Dietary Polyphenols Turn Fat "Brown": A Narrative Review of the Possible Mechanisms

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Abstract:

Background

Inducible brown adipocytes called beige adipocytes are found in white adipose tissue (WAT) depots. They express functional UCP1 and have thermogenic fat-burning capacities as also found in classical brown adipocytes in response to various stimuli. Beige adipocytes may also secrete certain factors that affect WAT function and systemic metabolism. Therefore, a white-to-brown fat conversion could be a novel therapeutic avenue for tackling obesity and metabolic disorders.

Scope and Approach

In this review, we examine the evidence supporting the concept that the anti-obesity action attributed to polyphenols might be contributed by their stimulation of WAT browning, and discuss the possible underlying mechanisms involved in this action.

Key Findings and Conclusions

Current evidence, mostly derived from animal models, strongly supports that dietary polyphenols may play roles in the browning of WAT. Studies also show multiple signaling pathways, receptors, and transcription factors have been associated with the browning effects of dietary polyphenols. In conclusion, polyphenol compounds and their principal metabolites may contribute to counteracting human obesity *via* promoting WAT browning.

Keywords: Polyphenols; Beige adipocytes; Browning; Energy metabolism; Obesity

1 Introduction

Obesity, which is accompanied by low-grade inflammation, insulin resistance, type 2 diabetes, hyperglycemia, hyperlipidemia, atherosclerosis, metabolic syndromes and decrease in life expectancy, has grown into a worldwide epidemic affecting large numbers of people (Engin, 2017). Current understanding indicates that the disruption of energy homeostasis leads to obesity (J. Gao, Ghibaudi, van Heek, & Hwa, 2002; Hall et al., 2011). Adipose tissues with different color, morphology, metabolic function, biochemical characteristics and gene expression patterns exist in mammals (including humans and mice), and have been mainly divided into two types of fat, namely white adipose tissue (WAT) and brown adipose tissue (BAT) (Lidell et al., 2013; Rosell et al., 2014). An excess of energy is primarily stored in subcutaneous and visceral WAT. In the last decade, functional BAT, which contains a large number of mitochondria and expresses the BAT-specific gene uncoupling protein-1 (*UC*P1) to produce heat, was found in healthy adults. Moreover, after the classical BAT was identified in human adults (originating from myf5+ precursors), there is sufficient evidence to suggest the presence of brown-like (beige) adipocytes (originating from myf5- precursors) in subcutaneous WAT depots, especially upon cold exposure or β-adrenergic stimulation (Table 1) (Cedikova et al., 2016; Park, Kim, & Bae, 2014). Although classical BAT and beige adipose tissue (BeAT) share many similarities, they still exhibit differences in their morphology and functions (Kissig, Shapira, & Seale, 2016), as illustrated in Figure 1. However, current evidence suggests that a number of the transcriptional regulators and coregulators that determine the differentiation of classic brown adipocytes are also key factors in the conversion of white adipocytes into beige adipocytes (beige adipogenesis) (Harms & Seale, 2013; Kiskinis et al., 2014; W. Wang & Seale, 2016; Wu, Jun, & McDermott, 2015). For example, key regulators of brown adipocyte differentiation including CCAAT-enhancer-binding protein β (*C/EBP*β), PR domain-containing 16 (*PRDM*16), peroxisome proliferator-activated receptor γ (*PPAR*γ), and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (*PGC1α*), were also identified as main targets for WAT transdifferentiation (Kajimura et al., 2009; Seale et al., 2007; Villanueva et al., 2013). *PPAR*γ agonists or ectopic expression of *PGC*1α promotes adipose browning; while the ablation of *PRDM*16 or *PGC*1α in white adipocytes inhibits formation and function of beige adipocytes (Ohno, Shinoda, Spiegelman, & Kajimura, 2012; Tiraby et al., 2003; Seale et al., 2011; Kleiner et al., 2012). Meanwhile, *PRDM*16 can also repress white adipocyte specific genes through its association with C-terminal binding proteins (Kajimura et al., 2008). Moreover, hormones and cytokines such as noradrenaline (NA), bone morphogenetic protein 7 (*BMP*7) and fibroblast growth factor 21 (*FGF*21) also play key roles in inducing white-to-brown conversion (Hu & Christian, 2017; Y. H. Lee, Jung, & Choi, 2014; Wu et al., 2015) (Figure 1). Since the discovery of inducible beige adipocytes, modulation of adipose tissue browning to increase energy consumption, especially *via* dietary intervention, has become an attractive idea due to its promising application in obesity and metabolic diseases prevention and treatment (S. Wang et al., 2014). Indeed, beige adipocytes are functionally very similar to classical brown adipocytes upon various stimuli (such as cold exposure) and can contribute to energy expenditure through heat production, therefore, they are also categorized as thermogenic adipocytes (Scheja & Heeren, 2016). The contribution of beige adipocytes to whole body energy balance is yet to be fully determined. However, mice with specific inactivation of beige adipocytes through ablation of *PRDM*16 (with minimal effects on classical BAT) become more obese and severely insulin resistant on a high fat diet (Cohen et al., 2014) clearly indicating an important role of these cells in whole-body energy homeostasis.

Polyphenols are a class of secondary metabolite compounds widely present in plants (Z. Wang et al., 2019). Currently, there are over 8,000 identified polyphenols found in foods such as fruits, vegetables, tea, wine, chocolate, nuts, seeds, and even spices and seasonings (X. Z. Han, Shen, & Lou, 2007). Polyphenols can be divided into four categories: flavonoids; phenolic acids; stilbenes and lignans (Figure 2). Aside from their well-known anti-oxidative functions, recent studies have suggested further mechanisms whereby polyphenols exert their beneficial health effects. Recent evidence challenges the concept that the health benefits of polyphenols are mainly attributed to their scavenging of free radicals, which may be an oversimplified view. Indeed, cells responding to polyphenol treatment can elicit changes in a number of receptors or enzymes involved in signal transduction (Scalbert, Johnson & Saltmarsh, 2005). In addition, polyphenols can also potentially bind directly to membrane components such as lipids, proteins and receptors (eg. EGCG was identified as the agonist of laminin receptor (67LR) with high affinity (in nanomolar K_d value) (Tachibana, Koga, Fujimura, & Yamada, 2004)). Furthermore, polyphenols may also undergo extensive biotransformation including phase I and phase II metabolism reactions in enterocytes and liver and be fermented by gut microbiota *in vivo*, to form a range of metabolites (Luca et al., 2019). Studies have also revealed that plant polyphenols may help the body to produce and utilize short-chain fatty acids (SCFAs) in the gut (Parkar, Trower, & Stevenson, 2013), which is associated with a range of potential health benefits and act as the natural ligands for GPR41/43 (Li et al., 2018; Hu, Lin, Zheng, & Cheung, 2018). Along with the advancing research on the biological effects of polyphenols and their metabolites, increasing evidence has highlighted the capacity of dietary polyphenols to promote adipose tissue browning and thereafter improve metabolic homeostasis and decrease body weight. In the current review, we critically evaluate the previous studies reporting the possible mechanisms of dietary polyphenols promoting WAT browning.

