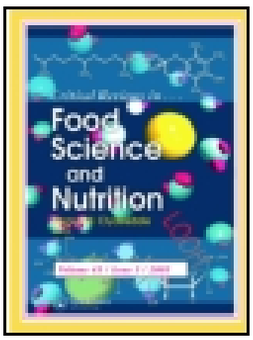

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REVIEW

Effects and mechanisms of edible and medicinal plants on obesity: an updated review

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ABSTRACT

In recent years, obesity has become a global public health issue. It is closely associated with the occurrence of several chronic diseases, such as diabetes and cardiovascular diseases. Some edible and medicinal plants show anti-obesity activity, such as fruits, vegetables, spices, legumes, edible flowers, mushrooms, and medicinal plants. Numerous studies have indicated that these plants are potential candidates for the prevention and management of obesity. The major anti-obesity mechanisms of plants include suppressing appetite, reducing the absorption of lipids and carbohydrates, inhibiting adipogenesis and lipogenesis, regulating lipid metabolism, increasing energy expenditure, regulating gut microbiota, and improving obesity-related inflammation. In this review, the anti-obesity activity of edible and medicinal plants was summarized based on epidemiological, experimental, and clinical studies, with related mechanisms discussed, which provided the basis for the research and development of slimming products. Further studies should focus on the exploration of safer plants with anti-obesity activity and the identification of specific anti-obesity mechanisms.

KEYWORDS

Anti-obesity; appetite; energy expenditure; mechanisms; plants

Introduction

Obesity is a major risk factor for many metabolic disorders and chronic diseases like diabetes, cardiovascular diseases, and certain cancers (Guo et al. 2018). In recent years, obesity has become a serious public health issue, with an estimated 107.7 million children and 603.7 million adults becoming obese in 2015 worldwide (Afshin et al. 2017). It is stated that obesity is characterized by increased body weight and adipose tissue due to the chronical energy intake exceeding body energy expenditure (Spiegelman and Flier 2001). The consequence of energy imbalance is the excessive energy storage in adipocytes, in which the accumulation of triglycerides leads to its hypertrophy, and adipocyte excessive differentiation leads to its hyperplasia (Hara-Chikuma et al. 2005; Kubota et al. 1999). The hypertrophy, hyperplasia, and the related intracellular dysfunction of adipocytes trigger the production of adipocytokines, free fatty acids, and inflammatory mediators, leading to systemic dysfunction and the initiation of obesity (De Ferranti and Mozaffarian 2008). Currently, pharmacotherapy is a common treatment strategy, but most synthetic drugs have side effects (Fu et al. 2016; Schroll, Penninga, and Gotzsche 2016). For example, the common anti-obesity drug orlistat is effective in treating obesity by inhibiting lipase activity and reducing the absorption of long-chain triglycerides, however, it also shows certain adverse effects, such as gastrointestinal reactions, which are harmful to human health (Sjostrom et al. 1998).

Dietary supplement is a product aiming to supplement one or more dietary components, including vitamins, minerals, protein, weight loss, and sports nutrition products (Ahmad et al. 2020). The consumption of natural supplements has been widely popular in the world. The global dietary supplement market is estimated at about 123 billion dollars by the end of 2015, and weight-loss products are one of the major contributors (Sun, Wu, and Chau 2016). Due to the non-toxicity or low toxicity, edible and medicinal plants and their bioactive components have gained increasing attention in the prevention and management of chronic diseases (Shang et al. 2019; Xu et al. 2018, 2020; Zheng et al. 2017). Also, several plants have been developed as natural dietary supplements for weight loss, such as green tea, garcinia, Yerba Maté, and white bean (Barrett and Udani 2011; Jayawardena et al. 2020; Kim et al. 2015). A number of studies have reported that many other edible and medicinal plants can fight against obesity, such as lingonberry, red cabbages, ginger, aloe vera, and omija fruits (Kowalska et al. 2019; Mao et al. 2019; Park et al. 2017; Podsędek, Majewska, and Kucharska 2017; Walid et al. 2018). In addition, some

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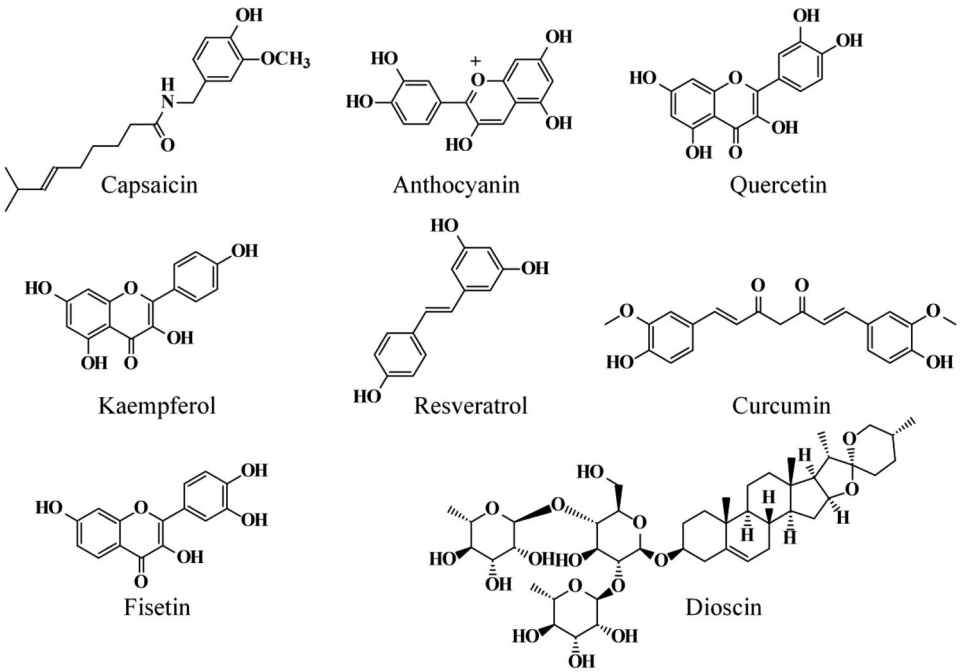

Figure 1. The chemical structures of representative bioactive compounds with anti-obesity activity.

bioactive compounds (Figure 1) derived from plants, such as capsaicin, anthocyanin, quercetin, dioscin, and kaempferol, have also shown anti-obesity activity (Badshah et al. 2013; Poudel et al. 2014; Seo et al. 2015; Torres-Villarreal et al. 2019; Tremblay, Arguin, and Panahi 2016). Moreover, the anti-obesity mechanisms mainly include the inhibition of appetite, reduction of the absorption of lipids and carbohydrates, inhibition of adipogenesis and lipogenesis, regulation of lipid metabolism, increase in energy consumption, regulation of gut microbiota, and improvement of obesity-related inflammation (Muccioli et al. 2010; Poudel et al. 2014; Tung et al. 2017; Walid et al. 2018). In order to provide an updated understanding of the relationship between plants and obesity, this review discusses the anti-obesity activity of representative edible and medicinal plants, with highlighting their related mechanisms. We hope that this review can be helpful in future research to develop dietary supplements for the prevention and management of obesity and obesity-related diseases.

Epidemiological studies

Many epidemiological studies have shown that the intake of edible and medicinal plants has a positive effect on weight loss. For example, an analysis of the children aged 2–18 years ($N = 14{,}690$) showed that the children consuming oatmeal had a lower risk of central adiposity and obesity (O'Neil et al. 2015). Moreover, a study revealed that a lower risk of obesity was associated with the intake of oat-based cereal (OR 0.71; 95% CI 0.55–0.90), muesli (OR 0.57; 95% CI 0.43–0.75), and all-bran (OR 0.62; 95% CI 0.44–0.87) in breakfast of mid-aged participants (Quatela et al. 2017). Therefore, the consumption of certain cereals in the daily diet, especially oats, may help maintain a healthy weight. Another study showed that the intake of tomato before lunch for 4 weeks significantly reduced body weight and fat percentage by 1.09 ± 0.12 kg and $1.54\% \pm 0.52\%$ in young women, respectively (Vinha et al. 2014). This suggests that more studies can be done to investigate whether eating other vegetables or fruits before meals have the same anti-obesity effect because they are rich in dietary fiber and can improve satiety, but it is important to consider that some fruits are high in carbohydrates and energy. In addition, a meta-analysis suggested that supplements of capsaicin or capsinoids could increase the energy consumption for 58.56 kcal/day and decrease the respiratory quotient by 0.216, indicating an increase in fat oxidation (Zsiborás et al. 2018). Hence, the spicy food may help lose weight.

In general, epidemiological studies suggest that certain plants have anti-obesity activity, such as several cereals, vegetables, and spices. In addition, the increase in the proportion of these plants in diets can play a positive role in weight loss, which should be further verified in epidemiological studies, as the results providing critical references for the public to consume an obesity-loss diet when necessary.

