Recent developments in natural products for white adipose tissue browning

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Available online 20 Nov., 2020

[ABSTRACT] Excess accumulation of white adipose tissue (WAT) causes obesity which is an imbalance between energy intake and energy expenditure. Obesity is a serious concern because it has been the leading causes of death worldwide, including diabetes, stroke, heart disease and cancer. Therefore, uncovering the mechanism of obesity and discovering anti-obesity drugs are crucial to prevent obesity and its complications. Browning, inducing white adipose tissue to brown or beige (brite) fat which is brown-like fat emerging in WAT, becomes an appealing therapeutic strategy for obesity and metabolic disorders. Due to lack of efficacy or intolerable side-effects, the clinical trials that promote brown adipose tissue (BAT) thermogenesis and browning of WAT have not been successful in humans. Obviously, more specific means still need to be developed to activate browning of white adipose tissue. In this review, we summarized seven kinds of natural products (alkaloids, flavonoids, terpenoids, long chain fatty acids, phenolic acids, else and extract) promoting white adipose tissue browning which can ameliorate the metabolic disorders, including obesity, dislipidemia, insulin resistance and diabetes. Since natural products are important drug sources and the browning property plays a significant role in not only obesity treatment but also in type 2 diabetes (T2DM) improvement, natural products of inducing browning may be an irreplaceable drug discovery orientation for obesity, diabetes and even other metabolic disorders.

[KEY WORDS] Natural products; Browning; Brown adipose tissue; White adipose tissue; Obesity


Introduction

Obesity is a serious concern as it induces metabolic disorders associated with high morbidity and mortality, including diabetes, hyperlipidemia, heart disease, stroke and cancer, which makes it a pathological condition worldwide. It is reported that the amount of obese people in over 70 countries has been doubled over the past 25 years [1]. Uncovering the mechanism of obesity and exploring the therapeutic strategy are crucial to prevent obesity and its complications.

White adipose tissue, including subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), plays a central role in energy storage and endocrine function [2]. However, brown adipose tissue (BAT) is characterized by the energy expenditure and adipose thermogenesis with unique marker of uncoupling protein-1 (UCP1). BAT can be activated then “burned” under stimulus of exercise, cold exposure or norepinephrine [3]. In addition, inducing VAT to beige (brite) fat which is brown-like fat appearing in VAT becomes a hot research spot of metabolic disorders with the upregulated UCP1 expression in VAT, as well as other thermogenic markers, such as PR domain containing-16 (PRDM-16), peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC1α) and cell death inducing DFFA like effector a (CIDEA) [4].

In recent years, piles of agents with activating adipose tissue burning have been discovered from synthetic chemicals and natural products. They either mediate BAT into beige fat or promote BAT combustion. However, since the volume of BAT in adult humans is much less than VAT, and white fat (particularly visceral fat) is positively associated with metabolic disorders, inducing VAT into BAT becomes a therapeutic strategy of combating obesity [5]. As an irreplaceable drug discovery source, natural products have been exhibiting a great deal of diverse pharmacological activities, like
antibiotic, hepatoprotection, immunomodulatory and anti-cancer effects [6]. The advantage of multi-target and safety makes the natural products worthy of future investigation.

Here we summarize the main kinds of natural products that can induce WAT browning, which may lay the foundation for anti-obesity drug development.

**Alkaloid**

Alkaloids are an important class of naturally occurring organic nitrogen-containing bases, which is found primarily in plants, especially in certain flowering plants, such as opium and ephedrine [7]. Well-known alkaloids include morphine, strychnine, quinine, ephedrine, and nicotine, which exhibit the important and diverse biological activities. Additionally, the novel browning activities of alkaloids will be summarized.

**Capsaicin**

Capsaicin, as a well-known pungent alkaloid molecule found in any fruit belonging to the genus Capsicum (family Solanaceae), is currently used to mitigate pain in neuralgias and neuropathies, induce apoptosis of cancer cells. Regarding the treatment of metabolic disorders, capsaicin can boost glucose uptake, inhibit glucose absorption and stimulate BAT thermogenesis and has been appearing on the marker to treat diabetic neuropathy [9]. Baskaran et al. firstly revealed that capsaicin stimulated browning of WAT via activating transient receptor potential cation channel subfamily V member 1 (TRPV1). 32-Week administration of 0.01% capsaicin led to higher basal metabolism with less weight gain, enhanced heat production and respiratory quotient in diet-induced obesity (DIO) mice. Mechanismly, capsaicin activated TRPV1 channel which induced phosphorylation of peroxisomal proliferator-activated receptor-γ (PPAR-γ) and PRDM-16 through calcium/calmodulin-dependent protein kinase type II alpha chain/5′ adenosine monophosphate-activated protein kinase α (CaMKIIα/AMPKα)-dependent NAD-dependent deacetylase sirtuin-1 (SIRT-1) pathway. Subsequently, the upregulated PGC-1α and PRDM-16 in adipose tissue triggered the molecular process of browning [9]. Moreover, Ritesh et al. demonstrated the browning effects of capsaicin may be correlated with gut microbial, which anti-obesity bacteria Lactobacillus and Bacteroidetes abundance increased while obesity-inducing bacteria Enterobacteriaceae and Firmicutes decreased [10]. Recently, a recruiting clinical trial sponsored by Northwestern University in US contrived to affirm the BAT activation and even generation activity of capsaicin to resist obesity and nutrition disorders in humans [11]. Apart from capsaicin, a nonpungent capsaicin analog of capsiate can also temporarily increase UCP1 expression in BAT but without effects on WAT [12].

**Bouchardatine**

The plant Bouchardatia neurococca contains a lot of bouchardatine with pharmacological activities of anti-inflammation and anti-cardiovascular diseases [13]. Additionally, recent study showed that bouchardatine and its derivatives may reduce lipid accumulation in 3T3-L1 adipocytes mediated by SIRT-1 activation. Male C57BL/6J mice fed on high fat diet (HFD) were intraperitoneally injected with 50 mg·kg⁻¹ bouchardatine every other day. It was observed that body weight gain, glucose and lipid disorders were attenuated with ameliorating fatty liver, glucose tolerance and insulin resistance. More importantly, bouchardatine induced BAT activation and WAT browning with upregulation of UCP1 expression, and prompted mitochondrial biogenesis as well. SIRT1-liver kinase B1 (LKB1)-AMPK axis was responsible for these effects [14].

**Harmine**

Harmine, an alkaloid from South American vine Banisteriopsis caapi, harmal or Syrian rue (Peganum harmala) and tobacco, is characterized as psychoactive component and monoamine oxidase (MAO) inhibitor [15]. In addition, previous studies demonstrated that harmine can make insulin receptor sensitive in db/db mice by regulating PPAR-γ expression [16]. Recently, Nie, et al found that harmine administration (50 mg·kg⁻¹ for 8 weeks) was able to resist HFD-induced obesity and metabolism disorders through gaining less weight, decreasing free fatty acid, steroid and triglyceride (TG) in plasma and improving insulin sensitivity. Energy metabolism with O₂ consumption and heat generation was significantly increased. Besides PRDM-16 in epidymidal fat tissue, UCP1, PGC1-α and CIDEA expression was upregulated in both WAT and BAT along with reduction of white adipocytes surface area, suggesting that harmine induced browning of WAT. Furthermore, RAC1-MEK-ERK pathway mediated the browning process with chromodomain helicase DNA binding protein 4 (CHD4) as the downstream target, rather than the classical MAO-A inhibition [17].

