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Narrative Review

Polyphenols in the prevention and treatment of non-alcoholic fatty liver disease: An update of preclinical and clinical studies

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SUMMARY

Background & aims: The prevention and treatment of non-alcoholic fatty liver disease (NAFLD) has become one of the most urgent problems to be solved. To date, only a lifestyle modification related to diet and physical activity is considered for these patients. Polyphenols are a group of plant natural products that when regularly consumed has been related to a reduction in the risk of several metabolic disorders associated with NAFLD. In this study, we aimed to present an overview of the relationship between polyphenols and NAFLD with current approaches.

Methods: We performed a comprehensive literature search for articles on polyphenols and NAFLD published in English between January 2018 to August 2020. Keywords included in this review: "Phenolic" OR "Polyphenol" AND "Non-Alcoholic Fatty Liver Disease". The editorials, communications and conference abstracts were excluded.

Results: Different polyphenols decreased the pro-inflammatory cytokines in both serum and liver that contribute to a decrease in fatty liver dysfunction. Additionally, polyphenols may improve the regulation of adipokines and prevent hepatic steatosis. According to human clinical studies, polyphenols are promising for NAFLD patients and associated diseases that lead to NAFLD.

Conclusion: Preclinical and clinical studies suggest that various polyphenols could prevent steatosis and its progression to non-alcoholic steatohepatitis, as well as ameliorate NAFLD. However, more clinical studies are needed to confirm this hypothesis.

1. Introduction

In recent years, non-alcoholic fatty liver disease (NAFLD) has attracted considerable attention in research studies and clinical practice. NAFLD is the most common liver disease due to its high prevalence worldwide. It's characterized by lipid accumulation of more than 5% of the total organ weight in the absence of excess alcohol intake in the liver [1]. NAFLD is generally in the form of 90–95% steatosis and comprises a broad spectrum, from simple steatosis to non-alcoholic steatohepatitis (NASH). NASH often progresses to cirrhosis and hepatocellular carcinoma [1,2]. NAFLD is a major public health issue in industrialized countries. According to the diagnostic method, the frequency of NAFLD in the general population has been reported as 25% [2,3]. Generally, NAFLD patients are clinically asymptomatic with approximately 10–25% progressing to NASH and 5–8% progressing to cirrhosis within 5 years [4].

NAFLD is considered to be a part of metabolic syndrome that is characterized by obesity, insulin resistance, dyslipidemia, diabetes, and visceral fat mass. Today, as the epidemics of obesity, type II diabetes mellitus (T2DM), insulin resistance, and dyslipidemia increase day by day, the risk of NAFLD is increasing proportionally [1,5].

NAFLD is a global health burden, impacting millions of patients each year, thus the prevention and treatment of NAFLD have become one of the most urgent problems needing to be solved [6]. To date, there are no effective treatments for patients with NAFLD. Only lifestyle modification related to diet and physical activity is

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considered the treatment for NAFLD [7]. Therefore, different approaches are important for these patients.

Today, polyphenols are known as functional foods and have been popular due to the increasing interest in healthy diets [8]. Also, regular consumption of polyphenols has been associated with a reduction in the risk of several metabolic diseases, including obesity, insulin resistance, hypertension and cardiovascular diseases [9–11]. Thus, it may contribute to the reduction of NAFLD components. The aim of this review is to present an overview of the relationship between polyphenols and NAFLD with current approaches.

2. Methods

In the current comprehensive review study, electronic searches were carried out using Scopus, ScienceDirect and PubMed databases, to identify relevant studies published from January 2018 to August 2020. The search was restricted to English language studies. Keywords included in this review: "Phenolic" OR "Polyphenol" AND "Non-Alcoholic Fatty Liver Disease". The editorials, communications and conference abstracts were excluded. The inclusion criteria were *in vivo* studies or human clinical studies reporting the effects of polyphenols on NAFLD. In total 61 preclinical studies and 9 clinical studies were included in this review.

3. Overview of non-alcoholic fatty liver disease pathophysiology

Early theories on the pathophysiology of NAFLD and NASH were described as the "two-hit model". "The first hit" is generally defined as the accumulation of lipids such as triglycerides (TGs), free fatty acids (FFAs) and cholesterol in hepatocytes. This increases the sensitivity to injuries caused by "the second hit" in the liver. "The second hit" includes inflammation, mitochondrial dysfunction and oxidative stress [12]. Recently, this "two-hit model" hypothesis has turned into "the three-hit" and "the multiple-hit" hypotheses. It has been suggested that defective hepatocyte regeneration is "the third-hit" in the development of NAFLD. Insulin resistance, lipotoxicity, secreting inflammatory mediators from adipose tissues, nutritional status, fatty acids, intestinal microbiota, genetic and epigenetic factors are "the multiple hit" contributing to the prognosis of NAFLD and fibrosis [13].

4. Overview of polyphenols

Phenolic compounds are described as secondary metabolites that are found abundantly in fruits and vegetables as well as coffee, tea, red wine, and dark chocolate [8,14,15]. Phenolic compounds commonly referred to as polyphenols are described according to their chemical structures: flavonoids and non-flavonoids [16].

Flavonoids include 15 carbons (C6–C3–C6) with two aromatic rings connected by a three-carbon bridge. The main sub-groups are flavonols (kaempferol, quercetin, isorhamnetin, and myricetin) abundant in onions and broccoli, flavones (luteolin, apigenin, nobiletin and tangeretin) predominantly in celery, parsley and some herbs, flavan-3-ols (e.g. (+)-catechin, (−)-epicatechin, epigallocatechin) predominantly in cocoa and green tea, flavanones (e.g. naringenin and hesperidin) almost exclusively found in citrus fruits (such as orange and grapefruit), isoflavones (e.g. genistein and daidzein) generally in leguminous plants, soybeans and soy products and anthocyanidins (pelargonidin, cyanidin, delphinidin, peonidin, petunidin, and malvidin) found in berry and cherry fruits and red wine, whereas minor flavonoids are flavan-3,4-diols, dihydroflavonols, chalcones, dihydrochalcones, coumarins and aurones (Fig. 1) [9,11,14,17].

Non-flavonoids include two sub-groups: phenolic acids and stilbenes. Phenolic acids comprise hydroxybenzoic acids (C6–C1) and hydroxycinnamic acids (C6–C3). Hydroxybenzoic acids (e.g. gallic acid, ellagitannins) are found in a diversity of foods such as pomegranate, strawberry, raspberries, blackberries, walnuts, and hazelnuts. Hydroxycinnamic acids (e.g. chlorogenic acids such as tartaric acid or quinic acid) abundant in coffee beans, red and white wines. Stilbenes include 14 carbons (C6–C2–C6), and resveratrol (almost exclusively found in red wines) is the main stilbene (Fig. 1) [9,11,17].

According to the literature, polyphenols have therapeutic effects including antioxidant, anti-inflammatory, anti-tumor, ameliorating lipid, carbohydrate and amino acid metabolism, inhibiting platelet aggregation and improving endothelin function [15,18,19]. Therefore, it is important to determine their effect on NAFLD by their potential mechanisms.

5. Preclinical studies

Preclinical studies evaluating the effects of different polyphenols on NAFLD are quite common in various animal models. Animal models of the studies are generally divided by cause into three main categories: (a) nutritional or pharmacological supplementation, (b) genetic mutation, or (c) a combination of both. Generally, to mimic NAFLD and NASH models in humans, different diet models containing high fat or sugar (cholesterol, fructose, sucrose, Western, Atherogenic, cafeteria, AIN-93G) have been used, which has identified obesity and insulin resistance as issues of concern in preclinical studies (Table 1).

5.1. Antioxidant effects of non-alcoholic fatty liver disease progression

Fat accumulation in the liver causes an increase in lipotoxicity from high levels of FFAs, free cholesterol and other lipid metabolites. Therefore, oxidative stress occurs, and reactive oxygen species increase along with endoplasmic reticulum stress-related mechanism and mitochondrial dysfunction being activated [13]. In this manner, an increase in free radicals and lipid peroxidation products along with reduced antioxidants have been found in animal models and NAFLD patients.

Nuclear factor-erythroid 2-related factor 2 (nrf-2) is the fundamental transcription factor that maintains the cellular reduction and oxidation (redox) status. It has been reported that various polyphenols can activate nrf2 and related genes (heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase (NQO1), glutamate-cysteine ligase catalytic (GCLC)) which in turn enhance the antioxidant defense enzymes that lead to a reduction in oxidative stress. For example, increased nrf-2 levels and related genes (HO-1, NQO1, GCLC) were observed in CCl_4-induced rats with oral administration of 95% methanol extract of dried *Periploca hydaspidis* (200 or 400 mg/kg body weight *(bw)*/three times a week for 4 weeks) regardless of dose [20] and chlorogenic acid supplementation with gavage (15, 30, or 60 mg/kg *bw*/d for 7 days) enhanced nrf-2 protein expression, depending on the dose [21]. Similarly, polyphenols isolated from dried *Coreopsis tinctoria* buds (150 or 600 mg/kg *bw*/d for 7 days, intragastrically) enhanced nrf-2 mRNA levels. Higher doses were observed to be more effective in D-galactosamine (D-GalN)/lipopolysaccharide (LPS) induced mice [22]. Hydroxytyrosol supplementation with 5 mg/d in mice fed with a high-fat diet (HFD) for 12 weeks increased nrf-2 mRNA levels [23]. In another study, after 12 weeks of administration of polyphenol extract of *Ampelopsis grossedentata* (200 or 400 mg/kg *bw*/d) with a gastric gavage, showed an increase in nrf-2 protein expression and HO-1 levels in low-density lipoprotein (LDL)r−/− mice fed with HFD [24].

