REVIEW

Differential effects of dietary flavonoids on adipogenesis

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Abstract

Propose Obesity is a fast growing epidemic worldwide. During obesity, the increase in adipose tissue mass arise from two different mechanisms, namely, hyperplasia and hypertrophy. Hyperplasia which is the increase in adipocyte number is characteristic of severe obese patients. Recently, there has been much interest in targeting adipogenesis as therapeutic strategy against obesity. Flavonoids have been shown to regulate several pathways and affect a number of molecular targets during specific stages of adipocyte development.

Methods Presently, we provide a review of key studies evaluating the effects of dietary flavonoids in different stages of adipocyte development with a particular emphasis on the investigations that explore the underlying mechanisms of action of these compounds in human or animal cell lines as well as animal models.

Results Flavonoids have been shown to regulate several pathways and affect a number of molecular targets during specific stages of adipocyte development. Although most of the studies reveal anti-adipogenic effect of flavonoids, some flavonoids demonstrated proadipogenic effect in mesenchymal stem cells or preadipocytes.

Conclusion The anti-adipogenic effect of flavonoids is mainly via their effect on regulation of several pathways such as induction of apoptosis, suppression of key adipogenic transcription factors, activation of AMPK and Wnt pathways, inhibition of clonal expansion, and cell-cycle arrest.

Keywords Adipogenesis · Flavonoids · Obesity · Hyperplasia · Adipocyte

Abbreviations

FABP4 Fatty acid-binding protein 4
hBM-MSCs Human bone marrow mesenchymal stem cells
LPL Lipoprotein lipase
ChREBP Carbohydrate response element-binding protein
EGCG Epigallocatechin gallate
FASN Fatty acid synthase
GPDH Glycerol-3-phosphate dehydrogenase
T2DM Type 2 diabetes mellitus
C/EBP CCAT/enhancer-binding protein
Cdns Cyclin-dependent kinases
Rb Retinoblastoma
ERK Extracellular signal-regulated kinase
KLFs Kruppel-like factors
Pref-1 Preadipocyte factor-1
CREB Cyclic AMP response element-binding protein
EPAS1 Endothelial PAS domain protein 1
BMAL1 Brain and muscle Arnt-like protein 1
FOXO1 Forkhead box O1
FOXO2 Forkhead box A2
TRAP220 Thyroid receptor-associated protein complex 220
TAF8 TATA-binding protein-associated factor-8
HDACs Histone deacetylases
NCoR Nuclear receptor co-repressors
mTOR Mammalian target of rapamycin
ADD-1 Adipocyte determination and differentiation-dependent factor 1
TCF/LEF T-cell factor/lymphoid enhancer factor

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Introduction

Obesity, which can be defined as increased body mass index (greater than 30 kg/m²), has been identified as a risk factor for the pathogenesis of many chronic diseases including cancer, hypertension, osteoarthritis, and cardiovascular diseases. It is also closely linked with metabolic disorders including insulin resistance and type 2 diabetes mellitus (T2DM) [1]. Obesity has been considered the fastest growing epidemic worldwide. According to the World Health Organization, in year 2014, more than 1.9 billion adults were overweight of which over 600 million were obese [2]. In the United States, the prevalence of adult obesity is greater than one-third (34.9%) of the population [3].

In obesity, the increase in adipose tissue mass arise via two main distinct mechanisms, increasing adipocyte number (hyperplasia) and/or increasing adipocyte volume (hypertrophy) [4, 5]. Hypertrophy occurs in overweight individuals and prolonged period of weight gain in adulthood leads to hyperplasia. Hyperplasia is mostly associated with severity of obesity and is the characteristic of morbidly obese individuals [6]. Hyperplasia takes place through adipogenesis that involves a cascade of transcriptional factors and cell-cycle proteins which leads to development of mature adipocyte [7]. This process can be divided into three main phases: growth arrest, clonal expansion, and terminal differentiation. Inhibition of adipocyte differentiation by interrupting any of these stages may serve as potential therapeutic strategy against adipogenesis and hence obesity.

Pharmaceutical approaches for weight management include altering metabolism, appetite, or fat absorption. Currently available drugs such as central nervous system stimulants, or peripherally acting anti-obesity drugs, are associated with several adverse effects such as hyperthyroidism, palpitations, anxiety, insomnia, and diarrhea [8]. The development of new and safe anti-obesity agent has become a necessity. Several studies have shown the potential of natural products to counteract obesity. Flavonoids represent the most researched groups of phytochemicals with regards to their effects on weight management. Studies have shown fruits and vegetables rich in several flavonoid subclasses, particularly flavonols, anthocyanins, and flavones are associated with less weight gain. A study which assessed the associations between habitual consumption of all flavonoid subclasses and weight gain among 124,086 American men and women over a period of 24 years showed higher intake of foods rich in flavonols, flavan-3-ols, anthocyanins, and flavonoid polymers may contribute to weight maintenance in adulthood after adjustment for changes in other lifestyle factors such as diet, smoking status, and physical activity [9]. Several other studies on human and rodents provide evidence that flavonoids can cause suppression of appetite [10–12], increase glucose uptake in muscle [13], decrease fat absorption [14], and inhibit adipogenesis [15, 16].

A prospective cohort study indicates that obesity is associated with shorten life expectancy and indeed this study divulges that obesity in adulthood is a powerful predictor of death at older ages [17]. Flavonoids have been reported to affect health and life span of various model organisms through different mechanisms including energy-restriction like effects [18]. In this context, some of the molecular targets of the anti-adipogenic effects of flavonoids which overlap with some energy-restriction mimetics could be in part explain their lifespan extending properties [18].

This review summarizes the mechanisms of adipogenesis and highlights the anti-adipogenic effect of flavonoids and their corresponding underlying mechanisms of actions.

Overview of adipogenesis

Adipogenesis occurs in two differentiation stages in which an undifferentiated multipotent mesenchymal stem cell transforms into a ‘determined’ or ‘committed’ preadipocyte, which then undergoes a secondary differentiation stage to become a lipid laden adipocyte [19, 20]. During the determination stage, multipotent mesenchymal stem cells (MSCs) differentiate and convert to committed preadipocytes under the influence of hormones, insulin, and growth factors [19]. Subsequent stage is mitotic clonal expansion in which growth-arrested preadipocytes undergo...
several rounds of mitotic division which is a necessary step in the adipocyte differentiation program [21]. Following mitotic clonal expansion, the preadipocytes leave the cell cycle and undergo terminal differentiation, lose their fibroblastic morphology, accumulate cytoplasmic triglyceride, and acquire the metabolic features of mature adipocytes. Adipocyte-specific genes are also highly expressed by mature adipocytes [19]. Adipocyte differentiation is closely regulated by a cascade of transcription factors, amongst which peroxisome proliferator-activated receptor gamma (PPARG) and CAAT/enhancer-binding proteins (C/EBPs) are key players of adipocyte fate.

Furthermore, to achieve successful transformation to mature adipocytes, fibroblastic preadipocytes undergo transformation into spherical cell shape [22, 23]. Proteolytic degradation of the stromal extracellular matrix (ECM) of preadipocyte by the plasminogen cascade is essential for changes in cell morphology, the expression of adipocyte-specific genes, and lipid accumulation [24]. Following changes in ECM, C/EBPα, and PPARG are then activated [25].

**Role of transcription factors in adipogenesis**

Adipogenesis is tightly controlled by the activity of transcription factors which activate or repress each other in a sequential manner. The key transcription factors that are involved in adipogenesis include C/EBP family members (C/EBPα, C/EBPβ, and C/EBPδ) and PPARG. At large, adipogenic program is driven by at least two waves of transcription factors. Adipogenic stimuli (hormones, growth factors, and cytokine) initiated the first wave which amongst others includes C/EBPβ and C/EBPδ. These proteins subsequently induce expression of the second wave of transcription factors of which PPARG and C/EBPα are the most important (Fig. 1). These two central adipogenic regulators positively control each other and cooperate to orchestrate expression of the full adipogenic program [7].

In addition to the above, an array of other important transcription factors function as regulators of adipogenesis. Krüppel-like factors (KLFs) are expressed in adipose tissue and are either activators or repressors of transcription. KLF4, KLF5, KLF6, KLF9, and KLF15 are positive regulators of adipogenesis [26]. KLF5 which is induced early during adipogenesis serves as a positive role in adipogenesis, whereas other transcriptional factors such as KLF2 and GATA2/3 suppress adipogenesis. CEBP CCAT/enhancer-binding protein, PPARγ peroxisome proliferator-activated receptor-gamma, ERK extracellular signal-regulated kinase, KLFs Kruppel-like factors, CREB cyclic AMP response element-binding protein, FOXO1 forkhead box O1, TCF/LEF T-cell factor/lymphoid enhancer factor, MAPK mitogen-activated protein kinase, Wnt wingless-type MMTV integration site family, PKA protein kinase A, GR glucocorticoid receptor, DRI direct repeat type 1 element.
adipogenesis by C/EBPβ and C/EBPε activates the Pparg2 promoter [27]. KLF6 suppresses the expression of preadipocyte factor-1 (Pref-1) which is known to inhibit adipogenesis [28]. Other proadipogenic transcription factors include sterol regulatory element-binding protein 1 (SREBP1) and cyclic AMP response element-binding protein (CREB). SREBP1 promotes early adipocyte differentiation and can induce expression of PPARG and facilitates fatty acid metabolism [29], while the expression of CREB in preadipocytes is necessary to induce adipocyte differentiation. Accordingly, the absence of CREB inhibits adipocytes differentiation [30, 31].

Signals that repress adipocyte development may have profound implications for human health. Amongst the myriad of transcription factors that are known to be repressors of adipocyte differentiation are several members of the KLF (KLF2 and KLF7) [32, 33], globin transcription factor (GATA2 and GATA3), and forkhead (Forkhead Box O1 (FOXO1) and Forkhead Box A2 (FOXA2)) families. GATA2 and GATA3 are known to inhibit terminal differentiation via repressing transcription of PPARG [34].

Role of transcription cofactors in adipogenesis

Transcription cofactors are proteins that interact with transcription factors and may affect transcription of specific genes in a positive or negative manner and thus play an important role in adipogenesis. Amongst the transcription co-activators, thyroid receptor-associated protein complex 220 (TRAP220) is a known binding partner of PPARG, the absence of which prevents adipocyte differentiation [35]. Other significant co-activators include TATA-binding protein-associated factor-8 (TAF8) which is upregulated during adipogenesis [36]. Hitherto and several other cofactors have been identified to play a role in preadipocyte differentiation that contribute to the intricacies of adipogenesis. The cyclin D3-cyclin-dependent kinase-6 complex can bind to and phosphorylate PPARG, and eventually leads to induction of preadipocyte differentiation [37]. Cyclin-dependent kinase 4 (CDK4) has also been reported to activate PPARG via its kinase domain [38].

By contrast, some cofactors may act as inhibitors of adipogenesis. For instance, cyclin D1 and transcriptional co-activator with PDZ-binding motif (TAZ) suppress PPARG activity and block adipocyte differentiation [39]. Some corepressors recruit histone deacetylases (HDACs) to target promoters, which in turn result in blockade of transcription. Mammalian sirtuin 1 (SIRT1) with HDAC activity interacts with PPARG and therefore inhibits preadipocyte differentiation. Furthermore, nuclear receptor co-repressors (NCoR) and silencing mediator of retinoid and thyroid hormone receptors can also act as anti-adipogenics [40].

Cell-cycle proteins

Cyclin-dependent kinases (Cdks) regulate the progression of preadipocytes through the cell division cycle [41]. Cdks when activated phosphorylate retinoblastoma family (Rb) members, including the retinoblastoma protein p130 and p107. This leads to the release of E2 promoter-binding factors (E2Fs) from inhibitory interaction with Rb, enabling E2F family to activate transcription of genes that allows the cells to enter S phase [42]. Cyclins are documented to be downstream targets of c-Myc protein, which has been shown to activate cell cycle and induces DNA synthesis in serum-starved 3T3-L1 cells [43]. Nonetheless, overexpression of c-Myc inhibits differentiation of preadipocytes possibly by inhibiting the cell to enter into a distinct predifferentiation stage in G0/G1 [44]. During conversion from G1 to S stage, p38 mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase (ERK), and glycogen synthase kinase-3B (GSK3B) phosphorylate and activate C/EBPβ which eventually leads to expression of Pparg and Cebpa [45].

