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Review article

Polyphenols regulating microRNAs and inflammation biomarkers in obesity

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ABSTRACT

Obesity is one of the most prevalent health problems worldwide. It is a complex disease that is generally accompanied by insulin resistance, increases in oxidative stress and inflammation biomarkers, and potentially, microRNA (miRNA) dysregulation. Polyphenols may act on obesity and its metabolic consequences. Circulating miRNAs have been studied as potential biomarkers for inflammatory and metabolic diseases, and their use may improve the diagnostic tools currently available and the ability to diagnose specific diseases. To our knowledge, data regarding the link between the consumption of polyphenols from food sources, miRNA expression, and inflammation biomarkers related to obesity is scarce, and most data available describing this relationship are found in cancer studies. This review focuses on the polyphenols that modulate the metabolism, inflammation, or both related to obesity to understand the extent to which miRNA expression can be modulated by dietary interventions.

Introduction

Inflammation biomarkers in obesity

Obesity is a serious public health problem with epidemic proportions in both developed and developing countries. In 2016, it was estimated that >1.9 billion adults were overweight (i.e., 39% of adults were overweight worldwide), of which more than 650 million, ~13%, were obese [1]. Obesity with fat accumulation in the abdominal area, especially viscerally, is strongly associated with an increased risk for type 2 diabetes (T2D), hypertension, atherosclerosis, cardiovascular disease (CVD), and cancer [2].

Chronic low-grade inflammation, a characteristic of obesity, may be a critical player in the initiation, propagation, and development of metabolic disorders, such as insulin resistance (IR) and dyslipidemia [3]. Low-grade inflammation leads to increased immune system cell infiltration and the production of inflammatory cytokines in adipose tissue [4]. In response to inflammatory signals, the adipose tissue releases inflammatory mediators and acute-phase proteins, such as tumor necrosis factor (TNF)-α; plasminogen activator inhibitor (PAI)-1; interleukin (IL)-6, IL-1 β, and IL-8; and inflammatory modulators, such as leptin, resistin, and adiponectin, which have been identified as the main factors that link obesity to its related complications [5,6]. In individuals with T2D [7], reduction in serum IL-1 β levels was one of the factors determining the success of T2D remission after metabolic surgeries. The reduced IL-1 β after surgery may have a systemic effect, reducing IL-1 β-induced toxicity on pancreatic β cells and the inflammation in adipose tissue, whose fact contributes to the normalization of blood glucose.

TNF-α, mainly derived from infiltrated macrophages, is involved in chronic inflammation and is responsible for inducing IR in the adipose tissue of obese individuals [8]. TNF-α acts on TNF receptors (TNFRs) by inducing the production of inflammatory cytokines and lipolysis along with the release of saturated fatty acids from adipocytes, which serve as ligands for toll-like receptors (TLR)-4, whose ligands induce the release of inflammation products, such as TNF-α, IL-6, and monocyte chemoattractant protein (MCP)-1. The presence of saturated fatty acids and TNF-α creates a vicious cycle characterized by the exacerbation of inflammatory cytokines, the inhibition of gene expression, and the synthesis of adiponectin (Fig. 1) [9].

TNF-α stimulates a chronic inflammation environment in obese adipose tissue by blocking the expression of adipogenic genes, such as the peroxisome proliferator-activated receptor γ gene (*PPARγ*), *C/EBPα*, and *FABP4* [6,10]. The release of fatty acids from adipocytes for circulation favors IR and contributes to liver steatosis and non-alcoholic fatty liver disease (NAFLD) [11]. The inflammatory environment in adipose tissue also induces oxidative stress and endothelial dysfunction, increasing the risk for CVD [3]. On the other hand, adiponectin increases the expression of IL-10, an anti-inflammatory cytokine, in human macrophages [12]. The antihypertensive and antiatherogenic properties of adiponectin can be

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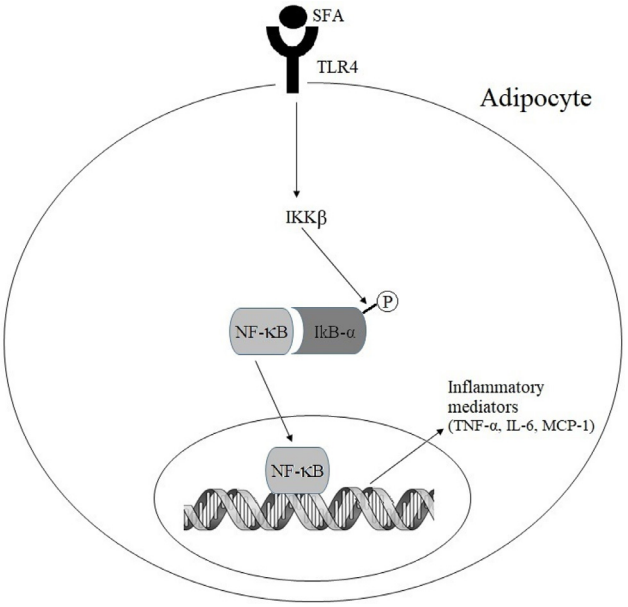