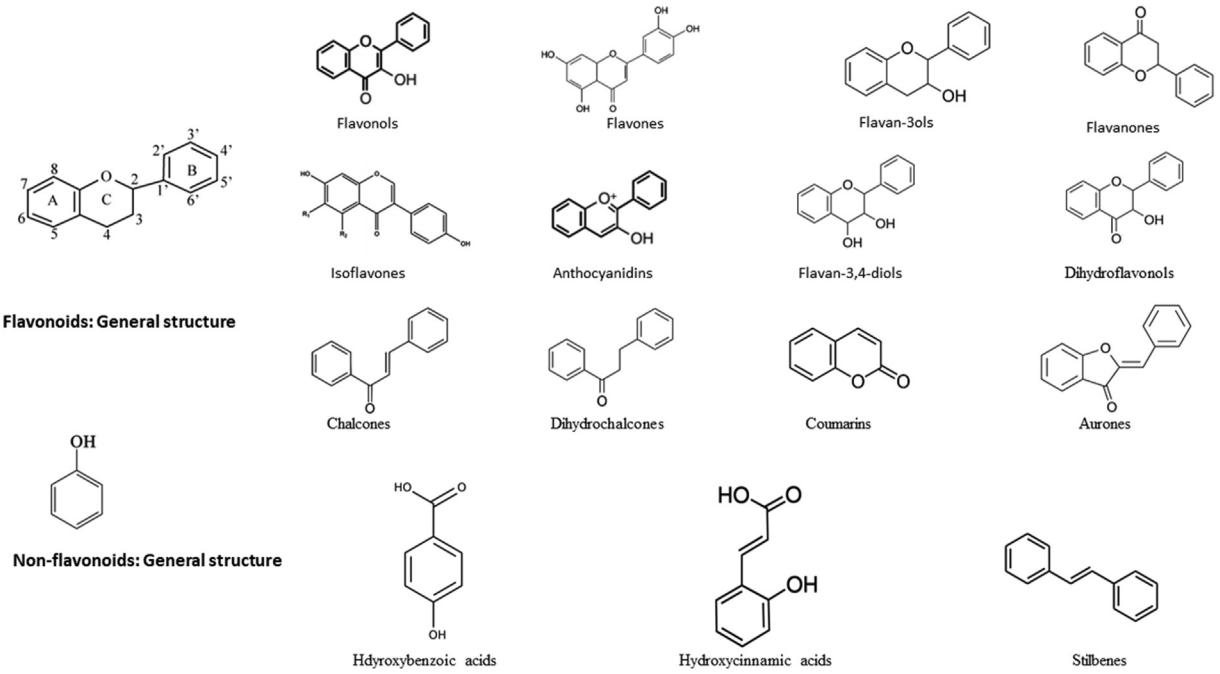

Fig. 1. Chemical structure of polyphenols.

Additionally, orally administered doses of 25, 50, or 100 μg/mL/d polyphenol extract of *Polygonum multiflorum thunb.*, increased nrf-2 and HO-1 mRNA levels within larval zebrafish fed high cholesterol diet for 10 days related to the doses [6].

Moreover, the antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) peroxidase (GpX), etc.) increased depending on the different polyphenols supplementation utilized [6,20–22,24–41].

5.2. Anti-inflammatory effects of non-alcoholic fatty liver disease progression

According to NAFLD pathophysiology, lipotoxicity, insulin resistance, and other factors (such as endotoxins and genetics) activate the pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-6 (IL-6), resistin, etc). Inflammation is especially the predominant factor of the progression from steatosis to NASH [12]. Also, TNF-α with its receptor inhibits insulin receptors and activates nuclear factor kappa B (NF-κB) transcription factor [24].

Intraperitoneal administration of 200 or 400 mg/kg *bw*/d of 70% ethanol extract of *Malva sylvestris* decreased TNF-α levels in rats with nephrotoxicity induced by gentamicin with 400 mg/kg dose being more effective [42]. The doses of 50 or 150 mg/kg *bw*/d of procyanidin B2 with oral gavage for 10 weeks decreased TNF-α and IL-6 levels in mice fed with HFD [41]. Also, oral administration of 0.5%, 1%, or 2% of the total energy of aqueous extract of dried *Morus alba* leaves for 14 weeks caused a reduction in IL-6 and TNF-α levels in rats fed with HFD at similar rates [39]. TNF-α and IL-6 levels were reduced after the 5 g/L of 95% ethanol extract of *Vaccinium* spp. after 18 weeks in mice fed with HFD [43]. In another study, reduced IL-6 level was observed after 12 weeks in obese diabetic (db/db) male mice due to 100 g/d of non-anthocyanin phenolics isolated from the dried powder of *Prunus avium* L. supplementation [40]. Oral administration of *Myrciaria jaboticaba* berry peel (4% of *bw*, for 10 weeks) reduced IL-6, TNF-α, and IL-1β levels in mice fed with HFD [38]. Also, pro-IL-1β and IL-1β, TNF-α, IL-6 were decreased with the chlorogenic acid supplementation (60 mg/kg *bw*/d) after 7 days in CCl_4 induced rats [21]. The dose of 6 g/kg *bw*/d of decaffeinated coffee supplementation decreased IL-6 and IL-1β levels in mice fed with a high fat + high cholesterol + high fructose diet for 6 weeks [44]. Resveratrol supplementation (50 or 100 mg/kg *bw*/d for 6 weeks, intragastrically) showed the same results and decreased TNF-α, IL-1β, and IL-6 levels in rats fed with HFD regardless of dose [45]. Similarly, polyphenol extract of *P. multiflorum thunb.* (25, 50, or 100 μg/mL/d, oral, 10 days) reduced IL-6, IL-1β, and TNF-α levels in larval zebrafish fed with high cholesterol diet depending on dose [6]. Administration of doses of 200 or 400 mg/kg *bw*/d of polyphenol extract of *A. grossedentata* with gastric gavage showed antioxidant effects with the reduction of TNF-α, IL-6, and NF-κB levels in LDLr−/− mice fed with HFD after 12 weeks with the dose of 400 mg/kg being more effective [24]. Reduced IL-1α levels were observed after oleuropein supplementation with 0.03% of *bw* after 8 weeks in mice fed with HFD [26]. Orally administrated doses of 200 or 400 mg/kg *bw*/three times a week of 95% methanol extract from dried *P. hydaspidis*, reduced TNF-α, transforming growth factor-beta 1 (TGF-β1), and resistin levels in CC_4 induced rats for 4 weeks depending on dose [20].

Bcl-2 and bax are proteins modulating apoptosis. When the ratio of bcl-2/bax protein expression decreases, cells are more likely to undergo apoptosis. Intragastrically procyanidin B2 with a dose of 30 mg/kg *bw*/d reduced IL-6 levels and bcl-2/bax ratio in rats with alpha-toxin-induced liver damage after 7 days [28].

Inhibitor kappa B kinase-β (IKKβ) is an essential kinase of NF-κB which activates the NF-κB and IκB protein causing the secretion and expression of inflammatory factors to increase [6]. Cyclooxygenase-2 (COX-2) is an important inflammatory marker that can be activated by IL-1β and TNF-α [31]. A study showed that the supplementation of kiwifruit seed oil (1 or 3 mL/kg *bw*/d for 12 weeks) reduces TNF-α, IL-6, IL-1β, and COX-2 levels in mice fed with HFD related to the doses [31].

Table 1
Summary of preclinical studies.

