Pol. J. Food Nutr. Sci., 2021, Vol. 71, No. 4, pp. 353–381
On-line ISSN: 2083-6007
Print ISSN: 1230-0322
DOI: 10.31883/pjfns/143164
http://journal.pan.olsztyn.pl

Review article
Section: Nutrition

Diet-Induced Adipocyte Browning

Oskar Wojciech Wiśniewski[1], Aleksander Rajczewski[1], Agnieszka Szumigała[1], Magdalena Gibas-Dorna[2]*

[1]Students' Scientific Society, Faculty of Medicine, Poznan University of Medical Sciences, 10 Fredry Street, 61–701 Poznan, Poland
[2]Department of Applied and Clinical Physiology, Collegium Medicum, University of Zielona Gora, 28 Zyty Street, 65–046 Zielona Gora, Poland

Key words: adipocyte browning, beige adipose tissue, brite adipose tissue, diet, diet therapy, obesity

The adipocyte browning process is a phenomenon that consists in the molecular and morphological remodeling of preadipocytes or mature white adipocytes into multilocular beige fat cells expressing thermogenesis-associated genes. Adipocyte browning may occur physiologically, mainly upon cold or exercise stimulation. However, it can also be induced by exogenous compounds, such as drugs or dietary components. Since adipocyte browning is followed by increased energy expenditure, weight loss, and improved metabolic health, it emerges as a novel therapeutic target in the treatment of obesity and obesity-related diseases. In addition, it contributes to the lowering of both systemic and adipose tissue inflammation, which are promoted in obese states. Thus, the role of adipocyte browning should be emphasized in the context of a dramatically increasing population of obese individuals. In this paper, we focus on dietary components and general dietary modifications, which may affect adipocyte browning by its stimulation or inhibition. We discuss browning properties of amino acids, carbohydrates, fatty acids, and retinoids, as well as present adipocyte browning potential of the wide range of non-nutrients, including glucosinolates, alkaloids, terpenes and terpenoids, flavonoids and other phenolic compounds. We also demonstrate the influence of edible plant extracts and food ingredients of animal origin on adipose tissue browning. Finally, we analyze browning effects of caloric restriction, intermittent fasting and various dietary macronutrient compositions, as well as the significance of microbiota in adipocyte browning process.

ABBREVIATIONS

AMPK: 5'-AMP-activated protein kinase; β_3-AR: β_3-adrenergic receptor; BAT: brown adipose tissue; C/EBPα: CCAAT/enhancer-binding protein α; CIDEA: cell death activator CIDE-A; CITED1: Cbp/p300-interacting transactivator 1; COX7A1: cytochrome c oxidase subunit 7A1, mitochondrial; COX8B: cytochrome c oxidase subunit 8B, mitochondrial; CPT1A: carnitine *O*-palmitoyltransferase 1, liver isoform; CPT1B: carnitine *O*-palmitoyltransferase 1, muscle isoform; Cyt C: cytochrome c; DHA: docosahexaenoic acid; DIO2: type II iodothyronine deiodinase; ELOVL3: elongation of very long chain fatty acids protein 3; EPA: eicosapentaenoic acid; eWAT: epididymal white adipose tissue; FGF21: fibroblast growth factor 21; GPRs: G protein-coupled receptors; HDL-C: high-density lipoprotein cholesterol; IL-6: interleukin 6; iWAT: inguinal white adipose tissue; LDL-C: low-density lipoprotein cholesterol; NRF1: nuclear respiratory factor 1; NRF2: nuclear respiratory factor 2; PGC1α: peroxisome proliferator-activated receptor γ coactivator 1-α; PPARα: peroxisome proliferator-activated receptor α; PPARγ: peroxisome proliferator-activated receptor γ; PRDM16: PR domain-containing protein 16; rWAT: retroperitoneal white adipose tissue; sWAT: subcutaneous WAT; TBX1: T-box transcription factor TBX1; TFAM: transcription factor A, mitochondrial; TMEM26: transmembrane protein 26; TNF-α: tumor necrosis factor α; UCP1: uncoupling protein 1; WAT: white adipose tissue.

INTRODUCTION

Over the last decades, the understanding of adipose tissue has changed unquestionably. Gradually, it came out that it is not only the storage site of lipids but also an active endocrine organ, which modulates the functioning of the whole organism [Luo & Liu, 2016]. In addition, recent years of preclinical trials have proven that white adipose tissue (WAT) has a transformative potential, as it can differentiate into beige adipose tissue upon definite stimulation in the process called adipocyte browning (also known as beiging or britening) [Rosenwald *et al.*, 2013].

More precisely, the adipocyte browning process is a phenomenon, which involves not only already existing white

* Corresponding Author:
E-mail: wisniewski.oskar@outlook.com (O.W. Wiśniewski)

Submitted: 8 July 2021
Accepted: 18 October 2021
Published on-line: 15 November 2021

adipocytes, but also preadipocytes, which can differentiate into both white or beige fat cells [Harms & Seale, 2013]. During the adipocyte browning, the clusters of stimulated cells undergo histological, cytological, and molecular changes, finally acquiring the beige adipose tissue phenotype [Wu *et al.*, 2012].

Beige adipose tissue (also called brite adipose tissue, brown-like adipose tissue, inducible-brown adipose tissue) is a subtype of brown adipose tissue (BAT), which contains adipocytes that share features of both white and "classical" brown fat cells [Lidell *et al.*, 2013]. Their unique gene expression pattern includes genetic hallmarks specific for beige adipocytes as well as genes expressed in both "classical" brown and beige fat cells (Table 1) [Wu *et al.*, 2012]. In contrast to white adipocytes, beige cells are abundant with uncoupling protein 1 (UCP1)-positive mitochondria, which enables the process called non-shivering thermogenesis [Shabalina *et al.*, 2013]. Heat generation and distribution as a key function of beige cells, is associated with their high degree of sympathetic innervation and vascularization [Kajimura *et al.*, 2015]. As compared with WAT cells, beige adipocytes contain more, but smaller in size, lipid droplets, which results in multilocular morphology of beige adipose tissue (in contrast to unilocular WAT) [Harms & Seale, 2013]. These lipid droplets are rich in triglycerides that supply an energy for thermogenesis.

Taken together, the adipocyte browning process that occurs when body's demands for heat generation and dissipation are greatly elevated, involves induction of mitochondrial biogenesis, UCP1 expression, triggered β-oxidation, angiogenesis and enhanced sympathetic innervation [Harms & Seale, 2013].

The assessment of gene expression alterations is essential to confirm adipocyte browning, therefore detailed knowledge about genes involved in this process is necessary to interpret the scientific results (Table 1). *Cd137, Tbx1,* and *Tmem26* seem to be specific markers for beige adipocytes, while the expression of other genes differs a lot when most prevalent WAT depots are considered: epididymal, inguinal and retroperitoneal WAT (eWAT, iWAT, and rWAT, respectively) [de Jong *et al.*, 2015].

There is a wide range of browning activators including endogenous (hormones, growth factors, or cytokines) and exogenous (mostly dietary components or pharmacological agents) factors, whereas browning inhibitors are relatively rare [Wisniewski *et al.*, 2018]. The most studied and presumably the most potent browning-positive effect is associated with increased sympathetic nervous system activity and β_3-adrenergic signaling pathway in response to cold [Contreras *et al.*, 2014]. Importantly, adipocyte browning is reversible, and so-called whitening of beige adipocytes may occur, depending on environmental conditions [Rosenwald *et al.*, 2013].

The clinical significance of adipocyte browning is associated with an improvement of metabolic health [Wisniewski *et al.*, 2018; Wisniewski, 2019]. Induction of beige fat thermogenesis results in increased lipolysis and energy expenditure, followed by reduced adiposity and weight loss [Yoneshiro *et al.*, 2013]. Furthermore, adipocyte browning decreases low-grade systemic inflammation by diminishing proinflammatory cytokine concentrations and enhancing anti-inflammatory adipokines production [Min *et al.*, 2016; Zhuang *et al.*, 2019], as well as improves glucose tolerance [Chondronikola *et al.*, 2014]. Hence, adipocyte browning emerges as a novel therapeutic approach to obesity and obesity-related complications, such as type 2 diabetes, hypertension, dyslipidemia, or non-alcoholic steatohepatitis [Wisniewski *et al.*, 2018].

In order to summarize the knowledge and inspire further research, we aimed to present a comprehensive review of the current literature about dietary components and dietary interventions that may elicit adipocyte browning.

AMINO ACIDS

Betaine

Betaine (trimethylglycine) is a common natural amino acid mostly found in wheat, spinach, beetroots, and shellfish [Ross *et al.*, 2014]. In humans, it is well known as an intermediate product of choline degradation, although it exhibits multiple positive metabolic effects by itself [Ueland, 2011]. Apart from improving insulin sensitivity, blood lipid profile, and anti-inflammatory activity, betaine affects adipogenesis and promotes adipocyte browning [Du *et al.*, 2018]. Du *et al.* [2018] proved that betaine suppresses proliferation and differentiation of 3T3-L1 preadipocytes by cell cycle blockage between G1/S phases and downregulation of C/EBPα and PPARγ. Furthermore, betaine upregulates *Ucp1*, *Pparg*, *Ppargc1a*, *Cidea,* and *Cd137*, as well as stimulates mitochondrial biogenesis, in Kunming mice after 13-week administration of a high-fat diet and 1% betaine in water, which, in turn, results in reduced body fat, lowered lipid accumulation and increased β-oxidation in myocytes mass [Du *et al.*, 2018].

Leucine

Leucine is an essential branched-chain amino acid with the highest content in proteins of soybeans, meat, eggs, and nuts [Rondanelli *et al.*, 2021]. Unlike another essential amino acid – methionine, there are many significant inconsistencies in the role of leucine in the adipocyte browning process.

Two studies confirm the browning properties of leucine supplementation [Binder *et al.*, 2014; Jiao *et al.*, 2016]. The first one revealed that 21-week supplementation of C57BL/6J mice with 1.5% L-leucine resulted in increased *Ucp1, Ucp3,* and *Cpt1* mRNAs in eWAT, albeit these changes were not associated with elevated energy expenditure and weight loss [Binder *et al.*, 2014]. The other research evidenced reduced body weight and enhanced expression of browning-related proteins, such as UCP1, PGC1α, β_3-AR, and FGF21, in eWAT and BAT of C57BL/6J mice after 24 weeks of dietary intervention with both 1.5% or 3.0% L-leucine [Jiao *et al.*, 2016]. Furthermore, decreased adipocyte size, lowered concentrations of lipogenic enzymes (acetyl-CoA carboxylase and fatty acid synthase) as well as encouraging lipolysis by increasing adipose triglyceride lipase and phosphorylated hormone-sensitive lipase at the protein level were found upon diet supplementation with both 1.5% or 3.0% L-leucine. Thus, the signs of adipocyte browning, raised thermogenesis, and adipose tissue remodeling were reported [Jiao *et al.*, 2016].

TABLE 1. Genes used in adipocyte browning research (based on UniProt database).

Gene names *HUMAN (Murine)*	Encoded protein	Abbreviation
Genes highly expressed in both beige and "classical" brown adipocytes		
ADRB3 (Adrb3)	β_3-adrenergic receptor	β_3-AR
CIDEA (Cidea)	Cell death activator CIDE-A	CIDEA
DIO2 (Dio2)	Type II iodothyronine deiodinase	DIO2
EBF2 (Ebf2)	Early B-cell factor 2	EBF2
ELOVL3 (Elovl3)	Elongation of very long chain fatty acids protein 3	ELOVL3
PPARA (Ppara)	Peroxisome proliferator-activated receptor α	PPARα
PPARG (Pparg)	Peroxisome proliferator-activated receptor γ	PPARγ
PPARGC1A (Ppargc1a)	Peroxisome proliferator-activated receptor γ coactivator 1-α	PGC1α
PRDM16 (Prdm16)	PR domain-containing protein 16	PRDM16
UCP1 (Ucp1)	Uncoupling protein 1	UCP1
Genes specific for beige adipocytes		
CD137 (Cd137)	CD137	CD137
CITED1 (Cited1)	Cbp/p300-interacting transactivator 1	CITED1
FGF21 (Fgf21)	Fibroblast growth factor 21	FGF21
HOXC9 (Hoxc9)	Homeobox protein Hox-C9	HOXC9
TBX1 (Tbx1)	T-box transcription factor TBX1	TBX1
TMEM26 (Tmem26)	Transmembrane protein 26	TMEM26
Genes specific for "classical" brown adipocytes		
EVA1 (Eva1)	Protein eva-1	EVA1
LHX8 (Lhx8)	LIM/homeobox protein Lhx8	LHX8
ZIC1 (Zic1)	Zinc finger protein ZIC 1	ZIC1
Genes strongly associated with mitochondrial biogenesis		
NRF1 (Nrf1)	Nuclear respiratory factor 1	NRF1
NRF2 (Nrf2)	Nuclear respiratory factor 2	NRF2
TFAM (Tfam)	Transcription factor A, mitochondrial	TFAM
Genes strongly associated with β-oxidation and mitochondrial activity		
ACADM (Acadm)	Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	MCAD
COX7A1 (Cox7a1)	Cytochrome c oxidase subunit 7A1, mitochondrial	COX7A1
(Cox8b)	Cytochrome c oxidase subunit 8B, mitochondrial	COX8B
CPT1A (Cpt1a)	Carnitine *O*-palmitoyltransferase 1, liver isoform	CPT1A
CPT1B (Cpt1b)	Carnitine *O*-palmitoyltransferase 1, muscle isoform	CPT1B
CYCS (Cycs)	Cytochrome c	Cyt C
Genes highly expressed in white adipocytes		
ALDH1A1 (Aldh1a1)	Retinal dehydrogenase 1	ALDH1
CEBPA (Cebpa)	CCAAT/enhancer-binding protein α	C/EBPα
FABP4 (Fabp4)	Fatty acid-binding protein type 4	FABP4
LPIN1 (Lpin1)	Phosphatidate phosphatase LPIN1	LIPIN1
PSAT1 (Psat1)	Phosphoserine aminotransferase	PSAT1
RETN (Retn)	Resistin	
SREBP1 (Srebp1)	Sterol regulatory element-binding protein 1	SREBP1
(Zfp423)	Zinc finger protein 423	ZFP423

However, another two study groups have indicated that adipocyte browning is induced by leucine restriction rather than by supplementation [Cheng *et al.*, 2010; Wanders *et al.*, 2015]. Two papers described elevated expression of UCP1 at both protein and mRNA levels as well as upregulated *Ppargc1a, Pparg,* and *Adrb3* in BAT of C57BL/6J mice after 1-week of total leucine restriction [Cheng *et al.*, 2010, 2011]. Moreover, the same alterations of the abovementioned lipogenic and lipolytic enzymes, as well as weight loss and diminished adipocyte size, were observed. In addition, a significant increase in UCP1 at both mRNA and protein levels in iWAT and BAT of C57BL/6J mice as well as a raised transcription of *Cidea, Cox7a,* and *Cox8b* in iWAT were detected upon 8 weeks of leucine restriction by 85% [Wanders *et al.*, 2015]. Similarly, a low-leucine diet resulted in broadened deposits of multilocular adipocytes, nevertheless heightened acetyl-CoA carboxylase and fatty acid synthase mRNAs were noted in eWAT and iWAT contrarily [Wanders *et al.*, 2015]. Taken together, based on the presented data, the impact of leucine on adipocyte browning remains not fully recognized.

Similarly as for methionine restriction, FGF21 overexpression and sympathetic nervous system activation were suggested as the possible mechanisms of the adipocyte browning in the case of leucine deprivation [Cheng *et al.*, 2010, 2011; Wanders *et al.*, 2015], while no mechanisms supporting the browning on leucine-rich diet were presented [Binder *et al.*, 2014; Jiao *et al.*, 2016].

Positive effects resulting from leucine administration or restriction beneficially influence metabolic outcomes. Upon prolonged leucine supplementation, decreased production of proinflammatory cytokines, diminished circulating leptin and leptin resistance were reported [Binder *et al.*, 2014; Jiao *et al.*, 2016]. Nevertheless, there are discrepancies, whether higher or lower leucine intake contributes to improved glucose metabolism [Binder *et al.*, 2014; Cheng *et al.*, 2011; Jiao *et al.*, 2016].

Methionine

Eggs, meat, grain, and dairy products are the predominant source of dietary methionine, an essential amino acid which profoundly modulates human metabolism [Górska-Warsewicz *et al.*, 2018]. However, recent data suggest that methionine restriction may also be beneficial in obesity and obesity-related diseases due to adipocyte browning stimulation [Jiang *et al.*, 2015; Stone *et al.*, 2015; Wanders *et al.*, 2017]. Over a 5-fold reduction in dietary methionine intake significantly elevated *Ucp1*, *Ppargc1a*, *Cidea, Cox7a1, Cox8b,* and *Adrb3* mRNAs in murine iWAT *in vivo* [Stone *et al.*, 2015; Wanders *et al.*, 2017]. Furthermore, the upregulation of *Ucp1, Cidea,* and *Elovl3* was also present in BAT. In addition, methionine restriction activates sympathetic drive and leads to the liver overexpression of FGF21 [Stone *et al.*, 2015; Wanders *et al.*, 2017], which is recognized as an independent activator in browning processes [Fisher *et al.*, 2012]. As a result of the adipocyte browning and pleiotropic functions of FGF21 itself, improved insulin sensitivity, weight loss, and a reduction in plasma and hepatic triglycerides were also reported [Stone *et al.*, 2015; Wanders *et al.*, 2017]. Similar browning and metabolic effects (↑ UCP1 and FGF21; ↓ body mass, glucose, and hepatic triglycerides) were also evidenced in mice with impaired intestinal and renal methionine absorption due to methionine transporter knockdown [Jiang *et al.*, 2015].

Taurine

Seafood is the primary source of exogenous taurine, one of the most common amino acids in the human body composition [Laidlaw *et al.*, 1990]. Guo *et al.* [2019] studied the impact of taurine on adipocyte browning and reported that intraperitoneal taurine administration resulted in the upregulation of *Ucp1*, *Ppargc1a*, *Tfam*, and *Cpt1b* expression in iWAT, eWAT, and BAT of C57BL6 mice. The same alterations of browning-specific genes were observed in C3H10T1/2 cells upon taurine supplementation [Guo *et al.*, 2019]. Consequently, dietary taurine promoted mitochondrial biogenesis, increased β-oxidation, and raised energy expenditure, leading to higher free fatty acids utilization, reduced adiposity, and weight loss with improved glucose tolerance and insulin sensitivity. Mechanistically, taurine stimulates AMPK phosphorylation, thus activating the AMPK/PGC1α pathway [Guo *et al.*, 2019].

CARBOHYDRATES

L-Rhamnose

L-Rhamnose is a monosaccharide that is a component of plant cell walls and bacteria [Jiang *et al.*, 2021]. It is used as a sweetener that is able to reduce both cholesterogenesis and triacylglycerol synthesis [Bai *et al.*, 2015]. In addition, 3T3-L1 preadipocyte supplementation with L-rhamnose resulted in an elevated concentration of browning-related proteins such as UCP1, PRDM16, and PGC1α as well as *Cd137*, *Cited1*, *Prdm16*, *Tbx1,* and *Tmem26* mRNAs [Choi *et al.*, 2018]. Several different signaling pathways, including β_3-AR, SIRT1, PKA, and p-38, take part in this process. L-Rhamnose administration was associated with activation of the AMPK and acetyl-CoA carboxylase proteins, increased acyl-coenzyme A oxidase, carnitine *O*-palmitoyltransferase 1, and phosphorylated hormone sensitive lipase levels. What is more, L-rhamnose activated HIB1B brown adipocytes by increasing expression of brown-fat markers (UCP1, PRDM16, and PGC1α) and changing morphology of fat cells [Choi *et al.*, 2018].

Trehalose

Trehalose is an anti-inflammatory disaccharide [Arai *et al.*, 2019] present in honey, fungi and yeast [Oku & Nakamura, 2000] that exhibits the ability to reduce insulin secretion and improve glucose tolerance [Arai *et al.*, 2019]. A 16 weeks of drinking water with trehalose resulted in WAT browning in experimental mice, which was confirmed by increased expression of *Cidea* and *Ucp1* mRNAs in iWAT [Arai *et al.*, 2019]. Similar but not significant tendency was observed in the mesenteric adipose tissue. Trehalose-induced WAT browning was accompanied with reduced serum glucose and elevated core temperature as a consequence of thermogenesis intensification. Moreover, trehalose caused the expansion of multilocular UCP1-positive adipocytes in both iWAT

and mesenteric WAT. Also, possible fibroblast growth factor 21 (FGF21) involvement in trehalose-induced adipocyte browning was investigated, though its concentration did not increase during the experiment, suggesting a different underlying mechanism [Arai *et al.*, 2019].

Inulin

Over 30,000 plant species (*e.g.*, *Cichorium intybus, Asparagus* sp., *Allium* sp.) are sources of inulin, a non-digestible carbohydrate known especially as a prebiotic and dietary sugar replacer in diabetics [Shoaib *et al.*, 2016]. A recent study by Weitkunat *et al.* [2017] evidenced browning properties of inulin, mainly attributed to short-chain fatty acids production. The 30-week inulin supplementation significantly raised *Ucp1*, *Ppargc1a* and *Cidea* mRNA levels in sWAT of C57BL/6JRj mice. Moreover, inulin ameliorated high-fat diet induced adipocyte hyperplasia and altered fecal microbiota composition, preferring overgrowth of *Bifidobacterium* [Weitkunat *et al.*, 2017].

FATTY ACIDS

α-Linolenic, γ-linolenic and pinolenic acids

Primary subcutaneous adipocytes of C57BL/6 mice were reported to upregulate the expression of *Ucp1* upon *in vitro* α-linolenic acid, γ-linolenic acid or pinolenic acid administration, which are different octadecatrienoic acid isomers, found mainly in the wide range of seeds [Shin & Ajuwon, 2018a]. Moreover, an insignificant increase in *Ppargc1a* mRNA was noted. However, only the pinolenic acid potentiated the browning effect of norepinephrine associated with sympathetic nervous system stimulation, while γ-linolenic acid additionally decreased *Cidea* transcription [Shin & Ajuwon, 2018a]. Furthermore, γ-linolenic acid slightly but insignificantly elevated *Ucp1* in both 3T3-L1 and 10T1/2 adipocytes [Shin & Ajuwon, 2018a].

Linoleic and conjugated linoleic acids

Conjugated linoleic acid is a mixture of linoleic acid isomers, mostly *cis*-9, *trans*-11 and *trans*-10, *cis*-12, derived from sunflower oil, ruminant meats, or dairy products [Shen & McIntosh, 2016]. Results obtained in murine trials proved that conjugated linoleic acid is an adipocyte browning inductor since it increased mRNAs of *Ucp1*, *Ppargc1a*, and *Cpt1b* in epididymal WAT as well as energy expenditure [Wendel *et al.*, 2009]. The possible mechanism of browning initiation might be connected with β_3-adrenergic activity but the effect is rather short lasting and not maintained over a few weeks of conjugated linoleic acid supplementation [Wendel *et al.*, 2009]. Therefore, the other pathways play a significant role in conjugated linoleic acid-driven browning process. In addition, results of conjugated linoleic acid administration may be partially mediated by a group of G protein-coupled receptors (GPRs) [Sauer *et al.*, 2004]. The conjugated linoleic acid browning properties were indirectly observed in several clinical trials reporting significant weight loss in conjugated linoleic acid subjects [Blankson *et al.*, 2000; Smedman & Vessby, 2001; Watras *et al.*, 2007]. Apart from the adipocyte browning promotion, conjugated linoleic acid elevated lipolysis, β-oxidation, white adipocyte apoptosis, and decreased adipogenesis [Hargrave *et al.*, 2002; LaRosa *et al.*, 2006]. Interestingly, a few research disclosed raised inflammatory markers, such as C-reactive protein, upon dietary interventions with conjugated linoleic acid [Steck *et al.*, 2007].