Fig. 1. Effect of saturated fatty acid on the TLR4 pathway. The TLR4 pathway increases the expression of proinflammatory biomarkers, such as TNF-α, IL-6 and MCP-1, by activating the transcription factors NF-κB. IKK, IkappaB kinase; IL, interleukin; MCP, monocyte chemoattractant protein; NF, nuclear factor; SFA, saturated fatty acid; TLR, toll-like receptor.

explained by their ability to stimulate nitric oxide production and reduce the expression of adhesion molecules on the endothelial cells [13].

microRNAs in inflammation related to obesity

microRNAs (miRNAs) regulate several cellular processes, such as growth, proliferation, differentiation, and apoptosis. They also are important for adipogenesis and the regulation of metabolic and endocrine functions in cells [3]. miRNAs have been associated with inflammation, oxidative stress, impaired adipogenesis, insulin signaling, apoptosis, and angiogenesis in obesity [14]. As miRNAs are involved in almost all biological processes and affect most metabolic pathways, the dysregulation of some miRNAs can lead to metabolic disorders and other diseases such as obesity, CVD, NAFLD, and T2D [15].

miRNAs are small noncoding RNAs (~22 nucleotides in length) that modulate gene expression. They are initially transcribed from DNA by RNA polymerase II in the nucleus, forming 'primary miRNA transcript' (pri-miRNA). This transcript is then cleaved by microprocessor complex, which comprises the double-stranded RNase III enzyme DROSHA and its essential cofactor, the DiGeorge syndrome critical region 8 (DGCR8), originating a shorter sequence called the 'miRNA precursor' (pre-miRNA), which displays a hairpin-like secondary structure. The pre-miRNAs are then exported to the cytoplasm by Exportin-5 and cleaved by RNase III Dicer to generate mature and functional miRNAs. Through an association with the Argonaute family of proteins, mature miRNAs are incorporated in the RNA-induced silencing complex (RISC), which binds to the 3′ untranslated region of the target mRNA. Subsequently, miRNAs regulate the expression of proteins by cleaving mRNA or repressing its translation, depending on the level of complementarity between the miRNA and the target mRNA. miRNAs can regulate >60% of all human genes [16–19]. Each miRNA can regulate several genes, and several miRNAs can act on the same gene. miRNAs can act directly on the target mRNA or indirectly by regulating intermediate components, such as transcribers that encode transcription factors, which in turn control the expression of genes. miRNAs also can change the expression of proteins that influence cell function and affect the expression of miRNA [3].

miRNAs can act in the cell in which they were produced, or they may be released into the blood, regulating gene expression in other cells. Circulating miRNAs are stable because they circulate inside microparticles, such as microvesicles and apoptotic bodies; some are associated with Argonaute2 or RNA-binding proteins or are linked to extracellular protein complexes, such as high-density lipoprotein (HDL). These structures protect the circulating miRNAs from ribonuclease activity and degradation [3,20]. miRNAs may be directly involved in the development of diseases such as cancer, T2D, and CVD [16].

miRNAs may play a role in the communication between adipocytes as well as between the adipose tissue and other tissues. The transfer of miRNAs appears to be involved in the transcription of multiple genes needed for lipid synthesis and cellular growth. miRNAs contained in exosomes from adipocytes can control the storage of lipids in the adipocytes and the size of these cells. Notably, miRNAs can act as potential diagnostic biomarkers because they fulfill most of the criteria that define a good biomarker (i.e., they can be rapidly and accurately detected by non-invasive methods, they have high sensitivity and specificity for the disease of interest, they allow for early detection, and they have a long half-life in samples). As such, the identification of dysregulated miRNAs during the development of obesity may provide early biomarkers for the clinical diagnosis of obesity [21–23].

miRNAs are closely associated with the inflammation arising from obesity in vitro [24–27], in vivo [4,8,28], and in clinical trials [3,29]. The miRNA profile was evaluated in human adipocytes and THP-1 cells (a macrophage cell line) at baseline and after stimulation with lipopolysaccharide (LPS; 10 ng/mL). The miRNAs that changed most significantly were subsequently studied in human subcutaneous adipose tissue, before the weight loss induced by bariatric surgery and 2 y after the surgery. In the in vitro study, the adipocytes and M1 macrophages presented an increased expression of a number of miRNAs, including miR-221, miR-222, and miR-155, as well as increased expression of the genes encoding IL-6 and TNF-α. The analysis of the subcutaneous adipose tissue showed a reduction in the number of macrophages and in the expression of inflammatory genes after weight loss. These results suggest that inflammation can alter the miRNA profile in adipocytes [30].

Several nutrients and non-nutrients, including polyphenols, can regulate signaling pathways involved in the inflammatory response, in the reduction of oxidative stress, and in the modulation of miRNA expression, contributing to the control of inflammation in the white adipose tissue of obese individuals.

Polyphenols, obesity-related miRNAs, and health

Polyphenols are the most abundant phytochemicals in fruits and vegetables. They represent a wide variety of compounds, separated into classes, according to their chemical structure as follows: phenolic acids (hydroxybenzoic and hydroxycinnamic acids), flavonoids (flavonols, flavanols, flavones, isoflavones, flavanones, and anthocyanins), stilbenes, lignans, and curcuminoids. It is estimated that the dietary intake of these compounds is 1 to 1.2 g/d, of which 40% are flavonoids [19,31]. Most polyphenols are present in food in the conjugated form with sugars and organic acids, or as polymers in the case of flavonoids. It is estimated that 5% to 10% of polyphenols are absorbed in the small intestine. After absorption, they undergo conjugation in the small intestine, liver, or both. Most

polyphenols reach the colon, where they are metabolized extensively by enzymes produced by the intestinal microbiota. As such, polyphenols reach blood circulation and target tissues in their conjugated metabolite form, mainly glucuronidated, sulfated, or methylated, and are chemically distinct from those ingested with food [19,32].

