Food Phenolics Stimulate Adipocyte Browning via Regulating Gut Microecology

Zhenyu Wang\textsuperscript{a, b}, Maomao Zeng\textsuperscript{a, b}, Zhaojun Wang\textsuperscript{a, b}, Fang Qin\textsuperscript{a, b}, Yongzhi Wang\textsuperscript{c}, Jie Chen\textsuperscript{a, b}, Mark Christian\textsuperscript{*, d}, Zhiyong He\textsuperscript{*, a, b}

\textsuperscript{a}State Key Laboratory of Food Science and Technology, Jiangnan University, Wuxi, Jiangsu 214122, China

\textsuperscript{b}International Joint Laboratory on Food Safety, Jiangnan University, Wuxi, Jiangsu 214122, China

\textsuperscript{c}Food and Beverage Department of Damin Food (Zhangzhou) Co., Ltd., Zhangzhou, Fujian 363005, China

\textsuperscript{d}School of Science and Technology, Nottingham Trent University, Clifton, Nottingham, NG11 8NS, United Kingdom

\textsuperscript{*}Corresponding author. Tel: +86 510 8591 9065; fax: +86 510 8591 9065.

E-mail address: zyhe@jiangnan.edu.cn (He Z.), mark.christian@ntu.ac.uk (M. Christian)
Abstract

Fat browning has piqued the interest of researchers as a potential target for treating obesity and related metabolic disorders. Recruitment of brown adipocytes leads to enhanced energy dissipation and reduced adiposity, thus facilitating the maintenance of metabolic homeostasis. Evidence is increasing to support the crucial roles of polyphenols and gut microecology in turning fat “brown”. However, it is not clear whether the intestinal microecology is involved in polyphenol-mediated regulation of adipose browning, so this concept is worthy of exploration. In this review, we summarise the current knowledge, mostly from studies with murine models, supporting the concept that the effects of food phenolics on brown fat activation and white fat browning can be attributed to their regulatory actions on gut microecology, including microbial community profile, gut metabolites, and gut-derived hormones. Furthermore, the potential underlying pathways involved are also discussed. Basically, understanding gut microecology paves the way to determine the underlying roles and mechanisms of food phenolics in adipose browning.

Keywords: Polyphenols, Gut microecology, Microbiota, Metabolites, Hormones, Adipose browning
1. Introduction

The onset of obesity is attributed to energy intake exceeding energy expenditure, which leads to serious complications, such as diabetes, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), and cancer (Kayser and Verges, 2013; Wang et al. 2021a). The abnormal or excessive fat accumulation driven by overconsumption of a high-calorie diet (rich in sugar and fat) is mainly responsible for the development of obesity (Júnior et al. 2021; Wang et al. 2020). According to its origin and functional and morphological differences, adipose tissue can be categorized into three types: white, brown and beige/brite (‘brown-in-white’) (Figure 1) (Wu, Yu, and Sun 2021). Mounting evidence suggests that the occurrence of the metabolic syndrome is partly attributed to the different roles of white adipose tissue (WAT) and brown adipose tissue (BAT) (Bartelt and Heeren 2014). Classical brown adipocytes contain multilocular lipid droplets and large numbers of mitochondria enriched with uncoupling protein 1 (UCP1), which release energy in the form of heat by uncoupling adenosine triphosphate (ATP) production (Hu et al. 2020). Inducible beige adipocytes occur in WAT upon cold exposure or β-adrenergic signaling, and present similar properties to those of classical brown fat, including multilocular lipid droplets and abundant UCP1, which leads to increased energy expenditure (Wu et al. 2012). Research on links between BAT and obesity has gained increasing attention (Figure 2A). With increasing age, dysfunction of BAT occurs and this is highly correlated to visceral fat accumulation (Yoneshiro et al. 2011). Data from murine models indicates that the elimination of BAT thermogenic capability or WAT browning results in
obesity and insulin resistance (Cohen et al. 2014; Tomilov et al. 2014). Furthermore, BAT transplantation has inhibitory effects on increases in body weight and fat mass and promotes oxygen consumption, eventually ameliorating obesity (Liu et al. 2013). Accordingly, new strategies, such as the recruitment of BAT and the “browning” of white fat, are positioned as prospective treatments for obesity and associated metabolic abnormalities. Importantly, browning/beiging and thermogenesis are processes induced by endogenous factors (e.g., thyroid hormones, catecholamines, peroxisome proliferator-activated receptor (PPAR)γ agonists) (Enerbäck 2010; Ohno et al. 2012), external factors (e.g., cold exposure, intermittent fasting, and physical exercise) (Liu et al. 2019; Peres Valgas da Silva 2019), or pharmacologically (e.g., indomethacin, isoproterenol, l组织开展zagon, sitagliptin and Chinese medicine Jinlida granules) (Hao et al. 2018; Lucchini et al. 2020; Prakash et al. 2020; Zhang et al. 2019). Nevertheless, some of these treatments are either unrealistic (e.g., cold) or cause adverse side effects once doses are supraphysiologica (e.g., thyroid) (Enerbäck 2010). It is encouraging that there is increasing evidence to support that natural phytochemicals, including alkaloids (e.g., berberine, bouchardatine, nicotine, ephedrine) (Horvath et al. 2020), terpenoids (e.g., cordycepin, ginsenoside, fucoxanthin) (Ma et al. 2020), long-chain fatty acids (e.g., n-3 polyunsaturated fatty acids) (Fan et al. 2019), saponins (e.g., platycodin D, ginsenoside Rg1, ginsenoside Rb1) (Fan et al. 2021; Kim et al. 2019), phytosterols (e.g., guggulsterone) (Azhar et al. 2016), and others (e.g., genipin, L-rhamnose, ostreolysin, glucoraphanin, cinnamaldehyde, D-mannitol) also effectively promote adipose browning (Jeon et al. 2019).
2021; Lee et al. 2019; Ma et al. 2020). Among these agents, polyphenols play a particularly significant role in inducing brown fat thermogenesis and the browning of WAT both *in vitro* and *in vivo* (Chen et al. 2021; Hu et al. 2020; Sudhakar et al. 2020). Gut microecology, a pivotal regulator of the host's energy homeostasis, correlates with disorders of glucomlipid metabolism (Xiao and Kang 2020). Recent evidence supports the view that polyphenols can beneficially modulate the gut microbiota profile, alleviate dysbacteriosis, and suppress body weight gain (T. Zou et al. 2020). Moreover, polyphenols also impact gut-derived metabolites and hormones with biological activities beneficial for human health, such as interfering with lipopolysaccharide (LPS) absorption to mitigate systemic inflammation, affecting bile acid (BA) biosynthesis to regulate glycolipid metabolism, stimulating short-chain fatty acid (SCFA) production to control appetite and energy balance, and promoting glucagon-like peptide 1 (GLP-1) secretion to boost insulin release and restore glucose homeostasis (Canfora et al. 2019; Hersoug, Møller and Loft 2016; Vallianou et al. 2019). Interestingly, the intestinal microbiota has been regarded as a novel endogenous system that modulates the activity of BAT and the beiging/browning process of WAT (Moreno-Navarrete and Fernandez-Real 2019). For example, antibiotic-induced depletion of gut microbiota, especially the elimination of SCFA butyrate-producing bacteria, is detrimental to BAT thermogenesis and formation of beige adipocytes, evidenced by downregulated UCP1 expression (Li et al. 2019). The growing evidence from animal and clinical experiments strongly supports the promoting effects of phenolic compounds on brown adipogenesis. However, to the
best of our knowledge, how polyphenols modify brown and beige adipose tissue via the intestinal microbiota, metabolites or gut hormones to influence nonshivering thermogenesis has, to date, not been extensively reviewed. Therefore, we focus on findings reported of the relationship between food phenolics and adipose browning from the perspective of gut microecology and investigate the proposed underlying mechanisms supporting this relationship.

2. Polyphenols induce browning features in adipose tissue in vivo animal and human studies

Whole-body energy expenditure can be boosted by fat thermogenesis and lipolysis driven by BAT activation and/or recruitment of brown-like adipocytes within WAT depots (Wu et al. 2014; Yoneshiro et al. 2011). In view of the physiological importance of fat browning, many efforts have been made to explore strategies to promote brown adipogenesis as possible therapeutic approaches for regulating metabolism and, ultimately, body weight. In recent years, the ability of polyphenols to promote “browning” of BAT and energy expenditure has become a key research focus (Figure 2B). As summarized in Table 1, phenolic compounds derived from fruits, vegetables, tea, herbs, and other food plants, including phenolic acids (hydroxycinnamic and hydroxybenzoic acids) (Hu et al. 2020), flavonoids (flavones, flavonols, flavanones, flavanones, isoflavones, chalcones, flavanols (flavan-3-ols), and anthocyanins) (Mele et al. 2017), stilbenes (Horvath et al. 2020), and lignans (Dong et al. 2021; Duan et al. 2020; Kang et al. 2020), have been consistently found
to be responsible for brown and beige fat enrichment in *in vivo* animal and humans models. Several key regulators of brown cell differentiation, such as PR domain-containing (PRDM) 16, CCAAT enhancer-binding protein α (C/EBPα), PPARγ, and peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) (factors also identified as main targets for WAT transdifferentiation), can be beneficially modulated by food phenolics *via* multiple pathways, including cyclic adenosine monophosphate (cAMP), AMP-activated protein kinase (AMPK), mitogen-activated protein kinases (MAPK), protein kinase A (PKA), β3-adrenergic receptor, and TRP vanilloid 1 (TRPV1)-mediated signals. However, polyphenols are extensively metabolized in the intestine due to their relatively low absorption. Thus, the underlying mechanisms of action of food phenolics in fat browning from the perspective of gut microecology are worthy of exploration.

