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Review

The effect of adiponectin in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) and the potential role of polyphenols in the modulation of adiponectin signaling

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide, as it affects up to 30 % of adults in Western countries. Moreover, NAFLD is also considered an independent risk factor for cardiovascular diseases. Insulin resistance and inflammation have been identified as key factors in the pathophysiology of NAFLD. Although the mechanisms associated with the development of NAFLD remain to be fully elucidated, a complex interaction between adipokines and cytokines appear to play a crucial role in the development of this condition. Adiponectin is the most common adipokine known to be inversely linked with insulin resistance, lipid accumulation, inflammation and NAFLD. Consequently, the focus has been on the use of new therapies that may enhance hepatic expression of adiponectin downstream targets or increase the serum levels of adiponectin in the treatment NAFLD. While currently used therapies show limited efficacy in this aspect, accumulating evidence suggest that various dietary polyphenols may stimulate adiponectin levels, offering potential protection against the development of insulin resistance, inflammation and NAFLD as well as associated conditions of metabolic syndrome. As such, this review provides a better understanding of the role polyphenols play in modulating adiponectin signaling to protect against NAFLD. A brief discussion on the regulation of adiponectin during disease pathophysiology is also covered to underscore the potential protective effects of polyphenols against NAFLD. Some of the prominent polyphenols described in the manuscript include aspalathin, berberine, catechins, chlorogenic acid, curcumin, genistein, piperine, quercetin, and resveratrol.

Abbreviations: ABCA1, adenosine triphosphate -binding cassette transporter A1; ACC, AMPK 5′ adenosine monophosphate-activated protein kinase; ACO, Acyl-CoA oxidase; APO A-I, apolipoprotein A-I; AOX1, aldehyde oxidase 1; ATP, adenosine triphosphate; ACC1, acetyl-CoA carboxylase 1; ACSL-1, acyl-CoA synthetase long-chain family member 1; AdipoR1, adiponectin receptor 1; AdipoR2, adiponectin receptor 2; AMP, adenosine monophosphate; CAT, catalase; CD36, cluster of differentiation 36; CETP, cholesteryl ester transfer protein; COX-2, cyclooxygenase-2; CPT1, carnitine palmitoyltransferase 1; CRP, C-reactive protein; CVD, cardiovascular disease; DNL, *de novo* lipogenesis; HDL, high density lipoprotein; HFD, high fat diet; HFHS, high fat high sugar diet; HFR, high fructose diet; GLUT2, glucose transporter 2; GLUT4, glucose transporter 4; G6P, Glucose-6- phosphate; G6Pase, glucose-6-phosphatase; FAO, fatty acid oxidation; FAS, fatty acid synthase; FFAs, free fatty acids; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HMW, high-molecular weight; HSL, hormone-sensitive lipase; IR, Insulin resistance; IL, interleukin; IFN-gamma, interferon-gamma; JNK, c-Jun N-terminal kinase; KLF7, Kruppel-like factor 7; LDL, low-density lipoprotein; LPL, lipoprotein lipase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steotohepatitis; NF-κB, nuclear factor-κB; NO, nitric oxide; PCOS, polycystic ovary syndrome; PPAR-α, peroxisome proliferator-activated receptor-alpha; PEPCK, phosphoenolpyruvate carboxy kinase; PI3K, phosphatidylinositol 3-kinase; SCD-1, sterol-CoA desaturase 1; SREBP-1C, sterol regulatory element-binding protein 1; TNF-α, tumor necrosis factor-alpha; TAGs, triglycerides; VLDL, very low-density lipoprotein.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver injury, globally, with an estimated prevalence of 24–30 % [1]. Over the past two decades, NAFLD cases have dramatically increased with the growing epidemic of obesity and related metabolic diseases [2]. It has been estimated that 90 % of patients with NAFLD are obese and of these, about 70 % are insulin resistant (IR) or have Type 2 Diabetes (T2D) [3,4]. This upsurge in the prevalence of NAFLD has led to increased research efforts aimed at better understanding the underlying pathophysiology of obesity-induced NAFLD. This is especially important since NAFLD is considered an independent risk factor for cardiovascular diseases (CVD) [5]. Currently, the mechanisms linking NAFLD with CVD have not been fully elucidated, however, it is well-accepted that abnormalities in hepatic lipid accumulation, enhanced inflammation, and subsequent liver fibrosis are prominent in conditions of CVD associated with NAFLD [6–8].

NAFLD is be defined as the hepatic manifestation of the metabolic syndrome that is characterized by increased hepatic lipid accumulation in the absence of excessive alcohol consumption. The histologic spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), which may advance to cirrhosis and hepatocellular carcinoma [9,10]. It has been reported that around 20–30 % of NAFLD patients will develop NASH in a few years [11]. Moreover, patients with NAFLD have an increased risk of developing CVD [12–14]. Furthermore, it has been argued that NAFLD increases the CVD risk independent of coronary heart disease and metabolic syndrome [15]. As such, it is important to understand the early disease pathophysiology of NAFLD in order to develop interventions to decrease CVD risk.

Accumulating evidence suggests that pathophysiological mechanisms of NAFLD are mainly driven by an augmented influx of lipids into the liver along with enhanced *de novo* lipogenesis (DNL), that may occur concurrent with the reduction of fatty acid oxidation (FAO) [16,17]. Increased consumption of high-energy-dense-food and sugar-sweetened-beverages are the key mediators of obesity and related hepatic lipid influx [18–20]. For example, the consumption of a high-fat, high-sugar (HFHS) diet for eight months has been associated with hypertriglyceridemia, hypercholesterolemia and increased oxidative stress, inflammation, and liver steatosis in Wistar rats [18]. This consequent has been confirmed by others showing that HFHS diet promotes elevation of serum levels of triglycerides (TAGs), total cholesterol, along with hepatic insulin resistance and liver damage, and the associated development of hepatic steatosis as a consequence [19,20]. Alternatively, enhanced adipokine levels, more specifically, adiponectin concentrations, can exert favorable effects, leading the amelioration of NAFLD and its linked complications [21].

Different molecules secreted from the adipose tissue such as adiponectin, leptin, resistin and visfatin and pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), and interleukins (ILs), can be involved in the pathogenesis of NAFLD [22]. In particular, adiponectin levels are inversely correlated to cardiovascular risk factors, and positively linked to high density lipoprotein-cholesterol (HDL-c) levels [23]. The adiponectin anti-inflammatory properties have been demonstrated in primary human monocytes, macrophages and dendritic cells. In fact, increased adiponectin levels has been shown to induce an anti-inflammatory response, whilst, impairing the production of IFN-alpha in the mentioned cells [24,25]. Thus, there has been an interest in understanding the protective properties of adiponectin (encoded by AdipoQ gene), as it is known to play a major role in the regulation of hepatic glucose and lipid metabolism. Apparently, reduced serum adiponectin levels in patients with NAFLD have been linked with increased susceptibility to CVD [13]. Nonetheless, the interplay between the regulation of adiponectin levels, pathogenesis of NAFLD and the development of CVD remains to be fully elucidated.

Several reviews have been published to describe the role of adipokines, including adiponectin, in the pathogenesis of NAFLD. Notably, a combination of high leptin, resistin, and low adiponectin can favor the development of NAFLD [26–28]. As one of the proposed mechanisms investigated, it has been reported that adiponectin can promote FAO and prevent DNL, leading to improved insulin sensitivity and reduced CVD risk [29]. As such, pharmacological interventions aimed at increasing adiponectin levels in conditions of metabolic disorder might hold the key to alleviate NAFLD-related complications [30–32].

There has been a stimulated interest in the role polyphenols play in preventing metabolic complications, as well as their impact on increasing adiponectin levels to improve metabolic health. As a prime example, resveratrol treatment has been shown to improve hepatic steatosis by increasing serum adiponectin levels in addition to inducing the expression of energy regulating mechanisms such as 5′ adenosine monophosphate-activated protein kinase (AMPK) during diet-induced obesity in mice [33]. Similarly, quercetin supplementation has been reported to improve adiponectin signaling by increasing hepatic expression of its receptors, along with AMPK activation in peripheral blood mononuclear cells of women diagnosed with polycystic ovary syndrome (PCOS) [34]. Although preclinical benefits are observed with the use of some polyphenolic compounds to modulate adiponectin levels in conditions of metabolic syndrome, such information has not been critically scrutinized to inform on the therapeutic potential of these compounds against NAFLD. Therefore, this review aims to provide a brief overview of the pathogenesis of NAFLD, while importantly, discussing the therapeutic role major polyphenols have on the regulation of adiponectin levels in conditions of NAFLD.

Prominent databases such as PubMed, Google Scholar and Embase were searched for relevant studies reporting on adiponectin levels and polyphenols in conditions of NAFLD. The search was extended to cover original articles and grey literature such as preprints, while reviews and books were screened for primary findings. Briefly, a search for the effect of polyphenols on adiponectin signaling pathway with regards to NAFLD was conducted using the following search terms and synonyms: “NAFLD”, “fatty liver”, “adiponectin”, “lipid metabolism”, “inflammation”, “insulin resistance” and “polyphenols” and their corresponding synonyms. The first section of the review will briefly discuss the pathogenesis of NAFLD and the involvement of adiponectin, to underscore and emphasize the potential benefits of polyphenols in regulating this adipokine to protect against liver injury.