Experimental studies

The anti-obesity activity of many edible and medicinal plants has been evaluated by experimental studies, including *in vitro* cellular experiments and *in vivo* animal models (Table 1). The related anti-obesity mechanisms are discussed and highlighted below.

Suppressing the appetite

A stimulated appetite increases the consumption of foods, which might cause the energy intake to exceed the expenditure, finally leading to obesity (Timper and Bruning 2017).

Table 1. The anti-obesity activity of edible and medicinal plants in experimental studies.

Plants	Main anti-obesity molecules	Study type	Models and inducers	Doses	Main effects and mechanisms	Ref.
Fruits						
Cranberry (*Oxycoccus quadripetalus*)	Polyphenols	*In vitro*	3T3-L1 cells	5, 10, and 20 mg/mL	Suppressing adipogenesis and lipogenesis Reducing the expression of adipogenic transcription factors, such as PPAR-γ, C/EBP-α, and SREBP-1	Kowalska et al. (2014)
Korean white mulberry (*Morus alba*)	Polysaccharide JS-MP-1	*In vitro*	3T3-L1 cells	50, 100, 200, and 500 μg/mL	Inhibiting the proliferation of 3T3-L1 cells Inducing the mitochondrial dysfunction and apoptosis of 3T3-L1 cells Increasing the expression of the cleavage of caspases 3, caspases 9, and poly (ADP-ribose) polymerase Reducing the ratio of Bcl-2 to Bax	Choi et al. (2016)
Lingonberry (*Vaccinium vitis-idaea*)	Flavonols, phenolic acids, anthocyanins, proanthocyanidins	*In vitro*	3T3-L1 cells RAW 264.7 macrophages	0.05, 0.5, and 1 mg/mL; 1, 2.5, and 5 mg/mL	Reducing intracellular ROS generation Increasing SOD, catalase, glutathione peroxidase, and suppressing NADPH oxidase 4 Decreasing the expression of IL-6, TNF-α, IL-1β, MCP-1, COX-2, and iNOS	Kowalska et al. (2019)
Lychee seed (*Litchi chinensis*)	Flavonoids	*In vitro*	3T3-L1 cells	8, 40, and 200 μg/mL	Inhibiting the differentiation of adipocytes Downregulating PPAR-γ, C/EBP-α, -β, -δ and KLF9	Qi et al. (2015)
Tamarind (*Tamarindus indica*)		*In vitro*	Pancreatic lipase, α-amylase		Inhibiting the activity of pancreatic lipase, α-amylase	Buchholz and Melzig (2016)
Carbohydrate-free peach (*Prunus persica*) and plum (*Prunus domestica*) juice	Polyphenols	*In vivo*	5- to 6-week-old male Zucker-Lepr^{fa}/Lepr^{+} rats		Regulating gut microbiota Increasing the levels of *Lactobacillus* and *Ruminococcus* family in their feces	Noratto et al. (2014)
Tejocote (*Crataegus pubescens*)	Gallic acid	*In vivo*	Male Wistar rats	Administered *ad libitum*	Increasing excretion of fecal triacylglycerol Decreasing the accumulation of adipose tissue	Perez-Ramirez et al. (2017)
Grapes (*Vitis vinifera*)	Resveratrol	*In vivo*	Standard diet-fed 4-week-old male mice	0.4% wt/wt	Decreasing the fat accumulation Increasing thermogenesis Upregulating the expression of UCP1 and SIRT1	Andrade et al. (2014)
Red pitaya (*Hylocereus polyrhizus*)	Betacyanins	*In vivo*	HFD-fed male C57BL/6J mice	200 mg/kg	Reducing body weight gain Modulating gut microbiota Downregulating the ratio of *Firmicutes* and *Bacteroidetes* Increasing *Akkermansia*	Song et al. (2016)
Raspberry (*Rubus idaeus*)	Polyphenols	*In vivo*	HFD-fed wild-type and AMPK$\alpha1^{-/-}$ mice	5%	Decreasing ectopic lipid deposition Improving inflammatory responses	Zhao et al. (2018)
Rubi Fructus (*Rubus coreanus*)	Ellagic acid	*In vivo*	HFD-fed male C57BL/6 mice	100 mg/kg	Reducing the weight of body and adipose tissue Decreasing the expression of FAS, SREBP-1c, LXR, ACC, and LPL	Nam et al. (2014)
Persimmon fruit (*Diospyros kaki*) and mandarin peel (*Citrus unshiu*)	Polyphenols	*In vitro*	Porcine pancreatic lipase	100, 250, 500, and 1000 μg/mL	Inhibiting the activity of lipase	Kim et al. (2016)
		In vivo	HFD-fed 4-week-old male ICR mice	50 and 200 mg/kg B.W.	Reducing the levels of serum TC, TG, and visceral fat weight	
Vegetables						
Borage (*Borago officinalis*)	Phenols	*In vitro*	α-amylase	31.25–1000 μg/mL	Suppressing the activity of α-amylase	Marrelli et al. (2014)
Red cabbage (*Brassica oleracea*)	Anthocyanins	*In vitro*	α-glucosidase, α-amylase, lipase		Suppressing the activity of α-glucosidase, α-amylase	Podsędek, Majewska, and Kucharska (2017)
Watercress (*Nasturtium officinale*)	Polyphenols	*In vitro*	α-glucosidase, α-amylase, lipase		Inhibiting the activity of α-glucosidase	Spinola, Pinto, and Castilho (2017)
Cruciferous vegetables	Sulforaphanes	*In vivo*	HFHS-fed male C57BL/6J mice	0.5 mg/kg B.W.	Suppressing appetite and the cumulative food intake	Shawky and Segar (2018)
		In vivo			Decreasing body weight gain	Han et al. (2018)

(*continued*)

Table 1. Continued.

Plants	Main anti-obesity molecules	Study type	Models and inducers	Doses	Main effects and mechanisms	Ref.
Purple lettuce (*Lactuca sativa*)	Esculin, chlorogenic acid		4-week-old male C57BL/6J mice	2.5, 5, and 10%	Reducing fat accumulation Increasing energy consumption Regulating gut microbiota	
Purple sweet potato (*Ipomoea batatas*)	Anthocyanins	*In vivo*	HFD-fed C57BL/6J mice	15 and 30%	Reducing HFD-induced obesity Decreasing body weight and fat accumulation Regulating energy expenditure	Ju et al. (2017)
Cereal						
Wheat (*Triticum aestivum*)	Alkylresorcinols	*In vivo*	HFHS-fed 3-week-old male C57BL/6J mice	0.4% wt/wt	Alleviating diet-induced obesity Inhibiting the absorption of intestinal cholesterol Increasing fecal cholesterol excretion	Oishi et al. (2015)
Legumes						
Black soybean seed coat (*Glycine max*)	Anthocyanins	*In vivo*	Male Sprague-Dawley rats	6 and 24 mg/kg B.W.	Suppressing appetite Reducing body weight and food intake Downregulating the expression of NPY and upregulating $GABA_{B1}R$ Decreasing the expression of protein kinase A-α and p-CREB	Badshah et al. (2013)
	Cyanidin 3-glucoside, procyanidins	*In vivo*	HFD-fed 4-week-old male C57BL/6 mice	0, 0.2, 1, and 2% wt/wt	Elevating UCP1 in BAT Elevating UCP2 in WAT Decreasing inflammatory cytokines	Kanamoto et al. (2011)
Soymilk residue Okara (*Glycine max*)	Dietary fiber	*In vivo*	HFD-fed 4-week-old male Jcl:ICR mice	10% wt/vol suspension as a drinking water	Reducing the triglyceride in the blood Decreasing the digestion and absorption of lipids Suppressing the activity of lipase	Nishibori, Kishibuchi, and Morita (2018)
Spices						
Alligator pepper seed (*Amomum melegueta*)	6-Paradol	*In vivo*	HFD-fed 5-week-old male C57BL/6J mice	0.1% (0.1 g extract/100 g HFD)	Enhancing thermogenesis and energy expenditure in BAT Upregulating the expression of UCP-1	Haratake et al. (2014)
CH-19 sweet peppers (*Capsicum annuum*)	Capsinoids	*In vivo*	HFD-fed 9-week-old male *UCP1*-KO mice, C57BL/6J mice	0.3% wt/wt	Decreasing body weight gain Attenuating adiposity and fatty liver Targeting the UCP1 protein in BAT	Okamatsu-Ogura et al. (2015)
Clove (*Syzygium aromaticum*)	Eugenol, β-caryophyllene	*In vivo*	HFD-fed 5-week-old male C57BL/6J mice	1% (1 g extract/100 g HFD)	Reducing lipid accumulation Decreasing the weights of body and abdominal adipose tissue Reducing the lipid deposition Regulating TG, LDL-C	Ding et al. (2017)
Ginger (*Zingiber officinale*)	6-Gingerol	*In vivo*	45% HFD-fed Sprague-Dawley rats	8 g/kg diet	Improving obesity and inflammation Downregulating the expression of microRNA-21/132 and activating AMPK in WAT	Kim et al. (2018)
Tulsi plant (*Ocimum sanctum*)	Ellagic acid, epigallocatechin gallate, rutin	*In vivo*	Male Wistar rats	Administered *ad libitum*	Increasing excretion of fecal triacylglycerol Decreasing the accumulation of adipose tissue,	Perez-Ramirez et al. (2017)
Cinnamon (*Cinnamomum zeylanicum*)	Cinnamaldehyde	*In vitro*	MGN3-1 cells (mouse ghrelinoma 3-1)	100 mM	Increasing the expression of TRPA1 Decreasing the secretion of octanoyl ghrelin and total ghrelin	Camacho et al. (2015)
		In vivo	HFD-fed C57BL6/J mice, C57BL/6NTac mice, $TRPA1^{-/-}$ mice	0.2% wt/wt	Reducing body weight gain Inhibiting the accumulative food intake Decreasing the secretion of ghrelin Reducing the gastric emptying	
Flowers						
Roselle (*Hibiscus sabdariffa*)	Hibiscus acid	*In vitro*	Porcine pancreatic lipase α-amylase		Inhibiting activities of pancreatic lipase and α-amylase	Buchholz and Melzig (2016)
	Flavonoids	*In vitro*			Increasing the phosphorylation of AMPK	Liu et al. (2017)

