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Review

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Natural Products with Anti-obesity Effects and Different Mechanisms of Action

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ABSTRACT: Obesity, a primary influence on health condition, causes numerous comorbidities and complications and, therefore, pharmacotherapy is considered a strategy for its treatment. However, the adverse effects of most chemical drugs targeting weight loss complicate their approval by regulatory authorities. Recently, interest has increased in the development of ingredients from natural sources with fewer adverse effects for preventing and ameliorating obesity. This review provides an overview of current anti-obesity drugs and natural products with anti-obesity properties as well as their mechanisms of action, which include interfering with nutrient absorption, decreasing adipogenesis, increasing energy expenditure (thermogenesis), appetite suppression, modifying intestinal microbiota composition, and increasing fecal fat excretion.

KEYWORDS: *obesity, pharmacotherapy, mechanism, chemical drug, natural product*

INTRODUCTION

Obesity is a condition of excessive body fat due to extreme disequilibrium between energy uptake and expenditure, and it is a global epidemic.[1] Moreover, obesity contributes to various chronic diseases, such as type 2 diabetes (T2D), hyperlipidemia, cardiovascular disease (CVD), hypertension, cerebrovascular incidents, and obstructive sleep apnea.[2]

Food consumption is thought to drive hormone peptide regulation in the hypothalamus and gut with regard to appetite modulation,[3] and "palatable foods" induce hyperphagia and excessive fat accumulation, as well as increased fatty acid oxidation within muscles and decreased anorexigenic hormones, such as cholecystokinin (CCK).[4]

Currently, multiple therapeutic options are available to treat obesity such as diet modification, exercise, behavioral changes, surgery, and pharmacotherapy. Among these, pharmacotherapy is the most common, although numerous drugs used to reduce weight have associated side effects[5] and ,specifically, fenfluramine,[6] rimonabant, and sibutramine[7] were withdrawn from the market because of dangerous side effects. Therefore, orlistat is the only medication approved for long-term use worldwide, although uncomfortable adverse events are associated with its use.[8] Furthermore, lorcaserin and the fixed-dose drugs phentermine and topiramate were approved for weight loss,[9] but their side effects were problematic. Therefore, other sources of weight loss drugs, such as natural products, are being investigated.[10−12]

In this review, we focused on the mechanisms of action of the anti-obesity drugs shown in Table 1 and included descriptions of natural products with potential anti-obesity properties, which are summarized in Tables 2 and 3. The active ingredients from natural products are categorized on the basis of their effects as follows: (1) interfering with nutrient absorption, (2) decreasing adipogenesis and enhancing energy expenditure (thermogenesis), (3) suppressing the appetite, and (4) modifying the intestinal microbiota composition and increasing fat excretion.

MECHANISMS OF ANTI-OBESITY EFFECT OF CHEMICAL DRUGS

Signal Transduction. The 5-hydroxytryptamine (5-HT, serotonin) receptor agonists, fenfluramine and lorcaserin, show their anti-obesity effect by promoting 5-HT release and reducing food intake in rodents in a manner consistent with increased satiety.[13] However, fenfluramine showed a specific toxicity in the form of cardiac valvulopathy, which prompted the manufacturers to withdraw it from the market.[14] Lorcaserin is a selective 5-HT_{2C}-receptor agonist, and its characteristic minimal activity at both the 5-HT_{2A} and 5-HT_{2B} receptors, which are linked to the development of valvular heart disease,[15] contributed to its approval in 2012.[16,17] Rimonabant is a selective reverse agonist of the cannabinoid receptor type 1 (CB1) receptor, which increases during the differentiation of pre-adipocytes and the biosynthesis of triacylglycerol (TG) and fatty acid.[18] It was approved for the treatment of obesity in 2006;[19] however, anxiety, suicidal thoughts, depressive disorders,[20] and related cardiometabolic risk abnormalities were reported,[21] and hence the drug was removed from the market. The inhibition of pancreatic lipase suppresses the intestinal absorption of dietary TGs to reduce fat absorption.[22] Orlistat was the first selective irreversible lipase inhibitor[23] to be approved in 1999,[14,24] and compared with other anti-obesity drugs, its side effects are limited.[25] Cetilistat is another pancreatic lipase inhibitor that is currently in phase III clinical trials. Compared with orlistat, the tolerability of cetilistat appears to be better,[26] and its adverse effects are mild to moderate.[27] Nevertheless, more studies are still required to confirm its safety in humans. Glucagon-like peptide-1 (GLP-1) is a gut hormone released from the intestine, which facilitates

