular mechanisms underlying their effects are herein reviewed.

2. FLAVONOIDS

Flavonoids are a large class of naturally occurring compounds widely present in fruits, vegetables and beverages derived from plants. The basic structure of these polyphenolic compounds consist of a 15-carbon skeleton that can have numerous substituents, determining the subclass of flavonoid and the specific compound within each class (Fig. **2**). The effects of the main subclasses of flavonoids (flavones, flavonols, flavanols, isoflavones, flavanones and anthocyanidins) on *in vivo* models of NAFLD are summarized in Table **1** (flavonols) and Table **2** (flavones, flavanones, flavanols, isoflavones and anthocyanidins), while effects on *in vitro* models of NAFLD are depicted in Table **3**, being all of them described below.

2.1. Flavonols

Quercetin, one of the most studied flavonoids, has a variety of biological functions, including well-known anti-inflammatory and antioxidant capacities, as well as antiviral activity [17, 21-24]. A comparative study of the role of pioglitazone, quercetin and hydroxy citric acid on steatosis, inflammation, cytochrome P450 (CYP) 2E1 expression and various biochemical parameters in rats fed with high fat diet (HFD), has shown a protective effect of these compounds against non-alcoholic steatohepatitis (NASH), being evident an optimal protection after quercetin treatment compared with pioglitazone or hydroxy citric acid [25, 26]. Several studies have demonstrated that quercetin is able to improve insulin resistance and hepatic lipid accumulation in different models of NAFLD [16, 27-32]. Recently, it has been reported the involvement of SREBP-1c and FAS upregulation in the increase of the lipid content in an *in vitro* model of free fatty acid- and insulin-induced NAFLD. After treatment with quercetin at different concentrations, ranging from 0.1 to 100 µM, the intracellular lipid content was reduced in a dose-dependent manner and the expression of these genes was inhibited, showing that quercetin improved hepatic lipid accumulation by regulating SREBP-1c- and FAS-mediated fatty acid synthesis. Moreover, quercetin induced the phosphorylation of insulin receptor (IR) β and insulin receptor substrate 1 (IRS1), which suggests that the flavonoid improves insulin resistance by enhancing insulin signal transduction [27]. This effect on lipid accumulation and insulin resistance has also been observed in similar *in vitro* models after a treatment with quercetin, showing in addition a reversion of increased lipid peroxidation, DNA fragmentation and inflammatory cytokine secretion, as well as an improvement of antioxidant enzymes levels [28], with a high correlation between inhibitory effects on reactive oxygen species (ROS) generation and intracellular triglyceride levels [33]. In a study about quercetin effect on HFD-induced NAFLD, it has been observed a quercetin-induced regulation of inflammatory cytokines balance that might help to delay the progression of NAFLD through the modulation of liver inflammation and steatosis [34]. These results are in accordance with studies in various nutritional models of NASH that demonstrate an improvement of serum biochemical markers and lipid accumulation in the liver after a treatment with quercetin. The flavonoid is able to reduce biomarkers of liver fibrosis as well as the expression of inflammatory-related genes such as toll-like receptor (TLR)-4, interleukin (IL)-6 or tumor necrosis factor (TNF) α. Beneficial effects of quercetin on fibrogenesis and inflammatory state might be related to the reduction of c-Jun terminal kinase (JNK) phosphorylation and the inactivation of nuclear

factor kappa B (NF-κB)/inducible nitric oxide synthase (iNOS) pathway through the upregulation of silent mating type information regulation 2 homolog 1 (SIRT1) expression, leading to lower inflammatory cytokine transcription [16, 21, 35]. A reduced fibrosis and improvement in liver function has been reported in a model of NAFLD in rats after a treatment with quercetin [29]. Furthermore, in agreement with other studies, authors reported an anti-inflammatory role of quercetin through hepatic NF-κB downregulation, besides an upregulation of nuclear factor (erythroid-derived 2)-related factor-2 (Nrf2) and subsequent heme oxygenase-1 (HO-1) increase, which contribute to cellular stress reduction; moreover, quercetin might attenuate steatosis by increasing fatty acid oxidation through CPT1 upregulation and removing steatotic cells from the liver due to an enhancement of caspase-3 expression-induced apoptosis [29]. On the other hand, an inhibitory effect of quercetin on caspase-1 expression, by suppressing the overexpression of hepatic thioredoxin-interacting protein (TXNIP) and subsequent NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation, could contribute to its lipid-lowering capacity, through downregulation of SREBP-1c and SREBP-2 [32]. Quercetin also reduces plasma and liver free fatty acids, cholesterol and triglyceride levels, by modulating lipid metabolism-related gene expression, preventing PPARα reduction, increasing paraoxonase 1 (PON1) and farnesyltransferase/geranylgeranyltransferase type-1 subunit alpha (FNTA) expressions and suppressing expression of aldehyde dehydrogenase (ALDH) 1B1, apolipoprotein (Apo) A4, ATP-binding cassette (ABC) G5, glycerol-3-phosphate acyltransferase 1 mitochondrial (GPAM), acetyl-CoA carboxylase (ACC), farnesyl-diphosphate farnesyltransferase 1 (FDFT1), PPARγ, FAS, FAT/CD36, CCAAT/enhancer binding protein (C/EBP) α and LXRα [30, 32].

Morin (3,5,7,20,40-pentahydroxyflavone) is a flavonoid isolated from Chinese herbs of the Moraceae family. In high fructose-fed rats morin reduced systemic inflammation, dyslipidemia and insulin and leptin resistance; it also diminished hepatic lipid accumulation through upregulation of PPARα and CPT1 expression, and downregulation of SREBP-1c and stearoyl-CoA desaturase-1 (SCD1) expression. The elevation of hepatic levels of IL-1β, IL-6 and TNFα in high fructose-fed rats was attenuated by morin through inhibiting hepatic sphingosine kinase 1 (SphK1)/sphingosine 1-phosphate (S1P) signaling pathway and subsequent hepatic NF-κB activation. These effects of morin were afterwards confirmed in a cell model stimulated with fructose [36].

Rutin is a glycoside of quercetin that can be found in onions, apples, tea or red wine. This flavonol slightly reduces ROS generation and triglyceride accumulation in an oleic acid-induced hepatic steatosis in an *in vitro* model [33]. Rutin is able to effectively attenuate *in vivo* diet-induced metabolic syndrome, NASH and cardiovascular abnormalities, reducing liver and body weights and plasma triglycerides or free fatty acids and cholesterol levels increase, improving impaired glucose tolerance and antioxidant status, and diminishing steatosis, inflammation and fibrosis in the liver. Rutin could attenuate liver steatosis by upregulating caspase-3-mediated apoptosis of fat-containing hepatocytes, and reduce oxidative stress, as indicated by the increase of heat shock protein (HSP) 70 expression. This flavonol also recovers cardiovascular structure and function, displaying a reduction in systolic blood pressure and an improvement of endothelial function, probably by scavenging free radicals that could in turns increase the nitric oxide bioavailability [37]. Troxerutin, a derivative of rutin, is also able to improve antioxidant

enzymes levels and hepatic lipid homeostasis, and restore insulin signaling and glycometabolism in HFD-induced NAFLD. The mechanism underlying its beneficial effect could implicate the suppression of oxidative stress-mediated NAD^+ depletion by increasing nicotinamide phosphoribosyltransferase (NAMPT) expression and decreasing poly (ADP-ribose) polymerase-1 (PARP1), thereby promoting SIRT1-mediated AMP-activated protein kinase (AMPK) activation to inhibit mammalian target of rapamycin (mTOR) signaling; this in turn enhances nuclear lipin1 localization, increasing fatty acid oxidation and triglyceride secretion and suppressing lipogenesis in the liver [38].

Kaempferol, a flavonoid present in several natural sources such as tea, beans, tomatoes, onions, leeks or apples, displays multiple beneficial effects in cardiovascular and nerve systems, and it has also been reported to suppress the lipid accumulation in macrophages through the modulation of the expression of genes implicated in fatty acid uptake such as FAT/CD36 [39]. *In vitro* studies in HepG2 with induced-lipid accumulation shows that kaempferol, at concentrations ranging from 50 to 150 µM, presents a high inhibitory effect on cellular triglyceride levels and produces a dose-dependent decrease of intracellular ROS [33].

Isorhamnetin, an O-methylated flavonol aglycone, has been reported to show cardio-protective, anti-adipogenic, anti-tumor and anti-inflammatory effects [40-43]. This flavonol is very efficient in reducing triglyceride overaccumulation and ROS generation *in vitro* after oleic acid-induced hepatic steatosis [33], and it has been suggested that the Ca^{2+}/calmodulin-dependent protein kinase kinase-2 (CaMKK2)-mediated AMPK activation is involved in the mechanism underlying the beneficial effect of isorhamnetin in the liver [44].

Tea, berries and other fruits and vegetables contain high concentration of myricetin. This molecule may have a protective effect against diet-induced obesity and insulin resistance partly by improving lipid profile and reducing serum proinflammatory cytokine levels, as well as ameliorating liver steatosis through the increase of fatty acid oxidation by PPARα upregulation and downregulation of SREBP-1 and SREBP-2 [45, 46], also showing antioxidant and lipid-lowering effects *in vitro* [33].

The flavonol galangin is the major component of *Alpinia officinarum*, widely used in traditional Chinese medicine for the treatment of several conditions. The *Alpinia officinarum* extract is able to efficiently suppress the expressions of C/EBPα, FAS, SREBP-1 and PPARγ in the liver and adipose tissue of HFD-fed mice, contributing to its antiobesity effect [47]. Nevertheless, the use of galangin at doses ranging from 1 to 40 µM fails to diminish oleic acid-induced triglyceride accumulation in an *in vitro* model, displaying only a slight reduction of ROS overproduction [33].

2.2. Flavones

Chrysin (5,7-di-OH-flavone) has been reported to be involved in various biological activities [48-50], and it seems to activate PPARγ in macrophages [51]. This flavone could ameliorate HFD-induced liver steatosis and inflammation, reducing pro-inflammatory cytokines and inducing anti-inflammatory cytokines and adiponectin levels, via induction of anti-inflammatory M2 phenotype and inhibition of pro-

inflammatory M1 phenotype of macrophages through PPARγ upregulation [52]. On the contrary, chrysin displays a lacking triglyceride-lowering effect and a pro-oxidant activity i*n vitro* at concentrations of 1-15 µM [33].

Apigenin (4',5,7-trihydroxyflavone) is a flavonoid found in many fruits and vegetables, being parsley and chamomile the most abundant sources. This flavone has been documented to present anti-inflammatory [53, 54] and anticancer properties [55-57]. In spite of its gluconeogenic and lipogenic reduction-mediated antidiabetic capacity reported in human cells [58], it does not seem to be able to reduce triglyceride overaccumulation in oleic acid-treated HepG2 cells, showing also a remarkable dose-dependent induction of ROS levels at concentrations ranging from 10 to 125 µM [33].

Luteolin (3',4',5,7,-tetrahydroxyflavone) is one of the most common polyphenolic flavonoids present in many edible plants such as carrots, peppers, celery, olive oil, peppermint, thyme, rosemary and oregano [59]. Similarly to apigenin, luteolin presents anti-inflammatory [60] and anticancer [61, 62] properties and a gluconeogenic and lipogenic reduction-mediated antidiabetic capacity *in vitro* [58], but unlike apigenin, luteolin is able to reduce *in vitro* ROS production and triglyceride overaccumulation [33, 63], probably through the downregulation of SREBP-1c and FAS gene expressions and the AMPK-mediated upregulation of CPT1 [63].

2.3. Flavanones

Naringenin is a citrus-derived flavonoid, that has been reported to attenuate dyslipidemia and improve insulin resistance in addition to steatosis, by increasing hepatic fatty acid oxidation and preventing SREBP-1c-mediated lipogenesis in several *in vivo* models [64]. Nevertheless, its use in an *in vitro* model of oleic acid-induced hepatic steatosis fails to decrease triglyceride content and displays a pro-oxidant effect [33].

Another flavonoid found abundantly in citrus fruits is hesperetin. This flavanone has shown antioxidant [65], anti-inflammatory [66], anticancer [67], antiallergic [68] and neuroprotective [69] properties, but little is known about its effect on NAFLD models. A treatment with hesperetin in an *in vitro* model of hepatic steatosis could not reduce triglyceride increase and slightly suppressed intracellular ROS [33].

The flavanone taxifolin shows a high antioxidant and antilipogenic effects *in vitro*, reducing the induced triglyceride overaccumulation [33], an effect that could be mediated, at least in part, by its ability to inhibit diacylglycerol acyltransferase (DGAT) and FAS activities [70, 71].

2.4. Flavanols

Recently, the effect of (-)-epigallocatechin-3-gallate (EGCG) on steatosis, liver fibrosis and tumorigenesis has been studied using a new model of NASH based on obese and hypertensive rats treated with HFD and carbon tetrachloride. Authors observed a fibrogenesis inhibition effect of EGCG by targeting the activation of the renin-angiotensin system through the reduction of serum levels of

angiotensin-II (AT-II) and the suppression of angiotensin-converting enzyme (ACE) and AT-II type 1 receptor (AT-1R) expressions. EGCG also reduced inflammation, oxidative stress and lipid peroxidation, preventing NASH-related liver fibrosis and subsequent tumorigenesis as it was demonstrated by the inhibition of the development of hepatic premalignant lesions [72]. Transforming growth factor (TGF)/SMAD, phosphatidylinositol 3-kinase (PI3K)/AKT/forkhead box protein O1 (FOXO1) and NF-κB pathways could be also implicated in the beneficial effect of EGCG on fibrosis, oxidative stress and inflammation [73]. Moreover, EGCG plays a positive role in diminishing triglyceride levels *in vitro* at concentrations under 25 μM, but it reflects a negative effect at higher concentrations. As EGCG, the flavanols (+)-catechin and (-)-epicatechin display a triglyceride-lowering effect in the same *in vitro* model [33].

The major active component of Flavangenol®, one of several pine bark extract products, is the procyanidin B1. This catechin is able to reduce palmitic acid-induce triglyceride accumulation in HepG2 cells by enhancing the β-oxidation of fatty acids through the gene expression upregulation of key enzymes involved in this process [74].