Contrary to conjugated linoleic acid, the linoleic acid supplementation evoked accumulation of fat and increased body mass as well as diminished thermogenesis and oxygen consumption in the C57BL/6 mice model [Shin & Ajuwon, 2018b]. Furthermore, no signs of browning-specific gene upregulation were noted. Nevertheless, linoleic acid addition to murine primary subcutaneous adipocytes *in vitro* resulted in *Ucp1* overexpression and insignificant *Ppargc1a* mRNA elevation [Shin & Ajuwon, 2018a]. Thus, the discrepancy between conjugated linoleic acid and linoleic acid browning properties *in vivo* may be attributed to the fact that high-fat diet itself leads to adipocyte browning inhibition, and linoleic acid is not capable of attenuating high-fat diet-induced alterations [Shin & Ajuwon, 2018b].

10-Oxo-12(*Z*)-octadecenoic acid

10-Oxo-12(*Z*)-octadecenoic acid is a product of saturation metabolism of linoleic acid by gut microbiota, especially *Lactobacillus* spp. [Kishino *et al.*, 2013]. Upon its administration, a significant increase in expression of *Ucp1, Prdm16, Ppargc1a, Tbx1, Cpt1b,* and *Adrb3* in iWAT, as well as BAT, of C57BL/6 mice was observed [M. Kim *et al.*, 2017]. 10-Oxo-12(*Z*)-octadecenoic acid induced adipocyte browning and weight loss *via* gastrointestinal TRPV1 receptors, which activated β_3-adrenergic signaling, a potent browning stimulator. Furthermore, its supplementation reduced blood glucose and triglycerides [M. Kim *et al.*, 2017].

Oleic acid

Olive oil is the most common source of oleic acid, a monounsaturated *n*-9 fatty acid, and a crucial element of the Mediterranean diet [Marcelino *et al.*, 2019]. Regarding adipocyte browning, oleic acid administration resulted in marginally augmented *Ucp1* expression in 3T3-L1 adipocytes, while no effect of oleic acid was observed in 10T1/2 cells or murine primary subcutaneous adipocytes *in vitro* [Shin & Ajuwon, 2018a]. Surprisingly, oleic acid did not show a potent browning-inducing effect, in contrast to the outcomes of olive oil supplementation (see: *Olive oil* section) [Shin & Ajuwon, 2018b].

Stearic acid

Animal fats, as well as cocoa and shea butter, are products abundant in stearic acid, which acts as a potent adipocyte browning inhibitor [Shin & Ajuwon, 2018b]. Stearic acid-rich diet based on high shea butter intake resulted in diminished *Ucp1, Ppargc1a,* and *Adrb3* expression in eWAT and also lowered the *Ucp1* mRNA level in sWAT of C57BL/6 mice [Shin & Ajuwon, 2018b]. Interestingly, shea butter diet significantly upregulated *Prdm16* in eWAT and *Tfam* in sWAT, although increased content of WAT and total body weight were noticed. Moreover, no alterations of browning-specific genes were observed in murine primary subcutaneous adipocytes as

well as 3T3-L1 and 10T1/2 cell lines *in vitro*, except for *Cidea* downregulation in primary subcutaneous adipocytes [Shin & Ajuwon, 2018a]. In addition, stearic acid supplementation led to elevated triglycerides accumulation in the liver as well as raised blood glucose and insulin [Shin & Ajuwon, 2018b].

Arachidonic acid

Arachidonic acid is a product of linoleic acid metabolism, which serves as a substrate for prostaglandins production [Sonnweber *et al.*, 2018]. Common dietary sources of arachidonic acid are eggs, fishes, meat and poultry [Taber *et al.*, 1998]. Recent research revealed that intake of arachidonic acid may inhibit adipocyte browning in human multipotent adipose-derived stem cells, which was manifested by decreased UCP1 at both mRNA and protein levels [Pisani *et al.*, 2014]. In addition, a significant decline in mitochondrial activity, as well as impaired browning upon β_3-AR agonist, was observed. Since elevated expression of both isoforms of cyclooxygenase (COX-1 and COX-2) and increased concentrations of prostaglandins E2 and F2α were noted in adipocytes, a prostaglandins-dependent pathway was suggested as the mechanism of browning suppression [Pisani *et al.*, 2014]. However, the same prostaglandin E2 was previously considered as a browning activator in both human and murine models [García-Alonso *et al.*, 2013, 2016]. This discrepancy might be attributed to the stimulation of different receptors for prostaglandin E2. High affinity EP4 receptor activity was recognized to promote cAMP signaling and stimulate browning, while low affinity EP1 receptor working through calcium signaling pathway evoked the opposite effect [Pisani *et al.*, 2014].

Moreover, the suppressive effect of arachidonic acid on the adipocyte browning was also reported in interscapular WAT of C57BL/6J mice (↓ UCP1, PRDM16, PGC1α, C/EBPβ), while in gonadal WAT molecular signs of browning (↑ UCP1, PRDM16, PGC1α, C/EBPβ, CIDEA) were found [Zhuang *et al.*, 2017]. Interestingly, arachidonic acid supplementation showed gender-specific effects on metabolic outcomes and inflammation. Arachidonic acid beneficially modulated insulin sensitivity and adipose tissue inflammation in female mice, and did the opposite in males [Zhuang *et al.*, 2017]. Possibly this is due to altered composition of gut microbiota in female mice (reduced Firmicutes/Bacteroidetes ratio), as a result of gender-dependent arachidonic acid interaction [Zhuang *et al.*, 2017].

Docosahexaenoic and eicosapentaenoic acids

n-3 Long-chain polyunsaturated fatty acids, such as docosahexaenoic and eicosapentaenoic acids (DHA and EPA, respectively), are well-known metabolism regulators found mainly in fish oil [Kris-Etherton *et al.*, 2009]. Recent research has suggested that positive metabolic effects of DHA and EPA might be associated with stimulation of the adipocyte browning [Bargut *et al.*, 2019; Laiglesia *et al.*, 2016; Zhao & Chen, 2014].

Both DHA and EPA, as well as a mixture of DHA with EPA, reduced adipocyte size and significantly increased expression of browning-specific genes, such as *Ucp1, Cd137, Ppargc1a, Nrf1, Tfam, Ppara, Pparg*, in iWAT of C57BL/6 mice [Bargut *et al.*, 2019]. Interestingly, the most potent effect was exerted by EPA itself, while DHA+EPA supplementation resulted mostly in significantly smaller gene upregulation than single EPA or DHA. Similarly, the above-mentioned genes were also overexpressed in BAT in response to both DHA and EPA as well as its mixture, except for insignificant *Ppargc1a* alteration upon DHA+EPA [Bargut *et al.*, 2019]. Furthermore, both DHA and EPA raised *Prdm16, Cidea, Cpt1b,* and *Cox8b* in iWAT of C57BL/6 mice; however, only the DHA-treated group showed a decreased fat mass and adipocyte volume as well as upregulation of *Cebpb* and bone morphogenetic protein 7 [Zhuang *et al.*, 2019]. Moreover, both DHA and EPA were responsible for the elevated expression of *Ucp1, Ppargc1a, Pparg, Cidea, Cpt1b,* and *Cox8b* in 3T3-L1 adipocytes [Zhuang *et al.*, 2019]. Nevertheless, DHA supplementation increased the expression of those genes to a greater extent than EPA and initiated the adipocyte browning a few days earlier [Zhuang *et al.*, 2019], suggesting DHA to be a more potent browning activator than EPA, on the contrary to the previously described paper [Bargut *et al.*, 2019].

Signs of adipocyte browning were also reported in human differentiated subcutaneous adipocytes upon EPA administration *in vitro* [Laiglesia *et al.*, 2016]. The addition of EPA to the medium was associated with an enhanced expression of *UCP1, PRDM16, CIDEA, CD137, TBX1, NRF1, TFAM,* and *CPT1A,* which is in line with the results obtained on murine model [Zhao & Chen, 2014].

However, one of the *in vivo* studies completely denied EPA-induced adipocyte browning presenting no effect of EPA in upregulating *Ucp1, Prdm16, Ppargc1a, Pparg, Cidea*, *Elovl3,* and *Fgf21* genes in murine iWAT, while showing that all of them were significantly enhanced in BAT [Pahlavani *et al.*, 2017].

There are also inconsistencies regarding the role of DHA and EPA in lipolysis and lipogenesis. Two of the studies report significant elevation in hormone-sensitive lipase expression [Bargut *et al.*, 2019], with concomitant increase in the lipolytic rate and inhibition of lipogenic enzymes, including fatty acid synthase [Laiglesia *et al.*, 2016]. On the other hand, another study showed inhibition of hormone-sensitive lipase and adipose triglyceride lipase, indicating lipolysis suppression, as well as overexpression of glycerol-3-phosphate acyltransferase 1 and 3 involved in lipogenesis [Zhao & Chen, 2014].

Furthermore, DHA, and EPA elevated serum adiponectin and decreased leptin [Bargut *et al.*, 2016; Zhuang *et al.*, 2019]. Interestingly, DHA also reduced the level of low-grade systemic inflammation, diminishing tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) concentrations, and increasing anti-inflammatory IL-10 [Zhuang *et al.*, 2019]. Moreover, EPA enhanced glucose transporter type 4 and lipoprotein lipase mRNAs, which might contribute to lowered blood glucose, low-density lipoprotein cholesterol (LDL-C), and total cholesterol [Bargut *et al.*, 2019; Zhao & Chen, 2014].

Several mechanisms of DHA and EPA-induced adipocyte browning have been proposed so far. First of them is the activation of the sympathetic nervous system, which might be a result of β_3-AR or TRPV1 receptors stimulation or FGF21 action [Bargut *et al.*, 2016; Kim *et al.*, 2015]. Another possible

TABLE 2. Summary of *in vivo* studies of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) regarding adipocyte browning stimulation.

Substance	Dose (g/kg/day)	Duration (week)	Research material	Adipose tissue deposit	Genes/mRNAs alterations	Reference
DHA	8.47	5	C57BL/6 mice	iWAT and BAT	↑↑ *Ucp1, Cd137, Ppargc1a, Nrf1, Tfam, Ppara, Pparg* ↑ *Fndc5, Hsl*	Bargut *et al.* [2019]
DHA	10	15	C57BL/6J mice	iWAT	↑ *Prdm16, Cidea, Cpt1b, Cox8b*	Zhuang *et al.* [2019]
EPA	8.47	5	C57BL/6 mice	iWAT and BAT	↑↑↑ *Ucp1, Cd137, Ppargc1a, Nrf1, Tfam, Ppara, Pparg* ↑ *Fndc5, Hsl*	Bargut *et al.* [2019]
EPA	10	15	C57BL/6J mice	iWAT	↑ *Prdm16, Cidea, Cpt1b, Cox8b*	Zhuang *et al.* [2019]
EPA	36	11	C57BL/6J mice	iWAT	↔ *Ucp1, Prdm16, Ppargc1a, Pparg, Cidea*, *Elovl3, Fgf21* ↔ *Fndc5*	Pahlavani *et al.* [2017]
EPA	36	11	C57BL/6J mice	BAT	↑ *Ucp1, Prdm16, Ppargc1a, Pparg, Cidea*, *Elovl3, Fgf21* ↔ *Fndc5*	Pahlavani *et al.* [2017]
DHA + EPA	4.235 + 4.235	5	C57BL/6 mice	iWAT	↑ *Ucp1, Cd137, Ppargc1a, Nrf1, Tfam, Ppara, Pparg* ↑ *Fndc5,* ↓ *Hsl*	Bargut *et al.* [2019]
DHA + EPA	4.235 + 4.235	5	C57BL/6 mice	BAT	↑ *Ucp1, Cd137, Nrf1, Tfam, Ppara, Pparg*	Bargut *et al.* [2019]

BAT: brown adipose tissue; *Cidea*: cell death activator CIDE-A; *Cox8b*: cytochrome c oxidase subunit 8B, mitochondrial; *Cpt1b*: carnitine *O*-palmitoyltransferase 1, muscle isoform; *Elovl3*: elongation of very long chain fatty acids protein 3; *Fgf21*: fibroblast growth factor 21; *Fndc5*: fibronectin type III domain-containing protein 5; *Hsl*: hormone-sensitive lipase; iWAT: inguinal white adipose tissue; *Nrf1*: nuclear respiratory factor 1; *Ppara*: peroxisome proliferator-activated receptor α; *Pparg*: peroxisome proliferator-activated receptor γ; *Ppargc1a*: peroxisome proliferator-activated receptor γ coactivator 1-α; *Prdm16*: PR domain-containing protein 16; *Tfam*: transcription factor A, mitochondrial; *Ucp1*: uncoupling protein 1.

mechanism involves AMPK/PGC1α or SIRT1/PGC1α pathways, which play role in mitochondrial biogenesis [Laiglesia *et al.*, 2016; Zhao & Chen, 2014]. Interestingly, AMPK/PGC1α signaling may be partially induced by apelin, which secretion might be augmented in response to fish oil consumption [Yuzbashian *et al.*, 2018]. Moreover, the action of DHA and EPA is associated with the GPR120 receptor, which promotes microRNAs miR-30b and miR-378 to modulate gene expression as well as may be linked with FGF21 activity and attenuation of inflammation-related browning inhibition [Kim *et al.*, 2016; Lund *et al.*, 2018; Quesada-López *et al.*, 2016].

In addition, both DHA and EPA, as well as DHA+EPA, were found to elevate fibronectin type III domain-containing protein 5 expression in murine iWAT, a precursor of irisin, which is capable of adipocyte browning stimulation itself [Bargut *et al.*, 2019]. However, other studies failed to detect changes in irisin concentrations in iWAT and BAT upon EPA supplementation [Pahlavani *et al.*, 2017].

The summary of the above-mentioned *in vivo* and *in vitro* studies concerning DHA and EPA browning potential is presented in Table 2 and Table 3, respectively.

Palmitoyl lactic acid

Palmitoyl lactic acid is often used as an emulsifying agent of food [Unno *et al.*, 2018]. Using the 3T3-L1 preadipocytes model, Unno *et al.* [2018] revealed that palmitoyl lactic acid as a substantial component of krill *Euphausia superba* oil fraction had adipocyte browning properties. Through unknown mechanism, palmitoyl lactic acid increased UCP1, PRDM16, PPARγ, and PGC1α at both mRNA as well as protein levels and upregulated expression of *Cidea*, *Cited1, Cox7a1*, *Fgf21,* and *Tmem26* after 7 days of administration. Moreover, it stimulated adipogenesis, inducing perilipin and fatty acid-binding protein 4, as well as elevated accumulation of lipids in small droplets. Interestingly, palmitoyl lactic acid is the only fatty acid so far that boosted adipogenesis in the presence of dexamethasone [Unno *et al.*, 2018].

Short-chain fatty acids

Short-chain fatty acids originate from dietary fibers during intestinal fermentation, and are an essential source of energy for colonocytes [Wong *et al.*, 2006]. Acetic, propionic, and butyric acids are the most prevalent short-chain fatty acids [Tazoe *et al.*, 2008]. Recently, Lu *et al.* [2016] proved that short-chain fatty acids also participated in adipocyte browning, leading to enhanced expression of *Ppargc1a*, *Tbx1*, *Tmem26*, *Cd137*, *Nrf1*, *Tfam,* as well as increased β-oxidation and mitochondrial biogenesis, in eWAT of C57BL/6J male mice. Moreover, Hu *et al.* [2016] confirmed that acetic acid administration resulted in elevated UCP1 and PGC1α, both at mRNA and protein level in immortalized brown adipocytes, while Weitkunat *et al.* [2017] reported upregulation of *Ppargc1a* mRNA and cytochrome c oxidase activity in sWAT of C57BL/6JRj mice. Interestingly, short-chain fatty acids reversed high-fat diet-induced adipocyte hyperplasia and altered microbiota composition, preferring overgrowth of *Bifidobacterium* [Weitkunat *et al.*, 2017] and reducing Firmicutes/Bacteroidetes ratio [Lu *et al.*, 2016]. Furthermore, propionic acid was found to increase transcription of neuregulin 4 [Weitkunat *et al.*, 2017], a batokine considered as an inhibitor of hepatic lipogenesis [Villarroya *et al.*, 2017]; however, only acetic acid supplementation resulted in the suppression of lipogenesis in the liver [Weitkunat *et al.*, 2017]. In addition,

TABLE 3. Summary of *in vitro* studies of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) regarding adipocyte browning stimulation.

Substance	Concentration (μM)	Duration (day)	Research material	Genes/mRNAs alterations	Protein alterations	Reference
DHA	100	8	3T3-L1 cells	↑↑↑ *Ucp1, Ppargc1a, Pparg, Cidea, Cpt1b, Cox8b*	Not studied	Zhuang *et al.* [2019]
EPA	100	8	3T3-L1 cells	↑ *Ucp1, Ppargc1a, Pparg, Cidea, Cpt1b, Cox8b*	Not studied	Zhuang *et al.* [2019]
EPA	200	8	iWAT-derived SVC	↑ *Ucp1, Prdm16, Ppargc1a, Cidea, Cd137, Nrf1, Tfam, Tbx1, Cpt1a* ↓ *Hsl, Atgl*	Not studied	Zhao & Chen [2014]
EPA	100	1	overweight female-derived sWAT	↑ *UCP1, PRDM16, CIDEA, CD137, TBX1, NRF1, TFAM, TMEM26, CPT1A*	Not studied	Laiglesia *et al.* [2016]

Atgl: adipose triglyceride lipase; *Cidea*: cell death activator CIDE-A; *Cox8b*: cytochrome c oxidase subunit 8B, mitochondrial; *Cpt1a*: carnitine *O*-palmitoyltransferase 1, liver isoform; *Cpt1b*: carnitine *O*-palmitoyltransferase 1, muscle isoform; *Hsl*: hormone-sensitive lipase; iWAT: inguinal white adipose tissue; *Nrf1*: nuclear respiratory factor 1; *Ppara*: peroxisome proliferator-activated receptor α; *Pparg*: peroxisome proliferator-activated receptor γ; *Ppargc1a*: peroxisome proliferator-activated receptor γ coactivator 1-α; *Prdm16*: PR domain-containing protein 16; SVC: stromal vascular cells; sWAT: subcutaneous white adipose tissue; *Tbx1*: T-box transcription factor TBX1; *Tfam*: transcription factor A, mitochondrial; *Tmem26*: transmembrane protein 26; *Ucp1*: uncoupling protein 1.

short-chain fatty acids improved carbohydrate and lipid metabolism as well as reduced the concentration of proinflammatory cytokines [Lu *et al.*, 2016; Weitkunat *et al.*, 2017].

All effects of short-chain fatty acids are likely mediated by GPR43, which promotes phosphorylation of extracellular signal-regulated kinases 1/2 and cAMP response element--binding protein [Hu *et al.*, 2016], while the role of GPR41 remains unclear [Hu *et al.*, 2016; Lu *et al.*, 2016]. Taken together, short-chain fatty acids attenuated weight gain in high-fat diet mice [Lu *et al.*, 2016; Weitkunat *et al.*, 2017], and acetic acid was found to have the highest impact [Lu *et al.*, 2016].

RETINOIDS

All-*trans* retinoic acid is a bioactive form of vitamin A, the latter found primarily in vegetables, fruits, dairy products, eggs, and meat in the form of retinol and its esters, or provitamin A [Dawson, 2000]. While the role of all-*trans* retinoic acid in the treatment of acute promyelocytic leukemia and acne is well known [Bershad *et al.*, 1999; Meng-er *et al.*, 1988], recent studies revealed its involvement in adipocyte browning activation [Guo *et al.*, 2016; Murholm *et al.*, 2013; Tourniaire *et al.*, 2015; Wang *et al.*, 2017].

Administration of all-*trans* retinoic acid significantly upregulated expression of *Ucp1, Prdm16, Pparg, Cidea, Elovl3,* and *Cox7a1* in iWAT of C57BL6 mice *in vivo* and iWAT-derived stromal vascular cells *in vitro* [Wang *et al.*, 2017]. Furthermore, a similar increase of BAT markers, including *Ucp1, Ppargc1a, Ppara,* and *Cd137,* was observed in eWAT and rWAT of Naval Medical Research Institute mice [Mercader *et al.*, 2006; Tourniaire *et al.*, 2015]; however no molecular signs of the adipocyte browning were reported in human multipotent adipose-derived stem cells or human preadipocytes upon all-*trans* retinoic acid supplementation [Murholm *et al.*, 2013]. In addition, all-*trans* retinoic acid induced mitochondrial biogenesis, β-oxidation, and oxidative phosphorylation capacity in murine *in vivo* and *in vitro* models [Tourniaire *et al.*, 2015]. Finally, all-*trans* retinoic acid altered adipocyte morphology to multilocular and elevated angiogenesis by upregulation of vascular endothelial growth factor A and its receptors [Mercader *et al.*, 2006; Wang *et al.*, 2017]. All actions of all--*trans* retinoic acid resulted in decreased adiposity, weight loss, reduced plasma glucose and triglycerides, as well as improved insulin sensitivity [Berry & Noy, 2009; Wang *et al.*, 2017].

The main mechanism of all-*trans* retinoic acid is associated with direct stimulation of retinoic acid response elements by binding to retinoic acid receptors, which form complexes with retinoid X receptors in promoter/enhancer regions of all-*trans* retinoic acid-dependent genes [Murholm *et al.*, 2013]. Thus, the downstream mechanism of all-*trans* retinoic acid-induced adipocyte browning at least partially refers to the activation of retinoic acid response elements on *Ucp1, Prdm16,* vascular endothelial growth factor A, and lipocalin 2 genes [Guo *et al.*, 2016; Murholm *et al.*, 2013; Wang *et al.*, 2017].

GLUCOSINOLATES AND OTHER SULFUR--CONTAINING PLANT SECONDARY METABOLITES

Glucoraphanin and sulforaphane

Broccoli and cauliflower are the sources of glucosinolates, including glucoraphanin, which is a precursor of biologically active sulforaphane – an activator of *Nrf2* [Houghton *et al.*, 2016]. Bioavailability of glucoraphanin ranges from 10% to 40% [Fahey *et al.*, 2015], the latter achieved upon plant myrosinase addition, which enhances glucoraphanin conversion to sulforaphane [Shapiro *et al.*, 2001]. Nagata *et al.* [2017] tested glucoraphanin supplementation in wild-type and *Nrf2* knockout ($Nrf2^{-/-}$) mice. They found that the glucoraphanin-rich diet mitigated decreased UCP1 levels in eWAT and iWAT of high-fat diet wild-type mice through the NRF2--related pathway. The browning-positive effect of glucoraphanin was confirmed with enhanced expression of *Nqo1* (target gene of NRF2) and browning-specific genes, such as *Ucp1, Prdm16, Cidea,* and *Elovl3,* after sulforaphane administration. Interestingly, BAT in wild-type mice was not affected by glucoraphanin supplementation since no differences were noticed in mRNA levels of *Ucp1* and *Ppargc1a* [Nagata *et al.*, 2017]. Furthermore, *in vitro* studies on 3T3-L1 adipocytes evidenced

that sulforaphane upregulated expression of UCP1, SIRT1, PGC1α, NRF1, and NRF2 proteins, suggesting the activation of Sirt1/PGC1α pathway and NRF-mediated mitochondrial biogenesis as a primary mechanism of sulforaphane-induced adipocyte browning [H. Q. Zhang *et al.*, 2016].