3. Overview of absorption and metabolism of polyphenols in the intestine

Only 5~10% of total polyphenols, mainly polyphenol aglycones, can be absorbed by the gastrointestinal tract after oral consumption, and the remaining 90~95% of phenolics accumulate in the colon, where they are metabolised and transformed by the gut microbial community (Wang et al. 2021b). As shown in Figure 3, glycoside polyphenols can be hydrolyzed by enzymes located in the intestinal mucosa, leading to the release of their glycoside fraction before absorption. The released diholosides and oligosides can be rapidly fermented to produce SCFAs (Jenner, Rafter, and Halliwell 2005). Furthermore, most polyphenols in conjugated and esterified forms
are dehydroxylated, decarboxylated, and ring-broken by the colon microbiota, resulting in generation of simpler phenolic compounds, such as chlorogenic acid which is converted to dihydroferulic acid and dihydrocaffeic acid (Liu et al. 2020; Zhang et al. 2020). These bacterial metabolites, particularly those with low molecular weights, are easily absorbed by colonocytes, conjugated by liver phase I/II enzymes and then transferred into target tissues/organs, where they exert biological effects before being eliminated in bile or urine (Monagas et al. 2010). Although the mechanisms involved in production of these bacterial metabolites are not entirely understood, research shows that keeping the gut healthy might impact their bioactivity.

Generally speaking, polyphenols and the intestinal microbiota interact with each other. Bifidobacterium and Lactobacillaceae species with high β-glucosidase activity are able to deglycosylate flavonoids; Eggerthella lenta and Adlercreutzia equolifaciens are capable of dehydroxylating flavan-3-ols at the B-ring (Braune and Blaut 2016). Evidence from humans and animal models also demonstrates that food phenolics beneficially modifying the microbiota profile, especially the Firmicutes/Bacteroides ratio (Duarte et al. 2021a).

4. The relationship between gut microecology and fat browning

“Gut microecology” consists of three parts: the gut microbiota, gut epithelium, and mucosal immune system (Lin et al. 2019). There is growing recognition of the involvement of the symbiotic action between the host’s metabolism and gut
microecology and that this relationship plays a role in metabolic health and illness. The intestinal microbes ($10^{14}$ in humans) help to maintain energy homeostasis, and bacterial dysbiosis may cause adipose tissue hypertrophy (Turnbaugh and Gordon 2009). As a vital endocrine organ, the gastrointestinal tract also releases a variety of regulatory peptide hormones that affect a series of physiological processes, including systemic energy metabolism (Melvin, le Roux, and Docherty 2016). Given the protective role of intestinal microecology in energy homeostasis, there is potential for microflora-dependent regulation of BAT biology or white fat browning. Evidence shows that microbiome depletion helps to stimulate the development of beige fat (upregulation of UCP1, cell death-inducing DNA fragmentation factor alpha-like effector A [Cidea], PGC-1α, PPARγ, and fatty acid-binding protein 4 [Fabp4]) and ameliorate obesity in thermoneutral and obese mice (Suárez-Zamorano et al. 2015). However, a study on rodents demonstrated that transplantation of a microbiome into germ-free mice markedly enhanced insulin sensitivity, energy combustion and fat loss in recipient mice by promoting WAT browning and brown adipogenesis (Chevalier et al. 2015). These observations strongly indicate that the changes in intestinal microbes are closely linked to the induction of browning activity. In addition, studies have addressed the key roles of hormones secreted by gut epithelial cells or the gut microbiota, including cholecystokinin (CCK), GLP-1, and ghrelin, on BAT activity and energy dissipation (Hu and Christian 2017). Collectively, it can be concluded that gut microecology regulates browning in adipocytes, which may alter the host response to obesity-associated metabolic dysfunction.
5. Mechanism of adipose tissue browning via food phenolics-dependent modulation of gut microecology

5.1. Gut microbiota

To date, a plethora of convincing evidence from clinical and experimental trials investigating the role of gut microbiota in caloric restriction-metabolic improvement, supports that compositional and functional alterations in gut microbiota are necessary to enhance fat browning and energy expenditure (Li et al. 2019; Mestdagh et al. 2012). Of particular significance, \textit{A. muciniphila}, an intestinal symbiont colonizing the mucosa layer, can function to improve metabolic disorders (obesity, hyperglycemia, and insulin resistance), and its abundance is positively correlated with white fat browning (Schneeberger et al. 2015). The growth of \textit{A. muciniphila} contributes to upregulating expressions of UCP1, Cidea, PGC-1\(\alpha\), PRDM16 and PPAR\(\gamma\) in BAT and diminishing adipocyte size in WAT (Deng et al. 2020). In obese mice, the relative abundance of the genus \textit{Oscillospira} was found to be inversely correlated with BAT weight, and significant positive correlations were observed between the relative abundance of an unclassified genus from \textit{Clostridiaceae} and BAT weight (Xian et al. 2021). Importantly, in a clinical intervention study with obese human subjects, the phylum \textit{Firmicutes}, specifically the \textit{Ruminococcaceae} family, was also shown to be highly associated with the browning of subcutaneous WAT, as confirmed by upregulation of the beige/brown marker PRDM16 (Moreno-Navarrete et al. 2018). Together, these data clearly imply that a particular type or group of bacteria closely correlates with body energy expenditure, regulating the thermogenic process in fat
depots.

Since phenolic chemicals possess poor bioavailability, the metabolic impacts of polyphenol-rich matrices appear to be caused by changes in gut microbiota composition and activity (Duarte et al. 2021a). Recent evidence, primarily from investigations in animal models, indicates that frequent consumption of food phenolics leads to thermogenesis and browning of adipocytes by modulating the gut microbiome (Table 2). Pro-thermogenic properties of tea polyphenols have been reported in diet-induced obese mice. The growth of *A. muciniphila* and *F. prausnitzii* was responsible for the enhancement of lipid oxidation and WAT browning (Gao et al. 2018). Furthermore, supplementation with blueberry polyphenol extracts (219.24mg/g of anthocyanins, 161.8mg/g of proanthocyanidins, 77.91 mg/g of phenolic acids, and 101.88 mg/g of flavanols) for 8 weeks lowered fat storage and promote the activation of BAT and browning of inguinal WAT (iWAT) (J. Guo et al. 2019). Mechanistic analysis reveals that overexpression of UCP1 and PGC-1α mRNA in BAT may correlate with the higher abundance of *Bifidobacteria* and *Lactobacillus* (J. Guo et al. 2019). Of particular note, a study using microbiota transplanted from 0.4% resveratrol-treated HFD fed mice into recipient mice demonstrated that resveratrol fecal transplants mitigated fat accumulation and induced the browning of WAT involving alterations of the gut microbiota profile (Liao et al. 2018). A decrease in the *Firmicutes/Bacteroidetes* ratio and *Proteobacteria* abundance might be the triggering factor for emergence of brown adipocytes in WAT (Liao et al. 2018). Consistent with these findings, fecal transplants of nobiletin-treated mice also upregulated factors
involved in thermogenesis and mitochondrial biogenesis, including UCP1, PRDM16, Cidea, mitochondria transcription factor A [Tfam], and nuclear respiratory factor 1 [NRF1]), in BAT and iWAT of HFD-fed recipient mice (Kou et al. 2021). Thus, evidence from a range of studies supports the beneficial effects of food phenolics on fat browning may be due, at least in part, to the regulatory actions of gut bacteria. However, a noteworthy point is that identifying whether intestinal flora involved in polyphenol regulatory BAT activity is relevant in specific disease models, as Ahmed et al. (2021) argues that BAT activity is independent of intestinal flora in a NAFLD mouse model. Additionally, humans have important differences in intestinal microbial communities and relatively low expression of brown/beige adipose markers compared to laboratory mice. Therefore, further clinical studies to validate this finding is warranted. Importantly, it is still uncertain whether the microbiota itself or its metabolites leads to brown-promoting effect, so in-depth studies are required.

5.2. Gut-derived metabolites

Gut metabolites serve a vital role in the physiology and pathophysiology of metabolic abnormalities. These metabolites described below, particularly LPS, BAs, SCFAs, unsaturated fatty acids (UFAs), branched-chain amino acids (BCAAs), trimethylamine N-oxide (TMAO), and their host receptors, possibly in combination with dietary polyphenols, are implicated in BAT activity and mitochondrial function, which may provide promising targets for obesity treatment.

5.2.1. Lipopolysaccharide

LPS is a major part of the gram-negative bacterial outer membrane (e.g.,
Bacteroidetes and E.coli) that facilitates the secretion of inflammatory cytokines by binding to toll-like receptors (TLRs) (Funakoshi-Tago et al. 2020). Dysbiosis of intestinal flora, especially the imbalance in A. muciniphila, F. prausnitzii, Bifidobacterium, and lactobacillus (Liu et al. 2017), leads to the production of bacteria-derived pathogens (e.g., LPS) accompanied with an inflammatory response, such as increase in interleukin [IL]-1β, IL-6, tumor necrosis factor-α [TNF-α], and monocyte chemotactic protein 1 [MCP1] levels (Corrêa et al. 2019). In an in vitro cell model, the impairment of UCP1 in brown/beige adipocytes by stimulation with LPS, IL-1β, or TNF-α has also been shown (Nøhr et al. 2017; Valladares et al. 2001). Furthermore, the genetic deletion of TLR4 contributes to beige cell differentiation and protection on mitochondrial function in LPS-induced adipocytes (Okla et al. 2018).

Importantly, in animal experiments, it was found that TLR4 stimulation by HFD or LPS were both associated with diminished body temperature and impaired thermogenesis in correlation with decreased expression of brown-specific markers in subcutaneous WAT (sWAT) (Bae et al. 2014). The elevated expression of proinflammatory cytokines/chemokines (e.g., MCP-1, IL-6, TNF-α, and RANTES) following TLR4 activation inhibits mitochondrial respiration and downregulates UCP1 expression. Therefore, the LPS-TLR4 axis may be an important pathway involved in beige fat formation regulated by polyphenols.

