Food Phenolics Stimulate Adipocyte Browning via Regulating Gut Microecology

Zhenyu Wang[a, b], Maomao Zeng[a, b], Zhaojun Wang[a, b], Fang Qin[a, b], Yongzhi Wang[c], Jie Chen [a, b], Mark Christian[*, d], Zhiyong He[*, a, b]

[a]State Key Laboratory of Food Science and Technology, Jiangnan University, Wuxi, Jiangsu 214122, China

[b]International Joint Laboratory on Food Safety, Jiangnan University, Wuxi, Jiangsu 214122, China

[c]Food and Beverage Department of Damin Food (Zhangzhou) Co., Ltd., Zhangzhou, Fujian 363005, China

[d]School of Science and Technology, Nottingham Trent University, Clifton, Nottingham, NG11 8NS, United Kingdom

[*]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, lobeglitazone, 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 supraphysiological (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.

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 glucolipid 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, flavanonols, 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, *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 *A. muciniphila* contributes to upregulating expressions of UCP1, Cidea, PGC-1α, PRDM16 and PPARγ in BAT and diminishing adipocyte size in WAT (Deng et al. 2020). In obese mice, the relative abundance of the genus *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 *Clostridiaceae* and BAT weight (Xian et al. 2021). Importantly, in a clinical intervention study with obese human subjects, the phylum *Firmicutes*, specifically the *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). The

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 meditated 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 to 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 Grefhorst 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 food phenolics 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 consum 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 gastrointestine 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

Acknowledgment

The authors acknowledge financial support from the National Natural Science Foundation of China (No. 31771978), the Six Talent Peaks Project in Jiangsu Province (No. NY-095), the National First-class Discipline Program of Food Science and Technology (No. JUFSTR20180201), the Innovation and Exploration Fund of State Key Laboratory of Food Science and Technology, Jiangnan University (No. SKLF-ZZB-202102) and the Fundamental Research Funds for the Central Universities (No. JUSRP21802). Mark Christian was supported by BBSRC grant BB/P008879/2.

References

Abdullahi, A., and M. G. Jeschke. 2016. White Adipose Tissue Browning: A Double-edged Sword. *Trends in Endocrinology & Metabolism* 27: 542-552. doi: 10.1016/j.tem.2016.06.006

Agarwal, R., M. Wiessler, E. Hecker, and S. Bhide. 1986. Tumour-promoting effects of chilli extracts in BALB/c mice. *International Journal of Cancer* 38: 689-695. doi: 10.1002/ijc.2910380512

Ahmed, B. A., F. J. Ong, N. G. Barra, D. P. Blondin, E. Gunn, S. M. Oreskovich, J. C. Szamosi, S. A. Syed, E. K. Hutchings, N. B. Konyer, et al. 2021. Lower brown adipose tissue activity is associated with non-alcoholic fatty liver disease but not changes in the gut microbiota. *Cell Reports Medicine* 2: 100397. doi:10.1016/j.xcrm.2021.100397

Andrade, J. M. O., A. S. Barcala-Jorge, G. C. Batista-Jorge, A. F. Paraíso, K. M. d. Freitas, D. d. F. Lelis, A. L. S. Guimarães, A. M. B. de Paula, and S. H. S. Santos. 2019. Effect of resveratrol on expression of genes involved thermogenesis in mice and humans. *Biomed Pharmacother* 112:108634. doi: 10.1016/j.biopha.2019.108634

Anhê, F. F., R. T. Nachbar, T. V. Varin, J. Trottier, S. Dudonné, M. Le Barz, F. Feutry, G. Pilon, O. Barbier, Y. Desjardins, et al. 2019. Treatment with camu camu (Myrciaria dubia) prevents obesity by altering the gut microbiota and increasing energy expenditure in diet-induced obese mice. *Gut* 68(3): 453-464. doi:10.1136/gutjnl-2017-315565.

Anhê, F. F., T. V. Varin, M. Le Barz, Y. Desjardins, E. Levy, D. Roy, and A. Marette. 2015. Gut Microbiota Dysbiosis in Obesity-Linked Metabolic Diseases and Prebiotic Potential of Polyphenol-Rich Extracts. *Current Obesity Reports* 4(4): 389-400. doi:10.1007/s13679-015-0172-9

Ansari, V. 2015. Curcuma longa: Boon for health care system with its biomedical application. *International Journal of Pharmaceutical Sciences and Research 6:* 4168-4173. doi:10.13040/IJPSR.0975-8232.

Ardid-Ruiz, A., M. Ibars, P. Mena, D. Del Rio, B. Muguerza, C. Bladé, L. Arola, G. Aragonès, and M. Suárez. 2018. Potential Involvement of Peripheral Leptin/STAT3 Signaling in the Effects of Resveratrol and Its Metabolites on Reducing Body Fat Accumulation. *Nutrients* 10(11): 1757. doi:10.3390/nu10111757

Argentato, P. P., C. A. Morais, A. B. Santamarina, H. d. C. César, D. Estadella, V. V. de Rosso, and L. P. Pisani. 2017. Jussara (Euterpe edulis Mart.) supplementation during pregnancy and lactation modulates UCP-1 and inflammation biomarkers induced by trans-fatty acids in the brown adipose tissue of offspring. *Clinical Nutrition Experimental* 12: 50-65. doi:10.1016/j.yclnex.2016.12.002

Asakawa, A., A. Inui, H. Yuzuriha, N. Ueno, G. Katsuura, M. Fujimiya, M. A. Fujino, A. Niijima, M. M. Meguid, and M. Kasuga. 2003. Characterization of the effects of pancreatic polypeptide in the regulation of energy balance.

Gastroenterology 124(5): 1325-1336. doi:10.1016/S0016-5085(03)00216-6

Attele, A. S., Z. Q. Shi, and C.-S. Yuan. 2002. Leptin, gut, and food intake. *Biochemical Pharmacology* 63(9): 1579-1583. doi:10.1016/S0006-2952(02)00883-3

Azhar, Y., A. Parmar, C. N. Miller, J. S. Samuels, and S. Rayalam. 2016. Phytochemicals as novel agents for the induction of browning in white adipose tissue. *Nutrition & Metabolism* 13: 89. doi: 10.1186/s12986-016-0150-6

Baboota, R. K., N. Murtaza, S. Jagtap, D. P. Singh, A. Karmase, J. Kaur, K. K. Bhutani, R. K. Boparaid, L. S. Premkumar, K. K. Kondepudia, et al. 2014. Capsaicin-induced transcriptional changes in hypothalamus and alterations in gut microbial count in high fat diet fed mice. *The Journal of Nutritional Biochemistry* 25(9): 893-902. doi:10.1016/j.jnutbio.2014.04.004

Bae, J., C. J. Ricciardi, D. Esposito, S. Komarnytsky, P. Hu, B. J. Curry, P. L. Brown, Z. Gao, J. P. Biggerstaff, J. Chen. et al. 2014. Activation of pattern recognition receptors in brown adipocytes induces inflammation and suppresses uncoupling protein 1 expression and mitochondrial respiration. *American Journal of Physiology-Cell Physiology* 306(10): C918-C930. doi:10.1152/ajpcell.00249.2013

Bahadoran, Z., P. Mirmiran, and F. Azizi. 2013. Dietary polyphenols as potential nutraceuticals in management of diabetes: a review. *Journal of Diabetes & Metabolic Disorders* 12: 43.doi: 10.1186/2251-6581-12-43

Bartelt, A., and J. Heeren. 2014. Adipose tissue browning and metabolic health. Nature Reviews Endocrinology 10(1): 24-36. doi:10.1038/nrendo.2013.204

Barthichoto, M., T. L., Moretto, F. P. de Carvalho, I. D. Benfato, V. V. de Rosso, D. A. Ribeiro, D. Estadella, L. Le Sueur-Maluf, L. P. Pisani, and , C. A. M. J. N. de Oliveira. 2021. Juçara (Euterpe edulis Mart.) supplementation reduces body weight gain and protects mice from metabolic complications induced by high-fat diet. *Nutrire* 46:1-11. doi:10.1186/s41110-021-00135-7

Baskaran, P., V. Krishnan, J. Ren, and B. Thyagarajan. 2016. Capsaicin induces browning of white adipose tissue and counters obesity by activating TRPV1 channel-dependent mechanisms. *British Journal of Pharmacology 173*(15): 2369-2389. doi: 10.1111/bph.13514

Beaudry, J. L. K. D. Kaur, E. M. Varin, L. L. Baggio, X. Cao, E. E. Mulvihill, H. E. Bates, J. E. Campbell, and D. J. Drucker. 2019. Physiological roles of the GIP receptor in murine brown adipose tissue. *Molecular Metabolism* 28:14-25. doi:10.1016/j.molmet.2019.08.006

Blouet, C., and G. J. Schwartz. 2012. Duodenal Lipid Sensing Activates Vagal Afferents to Regulate Non-Shivering Brown Fat Thermogenesis in Rats. *Plos One* 7(12): e51898. doi:10.1371/journal.pone.0051898

Boix Castejón, M., M. Herranz Lopez, J. A. Pérez-Gago, M. Olivares-Vicente, N. Caturla, E. Roche, and V. Micol. 2018. Hibiscus and lemon verbena polyphenols modulate appetite-related biomarkers in overweight subjects: A randomized controlled trial. *Food & Function* 9(6): 3173-3184. doi:10.1039/C8FO00367J

Bolin, A. P., C. P. B. Sousa-Filho, G. T. N. dos Santos, L. T. Ferreira, P. B. M. de Andrade, A. C. M. Figueira, et al. 2020. Adipogenic commitment induced by green tea polyphenols remodel adipocytes to a thermogenic phenotype. The *Journal of Nutritional Biochemistry* 83: 108429. doi: 10.1016/j.jnutbio.2020.108429

Commins, S. P., P. M. Watson, M. A. Padgett, A. Dudley, G. Argyropoulos, and T. W. Gettys. 1999. Induction of Uncoupling Protein Expression in Brown and White Adipose Tissue by Leptin. *Endocrinology 140*(1): 292-300. doi:10.1210/endo.140.1.6399

Bortolin, R. C., A. R.Vargas, V. de Miranda Ramos, J. Gasparotto, P. R. Chaves, C. E. Schnorr, K. D. B. Martinello, , A. K. Silveira, H. M. Gomes, T. K. Rabelo, et al. 2019. Guarana supplementation attenuated obesity, insulin resistance, and adipokines dysregulation induced by a standardized human Western diet via brown adipose tissue activation. *Phytotherapy Research* 33(5): 1394-1403. doi:10.1002/ptr.6330

Braune, A., and M. Blaut. 2016. Bacterial species involved in the conversion of dietary flavonoids in the human gut. *Gut Microbes* 7(3): 216-234. doi:10.1080/19490976.2016.1158395

Broeders, Evie P. M., Emmani B. M. Nascimento, B. Havekes, B. Brans, Kay H. M. Roumans, A. Tailleux, G. Schaart, M. Kouach, J. Charton, B. Deprez, et al. 2015. The Bile Acid Chenodeoxycholic Acid Increases Human Brown Adipose Tissue Activity. *Cell Metabolism* 22(3): 418-426. doi:10.1016/j.cmet.2015.07.002

Canfora, E. E., R. C. R. Meex, K. Venema, and E. E Blaak. 2019. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nature Reviews Endocrinology* 15(5): 261-273. doi:10.1038/s41574-019-0156-z

Cani, P. D., A. Everard, and T. Duparc. 2013. Gut microbiota, enteroendocrine functions and metabolism. *Current Opinion in Pharmacology* 13: 935-940. doi:10.1016/j.coph.2013.09.008

Cardona, F., C.Andrés-Lacueva, S. Tulipani, F. J. Tinahones, and M. I. Queipo-Ortuño. 2013. Benefits of polyphenols on gut microbiota and implications in human health. *The Journal of Nutritional Biochemistry* 24(8): 1415-1422. doi:10.1016/j.jnutbio.2013.05.001

Castro-Acosta, M. L., S. G. Stone, J. E. Mok, R. K. Mhajan, C. I. Fu, G. N. Lenihan-Geels, C. P. Corpe, and W. L. Hall. 2017. Apple and blackcurrant polyphenol-rich drinks decrease postprandial glucose, insulin and incretin response to a high-carbohydrate meal in healthy men and women. *The Journal of Nutritional Biochemistry* 49: 53-62. doi: 10.1016/j.jnutbio.2017.07.013

Chen, M. L., L. Yi, Y. Zhang, X. Zhou, L. Ran, J. Yang, J. D. Zhu, Q. Y. Zhang, and M.T. Mi. 2016. Resveratrol attenuates trimethylamine-N-oxide (TMAO)-induced atherosclerosis by regulating TMAO synthesis and bile acid metabolism via remodeling of the gut microbiota. *MBio* 7(2). doi:10.1128/mBio.02210-15

Chen, S., X. Liu, C. Peng., C. Tan, H. Sun, H. Liu, Y. Zhang, P. Wu, C. Cui, C. Liu, et

al. 2021. The phytochemical hyperforin triggers thermogenesis in adipose tissue via a Dlat-AMPK signaling axis to curb obesity. *Cell Metabolism* 33(3): 565-580.e567. doi:10.1016/j.cmet.2021.02.007

Cheng, Y., Q. Meng, C. Wang, H. Li, Z. Huang, S. Chen, F. Xiao, and F. Guo. 2010. Leucine deprivation decreases fat mass by stimulation of lipolysis in white adipose tissue and upregulation of uncoupling protein 1 (UCP1) in brown adipose tissue. *Diabete* 59(1): 17-25. doi:10.2337/db09-0929

Chevalier, C., O. Stojanović, Didier J. Colin, N. Suarez-Zamorano, V. Tarallo, C. Veyrat-Durebex, D. Rigo, S. Fabbiano, A. Stevanović, S. Hagemann, et al. 2015. Gut Microbiota Orchestrates Energy Homeostasis during Cold. *Cell* 163(6): 1360-1374. doi:10.1016/j.cell.2015.11.004

Chiva-Blanch, G., and L. Badimon. 2017. Effects of Polyphenol Intake on Metabolic Syndrome: Current Evidences from Human Trials. *Oxidative Medicine and Cellular Longevity* 2017: 5812401. doi:10.1155/2017/5812401

Chondronikola, M., C. Porter, I. Malagaris, A. A. Nella, and L. S. Sidossis. 2017. Brown adipose tissue is associated with systemic concentrations of peptides secreted from the gastrointestinal system and involved in appetite regulation. *European Journal of Endocrinology* 177(1): 33-40. doi:/10.1530/EJE-16-0958

Cohen, P., Julia D. Levy, Y. Zhang, A. Frontini, Dmitriy P. Kolodin, Katrin J. Svensson, James C. Lo, X. Zeng, L. Ye, Melin J. Khandekar, et al. 2014. Ablation of PRDM16 and Beige Adipose Causes Metabolic Dysfunction and Subcutaneous to Visceral Fat Switch. *Cell* 156(1): 304-316. doi:10.1016/j.cell.2013.12.021

Corrêa, T. A. F., M. M. Rogero, N. M. A. Hassimotto, and F. M. Lajolo. 2019. The Two-Way Polyphenols-Microbiota Interactions and Their Effects on Obesity and Related Metabolic Diseases. *Frontiers in Nutrition* 6:188 doi:10.3389/fnut.2019.00188

Cory, H., S. Passarelli, J. Szeto, M. Tamez, and J. Mattei. 2018. The Role of Polyphenols in Human Health and Food Systems: A Mini-Review. *Frontiers in Nutrition* 5: 87. doi: 10.3389/fnut.2018.00087

Cottart, C. H., V. Nivet-Antoine, C. Laguillier-Morizot, and J. L. Beaudeux. 2010. Resveratrol bioavailability and toxicity in humans. *Molecular Nutrition & Food Research* 54(1): 7-16. doi:10.1002/mnfr.200900437

Daveri, E., E. Cremonini, A. Mastaloudis, S. N. Hester, S. M. Wood, A. L. Waterhouse, M. Anderson, C. G. Fraga, and P. I. Oteiza. 2018. Cyanidin and delphinidin modulate inflammation and altered redox signaling improving insulin resistance in high fat-fed mice. *Redox Biology* 18: 16-24. doi: 10.1016/j.redox.2018.05.012

Deng, L., Z. Ou, D. Huang, C. Lix, Z. Lu, W. Liu, F. Wu, C. Nong, J. Cao, and Y. Peng. 2020. Diverse effects of different Akkermansia muciniphila genotypes on Brown adipose tissue inflammation and whitening in a high-fat-diet murine model. *Microbial Pathogenesis* 147:104353. doi:10.1016/j.micpath.2020.104353

Depommier, C., M. Van Hul, A. Everard, N. M. Delzenne, W. M. De Vos, and P. D.