Allicin

Allicin is a substance found in garlic and known for its antimicrobial properties since decades [Cavallito & Bailey, 1944]. The bioavailability of allicin is the highest when garlic is consumed raw (80%), and diminishes significantly when it is roasted (30%), pickled (19%) or boiled (16%) [Lawson & Hunsaker, 2018]. Recent studies show that allicin may affect the adipocyte browning, increasing *Ucp1, Prdm16,* and *Ppargc1a* mRNAs as well as mitochondria mass in differentiated 3T3-L1 adipocytes [Lee *et al.*, 2019]. In addition, its browning-positive effect was evidenced in iWAT of C57BL/6J mice. Upon 8-week supplementation with allicin, multilocular morphology of the adipocytes, elevated expression of *Ucp1, Prdm16,* and *Ppargc1a*, and attenuated weight gain were observed [Lee *et al.*, 2019].

Overexpression of the KLF15 transcription factor and its enhanced binding to the *Ucp1* promoter at the Sp1ER site was suggested as a part of the allicin-induced adipocyte browning mechanism [Lee *et al.*, 2019]. Moreover, allicin activated the extracellular signal-regulated kinases 1/2 pathway, which additionally intensified the expression of browning activators, including KLF15.

Interestingly, allicin reduced serum triglycerides and free fatty acids concentrations, not only preventing obesity but also improving metabolic health [Lee *et al.*, 2019].

VOLATILE ORGANIC COMPOUNDS

D-Limonene

D-Limonene is the major constituent of citrus oils, found in orange, mandarin, lemon, grapefruit and lime [Sun, 2007]. After oral administration, 43% of ingested D-limonene is bioavailable, according to a rat study [Chen *et al.*, 1998]. An *in vitro* study on 3T3-L1 adipocytes showed that limonene stimulates transcription of *Ucp1*, *Prdm16, Pparg*, *Cited1*, *Cidea*, *Fgf21* as well as translation of UCP1, PRDM16, PGC1α, and C/EBPβ, all indicative of adipocyte browning [Lone & Yun, 2016]. Mechanistically, the activation of β_3-AR signaling and mitogen-activated protein kinase/extracellular signal-regulated kinases pathway was suggested in D-limonene's browning-positive effects. In addition, limonene supplementation elevated phosphorylation of AMPK and acetyl-CoA carboxylase, which stimulated lipolysis and provided a supply of fatty acids as a source of energy for thermogenesis [Lone & Yun, 2016].

Menthol

Menthol, an agonist of the TRPM8 receptor, is derived from *i.a.* peppermint, or corn mint [Peier *et al.*, 2002]. After ingestion, the mean recovery of menthol as glucuronide ranged from 45.6% (menthol capsule) to 56.6% (mint candy/tea) [Gelal *et al.*, 1999]. Jiang *et al.* [2017] examined whether WAT adipocytes could be deluded by menthol mimicking cold exposure *via* TRPM8-related cooling sensation and induce adipocyte browning. Results of their *in vitro* study on murine white adipocytes revealed that menthol stimulation increased mRNAs of *Ucp1* and *Pgc1α* unless TRPM8 was blocked, supporting the role of TRPM8 in adipocyte browning. Mechanistically, TRPM8 activation resulted in higher cytoplasmic content of calcium, which energized PKA in an unknown pathway [Jiang *et al.*, 2017]. Interestingly, the contribution of TRPA1 in mediating menthol-induced adipocyte browning is also under consideration [Farco & Grundmann, 2013]. Menthol's browning-positive effect was also corroborated *in vivo* since its supplementation enhanced expression of *Ppargc1a, Ucp1, Prdm16, Trpm8,* and *Adrb3* in both eWAT and sWAT of high-fat diet mice, while transcription of *Pparg* remained unchanged [Jiang *et al.*, 2017]. Additionally, menthol counteracted adipocyte hypertrophy, leading to a reduced diameter of fat cells. Of note, there is also evidence of menthol-mediated browning in human adipocytes *in vitro* [Rossato *et al.*, 2014].

Phytol

Phytol, a branched-chain fatty alcohol present in chlorophyll molecules, improves glucose tolerance, expression of β-oxidation enzymes, and reduces serum fatty acid concentrations [Zhang *et al.*, 2018]. Rat studies revealed that bioavailability of phytol given orally varies between 30–66% [Mize *et al.*, 1966]. Its derivative is phytanic acid, known for WAT browning and increasing the expression of the UCP1 in HIB1B cells [Schluter *et al.*, 2002]. Major food sources of phytanic acid are dairy lipids and ruminant meat [Verhoeven & Jakobs, 2001].

Reduction of adipocyte diameter and formation of multilocular adipocytes, as well as increased expression of UCP1, PRDM16, PGC1α, Cyt C, and pyruvate dehydrogenase, also suggest the participation of phytol in the browning process in both iWAT of C57BL/6J mice and 3T3-L1 cells [Zhang *et al.*, 2018]. Additionally, overexpression of *Cidea*, *Elovl3*, *Cd137* and *Tmem26* mRNAs was observed in 3T3-L1 preadipocytes. Furthermore, the administration of phytol also multiplied mitochondrial content and O_2 consumption, resulting in better weight cont. Activation of the AMPKα pathway is considered as an underlying mechanism of phytol-induced adipocyte browning [Zhang *et al.*, 2018].

Thymol

Thymol is a phenolic monoterpene component obtained from the *Thymus* species, which is used as a food additive or aroma [Choi *et al.*, 2017]. Its bioavailability after oral administration is at least 16% [Kohlert *et al.*, 2002]. It acts as a pleiotropic agent, exerting neuroprotective, anti-inflammatory, antibacterial, and anti-diabetic effects. Recent studies reported, it may also lead to the browning of WAT [Choi *et al.*, 2017].

Upon 6- to 8-day thymol administration, the expression of BAT-specific genes, such as *Ucp1*, *Prdm16*, *Ppargc1a*, *Tbx1, Tmem26*, *Cidea*, *Cited1,* and *Fgf21*, significantly increased in 3T3-L1 adipocytes [Choi *et al.*, 2017]. Elevated concentrations of UCP1, PRDM16, PGC1α, PPARγ, and C/EBPβ proteins were also observed. In addition, a substantial rise

in mitochondrial biogenesis occurred due to the upregulation of the *Tfam* and *Nrf1* genes.

The activation of β_3-AR, resulting in the activation of PKA and p38 mitogen-activated protein kinase, as well as enhanced phosphorylation of AMPK, was suggested as a possible mechanistic explanation of thymol-induced adipocyte browning [Choi *et al.*, 2017].

By raising the level of carnitine *O*-palmitoyltransferase 1 and acyl-coenzyme A oxidase thymol intensified β-oxidation [Choi *et al.*, 2017]. A reduction in triglycerides and lipoprotein lipase levels and an increment in hormone sensitive lipase and perilipin were also noted.

trans-Anethole

trans-Anethole is a compound of essential oils derived from *i.a.*: anise, star anise, and fennel [Bartoňková & Dvořák, 2018], characterized with very high bioavailability of 95% when administered orally [Bounds & Caldwell, 1996]. Kang *et al.* [2018] provided evidence of its browning properties in the C57BL/6 mice model and 3T3-L1 adipocytes. *trans*-Anethole increased BAT marker protein levels PGC1α, UCP1, PRDM16, and upregulated beige adipose tissue-selective genes (*Cd137*, *Cited1*, *Tbx1*, *Tmem26)* by activation of β_3-AR and SIRT1 pathways. In addition, *trans*-anethole not only induced browning and elevated BAT mass, but also activated brown cells and decreased WAT depots and body weight [Kang *et al.*, 2018].

PHENOLIC COMPOUNDS

Phenolic acids

Ellagic acid is an anti-oxidative phenolic compound of nuts, raspberries, and other plants or fruits [Vattem & Shetty, 2005]. However its bioavailability from the diet is low, only 10% [Doyle & Griffiths, 1980]. Its adipocyte browning potential was studied in male rats in the timespan of 24 weeks [L. Wang *et al.*, 2019]. Results revealed that administration of ellagic acid evoked browning of iWAT in high-fat diet animals, which was proved by increased expression of PGC1α, UCP1, *Ppara, Prdm16, Cidea, Tmem26,* and *Cd137,* whereas C/EBPβ, PPARγ, and C/EBPα were decreased. This phenomenon could be explained by lowered levels of zinc finger protein 423 and retinal dehydrogenase 1 mRNAs since both are responsible for preserving the white adipocyte phenotype [L. Wang *et al.*, 2019]. Hence, suppression of these molecules by ellagic acid is considered as the principal mechanism of ellagic acid-related browning. In addition, ellagic acid promoted activation of BAT and improved metabolism, leading to reduced weight, insulin resistance as well as lowered accumulation of lipids in the liver [L. Wang *et al.*, 2019]. Interestingly, ellagic acid supplementation altered adipokines profile, decreasing plasma concentration of "white" adipogenic marker – resistin, without changing adiponectin which might possibly prevent effects of resistin on liver steatosis [L. Wang *et al.*, 2019]. Notably, gut microbiota transforms ellagic acid into urolithin A [Bialonska *et al.*, 2009], characterized with higher bioavailability than the ellagic acid [Landete, 2011]. Thus, it needs to be elucidated if the latter contributes to the browning and metabolic effects of ellagic acid.

Flavonoids

Flowers, honeycombs, and mushrooms are the sources of the chrysin, which carries numerous health benefits, including anti-cancer, anti-inflammatory, anti-diabetic, hypolipidemic, and hypocholesterolemic effects [Choi & Yun, 2016]. At the same time, the bioavailability of chrysin in humans is very low (0.003–0.02%) [Walle *et al.*, 2001]. Studies on 3T3-L1 cells showed that it is also engaged in adipocyte browning by increasing the expression of BAT-specific proteins (UCP1, PRDM16, PGC1α, PPARγ, C/EBPβ) and genes (*Ucp1*, *Ppargc1a*, *Prdm16*, *Cidea*, *Cited1*, *Fgf21*, *Tbx1*, *Tmem26*) [Choi & Yun, 2016]. Chrysin stimulated this process by activating the AMPK pathway. The expansion of multilocular adipocytes was also reported. Moreover, an increment in hormone-sensitive lipase, perilipin, lipoprotein lipase, carnitine *O*-palmitoyltransferase 1 and acyl-coenzyme A oxidase levels was observed, as well as acetyl-CoA carboxylase phosphorylation, which indicates its influence on lipid metabolism [Choi & Yun, 2016].

Cacao and tea are the rich sources of (–)-epicatechin [Bártíková *et al.*, 2017; Ramiro-Puig & Castell, 2009]. The bioavailability of this flavan-3-ol was described by urinary recovery ranging from 24.1 to 29.8%, 24 h after ingestion of cacao or chocolate, respectively, while the majority of (–)-epicatechin metabolites (80%) are eliminated in just 8 h [Baba *et al.*, 2000]. (–)-Epicatechin was tested on human adipocytes (isolated from sWAT during surgery) and adipocytes from obese C57BL/6 mice [Varela *et al.*, 2017]. (–)-Epicatechin provoked adipocyte browning in both groups, which was demonstrated with higher levels of BAT hallmarks, such as UCP1, PRDM16, and DIO2. There are a few possible mechanisms of (–)-epicatechin-induced adipocyte browning: raised phosphorylation of AMPK and acetyl-CoA carboxylase, lower acetylation of PPARγ and PGC1α, as well as the promotion of mitochondrial biogenesis [Varela *et al.*, 2017]. Moreover, (–)-epicatechin multiplies mitochondrial activity and intensifies fatty acid oxidation. Interestingly, (–)-epicatechin reduced TNF-α and IL-6 plasma concentrations, additionally providing an anti-inflammatory effect [Varela *et al.*, 2017].

Genistein belongs to isoflavones, phytoestrogens derived from *Fabaceae, e.g.*, *Soiae semen* [Jaiswal *et al.*, 2019]. Its absolute bioavailability in mice was found to be 89%; however, only 9.4% maintained the biologically active aglycone form [Andrade *et al.*, 2010]. After genistein administration under both, control and peroxidative stress conditions, Grossini *et al.* [2018] reported a dose-dependent increase in UCP1 expression in human preadipocytes isolated from visceral WAT. The same effect was also observed in differentiated brown adipocytes, but to a greater extent, determining genistein as a potent adipocyte browning inductor even in the case of oxidative stress [Grossini *et al.*, 2018]. At the molecular level, browning properties of genistein were associated with activation of Akt and AMPKα/β and subsequent elevation of mitofusin-2. In addition, the browning potential of genistein was also studied *in vivo* on female Wistar rats after ovariectomy [Shen *et al.*, 2019]. Genistein was found to increase translation of UCP1, PRDM16, PGC1α, CIDEA, NRF1, and TFAM, as well as a transcription of *Ppargc1a, Ucp1,* and *Tbx1* in iWAT after 4-week therapy. The promotion

of adipocyte browning resulted in upregulation of both nuclear estrogen receptor-α (ERα) and plasma irisin [Shen *et al.*, 2019], a browning-inducing myokine [Boström *et al.*, 2012]. Moreover, genistein exerted an anti-inflammatory effect, improved insulin sensitivity, mitigated lipogenesis in the liver, and facilitated weight reduction [Shen *et al.*, 2019]. Thus, genistein appeared to be beneficial particularly in postmenopausal conditions.

Hesperidin, a citrus flavanone, regulates metabolic processes, prevents obesity, sensitizes cells to insulin, and acts as an antioxidant [Mosqueda-Solís *et al.*, 2018]. Its bioavailability is variable and depends, to a great extent, on the composition of the intestinal flora [Mas-Capdevila *et al.*, 2020]. According to recent research, hesperidin lessened adipocyte size in both rWAT and iWAT of Wistar rats after 8-week supplementation [Mosqueda-Solís *et al.*, 2018]. Besides, multilocular cells exhibiting positive staining for UCP1 and CIDEA were detected in the latter. However, hesperidin caused no difference in the expression of *Ucp1*, *Ppargc1a*, *Prdm16,* and *Cidea* mRNAs in iWAT. CIDEA protein concentrations did not significantly increase in rWAT, while in iWAT there was a substantial rise after administration of hesperidin. In BAT, total UCP1 protein level was higher compared to the control group. It is also worth noting that after hesperidin supplementation rats did not demonstrate a reduction in body fat percentage [Mosqueda-Solís *et al.*, 2018].

Licochalcone A is found in *Glycyrrhiza uralensis*. This chalcone is known for its anti-oxidative and immunomodulatory effects [Jia *et al.*, 2017], despite its poor bioavailability of 3.3% after oral administration [Weng *et al.*, 2019]. It was also reported to enhance expression of UCP1 in 3T3-L1 adipocytes after 4 days of exposure [Lee *et al.*, 2018]. Its browning potential was confirmed by histological and immunochemical signs of browning in iWAT after 19 days of its peritoneal administration to C57BL/6 mice. PRDM16 and PGC1α levels were increased as well, which may partly explain the mechanism of browning. Another mechanistic evidence might be attributed to the downregulation of PPARγ, C/EBPα, and sterol regulatory element-binding protein 1c, which was reported in 3T3-L1 adipocytes by Quan *et al.* [2012]. Interestingly, licochalcone A was also found to multiply the browning effects of two browning activators: triiodothyronine and rosiglitazone [Lee *et al.*, 2018]. Moreover, it may exert beneficial effects on metabolic health, leading to the weight loss, improvement of dyslipidemia and insulin resistance.

Luteolin is a flavone found in plants such as peppermint, broccoli, celery, and oregano [Hostetler *et al.*, 2017]. When administered orally at the dosage of 50 mg/kg per rat body weight, only low bioavailability of 4.10% was achieved [Sarawek *et al.*, 2008]. X. Zhang *et al.* [2016] proved that luteolin enhanced expression of *Ucp1, Ppargc1a, Ppara, Cidea, Elovl3, Tmem26, Cd137, Cited1,* and *Sirt1* in sWAT, but not in eWAT, of C57BL/6 mice fed a high-fat diet. They also demonstrated a significant increase in UCP1 and a change in sWAT adipocyte phenotype (multilocular morphology). Moreover, luteolin was found to enhance the thermogenic activity of BAT by upregulating *Ucp1, Ppargc1a, Ppara, Cidea,* and *Sirt1,* though *Elovl3* and *Prdm16* were not affected. Interestingly, the browning-positive effect of luteolin was also evidenced in mice administered a low-fat diet [X. Zhang *et al.*, 2016]. The action of luteolin is tightly connected with AMPK phosphorylation, which results in the induction of PGC1α and promotes thermogenesis [X. Zhang *et al.*, 2016]. Of note, the effect of luteolin on *Prdm16* mRNA needs to be elucidated since its elevation was noticed only *in vitro* [X. Zhang *et al.*, 2016].

Nobiletin and naringenin are citrus flavonoids that positively influence glucose and lipid metabolism, as well as reduce oxidative stress [Gandhi *et al.*, 2020]. According to rat studies, they are characterized with similar bioavailability of 20–30% after oral administration [Felgines *et al.*, 2000; Zhang *et al.*, 2020]. The browning potential of nobiletin was demonstrated in 3T3-L1 adipocytes *in vitro* [Lone *et al.*, 2018]. By activating PKA and p-AMPK pathways, it enhanced mitochondrial biogenesis and elevated expression of transcriptional factors involved in browning: C/EBPβ, PPAR , PPARα. Furthermore, upon nobiletin supply, *Cd137, Cidea,* and *Tmem26* mRNAs, as well as PGC1α, PRDM16, UCP1, and FGF21 concentrations, increased. Additionally, nobiletin activated HIB1B brown adipocytes, upregulating expression of PRDM16, UCP1, and PGC1α [Lone *et al.*, 2018]. However, a study on Ldlr-/- mice *in vivo* questions its browning effect since no significant browning-specific features were found [Burke *et al.*, 2018]. Thus, the exact impact of nobiletin on adipocyte browning remains inconsistent and requires further studies. Similarly, there is a discrepancy concerning the browning characteristics of naringenin. A study on C57BL6/J mice *in vivo* disclosed increased *Ucp1* levels in epididymal WAT [Assini *et al.*, 2015], which was not confirmed in the *in vivo* study performed on Ldlr-/- mice [Burke *et al.*, 2018]. Nevertheless, beneficial metabolic effects of both nobiletin and naringenin were observed by Burke *et al.* [2018], despite the lack of adipocyte browning evidence at the molecular level. Reduced insulin resistance, improved lipid profile, ameliorated lipid accumulation in the liver and weight loss were reported.

Quercetin is a flavonol present in onion peel, apples, berries, and leafy vegetables [Silvester *et al.*, 2019] with antioxidant, anti-inflammatory [Lee *et al.*, 2017], and insulin resistance-reducing properties that can affect adipocyte browning [Forney *et al.*, 2018]. Its bioavailability is influenced by various factors, such as the content of lipids or indigestible fiber in the diet [Kaşıkcı & Bağdatlıoğlu, 2016]. The absolute bioavailability of quercetin in rats is estimated at 16.0–27.5%, depending on the solvent [Khaled *et al.*, 2003]. According to a 9-week study on C57BL/6J mice, the supply of quercetin resulted in iWAT and eWAT decrement, as well as the expansion of multilocular cells, increased number and diminished size of adipocytes in iWAT and eWAT [Forney *et al.*, 2018]. What is more, quercetin supplementation led to an attenuated expression of pro-inflammatory genes, such as *Cd11b*, *Cd68* in iWAT, while in eWAT there was a depletion in monocyte chemoattractant protein 1 and *Cd68* levels. Additionally, quercetin administration contributed to a decline in the serum leptin concentration [Forney *et al.*, 2018].

Pentamethylquercetin is the cardioprotective flavonoid found in the sea buckthorn [Mao *et al.*, 2009]. Due to the presence of additional methyl groups, its bioavailability is higher than that of quercetin [Chen *et al.*, 2011].

Pentamethylquercetin is known as an anti-diabetic [Wang *et al.*, 2011] and anti-obesity agent that reduces serum glucose, triglycerides, total cholesterol and LDL-C concentrations [Han *et al.*, 2017]. It was also found to reduce intracellular triglyceride concentration without enhancing lipolysis in 3T3-L1 adipocytes [Han *et al.*, 2017]. Administration of pentamethylquercetin was associated with elevated levels of *Cebpa* and *Pparg* mRNAs, and PPARγ protein, therefore, it was revealed that it did not lower the triglyceride levels by inhibiting their expression. It was also shown to upregulate *Ucp1*, *Ppargc1a*, *Cidea*, *Prdm16,* and increase the size and density of eWAT adipocytes in C57BL/6 mice, which was indicative of adipocyte browning [Han *et al.*, 2017]. Consequently, the number of cells showing multilocular morphology was multiplied due to pentamethylquercetin supplementation. Besides, an increment in interscapular BAT with simultaneous decline in eWAT mass was noted, compared to the control administered a high-fat diet [Han *et al.*, 2017].

Other phenolic compounds

Curcumin (diferuloylmethane) is an anti-inflammatory, anticancerous [Lone *et al.*, 2016], antidiabetic, and antiobesity turmeric-derived curcuminoid [Silvester *et al.*, 2019; Shan Wang *et al.*, 2015], known for its ability to inhibit adipogenesis and adipocyte differentiation [Lone *et al.*, 2016]. Unfortunately, its bioavailability in both humans and rats is poor, though may be enhanced by concomitant piperine administration [Shoba *et al.*, 1998]. Curcumin is often used as an ingredient in dietary supplements and flavor/color-enhancers for foods, such as curry powders, mustards, butters, cheeses [Lone *et al.*, 2016]. Recent studies revealed that its supply resulted in overexpression of the *Ucp1*, *Ppargc1a*, *Prdm16,* and *Cidea* genes in C57BL/6 mice iWAT [Shan Wang *et al.*, 2015], as well as 3T3-L1 cells and primary white adipocytes from iWAT of rats [Lone *et al.*, 2016]. Intensified mitochondrial biogenesis was also demonstrated, indicated by accretion in PGC1α amount [Lone *et al.*, 2016; Shan Wang *et al.*, 2015]. In C57BL/6 mice, curcumin supplementation was also found to increase the expression of thermogenic genes regulating adaptive thermogenesis and to beneficially influence weight and fat mass. These effects were observed in iWAT [Shan Wang *et al.*, 2015]. In cultured white 3T3-L1 adipocytes and in primary white adipocytes isolated from iWAT of rats, curcumin administration enhanced the expression of genes and increased contents of protein markers specific for BAT. Higher expression of *Pparg*, *Tmem26, Fgf21,* and *Cidea* genes and significant rise of UCP1, PGC1α, PRDM16, and C/EBPβ was noted [Lone *et al.*, 2016]. Furthermore, the addition of curcumin resulted in a substantial rise in levels of carnitine *O*-palmitoyltransferase 1, Cyt C, hormone sensitive lipase, and phospho-acetyl-CoA carboxylase, which suggests an intensified mitochondrial oxidation, as well as reinforced lipolysis and reduced fatty acid synthesis [Lone *et al.*, 2016]. Two different mechanisms leading to the occurrence of the above effects are considered. The first one indicates the activation of the AMPK pathway [Lone *et al.*, 2016], while the second suggests the influence of an elevated noradrenaline level on β_3-AR [Okla *et al.*, 2017; Shan Wang *et al.*, 2015].