Role of microRNAs in adipogenesis

MicroRNAs (miRNAs) are small non-coding RNAs that regulate different biological processes at post-translational modification state [46]. In addition, they play a role in a variety of human diseases such as obesity and diabetes mellitus [47]. The miRNA profile of human adipose tissue has been demonstrated to be different in obese patients [48–50]. One of the major functions of miRNAs in adipose tissue is to inhibit or stimulate the differentiation of adipocytes. There are numerous inhibitory and promoting miRNAs that contribute to the regulation of adipogenesis, in the commitment stage and in terminal differentiation (Fig. 2). The expression pattern of 70 miRNAs has been shown to be either upregulated or downregulated during adipogenesis in subcutaneous fat cells [49]. In mouse embryonic stem cells, 129 miRNAs expression are altered at distinct time points during conversion of mesodermal progenitor cells to mature adipocyte [51, 52]. MiR-103 is upregulated in rodents epidydimal adipocytes during adipogenesis and its ectopic expression increase triglyceride accumulation in the early stage of adipogenesis [53]. However, the expression of miR-103 remains unchanged during adipogenesis in human subcutaneous adipocytes [49]. The reason for the lack of inconsistencies between studies is not known but could be due to differences in fat depots in mice and humans.

MiR-30 family is upregulated during adipogenesis, and it increases adipogenesis via targeting run-related transcription factor 2 (RUNX2) [54]. RUNX2 is an osteogenesis regulator that promotes adipocytes differentiation when it is down-regulated. Similarly, miR-204 directly targets RUNX2.
Overexpression of miR-204 in MSCs promotes adipogenesis, whereas its inhibition favors osteogenesis [55, 56]. The miR 17–92 cluster is highly expressed during clonal expansion in preadipocytes and enhances adipogenesis through inhibiting the tumor suppressor, Rb2/p130 during the early clonal expansion of preadipocytes [51, 52].

MiRNAs known to inhibit adipogenesis include miR-27, miR-30, microRNA Let-7, and miR-448. Forced expression of miR-27 suppresses adipogenesis in multipotent adipose-derived stem cells and 3T3-L1 cell line [57, 58] by directly targeting Pparg and Cebpα mRNA [59], whilst miR-130 targets Pparg. Others such as microRNA Let-7 inhibit clonal expansion and terminal differentiation in 3T3-L1 cells [60], and miR-448 is reported to inhibit adipogenesis by targeting KLF5 [61].

MiRNAs have also been demonstrated to modulate adipogenesis by targeting Wnt pathway. Wnt proteins are factors in the external environment that can affect the differentiation potential of preadipocytes. MiRNA microarray results revealed increased expression of 18 miRNAs including miR-148a, miR-210, miR-194, and miR-322 that repress Wnt signaling and thus increase adipogenesis [46]. Conversely, 29 miRNAs including miR-27, miR-181, and miR-344 were identified to activate Wnt pathway and suppress adipogenesis [46].

**Role of circadian genes in adipogenesis**

It has been documented that in human adipose tissue explants, the circadian genes can oscillate independently of the central nervous system which may regulate the timing of clock-controlled genes such as Pparg. Several proteins including nocturnin, period circadian protein homolog 3 (PER3), and brain and muscle Arnt-like protein-1 (BMAL1) that are involved in the regulation of circadian rhythm can influence adipogenesis. Nocturnin, which is a circadian regulated gene, has been reported to facilitate adipogenesis in 3T3-L1 cells via stimulation of PPARγ nuclear translocation [62], whereas PER3 was shown to have a negative role in differentiation of MSCs to adipocytes; and besides, the protein can form a complex with PPARγ which inhibits PPARγ-mediated transcriptional activation via Pparg response elements [63]. Similarly, BMAL1 is a negative regulator of adipogenesis. BMAL1 deficiency in mice embryonic
fibroblast cells results in increased expression of Cebpβ and Pparg, and these adipogenic markers are increased even before induction of adipogenesis which suggests spontaneous differentiation of these cells with complete deficiency of BMAL1. BMAL1 has been shown to suppress adipogenesis by direct transcriptional regulation of genes of the Wnt signaling pathway [64]. However, another study showed conflicting results, Bmal1 knockout C3H10T1/2 cells failed to be differentiated into mature adipocytes [65].

Other factors in regulation of adipogenesis

In addition to the role of transcriptional factors, preadipocyte differentiation may be influenced by a number of hormones, growth factors and cytokine. Insulin, insulin-like growth factor-1 (IGF-1), thyroid hormones, mineralocorticoids, glucocorticoids (GCs), and PPARG agonists have important role in promoting adipogenesis. Insulin is an important positive regulator of adipogenesis [66]. Downstream molecules of the insulin signaling cascades such as phosphatidylinositol-3 kinase (PI3K), mammalian target of rapamycin (mTOR), and protein kinase B (PKB) are essential for preadipocyte differentiation [67, 68]. Thyroid hormone (T3), which plays a vital role in the control of metabolic homeostasis, promotes adipogenesis via thyroid receptor α1-induced lipogenic gene expression [69]. Likewise, GCs, which are positive regulator of adipogenesis, promote differentiation of preadipocytes by increasing the expression of Cebpδ and Pparg. Fibroblast growth factors (FGFs) including FGF1, FGF2, and FGF10 have been shown to have proadipogenic activity, since neutralization of these fibroblast growth factors can block adipogenesis [70–72].

Contrariwise, various extranuclear factors are shown to be negative regulators of adipogenesis. The wingless-type MMTV integration site family (Wnt) acts through autocrine or paracrine manner to regulate cell growth and cell fate in many cell types. Wnt signaling proceeds through canonical (β-catenin) or non-canonical pathways. In the canonical pathway, binding of Wnt to frizzled receptors on the cell surface causes the translocation of β-catenin to the nucleus where it interacts with the T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors to inhibit adipogenesis through blockade of C/EBPδ and PPARγ [73, 74]. In myometrial tissue, the absence of β-catenin leads to its conversion to adipose tissue, which highlights the importance of Wnt-β-catenin pathway in regulation of adipogenesis [32]. Suggestion has been put forward that the receptors that initiate the Wnt reside on primary cilia on adipocyte surface. This is based on the fact that the increased adipogenesis observed in obese patients with the inherited ciliopathy Bardet–Biedl syndrome may be due to impaired cilia formation which leads to increased expression of PPARγ [75].

Transforming growth factor β (TGF-β) is another negative regulator of adipocyte differentiation. TGF-β inhibits adipogenesis through Smad3 which interacts with C/EBPβ and C/EBPδ and represses C/EBP transcription activity [76]. Besides, it may also suppress adipogenesis via induction of c-Myc expression [77]. A soluble form of preadipocyte factor 1 (Pref-1) was shown to reduce adipose tissue mass and this factor negatively regulates adipogenesis via interaction with Notch [78]. Finally, proinflammatory cytokines inhibit adipogenesis via activation of several intracellular signaling pathways. Proinflammatory cytokines were proven to decrease PPARG and C/EBPα expression in preadipocytes and block insulin action [78–80].

Conceivably, PPARγ plays a major role in adipogenesis and most of the above factors that influence adipogenesis play their positive or negative role in adipogenesis by ultimately targeting PPARγ, and hence, in the next section, we look at PPARγ more closely.

PPARγ as a master key of adipogenesis

PPARγ which is abundantly expressed in adipose tissue is a master key of adipogenesis [81, 82] and contributes to whole-body insulin sensitivity and glucose homeostasis [81]. Activation of PPARγ by ligands such as fatty acids and the antidiabetic drugs, and thiazolidinediones (TZDs) lead to adipocyte differentiation and fatty acid storage. Therefore, intake of high fat food exposes people to prolonged high level of fatty acid (PPARG ligand), which most likely results in obesity [83].

Given that PPARγ is an essential regulator of adipogenesis, it has been the target of anti-obesity research. PPARγ can be either modulated directly, or indirectly by targeting its upstream factors or pathways which ultimately affect the activity of this crucial regulator of adipogenesis. In this regard, the expression or activity of PPARγ can be suppressed through inhibition of C/EBPβ, the increased expression of GATA2 and GATA3, regulation of mitogen-activated protein kinase (MAPK), and the activation of the Wnt/β-catenin pathway. Another group of proteins that may play a regulatory role in PPARγ transcriptional activity are the sirnuins (SIRT), especially SIRT1. SIRT1, an NAD+-dependent deacetylase, impaired adipogenesis by directly acting as a PPARγ co-repressor, thus, counteracting obesity [84, 85]. Still, PPARγ may possibly be regulated by post-translational modifications including phosphorylation which, in theory, is a distinct feature that can be subjected for cell- or tissue-specific modulation of this molecule [86, 87]. Phosphorylation of PPARγ at Ser273 by CDK5 has been reported to selectively decrease expression of a subset of PPARγ-target genes in adipocytes and pharmacological inhibition of Ser273 phosphorylation confers insulin sensitizing effects [88]. Nonetheless, Ser273 phosphorylation does not affect regulation of adipogenesis by PPARγ, suggesting that the
antidiabetic and proadipogenic roles can be independently manipulated by pharmacological agents.

## Dietary flavonoids

Flavonoids are a class of plant secondary metabolites that are widely distributed in a variety of vegetables and fruits [89]. Flavonoids have a wide range of biological functions, including coloration of flowers, protection against ultraviolet radiation and phytopathogens, signaling during nodulation, and auxin transport [90, 91]. Dietary flavonoids have been shown to possess an array of pharmacological activities including anti-inflammatory, antithrombotic, antitumor, antiviral, anti-atherosclerotic, antidiabetic, and anti-adipogenic effects [92–98].

Chemically, flavonoids have the basic structure of a 15-carbon skeleton consisting of two aromatic rings (A and B rings) connected through a heterocyclic pyrane ring (C ring) (Fig. 3). Flavonoids encompass a number of subclasses which are classified based on the level of oxidation and pattern of substitution of the C ring. The six diet-derived flavonoid subclasses include isoflavones, flavan-3-ols, anthocyanidins, flavanones, flavones, and flavonols [99, 100]. Each subclass consist of individual compounds, characterized based on specific hydroxylation and conjugation patterns [99]. The classification of dietary flavonoids, their chemical structures, individual compounds, and dietary source of these subgroups are shown in Table 1.

The structure of flavonoids reveals useful information on their anti-adipogenic effect. A comparative study investigated the anti-adipogenic effect of 44 flavonoids in 3T3-L1 cells and concluded that flavonols with a methoxy group at the 3-position possess the strongest anti-adipogenic effect. In addition, the presence of methoxy groups at the B ring contributes to the anti-adipogenic effect of flavonols. On the

![Fig. 3 Basic structure of flavonoids](image)

### Table 1 Flavonoid subclasses and their dietary sources

| Flavonoids     | C ring functional group | Dietary source                              | Compound          | Chemical formula |
|----------------|-------------------------|---------------------------------------------|-------------------|------------------|
| Anthocyanidins | 3-Hydroxy               | Cherry, berries, and red wine               | Cyanidin          | C₁₀H₁₀O₅⁺       |
|                |                         |                                             | Delphinidin       | C₁₀H₁₀O₅⁺       |
|                |                         |                                             | Malvidin          | C₁₀H₁₀O₅⁺       |
|                |                         |                                             | Pelargonidin      | C₁₀H₁₀O₅⁺       |
|                |                         |                                             | Petunidin         | C₁₀H₁₂O₆⁺       |
|                |                         |                                             | Peonidin          | C₁₀H₁₂O₆⁺       |
| Flavones       | 4-Oxo                   | Carrots, olive oil, peppers, rosemary       | Apigenin          | C₁₀H₁₀O₅       |
|                |                         | peppermint, and celery                      | Luteolin          | C₁₀H₁₀O₆       |
| Flavan-3-ols   | 3-Hydroxy               | Tea, chocolate and cocoa                    | (+)-Catechin      | C₁₀H₁₂O₆       |
|                | 3-O-gallate             |                                             | (+)-Gallocatechin | C₁₀H₁₂O₇       |
|                |                         |                                             | (-)-Epicatechin-3-gallate | C₁₀H₁₀O₁₀ |
|                |                         |                                             | (-)-Epigallocatechin-3-gallate | C₁₀H₁₀O₁₁ |
| Flavonols      | 3-Hydroxy, 4-Oxo        | Onion, olive oil, and berries               | Fisetin           | C₁₀H₁₅O₆       |
|                |                         |                                             | Isorhamnetin      | C₁₀H₁₅O₇       |
|                |                         |                                             | Kaempferol        | C₁₀H₁₅O₆       |
|                |                         |                                             | Myricetin         | C₁₀H₁₅O₈       |
|                |                         |                                             | Quercetin         |                 |
| Flavanones     | 4-Oxo                   | Citrus fruits                               | Hesperetin        | C₁₀H₁₅O₆       |
|                |                         |                                             | Naringenin        | C₁₀H₁₅O₆       |
| Isoflavones    | 4-Oxo                   | Soy bean and leguminous plants              | Daidzein          | C₁₀H₁₅O₈       |
|                |                         |                                             | Genistein         | C₁₀H₁₅O₈       |
|                |                         |                                             | Glycitein         | C₁₀H₁₅O₈       |
|                |                         |                                             | Biochanin A       | C₁₀H₁₅O₈       |
|                |                         |                                             | Formononetin      | C₁₀H₁₅O₈       |
contrary, flavonoids with hydroxy groups show little or no anti-adipogenic effect [101].