Cani. 2020. Pasteurized Akkermansia muciniphila increases whole-body energy expenditure and fecal energy excretion in diet-induced obese mice. *Gut Microbes* 11(5): 1231-1245. doi:10.1080/19490976.2020.1737307

Devillard, E., F. M. McIntosh, S. H. Duncan, and R. J. Wallace. 2007. Metabolism of Linoleic Acid by Human Gut Bacteria: Different Routes for Biosynthesis of Conjugated Linoleic Acid. *Journal of Bacteriology* 189(6): 2566-2570. doi:10.1128/JB.01359-06

Dong, S., W. Bai, J. Chen, L. Zhang, W. Sheng, and R. Feng. 2021. Secoisolariciresinol Diglucoside Regulates Adipose Tissue Metabolic Disorder in Obese Mice Induced by a Western Diet. *Journal of Food Quality* 2021: 5580772. doi: 10.1155/2021/5580772

Dowal, L., P. Parameswaran, S. Phat, S. Akella, I. D. Majumdar, J. Ranjan, C. Shah, S. Mogre, K. Guntur, S. Gesta, et al. 2017. Intrinsic Properties of Brown and White Adipocytes Have Differential Effects on Macrophage Inflammatory Responses. *Mediators of Inflammation* 2017:9067049. doi:10.1155/2017/9067049

Druart, C., E. M. Dewulf, P. D. Cani, A. M. Neyrinck, J. P. Thissen, and N. M. Delzenne. 2014. Gut Microbial Metabolites of Polyunsaturated Fatty Acids Correlate with Specific Fecal Bacteria and Serum Markers of Metabolic Syndrome in Obese Women. *Lipids* 49(4):397-402. doi:10.1007/s11745-014-3881-z

Du, H., Q. Wang, T. Li, D. Ren, and X. Yang. 2021. Grape seed proanthocyanidins reduced the overweight of C57BL/6J mice through modulating adipose thermogenesis and gut microbiota. *Food & Function* 12: 8467-8477. doi: 10.1039/D1FO01361K

Du, Y., Q. Meng, Q. Zhang, and F. Guo. 2011. Isoleucine or valine deprivation stimulates fat loss via increasing energy expenditure and regulating lipid metabolism in WAT. *Amino Acids* 43: 725-734. doi:10.1007/s00726-011-1123-8

Duarte, L., N. Gasaly, C. Poblete-Aro, D. Uribe, F. Echeverria, M. Gotteland, and D. F. Garcia-Diaz. 2021a. Polyphenols and their anti-obesity role mediated by the gut microbiota: a comprehensive review. *Reviews in Endocrine and Metabolic Disorders* 22*:367–388*. doi:10.1007/s11154-020-09622-0

Duan, Y. N., X. Ge, H. W. Jiang, H. J. Zhang, Y. Zhao, J. L. Li., W. Zhang, and , J. Y. Li. 2020b. Diphyllin Improves High-Fat Diet-Induced Obesity in Mice Through Brown and Beige Adipocytes. *Frontiers in endocrinology* 11: 592818-592818. doi: 10.3389/fendo.2020.592818

Duarte, L., J. Quezada, L. A. Ramirez, K. Vasquez, J. F. Orellana, V. Villanueva, F. Perez-Bravo, D. F. Garcia-Diaz. 2021. The treatment with an extract from Calafate (Berberis microphylla) induces transcript and protein expression of molecules involved in thermogenesis and adipocyte browning in adipose tissue from obese mice. *Journal of Berry Research, Preprint*, 1-11. doi:10.3233/JBR-200670

Dulloo, A. G., C. Duret, D. Rohrer, L. Girardier, N. Mensi, M. Fathi, P. Chantre, and J.

Vandermander. 1999. Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *The American Journal of Clinical Nutrition* 70(6):1040-1045. doi:10.1093/ajcn/70.6.1040

Enerbäck, S. 2010. Human Brown Adipose Tissue. *Cell Metabolism* 11: 248-252. doi: 10.1016/j.cmet.2010.03.008

Esteban-Fernández, A., I. Zorraquín-Peña, M. D. Ferrer, A. Mira, B. Bartolomé, D. González de Llano, and M. V. Moreno-Arribas. 2018. Inhibition of Oral Pathogens Adhesion to Human Gingival Fibroblasts by Wine Polyphenols Alone and in Combination with an Oral Probiotic. *Journal of Agricultural and Food Chemistry* 66(9): 2071-2082. doi:10.1021/acs.jafc.7b05466

Fan, Q., P. Xi, D. Tian, L. Jia, Y. Cao, K. Zhan, T. Sun, Y. Zhang, and Q. Wang. 2021. Ginsenoside Rb1 Facilitates Browning by Repressing Wnt/β-Catenin Signaling in 3T3-L1 Adipocytes. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* 27: e928619-e928619. doi:10.12659/MSM.928619

Fan, R., K. Koehler, and S. Chung. 2019. Adaptive thermogenesis by dietary n-3 polyunsaturated fatty acids: Emerging evidence and mechanisms. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1864: 59-70. doi: 10.3390/nu12010136

Fang, S., J. M. Suh, S. M. Reilly, E. Yu, O. Osborn, D. Lackey, E. Yoshihara, A. Perino, S. Jacinto, Y. Lukasheva, et al. 2015. Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. *Nature Medicine* 21(2): 159-165. doi:10.1038/nm.3760

Faria, A., I. Fernandes, S. Norberto, N. Mateus, and C. Calhau. 2014. Interplay between Anthocyanins and Gut Microbiota. *Journal of Agricultural and Food Chemistry* 62(29): 6898-6902. doi:10.1021/jf501808a

Fedorenko, A., Polina V. Lishko, and Y. Kirichok. 2012. Mechanism of Fatty-Acid-Dependent UCP1 Uncoupling in Brown Fat Mitochondria. *Cell* 151(2): 400-413. doi:10.1016/j.cell.2012.09.010

Funakoshi-Tago, M., Y. Nonaka, K. Tago, M. Takeda, Y. Ishihara, A. Sakai, M. Matsutaka, K. Kobata, and H. Tamura. 2020. Pyrocatechol, a component of coffee, suppresses LPS-induced inflammatory responses by inhibiting NF-κB and activating Nrf2. *Scientific Reports* 10(1): 2584. doi:10.1038/s41598-020-59380-x

Gao, X., Q. Xie, P. Kong, L. Liu, S. Sun, B. Xiong, B. Huang, L.Yan, J. Sheng, H. Xiang. 2018. Polyphenol- and Caffeine-Rich Postfermented Pu-erh Tea Improves Diet-Induced Metabolic Syndrome by Remodeling Intestinal Homeostasis in Mice. *Infection and Immunity* 86(1): e00601-00617. doi:10.1128/IAI.00601-17

Guo, B., B. Liu, H. Wei, K. W. Cheng, and F. Chen. 2019. Extract of the Microalga Nitzschia laevis Prevents High-Fat-Diet-Induced Obesity in Mice by Modulating the Composition of Gut Microbiota. *Molecular Nutrition and Food Research* 63(3): 1800808. doi:10.1002/mnfr.201800808

Guo, J., X. Han, H. Tan, W. Huang, Y. You, and J. Zhan. 2019. Blueberry Extract Improves Obesity through Regulation of the Gut Microbiota and Bile Acids via Pathways Involving FXR and TGR5. *iScience* 19: 676-690. doi:10.1016/j.isci.2019.08.020

Han, X., J. Guo, Y. Gao, W. Huang, Z. Jicheng, and Y. You. 2021. Gentisic acid prevents diet-induced obesity in mice by accelerating the thermogenesis of brown adipose tissue. *Food & Function* 12(3): 1262-1270. doi:10.1039/D0FO02474K

Han, X., J. Guo, M. Yin, Y. Liu, Y. You, J. Zhan, and W. Huang. 2020a. Grape Extract Activates Brown Adipose Tissue Through Pathway Involving the Regulation of Gut Microbiota and Bile Acid. *Molecular Nutrition & Food Research* 64(10): 2000149. doi:10.1002/mnfr.202000149

Han, X., J. Guo, Y. You, M. Yin., J. Liang, C. Ren, J. Zhan, and W. Huang. 2018b. Vanillic acid activates thermogenesis in brown and white adipose tissue. *Food & Function* 9(8): 4366-4375. doi:10.1039/C8FO00978C

Han, X., J. Guo, Y. You., J. Zhan, and W. Huang. 2020. p-Coumaric acid prevents obesity via activating thermogenesis in brown adipose tissue mediated by mTORC1-RPS6. *The FASEB Journal* 34(6): 7810-7824. doi:10.1096/fj.202000333R

Han, Y., J. Z. Wu, J.Z. Shen, L. Chen, T. He, M. W. Jin, and H. Liu. 2017. Pentamethylquercetin induces adipose browning and exerts beneficial effects in 3T3-L1 adipocytes and high-fat diet-fed mice. *Scientific Reports* 7:1123. doi: 10.1038/s41598-017-01206-4

Han, Z., L.Yao, Y. Zhong, Y. Xiao, J. Gao, Z. Zheng, S. Fan, Z. Zhang, S. Gong, S. Chang, et al. 2021. Gut microbiota mediates the effects of curcumin on enhancing Ucp1-dependent thermogenesis and improving high-fat diet-induced obesity. *Food & Function* 12: 6558-6575. doi: 10.1039/D1FO00671A

Hao, L., J. Kearns, S. Scott, D. Wu, S. D. Kodani, C. Morisseau, B. D. Hammock, X. Sun, L. Zhao, and S. Wang. 2018. Indomethacin Enhances Brown Fat Activity. *Journal of Pharmacology and Experimental Therapeutics* 365(3): 467-475. doi: 10.1124/jpet.117.246256

Hanatani, S., H. Motoshima, Y. Takaki, S. Kawasaki, M. Igata, T. Matsumura, T. Kondo, T. Senokuchi, N. Ishii, J. Kawashima, et al. 2016. Acetate alters expression of genes involved in beige adipogenesis in 3T3-L1 cells and obese KK-Ay mice. *Journal of Clinical Biochemistry and Nutrition* 59(3): 207-214. doi:10.3164/jcbn.16-23

He, X., S. Zheng, Y. Sheng, T. Miao, J. Xu, W. Xu, K. Huang, and C. Zhao. 2021. Chlorogenic acid ameliorates obesity by preventing energy balance shift in high-fat diet induced obese mice. *Journal of the Science of Food and Agriculture* 101(2): 631-637. doi:10.1002/jsfa.10675

Heppner, K. M., S. Marks, J. Holland, N. Ottaway, D. Smiley, R. Dimarchi, and D. Perez-Tilve. 2015. Contribution of brown adipose tissue activity to the control of energy balance by GLP-1 receptor signalling in mice. *Diabetologia* 58(9):

2124-2132. doi:10.1007/s00125-015-3651-3
Hersoug, L.-G., P. Møller, and S. Loft. 2016. Gut microbiota-derived lipopolysaccharide uptake and trafficking to adipose tissue: implications for inflammation and obesity. *Obesity Reviews* 17(4): 297-312. doi:10.1111/obr.12370
Hirano, S., and N. Masuda. 1982. Enhancement of the 7 alpha-dehydroxylase activity of a gram-positive intestinal anaerobe by Bacteroides and its significance in the 7-dehydroxylation of ursodeoxycholic acid. *Journal of Lipid Research* 23(8): 1152-1158. doi:10.1016/S0022-2275(20)38052-4
Holzer, P., F. Reichmann, and A. Farzi. 2012. Neuropeptide Y, peptide YY and pancreatic polypeptide in the gut–brain axis. *Neuropeptides* 46(6): 261-274. doi:10.1016/j.npep.2012.08.005
Horvath, C., and C. Wolfrum. 2020. Feeding brown fat: Dietary phytochemicals targeting non-shivering thermogenesis to control body weight. *Proceedings of the Nutrition Society* 79: 338-356. doi:10.1017/S0029665120006928
Hu, J., and M. Christian. 2017. Hormonal factors in the control of the browning of white adipose tissue. *Hormone Molecular Biology and Clinical Investigation* 31(1). doi:10.1515/hmbci-2017-0017
Hu, J., I. Kyrou, B. K. Tan, G. K. Dimitriadis, M. Ramanjaneya, G. Tripathi, Y. Patel, S. James, M. Kawan, J. Chen, et al. 2016. Short-Chain Fatty Acid Acetate Stimulates Adipogenesis and Mitochondrial Biogenesis via GPR43 in Brown Adipocytes. *Endocrinology* 157(5): 1881-1894. doi:10.1210/en.2015-1944
Hu, J., Z. Wang, B. K. Tan, and M. Christian. 2020. Dietary polyphenols turn fat “brown”: A narrative review of the possible mechanisms. *Trends In Food Science & Technology* 97: 221-232. doi:10.1016/j.tifs.2020.01.013
Hu, T., X. Yuan, G. Wei, H. Luo, H. J. Lee, and W. Jin. 2018. Myricetin-induced brown adipose tissue activation prevents obesity and insulin resistance in db/db mice. *European Journal of Nutrition* 57(1): 391-403. doi:10.1007/s00394-017-1433-z
Hu, T., X. Yuan, R. Ye, H. Zhou, J. Lin, C. Zhang, H. Zhang, G. Wei, M. Dong, Y. Huang, et al. 2017. Brown adipose tissue activation by rutin ameliorates polycystic ovary syndrome in rat. *The Journal of Nutritional Biochemistry* 47: 21-28. doi:10.1016/j.jnutbio.2017.04.012
Hui, S., Y. Liu, L. Huang, L. Zheng, M. Zhou, H. Lang, X. Wang, L. Yi, and M. Mi. 2020. Resveratrol enhances brown adipose tissue activity and white adipose tissue browning in part by regulating bile acid metabolism via gut microbiota remodeling. *International Journal of Obesity* 44(8): 1678-1690. doi:10.1038/s41366-020-0566-y
Ikeda, K., P. Maretich, and S. Kajimura. 2018. The Common and Distinct Features of Brown and Beige Adipocytes. *Trends in Endocrinology & Metabolism* 29(3): 191-200. doi:10.1016/j.tem.2018.01.001
Ishii, M., T. Toda, N. Ikarashi, Y. Kusunoki, R. Kon, W. Ochiai, Y. Machida, and K. Sugiyama. 2014. Gastrectomy increases the expression of hepatic cytochrome P450 3A by increasing lithocholic acid-producing enteric bacteria in mice.