**Berberine**

Berberine is a commercially available diarrhea drug and isolated from medicinal plants such as Hydrastis canadensis, Berberis aristata and Phellodendron chinense, which belongs to benzylisoquinoline alkaloids and exhibits cholesterol-lowering, anti-inflammatory and anti-cancer activities [18,19]. New publication showed that berberine treatment increased thermogenesis in both WAT and BAT. In HFD-induced obesity mice, berberine (100 mg·kg⁻¹·d⁻¹) improved hyperinsulinemia, relieved fatty deposit and stimulated browning and metabolism by upregulating UCP1 and tyrosine hydroxylase (TH) expression in extraperitoneal and subcutaneous WAT [20]. Further research [20] in db/db mice also suggested that berberine could inhibit body weight gain, reduce fat tissue percentage and serum insulin, improve insulin and glucose tolerance, increase rectal temperature, boost mitochondrial biogenesis as well as upregulation of UCP1 and PCG-1α expression in inguinal adipose tissue, instead of epididymal WAT (eWAT). In vitro C3H10T1/2 adipocytes also evidenced that berberine induced UCP1 expression of browning through activating AMPK and recruiting PGC-1α [20]. Besides, berberine exerted anti-inflammation by recruiting M2 macrophages and blocking M2 macrophage po-
larization in WAT \[31\].

Nicotine

Nicotine is one of the most famous addictive natural agents from tobacco plants with nicotine abuse as a kind of incentive of cancer and cardiovascular disease \[21\]. Given that smokers often exhibit less body weight than nonsmokers \[22\], so which ingredient should be responsible for the effect? Researches uncovered the answer. Female KK mice gained significantly less weight and had less WAT than control mice after being injected subcutaneously with nicotine at 1.0 mg·kg\(^{-1}\)·d\(^{-1}\) for the first three months and then 1.2 mg·kg\(^{-1}\)·d\(^{-1}\) for the second three months. In addition, nicotine-treated mice expressed more UCP1 mRNA in not only interscapular, subcutaneous, retroperitoneal WAT and BAT, but also gastrocnemius muscle \[23\]. Since the browning program may not depend on leptin \[24\], the exact molecular mechanism is still unclear. Nevertheless, the potential side effect of nicotine will limit the development for anti-obesity drug.

Flavonoids

Flavonoids are a series of compounds in which two benzene rings (A- and B-rings) with a phenolic hydroxyl group are linked to each other by three-carbon chain, such as hesperidin and quercetin. Flavonoids exist in the diverse kinds of plants, such as fruits, vegetables, grains, herbs, which play a significant pharmacological role \[25\], including improving the cognitive function, Parkinson disease and some cancers \[26-27\]. Besides, we summarized the following kinds of flavonoids newly reported to be concerned with thermogenesis of white adipose tissue.

Genistein

Genistein is one of the isoflavones mainly found in soybean which mimics 17β-estradiol and activates the estrogen receptor (ER) \[28\]. Therefore, genistein can improve estrogen deficiency-induced type 2 diabetes as phytoestrogen. In the ovariectomized rats, genistein treatment (oral gavage of 15 or 30 mg·kg\(^{-1}\)·d\(^{-1}\)) inhibited body weight gain, reduced perirenal, retroperitoneal and mesenteric adipose weight, reduced adipocytes size, and elevated plasma irisin and browning markers expression in inguinal WAT (iWAT) through modulation of nuclear ERα. Additionally, genistein can also inhibit the adipose tissue inflammation as well as improve insulin sensitivity with boosting insulin signaling of phosphorylated insulin receptor substrate 1 (p-IRS1) and phosphorylated protein kinase B (p-AKT) \[29\]. 3T3-L1 cells expressed the upregulated CD-137 and UCP1 mRNA after treatment with genistein (50 or 100 μmol·L\(^{-1}\)) even though the estrogen receptor was blocked, indicating of being independent of classical estrogen receptor pathway. Furthermore, genistein promoted the visceral preadipocytes differentiation, increased mitochondrial membrane potential and upregulated UCP1 expression in human BAT and WAT. Mechanism investigation suggested that activation of AKT and AMPK signaling were involved in browning of WAT and thermogenesis of BAT \[30\], while gut microbiota diversity may be involved in anti-obesity process \[31\].

Licochalcone A

Licochalcone A (3-α,α-dimethylallyl-4',4'-dihydroxy-6-methoxychalcone) is a characteristic flavonoid isolated from Licorice. The previous studies focused on its anti-inflammatory, anti-tumorigenic and anti-malarial effects \[32\]. However, a recent study figured out that the intraperitoneal injection of licochalcone A (10 mg·kg\(^{-1}\)) prevented body weight gain, improved metabolic disorder, and more importantly induced white fat browning in DIO mice. Browning induction of licochalcone A was confirmed in 3T3-L1 adipocytes with the up-regulation of UCP1 and PRDM-16 expression. Actually, another flavonoid extract of *licorice*, such as isoliquiritigenin and liquiritigenin, exerted the similar effects as licochalcone A. However, no more evidences uncovered the potential molecular mechanism \[33\].

Quercetin

Quercetin (3,5,7,3',4'-pentahydroxyflavone) is a polyphenol of flavonoids existing in onions, broccoli, tomatoes and apples. As a strong antioxidant, quercetin can protect against pancreas and brain injury and alleviate oxidative stress \[34\]. Instead of isosquercetin, quercetin isolated from onion peel was recently revealed to upregulate the brown-like adipocytes specific genes in 3T3-L1 cells depending on AMPK/PPAR-γ pathway after sympathetic stimulation. In HFD-fed obese mice, both WAT and BAT could be induced to express more browning or thermogenesis-related genes expression of PPAR-γ, PGC-1α, transcription factor A (Tfam), PRDM-16, CIDEA without suppressing food intake \[35\]. Specifically, quercetin (50 or 100 μmol·L\(^{-1}\)) was able to upregulate UCP1 expression in 3T3-L1 adipocytes \[36\]. However, Kuipers et al. found that only SAT browning could be induced in 0.1% quercetin-treated C57BL/6J mice without any change in BAT and VAT. Meanwhile, plasma TG was decreased through downregulating hepatic apolipoprotein B (Apob) expression and increasing the intestinal fatty acid absorption \[37\]. Whereas, p-AMPK (Thr172)/AMPK ratio in SAT was not affected. Quercetin might be prospective for preventing obesity and metabolic syndrome. In addition, pentamethylerucetin, another kind of quercetin derivative, exhibited the similar browning effect with reduction of waist circumference, cellular TG and WAT weight, and increase of glucose consumption and BAT mass as well \[38\].

Chrysins

Chrysins (5,7-dihydroxyflavone) is a natural flavonoid with skin photoprotection, hepatoprotection and osteogenic differentiation activities existing in flowers, honeycombs and mushrooms \[39\]. Recently, Jae et al revealed its novel browning effect. Apart from the cytotoxicity of 100 μmol·L\(^{-1}\) chrysin, 50 μmol·L\(^{-1}\) chrysin induced UCP1, PRDM16 and PGC-1α expression upregulation in 3T3-L1 adipocytes. Furthermore, chrysin reduced lipid accumulation and TG via upregulating PPAR-α, PPAR-γ and PPAR-β. Further investigation suggested AMPK pathway was involved in the underlying
Tea polyphenols

Green tea is not only a well-known Chinese drink from the dried leaves of Camellia sinensis, but also a treasure of modern medicine. For a long time, it is believed that caffeine in green tea plays a role in thermogenesis. However, catechin, as the major polyphenols of green tea, especially epigallocatechin gallate (EGCG), is a plasma lipid regulation supplement on Chinese market, was identified to be the important inducer of thermogenesis. 8-Week oral administration of catechin (7.5 or 155 mg kg⁻¹ d⁻¹) reduced the adipose tissue weight, alleviated the inflammation and induced the browning of SAT in DIO mice. Moreover, (-)-epicatechin upregulated UCP1, irisin and UCP2 expression of mice after treatment with (-)-epicatechin at 1 mg kg⁻¹ d⁻¹ for 15 days. Three key pathway enzymes related to fatty acid oxidation (acyl-CoA dehydrogenase very long chain, acyl-CoA dehydrogenase medium chain and hydroxacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha) (ACADVL, ACADM and HADHA) increased about 25%. Accordingly, low-density lipoprotein (LDL) and total TG levels decreased. Further investigation showed AMPK pathway mediated the browning induction of (-)-epicatechin. Besides green tea, some fully or partially oxidized tea, like oolong, black and Pu-erh tea, which could protect against obesity and hyperlipidemia with the reduction of retroperitoneal, epididymal and mesenteric WAT weight as well as plasma cholesterol level. Similarly, black and Pu-erh tea induced browning with UCP1 upregulation in mesenteric WAT mediated by AMPK pathway.

