Clinical and Experimental Health Sciences

Possible Anti-Obesity Role of Flavonoids Through Brown Adipose Tissue

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ABSTRACT

Worldwide, the incidence of overweight and obesity is increasing day by day, and this makes the control of body weight and complications a primary health problem. Weight loss diet therapy has long been a primary role in the prevention and management of obesity. Evidence supporting the specific anti-obesity effects of certain nutrient components, in particular, polyphenolic compounds, are increasing, as well as a strategy to limit energy intake to achieve control of body weight. Active brown adipose tissue in adult individuals is gaining interest as a new and feasible target for controlling body weight by triggering and increasing energy expenditure. Flavonoids are one of the polyphenolic compounds that draw attention by regulating non-shivering thermogenesis. Although each flavonoid has its health benefits; many phytochemical compounds classified as flavonoids have an anti-obesity effect by regulating oxidation, synthesis, uptake, and transport of fatty acids. In this study, current studies on the therapeutic effect of flavonoids on obesity by regulating energy expenditure through various mechanisms of action in brown adipose tissue are reviewed.

Keywords: Flavonoids; brown adipose tissue; obesity; thermogenesis.

1. INTRODUCTION

Obesity is defined as abnormal or excessive fat accumulation that presents a health risk, and a body mass index (BMI) above 30 kg/m^2 is classified as to have obesity. According to this criterion, the World Health Organization (WHO) states that 13% of the adult population in theworld has obesity and that obesity and its complications are one of the most difficult public health problems (1). Although energy restriction is the best-known dietary intervention to reduce the prevalence of obesity, potential anti-obesity effects of bioactive or functional food components such as polyphenols are also discussed (2-4).

Flavonoids are plant pigments groups that are responsible for the colors in many fruits and flowers. Flavonoids, estimated to be over 4000, are abundant in tea, apples, onions, legumes, tomatoes and red wine. In various studies, it is stated that besides the antioxidant properties offlavonoids, they have anti-obesity, anti-inflammatory, antiviral, anti-allergic, antithrombotic and other functions (5-8).

The discovery of the presence of brown adipose tissue (BAT) in neonates and adult individuals has led to an increase in research into the development of a new therapeutic approach to fighting obesity (9). Increasing energy expenditure with BAT activation is thought to be promising for the control of obesity (10). BAT's capacity to influence energy expenditure is based on the ability to dissipate energy as heat and depends on the expression of the uncoupling protein-1 (UCP-1) in brown adipocytes. UCP-1 separates the electron transport system (ETS) from ATP synthesis, thus dissipating energy (11). The presence of BAT in human tissue correlates negatively with BMI, body fat mass percentage, and plasma glucose (12-14).

This review presents a critical review of the literature describing the possible role of flavonoids in therapeutic strategies against obesity through BAT activation and browning.

In this review, studies included in the databases Pubmed, Science Direct, Web of Science, and Google Scholar were

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evaluated, which were performed until December 2021 with no time limitation. In vivo and in vitro studies written in English, and review articles about flavonoids and obesity are included in the study. A comprehensive study was carried out by two researchers. For flavonoids the keywords 'flavonoids', 'flavones', 'flavonols', 'flavanones', 'flavanols', 'anthocyanins', 'isoflavones', and for anti-obesity role the keywords 'brown adipose tissue', 'brown adipose tissue mechanism of action', 'browning', 'obesity', 'thermogenesis', 'non-shivering thermogenesis', and 'uncoupling protein-1' were scanned by using the conjunctions 'AND' and 'OR'. Titles of the articles were reviewed, and the first elimination was performed during the article evaluation process according to our specific subject. After that, abstracts were reviewed, and the articles eliminated were either included in the study over full text or excluded.

1.1. Properties of Adipose Tissue

Adipose tissue has an important role in regulating biological functions and especially energy metabolism with the enzyme, cytokine, growth factor and hormones it secretes. Adipocytes are made by lipoblasts differentiating from mesenchymal cells. Lipoblasts are transformed into two different adipose tissues, namely white adipose tissue (WAT) and BAT, with different functions and morphology in mammals (15, 16). Respectively, storing energy and preventing hypothermia are the main tasks of these tissues (17). In addition to WAT and BAT, the third type of adipose tissue called 'beige' has recently been identified. Adipocytes in the stores of beige adipose tissue (BeAT) are similar to white adipocytes but have the classic features of brown adipocytes (18, 19). The transformation of WAT into BAT, that is, the formation of BeAT, occurs as a result of increased expression of the UCP-1 pump in WAT cells via the irisin hormone stimulated by exercise and cold. WAT cells with increased UCP-1 pump in their mitochondria are referred to as BeAT. These cells work like BAT cells. Increased UCP-1 expression inhibits ATP synthesis, and heat production, which causes energy consumption in the cell, to increase, providing thermogenesis and glucose homeostasis (20-22). The characteristics of WAT, BAT, and BeAT are summarized in Table 1 (23, 24).