2. Non-alcoholic fatty liver diseases: prevalence

The estimated global prevalence of NAFLD is between 24-30 %, whilst in Africa it is 13.5 % compared to the Middle East, Europe and America with rates of 31.8 %, 23.7 % and 30.4 %, respectively [35,36]. Apart from the variation observed between continents, the prevalence of NAFLD varies with gender and age. Males are at higher risk of developing NAFLD compared to their female counterparts [37,38], which is thought to be linked to the protective effects of estrogen in pre-menopausal females. However, post-menopause, the prevalence of NAFLD gradually increases in women exceeding that of their male counterparts [39,40]. According to Tominaga [41], the prevalence of NAFLD increases with age, with a <1% chance of developing NAFLD in individuals younger than 20 years compared to a 8% and 39 % risk in those between 40−60-years of age. In this context, the prevalence of NAFLD is reported to be highest in developing middle-eastern countries compared to developed countries, due to changes in dietary habits and lifestyle [42].

2.1. Pathogenesis of non-alcoholic fatty liver

The pathogenesis of NAFLD has been described based on the “2-hits hypothesis”, which was first proposed by Day and James [43]. The “1st hit” is characterized by the accumulation of TAGs in hepatocytes (steatosis) and the development of hepatic insulin resistance, which increases vulnerability of the liver to secondary injury or insults. The

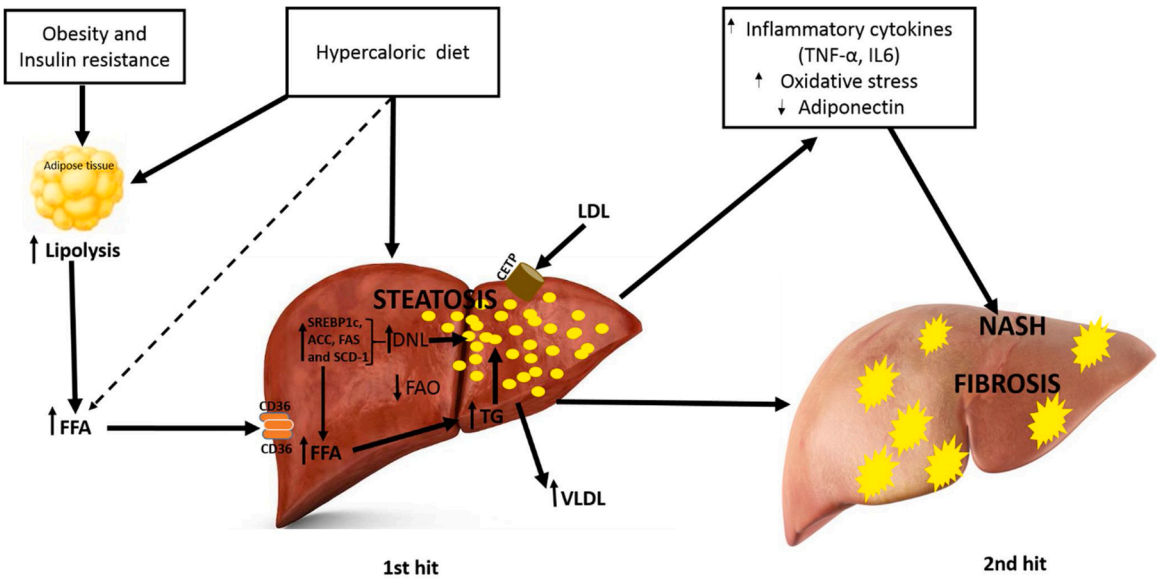

Fig. 1. Pathogenesis of NAFLD. The pathogenesis of NAFLD is suggested to be driven by two hit 1st and 2nd hit. The 1st hit involved accumulation of free fatty acids (FFAs) in the liver resulting in simple steatosis. Circulating free fatty acids and low-density lipoproteins (LDL) are thought to enter the liver via the cluster of differentiation 36 (CD36) and cholesteryl ester transfer protein (CETP), respectively. Overloaded of FFAs can activate the expression of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), as well the generation of reactive oxygen species (ROS) resulting in chronic inflammation, oxidative stress, lipid peroxidation and activation of fibrogenesis (2nd hit).

"2nd hit" occurs as a result of secondary injuries mediated by the "1st hit", which include altered production of adipokines, increased inflammation, oxidative stress, apoptosis and liver fibrosis. However, the 'two-hit' hypothesis is believed to not explain all the molecular and metabolic changes involved in NAFLD. Thus, it has recently been modified to a 'multiple hit' hypothesis, hypothesis which provides a more accurate explanation of NAFLD. The latter describes insulin resistance as the main factor which leads to increased DNL and lipolysis in adipose tissue, promoting efflux of free fatty acids (FFAs) to the liver via portal vein. This theory was proposed since the accumulation of TAGs in hepatocytes may be a protective mechanism against liver damage, while exacerbated inflammation may be the process leading to hepatic steatosis [44]. The "multiple hit" theory considers various insults acting together in synergy to induce NAFLD; these includes insulin resistance, adipokines secreted from the adipose tissue, as well as the interplay between environmental (diet) and genetic factors such as those involving epigenetics [45]. Furthermore, it has been increasingly recognized that the gut-liver axis play a critical roles in the pathogenesis and progression of the most common causes of NAFLD [46,47]. Notably, gut-liver axis has been shown to facilitate intestinal dysbiosis resulting in the disruption of the symbiotic relationship between gut resident microbial population and the host, leading to the dysfunction of host immune response, thereby contributing to pathogenesis of NAFLD [46, 47].

2.1.1. *Lipid metabolism and NAFLD (1st hit)*

The hallmark of NAFLD is hepatic lipid accumulation, which results due to increased lipolysis in adipose tissue that results in the hydrolysis of glycerol and influx of FFA into the liver at a rate that exceeds FAO (Fig. 1) [48]. This hepatic FFA influx occurs mainly through cluster of differentiation 36 (CD36) glycoprotein and cholesteryl ester transfer protein (CETP), which subsequently promotes the accumulation of TAGs whilst increasing DNL in the liver. Consistently, a hypercaloric diet and insulin resistance are well-known factors associated with impaired lipid metabolism in the liver [49,50]. The inability of insulin to suppress lipolysis in adipose tissue is thought to be the main source of enhanced circulating FFAs and inflammatory responses, which have been shown to contribute to approximately 60 % of hepatic lipid content [51]. Lambert and coworkers [52] and later Solinas and colleagues [53] reported that DNL contributes about 25 % of hepatic lipids in a patients with NAFLD. Besides, it is well-documented that hypercaloric diets contribute to hepatic steatosis by stimulating the lipogenic transcriptional factor, sterol response element-binding protein 1c (SREBP1-C), which is a master regulator of lipid synthesis [54,55]. Activated SREBP1-C can upregulate the expression of stearyl CoA desaturase 1 (SCD 1), acetyl-CoA carboxylase 1 (ACC1) and fatty acid synthase (FAS), which are essential enzymes involved in *de novo* fatty acids synthesis. In addition, increased DNL can activate ACC1 that increases malonyl-CoA levels in the cytoplasm, in a systematic process that blocks carnitine palmitoyltransferase-1 (CPT-1), the rate-limiting enzyme of FAO in the mitochondria [53].

2.1.2. *Impact of inflammation in NAFLD (2nd hit)*

It is well-established that overload of FFAs activate the expression of pro-inflammatory cytokines such as TNF-α and pro-inflammatory ILs, leading to chronic inflammation in the liver, a hallmark of NAFLD [56]. Inflammation appears to be the most important mechanism involved in the pathogenesis of NAFLD and has been considered as the hallmark of most chronic diseases, including CVD. Excessive lipid accumulation leads to hepatocellular damage and activation of an inflammatory response that triggers the progression of liver diseases and CVD [16]. In fact, it has been established that high fat diet (HFD) alters the levels of pro- and anti-inflammatory adipokines, concomitant to the exacerbation of hepatic inflammation and NAFLD [57]. Pro-inflammatory adipokines such as TNF-α, IL-6 and members of the IL-1 cytokine family, are reported to be increased by HFD, whereas anti-inflammatory adipokines (adiponectin, IL-10 and resistin) are said to be reduced [28,58–61]. Other studies have shown that lipid accumulation can promote TNF-α production in the liver, which in turn activates various inflammatory signaling pathways (including nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK) signaling mechanisms thus resulting in the development of IR and subsequently NAFLD [62,63]. Available evidence [64] show that circulating levels of TNF-α are positively associated with the degree of liver fibrosis in patients with NASH. Likewise, Mirea and co-workers [61] reviewed and provided evidence that IL-1 is crucial for the induction of hepatic inflammation and progression into liver