Based on currently available data, polyphenol monomers and phenolic-rich extracts function as modulator of gut microorganisms that may be related to gastrointestinal immunity and defence against inflammation (Martín and Ramos 2021).
improvement of gut flora composition induced by polyphenols can attenuate the LPS-induced inflammatory response to improve adipocyte browning and obesity (Corrêa et al. 2019; Seo et al. 2021). Interestingly, research has provided evidence that LPS-TLR4 signaling-induced reduction of thermogenic genes (e.g., UCP1) in sWAT of mice can be reversed by resveratrol, but in interscapular BAT (iBAT), the TLR4 signal is not involved in this process (Nøhr et al. 2017). This may be indicative of a greater inflammatory response in WAT compared to BAT (Dowal et al. 2017). Evidence to strengthen this concept comes from the elegant study by Neyrinck et al. (2017), in which the authors highlighted that epigallocatechin-3-gallate (EGCG)-rich green tea extracts diminished production of inflammatory cytokines (e.g., IL-1β, Mcp1) in the sWAT but not in BAT, which may contribute to browning process of WAT (Neyrinck et al. 2017). A similar phenomenon has been also observed in HFD-induced mice in which oral administration of polyphenol-rich green tea extract facilitated brown adipogenic and thermogenic markers in epididymal WAT (eWAT) via activation of the Sirt1/AMPK/PGC1α/PPARα pathway by inhibiting TLR4/TNF-α mediated miR-335 signaling (Otton et al. 2018). A recent report found that overexpression of cyclooxygenase (COX)2/prostaglandin (PG)E2 in IL-1β-treated primary human adipocytes by apigenin can induce cAMP signaling and subsequent upregulation of p-CREB, thereby, activating browning (Okla et al. 2020). These observations provide strong evidence for cross-talk between pro-inflammatory agents and white adipocytes, which may be an important target for the brown-promoting property of polyphenols. Strikingly, consumption of jussara fruit, which is rich in
phenolics (415.1 mg/100 g), augmented the level of the anti-inflammatory cytokine IL-10, thus driving beige adipogenesis, accompanied by an increase in energy expenditure (Argentato et al. 2017). Collectively, different studies point to a relevant role of LPS-associated signaling on the WAT browning process, demonstrating that the inhibition of the LPS-TLR4 axis by polyphenols and important mediators of this pathway have positive effects. Figure 4 shows the possible mechanism of the action of dietary polyphenols in promoting white fat browning via ameliorating dysbacteriosis and associated inflammatory signals.

5.2.2. Short chain fatty acids

There is broad agreement that microbial metabolites, particularly SCFAs, may serve an essential role in the cross-talk between the intestinal microflora and target organs (Wu et al. 2019; Zhang et al. 2021). Acetate, propionate and butyrate, as the major SCFAs present in serum and the cecum, have numerous benefits for metabolic health, including inducing WAT browning and activating BAT thermogenesis. Higher levels of acetate, propionate, and butyrate are accompanied by upregulated expression of UCP1 (Li et al. 2019). Investigations of acetate (1.0 mM)-stimulated 3T3-L1 cells and acetate (0.6%)-treated KK-Ay mice support this SCFA elevating the expression of brown/beige markers, including UCP1, PRDM16, PPARα, Dio2, and Cidea (Hanatani et al. 2016). Furthermore, a recent study conducted on obese humans revealed that acetate biosynthesis was mainly derived from the Ruminococcaceae family and that augmented plasma acetate levels led to overexpression of PRDM16 in subcutaneous WAT (Moreno-Navarrete et al. 2018). The likely mechanism of the action of acetate in
adipose tissue browning involves its activation of G protein-coupled receptor 43 (GPR43) (Hu et al. 2016). A previous study that monitored $^{13}$C-butyrate metabolic flux analysis observed faster uptake and utilization of butyrate by the brain than in BAT and WAT after entering the circulation (Li et al. 2019). This indicates that the brain is an important mediator of the effects of butyrate on BAT thermogenesis and WAT browning. Actually, the gut-brain neural circuit, that is, vagal nerve signaling, is considered the key pathway for butyrate-induced BAT activation, as shown by the increased thermogenic capacity (UCP1 upregulation) and sympathetic outflow towards BAT (Li et al. 2018). With regard to propionate, it may elicit sympathetic nervous system activity via GPR41, which is associated with energy expenditure, providing indirect evidence for its role in adaptive thermogenic capability (Kimura et al. 2011).

Polyphenols may be metabolised by the intestinal microbiota and further transformed into small-molecule metabolites such as organic acids (lactate, succinate, pyruvate, butyrate, and acetate). Flavonoid-degrading bacteria, such as *E. ramulus* and *Flavonifractor plautii*, can decompose phloroglucinol into SCFAs (Braune and Blaut 2016). As polyphenols also lead to beneficial changes in SCFA-producing microbiota (e.g., *Lactobacillus, A. muciniphila*, and *Blautia*) (Wang et al. 2021b), it is worthwhile investigating whether these compounds improve BAT activity and function associated with SCFA production. Growing evidence indicates that frequent consumption of resveratrol promotes energy expenditure and combats obesity by promoting BAT activity and beige adipogenesis, which are involved in the activation of
AMPK/Sirt1/PGC-1α signaling via the gut microbiota (SCFA)-adipose tissue axis (Zhou et al. 2019). Of interest, capsaicin (a polyphenolic compound with an alkaloid structure) promoted the expression of genes associated with mitochondrial biogenesis and thermogenesis in sWAT, including UCP1, Cidea, and PGC-1α, and the increased abundance of *A. muciniphila* and acetate production may be important for its mechanism of inducing browning (Baboota et al. 2014; S. Wang et al. 2019). Microbiota-generated acetate is regarded as the important factor for nobiletin-induced thermogenesis and BAT activation in HFD-fed mice by activating GPR43 (Kou et al. 2021). Based on the information above, polyphenols may stimulate SCFAs production to regulate transcription factors associated with adipogenesis and mitochondrial biogenesis in BAT through GPR41/43 signaling, vagal nerve signaling or their combination (Figure 5). However, it is difficult to establish to what degree the adaptive thermogenesis identified in different models of polyphenols supplementation may be ascribed specifically to the release of SCFAs. Nonetheless, the relationship between SCFAs and thermogenic potential (both by BAT recruitment and WAT browning) is evident. Consequently, regulating the composition of SCFAs by dietary phenolics is an intriguing physiological way to influence energy metabolism, particularly adaptive thermogenesis.

### 5.2.3. Bile acids

BAs are first produced by the liver and then reach the intestine through the portal vein, where they are transformed into secondary BAs by gut microbiota. There is evidence that *Bacteroides*, which has higher abundance in the intestine, can convert primary
BA chenodeoxycholic acid (CDCA)/ursodeoxycholic acid (UDCA) to secondary BA lithocholic acid (LCA), and primary BA cholic acid (CA) to secondary BA deoxycholic acid (DCA) via bacterial 7α/β-dehydroxylase activity (Hirano and Masuda 1982; Ishii et al. 2014). Moreover, the levels of primary/secondary BAs, including CDCA, LCA, α/β muricholic acid (MCA), and allocholic acid (ACA) are considered to be negatively correlated with bacterial phylum *Firmicutes* (Hui et al. 2020). Intriguingly, supplementation with BAs, for example CDCA and LCA, is reported to promote mitochondrial uncoupling in brown adipocytes and increase BAT activity by acting at the BA receptor Takeda G-protein coupled receptor 5 (TGR5) in mice and humans (Broeders et al. 2015; Moreno-Navarrete and Fernandez-Real 2019; Teodoro et al. 2014). The activation of TGR5 induces the overexpression of type 2 iodothyronine selenodeiodinase (D2), thereby stimulating thermogenesis-related markers such as PRDM16 and UCP1 (Broeders et al. 2015; Han et al. 2020a).

In this way, the beneficial effects of food phenolics on brown and thermogenic markers in WAT or/and BAT are proposed to correlate with alteration of the BA pool size (Anhê et al. 2019; Kirkwood et al. 2013). A recent study by Kuang and collaborators showed the bioactive compound theabrownin induces gut microbiota to produce non-12OH-BA (taurochenodeoxycholic acid [TCDCA], tauroursodeoxycholic acid [TUDCA]), resulting in improved energy metabolism in WAT and BAT (Kuang et al. 2020). Notably, the changes in BA promotes TGR5 expression in BAT. It has been shown that grape extract activates brown fat *via* mechanisms associated with alteration of BA and gut microbiota, implicating BA and
TGR5 signaling in the actions of grape polyphenols to promote thermogenesis (Han et al. 2020a). The overexpression of PPARγ, UCP1 and PGC-1α in iBAT was reported following administration of a chokeberry extract. This effect may be attributed to the decreased levels of CA and DCA and the elevated CDCA content regulated by Bacteroides, Prevotella, Clostridium, Eubacterium, and Ruminococcaceae via activation of the TGR-5 signaling pathway (Zhu et al. 2020). Additionally, one of the potential mechanism of the brown-promoting effects of resveratrol or curcumin was confirmed to be due to its regulation of LCA-TGR5 signaling mediated by gut microbiota remodeling (i.e., Firmicutes, Bacteroidaceae, Bacteroides, or Akkermansia) (Z. Han et al. 2021; Hui et al. 2020). Collectively, food phenolics may contribute to the activation of BAT, in part, via BA-TGR5 signaling (Figure 6). However, it is important to note that food phenolics also improve obesity through farnesoid X receptor (FXR) pathway-modulated BA metabolism (J. Guo et al. 2019). Activation of the BA sensor FXR has been shown to reduce weight gain, systemic inflammation and glucose production, and stimulate thermogenesis and WAT browning (Fang et al. 2015). Hence, whether polyphenols promote fat browning by acting on the BA sensor FXR is worthy of specific investigation. Importantly, because of the substantive variations in murine and human BA structure, BA-related metabolic alterations identified in mice models so far do not mirror equivalent changes in BA profiles in humans. In this sense, human trials and large prospective cohorts are crucial to establish a positive association between polyphenols and BA and their beneficial effects on BAT at different levels.
5.2.4. Unsaturated fatty acids

Gut bacteria are also responsible for the production of UFAs, such as linoleic acid (Devillard et al. 2007). Negative correlations have been found between some gut bacterial metabolites (especially trans monounsaturated fatty acids and conjugated linoleic acid) and blood lipid levels, indicating the possible fat-lowering effects of UFAs (Druart et al. 2014). Use of patch-clamp technology confirms that unsaturated long-chain fatty acids (LCFAs) may serve as a physiological mechanism of UCP1 regulation (Fedorenko, Lishko, and Kirichok 2012). For example, conjugated linoleic acid (CLA) increased multiple markers of WAT browning and mitochondrial respiration in mice, including UCP1, elongation of very long-chain fatty acids 3 protein (ElovL3), Cidea, cytochrome c oxidase subunit VIII b (Cox8b), carnitine palmitoyltransferase (CPT) 1β, and PPARα (Shen et al. 2013). In humans, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) concentrations are also positively associated with BAT activity determined through PET/CT imaging (Xiang et al. 2020). The antiobesity effects of 10-oxo-12(Z)-octadecenoic acid (a linoleic acid metabolite produced by gut lactic acid bacteria) were considered to be due to upregulated UCP1 expression in BAT and iWAT via activation of transient receptor potential vanilloid 1 (TRPV1) (M. Kim et al. 2017). Consequently, UFAs play an essential role in BAT and mitochondrial activities, and the intestine-derived UFAs pathway may be an important route for the regulation of fat browning by polyphenols. Currently, there is broad agreement that food phenolics, including green tea polyphenols (Wang et al. 2016), flavan-3-ol enriched grape seed extract (Tabasco
et al. 2011), facilitate the growth of lactic acid bacteria, which may contribute to the production of UFAs. Evidence has emerged that ginseng extract containing phenolics (248.47~2820.69 μg/g) can induce *Enterococcus faecalis* to produce myristoleic acid (an unsaturated LCFA) by overexpressing the *E. faecalis* gene encoding acyl-CoA thioesterase (ACOT). Both *E. faecalis* and its metabolite myristoleic acid are considered important components of ginseng extract that can mitigate adiposity by activating BAT and potentiate beiging of WAT (Quan et al. 2020).