Biological and Pharmaceutical Bulletin 37: 298-305. doi:10.1248/bpb.b13-00824

Jenner, A. M., J. Rafter, and B. Halliwell. 2005. Human fecal water content of phenolics: The extent of colonic exposure to aromatic compounds. *Free Radical Biology and Medicine* 38(6): 763-772. doi:10.1016/j.freeradbiomed.2004.11.020

Jeon, H. J., D. K. Choi, J. Choi, S. Lee, H. Lee, J. H. Yu, and S. H. Min. 2021. D-Mannitol Induces a Brown Fat-like Phenotype via a β3-Adrenergic Receptor-Dependent Mechanism. *Cells* 10(4): 768. doi:10.3390/cells10040768

Jiao, X., Y. Wang, Y. Lin, Y. Lang, E. Li, X. Zhang, Q. Zhang, Y. Feng, X. Meng, and B. Li. 2019. Blueberry polyphenols extract as a potential prebiotic with anti-obesity effects on C57BL/6 J mice by modulating the gut microbiota. *The Journal of Nutritional Biochemistry* 64: 88-100. doi:10.1016/j.jnutbio.2018.07.008

Jung, Y., J. Park, H. L. Kim, J. E. Sim, D. H. Youn, J. Kang, S. Lim, M. Y. Jeong, W. M. Yang, S. G. Lee, et al. 2018. Vanillic acid attenuates obesity via activation of the AMPK pathway and thermogenic factors in vivo and in vitro. *The FASEB Journal* 32(3): 1388-1402. doi:10.1096/fj.201700231RR

Júnior, R. E. M., L. M. de Carvalho, D. Carlos dos Reis, G. D. Cassali, A. M. C. Faria, T. U. Maioli, and A. L. B. Godard. 2021. Diet-induced obesity leads to alterations in behavior and gut microbiota composition in mice. *The Journal of Nutritional Biochemistry* 92:108622. doi:10.1016/j.jnutbio.2021.108622

Kábelová, A., H. Malínská, I. Marková, O. Oliyarnyk, B. Chylíková, and O. Šeda. 2021. Ellagic Acid Affects Metabolic and Transcriptomic Profiles and Attenuates Features of Metabolic Syndrome in Adult Male Rats. *Nutrients* 13(3):804. doi:10.3390/nu13030804

Kamiya, T., R. Nagamine, M. Sameshima-Kamiya, M. Tsubata, M. Ikeguchi, and K. Takagaki. 2012. The isoflavone-rich fraction of the crude extract of the Puerariae flower increases oxygen consumption and BAT UCP1 expression in high-fat diet-fed mice. *Global Journal of Health Science* 4(5): 147-155. doi:10.5539/gjhs.v4n5p147

Kang, J., J. Park, W. Y. Park, W. Jiao, S. Lee, Y. Jung, D. H. Youn, G. Song, S. Y. Cho, W. Y. Kim, et al. 2020. A phytoestrogen secoisolariciresinol diglucoside induces browning of white adipose tissue and activates non-shivering thermogenesis through AMPK pathway. *Pharmacological Research* 158: 104852. doi:10.1016/j.phrs.2020.104852

Kayser, B., and S. Verges. 2013. Hypoxia, energy balance and obesity: from pathophysiological mechanisms to new treatment strategies. *Obesity Reviews* 14: 579-592. doi:10.1111/obr.12034

Kim, H. L., J. Park, Y. Jung, K. S. Ahn, and J. Y. Um. 2019. Platycodin D, a novel activator of AMP-activated protein kinase, attenuates obesity in db/db mice via regulation of adipogenesis and thermogenesis. *Phytomedicine* 52: 254-263. doi:10.1016/j.phymed.2018.09.227

Kim, H. Y., K. Kim, Y. M. Lee, and H. Cho. 2017. Aster pseudoglehni extract

stimulates cholecystokinin and serotonin secretion in vitro and reduces gastric emptying in vivo. *Journal of Functional Foods* 35: 436-446. doi:10.1016/j.jff.2017.06.014

Kim, M., T. Furuzono, K. Yamakuni, Y. Li, Y. I. Kim, H. Takahashi, R. Ohue-Kitano, H.-F. Jheng, N. Takahashi, Y. Kano, et al. 2017. 10-oxo-12(Z)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, enhances energy metabolism by activation of TRPV1. *The FASEB Journal* 31(11): 5036-5048. doi:10.1096/fj.201700151R

Kimura, I., D. Inoue, T. Maeda, T. Hara, A. Ichimura, S. Miyauchi, M. Kobayashi, A. Hirasawa, and G. Tsujimoto. 2011. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proceedings of the National Academy of Sciences of the United States of America* 108: 8030-8035.

Kou, G., P. Li, Y. Hu, H. Chen, A. Nyantakyiwaa Amoah, S. Seydou Traore, Z. Cui, Q. Lyu. 2021. Nobiletin activates thermogenesis of brown and white adipose tissue in high-fat diet-fed C57BL/6 mice by shaping the gut microbiota. *The FASEB Journal* 35(2): e21267. doi:10.1096/fj.202002197R

Krieger, J.-P., E. P. S. d. Conceição, G. Sanchez-Watts, M. Arnold, K. G. Pettersen, M. Mohammed, S. Modica, P. Lossel, S. F. Morrison, C. J. Madden, A. G. Watts, W. Langhans, and S. J. Lee. 2018. Glucagon-like peptide-1 regulates brown adipose tissue thermogenesis via the gut-brain axis in rats. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 315(4): R708-R720. doi:10.1152/ajpregu.00068.2018

Kuang, J., X. Zheng, F. Huang, S. Wang, M. Li, M. Zhao, C. Sang, K. Ge, Y. Li, J. Li, et al. 2020. Anti-Adipogenic Effect of Theabrownin Is Mediated by Bile Acid Alternative Synthesis via Gut Microbiota Remodeling. *Metabolites* 10: 475. doi:10.3390/metabo10110475

Kwon, E. Y., and M. S. Choi. 2019. Dietary Eriodictyol Alleviates Adiposity, Hepatic Steatosis, Insulin Resistance, and Inflammation in Diet-Induced Obese Mice. *International Journal of Molecular Sciences* 20(5): 1227. doi:10.3390/ijms20051227

La Spina, M., E. Galletta, M. Azzolini, S. Gomez Zorita, S. Parrasia, M. Salvalaio, A. Salmaso, and L. Biasutto. 2019. Browning Effects of a Chronic Pterostilbene Supplementation in Mice Fed a High-Fat Diet. *International Journal of Molecular Sciences* 20(21): 5377. doi:10.3390/ijms20215377

Lee, K., Y. J. Seo, J. H. Song, S. Chei, and B. Y. Lee. 2019. Ginsenoside Rg1 promotes browning by inducing UCP1 expression and mitochondrial activity in 3T3-L1 and subcutaneous white adipocytes. *Journal of Ginseng Research* 43: 589-599. doi: 10.1016/j.jgr.2018.07.005

Lee, M.-S., Y. Shin, S. Jung, and Y. Kim. 2017. Effects of epigallocatechin-3-gallate on thermogenesis and mitochondrial biogenesis in brown adipose tissues of diet-induced obese mice. *Food & Nutrition Research* 61(1): 1325307. doi:10.1080/16546628.2017.1325307

Lee, S., G. Sanchez-Watts, J.-P. Krieger, A. Pignalosa, P. Norell, A. Cortella, K. G.

Pettersen, D. Vrdoljak, M. Hayes, S. Kanoski, et al. 2018. Loss of dorsomedial hypothalamic GLP-1 signaling reduces BAT thermogenesis and increases adiposity. *Molecular Metabolism* 11:33-46. doi:10.1016/j.molmet.2018.03.008

Li, B., L. Li, M. Li, S. M. Lam, G. Wang, Y. Wu, H. Zhang, C. Niu, X. Zhang, X. Liu, et al. 2019. Microbiota Depletion Impairs Thermogenesis of Brown Adipose Tissue and Browning of White Adipose Tissue. *Cell Reports* 26(10): 2720-2737. doi:10.1016/j.celrep.2019.02.015

Li, C., H. Zhang, and X. Li. 2020. The Mechanism of Traditional Chinese Medicine for the Treatment of Obesity. *Diabetes, Metabolic Syndrome and Obesity : Targets and Therapy* 13:3371-3381. doi:10.2147/DMSO.S274534

Li, Y., X. Ji, H. Wu, X. Li, H. Zhang, and D. Tang. (2021). Mechanisms of traditional Chinese medicine in modulating gut microbiota metabolites-mediated lipid metabolism. *Journal of Ethnopharmacology, 278*, 114207. doi:10.1016/j.jep.2021.114207

Li, Y., K. Schnabl, S. M. Gabler, M. Willershäuser, J. Reber, A. Karlas, S. Laurila, M. Lahesmaa, M. Din, A. Bast-Habersbrunner, et al. 2018. Secretin-Activated Brown Fat Mediates Prandial Thermogenesis to Induce Satiation. *Cell* 175(6): 1561-1574. doi:10.1016/j.cell.2018.10.016

Li, Z., C. X. Yi, S. Katiraei, S. Kooijman, E. Zhou, C. K. Chung, Y. Gao, J. K. van den Heuvel, O. C. Meijer, J. F. P. Berbée, et al. 2018. Butyrate reduces appetite and activates brown adipose tissue via the gut-brain neural circuit. *Gut* 67(7): 1269-1279. doi:10.1136/gutjnl-2017-314050

Liao, W., X. Yin, Q. Li, H. Zhang, Z. Liu, X. Zheng, L. Zheng, and X. Feng. 2018. Resveratrol-Induced White Adipose Tissue Browning in Obese Mice by Remodeling Fecal Microbiota. *Molecules* 23(12): 3356. doi:10.3390/molecules23123356

Lin, H. V., A. Frassetto, E. J. Kowalik Jr, A. R. Nawrocki, M. M. Lu, J. R. Kosinski, J. A. Hubert, D. Szeto, X. Yao, G. Forrest, et al. 2012. Butyrate and Propionate Protect against Diet-Induced Obesity and Regulate Gut Hormones via Free Fatty Acid Receptor 3-Independent Mechanisms. *Plos One* 7(4):e35240. doi:10.1371/journal.pone.0035240

Lin, L., P. K. Saha, X. Ma, I. O. Henshaw, L. Shao, B. H. J. Chang, E. D. Buras, T. Qiang, L. Chan, and Y. Sun. 2011. Ablation of ghrelin receptor reduces adiposity and improves insulin sensitivity during aging by regulating fat metabolism in white and brown adipose tissues. Plos One 10(6): 996-1010. doi:10.1111/j.1474-9726.2011.00740.x

Lin, R., W. Liu, M. Piao, and H. Zhu 2017. A review of the relationship between the gut microbiota and amino acid metabolism. *Amino Acids* 49(12): 2083-2090. doi:10.1007/s00726-017-2493-3

Lin, S., Z. Wang, K. L. Lam, S. Zeng, B. K. Tan, and J. Hu. 2019. Role of intestinal microecology in the regulation of energy metabolism by dietary polyphenols and their metabolites. *Food & Nutrition Research* 63 doi:10.29219/fnr.v63.1518

Liu, B., A. J. Page, A. T. Hutchison, G. A. Wittert, and L. K. Heilbronn. 2019.

Intermittent fasting increases energy expenditure and promotes adipose tissue browning in mice. *Nutrition* 66: 38-43. doi: 10.1016/j.nut.2019.03.015

Liu, J., Z. He, N. Ma, and Z. Y. Chen. 2020. Beneficial Effects of Dietary Polyphenols on High-Fat Diet-Induced Obesity Linking with Modulation of Gut Microbiota. *Journal of Agricultural and Food Chemistry* 68(1): 33-47. doi.:10.1021/acs.jafc.9b06817

Liu, X., Z. Zheng, X. Zhu, M. Meng, L. Li, Y. Shen, Q. Chen, D. Wang, ,Z. Zhang, C. Li, et al. 2013. Brown adipose tissue transplantation improves whole-body energy metabolism. *Cell Research* 23(6): 851-854. doi:10.1038/cr.2013.64

Liu, Z., D. D. Li, Y. Liu, and L. L. Zhu. 2017. Apigetrin attenuates high fat diet-induced intestinal inflammation and nonalcoholic fatty liver disease (NAFLD) process. *Oncotarget* 5. doi:10.18632/oncotarget.23544

Lucchini, F. C., S. Wueest, T. D. Challa, F. Item, S. Modica, M. Borsigova, Y. Haim, C. Wolfrum, A. udich, and D. Konrad. 2020. ASK1 inhibits browning of white adipose tissue in obesity. *Nature Communications* 11: 642. doi: 10.1038/s41467-020-15483-7

Ma, Y., M. Gao, and D. Liu. 2015. Chlorogenic Acid Improves High Fat Diet-Induced Hepatic Steatosis and Insulin Resistance in Mice. *Pharmaceutical Research* 32: 1200-1209. doi: 10.1007/s11095-014-1526-9

Ma, P., P. He, C. Y. Xu, B. Y. Hou, G. F. Qiang, and G. H. Du. 2020. Recent developments in natural products for white adipose tissue browning. *Chinese Journal of Natural Medicines* 18(11): 803-817. doi:10.1016/S1875-5364(20)60021-8

Madden, C. J. 2013. Systemic CCK increases brown adipose tissue sympathetic nerve activity. *The FASEB Journal* 27(S1): 1120.5-1120.5. doi:10.1096/fasebj.27.1_supplement.1120.5

Mano-Otagiri, A., A. Iwasaki-Sekino, T. Nemoto, H. Ohata, Y. Shuto, H. Nakabayashi, H. Sugihara, S. Oikawa, and T. Shibasaki. 2010. Genetic suppression of ghrelin receptors activates brown adipocyte function and decreases fat storage in rats. *Regulatory Peptides* 160(1): 81-90. doi:10.1016/j.regpep.2009.11.010

Martín, M. Á., and S. Ramos. 2021. Impact of Dietary Flavanols on Microbiota, Immunity and Inflammation in Metabolic Diseases. *Nutrients* 13(3): 850. doi:10.3390/nu13030850

Mele, L., G. Bidault, P. Mena, A. Crozier, F. Brighenti, A. Vidal-Puig, and D. Del Rio. 2017. Dietary (Poly)phenols, Brown Adipose Tissue Activation, and Energy Expenditure: A Narrative Review. *Advances in Nutrition* 8: 694-704. doi: 10.3945/an.117.015792

Melguizo Rodríguez, L., R. Illescas-Montes, V. J. Costela-Ruiz, and O. García-Martínez. 2020. Stimulation of brown adipose tissue by polyphenols in extra virgin olive oil. *Critical Reviews in Food Science and Nutrition* 1-8. doi:10.1080/10408398.2020.1799930

Melvin, A., C. W. le Roux, and N. G. Docherty. 2016. The Gut as an Endocrine Organ: Role in the Regulation of Food Intake and Body Weight. *Current Atherosclerosis Reports* 18(8): 49. doi:10.1007/s11883-016-0599-9

Mestdagh, R., M. E. Dumas, S. Rezzi, S. Kochhar, E. Holmes, S. P. Claus, and J. K. Nicholson. 2012. Gut Microbiota Modulate the Metabolism of Brown Adipose Tissue in Mice. *Journal of Proteome Research* 11(2): 620-630. doi:10.1021/pr200938v

Mizunoya, W., H. Miyahara, S. Okamoto, M. Akahoshi, T. Suzuki, M. K. Q., Do, H. Ohtsubo, Y. Komiya, M. Lan, T. Waga, et al. 2015. Improvement of Endurance Based on Muscle Fiber-Type Composition by Treatment with Dietary Apple Polyphenols in Rats. *Plos One* 10: e0134303. doi:10.1371/journal.pone.0134303

Monagas, M., M. Urpi-Sarda, F. Sánchez-Patán, R. Llorach, I. Garrido, C. Gómez-Cordovés, C. Andres-Lacueva, and B. Bartolomé. 2010. Insights into the metabolism and microbial biotransformation of dietary flavan-3-ols and the bioactivity of their metabolites. *Food & Function* 1(3): 233-253. doi:10.1039/C0FO00132E

Monfort-Pires, M., M. U-Din, G. A. Nogueira, J. de Almeida-Faria, D. Sidarta-Oliveira, M. R. Sant'Ana, J. C. De Lima-Júnior, D. E. Cintra, H. P. de Souza, S. R. G. Ferreira, et al. 2020. Short Dietary Intervention with Olive Oil Increases Brown Adipose Tissue Activity in Lean but not Overweight Subjects. *The Journal of Clinical Endocrinology & Metabolism* 106: 472-484.

Moreno-Navarrete, J. M., and J. M. Fernandez-Real. 2019. The gut microbiota modulates both browning of white adipose tissue and the activity of brown adipose tissue. *Reviews in Endocrine and Metabolic Disorders* 20(4): 387-397. doi:10.1007/s11154-019-09523-x

Moreno-Navarrete, J. M., M. Serino, V. Blasco-Baque, V. Azalbert, R. H. Barton, M. Cardellini, J. Latorre, F. Ortega, M. Sabater-Masdeu, R. Burcelin, et al. 2018. Gut Microbiota Interacts with Markers of Adipose Tissue Browning, Insulin Action and Plasma Acetate in Morbid Obesity. *Molecular Nutrition & Food Research* 62(3):1700721. doi:10.1002/mnfr.201700721

Mosqueda-Solís, A., J. Sánchez, M. P. Portillo, A. Palou, and C Picó. 2018. Combination of Capsaicin and Hesperidin Reduces the Effectiveness of Each Compound To Decrease the Adipocyte Size and To Induce Browning Features in Adipose Tissue of Western Diet Fed Rats. *Journal of Agricultural and Food Chemistry* 66(37): 9679-9689. doi:10.1021/acs.jafc.8b02611

Neyrinck, A. M., L. B. Bindels, L. Geurts, M. Van Hul, P. D. Cani, and N. M. Delzenne. 2017. A polyphenolic extract from green tea leaves activates fat browning in high-fat-diet-induced obese mice. *The Journal of Nutritional Biochemistry* 49: 15-21. doi:10.1016/j.jnutbio.2017.07.008

Nøhr, M. K., N. Bobba, B. Richelsen, S. Lund, and S. B. Pedersen. 2017. Inflammation Downregulates UCP1 Expression in Brown Adipocytes Potentially via SIRT1 and DBC1 Interaction. *International Journal of Molecular Sciences* 18(5): 1006. doi:10.3390/ijms18051006

Nomura, S., T. Ichinose, M. Jinde, Y. Kawashima, K. Tachiyashiki, and K. Imaizumi. 2008. Tea catechins enhance the mRNA expression of uncoupling protein 1 in rat brown adipose tissue. *The Journal of Nutritional Biochemistry* 19(12):

840-847. doi:10.1016/j.jnutbio.2007.11.005

Ohno, H., K. Shinoda, Bruce M. Spiegelman, and S. Kajimura. 2012. PPARγ agonists Induce a White-to-Brown Fat Conversion through Stabilization of PRDM16 Protein. *Cell Metabolism* 15:395-404. doi: 10.1016/j.cmet.2012.01.019

Okla, M., J. O. Al Madani, S. Chung, and M. Alfayez. 2020. Apigenin Reverses Interleukin-1β-Induced Suppression of Adipocyte Browning via COX2/PGE2 Signaling Pathway in Human Adipocytes. *Molecular Nutrition & Food Research* 64(1):1900925.