**Interventional studies in adipocyte development by dietary flavonoids**

**Anthocyanidins**

Anthocyanidins are common plant pigments which are present in many fruits, vegetables, and red wine. To date, about 365 anthocyanin compounds have been identified [102]. Cyanidin, peonidin, malvidin, delphinidin, pelargonidin, and petunidin are the most common anthocyanidins [103]. Human and animal studies have indicated the anti-obesity effect of anthocyanins [92, 103] which have recently attracted attention as potential novel anti-adipogenic agents. Cyanidin has been reported to reduce adipogenesis in 3T3-L1 cells by interfering with extracellular matrix and also decreasing carbohydrate response element-binding protein (ChREBP) expression level [93]. Anthocyanins derived from black soybean such as cyanidin-3-glucoside, delphinidin-3-O-glucoside, and petunidin-3-O-glucoside have been shown to reduce preadipocyte differentiation through suppression of PPARγ [94]. Extracts from *Oryza sativa* L. containing cyanidin-3-O-glucoside and peonidin-3-O-glucoside have been demonstrated to inhibit the differentiation of mesenchymal C3H10T1/2 cells to preadipocytes [104]. However, a more recent study showed treatment of preadipocytes with black soybean cyanidin-3-glucoside alone paradoxically increases the expression of *Pparg* and *Cebpa* and induces adipogenesis [95]. The discrepancy may be explained by the synergistic anti-adipogenic effects of other anthocyanins present in black soybean extract in the former study [105], where treatment of preadipocytes with the combination of these compounds results in inhibition of adipogenesis. Other possible anti-adipogenic mechanism of anthocyanidins such as cyanidin-3-O-glucoside and peonidin-3-O-glucoside include activation of Wnt-specific target genes such as *Axin2, Cyclin d1, and Wisp2* [104].

**Flavones**

Flavones are present in many herbs including parsley and celery. Apigenin and luteolin are the main dietary flavones [96]. Flavones have shown promising effects in inhibiting adipogenesis. For instance, apigenin suppresses adipogenesis in 3T3-L1 cells via activation of AMP-activated protein kinase (AMPK) pathway [97]. Activation of this pathway has been suggested to inhibit clonal expansion phase and thus adipocyte differentiation [98]. Indeed, apigenin arrests the cell cycle at the G<sub>0</sub>/G<sub>1</sub> phase which is associated with reduced cyclin D1 and CDK4 expression. Moreover, the exposure of these cells to apigenin reduces expression of PPARγ and C/EBPβ [106]. The reduction of C/EBPβ was shown to be due to upregulation of C/EBP inhibitors such as C/EBP homologous protein and the phospho-liver-enriched inhibitory protein isoform of C/EBPβ [107]. Similarly, luteolin inhibits adipogenesis by attenuating the expression of C/EBPα and PPARγ. Notably, the PPAR agonist, rosiglitazone-induced adipogenic differentiation in preadipocytes is inhibited by luteolin [108].

**Flavan-3-ols**

Flavan-3-ols are widely distributed in human diet and have been shown to be the dominant flavonoid intake by the U.S. adults compared to other flavonoid subclasses [109]. Flavan-3-ols can be found in many fruits including cocoa and tea. The main flavan-3-ols in fruits and cocoa are catechin and epicatechin. Epicatechin gallate (ECG), epigallocatechin (EGC), galloallocatechin, and epigallocatechin gallate (EGCG) are mainly present in tea [110]. Many studies demonstrated that catechin possesses anti-adipogenic effect. Tea catechin, in particular (−)-catechin 3-gallate and (−)-epigallocatechin, have been shown to suppress adipogenesis in 3T3-L1 cells via downregulation of PPARγ2, C/EBPα, and GLUT4 [111]. However, (−)-catechin derived from green tea has been shown to induce adipocyte differentiation in human bone marrow mesenchymal stem cells (hBM-MSCs) via stimulation of transcriptional activity of PPAR. In addition, the level of adipogenic markers such as adiponectin (*Adipoq*), fatty acid-binding protein 4 (*Fabp4*), and lipoprotein lipase (*Lpl*) are markedly increased. Nevertheless, its stereoisomer (+)-catechin does not show any proadipogenic effect which suggests the possibility of a direct pharmacological target regulated by (−)-catechin [105].

EGCG, the most abundant catechin in green tea, inhibits adipogenesis by reducing the expression of PPARγ, C/EBPα, FABP4, and fatty acid synthase while increasing the level of β-catenin in the nucleus. Knocking down of β-catenin using siRNA recovers the expression of these adipogenic markers and attenuates the anti-adipogenic effect of EGCG suggesting Wnt/β-catenin pathway as the anti-adipogenic mechanism of EGCG [112]. EGCG has also been shown to increase apoptosis in mature adipocytes without affecting viability of preadipocytes [113]. However, contradictory result has been obtained with EGCG; Sakuri et al. claimed that EGCG enhances the expression of the genes involved in adipocyte differentiation. The expression of *Pparg1, Pparg2, Cebps*, and *Ppargelα* was shown to be increased by EGCG treatment. Nonetheless, these effects are only observed at the early and not late stages of adipogenesis [104].
Flavonols

Flavonols are the most widely distributed flavonoids in the plant kingdom with the exception of algae and fungi. Quercetin, kaempferol, isorhamnetin, fisetin, and myricetin are the main dietary flavonols that can be found in berries, onions, and olive oil. A number of dietary flavonols investigated showed anti-adipogenic effects by interruption of both the conversion of mesenchymal cells to preadipocytes and the differentiation of preadipocytes to mature adipocytes. In vitro studies have indicated that isorhamnetin treatment of preadipocytes results in downregulation of *Pparg* and *Cebpα* without affecting regulation of *Cebpβ* and *Cebpδ*. In addition, this flavonol decreases expression of PPARγ-target genes such as liver X receptor-alpha (*Lxr-α*), *Lpl*, and *Fabp4* suggesting PPARγ inhibition as a possible mechanism underlying the anti-adipogenic effect of isorhamnetin [114]. Another study conducted by the same group showed that isorhamnetin inhibits differentiation of human adipose tissue-derived mesenchymal stem (hA-MSCs) cells to preadipocytes, wherein it downregulates the mRNA levels of Wnt antagonist such as secreted frizzled-related protein 1 (*Sfrp1*) and dickkopf-1 (*Dkk1*). Furthermore, isorhamnetin stabilizes β-catenin which suggests Wnt signaling pathway as the mechanism responsible for isorhamnetin anti-adipogenic effect in mesenchymal stem cells [115]. Myricetin inhibits hA-MSCs differentiation to preadipocytes and significantly reduces *Pparg*, *Cebpα*, and *Fabp4* gene expression [116]. Besides inhibiting mesenchymal stem cell differentiation, Wang et al. demonstrated the anti-adipogenic effect of myricetin on preadipocyte differentiation. Myricetin-treated 3T3-L1 cells downregulates transcription factors such as *Pparg*, *Cebpα*, *Cebpβ*, *Lpl*, *Fabp4*, *Glut4*, and *Srebp-1c*. Other anti-adipogenic targets of myricetin include inhibition of ERK and c-Jun N-terminal kinase (JNK) phosphorylation during the differentiation process [117]. Microarray analysis revealed that kaempferol decreases expression of adipogenic transcription factors and triglyceride synthesis-related genes and, conversely, increases gene involved in lipolysis [106]. Many transcriptional factors such as C/EBPβ, KLF4, and KLF5 are downregulated by kaempferol treatment, while negative regulators of adipogenesis such as KLF2 and Pref-1 are upregulated during the early adipogenesis [118]. As with many flavonoids, the anti-adipogenic mechanisms of kaempferol are several. Kaempferol also prevents adipocyte differentiation by inhibiting cell-cycle progression via regulation of cyclins. In addition, kaempferol treatment during early adipogenesis inhibits phosphorylation of AKT and mTOR signaling pathways. Fisetin was reported to induce cell-cycle arrest in preadipocytes by suppressing cell-cycle regulatory proteins such as cyclin A, cyclin D1, and CDK4 expression [119]. Nonetheless, another study reported that fisetin reduces adipogenesis by suppression of mTORC1 activity, wherein the flavonol inhibits mTOR phosphorylation and its downstream molecules such as p70 ribosomal S6 kinase which in turn decreases Cebpα gene expression [120, 121]. Rhamnetin blocks adipocyte differentiation during the early stage of adipogenesis program by inhibition of clonal expansion. The expression level of adipogenic transcription factors in the presence of rhamnetin also declines during the early adipogenesis [122].

A comparative study investigated and compared the inhibitory effects of flavonoids (rutin, naringenin, hesperidin, quercetin, naringin, and resveratrol) on adipocyte differentiation, as indicated by the decreases in triglyceride accumulation and GPDH activity [123]. In this study, rutin, a flavonol glycoside, exhibits the highest anti-adipogenic effect characterized by downregulation of adipogenic transcription factors and leptin, and upregulation of adiponectin [124]. Choi et al. investigated the anti-adipogenic effect of rutin in preadipocytes and HFD-induced obese animals. The results indicates that rutin decreases the expression of key adipogenic transcription factors. Experimental animals which received rutin gain less body weight and have lower blood cholesterol [125]. However, rutin was shown to be slowly and poorly absorbed in human [126] as it has to be hydrolysed by the intestinal microflora. These findings may limit the effectiveness of rutin as anti-adipogenic agent following dietary consumption.

Several mechanisms contribute to the anti-adipogenic effect of quercetin. Exposure of mouse preadipocytes to quercetin leads to activation of AMPKα and β and phosphorylation of their substrate, acetyl-CoA carboxylase. In addition, quercetin reduces adipocyte differentiation by inhibiting clonal expansion during the early adipogenesis via suppression of cyclin A [127]. A recent study indicated that quercetin prevents differentiation of OP9 mouse stromal cells into mature adipocytes through downregulation of adipogenic transcription factors, FABP4, LPL, and upregulation of adipose triglyceride and hormone sensitive lipases [128]. Quercetin may reduce adipose tissue mass not only by inhibiting adipogenesis, but this flavonol also induces apoptosis in mature adipocytes by modulating mitogen-activated protein (MAP) kinases, in particular ERKs and JNK pathway [129].

Flavanones

Flavanones are a subclass of dietary flavonoids that are found to be rich in citrus fruits. The major dietary flavanones are naringin and hesperidin [110]. Although naringin and hesperidin have shown promising effects in preventing obesity, limited studies have been conducted to investigate the anti-adipogenic effect of these flavanones. Hesperetin, an aglycone of hesperidin, inhibits adipogenesis in hBM-MSCs by reducing resistin (*Retn*), *Adipoq*,...
polyunsaturated fatty acids. Furthermore, mice with adipose tissue-specific SIRT1 deletion exhibit greater adiposity and metabolic dysregulation, including insulin resistance [135]. Other study investigated the role of SIRT1 in curbing adipocyte hyperplasia; SIRT1 knockdown results in hyperplastic, small, and inflamed adipocytes that appear to be dysfunctional metabolically and physiologically [136]. This study demonstrated that reduced levels of SIRT1 cause c-Myc to become hyperacetylated, which leads to higher preadipocyte proliferation potential and enhanced adipocyte mitotic clonal expansion during differentiation, which eventually results in dysfunctional hyperplastic adipocytes. Indeed, SIRT1 levels are reduced in mice-fed high fat diet which triggers inflammation-induced cleavage and inactivation of SIRT1 [135]. In this context, some of the anti-adipogenic effects of flavonoids mentioned above may very well be due to their actions on SIRT1; quercetin and apigenin have been shown to increase NAD+ levels which leads to activation of SIRT1 [137]. It has been reported that resveratrol inhibits human preadipocyte proliferation and adipogenesis in a SIRT1-dependent manner [116]. Fisetin suppresses the early stages of adipogenesis through SIRT1-mediated deacetylation of PPARγ and FoxO1, and enhances the association of SIRT1 with the PPARγ promoter, leading to suppression of PPARγ transcriptional activity [117].