Raspberry ketone is a food additive used in beverages and sweets which is sourced from *Rubus idaeus* [Leu *et al.*, 2018]. According to the murine study, its bioavailability is very high and its metabolism is rapid [Zhao *et al.*, 2019]. The effect of its administration on the browning of 3T3-L1 adipocytes was investigated by Leu *et al*. [2018], who demonstrated elevated levels of browning-specific proteins: UCP1, PGC1α, PRDM16, and C/EBPβ. What is more, raspberry ketone suppressed adipocyte autophagy, which normally is involved in WAT adipocyte differentiation and adipogenesis, and, in turn, increased the activity of BAT. Similarly, a substantial rise of PRDM16 and PGC1α was observed in iWAT of Wistar rats with ovariectomy-induced obesity [Leu *et al.*, 2018].

Red wine and grapes skin are rich in a natural phenolic compound named resveratrol, which belongs to stilbenoids [S. Wang *et al.*, 2015; Zou *et al.*, 2017; Zu *et al.*, 2018]. Despite over 70% absorption, bioavailability of oral resveratrol is very low, but it has been shown to accumulate in the cells of the gastrointestinal tract [Walle *et al.*, 2004]. Resveratrol has a beneficial influence on metabolism, preventing obesity and inhibiting adipogenesis [Rayalam *et al.*, 2008]. Studies revealed that its properties result mostly from involvement in WAT browning activation [Andrade *et al.*, 2019; S. Wang *et al.*, 2015; Zou *et al.*, 2017]. In CD1 mice, a 4-week supplementation with resveratrol attenuated weight gain, and lowered insulin and triglyceride serum levels [S. Wang *et al.*, 2015]. Additionally, its administration contributed to the expansion of smaller, multilocular adipocytes in iWAT, which are typically found in BAT. Besides, increased UCP1, PRDM16, and Cyt C contents with overexpression of phosphorylated AMPKα were observed, without affecting PPARγ and fatty acid-binding protein 4 concentrations. Resveratrol-supplemented mice consumed significantly more oxygen, with the level of CO_2 excreted being the same as in the control group, suggesting that fatty acid oxidation was the main source of energy [S. Wang *et al.*, 2015]. Thus, the average heat production was intensified. Furthermore, iWAT-derived stromal vascular cell analysis evidenced that resveratrol inhibited the expression of adipogenic markers, such as *Pparg* and fatty acid-binding protein 4, and prevented lipid accumulation, but only when used in higher concentrations (20 μM or 40 μM) [S. Wang *et al.*, 2015]. Resveratrol enhanced the expression of BAT hallmarks (*Ucp1*, *Prdm16*, *Cidea*, *Elovl3*) as well as *Ppargc1a*, which is crucial for mitochondrial biogenesis and intense oxidative phosphorylation. Beige fat markers, such as *Cd137*, *Tbx1*, and *Tmem26*, were also elevated and UCP1, PRDM16, Cyt C, and pyruvate dehydrogenase protein levels were raised. Finally, it augmented oxygen consumption. The effects of resveratrol on metabolic health are due to multiple mechanisms, including activation of AMPK pathway [S. Wang *et al.*, 2015]. Interestingly, pregnant mice supplementation with resveratrol induced browning and increased BAT metabolic activity in their offspring [Zou *et al.*, 2017]. This effect contributed to enhanced expression of UCP1 protein and *Ucp1, Ppargc1a, Prdm16, Cidea, Elovl3* mRNAs in BAT, iWAT, and eWAT of their offspring. Upregulation of *Cox7a1* was also observed in BAT, while an accretion of Cyt C, *Cd137*, *Tbx1,* and *Tmem*26 was demonstrated in both iWAT and eWAT where fatty

TABLE 4. Summary of *in vivo* studies of resveratrol regarding adipocyte browning stimulation.

Dose	Duration (week)	Research material	Adipose tissue deposit	Genes/mRNAs alterations	Protein alterations	Reference
100 (mg/kg/day)	4	CD1 mice	iWAT	Not studied	↑ UCP1, PRDM16, Cyt C ↔ PPARγ, FABP4	S. Wang *et al.* [2015]
200 (mg/kg/day)	3	C57BL/6J mice (pregnant)	iWAT and eWAT	↑ *Ucp1, Ppargc1a, Prdm16, Cidea, Elovl3, Cyt C, Cd137, Tbx1, Tmem26* ↔ *Fabp4, Pparg*	↑ UCP1, Cyt C ↔ PPARγ, FABP4	Zou *et al.* [2017]
			BAT	↑ *Ucp1, Ppargc1a, Prdm16, Cidea, Elovl3, Cox7a1*	↑ UCP1	
			sWAT	↑ *Ucp1, Prdm16, Sirt1, Fndc5* ↔ *Ppargc1a*	Not studied	
400 (mg/kg/day)	8	FVB/N mice	vWAT	↑ *Prdm16, Sirt1* ↔ *Ucp1, Ppargc1a, Fndc5*	Not studied	Andrade *et al.* [2019]
			BAT	↑ *Ucp1, Prdm16, Sirt1* ↔ *Ppargc1a, Fndc5*	Not studied	
500 (mg/day)	4	human	sWAT	↑ *UCP1, PRDM16, FNDC5, SIRT1* ↔ *PPARGC1A*	Not studied	Andrade *et al.* [2019]

BAT: brown adipose tissue; *Cidea*: cell death activator CIDE-A; *Cyt C*: cytochrome c; *Elovl3*: elongation of very long chain fatty acids protein 3; eWAT: epididymal white adipose tissue; *Fabp4*: Fatty acid-binding protein type 4; *Fndc5*: fibronectin type III domain-containing protein 5; iWAT: inguinal white adipose tissue; *Pparg*: peroxisome proliferator-activated receptor γ; *Ppargc1a*: peroxisome proliferator-activated receptor γ coactivator 1-α; *Prdm16*: PR domain-containing protein 16; *Sirt1*: sirtuin 1; sWAT: subcutaneous white adipose tissue; *Tbx1*: T-box transcription factor TBX1; *Tmem26*: transmembrane protein 26; *Ucp1*: uncoupling protein 1; vWAT: visceral white adipose tissue.

acid-binding protein 4, *Pparg* mRNAs and their protein levels were not affected by resveratrol. What is more, resveratrol administration reversed high-fat diet-induced attenuation of AMPKα phosphorylation in BAT, iWAT, and eWAT, and also decreased serum triglyceride and insulin, but not glucose [Zou *et al.*, 2017]. Most of the above-described alterations, except for those present in eWAT, were also demonstrated in 3-month-old adult descendants, which implies a significant long-term effect of resveratrol supplementation in pregnant mice on the metabolic processes of the offspring [Zou *et al.*, 2017]. It is worth noting that there are forms of resveratrol characterized by greater bioavailability, stability, and solubility than the free resveratrol – resveratrol encapsulated lipid nanocarriers and resveratrol encapsulated liposomes [Zu *et al.*, 2018]. Both of them dose-dependently stimulated expression of *Ucp1* mRNA and other browning markers, although resveratrol encapsulated liposomes exhibited greater biological activity. These compounds may be degraded in the digestive system, therefore to evoke a full browning effect they should be administered intravenously, which is invasive, carries a risk of complications and generates higher costs [Zu *et al.*, 2018]. An 8-week resveratrol supplementation was also assessed in Friend Virus B NIH mice [Andrade *et al.*, 2019], and was found to cause a substantial reduction in body adiposity and an increment of BAT mass. Moreover, upregulation of *Ucp1, Prdm16,* and *Sirt1* mRNAs in BAT and sWAT, as well as elevation of adiponectin concentration and decline in glucose and insulin levels were demonstrated in the resveratrol-supplemented high-fat diet group. Furthermore, the enhancement of *Prdm16* and *Sirt1* expression was observed in visceral WAT in the mice administered the resveratrol-supplemented high-fat diet [Andrade *et al.*, 2019]. In the human study, 4-week administration of resveratrol to obese study participants demonstrated overexpression of *UCP1*, *PRDM16*, *SIRT1*, and fibronectin type III domain-containing protein 5, and no change in *PPARGC1A*, regardless of resveratrol intake [Andrade *et al.*, 2019]. Overall, the researchers concluded that the effects of resveratrol are likely related to the activation of thermogenesis genes and fibronectin type III domain-containing protein 5 [Andrade *et al.*, 2019]. Crucial data on resveratrol-induced adipocyte browning are summarized in Table 4 (*in vivo* studies) and Table 5 (*in vitro* studies).

ALKALOIDS

Caffeine

As a component of coffee and some beverages, caffeine seems to be a common adipocyte browning stimulant characterized by more than 99% bioavailability upon oral administration [Bonati *et al.*, 1982]. Velickovic *et al.* [2019] demonstrated that drinking 65 mg of caffeine (the equivalent of a cup of coffee) resulted in a significantly higher temperature of the supraclavicular region (the vital BAT location) in young adults with BMI within the normal limits, assessed after 30 min. Furthermore, when testing the effect of caffeine *in vitro,* using mouse mesenchymal stem cells and human bone marrow-derived stem cells, they found an increase in UCP1 levels confirming caffeine as a browning inductor. Mechanistically, caffeine exerted its browning-positive effect by upregulation of PGC1α, *Pparg*, *Prdm16,* and *Adrb3*, as well as downregulation of *Adra2* and *Trpv2* [Velickovic *et al.*, 2019]. In addition, enhanced expression of β_3-AR and diminished of α_2-AR, acting antagonistically to β_3-AR [Lafontan *et al.*, 1997], may potentiate adipocyte browning in response to β-adrenergic stimulation, *e.g.*, during cold exposure [Velickovic *et al.*, 2019]. Nevertheless, it needs to be highlighted that elevated temperature of the skin could be evoked by an increase in blood flow rather than BAT activity, although Velickovic *et al.* [2019] undermined this possibility.

TABLE 5. Summary of *in vitro* studies of resveratrol regarding adipocyte browning stimulation.

Substance	Concentration (μM)	Duration (day)	Research material	Genes/mRNAs alterations	Protein alterations	Reference
Resveratrol	10	7	iWAT-derived SVC	↑ *Ucp1, Prdm16, Cidea, Elovl3, Ppargc1a, Cd137, Tbx1, Tmem26* ↔ *Fabp4, Pparg*	↑ UCP1, PRDM16, Cyt C	S. Wang *et al.* [2015]
Resveratrol	20 or 40	7	iWAT-derived SVC	↑ *Ucp1, Prdm16, Cidea, Elovl3, Ppargc1a, Cd137, Tbx1, Tmem26* ↓ *Fabp4, Pparg*	↑ UCP1, PRDM16, Cyt C	S. Wang *et al.* [2015]
Resveratrol Resveratrol (nanocarriers) Resveratrol (liposomes)	5 or 10 or 20	7	3T3-L1 cells	↑ *Prdm16* ↔ *Ucp1, Pparg, Ppargc1a, Cd137, Tmem26, Tfam*	Not studied	Zu *et al.* [2018]

Cidea: cell death activator CIDE-A; *Cyt C*: cytochrome c; *Elovl3*: elongation of very long chain fatty acids protein 3; *Fabp4*: Fatty acid-binding protein type 4; iWAT: inguinal white adipose tissue; *Pparg*: peroxisome proliferator-activated receptor γ; *Ppargc1a*: peroxisome proliferator-activated receptor γ coactivator 1-α; *Prdm16*: PR domain-containing protein 16; SVC: stromal vascular cells; *Tbx1*: T-box transcription factor TBX1; *Tmem26*: transmembrane protein 26; *Ucp1*: uncoupling protein 1.

Capsaicin

Capsaicin, a TRPV1 agonist, is an ingredient present in chili peppers [Baboota *et al.*, 2014] with anti-inflammatory, antioxidant, antiobesity, and antidiabetic properties [Mosqueda-Solís *et al.*, 2018]. Regarding bioavailability, nearly 94% of the oral capsaicin dosage was rapidly absorbed from the gastrointestinal tract of Wistar rats and just as fast metabolized in the liver, reaching 24.4% of maximum tissue distribution an 1 h after the administration [Suresh & Srinivasan, 2010]. Capsaicin exhibits a dose-dependent effect on lipid accumulation in 3T3-L1 preadipocytes – low concentrations suppress, whereas higher intensify that process [Baboota *et al.*, 2014]. Both small and large quantities increase the expression of *Pparg*, but *Ucp1*, *Ppargc1a*, *Prdm16*, *Dio2* and *Ppara,* are raised only at a low dose of capsaicin. Surprisingly, its low dose caused the enhanced expression of *Ucp1* negative regulator – vitamin D receptor, as well as the increment of anti-adipogenic genes, while the addition of its high dose caused a significant decrement. Browning-positive effects of capsaicin were associated with TRPV1 overexpression on adipocytes [Baboota *et al.*, 2014].

The influence of capsaicin on sWAT was also investigated, and it was shown that a 3-month consumption resulted in augmented expression of the BAT genes – *Ucp1*, *Ppargc1a*, *Cidea*, prostaglandin-endoperoxide synthase 2, and brain-derived neurotrophic factor in Laboratory Animal Centre A-strain (LACA) mice [Baboota *et al.*, 2014].

MIXTURES OF COMPOUNDS

A few studies investigated the mutual effects of well-established adipocyte browning activators (Table 6). Simultaneous administration of resveratrol and quercetin were evidenced to synergistically induce adipocyte browning, leading to more expressed features of beige adipose tissue and better metabolic outcomes than each of the substances separately [Arias *et al.*, 2017]. On the other hand, combination of hesperidin and capsaicin restricted their browning activities, compared to both isolated hesperidin and capsaicin [Mosqueda-Solís *et al.*, 2018]. Thus, before implementation of any treatment with a mixture of compounds, the interactions between browning activators should be studied, since the cumulative effect may appear far less significant than expected.

EDIBLE PLANT EXTRACTS/PARTS

Cinnamon extract

Cinnamon is a spice obtained from the bark of the cinnamon tree with anti-cancer, antibacterial, and anti-inflammatory properties [Gruenwald *et al.*, 2010]. It turns out that it also affects the process of browning adipocytes [Kwan *et al.*, 2017]. According to the study by Helal *et al.* [2014], the bioavailability of the constituents of the cinnamon extract was 53%, 22%, 47%, 90%, and 64% for quercetin 3-rhamnoside, syringic and coumaric acids, kaempferol and cinnamaldehyde, respectively.

Multilocular morphology of adipocytes was observed 24 h after cinnamon extract was added to 3T3-L1 cells [Kwan *et al.*, 2017]. Bioactive compounds identified in the cinnamon extract were protocatechuic acid, (+)-catechin, chlorogenic acid, esculetin, quercetin, and icariin. Cinnamon extract increased the expression of *Ucp1* mRNA and UCP1 protein as well as specific for BAT genes including *Prdm16*, *Ppargc1a, Pparg*, *Cidea,* and *Cpt1*. Enhanced mitochondrial protein production was also observed. Furthermore, cinnamon extract augmented the promoter activity of the UCP1 gene in HEK293 cells and 3T3-L1 adipocytes [Kwan *et al.*, 2017]. Mechanistically, β_3-adrenergic stimulation was involved. In mature subcutaneous adipocytes obtained from C57BLKS db/db mice, there was an increase in UCP1 protein, *Prdm16,* and *Cidea* expression after 24 h cinnamon extract supplementation, which was not observed in eWAT [Kwan *et al.*, 2017]. In addition, in diet-induced obese mice, cinnamon extract enhanced UCP1 protein level as well as *Ucp1*, *Prdm16,* and *Cidea* mRNAs in sWAT, but not eWAT or perirenal adipocytes [Kwan *et al.*, 2017]. Oral administration of cinnamon extract for 15 days resulted in weight loss without reducing organ weight or food intake.

TABLE 6. Summary of the selected mixtures of components influencing adipocyte browning.

Substance	Dose	Test subjects	Duration (week)	Results of mixture therapy (*vs*. each substance separately)	Reference
Resveratrol + quercetin	15 mg resveratrol/kg/day 30 mg quercetin/kg/day	Rats	6	Attenuation of weight gain Reduction of subcutaneous WAT and abdominal WAT depots Increase in multilocular adipocytes	Arias *et al.* [2017]
Hesperidin + capsaicin	100 mg hesperidin/kg/day 4 mg capsaicin/kg/day	Wistar rats	8	Lesser adipocyte size Weaker browning-inducing properties	Mosqueda-Solís *et al.* [2018]

WAT: white adipose tissue.

Germinated soy germ extract

Germinated soy germ extract (rich in nutrients and bioactive compounds, such as linoleic and linolenic acids, isoflavones, tocopherols, and free amino acids, including γ-aminobutyric acid) [Kim *et al.*, 2013] was tested *in vitro* and *in vivo* on 3T3-L1 preadipocytes and high-fat diet fed mice, showing its ability to promote UCP1 expression and adipocyte browning [Kim *et al.*, 2019]. Moreover, it upregulated β-oxidation and lipolysis in beige adipocytes [Kim *et al.*, 2019]. In addition, germinated soy germ extract affected transcription and translation of endocannabinoid system genes encoding cannabinoid receptor type 2, *N*-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D, diacylglycerol lipase-α, and fatty-acid amide hydrolase 1 proteins [Kim *et al.*, 2019], which are likely to mediate germinated soy germ extract browning properties since cannabinoids could induce adipocyte browning itself [Rossi *et al.*, 2018].

Ginger rhizome

Ginger is a widely used spice obtained from the rhizome of *Zingiber officinale Rosco*, that may have beneficial effects in reducing obesity [J. Wang *et al.*, 2017]. It appears to have the ability to induce WAT browning and improve BAT function by increasing brown and beige key proteins and genes, including UCP1, PRDM16, as well as *Cidea*, *Tmem26,* and *Cited1*, in both BAT and WAT of ginger-supplemented C57BL/6J mice [J. Wang *et al.*, 2019]. The underlying mechanism was the AMPK activation. Moreover, 16-week ginger supplementation upregulated *Tfam* and *Nrf1* genes, as well as *Ppargc1a* mRNA, involved in mitochondrial biogenesis and oxidative phosphorylation [J. Wang *et al.*, 2019]. As a result, not only decreased levels of serum glucose, triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-C) but also attenuated body weight gain and intensified energy expenditure were observed.

***Glycyrrhiza uralensis* extract**

A methyl dichloride fraction of *Glycyrrhiza uralensis* containing licochalcone A, isoliquiritigenin, and liquiritigenin was tested alongside licochalcone A in the abovementioned study by Lee *et al.* [2018]. The same results as for licochalcone A were obtained, providing evidence that the *Glycyrrhiza uralensis* extract has the ability to induce adipocyte browning. Upregulation of PRDM16 and PGC1α, as well as browning-specific adipose tissue remodeling were followed by weight loss and improvement in glucose and lipid metabolism [Lee *et al.*, 2018].

Grape extracts

An extract from grape pomace contains many flavonoids and phenolic caids, of which (–)-epicatechin, quercetin, (+)-catechin, and syringic acid are the most abundant [Rodriguez Lanzi *et al.*, 2016]. The research on spontaneously hypertensive rats, characterized by increased sympathetic nervous system drive, and normotensive Wistar–Kyoto rats, showed browning of eWAT in the spontaneously hypertensive group after 10 weeks of grape pomace extract supplementation to high-fat diet [Rodriguez Lanzi *et al.*, 2018]. The browning was evidenced with augmented levels of BAT marker proteins: UCP1, PRDM16, PGC1α, and PPARγ. On the contrary, rats of the Wistar–Kyoto fed with the same diet as spontaneously hypertensive rats displayed an elevated concentration of PPARγ and only a slight increase in UCP1. Nevertheless, they also (as well as spontaneously hypertensive rats) profited from the grape pomace extract administration, achieving healthier eWAT expansion – favoring adipocyte hyperplasia over hypertrophy, which lessened WAT inflammation. In addition, grape pomace extract effects on browning and the activation of β-adrenergic receptors were studied on 3T3-L1 adipocytes [Rodriguez Lanzi *et al.*, 2018]. The results disclosed elevated expression of UCP1 following an increase in p38 and extracellular signal-regulated kinases 1/2 activity. Thus, the mechanism of grape pomace extract-mediated adipocyte browning is tightly connected with β-adrenergic stimulation and its downstream cascade.

On the other hand, a similar *in vivo* study describing the influence of grape seed proanthocyanidin extract on rats revealed no browning effects in retroperitoneal WAT [Pascual-Serrano *et al.*, 2018]. Nevertheless, grape seed proanthocyanidin extract altered adipogenesis, promoting adipocytes hyperplasia rather than hypertrophy, which is considered to be protective in the context of metabolic complications related to obesity [Blüher, 2013]. Considering the abovementioned studies, it seems that some components of grape pomace, but not grape seeds, are associated with adipocyte browning.

Green tea extract

Flavan-3-ols are major constituents of green tea extract [Chen *et al.*, 2001]. The bioavailability of compounds of this flavonoid class is rather low. Chen *et al.* [1997] reported that

only 13.7% of (–)-epigallocatechin, 31.2% of (–)-epicatechin, and 0.1% of (–)-epigallocatechin-3-gallate administrated to rats within portion of 200 mg/kg of decaffeinated green tea were bioavailable. Nevertheless, green tea extract was found to stimulate adipocyte browning in male C57BL/6J mice, which was confirmed with an elevated transcription of *Ppargc1a, Prdm16,* and *Cited1,* as well as increased UCP1 concentration, in subcutaneous WAT of the green tea extract-supplemented mice [Neyrinck *et al.*, 2017]. Moreover, the addition of green tea extract to high-fat diet was able to reverse adipocyte whitening in iBAT by increasing *Ppargc1a* and inhibiting fatty acid-binding protein 4 expression [Neyrinck *et al.*, 2017]. Interestingly, tea polyphenols increased the amount of *Akkermansia muciniphila* in the gut microbiota of high-fat diet mice [Liu *et al.*, 2017], which is believed to be positively correlated with the browning of WAT [Gao *et al.*, 2018]. On the contrary, C57BL/6J mice, treated with decaffeinated green tea extract (a mixture of (–)-epigallocatechin, (–)-epicatechin-3-gallate, (–)-epigallocatechin-3-gallate, and (–)-epicatechin), did not present higher levels of *Ucp1* under similar conditions [Sae-Tan *et al.*, 2015]. In this study, caffeine was likely to interfere with tea flavan-3-ols by increasing sympathetic drive and browning effects. Further research is, however, needed to study the browning properties of tea polyphenols in details.

Immature *Citrus reticulata* fruit extract

Synephrine (16 mg/g), hesperidin (9.14 mg/g), narirutin (4.52 mg/g), nobiletin (2.54 mg/g), and tangeretin (1.67 mg/g) were the predominant phenolic compounds of immature *Citrus reticulata* fruit water extract [Chou *et al.*, 2018]. Interestingly, the content of synephrine, nobiletin and tangeretin in the immature *Citrus reticulata* fruit extract was significantly higher than in other *Citrus* species [Sun *et al.*, 2013]. Chou *et al.* [2018] proved the browning effects of the immature *Citrus reticulata* extract-rich diet on murine (C57BL/6) iWAT. After 11 weeks of immature *Citrus reticulata* extract supplementation, adipocytes became multilocular, and concentrations of PGC1α and UCP1 proteins increased. In addition, immature *Citrus reticulata* extract supplementation was responsible for the upregulation of thermogenic genes and beige adipose tissue hallmarks, such as *Cidea*, *Tmem26, Prdm16,* and *Cd137*. The mechanism of browning is most likely linked with *p*-synephrine, almost selective ligand to β_3-AR [Chou *et al.*, 2018]. Furthermore, other components of immature *Citrus reticulata* extract, naringin and hesperidin, were reported to strengthen the thermogenic effect of *p*-synephrine [Stohs *et al.*, 2011]. Besides adipocyte browning, immature *Citrus reticulata* extract can improve metabolic health by reducing dyslipidemia, insulin resistance, obesity, and lipid accumulation in the liver [Chou *et al.*, 2018].

