

Review Article

Econutrition, brown and beige fat tissue and obesity

Kelei Li PhD¹, Chunxiao Liu MM¹, Mark L Wahlqvist MD^{1,2,3,4}, Duo Li PhD^{1,5,6}

¹Institute of Nutrition and Health, Qingdao University, Qingdao, China

²Monash Asia Institute, Monash University, Melbourne, Australia

³China Medical University, Taichung, Taiwan

⁴National Health Research Institutes, Zhunan, Taiwan

⁵Department of Food Science and Nutrition, Zhejiang University, Hangzhou, China

⁶Department of Nutrition, Dietetics and Food, Monash University, Melbourne, Australia

Background and Objectives: Obesity is caused by excessive fat accumulation or abnormal fat distribution and has become one of the biggest health challenges worldwide. Considering the high thermogenic ability of brown fat tissue (BAT) and the plasticity of fat tissue, to induce the browning of white fat tissue (WAT), so increasing BAT activity provides an attractive option for the prevention and resolution of obesity. The aim of the present narrative review was to understand the relationship between diet, BAT, and obesity. **Methods and Study Design:** PubMed and Embase databases were searched to identify eligible studies. **Results:** Although cold exposure has long been known to be effective in the browning of WAT and activation of BAT, it is societally impractical for everyday body weight management aside from the tolerance of ambient temperature. An alternative is to identify specific dietary components with similar effects to cold exposure on BAT. Current evidence indicates that capsaicin and capsinoids, catechins, curcumin, quercetin, berberine, lipoic acid, polyunsaturated fatty acids, royal jelly, and some natural sweeteners are effective promoters of WAT browning, increase BAT activity and improve obesity related traits. However, only capsaicin, capsinoids, and catechins have demonstrated efficacy in clinical trials. Evidence for effects of curcumin, quercetin, berberine, lipoic acid, polyunsaturated fatty acids, royal jelly and natural sweeteners on BAT have only been observed in animal or in vitro studies, with clinical trials awaited for verification. **Conclusions:** Several dietary components can induce WAT browning and activate BAT, offering potential targets for obesity prevention and management.

Key Words: diet, brown fat tissue, energy metabolism, obesity, overweight

INTRODUCTION

Obesity is a chronic metabolic disease, caused by excessive fat accumulation or abnormal fat distribution. When the body intakes more energy than it consumes, excess energy will be stored in the form of fat, eventually leading to obesity. Obesity has become one of the biggest health challenges worldwide and is associated with many disorders and diseases, such as metabolic syndromes, hypertension, type 2 diabetes mellitus, cardiovascular disease, some cancers, neurodegenerative diseases and problems with mental health.^{1,2} In 2010, it was estimated that global overweight and obesity resulted in 3.4 million deaths.³

Adipose tissue types are referred to as white adipose tissue (WAT) and brown adipose tissue (BAT). White fat that undergoes browning in response to environmental and physiological stimuli is referred to as beige fat.^{4,6} White fat can store excess food energy in the form of triglycerides, while brown fat is a specialized thermogenic organ that can burn energy mainly through the oxidation of lipids (and possibly glucose) coming from blood to generate heat, which is necessary for mammals to maintain body temperature in the cold.^{6,7} The intake of certain dietary components⁸ or specific diets⁹ can lead to browning of WAT. Therefore, brown fat activation through diet

might be an attractive target in the prevention and therapy of obesity.¹⁰ The present study systematically reviews recent evidence for relationships between diet, BAT, and obesity.

Brown adipose tissue

BAT is formed by multilocular brown adipocytes, and mainly distributed in intrascapular, axillae, paravertebral, and perirenal regions in humans.⁴ It is present in rodents throughout life, but in humans is found mainly in newborns and degenerates with age.^{4,11} An autopsy study confirmed the presence of BAT in young adults but not the elderly.¹² BAT is a main thermogenic site in mammals. It is estimated that the heat produced by BAT is up to 300 times of that produced by most other tissues of the same weight.¹³ It contains a large number of mitochondria enriched in uncoupling protein 1 (UCP1) and has a relative-

Corresponding Author: Prof Duo Li, Institute of Nutrition and Health, Qingdao University, 308 Ningxia Road, Qingdao 266071, China.

Tel: +86 532 82991018

Email: duoli@qdu.edu.cn

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ly small capacity for fat storage.^{4,14} UCP1 is a transmembrane protein in the mitochondrial inner membrane and exclusively expressed in brown adipocytes. It can uncouple adenosine triphosphate (ATP) production from lipid and carbohydrate catabolic pathways, and thus lead to conversion of chemical energy to heat.^{15,16}

Fat tissue has plasticity (Figure 1). After various environmental and physiological stimuli, brown adipocytes may appear, which is referred to browning of WAT or the development of beige fat.⁷ Cold exposure could recruit BAT even in middle-aged and elderly subjects.^{5,17,18} A randomized controlled trial has indicated that a β 3-adrenergic receptor agonist, effective in the treatment of overactive bladder, could lead to higher BAT metabolic activity compared to placebo.¹⁹ Certain dietary components⁸ or specific diet⁹ intake have similar effects.