Paulownia (*Paulownia fortunei*)			Human HepG2 hepatocytes	10, 25, 50, and 100 g/mL	Decreasing fat deposits	
		In vivo	HFD-fed male ICR mice	50 and 100 mg/kg	Decreasing the gain of body weight Decreasing lipid accumulation	
Goldenrod (*Solidago virgaurea*)	Keampferol-3-O-rut-inoside, chlorogenic acid, protocatechuic acid	*In vitro* *In vivo*	3T3-L1 cells HFD-induced obese 5-week-old male C57BL/6 N mice	10 μg/mL 0.5 and 2 % wt/wt	Inhibiting adipogenesis Decreasing the body weight gain, the weight of liver and the size of adipose tissue Inhibiting genes related to adipogenesis, including fatty acid-binding protein-4, PPAR-γ, C/EBP-α, FAS, SCD-1, SREBP-1c, and CD36 in WAT and liver	Wang et al. (2017)
Medicinal plants						
Sojutsu (*Atractylodes lancea*)	Atractylodin	*In vitro*	Human pancreatic lipase		Suppressing the activity of human pancreatic lipase	Jiao et al. (2014)
Caper (*Capparis sicula*)	Rutin	*In vitro*	Pancreatic lipase		Suppressing the activity of pancreatic lipase	Marrelli et al. (2014)
Calabash (*Lagenaria siceraria*)	Fatty acids	*In vitro*	Porcine pancreatic lipase	25–600 μg/mL	Suppressing the activity of pancreatic lipase	Maqsood et al. (2017)
Turmeric (*Curcuma longa*)	Curcumin	*In vitro*	3T3-L1 cells and white adipocytes	1–20 μM	Changing into brown fat-like phenotype in white adipocytes Upregulating the expression of *Tmem26*, *Cidea*, *Fgf21*, and *Cited1* Increasing the brown adipocytes marker proteins, such as C/EBP-β, PGC-1α, PRDM16 and UCP1	Lone et al. (2016)
Ba Qia (*Smilax china*)	Polyphenols	*In vitro*	3T3-L1 cells	0.05, 0.1, and 0.25 mg/mL	Increasing lipolysis Activating hormone-sensitive lipase via the β-adrenergic receptor-cAMP-PKA pathway	Kang et al. (2015)
Aloe vera gel (*Aloe barbadensis*)	Gallic acid, quercetin	*In vivo*	4-week-old male Wistar rats	100 and 200 mg/kg B.W.	Decreasing fat accumulation Activating adipose lipolysis Improving oxidative stress	Walid et al. (2018)
Sifangshuiniuji-ao (*Caralluma quadrangular*)	Russelioside B	*In vivo*	Male Wistar rats	25 and 50 mg/kg B.W.	Decreasing body weight gain Increasing energy expenditure Enhancing the expression of UCP1 and CPT-1 in the BAT	Abdel-Sattar et al. (2018)
Ulam Raja (*Cosmos caudatus*)	Polyphenols	*In vivo*	HFD-fed 5- to 6-week-old male Sprague dawley rats	175 and 350 mg/kg B.W.	Decreasing body weight gain Increasing the excretion of fecal fat	Rahman et al. (2017)
Zhemu fruit (*Cudrania tricuspidata*)	6,8-Diprenylgenist-ein	*In vivo*	HFD-fed male C57BL/6J mice	10 and 30 mg/kg	Decreasing body weight and fat accumulation Reducing PPAR-γ and C/EBPα Reducing leptin and adiponectin Modulating ACC and HMGCR by activating AMPK	Jo et al. (2015)
Curry leaves (*Murraya koenigii*)	Mahanimbine	*In vivo*	HFD-fed 7–8 weeks old both sex Swiss albino mice	2 and 4 mg/kg B.W.	Reducing body weight gain Decreasing the dietary fat absorption Increasing fat excretion in HFD-fed mice	Jagtap et al. (2017)
Sweet tea tree (*Cyclocarya paliurus*)	Polysaccharides	*In vivo*	7-week-old male SHR.Cg-Leprcp/NDmcr rats	0.5 g/kg B.W.	Reducing appetite Activating the insulin-signaling pathway Upregulating p-Akt and sequentially phosphorylating FoxO1 Increasing POMC and decreasing NPY in the hypothalamus	Xu et al. (2017)
Kokum fruit rind (*Garcinia indica*)	Garcinol	*In vivo*	HFD-fed 5-week-old male C57BL/6 mice	0.1 and 0.5%	Modulating gut microbiota Improving gut dysbiosis	Lee et al. (2019)
Omija (*Schisandra chinensis*)	Phenols	*In vivo*	HFD-fed C57BL/6J mice	500 mg/kg B.W.	Inducing the browning of WAT Increasing the expression of *Cidea* and *Cox8*β Increasing energy expenditure	Park et al. (2017)
Mondo grass (*Ophiopogon japonicas*)	MDG-1	*In vivo*	HFD-fed 8-week-old male C57BL/6J mice	300 mg/kg B.W.	Decreasing the weight of body and adipose tissue Enhancing the energy expenditure and oxygen consumption	Wang et al. (2014)
Matarique root (*Psacalium decompositum*)	Fructo-oligosaccha-rides	*In vivo*	Fructose-induced obese male Wistar rats	150 mg/kg	Reducing body weight, TC and TG	Merino-Aguilar et al. (2014)

(*continued*)

Table 1. Continued.