Table 1. *General characteristics of white, brown and beige adipose tissue*

	White Adipose Tissue (WAT*)	Brown Adipose Tissue (BAT*)	Beige Adipose Tissue (BeAT*)
Location	**Visceral WAT:** Around the organs (mesenteric, omental, perigonadal and retroperitoneal) **Subcutaneous WAT:** Inguinal, intramuscular	Interscapular, perirenal	Neck and supraclavicular region
Morphology	Unilocular/Large lipid droplets	Multilocular/Small lipid droplets	Unilocular, large/multiple small lipid droplets
Lipid content	Single large droplet covering 90% of cell volume	Multiple small lipid droplets	Uncertain
Function	Energy storage Endocrine organ	Heat production	Adaptive thermogenesis
Mitochondria number	+	+++	++
UCP-1	-	+++	++
Vascularization	Few	Abundant	Uncertain
Obesity	Positive	Negative	Negative
Insulin resistance	Positive	Negative	Negative
Activators	High-fat diet	Cold, thyroid hormone, thiazolidinediones, FGF21*, BMP7*, BMP8b*, natriuretic peptide	Cold, thiazolidinediones, a natriuretic peptide, FGF21*, irisin, catecholamines, β-adrenergic receptor agonists

** BAT; brown adipose tissue, BeAT; beige adipose tissue, BMP7; bone morphogenetic protein 7, BMP8b; bone morphogenetic protein 8b, FGF21; fibroblast growth factor 21, UCP-1; uncoupling protein-1, WAT; white adipose tissue.*

1.2. Effect Mechanism of Brown Adipose Tissue

Brown adipose tissue has a negative correlation with BMI, fat mass percentage and plasma glucose. It contributes to energy expenditure by using energy as heat energy. This effect is due to UCP-1 expression in BAT. UCP-1, which is capable of separating ATP production from mitochondrial respiration, dissipates large amounts of stored energy as heat by allowing protons to re-enter the matrix (25).

Norepinephrine is released near the postganglionic nerve endings in BAT to increase activation of the sympathetic nervous system and situations requiring increased body temperature (26). Norepinephrine binds to the b3-adrenergic receptor (b3AR) on the surface of brown adipocytes.

Binding to b3AR provides cyclic AMP (cAMP) to be produced by adenylate cyclase. Increasedintracellular cAMP concentrations activate hormone-sensitive lipase (HSL) and protein kinase A (PKA) which phosphorylated perilipin to promote triglyceride hydrolysis. Then the releasedfree fatty acids (FFAs) are opened to the mitochondria via carnitine palmitoyltransferase-1 (CPT-1). In mitochondria, FFAs activate UCP-1 and fatty acid oxidation produce cofactors forETS. UCP-1 uses the proton gradient generated by ETS to produce heat and thus dissipates energy (27, 28).

In parallel with the direct activation of thermogenesis, norepinephrine stimulation leads to transcriptional regulation of genes important for thermogenesis, that is, the induction of the "thermogenic program". The activated PKA also activates cAMP response element-binding protein (CREB) and p38 mitogen-activated protein kinase by phosphorylating the transcription factor. Respectively, the p38 mitogen-activated protein kinase phosphorylates transcription factors such as activating transcription factor 2 or transcriptional coactivator PPAR-g coactivator 1a (PGC-1a) to induce UCP-1 expression. Phosphorylated CREB enhances transcription of type 2 iodothyronine deiodinase, which converts inactive tetraiodothyronine to triiodothyronine (T3), which promotes binding of T3 receptor. When the receptor is not bound to T3, it acts as a UCP-1 transcriptional suppressor. Therefore, T3 indirectly increases UCP-1 expression (Figure 1) (27, 29, 30).

