

1 **Dietary Polyphenols Turn Fat “Brown”: A Narrative Review of the Possible Mechanisms**

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14  
15 **Abstract:**

16 *Background*

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

22 *Scope and Approach*

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

26 *Key Findings and Conclusions*

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

32  
33 **Keywords:** Polyphenols; Beige adipocytes; Browning; Energy metabolism; Obesity

## 35 **1 Introduction**

36 Obesity, which is accompanied by low-grade inflammation, insulin resistance, type 2 diabetes,  
37 hyperglycemia, hyperlipidemia, atherosclerosis, metabolic syndromes and decrease in life  
38 expectancy, has grown into a worldwide epidemic affecting large numbers of people (Engin, 2017).  
39 Current understanding indicates that the disruption of energy homeostasis leads to obesity (J. Gao,  
40 Ghibaudi, van Heek, & Hwa, 2002; Hall et al., 2011). Adipose tissues with different color,  
41 morphology, metabolic function, biochemical characteristics and gene expression patterns exist in  
42 mammals (including humans and mice), and have been mainly divided into two types of fat, namely  
43 white adipose tissue (WAT) and brown adipose tissue (BAT) (Lidell et al., 2013; Rosell et al., 2014).  
44 An excess of energy is primarily stored in subcutaneous and visceral WAT. In the last decade,  
45 functional BAT, which contains a large number of mitochondria and expresses the BAT-specific  
46 gene uncoupling protein-1 (*UCP1*) to produce heat, was found in healthy adults. Moreover, after the  
47 classical BAT was identified in human adults (originating from *myf5*<sup>+</sup> precursors), there is sufficient  
48 evidence to suggest the presence of brown-like (beige) adipocytes (originating from *myf5*-  
49 precursors) in subcutaneous WAT depots, especially upon cold exposure or  $\beta$ -adrenergic stimulation  
50 (Table 1) (Cedikova et al., 2016; Park, Kim, & Bae, 2014). Although classical BAT and beige  
51 adipose tissue (BeAT) share many similarities, they still exhibit differences in their morphology and  
52 functions (Kissig, Shapira, & Seale, 2016), as illustrated in Figure 1. However, current evidence  
53 suggests that a number of the transcriptional regulators and coregulators that determine the  
54 differentiation of classic brown adipocytes are also key factors in the conversion of white adipocytes  
55 into beige adipocytes (beige adipogenesis) (Harms & Seale, 2013; Kiskinis et al., 2014; W. Wang  
56 & Seale, 2016; Wu, Jun, & McDermott, 2015). For example, key regulators of brown adipocyte  
57 differentiation including CCAAT-enhancer-binding protein  $\beta$  (*C/EBP* $\beta$ ), PR domain-containing 16  
58 (*PRDM16*), peroxisome proliferator-activated receptor  $\gamma$  (*PPAR* $\gamma$ ), and peroxisome proliferator-  
59 activated receptor gamma coactivator-1 alpha (*PGC1* $\alpha$ ), were also identified as main targets for  
60 WAT transdifferentiation (Kajimura et al., 2009; Seale et al., 2007; Villanueva et al., 2013). *PPAR* $\gamma$   
61 agonists or ectopic expression of *PGC1* $\alpha$  promotes adipose browning; while the ablation of  
62 *PRDM16* or *PGC1* $\alpha$  in white adipocytes inhibits formation and function of beige adipocytes (Ohno,  
63 Shinoda, Spiegelman, & Kajimura, 2012; Tiraby et al., 2003; Seale et al., 2011; Kleiner et al., 2012).  
64 Meanwhile, *PRDM16* can also repress white adipocyte specific genes through its association with  
65 C-terminal binding proteins (Kajimura et al., 2008). Moreover, hormones and cytokines such as  
66 noradrenaline (NA), bone morphogenetic protein 7 (*BMP7*) and fibroblast growth factor 21 (*FGF21*)  
67 also play key roles in inducing white-to-brown conversion (Hu & Christian, 2017; Y. H. Lee, Jung,  
68 & Choi, 2014; Wu et al., 2015) (Figure 1). Since the discovery of inducible beige adipocytes,  
69 modulation of adipose tissue browning to increase energy consumption, especially *via* dietary  
70 intervention, has become an attractive idea due to its promising application in obesity and metabolic  
71 diseases prevention and treatment (S. Wang et al., 2014). Indeed, beige adipocytes are functionally  
72 very similar to classical brown adipocytes upon various stimuli (such as cold exposure) and can  
73 contribute to energy expenditure through heat production, therefore, they are also categorized as  
74 thermogenic adipocytes (Scheja & Heeren, 2016). The contribution of beige adipocytes to whole  
75 body energy balance is yet to be fully determined. However, mice with specific inactivation of beige  
76 adipocytes through ablation of *PRDM16* (with minimal effects on classical BAT) become more  
77 obese and severely insulin resistant on a high fat diet (Cohen et al., 2014) clearly indicating an  
78 important role of these cells in whole-body energy homeostasis.

79

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

103

## 104 **2 Dietary polyphenols induce browning of white adipose tissue (WAT)**

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

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

135

### 136 **2.1 Dietary polyphenols increase sympathetic activity**

137 Neuronal release of noradrenaline (sympathetic nervous system activation) has been demonstrated  
138 to be one of the most important factors regulating WAT browning upon cold stimulation. Evidence  
139 has shown that dietary polyphenols may influence this browning by increasing sympathetic nervous  
140 system activity. For example, as catechin-polyphenols can function to inhibit catechol-O-methyl-  
141 transferase (the enzyme that catalyzes noradrenaline degradation) (Shixian, VanCrey, Shi, Kakuda,  
142 & Jiang, 2006), they have the potential to increase sympathetic activity representing an important  
143 mechanism for dietary polyphenols inducing WAT browning. In addition, using pre-adipocytes  
144 models, *trans*-cinnamic acid was found to induce browning of white adipocytes by activating  
145 the  $\beta$ 3-AR and *AMPK* signaling pathways, suggesting its potential to directly activate adrenergic  
146 receptors in adipocytes (Kang, Mukherjee, & Yun, 2019).