The average daily intake of polyphenols required to obtain benefits is extremely difficult to estimate, for many reasons, including structural diversity of polyphenols, lack of standardized analytical methods, and variation of content in a particular foodstuff. The biological effects of polyphenols not only depend on the amount of the polyphenols ingested, but also on the metabolites that are produced either in tissues or by the colonic microbiota [33]. Genetic predisposition and environmental factors may affect the biological outcome and lead to further complications for establishing dose–effect relationships [34].

Epidemiologic studies suggest that a high intake of dietary polyphenols is associated with a reduced risk for CVD, inflammatory and metabolic diseases, and some types of cancer. Polyphenols can interact with cell-signaling pathways, modulate the activity of transcription factors, and consequently, the expression of genes [19,31]. Polyphenols can reduce the risk for diseases associated with excessive reactive species [35]; they also change lipid metabolism, reduce low-density lipoprotein cholesterol (LDL-C) oxidation, delay the development of atherosclerotic lesions, improve endothelial function, reduce blood pressure, inhibit platelet aggregation, reduce IR, and regulate inflammation [19]. Polyphenols can exert beneficial effects against obesity by modulating the development of adipose tissue, oxidation, and inflammation markers [36]. Within polyphenols, flavonoids, such as epigallocatechin 3-gallate (EGCG), deserve special attention as they improve glucose homeostasis, lipid metabolism, and endothelial function. They also can reduce oxidative stress and blood pressure. Health effects of flavonoids have been mainly attributed to the modulation of gene expression that codes key metabolic proteins. These gene modifications can result from the interaction of flavonoids with signaling cascades or with epigenetic factors such as miRNAs [20].

More than 100 miRNAs that are involved in the control of different cell processes, such as inflammation and apoptosis, have been shown to be modulated by polyphenols [37]. The molecular structure of the polyphenol determines the nature of its association with certain miRNAs. miRNA modulation by polyphenols appears to be a new strategy for regulating metabolism and related diseases [15]; however, it is not yet known which mechanisms are involved in this regulation [19,32]. Possibly, the interaction between polyphenols and miRNAs influences the functionality of the miRNA by altering its binding to the seed sequence of the mRNA related to the target gene. Alternatively, the polyphenols may bind to a component involved in miRNA biogenesis, such as Dicer or RISC [15,32,38]. Most studies investigating miRNAs as mediators of the effects of polyphenols in cells have been conducted in the context of cancer; only a few studies have focused on metabolic diseases.

In vitro studies

There is evidence that cyanidin-3-glucoside (C3G) protects against oxidative damage in human erythrocytes, reduces the risk for obesity, decreases weight and adipose tissue, and ameliorates hyperglycemia in mice, improving IR. This molecule also improves endothelial vascular integrity and reduces the risk for inflammatory diseases [35,39]. C3G and delphinidin-3-glucoside have been shown to induce the secretion of insulin and possess antidiabetic activity [35]. The treatment of mice 3 T3-L1 adipocytes with açaí (*Euterpe oleracea* Martius) extract (particularly cyanidin-3-rutinoside and C3G), which is a source of anthocyanidins, resulted in reduced levels of leptin and PAI-1 and increased levels of adiponectin. Furthermore, this extract reduced oxidative stress and inhibited the nuclear factor-kappa B (NF-κB) pathway along with the expression of its target genes *TNF-α, MCP-1, IL-6, IL-8, IL-1 β,* and *INF-β* (interferon-β), demonstrating the importance of polyphenols for reducing inflammation in adipose tissue [6].

The effects of EGCG, the main polyphenol in green tea, were evaluated in HepG2 cells using several concentrations and times. The expression of five miRNAs was reduced after treatment with 50 μM EGCG for 5 h (miR-30 b*, miR-453, miR-520 e, miR-629, and miR-608). Using 100 μM EGCG for 24 h, the expression of 13 miRNAs was upregulated (e.g., let-7 a, miR-16, miR-221), and the expression of 48 miRNAs was downregulated (including miR-18 a, miR-34 b, miR-193 b, miR-222, and miR-342). Therefore, the number and types of miRNAs regulated by EGCG depend on the exposure time and the concentration of EGCG [40].

Quercetin, the largest representative of flavonols in the human diet, is found in onion, apple, tea, and red wine and appears to modulate miRNAs. The treatment of murine macrophages with quercetin after stimulation with LPS resulted in attenuation of the expression of inflammatory genes, as demonstrated by the downregulation of TNF-α, inducible nitric oxide synthase, IL-1 β, IL-6, macrophage inflammatory protein-1 α, and the inhibition of NF-κB and activation of the Nrf2 pathway. Quercetin also decreased the expression of miR-155 after LPS stimulation of macrophages [41]. Human adipocytes treated with C3G, at a concentration of 10 or 30 μmol/L, presented a lower expression of the genes encoding MCP-1 and IL-1 β induced by TNF-α [42].