2 Dietary polyphenols induce browning of white adipose tissue (WAT)

Both classical brown adipocytes and beige adipocytes are found to induce lipid mobilization to produce heat, a function mediated by *UCP1* which is located on the inner membrane of mitochondria (Lo & Sun, 2013). Various nutritional agents that promote the conversion of white adipocytes to brown adipocytes also display the ability to induce thermogenesis (Azhar, Parmar, Miller, Samuels, & Rayalam, 2016; Bonet, Oliver, & Palou, 2013; P. Lee & Greenfield, 2015; Merlin et al., 2016). BAT is a highly metabolically active tissue important for heat production and its contribution to thermogenesis in humans could range from 27-123 kcal per day at room temperature and 46-211 kcal per day during mild cold exposure (Carpentier et al., 2018). Interestingly, the reduction in BAT volume and/or activity in human has been associated with both adiposity (van Marken Lichtenbelt et al., 2009) and diabetic status (Ouellet et al., 2011). Furthermore, a recent study demonstrated induced pluripotent stem cells reprogrammed from adipogenic precursors of patients with type 2 diabetes can be induced into beige adipocytes with increased thermogenic function and anti-diabetic secretion (Su et al., 2018). Therefore, increasing the number or activity of brown adipocytes (as well as beige adipocytes) may be a safe and sustainable way to combat obesity and diabetes. A number of studies have observed that food-derived ingredients, such as saponins (eg. soyasaponin Ab), fatty acids (eg. eicosapentaenoic acid) and even plant pigments (eg. fucoxanthin) effectively activate adipose tissue browning (Kim et al., 2019; Fleckenstein-Elsen et al., 2016; Woo et al., 2009). Among these studies, polyphenols were consistently found as phytochemicals inducing browning in WAT.

For example, resveratrol was found to be capable of stimulating energy expenditure and ameliorating WAT deposition by browning adipose tissue (Zou et al., 2017); in high-fat and high-fructose diet fed mice vanillic acid could accelerate thermogenesis and mitochondrial synthesis in both classical BAT and inguinal WAT (X. Han et al., 2018). Similarly, cinnamaldehyde also dose-dependently decreased visceral WAT deposition, partly mediated by activating interscapular BAT, as evidenced by increased *UCP1* expression (Tamura, Iwasaki, Narukawa, & Watanabe, 2012). A polyphenol mixture can also relieve obesity and lipid accumulation through induction of beige adipocytes. For example, a recent study showed a water extraction of immature *Citrus reticulata* rich in synephrine, narirutin, hesperidin, nobiletin, and tangeretin can markedly relieve HFD induced obesity in C57BL/6 Mice by promoting browning of inguinal WAT (Chou, Ho, & Pan, 2018). Therefore, a positive relationship may exist between dietary polyphenols and WAT browning, and the underlying mechanisms are worthy of exploration.

2.1 Dietary polyphenols increase sympathetic activity

Neuronal release of noradrenaline (sympathetic nervous system activation) has been demonstrated to be one of the most important factors regulating WAT browning upon cold stimulation. Evidence has shown that dietary polyphenols may influence this browning by increasing sympathetic nervous system activity. For example, as catechin-polyphenols can function to inhibit catechol-O-methyl-transferase (the enzyme that catalyzes noradrenaline degradation) (Shixian, VanCrey, Shi, Kakuda, & Jiang, 2006), they have the potential to increase sympathetic activity representing an important mechanism for dietary polyphenols inducing WAT browning. In addition, using pre-adipocytes models, *trans*-cinnamic acid was found to induce browning of white adipocytes by activating the β3-AR and *AMPK* signaling pathways, suggesting its potential to directly activate adrenergic receptors in adipocytes (Kang, Mukherjee, & Yun, 2019).

2.2 Dietary polyphenols activate *AMPK-SIRT*1-*PGC1α* pathway

The pathway of *AMPK–SIRT1–PGC1α* axis is believed to function as a metabolic sensor involved in the regulation of brown or beige adipogenesis (Mele et al., 2017). *AMPK* phosphorylation is often strongly associated with the browning of adipose tissue accompanied with upregulation of thermogenic markers (Hutchinson, Chernogubova, Dallner, Cannon, & Bengtsson, 2005; Mulligan, Gonzalez, Stewart, Carey, & Saupe, 2007; X. Zhang et al., 2016). Consequently, *AMPK* activators (eg. 5-aminoimidazole-4-carboxamide ribonucleotide) are found to promote the acquisition of BAT-like characteristics in the WAT of mice (Vila-Bedmar, Lorenzo, & Fernández-Veledo, 2010). Furthermore, Mottillo *et al.* reported that adipocyte-specific deletion of *AMPK* resulted in a reduction in thermogenesis (Mottillo et al., 2016), suggesting a significant role of *AMPK* in BAT activation. *AMPK* activation also promotes the enhancement of sirtuin 1 (*SIRT*1) activity by upregulating cellular NAD^+ levels, decreasing NAM levels and phosphorylation of *PGC1α* (Borriello, Cucciolla, Della Ragione, & Galletti, 2010). In adipocytes it was also found that *SIRT*1 activation increased *AMPK* activity and *SIRT*1 inhibitors decreased *AMPK* activity. Since *AMPK* and *SIRT*1 can regulate each other reciprocally, this hints *AMPK* and *SIRT*1 could partner as cellular energy status sensors (AMP/ATP; NAD^+/NAM) to regulate adipocyte browning. Furthermore, as a histone/protein deacetylase, *SIRT*1 can also enhance WAT browning by deacetylating PPARγ on Lys268 and Lys293 and recruiting *PRDM*16, a key coactivator for the modulation of mitochondrial function and development of BAT (Qiang et al., 2012).

Interestingly, a considerable amount of literature has been published that polyphenols play an important role in activating the *AMPK-SIRT*1-*PGC1α* pathway (Mele et al., 2017; Silvester, Aseer, & Yun, 2019). For example, improved glucose homeostasis and insulin sensitivity were obtained with gallic acid administration (at 10 mg/kg body weight) to C57BL/6 mice fed high-fat diet (HFD) for 9 weeks. The resulting body weight loss and metabolic improvement is likely due to the upregulation of thermogenesis-related genes (*UCP1*, *PGC1α*, and *PPARγ*), which were related to increased *AMPK* phosphorylation and *SIRT*1 and *PGC1α* protein levels, suggesting the critical role of the *AMPK-SIRT*1-*PGC1α* pathway in gallic acid's action (Doan et al., 2015). Accumulating evidence also indicates favorable effects of resveratrol on metabolic syndromes including obesity and type 2 diabetes. Wang *et al.* found that resveratrol induced the browning of inguinal white adipocytes via *AMPK* activation that led to enhanced expression of a number of beige-specific gene markers (*SIRT1, PRDM16*, *PGC1α*, *PDH* and *UCP1*), suggesting its beneficial anti-obesity effects may be partly ascribed to WAT browning (S. Wang et al., 2015). The flavonoid and phenolic acid-rich oolong, pu-erh, and particularly black tea have the potential to exert anti-obesity properties. This is also partly associated with *AMPK* activation in WAT and the browning of mesenteric WAT (Yamashita et al., 2014). In agreement with these studies, chrysin was also found to induce 3T3-L1 adipocyte browning through *AMPK* activation and elevating *PGC1α* expression (Choi J, & Yun J, 2019). Collectively, these findings indicate that natural polyphenols may activate the browning of adipose tissues based on signaling through *AMPK-SIRT1-PGC1α* (Figure 3).