2.5. Isoflavones

In vivo and *in vitro* studies about beneficial relation of isoflavones and NAFLD and adiposity have been summarized in a review of Kim and Kang [75], putting special emphasis in the effect of these compounds via ChREBP and Wnt signaling.

One of the most prevalent isoflavones in soy is daidzein [76]. It has been reported that daidzein supplementation might alleviate HFD-induced NAFLD in mice by regulating *de novo* lipogenesis and improving insulin resistance, as well as modulating adipocyte metabolism. The mechanism underlying this effect could implicate LXRβ and ChREBP downregulation, fatty acid β-oxidation-related gene expression upregulation and the increase of leptin and adiponectin but the reduction of ghrelin levels [77]. Daidzein is also documented to reduce in a dose-dependent manner both triglyceride and ROS levels in an *in vitro* model of oleic acid-induced steatosis [33].

The use of puerarin, the major active component isolated from *Pueraria lobata,* is reported to show beneficial effects in several models of NAFLD. This isoflavone is able to diminish steatosis, inflammation and ballooning by reducing triglyceride and cholesterol levels and TNFα expression in the liver, and improving leptin signal transduction through janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathways [78-80].

Another of most abundant isoflavones in soy is genistein [76]. Its use in *in vitro* [33] and *in vivo* [81, 82] models reveals multiple benefits in NAFLD. Genistein reduces body and liver weights increase and visceral fat pads, improves insulin resistance, serum lipid profile, antioxidant status and NAFLD activity score by diminishing cholesterol, triglycerides and free fatty acids in the liver in addition to TNFα and IL-6 gene expressions. Moreover, it induces an increase in the expression of adiponectin, which functions as an anti-fibrogenic and anti-inflammatory cytokine. The enhancement of fatty acid β-oxidation and the

reduction of lipogenesis in adipose tissue, mediated by the upregulation of AMPK, PPARα and very long-chain acyl-CoA dehydrogenase (VLCAD) and the repression of ACC2, retinoid X receptor (RXR) α, LXRα, SREBP-1c, C/EBPβ and PPARγ could also contribute to the beneficial effects of genistein, leading to a diminution of visceral fat mass [82].

2.6. Anthocyanidins

Cyanidin is an anthocyanidin commonly found in fruits and vegetables. The antioxidant enzyme activation through extracellular signal-regulated kinase (ERK) and JNK pathways and Nrf2 upregulation in addition to ameliorated cytotoxicity and the improvement of the perturbation of genes involved in lipid metabolism, could contribute to its beneficial effects on NASH [83].

A glycoside of cyanidin, cyanidin-3-O-β-glucoside, is able to improve obesity and triglyceride metabolism in KKAy mice, reducing body and liver weights and fat pads, and hepatic and serum triglyceride content. These actions may be mediated by an increase in lipoprotein lipase (LPL) activity in plasma and skeletal muscle and inhibition of LPL in adipose tissue through the activation of AMPK [84]. Furthermore, this anthocyanin decreases hepatic glycerol-3-phosphate acyltransferase 1 (GPAT1) activity and its translocation to the outer mitochondrial membrane, diminishing triglyceride synthesis and thereby attenuating hepatic steatosis [85]. *In vitro* studies show the hepatoprotective effect of cyanidin-3-O-β-glucoside against hyperglycemia-accelerated steatohepatitis in NAFLD, process mediated, at least in part, by the improvement of antioxidant status and the inhibition of the mitochondria-mediated apoptotic pathway through AKT activation and JNK inactivation [86]. This anthocyanin has been also used combined with others such as cyanidin-3-rutinoside and pelargonidin-3-glucoside, displaying a protective effect against diet-induced body weight gain [87].

More recently, a further review about the effect of anthocyanins on hepatic lipid accumulation and lipotoxicity associated with NAFLD in both *in vitro* and *in vivo* models, has proposed the possible mechanism underlying the beneficial effects of anthocyanins, based on available studies. This includes the AMPK activation-mediated lipogenesis inhibition and lipolysis promotion by reducing SREBP-1c and inducing PPARα activity respectively, in addition to the reduction of oxidative stress by the induction of antioxidant enzymes [88].
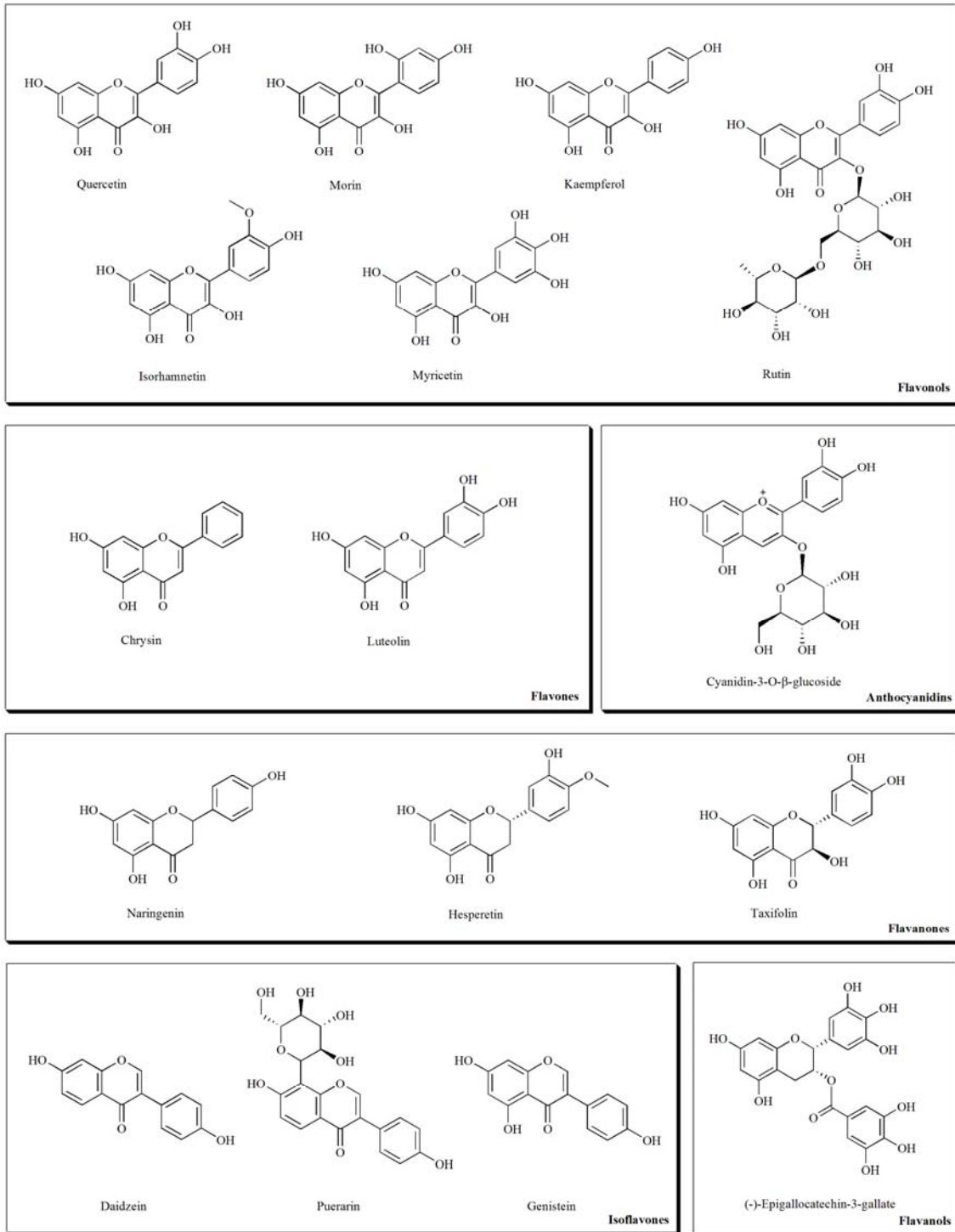
Fig (2). Representative compounds of the major classes of flavonoids with known effects on NAFLD.

Table **1**. Effects of flavonols on *in vivo* models of NAFLD.

Flavonoid treatment	Model	Physiological variables	Blood parameters	Histopathology and gene expression	Ref.
Quercetin 20 mg/kg b.w./day (last 4 weeks)	Wistar rats. HFD feeding (8 weeks)		↑AST, ALT, γGT (Q↓) ↑LDL (Q↓) ↑Glucose (Q↓) ↑Albumin, creatinine, urea, uric acid, bilirubin (Q↓)	↑Steatosis (Q↓) ↑Inflammation (Q↓) ↑CYP2E1 (Q↓)	[25, 26]
Quercetin 75 and 300 mg/Kg b.w./day (last 8 weeks)	Sprague-Dawley rats. HFD feeding (12 weeks)	↑Liver index (Q↓)	↑IL-18 (Q↓) ↓IL-10 (Q↑) ↑Glucose (Q↓)	↑Steatosis (Q↓) ↑Inflammation (Q↓)	[34]
Quercetin 15, 30 and 60 mg/Kg b.w./day (last 2 weeks)	Gerbils. HFD feeding (4 weeks)		↑AST, ALT (Q↓) ↑TG, cholesterol (Q↓) ↑LDL (Q↓) ↑Glucose (Q↓) --Albumin, bilirubin, ammonia (Q--) ↑TNFα, IL-6 (Q↓)	↑Fibrosis (Q↓) ↑Steatosis (Q↓) ↑Inflammation (Q↓) ↓SIRT1 (Q↑) ↑NF-κB p65, iNOS (Q↓)	[16]
Quercetin 50 mg/Kg b.w./day (4 weeks)	C57BL/6J mice. MCD-feeding (4 weeks)	↓Body weight (Q--) ↓Liver weight (Q--)	↑AST, ALT (Q↓)	↑NAS (Q↓) ↑TBARS (Q↓) ↑α-SMA (Q↓) ↑TLR-4, HMGB1, IL-6, TNFα, COX-2 (Q↓) ↑COL1A1, COL3A1, PLOD3, TGFβ1, SMAD3, SMAD7, TIMP1, MMP9, CTGF, AREG, PDGFB (Q↓) ↑NF-κB p65, pJNK (Q↓)	[21]
Quercetin 800 mg/Kg food (last 8 weeks)	Wistar rats. High carbohydrate HFD-feeding (16 weeks)	↑Body weight (Q--) ↑Liver weight (Q↓) ↑BMI (Q--) ↑Fat pads (Q↓)	↑ALT, ALP, LDH (Q↓) ↑AST (Q--) ↑TG (Q↑) ↑FFA, cholesterol (Q--) ↑Glucose (Q↓) ↓Urea (Q↑) ↑Uric acid (Q↓) --Bilirubin (Q↓)	↑Fibrosis (Q↓) ↑Steatosis (Q↓) ↑Inflammation (Q↓) ↓Nrf2, HO-1 (Q↑) ↓CPT1 (Q↑) ↓Caspase-3 (Q↑) ↑NF-κB (Q↓)	[29]
Quercetin 250 mg/Kg food (9 weeks)	C57BL/6 J mice. HFD-feeding (9 weeks)	↑Body weight (Q↓) ↑Liver weight (Q↓)	↑TG, cholesterol (Q↓) ↑TBARS (Q↓)	↑Steatosis (Q↓) ↑TG (Q↓) ↓CYP2C50, PON1, FNTA, PPARα, PPARδ (Q↑) ↑ALDH1B1, ApoA4, ABCG5, GPAM, ACC, FDFT1, VCAM1, PPARγ, FAT/CD36, FAS, C/EBPα (Q↓)	[30]

Quercetin 75 and 300 mg/Kg b.w./day (last 8 weeks)	Sprague-Dawley rats. HFD-feeding (12 weeks)		Resistin (Q↓) IL-18 (Q↓) Glucose, insulin (Q↓) HOMA-IR (Q↓) TG (Q↓) MDA (Q↓)		[31]
Quercetin 25, 50 and 100 mg/Kg b.w./day (7 weeks)	Sprague-Dawley rats. Streptozotocin-induced diabetes	↓Body weight (Q↑) ↑Liver weight (Q↓)	↑AST, ALT, ALP (Q↓) ↑TG, FFA, cholesterol (Q↓) ↑Glucose (Q↓) ↑IL-18, IL-1β (Q↓)	↑NAS (Q↓) ↑TG, FFA, cholesterol (Q↓) ↑IL-18, IL-1β (Q↓) ↑ROS (Q↓) ↑XO, XDH, XO/XDH (Q↓) ↑TXNIP, NLRP3, ASC, caspase-1 (Q↓) ↑SREBP-1c, SREBP-2, FAS, LXRα (Q↓) ↓PPARα (Q↑)	[32]
Quercetin (2 weeks)	Swiss mice. HFD-feeding (2 weeks)			↑ROS (Q↓) ↓Antioxidant profile (Q↑) ↑Lipid peroxidation (Q↓) ↑Inflammation (Q↓) ↑NF-κB (Q↓)	[35]
Morin 30 and 60 mg/Kg b.w./day (last 4 weeks)	Sprague-Dawley rats. High fructose diet (10% in drinking water) (8 weeks)	--Body weight (M--)	↑TG, cholesterol (M↓) ↑VLDL (M↓) ↑Glucose, insulin (M↓) ↑Leptin (M↓) ↑ TNFα, IL-6, IL-1β (M↓)	↑Steatosis (M↓) ↑Inflammation (M↓) ↑TG, cholesterol (M↓) ↑VLDL (M↓) ↑SREBP-1c, SCD1 (M↓) ↓PPARα, CPT1 (M↑) ↑TNFα, IL-6, IL-1β (M↓) ↓IκBα (M↑) ↑pIκBα, pIKKβ, nuclear NF-κB (M↓)	[36]
Rutin 1.6 g/Kg food (last 8 weeks)	Wistar rats. High carbohydrate HFD-feeding (16 weeks)	↑Body weight (R↓) ↑Liver weight (R↓) ↑BMI (R↓) ↑Fat pads (R↓)	↑AST, ALT, ALP, LDH (R↓) ↑TG, FFA, cholesterol (R↓) ↑Glucose, insulin (R↓) ↑O⁻₂ (R↓) ↑MDA (R↓) ↓GPx (R↑) ↓Urea (R↑) ↑Uric acid, bilirubin (R↓) --Albumin (R--)	↑Fibrosis (R↓) ↑Steatosis (R↓) ↑Inflammation (R↓) ↓Caspase-3, HSP70, ERK1/2(R↑)	[37]