Okla, M., W. Wang, I. Kang, A. Pashaj, T. Carr, and S. Chung. 2015. Activation of Toll-like receptor 4 (TLR4) attenuates adaptive thermogenesis via endoplasmic reticulum stress. *Journal of Biological Chemistry* 290: 26476-26490. doi: 10.1074/jbc.M115.677724

Otton, R., A. P. Bolin, L. T. Ferreira, M. P. Marinovic, A. L. S. Rocha, and M. A. Mori. 2018. Polyphenol-rich green tea extract improves adipose tissue metabolism by down-regulating miR-335 expression and mitigating insulin resistance and inflammation. *The Journal of Nutritional Biochemistry 57*: 170-179. doi:10.1016/j.jnutbio.2018.03.024

Palacios-González, B., A. Vargas-Castillo, L. A. Velázquez-Villegas, S. Vasquez-Reyes, P. López, L. G. Noriega, G. Aleman, C. Tovar-Palacio, I. Torre-Villalvazo, L. J. Yang, et al. 2019. Genistein increases the thermogenic program of subcutaneous WAT and increases energy expenditure in mice. *The Journal of Nutritional Biochemistry* 68:59-68. doi:10.1016/j.jnutbio.2019.03.012

Park, E. J., and J. M. Pezzuto. 2015. The pharmacology of resveratrol in animals and humans. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* 1852(6):1071-1113. doi:10.1016/j.bbadis.2015.01.014

Park, H. J., H. J. Kim, S. R. Kim, M. S. Choi, and U. J. Jung. 2017. Omija fruit ethanol extract improves adiposity and related metabolic disturbances in mice fed a high-fat diet. *The Journal of Nutritional Biochemistry* 41: 137-141. doi: 10.1016/j.jnutbio.2016.12.016

Paraíso, A. F., J. N. Sousa, J. M. O. Andrade, E. S. Mangabeira, D. d. F. Lelis, A. M. B. de Paula, A. M. E. B. L. Martins, W. J. N. Lima, A. L. S. Guimarães, G. A. Melo, et al. 2019. Oral gallic acid improves metabolic profile by modulating SIRT1 expression in obese mice brown adipose tissue: A molecular and bioinformatic approach. *Life Sciences* 237:116914. doi:10.1016/j.lfs.2019.116914

Pei, L., T. Wan, S. Wang, M. Ye, Y. Qiu, R. Jiang, N. Pang, Y. Huang, Y. Zhou, R. Jiang, et al. 2018. Cyanidin-3-O-β-glucoside regulates the activation and the secretion of adipokines from brown adipose tissue and alleviates diet induced fatty liver. *Biomedicine & Pharmacotherapy* 105: 625-632. doi:10.1016/j.biopha.2018.06.018

Pei, Y., D. Otieno, I. Gu, S. O. Lee, J. S. Parks, K. Schimmel, and H. W. Kang. 2021. Effect of quercetin on nonshivering thermogenesis of brown adipose tissue in high-fat diet-induced obese mice. *The Journal of Nutritional Biochemistry* 88:

108532. doi:10.1016/j.jnutbio.2020.108532

Peres Valgas da Silva, C., D. Hernández-Saavedra, J. D. White, and K. I. Stanford. 2019. Cold and Exercise: Therapeutic Tools to Activate Brown Adipose Tissue and Combat Obesity. *Biology 8*(1): 9 doi: 10.3390/biology8010009

Prakash, S., U. Rai, A. Uniyal, V. Tiwari, and S. Singh. 2020. Sitagliptin mitigates oxidative stress and up-regulates mitochondrial biogenesis markers in Brown adipose tissues of high-fat diet fed obese mice through AMPK phosphorylation. *Obesity Medicine* 19: 100265. doi: 10.1016/j.obmed.2020.100265

Psichas, A., M. L. Sleeth, K. G. Murphy, L. Brooks, G. A. Bewick, A. C. Hanyaloglu, M. A. Ghatei, S. R. Bloom, and G. Frost. 2015. The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. *International Journal of Obesity* 39(3): 424-429. doi:10.1038/ijo.2014.153

Quan, L. H., C. Zhang, M. Dong, J. Jiang, H. Xu, C. Yan, X. Liu, H. Zhou, H. Zhang, L. Chen, et al. 2020. Myristoleic acid produced by enterococci reduces obesity through brown adipose tissue activation. *Cut* 69(7):1239-1247. doi:10.1136/gutjnl-2019-319114

Ramirez, L. A., J. Quezada, L. Duarte, F. Concha, L. Escobillana, M. A. Rincon-Cervera, F. Perez-Bravo, A. A. Elorza, R. Bravo-Sagua, and D. F. Garcia-Diaz. 2021. The administration of an extract from Berberis microphylla stimulates energy expenditure, thermogenesis and mitochondrial dynamics in mice brown adipose tissue. *Food Bioscience* 41:100988. doi:10.1016/j.fbio.2021.100988

Raybould, H. E. 2007. Mechanisms of CCK signaling from gut to brain. *Current Opinion in Pharmacology* 7(6): 570-574. doi:10.1016/j.coph.2007.09.006

Rodríguez, A., S. Becerril, L. Méndez-Giménez, B. Ramírez, N. Sáinz, V. Catalán, J. Gómez-Ambrosi, and G. Frühbeck. 2015. Leptin administration activates irisin-induced myogenesis via nitric oxide-dependent mechanisms, but reduces its effect on subcutaneous fat browning in mice. *International Journal of Obesity* 39(3):397-407. doi:10.1038/ijo.2014.166

Rodriguez Lanzi, C., D. J. Perdicaro, J. Gambarte Tudela, V. Muscia, A. R. Fontana, P. I. Oteiza, M. A.V. Prieto. 2020. Grape pomace extract supplementation activates FNDC5/irisin in muscle and promotes white adipose browning in rats fed a high-fat diet. *Food & Function* 11:1537-1546. doi: 10.1039/c9fo02463h

Saito, M., M. Matsushita, T. Yoneshiro, and Y. Okamatsu-Ogura. 2020. Brown Adipose Tissue, Diet-Induced Thermogenesis, and Thermogenic Food Ingredients: From Mice to Men. *Frontiers in Endocrinology* 11: 222. doi:10.3389/fendo.2020.00222

Schnabl, K., Y. Li, and M. Klingenspor. 2020. The gut hormone secretin triggers a gut–brown fat–brain axis in the control of food intake. *Experimental Physiology* 105(8): 1206-1213. doi:10.1113/EP087878

Schalla, M. A., and A. Stengel. 2020. Effects of microbiome changes on endocrine ghrelin signaling–A systematic review. *Peptides* 133: 170388.

doi:10.1016/j.peptides.2020.170388

Schneeberger, M., A. Everard, A. G. Gómez-Valadés, S. Matamoros, S. Ramírez, N. M. Delzenne, R. Gomis, M. Claret, and P. D. Cani. 2015. Akkermansia muciniphila inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. *Scientific Reports* 5(1):16643. doi.:10.1038/srep16643

Schugar, R. C., D. M. Shih, M. Warrier, R. N. Helsley, A. Burrows, D. Ferguson, A. L. Brown, A. D. Gromovsky, M. Heine, A. Chatterjee, et al.. 2017. The TMAO-Producing Enzyme Flavin-Containing Monooxygenase 3 Regulates Obesity and the Beiging of White Adipose Tissue. *Cell Reports* 19(12): 2451-2461. doi: 10.1016/j.celrep.2017.05.077

Seo, S. H., S. M. Jo, T. T. M. Truong, G. Zhang, D.-S. Kim, M. Lee, Y. Lee, and I. Kang. 2021. Peanut sprout rich in p-coumaric acid ameliorates obesity and lipopolysaccharide-induced inflammation and the inhibition of browning in adipocytes via mitochondrial activation. *Food & Function* 12: 5361-5374. doi: 10.1039/D1FO00342A

Septembre-Malaterre, A., F. Le Sage, S. Hatia, A. Catan, L. Janci, and M. P. Gonthier. 2016. Curcuma longa polyphenols improve insulin-mediated lipid accumulation and attenuate proinflammatory response of 3T3-L1 adipose cells during oxidative stress through regulation of key adipokines and antioxidant enzymes. *Biofactors* 42(4): 418-430. doi:10.1002/biof.1288

Shen, H. H., S. Y. Huang, C. W. Kung, S. Y. Chen, Y. F. Chen, P. Y. Cheng, K. K. Lam, and Y. M. Lee. 2019. Genistein ameliorated obesity accompanied with adipose tissue browning and attenuation of hepatic lipogenesis in ovariectomized rats with high-fat diet. *The Journal of Nutritional Biochemistry* 67: 111-122. doi:10.1016/j.jnutbio.2019.02.001

Shen, W., C. C. Chuang, K. Martinez, T. Reid, J. M. Brown, L. Xi, L. Hixson, R. Hopkins, J. Starnes, and M. McIntosh. 2013. Conjugated linoleic acid reduces adiposity and increases markers of browning and inflammation in white adipose tissue of mice. *Journal of Lipid Research* 54(4): 909-922. doi:10.1194/jlr.M030924

Sheng, Y., J. Liu, S. Zheng, F. Liang, Y. Luo, K. Huang, W. Xu, and X. He. 2019. Mulberry leaves ameliorate obesity through enhancing brown adipose tissue activity and modulating gut microbiota. *Food & Function* 10(8): 4771-4781. doi:10.1039/C9FO00883G

Shin, C. M., D. H. Lee, A. Y. Seo, H. J. Lee, S. B. Kim, W. C. Son, Y. Kim, S. Lee, S. H. Park, N. Kim, et al. 2018. Green tea extracts for the prevention of metachronous colorectal polyps among patients who underwent endoscopic removal of colorectal adenomas: A randomized clinical trial. *Clinical Nutrition* 37(2): 452-458. doi:10.1016/j.clnu.2017.01.014

Simó, C., and V. García-Cañas. 2020. Dietary bioactive ingredients to modulate the gut microbiota-derived metabolite TMAO. New opportunities for functional food development. *Food & Function* 11(8): 6745-6776. doi:10.1039/D0FO01237H

Song, N. J., S. Choi, P. Rajbhandari, S. H. Chang, S. Kim, L. Vergnes, S. M. Kwon, J. H. Yoon, S. Lee, J. M. Ku, et al. 2016. Prdm4 induction by the small molecule butein promotes white adipose tissue browning. *Nature Chemical Biology* 12, 479-481. doi: 10.1038/nchembio.2081

Song, Z., X. Revelo, W. Shao, L. Tian, K. Zeng, H. Lei, H. S. Sun, M. Woo, D. Winer, and T. Jin. 2018. Dietary Curcumin Intervention Targets Mouse White Adipose Tissue Inflammation and Brown Adipose Tissue UCP1 Expression. *Obesity* 26(3): 547-558. doi:10.1002/oby.22110

Suárez-Zamorano, N., S. Fabbiano, C. Chevalier, O. Stojanović, D. J. Colin, A. Stevanović, C. Veyrat-Durebex, V. Tarallo, D. Rigo, S. Germain, et al. 2015. Microbiota depletion promotes browning of white adipose tissue and reduces obesity. *Nature Medicine* 21(12): 1497-1501. doi:10.1038/nm.3994

Sudhakar, M., S. J. Sasikumar, S. Silambanan, D. Natarajan, R. Ramakrishnan, A. J. Nair, and M. S. Kiran. 2020. Chlorogenic acid promotes development of brown adipocyte-like phenotype in 3T3-L1 adipocytes. *Journal of Functional Foods* 74:104161. doi:10.1016/j.jff.2020.104161

Sugita, J., T. Yoneshiro, T. Hatano, S. Aita, T. Ikemoto, H. Uchiwa, T. Iwanaga,T. Kameya, Y. Kawai, and M. Saito. 2013. Grains of paradise (Aframomum melegueta) extract activates brown adipose tissue and increases whole-body energy expenditure in men. *British Journal of Nutrition* 110(4): 733-738. doi: 10.1017/s0007114512005715Sun

Sun, E. W. L., A. M. Martin, R. L. Young, and D. J. Keating. 2019. The Regulation of Peripheral Metabolism by Gut-Derived Hormones. *Frontiers in endocrinolog*y 9: 754. doi:10.3389/fendo.2018.00754

Sun, Y. S., and W. Qu. 2019. Dietary Apigenin promotes lipid catabolism, thermogenesis, and browning in adipose tissues of HFD-Fed mice. *Food and Chemical Toxicology* 133:110780. doi:10.1016/j.fct.2019.110780

Tabasco, R., F. Sánchez-Patán, M. Monagas, B. Bartolomé, M. Victoria Moreno-Arribas, C. Peláez, and T. Requena. 2011. Effect of grape polyphenols on lactic acid bacteria and bifidobacteria growth: Resistance and metabolism. *Food Microbiology* 28(7):1345-1352. doi:10.1016/j.fm.2011.06.005

Tamura, Y., S. Tomiya, J. Takegaki, K. Kouzaki, A. Tsutaki, and K. Nakazato. 2020. Apple polyphenols induce browning of white adipose tissue. The Journal of *Nutritional Biochemistry* 77: 108299. doi:10.1016/j.jnutbio.2019.108299

Teodoro, J. S., P. Zouhar, P. Flachs, K. Bardova, P. Janovska, A. P. Gomes, F. V. Duarte, A. R.Varela, A. P. Rolo, C. M. Palmeira, et al. 2014. Enhancement of brown fat thermogenesis using chenodeoxycholic acid in mice. International *Journal of Obesity* 38(8): 1027-1034. doi:10.1038/ijo.2013.230

Thaiss, C. A., S. Itav, D. Rothschild, M. T. Meijer, M. Levy, C. Moresi, L. Dohnalová, S. Braverman, S. Rozin, S. Malitsky, et al. 2016. Persistent microbiome alterations modulate the rate of post-dieting weight regain. *Nature* 540: 544-551. doi: 10.1038/nature20796

Thondam, S. K., D. J. Cuthbertson, and J. P. H. Wilding. 2020. The influence of Glucose-dependent Insulinotropic Polypeptide (GIP) on human adipose tissue

and fat metabolism: Implications for obesity, type 2 diabetes and Non-Alcoholic Fatty Liver Disease (NAFLD). *Peptides* 125: 170208. doi: 10.1016/j.peptides.2019.170208

Tomilov, A., A. Bettaieb, K. Kim, S. Sahdeo, N. Tomilova, A. Lam, K. Hagopian, M. Connell, J. Fong, D. Rowland, et al. 2014. Shc depletion stimulates brown fat activity in vivo and in vitro. *Aging Cell* 13. https://doi.org/10.1111/acel.12267

Ueno, H., H. Yamaguchi, M. Mizuta, and M. Nakazato. 2008. The role of PYY in feeding regulation. *Regulatory Peptides* 145(1): 12-16. doi:10.1016/j.regpep.2007.09.011

Ullmer, C., R. Alvarez Sanchez, U. Sprecher, S. Raab, P. Mattei, H. Dehmlow, S. Sewing, A. Iglesias, J. Beauchamp, and K. Conde-Knape. 2013. Systemic bile acid sensing by G protein-coupled bile acid receptor 1 (GPBAR1) promotes PYY and GLP-1 release. *British Journal of Pharmacology* 169(3): 671-684. doi:10.1111/bph.12158.