Olive oil

Olive oil, composed of tri-, di-, and monoacylglycerols build up with mainly oleic, linoleic, palmitic, and stearic acids, as well as containing a wide range of sterols, tocopherols, and phenolic compounds, including hydroxytyrosol and oleuropein, is one of the fundamental and highly bioavailable constituents of the Mediterranean diet [Boskou *et al.*, 2006; Vissers *et al.*, 2004]. Its consumption reduces inflammation and prevents from civilization diseases, such as cardiovascular and neurodegenerative ones [Angeloni *et al.*, 2017; Marcelino *et al.*, 2019]. In addition, recent research reported that dietary supplementation with olive oil in C57BL/6 mice reduced weight gain and adipose tissue expansion, which coexisted with increased thermogenesis and oxygen consumption [Shin & Ajuwon, 2018b]. Nevertheless, these changes were not supported with overexpression of browning-specific genes, such as *Ucp1, Prdm16,* and *Ppargc1a,* in sWAT and BAT, while *Ppargc1a, Tfam, Adrb3,* and *Cpt1a* were upregulated in eWAT. However, a significant surge in *Ucp1* mRNA, but not protein, was found in BAT of Wistar rats upon 4-week olive oil supplementation [Rodríguez *et al.*, 2002]. Finally, olive oil administration slightly attenuated high-fat diet-induced increase in blood glucose and insulin [Shin & Ajuwon, 2018b].

Onion peel extracts

Flavonols (quercetin and isoquercetin) and anthocyanins are major constituents of onion peel extract [Krithika *et al.*, 2020; Wijerathne *et al.*, 2019]. A study on C57BL/6 mice showed no change in body mass, the weight of eWAT and rWAT, after 8-week supplementation with onion peel extract compared to the high-fat control diet [Lee *et al.*, 2017]. Nevertheless, it revealed the influence of the onion peel extract on gene expression, which included *Ucp1*, *Prdm16*, *Cidea,* and *Ppargc1a* increment in rWAT, while in sWAT there was no change in *Prdm16* and *Ppargc1a* levels, but *Ucp1* and *Cidea* were raised. Furthermore, elevated *Ucp1, Ppargc1a, Tbx1*, and *Cpt1a* expression was reported in 3T3-L1 preadipocytes upon onion peel extract administration [Lee *et al.*, 2017].

In addition, fractions of onion peel extract were also investigated by Lee *et al.* [2017] on 3T3-L1 cells. Onion peel ethyl acetate fraction, containing quercetin and isoquercetin, increased *Tbx1*, *Cpt1a*, and *Ppargc1a* transcription, as well as inhibited fatty acid synthase and acetyl-CoA carboxylase. On the contrary, onion peel water fraction, consisting of isoquercetin only, did not induce such changes. Nevertheless, both onion peel water and ethyl acetate fractions were capable of dose-dependent enhancement of *Ucp1* expression [Lee *et al.*, 2017].

Taken together, it seems that quercetin was the component of onion peel extracts, which played the pivotal role in adipocyte browning stimulation. Therefore, activation of the AMPK pathway is presumably the browning mechanism of the presented onion extracts [Lee *et al.*, 2017].

Raspberry fruits

Raspberry fruits represent a rich source of antioxidants and anti-inflammatory phenolic compounds [Xing *et al.*, 2018], such as flavan-3-ols, flavonols, phenolic acids, and anthocyanins [Pap *et al.*, 2021], which are also known to have the ability to induce browning of WAT [Zou *et al.*, 2018]. C57BL/6 mice treated with raspberry fruits for 10 weeks presented decreased iWAT, eWAT, and body weights, with a concomitant increment in BAT mass, greater oxygen uptake and CO_2 excretion, as well as intensified heat production [Zou *et al.*, 2018]. Lowered insulin, triglycerides, total cholesterol and free fatty acids serum levels were also noted. Furthermore, raspberry supplementation enhanced mRNA

and protein expression of *Ucp1*, *Prdm16, Ppargc1a mRNA* and Cyt C, in both BAT and iWAT [Zou *et al.*, 2018]. In iWAT, it upregulated *Elovl3*, *Cd137*, *Tbx1,* and *Tmem26*, while in BAT – *Cidea* and *Cox7al*. Moreover, raspberry administration resulted in diminished adipocyte size in iWAT [Zou *et al.*, 2018] and eWAT [Xing *et al.*, 2018].

Another 12-week study conducted on C57BL/6J high-fat diet mice showed that raspberry fruit administration caused a decline in monocyte chemoattractant protein 1, *Cd14*, *Cd68* mRNAs, as well as IL-6, IL-18, IL-1β concentrations, and macrophages abundance in iWAT [Xing *et al.*, 2018]. What is more, glucose transporter type 4 accretion resulted in improved insulin sensitivity.

It was suggested that raspberry fruits trigger adipocyte beiging by stimulating the AMPK pathway [Xing *et al.*, 2018; Zou *et al.*, 2018] and activating p38 and extracellular signal-regulated kinases 1/2 signaling, which take part in irisin-induced browning [Xing *et al.*, 2018].

Rose hip

Rose hip is the fruit of diverse plants belonging to the genus *Rosa*, which contains a wealth of ascorbic acid [Strålsjö *et al.*, 2003], carotenoids [Hodisan *et al.*, 1997], and phenolic compounds [Daels-Rakotoarison *et al.*, 2002]. The addition of rose hip to high-fat diet of C57BL/6J mice resulted in increased expression of brown and beige adipose tissue-specific genes in inguinal subcutaneous WAT, such as *Ucp1*, *Tbx15*, *Cidea*, *Cpt1,* and bone morphogenetic protein 7, which was mediated by AMPK related pathway [Cavalera *et al.*, 2016]. Surprisingly, neither *Ppargc1a* nor *Prdm16* mRNAs were elevated. Furthermore, no changes in gene expression were found in BAT deposits. Interestingly, feces of mice fed a high-fat diet with rose hip addition had much more energy value than these of mice fed only with the high-fat diet [Cavalera *et al.*, 2016]. Hence, the lower body mass of the rose hip-supplemented group should be attributed not only to elevated energy expenditure because of adipocyte browning but also to reduced effective energy intake due to impaired intestinal absorption. Measurements of fecal content are rarely used in adipocyte browning studies, although they might be useful for providing more comprehensive results of future research.

DIETARY INGREDIENTS OF ANIMAL ORIGIN

Fish oils

DHA, EPA, α-linolenic and linoleic acids are major constituents of fish oil [Kowalski *et al.*, 2019]. The browning-positive effect of fish oil was studied in C57BL/6 mice fed with fish oil-rich diet [Bargut *et al.*, 2016] or DHA/EPA-enriched fish oil [Kim *et al.*, 2015]. Fish oil supplementation elevated UCP1 concentration at both mRNA and protein levels as well as *Prdm16, Cidea, Cpt1b, Adrb3,* and *Fgf21* mRNAs in iWAT and BAT [Kim *et al.*, 2015]. Furthermore, increased transcription and translation of *Ppargc1a, Ppara, Pparg,* and *Adrb3* in BAT [Bargut *et al.*, 2016], and overexpression of *Tbx1* in iWAT, were observed [Kim *et al.*, 2015].

Same as for isolated DHA and EPA, fish oil enhanced glucose transporter type 4 and lipoprotein lipase mRNAs, and therefore lowered blood glucose and improved lipid profile [Bargut *et al.*, 2019; Zhao & Chen, 2014]. Additionally, fish oil elevated serum level of adiponectin and decreased that of leptin [Bargut *et al.*, 2016; Zhuang *et al.*, 2019].

Milk fat globule membrane substances

Milk fat globule membrane is composed of three layers built-up of lipids and proteins, and originates from the apical part of mammary apocrine glands [Fong *et al.*, 2007]. Since a few substances included in milk fat globule membrane may exert beneficial effects, Li *et al.* [2018] studied the outcomes of the whole complex milk fat globule membrane (the naturally ingested from) administration to high-fat diet C57BL/6 mice. They found that milk fat globule membrane reduced fat mass by both inhibiting adipogenesis in eWAT and inducing adipocyte browning in iWAT. Mechanistically, all results of milk fat globule membrane supplementation were mediated by the AMPK pathway, which led to the downregulation of PPARγ, C/EBPα, and sterol regulatory element-binding protein 1c in epididymal WAT as well as increased UCP1 in inguinal WAT and BAT. In addition, milk fat globule membrane altered lipid profile to less atherogenic (↓ triglycerides, LDL-C; ↑ HDL-C/LDL-C) and declined the content of free fatty acids [Li *et al.*, 2018].

Scallop shell

Scallops are a popular delicacy in Japan, therefore, their shells, which are composed of calcium carbonate (98%) and organic ingredients (2%), make up copious industrial waste [Liu *et al.*, 2006; Liu & Hasegawa, 2006]. While looking for a way to use them, it was suggested that they might improve metabolic health. Recent studies revealed that scallop shell powder intensifies lipolysis in 3T3-L1 cells [Liu & Hasegawa, 2006] as well as in Wistar rats [Liu *et al.*, 2006]. Moreover, reduced iWAT, eWAT, perirenal WAT, and body weights, along with no changes in the BAT mass, were observed in the group supplementing scallop shell powder for 5 weeks [Liu *et al.*, 2006; Liu & Hasegawa, 2006]. Furthermore, applying this ingredient resulted in a decreased serum leptin concentration [Liu *et al.*, 2006]. Among scallop shell-treated animals, it was noted that in BAT there were no alterations in the *Ucp1* level, while *Ucp2* was downregulated. However, both of them were elevated in eWAT. Though the exact mechanism leading to metabolic changes caused by scallop shell is not known, it is probably distinct from β_3-adrenergic stimulation and G protein-coupled receptors activation [Liu *et al.*, 2006].

GENERAL DIETARY MODIFICATIONS

Caloric restriction

Limiting caloric intake can prevent obesity, insulin resistance, metabolic and cardiovascular diseases [Golbidi *et al.*, 2017]. A recent study shows that it can also promote adipocyte browning [Fabbiano *et al.*, 2016]. Among the C57BL/6J mice subjected to caloric restriction, increased glucose uptake in WAT, which deposits were smaller and denser, was observed. In the caloric restriction group, the number of adipocytes raised. They were also shrunken and multilocular compared to the control mice in both inguinal subcutaneous

adipose tissue and perigonadal visceral fat. In those deposits, caloric restriction resulted in upregulation of *Ucp1*, *Cidea*, *Ppargc1a*, *Ppara*, *Prdm16*, *Pparg*, *Tbx1,* and fatty acid-binding protein 4 – the BAT hallmarks. *Cd137* and *Tmem26* expression was also enhanced in perigonadal visceral adipose tissue. The above changes appeared after one week of caloric restriction, reached their maximum after 4 weeks, and gradually disappeared after cessation of the diet. Similar consequences were noticed in the caloric restriction group kept in the thermoneutral environment and obese leptin-deficient (ob/ob) mice [Fabbiano *et al.*, 2016].

Moreover, using caloric restriction was connected with lipolysis intensification as a result of improved response to β-adrenergic stimulation [Fabbiano *et al.*, 2016]. Importantly, caloric restriction mice were able to maintain a constant body temperature, unlike the controls. Consequently, it proves the activity of the newly formed beige adipose tissue in caloric restriction mice [Fabbiano *et al.*, 2016].

Interestingly, WAT browning caused by caloric depletion was associated with augmented SIRT1 expression on macrophages and activation of type 2 immune signaling, including enhanced infiltration of eosinophils, macrophages, and increased secretion of cytokines (IL-4, IL-5, IL-13) in both inguinal subcutaneous adipose tissue and perigonadal visceral adipose tissue [Fabbiano *et al.*, 2016]. The study also revealed that caloric restriction-dependent browning occurred regardless of the proportion of diet components.

Dietary macronutrient composition

The influence of low-protein, high-carbohydrate diet on browning processes was studied by Pereira *et al.* [2017]. They found that low-protein, high-carbohydrate diet-fed rats presented a lower body weight but higher iWAT mass compared to the control group, while lipid content was similar in both iWAT and perigonadal WAT. Moreover, expansion of multilocular adipocytes as well as elevated levels of UCP1, TBX1, PRDM16, and β_1-AR were observed in the latter. Besides, the content of β_3-AR and PKA was comparable to control, but it was reduced in iWAT of low-protein, high-carbohydrate diet-fed rats. Additionally, this regimen resulted in adipose triglyceride lipase and phosphoenolpyruvate carboxykinase increment in iWAT, as well as lipoprotein lipase accretion in perigonadal WAT. Among low-protein, high-carbohydrate diet-fed rodents, FGF21 serum level increased, so did pAMPK/AMPK ratio in iWAT, whereas it was lessened in the second fat pad [Pereira *et al.*, 2017].

Effects of a high-carbohydrate diet were also determined in a 6-week study on wild-type and perulipin-2-null mice, treated with a 20% sucrose solution [Libby *et al.*, 2018]. This resulted in an elevated level of genes, such as *Ucp1*, *Elovl3*, *Cidea*, *Dio2*, *Cpt1b*, *Ppargc1a*, and *Ppara*. Moreover, the number of adipocytes with many lipid droplets increased in iWAT. Also, a diminution in iBAT, iWAT, and eWAT weights was demonstrated in animals with perilipin-2 deletion. Additionally, improvement in insulin sensitivity was observed due to, *inter alia*, augmented glucose transporter type 4 expression. It was also revealed that the increase in FGF21, which occurred in iWAT, BAT, and the liver under the influence of sucrose, was probably the underlying mechanism of browning [Libby *et al.*, 2018].

According to recent research, the type of diet may also affect the expression of irisin, fibronectin type III domain-containing protein 5 proteolytic cleavage product produced in muscles and adipocytes both in mice and humans [de Macêdo *et al.*, 2017]. A 60-day study conducted on Friend Virus B NIH mice revealed an increment in fibronectin type III domain-containing protein 5 and irisin concentration induced by a high-protein diet. It also turned out that their elevation was probably modulated by the *Ucp1* and *Ppara* genes, which are typical of BAT, suggesting that high-protein diet might have augmented their expression. Thus, these results differ from the conclusions presented by Pereira *et al.* [2017], who described low-protein, high-carbohydrate diet as the one that leads to browning activation. In addition, it was observed that both high-protein diet and high-carbohydrate diet increased the BAT mass, however, it was more significant in the first group [de Macêdo *et al.*, 2017]. Finally, higher HDL-C concentrations were noted in the high-carbohydrate diet-fed mice compared to the high-protein diet group. Although both high-carbohydrate diet and high-protein diet led to elevated glucose levels, the insulin sensitivity test showed no differences between the groups [de Macêdo *et al.*, 2017].

Intermittent fasting

Fasting is recognized as a factor that positively influences metabolism and prevents insulin resistance or fatty liver disease by leading to WAT browning [Li *et al.*, 2017]. A study conducted on growing C57BL/6N mice subjected to 15-cycle every other day fasting showed higher rectal temperatures compared to the control animals [Li *et al.*, 2017]. It also enhanced lipid utilization and reduced body weight with no effect on food intake. Comparing fat mass, the eWAT mass decreased, while the BAT weight rose. Interestingly, in BAT, there was no increment in the expression of BAT-specific genes, such as *Ucp1*, *Ppargc1a, Dio2*. What is more, every other day fasting inhibited norepinephrine and did not affect *Adrb3* expression [Li *et al.*, 2017]. However, when iWAT was examined, the features of browning, such as the occurrence of multilocular adipocytes and augmented expression of UCP1, were observed. Although every other day fasting discontinuation returned *Ucp1* mRNA to baseline values after 15 days, reduced weight was still observed. Furthermore, it was described that WAT browning was responsible for the increased energy consumption and occurred in the FGF21-independent pathway [Li *et al.*, 2017].

It seems that the intestinal microflora plays an important role in the WAT browning process caused by every other day fasting since an increased abundance of Firmicutes and inhibition of other phyla were observed upon fasting [Li *et al.*, 2017]. Moreover, microbiota in every other day fasting mice was responsible not only for intensification of lactate and acetate production, which are known to be factors leading to the beiging of adipose tissue, but also enhanced expression of the monocarboxylate transporter 1 gene, which encodes the protein transporting those molecules into the adipocytes [Li *et al.*, 2017].

MICROBIOTA

The intestinal microflora is closely related to human physiology and health [Moreno-Navarrete *et al.*, 2018] as it influences various metabolic processes in the body [Suárez--Zamorano *et al.*, 2015]. Its composition is significantly affected by diet or medicines [Moreno-Navarrete *et al.*, 2018]. The dominant types of bacteria are Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. Studies on rodents showed that Firmicutes increment and Bacteroidetes decrease was related to obesity, which was also observed in humans. However, some research has also shown an inverse relationship [Jumpertz *et al.*, 2011; Patil *et al.*, 2012]. According to the study conducted on humans, Firmicutes relative abundance increased the expression of BAT markers such as *UCP1*, *PRDM16,* and *DIO2* in subcutaneous adipose tissue [Moreno-Navarrete *et al.*, 2018]. In contrast, obese people with insulin resistance had lowered Firmicutes and increased Bacteroidetes, which correlated negatively with BAT markers.

It seems that the mechanistic link between Firmicutes relative abundance and brown adipocyte differentiation is connected with the acetate production since its concentration correlated positively with Firmicutes relative abundance, insulin sensitivity, and *PRDM16* mRNA level in subcutaneous adipose tissue [Moreno-Navarrete *et al.*, 2018]. Interestingly, at Firmicutes relative abundance, the levels of acetate, UCP1, and PRDM16 varied with age, gender, BMI, type 2 diabetes, and antihypertensive therapy.

In addition, an experiment on C57BL/6J mice, administered water containing antibiotics, revealed that microbiota depletion led to WAT browning and metabolic changes [Suárez--Zamorano *et al.*, 2015]. According to this study, improved insulin sensitivity and augmented WAT glucose uptake, as well as decreased weight and volume of inguinal subcutaneous adipose tissue and perigonadal visceral adipose tissue, were observed in microbiota-depleted mice despite increased food intake. Besides, their adipocytes were darker and smaller with multilocular phenotype. Furthermore, the upregulation of primary BAT proteins, such as UCP1, was demonstrated. Ten days after recolonization of the antibiotic-treated mice with microbes, the elevated level of browning markers and greater cold resistance were still noted, which was due to the development of functional beige adipocytes promoted by the depletion of microbiota [Suárez-Zamorano *et al.*, 2015]. Moreover, adipocytes derived from microbiota-depleted mice responded more strongly to β-adrenergic stimulation than control mice, indicating higher thermogenic capacity. Described metabolic changes occurred as a result of enhanced type 2 cytokine signaling, including secretion of interleukins IL-4, IL-5, IL-13, and infiltrations from eosinophils in inguinal subcutaneous adipose tissue [Suárez-Zamorano *et al.*, 2015].

CONCLUSIONS

There is a wide range of dietary substances that may participate in adipocyte browning induction, including amino acids, carbohydrates, lipids, phenolic compounds, and many others. Each of the described components upregulated BAT-specific genes in different WAT depots or cell lines. Numerous research also evidenced signs of adipose tissue remodeling associated with britening stimulated by different food ingredients, and increased BAT activation. Moreover, improved metabolic parameters, such as lipid profile or glucose concentration, were frequently observed.

However, the vast majority of the molecules were investigated based on murine models. Nevertheless, most of the papers focused on the impact of dietary intervention in obesity-induced animals, which closely resemble the obese state in humans, albeit interspecies differences should always be taken into consideration when analyzing the results.

Evidence regarding diet-induced adipocyte browning in humans or human cell cultures is rather scarce, including studies on caffeine, EPA, (–)-epicatechin, genistein, or resveratrol. Among them, EPA appears the most promising browning activator, since it upregulated not only the pivotal adipocyte browning genes (*UCP1, PRDM16*), but also genes involved in mitochondrial biogenesis (*NRF1, TFAM*) and β-oxidation (*CPT1A*), being responsible for the complete thermogenesis-related metabolic change. In addition, adipocyte browning upon EPA administration was evidenced with highly-specific beige adipose tissue markers (*CD137, TBX1*). Finally, the browning properties of EPA were investigated on the fully differentiated subcutaneous adipocytes, confirming its ability to stimulate adipocyte transdifferentiation, which seems to be the most relevant when considering potential clinical application in adults. Another optimistic data is associated with resveratrol, which also enhanced the expression of browning-fundamental genes (*UCP1*, *PRDM16*). Furthermore, the research with the use of resveratrol was performed on humans *in vivo* and carefully designed. Moreover, it revealed that even a small dose of resveratrol (500 mg/day) may contribute to adipocyte browning, which appears crucial, concerning its limited bioavailability. Additionally, resveratrol elevated the expression of fibronectin type III domain--containing protein 5, potentially initiating other mechanisms leading to adipocyte browning *via* irisin formation. Favorable outcomes were also reported about (–)-epicatechin, which increased essential proteins concentrations (UCP1, PRDM16) in fully differentiated subcutaneous adipocytes. Apart from adipocyte browning stimulation, the anti-inflammatory effect of (–)-epicatechin was observed. More studies are needed to appropriately establish the role of caffeine and genistein on adipocyte browning in humans. However, limited data indicate their ability to raise the level of UCP1.

In our opinion, future research should elucidate the outcomes of the acknowledged browning activators in human WAT and cell lines to provide novel therapeutic agents for the treatment of obesity and obesity-related diseases. Furthermore, the safety doses of dietary substances should be determined. Simultaneously, more compounds should be screened for browning-positive effects.

ACKNOWLEDGEMENTS

The authors thank Ms. Malwina Malinowska for writing assistance.

RESEARCH FUNDING

The publication of this review paper was funded from the budget of Vice-Rector for Student Affairs at Poznan University of Medical Sciences (ID: 4317).