Troxerutin 150 mg/Kg b.w./day (20 weeks)	ICR mice. HFD-feeding (20 weeks)	↑Body weight (Tx↓) ↑Liver index (Tx↓) ↑Fat pads (Tx↓)	↑TG, FFA, cholesterol (Tx↓) ↑Glucose, insulin (Tx↓) ↑ALT (Tx↓)	↑NAS (Tx↓) ↑TG, FFA, cholesterol (Tx↓) ↑ROS (Tx↓) ↑4-HNE (Tx↓) ↓GSH, GPx, SOD1 (Tx↑) ↓NAD$^+$, NAMPT, SIRT1, pAMPK, p-raptor, nuclear lipin1 (Tx↑) ↑PARP1, p-mTOR, cytoplasmic lipin1 (Tx↓) ↓PPARα, PGC1α, CPT1A, pACC, ApoB100 (Tx↑) ↑SREBP-1c, FAS (Tx↓)	[38].
Myricetin 0.6 and 1 g/Kg food (12 weeks)	C57BL/6J mice. High sucrose HFD-feeding (12 weeks)	↑Body weight (My↓) ↑Fat pads (My↓)	↑TG, cholesterol (My↓) --HDL (My--) ↑Glucose, insulin (My↓) ↑HOMA-IR (My↓) ↑Leptin (My↓) --Adiponectin, MCP-1 (My--) ↑ TNFα, IL-6 (My↓)		[45]
Myricetin 75, 150 and 300 mg/Kg b.w./day (last 8 weeks)	Wistar rats. HFD-feeding (10 weeks)	↑Body weight (My↓) ↑Fat pads (My↓)	↑TG, FFA, cholesterol (My↓) ↑LDL (My↓) ↓HDL (My↑)	↑Steatosis (My↓) ↑TG, cholesterol (My↓) ↓PPARα, ACO, CYP4A (My↑) ↑SREBP-1, SREBP-2 (My↓)	[46]

4-HNE, 4-hydroxy-2'-nonenal; **ABC**, ATP-binding; **ACC**, acetyl-CoA carboxylase; **ACO**, acyl-CoA oxidase; **ALDH**, aldehyde dehydrogenase; **ALP**, alkaline phosphatase; **ALT**, alanine aminotransferase; **AMPK**, AMP-activated protein kinase; **Apo**, apolipoprotein; **AREG**, amphiregulin; **ASC**, apoptosis-associated speck-like protein containing a caspase recruitment domain; **AST**, aspartate aminotransferase; **BMI**, body mass index; **C/EBPα**, CCAAT/enhancer binding protein alpha; **COL**, collagen; **COX-2**, cyclooxygenase-2; **CPT1**, carnitine palmitoyltransferase 1; **CTGF**, connective tissue growth factor; **CYP**, cytochrome P450; **ERK**, extracellular signal-regulated kinase; **FAS**, fatty acid synthase; **FAT/CD36**, fatty acid translocase CD36; **FDFT1**, farnesyl-diphosphate farnesyltransferase 1; **FFA**, free fatty acid; **FNTA**, farnesyltransferase/geranylgeranyltransferase type-1 subunit alpha; **GPAM**, glycerol-3-phosphate acyltransferase 1 mitochondrial; **GPx**, glutathione peroxidase; **GSH**, glutathione; **HDL**, high density lipoprotein; **HFD**, high fat diet; **HMGB1**, high-mobility group box 1 protein; **HO-1**, heme oxygenase-1; **HOMA-IR**, homeostasis model assessment for insulin resistance; **HSP**, heat shock protein; **IKKβ**, inhibitor κB kinase β; **IL**, interleukin; **iNOS**, inducible nitric oxide synthase; **IκBα**, inhibitor of NF-κB alpha; **JNK**, c-Jun terminal kinase; **LDH**, lactate dehydrogenase; **LDL**, low density lipoprotein; **LXRα**, liver X receptor alpha; **M**, morin; **MCD**, methionine and choline deficient; **MDA**, malondialdehyde; **MMP**, matrix metalloproteinase; **mTOR**, mammalian target of rapamycin; **My**, myricetin; **NAMPT**, nicotinamide phosphoribosyltransferase; **NAS**, NAFLD activity score; **NF-κB**, nuclear factor kappa B; **NLRP3**, NOD-like receptor family, pyrin domain-containing 3; **Nrf2**, nuclear factor (erythroid-derived 2)-related factor-2; **PARP**, poly (ADP-ribose) polymerase; **PDGFB**, platelet-derived growth factor subunit B; **PGC1α**, PPARγ coactivador-1 alpha; **PLOD3**, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3; **PON1**, paraoxonase 1; **PPARα**, peroxisome proliferator-activated receptor alpha; **PPARδ**, peroxisome proliferator-activated receptor delta; **PPARγ**, peroxisome proliferator-activated receptor gamma; **Q**, quercetin; **R**, rutin; **Raptor**, regulatory associated protein of mTOR; **ROS**, reactive oxygen species; **SCD1**, stearoyl-CoA desaturase-1; **SIRT1**, silent mating type information regulation 2 homolog1; **SOD**, superoxide dismutase; **SREBP**, sterol regulatory element-binding protein; **TBARS**, thiobarbituric acid-reactive substance; **TG**, triglyceride; **TGF**, transforming growth factor; **TIMP**, tissue inhibitor of metalloproteinases; **TLR**, toll-like receptor; **TNFα**, tumor necrosis factor alpha; **Tx**, troxerutin; **TXNIP**, thioredoxin-interacting protein; **VCAM1**, vascular cell adhesion protein 1; **VLDL**, very low density lipoprotein; **XDH**, xanthine dehydrogenase; **XO**, xanthine oxidase; **α-SMA**, alpha-smooth muscle actin; **γGT**, gamma glutamyl transferase; ↑, increase; ↓, decrease; **--**, no effect.

Table **2**. Effects of flavones, flavanones, flavanols, isoflavones and anthocyanidins on *in vivo* models of NAFLD.

Group	Flavonoid treatment	Model	Physiological variables	Blood parameters	Histopathology and gene expression	Ref.
Flavones	Chrysin 25 and 30 mg/Kg b.w./day (last 2 weeks)	C57BL/6J mice. HFD-feeding (17 weeks)	↑Body weight (C--)	↑AST, ALT (C↓) ↑IL-1β, TNFα (C↓) ↓IL-10 (C↑) ↓Adiponectin (C↑)	↑Steatosis (C↓) ↑Inflammation (C↓) ↑PPARγ (C↑)	[52]
Flavanones	Naringenin 10 and 30 g/Kg food (4 weeks)	Ldlr $^{-/-}$ mice. HFD-feeding (4 weeks)	↑Body weight (N↓) --Liver weight (N--) ↑Fat pads (N↓)	↑TG, cholesterol (N↓) --FFA (N--) ↑LDL, VLDL (N↓) --HDL (N--) ↑Glucose, insulin (N↓) ↑HOMA-IR (N↓) ↑Leptin (N↓)	↑Steatosis (N↓) ↑Cholesterol, TG (N↓) ↑SREBP-1c (N↓) ↓PGC1α (N↑) --PPARα (N--) --ACO (N↑)	[64]
	Naringenin 10 and 30 g/Kg food (30 weeks)	C57BL/6J mice. HFD-feeding (30 weeks)	↑Body weight (N↓) ↑Liver weight (N↓) ↑Fat pads (N↓)	↑TG, cholesterol (N↓) ↑LDL, VLDL (N↓) --HDL (N--) ↑Glucose, insulin (N↓)	↑TG, cholesterol (N↓)	[64]
Flavanols	EGCG 0.1 % in drinking water (8 weeks)	SHRSP-ZF rats. HFD-feeding (8 weeks) and CCl$_4$ (twice a week, 8 weeks)	↑Body weight (EGCG↑) ↑Liver weight (EGCG↑)	↑AST, ALT (EGCG--) ↑TG, cholesterol (EGCG--) ↑FFA (EGCG↓) ↑Glucose, insulin (EGCG--) ↑Leptin (EGCG--) ↓Adiponectin (EGCG--) ↑TNFα, IL-6 (EGCG--) ↑Hydroxyproline (EGCG↓)	↑NAS (EGCG↓) ↑Fibrosis (EGCG↓) ↑Hydroxyproline (EGCG↓) ↑MDA, 4-HNE (EGCG↓) ↑8-OHdG (DNA damage) (EGCG↓) ↑α-SMA (EGCG↓) ↑MMP2, MMP9, TIMP1, TIMP2, procollagen-1, TGFβ1, PAI-1 (EGCG↓) ↑CYP2E1, pJNK (EGCG↓) ↑ TNFα, IL-6, IL-1β, MCP-1 (EGCG↓) ↓CAT, GPx (EGCG↑)	[72]
	EGCG 50 mg/Kg b.w./day (3 times per week, 8 weeks)	Sprague-Dawley rats. HFD-feeding (8 weeks)	--Body weight (EGCG↓)	↑ALT/AST (EGCG↓)	↑NAS (EGCG↓) ↑Fibrosis (EGCG↓) ↑TGFβ1, α-SMA, SMAD2, SMAD4 MMP2, TIMP2 (EGCG↓) ↑pFOXO1,pPI3K, pAKT, NF-κB (EGCG↓) ↑iNOS, COX-2, TNFα (EGCG↓) ↑3-NT (EGCG↓) ↓CAT, GPx (EGCG↑) --SOD (EGCG--)	[73]

Isoflavones	Daidzein 0.1-2 g/Kg food (12 weeks)	C57BL/6J mice. HFD-feeding (12 weeks)		Glucose, insulin (D↓) HOMA-IR (D↓)	↑Steatosis (D↓) LXRβ, ChREBP (D↓) TNFα (D↓) Leptin, adiponectin (D↑) Ghrelin (D↓)	[77]
	Puerarin	Sprague-Dawley rats. HFD-feeding (4 weeks)		↑Leptin (P↓)	↑Steatosis (P↓) ↑Inflammation (P↓) ↑TG, cholesterol (P↓) ↓Leptin receptor (P↑) ↓pJAK2, pSTAT (P↑)	[78, 79]
	Puerarin 900 mg/Kg b.w./day (2 weeks)	C57BL/6J mice. MCD-feeding (2 weeks)		--TG, cholesterol (P↓) ↓HDL (P--) ↑LDL (P↓) ↑TNFα (P↓) ↑IL-6 (P--)	↑NAS (P↓) ↓PPARγ (P↑) ↑NF-κB (P--)	[80]
	Genistein 1 mg/Kg b.w./day (60 days)	Wistar rats. High fructose diet-feeding (60 days)	↑Body weight (G↓) ↑Liver weight (G↓)	↑AST, ALT, γGT, LDH (G↓) ↑TG, FFA, cholesterol (G↓) ↑Phospholipids (G↓) ↑LDL, VLDL (G↓) ↓HDL (G↑) ↑Glucose, insulin (G↓) ↑HOMA-IR (G↓) ↑TNFα, IL-6 (G↓) ↑TBARS (G↓) ↓Vit C, Vit E, GSH (G↑) ↓Nitrite (G↑) ↑Nitrosothiol (G↓)	↑NAS (G↓) ↑LDH (G↓) ↑TG, FFA, cholesterol (G↓) ↓Phospholipids (G↑) ↑TBARS(G↓) ↑3-NT (G↓) ↓Nitrite (G↑) ↑Nitrosothiol (G↓) ↓GPx, GR, Vit C, Vit E, GSH (G↑)	[81]
	Genistein 1, 2 and 4 g/Kg food (12 weeks)	C57BL/6J mice. HFD-feeding (12 weeks)	↑Body weight (G↓) ↑Fat pads (G↓)	↑ALT (G↓) --AST (G--) ↓TG (G↓) ↑FFA, cholesterol (G↓) ↑LDL (G↓) ↓HDL (G↑)	↑NAS (G↓) ↑TG, cholesterol (G↓)	[82]

Anthocyanidins	Cy-3-g 1 g/Kg food (12 weeks)	KKAy mice	Body weight (Cy-3-g↓) Liver weight (Cy-3-g↓) Fat pads (Cy-3-g↓)	Cholesterol (Cy-3-g--) LDL, HDL (Cy-3-g--) TG (Cy-3-g↓) LPL (Cy-3-g↑)	Steatosis (Cy-3-g↓) TG (Cy-3-g↓)	[84]
	Cy-3-g 100 mg/Kg food (12 weeks)	KKAy mice		TG (Cy-3-g↓) Glucose (Cy-3-g --)	↑Steatosis (Cy-3-g↓) ↑TG (Cy-3-g↓) --pPKCζ/PKCζ (Cy-3-g↑) ↑mtGPAT1 (Cy-3-g↓)	[85]

3-NT, 3-nitrotyrosine; **4-HNE**, 4-hydroxy-2'-nonenal; **8-OHdG**, 8-hydroxy-2'-deoxyguanosine; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **C**, chrysin; **CAT**, catalase; **ChREBP**, carbohydrate responsive element binding protein; **COX-2**, cyclooxygenase-2; **Cy-3-g**, cyanidin-3-O-β-glucoside; **CYP**, cytochrome P450; **D**, daidzein; **EGCG**, (-)-epigallocatechin-3-gallate; **FFA**, free fatty acid; **FOXO1**, forkhead box protein O1; **G**, genistein; **GPx**, glutathione peroxidase; **GR**, glutathione reductase; **GSH**, glutathione; **HDL**, high density lipoprotein; **HFD**, high fat diet; **HOMA-IR**, homeostasis model assessment for insulin resistance; **IL**, interleukin; **iNOS**, inducible nitric oxide synthase; **JAK2**, janus kinase 2; **JNK**, c-Jun terminal kinase; **LDH**, lactate dehydrogenase; **LDL**, low density lipoprotein; **LPL**, lipoprotein lipase; **LXRβ**, liver X receptor beta; **MCP-1**, monocyte chemoattractant protein-1; **MDA**, malondialdehyde; **MMP**, matrix metalloproteinase; **mtGPAT1**, glycerol-3-phosphate acyltransferase 1 mitochondrial; **N**, naringenin; **NAS**, NAFLD activity score; **NF-κB**, nuclear factor kappa B; **P**, puerarin; **PAI-1**, plasminogen activator inhibitor-1; **PI3K**, phosphatidylinositol 3-kinase; **PKCζ**, protein kinase C zeta; **PPARγ**, peroxisome proliferator-activated receptor gamma; **SOD**, superoxide dismutase; **STAT**, signal transducer and activator of transcription; **TBARS**, thiobarbituric acid-reactive substance; **TG**, triglyceride; **TGF**, transforming growth factor; **TIMP**, tissue inhibitor of metalloproteinases; **TNFα**, tumor necrosis factor alpha; **VLDL**, very low density lipoprotein; **α-SMA**, alpha-smooth muscle actin; **γGT**, gamma glutamyl transferase; ↑, increase; ↓, decrease; --, no effect.