Butein

Butein, one of chalcone flavonoids, is found in the heartwood of Dalbergia odorifera, Caragana jubata and Rhus verniciflua Stokes, and the stem bark of cashews (Semen carpini anacardium) with antioxidant activity, aldose reductase and advanced glycation endproducts (AGEs) inhibitory effects. Recently, the novel property of small molecule butein was firstly discovered by Song et al. in C3H10T1/2 adipocytes which expressed more UCP1 mRNA after treatment with butein. In vivo, 2-week intraperitoneal injection of butein (15 mg kg⁻¹ d⁻¹) significantly promoted thermogenesis of BAT and induced browning of WAT in wild-type lean mice. In addition, 8-week injection of butein (5 or 15 mg kg⁻¹ d⁻¹) significantly reduced weight gain, improved energy expenditure and insulin resistance in HFD-fed mice. What’s more, they affirmed that Prdm4-dependent pathway, instead of other Prdms-dependent pathways, mediated the thermogenic effects of butein in BAT and WAT. More studies need to confirm the pharmacological effects of butein in promoting thermogenesis and browning.

Formononetin

Formononetin is isolated from Astragalus membranaceus which is a traditional Chinese herb for immunity regulation, anit-asthma and anti-bacterial effect. Actually, a recent study showed that formononetin was also able to induce browning program. In vitro, formononetin dose-dependently upregulated UCP1 and other browning protein expression in differentiated 3T3-L1 adipocytes after treatment for 6 days, compared with other Astragalus membranaceus extract. In vivo, 8-week oral gavage of formononetin reduced SAT weight, especially SAT and VAT with boosting energy expenditure in DIO mice. Although formononetin may be the ERs, aryl hydrocarbon receptors (AhR) and PPAR-α/γ's further investigation suggested that PPAR-γ mediated the effects of formononetin on WAT browning and BAT thermogenesis. However, the underlying mechanism is still unclear yet.

Rutin

Rutin (quercetin-3-O-rutinoside) is found in citrus fruits, onion, wine, grape, buckwheat and mulberry and used to protect against inflammatory injury and neurotoxicity. Yuan et al. firstly revealed that rutin (1 mg mL⁻¹ in drinking water) strengthened energy consumption, maintained glucose homeostasis and inhibited body weight gain with improving glucose tolerance and increasing body temperature, mitochondrial copy number and oxygen expenditure in db/db mice and DIO mice. Further investigation demonstrated that rutin promoted thermogenesis of BAT and induced browning of SAT with the upregulated BAT-specific markers of UCP1, PGC-1α etc, as well as beige cell markers of CD137 and T-box transcriptional factor (TBX). Meanwhile, SIRT1 stabilization and SIRT1/PGC1α/Tfam signaling pathway were found to mediate these programs.

Terpenoids

Terpenoids, also named as isoprenoids, derive from five-carbon isoprene units and are characteristic as the molecular formula of (C₅H₈)ₙ. They abound in diverse kinds of plants and animal metabolic products. According to the amount of isoprene, they are classified as hemi-terpenes, monoterpenes and so on. Cannabis, cyanobacteria, Mallotus compricus and some cooking oil are the sources of terpenoids.

Cordycepin

Cordycepin is the natural derivatives of adenosine existing in the metabolic products of caterpillar fungus Cordyceps militaris with tumor inhibition, immunity modulation and inflammation suppression. A recent study demonstrated that cordycepin can remarkably induce browning with upregulation of UCP1 expression in WAT. In C57BL/6 male mice, 3-week oral administration of cordycepin at 40 mg kg⁻¹ largely inhibited body weight gain, particularly SAT weight, reduced liver TG and total cholesterol (TC), increased skin temperature as well as induced the browning of WAT, especially iWAT without affecting food intake. Further study in 3T3-L1 adipocytes showed that the browning markers of PGC-1α, UCP1 and so forth were significantly upregulated. Meanwhile, mtDNA copy number and citrate synthase activity were significantly increased after cordycepin treatment through AMPK activation. In addition, regulation of gut microbiota also accounted for the body weight reduction of
cordycepin. It still needs more evidences to clarify the relationship between browning and gut microbiota.

**Ginsenoside**

Ginsenoside is isolated from one well-known traditional Chinese herb, ginseng and *Panax notoginseng* with anti-epileptic and anti-Alzheimer’s disease and cardiovascular-protective effects. Among various kinds of ginsenoside, ginsenoside Rb1 and Rb2 have been approved the activity of WAT browning. 10 μmol·L⁻¹ ginsenoside Rb1-treated 3T3-L1 adipocytes for 10 days upregulated UCP1, PGC-1α and PRDM-16 expression. Besides, the basal glucose intake, mitochondrial respiration and energy expenditure were significantly prompted. Moreover, the browning effect of ginsenoside Rb1 was mediated by PPARγ-dependent pathway. Similarly, Rb2 exhibited the same effects in DIO mice. 40 mg kg⁻¹·d⁻¹ of Rb2 (i.p.) reduced the body weight and adipose tissue weight of iWAT, eWAT and BAT. In differentiated 3T3-L1 and C3H10T1/2 adipocytes, the expression of UCP1 and PGC-1α was significantly upregulated by Rb1 via AMPK signaling pathway.

**Phytol**

As part of the chlorophyll molecule, phytol is found in all green vegetables with the activities of anti-melanogenesis, anti-bacterial and lipid metabolism regulation. Actually, a dietary supplement with phytol functioning as lowering plasma lipid has been approved on Chinese market. Additionally, Zhang *et al.* reported phytol treatment (100 μmol·L⁻¹) induced the upregulation of BAT or beige adipocyte-related markers, such as UCP1, PRDM-16, PGC-1α expression in 3T3-L1 adipocytes. Meanwhile, the energy metabolism efficiency with mitochondrial number and oxygen expenditure was also increased. DIO mice treated with phytol (500 mg·kg⁻¹·d⁻¹) gained less body weight and induced browning of iWAT. Further study showed that the inhibitor of AMPKα pathway can abolish the activated effects of phytol, suggesting that phytol may induce browning via AMPKα signaling pathway.

**Menthol**

Menthol is one of cyclic monoterpen alcohol, found in the oils of corn mint, peppermint, or other mints. As an aromatic cooling element, menthol is applied to enhance athletic performance, reduce topical pain and influence the metabolism of nicotine. Actually, the study in obese mice proved the improved glucose metabolism and browning of WAT after 8-week HFD and 1% menthol treatment with the significantly upregulated UCP1 expression in both SAT and VAT. Furthermore, it was indicated that transient receptor potential melastatin 8 (TRPM8) of Ca²⁺ channel and PKA phosphorylation were involved in the browning process. In particular, L-menthol played a significant role in thermogenic program of subcutaneous adipocytes through transient receptor potential ankyrin 1 (TRPA1)-dependent pathway. Interestingly, the findings in humans showed that transdermal absorption of L-menthol exerted more significant effects than oral administration.