2.3 Dietary polyphenols activate the Protein kinase A (PKA) Signaling Pathway

Protein kinase A (*PKA*) is a downstream target of β3-adrenergic receptor (β3AR) signaling, which is expressed primarily in adipocytes (Klein et al., 1999). As shown in Figure 4, activated PKA is able to phosphorylate cAMP-response element binding protein (*CREB*) and trigger enhanced expression of thermogenesis and mitochondrial biogenesis related genes (Kim & Park, 2010; van Dam, Kooijman, Schilperoort, Rensen, & Boon, 2015; Wood Dos Santos et al., 2018). Moreover, PKA also activates hormone sensitive lipase (*HSL*), which stimulates lipolysis from stored energy in adipocytes providing free fatty acids for heat production *via* uncoupled respiration or ATP synthesis (Lowell & Spiegelman, 2000). There is evidence that some polyphenols may increase cAMP levels to activate the *PKA* pathway and consequently induce thermogenic gene expression (da-Silva et al., 2007; Tennen, Michishita-Kioi, & Chua, 2012). Thus, activating the PKA signaling pathway could be another possible mechanism for browning adipose tissues by phenolics. For example, the monoterpene phenolic compound thymol has been demonstrated to exert a browning action via activation of the β-adrenergic receptor and phosphorylated *PKA*, thereby triggering *UCP1* expression in 3T3-L1 adipocytes, suggesting that PKA signaling may be indispensable for thymol exerting its effects (J. H. Choi, Kim, Yu, & Yun, 2017). Similarly, it has been reported that quercetin increases the levels of *UCP1* in both WAT and BAT of HFD-fed mice accompanied by increases in the transcription of thermogenesis-related genes (eg., *PRDM16*, *CIDEA*, *TFAM*, *NRF-1*, *PGC1α*), which is associated with sympathetic stimulation through β3AR signaling-induced *PKA* activation (H. Choi, Kim, & Yu, 2019). In addition, nobiletin, a polymethoxylated flavone, has been reported to show anti-obesity effects, which were relevant to its positive effect on activating adipose browning. As reported by Lone J *et al.* , nobiletin

promoted the browning of 3T3-L1 adipocytes with increased expression of beige-specific genes including *CD137*, *CIDEA*, *TBX1*, and *TMEM26 via* the *PKA* signaling pathway (Jameel Lone, Parray, & Yun, 2018). Based on the above reports, dietary polyphenols may act as browning and thermogenic activators and their actions can be explained, at least in part, by activation of *PKA* signaling.

2.4 Dietary polyphenols activate *MAPK* Signaling Pathway

Mitogen-activated protein kinases (*MAPK*) are a type of serine/threonine protein kinases (Johnson & Lapadat, 2002). Activation of *MAPK*s, especially *p38*, were found to drive the browning process of adipocytes (Cao et al., 2004; Robidoux et al., 2005). *MAPK* is associated with phosphorylation of the transcription factor *CREB*, which was identified as a key modulator for *UCP1* transcription during brown and beige adipogenesis (Martinez-deMena & Obregon, 2005; Muller et al., 2013). In addition, the *MAPK* pathway was also found to turn on transcription of *PPARγ*, *PGC1α* and *UCP1 via* phosphorylating the cAMP-dependent transcription factor *ATF-2* (Cao et al., 2004). Polyphenols are reported to influence browning of adipocytes by activating the *MAPK* signaling pathway. Indeed, grape pomace extract, which is rich in a wide variety of phenolics and flavonoids, can stimulate the recruitment of beige adipocytes *in vitro* and in HFD-fed rats. The underlying mechanisms can be partly attributed to the activation of *p38* and *ERK1/2* (C. Rodriguez Lanzi et al., 2017; C. Rodriguez Lanzi et al., 2018). Another interesting case reported by Cong et al., showed Pycnogenol, a mixture of procyanidins, phenolic acids, and bioflavonoids promotes browning, which was tightly coordinated with phosphorylation of *PKA* as well as *p38* proteins (Cong et al., 2018) Thus, *MAPK* activation by polyphenols may represent an important signaling event to coordinate the recruitment of beige adipocytes in WAT.

2.5 Dietary polyphenols modulate epigenetic processes

Epigenetic processes including DNA methylation histone modifications and miRNAs are also involved in the control of WAT transdifferentiation. Evidence supports that polyphenol-related epigenetic modifications may also associate with their WAT “browning” activity. For example, apple polyphenols affect *PGC1α* promoter methylation levels and consequently increase its mRNA expression in epididymal adipocytes from high-fat sucrose fed rats (Boqué et al., 2013). Considering the importance of *PGC1α* in WAT browning, it is highly possible that apple polyphenols may affect WAT browning *via* this epigenetic modulation, although direct evidence may be still inadequate.

miRNA networks also represent a fundamental layer in the regulation of gene expression (Bartel, 2004). With understanding of the mechanisms behind the "browning" process increasing, the correlation between miRNAs and beige adipogenesis has been identified (Goody & Pfeifer, 2019). They either enhance or suppress brown/beige adipogenesis *via* regulating genes involved in this process (Chen, Pan, & Pfeifer, 2017). Notably, an adipocyte-specific *Dicer* ablation led to the “whitening” of murine interscapular BAT (Mori et al., 2012), also demonstrating the requirement of miRNA processing for brown adipogenesis. Evidence indicates that phenolics may regulate the browning *via* affecting miRNAs. Resveratrol reduces obesity alongside increasing miRNAs (miR-129, miR-328-5p and miR-539-5p), whose predicted target genes are key regulators of browning including *PPARγ* and *HSL* (Gracia et al., 2016). In addition, polyphenol-rich green tea extract also showed pro-browning effects by down-regulating miR-335 expression (Otton et al., 2018). These pieces of evidence together indicate the importance of the regulatory effects of miRNAs in

mediating the actions of dietary phenolics in the browning process of white adipocytes.

2.6 Dietary polyphenols increase cyclooxygenase-2 activity

Cyclooxygenase (*COX*)-2, a rate-limiting enzyme for prostaglandin synthesis, has been shown to regulate whole-body energy homeostasis (Vegiopoulos et al., 2010). In particular, increased COX-2 activity is related to the emergence of brown fat features in WAT by inducing brown adipogenic gene expression (Vegiopoulos et al., 2010). Madsen *et al.* also found that decreased *Cox-2* activity caused weight gain along with lowered diet-induced *UCP1* expression in inguinal WAT (Madsen et al., 2010). This indicates *COX-2* activation seems to be a vital mechanism involved in beige adipogenesis. Interestingly, the combination of resveratrol and quercetin has been found to induce a brown-like remodeling in perirenal WAT with the upregulated expression of *UCP1* protein (Arias et al., 2017). The increased mitochondrial activity was co-incident with increased *Cox-2* expression. A similar observation was reported in quercetin-treated rats where the expression of *Cox-2* was modestly increased (Arias, Macarulla, Aguirre, Martinez-Castano, & Portillo, 2014). Therefore, manipulation of *Cox-2* expression seems to be another possible way for dietary polyphenols to enhance BAT activity and WAT browning, which protects against energy surplus and body weight gain.

2.7 Dietary polyphenols increase Glucagon-Like Peptide-1

Glucagon-like peptide 1 (*GLP-1*) is an incretin hormone released by L-cells (Drucker, 2007; Goke, Fehmann, & Goke, 1991). *GLP-1* binds to the *GLP-1* receptor (Campbell & Drucker, 2013; J. Zhang et al., 2018), and ameliorates obesity *via* numerous physiological effects. Although its most striking characteristic may be the stimulatory effects on insulin secretion, *GLP-1* anti-obesity effects also partly result from increasing thermogenesis and browning (Gu et al., 2011; Lockie et al., 2012; J. Zhang et al., 2018). Evidence also points to inhibition of dipeptidyl peptidase-4 (*DPP-4*) (the enzyme that efficiently degrades *GLP-1 in vivo* and thus shortens the circulation half-life of *GLP-1* to less than 2 min (Deacon et al., 1995)), as a mechanism by which polyphenols increase *GLP-1* and leads to elevated expression of *PPARα*, *PGC1α* and *UCPs* in BAT of obese mice (Shimasaki et al., 2013) and increased metabolic gene expression in human (pre)adipocytes *via* upregulating PGC1α.

Dietary phenolics such as curcumin and caffeoylquinic acid derivatives are reported to possess *GLP-1* secretion-stimulating functions (Tsuda, 2015); in addition, polyphenols such as resveratrol, luteolin and apigenin also can exert DPP-4 inhibitory effects, leading to a prolonged action of *GLP-1* (Habtemariam & Varghese, 2014; Pinent, Blay, Serrano, & Ardevol, 2017). Another study also found grape seed extract containing abundant procyanidins resulted in increased levels of active *GLP-1* by lowering *DPP-4* activity (Gonzalez-Abuin et al., 2014). A study in HFD-fed mice also demonstrated that the flavonoid eriodictyol can exert beneficial effects on alleviating adiposity by significantly increasing the levels of *UCP1* in epididymal WAT, which was accompanied by increased circulating *GLP-1* (Kwon & Choi, 2019). However, more studies are needed to elucidate the relationship between dietary phenolics, *GLP-1* activity and beige adipogenesis.