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

ORCID IDs

M. Gibas-Dorna https://orcid.org/0000-0002-8408-2829
A. Rajczewski https://orcid.org/0000-0001-8022-3148
A. Szumigała https://orcid.org/0000-0002-3591-1539
O.W. Wiśniewski https://orcid.org/0000-0001-6262-5119

REFERENCES

1. Andrade, J.E., Twaddle, N.C., Helferich, W.G., Doerge, D.R. (2010). Absolute bioavailability of isoflavones from soy protein isolate-containing food in female BALB/c mice. *Journal of Agricultural and Food Chemistry, 58*(7), 4529–4536. https://doi.org/10.1021/jf9039843
2. Andrade, J.M.O., Barcala-Jorge, A.S., Batista-Jorge, G.C., Paraíso, A.F., Freitas, K.M. de, Lelis, D. de F., Guimarães, A.L.S., de Paula, A.M.B., Santos, S.H.S. (2019). Effect of resveratrol on expression of genes involved thermogenesis in mice and humans. *Biomedicine & Pharmacotherapy, 112*, art. no. 108634. https://doi.org/10.1016/j.biopha.2019.108634
3. Angeloni, C., Malaguti, M., Barbalace, M.C., Hrelia, S. (2017). Bioactivity of olive oil phenols in neuroprotection. *International Journal of Molecular Sciences, 18*(11), art. no. E2230. https://doi.org/10.3390/ijms18112230
4. Arai, C., Arai, N., Arai, S., Yoshizane, C., Miyata, S., Mizote, A., Suyama, A., Endo, S., Ariyasu, T., Mitsuzumi, H., Ushio, S. (2019). Continuous intake of trehalose induces white adipose tissue browning and enhances energy metabolism. *Nutrition & Metabolism, 16*, art. no. 45. https://doi.org/10.1186/s12986-019-0373-4
5. Arias, N., Picó, C., Teresa Macarulla, M., Oliver, P., Miranda, J., Palou, A., Portillo, M.P. (2017). A combination of resveratrol and quercetin induces browning in white adipose tissue of rats fed an obesogenic diet. *Obesity (Silver Spring, Md.), 25*(1), 111–121. https://doi.org/10.1002/oby.21706
6. Assini, J.M., Mulvihill, E.E., Burke, A.C., Sutherland, B.G., Telford, D.E., Chhoker, S.S., Sawyez, C.G., Drangova, M., Adams, A.C., Kharitonenkov, A., Pin, C.L., Huff, M.W. (2015). Naringenin prevents obesity, hepatic steatosis, and glucose intolerance in male mice independent of fibroblast growth factor 21. *Endocrinology, 156*(6), 2087–2102. https://doi.org/10.1210/en.2014-2003
7. Baba, S., Osakabe, N., Yasuda, A., Natsume, M., Takizawa, T., Nakamura, T., Terao, J. (2000). Bioavailability of (–)-epicatechin upon intake of chocolate and cocoa in human volunteers. *Free Radical Research, 33*(5), 635–641. https://doi.org/10.1080/10715760000301151
8. Baboota, R.K., Singh, D.P., Sarma, S.M., Kaur, J., Sandhir, R., Boparai, R.K., Kondepudi, K.K., Bishnoi, M. (2014). Capsaicin induces "brite" phenotype in differentiating 3T3-L1 preadipocytes. *PLoS One, 9*(7), art. no. e103093. https://doi.org/10.1371/journal.pone.0103093
9. Bai, W., Shen, J., Zhu, Y., Men, Y., Sun, Y., Ma, Y. (2015). Characteristics and kinetic properties of L-rhamnose isomerase from *Bacillus subtilis* by isothermal titration calorimetry for the production of D-allose. *Food Science and Technology Research, 21*(1), 13–22. https://doi.org/10.3136/fstr.21.13
10. Bargut, T.C.L., Martins, F.F., Santos, L.P., Aguila, M.B., Mandarim-de-Lacerda, C.A. (2019). Administration of eicosapentaenoic and docosahexaenoic acids may improve the remodeling and browning in subcutaneous white adipose tissue and thermogenic markers in brown adipose tissue in mice. *Molecular and Cellular Endocrinology, 482*, 18–27. https://doi.org/10.1016/j.mce.2018.12.003
11. Bargut, T.C.L., Silva-e-Silva, A.C.A.G., Souza-Mello, V., Mandarim-de-Lacerda, C.A., Aguila, M.B. (2016). Mice fed fish oil diet and upregulation of brown adipose tissue thermogenic markers. *European Journal of Nutrition, 55*(1), 159–169. https://doi.org/10.1007/s00394-015-0834-0
12. Bártíková, H., Boušová, I., Matoušková, P., Szotáková, B., Skálová, L. (2017). Effect of green tea extract-enriched diets on insulin and leptin levels, oxidative stress parameters and antioxidant enzymes activities in obese mice. *Polish Journal of Food and Nutrition Sciences, 67*(3), 233–240. https://doi.org/10.1515/pjfns-2017-0004
13. Bartoňková, I., Dvořák, Z. (2018). Essential oils of culinary herbs and spices display agonist and antagonist activities at human aryl hydrocarbon receptor AhR. *Food and Chemical Toxicology, 111*, 374–384. https://doi.org/10.1016/j.fct.2017.11.049
14. Berry, D.C., Noy, N. (2009). All-*trans*-retinoic acid represses obesity and insulin resistance by activating both peroxisome proliferation-activated receptor beta/delta and retinoic acid receptor. *Molecular and Cellular Biology, 29*(12), 3286–3296. https://doi.org/10.1128/MCB.01742-08
15. Bershad, S., Poulin, Y.P., Berson, D.S., Sabean, J., Brodell, R.T., Shalita, A.R., Kakita, L., Tanghetti, E., Leyden, J., Webster, G.F., Miller, B.H. (1999). Topical retinoids in the treatment of acne vulgaris. *Cutis, 64*(2 Suppl), 8–20.
16. Bialonska, D., Kasimsetty, S.G., Khan, S.I., Ferreira, D. (2009). Urolithins, intestinal microbial metabolites of *Pomegranate* ellagitannins, exhibit potent antioxidant activity in a cell-based assay. *Journal of Agricultural and Food Chemistry, 57*(21), 10181–10186. https://doi.org/10.1021/jf9025794
17. Binder, E., Bermúdez-Silva, F.J., Elie, M., Leste-Lasserre, T., Belluomo, I., Clark, S., Duchampt, A., Mithieux, G., Cota, D. (2014). Leucine supplementation modulates fuel substrates utilization and glucose metabolism in previously obese mice. *Obesity (Silver Spring, Md.), 22*(3), 713–720. https://doi.org/10.1002/oby.20578
18. Blankson, H., Stakkestad, J.A., Fagertun, H., Thom, E., Wadstein, J., Gudmundsen, O. (2000). Conjugated linoleic acid reduces body fat mass in overweight and obese humans. *The Journal of Nutrition, 130*(12), 2943–2948. https://doi.org/10.1093/jn/130.12.2943

19. Blüher, M. (2013). Adipose tissue dysfunction contributes to obesity related metabolic diseases. *Best Practice & Research. Clinical Endocrinology & Metabolism, 27*(2), 163–177. https://doi.org/10.1016/j.beem.2013.02.005
20. Bonati, M., Latini, R., Galletti, F., Young, J.F., Tognoni, G., Garattini, S. (1982). Caffeine disposition after oral doses. *Clinical Pharmacology and Therapeutics, 32*(1), 98–106. https://doi.org/10.1038/clpt.1982.132
21. Boskou, D., Blekas, G., Tsimidou, M. (2006). Olive oil composition. In D. Boskou (Eds.), *Olive Oil: Chemistry and Technology*, AOCS Press, Boca Raton, USA, pp. 41–72. https://doi.org/10.4324/9781003040217
22. Boström, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Boström, E.A., Choi, J.H., Long, J.Z., Kajimura, S., Zingaretti, M.C., Vind, B.F., Tu, H., Cinti, S., Højlund, K., Gygi, S.P., Spiegelman, B.M. (2012). A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature, 481*(7382), 463–468. https://doi.org/10.1038/nature10777
23. Bounds, S.V., Caldwell, J. (1996). Pathways of metabolism of [1'-14C]-*trans*-anethole in the rat and mouse. *Drug Metabolism and Disposition, 24*(7), 717–724.
24. Burke, A.C., Sutherland, B.G., Telford, D.E., Morrow, M.R., Sawyez, C.G., Edwards, J.Y., Drangova, M., Huff, M.W. (2018). Intervention with citrus flavonoids reverses obesity and improves metabolic syndrome and atherosclerosis in obese Ldlr-/- mice. *Journal of Lipid Research, 59*(9), 1714–1728. https://doi.org/10.1194/jlr.M087387
25. Cavalera, M., Axling, U., Berger, K., Holm, C. (2016). Rose hip supplementation increases energy expenditure and induces browning of white adipose tissue. *Nutrition & Metabolism, 13*, art. no. 91. https://doi.org/10.1186/s12986-016-0151-5
26. Cavallito, C.J., Bailey, J.H. (1944). Allicin, the antibacterial principle of *Allium sativum*. I. Isolation, physical properties and antibacterial action. *Journal of the American Chemical Society, 66*(11), 1950–1951. https://doi.org/10.1021/ja01239a048
27. Chen, H., Chan, K.K., Budd, T. (1998). Pharmacokinetics of D-limonene in the rat by GC-MS assay. *Journal of Pharmaceutical and Biomedical Analysis, 17*(4–5), 631–640. https://doi.org/10.1016/S0731-7085(97)00243-4
28. Chen, L., Lee, M.J., Li, H., Yang, C.S. (1997). Absorption, distribution, elimination of tea polyphenols in rats. *Drug Metabolism and Disposition, 25*(9), 1045–1050.
29. Chen, X., Li, D., Hu, Y., Jin, M., Zhou, L., Peng, K., Zheng, H. (2011). Simultaneous determination of 3,3',4',5,7-pentamethylquercetin and its possible metabolite 3,3',4',7-tetramethylquercetin in dog plasma by liquid chromatography-tandem mass spectrometry and its application to preclinical pharmacokinetic study. *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences, 879*(23), 2339–2344. https://doi.org/10.1016/j.jchromb.2011.06.019
30. Chen, Z., Zhu, Q.Y., Tsang, D., Huang, Y. (2001). Degradation of green tea catechins in tea drinks. *Journal of Agricultural and Food Chemistry, 49*(1), 477–482. https://doi.org/10.1021/jf000877h
31. Cheng, Y., Meng, Q., Wang, C., Li, H., Huang, Z., Chen, S., Xiao, F., Guo, F. (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. *Diabetes, 59*(1), 17–25. https://doi.org/10.2337/db09-0929
32. Cheng, Y., Zhang, Q., Meng, Q., Xia, T., Huang, Z., Wang, C., Liu, B., Chen, S., Xiao, F., Du, Y., Guo, F. (2011). Leucine deprivation stimulates fat loss *via* increasing CRH expression in the hypothalamus and activating the sympathetic nervous system. *Molecular Endocrinology (Baltimore, Md.), 25*(9), 1624–1635. https://doi.org/10.1210/me.2011-0028
33. Choi, J.H., Kim, S.W., Yu, R., Yun, J.W. (2017). Monoterpene phenolic compound thymol promotes browning of 3T3-L1 adipocytes. *European Journal of Nutrition, 56*(7), 2329–2341. https://doi.org/10.1007/s00394-016-1273-2
34. Choi, J.H., Yun, J.W. (2016). Chrysin induces brown fat-like phenotype and enhances lipid metabolism in 3T3-L1 adipocytes. *Nutrition, 32*(9), 1002–1010. https://doi.org/10.1016/j.nut.2016.02.007
35. Choi, M., Mukherjee, S., Kang, N.H., Barkat, J.L., Parray, H.A., Yun, J.W. (2018). L-rhamnose induces browning in 3T3-L1 white adipocytes and activates HIB1B brown adipocytes. *IUBMB Life, 70*(6), 563–573. https://doi.org/10.1002/iub.1750
36. Chondronikola, M., Volpi, E., Børsheim, E., Porter, C., Annamalai, P., Enerbäck, S., Lidell, M.E., Saraf, M.K., Labbe, S.M., Hurren, N.M., Yfanti, C., Chao, T., Andersen, C.R., Cesani, F., Hawkins, H., Sidossis, L.S. (2014). Brown adipose tissue improves whole-body glucose homeostasis and insulin sensitivity in humans. *Diabetes, 63*(12), 4089–4099. https://doi.org/10.2337/db14-0746
37. Chou, Y.-C., Ho, C.-T., Pan, M.-H. (2018). Immature *Citrus reticulata* extract promotes browning of beige adipocytes in high-fat diet-induced C57BL/6 mice. *Journal of Agricultural and Food Chemistry, 66*(37), 9697–9703. https://doi.org/10.1021/acs.jafc.8b02719
38. Contreras, G.A., Lee, Y.-H., Mottillo, E.P., Granneman, J.G. (2014). Inducible brown adipocytes in subcutaneous inguinal white fat: the role of continuous sympathetic stimulation. *American Journal of Physiology. Endocrinology and Metabolism, 307*(9), E793–E799. https://doi.org/10.1152/ajpendo.00033.2014
39. Daels-Rakotoarison, D.A., Gressier, B., Trotin, F., Brunet, C., Luyckx, M., Dine, T., Bailleul, F., Cazin, M., Cazin, J.-C. (2002). Effects of *Rosa canina* fruit extract on neutrophil respiratory burst. *Phytotherapy Research, 16*(2), 157–161. https://doi.org/10.1002/ptr.985
40. Dawson, M.I. (2000). The importance of vitamin A in nutrition. *Current Pharmaceutical Design, 6*(3), 311–325. https://doi.org/10.2174/1381612003401190
41. de Jong, J.M.A., Larsson, O., Cannon, B., Nedergaard, J. (2015). A stringent validation of mouse adipose tissue identity markers. *American Journal of Physiology. Endocrinology and Metabolism, 308*(12), E1085–1105. https://doi.org/10.1152/ajpendo.00023.2015
42. de Macêdo, S.M., Lelis, D. de F., Mendes, K.L., Fraga, C.A. de C., Brandi, I.V., Feltenberger, J.D., Farias, L.C., Guimarães, A.L.S., de Paula, A.M.B., Santos, S.H. de S. (2017). Effects of dietary macronutrient composition on FNDC5 and irisin in mice skeletal muscle. *Metabolic Syndrome and Related Disorders, 15*(4), 161–169. https://doi.org/10.1089/met.2016.0109

43. Doyle, B., Griffiths, L.A. (1980). The metabolism of ellagic acid in the rat. *Xenobiotica, 10*(4), 247–256. https://doi.org/10.3109/00498258009033752
44. Du, J., Shen, L., Tan, Z., Zhang, P., Zhao, X., Xu, Y., Gan, M., Yang, Q., Ma, J., Jiang, A., Tang, G., Jiang, Y., Jin, L., Li, M., Bai, L., Li, X., Wang, J., Zhang, S., Zhu, L. (2018). Betaine supplementation enhances lipid metabolism and improves insulin resistance in mice fed a high-fat diet. *Nutrients, 10*(2), art. no. 131. https://doi.org/10.3390/nu10020131
45. Fabbiano, S., Suárez-Zamorano, N., Rigo, D., Veyrat-Durebex, C., Stevanovic Dokic, A., Colin, D.J., Trajkovski, M. (2016). Caloric restriction leads to browning of white adipose tissue through type 2 immune signaling. *Cell Metabolism, 24*(3), 434–446. https://doi.org/10.1016/j.cmet.2016.07.023
46. Fahey, J.W., Holtzclaw, W.D., Wehage, S.L., Wade, K.L., Stephenson, K.K., Talalay, P. (2015). Sulforaphane bioavailability from glucoraphanin-rich broccoli: control by active endogenous myrosinase. *PLoS One, 10*(11), art. no. e0140963. https://doi.org/10.1371/journal.pone.0140963
47. Farco, J.A., Grundmann, O. (2013). Menthol – pharmacology of an important naturally medicinal "cool." *Mini Reviews in Medicinal Chemistry, 13*(1), 124–131. https://doi.org/10.2174/138955713804484686
48. Felgines, C., Texier, O., Morand, C., Manach, C., Scalbert, A., Régerat, F., Rémésy, C. (2000). Bioavailability of the flavanone naringenin and its glycosides in rats. *American Journal of Physiology. Gastrointestinal and Liver Physiology, 279*(6), G1148–1154. https://doi.org/10.1152/ajpgi.2000.279.6.G1148
49. Fisher, F.M., Kleiner, S., Douris, N., Fox, E.C., Mepani, R.J., Verdeguer, F., Wu, J., Kharitonenkov, A., Flier, J.S., Maratos-Flier, E., Spiegelman, B.M. (2012). FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. *Genes & Development, 26*(3), 271–281. https://doi.org/10.1101/gad.177857.111
50. Fong, B.Y., Norris, C.S., MacGibbon, A.K.H. (2007). Protein and lipid composition of bovine milk-fat-globule membrane. *International Dairy Journal, 17*(4), 275–288. https://doi.org/10.1016/j.idairyj.2006.05.004
51. Forney, L.A., Lenard, N.R., Stewart, L.K., Henagan, T.M. (2018). Dietary quercetin attenuates adipose tissue expansion and inflammation and alters adipocyte morphology in a tissue-specific manner. *International Journal of Molecular Sciences, 19*(3), art. no. 895. https://doi.org/10.3390/ijms19030895
52. Gandhi, G.R., Vasconcelos, A.B.S., Wu, D.-T., Li, H.-B., Antony, P.J., Li, H., Geng, F., Gurgel, R.Q., Narain, N., Gan, R.-Y. (2020). Citrus flavonoids as promising phytochemicals targeting diabetes and related complications: a systematic review of *in vitro* and *in vivo* studies. *Nutrients, 12*(10), E2907. https://doi.org/10.3390/nu12102907
53. Gao, X., Xie, Q., Kong, P., Liu, L., Sun, S., Xiong, B., Huang, B., Yan, L., Sheng, J., Xiang, H. (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), art. no. e00601–17. https://doi.org/10.1128/IAI.00601-17
54. García-Alonso, V., López-Vicario, C., Titos, E., Morán-Salvador, E., González-Périz, A., Rius, B., Párrizas, M., Werz, O., Arroyo, V., Clària, J. (2013). Coordinate functional regulation between microsomal prostaglandin E synthase-1 (mPGES-1) and peroxisome proliferator-activated receptor γ (PPARγ) in the conversion of white-to-brown adipocytes. *The Journal of Biological Chemistry, 288*(39), 28230–28242. https://doi.org/10.1074/jbc.M113.468603
55. García-Alonso, V., Titos, E., Alcaraz-Quiles, J., Rius, B., Lopategi, A., López-Vicario, C., Jakobsson, P.-J., Delgado, S., Lozano, J., Clària, J. (2016). Prostaglandin E2 exerts multiple regulatory actions on human obese adipose tissue remodeling, inflammation, adaptive thermogenesis and lipolysis. *PLoS One, 11*(4), art. no. e0153751. https://doi.org/10.1371/journal.pone.0153751
56. Gelal, A., Jacob, P., Yu, L., Benowitz, N.L. (1999). Disposition kinetics and effects of menthol. *Clinical Pharmacology and Therapeutics, 66*(2), 128–135. https://doi.org/10.1053/cp.1999.v66.100455001
57. Golbidi, S., Daiber, A., Korac, B., Li, H., Essop, M.F., Laher, I. (2017). Health benefits of fasting and caloric restriction. *Current Diabetes Reports, 17*(12), art. no. 123. https://doi.org/10.1007/s11892-017-0951-7
58. Górska-Warsewicz, H., Laskowski, W., Kulykovets, O., Kudlińska-Chylak, A., Czeczotko, M., Rejman, K. (2018). Food products as sources of protein and amino acids – The case of Poland. *Nutrients 10*(12), art. no. 1977. https://doi.org/10.3390/nu10121977
59. Grossini, E., Farruggio, S., Raina, G., Mary, D., Deiro, G., Gentilli, S. (2018). Effects of genistein on differentiation and viability of human visceral adipocytes. *Nutrients, 10*(8), art. no. 978. https://doi.org/10.3390/nu10080978
60. Gruenwald, J., Freder, J., Armbruester, N. (2010). Cinnamon and health. *Critical Reviews in Food Science and Nutrition, 50*(9), 822–834. https://doi.org/10.1080/10408390902773052
61. Guo, H., Foncea, R., O'Byrne, S.M., Jiang, H., Zhang, Y., Deis, J.A., Blaner, W.S., Bernlohr, D.A., Chen, X. (2016). Lipocalin 2, a regulator of retinoid homeostasis and retinoid-mediated thermogenic activation in adipose tissue. *The Journal of Biological Chemistry, 291*(21), 11216–11229. https://doi.org/10.1074/jbc.M115.711556
62. Guo, Y.-Y., Li, B.-Y., Peng, W.-Q., Guo, L., Tang, Q.-Q. (2019). Taurine-mediated browning of white adipose tissue is involved in its anti-obesity effect in mice. *The Journal of Biological Chemistry, 294*(41), 15014–15024. https://doi.org/10.1074/jbc.RA119.009936
63. Han, Y., Wu, J.-Z., Shen, J.-Z., Chen, L., He, T., Jin, M.-W., Liu, H. (2017). Pentamethylquercetin induces adipose browning and exerts beneficial effects in 3T3-L1 adipocytes and high-fat diet-fed mice. *Scientific Reports, 7*(1), art. no. 1123. https://doi.org/10.1038/s41598-017-01206-4
64. Hargrave, K.M., Li, C., Meyer, B.J., Kachman, S.D., Hartzell, D.L., Della-Fera, M.A., Miner, J.L., Baile, C.A. (2002). Adipose depletion and apoptosis induced by *trans*-10, *cis*-12 conjugated linoleic acid in mice. *Obesity Research, 10*(12), 1284–1290. https://doi.org/10.1038/oby.2002.174
65. Harms, M., Seale, P. (2013). Brown and beige fat: development, function and therapeutic potential. *Nature Medicine, 19*(10), 1252–1263. https://doi.org/10.1038/nm.3361