Resveratrol (3,4′,5-trihydroxystilbene), the main component of stilbenes, is found naturally in grapes and other berries, red wine, and peanuts and has anti-inflammatory, antioxidant, and antiproliferative activity [19]. The biological effects of resveratrol appear to be associated with the regulation of cell-signaling pathways and gene expression. This compound has anti-obesity properties, as demonstrated by a reduction in the proliferation and differentiation of preadipocytes, increased apoptosis of adipocytes, mobilization of lipids, oxidation of fatty acids, and reduction of de novo lipogenesis [43]. Resveratrol has been widely studied in relation to miRNAs [19,20,32,37,38,43–45].

The curcuminoids, particularly curcumin, are known for their anti-inflammatory, antioxidant, immunomodulatory, and antiangiogenic activities [19]. Curcumin, found mainly in the rhizome of the *Curcuma longa*, modulates the inflammation induced by obesity in the adipose tissue and liver, improving glycemic control and diminishing weight gain in obese animals. Septembre-Malaterre et al. [36] studied the effects of *Curcuma longa* polyphenols (12.5 μM) on 3 T3-L1 adipocytes submitted to oxidative stress induced by hydrogen peroxide (200 μM). The authors verified that curcuminoids upregulated *PPARγ* gene expression and adiponectin secretion. Curcuminoids also attenuated the production of IL-6 and MCP-1 and downregulated *NF-κB* gene expression rate when induced by oxidative stress. Moreover, curcuminoids reduced intracellular concentration of reactive oxygen species (ROS) and modulated the expression of superoxide dismutase (SOD) and catalase genes.

Analyzing the effects of curcumin and resveratrol on NF-κB activation in adipocytes treated with TNF-α, Gonzales and Orlando [46] observed that these polyphenols inhibited NF-κB translocation to the nucleus and the expression of inflammatory genes (*TNF-α, IL-1 β, IL-6* and cyclooxygenase 2 [*COX-2*]). The incubation of adipocytes with TNF-α elevated the expression of the *IL-6* and *COX-2* genes, in addition to activating *IL-1 β* gene expression and increasing the translocation of NF-κB. However, when the adipocytes

were treated with TNF-α and curcumin or resveratrol, there was inhibition of IκB degradation and consequently translocation of NF-κB. The activation of NF-κB is responsible for the production of several inflammatory cytokines and chemokines. Because the action of several miRNAs (such as miR-132, miR-146 b, miR-155, and miR-181 b) can modulate a number of physiological functions that are regulated by the NF-κB pathway, such as the immune response, proliferation, cell death, and inflammation, the action of polyphenols on the NF-κB pathway can enable or inhibit the inflammatory response in adipocytes (Fig. 2) [14,25,26]. Table 1 presents the summary of findings from in vitro studies.

In vivo studies

Grape polyphenols are reported to have an anti-inflammatory effect in adipose tissue. Obese mice fed a high-fat diet (HFD) plus 3% grape powder for 18 wk showed a reduction in the mRNA concentrations of TNF-α and MCP-1 and the two markers of macrophage recruitment and infiltration, CD11 c and F4/80, in epididymal adipose tissue [42]. The addition of grape polyphenols to the HFD (44% of kcal from fat), supplied to C57 BL/6 J mice for 16 wk, also reduced weight gain, body fat percentage, adipose tissue volume, IR, hepatic steatosis, and chronic inflammation in adipose tissue [47]. Grape fractions, rich in polyphenols, can reduce the metabolic consequences of an HFD by reducing adiposity, IR, and inflammatory markers. Among the polyphenols present in grapes, resveratrol has received special attention because of its performance in adipose tissue. The ingestion of resveratrol fed in conjunction with an obesogenic ration (rich in sucrose and lipids) reduced body weight and the volume of the adipose tissue in mice, in addition to modifying the expression of 16 miRNAs in the adipose tissue. An increase in the expression of miR-539, induced by resveratrol, was associated with the inhibition of de novo lipogenesis [43].

In addition to their effects in adipose tissue, polyphenols also may play an important role in miRNA modulation and liver metabolism. In the murine liver, miR-122 is the target of different types of polyphenols, including the polyphenol extract from