2.8 Dietary polyphenols promote irisin secretion

The myokine irisin (Bostrom et al., 2012), which is cleaved from the transmembrane protein

fibronectin type III domain-containing protein 5 (*FNDC5*), was discovered as the key factor regulating exercise-induced browning of WAT (Mahajan & Patra, 2013; McMillan & White, 2015; Y. Zhang et al., 2016). *FNDC5*/irisin is mainly secreted by skeletal muscle upon exercise and facilitates white adipocyte browning *via* activating *p38* and *ERK* signal pathways (Y. Zhang et al., 2014). The researchers confirmed that intravenous injection of irisin-expressing adenovirus can induce brown-fat-like development with increased thermogenic gene expression and energy expenditure (Bostrom et al., 2012). Therefore, the intake of irisin-activating ingredients is a mechanism to activate browning of adipose tissues, which would lead to accelerated metabolism and reduced body weight and fat. Some reports claim that polyphenols such as quercetin, apigenin, dihydromyricetin can promote irisin secretion (Jang et al., 2017; Leiherer et al., 2016; Zhou et al., 2015). Genistein was also found to promote browning of subcutaneous WAT in mice through induction of *FNDC5* expression in skeletal muscle and increasing irisin levels (Palacios-González et al., 2019). In one study, obese mice treated with leucine-resveratrol combinations for 6 weeks showed two-fold increase in *PGC1α* and augmented *UCP1* expression in WAT accompanied by elevated plasma irisin levels, showing the treatment combination may lead to browning of adipose tissue *via* promotion of irisin secretion (Baggett, Bruckbauer, & Zemel, 2013). Similarly, raspberry supplementation, which contains high amounts of polyphenols, also drove the browning of WAT, which was associated with elevated irisin (Xing et al., 2018). Therefore, polyphenols may stimulate browning of WAT due to a positive action on irisin secretion.

2.9 Capsaicin activates transient receptor potential cation channel subfamily V member 1 (*TRPV1*)

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is an active constituent of hot pepper, which provides an example of a phenolic compound that promotes browning *via* binding to membrane receptors (Yang et al., 2015). Capsaicin has elicited interest in anti-obesity research for a long time due to the capability to enhance energy expenditure (Ohnuki et al., 2001). Consumption of capsaicin was found to increase energy expenditure and fat oxidation in human (Janssens et al., 2013). In particular, capsaicin can promote both brown and beige adipogenesis (Kawabata et al., 2009; Ohyama et al., 2016; Ono et al., 2011). Several mechanisms have been proposed. *TRPV1* receptors in the intestinal tract can be activated by the consumption of capsaicin or capsaicin-containing food. This causes stimulation of vagal afferent pathways which leads to the activation of neurons within the ventromedial hypothalamus, and thus activates adrenergic pathways to induce brown and beige adipogenesis (Ohyama et al., 2016; Ono et al., 2011). Moreover, Baboota *et al.* showed that capsaicin also triggered the beige phenotype in 3T3-L1 preadipocytes *via* its receptor *TRPV1 in vitro* (Baboota et al., 2014), suggesting the centrally mediated effect of capsaicin was not the only mechanism underlying the browning process.

2.10 Dietary polyphenols influence gut microbiota composition and short-chain fatty acid production

The gut microbiota has been recognized as an important modulator of energy balance (Koren et al., 2012; Ridaura et al., 2013). For example, evidence from fecal transplantation experiments suggested that gut microbiota may regulate host energy homeostasis and insulin resistance *via* a range of possible mechanisms including influencing gut physiology and gut motility, affecting calorie and nutrient harvest, and triggering innate immune responses (Ley et al., 2005; Singh et al., 2017).

Changes in gut microbiota composition show a strong interaction with expression of browning-specific genes in adipose tissue and energy homeostasis (Chevalier et al., 2015; Fabbiano et al., 2018). A recent study in obese subjects demonstrated a significant positive association between the relative abundance of *Firmicutes* and the expression of brown marker genes *PRDM16*, *DIO2* and *UCP1* in subcutaneous WAT (Moreno-Navarrete et al., 2018). Dietary polyphenols also play a crucial role in augmenting host-microbial interactions, ultimately resulting in beneficial effects including weight reduction (Valdes et al., 2015; Xue et al., 2016). Evidence suggests the combination of quercetin and resveratrol lowers the ratio of *Firmicutes* to *Bacteroidetes* and increases *Akkermansia* in HFD-fed rats and consequently decreasing body weight gain and visceral (epididymal, perirenal) adipose tissue weight (Zhao et al., 2017). Similarly, an investigation from Anhê *et al.* (Anhe et al., 2018) found that administration of crude extract of *Myrciaria dubia* containing proanthocyanidins, flavonols, and phenolic acids to HFD fed mice activated BAT and increased the browning of WAT, which may be related to alteration of the gut microbiota. Subsequent analyses provides more direct evidence that resveratrol induced the emergence of beige adipocytes in WAT by remodeling fecal microbiota (Liao et al., 2018); and similar phenomenon are also presented in the study carried out by Wang *et al.*(P. Wang et al., 2019) that resveratrol-induced microbiota changes are able to stimulate the development of beige adipocytes in WAT and modulate lipid metabolism. Collectively, polyphenols may function as a potential intervention to improve dysbiosis of the gut microbiota in obesity.

SCFAs trigger a variety of physiological responses, which play important roles in energy metabolism and body weight control (Hu, Lin, Zheng, & Cheung, 2018). Several studies have confirmed that SCFAs, such as butyrate and acetate, can stimulate brown and beige adipogenesis (Z. Gao et al., 2009; Hu et al., 2016; Sahuri-Arisoylu et al., 2016). Notably, polyphenols not only affect SCFA production *via* regulating gut microbiota, the polyphenols themselves can be broken down in the gut into SCFAs (Bauer, Williams, Smidt, Mosenthin, & Verstegen, 2006; Oteiza, Fraga, Mills, & Taft, 2018; Parkar, Trower, & Stevenson, 2013). Anaerobic bacteria have been reported to produce acetate and butyrate from several flavonoids by cleaving their ring structure of into hydroxyphenylacetic and hydroxyphenylpropionic acids (Blaut, Schoefer, & Braune, 2003). As reviewed by Reynes *et al.* (Reynes, Palou, Rodriguez, & Palou, 2018), prebiotics such as polyphenols can produce specific postbiotic SCFAs that regulate adaptive thermogenesis *via* influencing BAT recruitment and WAT browning. The important physiological roles that SCFAs play in regulation of transcription factors associated with adipogenesis and mitochondrial biogenesis in BAT may be through G protein-coupled receptor 41/43 (*GPR41/43*) signaling (Hu et al., 2016; Kimura et al., 2013; Lu et al., 2016), as shown in Figure 5. Moreover, it is important to consider that the relative abundance of individual SCFAs is affected by the gut microbiota profile. Bacteroidetes primarily generate acetate and propionate, whereas Firmicutes mainly produces butyrate (LeBlanc et al., 2017), which can be shaped by the polyphenol substrate. Thus, the production of SFCAs is a possible mechanism for polyphenols to activate browning of adipose tissues.