Relationship between brown adipose tissue and obesity

Observational studies indicate that BAT presence is associated with less obesity and metabolic dysfunction, evidenced by narrower waist circumference, along with lower body mass index (BMI), visceral fat areas, subcutaneous fat area, serum triglycerides and glucose, and increased high density lipoprotein cholesterol (HDL-C).²⁰⁻²² The effect of cold exposure on BAT activation is associated with BMI: lean men have a significantly higher BAT activity than do overweight/obese men after cold exposure, and higher BAT activity is associated with a lower BMI and percentage of body fat.²³

Animal study provides substantial evidence for a role of BAT in obesity. Lowell et al created two lines of transgenic mice, UCP-DTA and UCP-176, both of which exhibited BAT ablation at age 16 days.²⁴ Interestingly, UCP-DTA mice remained BAT deficient with age, while UCP-176 regenerated BAT by age 8 weeks. Both lines developed obesity with BAT ablation at age 16 days.

However, obesity in the UCP-176 line resolved with BAT regeneration by age 8 weeks, but not in mice line UCP-DTA.

Diet, brown adipose tissue and energy metabolism

Current evidence indicates that several diet components have beneficial effects on obesity by affecting BAT and energy metabolism, including capsaicin and capsinoids, catechins, curcumin, quercetin, polyunsaturated fatty acid (PUFA), berberine, lipoic acid, royal jelly, and natural sweeteners. The food sources²⁵⁻³⁵ and function of the potential BAT promoters above are shown in Table 1.

Capsaicin and capsinoids

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is an important active ingredient of chili pepper, which can be absorbed from the gastrointestinal tract.³⁶ It is an amide responsible for the pungent feeling with intake of the genus capsicum and can be used as a food additive.^{37,38} A randomized controlled trial (RCT) indicates that red pepper intake can increase thermogenesis and lipid oxidation.³⁹ Animal studies demonstrate that capsaicin can increase energy metabolism, induce browning of WAT and protect against obesity through β -adrenergic action and the transient receptor potential vanilloid 1 (TRPV1, a capsaicin receptor) channel.^{40,41} A cell study indicates that capsaicin can target late-stage brown adipogenesis by increasing the expression of fatty acid-binding protein 4 (FABP4) (a marker of maturation in white and brown adipocytes), peroxisome proliferator-activated receptor γ 2 (PPAR γ 2) (a master regulator of white and brown adipogenesis) and PPAR γ coactivator-1 α (PGC1 α , another principle gene for thermogenesis in brown adipocytes except UCP1).⁴²

RCTs indicate that capsinoids can increase body temperature and oxygen consumption, thermogenesis, energy

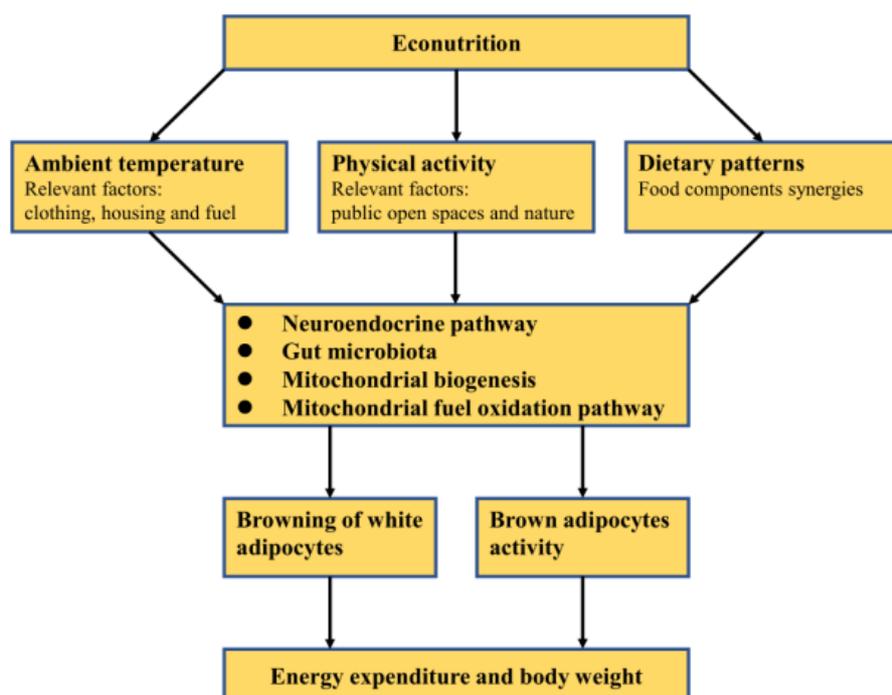


Figure 1. Summary of relationships between econutrition, BAT and body weight.