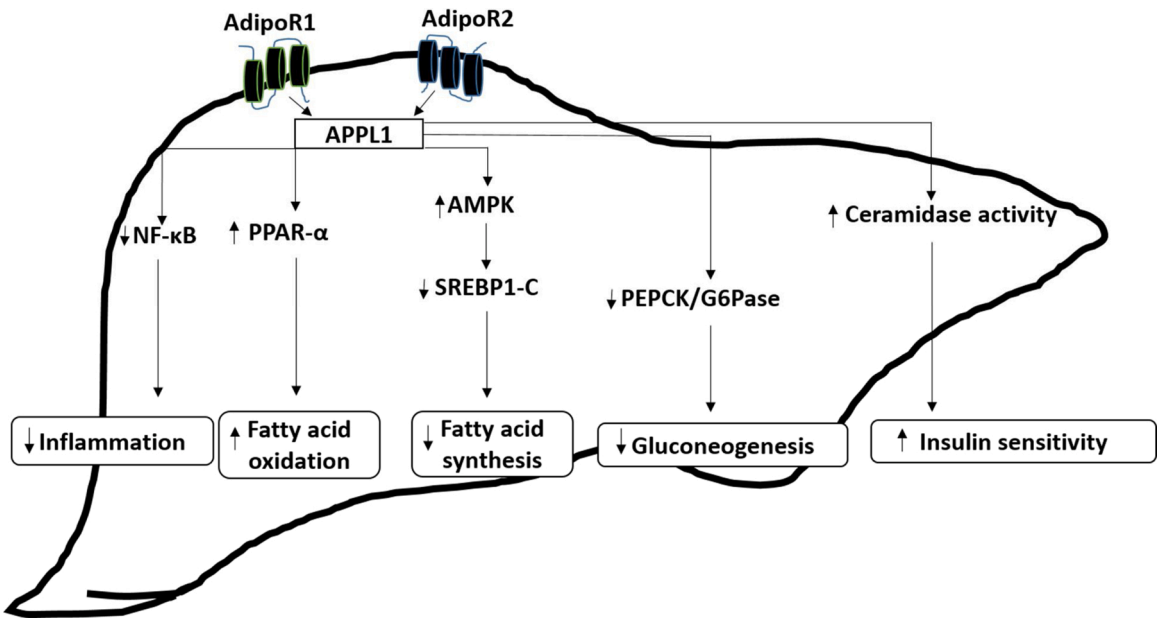

Fig. 2. The proposed adiponectin signaling pathway in conditions of nonalcoholic fatty acid liver disease (NAFLD). In the liver, adiponectin binds to its receptors (AdipoR1 and AdipoR2) which then interacts with the adaptor protein phosphotyrosine interaction (APPL1). This interaction results in the activation of various signaling pathways which include 5′ adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-alpha (PPAR-α) pathways. These pathways then suppress hepatic lipid accumulation by inhibiting sterol regulatory element-binding protein 1 (SREBP-1C) and acetyl-CoA carboxylase (ACC), also regulating glucose homeostasis through a decrease in PEPCK/G6Pase. Alternatively, adiponectin can also reduce inflammation by inhibiting tumor necrosis factor-alpha (TNF-α) through blocking Nuclear factor kappa B (NF-κB). Importantly, adiponectin also increases insulin sensitivity through effective regulation of ceramide levels.

fibrosis, while IL-1β is known to be involved in all stages of NAFLD development [65]. Moreover, NAFLD/NASH can extend broader range of FFA-induced metabolic dysregulations that enhance liver damage. For example, due to enhanced obesity-induced hepatic lipid accumulation, the mitochondrial respiratory oxidation is impaired concomitant to altered fat homeostasis, a process that generates lipid derived toxic metabolites and promotes ROS production [66]. Indeed, Buzzetti et al. [45] reported that hepatic fat accumulation, especially enhanced availability of triglycerides, cholesterol and other lipid metabolites, decrease mitochondrial dysfunction with a concomitant increased ROS production and endoplasmic reticulum stress. This has been confirmed by Cusi and co-workers [66], who showed that activation of inflammatory pathways contribute to hepatocytes necroinflammation [67], worsening mitochondrial damage. Similarly, this has been reported by Paradies and colleagues [68] who showed that a correlation exist between increased inflammatory response, mitochondrial dysfunction and insulin resistance. Furthermore, it has been reported that ROS, together with oxidized LDL particles, may activate Kupffer and hepatic stellate cells, leading to the progression of NASH [69]. Conversely, adiponectin, an anti-inflammatory adipokine was shown to have an inverse relationship with levels of liver enzymes associated with NAFLD [70,71]. Certainly, literature indicates that upregulation of adiponectin can have positive effects in ameliorating NAFLD by decreasing hepatic and systematic IR, while suppressing liver inflammation and subsequently fibrosis [72].

3. General overview of adiponectin and its physiological regulation

Adiponectin is the most abundant adipokine produced and secreted mainly by white adipose tissues. This bioactive protein was discovered in the mid-1990s [73–76]. Scherer [73] identified adiponectin from a subtractive cDNA library enriched in adipocyte-specific genes and named it adipocyte complement-related protein of 30 kDa (Acrp30). Subsequently, Maeda (1996), using a cDNA library construct from human adipose tissue samples, identified adiponectin as the most abundant transcript in these tissues and named it adipose most abundant gene transcript 1 (apM1) [75]. This was immediately followed by the work of Nakano and co-workers [76], who used protein sequencing to identify adiponectin. Since the initial discovery of adiponectin, many studies have focused on establishing its importance in metabolism in order to elucidate its mechanism of action [29,77,78]. As such, adiponectin has been implicated as a key adipokine that plays a significant role in the regulation of metabolic and inflammatory processes [79].

Adiponectin circulates at very high concentrations (2–30 μg/mL) and represents about 0.01 % of plasma proteins [76]. This adipokine occurs as a globular and full-length isoform within plasma [80]. The latter isoform is of interest, as it has been reported to circulate at a higher percentage than the globular isoform and is more potent in enhancing insulin sensitivity [81]. The full-length isoform exists in a wide range of oligomeric forms in blood, which includes a low molecular weight trimer (LMW), a middle molecular weight hexamer, and a high molecular weight (HMW) isoform [81]. The high molecular weight isoform has been proposed to be the most active isoform that plays a critical role in energy metabolism and has been implicated as an indicator of insulin sensitivity [82]. To confirm this, a recent study by Pandey et al. [83], reported that HMW adiponectin could alleviate inflammation and improve lipid metabolism, as well as insulin sensitivity via adaptor protein phosphotyrosine interaction pleckstrin homology domain and leucine zipper containing (APPL1)-AMPK-pathway in 3T3-L1 adipocytes exposed to high glucose and palmitate. Furthermore, studies have shown that the administration of adiponectin can reduce circulating FFAs and TAGs levels, while increasing serum concentrations of HDL in diabetic mice [84,85]. Adiponectin has been suggested to promote insulin sensitivity via activation of several signaling pathways, which includes insulin signaling and AMPK pathways.

Although adiponectin is mainly expressed in adipose tissue, its beneficial effects in the liver are mediated by its receptors (adiponectin receptor 1 (AdipoR1) and receptor 2 (AdipoR2)) and APPL1 [86,87].

Table 1
An overview of studies reporting on the effect of adiponectin on lipid metabolism, inflammation and insulin resistance.

Experimental model	Adiponectin dose and treatment	Findings	Reference
Human aortic endothelial cells (HAECs) exposed to human recombinant tumor necrosis factor alpha (TNF-α) time?	50 μg/mL for 18 h	Adiponectin supplementation suppressed nuclear factor kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκB-α) –nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway induced by tumor necrosis factor alpha (TNF-α) in HAECs cells Furthermore, adiponectin treatment dose-dependently increased cyclic adenosine monophosphate (cAMP) levels in HAECs, indicating that this adipokine inhibits inflammation through cAMP dependent pathway.	[89]
Human monocytes treated with lipopolysaccharide (LPS) or TNF-α for 16 h	20 μg/mL for 6 days	Adiponectin suppressed the release of pro-inflammatory cytokines interleukin 6 (IL-6), TNF-α, and interferon gamma (IFN-**γ**) while promoting the secretion of anti-inflammatory cytokines such as interleukin 10 and 1 (IL-10 and IL-1).	[112]
Human hepatoma cell line (HepG2) expose to liver X receptor (LXR) agonist	1,5 and 30 μg/mL for 24 h	Adiponectin promotes high-density lipoprotein (HDL) assembly through increased ATP binding cassette subfamily A Member 1 (ABCA1) expression and apolipoprotein A1 (APO A-I) synthesis in a dose-dependent manner.	[93]
10-week-old adiponectin transgenic obese diabetic *ob/ob* mice and *ob/ob* littermates fed a high fat diet (HFD) for 12 weeks	50 μg/kg body weight injection of a 1:1 mixture of 2 monoclonal adiponectin antibodies on days 1, 4, and 7 of the experiment.	Overexpression of adiponectin reduced serum levels of triglycerides (TAGs) and free fatty acids (FFAs), which was associated with improved hepatic insulin sensitivity as observed through increased protein expression of insulin receptor (IRS1), Protein kinase B (AKT/PKB) and glycogen synthase kinase 3 beta (GSK3-β).	[123]
C57BL/6 J i and HepG2 cells treated with actinomycin D and differentiated C2C12	Mice injected with 1×10^9 adenovirus-encoding adiponectin 3 days before experiments HepG2 and C2CL2 were	Adiponectin reduced serum levels of TAGs and circulating FFAs and increased HDL levels in mice. The *in vitro* study showed that	[85]