147

### 148 **2.2 Dietary polyphenols activate *AMPK-SIRT1-PGC1 $\alpha$* pathway**

149 The pathway of *AMPK-SIRT1-PGC1 $\alpha$*  axis is believed to function as a metabolic sensor  
150 involved in the regulation of brown or beige adipogenesis (Mele et al., 2017). *AMPK*  
151 phosphorylation is often strongly associated with the browning of adipose tissue accompanied with  
152 upregulation of thermogenic markers (Hutchinson, Chernogubova, Dallner, Cannon, & Bengtsson,  
153 2005; Mulligan, Gonzalez, Stewart, Carey, & Saupe, 2007; X. Zhang et al., 2016). Consequently,  
154 *AMPK* activators (eg. 5-aminoimidazole-4-carboxamide ribonucleotide) are found to promote the  
155 acquisition of BAT-like characteristics in the WAT of mice (Vila-Bedmar, Lorenzo, & Fernández-  
156 Veledo, 2010). Furthermore, Mottillo *et al.* reported that adipocyte-specific deletion of *AMPK*  
157 resulted in a reduction in thermogenesis (Mottillo et al., 2016), suggesting a significant role of  
158 *AMPK* in BAT activation. *AMPK* activation also promotes the enhancement of sirtuin 1 (*SIRT1*)  
159 activity by upregulating cellular NAD<sup>+</sup> levels, decreasing NAM levels and phosphorylation of  
160 *PGC1 $\alpha$*  (Borriello, Cucciolla, Della Ragione, & Galletti, 2010). In adipocytes it was also found that  
161 *SIRT1* activation increased *AMPK* activity and *SIRT1* inhibitors decreased *AMPK* activity. Since  
162 *AMPK* and *SIRT1* can regulate each other reciprocally, this hints *AMPK* and *SIRT1* could partner as  
163 cellular energy status sensors (AMP/ATP; NAD<sup>+</sup>/NAM) to regulate adipocyte browning.  
164 Furthermore, as a histone/protein deacetylase, *SIRT1* can also enhance WAT browning by  
165 deacetylating PPAR $\gamma$  on Lys268 and Lys293 and recruiting *PRDM16*, a key coactivator for the  
166 modulation of mitochondrial function and development of BAT (Qiang et al., 2012).

167

168 Interestingly, a considerable amount of literature has been published that polyphenols play an  
169 important role in activating the *AMPK-SIRT1-PGC1 $\alpha$*  pathway (Mele et al., 2017; Silvester, Aseer,  
170 & Yun, 2019). For example, improved glucose homeostasis and insulin sensitivity were obtained  
171 with gallic acid administration (at 10 mg/kg body weight) to C57BL/6 mice fed high-fat diet (HFD)  
172 for 9 weeks. The resulting body weight loss and metabolic improvement is likely due to the  
173 upregulation of thermogenesis-related genes (*UCPI*, *PGC1 $\alpha$* , and *PPAR $\gamma$* ), which were related to  
174 increased *AMPK* phosphorylation and *SIRT1* and *PGC1 $\alpha$*  protein levels, suggesting the critical role  
175 of the *AMPK-SIRT1-PGC1 $\alpha$*  pathway in gallic acid's action (Doan et al., 2015). Accumulating  
176 evidence also indicates favorable effects of resveratrol on metabolic syndromes including  
177 obesity and type 2 diabetes. Wang *et al.* found that resveratrol induced the browning of inguinal  
178 white adipocytes via *AMPK* activation that led to enhanced expression of a number of beige-  
179 specific gene markers (*SIRT1*, *PRDM16*, *PGC1 $\alpha$* , *PDH* and *UCPI*), suggesting its beneficial anti-  
180 obesity effects may be partly ascribed to WAT browning (S. Wang et al., 2015). The flavonoid  
181 and phenolic acid-rich oolong, pu-erh, and particularly black tea have the potential to exert anti-  
182 obesity properties. This is also partly associated with *AMPK* activation in WAT and the browning  
183 of mesenteric WAT (Yamashita et al., 2014). In agreement with these studies, chrysin was also  
184 found to induce 3T3-L1 adipocyte browning through *AMPK* activation and elevating *PGC1 $\alpha$*   
185 expression (Choi J, & Yun J, 2019). Collectively, these findings indicate that natural polyphenols  
186 may activate the browning of adipose tissues based on signaling through *AMPK-SIRT1-PGC1 $\alpha$*   
187 (Figure 3).

188

### 189 **2.3 Dietary polyphenols activate the Protein kinase A (PKA) Signaling Pathway**

190 Protein kinase A (*PKA*) is a downstream target of  $\beta$ 3-adrenergic receptor ( $\beta$ 3AR) signaling, which  
191 is expressed primarily in adipocytes (Klein et al., 1999). As shown in Figure 4, activated PKA is  
192 able to phosphorylate cAMP-response element binding protein (*CREB*) and trigger enhanced  
193 expression of thermogenesis and mitochondrial biogenesis related genes (Kim & Park, 2010; van  
194 Dam, Kooijman, Schilperoort, Rensen, & Boon, 2015; Wood Dos Santos et al., 2018). Moreover,  
195 PKA also activates hormone sensitive lipase (*HSL*), which stimulates lipolysis from stored  
196 energy in adipocytes providing free fatty acids for heat production *via* uncoupled respiration or  
197 ATP synthesis (Lowell & Spiegelman, 2000). There is evidence that some polyphenols may  
198 increase cAMP levels to activate the *PKA* pathway and consequently induce thermogenic gene  
199 expression (da-Silva et al., 2007; Tennen, Michishita-Kioi, & Chua, 2012). Thus, activating the  
200 *PKA* signaling pathway could be another possible mechanism for browning adipose tissues by  
201 phenolics. For example, the monoterpene phenolic compound thymol has been demonstrated to  
202 exert a browning action via activation of the  $\beta$ -adrenergic receptor and phosphorylated *PKA*,  
203 thereby triggering *UCPI* expression in 3T3-L1 adipocytes, suggesting that *PKA* signaling may  
204 be indispensable for thymol exerting its effects (J. H. Choi, Kim, Yu, & Yun, 2017). Similarly, it  
205 has been reported that quercetin increases the levels of *UCPI* in both WAT and BAT of HFD-fed  
206 mice accompanied by increases in the transcription of thermogenesis-related genes (eg.,  
207 *PRDM16*, *CIDEA*, *TFAM*, *NRF-1*, *PGC1 $\alpha$* ), which is associated with sympathetic stimulation  
208 through  $\beta$ 3AR signaling-induced *PKA* activation (H. Choi, Kim, & Yu, 2019). In addition, nobiletin,  
209 a polymethoxylated flavone, has been reported to show anti-obesity effects, which were relevant  
210 to its positive effect on activating adipose browning. As reported by Lone J *et al.* , nobiletin