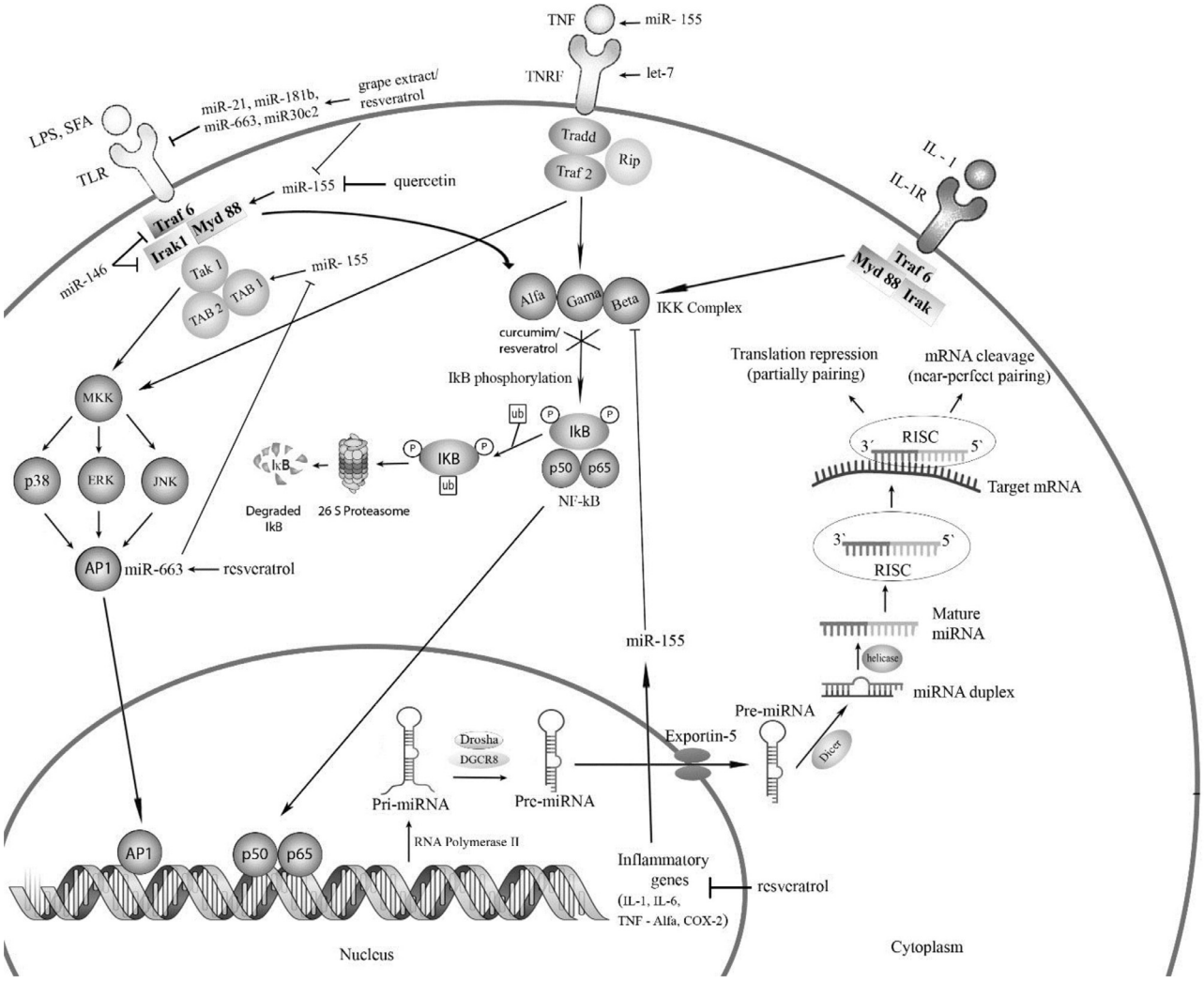

Fig. 2. Activation of the NF-κB and MAPKs pathways and modulation of the expression of inflammatory genes, miRNA biogenesis, and miRNA modulation by polyphenols. The interaction between LPS or SFAs and TLR; TNF and the TNFR; and IL-1 and the IL-1 R results in the activation of MAPKs and NF-κB pathways. The activation of these pathways upregulates the expression of inflammatory genes. After miRNA biogenesis, miRNAs may regulate the expression of proteins by cleaving mRNA or repressing its translation, depending on the level of complementarity between the miRNA and the target mRNA. Furthermore, polyphenols may modulate miRNA. COX, cyclooxygenase; ERK, extracellular signal-regulated kinase; IL, interleukin; IL-1 R, interleukin-1 receptor; IRAK, Interleukin-1 receptor-associated *kinase* 1; JNK, c-Jun N-terminal *kinase*; MAPK, mitogen-activated protein kinase; miRNA, microRNA; NF, nuclear factor; RISC, RNA-induced silencing complex; TAK, transforming growth factor beta–activated kinase; TLR, toll-like receptor; TNF, tumor necrosis factor; TRAF, TNF receptor-associated factor TNFR-associated factor; TNFR, TNF receptor; →, activation; ⊣ inhibition.

Table 1
Summary of findings from in vitro studies, which show the effect of polyphenols on inflammation and miRNAs expression

Polyphenol	Cell	Level	Results	Reference
Cyanidin-3-glucoside	3 T3-L1	2.5, 5, and 10 μg GAE/mL	↓ leptin and PAI-1 ↑ adiponectin ↓ oxidative stress ↓ expression of NF-κB along with the expression of its target genes (*TNF-α, MCP-1, IL-6, IL-8, IL-1 β*, and *INF*-β)	[6]
EGCG	HepG2	50 μM	↓ miR-30 b*, miR-453, miR-520 e, miR-629, and miR-608 ↑ 13 miRNAs (e.g., let-7 a, miR-16, miR-221)	[40]
		100 μM	↓ 48 miRNAs (e.g., miR-18 a, miR-34 b, miR-193 b, miR-222, and miR-342)	
Quercetin	Murine RAW264.7 macrophages stimulated with LPS	10 μM	↓ TNF-α, iNOS, IL-1 β, IL-6, and MIP-1 α Inhibition of NF-κB pathway Activation of Nrf2 ↓ miR-155 expression	[41]
Quercetin-3-glucoside	Human adipocytes	10 or 30 μM	↓ expression of the genes encoding MCP-1 and IL-1 β	[42]
Resveratrol	Rats 3 T3-L1	30 mg/ kg	↑ expression of miR-539-5p to Inhibition of de novo lipogenesis ↓ SREBP1 protein expression ↓ *fasn* gene expression ↓ fatty acid synthase activity	[43]
Curcuminoids	3 T3-L1 adipocytes submitted to oxidative stress induced by H_2O_2 (200 μM)	12.5 μM	↑ *PPARγ* gene expression ↑ adiponectin ↓ IL-6 and MCP-1 ↓ *NF-κB* gene expression ↓ ROS Modulation of *SOD* and *CAT* genes	[36]
Curcumin/resveratrol	Mouse 3 T3-L1 challenged with TNF-α	20 μM	Inhibition of NF-κB activation and expression of inflammatory genes (*TNF-α, IL-1 β, IL-6*, and *COX-2*)	[46]