Table 1. Food sources and function of potential BAT promoters

Potential BAT promoters	Common food sources	Function assessment			
		Study	Study design	Dose	Function
Capsaicin	<i>Capsicum</i> genus, such as chili pepper	Yoshioka et al. 1998 ³⁹	RCT with a parallel design	Single ingestion of a meal containing 10 g red pepper	Increase thermogenesis and lipid oxidation
		Baskaran et al. 2016 ⁴⁰	Mice study	Diet containing 0.01% capsaicin for 26 weeks	Induce browning of WAT and protect against obesity via activating TRPV1 channel
		Kawada et al. 1986 ⁴¹	Rats study	Single intraperitoneal injection of 3mg or 6 mg/kg capsaicin	6 mg/kg capsaicin treatment enhance energy metabolism via beta-adrenergic action
		Kida et al. 2016 ⁴²	Cell study	Culture medium containing 0.1, 1 or 10 μ M capsaicin for 12 days	Target late-stage brown adipogenesis by increasing the expression of FABP4, PPAR γ 2 and PGC1 α
Capsinoids	Non-pungent pepper, such as CH-19 sweet pepper	Josse et al. 2010 ⁴³	RCT with a crossover design	Single ingestion of 10 mg capsinoids	Increase adrenergic activity, oxygen consumption, and energy expenditure
		Ohnuki et al. 2001 ⁴⁴	RCT with a parallel design	Single ingestion of 0.1 g/kg CH-19 Sweet	Increase body temperature, oxygen consumption, thermogenesis and energy consumption
		Sun et al. 2018 ⁴⁵	RCT with a crossover design	Single ingestion of 12 mg capsinoids	Increase energy expenditure and weakly stimulate BAT
		Yoneshiro et al. 2013 ¹⁸	RCT with a crossover design	9 mg capsinoids/day for 6 weeks	Increase energy expenditure
		Shintaku et al. 2012 ⁴⁶	Cell study	Culture medium containing various concentrations of capsinoids to test dose-response relationship for TRP channel	Activate TRP channel
Catechins	Tea, legumes, apples, cocoa beans, grapes, buckwheat, litchis	Nagao et al. 2005 ⁵³	RCT with a parallel design	Tea containing 690 mg catechins/day for 12 weeks	Decrease body weight, BMI, waist circumference, body fat mass, and subcutaneous fat area
		Maki et al. 2009 ⁵⁴	RCT with a parallel design	Beverage containing 625 mg catechins/day for 12 weeks	Reduce total abdominal fat area, subcutaneous abdominal fat area and fasting serum triglycerides
		Nirengi et al. 2016 ⁵⁵	RCT with a parallel design	Beverage containing 540 mg catechin/day for 12 weeks	Increase BAT density and decrease extramyocellular lipid
Catechins		Yoneshiro et al. 2017 ⁵⁶	RCT with a crossover design	Single ingestion of beverage containing 615 mg catechin Ingestion of beverage containing 615 mg catechin 2 times/day for 5 weeks	Increase energy expenditure Increase cold-induced thermogenesis
		Nomura et al. 2008 ⁵⁷	Rats study	Diet containing 0.5% catechin for 8 weeks	Inhibit body fat accumulation in rats by increased expression of UCP1

BAT: brown fat tissue; RCT: randomized controlled trial; WAT: white adipose tissue; TRPV1: transient receptor potential vanilloid 1; FABP4: fatty acid-binding protein 4; PPAR γ 2: peroxisome proliferator-activated receptor; PGC1 α : PPAR γ coactivator-1 α ; UCP1: uncoupling protein 1; TG: triacylglycerol; HDL-C: high density lipoprotein cholesterol; PRDM16: PR domain-containing 16; AMPK: adenosine 5'-monophosphate-activated protein kinase; SBP: systolic blood pressure; PDH: pyruvate dehydrogenase; RBC: red blood cell; PUFA: polyunsaturated fatty acids; LC: long-chain; COX-IV: cytochrome c oxidase subunit IV.

Table 1. Food sources and function of potential BAT promoters (cont.)