Collectively, flavonoids exert their beneficial effects against adipogenesis through multiple pathways (Table 2). Although these findings are encouraging, most of their anti-adipogenic effects are identified from cellular models of adipogenesis and remains to be validated in vivo or in human cells. We must also keep in mind that much of these data are based on rodent models which cannot always be directly extrapolated to clinical effects. However, such studies elucidate different molecular mechanisms by which flavonoids, either as individual treatments or in combination, might be effective in prevention of adipocyte differentiation and ultimately obesity.

**Final remarks and conclusion**

Prolonged excessive energy intake without an increase in energy expenditure promotes the increase in adipocyte size and number. Hyperplasia is triggered by a network of signaling factors that induce conversion of MSCs to preadipocytes which then differentiate into mature adipocytes. Interrupting adipogenesis at any stage of adipocyte differentiation may

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**Isoflavones**

Dietary isoflavones are present in legumes, soy bean, and soy foods. As with many natural products, isoflavones such as genistein and daidzein can target more than one pathways in the development of adipocytes. Cultured human adipose-derived mesenchymal cells (hAD-MSCs) treated with genistein or daidzein maintain their fibroblast-like appearance and express Oct-4, the stem cell marker indicating the differentiation of these cells into preadipocytes is interrupted. Once the cells become committed to adipose lineage, genistein demonstrates anti-adipogenic effect by inhibition of *Pparg*, *Srebp-1c*, and *Glut 4* during intermediate phase of the adipogenesis program. Microarray result indicated that activation of Wnt pathway through estrogen receptor (ER)-dependent pathways including ERK/JNK signaling and LIF/TCF4 co-activators are amongst the mechanisms underlying the anti-adipogenic effect of genistein [131]. Recent studies have shown that hypoxic suppressions of adipocyte differentiation are associated with AMPK activation which, in turn, can impair mitotic clonal expansion during the early adipogenesis. In this context, genistein has been demonstrated to induce reactive oxygen species (ROS), which eventually leads to activation of AMPK and inhibition of mitotic clonal expansion. Furthermore, genistein was shown to activate AMPK comparable to 5-aminimidazole-4-carboxamide riboside (AICAR), a known activator of AMPK. Both genistein and daidzein also stimulate lipolysis [131]. Another study investigated the underlying mechanisms responsible for the anti-adipogenic effect of genistein. Genistein has been demonstrated to stimulate lipolysis by preventing the inhibitory effect of dexamethasone on eNOS expression and NO release in 3T3-L1 cells. In addition, pretreatment of preadipocytes with genistein has been reported to inhibit fatty acid synthase and suppress p38; expression of fatty acid synthase is associated with activation of p38 [119]. Indeed, phosphorylation of p38 mitogen-activated protein kinase is required for adipocyte differentiation during the early adipogenesis, wherein treatment of preadipocytes with p38 inhibitors suppressed adipogenesis [120]. Genistein also affects other pathway during adipocyte development; this flavonoid inhibits janus-activated kinase (JAK) 2 to attenuate the effect of growth hormones in promoting adipogenesis [121]. In addition, genistein was shown to suppress adipogenesis by induction of apoptosis in mature adipocytes [132, 133].

Recently, SIRTs, specifically SIRT1, have become a focus of intense anti-obesity research [134]. The NAD+-dependent deacetylase SIRT1 has been shown to maintain proper metabolic functions in many tissues to protect against obesity [84]. As a matter of fact, SIRT1 inhibits adipogenesis by repressing the transcriptional activity of PPARγ [85]. Furthermore, mice with adipose tissue-specific SIRT1 deletion exhibit greater adiposity and metabolic dysregulation, including insulin resistance [135]. Other study investigated the role of SIRT1 in curbing adipocyte hyperplasia; SIRT1 knockdown results in hyperplastic, small, and inflamed adipocytes that appear to be dysfunctional metabolically and physiologically [136]. This study demonstrated that reduced levels of SIRT1 cause c-Myc to become hyperacetylated, which leads to higher preadipocyte proliferation potential and enhanced adipocyte mitotic clonal expansion during differentiation, which eventually results in dysfunctional hyperplastic adipocytes. Indeed, SIRT1 levels are reduced in mice-fed high fat diet which triggers inflammation-induced cleavage and inactivation of SIRT1 [135]. In this context, some of the anti-adipogenic effects of flavonoids mentioned above may very well be due to their actions on SIRT1; quercetin and apigenin have been shown to increase NAD+ levels which leads to activation of SIRT1 [137]. It has been reported that resveratrol inhibits human preadipocyte proliferation and adipogenesis in a SIRT1-dependent manner [116]. Fisetin suppresses the early stages of adipogenesis through SIRT1-mediated deacetylation of PPARγ and FoxO1, and enhances the association of SIRT1 with the PPARγ promoter, leading to suppression of PPARγ transcriptional activity [117].

Collectively, flavonoids exert their beneficial effects against adipogenesis through multiple pathways (Table 2). Although these findings are encouraging, most of their anti-adipogenic effects are identified from cellular models of adipogenesis and remains to be validated in vivo or in human cells. We must also keep in mind that much of these data are based on rodent models which cannot always be directly extrapolated to clinical effects. However, such studies elucidate different molecular mechanisms by which flavonoids, either as individual treatments or in combination, might be effective in prevention of adipocyte differentiation and ultimately obesity.

**Final remarks and conclusion**

Prolonged excessive energy intake without an increase in energy expenditure promotes the increase in adipocyte size and number. Hyperplasia is triggered by a network of signaling factors that induce conversion of MSCs to preadipocytes which then differentiate into mature adipocytes. Interrupting adipogenesis at any stage of adipocyte differentiation may
Table 2  List of flavonoids and their underlying mechanisms of action in adipogenesis

| Flavonoids                    | Stages of adipogenesis | Effect                  | Pathways/target molecules                                                                 | Experimental model and dose applied                                                                 | Comments                                                                                                               | References |
|-------------------------------|------------------------|-------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|------------|
| Anthocyanidins                |                        |                         |                                           |                                                                                                       |                                                                                                                        |            |
| Cyanidin                      | Terminal differentiation | Anti-adipogenic         | Upregulation of ChREBP and interfering with the extracellular matrix                     | Preadipocytes obtained from subcutaneous and visceral human adipose explant tissue                   | Reduces adipogenesis via interfering with extracellular matrix and decreasing ChREBP expression level                | [93]       |
| Cyanidin-3-O-glucoside        | Terminal differentiation | Pro-adipogenic          | Upregulation of Pparg and Cebpα                                                              | 3T3-L1 cells (20 and 100 µM)/db/db mice (black soy bean extract 30 mg/kg, orally)                  | Increases Pparg and Cebpα expression, adiponectin secretion and activates insulin signaling cascade                  | [95]       |
| Determination                 | Anti-adipogenic         |                         | Activation of Wnt pathway                                                                    | C3H10T1/2 cells (black rice extract 10, 20, 40, and 80 µg/ml)/HFD mice (black rice extract, 100 mg/kg, orally) | Inhibits differentiation of mesenchymal cells to preadipocytes and induces Wnt-specific target genes such as Axin2, Wisp2, and Cyclin D1 | [138]      |
| Terminal differentiation      | Anti-adipogenic         | Suppression of PPARG    | 3T3-L1 cells (black soybean extract 12.5 and 50 µg/ml)                                      |                                                                                                       | Reduces lipid accumulation and suppresses PPARG expression                                                            | [94]       |
| Delphinidin-3-O-glucoside     | Terminal differentiation | Anti-adipogenic         | Suppression of PPARG                                                                        | 3T3-L1 cells (black soybean extract 12.5 and 50 µg/ml)                                            | Reduces lipid accumulation and suppresses PPARG expression                                                            | [94]       |
| Peonidin-3-O-glucoside        | Determination           | Anti-adipogenic         | Activation of Wnt pathway                                                                    | C3H10T1/2 cells (black rice extract 10, 20, 40, and 80 µg/ml)/HFD mice (black rice extract, 100 mg/kg, orally) | Inhibits differentiation of mesenchymal cells to preadipocytes and induces Wnt-specific target genes such as Axin2, Wisp2, and Cyclin D1 | [138]      |
| Flavones                      |                        |                         |                                           |                                                                                                       |                                                                                                                        |            |
| Apigenin                      | Clonal expansion        | Anti-adipogenic         | Inhibition of mitotic clonal expansion and cell-cycle arrest                                | 3T3-L1 cells (30 and 70 µM)                                                                         | Inhibits clonal expansion, arrests cell cycle at the G0/G1 phase and decreases PPARG and C/EBPβ levels             | [107]      |
|                              | Terminal differentiation | Anti-adipogenic         | Activation of AMPK                                                                          | 3T3-L1 cells (10, 50 µM)                                                                            | Induces activation of AMPK and decreases expression of adipogenic and lipolytic genes                               | [97]       |
| Luteolin                      | Terminal differentiation | Anti-adipogenic         | Inhibition of the transactivation of PPARG                                                   | 3T3-L1 cells                                                                                         | Attenuates PPARG and C/EBPγ expression                                                                                | [108]      |
| Baicalein                     | Clonal expansion        | Anti-adipogenic         | Suppression of Akt-C/EBPζ-GLUT4 signaling                                                    | 3T3-L1 cells (50 µM)                                                                                | Decreases the intracellular lipid accumulation by down-regulation of glucose uptake via repression of Akt-C/EBPζ-GLUT4 signaling | [133]      |
| Flavonoids                  | Stages of adipogenesis | Effect                | Pathways/target molecules                                      | Experimental model and dose applied                                                                 | Comments                                                                 | References |
|----------------------------|------------------------|-----------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|------------|
| Flavan-3-ols               |                        |                       |                                                                    |                                                                                                      |                                                                      |            |
| Catechin                   | Terminal differentiation| Anti-adipogenic       | Suppression of PPARG2, C/EBPα & GLUT4                           | 3T3-L1 cells (50, 75, 100 µM) / 3T3-L1 cells (30 µM)                                                | Inhibits adipogenesis via suppression of PPARG2, C/EBPα, and GLUT4   | [111, 139] |
| (−)-Catechin               | Determination           | Proadipogenic         | Upregulation of Pparg                                         | hBM-MSCs (1 and 100 µM)                                                                                        | Upregulates the mRNA levels of adipogenic markers, such as Adiposeq, Pparg, Fabp4, and Lpl in hBM-MSCs | [105]      |
| (−)-Epigallocatechin gallate | Terminal differentiation| Proadipogenic         | Upregulation of Pparg and Cebps                               | 3T3-L1 cells (0.5, 5, or 10 µM)                                                                            | Increases expression of Pparg1, Pparg2, and Cebps                  | [104]      |
| (−)-Epigallocatechin gallate | Terminal differentiation| Anti-adipogenic       | Activation of Wnt/β-catenin pathway                             | 3T3-L1 cells (100, 150, 200 µM)                                                                            | Reduces expression of adipogenic markers such as PPARG, C/EBPα, FABP4 and fatty acid synthase while increases β-catenin in the nucleus | [112]      |
| Flavonols                  | Terminal differentiation| Anti-adipogenic       | Apoptosis                                                      | 3T3-L1 cells (50–200 µM)                                                                                   | Increases apoptosis in mature adipocytes without affecting viability of preadipocytes | [113]      |
| Fisetin                    |                        |                       |                                                                    |                                                                                                      |                                                                      |            |
|                            | Clonal expansion        | Anti-adipogenic       | Inhibition of mitotic clonal expansion                          | 3T3-L1 cells (10, 30 µM)                                                                                   | Suppresses cell cycle regulatory proteins such as cyclin A, cyclin D1 and CDK4 expression and inhibits cell proliferation | [141]      |
|                            | Terminal differentiation| Anti-adipogenic       | Inhibition of mTORC1 signaling                                 | 3T3-L1 cells (50 µM) / HFD mice (HFD supplemented with 0.2% or 0.5% (w/w) fisetin)                      | Reduces adipogenesis by suppression of mTORC1 activity              | [140]      |
|                            |                        |                       |                                                                    |                                                                                                      |                                                                      |            |
|                            | Terminal differentiation| Anti-adipogenic       | Inhibition of mTOR-C/EBPα Signaling                            | 3T3-L1 cells (10 µM)                                                                                       | Downregulates Pparg and Cebpα expression during adipogenesis        | [142]      |
| Isorhamnetin               | Terminal differentiation| Anti-adipogenic       | Suppression of Pparg                                          | 3T3-L1 cells (50 µM)                                                                                       | Reduces Pparg and Cebpα expression. However Cebpβ and Cebpδ expression remains unchanged | [114]      |
| Determination/terminal differentiation | Anti-adipogenic     | Stabilization of β-catenin protein                           | hA-MSCs / 3T3-L1 cells (1, 25 µM)                                           | Inhibits Wnt receptor and co-receptor genes expression, increases β-catenin, but no effect on β-catenin mRNA levels | [115]      |