CAT, catalase; COX, cyclooxygenase; EGCG, epigallocatechin 3-gallate; H_2O_2, hydrogen peroxide; Hep G2, human liver cancer cell line; IL, interleukin; INF, interferon; iNOS, inducible nitric oxide synthase; LPS, lipopolyssacharide; NF, nuclear factor; Nrf2, nuclear *factor* erythroid 2 (NFE2)-related *factor* 2; miRNAs, microRNAs; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; PAI, plasminogen activator inhibitor; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SOD, superoxide dismutase; SREBP, sterol regulatory element-binding protein; TNF, tumor necrosis factor; ↑ increase; ↓ reduction; 3 T3-L1, cell line derived from (mouse) 3T3 cells that is used in biological research on adipose tissue

Hibiscus sabdariffa, quercetin, coffee polyphenols, and grape proanthocyanidins, all of which reduce the risk for diet-induced liver steatosis. miR-122 controls the biosynthesis of cholesterol, bile acids, and hepatic fatty acid oxidation and is related to NAFLD. The clinical manifestations of NAFLD include dyslipidemia, hypertension, and IR. Therefore, the benefits of polyphenols on these manifestations may be due to improved liver metabolism, resulting from miR-122 binding. With regard to lipid metabolism, proanthocyanidins reduce miR-33 expression, which plays an important role in cholesterol homeostasis and lipoprotein concentrations [20,32,48].

Obese rats fed an HFD supplemented with different concentrations of proanthocyanidin extract from grape seeds for 3 wk presented a dose-dependent reduction in hepatic steatosis in addition to a reduced expression of miR-33 a and miR-122 in the liver [48,49]. The intake of this extract also resulted in the normalization of the plasma concentrations of triacylglycerol (TG) and LDL-C and of total lipids and TG in the liver of the animals [61]. Resveratrol intake is also associated with reducing hepatic steatosis, mainly by reducing lipogenesis, increasing fatty acid oxidation, or both. Mice that ingested an obesogenic diet (45% of kcal from fat) supplemented with resveratrol for 6 wk showed downregulated expression of miR-103-3p, miR-107-3p, and miR-122-5p in the liver and a decreased expression of sterol regulatory element-binding protein (SREBP)-1 and an elevation of carnitine palmitoyltransferase (CPT) 1 a, an enzyme involved in fatty acid oxidation. miR-103-3p and miR-107-3p are considered to be positive regulators of the effect of resveratrol on sterol regulatory element-binding protein expression [50].

In addition to the miRNAs already mentioned, other miRNAs are also influenced by polyphenols in hepatic cells, specifically EGCG and ellagitannin, which modulate the expression of some compounds of the let-7 family and miR-210 in HepG2, where these miRNAs have been related to insulin sensitivity. miR-210 is upregulated in the liver of diabetic mice and downregulated in the adipose tissue of obese humans [20]. In the mouse liver, 137 miRNAs were modulated by polyphenols; stilbenes modulated 87 of these miRNAs, whereas 24 miRNAs were modulated by flavonoids, 6 by phenolic acids, and 20 by curcuminoids [38]. In C57 BL/6 J mice fed an HFD (60% of kcal from fat), the intake of quercetin and extracts of apple and cherry containing quercetin improved blood glucose, reduced the concentration of serum inflammation biomarkers (CRP and PAI-1) and the accumulation of lipids in hepatocytes, and increased the expression of obesity-related genes (*Cpt 1 a*, acyl-CoA oxidase [*Acox*] 1, and stearoyl-CoA desaturase [*SCD*] 1) [51].

Ellagic acid is found in fruits, such as pomegranates, berries, grapes, and mangos, as well as in walnuts. This polyphenol has antiproliferative, chemoprotective, and antiatherogenic activity in several types of cells. The main mechanism of action of ellagic acid is via the inhibition of oxidative stress and the attenuation of inflammatory damage by regulating the NF-κB pathway. Ellagic acid also inhibits the expansion of adipose tissue and attenuates the accumulation of hepatic lipids. Supplementation of rations rich in fats and sugars with ellagic acid was effective in reducing diet-induced metabolic stress in mice and attenuating stress in the endoplasmic reticulum, which is associated with hepatic steatosis, oxidative stress in the liver, hypertrophy of adipocytes, and inflammation in adipose tissue [52].