**Thymol**

Thymol (5-methyl 2-isopropylphenol), a natural monoterpene phenolic constituent, can be isolated from numerous aromatic plants, such as thyme species. Apart from biocide, the researches revealed its pharmacological activity of anti-depression, ultraviolet radiation protection and anti-diabetes. 20 μmol·L⁻¹ of thymol treatment improved lipid metabolism of 3T3-L1 adipocytes, promoted mitochondrial biogenesis and upregulated the browning marker genes and protein, like UCP1 and PPAR-γ, through activation of β3-adrenergic receptor, PKA and p38MAPK signaling pathway. Notably, the browning effect of thymol was more significant than the classical browning cocktail containing 50 nmol·L⁻¹ tridithoronylone and 1 μmol·L⁻¹ rosiglitazone.

**Fucoxanthin**

Fucoxanthin is a marine carotenoid isolated from macroalgae, such as *Laminaria japonica*, *Eisenia bicyclis*, and *Undaria pinnatifida*. Recently, it has been affirmed that fucoxanthin can treat hyperuricemia and improve both inflammation and cardiovascular dysfunction in obesity. Moreover, 0.05% fucoxanthin could upregulate UCP1, reduce the size and weight of VAT, decrease lipid-regulating enzyme activities, like glucose-6-phosphate dehydrogenase (G6PD) of VAT in male C57BL/6N mice. As early as 2005, Maeda *et al.* reported that after female obese KK-Ay mice were fed with 2% Undaria lipid for 4 weeks, the abdominal VAT weight was reduced and BAT weight was increased. More specifically, UCP1 expression of BAT was significantly upregulated and lipid metabolism was improved. There was still fewer research to investigate the underlying mechanism although Guo *et al.* reported fucoxanthin may restored the decreased abundance of cecal and fecal microbiota induced by HFD feeding.

**Long-chain fatty acids**

Long-chain fatty acids are a large group of natural products which are widely used as food and nutrient supplement from plenty kinds of plants or animals. Coconut oil, arachidonic acid (ARA) and so on have been proved to be browning inducet. As two double bonds more numerous aromatic plants, such as thyme species. Apart from biocide, the researches revealed its pharmacological activity of anti-depression, ultraviolet radiation protection and anti-diabetes. 20 μmol·L⁻¹ of thymol treatment improved lipid metabolism of 3T3-L1 adipocytes, promoted mitochondrial biogenesis and upregulated the browning marker genes and protein, like UCP1 and PPAR-γ, through activation of β3-adrenergic receptor, PKA and p38MAPK signaling pathway. Notably, the browning effect of thymol was more significant than the classical browning cocktail containing 50 nmol·L⁻¹ tridithoronylone and 1 μmol·L⁻¹ rosiglitazone.

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adipocytes were treated with 50 μmol·L⁻¹ of linoleic acid (18 : 2, Δ⁹,Δ₁₂), α-linolenic acid (18 : 3, Δ⁹,Δ₁₂,Δ₁₅), γ-linolenic acid (18 : 3, Δ⁵,Δ₈,Δ₁₂), or pinolenic acid (18 : 3, Δ⁵,Δ₈,Δ₁₂) for 24 h, the UCP1 and PGC1-α expression was significantly induced, instead of C3H10T1/2 or 3T3-L1 cells > T₁₂ or 3T3-L1 cells [47].

**Bitter melon seed oil (conjugated linoleic acid)**

Bitter melon (*Mormordica charantia*) is a common vegetable in Asia with the properties of anti-inflammation and anti-cancer. Interestingly, the oil isolated from bitter melon seed, which is rich in cis-9, trans-11, trans-13 conjugated linoleic acid, is able to attenuate fat accumulation in obese mice [50]. Another study showed WAT delipidation and browning effect on retroperitoneal WAT after feeding male C57BL/6Narl mice with bitter melon seed oil (BMSO) [79]. When 0.06% (low), 0.2% (intermediate) and 0.6% (high) doses of trans-10, cis-12 (10,12) conjugated linoleic acid (CLA) were fed to 129Sv male mice, intermediate and high doses reduced body weight gain and WAT depot weight, while low and intermediate doses induced browning program mediated by free fatty acid (FFA) receptors GPR120 and GPR40. However, high dose may cause hepatic steatosis, hepatomegaly and low-grade inflammation [78]. Additionally, another kind of CLA, called KetoA [10-oxo-12(Z)-octadecenoic acid] produced by gut microbiota, was reported to induce browning in BAT and iWAT mediated by the afferent vagus nerve pathway through activation of TRPV1 channel. However, browning did not display in TRPV1 KO mice treated with β-adrenoreceptor blocker, suggesting that the program may be related with TRPV1 and β-adrenoreceptor [79].

**Phenolic acids**

**Curcumin**

Curcumin is naturally occurring curcuminoid of turmeric isolated from rhizomes of *Curcuma* species with the property of anti-inflammation and dual effect on angiogenesis [80]. Lone et al. reported that 8-day treatment of curcumin (1, 20 μmol·L⁻¹) activated AMPK phosphorylation then boosted PRDM16 and PGC-1α in Sprague-Dawley rats inguinal adipocytes. Besides, curcumin (20 μmol·L⁻¹) augmented lipolysis and suppressed lipogenesis in primary rats inguinal adipocytes, which was mediated by hormone-sensitive lipase (HSL) [81]. In vivo, oral administration of curcumin (50 or 100 mg·kg⁻¹·d⁻¹) could reduce the body weight gain, increase mtDNA copy number and improve cold tolerance in C57BL/6 mice with iWAT browning via increasing plasma norepinephrine and upregulating β3 adrenergic receptor expression. However, eWAT browning was not induced by curcumin [82].

**Resveratrol**

Resveratrol (RES; 3,5,4′-trihydroxytrans-stilbene) is a dietary supplement for weight loss and widely distributed in natural plants, such as grapes, pines, knotweed and peanuts [83]. Since resveratrol exhibited the extensive activities of anti-inflammation, anti-cancer and anti-oxidative stress [84,85], much attention was paid to resveratrol recently. Several recent studies showed that resveratrol can mitigate obesity through inducing WAT browning. 8-Week administration of 0.4% resveratrol can reduce weight gain and gut dysbiosis in DIO mice. Mechanistically, WAT browning was involved in the anti-obesity effect of resveratrol with reversing UCP1 and SIRT1 down-regulation in the inguinal SAT and perigonadal VAT and upregulating PGC-1α and PPAR-γ protein expression [86]. Furthermore, resveratrol administration can improve the metabolic syndrome and promote thermogenesis in the offspring of HFD-fed female mice [86]. In adult healthy volunteers, 4-week oral administration of 500 mg trans-resveratrol significantly upregulated UCP1 expression in the SAT through SIRT1 pathway [87]. Another study suggested that AMPKα1 activation may be involved in the induction of browning program by resveratrol [88]. Not only resveratrol, but also its derivatives were affirmed the browning activity, such as oxyresveratrol and piceatannol. Oxyresveratrol administration (15 mg·kg⁻¹·d⁻¹ for 8 weeks) gained 18% less body weight and lowered blood glucose from 280 to 220 mg·dl⁻¹ in HFD-fed C57BL/6N mice with upregulation of UCP1 expression in eWAT mediated by Foxo3a [89]. Piceatannol was found to induce UCP1 expression in C₃H₁₀T₁/₂ adipocytes, which is the hydroxylate product of resveratrol isolated from passion fruit (*Passiflora edulis*) seeds [90]. It has been indicated that resveratrol could affect composition of anti-obesity related gut microbiota, although the detailed mechanism is still unclear [90].