Potential BAT promoters	Common food sources	Function assessment			Function
		Study	Study design	Dose	
		Kurogi et al. 2015 ⁵⁸	Cell study	Culture medium containing 2, 20, 100, or 200 µM epigallocatechin gallate	Activate the TRP channel
		Choo et al. 2003 ⁶⁰	Rats study	Diet containing 2% dry matter of water extract of green tea for 14 days	Inhibit high-fat-diet induced body fat gain, and increase energy expenditure and protein content in the interscapular BAT
Curcumin	Rhizome of <i>curcuma longa</i>	Saraf-Bank et al. 2019 ⁶²	RCT with a parallel design	500 mg tablet containing 95% turmeric extract/day for 10 weeks	Decrease BMI, waist and hip circumference, TG/HDL-C ratio; increase HDL-C
		Nishikawa et al. 2018 ⁶³	Mice study	Intragastric intubation of 1.5 or 4.5 mg native curcumin/kg per day for 4 weeks	Increase energy expenditure by inducing the formation of brown-like adipocytes
		Nishikawa et al. 2019 ⁶⁴	Mice study	1.5 mg/kg curcumin plus 5 mg/kg artemisinin C per day for 4 weeks	Enhance the formation of brown-like adipocytes
		Lone et al. 2016 ⁶⁵	Cell study	Culture medium containing 20 µM curcumin for 6-8 days	Induce WAT browning, increase mitochondrial biogenesis, suppress lipogenesis and up-regulated brown-specific markers such as UCP1, PGC1α, and PRDM16 by activating AMPK pathway
		Nalli et al. 2017 ⁶⁶	Cell study	Culture medium containing various concentrations of curcumin to test dose-response relationship for TRP channel	Act as a good modulator of TRPA1 channel (EC ₅₀ = 3.3 µM)
Quercetin	Fruits and vegetables, such as apples, berries, <i>Brassica</i> vegetables, capers, grapes, onions, shallots, tea, tomatoes	Huang et al. 2019 ⁶⁷	Meta-analysis of 9 RCTs	Dose ranging from 100-1000 mg/day; duration ranging from 4-12 weeks	Have no significant effect on weight loss
		Kim et al. 2015 ⁶⁸	RCT with a parallel design	100 mg quercetin-rich onion peel extract/day for 12 weeks	Reduce waist and hip circumference
		Lee et al. 2016 ⁶⁹	RCT with a parallel design	Onion peel extract containing 100 mg quercetin/day for 12 weeks	Reduce body weight and percentage of body fat; increase respiratory quotient
		Pfeuffer et al. 2013 ⁷⁰	RCT with a crossover design	150 mg/day quercetin for 8 weeks	Decrease waist circumference, SBP and TG; increase HDL-C
		Lee et al. 2017 ⁷¹	Mice study	Diet containing 0.5% onion peel extract	Induce WAT browning, up-regulate the expression of BAT specific genes by activating AMPK pathway

BAT: brown fat tissue; RCT: randomized controlled trial; WAT: white adipose tissue; TRPV1: transient receptor potential vanilloid 1; FABP4: fatty acid-binding protein 4; PPARγ2: peroxisome proliferator-activated receptor; PGC1α: PPARγ coactivator-1α; UCP1: uncoupling protein 1; TG: triacylglycerol; HDL-C: high density lipoprotein cholesterol; PRDM16: PR domain-containing 16; AMPK: adenosine 5'-monophosphate-activated protein kinase; SBP: systolic blood pressure; PDH: pyruvate dehydrogenase; RBC: red blood cell; PUFA: polyunsaturated fatty acids; LC: long-chain; COX-IV: cytochrome c oxidase subunit IV.

Table 1. Food sources and function of potential BAT promoters (cont.)

Potential BAT promoters	Common food sources	Function assessment			
		Study	Study design	Dose	Function
Berberine	Medicinal plants such as <i>hydrastis canadensis</i> , <i>berberis aristata</i> , <i>coptis chinensis</i> , <i>coptis japonica</i> , <i>phellodendron amurense</i> and <i>phellodendron chinense schneid</i>	Hu et al. 2012 ⁷²	Pilot study in humans and rats study	1500 mg berberine/day for 12 weeks in humans; 380 mg/kg berberine per day in rats	Protect against obesity and lower blood lipids in humans and rats
		Zhang et al. 2014 ⁷³	Mice and cell study	5 mg/kg berberine per day for 4 weeks in rats; 0.5 or 2.5 μM berberine for 24 h in cells	Enhance BAT activity and promote WAT browning by increasing AMPK phosphorylation and the expression of PGC1α and UCP1
		Wu et al. 2019 ⁷⁴	Human, mice and cell study	1.5 g berberine per day for 1 month in humans; 1.5 mg/kg berberine per day for 6 weeks in mice; 0.0625, 0.125, 0.25 or 0.5 μM berberine in cells	Activate BAT via AMPK-PRDM16 pathway
Lipoic acid	Green vegetables, organ meats and yeast	Huerta et al. 2015 ⁷⁵	RCT with a parallel design	0.3 g/day lipoic acid for 10 weeks	Lower body weight
		Koh et al. 2011 ⁷⁶	RCT with a parallel design	1.2 or 1.8 g/day lipoic acid for 20 weeks	1.8 g/d lipoic acid lower body weight
		Tajima et al. 2019 ⁷⁷	Mice study	30 mg/kg lipoic acid for 28 days	Restore BAT thermogenesis and improve age-associated obesity by increasing mitochondrial lipoylation and enzymatic activity of PDH
		Nikolai et al. 2014 ⁷⁸	Mice study	Diet containing 0.1 lipoic acid for 16 weeks	Increase energy expenditure and up-regulate the expression of thermogenic genes in BAT (such as UCP1 and PGC1α)
		Fernández-Galilea et al. 2015 ⁷⁹	Cell study	100 or 250 μM lipoic acid for 24 h	Increases mitochondrial biogenesis and promote beige adipose features in subcutaneous adipocytes
Phyllodulcin	Hydrangea	Kim et al. 2017 ³⁵		20 or 40 mg/kg phyllodulcin per day for 7 weeks	Shift the white adipose configuration to beige