3 Conclusions

Obesity arises from the imbalance between energy intake and consumption. Commercial anti-obesity drugs mainly target appetite suppression or inhibit nutrient absorbance. However, a number

of side effects have been associated with these drugs such as elevated blood pressure and heart rate, insomnia, stomach ache, constipation, and addiction (Kang & Park, 2012). Therefore, activating thermogenesis within white adipose tissue represents a future strategy for body weight control. Great efforts have been undertaken to search for natural compounds as "browning agents" to improve energy homeostasis. Although there is currently no evidence that supports any specific food ingredients or nutrients that can lead to weight loss, increasingly studies have pointed out that certain food components can influence the activation of beige adipose tissue. Dietary polyphenols in particular may be eligible candidates due to their capacity to enhance energy expenditure by activating brown adipogenesis. Polyphenols widely exist in fruits, vegetables, and plant-derived beverages and are the most abundant dietary antioxidant. It is estimated that healthy individuals can consume polyphenols up to 1 g/day (Perez-Jimenez et al., 2011). Many studies have demonstrated polyphenols can protect against the metabolic syndrome although research effort is still needed to evaluate the contribution of polyphenols to induction of WAT browning. Indeed, one study on healthy young women has shown that daily ingestion of a catechin-rich beverage increases brown adipose tissue density, supporting the regulatory effects of polyphenols on brown adipogenesis and browning of WAT may also be applied to humans (Nirengi et al., 2016).

Admittedly, the current knowledge may be still far away from elucidating the detailed mechanisms by which dietary phenolics exert their roles in beige adipogenesis. For example, polyphenols may have complex metabolic fates *in vivo* (van Duynhoven et al., 2011), making it difficult to determine whether metabolites or polyphenols themselves exert functional effects. Another major difficulty of elucidating the "browning" effects of polyphenols on WAT is polyphenols are extensively conjugated in the body, making it more difficult to explore the biological activities of these conjugated metabolites (Scalbert, Johnson & Saltmarsh, 2005). Moreover, with a deeper understanding towards the browning phenomenon, even evaluation of the browning effects may require considerable caution when drawing conclusions. For instance, certain high molecular weight polyphenols cannot be directly absorbed by the stomach and small intestine and they are metabolized in the colon (van Duynhoven et al., 2011). Therefore, the cell-autonomous browning effects observed in cellular models may not reflect the overall metabolic effects *in vivo*, especially when taking into consideration that browning is mainly a sympathetic event. Moreover, the search for browning agents has mostly been investigated in rodent models and there remains a paucity of human studies. Differences between humans and rodents cannot be overlooked. The activity of at least some "browning agents" may simply be a consequence of their epilating effects or curling the fur to cause cold stress in mice (Nedergaard & Cannon, 2014). Therefore, additional experiments may be needed to evaluate their browning effects in human. Another issue that cannot be ignored is phenolics usually possess a broad range of biological activities relevant to metabolic regulation (Pereira, Valentão, Pereira, & Andrade, 2009). Therefore, experiments are also required to assess whether the browning is the key cause of the observed metabolic changes. In order to fully understand the contribution of browning to the metabolic changes, the *UCP1* knock-out model may be a useful tool to dissect the links between the observation of beige adipocytes in white adipose tissue and the overall metabolic effects of the tested polyphenols (Nedergaard, Matthias, Golozoubova, Jacobsson, & Cannon, 1999).

In conclusion, current evidence strongly supports that dietary phenolics may play roles in the

browning of white adipose tissue, however, further exploration is needed to define the underlying mechanisms of polyphenols in the framework of WAT browning and BAT activation. More studies are also required to elucidate how much of a role polyphenol-activated browning may play in counteracting human obesity and correlate the biological effects of the polyphenol compounds with their principal metabolites.

Conflicts of Interest

The authors declare no conflicts of interest.

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Figure Legends

Fig. 1 **Key regulators during the transdifferentiation of white adipocytes into beige adipocytes; and the main differences in the morphology and functions between these two types of adipocytes.** WAT is classically spherical, it is full of single lipid droplet, and it contains few mitochondria. BAT is smaller than white. It contains a large number of mitochondria and contains multiple small lipid droplets. Blue: nucleus, green: mitochondria, and yellow: lipid droplets; *C/EBP*β: CCAAT-enhancer-binding protein β; *CtBP*1: C-terminal-binding protein 1; *PGC*1α: Peroxisome proliferator-activated receptor gamma coactivator-1 α; *PPAR*γ: Peroxisome proliferator-activated receptor γ; *PRDM*16: PR domain-containing 16.

Fig. 2 **Classification of polyphenols and the representative structures.**

Fig. 3 **The possible mechanisms for curcumin inducing "browning" *via* the *AMPK-SIRT1-PGC1α* pathway** (J. Lone, Choi, Kim, & Yun, 2016; Price et al., 2012; Yuan et al., 2017). (→) stimulatory, (⊥) inhibitory action, (↑) up-regulation. AMPK: AMP-activated protein kinase; *C/EBP*β: CCAAT-enhancer-binding protein β; *CIDEA*: Cell death-inducing DNA fragmentation factor, alpha subunit-like effector A; *CPT*1: Carnitine palmitoyl transferase I; HSL: hormone sensitive lipase; *FGF*21: fibroblast growth factor 21; *LKB*1: Liver kinase B1; NAD^+: Nicotinamide adenine dinucleotide (oxidized form); *NRF*1: Nuclear respiratory factor 1; *NRF*2: Nuclear respiratory factor 2; *PGC*1α: Peroxisome proliferator-activated receptor gamma coactivator-1 α; *PPAR*γ: Peroxisome proliferator-activated receptor γ; *PRDM*16: PR domain-containing 16; *SIRT*1: Sirtuin 1; *TBX*1: T-box protein 1; *TFAM*: Mitochondrial transcription factor A; *TMEM*26: Transmembrane protein 26; *UCP*1: Uncoupling protein 1;

Fig. 4 **Schematic representation of *PKA* pathways stimulated by polyphenols to activate mitochondrial biogenesis**. PKA: Protein kinase A; *CREB*: cAMP-response element binding protein; *NRF*1: Nuclear respiratory factor 1; *NRF*2: Nuclear respiratory factor 2; *PGC*1α: Peroxisome proliferator-activated receptor gamma coactivator-1 α; *TFAM*: Mitochondrial transcription factor A; mtDNA: Mitochondrial DNA.

Fig. 5 **Polyphenol metabolites SCFAs (eg. acetate and butyrate) stimulate brown adipogenesis and mitochondrial biogenesis *via GPR43* and controls mitochondrial biogenesis, resulting in increased BAT activity and adiposity reduction**. *GPR*43: G Protein-coupled Receptor 43; *PGC*1α: peroxisome proliferator-activated receptor gamma coactivator-1 α; NRF: Nuclear respiratory factor; *TFAM*: Mitochondrial transcription factor A.

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Figure 1

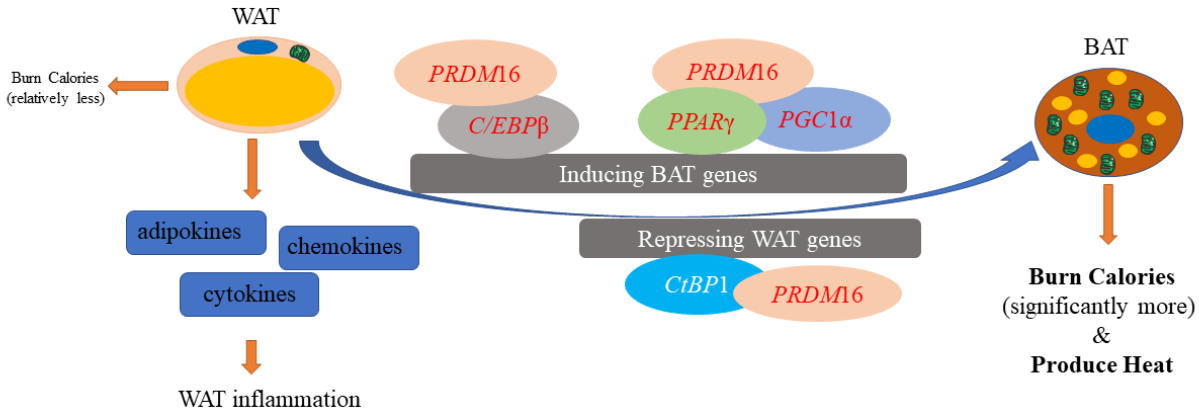

WAT
Burn Calories
(relatively less)
adipokines
chemokines
cytokines
WAT inflammation
PRDM16
C/EBPβ
PRDM16
PPARγ
PGC1α
Inducing BAT genes
Repressing WAT genes
CtBP1
PRDM16
BAT
Burn Calories
(significantly more)
&
Produce Heat