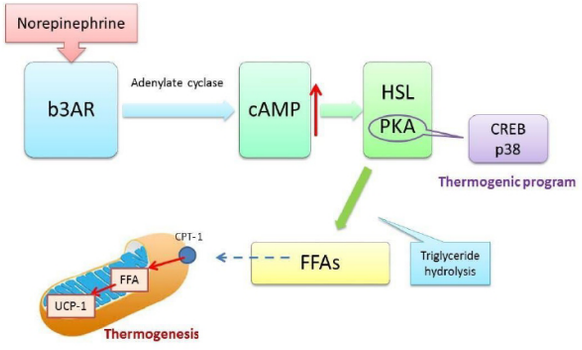

Figure. 1. *Brown adipose tissue's effect mechanism. b3AR; b3-adrenergic receptor, cAMP; cyclic AMP, HSL; hormone-sensitive lipase, PKA; protein kinase A, CREB; cAMP response element-binding protein, p38; p38 mitogen – activated protein kinase, FFAs; free fatty acids, CPT – 1; carnitine palmitoyltransferase-1, UCP-1; uncoupling protein-1.*

White adipocytes are highly sensitive to norepinephrine. It stimulates lipolysis through norepinephrine-like intracellular signaling events, thereby promoting the release of FFA, which is used as energetic substrates in BAT to maintain thermogenesis (27). In particular, it causes UCP-1 activation called "beige" or "brite" in subcutaneous and retroperitoneal stores in WAT(31). Beige adipocyte loss has been shown to cause obesity, but increasing the amount of beigeadipocyte in WAT may compensate for the thermogenic activity of descending BAT (24, 32). However, the increase in the amount of UCP-1 and adipocytes in human WAT is still highly debated and conflicting results have been reported (33, 34).

1.3. Flavonoids

Flavonoids are a group of plant pigments that are responsible for the colors in many fruits and flowers. They took 'flavonoid' name because they are yellow derived from 'flavus' which means yellow in Latin. They have 2-phenyl benzopyrone (diphenyl propane) structure of 15 carbon atoms (C6-C3-C6). Various flavonoids are formed by binding – OH groups to different carbons in the phenyl benzopyrone structure (35). Flavonoids, estimated to be over 4000, are abundant in tea, apples, onions, legumes, tomatoes and red wine. Flavonoids are composed of six subgroups; Flavones, Flavonols, Flavanones, Flavanols, Anthocyanins, and Isoflavones (35, 36).

The family of flavonoids has been shown to indicate some pharmacological activities that exhibit antioxidant, anti-inflammatory, anti-obesity, anti-carcinogenic, anti-diabetic, anti – allergic, anti-tumor properties (6, 8). While these properties may explain the success of some herbal medicines in the treatment of inflammatory and infectious diseases, their mechanism of action is often not fully understood (35, 37). The structural similarity between flavonoids, steroids and other cholesterol derivatives suggests that flavonoids may exert some of their effects through the nuclear receptor family. The random nature of the nuclear receptor ligand – binding domain is thought to facilitate direct transcriptional regulation of cells through the dietary intake of flavonoids (36).

1.4. Flavonoids and BAT Activation

The most studied species related to BAT activation from flavonoids are oligomers such as procyanidins (flavanol), catechins, epigallocatechin gallate (EGCG), theaflavins, quercetin. Activation of these flavonoid species on BAT is provided by biological pathways such as BAT thermogenesis, WAT browning, activation of the AMPK / SIRT1 / PGC-1α pathway, mitochondrial biogenesis, etc. (25).

Many mechanisms underlying the effects of flavonoids from dietary polyphenols on thermogenesis, lipid metabolism, and mitochondrial biogenesis. Selective activation of β3-AR leads to stimulation of lipolysis and thermogenesis; it provides the development of white-brown adipocyte phenotype in WAT. PKA then leads to increased lipolysis through HSL stimulation, a carrier enzyme for lipolysis. In conclusion, stimulation of PKA and HSL-mediated lipolysis causes increased mitochondrial respiration, in

fatty acids, proton's UCP-1-dependent mitochondrial entry and separation from ATP production. The stimulating effect of β3-AR on AMPK leads to activation of β-oxidation and provides to reduce lipid deposition. Provide full activation of PPAR ligands, including PPARα and PPARγ, is required (38-40). In particular, PPARα acts directly as the transcriptional master regulator of PGC1α gene transcription and plays a role in WAT browning, brown adipocyte determination, and function (41, 42). Induction of PPARγ ligand is a prerequisite for stimulated activation by stimulating the β-adrenergic receptor of brown adipocytes and also stimulates the formation of beige adipocytes in WAT. The coordination of all these processes results in increased thermogenic capacity and mitochondrial biogenesis, and it causes to browning of 3T3-L1 adipocytes. Furthermore, the B3-AR / PKA signaling pathway has been reported to stimulate the activation of p38 MAPK and the browning of white adipocytes, a target for PGC1α (Figure 2) (38, 43).