Table **3**. Effects of flavonoids on *in vitro* models of NAFLD.

Group	Flavonoid treatment	Model	Effects		Ref.
Flavonols	Quercetin 0.1-100 μM (48h)	HepG2. FFA 1 mM, insulin 50 nM (48h)	Q ↓ cell proliferation at 50 and 100 μM ↑Lipid accumulation (Q↓) ↑TG (Q↓) --IRβ, IRS1 (Q--)	↓pIRβ, pIRS1 (Q↑) ↑SREBP-1c, FAS (Q↓) --PPARα, CPT1, MTP, FABP1 (Q--)	[27]
	Quercetin 10 μM (24h)	HepG2. Oleic acid 2 mM (24h)	↓ cell proliferation (Q↑) ↑ALT (Q↓) ↑TG (Q↓) ↓Glucose uptake, urea, albumin (Q↑) ↑MDA (Q↓)	↑DNA fragmentation (Q↓) ↑TNFα, IL-18 (Q↓) ↓GSH (Q↑) ↑GSSG (Q↓) ↓CAT, GPx, SOD (Q↑)	[28]
	Quercetin 1-50 μM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (Q↓) ↑TG (Q↓)		[33]
	Rutin 25-200 μM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (R↓) ↑TG (R↓)		[33]
	Kaempferol 50-150 μM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (Kaempferol↓) ↑TG (Kaempferol↓)		[33]
	Isorhamnetin 10-150 μM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (Isorhamnetin↓) ↑TG (Isorhamnetin↓)		[33]
	Myricetin 10-150 μM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (My↓) ↑TG (My↓)		[33]
	Galangin 1-40 μM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (Galangin↓) ↑TG (Galangin --)		[33]
Flavones	Chrysin 1-15 μM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (C↑) ↑TG (C --)		[33]
	Apigenin 10-125 μM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (Apigenin↑) ↑TG (Apigenin --)		[33]
	Luteolin 10 and 20 μM (24h)	HepG2. Palmitate 0.4 mM (24h)	↑ROS (Luteolin↓) ↑Lipid accumulation (Luteolin↓) ↑TG (Luteolin↓) --pAMPKα, pACC (Luteolin↑) ↑SREBP-1c, FAS (Luteolin↓) ↑CPT1 (Luteolin↑)		[63]

	Luteolin 1-15 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (Luteolin↓) ↑TG (Luteolin↓)	[33]
Flavanones	Naringenin 10-150 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (N↑) ↑TG (N--)	[33]
	Hesperetin 5-75 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (Hesperetin↓) ↑TG (Hesperetin --)	[33]
	Taxifolin 10-150 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (Taxifolin ↓) ↑TG (Taxifolin↓)	[33]
Flavanols	EGCG 10-150 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (EGCG ↓) ↑TG (EGCG ↓)	[33]
	(+)-Catechin 25-200 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS ((+)-Catechin ↓) ↑TG ((+)-Catechin ↓)	[33]
	(-)-Epicatechin 50-200 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS ((-)-Epicatechin ↓) ↑TG ((-)-Epicatechin ↓)	[33]
	Procyanidin B1 10, 20 and 30 µM (48h)	HepG2. Palmitic acid 0.5 mM (48h)	↑TG (Procyanidin B1↓) --PPARα (Procyanidin B1 --) --CPT1, ACO (Procyanidin B1↑)	[74]
soflavones	Daidzein 10-150 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (D↓) ↑TG (D↓)	[33]
	Genistein 1-15 µM (24h)	HepG2. Oleic acid 1 mM (24h)	↑ROS (G↓) ↑TG (G--)	[33]
Anthocyanidins	Cy-3-g 50 µM (2h before glucose treatment)	Hepatocytes from C57BL/6J mice fed a HFD. Glucose 35 mM (12h)	↓Cell viability (Cy-3-g↑) ↑LDH (Cy-3-g↓) ↑ROS, carbonyl groups (Cy-3-g↓) ↑Apoptosis (Cy-3-g↓) ↑Procaspase-3, procaspase-8, procaspase-9, PARP cleavage (Cy-3-g↓) ↑Caspase-3, caspase-9 activities (Cy-3-g↓) --Caspase-8 activity (Cy-3-g--) ↓pAKT (Cy-3-g↑) ↑pJNK (Cy-3-g↓)	[86]

ACC, acetyl-CoA carboxylase; **ACO**, acyl-CoA oxidase; **ALT**, alanine aminotransferase; **AMPK**, AMP-activated protein kinase; **C**, chrysin; **CAT**, catalase; **CPT1**, carnitine palmitoyltransferase 1; **Cy-3-g**, cyanidin-3-O-β-glucoside; **D**, daidzein; **EGCG**, (-)-epigallocatechin-3-gallate; **FABP**, fatty acid binding protein; **FAS**, fatty acid synthase; **FFA**, free fatty acid; **G**, genistein; **GPx**, glutathione peroxidase; **GSH**, glutathione; **GSSG**, oxidized glutathione; **HFD**, high fat diet; **IL**, interleukin; **IRS1**, insulin receptor substrate 1; **IRβ**, insulin receptor beta; **JNK**, c-Jun terminal kinase; **LDH**, lactate dehydrogenase; **MDA**, malondialdehyde; **MTP**, microsomal triglyceride transfer protein; **My**, myricetin; **N**, naringenin; **PARP**, poly (ADP-ribose) polymerase; **PPARα**, peroxisome proliferator-activated receptor alpha; **Q**, quercetin; **R**, rutin; **ROS**, reactive oxygen species; **SOD**, superoxide dismutase; **SREBP**, sterol regulatory element-binding protein; **TG**, triglyceride; **TNFα**, tumor necrosis factor alpha; ↑, increase; ↓, decrease; **--**, no effect.

3. OTHER NATURAL COMPOUNDS

Silybum marianum, known as milk thistle, is a member of Asteraceae family that contains a mixture of flavonolignans named silymarin and two flavonoids (quercetin and taxifolin). Silymarin is a lipophilic extract composed of silybin A, silybin B, isosilybin A, isosilybin B, silychristin, silydianin and isosilychristin. Silibinin, a mixture of silybin A and silybin B, is the major constituent of silymarin. This mixture of flavonolignans displays a lipid-lowering effect in both *in vitro* and *in vivo* models of induced lipid accumulation [28, 89, 90]. It has been proven that silibinin administration counteracts the progression of liver injury in several nutritional models of NASH, by improving antioxidant status, insulin resistance, steatosis, ballooning and inflammation. This effect appears to be a consequence of the capacity of silibinin to reduce increased NF-κB activity and subsequent iNOS overexpression as well as ROS and reactive nitrogen species (RNS) levels. Moreover, the increased phosphorylation of JNK, which is associated with insulin resistance and inflammation, is attenuated by silibinin. Likewise, silibinin diminishes DNA damage and lipoperoxidation and increases SCD1 and FABP1 expressions, that are downregulated in NASH models [91-93]. SCD1 and FABP1 downregulation is associated with cell sensitization to saturated fatty acid-induced death [94] and lipotoxicity [95], respectively. Silymarin also displays antifibrogenic effects through the downregulation of TGFβ [96], one of the critical cytokines involved in fibrogenesis, and the suppression of hepatic stellate cells activation and α$_1$-procollagen production, although it can not completely block the histological appearance of liver fibrosis. Moreover, the increase in nuclear translocation of Nrf2, that may upregulate many antioxidant genes, might contribute to the antioxidant capacity of silymarin besides the reduction of TNFα expression, probably by reversing ERK activation [97]. On the contrary, non-effect of silymarin has been shown on phosphorylation levels of ERK, showing in addition an anti-apoptotic activity by lowering activation of procaspase-3 to active caspase-3 [96]. Silymarin has also been reported to display positive effects in patients with NAFLD [98, 99], in which the efficacy of this extract may be more readily observed compared with patients with hepatitis C, because of their higher plasma flavonolignan concentrations and more extensive enterohepatic cycling [100]. Combination of silibinin with phospholipids appears to increase its bioavailability [101]. Several clinical studies evidence the efficacy of silibinin combined with phospholipids and vitamin E in patients with NAFLD, who exhibit improvements in aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (γGT) levels, insulin resistance and liver histology in addition to the normalization of the cholestasis and cholesterol levels [102-105].

Curcumin is a polyphenol derived from *Curcuma longa* (turmeric), a food spice and colouring agent widely utilized in Indian and other South Asia countries. Its use in *in vivo* models of NASH reveals an improvement of steatosis, inflammation, ballooning and fibrosis, and a reduction of blood serum monocyte chemoattractant protein (MCP)-1, TNFα and IL-6 levels. Lipoperoxidation is attenuated, the antioxidant status is enhanced, and the expressions of NF-κB, suppressor of cytokine signaling 3 (SOCS3), SREBP-1c, FAS, ACC and 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase are decreased in the liver after curcumin treatment [80, 106, 107]. The beneficial effects of curcumin on steatosis and inflammation could be mediated by the STAT3 signaling activation and the improvement of

mitochondrial function [107]. *In vitro* studies show that curcumin is able to reduce induced lipid accumulation by downregulating lipogenic proteins and upregulating the expression of fatty acid β-oxidation-related genes as PPARα, via AMPK phosphorylation [108]. Moreover, this polyphenol seems to protect hepatocytes from lipoapoptosis [109] and iron-induced insulin resistance and oxidative stress in cells treated with stearic acid, probably reducing phosphorylated JNK levels [110].

Resveratrol (trans-3,4',5-trihydroxystilbene) is a polyphenol abundantly present in red wine and, to a lesser extent, in other foods such as grapes or nuts. This compound reduces body weight in obese mice, enhances antioxidant enzymes levels and diminishes lipoperoxidation, improving also serum lipid profile and hepatic steatosis through the increase of SIRT1 expression and phosphorylation levels of AMPK, and FOXO1, and promoting FOXO1 translocation from the nucleus to the cytoplasm [111]. Hepatoprotective actions of resveratrol and the mechanisms responsible of these beneficial effects, observed in *in vitro* and *in vivo* studies, have been recently reviewed [112]. A polyphenol extract also obtained from red wine is Provinol™, that contains proanthocyanidols, prodelphinidol, anthocyanins, catechin, resveratrol and others. This extract could help to prevent steatosis through SIRT1upregulation and subsequent AMPK and PPARγ coactivador (PGC) 1α increased expressions, leading to an enhanced fatty acid β-oxidation [113]. On the other hand, wine stored in oak barrels improves its organoleptic properties, including better taste. Indeed, many bioactives polyphenols contained in red wine derive from oak during the maturation. Oak bark extract treatment in a NAFLD model in rats displays multiple benefits, such as the reduction of body weight and abdominal fat pads, the improvement of insulin resistance, serum lipid profile and liver histology, as well as the recovery of cardiovascular structure and function [114].

Theaflavin is the major polyphenol derived from black tea, the most widely consumed tea in the world. Its use in a mouse model of fatty liver resulted in a decrease of hepatic steatosis, oxidative stress, inflammation and apoptosis, contributing to its protective effect against ischemia-reperfusion injury [115]. Green tea contents a high amount of catechins as EGCG, whose beneficial properties on NAFLD have been summarized herein. Several studies in murine models show the protective effect of green tea against induced non-alcoholic steatohepatitis [116, 117]. Likewise it has been reported an improved liver function and fatty liver status in patients with NAFLD after consuming green tea with high-density catechins for 12 weeks [118]. Previously, it had been published a further review about therapeutic potential of green tea and their catechins in this disease, based on studies carried out in *in vitro* and animal models. The mechanisms of action of green tea against NAFLD could implicate the prevention of steatosis through the reduction of intestinal lipid and carbohydrate absorption and the decrease of adipose lipolysis, in addition to the reduction of *de novo* lipogenesis and the enhancement of fatty acid oxidation and thermogenesis, as well as the improvement of insulin sensitivity. Moreover, antioxidant and anti-inflammatory activities could contribute to prevent the progression from simple steatosis to steatohepatitis [119].

The effects of various black soybean powder concentrations have been investigated in a model of NAFLD consisting of high cholesterol and HFD-fed mice. Black soybean, that presents a high content of isoflavones, was able to reduce body, liver and abdominal and epididymal adipose tissue weights gain in

a dose-dependent manner. Black soybean supplementation also reduced the levels of total cholesterol and triglyceride in the liver, with the subsequent decrease in the lipid droplets size. This cholesterol- and triglyceride-lowering effect was due, at least in part, to the reduction of the expression of SREBP-2, HMG-CoA reductase, PPARα and PPARγ as well as the increase of ABCA1 expression. The reduction in free fatty acids, glucose and insulin blood levels observed after black soybean treatment was the result of the increase of serum adiponectine levels, stimulating AMPK activation and improving insulin resistance. The improvement in cholesterol accumulation and insulin resistance, besides the antioxidant and antilipoperoxidative activities of black soybean, confer a protective capacity against NAFLD [120]. On the contrary, other studies have reported an induction of PPARα, in addition to ACO expressions by soybean, thereby diminishing lipid accumulation through the enhancement of fatty acid β-oxidation [121, 122].