*Note: HFD = High Fat Diet*
| Flavonoids | Stages of adipogenesis | Effect | Pathways/target molecules | Experimental model and dose applied | Comments | References |
|------------|------------------------|--------|---------------------------|-----------------------------------|----------|------------|
| Kaempferol | Clonal expansion        | Anti-adipogenic | Inhibition of cell-cycle progression, AKT and mTOR signaling pathway | 3T3-L1 cells (30 µM)/zebra fish (5, 10, 20 µM) | Inhibits cell-cycle progression via regulation of cyclins. In addition, inhibits phosphorylation of AKT and mTOR signaling pathway. Many transcriptional factors such as C/EBPβ, KLF4 and KLF5 are downregulated, while nKLF2 and Pref-1 are upregulated | [118] |
|            | Terminal differentiation | Anti-adipogenic | Suppression of Pparg | 3T3-L1 cells (40, 80 µM) | Downregulates expression of Pparg, Cebpβ, Srebp1, Rxrβ, Lxrβ, Rox1 and also genes involved in triglyceride biosynthesis such as Gpd1, Agpat2, Dgat2 | [106, 143] |
| Myricetin  | Terminal differentiation | Anti-adipogenic | Suppression of Pparg | 3T3-L1 cells (100 µM) | Reduces expression of Cebpa, Pparg, Cebpβ, Sreb1c, Fabp4, Lpl and Glut4. Also, inhibits phosphorylation of ERK and JNK during differentiation of adipocytes | [144] |
|            | Determination            | Anti-adipogenic | Suppression of Pparg | hA-MSCs (30 µM) | Reduces expression of Cebpa, Pparg, Lpl and Fabp | [145] |
| Rhamnetin  | Clonal expansion/terminal differentiation | Anti-adipogenic | Inhibition of mitotic clonal expansion, and suppression of Pparg | 3T3-L1 cells | Decreases expression of Pparg, Cebpα, and perilipin (Plin) Also completely inhibits triglyceride biosynthesis and clonal expansion | [122] |
| Rutin      | Terminal differentiation | Anti-adipogenic | Suppression of Pparg and Cebpα | 3T3-L1 cells (0.25, 0.5, 1.0 mg/ml)/3T3-L1 cells (10, 30, 100 µM)/HFD mice (25, 50 mg/kg, orally) | Reduces mRNA expression of Pparg and Cebpα | [125, 146] |
| Flavonoids     | Stages of adipogenesis | Effect               | Pathways/target molecules | Experimental model and dose applied | Comments                                                                 | References |
|---------------|------------------------|----------------------|---------------------------|------------------------------------|--------------------------------------------------------------------------|------------|
| Quercetin     | Terminal differentiation| Anti-adipogenic      | Activation of AMPK pathway | 3T3-L1 cells (10, 50, 100 µM)       | Stimulates activation of AMPK pathway and phosphorylation of acetyl-CoA carboxylase | [129]      |
| Clonal expansion | Anti-adipogenic       | Inhibition of mitotic clonal expansion | 3T3-L1 cells (50, 100 µM) | Decreases adipocyte differentiation by inhibition of clonal expansion during early adipogenesis via suppression of cyclin A | [147]      |
| Determination | Anti-adipogenic       | Suppression of PPARG, C/EBPα and SREBP-1c | OP9 mouse stromal cells (50 µM) | Downregulates mRNA and protein expression of C/EBPα, PPARG, SREBP-1c, FAS, FABP4 and mRNA level of Hsl and Lpl | [148]      |
| Flavanones    |                        |                      |                           |                                    |                                                                          |            |
| Hesperetin    | Determination          | Anti-adipogenic      | Apoptosis                 | hBM-MSCs (10, 20, 40, 80, 160 µM)  | Decreases expression of Adipoq, Retn, Fadh4, Pparγ, Lpl and Tnfα, while upregulates proapoptotic genes | [130]      |
| Naringenin    | Terminal differentiation | Anti-adipogenic     | Suppression of PPARG      | 3T3-L1 cells (25, 50 µg/ml)        | Reduces expression of FABP4, PPARG, STAT5A, and adiponectin              | [149]      |
| Isoflavones   |                        |                      |                           |                                    |                                                                          |            |
| Biochanin A   | Determination          | Anti-adipogenic      | Suppression of Pparγ      | hA-MSCs (0.1, 0.3, and 1 µM)       | Decreases Pparγ, Leptin (Lep), osteopontin (Opn) and Lpl expression    | [150]      |
| Daidzein      | Determination          | Anti-adipogenic      | Stimulation of lipolysis  | hA-MSCs (0.1–100 µM)              | Stimulates lipolysis by cAMP-dependent protein kinase-mediated hormone sensitive lipase | [131]      |
| Formononetin  | Terminal differentiation | Proadipogenic       | Upregulation of PPARG    | C3H10T1/2 cells (1–20 µM)          | Upregulates PPARG and its target genes such as Fabp4 and Glut4          | [151]      |
|               | Terminal differentiation | Proadipogenic       | Upregulation of PPARG    | 3T3-L1 cells (1–20 µM)             | Upregulates PPARG and its target genes such as Fabp4 and Glut4          | [152]      |
serve as potential therapeutic strategy against adipogenesis and obesity. In this context, dietary flavonoids have become the subject of increasing scientific interest due to their effects on adipogenesis. The anti-adipogenic effects of flavonoids are mainly via their effect on a number of molecular targets and regulation of several pathways such as induction of apoptosis [123], suppression of key adipogenic transcription factors [94, 95, 114, 144], activation of AMPK [97, 129], and Wnt [115, 138] pathways, inhibition of clonal expansion [147, 153, 155], cell-cycle arrest, and modulation of insulin signaling cascade [118], suggesting flavonoids as effective inhibitors of adipogenesis during determination and terminal differentiation stages.

Although these data are encouraging, further investigation is essential to gain insight into the molecular mechanisms that connect extranuclear and nuclear mediators of adipogenesis. Even though most of the studies have shown that flavonoids suppress the key adipogenic regulators such as PPARG and C/EBPα, the upstream mechanisms which led to suppression of these master regulators of adipogenesis are not fully investigated. In addition, the effect of flavonoids in areas such as microRNAs and circadian clock need to be more explored.

Strategies to develop flavonoids as treatment or as supplementary treatment of obesity will have to consider the pharmacokinetic aspects of the molecules, as well. We have to bear in mind that the in vitro evidence of flavonoids in suppressing adipogenesis might be somewhat of limited impact due to the fact that in vivo flavonoids are extensively metabolized to molecules with different structures and activities and, therefore, may preclude their use in humans [127]. Flavonoids are substrates for conjugating and hydrolyzing enzymes in the small intestine, liver, and colon. Conjugation of flavonoids first occurs in the small intestine followed by the liver where they are further metabolized and the produced glucuronides and sulfate derivatives facilitate their excretion via urine and bile. The compounds that are not absorbed in the intestine will reach the colon and be subjected to structural modifications by colonic microbiota. The flavonoid glucuronides that re-enter the enterohepatic circulation through bile excretion are hydrolyzed by the gut microbiota to aglycones that can further be catabolized to low-molecular-weight compounds that can readily be absorbed [128]. This bacterial conversion of flavonoids may have potential health consequences for the host. Therefore, the differences in intestinal microbiota composition among different species may result in different profiles of flavonoid metabolites with different bioactivity [156]. This emphasizes the importance of studying the pharmacokinetic profile of the various flavonoids in human subjects.

It is also important to determine the amount of flavonoids or bioactive compounds in foods or dietary supplement as well as their bioavailability. Despite the health benefits of

| Flavonoids          | States of adipogenesis | Effect                                      | Pathways/target molecules | Experimental model and dose          | Comments                                                                 | References |
|---------------------|------------------------|---------------------------------------------|----------------------------|--------------------------------------|--------------------------------------------------------------------------|------------|
| Genistein           | Clonal expansion/terminal differentiation | Anti-adipogenic                            | Inhibition of mitotic clonal expansion and PPARG expression | 3T3-L1 cells (5, 50, 100 µM) | Inhibits adipogenesis by inhibition of mitotic clonal expansion and PPARG expression | [153]      |
|                     |                       | Anti-adipogenic                            | Activation of MAPK and induction of apoptosis and inhibition of clonal expansion | 3T3-L1 cells (100 µM) | Increases nES expression, inhibits phosphorylation of JAK2 and decreases FAS expression | [119]      |
|                     |                       | Anti-adipogenic                            | Activation of MAPK and induction of apoptosis and inhibition of clonal expansion | hA-MSCs (0.1–100 µM) | Activates Wnt/β-catenin pathway, inhibits expression of Pparγ, Srebp-1c and Glut4 | [131]      |

Table 2 (continued)
flavonoids, the bioavailability of flavonoids is generally low and can vary drastically among different flavonoid classes as well as among compounds in a particular class. Flavonoids with complex structures and larger molecular weights may even have lower bioavailability [128]. In human diet, the concentration of flavonoids may be too low to generate adequate efficacy for their health benefits including anti-adipogenic properties. During the past few decades, dietary supplements have become increasingly popular as an alternative source to flavonoid-rich fruits and vegetables [157]. Even though consuming supplements can ensure us that we are getting our daily dose of flavonoids, toxicity issues as well as nutrient–drug interactions should be the subject of concern. Furthermore, the health promoting effects of some of dietary flavonoids are due to the synergistic effects of other flavonoids or compounds present in the food. Therefore, this complex mixture of secondary plant metabolites cannot be simply replaced by purified molecules as dietary supplements. Further investigations on the synergistic effects of flavonoids on adipogenesis are required. There is also a need for more studies assessing flavonoid absorption, organ- or tissue-specific distribution, and accumulation. Specifically, the availability of flavonoids or active metabolites to adipose tissues depends, amongst others, on the lipid solubility of the substance. flavonoids possessing a number of unsubstituted hydroxyl group and glycosides are polar and water-soluble. There is a negative correlation between the number of hydroxyl groups and the lipophilicity of flavonoids. Although most flavonoids are water-soluble, they possess some lipophilicity, as well. It is well known that flavonoid aglycones are only slightly soluble in water and show lipophilic properties. This lipophilic behavior of flavonoid aglycones may allow the uptake of flavonoids by adipose tissue. For instance, quercetin and its metabolites (isorhamnetin and tamarixetin) in their aglycone form were found in variable amount in most tissues in rat including white adipose tissue [132]. However, the lowest concentration was found in adipose tissue and brain [132]. Nevertheless, long-term intake of flavonoid-rich diet or supplements may result in adequate absorption and accumulation of anti-adipogenic concentration of flavonoids in adipose tissues.

Even though flavonoids have shown promising effect on inhibiting adipogenesis under experimental conditions, low bioavailability of some flavonoids needs to be enhanced for full exploitation of their benefits in prevention of adipogenesis. Therefore, more investigations on the appropriate dose of flavonoids in supplements and also methods to improve bioavailability and thus efficacy of certain flavonoids are warranted.

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Compliance with ethical standards

Conflict of interest The authors have declared that no competing interest exists.