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

216

#### 217 **2.4 Dietary polyphenols activate MAPK Signaling Pathway**

218 Mitogen-activated protein kinases (*MAPK*) are a type of serine/threonine protein kinases (Johnson  
219 & Lapadat, 2002). Activation of *MAPKs*, especially *p38*, were found to drive the browning process  
220 of adipocytes (Cao et al., 2004; Robidoux et al., 2005). *MAPK* is associated with phosphorylation  
221 of the transcription factor *CREB*, which was identified as a key modulator for *UCPI* transcription  
222 during brown and beige adipogenesis (Martinez-deMena & Obregon, 2005; Muller et al., 2013). In  
223 addition, the *MAPK* pathway was also found to turn on transcription of *PPAR $\gamma$* , *PGC1 $\alpha$*  and *UCPI*  
224 via phosphorylating the cAMP-dependent transcription factor *ATF-2* (Cao et al., 2004).  
225 Polyphenols are reported to influence browning of adipocytes by activating the *MAPK* signaling  
226 pathway. Indeed, grape pomace extract, which is rich in a wide variety of phenolics and flavonoids,  
227 can stimulate the recruitment of beige adipocytes *in vitro* and in HFD-fed rats. The underlying  
228 mechanisms can be partly attributed to the activation of *p38* and *ERK1/2* (C. Rodriguez Lanzi et al.,  
229 2017; C. Rodriguez Lanzi et al., 2018). Another interesting case reported by Cong et al., showed  
230 Pycnogenol, a mixture of procyanidins, phenolic acids, and bioflavonoids promotes browning,  
231 which was tightly coordinated with phosphorylation of *PKA* as well as *p38* proteins (Cong et al.,  
232 2018) Thus, *MAPK* activation by polyphenols may represent an important signaling event to  
233 coordinate the recruitment of beige adipocytes in WAT.

234

#### 235 **2.5 Dietary polyphenols modulate epigenetic processes**

236 Epigenetic processes including DNA methylation histone modifications and miRNAs are also  
237 involved in the control of WAT transdifferentiation. Evidence supports that polyphenol-related  
238 epigenetic modifications may also associate with their WAT “browning” activity. For example, apple  
239 polyphenols affect *PGC1 $\alpha$*  promoter methylation levels and consequently increase its mRNA  
240 expression in epididymal adipocytes from high-fat sucrose fed rats (Boqué et al., 2013). Considering  
241 the importance of *PGC1 $\alpha$*  in WAT browning, it is highly possible that apple polyphenols may affect  
242 WAT browning via this epigenetic modulation, although direct evidence may be still inadequate.

243 miRNA networks also represent a fundamental layer in the regulation of gene expression (Bartel,  
244 2004). With understanding of the mechanisms behind the "browning" process increasing, the  
245 correlation between miRNAs and beige adipogenesis has been identified (Goody & Pfeifer, 2019).  
246 They either enhance or suppress brown/beige adipogenesis via regulating genes involved in this  
247 process (Chen, Pan, & Pfeifer, 2017). Notably, an adipocyte-specific *Dicer* ablation led to the  
248 “whitening” of murine interscapular BAT (Mori et al., 2012), also demonstrating the requirement of  
249 miRNA processing for brown adipogenesis. Evidence indicates that phenolics may regulate the  
250 browning via affecting miRNAs. Resveratrol reduces obesity alongside increasing miRNAs (miR-129,  
251 miR-328-5p and miR-539-5p), whose predicted target genes are key regulators of browning  
252 including *PPAR $\gamma$*  and *HSL* (Gracia et al., 2016). In addition, polyphenol-rich green tea extract also  
253 showed pro-browning effects by down-regulating miR-335 expression (Otton et al., 2018). These  
254 pieces of evidence together indicate the importance of the regulatory effects of miRNAs in

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

256

## 257 **2.6 Dietary polyphenols increase cyclooxygenase-2 activity**

258 Cyclooxygenase (*COX*)-2, a rate-limiting enzyme for prostaglandin synthesis, has been shown to  
259 regulate whole-body energy homeostasis (Vegiopoulos et al., 2010). In particular, increased *COX*-  
260 2 activity is related to the emergence of brown fat features in WAT by inducing brown adipogenic  
261 gene expression (Vegiopoulos et al., 2010). Madsen *et al.* also found that decreased *Cox-2* activity  
262 caused weight gain along with lowered diet-induced *UCPI* expression in inguinal WAT (Madsen et  
263 al., 2010). This indicates *COX-2* activation seems to be a vital mechanism involved in beige  
264 adipogenesis. Interestingly, the combination of resveratrol and quercetin has been found to induce  
265 a brown-like remodeling in perirenal WAT with the upregulated expression of *UCPI* protein (Arias  
266 et al., 2017). The increased mitochondrial activity was co-incident with increased *Cox-2* expression.  
267 A similar observation was reported in quercetin-treated rats where the expression of *Cox-2* was  
268 modestly increased (Arias, Macarulla, Aguirre, Martinez-Castano, & Portillo, 2014). Therefore,  
269 manipulation of *Cox-2* expression seems to be another possible way for dietary polyphenols to  
270 enhance BAT activity and WAT browning, which protects against energy surplus and body weight  
271 gain.

272

## 273 **2.7 Dietary polyphenols increase Glucagon-Like Peptide-1**

274 Glucagon-like peptide 1 (*GLP-1*) is an incretin hormone released by L-cells (Drucker, 2007; Goke,  
275 Fehmann, & Goke, 1991). *GLP-1* binds to the *GLP-1* receptor (Campbell & Drucker, 2013; J. Zhang  
276 et al., 2018), and ameliorates obesity *via* numerous physiological effects. Although its most striking  
277 characteristic may be the stimulatory effects on insulin secretion, *GLP-1* anti-obesity effects also  
278 partly result from increasing thermogenesis and browning (Gu et al., 2011; Lockie et al., 2012; J.  
279 Zhang et al., 2018). Evidence also points to inhibition of dipeptidyl peptidase-4 (*DPP-4*) (the  
280 enzyme that efficiently degrades *GLP-1 in vivo* and thus shortens the circulation half-life of *GLP-1*  
281 to less than 2 min (Deacon et al., 1995)), as a mechanism by which polyphenols increase *GLP-1*  
282 and leads to elevated expression of *PPAR $\alpha$* , *PGC1 $\alpha$*  and *UCPs* in BAT of obese mice (Shimasaki et  
283 al., 2013) and increased metabolic gene expression in human (pre)adipocytes *via* upregulating  
284 *PGC1 $\alpha$* .