**Extract**

**Cinnamon extract**

Cinnamon is obtained from the inner bark of several tree species from the genus *Cinnamomum* family Lauraceae, one of the traditional Chinese medicine and spice, which was used as add-on medicine in type 2 diabetes [92]. Recent study demonstrated cinnamon extract (CE) can induce browning. Typical phenotype of brown adipocytes was observed in 3T3-L1 adipocytes after treatment with 80 μg·ml⁻¹ of CE for 3 days with the upregulated UCP1 mRNA and protein expression. Browning can be induced in subcutaneous adipocytes isolated from C57BLKS db/db mice, instead of epididymal adipocytes with the reduction of lipid content and body weight gain. Activation of AMP pathway then β3-adrenergic receptor were involved in the browning induction of CE [93].

**Ganoderma tsugae ethanol extract (GTEE)**

Ganoderma tsugae, a mushroom of the genus *Ganoderma* family Polyporaceae, also called *Lingzhi* or *Reishi*, is another kind of traditional herb used for life span extending and human health protection. The previous study revealed that it can treat physical frailty [94]. A recent study found that 0.2 mg·ml⁻¹ of GTEE induced browning with upregulating UCP1 and cytochrome c proteins in 3T3-L1 adipocytes and decreasing NADH/NAD⁺ ratio and NADH content. In vivo, GTEE helped male C57BL/6Narl mice to induce browning in inguinal and perirenal WAT, resist diet-induced obesity
ameliorate glucose and lipid disorders with reduction of fast-
ing blood glucose, TG, LDL. Meanwhile, AMPK pathway and SIRT1 may involve in the browning process [99].

**Immature citrus reticulata extract (ICRE)**

Citrus fruit is a main kind of commercial cultivars from family Rutaceae containing vitamins, minerals, pectin poly-
phenols, flavonoids, alkaloids and limonoids [96]. The extract, especially flavonoids, can treat ulcerative colitis and obe-
sity [97]. ICRE containing narirutin (4.52 ± 0.31 mg·g⁻¹), hes-
peridin (9.14 ± 0.32 mg·g⁻¹), nobiletin (2.54 ± 0.07 mg·g⁻¹) and tangeretin (1.67 ± 0.05 mg·g⁻¹) was administered to HFD-
fed mice. After 11-week treatment, the obesity-related lipid metabolism was improved with significant less body weight and lipid accumulation in liver and WAT than HFD group. Furthermore, the capacity for adaptive thermogenesis was en-
hanced with the significantly upregulated UCP1 and PGC-1α expression in iWAT, indicating browning of WAT [98]. There are fewer reports about its molecular mechanism.

**Microalgae extract**

Spirulina is a kind of microalga from family Oscillatori-
aceae for use as nutritional supplements. The previous studies suggested Spirulina extract has been ever used as natural angiotensin-converting enzyme inhibitor (ACEi) agent, lipid metabolism and gut microbiota modulator [98]. A recent study demonstrated that spirulina maximal 70% ethanol extract (SM70EE, 150 or 450 mg·kg⁻¹·d⁻¹ for 6 weeks) could lower subcutaneous and abdominal fat pad with the upregulated browning markers in HFD-induced obese mice of PRDM16, PGC-1α and UCP1 in WAT via AMPK pathway. It also im-
proved lipid metabolism with the increased HDL and de-
terased TG, TC and LDL [99]. Besides, another microalga, Phaeodactylum tricornutum containing diverse ω-3 fatty acids and carotenoids has been affirmed to exhibit anti-
obesity activity by inducing browning, stimulating BAT ther-
mosgenesis and lowering plasma lipid [100].

**Pycnogenol**

Pycnogenol® (PYC) is the extracted complex of French Maritime Pine bark of family Pinaceae with antioxidant, lipid regu-
ulatory, anti-atherosclerotic activity, which contains procyanidins, phenolic acids and bioflavonoids [100]. PYC has been marketing as lipid regulation dietary supplement in China [100]. Specifically, recent studies observed that Pycno-
genol could induce browning of WAT in high-cholesterol and high-fat diet (HCD)-fed apolipoprotein E (apoE)-deficient mice after oral gavage with 30 or 50 mg·kg⁻¹·d⁻¹ PYC. Be-
sides, body weight gain, epididymal fat gain and the ratio of adipocyte area augment were inhibited through PKA signal-
ing pathway [100].

**Water extract of Caulis Spatholobi (WECS)**

Caulis Spatholobi, also called Ji-Xue-Teng, is the vine stem of Spatholobus erectus of the family Leguminosae. Apart from the hematopoietic, antiviral and sedative-hypnot-
ic pharmacological activities [104], Zhang et al. recently demonstrated that water extract of Caulis Spatholobi (WECS) could ameliorate obesity through promoting thermogenesis and gut microbiota modulation. After DIO mice were fed with 1% (W/W) WECS in drinking water for 13 weeks, meta-
bolic disorders were improved with inhibition of weight gain, reduction of adiposity, improvement of glucose metabolism and hepatic steatosis. Mechanistically, sWAT browning and BAT thermogenesis were activated with the upregulated ther-
mosgenic and mitochondrial genes expression. Notably, WECS increased anti-obesity and anti-diabetes related bacte-
eria genus with the decreased ratio of Firmicutes to Bac-
teroidetes and the amount of bacteria from the Proteobacteria phylum in cecum feces [103]. The novel findings make Caulis Spatholobi to be the promising therapeutics for obesity and metabolic disorders.

**Berry extract**

Blueberries (Vaccinium spp.) is a well-known antioxidant plant of family Ericaceae with cardiovascular protective function [104]. A recent study reported that 10-week administra-
tion of 0.5% (W/I) blueberries extract could inhibit body weight gain of C57BL/6J db/db mice by inducing iWAT browning with the upregulated thermogenic gene expression of iWAT and enhancing body heat production with the in-
creased rectal temperature which was associated with gut micro-
biota and bile acids regulation. Meanwhile, lipid disorders were attenuated with the reduction of plasma TG and serum lipopolysaccharides (LPS) [103]. Another berry, methanolic ex-
tract of Strawberry was also found the browning-inducing property through AMPK pathway activation in 3T3-L1 cells after 100 μg·mL⁻¹ treatment [103]. Additionally, Park et al. ob-
served the significant beige adipocytes generation after treat-
ment with water extract of black raspberry in human mesen-
chymal stem cells (hMSCs) and 3T3-L1 cells, as well as C57BL/6J mice [109].

**Averrhoa bilimbi ethanolic leaf extract**

Averrhoa bilimbi, also known as bilimbi, is a tropical fruit tree of family Oxalidaceae with the hyperglycemic ef-
fect [110]. Recently, a Malaysia group reported that the ethan-
olic leaf extract of Averrhoa bilimbi (100 μg·mL⁻¹) induced browning process and improved mitochondria function in 3T3-L1 cells with the upregulation of UCP1, PRDM16, FNDC and PGC-1α protein. The underlying signaling pathway needs more investigation [111].

**Germinated soy germ extract**

Soybean (Glycine max) is of family Leguminosae with piles of uses. Germinated soy germ extract possesses diverse properties, such as osteoporosis protection, due to plenty of phytochemical enzymes [112]. The germinated soy germ extract (1 mg·kg⁻¹) prevented HFD-induced obesity and meta-
bolism syndrome along with prompting beige adipose genera-
tion in gWAT, inhibiting lipid accumulation and decreasing serum TC and LDL [110]. Germinated soy germ extract may become a prospective therapeutic strategy for weight loss or metabolism syndrome.