Figure 2

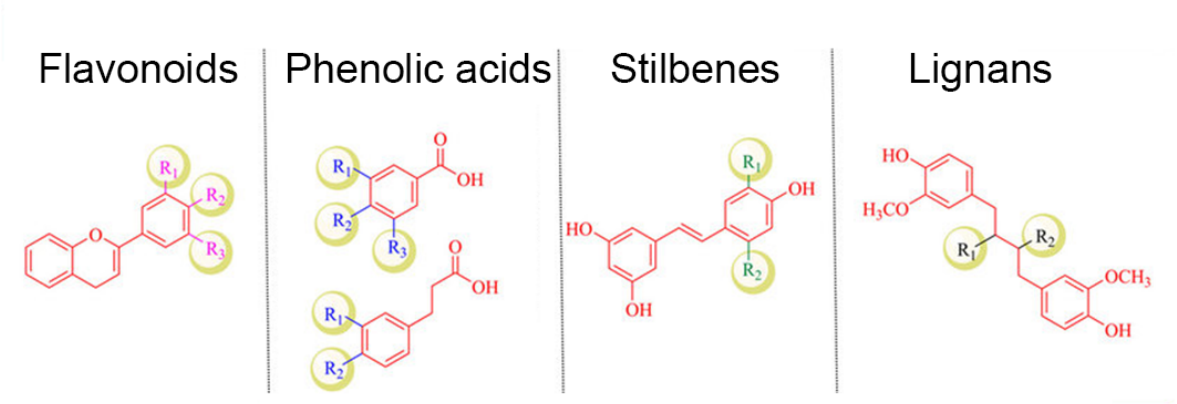


Figure 3

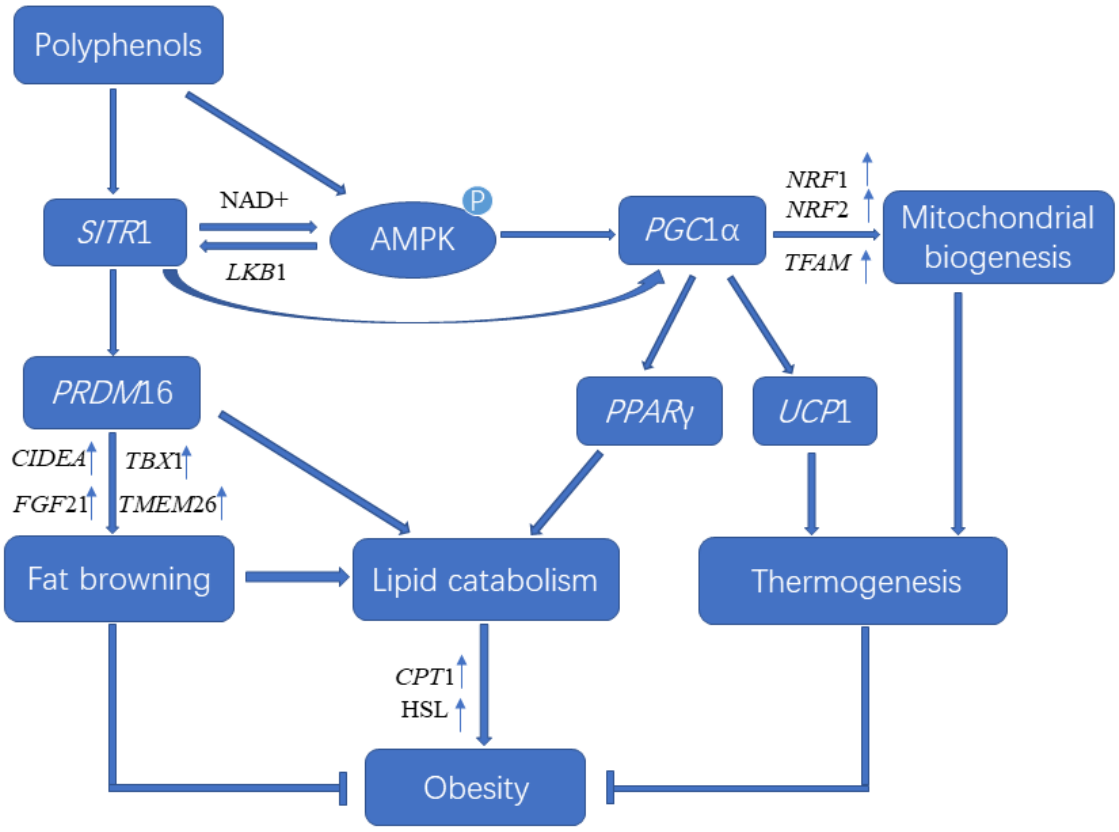

Polyphenols
SITR1
NAD+
LKB1
AMPK
P
PGC1α
NRF1
NRF2
TFAM
Mitochondrial biogenesis
PRDM16
CIDEA
TBX1
FGF21
TMEM26
PPARγ
UCP1
Fat browning
Lipid catabolism
Thermogenesis
CPT1
HSL
Obesity