285

286 Dietary phenolics such as curcumin and caffeoylquinic acid derivatives are reported to possess *GLP*-  
287 *1* secretion-stimulating functions (Tsuda, 2015); in addition, polyphenols such as resveratrol,  
288 luteolin and apigenin also can exert *DPP-4* inhibitory effects, leading to a prolonged action of *GLP*-  
289 *1* (Habtemariam & Varghese, 2014; Pinent, Blay, Serrano, & Ardevol, 2017). Another study also  
290 found grape seed extract containing abundant procyanidins resulted in increased levels of active  
291 *GLP-1* by lowering *DPP-4* activity (Gonzalez-Abuin et al., 2014). A study in HFD-fed mice also  
292 demonstrated that the flavonoid eriodictyol can exert beneficial effects on alleviating adiposity by  
293 significantly increasing the levels of *UCPI* in epididymal WAT, which was accompanied by  
294 increased circulating *GLP-1* (Kwon & Choi, 2019). However, more studies are needed to elucidate  
295 the relationship between dietary phenolics, *GLP-1* activity and beige adipogenesis.

296

## 297 **2.8 Dietary polyphenols promote irisin secretion**

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

299 fibronectin type III domain-containing protein 5 (*FNDC5*), was discovered as the key factor  
300 regulating exercise-induced browning of WAT (Mahajan & Patra, 2013; McMillan & White, 2015;  
301 Y. Zhang et al., 2016). *FNDC5*/irisin is mainly secreted by skeletal muscle upon exercise and  
302 facilitates white adipocyte browning *via* activating *p38* and *ERK* signal pathways (Y. Zhang et al.,  
303 2014). The researchers confirmed that intravenous injection of irisin-expressing adenovirus can  
304 induce brown-fat-like development with increased thermogenic gene expression and energy  
305 expenditure (Bostrom et al., 2012). Therefore, the intake of irisin-activating ingredients is a  
306 mechanism to activate browning of adipose tissues, which would lead to accelerated metabolism  
307 and reduced body weight and fat. Some reports claim that polyphenols such as quercetin, apigenin,  
308 dihydromyricetin can promote irisin secretion (Jang et al., 2017; Leiherer et al., 2016; Zhou et al.,  
309 2015). Genistein was also found to promote browning of subcutaneous WAT in mice through  
310 induction of *FNDC5* expression in skeletal muscle and increasing irisin levels (Palacios-González  
311 et al., 2019). In one study, obese mice treated with leucine-resveratrol combinations for 6 weeks  
312 showed two-fold increase in *PGC1α* and augmented *UCP1* expression in WAT accompanied by  
313 elevated plasma irisin levels, showing the treatment combination may lead to browning of adipose  
314 tissue *via* promotion of irisin secretion (Baggett, Bruckbauer, & Zemel, 2013). Similarly, raspberry  
315 supplementation, which contains high amounts of polyphenols, also drove the browning of WAT,  
316 which was associated with elevated irisin (Xing et al., 2018). Therefore, polyphenols may stimulate  
317 browning of WAT due to a positive action on irisin secretion.

318

## 319 **2.9 Capsaicin activates transient receptor potential cation channel subfamily V member 1** 320 **(*TRPV1*)**

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

335

## 336 **2.10 Dietary polyphenols influence gut microbiota composition and short-chain fatty acid** 337 **production**

338 The gut microbiota has been recognized as an important modulator of energy balance (Koren et al.,  
339 2012; Ridaura et al., 2013). For example, evidence from fecal transplantation experiments suggested  
340 that gut microbiota may regulate host energy homeostasis and insulin resistance *via* a range of  
341 possible mechanisms including influencing gut physiology and gut motility, affecting calorie and  
342 nutrient harvest, and triggering innate immune responses (Ley et al., 2005; Singh et al., 2017).



343 Changes in gut microbiota composition show a strong interaction with expression of browning-  
344 specific genes in adipose tissue and energy homeostasis (Chevalier et al., 2015; Fabbiano et al.,  
345 2018). A recent study in obese subjects demonstrated a significant positive association between the  
346 relative abundance of *Firmicutes* and the expression of brown marker genes *PRDM16*, *DIO2* and  
347 *UCPI* in subcutaneous WAT (Moreno-Navarrete et al., 2018). Dietary polyphenols also play a  
348 crucial role in augmenting host-microbial interactions, ultimately resulting in beneficial effects  
349 including weight reduction (Valdes et al., 2015; Xue et al., 2016). Evidence suggests the  
350 combination of quercetin and resveratrol lowers the ratio of *Firmicutes* to *Bacteroidetes* and  
351 increases *Akkermansia* in HFD-fed rats and consequently decreasing body weight gain and visceral  
352 (epididymal, perirenal) adipose tissue weight (Zhao et al., 2017). Similarly, an investigation from  
353 Anhe *et al.* (Anhe et al., 2018) found that administration of crude extract of *Myrciaria dubia*  
354 containing proanthocyanidins, flavonols, and phenolic acids to HFD fed mice activated BAT and  
355 increased the browning of WAT, which may be related to alteration of the gut microbiota.  
356 Subsequent analyses provides more direct evidence that resveratrol induced the emergence of beige  
357 adipocytes in WAT by remodeling fecal microbiota (Liao et al., 2018); and similar phenomenon are  
358 also presented in the study carried out by Wang *et al.* (P. Wang et al., 2019) that resveratrol-induced  
359 microbiota changes are able to stimulate the development of beige adipocytes in WAT and modulate  
360 lipid metabolism. Collectively, polyphenols may function as a potential intervention to improve  
361 dysbiosis of the gut microbiota in obesity.