Usdin, T. B., E. Mezey, D. C. Button, M. J. Brownstein, and T. I. Bonner. 1993. Gastric inhibitory polypeptide receptor, a member of the secretin-vasoactive intestinal peptide receptor family, is widely distributed in peripheral organs and the brain. *Endocrinology* 133(6): 2861-2870. doi:10.1210/en.133.6.2861

Valladares, A., C. Roncero, M. Benito, and A. Porras. 2001. TNF-α inhibits UCP-1 expression in brown adipocytes via ERKs: Opposite effect of p38MAPK. *Febs Letters* 493(1): 6-11. doi:10.1016/S0014-5793(01)02264-5

Vallianou, N., T. Stratigou, G. S. Christodoulatos, and M. Dalamaga. 2019. Understanding the Role of the Gut Microbiome and Microbial Metabolites in Obesity and Obesity-Associated Metabolic Disorders: Current Evidence and Perspectives. *Current Obesity Reports* 8(3): 317-332. doi:10.1007/s13679-019-00352-2

Van den Beukel, A., and A. Grefhorst. 2014. Interactions between the Gut, the Brain and Brown Adipose Tissue Function. *Frontiers of Hormone Research* 42: 107-122. doi:10.1159/000358320

Wang, L., Y. Wei, C. Ning, M. Zhang, P. Fan, D. Lei, J. Du, M. Gale, Y. Ma, and Y. Yang. 2019. Ellagic acid promotes browning of white adipose tissues in high-fat diet-induced obesity in rats through suppressing white adipocyte maintaining genes. *Endocrine Journal* 66(10): 923-936. doi.:10.1507/endocrj.EJ18-0467

Wang, L., B. Zeng, X. Zhang, Z. Liao, L. Gu, Z. Liu, Q. Zhong, H. Wei, and X. Fang. 2016. The effect of green tea polyphenols on gut microbial diversity and fat deposition in C57BL/6J HFA mice. *Food & Function* 7(12): 4956-4966. doi:10.1039/C6FO01150K

Wang, S., X. Liang, Q. Yang, X. Fu, C. J. Rogers, M. Zhu, B. D. Rodgers, Q. Jiang, M. V. Dodson, and M. Du. 2015. Resveratrol induces brown-like adipocyte formation in white fat through activation of AMP-activated protein kinase (AMPK) α1. *International Journal of Obesity* 39(6): 967-976. doi:10.1038/ijo.2015.23

Wang, S., X. Liang, Q. Yang, X. Fu, M. Zhu, B. D. Rodgers, Q. Jiang, M. Dodson,

and M. Du. 2017. Resveratrol enhances brown adipocyte formation and function by activating AMP-activated protein kinase (AMPK) α1 in mice fed high-fat diet. *Molecular Nutrition & Food Research* 61(4): 1600746. doi:10.1002/mnfr.201600746

Wang, S., M. H. Pan, W. L. Hung, Y. C. Tung, and C. T. Ho. 2019. From white to beige adipocytes therapeutic potential of dietary molecules against obesity and their molecular mechanisms. *Food & Function* 10(3): 1263-1279. doi:10.1039/C8FO02154F

Wang, Z., S. Li, S. Ge, and S. Lin. 2020. Review of Distribution, Extraction Methods, and Health Benefits of Bound Phenolics in Food Plants. *Journal of Agricultural and Food Chemistry* 68(11): 3330-3343. doi:10.1021/acs.jafc.9b06574

Wang, Z., M. Zeng, Z. Wang, F. Qin, J. Chen, and Z. He. 2021a. Dietary Luteolin: A Narrative Review Focusing on Its Pharmacokinetic Properties and Effects on Glycolipid Metabolism. *Journal of Agricultural and Food Chemistry* 69(5): 1441-1454. doi:10.1021/acs.jafc.0c08085

Wang, Z., M. Zeng, Z. Wang, F. Qin, J. Chen, and Z. He. 2021b. Dietary Polyphenols to Combat Nonalcoholic Fatty Liver Disease via the Gut–Brain–Liver Axis: A Review of Possible Mechanisms. *Journal of Agricultural and Food Chemistry* 69(12): 3585-3600. doi:10.1021/acs.jafc.1c00751

Wu, C., P. Yu, and R. Sun. 2021. Adipose tissue and age-dependent insulin resistance: New insights into WAT browning (Review). *International Journal of Molecular Medicine* 47(5): 71. doi:10.3892/ijmm.2021.4904

Wu, J., P. Boström, L. M. Sparks, L. Ye, J. H. Choi, A.-H. Giang, M. Khandekar, K. A. Virtanen, P. Nuutila, G. Schaart, et al. 2012. Beige Adipocytes Are a Distinct Type of Thermogenic Fat Cell in Mouse and Human. *Cell* 150(2): 366-376. doi:10.1016/j.cell.2012.05.016

Wu, M. V., G., Bikopoulos, S. Hung, and R. B. Ceddia. 2014. Thermogenic Capacity Is Antagonistically Regulated in Classical Brown and White Subcutaneous Fat Depots by High Fat Diet and Endurance Training in Rats: IMPACT ON WHOLE-BODY ENERGY EXPENDITURE*. *Journal of Biological Chemistry* 289(49):34129-34140. doi:10.1074/jbc.M114.591008

Wu, Y., N. Ma, P. Song, T. He, C. Levesque, Y. Bai, A. Zhang, and X. Ma. (2019). Grape Seed Proanthocyanidin Affects Lipid Metabolism via Changing Gut Microflora and Enhancing Propionate Production in Weaned Pigs. *The Journal of Nutrition* 149: 1523-1532. doi: 10.1093/jn/nxz102

Xia, B., X. C. Shi, B. C. Xie, M. Q. Zhu, Y. Chen, X. Y. Chu, G. H. Cai, M. Liu, S. Z. Yang, G. A. Mitchell, et al. 2020. Urolithin A exerts antiobesity effects through enhancing adipose tissue thermogenesis in mice. *Plos Biology* 18(3): e3000688. doi:10.1371/journal.pbio.3000688

Xian, Y., R. Fan, J. Shao, A. Mulcahy Toney, S. Chung, and A. E. Ramer-Tait. 2021. Polyphenolic fractions isolated from red raspberry whole fruit, pulp, and seed differentially alter the gut microbiota of mice with diet-induced obesity. *Journal of Functional Foods* 76: 104288. doi:10.1016/j.jff.2020.104288

Xiang, A. S., C. Giles, R. K. C. Loh, M. F. Formosa, N. Eikelis, G. W. Lambert, P. J. Meikle, B. A. Kingwell, and A. L. Carey. 2020. Plasma Docosahexaenoic Acid and Eicosapentaenoic Acid Concentrations Are Positively Associated with Brown Adipose Tissue Activity in Humans. *Metabolites* 10(10): 388. doi: 10.3390/metabo10100388

Xiao, H., and S. Kang. 2020. The Role of the Gut Microbiome in Energy Balance With a Focus on the Gut-Adipose Tissue Axis. *Frontiers in Genetics* 11: 297-297. doi:10.3389/fgene.2020.00297

Xu, J., J. Ge, X. He, Y. Sheng, S. Zheng, C. Zhang, W. Xu, and K. Huang. 2020. Caffeic acid reduces body weight by regulating gut microbiota in diet-induced-obese mice. *Journal of Functional Foods* 74: 104061. doi:10.1016/j.jff.2020.104061

Xu, Y., N. Wang, H.Y. Tan, S. Li, C. Zhang, Z. Zhang, and Y. Feng. 2020. Panax notoginseng saponins modulate the gut microbiota to promote thermogenesis and beige adipocyte reconstruction via leptin-mediated AMPKα/STAT3 signaling in diet-induced obesity. *Theranostics* 10(24): 11302-11323. doi:10.7150/thno.47746

Yabut, J. M., J. D. Crane, A. E. Green, D. J. Keating, W. I. Khan, and G. R. Steinberg. 2019. Emerging Roles for Serotonin in Regulating Metabolism: New Implications for an Ancient Molecule. *Endocrine Reviews* 40:1092-1107. doi: 10.1210/er.2018-00283

Yamazaki, T., Y. Morimoto-Kobayashi, K. Koizumi, C. Takahashi, S. Nakajima, S. Kitao, Y. Taniguchi, M. Katayama, and Y. Ogawa. 2019. Secretion of a gastrointestinal hormone, cholecystokinin, by hop-derived bitter components activates sympathetic nerves in brown adipose tissue. *The Journal of Nutritional Biochemistry* 64: 80-87. doi:10.1016/j.jnutbio.2018.10.009

Yao, H., C. Fan, X. Fan, Y. Lu, Y. Wang, R. Wang, T. Tang, and K. Qi. 2020. Effects of gut microbiota on leptin expression and body weight are lessened by high-fat diet in mice. *British Journal of Nutrition* 124(4): 396-406. doi:10.1017/S0007114520001117

Yasuda, T., T. Masaki, T. Kakuma, and H. Yoshimatsu. 2003. Centrally administered ghrelin suppresses sympathetic nerve activity in brown adipose tissue of rats. *Neuroscience Letters* 349(2): 75-78. doi:10.1016/S0304-3940(03)00789-4

Yoneshiro, T., S. Aita, M. Matsushita, T. Kameya, K. Nakada, Y. Kawai, and M. Saito. 2011. Brown Adipose Tissue, Whole-Body Energy Expenditure, and Thermogenesis in Healthy Adult Men. *Obesity* 19(1):13-16. doi:10.1038/oby.2010.105

Yoneshiro, T., Matsushita, M., Hibi, M., Tone, H., Takeshita, M., Yasunaga, K., Katsuragi, Y., Kameya, T., Sugie, H., and Saito, M. 2017. Tea catechin and caffeine activate brown adipose tissue and increase cold-induced thermogenic capacity in humans. *The American Journal of Clinical Nutrition* 105(4): 873-881. doi: 10.3945/ajcn.116.144972

Yoneshiro, T., Q. Wang, K. Tajima, M. Matsushita, H. Maki, K. Igarashi, Z. Dai. White P. J., McGarrah, R. W., Ilkayeva, O. R., et al. 2019. BCAA catabolism

in brown fat controls energy homeostasis through SLC25A44. *Nature* 572(7771): 614-619. doi:10.1038/s41586-019-1503-x

Yoshimatsu, H., M. Egawa, and G. A. Bray. 1992. Effects of cholecystokinin on sympathetic activity to interscapular brown adipose tissue. *Brain Research* 597(2): 298-303. doi:10.1016/0006-8993(92)91486-X

You, Y., X. Yuan, X. Liu, Liang, C., Meng, M., Huang, Y., Han, X., Guo, J., Ren, C., Zhang, Q., et al. 2017. Cyanidin-3-glucoside increases whole body energy metabolism by upregulating brown adipose tissue mitochondrial function. *Molecular Nutrition & Food Research* 61(11): 1700261. doi:10.1002/mnfr.201700261

Yu, Y. C., J. Li, M. Zhang, J. C. Pan, Y. Yu, J. B. Zhang, L. Zheng, J. M. Si, and Y. Xu 2019. Resveratrol Improves Brain-Gut Axis by Regulation of 5-HT-Dependent Signaling in the Rat Model of Irritable Bowel Syndrome. *Frontiers in Cellular Neuroscience* 13: 30. doi:10.3389/fncel.2019.00030

Yuan, X., Y. Wu, J. Liang, H. Yuan, X. Zhao, D. Zhu, H. Liu, J. Lin, S. Huang, X. Lai, et al. 2016. Phlorizin treatment attenuates obesity and related disorders through improving BAT thermogenesis. *Journal of Functional Foods* 27:429-438. doi:10.1016/j.jff.2016.09.022

Yue, S. J., J. Liu, A. T. Wang, X. T. Meng, Z. R. Yang, C. Peng, H. S. Guan, C. Y. Wang, D. Yan. 2019. Berberine alleviates insulin resistance by reducing peripheral branched-chain amino acids. *American Journal of Physiology-Endocrinology and Metabolism* 316(1): E73-E85. doi:10.1152/ajpendo.00256.2018

Zeng, S. L., S. Z. Li, P. T. Xiao, Y. Y. Cai, C. Chu, B. Z. Chen, P. Li, J. Li, and E. H Liu. 2020. Citrus polymethoxyflavones attenuate metabolic syndrome by regulating gut microbiome and amino acid metabolism. *Science Advances* 6(1). https://doi.org/10.1126/sciadv.aax6208

Zhang, F., F. He, L. Li, L. Guo, B. Zhang, S. Yu, and W. Zhao. 2020. Bioavailability Based on the Gut Microbiota: a New Perspective. *Microbiology and Molecular Biology Reviews* 84(2): e00072-00019. doi:10.1128/MMBR.00072-19

Zhang, H., Y. Hao, C. Wei, B. Yao, S. Liu, H. Zhou, D. Huang, C. Zhang, and Y. Wu, 2019. Chinese medicine Jinlida granules improve high-fat-diet induced metabolic disorders via activation of brown adipose tissue in mice. *Biomedicine & Pharmacotherapy* 114:108781. doi: 10.1016/j.biopha.2019.108781

Zhang, S., J. Zhao, F. Xie, H. He, L. J. Johnston, X. Dai, C. Wu, and X. Ma. 2021. Dietary fiber-derived short-chain fatty acids: A potential therapeutic target to alleviate obesity-related nonalcoholic fatty liver disease. *Obesity Reviews* e13316. doi: 10.1111/obr.13316

Zhang, Z., H. Zhang, B. Li, X. Meng, J. Wang, Y. Zhang, S. Yao, Q. Ma, L. Jin, J. Yang, et al. 2014. Berberine activates thermogenesis in white and brown adipose tissue. *Nature Communications* 5(1): 5493. doi:10.1038/ncomms6493

Zheng, J., S. Zheng, Q. Feng, Q. Zhang, and X. Xiao. 2017. Dietary capsaicin and its anti-obesity potency: from mechanism to clinical implications. *Bioscience*

Reports 37 (3): BSR20170286. doi: 10.1042/BSR20170286

Zhou, F., J. Guo, X. Han, Y. Gao, Q. Chen, W. Huang, J. Zhan, D. Huang, and Y. You. 2020. Cranberry Polyphenolic Extract Exhibits an Antiobesity Effect on High-Fat Diet–Fed Mice through Increased Thermogenesis. *The Journal of Nutrition* 150(8): 2131-2138. doi:10.1093/jn/nxaa163

Zhou, L., X. Xiao, Q. Zhang, J. Zheng, and M. Deng. 2019. Deciphering the Anti-obesity Benefits of Resveratrol: The "Gut Microbiota-Adipose Tissue" Axis. *Frontiers in Endocrinology* 10:413. doi:10.3389/fendo.2019.00413

Zhu, Y., J. Y. Zhang, Y. L. Wei, J. Y. Hao, Y. Q. Lei, W. B. Zhao, Y. H. Xiao, and A. D. Sun. 2020. The polyphenol-rich extract from chokeberry (Aronia melanocarpa L.) modulates gut microbiota and improves lipid metabolism in diet-induced obese rats. *Nutrition & Metabolism* 17(1): 54. doi:10.1186/s12986-020-00473-9

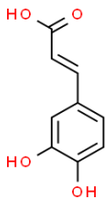
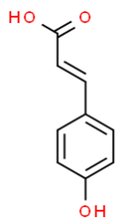
Zou, T., D. Chen, Q. Yang, B. Wang, M. J. Zhu, P. W. Nathanielsz, and M. Du. 2017. Resveratrol supplementation of high-fat diet-fed pregnant mice promotes brown and beige adipocyte development and prevents obesity in male offspring. *The Journal of physiology* 595(5):1547-1562. doi:10.1113/JP273478

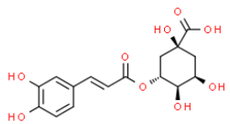
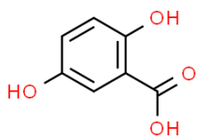
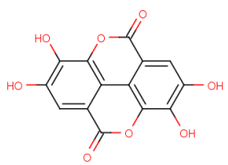
Zou, T., B. Wang, S. Li, Y. Liu, and J. You. 2020. Dietary apple polyphenols promote fat browning in high-fat diet-induced obese mice through activation of adenosine monophosphate-activated protein kinase α. *Journal of the Science of Food and Agriculture* 100(6): 2389-2398. doi:10.1002/jsfa.10248

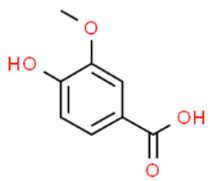
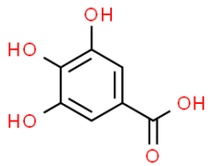
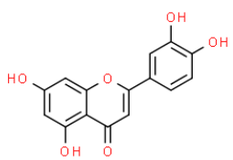
Zou, T., B. Wang, Q. Yang, J. M. de Avila, M. J. Zhu, J. You, D. Chen, and M. Du. 2018. Raspberry promotes brown and beige adipocyte development in mice fed high-fat diet through activation of AMP-activated protein kinase (AMPK) α1. *The Journal of Nutritional Biochemistr*y 55: 157-164. doi:10.1016/j.jnutbio.2018.02.005

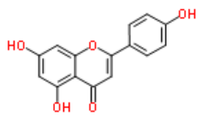
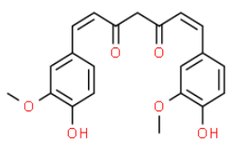
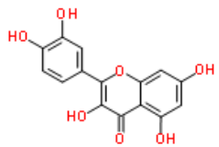
Zou, Y., X. Ju, W. Chen, J. Yuan, Z. Wang, R. E. Aluko, and R. He. 2020. Rice bran attenuated obesity via alleviating dyslipidemia, browning of white adipocytes and modulating gut microbiota in high-fat diet-induced obese mice. *Food & Function* 11(3): 2406-2417. doi:10.1039/C9FO01524H

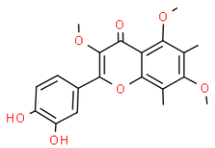
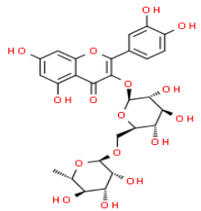
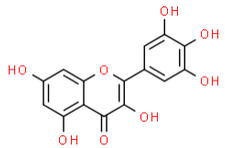
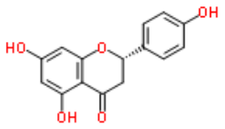
Table 1. Polyphenols function as bioactive substances promoting browning/beiging of WAT and activation of BAT in animal and human models.