Polyphenol/extract	Animal model	Administration dose, route and period	Effects	References
Polyphenol extract of *Polygonum multiflorum thunb.*	Larval zebrafish fed a high cholesterol diet (5%) or normal cholesterol diet (n = 150)	25, 50, or 100 μg/mL/d, oral, 10 days	Reduce TC, TG, ROS, MDA, NEFA, FASN, IKKβ, IL-6, IL-1β, TNF-α, SREBP1c; increase SOD, CPT1α, nrf2, HO-1, PPAR-α	[6]
95% methanol extract of dried *Periploca hydaspidis*	Male Sprague–Dawley rats with CCl_4 induced or control (n = 56)	200 or 400 mg/kg *bw*/three times a week, oral, 4 weeks	Reduce AST, ALT, ALP, LDL, TG, TC, TNF-α, TGF-β1, and resistin; increase SOD, CAT, peroxidase, IL-10, nrf2, adiponectin	[20]
Chlorogenic acid	Male Sprague–Dawley rats with CCl_4 induced (n = 18)	15, 30, or 60 mg/kg *bw*/d, gavage, 7 days	Reduce MDA, pro-caspase-1, caspase-1, pro-IL-1β and IL-1β TNF-α, IL-6; increase nrf2-related anti-oxidant genes (HO-1, NQO1, GCLC), nfr2 gene, GSH, SOD, CAT	[21]
Polyphenols isolated from dried *Coreopsis tinctoria* buds	Male Kunming mice with D-GalN/LPS induced or control (n = 45)	150 or 600 mg/kg *bw*/d, intragastrically, 7 days	Reduce liver injury, AST, ALT; increase nrf2, SOD, CAT, GSH	[22]
Hydroxytyrosol	Male C57BL/6J mice fed with HFD (60% fat, 20% protein, and 20% carbohydrate, with a caloric value of 5.24 kcal/g) or normal diet (10% fat, 20% protein, and 70% carbohydrate, with a caloric value of 3.85 kcal/g) (n = 40)	5 mg/d, gavage, 12 weeks	Reduce WAT, NF-κB, SREBP 1c, PPAR-γ; increase nrf2	[23]
Polyphenol extract of *Ampelopsis grossedentata*	Male LDLr−/− mice fed with HFD (21% fat and 0.21% cholesterol) (n = 40)	200 or 400 mg/kg *bw*/d, gastric gavage, 12 weeks	Reduce steatosis, inflammation and fibrosis, NF-kB, TG, TC, AST, ALT, MDA, TNF-α, IL-6, p65, SREBP-1c, C/EBPα, C/EBPβ; increase AMPKα1, AMPKα2, SIRT1, SOD, CAT GpX, liver kinase B1, CPT, Nrf2, HO-1	[24]
Anthocyanin extract of lyophilized *Zea mays* L. powder	Wistar Kyoto rats fed with HFD (60% energy from fat) or normal diet (13.2% energy from fat) (n = 15)	2.3 g/d, 8 weeks	Reduce AST, ALT, MDA, steatosis, SOD1 gene	[25]
Oleuropein	C57BL/6J mice fed with HFD (15.2% protein, 42.7% carbohydrate, 42.0% fat) or normal diet (24.0% protein, 58.0% carbohydrate, 18.0% fat) (n = 32)	0.03%, oral gavage, 8 weeks	Reduce steatosis (especially female mice), body, liver and hearth weights, AST, ALT, TG, IL-1α; increase HDL, SIRT1, SOD2 activity	[26]
70% ethanol extract of *Vaccinium corymbosum* L. leaves	Male Sprague–Dawley rats fed with HFD (15% lard (w/w), 2% cholesterol, 0.5% bile salt, and 5% yolk powder added a normal diet) or normal diet (n = 24)	100 or 400 mg/kg *bw*/d, oral gavage, 9 weeks	Reduce liver weight, AST, ALT, TC, TG, LDL, steatosis, MDA, MMP; increase SOD2 and AMPK/PGC-1α/SIRT3 pathway	[27]
Procyanidin B2	Sprague–Dawley rats with alpha-toxin-induced liver damage (n = 40)	30 mg/kg *bw*/d, intragastrically, 7 days	Reduce liver damage, ALT, AST, ALP, MDA, IL-6; increase CAT, GSH, SOD, bcl-2/bax ratio	[28]
Walnut green husk polysaccharide	Kunming male mice fed with HFD or high sucrose (n = 40)	200,400, or 800 mg/kg *bw*/d, intragastrically, 8 weeks	Reduce steatosis, liver weight, insulin resistance, plasma insulin, MDA, TG, TC, LDL, AST, ALT levels; increase SOD, GPx	[29]
Methanol extract of *Erica multiflora* leaf	Triton WR-1339-induced hyperlipidemic rats fed with commercial pellet diet and water ad libitum (n = 36)	150 or 250 mg/kg *bw*/d, intragastrically, a single dose	Reduce TG, TC, LDL, VLDL, AST, ALT, NO, MDA; increase SOD, CAT, GPx	[30]
Kiwifruit seed oil	C57BL/6 mice fed with HFD or normal diet (n = 40)	1 or 3 mL/kg *bw*/d, oral, 12 weeks	Reduce serum glucose, LDL, inguinal fat tissue, body weight, TG, TC, TNF-α, IL-6, IL-1β, COX-2, nitric oxide synthase, HOMA-IR, PPAR-γ; increase PGC1-α, PPAR-α, CAT, SOD, GPx	[31]
50% methanol extract of dried *Argyreia speciosa* seeds	Wistar rats with CCl_4 induced or normal (n = 30)	50 or 100 mg/kg *bw*/d, oral, 24 h	Reduce lipid peroxidation; increase SOD, GSH, CAT	[32]
80% ethanol extract of dried powder of *Cyclocarya paliurus* leaves	Female ICR mice were received 15 mL/kg *bw*/d distilled water or high-fat water (n = 60)	50, 300, and 600 mg/kg *bw*/d, intragastrically, 28 days	Reduce TG, TC, LDL in plasma and liver, lipid peroxidation, MDA; increase SOD, total antioxidant capability, GpX, HDL	[33]

Table 1 (*continued*)

Polyphenol/extract	Animal model	Administration dose, route and period	Effects	References
Cynara scolymus L.	Rats with CCl_4 induced (n = 72)	500 or 900 mg/kg *bw*/d, oral, 1 month	Reduce AST, ALT, ALP, MDA TG, TC, LDL; increase GSH	[34]
Aloe barbadensis Miller gel	Male Wistar rats fed with cafeteria diet (23% protein, 35% carbohydrate, and 42% fat) or normal diet (25% protein, 65% carbohydrate, and 10% fat) (n = 48)	100 or 200 mg/kg *bw*/d, oral, 8 weeks	Reduce body weight, MDA, PCAR, LPL, serum glucose, LDL, TG, TC; increase GSH	[35]
Aqueous extract of dried *Citrus maxima* leaves	Wistar rats fed with HFD and fructose (45% fructose) or normal diet (n = 24)	50 mg/kg *bw*/d, gavage, 45 days	Reduce lipid accumulation in hepatocytes, TG, TC, LDL, AST, ALT, MDA; increase adiponectin, GSH	[36]
Spirulina platensis fortified functional soy yogurts	Balb/c male mice fed with AIN-93G diet (1.25% cholesterol + 0.5% cholic acid) or normal diet (n = 36)	0.5, 1, or 1.5 g/100 g yogurt, oral, 8 weeks	Reduce steatosis, TC, TG, VLDL, LDL, MDA, AST, ALT, ALP, alkaline phosphatase, GGT and thiobarbituric acid; increase SOD, GSH, CAT	[37]
Myrciaria jaboticaba berry peel	Male Swiss mice fed with HFD (26.29% corn starch, 9.57% maltodextrin, 5.65% sucrose, 31% lard) or normal diet (44.56% corn starch, 14.83% maltodextrin, 9.57% sucrose, 3.73% cellulose, 4% MJP-composed of 1.27% insoluble fiber) (n = 40)	4% of *bw*, oral, 10 weeks	Reduce lipid accumulation, body weight, IL-6, TNF-α, IL-1β, AST, ALT, TG, TC, TBARS; increase SOD, CAT; GSH, GPx	[38]
Aqueous extract of dried *Morus alba* leaves	Wistar rats fed with HFD (normal diet supplemented 2% cholesterol and 20% lard oil) or normal diet (n = 40)	0.5%, 1%, or 2% of total energy, oral, 14 weeks	Reduce TG, TC, LDL, AST, ALT, lipid accumulation, FASN, HMGCoA, IL-6, TNF-α, leptin; increase CPT-1, SOD, adiponectin, PPAR-α	[39]
Non-anthocyanin phenolics isolated from the dried powder of *Prunus avium* L.	Obese diabetic (db/db) male mice (n = 30) lean mice (n = 10) fed with normal diet	100 g/d, oral, 12 weeks	Reduce lipid accumulation in hepatocytes, IL-6, FBG, TG, LDL, leptin; increase, CAT	[40]
Procyanidin B2	C57BL/6J mice fed with HFD or normal diet (n = 48)	50 or 150 mg/kg *bw*/d, oral gavage, 10 weeks	Reduce steatosis, PPAR-γ, C/EBPα, SREBP1-c, IL-6, TNF-α, TG, TC, leptin; increase GPx, SOD, CAT, adiponectin	[41]
70% ethanol extract of *Malva sylvestris*	Male Wistar rats fed with nephrotoxicity induced by gentamicin (n = 42)	200 or 400 mg/kg *bw*/d, intraperitoneally, 9 days	Reduce liver injury, MDA, AST, ALP, ALT, TNF-α	[42]
95% ethanol extract of *Vaccinium* spp.	Male C57BL/6J mice fed with HFD (60% fat) or normal diet (10% fat) (n = 16)	5 g/L of water, oral, 18 weeks	Reduce iWAT, eWAT, body and liver weights, TG, steatosis, AST, ALT, TNF-α, IL-6, SREBP-1c, PPARγ1, PPARγ2, FASN; increase CPT-1, PPAR-α, and ACS	[43]
Decaffeinated coffee	Female C57BL/6J mice fed with HFD + high cholesterol + high fructose (60% carbohydrate, 25% fat, 15% protein with 50% wt/wt fructose and 0.16% wt/wt cholesterol) or normal diet (n = 18)	6 g/kg *bw*/d, oral, 6 weeks	Reduce liver injury, lipid accumulation, IL-6, IL-1β, FBG, XBP1, NO-synthase protein levels and 3-nitrotyrosine protein; increase zonula occludens-1	[44]
Resveratrol	Male Sprague–Dawley rats fed with HFD (45% fat, 35% carbohydrate, 20% protein) or normal diet (10% fat, 70% carbohydrate, 20% protein) (n = 24)	50 or 100 mg/kg *bw*/d, intragastrically, 6 weeks	Reduce steatosis, fibrosis, body weight, liver index, hepatic lipid accumulation and inflammation, TNF-α, IL-1β, IL-6, FBG	[45]
Bound phenolics extracted from lotus seeds	ICR male mice fed with HFD (protein, 43.1% carbohydrate, and 18.4% fat) or normal diet (22.3% protein, 60.6% carbohydrate, and 4.0% fat) (n = 24)	400 mg/kg *bw*/d, oral gavage, 6 weeks	Reduce TG, TC, LDL, PPARγ, C/EBPα, SREBP-1c, FASN, LPL; increase HSL, PGC-1α, SIRT-1, CPT1α	[46]
70% ethanol extract of lyophilized *Valeriana fauriei*	Male C57BL/6J mice fed with HFD (45% fat and 0.5% cholesterol) or normal diet (n = 18)	125 or 250 mg/kg *bw*/d, oral, 8 weeks	Reduce TG, TC, lipid accumulation in hepatocytes, SCD1, and SREBP1c genes, mTORC1 activity; increase the number of autophagosome in hepatocytes	[47]