BAT: brown fat tissue; RCT: randomized controlled trial; WAT: white adipose tissue; TRPV1: transient receptor potential vanilloid 1; FABP4: fatty acid-binding protein 4; PPARγ2: peroxisome proliferator-activated receptor; PGC1α: PPARγ coactivator-1α; UCP1: uncoupling protein 1; TG: triacylglycerol; HDL-C: high density lipoprotein cholesterol; PRDM16: PR domain-containing 16; AMPK: adenosine 5'-monophosphate-activated protein kinase; SBP: systolic blood pressure; PDH: pyruvate dehydrogenase; RBC: red blood cell; PUFA: polyunsaturated fatty acids; LC: long-chain; COX-IV: cytochrome c oxidase subunit IV.

Table 1. Food sources and function of potential BAT promoters (cont.)

Potential BAT promoters	Common food sources	Function assessment			
		Study	Study design	Dose	Function
n-3 PUFA	LC n-3 PUFA (No. of carbons ≥ 20): sea-food, such as oily fish and algae. ALA: Flaxseed oil, walnut oil, echium oil, algae oil	Simopoulos et al. 2016 ⁸³	Review	NA	RBC membrane ratio of n-6/n-3 PUFA is positively associated with obesity risk; RBC n-3 PUFA is negatively associated with obesity risk (prospective studies in humans)
		Bender et al. 2014 ⁸⁴	Meta-analysis of RCTs	0.3 to 6 g n-3 PUFA/day; duration ranged from 21 to 1095 days	Lower body weight, BMI, body fat and waist circumference
		Sneddon et al. 2009 ⁸⁵	Rats study	Diet containing 1% conjugated linoleic acid and 1% n-3 LC PUFA for 12 weeks	Increase BAT weight and the expression of UCP1; decrease WAT weight, TG and cholesterol
Conjugated fatty acids	Conjugated linoleic acid: food from ruminant-animal origin, such as beef, sheep and goat meat and dairy products. Conjugated linolenic acid: Tung seed, bitter gourd seed, snake gourd seed, pomegranate seed, trichosanthes seed, pot marigold seed, jacaranda seed, and catalpa seed.	Sneddon et al. 2009 ⁸⁵	Rats study	Diet containing 1% conjugated linoleic acid and 1% n-3 LC PUFA for 12 weeks	Increase BAT weight and the expression of UCP1; decrease WAT weight, TG and cholesterol
Active ingredient on BAT is unknown	Royal jelly	Pourmoradian et al. 2012 ⁸⁷	RCT with a parallel design	1 g royal jelly/day for 8 weeks	Lower body weight
		Yoneshiro et al. 2018 ⁸⁸	Mice study	Diet with 5% royal jelly for 17 weeks	Suppress accumulation of WAT and hepatic TG; promote BAT thermogenesis; up-regulate the expression of UCP1 and COX-IV in BAT

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consumption, adrenergic activity and lipid oxidation.^{43,44}

An acute crossover study found that oral ingestion of capsinoids, non-pungent analogs of capsaicin, can increase energy expenditure (EE) and weakly stimulate BAT, but this effect of capsinoids on EE and BAT is less than that of cold exposure.⁴⁵ Similar effects of capsinoids on EE and BAT have been replicated in another crossover study.¹⁸ Like capsaicin, capsinoids can also activate TRPV1, which probably explains the similar effects of capsaicin and capsinoids on BAT thermogenesis.⁴⁶

Catechins

Catechins are polyphenols found in tea, including epicatechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate and their thermal isomers, such as catechin, catechin gallate, gallic acid, and gallic acid gallate.⁴⁷ Catechins are multifunctionally anti-oxidant, anti-inflammatory, anti-tumor, and obesity protectant, reducing insulin resistance, dyslipidemia, hypertension and atherosclerosis.⁴⁸⁻⁵²