### 5.2.5. Branched-chain amino acids

BCAAs can be biosynthesized by intestinal bacteria and have the capacity to negatively impact metabolic health. For instance, *Bacteroides* spp. improve efficiency of BCAAs generation, and higher circulating levels of BCAAs trigger the progression of obesity and type 2 diabetes mellitus (Cardona et al. 2013; Lin et al. 2017). Yoneshiro et al. (2019) documented the role of BCAAs as fuel for BAT thermogenesis. As one of the major BCAAs (leucine, isoleucine, and valine), deprivation of leucine reduces fat mass by facilitating lipolysis in WAT and upregulating UCP1 in BAT (Cheng et al. 2010). Additionally, isoleucine or valine elimination leads to fat loss by enhancing PGC-1α and UCP1 expression in BAT, thus burning energy (Du et al. 2011). Recent studies have pointed to a promising link between food phenolics and mitigating obesity-related insulin resistance, which may be attributed to altered BCAA degradation via modulating gut microbial functions (Anhê et al. 2015). Promisingly, citrus polymethoxyflavones (a complex of sinensetin, nobiletin, hepamethoxyflavone, and tangeretin) reduce adipose deposition and the cell size of
both WAT and BAT (Zeng et al. 2020). A possible mechanism that could explain this phenomenon is that polymethoxyflavones can modulate thermogenesis through regulating the gut microbiome (*B. vulgatus*) and BCAAs (isoleucine, leucine, valine, phenylalanine, tyrosine, and serine) metabolism. It is noteworthy that berberine (a polyphenolic compound and a plant alkaloid) supplementation alleviates obesity by reducing the abundance of BCAA-producing bacteria, including members of the order *Clostridiales*; families *Streptococcaceae*, *Clostridiaceae*, and *Prevotellaceae*; and genera *Streptococcus* and *Prevotella*, and the level of circulating BCAAs (valine, leucine, isoleucine); meanwhile, it also induces WAT browning and BAT activation, which provide a robust defense against obesity (Yue et al. 2019; Zhang et al. 2014). The fat browning induced by berberine treatment may be associated with decreased levels of circulating BCAAs, but further investigation is needed.

### 5.2.6. Trimethylamine N-oxide

TMAO, which is derived from gut microbiota metabolites, is a new potential therapeutic target for diabetes and obesity (Simó and García-Cañas 2020; Wu et al. 2020). *Enterococcus* were found to have a positive correlation with TMAO, while *Candidatus stoquefichus* showed the opposite effect (Simó and García-Cañas 2020). The changes in gut-derived TMAO may be involved in the regulation of WAT browning and BAT activity (Xiao and Kang 2020). A study confirmed that the TMAO signal along the microbe-to-host endocrine axis communicates with adipose tissue, as genetic knockdown of the TMAO-producing enzyme flavin-containing monooxygenase 3 (FMO3) stimulated adipocyte beiging and alleviated obesity
(Schugar et al. 2017). Studies on the regulation of lipid metabolism by microbial metabolites in traditional Chinese medicine found that natural herbal extracts and their active compounds, including polyphenols which reportedly control energy homeostasis in brown fat, may act in part by decreasing synthesis of gut-derived TMAO (Li et al. 2021). A example is that resveratrol can attenuate the production of TMAO by remodeling the gut microbiota (Chen et al. 2016), which may enhance BAT activity and WAT browning (Hui et al. 2020). Given the beneficial regulatory effects of polyphenols on the intestinal flora, inhibition of TMAO production by food phenolics may be helpful for fat browning; however, direct evidence is still lacking.

5.3. Gut-derived hormones

Enteroendocrine cells from the gut epithelium can secrete over 20 hormones depending on food intake and nutrient status (Sun et al. 2019). These hormones not only transmit signals from the gut to the brain but also act directly on metabolically vital peripheral targets in a highly coordinated manner to sustain energy homeostasis and induce brown/brite adipose development (Sun et al. 2019). Thus, the possibility that polyphenols regulate fat browning by modulating gut-derived hormones may exist.

5.3.1. GLP-1 and CCK and PYY

GLP-1 is secreted by intestinal L cells upon food intake and functions as a facilitator of energy expenditure and weight loss (Heppner et al. 2015). In this regard, it has been reported that administration of GLP-1 into the dorsomedial hypothalamus can
activate BAT thermogenesis and promote adipocyte browning to reduce adiposity (Lee et al. 2018). The promising effects of GLP-1 on fat browning may be attributed to the elevated firing of sympathetic nerves into the BAT depot by binding to GLP receptor (GLP-1R). In agreement with the findings of this study, intestinal GLP-1 has been shown to regulate energy expenditure and BAT thermogenesis through gut-brain-BAT communication involving vagal afferent neuron GLP-1R signaling (Krieger et al. 2018).

Intriguingly, basic research on traditional Chinese medicine in the treatment of obesity suggests phenolic extracts augment the secretion of GLP-1 by endocrine cells and thereby promote brown markers in WAT to stimulate thermogenesis through GLP-1-induced activation of AMPK pathway (Li, Zhang, and Li. 2020). Investigation from rodents has also demonstrated that the flavonoid eriodictyol can exert beneficial effects on ameliorating adiposity, as manifested by upregulated expression of fatty acid oxidation-related genes (UCP1, adrenoreceptor β3 [ADRB3], CPT1β and PGC-1α) in eWAT, which is accompanied by an augment level of circulating GLP-1 (Kwon and Choi 2019).

Furthermore, CCK is a peptide hormone that is expressed by intestinal endocrine cells (termed I cells) in response to intraluminal nutrients (Raybould 2007). Available evidence supports the importance of this vagal signaling in BAT thermogenesis, which can be attributed to the central effects of CCK (Blouet and Schwartz 2012; Yoshimatsu, Egawa, and Bray 1992). An earlier study showed that intravenous administration of CCK (0.5 μg/kg) could augment energy metabolism and BAT
thermogenesis via the vagus nerve (Madden 2013). Nutrient sensing in the gut may initiate CCK secretion via activation of the CCK receptor on vagal afferents to contribute to thermogenesis in BAT (Yamazaki et al. 2019). Importantly, CCK secretion from enteroendocrine cells can be stimulated by aster pseudoglehni extract (polyphenol content: 78.66 mg/g), which mainly contains chlorogenic acid (16.13 mg/g) and kaempferol (30.69 mg/g) (H. Kim et al. 2017). CCK upregulation may be responsible for energy expenditure and fat browning following oral administration of capsaicin and its activation of hypothalamic or gastrointestinal TRPV1, inducing a “browning” genotype in sWAT and triggering the expression of thermogenesis- and mitochondrial biogenesis-related genes in BAT (Baboota et al. 2014). However, it is still unclear whether CCK has a role in the brown-promoting effect of polyphenols. For further validation, the Otsuka Long Evans Tokushima Fatty (OLETF) rat is an ideal in vivo model to study the role of CCK on BAT activity due to its lack of a functional CCK1 receptor.

Equally important, peptide YY (PYY) is secreted primarily from L-cells within mucosa of the ileum and large intestine (Ueno et al. 2008). Release of the hormone is also affected by the intestinal microbiota (Holzer, Reichmann, and Farzi 2012). By univariate analysis, BAT volume was found to be correlated with a high level of PYY (Chondronikola et al. 2017). PYY deficiency may have an inhibitory effect on BAT activity (Van den Beukel and Greffhorst 2014). The beneficial effects of food phenolics on BAT are linked to stimulating SCFA generation and modulating BA metabolism (Liu et al. 2020). To a certain extent, SCFAs (butyrate, propionate, acetate)
can stimulate PYY secretion (Lin et al. 2012; Psichas et al. 2015). Additionally, BAs (DCA, taurocholic acid [TCA]), have been shown to stimulate PYY secretion from L-cells via G protein-coupled bile acid receptor 1 (GPBAR1) (Ullmer et al. 2013). It is therefore tempting to speculate that polyphenols reduce body weight and promote brown adipogenesis via PYY stimulation by SCFA and BA pathways. Indeed, capsaicin (chili pepper) promotes thermogenic fat activation by targeting the brown specific markers like PRDM16, PGC-1α, and UCP1, which may be associated with the upregulation of PYY and its receptor PYY-Y2 in the colon (Li, Zhang, and Li 2020). In line with the findings of this study, capsaicin supplementation induced PYY expression via activation of the gastrointestinal TRPV-nerve axis, which serves to stimulate thermogenesis both in WAT and BAT (Baboota et al. 2014). The capsaicin compound is a subclass of polyphenolic amides and whether its regulatory effect on PYY is due to its phenolic or alkaline structure is not known. Therefore other types of polyphenols without alkaline structure should be investigated.

To conclude, it seems that food phenolics induce BAT activity by modulating GLP-1, CCK and PYY signaling. A possible pathway is proposed, as shown in Figure 7, based on the abovementioned evidence. Unfortunately, most of these benefits have been reported in research employing cells in vitro and mice/rats in vivo, with very little comparable data in people. One of the explanations for this large gap might be associated with the limited approaches employed to measure human BAT.