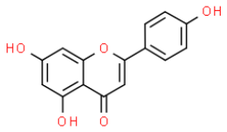
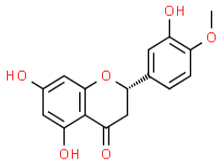
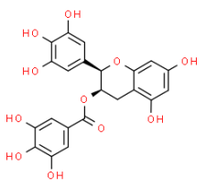
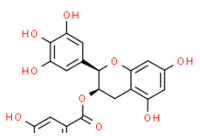
Polyphenols	Structure	Main source	Animal or humans Models	Dosage	Duration	Effects on adipose browning in WAT or/and BAT	References
Phenolic acids							
Hydroxycinnamic acids							
Caffeic acid		 Coffee beans, potatoes, grains, and vegetables	HFD-fed C57BL/6J mice	50mg/kg	8 weeks	Energy expenditure↑; Respiratory quotient values↑	(Xu et al. 2020)
p-Coumaric acid		 Fruits (apples, pears, grapes, oranges, tomatoes and berries), vegetables (e.g. beans, potatoes and onions) and cereals (e.g. maize, oats and wheat)	HFD-fed C57BL/6 Cnc mice	2mg/mL	6 weeks	Energy metabolism.↑; BAT: UCP1, Cidea, and PRDM16↑	(Han et al. 2020b)

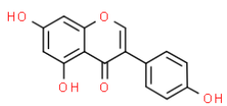
Chlorogenic acid		 Coffee, cherries, apples, honeysuckle and eucommia	HFD-fed C57BL/6 mice	100 mg/kg	15 weeks	Lipid accumulation in BAT↓	(Ma, Gao, and Liu. 2015)
Hydroxybenzoic acids							
Gentisic acid		 Blueberries, grapes, citrus fruits, and kiwi fruits	HFD-fed C57BL/6Cnc mice	2 mg/mL	12 weeks	Energy expenditure↑; BAT: UCP1, PRDM16, and PGC-1α↑	(X. Han et al. 2021)
Ellagic acid		 Pomegranates, grapes, raspberries, and walnuts	SHR-Zbtb16$^{Lx/k.o.}$	50 mg/kg	3 weeks	BAT: UCP1, PRDM16, PGC-1α, Tbx1, and NRF1↑ iWAT: brown/beige markers including UCP1, PRDM16, Cidea, PGC-1α, PPARα; including CD137 and Tmem26 ↑	(Kábelová et al. 2021) (L. Wang et al. 2019)
			HFD-fed SD rats	10 and 30 mg/kg/day	24 weeks		

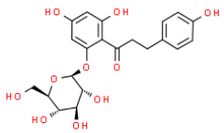
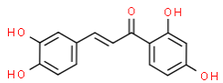
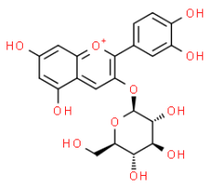
Vanillic acid		 Root of Angelica sinensis	HFD-C57BL/6J mice	0.5% w/w	13 weeks	iWAT: UCP1, PRDM16, Cidea, Tmem26, CD137, HOXC8 and Tbx1↑	(Han et al. 2018)
Gallic acid		 Red wine and grapes	HFD-C57BL/6J mice	100 mg/kg	60 days	BAT: Sirt1 and PGC-1α↑	(Paraíso et al 2019)
Flavonoids							
Flavones							
Luteolin		 Pepper, celery, thyme, peppermint and honeysuckle	HFD-fed C57BL/6 mice	0.01%	12 weeks	BAT and sWAT: AMPK/PGC-1α signaling↑	(Zhang et al. 2016)

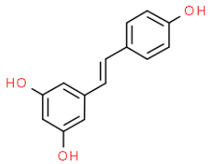
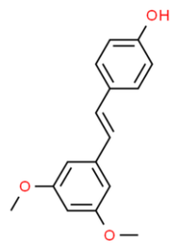
Apigenin		 Celery	HFD-fed C57BL/6 mice	0.04%	12 weeks	sWAT: ATGL, HSL, FOXO1, Sirt1, p-AMPK/AMPK, p-ACC/ACC↑; eWAT: ATGL, HSL, FOXO1, Sirt1, p-AMPK/AMPK, and p-ACC/ACC↑; BAT: HSL, Sirt1, FOXO1, p-AMPK/AMPK, p-ACC/ACC↑	(Sun and Qu 2019)
Curcumin		 Turmeric	HFD-fed C57BL/6J mice	1%	6 weeks	Energy expenditure↑; BAT: UCP1, PPARα, and PGC-1α↑	(Song et al. 2018)
Flavonols							
Quercetin		 Apples, cherries, berries, onions, asparagus, and red leaf lettuce	C57BL/6 inbred mice	1%	16 weeks	BAT: UCP1, PGC-1α, Cidea, and mtTFA ↑	(Pei et al. 2021)

Pentamethylquercetin			HFD-fed C57BL/6J mice	0.04%	17 weeks	eWAT: brown fat-selective genes (UCP1, C/EBPα, PGC-1α, Cidea, Bmp7, and Glut-4) ↑	(Han et al. 2017)
Rutin		 Passion flower, buckwheat, tea, and apple	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		 Berries, tea, fruits, wines and vegetables	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		 Citrus fruits, grapefruits, and tomato	C57Bl/6 mice	80 mg/kg	8 weeks	BAT: UCP1 ↑	(Thaiss et al. 2016)

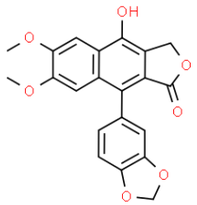
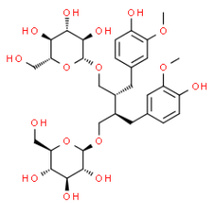
Apigenin		 Vegetables (parsley, celery, onions) fruits (oranges), herbs (chamomile, thyme, oregano, basil)	C57Bl/6 mice	80 mg/kg	8 weeks	BAT: UCP1 ↑	(Thaiss et al. 2016)
Hesperetin		 Sweet orange and lemon	Western diet fed wistar rats	100 mg/kg/day	8 weeks	iWAT: Cidea↑	(Mosqueda-Solís et al. 2018)
Flavanols (Flavan-3-ols)							
Epigallocatechin-3-gallate (EGCG)		 Black tea Green tea Oolong tea Yellow tea	HFD-fed C57BL/6J mice	0.2% (w/w) EGCG	8 weeks	BAT: UCP1, PRDM16, PGC-1α, NRF1, and Tfam↑	(Lee et al. 2017)
Catechins		 White tea Dark tea	Sprague-Dawley rats	500 mg/100 g chow	8 weeks	BAT: UCP mRNA↑	(Nomura et al. 2008)

			Healthy young male volunteers	Beverage contained 615 mg tea catechin and 77 mg caffeine	2 weeks	Whole-body energy expenditure↑; FDG uptake↑	(Yoneshiro et al. 2017)
Isoflavones							
Genistein		 Soy	Casein diet fed C57BL/6 mice	0.2%	8 weeks	sWAT:UCP1 and PGC-1α↑ BAT: UCP1↑	(Palacios-González et al. 2019)
			Ovx rats were fed with HFD	15 or 30 mg/kg	4 weeks	iWAT: UCP-1, PRDM-16, PGC-1α, Cidea, NRF1, Tfam, UCP-1 and Tbx-1↑	(Shen et al. 2019)
Chalcones							

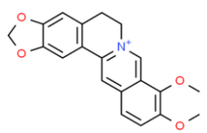
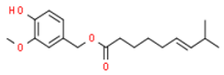
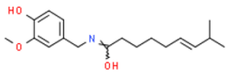
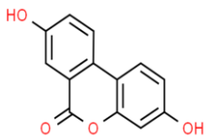
Phlorizin		 Apple	C57BL/6 mice were fed HFD	60 mg/kg	12 weeks	BAT: Tyk2/STAT3 signaling↑; UCP1, PPARα, and PRDM16↑	(Yuan et al. 2016)
Butein		 Cashews	C57BL/6N mice were fed HFD	5 and 15mg/kg	8 weeks	Energy expenditure↑; iWAT, eWAT and BAT:PRDM4 and UCP1↑	(Song et al. 2016)
Anthocyanins							
Cyanidin-3-O-β-Glucoside		 Colorful fruits, vegetables, red wine, and grains	db/db mice	1 mg/ml in water	16 weeks	BAT: UCP1, Sirt1 and PGC-1α, PPARα↑	(You et al. 2017)
			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)
Stilbenes							

			HFD-fed CD1 female mice	0.1% resveratrol	4 weeks	iWAT: p-AMPKα/t-AMPKα ratio↑ BAT: PRDM16, UCP-1, Cytochrome C, p-AMPKα/t-AMPKα↑	(Wang et al. 2015, 2017)
Resveratrol		 Polygonum cuspidatum	HFD fed C57BL/6 J mice	0.1~0.4%	11 weeks	iWAT and eWAT: UCP1, PRDM16, Sirt1, Fabp4, PPARγ, and p-AMPKα/t-AMPKα ratio↑	(Zou et al. 2017)
			Twenty male and female volunteers, aged 30–55 years (BMI ≥ 30 kg/m^2)	500 mg/day	8 weeks	sWAT: FNDC5, UCP1, PRDM16, and SIRT1↑	(Andrade et al. 2019)
Pterostilbene		 Grape and blueberries	HFD-fed C57BL/6 mice	352μmol/kg/day	30 weeks	iWAT: UCP1, Cidea, Ebf2, PGC-1α, PPARγ, Sirt1, and Tbx1↑	(La Spina et al. 2019)

Lignans

Diphyllin		 Justicia procumbens	HFD-fed C57BL/6J mice	100 mg/kg	7 weeks	Energy expenditure and adaptive thermogenesis↑; BAT: UCP1, Cox7a1, Cox78b↑; iWAT: UCP1 and Cox7a1↑; eWAT: UCP1, Cox7a1, and PGC-1α↑	(Duan et al. 2020)
Secoisolariciresinol diglucoside		 Flaxseed	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		 Coptis chinensis and Hydrastis canadensis	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		 Pepper	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		 Pomegranate	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) extract	 Berberis microphylla	HFD fed C57BL/6J mice	50mg/kg/day		Energy expenditure↑; BAT: UCP1, PPARα, and Sirt1↑ iWAT: PGC-1α, PPARα, PRDM16, Sirt1, and Dio2↑	(Duarte et al. 2021b)
		HFD-fed C57BL/6J mice	50 mg (total polyphenols) /kg/day		Energy expenditure↑ BAT: UCP1↑; Mitochondrial dynamics↑	(Ramirez et al. 2021)
Apple polyphenols	 Apple	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)	 Cranberry	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)

					Cd137, and Tbx1↑	
Raspberry	 Raspberry	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)
Grains of paradise (Aframomum melegueta) extract (15.2 % 6-gingerol and 12.5 % 6-paradol)	 Grains of paradise	Healthy male volunteers aged 20~32 years	40 mg	4 weeks	Energy expenditure↑; FDG uptake↑	(Sugita et al. 2013)

Isoflavone-rich *Puerariae* flower extract (63.11mg/100g)	 Puerariae flower	C57BL/6J mice were fed with HFD	1.355%	42 days	Oxygen consumption ↑; BAT:UCP1↑	(Kamiya et al. 2012)
Polyphenol-rich green tea (392 μg/mg of extract).	 Green tea	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)
Grape pomace extract	 Grape pomace	HFD-fed Sprague Dawley rats	300 mg/kg	6 weeks	eWAT: PGC-1α, PPARγ, PRDM16 and UCP1↑	(Rodriguez Lanzi et al. 2020)
Juçara (*Euterpe edulis* Mart.) containing 415.1 mg/g phenolics	 *Euterpe edulis* Mart.	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;eWAT, 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.

Polyphenols	Model	Dose	Duration	Microflora structure	Results of fat browning	References
Quercetin	HFD-fed C57BL/6 inbred mice	1%	16 weeks	*Firmicutes*/*Bacteroidetes* ratio↓; *Parabacteroides*↑; *Lactobacillus*↓	Energy expenditure↑; Thermogenesis genes in BAT↑	(Pei et al. 2021)
Resveratrol	HFD-fed C57BL/6J mice	0.4%	8 weeks	*Firmicutes*/*Bacteroidetes* ratio↓; *Proteobacteria*↑	Sirt1 signaling (UCP1, PGC-1α, PPARγ)↑	(Liao et al. 2018)
Nobiletin	HFD-fed C57BL/6J mice	50 mg/kg	12 weeks	*Akkermansia* and *Bacteroidetes*↑	BAT activity↑; Beige adipocytes formation↑	(Kou et al. 2021)
Caffeic acid	HFD-fed C57BL/6J mice	50 mg/kg	12 weeks	Anti-obesity related bacteria and butyrate-producing bacteria↑	Energy expenditure↑; BAT activity↑	(Xu et al. 2020)
Chlorogenic acid	HFD-fed C57BL/6J mice	100 mg/kg	13 weeks	Modification of microbiota structure in a unique way	Energy expenditure↑; BAT activity↑	(He et al. 2021)

Theabrownin	HFD-fed C57BL/6J mice	225 mg/kg/day	8 weeks	non-12OH-BAs produced microbiota (*Akkermansia muciniphila*, *Clostridium scindens*, and *Parabacteroides distasonis*)↑	Energy expenditure↑; UCP1 and Dio2 in BAT↑; UCP1 in WAT↑	(Kuang et al. 2020)
Curcumin	HFD-fed C57BL/6J mice	100 mg kg/day		*Akkermansia*↑	UCP1-dependent thermogenesis in BAT and iWAT↑	(Z. Han et al. 2021)
Grape extract	HFHS-fed C57BL/6Cnc mice	1%	13 weeks	*Bifidobacteria*, *Akkermansia*, and *Clostridia* genera↑	Energy expenditure↑; Thermogenesis genes in BAT↑	(Han et al. 2020a)
Polyphenols isolated from red raspberry fractions	HFD-fed C57BL/6 male mice	0.3% pulp; 0.1% seeds; 0.4% whole fruits	16 weeks	*Oscillospira*↓; *Clostridiaceae*↑	BAT weight↓	(Xian et al. 2021)
Blueberry extract	HFD-fed C57BL/6 male mice	0.5% (m/v)	10 weeks	*Bifidobacteria* and *Lactobacillus*↑	Energy expenditure↑; Brown-special factors in BAT and	(J. Guo et al. 2019)

					iWAT↑	
Blueberry polyphenols extract	HFD-fed C57BL/6 male mice	200 mg/kg	12 weeks	Change in microbiota profile (e.g., *Bifidobacterium*↑, *Coprobacillus*↓)	BAT weight↓	(Jiao et al. 2019)
Tea polyphenols	HFD-fed C57BL/6J male mice	250 mg/kg	12 weeks	*Akkermansia muciniphila* ↑; *Faecalibacterium prausnitzii*↑	UCP1, PGC-1α, Cidea, Tbx1, and Prdm16 in BAT↑	(Gao et al. 2018)
Extract of the Microalga Nitzschia laevis (13.83% polyphenols)	HFD-fed C57BL/6J mice	10 and 50mg/kg	8 weeks	*Firmicutes/Bacteroidetes* ratio↓; *Christensenellaceae*↓	UCP 1 and PGC-1α in BAT↑	(B. Guo et al. 2019)
Polyphenol-rich extract from chokeberry (2209.25 mg/100 g)	HFD-fed wistar rats	1000 mg/kg	40 days	Firmicutes/Bacteroidetes ratio, *Bacteroides*, *Prevotella*, *Akkermansia*↑	mRNA expression of PPARγ, UCP1 and PGC-1α in BAT↑	(Zhu et al. 2020)
Camu camu (Myrciaria dubia)	HFHS-fed C57Bl/6J male mice	200mg/kg	8 weeks	*Akkermansia muciniphila*↑; *Lactobacillus*↓	Energy expenditure↑; UCP1 in BAT↑	(Anhê et al. 2019)