The effect of catechins on BAT, energy metabolism and obesity are evident in several clinical trials. Tea rich in catechins significantly decreased body weight, BMI, waist circumference, body fat mass, and subcutaneous fat area in healthy men.⁵³ They facilitate a reduction of total abdominal fat area, subcutaneous abdominal fat area and fasting serum triglycerides in overweight and obese adults during exercise-induced weight loss compared with placebo.⁵⁴ An increase in BAT density and decreased extramyocellular lipid (EMCL) is found after 12 weeks of catechin-rich beverage intervention compared to placebo, and the changes in BAT density are negatively correlated with those in EMCL.⁵⁵ A crossover study found that catechin supplementation acutely increased EE and chronically increased cold-induced thermogenesis (CIT), a noninvasive predictive index for BAT activity.⁵⁶

The mechanisms by which catechins may affect BAT, energy metabolism and obesity are becoming clear. Catechins inhibit body fat accumulation in rats by increased expression of UCP1.⁵⁷ Cellular biology shows that catechins can activate the TRP channel,⁵⁸ which plays an important role in activation of BAT.⁵⁹ Green tea extracts inhibit high-fat-diet induced body fat gain in rats, and increase EE and protein content in the interscapular BAT by activating the β adrenoceptor.⁶⁰

Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is the main natural polyphenol in the rhizome of turmeric and other *Curcuma spp.*²⁵ Turmeric itself has a long and wide use in food preparation as a food ingredient and in traditional medicine. Curcumin can be used as a food additive.⁶¹

A RCT indicates that curcumin can decrease BMI, waist and hip circumference, increase HDL-C with a decrease in triacylglycerol (TG)/HDL-C ratio in obese and overweight girls.⁶² In an animal study, curcumin increased energy expenditure by inducing brown-like adipocytes formation.^{63,64} In a cell study, curcumin induced browning of WAT, increased mitochondrial biogenesis, suppressed lipogenesis and up-regulated brown-specific markers such as UCP1, PGC1 α , and PR domain-

containing 16 (PRDM16) by activating adenosine 5'-monophosphate-activated protein kinase (AMPK).⁶⁵ Curcumin can also modulate the TRP channel.⁶⁶ However, no human studies have evaluated the relationship between curcumin and BAT or WAT browning.

Quercetin

A meta-analysis of 9 RCTs found no significant effect of quercetin supplementation on weight loss.⁶⁷ Despite this, several RCTs indicate that quercetin improve several other obesity-related traits, such as body fat percentage, waist and hip circumferences, blood pressure, TG and HDL-C.⁶⁸⁻⁷⁰ Studies in animals and cells indicate that quercetin can induce WAT browning, up-regulate the expression of BAT specific genes, including PRDM16, UCP1, fibroblast growth factor 21 (FGF21), cell death-inducing DFFA-like effector (CIDEA), and PGC1 α by activating the AMPK signaling pathway.⁷¹ However, evidence in humans about the role of quercetin in WAT browning is still unavailable.

Berberine

Berberine, an alkaloid found in several traditional Chinese medicinal plants,³² has adipocyte browning properties. The anti-obesity and lipid-lowering effect of berberine has been observed in both human and animal studies.⁷² Previous studies in vivo and in vitro indicated that berberine could enhance BAT activity and promote WAT browning by increasing AMPK phosphorylation and the expression of PGC1 α and UCP1.⁷³ Human, animal and cell studies found that the activation effect of berberine on BAT is dependent on AMPK-PRDM16 pathway, that is, AMPK activation could lead to active DNA demethylation of PRDM16 promoter and thus up-regulate the expression of PRDM16, which could act as a master regulator of brown/beige adipogenesis through its interactions with transcriptional factors such as PPAR γ and PGC-1 α .⁷⁴ However, evidence in humans about the role of berberine in BAT activation or WAT browning is still unavailable.

Lipoic acid

Lipoic acid is the conjugate acid of lipoate, a cofactor of many mitochondrial enzymes usually binding to lysine in proteins.³³ It is found in green vegetables, organ meats and yeast.^{33,34} RCTs demonstrate that lipoic acid has a lowering effect on body weight.^{75,76} Animal study by Tajima et al. indicates that supplementation of lipoic acid can restore BAT thermogenesis and improve age-associated obesity in old mice without influencing BAT-specific thermogenic genes expression (such as UCP1), and the mechanism is that lipoic acid increases mitochondrial lipoylation and then enzymatic activity of pyruvate dehydrogenase (PDH) by enhancing the Bola3-dependent mitochondrial iron-sulfur (Fe-S) cluster formation pathway.⁷⁷ Another animal study found that lipoic acid could increase energy expenditure in mice fed by a high fat diet. However, up-regulation effect of lipoic acid on the expression of thermogenic genes in BAT (such as UCP1 and PGC1 α) was also observed in this study, which was contradictory to the study by Tajima et al.^{77,78} In vitro study indicates that lipoic acid increases mitochondrial biogenesis and promotes beige adipose features in subcu-