Table 1 (*continued*)

Experimental model	Adiponectin dose and treatment	Findings	Reference
	incubated with 10 μg/ml of recombinant human adiponectin for 24 h	adiponectin treatment for 24 h increases lipoprotein lipase (LPL) and very low-density lipoprotein (VLDL) expression in differentiated C2C12 myotubes. In cultured HepG2 cells, treatment with recombinant human adiponectin did no alter hepatic VLDL-TAGs secretion rates were also not altered by elevated plasma adiponectin.	
$^{+}Lepr^{db}/^{+}Lepr^{db}$ (*db/db*) mice and Rat Hepatoma Cell Line Derived from H35 Cells	Mice were injected with 3 μg/g bodyweight for 4 or 8 h. Hepatocytes were incubated 25 μg/mL of recombinant adiponectin for 4 and 8 h	Adiponectin treatment of *db/db* mice suppressed hepatic expression of sterol regulatory element-binding protein (SREBP-1C) gene and downstream effectors of SREBP-1C (Acetyl-CoA carboxylase 1 (ACC-1) and sterol-CoA desaturase 1 (SCD-1) were also reduced. Treatment of hepatocytes with adiponectin resulted in a decrease in SREBP-1C expression, while deletion of adiponectin receptor 1 (adipoR1) and liver kinase B1 (LKB1) deletion upregulated SREBP-1C expression, suggesting that adiponectin suppresses SREBP-1C mRNA expression through AdipoR1/LKB1/5′ adenosine monophosphate-activated protein kinase (AMPK) pathway.	[99]
$lep^{ob/ob}$ mice fed with an HFD, and $lep^{ob/ob}$ mice infected with AdipoR1 and AdipoR2 adenoviruses	Mice were injected once with 2 mg/kg of full-length adiponectin for 60 minutes	Administration of recombinant adiponectin effectively reduced hepatic ceramide content and improved hepatic insulin sensitivity in *ob/ob* mice. Also, infection of a mouse with adenoviruses carrying AdipoR1 and adiponectin receptor 2 (AdipoR2) resulted in a significant increase in hepatic ceramidase activity and improved insulin sensitivity.	[102]
Primary cultured calf hepatocytes obtained from the liver of a female Holstein calf.	Cells were exposed to either 16, 64 or 128 ng/ml of full-length adiponectin for 4 h	Administration of adiponectin enhanced mRNA expression of adiponectin receptors, AMPK and peroxisome proliferator-activated receptor-alpha (PPAR-α), as well as lipid oxidative enzymes	[77]

(*continued on next page*)

Table 1 (*continued*)

Experimental model	Adiponectin dose and treatment	Findings	Reference
		(Acyl-CoA oxidase (ACO), Carnitine palmitoyltransferase 1 (CPT-1) and acyl-CoA synthetase long-chain family member 1 (ACSL-1) while inhibiting lipogenic genes SREBP-1C, ACC-1, fatty acid synthase (FAS) and SCD-1) in a dose-dependent manner in primary cultured calf hepatocytes.	
Murine peritoneal macrophages isolated from female C57BL/6 mice exposed to LPS	Pre-treated with 0.1 μg/mL of globular adiponectin for 18 h	Adiponectin suppressed LPS-stimulated production of IL-1β through induction of autophagy and AMPK signaling pathway in macrophages. Also, adiponectin treatment suppressed caspase-1 and the inflammasome activation in murine peritoneal macrophage.	[113]

APPL1 is an insulin-sensitizing protein and a master mediator of the crosstalk between insulin and adiponectin [88]. This has also been suggested to mediate the positive effects of adiponectin on insulin sensitivity and other associated downstream signaling pathways involved in insulin signaling [86], such as TNF-α [89], AMPK, as well as peroxisome proliferator-activated receptor-alpha (PPAR-α) pathways [77]. Fig. 2 summarizes the proposed mechanisms impacted by adiponectin during the pathogenesis of NAFLD, including of FAO via regulating AMPK and PPAR-α, and the amelioration of oxidative stress by enhancing intracellular antioxidants such as superoxide dismutase (SOD).

3.1. Adiponectin and lipid metabolism

Findings by Combs and Marliss [90] and later Gamberi and colleagues [91] revealed that adiponectin protects the liver against hepatic steatosis by decreasing serum lipids and glucose production. Supporting these findings, Qiao and colleagues [85] showed that overexpression of adiponectin was linked to reduced levels of fasting plasma TAGs and FFAs, as well as elevated very low lipoprotein (VLDL) catabolism in skeletal muscle. In addition, a recent study by Coimbra and co-workers [92] reported that circulating adiponectin levels correlated positively with large HDL and negatively with body mass index (BMI) and VLDL in end-stage renal disease patients. Furthermore, work done by Mastuura and co-workers [93] showed that the possible mechanism by which adiponectin increases HDL-cholesterol is via enhancing the production of ATP-binding cassette transporter A1 (ABCA1) and apolipoprotein A-I (APO A-I) in the liver.

As illustrated in Fig. 2, adiponectin can prevent hepatic lipid accumulation by decreasing fatty acid synthesis while promoting FAO, thus leading to reduced hepatic TAG content. This effect of adiponectin in the liver is suggested to be mediated by its receptors, AdipoR1 and AdipoR2 as well as APPL1 through the activation of AMPK and PPAR- α signaling pathways [94]. Beyond their anticipation energy metabolism [95,96], AMPK pathways can regulate several effects of adiponectin in the liver such as inhibition of gluconeogenesis, lipogenesis as well as enhancing the rate of FAO. For instance, adiponectin-activated AMPK is mediated by AdipoR1, while AdipoR2 is involved in the activation of PPAR-α signaling pathway [97]. Activation of AMPK by AdipoR1 is associated with blockade of FFA synthesis, while concomitantly stimulating FOA by blocking SREBP-1C, which in turn has an inhibitory effect on ACC [98]. To confirm such a hypothesis, the administration of adiponectin was shown to suppress SREBP-1C expression via the activation of AMPK in the liver of type 2 diabetic (*db/db)* mice and cultured hepatocytes [99]. Additionally, it has been demonstrated that adiponectin activated-AMPK promote lipid oxidation by reducing the expression of SREBP-1C and its downstream enzymes, ACC and malonyl CoA [77]. Similar to AMPK pathway involvement, Chen and co-workers [77] demonstrated that treatment of bovine hepatocytes with adiponectin could significantly increase the expression of PPAR-α, acyl-CoA oxidase (ACO), CPT1 and acyl-CoA synthetase long-chain family member 1 (ACSL-1), whose activity is regulated by PPAR-α (Table 1). Montagner and colleagues [100] demonstrated that deletion of PPAR-α in hepatocytes could impair fatty acid catabolism, promote steatosis and subsequently, NAFLD in mice, thus emphasizing the importance of PPAR-α regulation in NAFLD.

3.2. Adiponectin and insulin resistance

The role of adiponectin as an insulin sensitizer has been widely reported [101–103]. Previous research showed that administration of adiponectin significantly ameliorated insulin resistance and hypertriglyceridemia in HFD-fed mouse [103]. Added to this, serum levels of adiponectin have been shown to negatively correlate with plasma glucose and insulin levels in T2D patients, thus emphasizing the beneficial role of this hormone in attenuating insulin resistance [101]. Although the mechanism by which adiponectin enhances insulin sensitivity is still not fully elucidated, studies have suggested that adiponectin increases glucose uptake through translocation of glucose transporters [104] and inhibition of TNF-α [105]. It has been reported that adiponectin enhanced basal glucose uptake and reversed the inhibitory effect of TNF-α on insulin-stimulated glucose uptake in mature rat adipocytes [105]. As demonstrated in Fig. 2, adiponectin is suggested to suppress glucose production, through the activation of AMPK and concomitant inhibition of gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6 phosphatase (G6pase) in type 2 diabetic mice [106,107]. Furthermore, adiponectin was shown to improve hepatic insulin sensitivity by directly inducing ceramidase activity, a rate-limiting enzyme that catalyzes the catabolism of ceramides [102]. The latter describes lipid molecules that affect insulin sensitivity by inhibiting the activity of the anabolic enzyme Protein kinase B (Akt/PKB) signaling [108]. Also, it is noteworthy that insulin resistance correlates with TAG content, thus the ability of adiponectin to increase the rate of FAO and decrease that of TAGs through activation of AMPK and PPAR-α is another mechanism by which this adipokine improves insulin sensitivity [58,77].