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References

1. Gil-Campos M, Canete RR, Gil A (2004) Adiponectin, the missing link in insulin resistance and obesity. Clin Nutr 23(5):963–974. https://doi.org/10.1016/j.clnu.2004.04.010
2. World Health Organization (2014) Obesity and overweight (Fact sheet No. 311). http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed 5 Feb 2016
3. Flegal KM, Carroll MD, Ogden CL, Curtin LR (2010) Prevalence and trends in obesity among US adults, 1999–2008. JAMA 303(3):235–241. https://doi.org/10.1001/jama.2009.2014
4. Jo J, Gavrilova O, Pack S, Jou W, Mullen S, Sumner AE, Cushman SW, Periwal V (2009) Hypertrophy and/or hyperplasia: dynamics of adipose tissue growth. PLoS Comput Biol 5(3):e1000324. https://doi.org/10.1371/journal.pcbi.1000324
5. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, Blomqvist L, Hofstedt J, Naslund E, Britton T, Concha H, Hassan M, Ryden M, Frisen J, Arner P (2008) Dynamics of fat cell turnover in humans. Nature 453(7196):783–787. https://doi.org/10.1038/nature06902
6. Hirsch J, Batchelor B (1976) Adipose tissue cellularity in human obesity. Clin Endocrinol Metab 5(2):299–311
7. Letierova M, Lazar MA (2009) New developments in adipogenesis. Trends Endocrinol Metab 20(3):107–114. https://doi.org/10.1016/j.tem.2008.11.005
8. Vroegrijk IO, van Diepen JA, van den Berg SA, Romijn JA, Havekes LM, van Dijk KW, Darland G, Konda V, Tripp ML, Bland JS, Voshol PJ (2013) META060 protects against diet-induced obesity and insulin resistance in a high-fat-diet fed mouse. Nutrition 29(1):276–283. https://doi.org/10.1016/j.nut.2012.05.004
9. Bertoia ML, Rimm EB, Mukamal KJ, Hu FB, Willett WC, Cassidy A (2016) Dietary flavonoid intake and weight maintenance: three prospective cohorts of 124,086 US men and women followed for up to 24 years. BMJ. https://doi.org/10.1136/bmj.j17
10. Badshah H, Ullah I, Kim SE, Kim TH, Lee HY, Kim MO (2013) Anthocyanins attenuate body weight gain via modulating neuroepitope Y and GABAB1 receptor in rats hypothalamus. Neuropeptides 47(5):347–353. https://doi.org/10.1016/j.nep.2013.06.001
11. Josic J, Olsson AT, Wickeberg J, Lindstedt S, Hlebowicz J (2010) Does green tea affect postprandial glucose, insulin and satiety in healthy subjects: a randomized controlled trial. Nutr J 9:63. https://doi.org/10.1186/1475-2891-9-63
12. Stendell-Hollis NR, Thomson CA, Thompson PA, Bea JW, Cussler EC, Hakim IA (2010) Green tea improves metabolic...
biomarkers, not weight or body composition: a pilot study in overweight breast cancer survivors. J Hum Nutr Diet 23(6):590–600. https://doi.org/10.1111/j.1365-277X.2010.01078.x

13. Ashida H, Furuyashiki T, Nagayasu H, Bessho H, Sakakibara H, Hashimoto T, Kanazawa K (2004) Anti-obesity actions of green tea: possible involvements in modulation of the glucose uptake system and suppression of the adipogenesis-related transcription factors. BioFactors 22(1–4):135–140

14. Westerterp-Plantenga MS, Lejeune MP, Kovacs EM (2005) Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. Obes Res 13(7):1195–1204. https://doi.org/10.1038/oby.2005.142

15. Moon J, Do HJ, Kim OY, Shin MJ (2013) Antiobesity effects of quercetin-rich onion peel extract on the differentiation of 3T3-L1 preadipocytes and the adipogenesis in high fat-fed rats. Food Chem Toxicol 58:347–354. https://doi.org/10.1016/j.fct.2013.05.006

16. Wolfram S, Raederstorff D, Wang Y, Teixeira SR, Elste V, Weber P (2005) TAVIGO (epigallocatechin gallate) supplementation prevents obesity in rodents by reducing adipose tissue mass. Ann Nutr Metab 49(1):54–63. https://doi.org/10.1159/000084178

17. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L (2003) Obesity in adulthood and its consequences for life expectancy: a life-table analysis. Ann Intern Med 138(1):24–32

18. Pallauf K, Duckstein N, Rimbach G (2017) A literature review of flavonoids and lifespan in model organisms. Proc Nutr Soc 76(2):145–162. https://doi.org/10.1017/S0033-838716000720

19. Niemela S, Miettinen S, Sarkanen JR, Ashammakhi N (2008) Adipose tissue and adipocyte differentiation: molecular and cellular aspects and tissue engineering In: Ashammakhi A, Reis R, Chiellini F (eds) Topics in tissue engineering, vol 4. University of Oulu, Oulu

20. Rayalam S, Della-Fera MA, Baile CA (2008) Phytochemicals and regulation of the adipocyte life cycle. J Nutr Biochem 19(11):717–726. https://doi.org/10.1016/j.jnutbio.2007.12.007

21. Patel YM, Lane MD (2000) Mitotic clonal expansion during preadipocyte differentiation: calpain-mediated turnover of p27. J Biol Chem 275(23):17653–17660. https://doi.org/10.1074/jbc.M910445199

22. Gregoire FM, Zhang F, Clarke HG, Gustafson TA, Sears DD, Faveluykis S, Lenhard J, Rentzeperis D, Clemens LE, Mu Y, Lavan BE (2009) A novel peroxisome proliferator-activated receptor-ligand with weak transactivation activity retains anti-diabetic properties in the absence of weight gain and edema. Mol Endocrinol 23(7):975–988. https://doi.org/10.1210/me.2008-0473

23. Moreno-Navarrete J, Fernández-Real J (2012) Adipocyte differentiation. In: Symonds ME (ed) Adipose tissue and adipocyte differentiation. In: Symonds ME (ed) Adipose tissue and adipocyte differentiation. Cell Metab 10(2):165–173

24. Ge K, Guermah M, Ge K, Chiang CM, Roeder RG (2003) The TBN protein, which is essential for early embryonic mouse development, is an inducible TAFII implicated in adipogenesis. Mol Biochemistry 44(33):11098–11105. https://doi.org/10.1021/bi050166f

25. Tong Q, Tsai J, Tan G, Dalgin G, Hotamisligil GÖ S (2005) Interaction between GATA and the C/EBP family of transcription factors is critical in GATA-mediated suppression of adipocyte differentiation. Mol Cell Biol 25(2):706–715. https://doi.org/10.1128/mcb.25.2.706-715.2005

26. Reusch JE, Colton LA, Klemm DJ (2000) CREB activation induces adipogenesis in 3T3-L1 cells. Mol Cell Biol 20(3):1008–1020

27. Zhang JW, Klemm DJ, Vinson C, Lane MD (2004) Role of CREB in transcriptional regulation of CCAAT/enhancer-binding protein beta gene during adipogenesis. J Biol Chem 279(6):4471–4478. https://doi.org/10.1074/jbc.M311327200

28. Kanazawa A, Kawamura Y, Sekine A, Iida A, Tsunoda T, Kashiwagi A, Tanaka Y, Babazono T, Matsuda M, Kawai K, Iizumi T, Fujioka T, Imanishi M, Kaku K, Iwamoto Y, Kawamori R, Kikkawa R, Nakamura Y, Maeda S (2005) Single nucleotide polymorphisms in the gene encoding Kruppel-like factor 7 are associated with type 2 diabetes. Diabetologia 48(7):1315–1322. https://doi.org/10.1007/s00125-005-1797-0