Guarana rich in catechins and methylxanthines	Western diet fed Wistar	0.5%	18 weeks	*Firmicutes/Bacteroidetes*↓; *Butyricicoccus*↑, *Holdemania*↓	BAT weight↑; UCP1 and Sirt 1↑	(Bortolin et al. 2019)
Mulberry leaves	HFD-fed C57BL/6J mice	20% mulberry leaf powder (w/w)	8 weeks	*Bacteroidetes*/*Firmicutes* ratio↑; *Akkermansia*↑	BAT activity↑	(Sheng et al. 2019)
Rice bran	HFD-fed C57BL/6 mice	300 mg/kg	39 days	*Firmicutes*/*Bacteroidetes*; *Akkermansia*↑	BAT activity and WAT browning↑	(Y. Zou et al. 2020)
Grape seed proanthocyanidins	HFD-fed C57BL/6 mice	100 or 200 mg/kg	8 weeks	*Alistipes and Ruminococcaceae*↑	Thermogenic activity of iBAT (PRDM16 and UCP1 expression) ↑	(Du et al. 2021)

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, thiiodothronine; 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

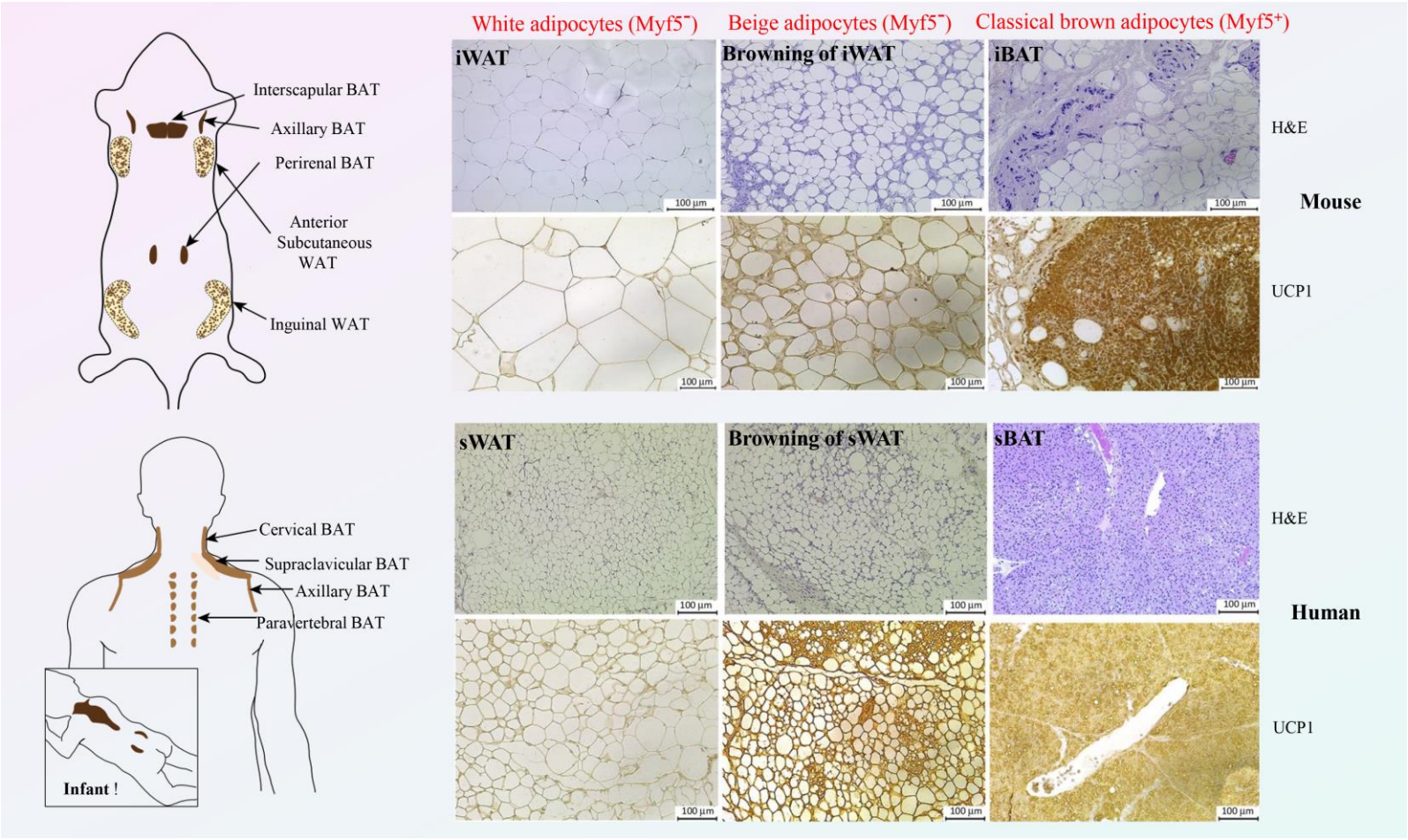
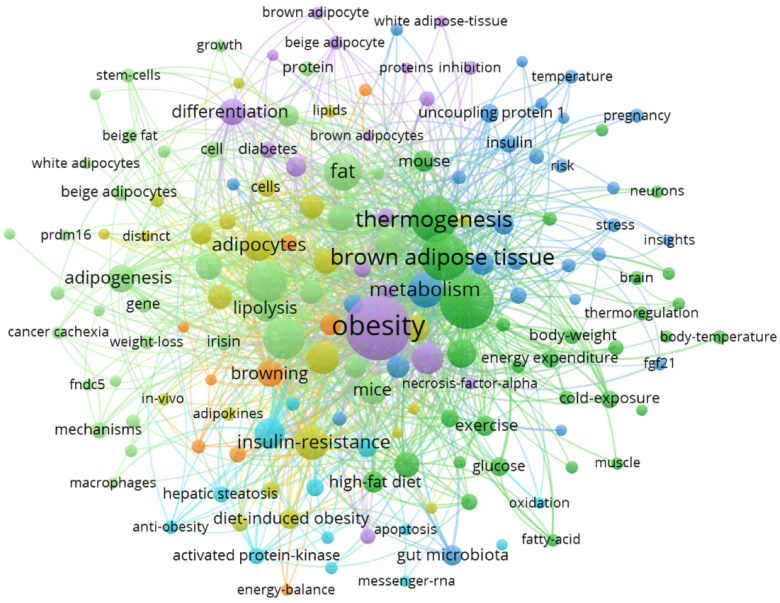

White adipocytes (Myf5⁻)
Beige adipocytes (Myf5⁻)
Classical brown adipocytes (Myf5⁺)
Interscapular BAT
Axillary BAT
Perirenal BAT
Anterior Subcutaneous WAT
Inguinal WAT
iWAT
Browning of iWAT
iBAT
H&E
UCP1
Mouse
Cervical BAT
Supraclavicular BAT
Axillary BAT
Paravertebral BAT
Infant !
sWAT
Browning of sWAT
sBAT
H&E
UCP1
Human
100 μm

Fig. 2

A


brown adipocyte
white adipose-tissue
growth
beige adipocyte
protein
proteins inhibition
temperature
stem-cells
differentiation
lipids
uncoupling protein 1
pregnancy
beige fat
brown adipocytes
insulin
cell
diabetes
white adipocytes
mouse
risk
fat
cells
neurons
beige adipocytes
thermogenesis
stress
prdm16
distinct
adipocytes
insights
brown adipose tissue
adipogenesis
brain
metabolism
gene
lipolysis
thermoregulation
cancer cachexia
obesity
body-weight
body-temperature
weight-loss
irisin
energy expenditure
fgf21
browning
fndc5
mice
necrosis-factor-alpha
in-vivo
cold-exposure
adipokines
exercise
mechanisms
insulin-resistance
glucose
muscle
macrophages
high-fat diet
hepatic steatosis
oxidation
anti-obesity
diet-induced obesity
apoptosis
fatty-acid
activated protein-kinase
gut microbiota
messenger-rna
energy-balance

B

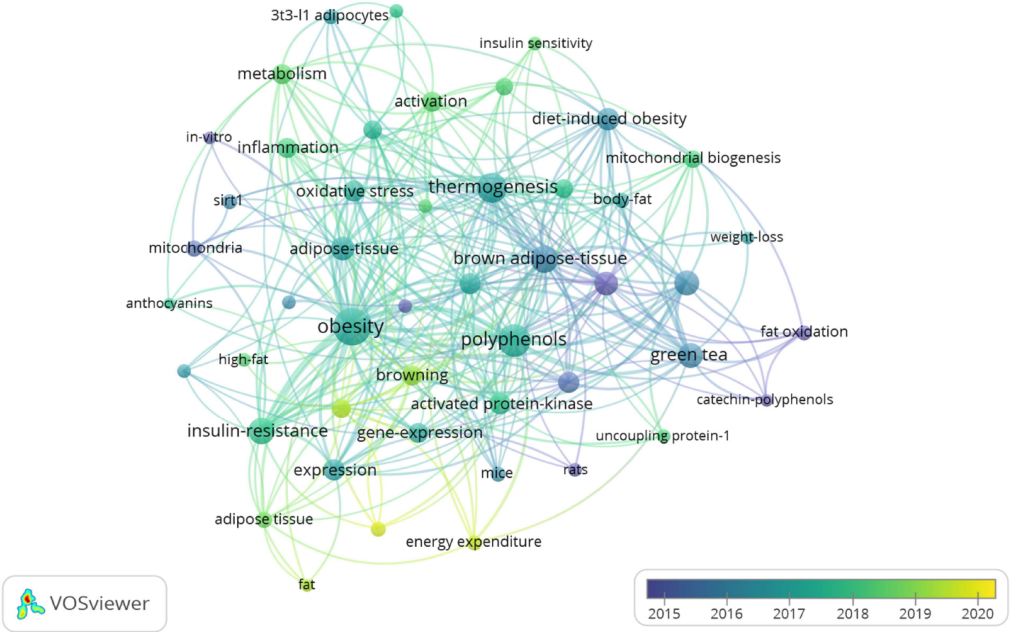

3t3-l1 adipocytes
insulin sensitivity
metabolism
activation
diet-induced obesity
in-vitro
inflammation
mitochondrial biogenesis
oxidative stress
thermogenesis
body-fat
sirt1
weight-loss
mitochondria
adipose-tissue
brown adipose-tissue
anthocyanins
obesity
polyphenols
fat oxidation
high-fat
green tea
browning
activated protein-kinase
catechin-polyphenols
insulin-resistance
gene-expression
uncoupling protein-1
expression
mice
rats
adipose tissue
energy expenditure
fat
VOSviewer
2015
2016
2017
2018
2019
2020

Fig. 3

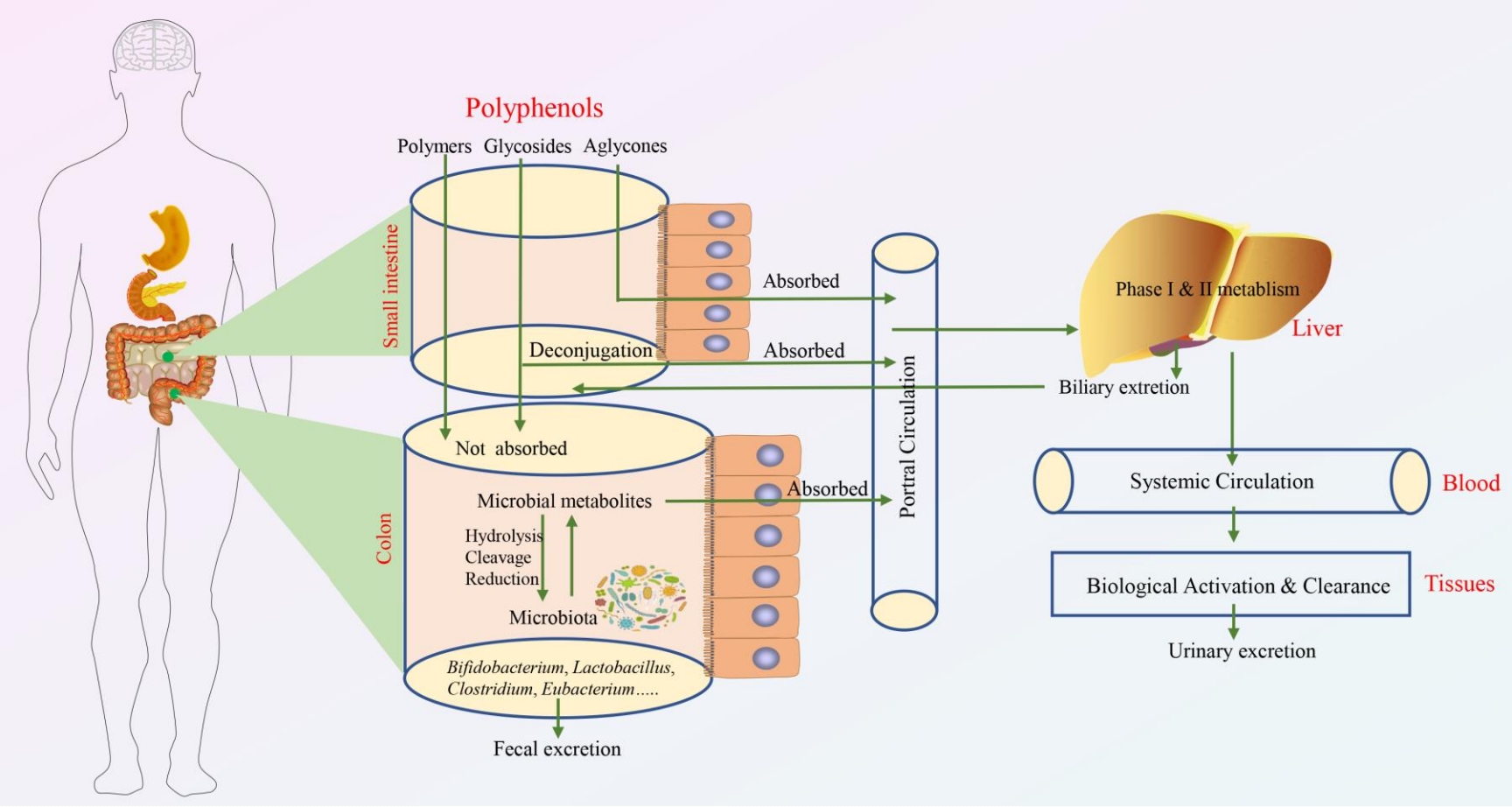

Polyphenols
Polymers Glycosides Aglycones
Small intestine
Absorbed
Deconjugation
Absorbed
Not absorbed
Colon
Microbial metabolites
Absorbed
Hydrolysis
Cleavage
Reduction
Microbiota
Bifidobacterium, Lactobacillus,
Clostridium, Eubacterium.....
Fecal excretion
Portral Circulation
Phase I & II metablism
Liver
Biliary extretion
Systemic Circulation
Blood
Biological Activation & Clearance
Tissues
Urinary excretion