There are many other species of plants proven to present preventive effects on NAFLD. Thus, *Taraxacum officinale* (dandelion) shows properties similar to black soybean, as it has been observed in murine models of NAFLD a significant reduction of hepatic lipid accumulation, body and liver weights and serum cholesterol, triglyceride, insulin and glucose levels, with an improved insulin resistance by AMPK pathway activation, after dandelion leaf extract treatment [123, 124]. *Myrcia bella* is a species belonging to the Myrtaceae family whose principle constituents are phenolic acids and flavonoids, such as quercetin and myricetin. The extract of leaves of this species presents hypoglycemic activity, probably due to the activation of the insulin signaling pathway involving PI3K/AKT proteins that leads in turn to the store and prevention of the degradation of glucose in the liver. Moreover, the extract can act as a hypolipidemic agent by reducing the levels of serum lipids [125]. In the same way, the effect of flavonoids obtained from *Rosa laevigata* Michx fruit, mainly rutin, quercetin, kaempferol, luteolin, apigenin and liquiritigenin, have been studied in a model of HFD-induced NAFLD in rats. It was observed a lower weight gain and a hepatoprotective effect showing a dose-dependent reduction of serum AST and ALT as well as blood lipid and glucose levels after flavonoids treatment. It was also shown a significant decrease in lipid peroxidation and CYP2E1 expression due to the antioxidant capacity of flavonoids. Expression of SREBP-1c, FASN, SCD1, PPARγ, long-chain fatty acyl-CoA ligase (ACSL) 5 and ACC was reduced and levels of pAMPKα, ACO1 and PPARα were increased in flavonoids-treated rats, reverting the effect of HFD. This led to a fatty acid synthesis downregulation and a fatty acid β-oxidation promotion with a subsequent lipid content reduction in hepatocytes [90]. *Phyllanthus urinaria*, a traditional medicinal plant, with a high amount of tannins and flavonoids, has also been documented to ameliorate the severity of steatohepatitis in *in vitro* and *in vivo* nutritional models. This effect seems to be attributed to the suppression of CYP2E1-mediated oxidative stress and JNK and NF-κB pathways-mediated inflammatory response, in addition to the induction of fatty acid oxidation through CYP4A10 upregulation and the suppression of lipogenic transcription factor C/EBPβ [126]. Likewise, *Ilex hainanensis* Merr., whose major bioactive components are chlorogenic acid, kaempferol-7-O-β-D-glucoside and ilexgenin A [127], displays preventive effects on hepatic induced steatosis by alleviating insulin resistance and regulating lipid metabolism, inflammation and oxidative stress, through the regulation of PPARα and CYP2E1 expressions [128, 129]. The lipid-lowering effect of *Ginkgo biloba*, whose principle active ingredients are quercetin, kaempferol and isorhamnetin, seems to be attributed to

the content of these flavonoids, through the CPT1A-mediated fatty acid oxidation enhancement [130, 131]. Furthermore, there are several traditional Chinese medicine formulas, as Salvia-*Nelumbinis naturalis* or Hugan Qingzhi tablet, with a lipid-lowering effect on induced steatosis, via enhancing hepatic insulin sensitivity and fatty acid oxidation or reducing lipogenesis [132, 133].

Flavangenol®, one of several pine bark extract products, is also reported to exert a lipid-lowering action in the liver of mice with insulin resistance, abnormalities of carbohydrate and lipid metabolism, hypertension and a marked fatty liver, by increasing the expression of fatty acid oxidation-related genes. The effect of Flavangenol® could be attributed in part to procyanidin B1, its major bioactive component [74]. Other authors explain the beneficial effects of total flavonoids from citrus on NASH in mice fed with a HFD by the modulation of the SIRT1/PGC-1α signal pathway, which might in turn be related to the improvement of oxidative stress and lipid peroxidation [134]. Polyphenols from pomegranate flowers seem to improve also insulin resistance and steatosis in rats with diabetes and non-alcoholic fat liver disease, probably by enhancing PON1 expression in the liver [135]. In the same way, polyphenolic extracts obtained from blueberries [136, 137], mulberries [137] and bayberries [138] show preventive effects on NAFLD, inhibiting body weight gain, decreasing serum cholesterol, reducing insulin resistance and attenuating lipid accumulation, as well as improving plasma antioxidant status and inhibiting the inflammatory and apoptotic responses. Likewise, polyphenolic extract from lotus root, the edible rhizome of *Nelumbo nucifera*, rich in proanthocyanidins, alleviates hepatic steatosis by suppressing lipogenic enzymes activities [139].

4. CONCLUSION

Polyphenols, as flavonoids and many other related natural compounds, display beneficial effects on NAFLD, preventing multiple disorders associated with the disease. These molecules possess the ability to modulate the expression of several genes whose deregulation contributes to lipid accumulation, fibrosis, inflammation, oxidative stress or insulin resistance. Their lipid-lowering effects seem to be associated with their capacity to regulate the expression of genes mainly involved in *de novo* lipogenesis and fatty acid β-oxidation, although the antioxidant and anti-inflammatory properties of these compounds might also contribute to this capacity (Fig. **3**). Overall, in view of results obtained in *in vitro* and *in vivo* models, as well as in patients with NAFLD, it may be concluded that the use of flavonoids and other natural substances should be considered as therapy for preventing NAFLD progression.
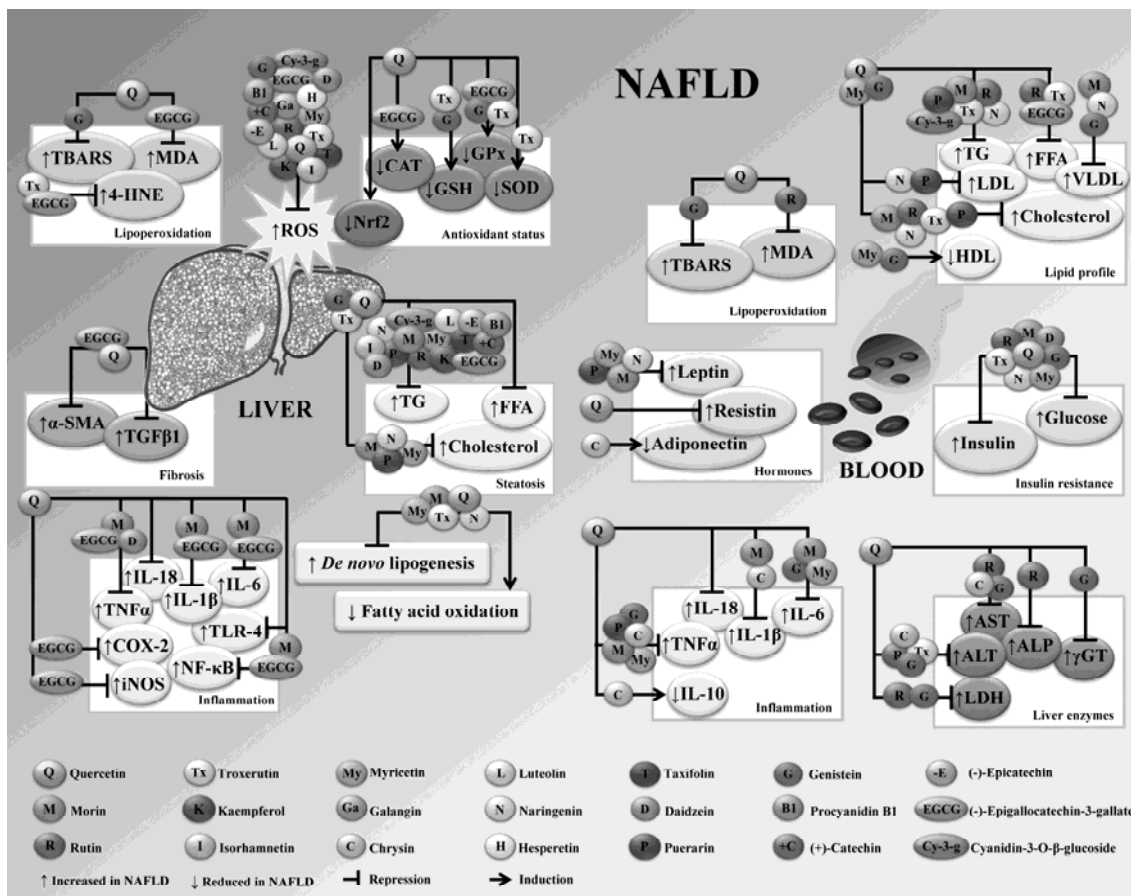
Fig (3). Overview of the mechanisms of action reported for different flavonoids. Most studied flavonoids are able to counteract blood parameter alterations and liver disorders associated with NAFLD progression. Lipid peroxidation is reduced, and antioxidant status enhanced, leading to a reduction of reactive oxygen species (ROS). Fibrosis and inflammation are ameliorated and steatosis is diminished, fundamentally through a reduction of triglyceride (TG) levels, probably mediated by modulation of *de novo* lipogenesis- and fatty acid oxidation-related gene expression, altered in NAFLD. Moreover, there is an improvement of insulin resistance, serum lipid profile and liver function, as shown by the normalization in the levels of liver enzymes.

CONFLICT OF INTEREST STATEMENT

All authors state no financial and personal relationships with other people or organizations that could inappropriately influence this work.

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ABBREVIATIONS

ABC	=	ATP-binding cassette
ACC	=	acetyl-CoA carboxylase
ACE	=	angiotensin-converting enzyme
ACO	=	acyl-CoA oxidase
ACSL5	=	long-chain fatty acyl-CoA ligase 5
ALDH	=	aldehyde dehydrogenase
ALT	=	alanine aminotransferase
AMPK	=	AMP-activated protein kinase
Apo	=	apolipoprotein
AST	=	aspartate aminotransferase;
AT-1R	=	AT-II type 1 receptor
AT-II	=	angiotensin-II
C/EBP	=	CCAAT/enhancer binding protein
CaMKK2	=	Ca2+/calmodulin-dependent protein kinase kinase-2
ChREBP	=	carbohydrate responsive element binding protein
CPT	=	carnitine palmitoyltransferase
CYP	=	cytochrome P450
DGAT	=	diacylglycerol acyltransferase
EGCG	=	(-)-epigallocatechin-3-gallate
ERK	=	extracellular signal-regulated kinase
FABP	=	fatty acid binding protein
FAS	=	fatty acid synthase
FAT/CD36	=	fatty acid translocase (FAT) CD36
FATP	=	fatty acid transport protein
FDFT1	=	farnesyl-diphosphate farnesyltransferase 1
FNTA	=	farnesyltransferase/geranylgeranyltransferase type-1 subunit
FOXO1	=	forkhead box protein O1
GPAM	=	glycerol-3-phosphate acyltransferase 1 mitochondrial
GPAT1	=	glycerol-3-phosphate acyltransferase 1
HFD	=	high fat diet
HMG-CoA	=	3-hydroxy-3-methylglutaryl-coenzyme A
HO-1	=	heme oxygenase-1
HSP	=	heat shock protein
IL	=	interleukin
iNOS	=	inducible nitric oxide synthase
IR	=	insulin receptor
IRS1	=	insulin receptor substrate 1
JAK2	=	janus kinase 2
JNK	=	c-Jun terminal kinase

LPL	=	lipoprotein lipase
MCAD	=	medium-chain acyl-CoA dehydrogenase
MCP-1	=	monocyte chemoattractant protein-1
mTOR	=	mammalian target of rapamycin
MTP	=	microsomal triglyceride transfer protein
NAFLD	=	non-alcoholic fatty liver disease
NAMPT	=	nicotinamide phosphoribosyltransferase
NASH	=	non-alcoholic steatohepatitis
NF-κB	=	nuclear factor kappa B
NLRP3	=	NOD-like receptor family pyrin domain-containing 3
Nrf2	=	nuclear factor (erythroid-derived 2)-related factor-2
PARP1	=	poly (ADP-ribose) polymerase-1
PGC1α	=	PPARγ coactivador-1 alpha
PI3K	=	phosphatidylinositol 3-kinase
PON1	=	paraoxonase 1
PPAR	=	peroxisome proliferator activated receptor
RNS	=	reactive nitrogen species
ROS	=	reactive oxygen species
RXRα	=	retinoid X receptor alpha
S1P	=	sphingosine 1-phosphate
SCD1	=	stearoyl-CoA desaturase-1
SIRT1	=	silent mating type information regulation 2 homolog1
SOCS3	=	suppressor of cytokine signaling 3
SphK1	=	sphingosine kinase 1
SREBP	=	sterol regulatory element binding protein
STAT	=	signal transducer and activator of transcription 3
TGF	=	transforming growth factor
TLR	=	toll-like receptor
TNFα	=	tumor necrosis factor alpha
TXNIP	=	thioredoxin-interacting protein
VLCAD	=	very long-chain acyl-CoA dehydrogenase
VLDL	=	very low density lipoprotein
γGT	=	gamma glutamyl transferase

REFERENCES

[1] Vernon, G.; Baranova, A.; Younossi, Z. M. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment. Pharmacol. Ther.* **2011**, *34*, 274-285.

[2] Machado, M.; Cortez-Pinto, H. Non-alcoholic steatohepatitis and metabolic syndrome. *Curr. Opin. Clin. Nutr. Metab. Care* **2006**, *9*, 637-642.

[3] Tiniakos, D. G.; Vos, M. B.; Brunt, E. M. Nonalcoholic fatty liver disease: pathology and pathogenesis. *Annu. Rev. Pathol.* **2010**, *5*, 145-171.

[4] Tilg, H.; Moschen, A. R. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology* **2010**, *52*, 1836-1846.

[5] Farrell, G. C.; Larter, C. Z. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* **2006**, *43*, S99-S112.

[6] Koo, S. H. Nonalcoholic fatty liver disease: molecular mechanisms for the hepatic steatosis. *Clin. Mol. Hepatol.* **2013**, *19*, 210-215.

[7] Neuschwander-Tetri, B. A. Nontriglyceride hepatic lipotoxicity: the new paradigm for the pathogenesis of NASH. *Curr. Gastroenterol. Rep.* **2010**, *12*, 49-56.

[8] Miquilena-Colina, M. E.; Lima-Cabello, E.; Sánchez-Campos, S.; García-Mediavilla, M. V.; Fernández-Bermejo, M.; Lozano-Rodríguez, T.; Vargas-Castrillón, J.; Buqué, X.; Ochoa, B.; Aspichueta, P.; González-Gallego, J.; García-Monzón, C. Hepatic fatty acid translocase CD36 upregulation is associated with insulin resistance, hyperinsulinaemia and increased steatosis in non-alcoholic steatohepatitis and chronic hepatitis C. *Gut* **2011**, *60*, 1394-1402.