29. Wu J, Srinivasan SV, Neumann JC, Lingrel JB (2005) The KLF2 transcription factor does not affect the formation of preadipocytes but inhibits their differentiation into adipocytes. Biochemistry 44(33):11098–11105. https://doi.org/10.1021/bi050166f
41. Grana X, Reddy EP (1995) Cell cycle control in mammalian cells: role of cyclins, cyclin dependent kinases (CDKs), growth suppressor genes and cyclin-dependent kinase inhibitors (CKIs). Oncogene 11(2):211–219
42. Hunter T, Pines J (1994) Cyclins and cancer. II: cyclin D and CDK inhibitors come of age. Cell 79(4):573–582
43. Heremekin H, Wolf DA, Kohlihuber F, Dickmanns A, Billaud M, Fanning E, Eick D (1994) Role of c-myc in simian virus 40 large tumor antigen-induced DNA synthesis in quiescent 3T3-L1 mouse fibroblasts. Proc Natl Acad Sci USA 91(22):10412–10416
44. Heath VJ, Gillespie DA, Crouch DH (2000) Inhibition of the terminal stages of adipocyte differentiation by cMyc. Exp Cell Res 254(1):91–98. https://doi.org/10.1006/excr.1999.4736
45. Tang QQ, Otto TC, Lane MD (2003) CCAAT/enhancer-binding protein b is required for mitotic clonal expansion during adipogenesis. Proc Natl Acad Sci USA 100:850–855
46. Qin L, Chen Y, Niu Y, Chen W, Wang Q, Xiao S, Li A, Xie Y, Li J, Zhao X, He Z, Mo D (2010) A deep investigation into the adipogenesis mechanism: profile of microRNAs regulating adipogenesis by modulating the canonical Wnt/beta-catenin signaling pathway. BMC Genom 11:320. https://doi.org/10.1186/1471-2164-11-320
47. Hamam D, Ali D, Kassem M, Aldahmash A, Alajez NM (2015) MicroRNA-204 inhibiting protein b is required for mitotic clonal expansion during adipogenesis. Proc Natl Acad Sci USA 102(34):12071–12076. https://doi.org/10.1073/pnas.0502318102
48. Klöting N, Berthold S, Kovacs P, Schön MR, Schön MR, Fasshauer M, Ottmann D, Schaffner F, Liedtke M, Fuhrmann G, Stumvoll M, Clemmons DR, Rosen CJ (2010) A circadian-regulated gene, Nocturnin, promotes adipogenesis by stimulating PPAR-gamma transcriptional activation. Proc Natl Acad Sci USA 107(23):10508–10513. https://doi.org/10.1073/pnas.1007881
49. Kawai M, Green CB, Lecka-Czernik B, Douris N, Gilbert MR, Kojima S, Ackert-Bicknell C, Garg N, Honzovitz MC, Adamo ML, Clemons DR, Rosen CJ (2010) Circadian rhythm gene period 3 is an inhibitor of the adipocyte cell fate. J Biol Chem 286(11):9063–9070. https://doi.org/10.1074/jbc.M110.164558
50. Guo B, Chatterjee S, Li L, Zhao X, Ji C, Guo X (2016) Adipogenic miRNA and meta-signature into the adipogenesis mechanism: profile of microRNAs regulating adipogenesis of mesenchymal stem cells. Stem Cells Dev 24(4):417–425. https://doi.org/10.1089/scd.2014.0331
51. Mercado C, Eades G, Zhou Q (2013) MicroRNAs: a new class of master regulators of adipogenesis. Hum Genet Embryol 3:108
52. Knelangen JM, van der Hoek MB, Kong WC, Owens JA, Fischer E, Borchardt RT, Wunderlich MT, Clemmons DR, Rosen CJ (2010) A circadian-regulated gene, Nocturnin, promotes adipogenesis by stimulating PPAR-gamma transcriptional activation. Proc Natl Acad Sci USA 107(23):10508–10513. https://doi.org/10.1073/pnas.1007881
53. Yoshimi S, Ishii N, Ohta Y, Ohno T, Watabe Y, Hayashi M, Wada T, Aoyagi T, Tetzuka M (2005) Brain and muscle Arnt-like 1, regulates adipogenesis via Wnt signaling pathway. FASEB J 26(8):3453–3463. https://doi.org/10.1096/fj.12-205781
54. Shima S, Ishii N, Ohta Y, Ohno T, Watabe Y, Hayashi M, Wada T, Aoyagi T, Tetzuka M (2005) Brain and muscle Arnt-like protein-1 (BMAL1), a component of the molecular clock, regulates adipogenesis. Proc Natl Acad Sci USA 102(34):12071–12076. https://doi.org/10.1073/pnas.0502318102
55. Bluher M, Michael MD, Peroni OD, Ueki K, Carter N, Kahn BB, Kahn CR (2002) Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. Dev Cell 3(1):25–38
56. Garofalo RS, Orena SJ, Rafidi K, Torchia AJ, Stock JL, Hildebrandt AL, Coskran T, Black SC, Brees DJ, Wicks JR, McNeech JD, Coleman KG (2003) Severe diabetes, age-dependent loss of insulin receptor-alpha1 gene expression than omental fat. Proc Natl Acad Sci USA 100:850–855
57. Kinoshita M, Ono K, Horie T, Nagao K, Nishi H, Kurosawa Y, Takanabe-Mori R, Hasegawa K, Kita T, Kimura T (2010) Regulation of adipocyte differentiation by activation of serotinin (5-HT) receptors 5-HT2AR and 5-HT2CR and involvement of microRNA-448-mediated repression of KLF5. Mol Endocrinol 24(10):1978–1987. https://doi.org/10.1210/me.2010-0054
58. Heath VJ, Gillespie DA, Crouch DH (2000) Inhibition of the terminal stages of adipocyte differentiation by cMyc. Exp Cell Res 254(1):91–98. https://doi.org/10.1006/excr.1999.4736
59. Hamam D, Ali D, Kassem M, Aldahmash A, Alajez NM (2015) MicroRNAs as regulators of adipogenic differentiation of mesenchymal stem cells. Stem Cells Dev 24(4):417–425. https://doi.org/10.1089/scd.2014.0331
60. Kawai M, Green CB, Lecka-Czernik B, Douris N, Gilbert MR, Kojima S, Ackert-Bicknell C, Garg N, Honzovitz MC, Adamo ML, Clemons DR, Rosen CJ (2010) Circadian rhythm gene period 3 is an inhibitor of the adipocyte cell fate. J Biol Chem 286(11):9063–9070. https://doi.org/10.1074/jbc.M110.164558
61. Guo B, Chatterjee S, Li L, Zhao X, Ji C, Guo X (2016) Adipogenic miRNA and meta-signature into the adipogenesis mechanism: profile of microRNAs regulating adipogenesis of mesenchymal stem cells. Stem Cells Dev 24(4):417–425. https://doi.org/10.1089/scd.2014.0331
62. Kinoshita M, Ono K, Horie T, Nagao K, Nishi H, Kurosawa Y, Takanabe-Mori R, Hasegawa K, Kita T, Kimura T (2010) Regulation of adipocyte differentiation by activation of serotinin (5-HT) receptors 5-HT2AR and 5-HT2CR and involvement of microRNA-448-mediated repression of KLF5. Mol Endocrinol 24(10):1978–1987. https://doi.org/10.1210/me.2010-0054
adipose-derived stem cells. Biochem Biophys Res Commun 359(2):239–244. https://doi.org/10.1016/j.bbrc.2007.05.070
72. Ohta H, Konishi M, Itoh N (2011) FGF10 and FGF21 as regulators in adipocyte development and metabolism. Endocr Metab Immune Disord Drug Targets 11(4):302–309
73. Moldes M, Zuo Y, Morrison RF, Silva D, Park BH, Liu J, Farmer SR (2003) Peroxisome-proliferator-activated receptor gamma suppresses Wnt/beta-catenin signalling during adipogenesis. Biochem J 376(Pt 3):607–613. https://doi.org/10.1042/bj20030426
74. Ross SE, Hemati N, Longo KA, Bennett CN, Lucas PC, Erickson RL, MacDougall OA (2000) Inhibition of adipogenesis by Wnt signaling. Science 289(5481):950–953
75. Marion V, Stoetzel C, Schlicht D, Messaddeq N, Koch M, Flori E, Danje ML, Mandel JL, Dollfus H (2009) Transient ciliogenesis involving Bardet-Biedl syndrome proteins is a fundamental characteristic of adipogenic differentiation. Proc Natl Acad Sci USA 106(18):1820–1825. https://doi.org/10.1073/pnas.0812518106
76. Choy L, Derynick R (2003) Transforming growth factor-beta inhibits adipocyte differentiation by Smad3 interacting with CCAAT/enhancer-binding protein (C/EBP) and repressing C/EBP transactivation function. J Biol Chem 278(11):9609–9619. https://doi.org/10.1074/jbc.M212259200
77. Ninomiya-Tsuji J, Torti FM, Ringold GM (1993) Tumor necrosis factor-induced c-myc expression in the absence of mitogenesis is associated with inhibition of adipocyte differentiation. Proc Natl Acad Sci USA 90(20):9611–9615
78. Yarmo MN, Landry A, Molgat AS, Gagnon A, Sorisky A (2009) Macrophage-conditioned medium inhibits differentiation-induced Rb phosphorylation in 3T3-L1 preadipocytes. Exp Cell Res 315(3):411–418. https://doi.org/10.1016/j.yexcr.2008.10.036
79. Constant VA, Gagnon A, Landry A, Sorisky A (2006) Macrophage-conditioned medium inhibits the differentiation of 3T3-L1 and human abdominal preadipocytes. Diabetologia 49(6):1402–1411. https://doi.org/10.1007/s00125-006-0253-0
80. Lumeng CN, Deyoun SM, Salitriet AR (2007) Macrophages block insulin action in adipocytes by altering expression of signaling and glucose transport proteins. Am J Physiol Endocrinol Metab 292(1):E166–E174. https://doi.org/10.1152/ajpendo.00284.2006
81. He W, Barak Y, Hevener A, Olson P, Liao D, Le J, Nelson M, Ong E, Olefsky JM, Evans RM (2003) Adipose-specific peroxisome proliferator-activated receptor gamma knockout causes insulin resistance in fat and liver but not in muscle. Proc Natl Acad Sci USA 100(26):15712–15717. https://doi.org/10.1073/pnas.2536821100
82. Leonardini A, Laviola L, Perrini S, Natalichio A, Giorgino F (2009) Cross-talk between PPARgamma and insulin signaling and modulation of insulin sensitivity. PPAR Res 2009:818945. https://doi.org/10.1155/2009/818945
83. Cock TA, Houten SM, Auwerx J (2004) Peroxisome proliferator-activated receptor-gamma: too much of a good thing causes harm. EMBO Rep 5(2):142–147. https://doi.org/10.1038/sj.embor.7400082
84. Guerante L (2006) Sirtuins as potential targets for metabolic syndrome. Nature 444(7121):868–874. https://doi.org/10.1038/nature05486
85. Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado de Oliveira R, Leid M, McBurney MW, Guerante L (2004) Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. Nature 429(6993):771–776
86. Qiang L, Wang L, Kon N, Zhao W, Lee S, Zhang Y, Rosenbaum M, Zhao Y, Gu W, Farmer SR, Accili D (2012) Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of PPARgamma. Cell 150(3):620–632. https://doi.org/10.1016/j.cell.2012.06.027
87. van Beekum O, Fleskens V, Kalkhoven E (2009) Posttranslational modifications of PPAR-gamma: fine-tuning the metabolic master regulator. Obesity (Silver Spring) 17(2):213–219. https://doi.org/10.1038/oby.2008.473
88. Choi JH, Banks AS, Estall JL, Kajimura S, Bostrom P, Laznik D, Ruas JL, Chalmers MJ, Kamenecka TM, Bluhm M, Griffin PR, Spiegelman BM (2010) Obesity-linked phosphorylation of PPARγ by cdk5 is a direct target of the anti-diabetic PPARγ ligands. Nature 466(7305):451–456. https://doi.org/10.1038/ nature09291
89. Cushnie TP, Lamb AJ (2005) Antimicrobial activity of flavonoids. Int J Antimicrob Agents 26(5):343–356
90. Palome Ferreyra ML, Rius SP, Casati P (2012) Flavonoids: biosynthesis, biological functions, and biotechnological applications. Front Plant Sci 3:222. https://doi.org/10.3389/fpls.2012.00222
91. Winkel-Shirley B (2001) Flavonoid biosynthesis. A colorful model for genetics, biochemistry, cell biology, and biotechnology. Plant Physiol 126(2):485–493. https://doi.org/10.1104/pp.126.2.485
92. Zhang ZF, Lu J, Zheng YL, Wu DM, Hu B, Shan Q, Cheng W, Li MQ, Sun YY (2013) Purple sweet potato color attenuates hepatic insulin resistance via blocking oxidative stress and endoplasmic reticulum stress in high-fat-diet-treated mice. J Nutr Biochem 24(6):1018–1018. https://doi.org/10.1016/j.jnutbio.2012.07.009
93. Pompei A, Toniato E, Innocenti P, I DA, Cellini C, Mattosio C, Cotellese R, Bosco D, Ciccarelli R, Dadorante V, N DO, Martinotti S, Robuffo I (2012) Cyanidin reduces preadipocyte differentiation and relative ChREBP expression. J Biol Regul Homeost Agents 26(2):253–264
94. Kim HK, Kim JN, Han SN, Nam JH, Na HN, Ha TJ (2012) Black soybean anthocyanins inhibit adipocyte differentiation in 3T3-L1 cells. Nutr Res 32(10):770–777. https://doi.org/10.1016/j.nutres.2012.06.008
95. Matsukawa T, Inaguma T, Han J, Villareal MO, Isoda H (2015) Cyanidin-3-glucoside derived from black soybeans ameliorate type 2 diabetes through the induction of differentiation of preadipocytes into smaller and insulin-sensitive adipocytes. J Nutr Biochem 26(8):860–867. https://doi.org/10.1016/j.jnutbio.2015.03.006
96. Crozier A, Jagnathan IB, Clifflord MN (2009) Dietary phenolics: chemistry, bioavailability and effects on health. Nat Prod Rep 26(8):1001–1043. https://doi.org/10.1039/b802662a
97. Ono M, Fujimori K (2011) Antiadipogenic effect of dietary apigenin through activation of AMPK in 3T3-L1 cells. J Agric Food Chem 59(24):13346–13352. https://doi.org/10.1021/jf203490a
98. Habinowski SA, Witters LA (2001) The effects of AICAR on adipocyte differentiation of 3T3-L1 cells. Biochem Biophys Res Commun 286(5):852–856. https://doi.org/10.1006/bbrc.2001.5484
99. Beecher GR (2003) Overview of dietary flavonoids: nomenclature, occurrence and intake. J Nutr 133(10):3248–3254
100. Hajighaiahiour F, Khalihipourfarshabi M, Arya A (2015) Modulation of glucose transporter protein by dietary flavonoids in type 2 diabetes mellitus. Int J Biol Sci 11(5):508–524. https://doi.org/10.7150/ijbs.11241
101. Matsuda H, Kogami Y, Nakamura S, Sugiyama T, Ueno T, Yoshikawa M (2011) Structural requirements of flavonoids for the adipogenesis of 3T3-L1 cells. Bioorg Med Chem 19(9):2835–2841. https://doi.org/10.1016/j.bmc.2011.03.040
102. He J, Giusti MM (2010) Anthocyanins: natural colorants with health-promoting properties. Annu Rev Food Sci Technol 1:163–187. https://doi.org/10.1146/annurev.food.080708.100754
103. Ghosh D, Konishi T (2007) Anthocyanins and anthocyanin-rich extracts: role in diabetes and eye function. Asia Pac J Clin Nutr 16(2):200–208
104. Sakurai N, Mochizuki K, Kameji H, Shimada M, Goda T (2009) (−)-Epigallocatechin gallate enhances the expression of genes related to insulin sensitivity and adipocyte differentiation in 3T3-L1 adipocytes at an early stage of differentiation. Nutrition 25(10):1047–1056. https://doi.org/10.1016/j.nut.2009.02.012
105. Shin DW, Kim SN, Lee SM, Lee W, Song MJ, Park SM, Lee TR, Baik JH, Kim HK, Hong JH, Noh M (2009) (−)-Catechin promotes adipocyte differentiation in human bone marrow mesenchymal stem cells through PPAR gamma transactivation. Biochem Pharmacol 77(1):125–133. https://doi.org/10.1016/j.bcp.2008.09.033
106. Park UH, Jeong JC, Jang JS, Sung MR, Youn H, Lee SJ, Kim EJ, Um SJ (2012) Negative regulation of adipogenesis by kaempferol, a component of Rhizoma Polygonati falcatum in 3T3-L1 cells. Biol Pharm Bull 35(9):1525–1533
107. Kim MA, Kang K, Lee HJ, Kim M, Kim CY, Nho CW (2014) Apigenin isolated from Daphne genkwa Siebold et Zucc. inhibits its 3T3-L1 preadipocyte differentiation through a modulation of mitotic clonal expansion. Life Sci 101:64–72
108. Park HS, Kim SH, Kim YS, Ryu SY, Hwang JT, Yang HJ, Kim GH, Kwon DY, Kim MS (2009) Luteolin inhibits adipogenic differentiation by regulating PPARgamma activation. BioFactors 35(4):373–379. https://doi.org/10.1002/biof.38
109. Chun OK, Chung SJ, Song WO (2007) Estimated dietary flavonoid intake and major food sources of U.S. adults. J Nutr 137:1244–1252
110. Babu PVA, Liu D, Gilbert ER (2013) Recent advances in understanding the anti-diabetic actions of dietary flavonoids. J Nutr Biochem. https://doi.org/10.1016/j.jnutbio.2013.06.003
111. Furuyashiki T, Nagayasu H, Aoki Y, Bessho H, Hashimoto T, Lee H, Bae S, Yoon Y (2013) The anti-adipogenic effects of green tea polyphenol bbb.68.2353. https://doi.org/10.1271/BiolPharmBull.13bb0249
112. Lin J, Della-Fera MA, Baile CA (2005) Green tea polyphenol epigallocatechin gallate inhibits adipogenesis and induces apoptosis in 3T3-L1 adipocytes. Obes Res 13(6):982–990. https://doi.org/10.1038/oby.2005.115
113. Lee H, Bae S, Yoon Y (2013) The anti-adipogenic effects of (−)-epigallocatechin gallate are dependent on the Wnt/beta-catenin pathway. J Nutr Biochem 24(7):1232–1240. https://doi.org/10.1016/j.jnutbio.2012.09.007
114. Lin J, Della-Fera MA, Baile CA (2005) Green tea polyphenol epigallocatechin gallate inhibits adipogenesis and induces apoptosis in 3T3-L1 adipocytes. J Nutr 135(9):2226–232. https://doi.org/10.1038/oby.2008.472
115. Lee H, Lee J, Jung E, Lee J, Kim S, Huh S, Kim Y, Kim Y, Byun SY, Kim YS, Park D (2009) Isohamnetin represses adipogenesis in 3T3-L1 cells. Obesity (Silver Spring) 17(2):226–232. https://doi.org/10.1038/oby.2008.472
116. Lee J, Lee J, Jung E, Hwang W, Kim YS, Park D (2010) Isohamnetin-induced anti-adipogenesis is mediated by stabilization of beta-catenin protein. Life Sci 86(11–12):416–423. https://doi.org/10.1016/j.lfs.2010.01.012
117. Fischer-Posovszky P, Kukulcs V, Tews D, Unterkircher T, Debatin KM, Fulda S, Wabitsch M (2010) Resveratrol regulates multiple signal pathways. Phytother Res 23(5):713–718. https://doi.org/10.1002/ptr.2724
118. Takenouchi T, Takayama Y, Takezawa T (2004) Co-treatment with dexamethasone and octanoate induces adipogenesis in 3T3-L1 cells. Cell Biol Int 28(3):209–216. https://doi.org/10.1016/j.cellbi.2003.11.020
119. Yarwood SJ, Sale EM, Sale GJ, Houslay MD, Kilgour E, Anderson NG (1999) Growth hormone-dependent differentiation of 3T3-F442A preadipocytes requires Janus kinase/signal transducer and activator of transcription but not mitogen-activated protein kinase or p70 S6 kinase signaling. J Biol Chem 274(13):8662–8668
120. Ji SY, Choi KM, Lee YS, Yu JY, Shin DM, Lee S, Yoo KS, Lee YM, Yun YP, Yoo HS (2012) Rhamnetin-induced suppression of clonal expansion during early stage of adipogenesis. Arch Pharm Res 35(6):1083–1089. https://doi.org/10.1007/s12277-012-0616-7
121. Hsu CL, Yen GC (2006) Induction of cell apoptosis in 3T3-L1 pre-adipocytes by flavonoids is associated with their antioxidant activity. Mol Nutr Food Res 50(11):1072–1079. https://doi.org/10.1002/mnr.200600040
122. Hsu CL, Yen GC (2007) Effects of flavonoids and phenolic acids on the inhibition of adipogenesis in 3T3-L1 adipocytes. J Agric Food Chem 55(21):8404–8410
123. Choi I, Park Y, Choi H, Lee EH (2006) Anti-adipogenic activity of rutin in 3T3-L1 cells and mice fed with high-fat diet. BioFactors 26(4):273–281
124. Manach C, Williamson G, Morand C, Scalbert A, Remédy C (2005) Bioavailability and bioefficacy of polyphenols in humans. J. Review of 97 bioavailability studies. Am J Clin Nutr 81(1):2305–2425
125. Serafini M, Peluso I, Ragazzini A (2010) Flavonoids as anti-inflammatory agents. Proc Nutr Soc 69(3):273–278. https://doi.org/10.1017/s002966511000162x
126. Thilakarathna SH, Rupasinghe HPV (2013) Flavonoid bioavailability and attempts for bioavailability enhancement. Nutrients 5(9):3367–3387. https://doi.org/10.3390/nu5093367
127. Ahn J, Lee H, Kim S, Park J, Ha T (2008) The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. J Biochem Biophys Res Commun 373(4):545–549
128. Subash-Babu P, Alshatwi AA (2015) Hesperetin inhibit adipocyte differentiation and enhance Bax- and p21-mediated adipolyis in human mesenchymal stem cell adipogenesis. J Biochem Mol Toxicol 29(3):99–108. https://doi.org/10.1002/jbt.21672
129. Kim MH, Park JS, Seo MS, Jung JW, Lee YS, Kang KS (2010) Genistein and daidzein repress adipogenic differentiation of human adipose tissue-derived mesenchymal stem cells via Wnt/beta-catenin signalling or lipolysis. Cell Prolif 43(6):594–605. https://doi.org/10.1111/j.1366-2464.2010.00709.x
130. de Boer VCIJ, Dihal AA, van der Woude H, Arts ICW, Wolfram S, Aink GM, Rietjens IMCM, Keijer J, Hollman PCH (2005) Tissue distribution of quercetin in rats and pigs. J Nutr 135(7):1718–1725. https://doi.org/10.1093/jn/135.7.1718
131. Nakao Y, Yoshihara H, Fujimori K (2016) Suppression of very early stage of adipogenesis by Baiacalein, a Plant-derived flavonoid through reduced Akt-C/EBPα-GLUT4 signaling-mediated glucose uptake in 3T3-L1 adipocytes. PLoS ONE 11(9):e0163640. https://doi.org/10.1371/journal.pone.0163640
132. Kurylowicz A (2016) In search of new therapeutic targets in obesity treatment: Sirtuins. Int J Mol Sci 17(4):572. https://doi.org/10.3390/ijms17040572