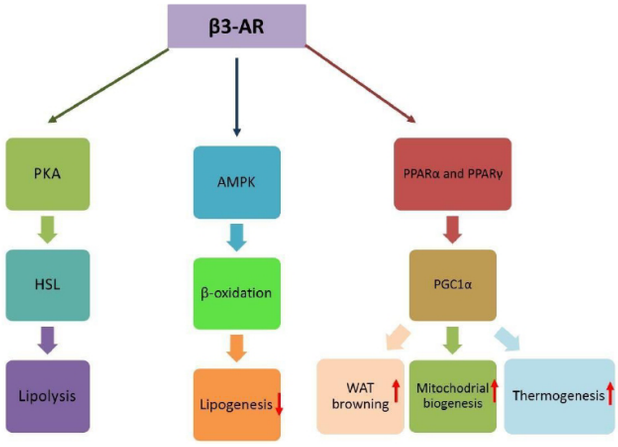

Figure. 2. *Flavonoids in BAT activation. ß3-AR; ß3-adrenergic receptor, PKA; protein kinase A, HSL; hormone-sensitive lipase, AMPK; AMP-activated protein kinase, PPARα; peroxisome proliferator-activated receptor – alpha, PPARγ; peroxisome proliferator – activated receptor gamma, PGC1α; peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, WAT; white adipose tissue.*

Besides, the efficacy of dietary flavonoids (e.g. flavan-3-ol, green tea catechins, quercetin, etc.) influences weight management by increasing BAT thermogenesis and provides white adipocyte browning. The different signaling pathways of BAT activation are effectively provided by forming different combinations of polyphenol subtypes in the diet. Mechanisms can act as a therapeutic task for stimulation of BAT thermogenesis, body weight loss and improved metabolic status. Therefore, diet modulation of brown and beige fat tissue development and metabolism is considered a promising target for the prevention and treatment of obesity (44).

1.4.1. Flavones

Flavone and flavone glycosides are light yellow compounds found in almost every plant formed by the coupling of the hydroxyl group to C3 atom. Flavones are much less common than other subclasses of flavonoids (45). Flavones are divided into various subgroups based on side chains attached to backbone molecules such as hydroxylation, methoxylation, isoprenylation and glycosylation (46). The major dietary sources of flavones are olives, extra virgin olive oil, essential oils derived from rosemary, parsley, celery, and citrus fruits. The main flavones are apigenin, luteolin, chrysin and tangeretin (47). Flavones are effective on BAT activation by increasing SIRT1, PGC1α, UCP-1, PRDM16 activation in white and beige adipose tissue (22, 48-51). In vitro studies in adipose cells, it has been reported that different flavon species (sudachitin; chrysin; luteolin) applied in various amounts (30 nM; 1-50 µM; 100 nM) increased UCP-1 secretion in adipose tissue, induced browning of white adipocytes through AMPK / SIRT1 / PGC-1α pathway activation (22, 48, 49). In studies in which animals are given high – fat diet and different flavon types, flavone groups' body weight, and fat percentage are reduced, WAT browning and, as a result, O2 consumption was found to increase (22, 48, 50). In Table 2, in vitro and in vivo studies related to the activity of flavones on BAT activation are summarized.

Table 2. *In vitro and in vivo studies on the effects of flavones on non-shivering thermogenesis*

Authors	Flavone Type	Study Group	Treatment	Result
Tsutsumi et al. 2014 (48)	Sudachitin	Primary myoblasts	30 nM	SIRT1*, PGC1α*, UCP-1* increase
Choi and Yun 2016 (49)	Chrysin	3T3-L1	1-50 µM	UCP-1, PGC1α, PRDM16*, FGF21* increase AMPK phosphorylation increase
Zhang et al. 2016 (22)	Luteolin	Primary adipocytes from BAT* and sWAT*	100 nM	UCP-1, PGC1αand SIRT1 increase AMPK* phosphorylation increase
Shen et al. 2014 (50)	Olive leaf extract (luteolin and apigenin)	C57BL/6N male mice	HFD* with 0.15% olive leaf extract 8 weeks	Body weight, fat percentage decrease Browning and mitochondrial biogenesis increase
Tsutsumi et al. 2014 (48)	Sudachitin	C57BL/6 and db/db mice	HFD with 5 mg/kg sudachitin 12 weeks	Body weight, fat percentage O2 consumption, and energy expenditure decrease UCP-1 in WAT* increase
Thaiss et al. 2016 (51)	Apigenin and naringenin	C57BL/6 male mice	80 mg/kg 2 weeks	UCP-1 in BAT increase
Zhang et al. 2016 (22)	Luteolin	C57BL/6 male mice	HFD with 0.01 % luteolin 12 weeks	O2 consumption and CO2 production increase BAT activation increase WAT browning increase AMPK / PGC1α signalization increase

**AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, FGF21; fibroblast growth factor 21, HFD; high-fat diet, PGC1α ; peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, PRDM16; positive regulatory domain containing 16, sWAT; subcutaneous white adipose tissue, SIRT1; silent mating type information regulation 2 homolog 1, UCP-1; uncoupling protein-1, WAT; white adipose tissue.*

1.4.2. Flavonols

Flavonol group compounds which are in the structure of 3-hydroxy flavone are commonly found in glycoside form in foods. Major flavonol species include quercetin, myricetin, kaempferol, and routine. Flavonols are mostly found in cabbage, onion, apple, tea, buckwheat and broccoli (52, 53). Studies have shown that flavonols increased non-shivering thermogenesis by increasing UCP-1, Cpt1α, Tbx1, PGC1α activation in general (54-60). In vitro studies have shown that flavonol species act through mechanisms that trigger BAT activation (54-57). In studies performed in experimental animals, increase in AMPK phosphorylation, SIRT1 and UCP-1 expression, BAT browning, O2 consumption, and body temperature were found, resulting in a decrease in body weight and white adipose tissue mass in flavonol-treated groups compared to HFD-fed groups (54-60). In vitro and in vivo studies associated with the efficacy of flavonols on BAT activation are summarized in Table 3.

1.4.3. Flavanones

Flavanones are flavonoids found in nature as aglycones and glycosides having an unsaturated carbon-carbon bond in the C ring (53). Naturally existing flavanones are naringenin, hesperidin, eriodicthiol, narirutin and erythocytin (61). As the main source, citrus fruits such as satsuma mandarin and valentine orange are examples of foods that contain narirutin and hesperidin (62). Hesperidin is insoluble in water and does not dissolve well in the intestine, however, G – hesperidin is water-soluble and absorbs faster than hesperidin. It has been shown in experimental studies that flavanone species, like other flavonoids, have potential effects on increasing energy expenditure and increase in body temperature as a result of increased BAT sympathetic nerve activity through BAT activation (63-65). Table 4 summarizes in vitro and in vivo studies about the efficacy of flavanones on BAT activation.

1.4.4. Flavanols

Flavanols, which is most common in foods, are flavonoid subclass called flavan-3-ol since they contain a group of – OH in the C3 atom (66). A study using data obtained from NHANES 1999 – 2002 showed that the average daily intake of flavan-3-ol was the highest among other flavonoids and accounted for 82% of average flavonoids intake (67). Flavanols are commonly found in tea, wine, apple and chocolate (68, 69). Flavanol monomers are classified as catechin, epicatechin, epigallocatechin (EGC), epicatechin gallate (EG) and EGCG (70). Flavanols have been shown to increase UCP-1 activation and BAT activation and thus be effective in energy expenditure (71-80). Experimental animal studies in which different types of flavanol are given have reported reducing body weight by triggering signaling pathways that increase the energy expenditure of flavanols (72, 80). While there are many in vitro and in vivo studies on the efficacy of flavonoids on energy expenditure, human studies are more limited. In a study examining EGCG activity in healthy young men, a gel capsule of green tea extract containing 1600 mg EGCG and 600 mg caffeine was given after 3 hours of cold exposure. It was observed that energy expenditure was increased in the group that received green tea extract and lipids had more contribution to total energy expenditure than placebo (74). In another study, it was found that BAT concentration increased in healthy young female subjects receiving catechin – enriched beverage (540 mg/day catechin) (78). In vivo studies regarding the effectiveness on BAT activation of flavanols are summarized in Table 5.