362

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

383

### 384 **3 Conclusions**

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

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

403

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

429

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

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

436

437 **Conflicts of Interest**

438 The authors declare no conflicts of interest.

439

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444

## 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/EBPβ*: CCAAT-enhancer-binding protein β; *CtBP1*: C-terminal-binding protein 1; *PGC1α*: Peroxisome proliferator-activated receptor gamma coactivator-1 α; *PPARγ*: Peroxisome proliferator-activated receptor γ; *PRDM16*: 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/EBPβ*: CCAAT-enhancer-binding protein β; *CIDEA*: Cell death-inducing DNA fragmentation factor, alpha subunit-like effector A; *CPT1*: Carnitine palmitoyl transferase I; HSL: hormone sensitive lipase; *FGF21*: fibroblast growth factor 21; *LKB1*: Liver kinase B1;  $\text{NAD}^+$ : Nicotinamide adenine dinucleotide (oxidized form); *NRF1*: Nuclear respiratory factor 1; *NRF2*: Nuclear respiratory factor 2; *PGC1α*: Peroxisome proliferator-activated receptor gamma coactivator-1 α; *PPARγ*: Peroxisome proliferator-activated receptor γ; *PRDM16*: PR domain-containing 16; *SIRT1*: Sirtuin 1; *TBX1*: T-box protein 1; *TFAM*: Mitochondrial transcription factor A; *TMEM26*: Transmembrane protein 26; *UCP1*: 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; *NRF1*: Nuclear respiratory factor 1; *NRF2*: Nuclear respiratory factor 2; *PGC1α*: 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.** *GPR43*: G Protein-coupled Receptor 43; *PGC1α*: peroxisome proliferator-activated receptor gamma coactivator-1 α; *NRF*: Nuclear respiratory factor; *TFAM*: Mitochondrial transcription factor A.