3.3. Adiponectin and inflammation

One of the mechanisms by which adiponectin suppresses inflammation is its ability to counter the detrimental effect of hepatic TNF-α expression [78,109–111]. TNF-α is an important marker of both systemic inflammation and insulin resistance. Hashimoto and colleagues reported that levels of TNF-α, FFAs and TAGs were increased in adiponectin-deficient mice and that this was concomitant to decreased expression of PPAR-α in the liver [111]. Moreover, adiponectin has been suggested to suppress the expression of IkappaB-alpha (IkBα) and subsequently inhibit TNF-α-induced NF-κB pathway in human aortic endothelial cells (HAECs) [62,89]. Adiponectin can further block the release of pro-inflammatory cytokines, IL-6 and interferon-gamma (IFN-γ), leading to enhanced secretion of anti-inflammatory cytokines which includes IL-10 and IL-1 in human leukocytes [112]. This has been confirmed by Kim (2017) [113], who showed that adiponectin suppressed the production of IL-1β through autophagy induction and AMPK

Table 2
An overview of studies reporting on the potential modulatory effect of polyphenols on adiponectin levels in non-alcoholic fatty liver disease (NAFLD).

Polyphenols	Plant source	Experimental model used	Treatment dose and intervention period	Review reporting of findings	Ref.
Aspalathin	*Aspalathus linearis*	H9c2 cardiac cells exposed to 33 mM glucose for 48 h	1 μM for 6 h	Aspalathin treatment for a period of 6 h increased the expression of adiponectin and peroxisome proliferator-activated receptor gamma (Pparγ) while decreasing that of sterol regulatory element-binding protein-1c (SREBP-1C) in cultured H9c2 cardiomyocytes. Also, treatment with aspalathin improved high-glucose induced inflammation as well as insulin resistance by decreasing the expression of pro-inflammatory cytokines (interleukins 3 and 6 (IL-3 and IL-6) and tumor necrosis factor (TNF-α) and phosphodiesterase 3B (Pde3b) in H9c2 cells.	[147]
Berberine	*Rhizoma coptidis*	Wistar rats fed with a high-fat diet (HFD) for 8 weeks	150 mg/kg and 380 mg/kg for 8 weeks	Berberine treatment increased serum levels of HMW adiponectin, while concomitantly increasing the expression of adiponectin receptor 1 (adipoR1), adiponectin receptor 2 (adipoR2) and 5′ adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscle and the liver of HFD-fed rats. Another important finding was that treatment with berberine improves glucose tolerance and insulin sensitivity.	[165]
Catechin	Green tea, cocoa, fruits, berries and red wines.	Wistar rats fed with high fructose (HFR) diet and 3T3-L1 cells expose to TNFα for 24 h	20 mg/kg and 1 and 10 μM for 6 weeks	Catechin supplement also improved protein expression and plasma levels of adiponectin in adipose tissue of HFR diet-fed rats. *In vitro* results showed that treatment with TNFα in 3T3-L1 cells decreased the secretion of adiponectin and treatment with catechin was able to increase adiponectin secretion in a dose-dependent manner. In addition, catechin supplement was also shown to suppress inflammation and improve metabolic factors associated with insulin sensitivity.	[175]
		Differentiating 3T3-L1 cells	5, 10, 50 and 100μM for 24 h.	Catechin supplement increased the secretion and protein expression of adiponectin while suppressing the expression of kruppel like factor 7 (KLF7) in differentiating 3T3-L1 cells. Also, administration of catechin increased glucose uptake into 3T3-L1 adipocytes in the presence of insulin, suggesting the role of catechin as an insulin-sensitizing material.	[174]
Chlorogenic acid	Fruits, vegetables, coffee and tea.	C57BL/BKS *db/db* mice	80 mg/kg/d for 12 weeks	Chlorogenic acid was found to increase adiponectin levels in visceral adipose tissue and enhanced protein expression of AdipoR2, AMPK and peroxisome proliferator-activated receptor alpha (PPAR-α) in the liver. At the same time, chlorogenic acid was found to improve hepatic glucose and lipid metabolism by increasing the expression of AMPK and reducing the expression of glucose 6-phosphatase (G6Pase) in the liver, while up-regulating glucose transport 4 (GLUT4)	[186]
		ICR mice model fed with an HFD for 6 weeks	150 mg/kg daily for 6 weeks	Consumption of chlorogenic acid daily for 6 weeks increased mRNA expression of adiponectin and PPAR-α while decreasing the expression of SREBP-1C, fatty acid synthase (FAS), lipoprotein lipase (LPL), adipocyte fatty acid-binding protein (AP2) as well as free fatty acid receptor 2 (FFAR2) in epididymal adipose tissue of HFD-fed mice. Further, it was found that berberine improved lipid metabolism by reduced plasma lipid levels in plasma and diminished hepatic steatosis.	[185]
Curcumin	*Curcumina longa*	Patients with metabolic syndrome	1 g/day for a period of 6 weeks	Supplementation of curcumin increased serum adiponectin concentrations in patients with metabolic syndrome.	[196]
		Obese diabetic (*ob/ob*) C57BL/6 J mice fed with an HFD-diet	3% by weight admixture of curcumin for 6 weeks	Post-treatment with curcumin for 6 weeks dramatically increases serum protein levels and the expression of mRNA of adiponectin in adipose tissue. Another important finding, curcumin prevented hepatic inflammation by decreasing the expression of hepatic TNF-α, suppressor of cytokine signaling-3 and monocyte chemotactic protein 1 (MCP-1) in *ob/ob* mice fed with a HFD-diet.	[198]
		Patients with non-alcoholic fatty liver diseases (NAFLD)	50 mg/day of pure curcumin for 8 weeks	Curcumin supplementation upregulated serum levels of adiponectin and reduced serum levels of leptin in patient with NAFLD. Also, curcumin administration in patient with NAFLD reduced serum levels of low-density lipoproteins (LDL), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and increased levels of high-density lipoproteins (HDL) but the changes were not statistically.	[197]
Piperine	*Piper nigrum*				[203]

(*continued on next page*)

Table 2 (*continued*)

Polyphenols	Plant source	Experimental model used	Treatment dose and intervention period	Review reporting of findings	Ref.
		C57BL/6 N mice fed with HFD for 13 weeks	50 mg/kg and 25 mg/kg for 10 weeks	Piperine treatment was found to prevent steatosis and hepatic insulin resistance through increased adiponectin serum levels and the hepatic expression of AdipoR1 and AdipoR2 in HFD-fed mouse.	
Quercetin	Fruits and vegetables	Wistar rats fed with a HFD for 4 weeks	25 mg/kg for 4 weeks	Dietary quercetin supplementation elevated both serum level and mRNA expression of adiponectin in adipose tissue of HFD-fed Wistar rats. This observed increase on the levels of circulating adiponectin was found to have a negative correlation with the insulin resistance index and serum levels of insulin.	[214]
		C57BL/6-Lep *ob/ob* mice fed with a HFD for 13 weeks	101 mg/kg (0.3 % w/w) daily for 10 weeks	Consumption of dietary quercetin for 10 weeks increased both serum level and protein expression of adiponectin in epididymal adipose tissue and decreased serum levels of TNF-α and MCP-1 levels in *ob/ob* mice. Further, quercetin treatment in HFD-fed *ob/ob* mice improved liver functioning by reducing hepatic contents of triglycerides, serum level of alanine aminotransferase (ALT) and alleviated hepatic steatosis.	[213]
		Humans with Polycystic ovary syndrome (PCOS)	500 mg/kg daily for 12 weeks	Quercetin supplementation increased the transcript expression of AdipoR1 and AdipoR2 as well as the expression of a downstream effector, AMPK in Peripheral blood mononuclear cells isolated from PCOS patients. These results suggested that quercetin supplementation exerts its beneficial metabolic effects in PCOS patients through improving adiponectin and AMPK signaling pathways.	[34]
Resveratrol	The skin of grapes and mulberry, and in red wine	C57BL/6 J mice fed with HFD for 6 weeks	8 mg/kg/day for 4 weeks	Resveratrol administration for 4 weeks increased serum levels of adiponectin and the expression of adiponectin in epididymis fat depots as well as the expression of PPAR-α PPARγ, sirtuin1 and AMPK. Furthermore, that resveratrol is shown to a significantly reduce serum FFAs and TAGs, whilst improving serum levels of liver function markers (ALT and aspartate aminotransferase (AST)).	[33]
		New Zealand White rabbits fed with Cholesterol for 8 weeks	200 or 400 mg/kg body for 8 weeks	Resveratrol supplementation reduced body weight, blood glucose and insulin levels, which correlated negatively with serum levels of adiponectin in cholesterol diet-fed rabbits. In parallel, the co-administration of resveratrol with cholesterol diet improved insulin sensitivity as could be observed through a decrease in both serum levels of insulin and glucose in rabbits.	[227]
		Patients with coronary artery disease	350 mg/day of resveratrol containing grape extract for 6 months, and 700 mg/day for following 6 months.	Chronic daily consumption of a resveratrol containing Grape extract (GE-RES) increased serum levels of adiponectin which correlated inversely with glucose level and hemoglobin A1c (HbA1c). Also, GE-RES inhibited circulation levels of activator protein 1(Ap-1, an inflammatory regulator known to promotes transcription of other pro-inflammatory cytokines.	[231]
		C57BL/6 J mice fed with low fat diet and 29 % ethanol for 3days	400 mg/kg body weight/day for 2 weeks	Administration of resveratrol in ethanol-fed mice upregulated serum levels of adiponectin and increased the expression of AdipoR1 and AdipoR2 in the liver. Also, resveratrol treatment increased hepatic sirtuin 1 (SIRT1) expression and AMPK while suppressing SREBP-1C and activation of peroxisome proliferator-activated receptor γ coactivator α (PGC-1α).	[228]