5.3.2. Ghrelin

Ghrelin is generated by endocrine cells in the gastrointestinal tract; its levels are
strongly correlated with the abundance of *Clostridium* and *Ruminococcus* and in contrast negatively correlated with SCFAs, *Bacteroidetes/Firmicutes* ratio and *Faecalibacterium* (Schalla and Stengel 2020). Ghrelin is considered to be the endogenous ligand for the growth hormone secretagogue receptor (GHS-R) and plays crucial roles in energy storage by modifying BAT function and locomotor activity (Mano-Otagiri et al. 2010). In an *in vitro* cell model, ghrelin was found to downregulate thermogenic genes, whereas a GHS-R antagonist reversed ghrelin’s effect and potentiated UCP1 expression (Lin et al. 2011). Data from a rodent model indicates that central administration of ghrelin to the third cerebral ventricle of Sprague-Dawley rats can alleviate energy consumption and thermogenesis in BAT via its inhibitory effect on BAT sympathetic nerve activity (Yasuda et al. 2003). A recent report on capsaicin revealed that polyphenols could increase browning markers (UCP1, PGC-1α, brain-derived neurotrophic factor [BDNF], and PPARα) in BAT and WAT and was, at least partially, mediated by the inactivation of ghrelin and GHS-R (Baboota et al. 2014). In parallel, combinational treatment of Hibiscus and Lemon verbena polyphenols reduced adipose fat mass and triggered energy expenditure in overweight subjects partly via decreasing the level of ghrelin hormone (Boix Castejón et al. 2018). Two possible mechanisms of this effect involve: 1) ghrelin directly suppressing noradrenaline release in BAT and 2) ghrelin acting on the sympathetic nerve activity innervating BAT. However, the specific pathways involved in the regulation of ghrelin by polyphenols remains unclear and therefore requires further confirmation.
5.3.3. Glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide (GIP) is synthesized by K cells in the duodenum and jejunum mucosa; its receptor has been detected both in WAT and BAT (Beaudry et al. 2019; Usdin et al. 1993). The secretion of GIP can be affected by gut microbiota species and their metabolites (SCFAs and BAs) (Cani, Everard, and Duparc 2013). Data emerging from human studies support an adipogenic role for GIP in white fat (Thondam, Cuthbertson, and Wilding 2020). In HFD-fed mice and brown pre-adipocyte cells, GIP deletion can upregulate mitochondrial and thermogenic gene expression, indicating that it regulates BAT function (Beaudry et al. 2019). Mounting evidence supports that food phenolics exert lipid- and glucose-lowering activity attributed to their action to reduce GIP levels (Bahadoran, Mirmiran, and Azizi 2013; Castro-Acosta et al. 2017). Notably, polyphenol-rich extract from omija fruit was able to impede the white fat gain by inducing the upregulation of brown-specific markers, which is partly due to decreased level of the incretin hormone GIP (Park et al. 2017).

Studies on rodents fed HFD have shown that anthocyanidins cyanidin and delphinidin (40 mg/kg/day) supplementation, possibly via alleviating the GIP signal, promote adipose browning, confirmed as reduced weight of BAT and WAT (Daveri et al. 2018).

5.3.4. Leptin

Leptin is produced predominantly by adipose tissues, but also present in the intestine (Attele, Shi, and Yuan 2002). The gut microbiota is also considered to affect levels of leptin hormone (Yao et al. 2020). Leptin signaling regulates sympathetic innervation
of adipose tissue (WAT and BAT) that is vital for energy homeostasis (Commins et al. 1999). As experimentally observed, intravenous leptin triggers a beige phenotype in subcutaneous adipocytes through the upregulation brown-specific genes (e.g., PRDM16 and UCP1) (Rodríguez et al. 2015). A similar phenomenon was also shown in an animal study via gut microbiota-mediated leptin/STAT3 signaling (Xu et al. 2020). One of potential mechanisms behind the green tea extract-induced weight loss and adipose browning appears to be related to improved leptin sensitivity in white fat (Neyrinck et al. 2017). Likewise, resveratrol and its metabolites (phase II and microbiota) attenuated eWAT mass by upregulating fatty-acid β-oxidation-related genes (e.g., PPARα and CPT1β) via leptin-STAT3 signaling (Ardid-Ruiz et al. 2018).

In addition, a 4-week clinical trial with extra virgin olive oil resulted in elevated leptin concentration in lean participants and therefore enhanced BAT activity (Melguizo Rodríguez et al. 2020), where the presence of phenolic acids and flavonoids is essential in this process (Monfort-Pires et al. 2020). Thus, polyphenols may recruit beige adipocytes through modulating leptin signaling. However, it remains unclear whether gut-derived or adipose-derived leptin signaling is involved in the browning process.

5.3.5. Secretin

The gut hormone secretin (SCT) is considered a non-adrenergic activator of brown fat and an inducer of thermogenesis (Schnbl, Li, and Klingenspor 2020). FDG-PET/CT scans following secretin infusion revealed direct evidence for its thermogenic action on BAT, with substantially enhanced fluorodeoxyglucose (FDG) uptake in human
supraclavicular BAT (Saito et al. 2020). The increase in circulating SCT-activated BAT thermogenesis is a consequence of binding to SCT receptor in brown adipocytes (Li et al. 2018). There is a high association between curcumin intake and UCP1 expression in BAT (Song et al. 2018). Furthermore, curcumin also exerts protective effects on the gastrointestinal tract, for example, by facilitating SCT secretion and improving mitochondrial metabolic activity (Ansari 2015; Septembre-Malaterre et al. 2016). Correspondingly, the SCT pathway may be a key component for curcumin-dependent activation of BAT. In lean and obese volunteers, the release of endogenous secretin induced by extra virgin olive oil was closely related to incremental BAT activity, and this beneficial effect may be due, in part, to the polyphenols in olive oil (Melguizo Rodríguez et al. 2020; Monfort-Pires et al. 2020).

6. Safety issues

The average daily polyphenol intake of an adult is estimated at 283~1000 mg in Europe, 240~350 mg in America, 50~1500 mg in East Asia, and 534 mg in Brazil, respectively (Chiva-Blanch and Badimon 2017). Polyphenols are often marketed as dietary supplements in the United States, and are only minimally limited, allowing for a larger range of health claims (Cory et al. 2018). Accumulating research, mostly from murine trials supports the promising effects of phenolic consumption on BAT activation. However, incremental energy metabolic rate by BAT activation requires more oxygen, and thus may cause side effects on other tissues of the body. Hence, consideration of the safe intake amount of foodphenolics is especially important.
Animal studies have reported that daily intake of 5% apple polyphenols (80% total phenolics and 5% phloridizine) (Mizunoya et al. 2015; Tamura et al. 2020), or 20% polyphenol-rich mulberry leaves can induce beige/brown adipocyte formation with mitochondrial thermogenesis, and no damage to internal organs (e.g., liver and kidney) was observed at this concentration (Sheng et al. 2019). The consumption of a resveratrol supplement enhances BAT activity and improves gut microflora without any adverse reactions found in animal and humans studies, indicating its beneficial effects and safe use (Cottart et al. 2010; Park and Pezzuto 2015). Green tea is popular among East Asians, particularly the Chinese and Japanese, and is consumed on a daily basis.

Clinical studies have shown the safety of green tea (capsule containing 90 mg EGCG) consumption and its aid in weight loss by sympathetic activation of thermogenesis and fat oxidation (Dulloo et al. 1999). Nevertheless, at this high dose (about 2.5 g of green tea extract), some adverse effects can occur such as hepatotoxicity, stomachache, insomnia and palpitations, which may be attributed to the oxidative stress incurred by caffeine and its metabolites (Cory et al. 2018; Shin et al. 2018). Likewise, in BALB/c mice, capsaicin or chilli extract was demonstrated as a potential promoter of stomach and liver carcinogenesis (Agarwal et al. 1986), although clinically beneficial for gut microbiota and BAT density (Zheng et al. 2017), so the appropriate dosage of chilli intake is essential. Collectively, in terms of browning-promoting effects, polyphenols at the safe and beneficial level added to foods for human consumption remain to be elucidated in more detail.
7. Conclusion and perspectives

Dissipation of energy through stimulating the recruitment and activation of brown/beige adipocytes is a promising strategy for treating obesity and associated metabolic diseases. A close relationship exists between food phenolics and non-shivering thermogenesis, as confirmed by boosted white fat browning and activated BAT. Alteration of microbial community structure, production of specific metabolites and hormones in the intestine by polyphenol intervention influences adipose tissue thermogenesis, modulates white-to-brown adipose tissue conversion and BAT activity, and eventually results in improvements in obesity-related metabolic diseases.

However, there are still some issues that need to be addressed. These issues include differences in intestinal microbes and metabolic enzymes that impact how and to what extent polyphenols effectively target adipose tissues (WAT and BAT). Secondly, it is necessary to clarify whether the bacterial structure itself, the metabolites produced by bacteria or their synergy upon polyphenol treatment are responsible for the brown-promoting effect. For example, *A. muciniphila* is reported to function in the activation of BAT, but pasteurized *A. muciniphila* does not modulate sWAT beiging or BAT function (Deng et al. 2020; Depommier et al. 2020). Thirdly, different subjects can possess different abilities to metabolize certain polyphenols, such as daidzein, catechins, and urolithins, due to interindividual variations in their microbiota profiles, which influence their bioactivity and bioavailability for brown-promoting ability. The different “metabotypes” need to be further specified according to their ability to
produce specific bioactive metabolites. In the intestine, polyphenols may undergo diverse intestinal transformations, e.g., structural conversion into simple phenols and phenolic and aromatic acids; thus, the metabolites may determine the biological efficacy of polyphenols (Esteban-Fernández et al. 2018). Anthocyanins have been shown to possess strong anti-obesity properties; they are not directly absorbed but are metabolized by intestinal microbes. Vanillic acid is one of the main metabolites of anthocyanins produced by microorganisms and can activate and recruit BAT and promote mitochondria- and thermogenesis-related factors in primary cultured brown adipocytes (Faria et al. 2014; Jung et al. 2018). Urolithin A, a gut microflora-derived metabolite of ellagic acid and ellagitannins is considered to enhance energy expenditure and thermogenesis both in vitro and in vivo because of its promotion of brown adipocytes (Manigandan and Yun 2020; Xia et al. 2020). Thus, the beneficial effects of ellagic acid are most likely due to the phenolic transformations performed in the gastrointestinal mainly via the action of gut bacteria rather than due to the original forms found in food. Moreover, although polyphenols modulate gut hormones to stimulate/inhibit BAT activity, the specific mechanisms (a central mechanism, a direct mechanism or both mechanisms) by which hormones modulate BAT are still largely unknown.