taneous adipocytes from overweight/obese subjects.⁷⁹ Previous animal studies indicate that the level of lysine-specific demethylase 1 (LSD1), enzyme that can selectively removes mono- and dimethyl groups from lysine 4 or lysine 9 of histone H3, decreases in inguinal white adipose tissue with aging accompanied by beige fat cell decline, while over-expression of LSD1 could turnover age-related decline of beige adipocytes, increase mitochondrial activity and limit weight gain induced by high-fat diet via targeting PPAR α , indicating that epigenetic modification of histone plays a crucial role in browning of WAT.^{80,81} Cell study found that lipoic acid could inhibit histone deacetylase activity and lead to hyperacetylation of histones.⁸² Considering the lysine bound property of lipoic acid, we hypothesize that affecting demethylation of lysine in histone by lipoic acid may be another possible mechanism for its activation effect on BAT and promotion effect on WAT browning, but this still needs further study to verify. No human study has evaluated the relationship between lipoic acid and WAT browning or BAT browning.

Polyunsaturated fatty acid

Prospective studies found a positive association between risk of obesity and red blood cell (RBC) membrane ratio of n-6/n-3 PUFA, while a negative association was found for RBC n-3 PUFA and obesity risk.⁸³ Meta-analysis based on RCTs indicates that n-3 PUFA supplementation can help lose 0.59 kg more body weight, 0.2 kg/m² more BMI, 0.4% more body fat, and 0.81 cm more waist circumference than controls.⁸⁴ In rats, supplementation with 1% conjugated linoleic acid and 1% n-3 long chain PUFA (n-3 LC PUFA) increases BAT weight, decreases WAT weight, TG and cholesterol, and increases the expression of UCPI.⁸⁵ The n-3 PUFA supplementation leads to an increased food intake without body weight increase compared with a control group.⁸⁵ However, no human study has evaluated the relationship between PUFA and WAT browning or BAT activity.

Royal jelly

Royal jelly is a white sticky substance secreted by the hypopharyngeal and mandibular glands of worker bees, which contains water (50%–60%), proteins (18%), carbohydrates (15%), lipids (3%–6%), mineral salts (1.5%), and vitamins.⁸⁶ An RCT has found a reduction by royal jelly in body weight.⁸⁷ An animal study shows that royal jelly suppresses high-fat-diet induced accumulation of WAT and hepatic TG, promoting BAT thermogenesis by up-regulating the expression of UCPI and mitochondrial cytochrome c oxidase subunit IV (COX-IV) in BAT.⁸⁸ However, no human study is available in support of a relationship between royal jelly and WAT browning or BAT activity.

Natural sweeteners

There is increasing recognition that taste and olfactory receptors are distributed in the body beyond the oro-nasal cavities. A case in point is the sweet receptor which may be present in adipose tissue. Phylloidalin, a natural non-nutritive sweetener, can shift the white adipose configuration to beige.³⁵ Of particular interest is that brain derived

neurotrophic factor (BDNF) is involved as it is in response to walking.^{89,90} The synergistic health possibilities of this conjunction are provocative, as are those for dietary taste preference.

Mechanisms for effects of dietary ingredients on brown adipose tissue

Based on published studies,^{59,74,77,81,91-95} we summarize mechanisms by which dietary factors might induce browning of WAT to become beige fat and activate BAT in Figure 2.

Environmental and behavioural determinants of thermogenic fat

Although most settled people do not have to contend with excessive cold ambient temperatures given their shelter, fuel and clothing, when they do, thermogenic fat tissue increases.¹⁷ The neuroendocrine pathways for regulation of fat type also provide for environmental and behavioral modulation of the amount and activity of brown and beige fat.⁶ Implicitly, opportunities for the regular and life-long stimulation of energy expenditure and fat store utilization through physical activity ought to be conducive to the maintenance of brown fat, rather than its decline, from childhood. Not only might physical activity itself contribute to thermogenic fat maintenance, but so might its type (aerobic, anaerobic or strength) on account of cytokine and hormonal connectedness between muscle, bone and fat⁹⁶ and its location in more or less natural surroundings.

Omental fat, with its neuroendocrine modulation in the hepatic portal circulation, may also be responsive to adipocyte browning with implications for amplification of environmental, behavioral and emotional inputs.⁹⁷

Human microbiomes represent a continuum between us and the ecosystem in which we live. These microbiomes, especially that of the gut, offer a pathway between our fat tissue type profile and the environment, most obviously the food system on which we depend.⁹⁸⁻¹⁰⁰ Xiao et al show that such an axis contributes to energy balance.⁹⁹

However, the maintenance of beige fat has not only to do with energy regulation, but also innate immunity and appropriate inflammatory responsiveness.¹⁰¹⁻¹⁰³

Browning of fat and its activity displays biorhythm, with relevance to sleep¹⁰⁴ further representing ecological connectedness.