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Table 1. Current Situation of Anti-obesity Drugs Based on Mechanisms[a]

mechanism	drug	efficacy (%)	safety and tolerability concerns	stage of development
signal transduction				
5-HT receptor agonist	fenfluramine	5−6	cardiac valvulopathy, pulmonary and hypertension	approved in 1973; withdrawn in 1997
	lorcaserin	3−4	dizziness, headache, insomnia, and possible risk of valvulopathy in obese type 2 diabetics	approved in 2012
CB1 receptor inhibitor	rimonabant	6−7	depression disorders, anxiety, suicidal thoughts, and related cardiometabolic risk abnormalities	approved in 2006; withdrawn in 2008
pancreatic lipase inhibitor	orlistat	3−4	malabsorption, vitamin deficiencies, oily stools, gastrointestinal tract discomfort	approved in 1999
	cetilistat	<5	steatorrhea and gastrointestinal side effects	phase III
GLP-1 receptor agonist	exenatide	4−6	transient nausea, vomiting, hypoglycaemia, and risk for pancreatitis	approved in 2005
	liraglutide	5−6	nausea, diarrhea, hypoglycemia, and risk for pancreatitis	approved in 2014
poly mechanisms				
5-HT/NA re-uptake inhibitor	sibutramine	5−6	serious cardiovascular complications, increased risk for stroke and myocardial infarction	approved in 1997; withdrawn in 2010
neuropeptide Y2/Y4 receptor agonist	obinepitide	<5	adverse cardiovascular effects	phase II
NA agent and anti-epileptic drug	phentermine with topiramate	9−10	paresthesia, constipation, dysgeusia, dizziness, insomnia, psychosis, and teratogenicity	approved in 2012
DA/NA re-uptake inhibitor and opioid receptor antagonist	bupropion with naltrexone	3−6	nausea, headache, vomiting, constipation, insomnia, risk of suicide and neuropsychosis	approved in 2014
5-HT/DA/NA re-uptake inhibitor	tesofensine	9−11	increased heart rate and blood pressure	phase III

[a]Sources: Rodgers et al;[14] Adan;[162] Shin and Gadde;[170] Solas et al;[171] Wong.[163]

the secretion of glucose-dependent insulin from pancreatic islet cells and represses glucagon release, leading to a subsequent glucose-dependent decrease in hepatic glucose production.[28] Moreover, GLP-1 receptor agonists have been shown to induce clinically relevant reductions in body weight by decreasing calorie intake.[29,30] Exenatide and liraglutide are GLP-1 receptor agonists approved by the U.S. Food and Drug Administration (FDA) for treating obesity and diabetes in 2005[31] and 2014,[32] respectively.