It is noteworthy that animal experiments are conducted in inbred lines with nearly identical genetic backgrounds, whereas in human subjects, interindividual discrepancies are more pronounced. These discrepancies are intensified by different study designs (duration, dose, ethnicity, formulation, etc.), which may lead to the
large variability found in fat browning among human studies. Another significant consideration is the relatively low expression of BAT markers in humans, suggesting that WAT browning in humans may be less relevant than that in mice. Thus, whether the effects of polyphenol-induced weight loss are positively related to the expression of brown/beige-related factors in humans remains to be fully elucidated. Also, sex as an important biological variable adds extra complexity to the interpretation of results. Therefore, for the study of isoflavones in fat browning, attention needs to be paid to the selection of animals (female>male) due to the estrogenic potential of these compounds. Of note, two gastrointestinal hormones, of which pancreatic polypeptides (PPs) are present in the colon and rectum at certain quantities (Holzer et al. 2012). Research on rodents addressing the effect of PP on BAT indicates that peripherally administered PP enhances the function of sympathetic nerves that innervate the BAT depot (Asakawa et al. 2003). Serotonin (5-hydroxytryptamine, 5-HT) is also expressed in duodenum, where it has as a crucial role in the energy balance (Yu et al. 2019). Recent studies highlight that serotonin can enter the bloodstream and interact with multiple organs, reducing lipolysis and the metabolic activity of brown and beige adipocytes (Yabut et al. 2019). However, whether food phenolics promote brown adipogenesis by regulating PP and 5-HT secretion is unclear and therefore warrants further investigation.

In conclusion, polyphenols, in a food matrix or as a supplement provided alone, play a pivotal role in preventing and managing obesity by activating BAT. These include food-derived compounds which should be considered as part of the nutritional regime.
in conjunction with physical exercise and pharmacological and surgical therapy. Further mechanistic investigations of BAT activation and beige cell recruitment induced by safe and effective natural active components has great potential for new and highly effective approaches for combating obesity.

**Declarations of competing interest**

The authors declare no conflicts of interest

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Table 1. Polyphenols function as bioactive substances promoting browning/beiging of WAT and activation of BAT in animal and human models.

<table>
<thead>
<tr>
<th>Polyphenols</th>
<th>Structure</th>
<th>Main source</th>
<th>Animal or humans Models</th>
<th>Dosage</th>
<th>Duration</th>
<th>Effects on adipose browning in WAT or/and BAT</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenolic acids</td>
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<tr>
<td>Hydroxycinnamic acids</td>
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<tr>
<td>Caffeic acid</td>
<td><img src="image" alt="Caffeic acid" /></td>
<td>HFD-fed C57BL/6J mice</td>
<td>50mg/kg</td>
<td>8 weeks</td>
<td>Energy expenditure↑; Respiratory quotient values↑</td>
<td>(Xu et al. 2020)</td>
<td></td>
</tr>
<tr>
<td>p-Coumaric acid</td>
<td><img src="image" alt="p-Coumaric acid" /></td>
<td>HFD-fed C57BL/6 Cnc mice</td>
<td>2mg/mL</td>
<td>6 weeks</td>
<td>Energy metabolism↑; BAT: UCP1, Cidea, and PRDM16↑</td>
<td>(Han et al. 2020b)</td>
<td></td>
</tr>
</tbody>
</table>
Chlorogenic acid

HFD-fed C57BL/6 mice 100 mg/kg 15 weeks Lipid accumulation in BAT↓ (Ma, Gao, and Liu. 2015)

Hydroxybenzoic acids

Gentisic acid

HFD-fed C57BL/6Cmc mice 2 mg/mL 12 weeks Energy expenditure↑; BAT: UCP1, PRDM16, and PGC-1α↑ (X. Han et al. 2021)

Ellagic acid

SHR-Zbtb16Δc/Δc k.o. 50 mg/kg 3 weeks BAT: UCP1, PRDM16, PGC-1α, Tbx1, and NRF1↑ (Kábelová et al. 2021)

HFD-fed SD rats 10 and 30 mg/kg/day 24 weeks iWAT: brown/beige markers including UCP1, PRDM16, Cidea, PGC-1α, PPARα; including CD137 and Tmem26↑ (L. Wang et al. 2019)
Vanillic acid

HFD-C57BL/6J mice 0.5% w/w 13 weeks iWAT: UCP1, PRDM16, Cidea, Tmem26, CD137, HOXC8 and Tbx1↑ (Han et al. 2018)

Gallic acid

HFD-C57BL/6J mice 100 mg/kg 60 days BAT: Sirt1 and PGC-1α↑ (Paraíso et al. 2019)

Flavonoids

Flavones

Luteolin

HFD-fed C57BL/6 mice 0.01% 12 weeks BAT and sWAT: AMPK/PGC-1α signaling↑ (Zhang et al. 2016)
Apigenin

HFD-fed C57BL/6 mice 0.04% 12 weeks

sWAT: ATGL, HSL, FOXO1, Sirt1,
p-AMPK/AMPK, p-ACC/ACC↑;
eWAT: ATGL, HSL, FOXO1, Sirt1, p-AMPK/AMPK, and p-ACC/ACC↑;
BAT: HSL, Sirt1, FOXO1, p-AMPK/AMPK, p-ACC/ACC↑

Curcumin

HFD-fed C57BL/6J mice 1% 6 weeks

Energy expenditure↑;
BAT: UCP1, PPARα, and PGC-1α↑

Flavonols

Quercetin

C57BL/6 inbred mice 1% 16 weeks

BAT: UCP1, PGC-1α, Cidea, and mtTFA ↑
Pentamethylquercetin | HFD-fed C57BL/6J mice | 0.04% | 17 weeks | C/EBPα, PGC-1α, Cidea, Bmp7, and Glut-4↑ (Han et al. 2017)

Rutin | Sprague-Dawley rats with polycystic ovary syndrome | 100 mg/kg | 3 weeks | BAT: Dio2, UCP1, PPARα, MCAD, PGC-1α, PGC-1β, and CPT1α↑ (Hu et al. 2017)

Myricetin | db/db mice | 400 mg/kg | 14 weeks | BAT and iWAT: UCP1, ATP5A, UQCRC2, SDHB, Sirt1, and PGC-1α↑ (Hu et al. 2018)

Flavanones

Naringenin | C57Bl/6 mice | 80 mg/kg | 8 weeks | BAT: UCP1↑ (Thaiss et al. 2016)
<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Treatment</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apigenin</td>
<td>C57Bl/6 mice</td>
<td>80 mg/kg 8 weeks</td>
<td></td>
<td>BAT: UCP1 ↑</td>
</tr>
<tr>
<td>Hesperetin</td>
<td>Western diet fed wistar rats</td>
<td>100 mg/kg/day 8 weeks</td>
<td></td>
<td>iWAT: Cidea↑</td>
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<tr>
<td>Flavanols (Flavan-3-ols)</td>
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<tr>
<td>Epigallocatechin-3-gallate (EGCG)</td>
<td>HFD-fed C57BL/6J mice</td>
<td>0.2% (w/w) 8 weeks</td>
<td></td>
<td>BAT: UCP1, PRDM16, PGC-1α, NRF1, and Tfam↑</td>
</tr>
<tr>
<td>Catechins</td>
<td>Sprague-Dawley rats</td>
<td>500 mg/100 g 8 weeks</td>
<td></td>
<td>BAT: UCP mRNA↑</td>
</tr>
</tbody>
</table>

(Thaiss et al. 2016)
(Mosqueda-Solís et al. 2018)
(Lee et al. 2017)
(Nomura et al. 2008)
Healthy young male volunteers

Beverage contained 615 mg tea catechin and 77 mg caffeine for 2 weeks.

Whole-body energy expenditure↑; FDG uptake↑ (Yoneshiro et al. 2017)

Isoflavones

Casein diet fed C57BL/6 mice for 8 weeks

sWAT: UCP1 and PGC-1α↑

BAT: UCP1↑ (Palacios-González et al. 2019)

Genistein

Ovx rats were fed with HFD for 4 weeks

iWAT: UCP-1, PRDM-16, PGC-1α, Cidea, NRF1, Tfam, UCP-1 and Tbx-1↑ (Shen et al. 2019)

Chalcones
Phlorizin
C57BL/6 mice were fed HFD 60 mg/kg 12 weeks UCP1, PPARα, and PRDM16↑ (Yuan et al. 2016)

Butein
C57BL/6N mice were fed HFD 5 and 15 mg/kg 8 weeks Energy expenditure↑;
iWAT, eWAT and BAT: PRDM4 and UCP1↑ (Song et al. 2016)

Anthocyanins
Cyanidin-3-O-β-Glucoside
db/db mice 1 mg/ml in water 16 weeks BAT: UCP1, Sirt1 and PGC-1α, PPARα↑ (You et al. 2017)

Stilbenes
C57BL/6 J mice were fed with a HFC diet 200 mg/kg 8 weeks BAT: UCP1, PGC-1α, NRG4, NAMPT, FGF21↑ (Pei et al. 2018)
<table>
<thead>
<tr>
<th>Compound</th>
<th>Treatment</th>
<th>Daily Dose</th>
<th>Duration</th>
<th>Outcome Note</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resveratrol</td>
<td>HFD-fed CD1 female mice</td>
<td>0.1% resveratrol</td>
<td>4 weeks</td>
<td>iWAT: p-AMPKα/t-AMPKα ratio↑</td>
<td>Wang et al. 2015</td>
</tr>
<tr>
<td></td>
<td>HFD fed C57BL/6 J mice</td>
<td>0.1–0.4%</td>
<td>11 weeks</td>
<td>BAT: PRDM16, UCP-1, Cytochrome C, p-AMPKα↑</td>
<td>Zou et al. 2017</td>
</tr>
<tr>
<td></td>
<td>Twenty male and female volunteers, aged 30–55 years</td>
<td>500 mg/day</td>
<td>8 weeks</td>
<td>iWAT and eWAT: UCP1, PRDM16, Sirt1, Fabp4, PPARγ, and p-AMPKα/t-AMPKα↑</td>
<td></td>
</tr>
<tr>
<td>Pterostilbene</td>
<td>HFD-fed C57BL/6 mice</td>
<td>352µmol/kg/da</td>
<td>30 weeks</td>
<td>sWAT: FNDC5, UCP1, PRDM16, and SIRT1↑</td>
<td>La Spina et al. 2019</td>
</tr>
<tr>
<td>Lignans</td>
<td>HFD-fed C57BL/6 mice</td>
<td>300 mg/day</td>
<td>12 weeks</td>
<td>sWAT: FNDC5, UCP1, PRDM16, and SIRT1↑</td>
<td></td>
</tr>
</tbody>
</table>
Diphyllin