**Others**

**Genipin**

Genipin is the major ingredient of Gardeniae fructus with
anti-cancer, hepatic injury protection and anti-inflammation properties \[^{[114]}\]. A recent study reported Genipin also exhibited browning property. After DIO rats were intraperitoneally injected with Genipin at 12.5 or 25 mg·kg\(^{-1}\)·d\(^{-1}\) for 12 days, obesity was prevented with less body weight gain, food intake and VAT mass. Meanwhile, glucose and lipid metabolism were significantly improved, including glucose intolerance, insulin resistance, adipocyte hypertrophy and hepatic steatosis. Genipin also exhibited anti-inflammatory effect with reduction of proinflammatory cytokines of tumor necrosis factor-alpha (TNF-\(\alpha\)) and interleukin-6 (IL-6) in WAT. What’s more, both UCP1 and PRDM16 genes expression in SAT showed upregulation, indicating WAT browning \[^{[115]}\].

\textbf{L-rhamnose}

L-rhamnose, a kind of rare sugar isolated from pectin in plants, is the component of lipopolysaccharides in Gram-negative bacteria. Previous studies suggested L-rhamnose can regulate lipid metabolism and relieve skin ageing \[^{[116]}\]. Interestingly, as sugar, L-rhamnose can also increase energy expenditure via inducing WAT browning. Treatment of L-rhamnose (10, 50, 100 μmol·L\(^{-1}\)) upregulated UCP1, PRDM16 expression in 3T3-L1 or HIB1B adipocytes, indicating WAT browning and BAT activation. Moreover, molecular docking analysis revealed \(\beta\)-3-AR, SIRT1, PKA and p-38 MAPK might be the potential targets through interaction with L-rhamnose \[^{[117]}\].

\textbf{Ostreolysin}

Ostreolysin is a kind of fungal protein with anti-cancer and intracellular Ca\(^{2+}\) regulatory activity, which is expressed in developmental stages of \textit{P. ostreatus} \[^{[109]}\]. 48-h Treatment of recombinant ostreolysin (10 μg·mL\(^{-1}\)) induced browning, increased mitochondrial biogenesis and alleviated inflammation in 3T3-L1 adipocytes mediated by phosphorylation of AMPK. \textit{In vivo}, 4-week intraperitoneal injection of recombinant ostreolysin (1 μg·g\(^{-1}\)·day\(^{-1}\)) reversed hepatic steatosis, improved insulin sensitivity as well as glucose resistance and alleviated chronic inflammation in adipose tissue in DIO mice \[^{[119]}\].

\textbf{Glucoraphanin}

As a kind of sulforaphane, glucoraphanin is a well-known nuclear factor-like 2 (Nrf2) inducer \[^{[120]}\] produced from gut microbiota or cruciferous vegetables, especially broccoli sprouts. Glucoraphanin has exhibited anti-cancer and antioxidant activities \[^{[121]}\]. 0.3% Glucoraphanin was demonstrated to prevent body weight gain, ameliorate glucose tolerance and induce browning by upregulating UCP1 expression in WAT of DIO mice. Keap1-Nrf2 pathway and increased Proteobacteria in the gut microbiomes were involved in the browning effect of glucoraphanin since browning could not be induced in the Nrf2-knockout mice \[^{[122]}\].

\textbf{Cannabidiol}

\textit{Cannabis sativa} is a famous addictive plant and treasure house for modern medicine, from which cannabidiol is isolated for schizophrenia and neuroprotective treatment. Brown-fat specific markers of UCP1, CIDEA, and PGC-1\(\alpha\) can be upregulated in 3T3-L1 adipocytes after 72-h cannabidiol treatment (1, 5, 10 μmol·L\(^{-1}\)) via activating PPARG and PI3K. Similarly, cannabidiol can also ameliorate lipid metabolic disorder with upregulation of a fatty acid oxidation-associated gene (CPT1) and other lipid metabolism genes \[^{[123]}\].

\textbf{Cinnamaldehyde}

Cinnamaldehyde (CA), a pungent component of the leaves of \textit{Cinnamomum osmophloeum}, is used for inflammatory regulation, insulin tolerance improvement and cancer therapy \[^{[124]}\]. In addition, browning effects were also revealed. After male C57BL/6J mice were administered with CA (40 mg·kg\(^{-1}\)·d\(^{-1}\)) for another 8 weeks after 12-week HFD feeding, the expression of UCP1 and PPARG was significantly upregulated in both WAT and BAT, indicative of “browning”. Besides browning, body weight, fat mass, food intake, serum lipid, free fatty acid and leptin levels were all reduced after CA treatment \[^{[125]}\].

\textbf{Honokiol}

Honokiol is a lignan, also biphenolic compound, isolated from bark of the genus Magnolia with antiallergic and anti-angiogenesis effects \[^{[126]}\]. Ding \textit{et al.} demonstrated after DIO mice were administrated with honokiol (200, 400 and 800 mg·kg\(^{-1}\)), obesity, inflammation, lipid and glucose metabolism got improved via gut microbiota regulation \[^{[127]}\]. Furthermore, a recent study suggested that honokiol exerted browning and dual effects on apoptosis in adipocytes. Honokiol treatment (1, 10, 20 μmol-L\(^{-1}\)) helped 3T3-L1 adipocytes to express more browning protein, like PGC-1\(\alpha\), PRDM16 and UCP1 through ERK activation, and induced thermogenesis in HIB1B cells. Interestingly, Honokiol prompted apoptosis in 3T3-L1 adipocytes while inhibited apoptosis in HIB1B adipocytes via AMPK pathway \[^{[128]}\].

\textbf{Conclusions}

Excess accumulation of white adipose tissue causes obesity which is an imbalance between energy intake and expenditure \[^{[129]}\]. Different from white adipose tissue, brown adipose tissue is responsible for both basal and inducible energy expenditure of thermogenesis mediated by UCP1, which was demonstrated to be metabolically important in adult humans with reduction yet presence in most overweight or obese subjects \[^{[130-131]}\]. Functional brown adipose tissue in adults makes it a potential target for treating obesity and its complications.

Browning, inducing WAT to brown or beige (brite) fat which is brown-like fat emerging in WAT, becomes an appealing therapeutic strategy for metabolic disorders \[^{[4]}\]. Physiological stimuli and chemical treatment were traditionally considered to induce the formation of beige adipocytes, including diet, cold exposure and exercise as well as adrenergic agonist stimulation, leading to alleviating obesity, insulin resistance, diabetes and other metabolic disorders \[^{[122-134]}\]. However, the therapeutic potential of activating brown fat-mediated thermogenesis in human has to be fulfilled. Due to lack of efficacy or intolerable side-effects, the clinical trials have not been successful. Mirabegron, as \(\beta\)-adrenergic agon-
To date, numerous “browning”-related agents have been discovered. All the above-mentioned natural products related to BAT and WAT browning are listed in the Table 1. Whereas, they still need to be further studied, including the mechanism, pharmacological effects and clinical trial. Indeed, it is difficult for some natural products to be developed for anti-obesity drug due to lack of natural resources and available chemical synthesis, such as cordycepin and ginsenoside. Some of them exhibited the poor pharmacological activities, such as Spirulina extract and Phaeodactylum tricornutum extract. Moreover, the adverse effects of addiction limit the clinical application of nicotine. Deep investigation needs to be done including seeking for more resources and more powerful natural products. Nevertheless, it is undeniable that natural products are important drug sources and the brown-