signaling pathway in macrophages treated with lipopolysaccharide (LPS). Other studies have demonstrated that adiponectin has an inverse correlation with C-reactive protein (CRP), a marker of systematic inflammation known to be mediated by IL-1β [114–116]. Furthermore, according to Skat-Rordam et al. [117] adiponectin and PPARγ serve as an emerging modulator of cellular metabolic functions within the liver. For example, TZD-induced activation of PPARγ enable local and systemic crosstalk by increasing adipocyte lipid uptake and release of inflammatory cytokine that consequently have an insulin sensitizing effect, preventing FFA-induced hepato-lipotoxicity [118]. Consequently, in the liver increased circulation of the fat derived hormone, adiponectin levels subsequently activate AMPK that induces FAO, whilst lowering proinflammatory cytokines and gluconeogenesis, preventing insulin resistance. This was confirmed in a study done on ob/ob mice where recombinant adiponectin was shown to lessen TNFα expression and hepatic steatosis whilst increasing β-oxidation through enhanced PPARα, supporting the direct effect of adiponectin on NAFLD [119]. This suggest that targeting PPARγ in adipose tissue through enhanced adiponectin signaling may mitigate the vicious circle of lipotoxicity and systemic insulin resistance. In this way, developing pharmacotherapeutic ligands that target integrated network of adiponectin and hepatic PPARs, may provide potential therapeutic perspectives for synthesizing anti-obesity as well as anti-inflammatory ligands for treatment of obesity and obesity-induced NAFLD [120–122].

Adiponectin levels are reported to be decreased between 20%–40% during the development of NAFLD [94]. As such, adiponectin is a key player in the management of NAFLD and its associated metabolic diseases. Therefore, interventions that increase adiponectin levels may be valuable for the improvement of NAFLD and its linked complications such as CVD. Thiazolidinediones (TZDs), well-known insulin sensitizers,

have been previously shown to improve adiponectin levels and reduce hepatic fat accumulation in patients with T2D [124–126]. However, many of these insulin sensitizers are associated with an increased risk of developing CVD [127,128]. This has stimulated interest in investigating alternative therapies such as instigating the role polyphenols might play in increasing adiponectin levels, whilst improving insulin sensitivity, lipid metabolism and inflammation in conditions of metabolic syndrome. This is particularly significant since polyphenols consumed in moderation are known to have fewer or no side effects. Therefore, in the following section, we reviewed the therapeutic potential of several polyphenols and their impact in regulating adiponectin levels, including it signaling in conditions of NAFLD.

4. The role of polyphenols in the regulation of adiponectin levels in conditions of metabolic syndrome

Polyphenols are naturally occurring phytochemicals and secondary metabolites found largely in fruits, vegetables, cereals and beverages as well as herbal medicines [129]. Generally, polyphenols have been categorized into different groups which include phenolic acids, flavonoids, stilbenes, and lignans [130]. These classes are based on the number of phenol rings they contain and the structural elements binding these rings to one another. Indeed, much experimental evidence shows that these secondary metabolites exhibit tremendous potency against the development of diseases such as diabetes, obesity, CVD, cancer and neurodegenerative diseases [131–133]. Consequently, polyphenols have gained the interest of public and scientific societies due to their potential health benefits in metabolic diseases. Our group has progressively investigated and scrutinized published literature reporting on the impact of polyphenols and their ameliorative effects against metabolic complications, whilst assessing their proposed therapeutic mechanisms of action [134–138]. In this review, we discuss the beneficial effects of several well-studied polyphenols and their impact on adiponectin levels, including ameliorative effects against lipid metabolism, inflammation and insulin resistance We discuss polyphenols such as aspalathin, berberine, catechins, chlorogenic acid, curcumin, genistein, piperine, quercetin, and resveratrol, and elaborate on their potential role in the treatment of metabolic diseases through the regulation of adiponectin signaling as summarized in Table 2.

4.1. Aspalathin targets NAFLD-related complications in preclinical settings but only increases adiponectin expression in cultured cardiomyocytes

Aspalathin is a flavonoid unique to *Aspalathus linearis,* a plant endemic to South Africa and commonly referred to as rooibos. Aspalathin has been shown to possess several biological activities such as antioxidant, anti-inflammatory, anti-diabetic, anti-mutagenic and cardio-protective properties [134,139–143]. In LPS-treated HUVECs, aspalathin suppressed inflammation by inhibiting Toll-like receptor 4 (TLR4) expression [140]. In cultured H9c2 cardiomyoblasts, aspalathin prevented doxorubicin-induced oxidative damage by increasing endogenous antioxidant content while inhibiting ROS production and lipid peroxidation [141]. Furthermore, Mazibuko et al. [144] reported on the ability of aspalathin to decrease lipid metabolism and increase glucose uptake by modulating key genes involved in energy metabolisms such as AMPK, PPAR-α and CPT1. Relevant to the liver, this dihydrochalcone ameliorated hepatic insulin resistance by stimulating the PI3K/AKT pathway in palmitate-exposed C3A hepatocytes [138]. While an aspalathin-enriched green rooibos extract ameliorated palmitate-induced alterations in glucose and lipid metabolism in part by modulation PI3K/AKT and AMPK mechanisms in C3A cells [145]. This extract could significantly reduce serum total cholesterol and iron levels, whilst enhancing that of alkaline phosphatase enzyme activity in Fischer rats [146]. Although not in the liver, aspalathin treatment increased adiponectin gene expression in cultured cardiac cells, concomitant to reducing that of peroxisome proliferator-activated receptor gamma (PPAR-γ), SREBP-1C and pro-inflammatory markers after high glucose exposure [147]. As recently reviewed [148], including evidence from *db/db* animals [147] suggest that aspalathin can ameliorate complications linked with metabolic syndrome in preclinical settings, as mainly demonstrated by its capability to reduce enhanced serum cholesterol levels. Available literature shows that this dihydrochalcone is able to activate the most important pathological processes in the etiology of NAFLD and so to downstream regulators of adiponectin. However, a paucity of data exist on the role aspalathin plays in adiponectin signaling as a potential therapy to improve NAFLD. As such, additional studies, especially clinical trials, are necessary to confirm the role of aspalathin in health as a dietary supplement, a preferable therapy for the treatment of NAFLD.

4.2. Berberine attenuates NAFLD-associated complications in part by increasing the expression of adiponectin and its downstream targeted genes in preclinical settings

Berberine is an isoquinoline alkaloid found in roots, rhizomes and stem barks of several plants [149]. This bioactive compound is known to have multiple beneficial effects, which include antioxidant, anti-inflammatory, hypoglycemic and cholesterol-lowering properties [150–152]. Recently, berberine was found to improve glucose and lipid metabolism through increased expression of glucose transporter 4 (GLUT4), mitogen-activated protein kinase 14 (MAPK14), MAPK8, JNK and PPARα in diabetic *KKAy* mice [153]. The antioxidant properties of berberine are related to increasing the messenger RNA (mRNA) expression of SOD, but decreasing that of GSH and GSH-Px levels in diabetic mice [154]. This alkaloid suppressed LPS-induced inflammation through inhibition of TNF-α, cyclooxygenase-2 (COX-2) and nitric oxide synthase (NOS) in murine BV-2 cells [155]. Such evidence has been confirmed by others showing that berberine attenuated inflammation by reducing TNF-α, IL-6, IL-1β, nitric oxide (NO), COX-2 and NOS mRNA expressions in LPS-stimulated RAW264.7 cells [156]. Additional studies have reported on the ability of this alkaloid to attenuate hepatic fat accumulation through the inhibition of lipogenesis and gluconeogenesis [157–159]. Of interest, the role of berberine in the management or treatment of NAFLD has been well-documented [157,160–164]. Briefly, berberine treatment reduced hepatic fat content and body weight, while improving glucose levels and lipid profiles in NAFLD patients [160]. It improved glucose control and decreased hepatic inflammation and steatosis in HFD-fed mice [162]. Mechanistically, berberine reduced lipid content and attenuated hepatic steatosis through overexpression of the intracellular antioxidant response system controlled by nuclear factor erythroid 2–related factor 2 (Nrf2) in HFD-fed in rats [164]. Interestingly, berberine treatment increased serum concentration of adiponectin and the expression levels of AdipoR1, AdipoR2 and AMPK in the kidney in HFD-fed Wistar rats [165]. Elsewhere, Wu and co-workers berberine improved insulin sensitivity by increasing the ratio of high-molecular-weight adiponectin level, as well as the expression of AdipoR1 and AdipoR2 in skeletal muscle and liver tissue of HFD-fed rats [166]. Taken together, these findings suggest that berberine treatment can abrogate hepatic manifestation of metabolic syndrome by improving glucose and lipid metabolism. As such, clinical studies would be an added advantage in the fight against hypercaloric diet induced lipotoxicity and subsequent NAFLD.