HFD-fed C57BL/6J mice

100 mg/kg

7 weeks

BAT: UCP1, Cox7a1, Cox7b1↑;

iWAT: UCP1 and Cox7a1↑;

eWAT: UCP1, Cox7a1, and PGC-1α↑

(Duan et al. 2020)

Secoisolariciresinol diglucoside

HFD-fed obese C57BL/6J mice

50 mg/kg

16 weeks

BAT: UCP1, PGC-1α and PRDM16↑

(Kang et al. 2020)

HFD-fed C57BL/6J mice

40 mg/kg/day

12 weeks

eWAT: PPARα and PGC-1α↑

(Dong et al. 2021)

Other phenolics
Berberine

Obese db/db mice 5 mg/kg/day 4 weeks BAT and iWAT: PGC-1α, UCP1, mtTFA, NRF-1, PPARα, CPT1β, Dio2, and Cox8b↑

(Zhang et al. 2014)

Capsiate

Healthy men 1.5 mg 4 weeks Energy expenditure↑; Eardrum and skin temperature↑; FDG uptake↑

(Yoneshiro et al. 2012)

Capsaicin

Wild-type and TRPV1−/− mice 0.01% 26 weeks eWAT: PGC-1α and SIRT-1↑

(Baskaran et al. 2016)

Urolithin A

HFD fed C57BL/6 mice 30 mg/kg/day 6 weeks Energy expenditure↑; BAT and iWAT: T3 and UCP1↑

(Xia et al. 2020)
Polyphenols extracts

Polyphenol-rich Calafate
(Berberis microphylla)

HFD fed C57BL/6J mice 50mg/kg/day

Energy expenditure↑; BAT: UCP1, PPARα, and Sirt1↑ (Duarte et al. 2021b)

iWAT: PGC-1α, PPARα, PRDM16, Sirt1, and Dio2↑

HFD-fed C57BL/6J mice 50 mg (total polyphenols)/kg/day

Energy expenditure↑; BAT: UCP1↑; Mitochondrial dynamics↑ (Ramirez et al. 2021)

Apple polyphenols

HFD-induced C57BL/6J mice 5 g/kg diet 10 weeks

Energy expenditure↑; BAT: PRDM16, PGC-1α, and Cidea↑ (T. Zou et al. 2020)

Cranberry Polyphenolic

Extract (CPE)

HFD-fed C57BL/6J mice 0.75% CPE in drinking water 16 weeks

iWAT: PGC-1α, Cidea, UCP1↑; eWAT: Tmem26, Cd137, and Hoxc8↑; BAT: PRDM16, PGC-1α, Cidea, UCP1, (Zhou et al. 2020)
HFD-fed C Wild-type and AMPKα1−/− C57BL/6 male mice 5% 10 weeks BAT and iWAT: AMPKα1 pathway↑; BAT: UCP1↑ (Zou et al. 2018)

Healthy male volunteers aged 20–32 years 40 mg 4 weeks Energy expenditure↑; FDG uptake↑ (Sugita et al. 2013)

Raspberry

Grains of paradise (Aframomum melegueta) extract (15.2 % 6-gingerol and 12.5 % 6-paradol)
| Isoflavone-rich | C57BL/6J mice were fed with HFD | 1.355% | 42 days | Oxygen consumption ↑; BAT:UCP1↑ | (Kamiya et al. 2012) |
| Pueraiae flower extract | Polyphenol-rich green tea (392 µg/mg of extract). | C57BL/6 mice fed with cafeteria diet | 500 mg/kg | 16 weeks | Energy expenditure↑; sWAT: PPARγ/FGF21/AMPK/UCP1 pathway↑; BAT: UCP1↑ | (Bolin et al. 2020) |
| Polyphenol-rich green tea (392 µg/mg of extract). | Grape pomace extract HFD-fed Sprague Dawley rats | 300 mg/kg | 6 weeks | eWAT: PGC-1α, PPARγ, PRDM16 and UCP1↑ | (Rodriguez Lanzi et al. 2020) |
| Grape pomace extract | Juçara (Euterpe edulis Mart.) containing 415.1 mg/g phenolics | HFD-fed C57BL/6 mice | 0.5% | 16 weeks | Energy expenditure↑; BAT: UCP1↑ | (Barthichoto et al. 2021) |

ACC, 1-aminocyclopropane-1-carboxylic acid; AMPK, AMP-activated protein kinase; ATGL, adipose triglyceride lipase; ATP5A, ATP synthase, H+ transporting, mitochondrial
F1 complex, alpha 1; BAT, brown adipose tissue; Bmp7, bone morphogenetic protein 7; Cd137, tumor necrosis factor receptor superfamily, member 9; C/EBPα, CCAAT enhancer-binding protein α; ChREBP, carbohydrate-responsive element-binding protein; Cidea, cell death-inducing DNA fragmentation factor alpha-like effector A; Cited1, gene encoding Cbp/p300-interacting transactivator 1; Cox7a1, cytochrome c oxidase polypeptide 7a1; Cox8b, cytochrome coxidase polypeptide 8b; CPT1α/β, carnitine palmitoyltransferase 1 α/β; Dio2, iodothyronine Deiodinase 2; Ebf2, early B cell factor-2; Elovl3, elongation of very long-chain fatty acids protein 3; cWAT, epididymal white adipose tissue; Fabp4, fatty acid-binding protein 4; FDG, fluorodeoxyglucose; FGF21, recombinant human fibroblast growth factor 21; FNDC5, fibronectin type III domain-containing protein 5; FOXO1, forkhead box O1; GLUT4, glucose transporter type 4; HFC, high fat-high-cholesterol; HFD, high fat diet; HOXC8, homeobox-containing protein C8; HSL, hormone-sensitive lipase; iWAT, inguinal WAT; MCAD, medium-chain acyl-CoA dehydrogenase; mtTFA, mitochondrial transcription factor A; NAMPT, nicotinamide phosphoribosyltransferase; NRF1, nuclear respiratory factor 1; NRG4, neuregulin 4; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 α; PDH, pyruvate dehydrogenase; PPARα/γ, peroxisome proliferator-activated receptor α/γ; PRDM16, PR domain-containing 16; SAT, subcutaneous adipose tissue; SDHB, succinate dehydrogenase [ubiquinone] iron–sulfur subunit, mitochondrial; Sirt1, sirtuin 1; STAT, signal transducer and activator of transcription; sWAT, subcutaneous WAT; T3, triiodothyronine, Tbx1, gene encoding T-box protein 1; Tfam, mitochondria transcription factor A; Tmem26, gene encoding transmembrane protein 26; TYK2, Tyrosine kinase 2; UCP1, uncoupling protein 1; UQCRC2, Cytochrome b-c1 complex subunit 2
Table 2. Polyphenol monomers or their extracts activate BAT or induce browning of WAT via modulating gut microbiota.