Plants	Main anti-obesity molecules	Study type	Models and inducers	Doses	Main effects and mechanisms	Ref.
					Downregulating the levels of inflammatory mediators, including inflammatory cytokines IL-1, IL-6, IFN-γ, MCP-1, and VEGF	
Kindal bark (*Terminalia paniculata*)	Polyphenols, triterphenoids	*In vivo*	HFD-fed 6- to 8-week-old male Sprague–Dawley rats	100, 150, and 200 mg/kg B.W.	Reducing body weight Inhibiting adipogenesis Decreasing the expression of FAS, leptin, adiponectin, PPAR-γ, and SREBP-1c, Increasing the expression of AMPK-1α	Mopuri et al. (2015)
Maidenhair fern (*Adiantum capillus-veneris*)	Chlorogenic acid, ellagic acid, ferulic acid	*In vitro*	Pancreatic lipase α-amylase/ α-glucosidase	0.24–100 mg/mL	Suppressing the activity of pancreatic lipase	Kasabri et al. (2017)
		In vivo	High cholesterol diet-fed male Wistar rats	500 mg/kg B.W. *ad libitum*	Decreasing body weight gain	
Sepiaria leaf (*Aegle marmelos*)	(3,3-dimethylallyl) halfordinol	*In vitro*	3T3-L1 cells	5–20 μg/mL	Stimulating lipolysis of adipocytes Decreasing the accumulation of triglyceride Increasing the release of glycerol	Saravanan et al. (2014)
		In vivo	High fat and fructose diet-induced obese C57/BL6J mice	50 mg/kg B.W.	Decreasing adipose tissue mass Reducing the expression of PPAR-γ, C/EBP-α, SREBP-1c, PPAR-α, and GLUT4	
Corn silk (*Zea mays*)	β-sitosterol	*In vitro*	3T3-L1 cells	600 and 800 μg/mL (corn silk extract); 50 and 100 μM (β-sitosterol)	Suppressing the adipogenesis Inhibiting the deposition of lipid Reducing the gene expression of galectin-12 Decreasing the expression of PPAR-γ, C/EBP-α, C/EBP-β, FAS, LPL, aP2, and adipsin	Hsu et al. (2018)
		In vivo	4-week-old C57BL/6 mice	400 mg/kg B.W. (corn silk extract); 5 and 10 mg/kg B.W. (β-sitosterol)	Reducing weight	
Chuanshanlong (*Dioscorea nipponica*) and Dunyeshuyu (*Dioscorea zingiberensis*)	Dioscin	*In vitro*	3T3-L1 cells	1, 2, and 4 μM	Suppressing the differentiation of 3T3-L1 cells Inhibiting adipogenesis by delaying the cell cycle at G_0/G_1 Decreasing the phosphorylation of MAPKs, ERK1/2, and p38 Increasing the phosphorylation of AMPK and ACC	Poudel et al. (2014)
		In vivo	HFD-fed 5-week-old male C57BL/6J mice	50 and 100 mg/kg	Reducing body weight gain	
		In vivo	HFD-fed 5-week-old male ob/ob mice and C57BL/6J mice	20, 40, and 80 mg/kg B.W.	Reducing body weight and liver lipid accumulation Increasing oxygen consumption and energy expenditure	Liu et al. (2015)
Fermented mixture of Tuoshu (*Cudrania tricuspidata*), Honeyberry (*Lonicera caerulea*), and soybean (*Glycine max*)	Flavonoid aglycones	*In vitro*	Porcine pancreatic lipase		Suppressing the activity of lipase	Suh et al. (2016)
		In vivo	HFD-fed male Sprague–Dawley rats	150 and 300 mg/kg B.W.	Reducing body weight and body weight gain. Increasing the expression of AMPK Decreasing the expression of PPAR-γ	
Purple perilla (*Perilla frutescens*)	Rosmarinic acid	*In vitro*	3T3-L1 cells	0.1, 0.25, 0.5, 0.75, and 1 mg/mL	Increasing the expression of lipolytic genes Reducing the lipid accumulation	Thomas et al. (2018)
		In vivo	HFD-fed 4-week-old C57BL/6J mice	100 and 400 mg/kg B.W.	Decreasing body weight gain Upregulating ATGL and HSL in the adipose tissue and liver	
Thunder god vine (*Tripterygium wilfordii*)	Celastrol	*In vitro*	LPS-treated murine macrophage cell line RAW264.7	0.25, 0.5, 0.75, and 1 μM	Inhibiting the pro-inflammatory M1 polarization Inhibiting MAPKs, including ERK1/2, JNK, and p38 Reducing the NF-κB p65 subunit, as well as activating Nrf2 and the expression of HO-1	Luo et al. (2017)
		In vivo			Decreasing fat accumulation	

			HFD-fed 3- to 4-week-old male C57BL/6N mice	5 and 7.5 mg/kg B.W.		
Niu-chang-chih (*Withania somnifera*)	Withaferin A	*In vitro*	3T3-F442A cell	0.25, 0.5 and 1 μM	Decreasing lipid accumulation Inhibiting adipogenesis Downregulating expressions of PPAR-γ and C/EBP-α	Khalilpourfarshbafi et al. (2019)
		In vivo	45 kcal% HFD-fed 4-week-old male C57BL/6J mice	6 mg/kg B.W. (intraperitoneal injection)	Decreasing body weight gain Reducing epididymal and mesenteric fat mass	
Others						
Fruits, vegetables and tea	Kaempferol	*In vitro*	3T3-L1 cells	60 μM	Inhibiting the adipocyte differentiation Decreasing the expression of C/EBPα Reducing lipid accumulation Increasing the mRNA levels of lipolysis genes, such as ATGL and HSL	Torres-Villarreal et al. (2019)
Cereals, bamboo and sugar cane	Tricin	*In vivo*	HFD-fed 4-week-old male C57BL/6 mice	50 and 200 mg/kg diet	Inhibiting the transcription factors related to the differentiation of adipocytes Reducing the expression of lipogenic enzymes of the fat synthesis in the mice liver, such as FAS, SCD-1, ELOVL6, GPAM, and DGAT	Lee and Imm (2018)
Fruits and vegetables	Fisetin	*In vivo*	HFD-fed 4-week-old male C57BL/6 mice	20 mg/kg B.W.	Decreasing weights of body and epididymal adipose tissue Increasing lipolysis in hepatocytes Improving the metabolism of hepatic lipid	Liou et al. (2018)
Fruits, vegetables cereals and bran	Oat β-glucan, fructo-oligosaccharide, apple pectin	*In vivo*	12-week-old outbred male Sprague Dawley rats	10% wt/wt	Suppressing appetite Reducing food intake and body weight	Adam et al. (2014)
Fruits, vegetables, leaves, and grains	Quercetin	*In vitro*	Pancreatic lipase 3T3-L1 cells	6.25, 12.5, and 25 μM	Decreasing lipid accumulation Inhibiting the ERK1/2, JNK, p38, MCP-1, and TNF-α	Seo et al. (2015)
		In vivo	HFD-fed mice	25, 50, and 100 mg/mL	Decreasing body weight Reducing obesity-induced inflammation	
Cruciferous vegetables	3,3′- diindolylmethane	*In vitro*	3T3-L1 cells	20, 40, and 60 μM	Inducing cell cycle arrest at G_1 phase Inhibiting the activity of USP2 Inducing the post-translational degradation of cyclin D1	Yang et al. (2017)
		In vivo	HFD-fed 6-week-old male C57BL/6N mice	10 and 50 mg/kg B.W.	Decreasing the weight of body and the epididymal WAT Inhibiting adipogenesis and lipogenesis	
Ryegrass (*Lolium multiflorum*)	Ferulic acid	*In vitro*	3T3-L1 cells	0.2, 0.4, 0.6, 0.8, 1, and 2 mM	Decreasing the deposition of lipid Decreasing the expressions of C/EBP-β, C/EBP-α, PPAR-γ, and SREBP-1	Ilavenil et al. (2017)
		In vivo	HFD-fed 5-week-old Swiss albino male mice	25 and 50 mg/kg B.W.	Reducing the body weight gain Decreasing the levels of TC and TG	

ACC, acetyl-CoA carboxylase; AGPAT, 1-acylglycerol-3-phosphate acyltransferase; AMPK, AMP-activated protein kinase; aP2, fatty acid binding protein-4; BAT, brown adipose tissue; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; B.W., body weight; CD36, fatty acid translocase; C/EBP, CCAAT/enhancer-binding protein; CPT-1, carnitine palmitoyltransferase 1; DGAT, diglyceride acyltransferase; ELOVL6, elongation of long-chain fatty acids family member 6; ERK1/2, extracellular-regulated kinase 1/2; FAS, fatty acid synthase; *Fgf21*, fibroblast growth factor 21; FoxO1, forehead box-containing protein of the O subfamily 1; $GABA_{B1}R$, γ-amino butyric acid receptor; GLUT4, glucose transporter 4; GPAM, glycerol-3-phosphate acyltransferase; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; HFHS, high-fat high-sucrose diet; HMGCoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HO-1, heme oxygenase-1; IFN, interferon; KLF9, kruppel-like factor 9; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; LPS, lipopolysaccharide; LXR, liver X receptor; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor-κB; Nfr1, nuclear respiratory factor 1; NPY, neuropeptide Y; Nrf2, nuclear factor (erythroid-derived 2)-related factor-2; p-Akt, phosphorylated protein kinase B; p-CREB, phosphorylated cAMP-response element binding protein; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1 α; POMC, proopiomelanocortin; PPAR, peroxisome proliferation-activated receptor; PRDM16, PR domain-containing 16; ROS, reactive oxygen species; SCD-1, stear-oyl-CoA desaturase-1; SIRT1, sirtuin 1; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element binding protein-1c; TC, total cholesterol; TG, total triglyceride; Tmem26, transmembrane protein 26; TNF-α, tumor necrosis factor-α; TRPA1, transient receptor potential-ankyrin receptor 1; UCP, uncoupling protein; USP2, ubiquitin specific peptidase 2; VEGF, vascular endothelial growth factor; WAT, white adipose tissue.