Drugs with Multiple Mechanisms of Action. Some drugs that influence energy balance via 5-HT and norepinephrine (NE) neural pathways in the central nervous system (CNS) have been studied for treating eating disorders and obesity.[33] The 5-HT-NE re-uptake inhibitor, sibutramine, approved by the FDA in 1997, was used as an anti-obesity drug because of its ability to influence feelings of hunger and satiety at the CNS level.[34] However, cardiovascular complications possibly arising from thrombus formation after sibutramine treatment led to its market withdrawal in 2010.[35] Synergism between neuropeptide Y2 and Y4 receptor signaling in controlling fat mass may be linked to differences in mitochondrial oxidative capacity, which increase peroxisome proliferator-activated receptor (PPAR)-γ gamma coactivator 1-α (PGC-1α) and mitochondrial respiratory chain complexes I and III.[36] A dual neuropeptide Y2/Y4 receptor agonist, obinepitide, has a long-term influence on suppressing appetite and reducing body weight in rodents and is presently in phase II clinical trials. Fixed-dose combination drugs such as phentermine plus topiramate and bupropion plus naltrexone have been of interest for promoting weight loss. Phentermine/topiramate, a sympathomimetic and antiepileptic drug combination, was approved in 2012 for weight management.[37] The combination of bupropion and naltrexone, which blocks dopamine (DA) and NE re-uptake and antagonizes opioid receptors, was approved in 2014.[38] However, there is a risk of suicide and neuropsychosis because of the bupropion component except for the common side effects.[38]

Some anti-obesity agents influence monoaminergic activity, and those that selectively inhibit the re-uptake of 5-HT, NE, and DA have been variously approved. Moreover, the combination of inhibitors of monoamine neurotransmitter transporters can synergistically increase anti-obesity effects.[39] Tesofensine, which inhibits the re-uptake process of DA, NE, and 5-HT, is under study as a weight loss aid[40] in phase III clinical trials.[41] In addition, the adverse effects and details of the anti-obesity effects of chemical drugs are summarized in Table 1.

MECHANISMS OF ANTI-OBESITY EFFECT OF NATURAL PRODUCTS

Inhibiting Digestive Enzyme Activity. *Pancreatic Lipase Inhibitors.* Most of the fat consumed in the Western diet comprises TGs or esters of a single molecule of glycerol and three fatty acids, which are metabolized and absorbed in the gut.[42] Dietary TGs that cannot be absorbed are hydrolyzed by pancreatic lipase secreted from the pancreas to promote their absorption in the small intestine.[43] TGs are separated by pancreatic lipase into monoacylglycerol and free fatty acids that are combined with bile acids, cholesterol, and lysophosphatidic acid (LPA) to form mixed micelles. Mixed micelles are assimilated into enterocytes, which ultimately resynthesize TGs stored in adipocytes[12] (Figure 1). However, the utilization of ingested lipids and absorbed sugars is diminished when lipid hydrolysis is inhibited by a pancreatic lipase inhibitor. Some natural products may inhibit pancreatic lipase[44] because reduced fat absorption can improve diabetes[45] and, therefore, may be an option for weight loss treatment.

As a pancreatic lipase inhibitor, orlistat, with a median inhibitory concentration (IC_{50}) of 0.7 μM, is the only anti-obesity agent approved by the FDA for long-term clinical use. Orlistat's side effects are unacceptable for numerous patients and, therefore, discovering new potent pancreatic lipase inhibitors (Table 2) with fewer adverse effects from plants is a desirable approach. Additionally, the mechanisms of action of

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Table 2. Active Ingredients for Anti-obesity Effect Based on Inhibiting Digestive Enzyme Activity