Springer
135. Chalkiadaki A, Guarente L (2012) High-fat diet triggers inflammation-induced cleavage of SIRT1 in adipose tissue to promote metabolic dysfunction. Cell Metab 16(2):180–188. https://doi.org/10.1016/j.cmet.2012.07.003

136. Abdesselem H, Madani A, Han I, Al-Noubi M, Goswami N, Ben Hamidane H, Billing AM, Pasquier I, Bonkowski MS, Halabi N, Delloul R, Shrieff MZ, Masaeti N, ElRayess M, Sinclair DA, Graumann J, Mazloum NA (2016) SIRT1 limits adipocyte hyperplasia through c-Myc inhibition. J Biol Chem 291(5):2119–2135. https://doi.org/10.1074/jbc.M115.675645

137. Escande C, Nin V, Price NL, Capellini V, Gomes AP, Barbosa MT, O’Neil L, White TA, Sinclair DA, Chini EN (2013) Flavonoid apigenin is an inhibitor of the NAD(+)ase CD38: implications for cellular NAD(+) metabolism, protein acetylation, and treatment of metabolic syndrome. Diabetes 62(4):1084–1093

138. Jang WS, Seo CR, Jang HH, Song NJ, Kim JK, Ahn JY, Han J, Seo WD, Lee YM, Park KW (2015) Black rice (Oryza sativa L.) extracts induce osteoblast differentiation and protect against bone loss in ovariectomized rats. Food Funct 6(1):265–275. https://doi.org/10.1039/c4fo00836g

139. Chein PO, Chen YC, Lu SC, Sheu F (2005) Dietary flavonoids suppress adipogenesis in 3T3-L1 preadipocytes. JFDA 13(2):168–175

140. Jung CH, Kim H, Ahn J, Jeon TI, Lee DH, Ha TY (2013) Fisetin regulates obesity by targeting mTORC1 signaling. J Nutr Biochem 24(8):1547–1554. https://doi.org/10.1016/j.jnutbio.2013.01.003

141. Lee Y, Bae EJ (2013) Inhibition of mitotic clonal expansion mediates fisetin-exerted prevention of adipocyte differentiation in 3T3-L1 cells. Arch Pharm Res 36(11):1377–1384. https://doi.org/10.1007/s12272-013-0226-z

142. Watanabe M, Hisatake M, Fujimori K (2015) Fisetin suppresses lipid accumulation in mouse adipocytic 3T3-L1 cells by repressing GLUT4-mediated glucose uptake through inhibition of mTORC/C/EBPalpha signaling. J Agric Food Chem 63(20):4979–4987. https://doi.org/10.1021/acs.jafc.5b00821

143. Jae-Sik J, Ji-Cheon J (2010) Anti-adipogenic effect of Kaempferol, a component of Polygonati Rhizoma. J Korean Orient Med 31(2):158–166

144. Wang Q, Wang ST, Yang X, You PP, Zhang W (2015) Myricetin suppresses differentiation of 3T3-L1 preadipocytes and enhances lipolysis in adipocytes. Nutr Res 35(4):317–327. https://doi.org/10.1016/j.nutres.2014.12.009

145. Bin H-S, Choi U-K (2012) Myricetin inhibits adipogenesis in human adipose tissue-derived mesenchymal stem cells. Food Sci Biotechnol 21(5):1391

146. Naowaboot J, Chung CH, Choi R (2015) Rutin stimulates adipocyte differentiation and adiponectin secretion in 3T3-L1 adipocytes. J Med Assoc Thai 98(Suppl 3):S1–S6

147. Swick J, Lee OK, Kim YC (2012) Quercetin exerts anti-adipogenic effects through modulation of 3T3-L1 preadipocyte proliferation and differentiation. FASEB J 26:644

148. Seo YS, Kang OH, Kim SB, Mun SH, Kang DH, Yang DW, Choi JG, Lee YM, Kang DK, Lee HS, Kwon DY (2015) Quercetin prevents adipogenesis by regulation of transcriptional factors and lipases in OP9 cells. Int J Mol Med 35(6):1779–1785. https://doi.org/10.3892/ijmm.2015.2185

149. Richard AJ, Amini-Vaughan Z, Ribnicky DM, Stephens JM (2013) Naringenin inhibits adipogenesis and reduces insulin sensitivity and adiponectin expression in adipocytes. Evid Based Complement Alternat Med 2013:549750. https://doi.org/10.1155/2013/549750

150. Su SJ, Yeh YT, Su SH, Chang KL, Shyu HW, Chen KM, Yeh H (2013) Biochanin A promotes osteogenic but inhibits adipogenic differentiation: evidence with primary adipose-derived stem cells. Evid Based Complement Alternat Med 2013:846039. https://doi.org/10.1155/2013/846039

151. Yu SY, Choi Y, Kwon YI, Wood R, Kim YC (2015) Formononetin enhances the expression of genes related to adipocyte differentiation and insulin sensitivity. FASEB J 29

152. Choi Y, Noh J, Yun SW, Kwon YI, Kim YC (2013) Effect of isoflavones from Astragalus membranaceus on 3T3-L1 adipocyte differentiation and insulin sensitivity. FASEB J 27:637–628

153. Harmon AW, Harp JB (2001) Differential effects of flavonoids on 3T3-L1 adipogenesis and lipolysis. Am J Physiol Cell Physiol 280(4):C807–C813

154. Hwang JT, Park II, Shin JI, Lee YK, Lee SK, Baik HW, Ha J, Park OJ (2005) Genistein, EGCG, and capsaicin inhibit adipocyte differentiation process via activating AMP-activated protein kinase. Biochem Biophys Res Commun 338(2):694–699. https://doi.org/10.1016/j.bbrc.2005.09.195

155. Lee K, Villena JA, Moon YS, Kim KH, Lee S, Kang C, Sul HS (2003) Inhibition of adipogenesis and development of glucose intolerance by soluble preadipocyte factor-1 (Pref-1). J Clin Invest 111(4):453–461. https://doi.org/10.1172/jci15924

156. Braune A, Blaut M (2016) Bacterial species involved in the conversion of dietary flavonoids in the human gut. Gut Microbes 7(3):216–234. https://doi.org/10.1080/19440077.2016.1158395

157. Egert S, Rimbach G (2011) Which sources of flavonoids: complex diets or dietary supplements? Adv Nutr 2(1):8–14. https://doi.org/10.3945/an.110.000026