An array of ecological and behavioral factors are in play with brown and beige fat in keeping with the understanding of ourselves as socioecological beings¹⁰⁵ and that our nutritional status merits an econutrition insight.^{106,107} In the meantime, while any one food component or food may not alone have the capacity to make a biologically meaningful change to fat browning, a bio-diverse food pattern may in aggregate make a useful contribution to energy regulation and the other functions of this fat tissue. This would be consistent with evidence that dietary diversity confers longer survival and reduced disability^{108,109} with favorable benefit-risk-cost ratios.¹¹⁰ Environmental and physiological factors can modulate beige fat status, and these are potentially amenable to place of abode, occupational, leisure-time and personal behavioral situation.¹⁷ This suggests that optimal health may be predicated on brown and beige fat maintenance

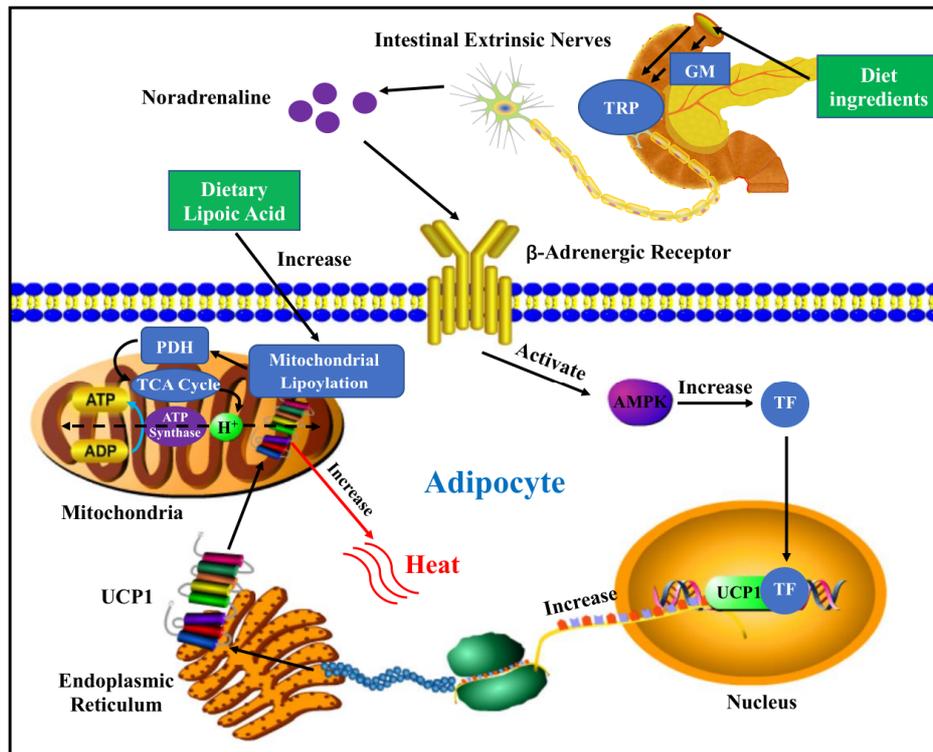


Figure 2. Mechanisms behind the effects of diet ingredients on BAT. Dietary intake of BAT promoters can activate intestinal TRP. BAT promoter intake can also modify the gut microbiome. Whether TRP activation is due to the direct effect of BAT promoters or modification of gut microbiome is still uncertain. The following signal transduction is conducted by intestinal extrinsic nerves, and the neural signal leads to the release of β -adrenergic agents, such as noradrenaline, and thus activates the β -adrenergic receptor of adipocytes. This can activate AMPK, then up-regulate the expression of several transcription factors, such as PPAR α , PPAR γ , PGC1 α and PRDM16, and thus increases the expression of BAT specific genes, especially UCP1. UCP1 can uncouple ATP production from lipid and carbohydrate catabolic pathways, leading to increased heat production. In addition, lipoic acid can elevate the mitochondrial protein lipoylation level, then increase the activity of PDH, and thus enhance mitochondrial fuel oxidation, including the TCA cycle. Enhanced fuel oxidation provides more NADH and FADH₂, which can transfer protons for heat production by UCP1. BAT, brown fat tissue; GM, gut microbiome; TRP, transient receptor potential; AMPK, adenosine 5'-monophosphate-activated protein kinase; PPAR, peroxisome proliferator-activated receptor; PGC1 α , PPAR γ coactivator-1 α ; PRDM16, PR domain-containing 16; UCP1, uncoupling protein 1; ATP, adenosine triphosphate; ADP, adenosine diphosphate; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid.

from early life.⁸¹ It would be a paradigm shift in body compositional nutrition if brown fatness were normalised as a life-long index of health.¹¹¹

Conclusion

Induction of WAT browning and increasing BAT activity by specific dietary factors and probably the foods in which they are found may be targeted for obesity prevention and management.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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