66. Helal, A., Tagliazucchi, D., Verzelloni, E., Conte, A. (2014). Bioaccessibility of polyphenols and cinnamaldehyde in cinnamon beverages subjected to *in vitro* gastro-pancreatic digestion. *Journal of Functional Foods, 7*(1), 506–516. https://doi.org/10.1016/j.jff.2014.01.005
67. Hodisan, T., Socaciu, C., Ropan, I., Neamtu, G. (1997). Carotenoid composition of *Rosa canina* fruits determined by thin-layer chromatography and high-performance liquid chromatography. *Journal of Pharmaceutical and Biomedical Analysis, 16*(3), 521–528. https://doi.org/10.1016/S0731-7085(97)00099-X
68. Hostetler, G.L., Ralston, R.A., Schwartz, S.J. (2017). Flavones: food sources, bioavailability, metabolism, and bioactivity. *Advances in Nutrition (Bethesda, Md.), 8*(3), 423–435. https://doi.org/10.3945/an.116.012948
69. Houghton, C.A., Fassett, R.G., Coombes, J.S. (2016). Sulforaphane and other nutrigenomic Nrf2 activators: can the clinician's expectation be matched by the reality? *Oxidative Medicine and Cellular Longevity, 2016*, art. no. 7857186. https://doi.org/10.1155/2016/7857186
70. Hu, J., Kyrou, I., Tan, B.K., Dimitriadis, G.K., Ramanjaneya, M., Tripathi, G., Patel, V., James, S., Kawan, M., Chen, J., Randeva, H.S. (2016). Short-chain fatty acid acetate stimulates adipogenesis and mitochondrial biogenesis *via* GPR43 in brown adipocytes. *Endocrinology, 157*(5), 1881–1894. https://doi.org/10.1210/en.2015-1944
71. Jaiswal, N., Akhtar, J., Singh, S.P., Badruddeen, Ahsan, F. (2019). An overview on genistein and its various formulations. *Drug Research, 69*(6), 305–313. https://doi.org/10.1055/a-0797-3657
72. Jia, T., Qiao, J., Guan, D., Chen, T. (2017). Anti-inflammatory effects of licochalcone A on IL-1β-stimulated human osteoarthritis chondrocytes. *Inflammation, 40*(6), 1894–1902. https://doi.org/10.1007/s10753-017-0630-5
73. Jiang, C., Zhai, M., Yan, D., Li, D., Li, C., Zhang, Y., Xiao, L., Xiong, D., Deng, Q., Sun, W. (2017). Dietary menthol-induced TRPM8 activation enhances WAT "browning" and ameliorates diet-induced obesity. *Oncotarget, 8*(43), 75114–75126. https://doi.org/10.18632/oncotarget.20540
74. Jiang, N., Dillon, F.M., Silva, A., Gomez-Cano, L., Grotewold, E. (2021). Rhamnose in plants - from biosynthesis to diverse functions. *Plant Science, 302*, art. no. 110687. https://doi.org/10.1016/j.plantsci.2020.110687
75. Jiang, Y., Rose, A.J., Sijmonsma, T.P., Bröer, A., Pfenninger, A., Herzig, S., Schmoll, D., Bröer, S. (2015). Mice lacking neutral amino acid transporter B(0)AT1 (Slc6a19) have elevated levels of FGF21 and GLP-1 and improved glycaemic control. *Molecular Metabolism, 4*(5), 406–417. https://doi.org/10.1016/j.molmet.2015.02.003
76. Jiao, J., Han, S.-F., Zhang, W., Xu, J.-Y., Tong, X., Yin, X.-B., Yuan, L.-X., Qin, L.-Q. (2016). Chronic leucine supplementation improves lipid metabolism in C57BL/6J mice fed with a high-fat/cholesterol diet. *Food & Nutrition Research, 60*, art. no. 31304. https://doi.org/10.3402/fnr.v60.31304
77. Jumpertz, R., Le, D.S., Turnbaugh, P.J., Trinidad, C., Bogardus, C., Gordon, J.I., Krakoff, J. (2011). Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *The American Journal of Clinical Nutrition, 94*(1), 58–65. https://doi.org/10.3945/ajcn.110.010132
78. Kajimura, S., Spiegelman, B.M., Seale, P. (2015). Brown and beige fat: physiological roles beyond heat generation. *Cell Metabolism, 22*(4), 546–559. https://doi.org/10.1016/j.cmet.2015.09.007
79. Kang, N.H., Mukherjee, S., Min, T., Kang, S.C., Yun, J.W. (2018). *trans*-Anethole ameliorates obesity *via* induction of browning in white adipocytes and activation of brown adipocytes. *Biochimie, 151*, 1–13. https://doi.org/10.1016/j.biochi.2018.05.009
80. Kaşıkcı, M.B., Bağdatlıoğlu, N. (2016). Bioavailability of quercetin. *Current Research in Nutrition and Food Science Journal, 4*(Suppl 2), 146–151. https://doi.org/10.12944/CRNFSJ.4.Special-Issue-October.20
81. Khaled, K.A., El-Sayed, Y.M., Al-Hadiya, B.M. (2003). Disposition of the flavonoid quercetin in rats after single intravenous and oral doses. *Drug Development and Industrial Pharmacy, 29*(4), 397–403. https://doi.org/10.1081/DDC-120018375
82. Kim, H.-J., Choi, E.-J., Kim, H.S., Choi, C.-W., Choi, S.-W., Kim, S.-L., Seo, W.-D., Do, S.H. (2019). Germinated soy germ extract ameliorates obesity through beige fat activation. *Food & Function, 10*(2), 836–848. https://doi.org/10.1039/C8FO02252F
83. Kim, J., Okla, M., Erickson, A., Carr, T., Natarajan, S.K., Chung, S. (2016). Eicosapentaenoic acid potentiates brown thermogenesis through FFAR4-dependent up-regulation of miR-30b and miR-378. *The Journal of Biological Chemistry, 291*(39), 20551–20562. https://doi.org/10.1074/jbc.M116.721480
84. Kim, M., Furuzono, T., Yamakuni, K., Li, Y., Kim, Y.-I., Takahashi, H., Ohue-Kitano, R., Jheng, H.-F., Takahashi, N., Kano, Y., Yu, R., Kishino, S., Ogawa, J., Uchida, K., Yamazaki, J., Tominaga, M., Kawada, T., Goto, T. (2017). 10-Oxo-12(*Z*)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, enhances energy metabolism by activation of TRPV1. *FASEB Journal, 31*(11), 5036–5048. https://doi.org/10.1096/fj.201700151R
85. Kim, M., Goto, T., Yu, R., Uchida, K., Tominaga, M., Kano, Y., Takahashi, N., Kawada, T. (2015). Fish oil intake induces UCP1 upregulation in brown and white adipose tissue *via* the sympathetic nervous system. *Scientific Reports, 5*, art. no. 18013. https://doi.org/10.1038/srep18013
86. Kim, S.-L., Lee, J.-E., Kwon, Y.-U., Kim, W.-H., Jung, G.-H., Kim, D.-W., Lee, C.-K., Lee, Y.-Y., Kim, M.-J., Kim, Y.-H., Hwang, T.-Y., Chung, I.-M. (2013). Introduction and nutritional evaluation of germinated soy germ. *Food Chemistry, 136*(2), 491–500. https://doi.org/10.1016/j.foodchem.2012.08.022
87. Kishino, S., Takeuchi, M., Park, S.-B., Hirata, A., Kitamura, N., Kunisawa, J., Kiyono, H., Iwamoto, R., Isobe, Y., Arita, M., Arai, H., Ueda, K., Shima, J., Takahashi, S., Yokozeki, K., Shimizu, S., Ogawa, J. (2013). Polyunsaturated fatty acid saturation by gut lactic acid bacteria affecting host lipid composition. *Proceedings of the National Academy of Sciences of the United States of America, 110*(44), 17808–17813. https://doi.org/10.1073/pnas.1312937110
88. Kohlert, C., Schindler, G., März, R.W., Abel, G., Brinkhaus, B., Derendorf, H., Gräfe, E.-U., Veit, M. (2002). Systemic availability and pharmacokinetics of thymol in humans. *Journal of Clinical Pharmacology, 42*(7), 731–737. https://doi.org/10.1177/009127002401102678

89. Kowalski, R., Kałwa, K., Wilczyński, K., Kobus, Z. (2019). The fatty acids composition of selected fish oils used as dietary supplements. *Polish Journal of Natural Sciences, 34*(1), 115–126.
90. Kris-Etherton, P.M., Grieger, J.A., Etherton, T.D. (2009). Dietary reference intakes for DHA and EPA. *Prostaglandins, Leukotrienes, and Essential Fatty Acids, 81*(2–3), 99–104. https://doi.org/10.1016/j.plefa.2009.05.011
91. Krithika, J., Sathiyasree, B., Teodore, B., Ramarajan, C., Gurushankar, K. (2020). Optimization of extraction parameters and stabilization of anthocyanin from onion peel. *Critical Reviews in Food Science and Nutrition,* 1–8. https://doi.org/10.1080/10408398.2020.1856772
92. Kwan, H.Y., Wu, J., Su, T., Chao, X.-J., Liu, B., Fu, X., Chan, C.L., Lau, R.H.Y., Tse, A.K.W., Han, Q.B., Fong, W.F., Yu, Z.-L. (2017). Cinnamon induces browning in subcutaneous adipocytes. *Scientific Reports, 7*(1), art. no. 2447. https://doi.org/10.1038/s41598-017-02263-5
93. Lafontan, M., Barbe, P., Galitzky, J., Tavernier, G., Langin, D., Carpéné, C., Bousquet-Melou, A., Berlan, M. (1997). Adrenergic regulation of adipocyte metabolism. *Human Reproduction (Oxford, England), 12*(Suppl 1), 6–20. https://doi.org/10.1093/humrep/12.suppl_1.6
94. Laidlaw, S.A., Grosvenor, M., Kopple, J.D. (1990). The taurine content of common foodstuffs. *JPEN – Journal of Parenteral and Enteral Nutrition, 14*(2), 183–188. https://doi.org/10.1177/0148607190014002183
95. Laiglesia, L.M., Lorente-Cebrián, S., Prieto-Hontoria, P.L., Fernández-Galilea, M., Ribeiro, S.M.R., Sáinz, N., Martínez, J.A., Moreno-Aliaga, M.J. (2016). Eicosapentaenoic acid promotes mitochondrial biogenesis and beige-like features in subcutaneous adipocytes from overweight subjects. *The Journal of Nutritional Biochemistry, 37*, 76–82. https://doi.org/10.1016/j.jnutbio.2016.07.019
96. Landete, J.M. (2011). Ellagitannins, ellagic acid and their derived metabolites: a review about source, metabolism, functions and healt. *Food Research International (Ottawa, Ont.), 44*(5), 1150–1160. https://doi.org/10.1016/j.foodres.2011.04.027
97. LaRosa, P.C., Miner, J., Xia, Y., Zhou, Y., Kachman, S., Fromm, M.E. (2006). *trans*-10, *cis*-12 Conjugated linoleic acid causes inflammation and delipidation of white adipose tissue in mice: a microarray and histological analysis. *Physiological Genomics, 27*(3), 282–294. https://doi.org/10.1152/physiolgenomics.00076.2006
98. Lawson, L.D., Hunsaker, S.M. (2018). Allicin bioavailability and bioequivalence from garlic supplements and garlic foods. *Nutrients, 10*(7), art. no. E812. https://doi.org/10.3390/nu10070812
99. Lee, C.G., Rhee, D.K., Kim, B.O., Um, S.H., Pyo, S. (2019). Allicin induces beige-like adipocytes *via* KLF15 signal cascade. *The Journal of Nutritional Biochemistry, 64*, 13–24. https://doi.org/10.1016/j.jnutbio.2018.09.014
100. Lee, H.E., Yang, G., Han, S.-H., Lee, J.-H., An, T.-J., Jang, J.-K., Lee, J.Y. (2018). Anti-obesity potential of *Glycyrrhiza uralensis* and licochalcone A through induction of adipocyte browning. *Biochemical and Biophysical Research Communications, 503*(3), 2117–2123. https://doi.org/10.1016/j.bbrc.2018.07.168
101. Lee, S.G., Parks, J.S., Kang, H.W. (2017). Quercetin, a functional compound of onion peel, remodels white adipocytes to brown-like adipocytes. *The Journal of Nutritional Biochemistry, 42*, 62–71. https://doi.org/10.1016/j.jnutbio.2016.12.018
102. Leu, S.-Y., Tsai, Y.-C., Chen, W.-C., Hsu, C.-H., Lee, Y.-M., Cheng, P.-Y. (2018). Raspberry ketone induces brown-like adipocyte formation through suppression of autophagy in adipocytes and adipose tissue. *The Journal of Nutritional Biochemistry, 56*, 116–125. https://doi.org/10.1016/j.jnutbio.2018.01.017
103. Li, G., Xie, C., Lu, S., Nichols, R.G., Tian, Y., Li, L., Patel, D., Ma, Y., Brocker, C.N., Yan, T., Krausz, K.W., Xiang, R., Gavrilova, O., Patterson, A.D., Gonzalez, F.J. (2017). Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut microbiota. *Cell Metabolism, 26*(4), 672–685.e4. https://doi.org/10.1016/j.cmet.2017.08.019
104. Li, T., Gao, J., Du, M., Song, J., Mao, X. (2018). Milk fat globule membrane attenuates high-fat diet-induced obesity by inhibiting adipogenesis and increasing uncoupling protein 1 expression in white adipose tissue of mice. *Nutrients, 10*(3), art. no. 331. https://doi.org/10.3390/nu10030331
105. Libby, A.E., Bales, E.S., Monks, J., Orlicky, D.J., McManaman, J.L. (2018). Perilipin-2 deletion promotes carbohydrate-mediated browning of white adipose tissue at ambient temperature. *Journal of Lipid Research, 59*(8), 1482–1500. https://doi.org/10.1194/jlr.M086249
106. Lidell, M.E., Betz, M.J., Leinhard, O.D., Heglind, M., Elander, L., Slawik, M., Mussack, T., Nilsson, D., Romu, T., Nuutila, P., Virtanen, K.A., Beuschlein, F., Persson, A., Borga, M., Enerbäck, S. (2013). Evidence for two types of brown adipose tissue in humans. *Nature Medicine, 19*(5), 631–634. https://doi.org/10.1038/nm.3017
107. Liu, J., Li, Y., Yang, P., Wan, J., Chang, Q., Wang, T.T.Y., Lu, W., Zhang, Y., Wang, Q., Yu, L.L. (2017). Gypenosides reduced the risk of overweight and insulin resistance in C57BL/6J mice through modulating adipose thermogenesis and gut microbiota. *Journal of Agricultural and Food Chemistry, 65*(42), 9237–9246. https://doi.org/10.1021/acs.jafc.7b03382
108. Liu, Y.C., Hasegawa, Y. (2006). Reducing effect of feeding powdered scallop shell on the body fat mass of rats. *Bioscience, Biotechnology, and Biochemistry, 70*(1), 86–92. https://doi.org/10.1271/bbb.70.86
109. Liu, Y.C., Satoh, K., Hasegawa, Y. (2006). Feeding scallop shell powder induces the expression of uncoupling protein 1 (UCP1) in white adipose tissue of rats. *Bioscience, Biotechnology, and Biochemistry, 70*(11), 2733–2738. https://doi.org/10.1271/bbb.60349
110. Lone, J., Choi, J.H., Kim, S.W., Yun, J.W. (2016). Curcumin induces brown fat-like phenotype in 3T3-L1 and primary white adipocytes. *The Journal of Nutritional Biochemistry, 27*, 193–202. https://doi.org/10.1016/j.jnutbio.2015.09.006
111. Lone, J., Parray, H.A., Yun, J.W. (2018). Nobiletin induces brown adipocyte-like phenotype and ameliorates stress in 3T3-L1 adipocytes. *Biochimie, 146*, 97–104. https://doi.org/10.1016/j.biochi.2017.11.021

112. Lone, J., Yun, J.W. (2016). Monoterpene limonene induces brown fat-like phenotype in 3T3-L1 white adipocytes. *Life Sciences, 153*, 198–206. https://doi.org/10.1016/j.lfs.2016.04.010
113. Lu, Yuanyuan, Fan, C., Li, P., Lu, Yanfei, Chang, X., Qi, K. (2016). Short chain fatty acids prevent high-fat-diet-induced obesity in mice by regulating G protein-coupled receptors and gut microbiota. *Scientific Reports, 6*, art. no. 37589. https://doi.org/10.1038/srep37589
114. Lund, J., Larsen, L.H., Lauritzen, L. (2018). Fish oil as a potential activator of brown and beige fat thermogenesis. *Adipocyte, 7*(2), 88–95. https://doi.org/10.1080/21623945.2018.1442980
115. Luo, L., Liu, M. (2016). Adipose tissue in control of metabolism. *The Journal of Endocrinology, 231*(3), R77–R99. https://doi.org/10.1530/JOE-16-0211
116. Mao, Z., Liang, Y., Du, X., Sun, Z. (2009). 3,3',4',5,7-Pentamethylquercetin reduces angiotensin II-induced cardiac hypertrophy and apoptosis in rats. *Canadian Journal of Physiology and Pharmacology, 87*(9), 720–728. https://doi.org/10.1139/Y09-069
117. Marcelino, G., Hiane, P.A., Freitas, K. de C., Santana, L.F., Pott, A., Donadon, J.R., Guimarães, R. de C.A. (2019). Effects of olive oil and its minor components on cardiovascular diseases, inflammation, and gut microbiota. *Nutrients, 11*(8), art. no. E1826. https://doi.org/10.3390/nu11081826
118. Mas-Capdevila, A., Teichenne, J., Domenech-Coca, C., Caimari, A., Del Bas, J.M., Escoté, X., Crescenti, A. (2020). Effect of hesperidin on cardiovascular disease risk factors: the role of intestinal microbiota on hesperidin bioavailability. *Nutrients, 12*(5), art. no. E1488. https://doi.org/10.3390/nu12051488
119. Meng-er, H., Yu-chen, Y., Shu-rong, C., Jin-ren, C., Jia-Xiang, L., Lin, Z., Long-jun, G., Zhen-yi, W. (1988). Use of all-*trans* retinoic acid in the treatment of acute promyelocytic leukemia. *Blood, 72*(2), 567–572. https://doi.org/10.1182/blood.V72.2.567.567
120. Mercader, J., Ribot, J., Murano, I., Felipe, F., Cinti, S., Bonet, M.L., Palou, A. (2006). Remodeling of white adipose tissue after retinoic acid administration in mice. *Endocrinology, 147*(11), 5325–5332. https://doi.org/10.1210/en.2006-0760
121. Min, S.Y., Kady, J., Nam, M., Rojas-Rodriguez, R., Berkenwald, A., Kim, J.H., Noh, H.-L., Kim, J.K., Cooper, M.P., Fitzgibbons, T., Brehm, M.A., Corvera, S. (2016). Human 'brite / beige' adipocytes develop from capillary networks and their implantation improves metabolic homeostasis in mice. *Nature Medicine, 22*(3), 312–318. https://doi.org/10.1038/nm.4031
122. Mize, C.E., Avigan, J., Baxter, J.H., Fales, H.M., Steinberg, D. (1966). Metabolism of phytol-U-14C and phytanic acid-U-14C in the rat. *Journal of Lipid Research, 7*(5), 692–697. https://doi.org/10.1016/S0022-2275(20)39252-X
123. Moreno-Navarrete, J.M., Serino, M., Blasco-Baque, V., Azalbert, V., Barton, R.H., Cardellini, M., Latorre, J., Ortega, F., Sabater-Masdeu, M., Burcelin, R., Dumas, M.-E., Ricart, W., Federici, M., Fernández-Real, J.M. (2018). Gut microbiota interacts with markers of adipose tissue browning, insulin action and plasma acetate in morbid obesity. *Molecular Nutrition & Food Research, 62*(3), art. no. 1700721. https://doi.org/10.1002/mnfr.201700721
124. Mosqueda-Solís, A., Sánchez, J., Portillo, M.P., Palou, A., Picó, C. (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. https://doi.org/10.1021/acs.jafc.8b02611
125. Murholm, M., Isidor, M.S., Basse, A.L., Winther, S., Sørensen, C., Skovgaard-Petersen, J., Nielsen, M.M., Hansen, A.S., Quistorff, B., Hansen, J.B. (2013). Retinoic acid has different effects on UCP1 expression in mouse and human adipocytes. *BMC Cell Biology, 14*, art. no. 41. https://doi.org/10.1186/1471-2121-14-41
126. Nagata, N., Xu, L., Kohno, S., Ushida, Y., Aoki, Y., Umeda, R., Fuke, N., Zhuge, F., Ni, Y., Nagashimada, M., Takahashi, C., Suganuma, H., Kaneko, S., Ota, T. (2017). Glucoraphanin ameliorates obesity and insulin resistance through adipose tissue browning and reduction of metabolic endotoxemia in mice. *Diabetes, 66*(5), 1222–1236. https://doi.org/10.2337/db16-0662
127. Neyrinck, A.M., Bindels, L.B., Geurts, L., Van Hul, M., Cani, P.D., Delzenne, N.M. (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. https://doi.org/10.1016/j.jnutbio.2017.07.008
128. Okla, M., Kim, J., Koehler, K., Chung, S. (2017). Dietary factors promoting brown and beige fat development and thermogenesis. *Advances in Nutrition (Bethesda, Md.), 8*(3), 473–483. https://doi.org/10.3945/an.116.014332
129. Oku, T., Nakamura, S. (2000). Estimation of intestinal trehalase activity from a laxative threshold of trehalose and lactulose on healthy female subjects. *European Journal of Clinical Nutrition, 54*(10), 783–788. https://doi.org/10.1038/sj.ejcn.1601091
130. Pahlavani, M., Razafimanjato, F., Ramalingam, L., Kalupahana, N.S., Moussa, H., Scoggin, S., Moustaid-Moussa, N. (2017). Eicosapentaenoic acid regulates brown adipose tissue metabolism in high-fat-fed mice and in clonal brown adipocytes. *The Journal of Nutritional Biochemistry, 39*, 101–109. https://doi.org/10.1016/j.jnutbio.2016.08.012
131. Pap, N., Fidelis, M., Azevedo, L., do Carmo, M.A.V., Wang, D., Mocan, A., Pereira, E.P.R., Xavier-Santos, D., Sant'Ana, A., Yang, B., Granato, D. (2021). Berry polyphenols and human health: evidence of antioxidant, anti-inflammatory, microbiota modulation, and cell-protecting effects. *Current Opinion in Food Science, 42*, 167–186. https://doi.org/10.1016/j.cofs.2021.06.003
132. Pascual-Serrano, A., Bladé, C., Suárez, M., Arola-Arnal, A. (2018). Grape seed proanthocyanidins improve white adipose tissue expansion during diet-induced obesity development in rats. *International Journal of Molecular Sciences, 19*(9), art. no. 2632. https://doi.org/10.3390/ijms19092632
133. Patil, D.P., Dhotre, D.P., Chavan, S.G., Sultan, A., Jain, D.S., Lanjekar, V.B., Gangawani, J., Shah, P.S., Todkar, J.S., Shah, S., Ranade, D.R., Patole, M.S., Shouche, Y.S. (2012). Molecular

analysis of gut microbiota in obesity among Indian individuals. *Journal of Biosciences, 37*(4), 647–657. https://doi.org/10.1007/s12038-012-9244-0