(*continued on next page*)

Table 1 (*continued*)

Polyphenol/extract	Animal model	Administration dose, route and period	Effects	References
Tannic acid	Male C57BL/6J mice fed with Western diet or normal diet (n = 38)	1% or 3% of *bw*, oral, 12 weeks	Reduce HAT activity, body weight, lipid accumulation in hepatocytes, AST, ALT, FASN, SREBP-1c, PPARγ mRNAs, TG, TC, LDL	[48]
Oxyresveratrol isolated from *Morus alba* L.	C57BL/6J male mice fed with HFD (60% of fat) or normal diet (n = 40)	10 or 30 mg/kg *bw*/d, oral, 4 weeks	Reduce steatosis, lipid accumulation in hepatocytes, FBG, TG, TC, LDL, SREBP-1c, LXR-α; increase AMPK activation	[49]
Musa sp.	C57BL/6J male mice fed with HFD (14% protein, 47% fat, 39% carbohydrate, total energy 22.2 kJ/g) or normal diet (14% protein, 9% fat, 77% carbohydrate, total energy 15.9 kJ/g) (n = 40)	15% of total energy, oral, 4 weeks	Reduce steatosis, TG in the liver, FASN; increase AMPKp/AMPK, HMG-CoA	[50]
Dieckol-enriched extraction from *Laminaria japonica*	Specific pathogen free male ICR mice fed with HFD (g/100 g; 23.5 fish meal, 57.8 corn flour, 3.0 wheat bran, 3.5 mineral mix, 1.0 vitamin mix, 10.0 lard oil, 1.0 cholesterol, 0.2 bile salts) or normal diet (g/100 g; 23.5 fish meal, 68,5 corn flour, 3.5 wheat bran, 3.5 mineral mix, 1.0 vitamin mix) (n = 20)	50 mg/kg *bw*/d, intragastrically, 4 weeks	Reduce steatosis, body weight gain, liver index, visceral fat index, TG, TC, LDL; increase PPAR-α, AMPK	[51]
Curcumin	Male C57BL/6J mice fed with HFD (high-fat diet and high fructose (30%)) or normal diet (n = 30)	50 or 100 mg/kg *bw*/d, oral gavage, 4 weeks	Reduce steatosis, TG, TC, NEFA, ALT, SREBP-1c, FASN, LXRα	[52]
Aqueous extract of *Coffea arabica* pulp	HFD-induced hypercholesterolemic rats fed with HFD (57.60% fat and 1.68% cholesterol) or normal diet (19.77% fat) (n = 25)	1000 mg/kg *bw*/d, oral gavage, 12 weeks	Reduce NPC1L1 membrane protein expression, body weight, LXR-α mRNA	[53]
Quercetin	Male Sprague–Dawley rats fed with HFD or normal diet (n = 40)	100 mg/kg *bw*/d, 8 weeks	Reduce TG, TC, VLDL, p62, IRE1α; increase XBP1, HDL	[54]
Cyanidin-3-glucoside	Male C57BL/6J mice fed with HFD (4.7 kcal/g, 25% fructose, and 25% lard) or normal diet (3.2 kcal/g, 4.5% fat) (n = 36)	1 mg/mL, oral, 12 weeks	Reduce steatosis, body weight, the size of the lipid droplets of BAT, iWAT and eWAT, TG, LDL, glucose; increase energy expenditure and thermogenic capacity of BAT, PGC1α, PGC1β, CPT1α, PPARα and HSL genes	[56]
100% methanol extract of *Rhamnus alaternus* leaves	Rats with hyperlipidemic or normal (n = 24)	200 or 400 mg/kg *bw*/d, oral gavage, 24 h	Reduce TG, TC; increase gene expression of CPT-1	[57]
Ethanol extract of *Zingiber officinale* Roscoe	Male Golden Syrian hamsters fed with HFD (standard chow + 3% cholesterol, and 15% butter) or normal diet (n = 21)	800 μg/kg *bw*/d, gavage, 5 weeks	Reduce NEFA, SCD1, TBARS, TG, TC; increase PON-1	[58]
Adansonia digitata fruit	Male Albino Wistar rats fed with high sucrose/HFD (2% cholesterol, 1% cholic acid, 10% of peanut oil, 40% of sucrose and 47% of standard laboratory diet) or normal diet (n = 42)	200, 400, or 800 mg/kg *bw*/d, intragastrically, 6 weeks	Reduce dyslipidemia, hyperglycemia, body and liver weights, creatinine, urea, LDL, TC, TG, FBG, AST, ALT, ALP, lesions in liver, kidney and heart; increase HDL	[60]
Gallic acid	Swiss male mice fed with HFD (24.55% carbohydrate, 14.47% protein, and 60.98% fat) or normal diet (54% carbohydrate, 26% protein, and 8% fat) (n = 24)	100 mg/kg *bw*/d, oral, 8 weeks	Reduce TC, steatosis, body and liver weights, plasma insulin, FBG, and FASN mRNA	[61]
Calyces of the flower of *Hibiscus sabdariffa* L.	Wistar rats fed with HFD and high fructose (20% lard, 18% fructose) (n = 32)	10.1 g or 6.2 g/100 g HFD, oral, 18 weeks	Reduce steatosis, TG in hepatocytes, body weight, FBG, insulin, HOMA-IR; increase GLP-1	[62]

Table 1 (*continued*)