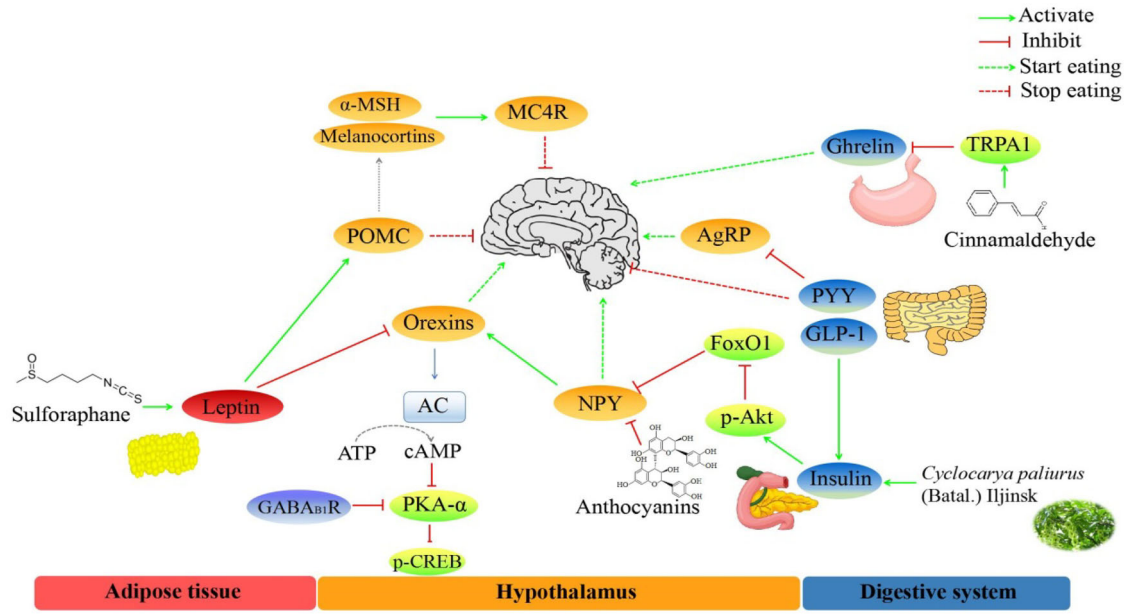

Figure 2. The mechanisms of edible and medicinal plants on the regulation of appetite. AC, adenylyl cyclase; AgRP, agouti gene-related protein; FoxO1, forehead box-containing protein of the O subfamily 1; $GABA_{B1}R$, γ-aminobutyric acid receptor; GLP-1, glucagon-likepeptide1; MC4R, melanocortin receptor 4; NPY, neuropeptide Y; p-Akt, phosphorylated protein kinase B; p-CREB, phosphorylated cAMP-response element-binding protein; PKA-α, protein kinase A-α; POMC, proopiomelanocortin; PPY, peptide YY; TRPA1, transient receptor potential ankyrin-1; α-MSH, α-melanocyte-stimulating hormone.

The control of appetite and the inhibition of over-eating in daily diet are considered an effective way to reduce weight gain (Zhang, Zhu, and Jiang 2014). Some current weight-loss drugs work as appetite suppressants, while many plants also can effectively prevent and manage obesity by suppressing the appetite. For example, the addition of three different soluble dietary fibers, including oat β-glucan, fructo-oligosaccharide, or apple pectin, to the regular feeding of rats, reduced food intake by 10%, 17%, and 19%, respectively, and also decreased the body weight of rats (Adam et al. 2014). Besides, resveratrol and pterostilbene could reduce the food intake and improve the seasonal spontaneous obesity of gray mouse lemurs (Dal-Pan, Blanc, and Aujard 2010).

Studies have shown that some neurotransmitters and hormones are the main factors in controlling appetite, satiety, and hunger (Camacho et al. 2015; Flier and Maratos-Flier 1998; Li et al. 2019; Shawky and Segar 2018). The neuropeptide Y (NPY)/agouti-related protein in the arcuate nucleus of hypothalamus are effective orexigenic neurotransmitter, and can promote food intake and delay satiety (Luquet et al. 2005). In addition, the proopiomelanocortin (POMC) in hypothalamus is a crucial anorexigenic neurotransmitter, and it can regulate food consumption, such as melanocortins and α-melanocyte-stimulating hormone (α-MSH), which act on melanocortin receptors and are also affected by leptin and insulin (Thornton et al. 1997). The aqueous extract of *Cyclocarya paliurus* (Batal.) Iljinsk inhibited the appetite via activating the insulin signaling pathway, upregulating phosphorylated protein kinase B, sequentially phosphorylating forehead box-containing protein of the O subfamily 1, increasing POMC expression, and decreasing NPY expression in the hypothalamus of SHR.Cg-Leprcp/NDmcr rats (Xu et al. 2017). Moreover, anthocyanins extracted from black soybean reduced food consumption and body weight of rats by downregulating the expression of NPY and increasing the receptor of γ-aminobutyric acid in the hypothalamus (Badshah et al. 2013). The same study also showed decreased expression of protein kinase A (PKA)-α and phosphorylated cAMP-response element-binding protein in the hypothalamus.

Some plants suppress appetite by regulating the secretion of POMC and NPY neurotransmitters in the hypothalamus, while other plants target hormones in adipose tissue and digestive system, which also affect satiety and hunger. Leptin, secreted by adipocytes, can act on the hypothalamus and control appetite. The sulforaphane from cruciferous vegetables enhanced the response to intraperitoneally-injected leptin and suppressed the cumulative food intake in diet-induced obese mice (Shawky and Segar 2018). Furthermore, the cinnamaldehyde commonly found in cinnamon inhibited the cumulative food intake of mice by decreasing the secretion of ghrelin in the stomach via activating the expression of transient receptor potential-ankyrin receptor 1 (Camacho et al. 2015).

Many people try to prevent obesity or lose weight by eating less, but the resulting hunger may lead to overeating afterward, while appetite suppression can reduce the discomfort of enduring hunger and making the process easier. Collectively, edible and medicinal plants can control appetite and feeding behavior by regulating NPY and POMC neurotransmitters, and several hormones, such as melanocortins, α-MSH, leptin, and insulin (Figure 2).

Reducing the digestion and absorption of lipids and carbohydrates

The digestion and absorption of lipids and carbohydrates are important processes for the development of obesity, and

the related digestive enzymes are crucial in this process (Marrelli et al. 2014; Rahman et al. 2017). For example, the lipases act on the digestion of lipids, while α-amylase and α-glucosidase contribute to the degradation of carbohydrates (Spinola, Pinto, and Castilho 2017). The dietary fats are hydrolyzed by lipases and bile salts into monoglycerides and fatty acids, which are absorbed in the small intestine and then resynthesized in the body, resulting in fat accumulation (De La Garza et al. 2011). The carbohydrates are hydrolyzed into monosaccharides by several specific enzymes, such as α-amylase and α-glucosidase, and some monosaccharides are synthesized into glycogen and converted into fat, thereby leading to obesity (Dhital et al. 2017; Tundis, Loizzo, and Menichini 2010). Therefore, suppressing the activity of enzymes and reducing the absorption of lipids and carbohydrates is an effective way to prevent obesity and lose weight.

Several edible and medicinal plants exhibit an anti-obesity effect via regulating the activities of relevant digestive enzymes in vitro. *Atractylodes lancea* rhizome extract markedly suppressed the activity of human pancreatic lipase (IC_{50} = 9.06 μg/mL), and its main compound atractylodin showed the highest inhibitory effect (IC_{50} = 39.12 μg/mL) on pancreatic lipase activity than other compounds in the extract (Jiao et al. 2014). Additionally, red cabbages showed inhibitory effects on digestive enzymes, and its total phenolics and diacylated anthocyanin content were positively associated with the suppression of α-glucosidase, while the inhibition of α-amylase was related to the content of monoacylated and diacylated anthocyanins (Podsędek, Majewska, and Kucharska 2017). Moreover, different solvents also affect enzyme inhibitory abilities of plants. For instance, the *Tamarindus indica* L. methanolic extract had a higher inhibitory activity on pancreatic lipase (IC_{50} = 152.0 ± 7.0 μg/mL) than the aqueous extract, while the latter had a higher inhibitory activity on α-amylase (IC_{50}=139.4 ± 9.0 μg/mL) (Buchholz and Melzig 2016). The specific compounds that inhibit the activity of enzymes need to be further investigated. Furthermore, the processing methods also had an impact on the inhibitory activity. The metabolites derived from the fermented mixture of *Cudrania tricuspidata*, *Lonicera caerulea*, and soybean exhibited a stronger inhibitory effect on lipase activity than unfermented mixture (Suh et al. 2016). More in vitro experiments on plants inhibited the pancreatic lipase, α-amylase, and α-glucosidase activity are presented in Table 1, including the *Diospyros kaki* fruit and *Citrus unshiu* peel mixture extract, *Capparis sicula* and *Borago officinalis* mixture extract, *Lagenaria siceraria* fruit, and water-cress juice (Kim et al. 2016; Maqsood et al. 2017; Marrelli et al. 2014; Spinola, Pinto, and Castilho 2017).