Table 1 Summary of natural products with browning activity

<table>
<thead>
<tr>
<th>Classification</th>
<th>Name</th>
<th>Source</th>
<th>Dose</th>
<th>Activity</th>
<th>Pathway</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
<td>Capsaicin</td>
<td>Any fruit belonging to the genus Capsicum (family Solanaceae)</td>
<td>0.01% capsaicin in high-fat diet for DIO mice</td>
<td>Inhibit glucose intake; Increase glucose expenditure</td>
<td>SIRT1 phosphorylation; Regulate gut microbiota</td>
<td>[9]</td>
</tr>
<tr>
<td></td>
<td>Bouchardatine</td>
<td>Bouchardatia neurococca</td>
<td>50 mg·kg⁻¹·i.p. once two days for C57BL/6J mice</td>
<td>Alleviate body weight gain; Dyslipidaemia and fatty liver; Mitochondrial biogenesis</td>
<td>SIRT1-LKB1-AMPK pathway</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>Harmine</td>
<td>South American vine Banisteropsis coaapi, harmaal or Syrian rue (Peganum harmala), tobacco</td>
<td>50 mg·kg⁻¹·d⁻¹ for C57BL/6J mice</td>
<td>Facilitate adipogenesis; Inhibit body weight gain; Decrease FFA, insulin, sterol and TG in plasma</td>
<td>RAC1-MEK-ERK pathway; Inhibit Wnt signaling pathway</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td>Berberine</td>
<td>Hydrastis canadensis, Berberis aristata and Phellondendron chinense</td>
<td>100 mg·kg⁻¹·d⁻¹ for DIO for C57BL/6J mice</td>
<td>Increase energy metabolism and glucose tolerance; Inhibit inflammation</td>
<td>Activate AMPK and recruit PGC-1α</td>
<td>[20]</td>
</tr>
<tr>
<td>Alkaloids</td>
<td>Nicotine</td>
<td>Tobacco plants</td>
<td>1.0 and then 1.2 mg·kg⁻¹·d⁻¹ for KK mice</td>
<td>Inhibit body weight gain; Induce BAT thermogenesis</td>
<td>Unclear</td>
<td>[23]</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Genistein</td>
<td>Soybean</td>
<td>15 or 30 mg·kg⁻¹·d⁻¹ p.o. for ovariectomized rats; 50 or 100 μmol·L⁻¹ for 3T3-L1 cell</td>
<td>Improve cell viability; Induce fat cell differentiation; Lead large droplets to multilocular distribution</td>
<td>Activate ER AKT and AMPK signaling; Regulate gut microbiota</td>
<td>[29]</td>
</tr>
<tr>
<td>Licochalcone A</td>
<td>Licorice</td>
<td>Licorice</td>
<td>10 mg·kg⁻¹·i.p. for 3T3-L1 cell</td>
<td>Prevente body weight gain, improve metabolic disorde</td>
<td>Unclear</td>
<td>[33]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Onions, broccoli, tomatoes, and apples</td>
<td>50 or 100 μmol·L⁻¹ for 3T3-L1 cell; 0.1% (W/V) for C57BL/6J mice</td>
<td>Decrease TG level</td>
<td>AMPK/PPARγ pathway</td>
<td>[37]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chrysin</td>
<td>Flowers, honeycombs, and mushrooms</td>
<td>1, 25 and 50 μmol·L⁻¹ for 3T3-L1 cell</td>
<td>Regulate lipid metabolism</td>
<td>AMPK pathway</td>
<td>[40]</td>
</tr>
<tr>
<td>Tea polyphenols</td>
<td>Dried leaves of Camellia sinensis</td>
<td>The heartwood of Dalbergia odorifera, Caragana jubata, and Rhus verniciflua and the stem bark of cashews (Semecarpus anacardium)</td>
<td>15 mg·kg⁻¹·d⁻¹ i.p. for wild type lean mice</td>
<td>Improve energy expenditure and insulin resistance</td>
<td>PRDM4-dependent pathway</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Butein</td>
<td>Astragalus membranaceus</td>
<td>1 μmol·L⁻¹ for 3T3-L1 cell</td>
<td>Reduce fat mass; Boost energy expenditure</td>
<td>PPARγ mediated pathway</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>Formononetin</td>
<td>Citrus fruits, onion, wine, grape, buckwheat and mulberry</td>
<td>1 mg·L⁻¹ in drinking water for db/db mice and C57BL/6J mice</td>
<td>Induce mitochondrial biogenesis; Induce BAT thermogenesis</td>
<td>SIRT1/PGC1α/Tfam signaling pathway</td>
<td>[50]</td>
</tr>
<tr>
<td>Classification</td>
<td>Name</td>
<td>Source</td>
<td>Dose</td>
<td>Activity</td>
<td>Pathway</td>
<td>Ref</td>
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</tr>
<tr>
<td>Terpenoids</td>
<td>Cordycepin</td>
<td>The metabolic product of caterpillar fungus <em>Cordyceps militaris</em></td>
<td>40 mg·kg⁻¹ for C57BL/6 male mice</td>
<td>Inhibit body weight gains; Regulate lipid metabolism</td>
<td>AMPK pathway</td>
<td>[55]</td>
</tr>
<tr>
<td></td>
<td>Ginsenoside Rb1</td>
<td>Ginseng and <em>Panax notoginseng</em></td>
<td>10 μmol·L⁻¹ for 3T3-L1 cell</td>
<td>Increase basal glucose uptake, mitochondria respiration and energy expenditure</td>
<td>PPAR-dependent pathway</td>
<td>[59]</td>
</tr>
<tr>
<td></td>
<td>Ginsenoside Rb2</td>
<td>Ginseng and <em>Panax notoginseng</em></td>
<td>40 mg·kg⁻¹·d⁻¹ i.p. for DIO mice</td>
<td>Reduce body weight, particularly iWAT, eWAT and BAT</td>
<td>AMPK pathway</td>
<td>[60]</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>Phytol</td>
<td>All green vegetables</td>
<td>100 μmol·L⁻¹ for 3T3-L1 cell</td>
<td>Increase mitochondria number and oxygen expenditure</td>
<td>AMPK pathway</td>
<td>[63]</td>
</tr>
<tr>
<td>Menthol</td>
<td></td>
<td>The oils of corn mint, peppermint, or other mints</td>
<td>HFD plus 1% menthol for obese mice 30 or 100 μmol·L⁻¹ for subcutaneous white adipocytes</td>
<td>Improve glucose metabolism</td>
<td>Activate TRPM8 then phosphorylate PKA</td>
<td>[65]</td>
</tr>
<tr>
<td>Thymol</td>
<td></td>
<td>Thyme species</td>
<td>20 μmol·L⁻¹ for 3T3-L1 cell</td>
<td>Promote mitochondrial biogenesis</td>
<td>β3-AR, AMPK, PKA, and p38 MAPK</td>
<td>[69]</td>
</tr>
<tr>
<td>Fucoxanthin</td>
<td></td>
<td><em>Laminaria japonica</em>, <em>Eisenia bicyclis</em>, and <em>Undaria pinnatifida</em></td>
<td>0.05% fucoxanthin for C57BL/6N mice</td>
<td>Improve lipid metabolism</td>
<td>Unclear</td>
<td>[71]</td>
</tr>
<tr>
<td>Long chain fatty acids</td>
<td></td>
<td>Animal, like fish, plants and secondary metabolite</td>
<td>50 μmol·L⁻¹ for murine primary adipocytes</td>
<td>Prevent body weight gain; Improve glucose tolerance and insulin resistance; Anti-inflammation; Lower metabolic risk factors</td>
<td>Unclear</td>
<td>[74]</td>
</tr>
<tr>
<td>Bitter melon seed oil</td>
<td></td>
<td>Bitter melon (<em>Mormordica charantia</em>)</td>
<td>0.06% and 0.2% p.o. (W/W) for 129Sv male mice</td>