Polyphenol/extract	Animal model	Administration dose, route and period	Effects	References
70% ethanol extract of peanut skin	C57BL/6 mice fed with Atherogenic (20.8% protein, 15.5% fat, 3.1% fiber, 45.6% carbohydrates, and 4.05 kcal/g of metabolizable energy with 1.25% cholesterol, 0.125% choline chloride, 7.5% cocoa butter fat, 2.5% glucose, and 1.625% sucrose) or normal diet (23.9% protein, 5.0% fat, 5.1% fiber, 48.7% carbohydrate, and 2.89 kcal/g of metabolizable energy) (n = 30)	0.78% of *bw*, oral, 16 weeks	Reduce body weight, FBG, hepatic glycogen, hepatic TC and lipid	[63]
Annatto-extracted tocotrienols and green tea polyphenols	Male C57BL/6J mice fed with HFD (20% carbohydrate, 22% protein, and 58% fat) (n = 48)	400 mg/kg *bw*/d tocotrienols or 0.5% (wt/vol) of green tea polyphenols, oral, 14 weeks	Reduce body weight (green tea), FBG (green tea), MDA (both); increase citrate synthase (both)	[64]
95% ethanol extract of dried *Morus alba* L. leaves	Female Wistar rats fed with a high cholesterol diet (17.48% protein, 6.85% fat, 10% cholesterol, 52.99% carbohydrate, 4.08% ash, and 2.16% minerals and vitamins) or normal diet (17.48% protein, 6.85% fat, 62.99% carbohydrate, 4.08% ash, and 2.16% minerals and vitamins) (n = 18)	100 mg/kg *bw*/d, gastric intubation, 8 weeks	Reduce body weight, TG, TC, atherogenic index, coronary artery indices, insulin resistance index, glucose, serum leptin; increase serum adiponectin level, and its mRNA expression in visceral adipose tissue	[65]
Silymarin isolated from *Silybum marianum*	Male Sprague–Dawley rats fed with HFD (5% beef tallow and 65% Laboratory rodent diet 5001, and total calorie 5.53 kcal/g) or normal diet (56.0% carbohydrate, 23.0% crude protein, 8.0% ash, 6.0% crude fiber, 4.5% crude fat, and 2.5% added minerals) (n = 54)	100, 200, or 400 mg/kg *bw*/d, oral, 8 weeks	Reduce lipid accumulation in hepatocytes, insulin resistance, HOMA-IR, serum glucose, insulin; increase SIRT-1	[66]
Sinapic acid and resveratrol	Male Wistar rats fed with HFD or normal diet (n = 30)	200 mg/kg *bw*/d sinapic acid, 400 mg/kg *bw*/d resveratrol	Reduce serum glucose (resveratrol), HOMA-IR (resveratrol), TG (sinapic acid), NEFA (sinapic acid), ROS activity in plasma and liver (sinapic acid), MDA (both); increase HDL (resveratrol)	[67]
Catalpol and stachyose are isolated from *Rehmanniae Radix*	Male Diabet C57BL/6J mice with streptozotocin-induced (n = 80)	Catalpol:stachyose (1:1, 1:2, 2:1), gavage, 6 weeks	Reduce body weight, blood glucose, kidney weight and liver weight index, TG, TC, ALT, total bile acid, urinary creatinine	[68]
Dry methanol extract of *Eclipta prostrata*	Albino rats fed with HFD (normal diet + cholesterol and cholic acid) or normal diet (n = 84)	50, 100, 200, or 300 mg/kg *bw*/d, oral, 8 weeks	Reduce TG, TC, LDL, AST, ALT; increase HDL	[69]
Dried *Salvia officinalis* L. essential oil leaves	Male Wistar rats with alloxan-induced or normal (n = 30)	2.5 μL/d, gavage, 1 month	Reduce serum α-amylase, lipase, serum glucose, the level of glycogen stored in the liver, AST, ALT	[70]
LC-PUFA (n-3) and flavan-3-ols (cocoa flavanol)	Male C57BL/6J mice fed with high fat/high fructose diet or normal diet (n = 50)	60, 7, 400, and 280 mg/kg *bw* of (−)-epicatechin, (+)-catechin, EPA and DHA, oral, 16 weeks	Reduce steatosis (n-3 and flavan-3ol combination), body and adipose tissue weights (flavan-3ol), serum insulin (flavan-3ol), SREBP-1c (n-3)	[71]
Trans-cinnamic acid	Male C57BL/6J mice fed with HFD (5.28 kcal per 1 g of a diet composed 35.2% of carbohydrate, 19.8% of protein, and 45.0% of fat) or normal diet (2.18 kcal per 1 g of a diet composed 60.6% carbohydrate, 22.3% protein, and 4.0% fat) (n = 18)	40 mg/kg *bw*/d, oral gavage, 17 weeks	Reduce TC, TG, LDL in plasma, body, liver and adipose tissue weights, hepatic steatosis and adipose hypertrophy	[72]
Polyphenol extract of *Scutellariae baicalensis*	Male C57BL/6J mice fed with HFD (60% fat) or normal diet (10% fat) (n = 40)	400 mg/kg *bw*/d, oral gavage, 12 weeks	Reduce TG, AST, ALT, cathepsin B release	[73]

(*continued on next page*)

Table 1 (*continued*)

Polyphenol/extract	Animal model	Administration dose, route and period	Effects	References
Theaphenon E, a standardized formulation of green tea extract	C57BL/6J mice fed with HFD (61.3% kcal fat, 18.4% kcal protein, and 20.3% kcal carbohydrate) or low-fat diet (10.5% kcal fat, 18.9% kcal protein, and 70.6% kcal carbohydrate) (n = 105)	2% of *bw*, oral, 35 weeks	Reduce lipid accumulation, ALT, AST, body and liver weights; increase DNA fragmentation marker	[74]
Green rooibos extract	Male Wistar rats fed with HFD (Holsum, 750 g), sucrose (sweetened condensed milk, Nestle™, 790 g), fructose (100 g, Merck) and cholesterol (10 g) or normal diet (n = 28)	60 mg/kg *bw*/d, intraperitoneally, 6 weeks	Reduce body and liver weights and steatosis	[75]
Freeze-dried apple pomace	Female Sprague–Dawley rats fed with Western Diet (45% fat, 33% sucrose by kcals) or normal diet (n = 32)	10% of *bw*, oral, 8 weeks	Reduce hepatic histological evidence of inflammation; increase total serum antioxidants	[76]
70% ethanol extract of freeze-dried *Fenugreek*	Female Wistar rats fed with HFD (Lard-2 kg, Sucrose-1/2 kg, Normal pellet (powdered)-11/2 kg, Casein-1/2 kg, Cholesterol-125 g, Cholic acid-2 g, Vitamin-50 ml, and DL-methionine-50 g) or normal diet (n = 30)	200, 300 or 400 mg/kg *bw*/d, oral, 12 weeks	Reduce TG, TC, LDL, AST, ALT; increase HDL	[77]
The pulp of *Litchi chinensis*	Male Wistar rats high sucrose (40% sucrose) or normal diet (n = 20)	40% p/v, oral, 5 weeks	Reduce TG, TC, adipose tissue weight; increase HDL	[78]
Aqueous extract of *Parkia biglobosa* seed	Wistar rats with diabetes (n = 30)	200,400, or 800 mg/kg *bw*/d, oral, 14 days	Reduce AST, ALT, ALP; ameliorate histological changes in hepatocytes	[79]
Foeniculum vulgare seed powder	Male lambs fed with normal diet (n = 15)	0.75% or 1.5% of total energy, oral, 80 days	Reduce liver weight, serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase in liver	[80]
Resveratrol	Male rabbits fed with HFD (10% groundnut oil, 20% groundnut meal, and 2% cholesterol) or normal diet (n = 30)	200 or 400 mg/kg *bw*/d, oral, 8 weeks	Reduce body weight	[81]

ACS, acetyl-coenzyme A synthetase; CCl_4, carbon tetrachloride; D-GalN, D-galactosamine; LPS, lipopolysaccharide; HFD, high-fat diet; LDL, low-density lipoprotein; TC, total cholesterol; TG, total triglycerides; VLDL, very low density lipoprotein; ROS, reactive oxygen species; MDA, malondialdehyde; NEFA, nonesterified fatty acids; FASN, fatty acid synthase; IKKβ, inhibitor kappa B kinase-β; IL-6, interleukin-6; IL-1β, interleukin-1β; IL-10, interleukin-10; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor-α; TGF-β1, transforming growth factor-beta 1; SREBP1c, sterol regulatory element-binding protein 1c; SOD, superoxide dismutase; CAT, catalase; GSH, glutathione; GpX, glutathione peroxidase; CPT1α, carnitine palmitoyltransferase-1α; nrf2, nuclear factor-erythroid 2-related factor 2; HO-1, heme oxygenase-1; NQO1, NAD(P)H quinone dehydrogenase; GCLC, glutamate-cysteine ligase catalytic; PPAR-α, peroxisome proliferator-activated receptor- α; PPAR-γ, peroxisome proliferator-activated receptor-γ; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; WAT, white adipose tissue; SIRT-1, sirtuin-1; SIRT-3, sirtuin-3; C/EBPα, CCAAT enhancer-binding proteins α; C/EBPβ, CCAAT enhancer-binding proteins β; AMPK, adenosine monophosphate kinase; AMPKα1, adenosine monophosphate-activated protein kinase α1; AMPKα2, adenosine monophosphate-activated protein kinase α2; MMP, matrix metalloproteinase; MJP, *Myrciaria jaboticaba* berry peel; NO, nitric oxide; COX-2, cyclooxygenase-2; LPL, lipoprotein lipase; TBARS, thiobarbituric acid reactive substance; HMGCoA, 3-hydroxy-3-methylglutaryl-coenzyme A; FBG, fasting blood glucose; XBP1, X-box binding protein 1; mTORC1, mammalian target of rapamycin complex 1; SCD1, stearoyl-CoA desaturase-1; LXR-α, liver X receptor-α; IRE1α, inositol-requiring; transmembrane kinase/endoribonuclease 1α; BAT, brown adipose tissue; PGC1β, peroxisome proliferator-activated receptor gamma coactivator 1 β; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; HSL, hormone sensitive lipase; PON-1, paraoxonase-1; HOMA-IR, homeostatic model assessment for insulin resistance.

5.3. Improvement of insulin sensitivity and β-fatty acid oxidation and de novo lipogenesis reduction

Obesity is characterized by increasing adipose tissue mass which results in an increase in mature adipose cells through adipogenesis and TG accumulation in the cytoplasm. It is reported that peroxisome proliferator-activated receptor-γ (PPAR-γ), CCAAT enhancer-binding proteins α (C/EBPα) gene, and sterol regulatory element-binding protein 1c (SREBP-1c) are the major transcription factors involved in adipocyte differentiation and lipid accumulation [24,46].