primary source (species)	active compounds	parts used	IC_{50} value	model	suitable dosage	duration	refs
pancreatic lipase inhibitors							
Platycodon grandiflorum (Campanulaceae)	platycodins	roots	20 mg/mL	hamsters	0.3−0.5% platycodin in aqueous extract of platycodi radix per day	4 weeks	46−48
				mice	5% aqueous extract of platycodi radix in high-fat diet per day (570 mg/kg/day)	5 weeks	
Acanthopanax sessiliflorus (Araliaceae)	sessiloside, chiisanoside, isochiisanoside	leaves	0.36, 0.75, 4.0 mg/mL	mice	100−300 mg/kg/day chiisanoside	4 h	49, 50
Acanthopanax senticosus (Araliaceae)	silphioside F, copteroside B	fruits	0.22, 0.25 mM	mice	500 mg/kg/day *A. senticosus* extract	12 weeks	51, 52
Alpinia officinarum (Zingiberaceae)	3-methyl ethergalangin, 5-hydroxy-7-(49-hydroxy-39-methoxyphenyl)-1-phenyl-3-heptanone	rhizome	1.30, 1.50 mg/mL	rats	3−5% (weight/diet weight, w/w) powdered *A. officinarum* ethanolic extract in high-fat diet per day	6 weeks	53−55
Clusia nemorosa (Clusiaceae)	betulinic acid (BA)	barks	21.1 μM	cell lines	1.5−100 μM BA	4 h	56, 57
				rats	50−100 mg/kg/day BA		
Gardenia jasminoides (Rubiaceae)	crocin, crocetin	fruits	2.10, 2.60 mg/mL	mice	50 mg/kg/day crocin, crocetin	5 weeks	58, 59
				rats	25−100 mg/kg/day crocin	10 days	
Panax ginseng (Araliaceae)	ginsenoside Rg3, ginsenoside Rh2, protopanaxadiol saponins, protopanaxatriol saponins	roots, berries	ginseng saponin, 0.5 mg/mL	mice	3% (w/w) ginseng saponin extract in high-fat diet per day	3 weeks	60
Panax quinquefolium (Araliaceae)	ginsenosides Rb1, Rb2, and Rc	stems, leaves	0.50 mg/mL	mice, rats	1000 mg/kg/day crude saponins	8 weeks	61
Panax japonicus (Araliaceae)	chikusetsusaponins III and IV	rhizomes	0.25, 0.50 mg/mL	mice	1−3% total chikusetsusaponins in high-fat diet per day	9 weeks	62
				rats	1000 mg/kg/day total chikusetsusaponins	5 h	
Aesculus turbinata (Hippocastanaceae)	escins Ib and IIa	seeds	m0.50 g/mL	mice	2% total escins in high-fat diet per day	11 weeks	63, 64
				rats	250−1000 mg/kg/day total escins	3 h	
green tea	(−)-epigallocatechin gallate	leaves	1.8 ± 0.57 μM	vitro	10−30 mg/mL, in drinking water	unclear	65
gomchui tea	di-*O*-caffeoylquinic acid	leaves	12.7−40.4 μM	vitro	10−30 mg/mL, in drinking water	unclear	65
oolong tea	oolonghomobisflavans A, oolonghomobisflavans B, oolongtheanin-3′-*O*-gallate	leaves	0.048, 0.108, 0.068 μM	vitro	6.67 mg/mL, in drinking water	unclear	66
Eisenia bicyclis	7-phloroeckol, fucofuroeckol A	leaves	12.7 ± 1.0, 37.2 ± 2.3 μM	vitro	unclear	unclear	67
Glycyrrhiza uralensis (Leguminosae)	licochalcone A	roots	103.4 μM	vitro	unclear	unclear	68
Acacia meansii (Acacia)	acacia polyphenol (AP)	barks	0.95 mg/mL	mice	250−1000 mg/kg/day APl, 2.5−5% AP in high-fat diet per day	7 weeks	69, 70
Actinidia arguta (Actinidiaceae)	ursolic acid	roots	51.21 μM	rats	50−100 mg/kg/day ursolic acid	4 h	71
Rosmarinus officinalis (Lamiaceae)	carnosic acid, carnosol	leaves	36, 13 μM	rats	20 mg/kg/day carnosic acid, 200 mg/kg/day *R. officinalis* extract	65 days	72
Salvia officinalis (Lamiaceae)	carnosic acid, carnosol	leaves	36, 13 μM	mice	5−20 mg/kg/day carnosic acid	14 days	73
Sapindus rarak (Sapindaceae)	rarasaponins I and II, raraoside A	pericarps	131, 172, 151 μM	vitro	unclear	unclear	74
Ginkgo biloba (Ginkgoaceae)	ginkgolide A and B, bilobalide	leaves	22.9, 90.0, 60.1 μg/mL	molecular modeling	1.56−100 μg/mL *G. biloba* extract	unclear	75
Calotropis procera (Asclepiadaceae)	2,4-bis(1,1-dimethylethyl) ester, 1,2-benzedenedi-carboxylic acid, bis(2-methylpropyl) ester	roots	purified diterpenoid fraction, 9.47 μg/mL	vitro	1−20 μg/mL *C. procera* crude extract	unclear	76
Dioscorea nipponica (Dioscoreaceae)	dioscin, diosgenin	roots, rhizomes	20.0, 28.0 μg/mL	mice	100 mg/kg/day dioscin and diosgenin	8 weeks	77
				rats	2−5% *D. nipponica* powder in high-fat diet per day	8 weeks	