Several miRNAs regulate NF-κB; therefore, it is possible that ellagic acid modulates the expression of miRNAs involved in the regulation of this pathway. miR-146, for example, is induced by TLR in an NF-κB dependent fashion. TRAF6 and IRAK1, two key molecules in the TLR/NF-κB pathway, are direct targets of miR-146 (Fig. 2). Therefore, an increase in the expression of this miRNA can inhibit these molecules, reducing NF-κB activity. miR-146 is related to β-pancreatic cell function, and an increase in this miRNA has been observed in pancreatic islets of db/db diabetic and obese mice. miR-181 b, an miRNA involved in the inflammatory process, is indirectly regulated by NF-κB. The transcription of this miRNA is increased by STAT3. Furthermore, miR-181 b inhibits the production of *CYLD*, thus inhibiting the activation of NF-κB. NF-κB increases the production of IL-6 and therefore favors the phosphorylation and activation of STAT3, increasing the expression of miR-181 b. In contrast, miR-21 increases the activity of NF-κB by inhibiting the expression of *PTEN*, which inhibits the phosphorylation of AKT and is responsible for the activation of NF-κB. miR-155, induced by inflammatory cytokines, can inhibit the expression of *IKKβ* and *IKKε*, thereby favoring the activation of NF-κB [53].

Human studies

Hesperidin and naringin, the major flavonoids present in orange juice, have been reported to reduce anthropometric and biochemical measurements. Basile et al. [54] verified a significant reduction in the waist circumference, serum total cholesterol, and LDL-C and an increase in HDL-C in women who ingested orange juice for 8 wk. In another study [55], reductions in weight, body mass index (BMI), waist circumference, blood pressure, plasma insulin, TG, and apoB were also observed after consumption of orange juice by overweight individuals. The intake of orange juice even improved the antioxidant defense system and protected against lipoperoxidation [56]. Green tea polyphenols were also reported to reduce body weight and improve lipid metabolism, as demonstrated by reductions in LDL-C and LDL/HDL [57].

The daily intake of one capsule of grape extract (139 mg) plus resveratrol (8.1 mg) by men with T2D, hypertension, and BMI >30 kg/m^2 for 6 mo and two capsules for another 6 mo resulted in the upregulation of miR-21, miR-181 b, miR-663, and miR-30 c2 and the downregulation of inflammatory cytokines (IL-6, CCL3, IL-1 β, and TNF-α) and miR-155 in peripheral blood mononuclear cells. The increase in these miRNAs was associated with a reduction in inflammation mediated by the regulation of the TLR and NF-κB pathways and inflammatory cytokine gene expression [45]. Table 2 shows the studies in which the miRNAs that are associated with obesity are modulated by polyphenols.

Polyphenol effect on the hypothalamic satiety

Food intake and satiety are mainly controlled by the hypothalamus, which controls energy homeostasis as well as the regulation of food intake generally by altering the expression of neurotransmitters. The arcuate nucleus contains neurons that express orexigenic (neuropeptides agouti-related protein, and neuropeptide Y [NPY]) and anorexigenic neuropeptides (proopiomelanocortin/alpha-melanocyte stimulating hormone). Also, ghrelin, an orexigenic peptide, can increase NPY and neuropeptides agouti-related protein expression in the arcuate nucleus [64]. Cholecystokinin acts on the peripheral vagal afferent receptors to inhibit food intake. Insulin, leptin, and peptide YY are important anorexigenic hormones [64,65].

To our knowledge, studies evaluating the effects of polyphenols in the central nervous system in regulating neuropeptides and neurohormones are scarce. However, some polyphenols clearly appear to have the potential to modulate the neuropeptides involved in food intake and satiety [64,65]. In this context, the polyphenol level in the brain is an important factor when evaluating the neural effects of any polyphenol. Also, there is evidence that polyphenols cross the blood–brain barrier, as assessed by ^{14}C-trans-resveratrol, ^{3}H-EGCG, ^{14}C-grape seed polyphenolic extract, and ^{3}H-trans-resveratrol in animal brains; however, the exact level of polyphenol concentration achieved in the brain is not clear [64].

Polyphenols can modulate insulin signaling in the brain. Several polyphenols either have insulin-potentiating effects or improve IR in individuals with obesity, T2D, metabolic syndrome, or all three. Cinnamon polyphenols may mimetic the insulin effects, which have been verified in cultures of neuronal cells [64]. Intake of cinnamon also can delay gastric emptying rate and decrease postprandial feeling of hunger by regulating plasma insulin and glucagon-like peptide (GLP)-1 levels in healthy individuals [66]. Likewise, the