134. Peier, A.M., Moqrich, A., Hergarden, A.C., Reeve, A.J., Andersson, D.A., Story, G.M., Earley, T.J., Dragoni, I., McIntyre, P., Bevan, S., Patapoutian, A. (2002). A TRP channel that senses cold stimuli and menthol. *Cell, 108*(5), 705–715. https://doi.org/10.1016/S0092-8674(02)00652-9
135. Pereira, M.P., Ferreira, L.A.A., da Silva, F.H.S., Christoffolete, M.A., Metsios, G.S., Chaves, V.E., de França, S.A., Damazo, A.S., Flouris, A.D., Kawashita, N.H. (2017). A low-protein, high-carbohydrate diet increases browning in perirenal adipose tissue but not in inguinal adipose tissue. *Nutrition, 42*, 37–45. https://doi.org/10.1016/j.nut.2017.05.007
136. Pisani, D.F., Ghandour, R.A., Beranger, G.E., Le Faouder, P., Chambard, J.-C., Giroud, M., Vegiopoulos, A., Djedaini, M., Bertrand-Michel, J., Tauc, M., Herzig, S., Langin, D., Ailhaud, G., Duranton, C., Amri, E.-Z. (2014). The ω6-fatty acid, arachidonic acid, regulates the conversion of white to brite adipocyte through a prostaglandin/calcium mediated pathway. *Molecular Metabolism, 3*(9), 834–847. https://doi.org/10.1016/j.molmet.2014.09.003
137. Quan, H.-Y., Baek, N.I., Chung, S.H. (2012). Licochalcone A prevents adipocyte differentiation and lipogenesis *via* suppression of peroxisome proliferator-activated receptor γ and sterol regulatory element-binding protein pathways. *Journal of Agricultural and Food Chemistry, 60*(20), 5112–5120. https://doi.org/10.1021/jf2050763
138. Quesada-López, T., Cereijo, R., Turatsinze, J.-V., Planavila, A., Cairó, M., Gavaldà-Navarro, A., Peyrou, M., Moure, R., Iglesias, R., Giralt, M., Eizirik, D.L., Villarroya, F. (2016). The lipid sensor GPR120 promotes brown fat activation and FGF21 release from adipocytes. *Nature Communications, 7*, art. no. 13479. https://doi.org/10.1038/ncomms13479
139. Ramiro-Puig, E., Castell, M. (2009). Cocoa: antioxidant and immunomodulator. *The British Journal of Nutrition, 101*(7), 931–940. https://doi.org/10.1017/S0007114508169896
140. Rayalam, S., Yang, J.-Y., Ambati, S., Della-Fera, M.A., Baile, C.A. (2008). Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. *Phytotherapy Research, 22*(10), 1367–1371. https://doi.org/10.1002/ptr.2503
141. Rodriguez Lanzi, C., Perdicaro, D.J., Antoniolli, A., Fontana, A.R., Miatello, R.M., Bottini, R., Vazquez Prieto, M.A. (2016). Grape pomace and grape pomace extract improve insulin signaling in high-fat-fructose fed rat-induced metabolic syndrome. *Food & Function, 7*(3), 1544–1553. https://doi.org/10.1039/C5FO01065A
142. Rodriguez Lanzi, C., Perdicaro, D.J., Landa, M.S., Fontana, A., Antoniolli, A., Miatello, R.M., Oteiza, P.I., Vazquez Prieto, M.A. (2018). Grape pomace extract induced beige cells in white adipose tissue from rats and in 3T3-L1 adipocytes. *The Journal of Nutritional Biochemistry, 56*, 224–233. https://doi.org/10.1016/j.jnutbio.2018.03.001
143. Rodríguez, V.M., Portillo, M.P., Picó, C., Macarulla, M.T., Palou, A. (2002). Olive oil feeding up-regulates uncoupling protein genes in rat brown adipose tissue and skeletal muscle. *The American Journal of Clinical Nutrition, 75*(2), 213–220. https://doi.org/10.1093/ajcn/75.2.213
144. Rondanelli, M., Nichetti, M., Peroni, G., Faliva, M.A., Naso, M., Gasparri, C., Perna, S., Oberto, L., Di Paolo, E., Riva, A., Petrangolini, G., Guerreschi, G., Tartara, A. (2021). Where to find leucine in food and how to feed elderly with sarcopenia in order to counteract loss of muscle mass: practical advice. *Frontiers in Nutrition, 7*, art. no. 622391. https://doi.org/10.3389/fnut.2020.622391
145. Rosenwald, M., Perdikari, A., Rülicke, T., Wolfrum, C. (2013). Bi-directional interconversion of brite and white adipocytes. *Nature Cell Biology, 15*(6), 659–667. https://doi.org/10.1038/ncb2740
146. Ross, A.B., Zangger, A., Guiraud, S.P. (2014). Cereal foods are the major source of betaine in the Western diet – analysis of betaine and free choline in cereal foods and updated assessments of betaine intake. *Food Chemistry, 145*, 859–865. https://doi.org/10.1016/j.foodchem.2013.08.122
147. Rossato, M., Granzotto, M., Macchi, V., Porzionato, A., Petrelli, L., Calcagno, A., Vencato, J., De Stefani, D., Silvestrin, V., Rizzuto, R., Bassetto, F., De Caro, R., Vettor, R. (2014). Human white adipocytes express the cold receptor TRPM8 which activation induces UCP1 expression, mitochondrial activation and heat production. *Molecular and Cellular Endocrinology, 383*(1–2), 137–146. https://doi.org/10.1016/j.mce.2013.12.005
148. Rossi, F., Punzo, F., Umano, G.R., Argenziano, M., Miraglia Del Giudice, E. (2018). Role of cannabinoids in obesity. *International Journal of Molecular Sciences, 19*(9), art. no. 2690. https://doi.org/10.3390/ijms19092690
149. Sae-Tan, S., Rogers, C.J., Lambert, J.D. (2015). Decaffeinated green tea and voluntary exercise induce gene changes related to beige adipocyte formation in high fat-fed obese mice. *Journal of Functional Foods, 14*, 210–214. https://doi.org/10.1016/j.jff.2015.01.036
150. Sarawek, S., Derendorf, H., Butterweck, V. (2008). Pharmacokinetics of luteolin and metabolites in rats. *Natural Product Communications, 3*(12), 2029–2036. https://doi.org/10.1177/1934578X0800301218
151. Sauer, L.A., Dauchy, R.T., Blask, D.E., Krause, J.A., Davidson, L.K., Dauchy, E.M., Welham, K.J., Coupland, K. (2004). Conjugated linoleic acid isomers and *trans* fatty acids inhibit fatty acid transport in hepatoma 7288CTC and inguinal fat pads in Buffalo rats. *The Journal of Nutrition, 134*(8), 1989–1997. https://doi.org/10.1093/jn/134.8.1989
152. Schluter, A., Giralt, M., Iglesias, R., Villarroya, F. (2002). Phytanic acid, but not pristanic acid, mediates the positive effects of phytol derivatives on brown adipocyte differentiation. *FEBS Letters, 517*(1–3), 83–86. https://doi.org/10.1016/S0014-5793(02)02583-8
153. Shabalina, I.G., Petrovic, N., de Jong, J.M.A., Kalinovich, A.V., Cannon, B., Nedergaard, J. (2013). UCP1 in brite/beige adipose tissue mitochondria is functionally thermogenic. *Cell Reports, 5*(5), 1196–1203. https://doi.org/10.1016/j.celrep.2013.10.044
154. Shapiro, T.A., Fahey, J.W., Wade, K.L., Stephenson, K.K., Talalay, P. (2001). Chemoprotective glucosinolates and isothiocyanates of broccoli sprouts: metabolism and excretion in humans. *Cancer Epidemiology, Biomarkers & Prevention, 10*(5), 501–508.
155. Shen, H.-H., Huang, S.-Y., Kung, C.-W., Chen, S.-Y., Chen, Y.-F., Cheng, P.-Y., Lam, K.-K., Lee, Y.-M. (2019). Genistein amelio-

rated 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. https://doi.org/10.1016/j.jnutbio.2019.02.001

156. Shen, W., McIntosh, M.K. (2016). Nutrient regulation: conjugated linoleic acid's inflammatory and browning properties in adipose tissue. *Annual Review of Nutrition, 36*, 183–210. https://doi.org/10.1146/annurev-nutr-071715-050924
157. Shin, S., Ajuwon, K.M. (2018a). Divergent response of murine and porcine adipocytes to stimulation of browning genes by 18-carbon polyunsaturated fatty acids and beta-receptor agonists. *Lipids, 53*(1), 65–75. https://doi.org/10.1002/lipd.12010
158. Shin, S., Ajuwon, K.M. (2018b). Effects of diets differing in composition of 18-C fatty acids on adipose tissue thermogenic gene expression in mice fed high-fat diets. *Nutrients, 10*(2), art. no. 256. https://doi.org/10.3390/nu10020256
159. Shoaib, M., Shehzad, A., Omar, M., Rakha, A., Raza, H., Sharif, H.R., Shakeel, A., Ansari, A., Niazi, S. (2016). Inulin: properties, health benefits and food applications. *Carbohydrate Polymers, 147*, 444–454. https://doi.org/10.1016/j.carbpol.2016.04.020
160. Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., Srinivas, P.S. (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Medica, 64*(4), 353–356. https://doi.org/10.1055/s-2006-957450
161. Silvester, A.J., Aseer, K.R., Yun, J.W. (2019). Dietary polyphenols and their roles in fat browning. *The Journal of Nutritional Biochemistry, 64*, 1–12. https://doi.org/10.1016/j.jnutbio.2018.09.028
162. Smedman, A., Vessby, B. (2001). Conjugated linoleic acid supplementation in humans – metabolic effects. *Lipids, 36*(8), 773–781. https://doi.org/10.1007/s11745-001-0784-7
163. Sonnweber, T., Pizzini, A., Nairz, M., Weiss, G., Tancevski, I. (2018). Arachidonic acid metabolites in cardiovascular and metabolic diseases. *International Journal of Molecular Sciences, 19*(11), art. no. E3285. https://doi.org/10.3390/ijms19113285
164. Steck, S.E., Chalecki, A.M., Miller, P., Conway, J., Austin, G.L., Hardin, J.W., Albright, C.D., Thuillier, P. (2007). Conjugated linoleic acid supplementation for twelve weeks increases lean body mass in obese humans. *The Journal of Nutrition, 137*(5), 1188–1193. https://doi.org/10.1093/jn/137.5.1188
165. Stohs, S.J., Preuss, H.G., Keith, S.C., Keith, P.L., Miller, H., Kaats, G.R. (2011). Effects of *p*-synephrine alone and in combination with selected bioflavonoids on resting metabolism, blood pressure, heart rate and self-reported mood changes. *International Journal of Medical Sciences, 8*(4), 295–301. https://doi.org/10.7150/ijms.8.295
166. Stone, K.P., Wanders, D., Calderon, L.F., Spurgin, S.B., Scherer, P.E., Gettys, T.W. (2015). Compromised responses to dietary methionine restriction in adipose tissue but not liver of ob/ob mice. *Obesity (Silver Spring, Md.), 23*(9), 1836–1844. https://doi.org/10.1002/oby.21177
167. Strålsjö, L., Alklint, C., Olsson, M.E., Sjöholm, I. (2003). Total folate content and retention in rosehips (*Rosa* ssp.) after drying. *Journal of Agricultural and Food Chemistry, 51*(15), 4291–4295. https://doi.org/10.1021/jf034208q
168. Suárez-Zamorano, N., Fabbiano, S., Chevalier, C., Stojanović, O., Colin, D.J., Stevanović, A., Veyrat-Durebex, C., Tarallo, V., Rigo, D., Germain, S., Ilievska, M., Montet, X., Seimbille, Y., Hapfelmeier, S., Trajkovski, M. (2015). Microbiota depletion promotes browning of white adipose tissue and reduces obesity. *Nature Medicine, 21*(12), 1497–1501. https://doi.org/10.1038/nm.3994
169. Sun, J. (2007). D-Limonene: safety and clinical applications. *Alternative Medicine Review: A Journal of Clinical Therapeutic, 12*(3), 259–264.
170. Sun, Y., Qiao, L., Shen, Y., Jiang, P., Chen, J., Ye, X. (2013). Phytochemical profile and antioxidant activity of physiological drop of citrus fruits. *Journal of Food Science, 78*(1), C37–42. https://doi.org/10.1111/j.1750-3841.2012.03002.x
171. Suresh, D., Srinivasan, K. (2010). Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. *The Indian Journal of Medical Research, 131*, 682–691.
172. Taber, L., Chiu, C.H., Whelan, J. (1998). Assessment of the arachidonic acid content in foods commonly consumed in the American diet. *Lipids, 33*(12), 1151–1157. https://doi.org/10.1007/s11745-998-0317-4
173. Tazoe, H., Otomo, Y., Kaji, I., Tanaka, R., Karaki, S.-I., Kuwahara, A. (2008). Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. *Journal of Physiology and Pharmacology, 59*(Suppl 2), 251–262.
174. Tourniaire, F., Musinovic, H., Gouranton, E., Astier, J., Marcotorchino, J., Arreguin, A., Bernot, D., Palou, A., Bonet, M.L., Ribot, J., Landrier, J.-F. (2015). All-*trans* retinoic acid induces oxidative phosphorylation and mitochondria biogenesis in adipocytes. *Journal of Lipid Research, 56*(6), 1100–1109. https://doi.org/10.1194/jlr.M053652
175. Ueland, P.M. (2011). Choline and betaine in health and disease. *Journal of Inherited Metabolic Disease, 34*(1), 3–15. https://doi.org/10.1007/s10545-010-9088-4
176. Unno, Y., Yamamoto, H., Takatsuki, S., Sato, Y., Kuranaga, T., Yazawa, K., Ono, Y., Wakimoto, T. (2018). Palmitoyl lactic acid induces adipogenesis and a brown fat-like phenotype in 3T3-L1 preadipocytes. *Biochimica Et Biophysica Acta. Molecular and Cell Biology of Lipids, 1863*(7), 772–782. https://doi.org/10.1016/j.bbalip.2018.04.003
177. Varela, C.E., Rodriguez, A., Romero-Valdovinos, M., Mendoza-Lorenzo, P., Mansour, C., Ceballos, G., Villarreal, F., Ramirez-Sanchez, I. (2017). Browning effects of (–)-epicatechin on adipocytes and white adipose tissue. *European Journal of Pharmacology, 811*, 48–59. https://doi.org/10.1016/j.ejphar.2017.05.051
178. Vattem, D.A., Shetty, K. (2005). Biological functionality of ellagic acid: a review. *Journal of Food Biochemistry, 29*(3), 234–266. https://doi.org/10.1111/j.1745-4514.2005.00031.x
179. Velickovic, K., Wayne, D., Leija, H.A.L., Bloor, I., Morris, D.E., Law, J., Budge, H., Sacks, H., Symonds, M.E., Sottile, V. (2019). Caffeine exposure induces browning features in adipose tissue *in vitro* and *in vivo*. *Scientific Reports, 9*(1), art. no. 9104. https://doi.org/10.1038/s41598-019-45540-1

180. Verhoeven, N.M., Jakobs, C. (2001). Human metabolism of phytanic acid and pristanic acid. *Progress in Lipid Research, 40*(6), 453–466. https://doi.org/10.1016/S0163-7827(01)00011-X
181. Villarroya, F., Cereijo, R., Villarroya, J., Giralt, M. (2017). Brown adipose tissue as a secretory organ. *Nature Reviews. Endocrinology, 13*(1), 26–35. https://doi.org/10.1038/nrendo.2016.136
182. Vissers, M.N., Zock, P.L., Katan, M.B. (2004). Bioavailability and antioxidant effects of olive oil phenols in humans: a review. *European Journal of Clinical Nutrition, 58*(6), 955–965. https://doi.org/10.1038/sj.ejcn.1601917
183. Walle, T., Hsieh, F., DeLegge, M.H., Oatis, J.E., Walle, U.K. (2004). High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metabolism and Disposition, 32*(12), 1377–1382. https://doi.org/10.1124/dmd.104.000885
184. Walle, T., Otake, Y., Brubaker, J.A., Walle, U.K., Halushka, P.V. (2001). Disposition and metabolism of the flavonoid chrysin in normal volunteers. *British Journal of Clinical Pharmacology, 51*(2), 143–146. https://doi.org/10.1111/j.1365-2125.2001.01317.x
185. Wanders, D., Forney, L.A., Stone, K.P., Burk, D.H., Pierse, A., Gettys, T.W. (2017). FGF21 mediates the thermogenic and insulin-sensitizing effects of dietary methionine restriction but not its effects on hepatic lipid metabolism. *Diabetes, 66*(4), 858–867. https://doi.org/10.2337/db16-1212
186. Wanders, D., Stone, K.P., Dille, K., Simon, J., Pierse, A., Gettys, T.W. (2015). Metabolic responses to dietary leucine restriction involve remodeling of adipose tissue and enhanced hepatic insulin signaling. *BioFactors (Oxford, England), 41*(6), 391–402. https://doi.org/10.1002/biof.1240
187. Wang, B., Fu, X., Liang, X., Deavila, J.M., Wang, Z., Zhao, L., Tian, Q., Zhao, J., Gomez, N.A., Trombetta, S.C., Zhu, M.-J., Du, M. (2017). Retinoic acid induces white adipose tissue browning by increasing adipose vascularity and inducing beige adipogenesis of PDGFRα+ adipose progenitors. *Cell Discovery, 3*, art. no. 17036. https://doi.org/10.1038/celldisc.2017.36
188. Wang, J., Ke, W., Bao, R., Hu, X., Chen, F. (2017). Beneficial effects of ginger *Zingiber officinale Roscoe* on obesity and metabolic syndrome: a review. *Annals of the New York Academy of Sciences, 1398*(1), 83–98. https://doi.org/10.1111/nyas.13375
189. Wang, J., Li, D., Wang, P., Hu, X., Chen, F. (2019). Ginger prevents obesity through regulation of energy metabolism and activation of browning in high-fat diet-induced obese mice. *The Journal of Nutritional Biochemistry, 70*, 105–115. https://doi.org/10.1016/j.jnutbio.2019.05.001
190. Wang, L., Wei, Y., Ning, C., Zhang, M., Fan, P., Lei, D., Du, J., Gale, M., Ma, Y., Yang, Y. (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. https://doi.org/10.1507/endocrj.EJ18-0467
191. Wang, S., Liang, X., Yang, Q., Fu, X., Rogers, C.J., Zhu, M., Rodgers, B.D., Jiang, Q., Dodson, M.V., Du, M. (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. https://doi.org/10.1038/ijo.2015.23
192. Wang, Shan, Wang, X., Ye, Z., Xu, C., Zhang, M., Ruan, B., Wei, M., Jiang, Y., Zhang, Y., Wang, L., Lei, X., Lu, Z. (2015). Curcumin promotes browning of white adipose tissue in a norepinephrine-dependent way. *Biochemical and Biophysical Research Communications, 466*(2), 247–253. https://doi.org/10.1016/j.bbrc.2015.09.018
193. Wang, Y., Xin, X., Jin, Z., Hu, Y., Li, X., Wu, J., Jin, M. (2011). Anti-diabetic effects of pentamethylquercetin in neonatally streptozotocin-induced diabetic rats. *European Journal of Pharmacology, 668*(1–2), 347–353. https://doi.org/10.1016/j.ejphar.2011.06.022
194. Watras, A.C., Buchholz, A.C., Close, R.N., Zhang, Z., Schoeller, D.A. (2007). The role of conjugated linoleic acid in reducing body fat and preventing holiday weight gain. *International Journal of Obesity (2005), 31*(3), 481–487. https://doi.org/10.1038/sj.ijo.0803437
195. Weitkunat, K., Stuhlmann, C., Postel, A., Rumberger, S., Fankhänel, M., Woting, A., Petzke, K.J., Gohlke, S., Schulz, T.J., Blaut, M., Klaus, S., Schumann, S. (2017). Short-chain fatty acids and inulin, but not guar gum, prevent diet-induced obesity and insulin resistance through differential mechanisms in mice. *Scientific Reports, 7*(1), art. no. 6109. https://doi.org/10.1038/s41598-017-06447-x
196. Wendel, A.A., Purushotham, A., Liu, L.-F., Belury, M.A. (2009). Conjugated linoleic acid induces uncoupling protein 1 in white adipose tissue of ob/ob mice. *Lipids, 44*(11), 975–982. https://doi.org/10.1007/s11745-009-3348-9
197. Weng, Q., Chen, L., Ye, L., Lu, X., Yu, Z., Wen, C., Chen, Y., Huang, G. (2019). Determination of licochalcone A in rat plasma by UPLC–MS/MS and its pharmacokinetics. *Acta Chromatographica, 31*(4), 262–265. https://doi.org/10.1556/1326.2018.00491
198. Wijerathne, T.D., Kim, J.H., Kim, M.J., Kim, C.Y., Chae, M.R., Lee, S.W., Lee, K.P. (2019). Onion peel extract and its constituent, quercetin inhibits human Slo3 in a pH and calcium dependent manner. *The Korean Journal of Physiology & Pharmacology, 23*(5), 381–392. https://doi.org/10.4196/kjpp.2019.23.5.381
199. Wisniewski, O., Malinowska, M., Gibas-Dorna, M. (2018). Physiologically-induced adipocyte browning. *Advances in Hygiene and Experimental Medicine, 72*, 499–511. https://doi.org/10.5604/01.3001.0012.0757
200. Wisniewski, O.W. (2019). Physiology of adipose tissue. In H. Krauss (Eds.), *Physiology of Nutrition*, PZWL Wydawnictwo Lekarskie, Warsaw, Poland, pp. 25–56.
201. Wong, J.M.W., de Souza, R., Kendall, C.W.C., Emam, A., Jenkins, D.J.A. (2006). Colonic health: fermentation and short chain fatty acids. *Journal of Clinical Gastroenterology, 40*(3), 235–243. https://doi.org/10.1097/00004836-200603000-00015
202. Wu, J., Boström, P., Sparks, L.M., Ye, L., Choi, J.H., Giang, A.-H., Khandekar, M., Nuutila, P., Schaart, G., Huang, K., Tu, H., van Marken Lichtenbelt, W.D., Hoeks, J., Enerbäck, S., Schrauwen, P., Spiegelman, B.M. (2012). Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell, 150*(2), 366–376. https://doi.org/10.1016/j.cell.2012.05.016

203. Xing, T., Kang, Y., Xu, X., Wang, B., Du, M., Zhu, M.-J. (2018). Raspberry supplementation improves insulin signaling and promotes brown-like adipocyte development in white adipose tissue of obese mice. *Molecular Nutrition & Food Research, 62*(5), art. no. 1701035. https://doi.org/10.1002/mnfr.201701035
204. Yoneshiro, T., Aita, S., Matsushita, M., Kayahara, T., Kameya, T., Kawai, Y., Iwanaga, T., Saito, M. (2013). Recruited brown adipose tissue as an antiobesity agent in humans. *The Journal of Clinical Investigation, 123*(8), 3404–3408. https://doi.org/10.1172/JCI67803
205. Yuzbashian, E., Zarkesh, M., Asghari, G., Hedayati, M., Safarian, M., Mirmiran, P., Khalaj, A. (2018). Is apelin gene expression and concentration affected by dietary intakes? A systematic review. *Critical Reviews in Food Science and Nutrition, 58*(4), 680–688. https://doi.org/10.1080/10408398.2016.1262325
206. Zhang, F., Ai, W., Hu, X., Meng, Y., Yuan, C., Su, H., Wang, L., Zhu, X., Gao, P., Shu, G., Jiang, Q., Wang, S. (2018). Phytol stimulates the browning of white adipocytes through the activation of AMP-activated protein kinase (AMPK) α in mice fed high-fat diet. *Food & Function, 9*(4), 2043–2050. https://doi.org/10.1039/C7FO01817G
207. Zhang, H.Q., Chen, S.Y., Wang, A.S., Yao, A.J., Fu, J.F., Zhao, J.S., Chen, F., Zou, Z.Q., Zhang, X.H., Shan, Y.J., Bao, Y.P. (2016). Sulforaphane induces adipocyte browning and promotes glucose and lipid utilization. *Molecular Nutrition & Food Research, 60*(10), 2185–2197. https://doi.org/10.1002/mnfr.201500915
208. Zhang, M., Xin, Y., Feng, K., Yin, B., Kan, Q., Xiao, J., Cao, Y., Ho, C.-T., Huang, Q. (2020). Comparative analyses of bioavailability, biotransformation, and excretion of nobiletin in lean and obese rats. *Journal of Agricultural and Food Chemistry, 68*(39), 10709–10718. https://doi.org/10.1021/acs.jafc.0c04425
209. Zhang, X., Zhang, Q.-X., Wang, X., Zhang, L., Qu, W., Bao, B., Liu, C.-A., Liu, J. (2016). Dietary luteolin activates browning and thermogenesis in mice through an AMPK/PGC1α pathway-mediated mechanism. *International Journal of Obesity 40*(12), 1841–1849. https://doi.org/10.1038/ijo.2016.108
210. Zhao, D., Yuan, B., Kshatriya, D., Polyak, A., Simon, J., Bello, N., Wu, Q. (2019). Bioavailability and metabolism of raspberry ketone with potential implications for obesity prevention (OR34–05–19). *Current Developments in Nutrition, 3*(Suppl. 1), art. no. nzz031.OR34–05–19. https://doi.org/10.1093/cdn/nzz031.OR34-05-19
211. Zhao, M., Chen, X. (2014). Eicosapentaenoic acid promotes thermogenic and fatty acid storage capacity in mouse subcutaneous adipocytes. *Biochemical and Biophysical Research Communications, 450*(4), 1446–1451. https://doi.org/10.1016/j.bbrc.2014.07.010
212. Zhuang, P., Lu, Y., Shou, Q., Mao, L., He, L., Wang, J., Chen, J., Zhang, Y., Jiao, J. (2019). Differential anti-adipogenic effects of eicosapentaenoic and docosahexaenoic acids in obesity. *Molecular Nutrition & Food Research, 63*(14), art. no. e1801135. https://doi.org/10.1002/mnfr.201801135
213. Zhuang, P., Shou, Q., Lu, Y., Wang, G., Qiu, J., Wang, J., He, L., Chen, J., Jiao, J., Zhang, Y. (2017). Arachidonic acid sex-dependently affects obesity through linking gut microbiota-driven inflammation to hypothalamus-adipose-liver axis. *Biochimica Et Biophysica Acta. Molecular Basis of Disease, 1863*(11), 2715–2726. https://doi.org/10.1016/j.bbadis.2017.07.003
214. Zou, T., Chen, D., Yang, Q., Wang, B., Zhu, M.-J., Nathanielsz, P.W., Du, M. (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. https://doi.org/10.1113/JP273478
215. Zou, T., Wang, B., Yang, Q., de Avila, J.M., Zhu, M.-J., You, J., Chen, D., Du, M. (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 Biochemistry*, *55*, 157–164. https://doi.org/10.1016/j.jnutbio.2018.02.005
216. Zu, Y., Overby, H., Ren, G., Fan, Z., Zhao, L., Wang, S. (2018). Resveratrol liposomes and lipid nanocarriers: Comparison of characteristics and inducing browning of white adipocytes. *Colloids and Surfaces B: Biointerfaces, 164*, 414–423. https://doi.org/10.1016/j.colsurfb.2017.12.044