The plants could also reduce the absorption of lipids and carbohydrates in vivo (Kasabri et al. 2017; Rahman et al. 2017). The wheat alkylresorcinols alleviated diet-induced obesity in mice by inhibiting the absorption of intestinal cholesterol and increasing fecal cholesterol excretion (Oishi et al. 2015). Moreover, feeding of soymilk residue reduced the triglyceride in the blood of high-fat diet (HFD)-fed mice, and decreased the digestion and absorption of lipids via suppressing the activity of lipase in the intestinal tract (Nishibori, Kishibuchi, and Morita 2018). Also, *Adiantum capillus-veneris*, *Cosmos caudatus* Kunth leaf, *Leopoldia comosa*, *Ocimum sanctum*, *Crataegus pubescens* and mahanimbine could ameliorate obesity and reduce the absorption of lipids and carbohydrates by acting on key enzymes relative to obesity in animal models (Table 1) (Casacchia et al. 2019; Jagtap et al. 2017; Kasabri et al. 2017; Perez-Ramirez et al. 2017; Rahman et al. 2017).

In short, some plants can play a crucial role in weight loss and reduce the absorption of lipids and carbohydrates by inhibiting digestive enzymes, like lipase, α-amylase, and α-glucosidase. These plants are also potential candidates for obesity treatment. Moreover, different methods for plant extraction also influence the activities of plants on the inhibition of digestive enzymes, leading to the differences in their anti-obesity activities, which should be further studied.

Inhibiting the growth of white adipose tissue

The expansion of white adipose tissue (WAT) is the characteristic of obesity, and the increase of WAT mass is closely related to the hypertrophy and hyperplasia of adipocytes (Ghaben and Scherer 2019). Recent findings reveal that plants demonstrate the anti-obesity effect via inhibiting the growth of WAT and regulating the lipid metabolism, including the inhibition of adipogenesis and lipogenesis, and promotion of lipid metabolism. However, it is worth noting that inhibiting the growth of WAT may induce some metabolic diseases, such as diabetes (Yun 2010). Therefore, there are potential risks for WAT inhibition by plants.

Inhibiting adipogenesis and lipogenesis

The inhibitory effects of edible and medicinal plants on the adipogenic differentiation of pre-adipocytes into mature adipocytes and the synthesis of fat in adipocytes have been extensively studied in vitro. For instance, the extract of cranberries decreased proliferation of 3T3-L1 pre-adipocytes and suppressed the adipogenesis by reducing the expression of several crucial adipogenic transcription factors, like peroxisome proliferation-activated receptor (PPAR)-γ, CCAAT/enhancer-binding protein (C/EBP)-α, and sterol regulatory element-binding protein (SREBP)-1 (Kowalska et al. 2014). The downregulation of PPAR-γ and C/EBP-α was also verified in the inhibition of 3T3-L1 cell differentiation by aqueous extract of lychee seed, and the expression of kruppel-like factor (KLF) 9 was also decreased (Qi et al. 2015). 3,3′-Diindolylmethane, the main metabolite of indole-3-carbinol in the stomach, not only reduced the expression of key transcription factors, but also induced cell cycle arrest at the G_1-phase thereby inhibiting adipogenesis in 3T3-L1 pre-adipocytes (Yang et al. 2017). In the same study, ubiquitin-specific peptidase 2 (USP2) was found to be involved in the regulation of adipogenesis, and the inhibition of USP2 led to the post-translational degradation of cyclin D1. Additionally, dioscin suppressed the differentiation of 3T3-L1 cells and suppressed the adipogenesis by decreasing the

phosphorylation of extracellular-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinases (MAPKs), also, the content of triglyceride and the lipid accumulation were reduced (Poudel et al. 2014). In addition, in vitro studies on the inhibition of adipocytes differentiation and the reduction of lipid accumulation by clove, corn silk, *Morus alba* L. polysaccharide, withaferin A are shown in Table 1 (Choi et al. 2016; Ding et al. 2017; Hsu et al. 2018; Khalilpourfarshbafi et al. 2019).

Meanwhile, the inhibition of adipogenesis, lipogenesis, and fat accumulation by plants has also been investigated in vivo. The extract of *Terminalia paniculata* bark decreased the body weight of HFD-induced obese rats, and inhibited the adipogenesis by decreasing the expression of fatty acid synthase (FAS), leptin, adiponectin, PPAR-γ, and SREBP-1c, and increasing AMPK-1α in HFD-fed rats (Mopuri et al. 2015). In another study, the administration of *Rubi Fructus* extract reduced the weight of body and adipose tissue in HFD-induced obese mice (Nam et al. 2014). It also decreased the expression of some lipogenic genes, such as *FAS*, *SREBP-1c*, liver X receptor (*LXR*), acetyl-CoA carboxylase, and lipoprotein lipase (*LPL*). *Solidago virgaurea* var. *gigantean* ethanolic extract decreased the gain in body weight without affecting the food intake in HFD-induced obese mice (Wang et al. 2017). Also, it inhibited several genes relative to adipogenesis, including *PPAR-γ*, *C/EBP-α*, fatty acid translocase and fatty acid-binding protein-4, and suppressed the genes related to the lipogenesis, such as *FAS*, steaoyl-CoA desaturase-1, and *SREBP-1c* in WAT and liver. Furthermore, the *Rubi Fructus*, purple perilla, *Paulownia fortune* flower, *Lolium multiflorum* ferulic acid, tricin and 6,8-diprenylgenistein also managed obesity by inhibiting WAT expansion, with the mechanisms of suppressing adipocyte differentiation by modulating adipogenesis and lipogenesis related genes and proteins, such as C/EBP-α, PPAR-γ, FAS, LXR, LPL, and SREBP-1c in animal studies (Ilavenil et al. 2017; Jo et al. 2015; Lee and Imm 2018; Liu et al. 2017; Nam et al. 2014; Thomas et al. 2018).

Regulating lipid metabolism in adipocytes

The hydrolysis of triglyceride and the degradation of fatty acids in adipocyte are closely associated with the maintenance of body energy balance. The promotion of lipolysis and fatty acid β-oxidation, and the reduction of the triglyceride accumulation are contributed to the diminishment of adipocytes size, thus suppressing the growth of WAT. Plants can inhibit obesity by regulating lipid metabolism both in vitro and in vivo. The water-soluble fraction of ethanolic extract of *Smilax china* L. leaf promoted the lipolysis and the release of glycerol, and decreased lipid accumulation in 3T3-L1 adipocytes (Kang et al. 2015). The mechanism of action may be the activation of hormone-sensitive lipase (HSL) via the β-adrenergic receptor-cAMP-PKA pathway. Moreover, purple perilla could decrease the lipid accumulation in adipocytes by regulating adipogenic and lipolytic genes (Thomas et al. 2018). It also increased the expression of lipolysis genes and fatty acid β-oxidation genes, such as adipose triglyceride lipase, *HSL*, carnitine palmitoyltransferase α (*CPT1α*) and cyl CoA oxidase (*ACOX*) in adipose tissue and liver of HFD-fed obese rats. In addition, kaempferol, (3,3-dimethylallyl) halfordinol and fisetin also had the abilities of promoting lipolysis and reducing lipid accumulation in adipocytes, while in vivo experiments confirmed that they could reduce body weight gain in HFD-fed obese mice (Liou et al. 2018; Saravanan et al. 2014; Torres-Villarreal et al. 2019). The lipid metabolism in adipocytes is a complex process, and illuminating the regulation of plants on this process is helpful to study their anti-obesity effect.

In summary, many plants have shown the characteristics of inhibiting the expansion of WAT, including suppressing adipogenesis and lipogenesis, and regulating lipid metabolism. Nevertheless, given the harmful effects of WAT dysfunction, the adipogenesis inhibitors or lipolysis inducer cannot be used as anti-obesity therapy.

Increasing energy expenditure

In addition to the control of energy intake, increasing energy expenditure is also a valid way to manage obesity (Ohyama et al. 2015). Generally, physical exercise is the main way to increase energy expenditure. Several edible and medicinal plants have been reported to consume energy by enhancing thermogenesis and help maintain the balance between energy generation and consumption without more physical activity. Moreover, two types of thermogenic adipocytes, brown adipocytes, and beige adipocytes have gained much attention due to their capacity of generating heat to consume energy, which is different from WAT (Ikeda, Maretich, and Kajimura 2018; Sanchez-Delgado et al. 2015).