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Figure 1

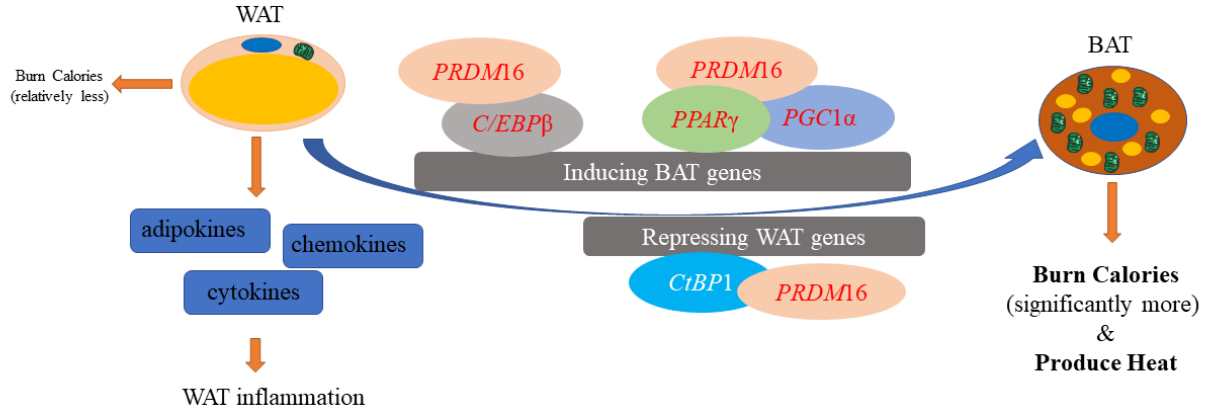


Figure 2

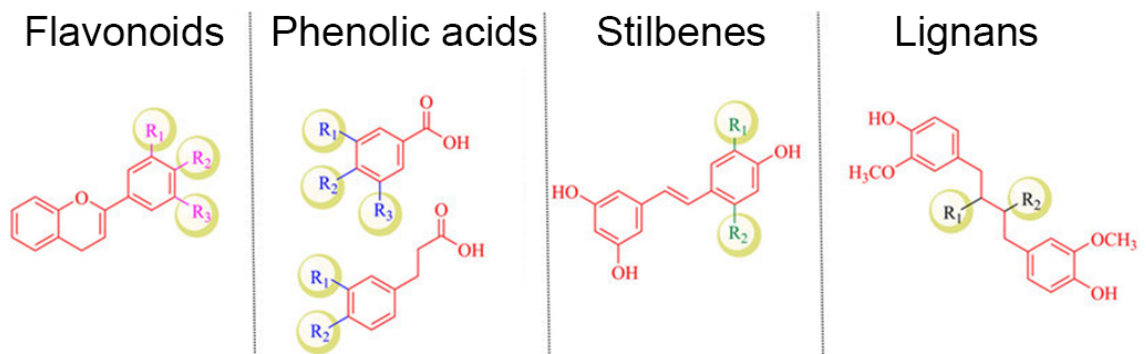


Figure 3

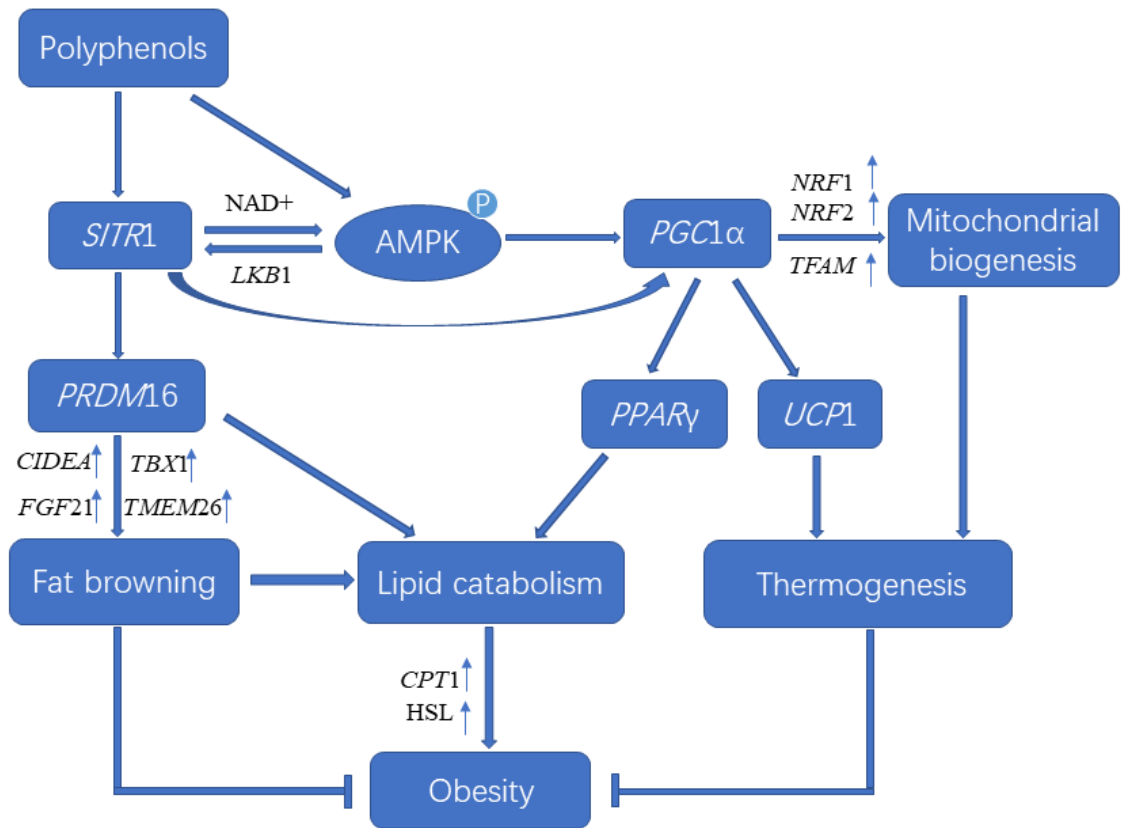


Figure 4

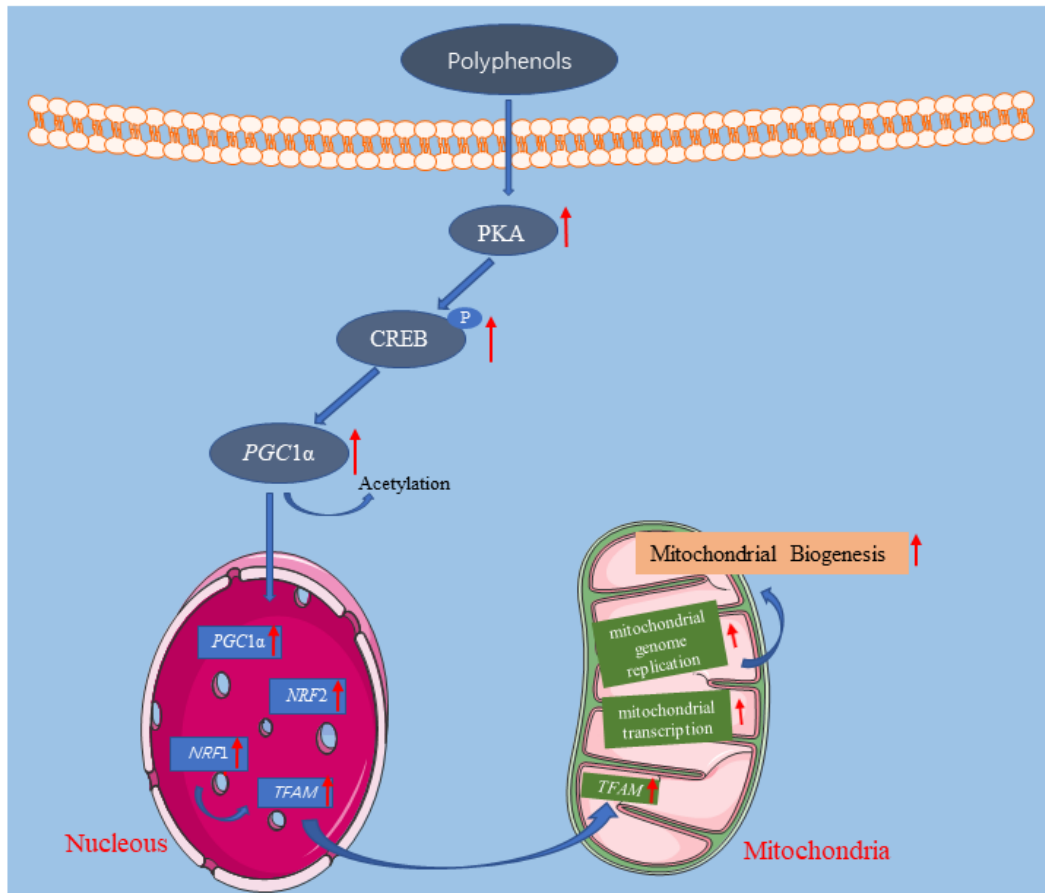


Figure 5

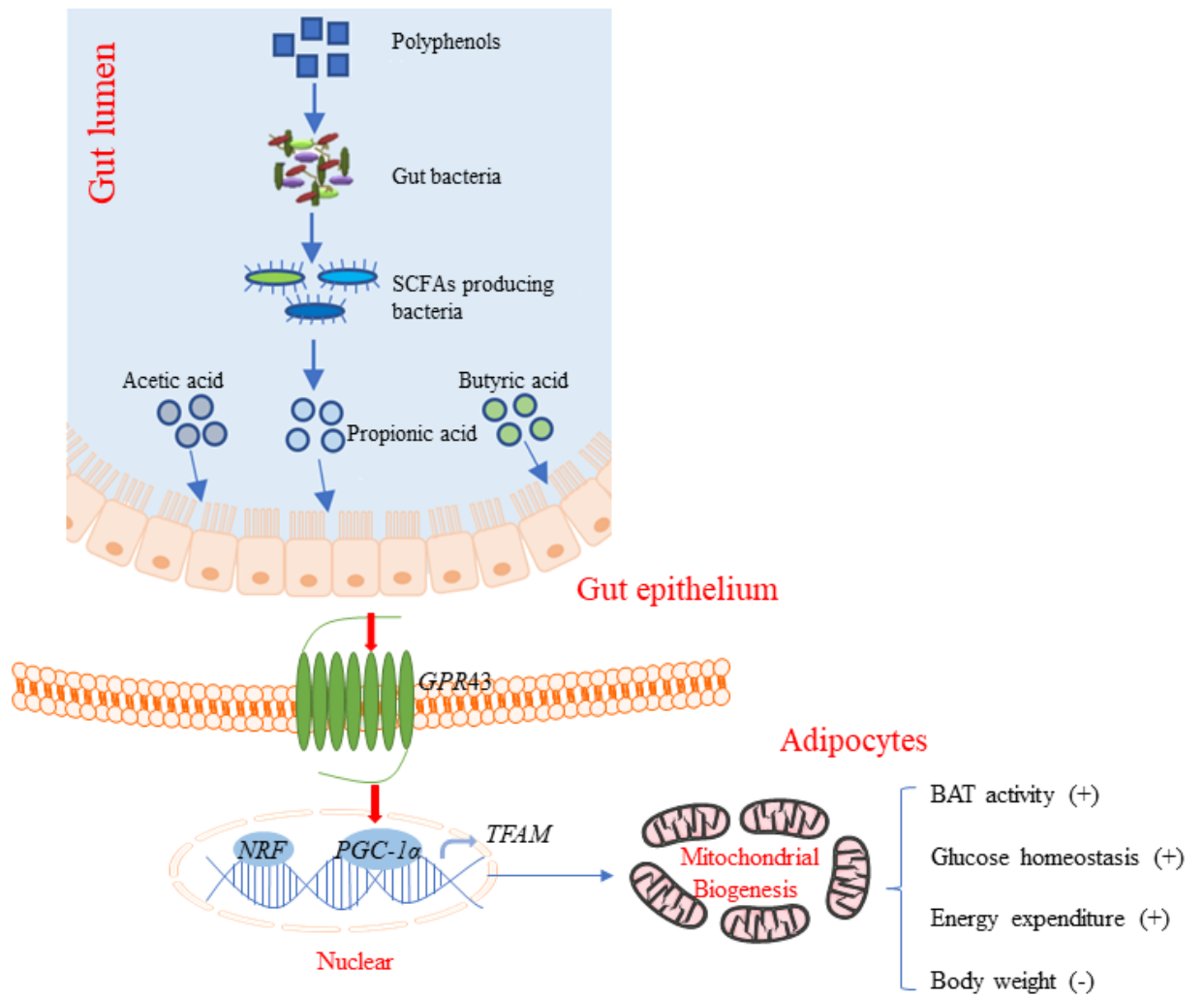
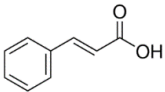
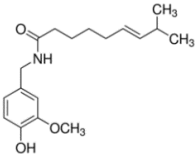
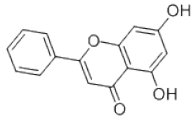
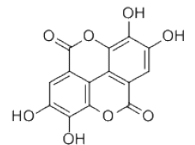
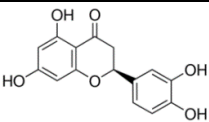
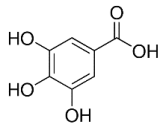
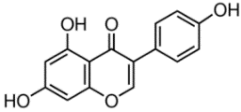
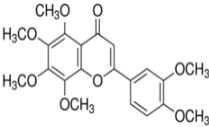
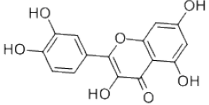
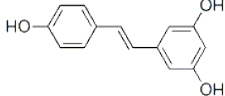


Table 1 The main location and characteristics of different adipose tissues in mammals.

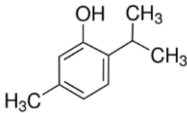
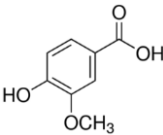
Adipose tissues		WAT	BAT	Beige AT
Localization	Mice	Omental, Perigonadal, Intramuscular, Retroperitoneal, Mesenteric, Inguinal	Interscapular, Perirenal	Subcutaneous WAT
	Humans	Epicardia, Retroperitoneal, Gluteal, Omental, Mesenteric, Gonadal, Subcutaneous abdominal, Femoral	Supraclavicular, Paravertebral, 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 $\mu$ M	4-8days	<i>UCP1</i> $\uparrow$ , <i>PRDM16</i> $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>CD137</i> $\uparrow$ , <i>CIDEA</i> $\uparrow$ , <i>CITED1</i> $\uparrow$ , <i>TBX1</i> $\uparrow$ , <i>TMEM26</i> $\uparrow$ , p-AMPK $\uparrow$ , and $\beta$ 3-AR $\uparrow$	Kang, Mukherjee, & Yun, 2019