Figure 4

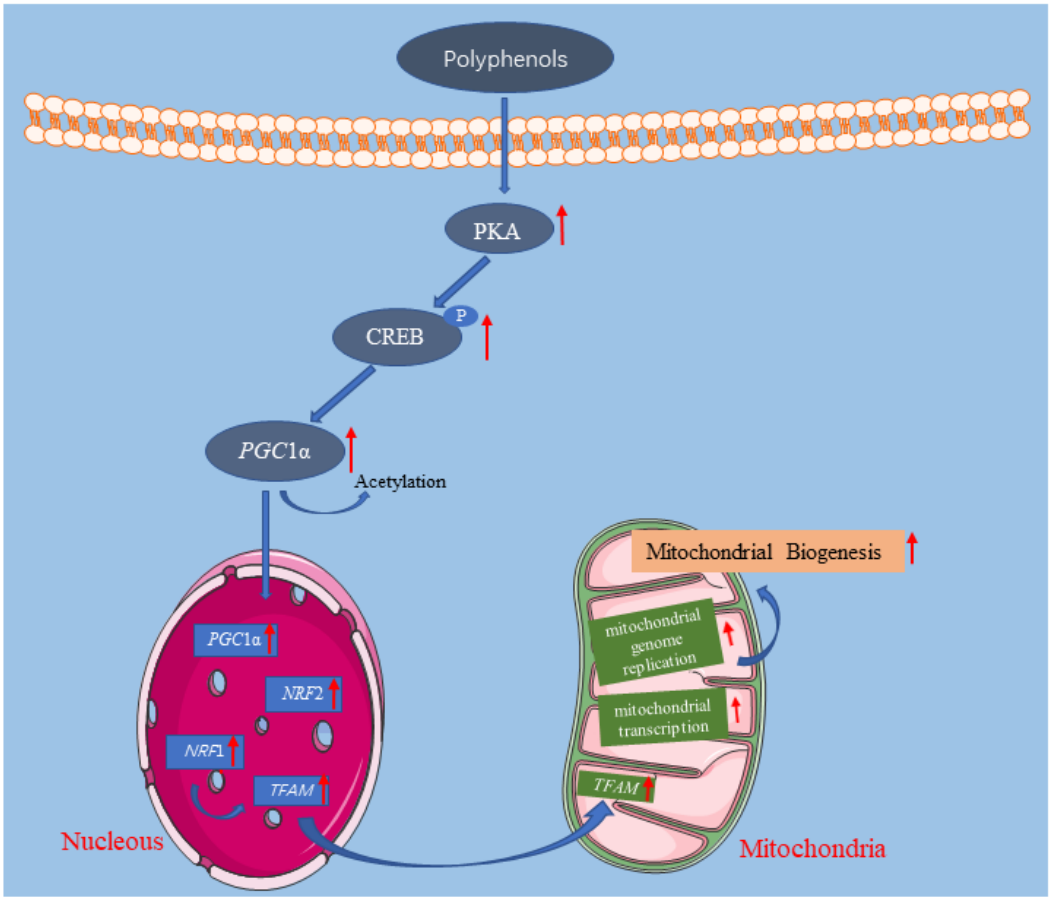

Polyphenols
PKA
CREB
P
PGC1α
Acetylation
PGC1α
NRF2
NRF1
TFAM
Nucleous
Mitochondrial Biogenesis
mitochondrial genome replication
mitochondrial transcription
TFAM
Mitochondria

Figure 5

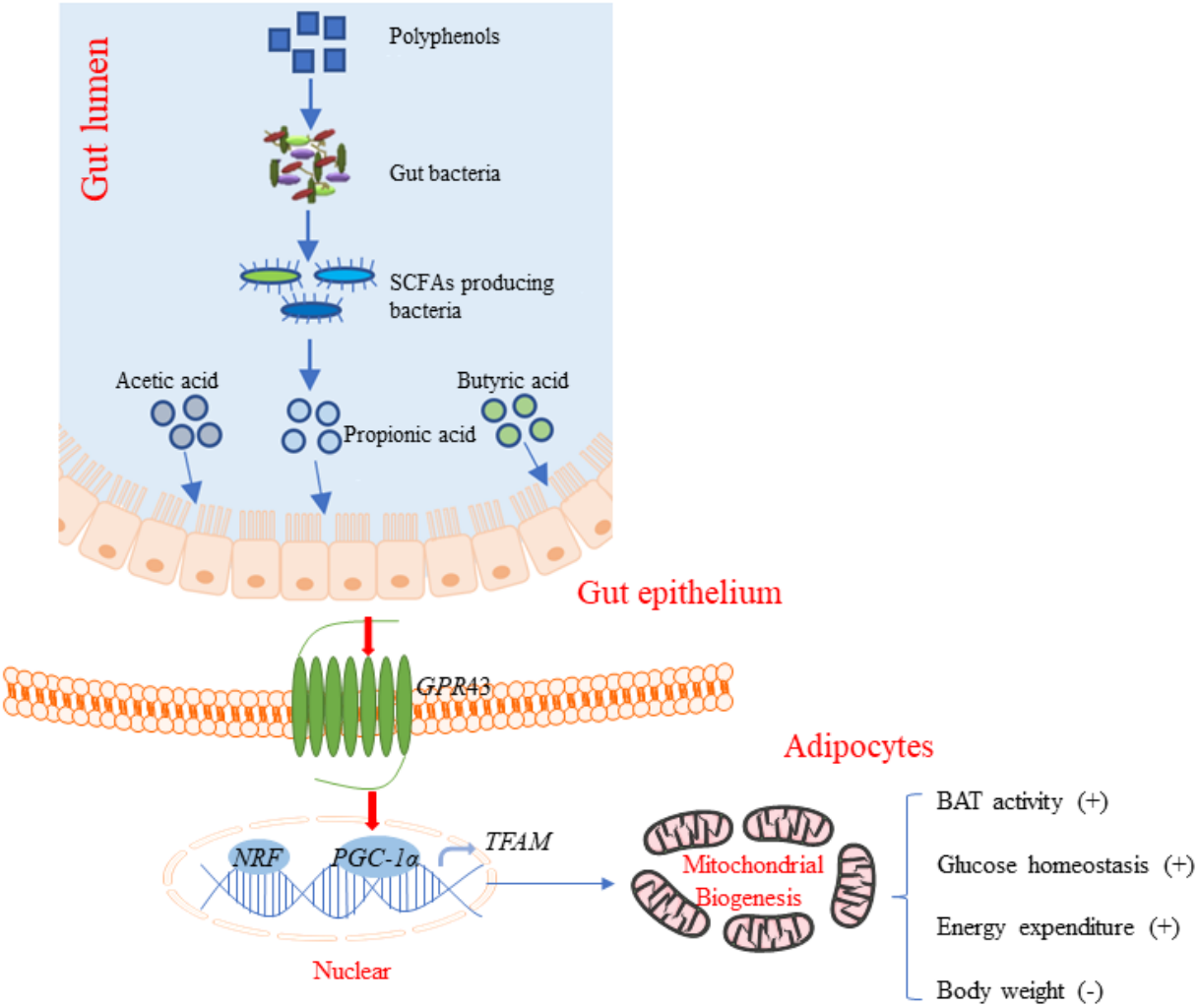
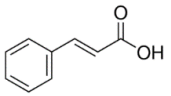
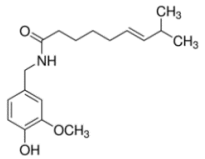
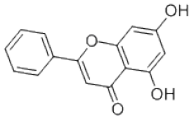
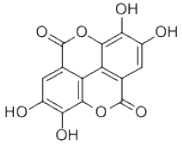
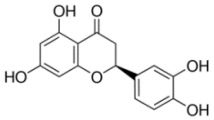
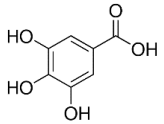
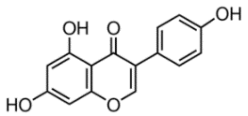
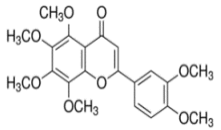
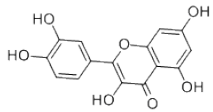
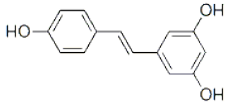

Gut lumen
Polyphenols
Gut bacteria
SCFAs producing bacteria
Acetic acid
Propionic acid
Butyric acid
Gut epithelium
GPR43
Adipocytes
TFAM
NRF
PGC-1α
Mitochondrial Biogenesis
Nuclear
BAT activity (+)
Glucose homeostasis (+)
Energy expenditure (+)
Body weight (-)

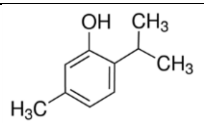
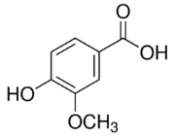
Table 1 The main location and characteristics of different adipose tissues in mammals.