Fig. 4

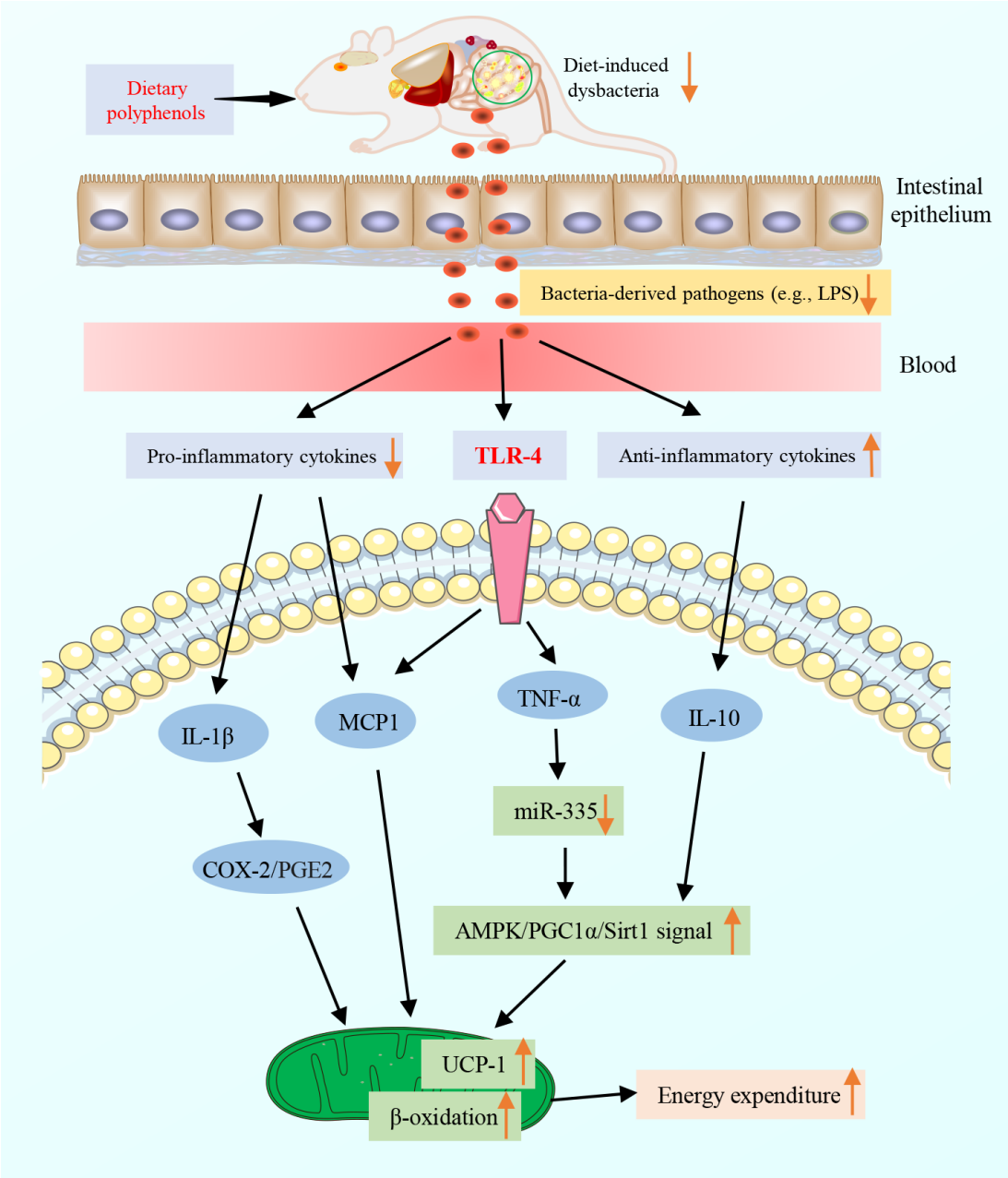

Dietary polyphenols
Diet-induced dysbacteria
Intestinal epithelium
Bacteria-derived pathogens (e.g., LPS)
Blood
Pro-inflammatory cytokines
TLR-4
Anti-inflammatory cytokines
IL-1β
MCP1
TNF-α
IL-10
miR-335
COX-2/PGE2
AMPK/PGC1α/Sirt1 signal
UCP-1
β-oxidation
Energy expenditure

Fig. 5

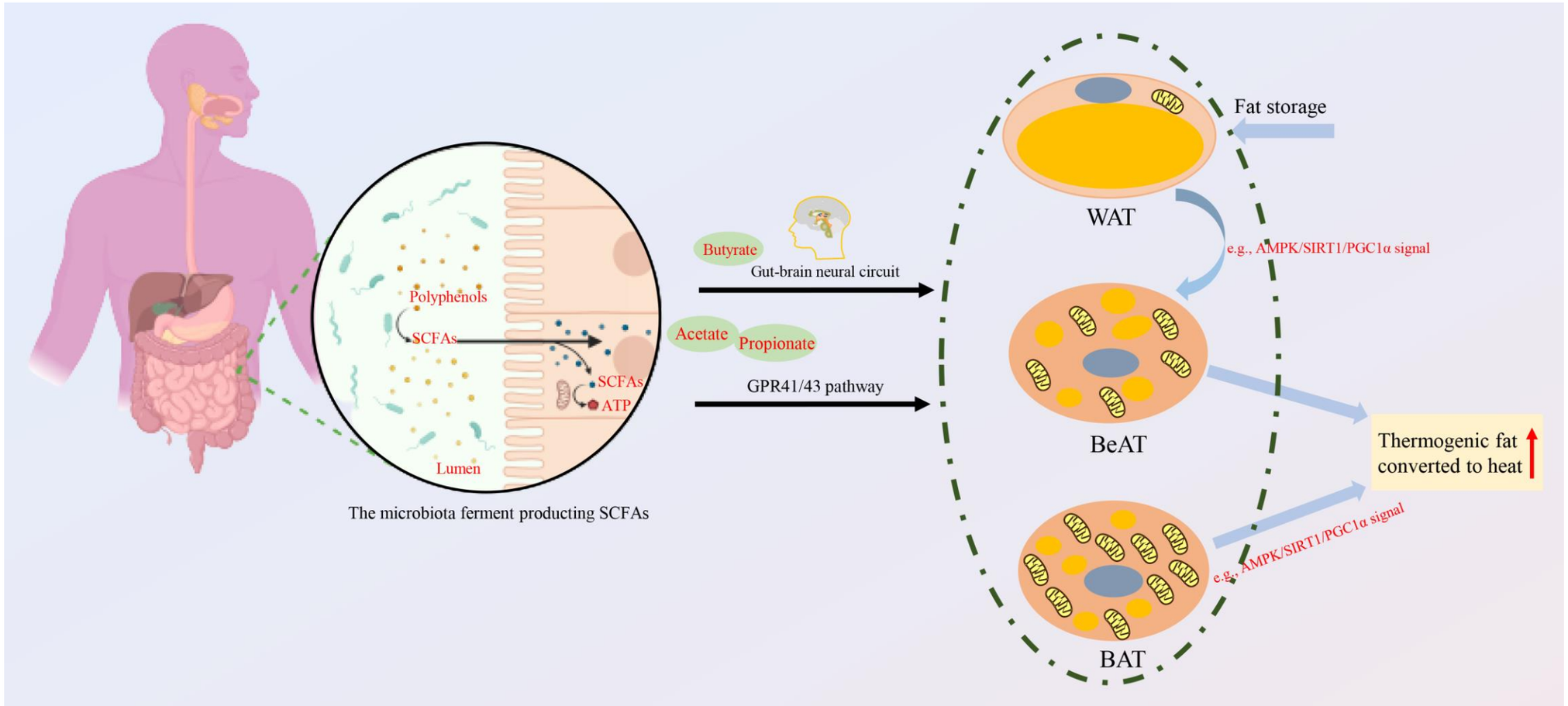

Polyphenols
SCFAs
SCFAs
ATP
Lumen
The microbiota ferment producting SCFAs
Butyrate
Gut-brain neural circuit
Acetate
Propionate
GPR41/43 pathway
Fat storage
WAT
e.g., AMPK/SIRT1/PGC1α signal
BeAT
Thermogenic fat converted to heat
e.g., AMPK/SIRT1/PGC1α signal
BAT

Fig. 6

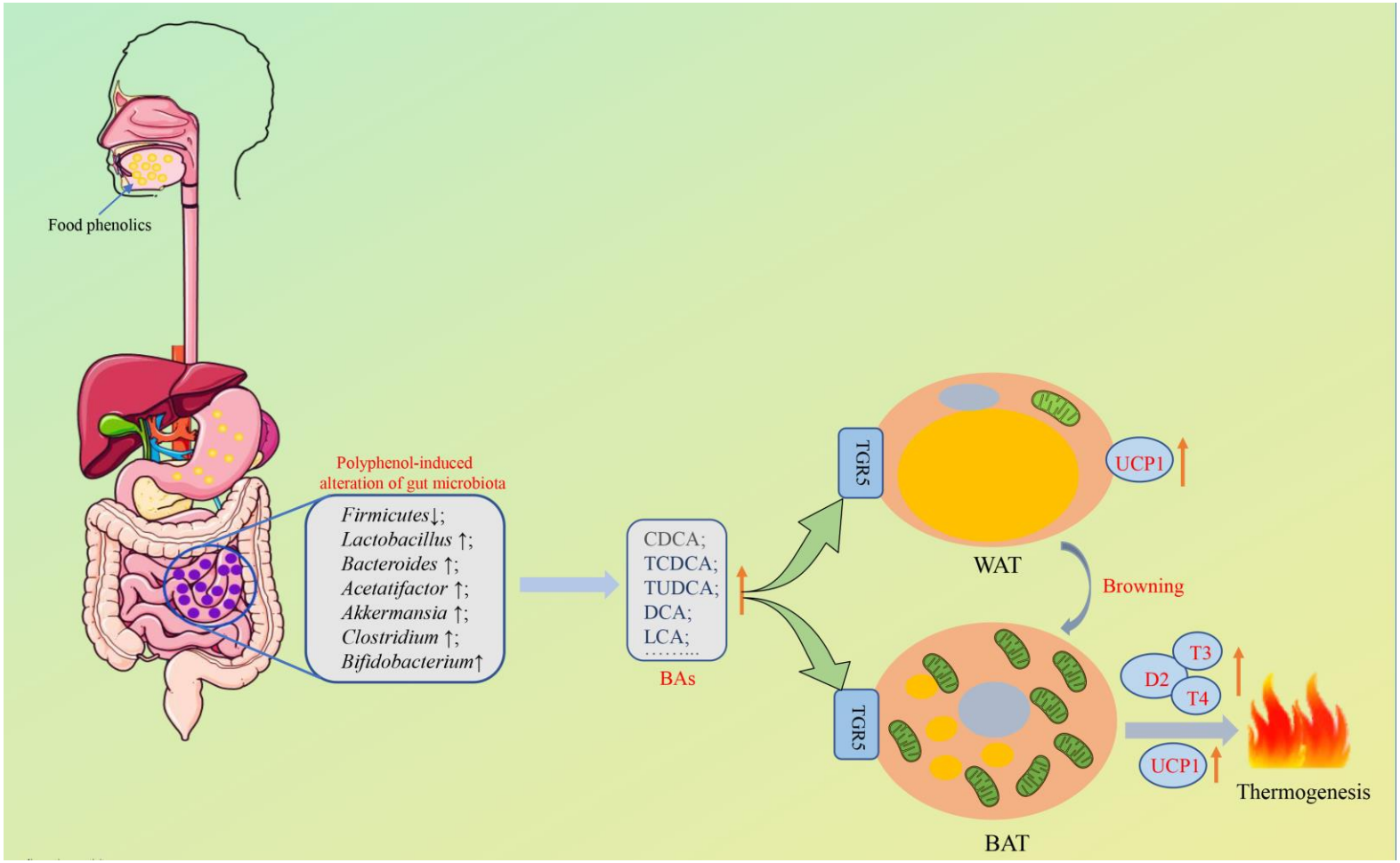
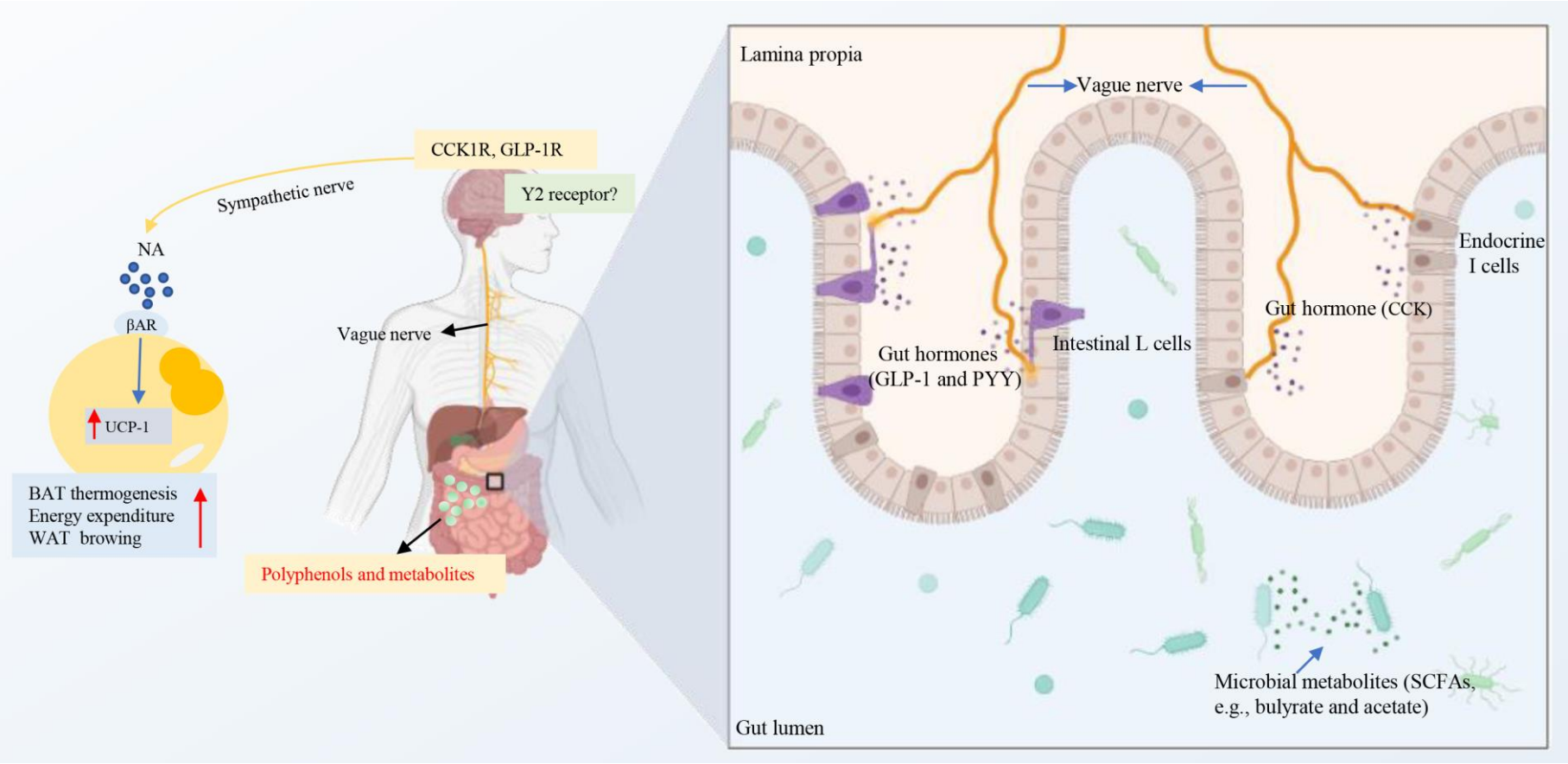

Food phenolics
Polyphenol-induced
alteration of gut microbiota
Firmicutes↓;
Lactobacillus ↑;
Bacteroides ↑;
Acetatifactor ↑;
Akkermansia ↑;
Clostridium ↑;
Bifidobacterium↑
CDCA;
TCDCA;
TUDCA;
DCA;
LCA;
BAs
TGR5
UCP1
WAT
Browning
TGR5
T3
D2
T4
UCP1
Thermogenesis
BAT

Fig. 7


CCK1R, GLP-1R
Y2 receptor?
Sympathetic nerve
NA
βAR
UCP-1
BAT thermogenesis
Energy expenditure
WAT browing
Vague nerve
Polyphenols and metabolites
Lamina propia
Vague nerve
Endocrine
I cells
Gut hormone (CCK)
Gut hormones
(GLP-1 and PYY)
Intestinal L cells
Microbial metabolites (SCFAs,
e.g., bulyrate and acetate)
Gut lumen