Uncoupling protein (UCP)-1 is a major contributor to the thermogenesis of brown adipose tissue (BAT). The stimulation of UCP-1 can increase respiration and promote the dissipation of energy in the form of heat (Rousset et al. 2004). 6-paradol enhanced the thermogenesis and energy expenditure in BAT in mice, with the mechanism relative to the enhanced expression of thermogenesis UCP1 by increasing the activity of sympathetic nerve (Haratake et al. 2014). The seed coat extract of black soybean increased the energy expenditure by elevating the expression of UCP1 in BAT and UCP2 in WAT of mice (Kanamoto et al. 2011). In addition, russelioside B could increase the expression of UCP1 in the BAT of HFD-fed rats, and it also up-regulated the expression of carnitine palmitoyltransferase-1 (CPT-1), which can promote fatty acid β-oxidation, suggesting the increase of energy expenditure (Abdel-Sattar et al. 2018). Moreover, the polysaccharide isolated from *Ophiopogon japonicas* decreased body weight and adipose tissue mass via enhancing the energy expenditure and oxygen consumption in HFD-fed mice (Wang et al. 2014). Likewise, resveratrol, dioscin, and capsinoids had the capacity to control obesity in vivo through increasing energy expenditure and producing heat (Andrade et al. 2014; Liu et al. 2015; Okamatsu-Ogura et al. 2015).

The brown adipocytes contain a large number of mitochondria, and UCPs on the mitochondrial inner membrane

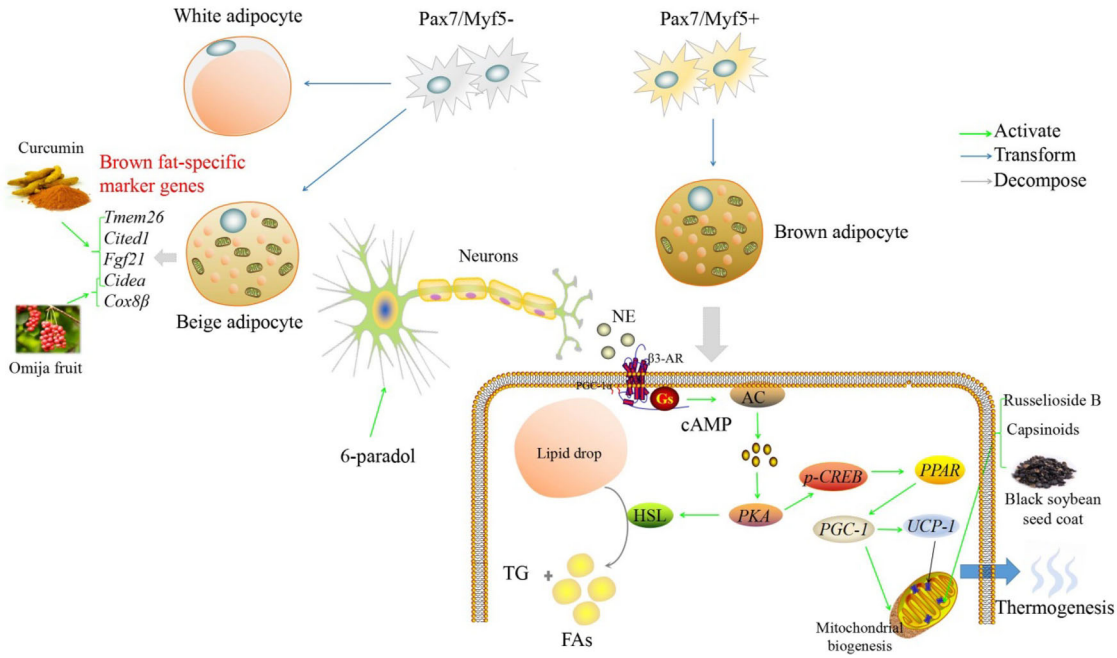

Figure 3. The mechanisms of edible and medicinal plants on increasing energy expenditure. During the process of energy consumption by brown adipocytes, peripheral sympathetic nerve endings are stimulated to release norepinephrine (NE), which acts on β3-adrenoceptor (AR) on the membrane, and then the intracellular concentration of cAMP is increased and activates protein kinase A (PKA). PKA upregulates the phosphorylation of hormone-sensitive triglyceride lipase (HSL), thereby promoting the decomposition of triglycerides in fat droplets into glycerol and fatty acids (FAs). On the other hand, PKA activates cAMP-response element-binding protein (CREB), which induces peroxisome proliferator-activated receptor (PPAR) to activate uncoupling protein 1 (UCP-1) and PPARγ coactivator-1α (PGC-1α). The PGC-1α can regulate the biosynthesis of mitochondria, and the UCP-1 in mitochondria increases energy consumption by generating heat. Additionally, the plants can upregulate the expression of gene encoding transmembrane protein 26 (*Tmem26*), encoding cell death-inducing DNA fragmentation factor alpha-like effector A (*Cidea*), gene encoding fibroblast growth factor 21 (*Fgf21*), gene encoding Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 1 (*Cited1*), and *Cox8β*, which all are the brown fat-specific genes.

are involved in heat generation. The beige adipocytes are another type of thermogenic adipocytes existing in the white fat depots, and the process of recruiting UCP1-positive beige adipocytes in WAT is known as browning or beiging (Brestoff et al. 2015; Wu et al. 2012). Curcumin could induce brown fat-like phenotype in WAT, and upregulate the expression of brown fat specific genes, such as the genes encoding transmembrane protein 26, cell death-inducing DNA fragmentation factor alpha-like effector A, fibroblast growth factor 21, and Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 1 (Lone et al. 2016). Curcumin also increased the expression of brown adipocyte marker proteins, such as C/EBP-β, PPAR-γ coactivator 1-α, PR domain-containing 16, and UCP1. Additionally, the omija fruit ethanolic extract induced the browning of WAT by increasing the expression of brown fat-selective genes, and enhanced fatty acid oxidation in mice, which was related to the increase in the energy expenditure (Park et al. 2017).

Overall, some plants, especially polysaccharides and polyphenols, can elevate energy expenditure by increasing fatty acid β-oxidation and heat production. UCP1 is an important target of thermogenesis in brown adipocytes and beige adipocytes. Additionally, plants can facilitate the browning of adipocytes in WAT, contributing to the anti-obesity effect (Figure 3).

Regulating gut microbiota

The gut microbiota has been shown to have a close relationship with obesity (Muccioli et al. 2010). Inflammation, gene, and hormone regulation are associated with the regulation of obesity by gut microbiota (Kallus and Brandt 2012). The edible and medicinal plants can change the abundance and composition of gut microbiota, suggesting their potential anti-obesity effect.

Recent findings revealed that *Firmicutes* and some species of *Lactobacillus* as well as *Bacteroidetes* were related to the promotion of obesity, while *Bifidobacterium*, most *Lactobacillus*, and some *Bacteroidetes* are associated with the inhibition of obesity (Cao et al. 2019). The increase of *Bifidobacterium*, *Lactobacillus*, and *Bacteroidetes*, as well as the decrease of *Firmicutes* can help regulate energy metabolic-related factors and pathways (including fasting-induced adipocyte factor, AMPK, and short-chain fatty acids), enhancing gut barrier function and decreasing low-grade inflammation (Tsai, Cheng, and Pan 2014). The rats administrated with carbohydrate-free peach and plum juice showed high levels of *Lactobacillus* and *Ruminococcus* family bacteria in their feces, and the rats in the group treated with plum significantly lost weight, which might be linked to the high content of polyphenols in the plum juice (Noratto et al. 2014). The *Firmicutes* and *Bacteroidetes* are both rich in genes that encode enzymes involved in the metabolism of lipids and carbohydrates, and *Firmicutes* contain far more metabolism-related genes than *Bacteroidetes*. Thus, *Firmicutes* are able to better metabolize the full energy intake, promoting efficient energy absorption and weight gain (Kallus and Brandt 2012). Garcinol modulated gut microbiota by reducing the ratio of *Firmicutes*-to-

Bacteroidetes and increasing the level of *Akkermansia*. After administration of garcinol, the body weight gain of HFD-fed mice was reduced and their gut dysbiosis was improved (Lee et al. 2019). Further, purple lettuces and betacyanins also regulated the gut microbiota and helped suppress obesity (Han et al. 2018; Song et al. 2016).

Overall, the gut microbiota is closely related to obesity. Plants can control obesity by modulating gut microbiota, such as reducing *Firmicutes* and increasing *Bifidobacterium*. The food matrix and gut microbiota should be a dynamic system, where they have interactions and produce metabolites that may influence human health. In the future, more plants should be explored to clarify the relationships among plants, gut microbiota, and obesity.

Improving obesity-related inflammation

Obesity causes the production of inflammatory cytokines and makes immune cells infiltrate into adipose tissue, resulting in chronic low-grade inflammation (Cao 2014). Inflammation plays a crucial role in the occurrence and progression of obesity and some edible and medicinal plants can reduce inflammatory response caused by obesity.