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Table 2. continued

primary source (species)	active compounds	parts used	IC_{50} value	model	suitable dosage	duration	refs
Cudrania tricuspidata (Moraceae)	cudraflavone C	leaves	9.91 μg/mL	rats	50−250 mg/kg/day *C. tricuspidata* extract	4 h	78
amylase inhibitors							
Salix matsudana (Berberidaceae)	apigenin-7-*O*-D-glucoside	leaves	0.20 mg/mL	mice	20−5% polyphenols of *S. matsudana* leaves in high-fat diet per day	9 weeks	80, 81
Phaseolus vulgaris (Fabaceae)	phytohemagglutinin	beans	unclear	rats	50−500 mg/kg/day *P. vulgaris* extract	22 days	79, 82
Nelumbo nucifera (Nymphaeaceae)	phenolic compounds	leaves	0.820 mg/mL	mice, rats	1.22 g/kg/day *N. nucifera* extract	6 weeks	83, 84
Araucaria angustifolia (Araucariaceae)	pinhão coat tannin	seeds	unclear	mice	250−500 mg/kg/day pinhão coat extract	6 h	85

active ingredients for inhibiting pancreatic lipase are shown in Figure 1.

Platycodins, a group of saponin glycosides from the root of *Platycodon grandiflorum* (family Campanulaceae) with an IC_{50} of 20 mg/mL, are considered partly responsible for decreasing dietary lipid digestion and absorption by inhibiting pancreatic lipase.[46] Compared to the control diet, platycodin-enriched diets (low, 0.3−0.5% platycodin in the aqueous extract of platycodi radix; high, 0.9−1.0% platycodin in crude platycodin-enriched saponins) reduced total cholesterol (TC) in the plasma (13−28%, $p < 0.05$) and the liver (41−79%, $p < 0.05$) and whole body cholesterol. Furthermore, it promoted the excretion of cholesterol ($p < 0.05$) and reduced the risk for cardiovascular diseases.[47] In addition, Han et al.[48] suggested that the study group treated with 5% platycodi radix aqueous extract (570 mg/kg) showed a reduction in final parametrial adipose tissue weights ($p < 0.05$) and decreased body weight ($p < 0.05$) as well as hepatic and plasma TG ($p < 0.05$) compared with the high-fat (HF) diet groups through suppressing the intestinal absorption of dietary lipids.

Saponins such as chiisanoside, sessiloside, and isochiisanoside (IC_{50} = 0.36, 0.75, and 4.0 mg/mL, respectively) have been isolated from the leaves of *Acanthopanax sessiliflorus* (family Araliaceae) and investigated for the suppression of pancreatic lipase.[49] Supplementation of an HF diet-induced obese mouse model with chiisanoside (100 or 300 mg/kg) lowered serum TG ($p < 0.05$), and the strongest effect was evident 4 h after administration. In addition, it lowered the elevated undigested TG ($p < 0.05$) in the intestinal lumen after oil gavage, suggesting that chiisanoside inhibited dietary fat absorption.[50] Fruits of another species of *Acanthopanax*, *Acanthopanax senticosus* (family Araliaceae), contain the major saponins silphioside F and copteroside B (IC_{50} = 0.22 and 0.25 mM, respectively). The free carboxylic acid groups at position 28 in these compounds increase their inhibition of pancreatic lipase.[51] According to Cha et al.,[52] the oral administration of *A. senticosus* extract (500 mg/kg) significantly reduced weight gain ($p < 0.05$), plasma low-density lipoprotein cholesterol (LDL-C, $p < 0.05$), and liver TG accumulation in HF diet-induced obese mice.