Capsaicin			Male C57BL/6J mice	0.3% capsinoids	4 weeks	Vagal afferent pathways $\uparrow$ , Adrenergic pathways $\uparrow$	Ohyama <i>et al.</i> , 2016;
			3T3-L1 preadipocytes	0.1-100 $\mu$ M	8 days	<i>UCP1</i> $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>PRDM16</i> $\uparrow$ , <i>DIO2</i> $\uparrow$ , <i>PPAR<math>\alpha</math></i> $\uparrow$ , <i>FOXC2</i> $\uparrow$	Baboota <i>et al.</i> , 2014
Chrysin	Flavonoids		3T3-L1 adipocytes	50 $\mu$ M	6-8days	p-AMPK $\uparrow$ , <i>PPAR<math>\alpha</math></i> $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>CIDEA</i> $\uparrow$ , <i>PRDM16</i> $\uparrow$ , <i>UCP1</i> $\uparrow$	Choi J, & Yun J, 2019
Ellagic acid	Phenolic acid		Male SD rats	10 or 30 mg/kg/d	24 weeks	<i>UCP1</i> $\uparrow$ , <i>PRDM16</i> $\uparrow$ , <i>CIDEA</i> $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>CD137</i> $\uparrow$ , <i>TMEM26</i> $\uparrow$ , <i>TFAM</i> $\uparrow$	Wang <i>et al.</i> , 2019
Eriodictyol	Flavonoids		Male C57BL/6N mice	0.005% (w/w) eriodictyol	16 weeks	GLP-1 $\uparrow$ , <i>UCP1</i> $\uparrow$	Kwon & Choi, 2019
Gallic acid	Phenolic acid		C57BL/6 mice	10 mg/kg bw	9 weeks	AMPK/ <i>SIRT1</i> / <i>PGC1<math>\alpha</math></i> pathway $\uparrow$	Doan <i>et al.</i> , 2015