Consumption of 70% ethanol extract of lyophilized *Valeriana fauriei* (125 or 250 mg/kg *bw*/d, orally, 8 weeks) reduced the SREBP1c gene in mice fed with HFD [47]. Reduced levels of SREBP-1c, C/EBPα and β were observed after supplementation of polyphenol extract of *A. grossedentata* (200 or 400 mg/kg *bw*/d, gastric gavage, 12 weeks) in LDLr−/− mice fed with HFD [24]. An administration dose of 400 mg/kg *bw*/d of bound phenolics extracted from the lotus seeds with oral gavage for 6 weeks decreased PPARγ, C/EBPα, and SREBP-1c levels in mice fed with HFD [46]. Likewise, a dose of 5 mg/d of hydroxytyrosol supplementation with gavage decreased SREBP 1c and PPAR-γ levels in mice fed with HFD [23]. After 12 weeks of administration of kiwifruit seed oil (1 or 3 mL/kg *bw*/d with oral) decreased PPAR-γ levels [31]. Oral administration of tannic acid (1% or 3% of *bw* for 12 weeks) decreased SREBP-1c and PPAR-γ levels in mice fed with a Western diet [48]. Similarly,

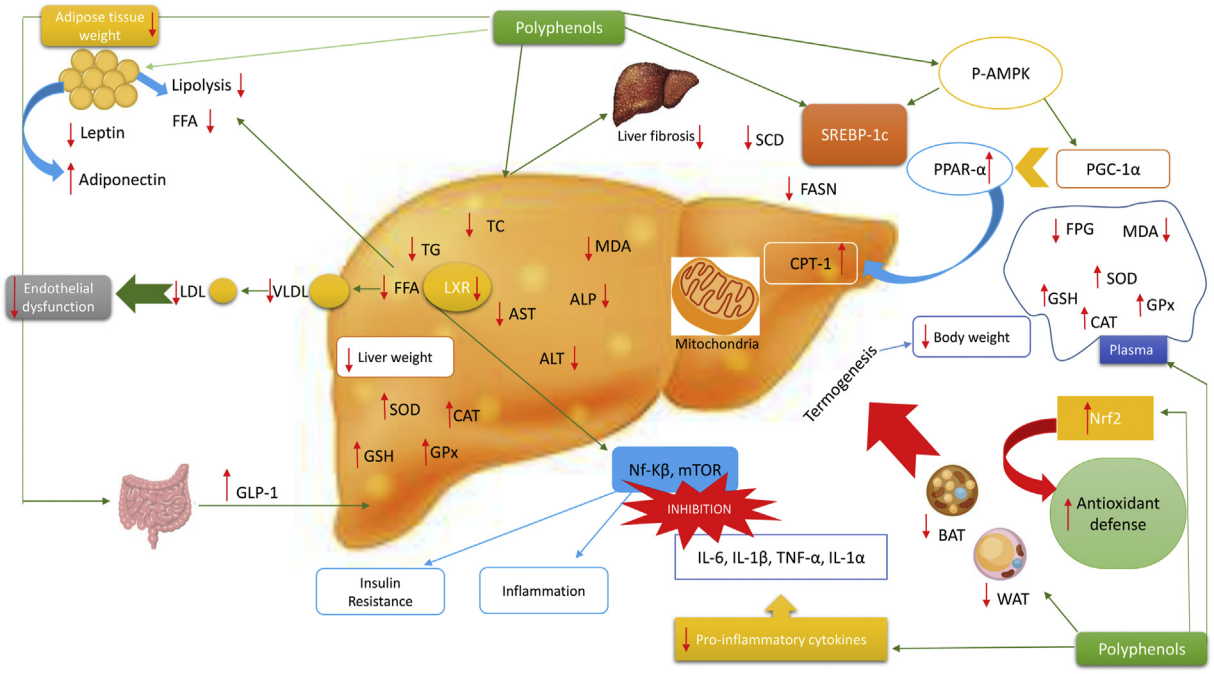

Fig. 2. Possible mechanisms of polyphenols effects on NAFLD according to preclinical studies.

procyanidin B2 supplementation with oral gavage (50 or 150 mg/kg *bw*/d) reduced PPAR-γ, C/EBPα, and SREBP1-c levels in mice fed with HFD after 10 weeks depending on dose [41].

It is well known that adenosine monophosphate kinase (AMPK) inhibits SREBP-1c expression through different paths including phosphorylation, reducing the mammalian target of rapamycin complex (mTORC) activity and liver X receptors (LXR). This leads to a decrease in fatty acid synthase (FASN) expression and lipid synthesis inhibition. Studies suggest that AMPK could be an attractive therapeutic target for NAFLD due to its mechanism [24,27,49–51]. Intragastric administration of 50 mg/kg *bw*/d of dieckol-enriched extract from Laminaria japonica increased AMPK in mice fed with HFD after 4 weeks [51]. Oxyresveratrol isolated from *M. alba* L. (10 or 30 mg/kg *bw*/d, oral, 4 weeks) increased AMPK activation and reduced LXRα levels in mice fed with HFD [49]. The doses of 50 or 100 mg/kg *bw*/d of curcumin reduced SREBP-1c and LXRα in mice fed with HFD after 4 weeks [52]. Oral administration of 15% of the total energy of *Musa* sp. increased AMPKp/AMPK ratio and FASN expression in mice fed with HFD after 4 weeks of supplementation [50]. Increased levels of AMPKα1, AMPKα2, and sirtuin-1 (SIRT-1) activity were observed after polyphenol extract of *A. grossedentata* supplementation (200 or 400 mg/kg *bw*/d, gastric gavage, 12 weeks) in LDLr−/− mice fed with HFD [24].

Peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) and sirtuin-3 (SIRT-3) are known mediators of AMPK which are up-regulated by AMPK phosphorylation. PGC-1α can also co-activated many nuclear receptors including estrogen-related receptor α (ERRα) (an important transducer in mitochondrial biogenesis), nrf1, nrf2, and SIRT-3 can activate antioxidant enzymes. In one study, doses of 100 or 400 mg/kg *bw*/d of 70% ethanol extract of *Vaccinium corymbosum* L. leaves administered by oral gavage, activated AMPK/PGC-1α/SIRT3 pathway in rats fed with HFD for 9 weeks [27].

Downregulated niemann-pick C1-like 1 (NPC1L1) expression can be mediated by increased LXRα mRNA [53]. One study demonstrated that oral gavage administrated in an aqueous extract of coffea arabica pulp with 1000 mg/kg *bw*/d for 12 weeks decreased NPC1L1 membrane protein expression and LXRα mRNA levels [53].

Additionally, inositol-requiring enzyme 1α (IRE1α) is responsible for endoplasmic reticulum stress [54]. The dose of 100 mg/kg *bw*/d of quercetin reduced IRE1α levels in rats fed with HFD after 8 weeks [54].

AMPK inhibits β-fatty acid (FA) oxidation indirectly due to targeting of peroxisome proliferator-activated receptor-α (PPAR-α), carnitine palmitoyltransferase-1α (CPT-1α), acetyl-CoA carboxylase and FA synthetase [55]. Similarly, cyanidin-3-glucoside supplementation of 1 mg/mL administered orally, enhanced PPAR-α levels in mice fed with HFD after 12 weeks [56]. Administered doses of 1 or 3 mL/kg *bw*/d of kiwifruit seed oil supplementation increased PPAR-α levels in mice fed with HFD for 12 weeks [31]. Another study found that 95% ethanol extract of *Vaccinium* spp. (5 g/L, oral for 18 weeks) increase carnitine palmitoyltransferase (CPT-1), PPAR-α, and acetyl-coenzyme A synthetase (ACS) levels in mice fed with HFD [43]. Intragastric administration of 50 mg/kg *bw*/d of dieckol-enriched extraction from *Laminaria japonica* increased PPAR-α in mice fed with HFD after 4 weeks [51]. Similarly, polyphenol extract of *P. multiflorum thunb.* (25, 50, or 100 μg/mL/d, oral, 10 days) increased PPAR-α expression in larval zebrafish fed high cholesterol diet [6].

3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase (HMCoAR) is an important enzyme regulating TG and cholesterol synthesis in addition to being a marker of lipogenesis [39]. Administration doses of 0.5%, 1%, or 2% of the total energy of aqueous extract of dried *M. alba* leaves reduced HMGCoAR and PPAR-α levels in rats fed with HFD for 14 weeks [39]. Another study showed that 15% of the total energy of *Musa* sp. supplementation for 4 weeks increase HMGCoA levels in mice fed with HFD [50]. After 24 h administration of 200 or 400 mg/kg *bw*/d of 100% methanol extract of *Rhamnus alaternus* leaves, led to an increase in CPT-1 in hyperlipidemia rats [57].

Stearoyl-CoA desaturase-1 (SCD1) is an enzyme that catalyzes the rate-limiting step in the formation of monounsaturated fatty acids, specifically oleate and palmitoleate from stearoyl-CoA and

Table 2
Summary of clinical studies.