<table>
<thead>
<tr>
<th>Polyphenols</th>
<th>Model</th>
<th>Dose</th>
<th>Duration</th>
<th>Microflora structure</th>
<th>Results of fat browning</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin</td>
<td>HFD-fed C57BL/6 inbred mice</td>
<td>1%</td>
<td>16 weeks</td>
<td>Firmicutes/Bacteroidetes ratio↓; Parabacteroides↑; Lactobacillus↓</td>
<td>Energy expenditure↑; Thermogenesis genes in BAT↑</td>
<td>(Pei et al. 2021)</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>HFD-fed C57BL/6J mice</td>
<td>0.4%</td>
<td>8 weeks</td>
<td>Firmicutes/Bacteroidetes ratio↓; Proteobacteria↑</td>
<td>Sirt1 signaling (UCP1, PGC-1α, PPARγ)↑</td>
<td>(Liao et al. 2018)</td>
</tr>
<tr>
<td>Nobiletin</td>
<td>HFD-fed C57BL/6J mice</td>
<td>50 mg/kg</td>
<td>12 weeks</td>
<td>Akkermansia and Bacteroidetes↑</td>
<td>BAT activity↑; Beige adipocytes formation↑</td>
<td>(Kou et al. 2021)</td>
</tr>
<tr>
<td>Caffeic acid</td>
<td>HFD-fed C57BL/6J mice</td>
<td>50 mg/kg</td>
<td>12 weeks</td>
<td>Anti-obesity related bacteria and butyrate-producing bacteria↑</td>
<td>Energy expenditure↑; BAT activity↑</td>
<td>(Xu et al. 2020)</td>
</tr>
<tr>
<td>Chlorogenic acid</td>
<td>HFD-fed C57BL/6J mice</td>
<td>100 mg/kg</td>
<td>13 weeks</td>
<td>Modification of microbiota structure in a unique way</td>
<td>Energy expenditure↑; BAT activity↑</td>
<td>(He et al. 2021)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Model</td>
<td>Dose/Concentration</td>
<td>Duration</td>
<td>Microbiota Changes</td>
<td>Energy Expenditure Changes</td>
<td>References</td>
</tr>
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<tr>
<td>Theabrownin</td>
<td>HFD-fed C57BL/6J mice</td>
<td>225 mg/kg/day</td>
<td>8 weeks</td>
<td>non-12OH-BAs produced microbiota (Akkermansia muciniphila, Clostridium scindens, and Parabacteroides distasonis)↑</td>
<td>Energy expenditure↑; UCP1 and Dio2 in BAT↑; UCP1 in WAT↑</td>
<td>(Kuang et al. 2020)</td>
</tr>
<tr>
<td>Curcumin</td>
<td>HFD-fed C57BL/6J mice</td>
<td>100 mg kg/day</td>
<td></td>
<td>Akkermansia↑</td>
<td>UCP1-dependent thermogenesis in BAT and iWAT↑</td>
<td>(Z. Han et al. 2021)</td>
</tr>
<tr>
<td>Grape extract</td>
<td>HFHS-fed C57BL/6Cnc mice</td>
<td>1%</td>
<td>13 weeks</td>
<td>Bifidobacteria, Akkermansia, and Clostridia genera↑</td>
<td>Energy expenditure↑; Thermogenesis genes in BAT↑</td>
<td>(Han et al. 2020a)</td>
</tr>
<tr>
<td>Polyphenols isolated from red raspberry fractions</td>
<td>HFD-fed C57BL/6 male mice</td>
<td>0.3% pulp; 0.1% seeds; 0.4% whole fruits</td>
<td>16 weeks</td>
<td>Oscillospira↓; Clostridiaceae↑</td>
<td>BAT weight↓</td>
<td>(Xian et al. 2021)</td>
</tr>
<tr>
<td>Blueberry extract</td>
<td>HFD-fed C57BL/6 male mice</td>
<td>0.5% (m/v)</td>
<td>10 weeks</td>
<td>Bifidobacteria and Lactobacillus↑</td>
<td>Energy expenditure↑; Brown-special factors in BAT and</td>
<td>(J. Guo et al. 2019)</td>
</tr>
<tr>
<td>Treatment</td>
<td>HFD/Fat-fed C57BL/6/J male mice</td>
<td>Dose (mg/kg)</td>
<td>Treatment Duration (weeks)</td>
<td>Change in microbiota profile (e.g.,)</td>
<td>BAT weight↓</td>
<td>References</td>
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<tr>
<td>Blueberry polyphenols extract</td>
<td>HFD-fed C57BL/6 male mice</td>
<td>200 mg/kg</td>
<td>12</td>
<td>Change in microbiota profile (e.g.,</td>
<td>Bifidobacterium↑, Coprobacillus↓)</td>
<td>(Jiao et al. 2019)</td>
</tr>
<tr>
<td>Tea polyphenols</td>
<td>HFD-fed C57BL/6J male mice</td>
<td>250 mg/kg</td>
<td>12</td>
<td>Akkermansia muciniphila↑; UCP1, PGC-1α, Cidea, Tbx1,</td>
<td>Faecalibacterium praunztizi↑ and Prdm16 in BAT↑</td>
<td>(Gao et al. 2018)</td>
</tr>
<tr>
<td>Extract of the Microalgae</td>
<td>HFD-fed C57BL/6J mice</td>
<td>10 and 50 mg/kg</td>
<td>8</td>
<td>Firmicutes/Bacteroidetes ratio↓; UCP 1 and PGC-1α in BAT↑</td>
<td>Christensenellaceae↓</td>
<td>(B. Guo et al. 2019)</td>
</tr>
<tr>
<td>Nitzschia laevis (13.83% polyphenols)</td>
<td></td>
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<tr>
<td>Polyphenol-rich extract from chokeberry (2209.25 mg/100 g)</td>
<td>HFD-fed wistar rats</td>
<td>1000 mg/kg</td>
<td>40</td>
<td>Firmicutes/Bacteroidetes ratio, Bacteroides, Prevotella,</td>
<td>mRNA expression of PPARγ, UCP1</td>
<td>(Zhu et al. 2020)</td>
</tr>
<tr>
<td>Camu camu (Myrciaria dubia)</td>
<td>HFHS-fed C57BI/6J male mice</td>
<td>200 mg/kg</td>
<td>8</td>
<td>Akkermansia muciniphila↑; Lactobacillus↓; Energy expenditure↑;</td>
<td>UCP1 in BAT↑</td>
<td>(Anhê et al. 2019)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Model</td>
<td>Diet/Intervention</td>
<td>Duration</td>
<td>Microbiota Changes</td>
<td>Additional Effects</td>
<td>Reference</td>
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<tr>
<td>Guarana rich in catechins</td>
<td>Western diet fed Wistar</td>
<td>0.5%</td>
<td>18 weeks</td>
<td>Firmicutes/Bacteroidetes↓; Bat weight↑; UCP1 and Sirt 1↑</td>
<td></td>
<td>(Bortolin et al. 2019)</td>
</tr>
<tr>
<td>and methylxanthines</td>
<td></td>
<td></td>
<td></td>
<td>Butyricoccus↑, Holdemania↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mulberry leaves</td>
<td>HFD-fed C57BL/6J mice</td>
<td>20% mulberry</td>
<td>8 weeks</td>
<td>Bacteroidetes/Firmicutes ratio↑; Bat activity↑</td>
<td></td>
<td>(Sheng et al. 2019)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>leaf powder (w/w)</td>
<td></td>
<td>Akkermansia↑</td>
<td></td>
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</tr>
<tr>
<td>Rice bran</td>
<td>HFD-fed C57BL/6 mice</td>
<td>300 mg/kg</td>
<td>39 days</td>
<td>Firmicutes/Bacteroidetes; Bat activity and WAT browning↑</td>
<td></td>
<td>(Y. Zou et al. 2020)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Akkermansia↑</td>
<td></td>
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</tr>
<tr>
<td>Grape seed</td>
<td>HFD-fed C57BL/6 mice</td>
<td>100 or 200 mg/kg</td>
<td>8 weeks</td>
<td>Alistipes and Ruminococcaceae↑</td>
<td>Thermogenic activity of iBAT (PRDM16 and UCP1 expression)↑</td>
<td>(Du et al. 2021)</td>
</tr>
</tbody>
</table>

Dio2, iodothyronine Deiodinase 2; HFD, high fat diet; HFHS, high fat/high sucrose diet; iBAT, intrascapular brown adipose tissue; iWAT, inguinal white adipose tissue; PGC1α, peroxisome proliferator-activated receptor gamma coactivator-1 α; PPARγ, peroxisome proliferator-activated receptor γ; PRDM16, PR domain-containing 16; Sirt1, Sirtuin 1; UCP1, uncoupling protein 1
Figure 1 Anatomical locations and characteristics of adipose tissue in mice and humans (Figure was reproduced with Copyright 2018 Elsevier (License number: 5078560921795) and Copyright 2016 Elsevier (License number: 5078790022377)) (Abdullahi and Jeschke 2016; Ikeda, Maretich, and Kajimura 2018). White adipocytes are mainly derived from the Myf5− progenitor cells and store excess energy in the form of triglyceride droplets. Brown adipocytes originated from Myf5+ progenitors contain high mitochondrial content and can convert stored energy into heat via UCP1 activation. Clusters of beige adipocytes with thermogenic capacity can appear within WAT. H&E, hematoxylin-eosin staining; iBAT, interscapular brown adipose tissues; sBAT, supraclavicular brown adipose tissues; iWAT: inguinal white adipose tissues; sWAT, subcutaneous white adipose tissues; UCP1, mitochondrial uncoupling protein-1.

Figure 2 VOSviewer co-occurrence network visualization of most frequent all keywords (minimum of 5 occurrences) of “brown adipose” research (A), and overlay visualization of most frequent all keywords (minimum of 5 occurrences) of “Polyphenols & brown adipose” research (Web of Science Core Collection) (B).

Figure 3 Absorption of food phenolics and their microbial transformation in the intestine. This figure was partly generated using ScienceSlides 2006 and adapted from (Liu et al. 2020).

Figure 4 Food phenolics improve diet-induced dysbacteriosis and ameliorate the production of gut bacteria-derived LPS. The decreased white fat browning and mitochondrial thermogenesis attributed to the inflammatory response along the
gut-adipose tissue axis can be overcome by food phenolics, which recruit brown-like adipocyte formation in WAT. This figure was partly generated using ScienceSlides 2006.

**Figure 5** Overview of the possible role of food phenolics in the brown adipogenesis via the gut microbiota (SCFA)-adipose tissue axis. The figure was partly created using BioRender (https://biorender.com/).

**Figure 6** The gut microbiota regulated by polyphenols modulates bile acid production and signaling via the bile acid receptor TGR5 to increase BAT activity (e.g., D2 and its target genes T3/T4) and WAT browning and promotes mitochondrial uncoupling. CDCA, chenodeoxycholic acid; D2, iodothyronine deiodinase; DCA, deoxycholic acid; LCA, lithocholic acid; T3, thiiodothyronine; T4, thyroxine; TCDCA, taurochenodeoxycholic acid; TUDCA, tauroursodeoxycholic acid

**Figure 7** Polyphenols and their metabolites can promote the secretion of gut hormones (CCK, GLP-1, and PYY) to stimulate fat browning possibly via central mechanisms. NA:noradrenaline. The figure was partly created using BioRender (https://biorender.com/).
Fig. 1

Interscapular BAT
Axillary BAT
Perirenal BAT
Anterior Subcutaneous WAT
Inginal WAT

Waite adipocytes (Myf5*)
Beige adipocytes (Myf5*)
Classical brown adipocytes (Myf5*)

Mouse
H&E
UCP1

Human
H&E
UCP1

iWAT
Browning of iWAT
iBAT

sWAT
Browning of sWAT
sBAT

Infant?
Fig. 2

A

B
Fig. 3

Polyphenols
- Polymers
- Glycosides
- Aglycones

Small intestine
- Absorbed
- Not absorbed

Deconjugation
- Absorbed

Colon
- Microbial metabolites
  - Hydrolysis
  - Cleavage
  - Reduction
- Microbiota
  - *Bifidobacterium*, *Lactobacillus*, *Clostridium*, *Eubacterium*...
- Fecal excretion

Portal Circulation
- Phase I & II metabolism
- Biliary excretion
- Systemic Circulation
- Biological Activation & Clearance
- Urinary excretion

Blood
Tissues
Fig. 5

The microbiota ferment producing SCFAs

- Butyrate
- Acetate
- Propionate

Gut-brain neural circuit
GPR41/43 pathway

WAT
BeAT
BAT

Fat storage
Thermogenic fat converted to heat
e.g., AMPK/SIRT1/PGC1α signal
e.g., AMPK/SIRT1/PGC1α signal
Fig. 6