Rhizomes of *Alpinia officinarum* (family Zingiberaceae) are rich in bioactive compounds, such as 3-methyl ethergalangin and 5-hydroxy-7-(49-hydroxy-39-methoxyphenyl)-1-phenyl-3-heptanone, and inhibit pancreatic lipase (IC_{50} = 1.30 and 1.50 mg/mL, respectively).[53,54] In an HF diet-induced animal model, *A. officinarum* ethanolic extract (3 and 5% w/w) significantly suppressed weight gain ($p < 0.05$) and reduced the epididymal and perirenal white adipose tissue (WAT, $p < 0.05$). In addition, it improved plasma lipids by reducing TC, TG, LDL-C, leptin, and serum atherogenic indices (all $p < 0.05$), as well as reversed pathological changes in the liver and adipose tissue.[55]

Betulinic acid (BA), a pentacyclic triterpenic acid, is widely distributed in various plants such as *Clusia nemorosa* (family Clusiaceae).[56] The anti-obesity effect of BA has been investigated with respect to the inhibition of pancreatic lipase and amylase.[57] BA inhibited pancreatic lipase (IC_{50}, 21.10 μM) at concentrations of 1.5−100 μM in a dose-dependent manner in vitro and significantly reduced serum TG ($p < 0.01$) 2 h after the administration of 50 or 100 mg/kg. The effect of BA in reducing TG is similar to that of orlistat (45 mg/kg, $p < 0.01$) compared to that observed in the untreated control groups. In addition, BA's lipolytic effect was mediated by suppressing

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Table 3. Active Ingredients for Anti-obesity Effect Based on Adipose Tissues and Appetite Regulation