Subjects	Study design	Polyphenol/extract	Administration dose	Effects	References
Subjects between 50 and 73 years with BMI 24.9 −29.9 kg/m^2 (n = 12)	Received a high-fat reference breakfast meal (RM; 910 kcal, 50% fat) or three isocaloric test meals incorporating CM, BM or LM to the high-fat breakfast	BM, LM and CM	BM and LM 100 g/d, CM 3 g/d	Reduce TAG (BM), TG (BM, LM), TC (BM), glycemic response (CM), postprandial endotoxemia (CM) and CRP (CM)	[82]
Subjects between 30 and 60 years with BMI ≥30 kg/m^2, and newly diagnosed with T2DM (n = 80)	A randomized, single-blind, placebo-controlled clinical study, 8 weeks	Ginger	600 mg of ginger powder 3 times a day (the total daily dose was 1.8 g)/in 3 doses daily	Reduce BMI, FBG, 2-h postprandial blood glucose, HbA1c, TC, LDL, TG, fasting insulin levels, and HOMA-IR; increase HDL, HOMA2-%β, HOMA2-%S	[83]
Subjects between 20 and 70 years; BMI ≥27 kg/m^2 and elevated FBG (≥5.6 −<7.0 mmol/L) or T2DM (confirmed by evidence of the previous diagnosis) and not taking any diabetes medication and/or HbA1c >10% (n = 76)	A randomized, double-blind, placebo-controlled study, 8 weeks	Almond	56 g/d	Reduce TG/HDL, = AST, ALT, HbA1c, body weight, inflammatory markers	[84]
Subjects with a mean age of 36.5 ± 1.8 years and BMI of 26.37 ± 1.79 kg/m^2, and have moderate or high cholesterol levels (n = 18)	A randomized, double-blind, placebo-controlled study, 2 weeks	*Citrus sinensis* L. var. *Navel late* beverage	500 mL/d	Reduce TC, LDL, LDL/HDL, TBARS, VCAM-1	[85]
Subjects between 35 and 60 years with mild elevated total cholesterol and LDL cholesterol (n = 76)	A randomized, double-blind, placebo-controlled study, 8 weeks	*Phoenix dactylifera* L. vinegar	30 mL/d	Reduce TG, TC, LDL, VLDL, CRP, NO, TNF-α, fibrinogen, = Apo B, Apo A-1, Apo E	[86]
Subjects with the age of≥ 18 years and BMI≥ 25 kg/m^2, and NAFLD diagnosis with ultrasound examination (n = 66)	A randomized, double-blind, placebo-controlled study, 12 weeks	Olive oil	20 g/d	Reduce fatty liver grade, body weight, waist circumference, and blood pressure AST, TG and body fat mass	[87]
Subjects with BMI ≥25 kg/m^2, and at least 12 months of T2DM and NAFLD diagnosis with abdominal ultrasound (n = 80)	A randomized, double-blind, placebo-controlled study, 16 weeks	BPF and/or CyC	300 mg/d	Reduce AST, ALT, GGT, ALP, MDA, TNF-α (BPF and CyC), fibrosis markers (HA, PC III ve IV-C); increase GpX (BPF and CyC combination) and SOD (BPF and CyC combination)	[88]
Subjects between 20 and 60 years with BMI 25 −35 kg/m^2 and NAFLD (n = 48)	A randomized, double-blind placebo-controlled clinical study, 8 weeks	Green coffee extract capsules	400 mg/d	Reduce FBG, HOMA-IR, BMI, waist circumference, leptin, = AST, ALT, hip/waist ratio	[89]
Subjects between 20 and 60 years with BMI 25 −35 kg/m^2 and NAFLD (n = 48)	A randomized, double-blind placebo-controlled clinical study, 8 weeks	Green coffee extract capsules	400 mg/d	Reduce body weight, BMI, TC, TG; increase HDL, = adiponectin, steatosis	[90]

BMI, body mass index; BM, bilberry; LM, lingonberry; CM, cinnamon; T2DM, type 2 diabetes mellitus; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, total triglycerides; LDL, low-density lipoprotein; TAG, triacylglycerol; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA2-%β, β cell function index; HOMA2-%S, insulin sensitivity index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBARS, thiobarbituric acid reactive substance; VCAM-1, vascular cell adhesion molecule 1; NAFLD, non-alcoholic fatty liver disease; VLDL, very low density lipoprotein; CRP, C-reactive protein; Apo A-1, apolipoprotein A-1; Apo E, apolipoprotein E; MDA, malondialdehyde; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; TNF-α, tumor necrosis factor-α; BPF, bergamot polyphenolic fraction; CyC, *Cynara cardunculus;* PC III, type III pre-collagen; IV-C, type IV collagen; GpX, glutathione peroxidase; SOD, superoxide dismutase.

palmitoyl-CoA. Consumption of 70% ethanol extract of lyophilized *V. fauriei* (125 or 250 mg/kg *bw*/d, oral for 8 weeks) reduced the SCD1 gene in mice fed with HFD [47]. Likewise, the dose of 800 μg/kg *bw*/d of ethanol extract of *Zingiber officinale* Roscoe with gavage, reduced SCD1 in hamsters with HFD after 5 weeks [58].

Postprandial insulin secretion modulates hepatic glucose uptake, while glycogen synthesis inhibits gluconeogenesis and actives SREBP-1c, which increases de novo lipogenesis [59]. Studies showed that different polyphenols decrease fasting blood glucose (FBG), insulin resistance, and homeostatic model assessment for insulin resistance (HOMA-IR). Therefore their consumption can be used for therapeutic purposes in NAFLD as well as having a positive effect on insulin mechanisms [29,31,40,44,45,49,56–71]. The positive effects of various polyphenols on NAFLD through different mechanisms are identified in Fig. 2. It is suggested that polyphenols reduce steatosis by regulating liver enzymes and reducing lipid accumulation [72–81].

5.4. Improvement of adipokine

Hepatic lipid accumulation stimulates oxidative stress and is associated with IL-6 and TNF-α which are regulated by leptin and

adiponectin [39]. Leptin regulates energy balance and body adiposity which is made by adipose tissue. Subjects with higher body fat tissue express higher leptin levels [40]. Adiponectin ameliorates hepatic and peripheral insulin resistance and also comprises in anti-inflammatory response. In addition, adiponectin could mediate by the activation of AMPK [13]. According to studies, adiponectin levels decrease as leptin levels increase in NAFLD patients. Various polyphenols could increase adiponectin levels and decrease leptin levels. For example, after 10 weeks of administration doses of 50 or 150 mg/kg *bw*/d procyanidin B2 with oral gavage, showed a reduction in leptin levels while increasing adiponectin levels in mice fed with HFD [41]. The dose of 100 mg/kg *bw*/d of 95% ethanol extract of dried *M. alba* L. leaves with gastric intubation for 8 weeks increased adiponectin levels, and decreased leptin levels in rats fed with high cholesterol [65]. Similarly, the aqueous extract of dried *M. alba* L. leaves (0.5%, 1%, or 2% of total energy, oral, 14 weeks) reduced leptin levels in rats fed with HFD [39]. An oral dose of 100 g/d of non-anthocyanin phenolics isolated from the dried powder of *P. avium* L. diminished leptin levels in obese diabetic mice [40]. The doses of 200 or 400 mg/kg *bw*/three times a week of 95% methanol extract of dried *P. hydaspidis* administered orally, increased adiponectin levels in CC_4 induced rats after 4 weeks [20]. Administrated dose of 50 mg/kg *bw*/d of water extract of dried *Citrus maxima* leaves by gavage showed identical results after 45 days in rats fed with high fat and fructose [36].

6. Clinical studies

Unlike preclinical studies, clinical studies are extremely limited. Most of the human studies consist of randomized controlled trials, all of which have been conducted not only in direct NAFLD patients but also in individuals with associated diseases that lead to NAFLD (Table 2).