A study showed that celastrol exhibited anti-obesity activity by inhibiting the pro-inflammatory M1 polarization of macrophage via inhibiting MAPKs, including ERK1/2, Jun N-terminal kinase (JNK) and p38, and reducing the nuclear translocation of nuclear factor-κB (NF-κB) p65 subunit, as well as activating nuclear factor (erythroid-derived 2)-related factor-2 and the expression of heme oxygenase-1 (Luo et al. 2017). Quercetin suppressed monocyte chemotactic protein-1 (MCP-1), which attracted macrophages to infiltrate adipose tissue, and alleviated obesity-induced inflammation via downregulating MAPK signaling pathway in adipocytes. It also decreased the levels of inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1 and IL-6, and increased the secretion of anti-inflammatory cytokines IL-10, both in vitro and in vivo (Seo et al. 2015). More studies have shown that raspberry, ginger, and *Psacalium decompositum* roots fructooligosaccharides had an effect on alleviating obesity and obesity-related inflammation (Kim et al. 2018; Merino-Aguilar et al. 2014; Zhao et al. 2018).

In brief, some natural plants play a critical role in weight loss by modulating the inflammatory response. The major mechanisms include the inhibition of MAPK signaling pathways (ERK1/2, JNK, and p38 MAPK) and downregulation of inflammatory mediators (IL-1, IL-6, TNF-α, and MCP-1). Therefore, plants with high anti-inflammatory effects may be effective to prevent and manage obesity.

Others obesity-related diseases

Obesity is associated with the occurrence and development of several diseases, such as diabetes, cardiovascular diseases, and osteoarthritis. The important role of edible and medicinal plants in the prevention and management of these obesity-related diseases has also received attention. For example, curcumin has been shown to reduce weight gain, improve insulin sensitivity, and prevent the development of diabetes in rodent models and in prediabetic human subjects (Jin et al. 2018). Several cohort studies demonstrated that daily consumption of tea (catechins) could help lose weight, improving metabolic syndrome, and reducing risk of diabetes and cardiovascular disease (Yang, Wang, and Sheridan 2018). In addition, herbal medicine can effectively combat obesity-related arthritis by reducing weight, regulating leptin signaling pathways, and modulating gut microbiota, instead of corticotherapies with severe side effects (Zeddou 2019). In summary, plants are hopeful to be developed as dietary supplements for preventing a variety of obesity-related diseases.

Clinical trials

Epidemiological and experimental studies have supported that edible and medicinal plants have anti-obesity activity, and clinical trials further verify the effects of plants on obesity as discussed below. In a double-blinded, randomized, parallel trial, 17 obese volunteers were given 900 mg of the polyphenolic drug Fiit-ns daily for 12 weeks, and the body figures and metabolic parameters of participants were significantly improved (Cases et al.2015). After a 12-week consumption of Yerba Maté (*Ilex paraguariensis*) capsules, 30 obese participants had a decrease in body fat mass, body fat percentage, and waist-hip ratio (Kim et al. 2015). In another trial, 22 obese patients were randomized to take *Fraxinus excelsior* L. seed/fruit extract capsules or placebo capsules for 3 weeks with one-week washout period, and the results displayed a significant increase in the ratio of adiponectin to leptin and a decrease in the fat mass (Zulet et al. 2014). Moreover, 56 overweight adults were given fruit and vegetable juices or placebo capsules daily for 8 weeks, with decreased obesity-related systemic inflammation, total cholesterol, low-density lipoprotein cholesterol, and TNF-α in the plasma (Williams et al. 2017). The same study also observed elevated expression of genes associated with adipogenesis, NF-κB, and AMPK signaling pathways. Furthermore, 7 obese Korean women aged from 40 to 65 years were given 4 g of *Ephedra sinica* aqueous extract daily for 8 weeks, and their body weight, body mass index, and body fat rate were decreased, and gut microbiota *Akkermansia*, *Subdoligranulum*, and *Oscillibacter* were reported to be associated with body weight, body mass index after taking ephedra (Kim, Song, and Kim 2014).

Overall, several edible and medicinal plants have been applied in the clinic and have positive effects on the prevention and management of obesity. In the future, the anti-obesity action of more plants should be confirmed by clinical studies. Importantly, the safe dose and side effects of plants are essential to be further investigated. Furthermore, most clinical trials currently focus on the anti-obesity effect of an individual plant, and the effects of the combination of two or more plants should be investigated to develop new anti-obesity treatments.

Conclusions

Obesity has become a global public health problem, and it can increase the risk of certain chronic diseases, such as cardiovascular diseases, diabetes, and some cancers. Considering the serious side effects of synthetic weight-loss drugs, edible and medicinal plants show great potential to prevent and manage obesity. At present, some plants, such as fruits, vegetables, legumes, spices, edible flowers, mushrooms, and medicinal plants have been demonstrated to possess anti-obesity property. Epidemiological studies have demonstrated that the consumption of some plants can lower the risk of obesity. Further, experimental studies reveal the anti-obesity mechanisms of plants, which are mainly related to the suppression of appetite, reduction in the absorption of lipids and carbohydrates, inhibition of adipogenesis and lipogenesis, regulation of lipid metabolism, increase in energy expenditure, modulation of gut microbiota, and improvement of obesity-related inflammation. AMPK is a crucial regulator of the energy metabolism balance in body. It is reported that gut microbiota exerts the anti-obesity effect by regulating AMPK pathway. AMPK pathway is also associated with the inhibition of adipogenesis, promotion of lipolysis, improvement of insulin resistance and elevation of energy expenditure. In addition, AMPK is related to the suppression of NF-κB signaling pathway, thereby alleviating obesity-related inflammation. The MAPK signaling pathways (ERK1/2, JNK, and p38 MAPK) are also participants of fighting against obesity, which is involved in the modulation of suppressing adipogenesis and reducing inflammation. Importantly, clinical trials are in accordance with the results of epidemiological and experimental studies and demonstrated the weight-control effects of several plants. According to the current literature, the increasing consumption of several edible plants in the diets, such as cereals, berries, cruciferous vegetables, and legumes, can maintain weight and prevent obesity, and the extracts from some medicinal plants can also be the potential anti-obesity products.

In the future, more plants need to be investigated on their anti-obesity activity, and their major anti-obesity compounds need to be isolated and identified, with clarifying the specific molecular mechanisms as well as the safe doses for humans. Moreover, the extract is the product of targeted acquisition and enrichment of one or more active ingredients (such as polyphenols, polysaccharides, terpenes, and alkaloids) in the raw materials, through physical or chemical extraction and separation processes. Although the extract may cause the loss of vitamins and minerals in foods, a small amount of extract with high purity and concentration can effectively supplement nutrients that would otherwise require a large intake of raw materials. Also, some parts of plants that cannot be eaten directly, such as branch, leaf, peel, and seed which contain abundant bioactive compounds, can also be made into extracts for effective utilization. It is necessary to explore effective methods to extract anti-obesity compounds from plants. It is of great significance to study the additive or synergistic effects of two or more plants on obesity. A single plant may require a high dose to achieve a significant anti-obesity effect, meanwhile it may also have serious adverse effects, while the combination of different plants may reduce their respective dosage, and alleviate side effects such as hepatorenal toxicity. Moreover, it should be pointed out that with the development of anti-obesity research, novel and reliable in vivo models of obesity are essential to be established to promote the research and development of anti-obesity agents. Currently, the fruit flies, zebrafish, mice, rats, pigs, and dogs are used in the establishment of obesity models, and the rodents are relatively common. In the future, more obesity animal models need to be developed to mimic the obesity of humans, and more time-saving and efficient modeling methods also need to be explored. Overall, edible and medicinal plants are promising anti-obesity agents and can be developed as dietary supplements or drugs for the prevention and management of obesity and obesity-related diseases.

Disclosure statement

The authors declare no conflict of interest.

Abbreviations

AMPK	AMP-activated protein kinase
BAT	brown adipose tissue
C/EBP	CCAAT/enhancer-binding protein
CPT-1	carnitine palmitoyltransferase 1
ERK1/2	extracellular-regulated kinase 1/2
FAS	fatty acid synthase
HFD	high-fat diet
HSL	hormone sensitive lipase
IFN	interferon
JNK	Jun N-terminal kinase
LPL	lipoprotein lipase
LXR	liver X receptor
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemotactic protein-1
NF-κB	nuclear factor-κB
Nfr1	nuclear respiratory factor 1
NPY	neuropeptide Y
PKA	protein kinase A
POMC	proopiomelanocortin
PPAR	peroxisome proliferation-activated receptor
SREBP-1c	sterol regulatory element binding protein-1c
TNF-α	tumor necrosis factor-α
UCP	uncoupling protein
USP2	ubiquitin specific peptidase 2
WAT	white adipose tissue
α-MSH	α-melanocyte-stimulating hormone

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