4.3. Catechin attenuates NAFLD-related complications in preclinical settings in part by increasing serum levels

Catechins are a group of polyphenols that includes (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin, (−)-epicatechin-3-gallate and (−)-epicatechin), found in green tea, cocoa, fruits, berries and red wines. Catechins, especially EGCG, are known to contain strong antioxidative and anti-inflammatory activities [167–169]. In cultured

3T3-L1 adipocytes, catechin attenuated TNF-α-induced pro-inflammatory responses by reducing IL-1α, IL-1β, IL-6, IL-12 and TNF-α cytokines [169]. Exposure to EGCG treatment inhibited the production of pro-inflammatory mediators such as NO and prostaglandins through decreased mRNA expression of NOS and COX-2 in LPS-stimulated murine macrophages [168]. The same compound was found to reduce fat accumulation by increasing lipolysis and hormone-sensitive lipase (HSL) gene expression in 3T3-L1 adipocytes [170]. In addition, catechin-rich green tea decreased hepatic lipogenesis through increasing the expression of AMPK-Thr^{172} while reducing that of ACC and SREBP1-C in rats with HFD-induced NAFLD [171]. Consistent with effects related to liver function, EGCG treatment improved lipid profiles, and attenuated hepatic steatosis through regulation of SREBP1-C and other lipid metabolic related genes including LXRα, FAS and SIRT1 in HFD- fed rat [172]. Importantly, a clinical trial by Sakata and co-workers [173] found that green tea with high-density catechin at a dose of 1080 mg/700 mL for 12 weeks improved liver function and reduced urinary 8-isoprostane excretion after 12 weeks of consumption in NAFLD patients. Interestingly, Cho and colleagues [174] showed catechin upregulated the expression of adiponectin by suppressing the Kruppel-like factor 7 (KLF7) expression, in 3T3-L1 adipocytes. Similarly, a study by Vazquez Prieto and colleagues [175] showed catechin treatment in high fructose (HFR) diet-fed rats upregulated serum levels and protein expression of adiponectin in adipose tissue. Taken together, catechins or catechin-rich foods might be the best candidate in the enhancement of adiponectin to attenuate NAFLD, however there is little or evidence about this from human studies.

4.4. Chlorogenic acid improves adiponectin signaling to attenuate NAFLD-related complications in preclinical settings

Chlorogenic acid is one of the abundant polyphenolics found in fruits and vegetables as well as coffee and tea. Chlorogenic acid is known to possess antioxidant, anti-inflammatory and anti-carcinogenic activities [176–179]. For example, chlorogenic acid reduced NO production, as well as the expression of pro-inflammatory cytokines (COX-2 and iNOS, IL-1β and TNF-α) in LPS-stimulated RAW 264.7 cells [177]. Reviewed evidence suggests that chlorogenic acid ameliorates metabolic complications by improving glucose and lipid metabolism [180]. For instance, Wan et al. [181] found that chlorogenic acids treatment prevented fat accumulation by decreasing plasma total cholesterol and LDL, while increasing the levels of HDL through increase expression of PPAR-α in hypercholesterolemic rats. Likewise, chlorogenic acids improved hepatic lipid metabolism through activation of AMPK and subsequent CPT-1 whilst inhibiting the expression of ACC1 in HFD-fed rats [182]. Consistently, chlorogenic acid prevented liver injury and insulin resistance by inhibiting the JNK pathway in HFD-induced NAFLD in rats [183]. Recently, chlorogenic acid in combination with telmisartan improved insulin resistance, histopathological alterations and reduced serum lipid content as well as liver enzymes (AST and ALT) in HFR-induced NAFLD in rats [184]. Interesting, this compound improved adiponectin signaling by upregulating the mRNA expression levels of this adipokine and PPAR-α, while reducing the levels of lipogenic genes including FAS and SREBP-1C in adipose tissue of HFD-fed mice [185]. In *db/db* mice, chlorogenic acid exerted anti-diabetic effects through increasing the expression of adiponectin in adipose tissue and that of AdipoR1, AdipoR2, AMPK and PPAR-α in the liver [186]. Although chlorogenic acid can affect the mRNA expression levels of adiponectin or that of its receptors to attenuate NAFLD-related complications in preclinical settings, such information is still to be confirmed human studies.

4.5. Curcumin improves liver function in conditions of NAFLD in part by increasing serum levels of adiponectin

Curcumin, also called diferuloylmethane, is the main natural polyphenol found in *Curcumina longa* (turmeric) used as a spice and food coloring agent. Curcumin is known to have strong antioxidant properties and anti-inflammatory effects [187,188]. Recent evidence demonstrated the antioxidant properties of curcumin are related to the suppression of ROS and malondialdehyde levels, and enhancements in antioxidants like SOD, CAT and GSH-Px in H_2O_2-treated RAW264.7 cells [189]. Curcumin improved lipid metabolism and attenuated inflammation by decreasing the levels of FFAs, LDL and TNF-α in T2D rats [190]. In particular, the effect of curcumin against NAFLD has been extensively reported [191–194]. For example, curcumin ameliorated the severity of steatosis by reducing hepatic lipid accumulation through upregulating mRNA expression of AMPK and decreased SREBP-1C, ACC, FAS, while inhibiting O-GlcNAcylation and NF-κB pathway in methionine and choline-deficient diet-fed mice [191]. A randomized trial conducted by Panahi et al. [194] found that short-term supplementation with curcumin at a dose of 1 000 mg/day ameliorated hepatic steatosis and improved the levels of AST and ALT transaminase levels in patients with NAFLD. Interestingly, clinical evidence suggests that curcumin elevates serum levels of adiponectin in patients with metabolic syndrome [195, 196]. In another randomized double blinded trial, curcumin supplement significantly increased serum levels of adiponectin in patient with NAFLD and decreased LDL, AST and AST but not significant [197]. In preclinical models, curcumin supplementation increased adiponectin production in the adipose tissue and reduced insulin resistance in HFD-fed C57BL/6 J mice [198]. All these studies clearly suggested the therapeutic potential of curcumin in the prevention and treatment of human disease, specifically NAFLD. Of interest, the beneficial role of curcumin on adiponectin levels was confirmed in clinical studies involving patient with metabolic diseases including NAFLD patient.

4.6. Piperine attenuates NAFLD-related complications in part by increasing serum levels of adiponectin in preclinical settings

Piperine is an important alkaloid found in plants of the *Piperaceae* family. It is the bioactive compound responsible for the pungency of black pepper [199]. Piperine displays a broad spectrum of anti-inflammatory and antioxidant properties in different experimental settings [151,152]. This compound reduced the expression of IL-6 and the migration of activator protein 1 (AP-1) in a dose-dependent manner in an experimental model of arthritis [200]. It attenuated microcystin-induced oxidative damage by increasing hepatic levels of GSH, SOD, CAT, and GSH-Px contents in mice [201]. Piperine also improved glucose and lipid metabolism in skeletal muscles during exercise in mice [202]. Most importantly, piperine treatment could reverse high fat diet-induced hepatic steatosis and insulin resistance in part by increasing serum levels of adiponectin and the hepatic expression of AdipoR1 and AdipoR2 in a dose-dependent manner in mice [203]. In a clinical setting, co-administration of curcumin (500 mg/day) and piperine at the dose of 5 mg/day for 12 weeks ameliorated hepatic steatosis severity, an effect that was related to the reduction of serum levels of AST, ALT, TC and LDL [204]. However, additional studies are needed to assess the therapeutic effects of piperine in modulating NAFLD-related complication, especially through the modulation of adiponectin.