Genistein	Flavonoids		Female C57BL/6J mice	0.25 g/kg	8 weeks	<i>UCP1</i> ↑, <i>CIDEA</i> ↑, <i>PGC1α</i> ↑, <i>PPARα</i> ↑	Zhou <i>et al.</i> , 2019
			Female Wistar rats	15 and 30 mg/kg	4 weeks	<i>UCP1</i> ↑, <i>PRDM16</i> ↑, <i>PGC1α</i> ↑, <i>CIDEA</i> ↑, <i>TBX1</i> ↑	Shen <i>et al.</i> , 2019
			3T3-L1 cells	0.5 mM	10 days	<i>Irisin</i> secretion↑, p-AMPK↑, <i>UCP1</i> ↑, <i>TMEM26</i> , <i>TBX1</i> ↑	Palacios-González <i>et al.</i> , 2019
			Male C57BL/6 mice	0.2% genistein	60 days		
Nobiletin	Flavonoids		3T3-L1 adipocytes	100 μM	6–8 days	<i>CD137</i> ↑, <i>CIDEA</i> ↑, <i>TBX1</i> ↑, <i>TMEM26</i> ↑.	Jameel Lone, Parray, & Yun, 2018
Quercetin	Flavonoids		Male C57BL/6 mice	0.05% (w/w) quercetin	9 weeks	$\beta$ 3-AR↑, PKA↑, p-AMPK↑, <i>UCP1</i> ↑	H. Choi, Kim, & Yu, 2019
Resveratrol	Stilbenes/ Flavonoids		CD1 mice	Each capsule contains 500 mg resveratrol	4 weeks	<i>SIRT1</i> ↑, <i>PRDM16</i> ↑, <i>PGC1α</i> ↑, <i>UCP1</i> ↑, Cytochrome C↑	S. Wang <i>et al.</i> , 2015
			Vascular cells isolated from iBAT	10 μM	9 days	<i>PRDM16</i> ↑, <i>UCP1</i> ↑, <i>PGC1α</i> ↑	
			Pregnant female C57BL/6J mice	Diet contains 0.2% (w/w) resveratrol	11 weeks	<i>PRDM16</i> ↑, <i>PGC1α</i> ↑, <i>UCP1</i> ↑	Zou <i>et al.</i> , 2017
Resveratrol (RSV) and Quercetin (Q)	Flavonoids		Rats	15 mg /kg/day RSV+30 mg /kg/day Q	6 weeks	COX-2↑, <i>CIDEA</i> ↑; <i>UCP1</i> ↑	Arias <i>et al.</i> , 2017



Thymol	Monoterpenols		3T3-L1 adipocytes	20 $\mu$ M thymol	6–8 days	$\beta$ 3-AR $\uparrow$ , p-AMPK $\uparrow$ , PKA $\uparrow$ , p-p38 $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>UCP1</i> $\uparrow$	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	<i>UCP1</i> $\uparrow$ , <i>NRF2</i> $\uparrow$ , <i>CIDEA</i> $\uparrow$ , <i>PRDM16</i> $\uparrow$	X. Han <i>et al.</i> , 2018
Immature <i>citrus reticulata</i> 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	<i>UCP1</i> $\uparrow$ , <i>TMEM26</i> $\uparrow$ , <i>CD137</i> $\uparrow$ , <i>CIDEA</i> $\uparrow$ , <i>PRDM16</i> $\uparrow$ , <i>NRF1</i> $\uparrow$	Chou, Ho, & Pan, 2018
Grape pomace extract	Rich in epicatechin and quercetin		3T3-L1 preadipocytes	30 mM	10 days	$\beta$ -adrenergic signaling cascade (PKA, AMPK, p38, ERK) $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>PRDM16</i> $\uparrow$ , <i>PPAR<math>\gamma</math></i> $\uparrow$ , <i>UCP1</i> $\uparrow$	C. Rodriguez Lanzi <i>et al.</i> , 2017; C. Rodriguez Lanzi <i>et al.</i> , 2018
Green tea extract	Rich in catechins		Spontaneously hypertensive rats	300 mg/kg/day	10 weeks		
			Male C57BL/6 mice	500mg/kg	12 weeks	miR-335 $\downarrow$ , <i>SIRT1</i> $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>FOXO1</i> , <i>PPAR<math>\alpha</math></i> $\uparrow$	Otton <i>et al.</i> , 2018
Pycnogenol	Mixture of procyanidins, phenolic acids, and bioflavonoids		ApoE-deficient mice	100mg/kg/day	10 weeks	p-p38 $\uparrow$ , p-PKA/PKA $\uparrow$ , <i>UCP1</i> $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>PRDM16</i> $\uparrow$	Cong <i>et al.</i> , 2018
Raspberry	Rich in anthocyanin		Wild-type C57BL/6J male mice	Diet contains 5% Raspberry	12 weeks	Irisin $\uparrow$ , <i>PGC1<math>\alpha</math></i> $\uparrow$ , <i>UCP1</i> $\uparrow$ , <i>PRDM16</i> $\uparrow$ , Cytochrome C $\uparrow$ , <i>CIDEA</i> $\uparrow$ , <i>ELVOL3</i> $\uparrow$	Xing <i>et al.</i> , 2018

Catechin-rich beverage	Healthy young women	540 mg/day	12 weeks	BAT density↑	Nirengi <i>et al.</i> , 2016
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**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; **CITED1**: Cbp/p300-Interacting Transactivator 1; **COX-1**: Cyclooxygenase 1; **COX-2**: Cyclooxygenase 2; **DIO2**, Iodothyronine Deiodinase 2; **ELVOL3**., ELOVL Fatty Acid Elongase 3; **ERK**: Extracellular signal-regulated kinases; **FOXC2**: Forkhead box protein C2; **FOXO1**: Forkhead box protein O1; GLP-1: Glucagon-like peptide-1; **NRF1**: Nuclear respiratory factor 1; **NRF2**: Nuclear respiratory factor 2; **p38**: p38 mitogen-activated protein kinases; **PGC1α**: Peroxisome proliferator-activated receptor gamma coactivator-1 α; **PKA**: Protein kinase A; **PPARα**: Peroxisome proliferator-activated receptor α; **PPARγ**: Peroxisome proliferator-activated receptor γ; **PRDM16**: PR domain-containing 16; **SIRT1**: Sirtuin 1; **TBX1**: T-box protein 1; **TFAM**: Mitochondrial transcription factor A; **TMEM26**: Transmembrane protein 26; **UCP1**: Uncoupling protein 1;