primary source	active compounds	parts used	molecular pathways	model	suitable dosage	duration	refs
reduce white adipose formation							
crab and shrimp shells	chitosan oligosaccharides (COS)	shells	decreases the mRNA expression of PPARγ, LXRα (both $p < 0.01$), inhibits the differentiation of adipocytes	rats	250−1000 mg/kg/day COS	6 weeks	93−97
Curcuma longa (Zingiberaceae)	curcumin	rhizomes	activates Wnt/β-catenin signaling and AMPK phosphorylation, increases carnitine palmitoyltransferase-1 expression ($p < 0.05$), decreases glycerol-3-phosphate acyl transferase-1, PPARγ and C/EBPα (all $p < 0.05$) expression, suppresses 3T3-L1 adipocytes differentiation	cell lines	5−25 μM curcumin	24 h	98−100
				mice	500 mg/kg/day curcumin	12 weeks	
black soybeans (Leguminosae)	anthocyanins (cyanidine-3-*O*-glucoside, delphinidin-3-*O*-glucoside, petunidin-3-*O*-gluco-side)	seeds	suppresses 3T3-L1 cells differentiationand lipid accumulation, decreases the expression of LXRα, PPARγ, C/EBPα, and SREBP-1c (all $p < 0.01$)	cell lines	10−50 μg/mL anthocyanins	24 h	108, 109
Salacia reticulata (Celastraceae)	mangiferin, (−)-epicatechin, (−)-epigallocatechin	roots, stems	represses fat accumulation, reduces the size of weight adipocytes ($p < 0.05$), decreases PPARγ, C/EBPα expression and glycerol-3-phosphate dehydrogenase (all $p < 0.05$), suppresses adipocyte differentiation	cell lines	10−100 μg/mL *S. reticulata* extract	96 h	110−112
				mice	1% *S. reticulata* extract per day	9 weeks	
Wasabia japonica (Cruciferae)	hot water extract	leaves, rhizomes	suppresses 3T3-L1 pre-adipocytes differentiation, decreases the regulation of PPARγ, SREBP-1c, fatty acid synthase, C/EBPαand adipocyte fatty acid binding protein 2 (all $p < 0.05$)	cell lines	667 μg/mL *W. japonica* extract	6 days	113, 114
				mice	5% *W. japonica* extract in high-fat diet	163 days	
Vitis vinifera (Vitaceae)	vitisin A	seeds	represses pre-adipocyte proliferation and differentiation via p21- and Rb-dependent cell cycle arrest, decreases lipid content ($p < 0.01$)	cell lines	1−10 μM vitisin A	8 days	115
Rosmarinus officinalis (Lamiaceae)	carnosic acid, carnosol	leaves	induces phase II enzymes, stimulares the metabolism of glutathione (GSH, $p < 0.01$), inhibits the PPARγ, fatty acid binding protein-4 expression (FABP4) (both $p < 0.01$), suppresses 3T3-L1 adipocyte differentiation	cell lines	5−10 μg/mL carnosic acid	5 days	116, 117
Platycodon grandiflorum (Campanulaceae)	platycodins	roots	inhibits 3T3-L1 pre-adipocyte differentiation and reduces fat accumulation ($p < 0.05$), decreases the size of subcutaneous adipocytes ($p < 0.05$)	rats	150 mg/kg/day *P. grandiflorum* extract	7 weeks	118
increase brown adipose tissue (increase thermogenesis)							
Capsicum annuum (Solanaceae)	capsaicin	fruits	increases the expression of browning-specific genes in subcutaneous white adipose, up-regulates UCP2 and UCP3 ($p < 0.01$ and <0.05, compared to the control and HF diet groups, respectively) (thermogenesis) expression, suppresses the differentiation of 3T3-L1 pre-adipocytes ($p < 0.05$)	cell lines	0.1−1 μM capsaicin	24 h	101−105
				mice	0.01% capsaicin in normal diet	6 weeks	
Tripterygium Wilfordi (Celastraceae)	celastrol	roots	thermogenesis, increases plasma leptin ($p < 0.001$), activates the HSF1-PGC1α transcriptional axis($p < 0.01$)	mice	1−3 mg/kg/day celastrol	2 weeks	106, 107
appetite suppression							
Garcinia Cambogia (guttiferae)	(−)-hydroxycitric acid (HCA)	fruits	suppresses the ATP-citratelyase, increases satiety, decreases [^{3}H]-5-HT uptake by 20% ($p < 0.01$), enhances the release of neurotransmitter	rats	300 μM HCA extract	14 days	131−134
Evodia rutaecarpa (Rutaceae)	evodiamine, rutecarpine	fruits	decreases the mRNA expression of NPY ($p < 0.05$) and AgRP ($p < 0.01$), decrease the protein expression of NPY peptide ($p < 0.001$), enhance leptin level ($p < 0.001$), decrease blood cholesterol, nonfasting glucose level	rats	40 mg/kg/day evodiamine	25 days	135, 136
				Mice	20−100 mg/kg/day rutecarpine	4 weeks	
				cell lines	10−100 μM	24 h	
Agave angustifolia and *Agave potatorum* (Agavaceae)	agavins	leaves	increases the anorexigenic GLP-1 (AASDP, 40.93%; APSDP, 93%, respectively, $p < 0.05$) and decreases the orexigenic ghrelin (AASDP, 16%; APSDP, 38%, respectively, $p < 0.05$)	mice	10% agavins in diet	5 weeks	137, 138
Catha edulis (theaceae)	cathinone	leaves	increases satiety, reduces the sense of hungry ($p < 0.05$)	humans	unclear	180 min	139, 140
Capsicum annuum (Solanaceae)	capsaicin and capsiate	fruits	increases the level of GLP-1 ($p < 0.05$), tended to decrease ghrelin content ($p = 0.07$)	humans	unclear	180 min	141, 142
Griffonia simplicifolia (Leguminosae)	5-hydroxytryptophan	seeds	increases satiety, lowers food intake	humans	unclear	4 weeks	143