4.7. Quercetin attenuates NAFLD-related complications in part by increasing the expression of adiponectin and its receptors

Quercetin (3,30,40,5,7-pentahydroxyflavone) is a potent plant-derived flavonoid with known anti-inflammatory properties both *in vitro* and *in vivo* [205–208]. The biological activities of quercetin are related to the suppression of TNF-α and NO levels in LPS stimulated macrophages [205]. This flavonol prevented ochratoxin A-induced inflammatory response by down-regulating COX-2 in hepatoma HepG2 cells [207]. In addition to its anti-inflammatory properties, the role of quercetin in hepatic lipid accumulation has been well demonstrated through various experimental models [209–211]. For example,

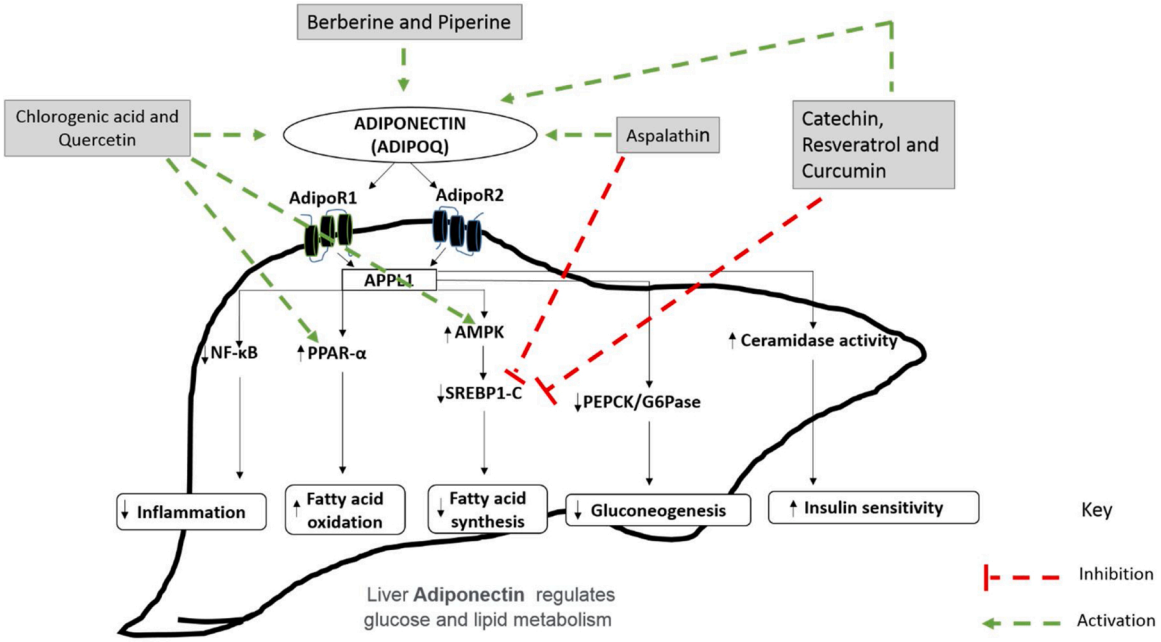

Fig. 3. The possible mechanism underlying the effect of polyphenols on adiponectin signaling in the liver. Polyphenols may prevent hepatic accumulation of lipid associated with NAFLD by increasing the serum levels of adiponectin as well as the expression of its downstream targeted genes such as adiponectin receptors (AdipoR1 and AdipoR2), AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-alpha (PPAR-α) while decreasing the expression of sterol regulatory element-binding protein 1 SREBP-1C, a gene that promotes lipogenesis and inhibit fatty acid oxidation.

Hoek-Van den Hil and co-workers [209] demonstrated that quercetin treatment reduced hepatic fat accumulation by regulating the gene response associated with lipid metabolism: acyl-CoA thioesterase 3 and fatty acid-binding protein 5 in HFHS-fed mice. Likewise, this flavonol improved hepatic lipid accumulation by reducing the mRNA expression of SREBP-1C and FAS in HepG2 cells [211]. Quercetin treatment ameliorated HFD-induced NAFLD through enhanced hepatic VLDL assembly in Wistar rats [212]. Apparently, increasing adiponectin levels to improve insulin and alleviating pro-inflammatory cytokines like TNF-α and MCP-1 is one of the mechanisms related with the therapeutic effects of quercetin against NAFLD in *ob/ob* Mice [213]. Certainly, dietary quercetin supplementation ameliorated insulin resistance by elevating both serum level and mRNA expression of adiponectin in HFD-fed Wistar rats [214]. Interestingly, in a clinical setting, quercetin supplementation (two 500 mg capsules daily for 12 weeks) ameliorated metabolic complications by upregulating the expression adiponectin receptors (AdipoR1 and AdipoR2) from peripheral blood mononuclear cells and serum AMPK in women diagnosed with polycystic ovary syndrome (PCOS) [34]. Although, the role of quercetin in NAFLD has been evaluated in preclinical settings, clinical studies are very limited.

4.8. Resveratrol attenuates NAFLD-linked complications in part by increasing serum levels of adiponectin and mRNA expression of downstream effectors

Resveratrol (3, 5, 4′-trihydroxystilbene) is a natural phytoalexin found in the skin of grapes, berries and red wine. Because of its potential as an antioxidant, anti-inflammatory, cardioprotective, and anti-cancer agent, resveratrol has gained popularity in both scientific and pharmaceutical industries [215–217]. For example, Guo and colleagues [218] showed that resveratrol treatment suppressed NADPH oxidase-derived ROS generation and increased the activity of SOD, CAT, and glutathione peroxidase in primary culture of neonatal rat cardiomyocytes exposed to high glucose. Moreover, comparative use of resveratrol and metformin has been recently reviewed to show beneficial effects in improving diabetes-associated complications in preclinical settings [219]. Some of the prominent mechanisms involved in the ameliorative effects of resveratrol include optimal regulation of glucose and lipid metabolism, as well as controlling dyslipidemia. Notably, resveratrol resulted in a dose-dependent reduction in total cholesterol, TG and LDL in HFHS-fed rats [220]. Consistently, resveratrol improved serum lipid profiles and decrease body fat deposition, which was associated with the decrease in FAS and PPARγ mRNA levels and increased CPT-1 in muscle and adipose tissues in experimental models of metabolic disease [221]. Furthermore, that resveratrol ameliorated hepatic steatosis by improving lipid metabolism and redox homeostasis through activation of PPARα in a rodent model of HFD-induced NAFLD [222]. It attenuated liver steatosis and improved insulin sensitivity by enhancing hepatic expression of AMPK and peroxisome proliferator-activated receptor- γ coactivator 1α (PGC-1α) in mice on a high-calorie diet [223]. Recently, it was shown that administration of 200 mg trans-resveratrol for 6 months protected the liver by reducing TAG accumulation and improved insulin sensitivity in a patient with NAFLD [224]. Importantly, numerous studies have suggested that resveratrol improves insulin sensitivity by increasing adiponectin levels [225–227]. Resveratrol administration has also been shown to enhance serum levels and mRNA expression of adiponectin and AMPK in adipose depots of HFHS-fed mice [33]. Elsewhere, resveratrol supplementation also increased serum levels of adiponectin while reducing blood glucose and insulin levels in cholesterol diet-fed rabbits [227]. Also, resveratrol supplementation increased circulating adiponectin levels and hepatic mRNA expression of AdipoR2 and AdipoR2 in ethanol-fed mice [228]. Evidence from randomized clinical trials has already demonstrated that resveratrol administration improves insulin sensitivity, as well as glucose and lipid metabolism in patients with NAFLD [229,230]. Relevant to adipokine regulation, dietary intervention with a resveratrol-containing grape extract dietary (grape phenolics plus 8 mg resveratrol for 6 months) increased serum levels of adiponectin which inversely correlated with glycated hemoglobin (HbAc1) and glucose levels in patients with coronary artery disease [231].

5. Conclusion

This study set out to provide a better understanding of the role

polyphenols plays in the modulation of adiponectin signaling and the effect thereof on the pathogenesis of NAFLD. There is increasing evidence that adiponectin serum level changes, which occur during the expansion of adipose tissue, contribute to the development not only of metabolic syndrome but also to the onset and progression of NAFLD to NASH and possibly to NASH-related cirrhosis [26,232]. In this way adiponectin can be a suitable disease-marker. As such, this study supports the notion that polyphenols such as resveratrol, berberine and catechin can protect against the development of NAFLD and associated complications. For example, beyond alleviating inflammation or effectively regulating lipid and glucose metabolism by modulating AMPK, these polyphenols may have enhanced potential to increase levels of adiponectin and the expression of its receptors to influence metabolic function. Interestingly, the therapeutic potential of these compounds is consistent with their regulatory effect of prime mechanisms involved in energy metabolism (Fig. 3). This review found that most of these studies were done using *in vitro* and *in vivo* animal models, while research on human subjects has been limited. Similarly, functional studies directly informing on how these polyphenols modulate adiponectin to improve liver functions under conditions of NAFLD are still scarce. As such, this study concludes that there is a need for researchers to focus on therapeutic interventions to enhance serum and hepatic expression levels of this adipokine for effective management of NAFLD and related complications.

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Authors contribution

S.C.S prepared and wrote the manuscript, R.J develop the concept and helped to draft the manuscript, P.V.D, L.M, A.P.K, A.K.B and C.P were involved in critically revising of the manuscript. All authors read and approved the final version to be submitted for publication.

Declaration of Competing Interest

The authors report no declarations of interest.

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