<td>Activate BAT thermogenesis; Decrease body weight gain and WAT depot weight</td>
<td>Unclear</td>
<td>[77]</td>
</tr>
<tr>
<td>Phenolic acids</td>
<td>Curcumin</td>
<td>Rhizomes of <em>Curcuma</em> species</td>
<td>1 and 20 μmol·L⁻¹ curcumin for 3T3-L1 cell</td>
<td>50 or 100 mg·kg⁻¹·d⁻¹ for C57BL/6J mice</td>
<td>Regulate lipid metabolism; Induce mitochondrial biogenesis; Decrease body weight and fat mass improve cold tolerance</td>
<td>AMPK pathway norepinephrine-β3 receptor</td>
</tr>
<tr>
<td>Resveratrol</td>
<td></td>
<td>Grapes, pines, knotweed and peanuts</td>
<td>0.4% in HFD for C57BL/6J mice</td>
<td>Inhibit HFD-induced body weight gain and the gut dysbiosis; Regulate glucose homeostasis</td>
<td>Remodel fecal microbiota</td>
<td>[83]</td>
</tr>
<tr>
<td>Extract</td>
<td>Cinnamon extract</td>
<td>the inner bark of several tree species from the genus <em>Cinnamomum</em> family Lauraceae</td>
<td>80 μg·mL⁻¹ for 3T3-L1 cell</td>
<td>upregulate UCP1, CIDEA and PRDM16</td>
<td>cAMP pathway</td>
<td>[93]</td>
</tr>
<tr>
<td>Extract</td>
<td><em>Ganoderma tsugae</em> ethanol extract (GTEE)</td>
<td>a mushroom of the genus <em>Ganoderma</em> family Polyporaceae</td>
<td>0.2 mg·mL⁻¹ for 3T3-L1 cell</td>
<td>Upregulate the levels of UCP1, CIDEA, HSP60, and cytochrome c proteins during 3T3-L1 adipogenesis</td>
<td>AMPK pathway; SIRT1</td>
<td>[95]</td>
</tr>
<tr>
<td>Extract</td>
<td>Immature citrus reticulata extract (ICRE)</td>
<td>Citrus fruits of family Rutaceae</td>
<td>HFD with 1% ICRE for C57BL/6 mice</td>
<td>Upregulate UCP1 and PGC-1α in iWAT</td>
<td>Unclear</td>
<td>[96]</td>
</tr>
<tr>
<td>Classification</td>
<td>Name</td>
<td>Source</td>
<td>Dose</td>
<td>Activity</td>
<td>Pathway</td>
<td>Ref</td>
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</tr>
<tr>
<td><strong>Spirulina extract</strong></td>
<td>family Spirulina</td>
<td></td>
<td></td>
<td>Regulate lipid accumulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phaeodactylym tricornutum extract</strong></td>
<td>Phaeodactylym tricornutum</td>
<td></td>
<td></td>
<td>Reduce adipocyte diameter; Activate BAT</td>
<td>unclear</td>
<td>[100]</td>
</tr>
<tr>
<td><strong>Extract</strong></td>
<td>Pycnogenol*</td>
<td>French maritime pine bark of family Pinaceae</td>
<td></td>
<td>Inhibit body weight gain and epididymal fat gain</td>
<td>PKA pathway</td>
<td>[103]</td>
</tr>
<tr>
<td><strong>Water extract of Caulis Spatholobi</strong></td>
<td>the vine stem of Spatholobus erectus</td>
<td></td>
<td></td>
<td>Improve glucose and insulin tolerance; Augmented BAT mitochondrial function and oxygen consumption; Inhibit body weight gain</td>
<td>Regulate gut microbiota</td>
<td>[105]</td>
</tr>
<tr>
<td><strong>Blueberry extract</strong></td>
<td>Blueberry (Vaccinium spp.) family Ericaceae</td>
<td>0.5% (W/W) in drinking water for DIO mice</td>
<td></td>
<td>Inhibit body weight gain</td>
<td>Regulate gut microbiota and bile acids</td>
<td>[107]</td>
</tr>
<tr>
<td><strong>Strawberry methanolic extract</strong></td>
<td>Strawberry (Fragaria × ananassa) family Rosaceae</td>
<td>1% (W/W) in drinking water for C57BL/6J mice</td>
<td></td>
<td>Augment BAT mitochondrial function and oxygen consumption</td>
<td>Regulate gut microbiota</td>
<td>[108]</td>
</tr>
<tr>
<td><strong>Black raspberry water extract</strong></td>
<td>the genus Rubus family Rosaceae</td>
<td>5 and 10 μg·mL⁻¹ for 3T3-L1 cell; 100 mg·kg⁻¹·d⁻¹ p.o. for C57BL/6J mice</td>
<td></td>
<td>Reduce lipid droplets accumulation</td>
<td>Unclear</td>
<td>[109]</td>
</tr>
<tr>
<td><strong>Averrhoa bilimbi ethanolic extract</strong></td>
<td>leaf of Averrhoa bilimbi</td>
<td>100 μg·mL⁻¹ for 3T3-L1 cell</td>
<td></td>
<td>Increase oxygen consumption</td>
<td>Unclear</td>
<td>[111]</td>
</tr>
<tr>
<td><strong>Germinated soy germ extract</strong></td>
<td>Soybean (Glycine max) family Leguminosae</td>
<td>0.1, 1 and 10 μg·mL⁻¹ for 3T3-L1 cell; HFD added 1 mg·kg⁻¹ for female C57BL/6J mice</td>
<td></td>
<td>Increase cell viability in premature period of 3T3-L1; Decrease lipid accumulation</td>
<td>unclear</td>
<td>[113]</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Genipin</td>
<td>The fruit of Gardenia jasminoides</td>
<td>12.5 or 25 mg·kg⁻¹·d⁻¹ i.p. for DIO Sprague-Dawley rat</td>
<td>Reduce body weight, food intake, and visceral fat mass; Ameliorate dyslipidemia, glucose intolerance, insulin intolerance, adipocyte hypertrophy, and hepatic steatosis; Reduce serum TNF-α level</td>
<td>Unclear</td>
<td>[115]</td>
</tr>
<tr>
<td><strong>L-rhamnose</strong></td>
<td>Lipopolysaccharides in Gram-negative bacteria and pectin in plants</td>
<td>10, 50 and 100 μmol·L⁻¹ for 3T3-L1 or HIB1B adipocytes</td>
<td></td>
<td>Upregulate PRDM16, TMEN26 and UCP1</td>
<td>SIRT1, PKA and P38 pathway</td>
<td>[117]</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Ostreolysin</td>
<td>Pleurotus ostreatus</td>
<td>10 μg·mL⁻¹ for 3T3-L1 cell</td>
<td>Induce mitochondrial biogenesis; Inhibit inflammation Reverse hepatic steatosis Improve insulin resistance</td>
<td>AMPK pathway</td>
<td>[119]</td>
</tr>
<tr>
<td><strong>Glucoraphanin</strong></td>
<td>Hydrolyzed product produced by gut microbiota</td>
<td>0.3% in HFD for DIO mice</td>
<td></td>
<td>Decreases weight gain and adiposity; Increases energy expenditure; Improve diet-induced insulin resistance and glucose tolerance</td>
<td>Keap1-Nrf2 pathway; Regulate gut microbiota</td>
<td>[122]</td>
</tr>
</tbody>
</table>
ing property plays a significant role in not only obesity but also in T2DM treatment. Thus, based on the safety and good efficacy, natural products of inducing browning may be an irreplaceable drug for obesity, diabetes and even other metabolic disorders in the future.

References


Menezes Maciel Bindes M, Hespanhol Miranda Reis M, Luiz Cardoso V, et al. Ultrasound-assisted extraction of bioactive compounds from green tea leaves and clarification with natural surfactants (chitosan and Moringa oleifera seeds) [J]. Ultrason Sonochem, 2019, 51: 111-119.


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