A study aimed to investigate the feasibility of using a high-fat/high-caloric breakfast challenge as a tool for assessing the cardiometabolic protective effects of cinnamon (CM) (3 g/d), bilberry (BM) (100 g/d) or lingonberry (LM) (100 g/d), found that bilberry reduces triacylglycerol (TAG), TG, total cholesterol (TC); lingonberry reduces TG and cinnamon reduces the glycemic response, postprandial endotoxemia and C-reactive protein (CRP). This study suggested that polyphenol-rich foods decrease cardiometabolic risk after a high-fat meal [82]. 600 mg of ginger powder administered three times a day reduced body mass index (BMI), 2-h postprandial blood glucose, HbA1c, TC, LDL, TG, fasting insulin levels, and HOMA-IR; increased high-density lipoprotein (HDL), β cell function index (HOMA2-%β) and insulin sensitivity index (HOMA2-%S) after 8 weeks in T2DM patients [83]. Daily consumption of almond with 56 g for 8 weeks, reduced TG/HDL ratio, whereas there was no statistically significant difference in the levels of HbA1c, glycemic variability, body weight and composition (fat-free mass, body fat mass, muscle mass), liver fat and aspartate aminotransferase (AST) and alanine aminotransferase (ALT), cardio-metabolic health and inflammatory markers (TNF-α and IL-6) in patients with T2DM [84]. A study found that 500 mL/d of low-alcohol beverage with *Citrus sinensis* L. var. and navel late decrease TC, LDL, LDL/HDL, thiobarbituric acid reactive substance (TBARS), vascular cell adhesion molecule 1 (VCAM-1) levels in patients with moderate or high cholesterol levels after 2 weeks [85]. *Phoenix dactylifera* L. vinegar with 30 mL/d reduced TG, TC, LDL, very low-density lipoprotein (VLDL), CRP, nitric oxide (NO), TNF-α, fibrinogen whereas it did not change the levels of Apolipoprotein (Apo) B, Apo A-1, Apo E in patients with mild elevated TC and LDL for 8 weeks [86]. The dose of 20 g/d of olive oil supplementation for 12 weeks reduced fatty liver grade, body weight, waist circumference, blood pressure, TG, and body fat mass in patients with NAFLD [87]. Another study indicated that the dose of 300 mg/d of bergamot polyphenolic fraction (BPF) and/or *Cynara cardunculus* (CyC) for 16 weeks ameliorate NAFLD with reduction of AST, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), malondialdehyde (MDA), TNF-α and fibrosis markers (hyaluronic acid, type III pre-collagen (PC III), and type IV collagen (IV-C)) and increasing GPx and SOD levels in patients with T2DM and NAFLD [88]. In other studies, a dose of 400 mg/d of green tea extract capsule was supplemented for 8 weeks in NAFLD patients decreased FBG, HOMA-IR, body mass index (BMI), waist circumference and leptin levels [89]. Another study showed reduced body weight, BMI, TC, TG levels held no statistical difference in adiponectin and steatosis levels [90]. According to the study, green tea supplementation could improve glycemic parameters and obesity therefore it may be useful in the management of NAFLD complications.

7. Discussion

The prevalence of NAFLD is not known accurately, but it is increasing and in parallel with diseases such as diabetes, dyslipidemia and obesity. The prevalence is believed to be 75% in obese patients and can increase up to 90% in morbidly obese patients [91]. Today, obesity is a pandemic effecting more than 1.9 billion overweight adults and 600 million obese adults [92]. It also plays a key role in the development of NAFLD in genetic predisposition as well as in the environment with dietary habits [93]. There are no pharmacological treatments for NAFLD. Only lifestyle modification with diet and increased physical activity are recommended for effected patients [7,15]. Thus, investigations are conducted for the discovery of further treatment options.

Since ancient times, medicinal plants and their isolated phytochemicals like polyphenols have been suggested as having several health-promoting effects. Fruits and vegetables are the basis of a healthy diet, in addition to being rich in polyphenols [15,94]. Here, we reviewed preclinical and clinical studies that assessed the effectiveness of pure polyphenols or isolated from different plant sources in NAFLD. Taken together, current preclinical and limited clinical studies suggest that various polyphenols could prevent steatosis and its progression to NASH. In addition, polyphenols could act through different mechanisms of action to improve the NAFLD (Fig. 2).

Accumulation of FFAs, free cholesterol, TGs and other lipid metabolites in hepatocytes is defined as “the first hit” of NAFLD that caused oxidative stress [12,13]. Many preclinical studies showed that nrf2 and related genes (HO-1, NQO1, and GCLC) enhance the antioxidant defense enzymes that lead to a reduction in oxidative stress [6,20–24]. These results found after the supplementation with isolated polyphenols or extracts of *P. multiflorum thunb., Zea mays* L., *A. grossedentata, V. corymbosum* L. leaves, walnut green husk polysaccharide, *Erica multiflora* leaves, kiwifruit seed oil, *Argyreia speciosa* seeds, *Cyclocarya paliurus* leaves, *Cynara scolymus* L., *Aloe barbadensis* miller, *Citrus maxima* leaves, *Spirulina platensis*, *M. jaboticaba berry*, *M. alba* leaves, *P. avium* L., *C. tinctoria* buds, *P. hydaspidis*, oleuropein, chlorogenic acid and procyanidin B2. Additionally, the antioxidant enzymes like SOD, CAT, GSH, and GpX were increased after the different polyphenols supplementation in both serum and liver [6,20–22,24–41]. These results suggest that different polyphenols have high antioxidant capacities and thus may have a decreasing effect on the progression of the disease even at the onset of NAFLD.

Under NAFLD pathophysiology, increased pro-inflammatory cytokine release is common with the predominant factor of progression from steatosis to NASH [12]. According to preclinical studies, it is reported that various polyphenols with different doses

reduce pro-inflammatory cytokine levels in both serum and liver, especially IL-6 and TNF-α [6,20,21,24,26,31,38–45]. Additionally, leptin and adiponectin regulate IL-6 and TNF-α levels [39] and polyphenols from *M. alba* L. and dried *Citrus maxima* leaves, *P. avium* L., and procyanidin B2 reduce leptin levels and increase adiponectin levels in rats and mice [20,36,39–41,65]. According to the results, polyphenols may significantly improve the regulation of adipokines and prevent hepatic steatosis with related mechanisms. Polyphenols have also been found to have a protective effect against apoptosis by providing a reduction on bcl-2/bax protein expression as a separate anti-inflammatory effect [28]. Moreover, kiwifruit seed oil supplementation decreased COX-2 levels which is responsible for IL-1β and TNF-α activation [31]. Although studies suggest that polyphenols play an anti-inflammatory effect in the pathogenesis of NAFLD through different mechanisms, human clinical studies are limited.

PPAR-γ, C/EBPα gene, and SREBP-1c are the major transcription factors involved in adipocyte differentiation and lipid accumulation [24,46]. The supplementation of *V. fauriei, A. grossedentata*, kiwifruit seed oil, procyanidin B2, tannic acid, hydroxytyrosol and bound phenolics extracted from the lotus seeds led to a reduction in these transcription factors in mice [23,24,31,41,46–48]. AMPK is an attractive therapeutic target for addressing NAFLD because it inhibits SREBP-1c expression through pathways that reduce lipid synthesis [24,27,49–51]. Laminaria japonica, *M. alba* L., *Musa* sp., *A. grossedentata, V. corymbosum* L., and curcumin increased AMPK activation in mice [24,27,50–52]. Another role of AMPK is that it inhibits β-FA oxidation indirectly due to mechanisms such as targeting of PPAR-α, CPT-1α, acetyl-CoA carboxylase, and FA synthetase [55]. These effects were found in mice, rats and larval zebrafish models with different polyphenols supplementation [6,31,43,51,56,57]. Additionally, *M. alba* leaves and *Musa* sp. could ameliorate lipogenesis with the effect on HMGCoA and HMGCoAR [39,50]. Further, *V. fauriei* and *Z. officinale* Roscoe reduced the SCD1 enzyme in both hamsters and mice that lead to a reduction in monounsaturated fatty acids [47,58]. According to preclinical reports, different polyphenols decreased FBG, insulin resistance and HOMA-IR, and had a positive effect on insulin mechanisms [29,31,40,44,45,49,56–71]. These results suggest that it provides an improvement in insulin sensitivity and β-FA oxidation and a decrease in de novo lipogenesis. Therefore, polyphenols are very promising in the prevention and treatment of NAFLD. Although preclinical studies are quite common, these results need to be supported by clinical studies.

Human clinical studies are limited in this subject. Therefore, were included with not only NAFLD patients but also patients with diseases that are associated with NAFLD. According to the human clinical studies, it is suggested that ginger, almonds, olive oil, *C. sinensis* L. var., navel late, *P. dactylifera* L., bergamot, *C. cardunculus*, and green tea show positive effects on NAFLD pathophysiology due to pharmacological activities such as decreasing glycemic response, HOMA-IR, HbA1c, body weight, BMI, lipid parameters, liver enzymes (AST, ALT, ALP) and pro-inflammatory markers, and increasing antioxidant enzymes [82–90]. Clinical studies have used non-invasive diagnostic methods such as ultrasound instead of the gold standard method "biopsy" when defining NAFLD. Therefore, these studies may not have precise data on the severity of NAFLD. Nevertheless, studies indicate that polyphenols are promising in treating NAFLD and associated diseases that lead to NAFLD.

The current study had some limitations. First, clinical studies are very limited and had a small sample size. The largest sample size amongst the included articles was only 80 [83,88]. Second, in human clinical studies, only two articles evaluated the effects of the same polyphenols (green coffee extract) [89,90]. Therefore, the data obtained from these studies may be considered controversial. Third, the short follow-up period is a limitation of the studies identified. No human clinical studies had a study duration greater than 6 months which makes the long-term effect of the polyphenols for treating NAFLD and associated diseases is unknown.

8. Conclusion

While the prevalence of NAFLD is increasing globally, no pharmacological treatments are currently available. Therefore, it is important to find alternative treatments for these patients. Currently, interest in "functional foods" has increased considerably and polyphenols that are found in fruits and vegetables, are thought as one of them, polyphenols have shown beneficial effects on NAFLD via different mechanisms. The natural sources of polyphenols are a part of the human diet and are generally safe. The addition of polyphenol-rich foods may be an appropriate recommendation for NAFLD patients. However, future clinical human studies are recommended for confirmation of the currently available data.

Statement of authorship

All authors contributed equally to conceptualization of the study, data acquisition and interpretation, and review and final approval of the manuscript.

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