[9] Lima-Cabello, E.; García-Mediavilla, M. V.; Miquilena-Colina, M. E.; Vargas-Castrillón, J.; Lozano-Rodríguez, T.; Fernández-Bermejo, M.; Olcoz, J. L.; González-Gallego, J.; García-Monzón, C.; Sánchez-Campos, S. Enhanced expression of pro-inflammatory mediators and liver X-receptor-regulated lipogenic genes in non-alcoholic fatty liver disease and hepatitis C. *Clin. Sci. (Lond)* **2011**, *120*, 239-250.

[10] García-Mediavilla, M. V.; Pisonero-Vaquero, S.; Lima-Cabello, E.; Benedicto, I.; Majano, P. L.; Jorquera, F.; González-Gallego, J.; Sánchez-Campos, S. Liver X receptor alpha-mediated regulation of lipogenesis by core and NS5A proteins contributes to HCV-induced liver steatosis and HCV replication. *Lab. Invest.* **2012**, *92*, 1191-1202.

[11] Uyeda, K.; Repa, J. J. Carbohydrate response element binding protein, ChREBP, a transcription factor coupling hepatic glucose utilization and lipid synthesis. *Cell. Metab.* **2006**, *4*, 107-110.

[12] Desvergne, B.; Wahli, W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr. Rev.* **1999**, *20*, 649-688.

[13] Hussain, M. M.; Shi, J.; Dreizen, P. Microsomal triglyceride transfer protein and its role in apoB-lipoprotein assembly. *J. Lipid Res.* **2003**, *44*, 22-32.

[14] Torres, D. M.; Harrison, S. A. Diagnosis and therapy of nonalcoholic steatohepatitis. *Gastroenterology* **2008**, *134*, 1682-1698.

[15] González-Gallego, J.; García-Mediavilla, M. V.; Sánchez-Campos, S.; Tuñón, M. J. Fruit polyphenols, immunity and inflammation. *Br. J. Nutr.* **2010**, *104 Suppl 3*, S15-27.

[16] Ying, H. Z.; Liu, Y. H.; Yu, B.; Wang, Z. Y.; Zang, J. N.; Yu, C. H. Dietary quercetin ameliorates nonalcoholic steatohepatitis induced by a high-fat diet in gerbils. *Food Chem. Toxicol.* **2013**, *52*, 53-60.

[17] Pisonero-Vaquero, S.; García-Mediavilla, M. V.; Jorquera, F.; Majano, P. L.; Benet, M.; Jover, R.; González-Gallego, J.; Sánchez-Campos, S. Modulation of PI3K-LXRalpha-dependent lipogenesis mediated by oxidative/nitrosative stress contributes to inhibition of HCV replication by quercetin. *Lab. Invest.* **2014**, *94*, 262-274.

[18] Bladé, C.; Baselga-Escudero, L.; Salvadó, M. J.; Arola-Arnal, A. miRNAs, polyphenols, and chronic disease. *Mol. Nutr. Food Res.* **2013**, *57*, 58-70.

[19] Eslamparast, T.; Eghtesad, S.; Hekmatdoost, A.; Poustchi, H. Probiotics and nonalcoholic fatty liver disease. *Middle East. J. Dig. Dis.* **2013**, *5*, 129-136.

[20] Kawabata, K.; Sugiyama, Y.; Sakano, T.; Ohigashi, H. Flavonols enhanced production of anti-inflammatory substance(s) by *Bifidobacterium adolescentis*: prebiotic actions of galangin, quercetin, and fisetin. *Biofactors* **2013**, *39*, 422-429.

[21] Marcolin, E.; San-Miguel, B.; Vallejo, D.; Tieppo, J.; Marroni, N.; González-Gallego, J.; Tuñón, M. J. Quercetin treatment ameliorates inflammation and fibrosis in mice with nonalcoholic steatohepatitis. *J. Nutr.* **2012**, *142*, 1821-1828.

[22] Crespo, I.; García-Mediavilla, M. V.; Almar, M.; González, P.; Tuñón, M. J.; Sánchez-Campos, S.; González-Gallego, J. Differential effects of dietary flavonoids on reactive oxygen and nitrogen species generation and changes in antioxidant enzyme expression induced by proinflammatory cytokines in Chang Liver cells. *Food Chem. Toxicol.* **2008**, *46*, 1555-1569.

[23] Tieppo, J.; Cuevas, M. J.; Vercelino, R.; Tuñón, M. J.; Marroni, N. P.; González-Gallego, J. Quercetin administration ameliorates pulmonary complications of cirrhosis in rats. *J. Nutr.* **2009**, *139*, 1339-1346.

[24] de David, C.; Rodrigues, G.; Bona, S.; Meurer, L.; González-Gallego, J.; Tuñón, M. J.; Marroni, N. P. Role of quercetin in preventing thioacetamide-induced liver injury in rats. *Toxicol. Pathol.* **2011**, *39*, 949-957.

[25] Surapaneni, K. M.; Jainu, M. Pioglitazone, quercetin and hydroxy citric acid effect on hepatic biomarkers in non alcoholic steatohepatitis. *Pharmacognosy Res.* **2014**, *6*, 153-162.

[26] Surapaneni, K. M.; Priya, V. V.; Mallika, J. Pioglitazone, quercetin and hydroxy citric acid effect on cytochrome P450 2E1 (CYP2E1) enzyme levels in experimentally induced non alcoholic steatohepatitis (NASH). *Eur. Rev. Med. Pharmacol. Sci.* **2014**, *18*, 2736-2741.

[27] Li, X.; Wang, R.; Zhou, N.; Wang, X.; Liu, Q.; Bai, Y.; Bai, Y.; Liu, Z.; Yang, H.; Zou, J.; Wang, H.; Shi, T. Quercetin improves insulin resistance and hepatic lipid accumulation in a NAFLD cell model. *Biomed. Rep.* **2013**, *1*, 71-76.

[28] Vidyashankar, S.; Sandeep Varma, R.; Patki, P. S. Quercetin ameliorate insulin resistance and up-regulates cellular antioxidants during oleic acid induced hepatic steatosis in HepG2 cells. *Toxicol. In. Vitro.* **2013**, *27*, 945-953.

[29] Panchal, S. K.; Poudyal, H.; Brown, L. Quercetin ameliorates cardiovascular, hepatic, and metabolic changes in diet-induced metabolic syndrome in rats. *J. Nutr.* **2012**, *142*, 1026-1032.

[30] Jung, C. H.; Cho, I.; Ahn, J.; Jeon, T. I.; Ha, T. Y. Quercetin reduces high-fat diet-induced fat accumulation in the liver by regulating lipid metabolism genes. *Phytother. Res.* **2013**, *27*, 139-143.

[31] Zhang, M. H.; Liang, Z. Q.; Qin, Q.; Li, S. L.; Zhou, D. S.; Tang, L. Effects of quercetin on serum levels of resistin and IL-18 and on insulin resistance in nonalcoholic fatty liver disease rats. *Zhonghua Gan Zang Bing Za Zhi* **2013**, *21*, 66-70.

[32] Wang, W.; Wang, C.; Ding, X. Q.; Pan, Y.; Gu, T. T.; Wang, M. X.; Liu, Y. L.; Wang, F. M.; Wang, S. J.; Kong, L. D. Quercetin and allopurinol reduce liver thioredoxin-interacting protein to alleviate inflammation and lipid accumulation in diabetic rats. *Br. J. Pharmacol.* **2013**, *169*, 1352-1371.

[33] Zhang, D.; Xie, L.; Jia, G.; Cai, S.; Ji, B.; Liu, Y.; Wu, W.; Zhou, F.; Wang, A.; Chu, L.; Wei, Y.; Liu, J.; Gao, F. Comparative study on antioxidant capacity of flavonoids and their inhibitory effects on oleic acid-induced hepatic steatosis in vitro. *Eur. J. Med. Chem.* **2011**, *46*, 4548-4558.

[34] Zhou, D. S.; Liang, Z. Q.; Qin, Q.; Zhang, M. H.; Li, S. L. Therapeutic efficacy and mechanisms of quercetin in a rat model of nonalcoholic fatty liver disease. *Zhonghua Gan Zang Bing Za Zhi* **2013**, *21*, 134-137.

[35] Das, N.; Sikder, K.; Bhattacharjee, S.; Majumdar, S. B.; Ghosh, S.; Majumdar, S.; Dey, S. Quercetin alleviates inflammation after short-term treatment in high-fat-fed mice. *Food Funct.* **2013**, *4*, 889-898.

[36] Wang, X.; Zhang, D. M.; Gu, T. T.; Ding, X. Q.; Fan, C. Y.; Zhu, Q.; Shi, Y. W.; Hong, Y.; Kong, L. D. Morin reduces hepatic inflammation-associated lipid accumulation in high fructose-fed rats via inhibiting sphingosine kinase 1/sphingosine 1-phosphate signaling pathway. *Biochem. Pharmacol.* **2013**, *86*, 1791-1804.

[37] Panchal, S. K.; Poudyal, H.; Arumugam, T. V.; Brown, L. Rutin attenuates metabolic changes, nonalcoholic steatohepatitis, and cardiovascular remodeling in high-carbohydrate, high-fat diet-fed rats. *J. Nutr.* **2011**, *141*, 1062-1069.

[38] Zhang, Z. F.; Fan, S. H.; Zheng, Y. L.; Lu, J.; Wu, D. M.; Shan, Q.; Hu, B. Troxerutin improves hepatic lipid homeostasis by restoring NAD(+)-depletion-mediated dysfunction of lipin 1 signaling in high-fat diet-treated mice. *Biochem. Pharmacol.* **2014**, *91*, 74-86.

[39] Li, X. Y.; Kong, L. X.; Li, J.; He, H. X.; Zhou, Y. D. Kaempferol suppresses lipid accumulation in macrophages through the downregulation of cluster of differentiation 36 and the upregulation of scavenger receptor class B type I and ATP-binding cassette transporters A1 and G1. *Int. J. Mol. Med.* **2013**, *31*, 331-338.

[40] Zhang, N.; Pei, F.; Wei, H.; Zhang, T.; Yang, C.; Ma, G.; Yang, C. Isorhamnetin protects rat ventricular myocytes from ischemia and reperfusion injury. *Exp. Toxicol. Pathol.* **2011**, *63*, 33-38.

[41] Kong, C. S.; Seo, Y. Antiadipogenic activity of isohamnetin 3-O-beta-D-glucopyranoside from Salicornia herbacea. *Immunopharmacol. Immunotoxicol.* **2012**, *34*, 907-911.

[42] Ramachandran, L.; Manu, K. A.; Shanmugam, M. K.; Li, F.; Siveen, K. S.; Vali, S.; Kapoor, S.; Abbasi, T.; Surana, R.; Smoot, D. T.; Ashktorab, H.; Tan, P.; Ahn, K. S.; Yap, C. W.; Kumar, A. P.; Sethi, G. Isorhamnetin inhibits proliferation and invasion and induces apoptosis through the

modulation of peroxisome proliferator-activated receptor gamma activation pathway in gastric cancer. *J. Biol. Chem.* **2012**, *287*, 38028-38040.

[43] Chirumbolo, S. Anti-inflammatory action of isorhamnetin. *Inflammation* **2014**, *37*, 1200-1201.

[44] Dong, G. Z.; Lee, J. H.; Ki, S. H.; Yang, J. H.; Cho, I. J.; Kang, S. H.; Zhao, R. J.; Kim, S. C.; Kim, Y. W. AMPK activation by isorhamnetin protects hepatocytes against oxidative stress and mitochondrial dysfunction. *Eur. J. Pharmacol.* **2014**, *740*, 634-640.

[45] Choi, H. N.; Kang, M. J.; Lee, S. J.; Kim, J. I. Ameliorative effect of myricetin on insulin resistance in mice fed a high-fat, high-sucrose diet. *Nutr. Res. Pract.* **2014**, *8*, 544-549.

[46] Chang, C. J.; Tzeng, T. F.; Liou, S. S.; Chang, Y. S.; Liu, I. M. Myricetin increases hepatic peroxisome proliferator-activated receptor alpha protein expression and decreases plasma lipids and adiposity in rats. *Evid Based. Complement. Alternat Med.* **2012**, *2012*, 787152.

[47] Jung, C. H.; Jang, S. J.; Ahn, J.; Gwon, S. Y.; Jeon, T. I.; Kim, T. W.; Ha, T. Y. *Alpinia officinarum* inhibits adipocyte differentiation and high-fat diet-induced obesity in mice through regulation of adipogenesis and lipogenesis. *J. Med. Food* **2012**, *15*, 959-967.

[48] Jiang, Y.; Gong, F. L.; Zhao, G. B.; Li, J. Chrysin suppressed inflammatory responses and the inducible nitric oxide synthase pathway after spinal cord injury in rats. *Int. J. Mol. Sci.* **2014**, *15*, 12270-12279.

[49] Yang, B.; Huang, J.; Xiang, T.; Yin, X.; Luo, X.; Huang, J.; Luo, F.; Li, H.; Li, H.; Ren, G. Chrysin inhibits metastatic potential of human triple-negative breast cancer cells by modulating matrix metalloproteinase-10, epithelial to mesenchymal transition, and PI3K/Akt signaling pathway. *J. Appl. Toxicol.* **2014**, *34*, 105-112.

[50] Sirovina, D.; Orsolic, N.; Koncic, M. Z.; Kovacevic, G.; Benkovic, V.; Gregorovic, G. Quercetin vs chrysin: effect on liver histopathology in diabetic mice. *Hum. Exp. Toxicol.* **2013**, *32*, 1058-1066.

[51] Liang, Y. C.; Tsai, S. H.; Tsai, D. C.; Lin-Shiau, S. Y.; Lin, J. K. Suppression of inducible cyclooxygenase and nitric oxide synthase through activation of peroxisome proliferator-activated receptor-gamma by flavonoids in mouse macrophages. *FEBS Lett.* **2001**, *496*, 12-18.

[52] Feng, X.; Qin, H.; Shi, Q.; Zhang, Y.; Zhou, F.; Wu, H.; Ding, S.; Niu, Z.; Lu, Y.; Shen, P. Chrysin attenuates inflammation by regulating M1/M2 status via activating PPARgamma. *Biochem. Pharmacol.* **2014**, *89*, 503-514.

[53] Wang, J.; Liu, Y. T.; Xiao, L.; Zhu, L.; Wang, Q.; Yan, T. Anti-inflammatory effects of apigenin in lipopolysaccharide-induced inflammatory in acute lung injury by suppressing COX-2 and NF-kB pathway. *Inflammation* **2014**.