1.4.5. Anthocyanins

As a flavonoid species, anthocyanins are water-soluble pigments that provide blue, purple and red colors in fruits such as blackberries, raspberries, pomegranates, black and red currants and in vegetables such as eggplant and red cabbage (81). Major anthocyanins are peonidine, pelargonidine, malvidine, cyanidine, petunidine and delphinidine (82). It has been reported they have many positive effects on health such as antioxidant, anti-inflammatory, antidiabetic and anti-carcinogenic properties (81). Anthocyanins have been shown to increase UCP-1, PGC1α, Cpt1α, PRDM16 expression in white and brown adipocytes, and increase energy expenditure by increasing body temperature (83-86). Cell studies have reported increased AMPK phosphorylation and mitochondrial biogenesis in studies of different doses of cyanidin (83, 84). In experimental animal studies where diverse anthocyanin varieties were applied in different amounts and time, it was observed that energy expenditure increased as a result of increased AMPK activity (85, 86).

1.4.6. Isoflavones

Isoflavones, known as phytoestrogens, are found in a variety of legumes, mainly soy and soybeans. Among the isoflavones, daidzein, genistein, glisitin, and formononetin are prominent (87). It increases O2 consumption and CO2 production by increasing UCP-1 function and affects BAT activation by increasing browning (88-92). In animal studies in which isoflavone subtypes were given, it was found that BAT browning and energy expenditure increased as a result of increased UCP-1 secretion (89-92). Table 6 summarizes in vitro and in vivo studies of the efficacy of anthocyanins and isoflavones on BAT activation.

Obesity is a disease in which adipocytes grow by accumulating excessive amounts of lipids and is characterized at the cellular level by an increase in the number and size of differentiated adipocytes in adipose tissues (2, 4, 16). As treating obesity with medications is often associated with negative side effects and little long-term efficacy, some study results suggest that the use of natural plant extracts may be an interesting alternative for long-term weight management, and flavonoids can be suggested as one possible source (69, 93). In vitro and in vivo studies examined in this review have shown that some of the dietary flavonoids are effective at clinical levels. However, the majority of data show the effects of flavonoids on BAT and browning WAT at pre-clinical levels using mammalian cells and animals (48-51). Some types of flavonoids are metabolized by intestinal bacteria in the large intestine and then absorbed into the body. This suggests that the effects of flavonoids on non-shivering thermogenesis may be regulated by indirect signaling cascades such as the microbiome (94). In addition, the efficacy of dietary flavonoids is controversial because the number of flavonoids taken with diet is not known clearly like supplements. Because it is difficult to measure the BAT activity of dietary flavonoids in humans, more clinical studies should be conducted to confirm the effect of flavonoids on non-shivering thermogenesis before flavonoids can be recommended for improving metabolic diseases (5, 69, 95).

Table 3. *In vitro and in vivo studies on the effects of flavonols on non-shivering thermogenesis*

Authors	Flavonol Type	Study Group	Treatment	Result
Moon et al. 2013 (54)	Quercetin (onionpeel)	3T3-L1	25-100 µg/mL	CPT1α* increase
Lee, Parks, and Kang 2017 (55)	Quercetin	3T3-L1	25-100 µM	UCP-1*, CPT1α, TBX1*, PGC1α*, PPARγ*, PRDM16 * increase
Yuan et al.	Rutin	C H T cells 3 10 1/2	0.1-100 µM	UCP-1, PRDM16, PGC1α increase
2017 (56)				Deacetylation of PGC1α by stabilizing SIRT1* increase
Hu et al. 2018 (57)	Myricetin	C H T cells 3 10 1/2	0.001-10 µM	UCP-1, PGC1α, SIRT1 increase Adiponectin increase
Varshney et al. 2019 (58)	Quercetin Rutin Myricetin Kaempferol	3T3-L1 and L6 cells	1,10,50 µM	PPARγ and Fabp4* decrease Lipid and triglyceride decrease AMPK* phosphorylation increase
Moon et al. 2013 (54)	Quercetin (onionpeel)	Sprague Dawley male mice	HFD* with 0.36% and 0.72% OPE* 8 weeks	Body weight and fat content decrease UCP-1 and CPT1α (epididymal WAT*) increase
Dong et al.	Quercetin	C57BL/6 male	HFD with	Body weight, epididymal WAT decrease
2014 (59)		mice	0.1%	AMPK* phosphorylation, SIRT1 expression
			Quercetin 12	and UCP-1 increase
			weeks	
Lee, Parks, and Kang 2017 (55)	Quercetin (onion peel)	C57BL/6 male mice	HFD with 0.5% OPE 8 weeks	Adipocyte browning increase
Yuan et al.	Rutin	C57BL/6 male	HFD with 1	Mitochondrial biogenesis and energy
2017 (56)		mice	mg/kg rutin	expenditure increase
		And db/db mice	10 weeks	BAT* and browning increase
Hu et al. 2017 (60)	Rutin	Female rats with PCOS	100 mg/kg rutin 3 weeks	UCP-1, PPARα*, PGC1α, and CPT1α increase Body temperature increase
Hu et al. 2018 (57)	Myricetin	db/db male mice	HFD with 400 mg/kg myricetin 14 weeks	Body weight, fat mass, blood glucose decrease d Body temperature, O_2 consumption, BAT activity increase Browning, mitochondrial biogenesis increase
Varshney et al. 2019 (58)	Quercetin Rutin Myricetin Kaempferol	C57BL/6 male mice	HFD with 25 mg/kg (each flavonols) 7 weeks	Body weight decrease Serum triglyceride, cholesterol, LDL Blood glucose level decrease Glucose tolerance, insulin sensitivity increase

**AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, Cpt1α; carnitine palmitoyltransferase 1 alpha, Fabp4; Fatty Acid-Binding Protein 4, HFD; high fat diet, OPE; onion peel extract, PGC1α ; peroxisome proliferator-activated receptor-gammacoactivator 1 alpha, PPARα; peroxisome proliferator-activated receptor – alpha, PPARγ; peroxisome proliferator – activated receptor gamma, PRDM16; positive regulatory domain containing 16, SIRT1; silent mating type information regulation 2 homolog 1, TBX1; T-box transcription factor, UCP-1; uncoupling protein-1, WAT; whiteadipose tissue.*

Table 4. *In vitro and in vivo studies on the effects of flavanones on non-shivering thermogenesis*

Authors	Flavanone Type	Study Group	Treatment	Result
Choi et al. 2016 (63)	Hesperidin	3T3-L1	12.5 and 50 µg/mL	UCP-1* and PRDM16* increase
Shen et al. 2009 (64)	G-hesperidin	Male Wistar rats	60 mg of oral G – hesperidin	BAT* sympathetic nerve activity increase Body temperature decrease Cutaneous sympathetic nerve activity decrease
Choi et al. 2017 (65)	Hesperidin	ICR male rats	HFD* with 50 and 200 mg/kg/day 7 weeks	Body weight, fat mass, insulin, TG* decrease AMPK* phosphorylation, and BAT activity increase

AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, HFD; high fat diet, PRDM16; positive regulatory domain containing 16, TG; triglyceride, UCP-1; uncoupling protein-1.

Table 5. *In vivo studies on the effects of flavanols on non-shivering thermogenesis*

Authors	Flavanol Type	Study Group	Treatment	Result
Dulloo et al. 2000 (71)	Green tea extract (catechin and EGCG*)	Male SD rats	0-200 µM	BAT* activation and O_2 uptake rate increase
Choo 2003 (72)	Green tea (EGCG)	Male SD rats	HFD* with 20 g/kg green tea extract	Body weight decrease Energy expenditure, BAT intensity increase
Nomura et al. 2008 (73)	Tea catechins (TC*)	Male SD rats	LFD* and HFD with 0.5% TC 5 weeks	UCP-1* (LFD with TC group) increase No difference in the HFD group (-)
Gosselin and Haman 2012 (74)	EGCG	Healthy young men	3 hours cold exposure 1600 mg EGCG and 600 mg caffeine	Energy expenditure increase Shivering thermogenesis decrease
Yan, Zhao, and Zhao 2013 (75)	Green tea catechins	Male SD rats	LFD and HFD with 100 mg/kg 5 weeks	PPARδ*, UCP-1, CPT1α* increase
Matsumura et al. 2014 (76)	Cocoa flavanols	Male ICR mice	10 mg/kg cocoa flavonoid	BAT activity, AMPK* phosphorylation increase Plasma catecholamine level increase
Yamashita et al. 2014 (77)	Oolong, black tea	Male ICR mice	Tea boiled with 2 g tea leaves in 100 mL 7 days	Weight of WAT* decrease AMPK phosphorylation and UCP-1 increase
Nirengi et al. 2016 (78)	Catechin	Healthy young women	540 mg/day catechin 12 weeks	BAT density increase
Rabadan – Chávez et al. 2016 (79)	Cocoa flavanols	Male Wistar rats	HFD with 1 g/kg cocoa powder, 100 mg/kg cocoa extract and 10 mg/kg epicatechin (EC*) 8 weeks	UCP-1, PPARγ*, PPARα*, SIRT1*, PGC1α* increase AMPK phosphorylation increase Plasma catecholamine level increase
Gutiérrez – Salmeán et al. 2014 (80)	Epicatechin	Male Wistar rats	HFD for 5 weeks with – EC (1 mg/kg) for an extra 2 weeks	Browning increase Body weight decrease

AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, CPT1α; carnitine palmitoyl transferase 1 alpha, EC; epicatechin*, EGCG;* Epigallocatechin gallate*, HFD; high fat diet, LFD; low fat diet, PGC1α ; peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, PPARα; peroxisome proliferator – activated receptor-alpha, PPARγ; peroxisome proliferator-activated receptor gamma, PPARδ; peroxisome proliferator-activated receptor sigma, SIRT1; silent mating type information regulation 2 homolog 1, TC; tea catechins, UCP-1; uncoupling protein-1.*

Table 6. *In vitro and in vivo studies on the effects of anthocyanins and isoflavones on non – shivering thermogenesis*

Authors	Type	Study Group	Treatment	Result
Anthocyanin				
You et al. 2015 (83)	Cyanidin	C_3 H_{10} $T_{1/2}$ cells	10 µg/mL mulberry extract, mulberry wine extract	Increase; UCP-1*, PGC1α*, Cpt1α*, PRDM16*p38 phosphorylation Cellular O_2 respiration
Matsukawa etal. 2017 (84)	Cyanidin	3T3-L1	50 or 100 µM	Increase; Cellular cAMP* concentration AMPK* phosphorylation UCP-1, PGC1α Mitochondrial biogenesis
Takikawa et al. 2010 (85)	Bilberry extract	Male KK-Ay mice	27 g/kg diet 5 weeks	AMPK in sWAT* and skeletal muscle increase
You et al. 2017 (86) t	Cyanidin	Male db/db mice	1 mg/mL 16 weeks	Energy expenditure, O_2 consumption increase BAT* activation, body temperature, mitochondrial biogenesis increase Browning increase Body weight gain, the weight of WAT* decrease

Table 6. *(Continued)*

Isoflavone				
Aziz et al. 2017 (88)	Genistein	3T3-L1	100 µM	UCP-1*, PGC1α*, SIRT1* increase O_2 consumption increase
Gautam et al. 2017 (89)	Formononetin	3T3-L1	10 nM	AMPK* phosphorylation and β – catenin expression increase
Lephart et al. 2004 (90)	Isoflavone mixture	Long-Evans male and female rats	600 µg/g phytoestrogens	Body temperature during the light cycle, UCP-1 increase
Crespillo et al. 2011 (91)	Daidzein	Male Wistar rats	LFD* and HFD* with 50 mg/kg 2 weeks	UCP-1 (in HFD) increase
Kamiya et al. 2012 (92)	Puerariae flower extract (PFE*) and PFE isoflavone – rich fraction (ISOF*)	C57BL/6J male mice	HFD with 5% PFE and HFD with ISOF 6 weeks	Energy expenditure, O_2 consumption increase UCP-1 increase
Gautam et al. 2017 (89)	Formononetin	C57BL/6J male mice	HFD with 0.1, 1 and 10 mg formononetin	Browning increase

AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, cAMP; cyclic AMP, CPT1α; carnitine palmitoyltransferase 1 alpha, HFD; high-fat diet, ISOF; isoflavone-rich fraction, LFD; low-fat diet, PFE; Puerariae flower extract, PGC1α; peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, PRDM16; positive regulatory domain containing 16, SIRT1; silent mating type information regulation 2 homolog 1, sWAT; subcutaneous white adipose tissue, UCP-1; uncoupling protein-1, WAT; white adipose tissue.

2. CONCLUSION

Increasing BAT activation and non-shivering thermogenesis is a potential approach to ameliorating metabolic diseases. While dietary energy restriction is the best-known intervention to reduce obesity, several studies have shown potential anti-obesity effects of bioactive or functional nutrient components such as flavonoids. Many flavonoid species are effective in activating some transcription factors in WAT browning, increasing BAT activation and thereby increasing energy expenditure. However, although flavonoids have a positive effect on energy metabolism by regulating non-shivering thermogenesis, low bioavailability of flavonoids and structure modification via the digestive system when taken into the body by diet should also beconsidered. More studies are needed to better understand the effects of flavonoids on anti – obesity in humans.

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