Table 2
miRNAs induced by polyphenols and associated with obesity

Polyphenols	miRNA	Expression pattern and/or function	Tissue or cell	References
Resveratrol (30 mg·kg·d^{-1})	↑miR-539-5p	Inhibition of de novo lipogenesis	3 T3-L1	[43]
Quercetin and isorhamnetin (10 μmol/L)	↓ miR-155	Inflammatory	Murine macrophages	[41]
Resveratrol (30 μmol/L)	↑ miR-663	Reduction of the miR-155 increase induced by LPS	Human THP-1 monocytes	[58]
Proanthocyanidins (5, 25, and 50 mg·kg·d^{-1})	↓ miR-33 a, miR-122	↓ Dyslipidemia	Liver	[48]
Anthocyanins + flavonols + phenolic acid derivatives	↓ miR-103, miR-107, miR-122	Prevention or attenuation of NAFLD	Liver	[59]
Grape seed extract (30 mg·kg·d^{-1})	↓ miR-33 a, miR-122	Improvement in dyslipidemia and oxidative and inflammatory processes	Liver	[60]
Resveratrol (30 mg·kg·d^{-1})	↓ miR-103, miR-107, miR-122	↓ Hepatic steatosis	Liver	[50]
Curcumin (2 or 10 μmol/L)	↓ miR-17 to 5 *P*	Inhibition of preadipocyte differentiation	3 T3-L1	[61]
Quercetin 3-rutinoside, rutin, and epicatechin (Lychee; (500 mg·kg·d^{-1})	↓ miR-33 a, miR-122	Hypolipidemic effect	Liver	[62]
Resveratrol (8.1 mg/d for 6 mo and 16.2 mg/d for additional 6 mo)	↑ miR-21, miR-181 b, miR-663, miR-30 c2 ↓ miR-155	Regulation of TLR and NF-κB pathways and the levels of inflammatory cytokines	PBMC	[45]
Persimmon tannin (20–60 μg/mL)	↑ miR-27 a, miR-27 b	Inhibition of preadipocyte differentiation	3 T3-L1	[63]
Resveratrol (25 μmol/L)	↑ miR-155	Inhibition of adipogenesis	3 T3-L1	[44]

LPS, lipopolysaccharide; NAFLD, non-alcoholic fatty liver disease; NF, nuclear factor; miRNA, microRNA; miRNAs, microRNAs; PBMC, peripheral blood mononuclear cell; TLR, toll-like receptor; ↑ increase; ↓ reduction; 3 T3-L1, cell line derived from (mouse) 3T3 cells that is used in biological research on adipose tissue; Hep G2, human liver cancer cell line

administration of resveratrol to diet-induced obese and diabetic mice normalized hyperglycemia and improved hyperinsulinemia. Also, there is evidence that green tea polyphenols improve insulin sensitivity and increase plasma GLP-1 levels in individuals with T2D. In this way, EGCG, the major compound in green tea, was found to induce the secretion of CCK and GLP-1 in Caco-2 cells [65].

Among commonly consumed foods, soy foods are uniquely rich sources of isoflavones. When all forms of the individual isoflavones are considered, the three isoflavones (genistein, daidzein, and glycitein) account for ~50%, 40%, and 10%, respectively, of the total soybean isoflavone content [67]. The potential effect of isoflavones on satiety was studied in 34 healthy postmenopausal women who received soy isoflavone (50 mg/d) for 8 wk. Their plasma PYY levels increased during isoflavone treatment. PYY may act on NPY receptors in the hypothalamus. Polyphenols may possibly modulate the actions of NPY and thus regulate energy homeostasis [68].

Toxicity related to polyphenols

Despite the benefits of polyphenols, they can cause adverse effects in certain vulnerable populations (those with genetic polymorphism in genes related to the polyphenol biotransformation pathway). They can cause drug–drug interactions and adverse effects in foods that are too highly fortified or when ingested as supplement. It should be noted that bioavailability is a relevant factor in the occurrence of toxic events [69]. When ingested as food components, polyphenols show low toxicity; however, the exact values will be different for each class of polyphenols and even individual compounds [34]. Toxicity findings have not been observed in human intervention studies [34,69].

Some polyphenols, such as caffeic acid, green tea catechins, and quercetin, may have genotoxic or carcinogenic effects at high doses, at which polyphenols may become pro-oxidant [70]. The toxicity of mega-doses of tea polyphenols is referred in cells and animals studies. The treatment of rat hepatocytes with 200 μM EGCG was pro-oxidant and caused cell death. In Beagle dogs, high doses of green tea-derived preparations (500 mg/kg) resulted in dose-dependent toxicity and death. Intraperitoneal administration of EGCG (>150 mg/kg) to mice resulted in dose-dependent lethality, which was related to hepatotoxicity. High doses of EGCG can induce toxicity in the liver, kidneys, and intestine of dogs [69].

High doses of polyphenols also may have antinutritional effects. Tea consumption with meals may increase the risk for iron depletion in individuals with marginal iron status. Polyphenols also may affect drug bioavailability and pharmacokinetics. However, most of these effects have been shown in in vitro or in vivo studies, and it has not been proven that these effects also occur in humans. Intakes from habitual diets are usually lower than the doses used in the studies, and food matrix also may influence the effects of polyphenols [70].

Conclusion

Obesity induces chronic, systemic, and low-grade inflammation, resulting in the production of several inflammatory cytokines. Obese individuals show alterations in the expression profile of miRNAs that have been related, in several studies, to the inflammation arising from obesity. Both inflammatory cytokines that modulate the expression of miRNAs and miRNAs, which partially control inflammation in the adipose tissue, can be modulated by polyphenols; however, studies of the effects of polyphenols on miRNAs have focused mainly on cancer. It should be noted that many of the available studies related to miRNAs and polyphenols are conducted in vitro and in animals. In humans, nutrition science studies may help identify new biomarkers and other possible mechanisms of action of polyphenols, with a view to understanding how polyphenols can control these small non-coding RNAs and regulate physiological mechanisms related to obesity. Such an understanding would allow for the development of dietary approaches to reduce the risk for obesity, as well as its metabolic complications.

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