[54] Zhang, X.; Wang, G.; Gurley, E. C.; Zhou, H. Flavonoid apigenin inhibits lipopolysaccharide-induced inflammatory response through multiple mechanisms in macrophages. *PLoS One* **2014**, *9*, e107072.

[55] Tong, X.; Pelling, J. C. Targeting the PI3K/Akt/mTOR axis by apigenin for cancer prevention. *Anticancer Agents Med. Chem.* **2013**, *13*, 971-978.

[56] Bao, Y. Y.; Zhou, S. H.; Fan, J.; Wang, Q. Y. Anticancer mechanism of apigenin and the implications of GLUT-1 expression in head and neck cancers. *Future Oncol.* **2013**, *9*, 1353-1364.

[57] Lefort, E. C.; Blay, J. Apigenin and its impact on gastrointestinal cancers. *Mol. Nutr. Food Res.* **2013**, *57*, 126-144.

[58] Bumke-Vogt, C.; Osterhoff, M. A.; Borchert, A.; Guzman-Perez, V.; Sarem, Z.; Birkenfeld, A. L.; Bahr, V.; Pfeiffer, A. F. The flavones apigenin and luteolin induce FOXO1 translocation but inhibit gluconeogenic and lipogenic gene expression in human cells. *PLoS One* **2014**, *9*, e104321.

[59] López-Lázaro, M. Distribution and biological activities of the flavonoid luteolin. *Mini Rev. Med. Chem.* **2009**, *9*, 31-59.

[60] Chen, D.; Bi, A.; Dong, X.; Jiang, Y.; Rui, B.; Liu, J.; Yin, Z.; Luo, L. Luteolin exhibits anti-inflammatory effects by blocking the activity of heat shock protein 90 in macrophages. *Biochem. Biophys. Res. Commun.* **2014**, *443*, 326-332.

[61] Kim, Y. S.; Kim, S. H.; Shin, J.; Harikishore, A.; Lim, J. K.; Jung, Y.; Lyu, H. N.; Baek, N. I.; Choi, K. Y.; Yoon, H. S.; Kim, K. T. Luteolin suppresses cancer cell proliferation by targeting vaccinia-related kinase 1. *PLoS One* **2014**, *9*, e109655.

[62] Osman, N. H.; Said, U. Z.; El-Waseef, A. M.; Ahmed, E. S. Luteolin supplementation adjacent to aspirin treatment reduced dimethylhydrazine-induced experimental colon carcinogenesis in rats. *Tumour Biol.* **2014**.

[63] Liu, J. F.; Ma, Y.; Wang, Y.; Du, Z. Y.; Shen, J. K.; Peng, H. L. Reduction of lipid accumulation in HepG2 cells by luteolin is associated with activation of AMPK and mitigation of oxidative stress. *Phytother. Res.* **2011**, *25*, 588-596.

[64] Mulvihill, E. E.; Allister, E. M.; Sutherland, B. G.; Telford, D. E.; Sawyez, C. G.; Edwards, J. Y.; Markle, J. M.; Hegele, R. A.; Huff, M. W. Naringenin prevents dyslipidemia, apolipoprotein B overproduction, and hyperinsulinemia in LDL receptor-null mice with diet-induced insulin resistance. *Diabetes* **2009**, *58*, 2198-2210.

[65] Esmaeili, A. H.; Hajizadeh Moghaddam, A.; Chaichi, M. J. Identification, determination, and study of antioxidative activities of hesperetin and gallic acid in hydro-alcoholic extract from flowers of *Eriobotrya japonica* (Lindl.). *Avicenna J. Phytomed* **2014**, *4*, 260-266.

[66] Fordham, J. B.; Naqvi, A. R.; Nares, S. Leukocyte production of inflammatory mediators is inhibited by the antioxidants phloretin, silymarin, hesperetin, and resveratrol. *Mediators Inflamm.* **2014**, *2014*, 938712.

[67] Palit, S.; Kar, S.; Sharma, G.; Das, P. K. Hesperetin induces apoptosis in breast carcinoma by triggering accumulation of ROS and activation of ASK1/JNK pathway. *J. Cell. Physiol.* **2014**.

[68] Lee, N. K.; Choi, S. H.; Park, S. H.; Park, E. K.; Kim, D. H. Antiallergic activity of hesperidin is activated by intestinal microflora. *Pharmacology* **2004**, *71*, 174-180.

[69] Choi, E. J.; Ahn, W. S. Neuroprotective effects of chronic hesperetin administration in mice. *Arch. Pharm. Res.* **2008**, *31*, 1457-1462.

[70] Casaschi, A.; Rubio, B. K.; Maiyoh, G. K.; Theriault, A. G. Inhibitory activity of diacylglycerol acyltransferase (DGAT) and microsomal triglyceride transfer protein (MTP) by the flavonoid, taxifolin, in HepG2 cells: potential role in the regulation of apolipoprotein B secretion. *Atherosclerosis* **2004**, *176*, 247-253.

[71]   Brusselmans, K.; Vrolix, R.; Verhoeven, G.; Swinnen, J. V. Induction of cancer cell apoptosis by flavonoids is associated with their ability to inhibit fatty acid synthase activity. *J. Biol. Chem.* **2005**, *280*, 5636-5645.

[72]   Kochi, T.; Shimizu, M.; Terakura, D.; Baba, A.; Ohno, T.; Kubota, M.; Shirakami, Y.; Tsurumi, H.; Tanaka, T.; Moriwaki, H. Non-alcoholic steatohepatitis and preneoplastic lesions develop in the liver of obese and hypertensive rats: suppressing effects of EGCG on the development of liver lesions. *Cancer Lett.* **2014**, *342*, 60-69.

[73]   Xiao, J.; Ho, C. T.; Liong, E. C.; Nanji, A. A.; Leung, T. M.; Lau, T. Y.; Fung, M. L.; Tipoe, G. L. Epigallocatechin gallate attenuates fibrosis, oxidative stress, and inflammation in non-alcoholic fatty liver disease rat model through TGF/SMAD, PI3 K/Akt/FoxO1, and NF-kappa B pathways. *Eur. J. Nutr.* **2014**, *53*, 187-199.

[74]   Shimada, T.; Tokuhara, D.; Tsubata, M.; Kamiya, T.; Kamiya-Sameshima, M.; Nagamine, R.; Takagaki, K.; Sai, Y.; Miyamoto, K.; Aburada, M. Flavangenol (pine bark extract) and its major component procyanidin B1 enhance fatty acid oxidation in fat-loaded models. *Eur. J. Pharmacol.* **2012**, *677*, 147-153.

[75]   Kim, M. H.; Kang, K. S. Isoflavones as a smart curer for non-alcoholic fatty liver disease and pathological adiposity via ChREBP and Wnt signaling. *Prev. Med.* **2012**, *54 Suppl*, S57-63.

[76]   Westmark, C. J. A hypothesis regarding the molecular mechanism underlying dietary soy-induced effects on seizure propensity. *Front. Neurol.* **2014**, *5*, 169.

[77]   Kim, M. H.; Park, J. S.; Jung, J. W.; Byun, K. W.; Kang, K. S.; Lee, Y. S. Daidzein supplementation prevents non-alcoholic fatty liver disease through alternation of hepatic gene expression profiles and adipocyte metabolism. *Int. J. Obes. (Lond)* **2011**, *35*, 1019-1030.

[78]   Zheng, P. Y.; Ma, Z. S.; Hua, Y. Q.; Liu, T.; Xing, L. J.; Ji, G. Effects of puerarin on expressions of leptin receptor mRNA, phosphorylated Janus kinase 2/phosphorylated signal transducers and activators of transcription 3 proteins in the liver of rats with non-alcoholic fatty liver. *Zhong Xi Yi Jie He Xue Bao* **2008**, *6*, 921-927.

[79]   Zheng, P.; Ji, G.; Ma, Z.; Liu, T.; Xin, L.; Wu, H.; Liang, X.; Liu, J. Therapeutic effect of puerarin on non-alcoholic rat fatty liver by improving leptin signal transduction through JAK2/STAT3 pathways. *Am. J. Chin. Med.* **2009**, *37*, 69-83.

[80]   Wang, Y.; Li, J.; Zhuge, L.; Su, D.; Yang, M.; Tao, S.; Li, J. Comparison between the efficacies of curcumin and puerarin in C57BL/6 mice with steatohepatitis induced by a methionine- and choline-deficient diet. *Exp. Ther. Med.* **2014**, *7*, 663-668.

[81]   Mohamed Salih, S.; Nallasamy, P.; Muniyandi, P.; Periyasami, V.; Carani Venkatraman, A. Genistein improves liver function and attenuates non-alcoholic fatty liver disease in a rat model of insulin resistance. *J. Diabetes* **2009**, *1*, 278-287.

[82]   Kim, M. H.; Kang, K. S.; Lee, Y. S. The inhibitory effect of genistein on hepatic steatosis is linked to visceral adipocyte metabolism in mice with diet-induced non-alcoholic fatty liver disease. *Br. J. Nutr.* **2010**, *104*, 1333-1342.

[83] Shih, P. H.; Hwang, S. L.; Yeh, C. T.; Yen, G. C. Synergistic effect of cyanidin and PPAR agonist against nonalcoholic steatohepatitis-mediated oxidative stress-induced cytotoxicity through MAPK and Nrf2 transduction pathways. *J. Agric. Food Chem.* **2012**, *60*, 2924-2933.

[84] Wei, X.; Wang, D.; Yang, Y.; Xia, M.; Li, D.; Li, G.; Zhu, Y.; Xiao, Y.; Ling, W. Cyanidin-3-O-beta-glucoside improves obesity and triglyceride metabolism in KK-Ay mice by regulating lipoprotein lipase activity. *J. Sci. Food Agric.* **2011**, *91*, 1006-1013.

[85] Guo, H.; Li, D.; Ling, W.; Feng, X.; Xia, M. Anthocyanin inhibits high glucose-induced hepatic mtGPAT1 activation and prevents fatty acid synthesis through PKCzeta. *J. Lipid Res.* **2011**, *52*, 908-922.

[86] Jiang, X.; Tang, X.; Zhang, P.; Liu, G.; Guo, H. Cyanidin-3-O-beta-glucoside protects primary mouse hepatocytes against high glucose-induced apoptosis by modulating mitochondrial dysfunction and the PI3K/Akt pathway. *Biochem. Pharmacol.* **2014**, *90*, 135-144.

[87] Wu, T.; Qi, X.; Liu, Y.; Guo, J.; Zhu, R.; Chen, W.; Zheng, X.; Yu, T. Dietary supplementation with purified mulberry (*Morus australis* Poir) anthocyanins suppresses body weight gain in high-fat diet fed C57BL/6 mice. *Food Chem.* **2013**, *141*, 482-487.

[88] Valenti, L.; Riso, P.; Mazzocchi, A.; Porrini, M.; Fargion, S.; Agostoni, C. Dietary anthocyanins as nutritional therapy for nonalcoholic fatty liver disease. *Oxid Med. Cell. Longev* **2013**, *2013*, 145421.

[89] Mao, Z. M.; Song, H. Y.; Yang, L. L.; Liu, T.; Li, D. F.; Zheng, P. Y.; Liu, P.; Ji, G. Effects of the mixture of *Swertia pseudochinensis* Hara and *Silybum marianum* Gaertn extracts on CCl(4)-induced liver injury in rats with non-alcoholic fatty liver disease. *Zhong Xi Yi Jie He Xue Bao* **2012**, *10*, 193-199.

[90] Zhang, S.; Zheng, L.; Dong, D.; Xu, L.; Yin, L.; Qi, Y.; Han, X.; Lin, Y.; Liu, K.; Peng, J. Effects of flavonoids from *Rosa laevigata* Michx fruit against high-fat diet-induced non-alcoholic fatty liver disease in rats. *Food Chem.* **2013**, *141*, 2108-2116.

[91] Salamone, F.; Galvano, F.; Cappello, F.; Mangiameli, A.; Barbagallo, I.; Li Volti, G. Silibinin modulates lipid homeostasis and inhibits nuclear factor kappa B activation in experimental nonalcoholic steatohepatitis. *Transl. Res.* **2012**, *159*, 477-486.

[92] Salamone, F.; Galvano, F.; Marino Gammazza, A.; Paternostro, C.; Tibullo, D.; Bucchieri, F.; Mangiameli, A.; Parola, M.; Bugianesi, E.; Li Volti, G. Silibinin improves hepatic and myocardial injury in mice with nonalcoholic steatohepatitis. *Dig. Liver Dis.* **2012**, *44*, 334-342.

[93] Yao, J.; Zhi, M.; Minhu, C. Effect of silybin on high-fat-induced fatty liver in rats. *Braz. J. Med. Biol. Res.* **2011**, *44*, 652-659.

[94] Li, Z. Z.; Berk, M.; McIntyre, T. M.; Feldstein, A. E. Hepatic lipid partitioning and liver damage in nonalcoholic fatty liver disease: role of stearoyl-CoA desaturase. *J. Biol. Chem.* **2009**, *284*, 5637-5644.

[95] Guzmán, C.; Benet, M.; Pisonero-Vaquero, S.; Moya, M.; García-Mediavilla, M. V.; Martínez-Chantar, M. L.; González-Gallego, J.; Castell, J. V.; Sánchez-Campos, S.; Jover, R. The human liver fatty acid binding protein (FABP1) gene is activated by FOXA1 and PPARalpha; and

repressed by C/EBPalpha: Implications in FABP1 down-regulation in nonalcoholic fatty liver disease. *Biochim. Biophys. Acta* **2013**, *1831*, 803-818.

[96] Aghazadeh, S.; Amini, R.; Yazdanparast, R.; Ghaffari, S. H. Anti-apoptotic and anti-inflammatory effects of *Silybum marianum* in treatment of experimental steatohepatitis. *Exp. Toxicol. Pathol.* **2011**, *63*, 569-574.

[97] Kim, M.; Yang, S. G.; Kim, J. M.; Lee, J. W.; Kim, Y. S.; Lee, J. I. Silymarin suppresses hepatic stellate cell activation in a dietary rat model of non-alcoholic steatohepatitis: analysis of isolated hepatic stellate cells. *Int. J. Mol. Med.* **2012**, *30*, 473-479.