Adipose tissues		WAT	BAT	Beige AT
Localization	Mice	Omental, Perigonadal, Intramuscular, Retroperitoneal, Mesenteric, Inguinal	Interscapular, Perirenal	Subcutaneous WAT
	Humans	Epicardia, Retroperitoneal, Gluteal, Omental, Mesenteric, Gonadal, Subcutaneous abdominal, Femoral	Supraclavicular, Paravertebral, Suprarenal,	Supraclavicular
Cellular composition		Single large lipid droplet; Few mitochondria; Flattened peripheral nucleus	Multiple small lipid droplets; A large of mitochondria; Oval central nucleus	Small lipid droplets; Mitochondria appear with stimulation
Function		Energy storage	Energy consumption and non-shivering thermogenesis	Thermogenesis potential

Table 2 Dietary polyphenols function as bioactive substances promoting browning of white fat

Polyphenols/ Polyphenol-rich foods	**Categories/ Identified polyphenols**	**Structure formula**	**Experimental models**	**Dosage**	**Duration**	**Effects**	**References**
trans-Cinnamic acid	Phenolic acid		3T3-L1 adipocytes	10, 50, 100, 200 μM	4-8days	*UCP*1↑, *PRDM*16↑, *PGC*1α↑ , CD137↑, *CIDEA*↑, *CITED*1↑, *TBX*1↑, *TMEM*26↑, p-AMPK↑, and β3-AR↑	Kang, Mukherjee, & Yun, 2019
Capsaicin			Male C57BL/6J mice	0.3% capsinoids	4 weeks	Vagal afferent pathways↑, Adrenergic pathways↑	Ohyama *et al.*, 2016;
			3T3-L1 preadipocytes	0.1-100 μM	8 days	*UCP*1↑, *PGC*1α↑, *PRDM*16↑, *DIO*2↑, *PPAR*α↑, *FOXC*2↑	Baboota *et al.*, 2014
Chrysin	Flavonoids		3T3-L1 adipocytes	50 μM	6-8days	p-AMPK↑, *PPAR*α↑, *PGC*1α↑, *CIDEA*↑, *PRDM*16↑, *UCP*1↑	Choi J, & Yun J, 2019
Ellagic acid	Phenolic acid		Male SD rats	10 or 30 mg/kg/d	24 weeks	*UCP*1↑, *PRDM*16↑, *CIDEA*↑, *PGC*1α↑, CD137↑, *TMEM*26↑, *TFAM*↑	Wang *et al.*, 2019
Eriodictyol	Flavonoids		Male C57BL/6N mice	0.005% (w/w) eriodictyol	16 weeks	GLP-1↑, *UCP*1↑	Kwon & Choi, 2019
Gallic acid	Phenolic acid		C57BL/6 mice	10 mg/kg bw	9 weeks	AMPK/*SIRT*1/*PGC*1α pathway↑	Doan *et al.*, 2015

Genistein	Flavonoids		Female C57BL/6Jmice	0.25 g/kg	8 weeks	*UCP*1↑, *CIDEA*↑, *PGC*1α↑, *PPAR*α↑	Zhou *et al.*, 2019
			Female Wistar rats	15 and 30 mg/kg	4 weeks	*UCP*1↑, *PRDM*16↑, *PGC*1α↑, *CIDEA*↑, *TBX*1↑	Shen *et al.*, 2019
			3T3-L1 cells	0.5 mM	10 days	Irisin secretion↑, p-AMPK↑, *UCP*1↑, *TMEM*26, *TBX*1↑	Palacios-González *et al.*, 2019
			Male C57BL/6 mice	0.2% genistein	60 days		
Nobiletin	Flavonoids		3T3-L1 adipocytes	100 μM	6–8 days	CD137↑, *CIDEA*↑, *TBX*1↑, *TMEM*26↑.	Jameel Lone, Parray, & Yun, 2018
Quercetin	Flavonoids		Male C57BL/6 mice	0.05% (w/w) quercetin	9 weeks	β3-AR↑, PKA↑, p-AMPK↑, *UCP*1↑	H. Choi, Kim, & Yu, 2019
Resveratrol	Stilbenes/ Flavonoids		CD1 mice	Each capsule contains 500 mg resveratrol	4 weeks	*SIRT*1↑, *PRDM*16↑, *PGC*1α↑, *UCP*1↑, Cytochrome C↑	S. Wang *et al.*, 2015
			Vascular cells isolated from iBAT	10 μM	9 days	*PRDM*16↑, *UCP*1↑, *PGC*1α↑	
			Pregnant female C57BL/6J mice	Diet contains 0.2% (w/w) resveratrol	11 weeks	*PRDM*16↑, *PGC*1α↑, *UCP*1↑	Zou *et al.*, 2017
Resveratrol (RSV) and Quercetin (Q)	Flavonoids		Rats	15 mg /kg/day RSV+30 mg /kg/day Q	6 weeks	COX-2↑, *CIDEA*↑; *UCP*1↑	Arias *et al.*, 2017

Thymol	Monoterpenols		3T3-L1 adipocytes	20 μM thymol	6–8 days	β3-AR↑, p-AMPK↑, PKA↑, p-p38↑, *PGC*1α↑, *UCP*1↑	J. H. Choi, Kim, Yu, & Yun, 2017
Vanillic acid	Phenolic acid		Male C57BL/6J mice	Diet contains 0.5% (w/w) vanillic acid	16 weeks	*UCP*1↑, *NRF*2↑, *CIDEA*↑, *PRDM*16↑	X. Han *et al.*, 2018
Immature *citrus reticulata* extract (IMRe)	Synephrine(16.0mg/g) Narirutin(4.52mg/g) Hesperidin(9.14mg/g)		Male C57BL/6 mice	Diet contains 1%(w/w) IMRe	11 weeks	*UCP*1↑, *TMEM*26↑, CD137↑, *CIDEA*↑, *PRDM*16↑, *NRF*1↑	Chou, Ho, & Pan, 2018
Grape pomace extract	Rich in epicatechin and quercetin		3T3-L1 preadipocytes	30 mM	10 days	β-adrenergic signaling cascade (PKA, AMPK, p38, ERK)↑, *PGC*1α↑, *PRDM*16↑, *PPARγ*↑, *UCP*1↑	C. Rodriguez Lanzi *et al.*, 2017; C. Rodriguez Lanzi *et al.*, 2018
			Spontaneously hypertensive rats	300 mg/kg/day	10 weeks		
Green tea extract	Rich in catechins		Male C57BL/6 mice	500mg/kg	12 weeks	miR-335↓, *SIRT*1↑, *PGC*1α↑, *FOXO*1, *PPARα*↑	Otton *et al.*, 2018
Pycnogenol	Mixture of procyanidins, phenolic acids, and bioflavonoids		ApoE-deficient mice	100mg/kg/day	10 weeks	p-p38↑, p-PKA/PKA↑, *UCP*1↑, *PGC*1α↑, *PRDM*16↑	Cong *et al.*, 2018
Raspberry	Rich in anthocyanin		Wild-type C57BL/6J male mice	Diet contains 5% Raspberry	12 weeks	Irisin↑, *PGC*1α↑, *UCP*1↑, *PRDM*16↑, Cytochrome C↑, *CIDEA*↑, *ELVOL*3↑	Xing *et al.*, 2018

Catechin-rich beverage	Healthy young women	540 mg/day	12 weeks	BAT density↑	Nirengi *et al.*, 2016

AMPK: AMP-activated protein kinase; **β3-AR**: β3-adrenergic receptor; **CD137**: Tumor necrosis factor receptor superfamily member 9; ***CIDEA***: Cell death-inducing DNA fragmentation factor, alpha subunit-like effector A; ***CITED*1**: Cbp/p300-Interacting Transactivator 1; ***COX*-1**: Cyclooxygenase 1; ***COX*-2**: Cyclooxygenase 2; ***DIO*2**, Iodothyronine Deiodinase 2; ***ELVOL*3**:, ELOVL Fatty Acid Elongase 3; **ERK**: Extracellular signal–regulated kinases; ***FOXC*2**: Forkhead box protein C2; ***FOXO*1**: Forkhead box protein O1; GLP-1: Glucagon-like peptide-1; ***NRF*1**: Nuclear respiratory factor 1; ***NRF*2**: Nuclear respiratory factor 2; **p38**: p38 mitogen-activated protein kinases; ***PGC*1α**: Peroxisome proliferator-activated receptor gamma coactivator-1 α; **PKA**: Protein kinase A; ***PPARα***: Peroxisome proliferator-activated receptor α; ***PPARγ***: Peroxisome proliferator-activated receptor γ; ***PRDM*16**: PR domain-containing 16; ***SIRT*1**: Sirtuin 1; ***TBX*1**: T-box protein 1; ***TFAM***: Mitochondrial transcription factor A; ***TMEM*26**: Transmembrane protein 26; ***UCP*1**: Uncoupling protein 1;