[98] Buturova, L. I.; Tsybizova, T. A.; Kalinin, A. V. Use of Legalon in non-alcoholic fatty liver disease. *Eksp. Klin. Gastroenterol.* **2010**, *(5)*, 69-75.

[99] Cacciapuoti, F.; Scognamiglio, A.; Palumbo, R.; Forte, R.; Cacciapuoti, F. Silymarin in non alcoholic fatty liver disease. *World J. Hepatol.* **2013**, *5*, 109-113.

[100] Schrieber, S. J.; Hawke, R. L.; Wen, Z.; Smith, P. C.; Reddy, K. R.; Wahed, A. S.; Belle, S. H.; Afdhal, N. H.; Navarro, V. J.; Meyers, C. M.; Doo, E.; Fried, M. W. Differences in the disposition of silymarin between patients with nonalcoholic fatty liver disease and chronic hepatitis C. *Drug Metab. Dispos.* **2011**, *39*, 2182-2190.

[101] Kidd, P. M. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. *Altern. Med. Rev.* **2009**, *14*, 226-246.

[102] Loguercio, C.; Andreone, P.; Brisc, C.; Brisc, M. C.; Bugianesi, E.; Chiaramonte, M.; Cursaro, C.; Danila, M.; de Sio, I.; Floreani, A.; Freni, M. A.; Grieco, A.; Groppo, M.; Lazzari, R.; Lobello, S.; Lorefice, E.; Margotti, M.; Miele, L.; Milani, S.; Okolicsanyi, L.; Palasciano, G.; Portincasa, P.; Saltarelli, P.; Smedile, A.; Somalvico, F.; Spadaro, A.; Sporea, I.; Sorrentino, P.; Vecchione, R.; Tuccillo, C.; Del Vecchio Blanco, C.; Federico, A. Silybin combined with phosphatidylcholine and vitamin E in patients with nonalcoholic fatty liver disease: a randomized controlled trial. *Free Radic. Biol. Med.* **2012**, *52*, 1658-1665.

[103] Iakimchuk, G. N.; Gendrikson, L. N. Study of clinical efficiency of essential phospholipids and silymarin combination in nonalcoholic and alcoholic steatohepatitis. *Eksp. Klin. Gastroenterol.* **2011**, *(7)*, 64-69.

[104] Federico, A.; Trappoliere, M.; Tuccillo, C.; de Sio, I.; Di Leva, A.; Del Vecchio Blanco, C.; Loguercio, C. A new silybin-vitamin E-phospholipid complex improves insulin resistance and liver damage in patients with non-alcoholic fatty liver disease: preliminary observations. *Gut* **2006**, *55*, 901-902.

[105] Trappoliere, M.; Federico, A.; Tuccillo, C.; de Sio, I.; Di Leva, A.; Niosi, M.; D'Auria, M.; Loguercio, C.; Real Sud Group 2 Effects of a new pharmacological complex (silybin + vitamin-E + phospholipids) on some markers of the metabolic syndrome and of liver fibrosis in patients with hepatic steatosis. Preliminary study. *Minerva Gastroenterol. Dietol.* **2005**, *51*, 193-199.

[106] Zeng, C. H.; Zeng, P.; Deng, Y. H.; Shen, N.; Peng, M. L.; Liu, Q.; Ren, H. The effects of curcumin derivative on experimental steatohepatitis. *Zhonghua Gan Zang Bing Za Zhi* **2011**, *19*, 454-459.

[107] Kuo, J. J.; Chang, H. H.; Tsai, T. H.; Lee, T. Y. Positive effect of curcumin on inflammation and mitochondrial dysfunction in obese mice with liver steatosis. *Int. J. Mol. Med.* **2012***, 30*, 673-679.

[108] Kang, O. H.; Kim, S. B.; Seo, Y. S.; Joung, D. K.; Mun, S. H.; Choi, J. G.; Lee, Y. M.; Kang, D. G.; Lee, H. S.; Kwon, D. Y. Curcumin decreases oleic acid-induced lipid accumulation via AMPK phosphorylation in hepatocarcinoma cells. *Eur. Rev. Med. Pharmacol. Sci.* **2013***, 17*, 2578-2586.

[109] Kuo, J. J.; Chang, H. H.; Tsai, T. H.; Lee, T. Y. Curcumin ameliorates mitochondrial dysfunction associated with inhibition of gluconeogenesis in free fatty acid-mediated hepatic lipoapoptosis. *Int. J. Mol. Med.* **2012***, 30*, 643-649.

[110] Messner, D. J.; Rhieu, B. H.; Kowdley, K. V. Iron overload causes oxidative stress and impaired insulin signaling in AML-12 hepatocytes. *Dig. Dis. Sci.* **2013***, 58*, 1899-1908.

[111] Zhu, W.; Chen, S.; Li, Z.; Zhao, X.; Li, W.; Sun, Y.; Zhang, Z.; Ling, W.; Feng, X. Effects and mechanisms of resveratrol on the amelioration of oxidative stress and hepatic steatosis in KKAy mice. *Nutr. Metab. (Lond)* **2014***, 11*, 35-7075-11-35. eCollection 2014.

[112] Aguirre, L.; Portillo, M. P.; Hijona, E.; Bujanda, L. Effects of resveratrol and other polyphenols in hepatic steatosis. *World J. Gastroenterol.* **2014***, 20*, 7366-7380.

[113] Aoun, M.; Michel, F.; Fouret, G.; Casas, F.; Jullien, M.; Wrutniak-Cabello, C.; Ramos, J.; Cristol, J. P.; Coudray, C.; Carbonneau, M. A.; Feillet-Coudray, C. A polyphenol extract modifies quantity but not quality of liver fatty acid content in high-fat-high-sucrose diet-fed rats: possible implication of the sirtuin pathway. *Br. J. Nutr.* **2010***, 104*, 1760-1770.

[114] Panchal, S. K.; Brown, L. Cardioprotective and hepatoprotective effects of ellagitannins from European oak bark (*Quercus petraea* L.) extract in rats. *Eur. J. Nutr.* **2013***, 52*, 397-408.

[115] Luo, X. Y.; Takahara, T.; Hou, J.; Kawai, K.; Sugiyama, T.; Tsukada, K.; Takemoto, M.; Takeuchi, M.; Zhong, L.; Li, X. K. Theaflavin attenuates ischemia-reperfusion injury in a mouse fatty liver model. *Biochem. Biophys. Res. Commun.* **2012***, 417*, 287-293.

[116] Chung, M. Y.; Park, H. J.; Manautou, J. E.; Koo, S. I.; Bruno, R. S. Green tea extract protects against nonalcoholic steatohepatitis in ob/ob mice by decreasing oxidative and nitrative stress responses induced by proinflammatory enzymes. *J. Nutr. Biochem.* **2012***, 23*, 361-367.

[117] Park, H. J.; Lee, J. Y.; Chung, M. Y.; Park, Y. K.; Bower, A. M.; Koo, S. I.; Giardina, C.; Bruno, R. S. Green tea extract suppresses NFkappaB activation and inflammatory responses in diet-induced obese rats with nonalcoholic steatohepatitis. *J. Nutr.* **2012***, 142*, 57-63.

[118] Sakata, R.; Nakamura, T.; Torimura, T.; Ueno, T.; Sata, M. Green tea with high-density catechins improves liver function and fat infiltration in non-alcoholic fatty liver disease (NAFLD) patients: a double-blind placebo-controlled study. *Int. J. Mol. Med.* **2013***, 32*, 989-994.

[119] Masterjohn, C.; Bruno, R. S. Therapeutic potential of green tea in nonalcoholic fatty liver disease. *Nutr. Rev.* **2012***, 70*, 41-56.

[120] Jung, J. H.; Kim, H. S. The inhibitory effect of black soybean on hepatic cholesterol accumulation in high cholesterol and high fat diet-induced non-alcoholic fatty liver disease. *Food Chem. Toxicol.* **2013***, 60*, 404-412.

[121] Badger, T. M.; Ronis, M. J.; Wolff, G.; Stanley, S.; Ferguson, M.; Shankar, K.; Simpson, P.; Jo, C. H. Soy protein isolate reduces hepatosteatosis in yellow Avy/a mice without altering coat color phenotype. *Exp. Biol. Med. (Maywood)* **2008**, *233*, 1242-1254.

[122] Leng, L.; Jiang, Z. Q.; Ji, G. Y. Effects of soybean isoflavone on liver lipid metabolism in nonalcoholic fatty liver rats. *Zhonghua Yu Fang Yi Xue Za Zhi* **2011**, *45*, 335-339.

[123] Davaatseren, M.; Hur, H. J.; Yang, H. J.; Hwang, J. T.; Park, J. H.; Kim, H. J.; Kim, M. J.; Kwon, D. Y.; Sung, M. J. *Taraxacum official* (dandelion) leaf extract alleviates high-fat diet-induced nonalcoholic fatty liver. *Food Chem. Toxicol.* **2013**, *58*, 30-36.

[124] Davaatseren, M.; Hur, H. J.; Yang, H. J.; Hwang, J. T.; Park, J. H.; Kim, H. J.; Kim, M. S.; Kim, M. J.; Kwon, D. Y.; Sung, M. J. Dandelion leaf extract protects against liver injury induced by methionine- and choline-deficient diet in mice. *J. Med. Food* **2013**, *16*, 26-33.

[125] Vareda, P. M.; Saldanha, L. L.; Camaforte, N. A.; Violato, N. M.; Dokkedal, A. L.; Bosqueiro, J. R. *Myrcia bella* leaf extract presents hypoglycemic activity via PI3k/Akt insulin signaling pathway. *Evid Based. Complement. Alternat Med.* **2014**, *2014*, 543606.

[126] Shen, B.; Yu, J.; Wang, S.; Chu, E. S.; Wong, V. W.; Zhou, X.; Lin, G.; Sung, J. J.; Chan, H. L. *Phyllanthus urinaria* ameliorates the severity of nutritional steatohepatitis both in vitro and in vivo. *Hepatology* **2008**, *47*, 473-483.

[127] Yang, J.; Lv, F.; Chen, X. Q.; Cui, W. X.; Chen, L. H.; Wen, X. D.; Wang, Q. Pharmacokinetic study of major bioactive components in rats after oral administration of extract of *Ilex hainanensis* by high-performance liquid chromatography/electrospray ionization mass spectrometry. *J. Pharm. Biomed. Anal.* **2013**, *77*, 21-28.

[128] Cui, W. X.; Yang, J.; Chen, X. Q.; Mao, Q.; Wei, X. L.; Wen, X. D.; Wang, Q. Triterpenoid-rich fraction from *Ilex hainanensis* Merr. attenuates non-alcoholic fatty liver disease induced by high fat diet in rats. *Am. J. Chin. Med.* **2013**, *41*, 487-502.

[129] Li, J. J.; Yang, J.; Cui, W. X.; Chen, X. Q.; Chen, G. L.; Wen, X. D.; Wang, Q. Analysis of therapeutic effect of *Ilex hainanensis* Merr. extract on nonalcoholic fatty liver disease through urine metabolite profiling by ultraperformance liquid chromatography/quadrupole time of flight mass spectrometry. *Evid Based. Complement. Alternat Med.* **2013**, *2013*, 451975.

[130] Wang, S. D.; Xie, Z. Q.; Chen, J.; Wang, K.; Wei, T.; Zhao, A. H.; Zhang, Q. H. Inhibitory effect of *Ginkgo biloba* extract on fatty liver: regulation of carnitine palmitoyltransferase 1a and fatty acid metabolism. *J. Dig. Dis.* **2012**, *13*, 525-535.

[131] Wei, T.; Xiong, F. F.; Wang, S. D.; Wang, K.; Zhang, Y. Y.; Zhang, Q. H. Flavonoid ingredients of. *J. Biomed. Sci.* **2014**, *21*, 87.

[132] Zhang, L.; Xu, J.; Song, H.; Yao, Z.; Ji, G. Extracts from Salvia-*Nelumbinis naturalis* alleviate hepatosteatosis via improving hepatic insulin sensitivity. *J. Transl. Med.* **2014**, *12*, 236-014-0236-8.

[133] Yin, J.; Luo, Y.; Deng, H.; Qin, S.; Tang, W.; Zeng, L.; Zhou, B. Hugan Qingzhi medication ameliorates hepatic steatosis by activating AMPK and PPARalpha pathways in L02 cells and HepG2 cells. *J. Ethnopharmacol.* **2014**, *154*, 229-239.

[134] Chen, Z. Y.; Li, J. S.; Jiang, J. P.; Yan, M. X.; He, B. H. Effect of pure total flavonoids from citrus on hepatic SIRT1/PGC-1alpha pathway in mice with NASH. *Zhongguo Zhong Yao Za Zhi* **2014**, *39*, 100-105.

[135] Wei, Y. Y.; Yan, D.; Japar, A.; Qu, S. S.; Haji, A. A.; Parhat, K. Effects of pomegranate flowers polyphenols on liver PON expression of diabetes combining non-alcoholic fat liver diseases rats. *Yao Xue Xue Bao* **2013**, *48*, 71-76.

[136] Liu, Y.; Wang, D.; Zhang, D.; Lv, Y.; Wei, Y.; Wu, W.; Zhou, F.; Tang, M.; Mao, T.; Li, M.; Ji, B. Inhibitory effect of blueberry polyphenolic compounds on oleic acid-induced hepatic steatosis in vitro. *J. Agric. Food Chem.* **2011**, *59*, 12254-12263.

[137] Wu, T.; Tang, Q.; Gao, Z.; Yu, Z.; Song, H.; Zheng, X.; Chen, W. Blueberry and mulberry juice prevent obesity development in C57BL/6 mice. *PLoS One* **2013**, *8*, e77585.

[138] Guo, H.; Zhong, R.; Liu, Y.; Jiang, X.; Tang, X.; Li, Z.; Xia, M.; Ling, W. Effects of bayberry juice on inflammatory and apoptotic markers in young adults with features of non-alcoholic fatty liver disease. *Nutrition* **2014**, *30*, 198-203.

[139] Tsuruta, Y.; Nagao, K.; Kai, S.; Tsuge, K.; Yoshimura, T.; Koganemaru, K.; Yanagita, T. Polyphenolic extract of lotus root (edible rhizome of *Nelumbo nucifera*) alleviates hepatic steatosis in obese diabetic db/db mice. *Lipids Health. Dis.* **2011**, *10*, 202-511X-10-202.