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Table 3. continued

primary source	active compounds	parts used	molecular pathways	model	suitable dosage	duration	refs
Panax ginseng (Araliaceae)	ginseng crude saponins (protopanaxadiol, protopanaxatriol)	roots, berries	decreases the NPY expression and leptin level (both $p < 0.05$), increases the level of CCK ($p < 0.05$), suppresses energy gain	rats	200 mg/kg/day ginseng crude saponins, 50 mg/kg/day protopanaxadiol or protopanaxatriol	3 weeks	144, 145
Gymnema sylvestre (Asclepiadaceae)	gymnemic acids	leaves	prevents sugar molecular absorption, reduces food intake	mice	1000 mg/kg/day *G. sylvestre* extract	4 weeks	146, 147
Phaseolus vulgaris (Fabaceae)	phytohemagglutinin	beans	inhibits ghrelin secretion ($p < 0.05$), reduces food intake, increases satiety sensations	humans	unclear	120 min	148
Benincasa hispidan (Cucurbitaceae)	methanol extract	fruits	stimulates central nervous system, reduces food intake (27− 54%, $p < 0.001$)	mice	200−1000 mg/kg/day *B. hispidan* extract	7 h	149

cyclic adenosine monophosphate (cAMP)-dependent phosphodiesterase ($p < 0.01$), and it may accelerate lipid mobilization by increasing lipolysis in adipose tissues.[57]

Crocin and crocetin are bioactive ingredients isolated from *Gardenia jasminoides* (family Rubiaceae). They inhibited pancreatic lipase (IC_{50} = 2.1 and 2.6 mg/mL, respectively), reduced weight gain ($p < 0.05$) and epididymal fat pad mass elevation ($p < 0.05$), and suppressed serum TG ($p < 0.05$), TC, and LDL-C ($p < 0.05$) at a dose of 50 mg/kg in hyperlipidemic mice.[58] Furthermore, they increased fecal excretion of fat ($p < 0.05$) and cholesterol ($p < 0.01$) at a dose range of 25−100 mg/kg in rats,[59] which are similar to the effects of xenical and lovastatin (both 10 mg/kg, $p < 0.05$) and may improve obesity pathophysiology.

The active ingredients of *Panax ginseng*,[60] *Panax quinquefolium*,[61] *Panax japonicus*,[62] *Aesculus turbinata*,[63,64] green tea, gomchui,[65] and oolong teas,[66] *Eisenia bicyclis*,[67] *Glycyrrhiza uralensis*,[68] *Acacia mearnsii*,[69,70] *Actinidia arguta*,[71] *Rosmarinus officinalis*,[72] *Salvia officinalis*,[73] *Sapindus rarak*,[74] *Ginkgo biloba*,[75] *Calotropis procera*,[76] *Dioscorea nipponica*,[77] and *Cudrania tricuspidata*[78] as well as their plant parts used are shown in Table 2. These extracts inhibit pancreatic lipase to reduce plasma TGs and fat absorption, which reduces calories from fat intake.

Amylase Inhibitors. For many individuals, carbohydrates are the most abundant source of calories. Because carbohydrates range from monosaccharides to polysaccharides, such as polyhydroxy aldehydes, ketones, alcohols, and acids, which can be degraded into monosaccharides by amylase, the blockade of amylase may inhibit carbohydrate absorption.[79] Therefore, amylase inhibitors (Table 2) may contribute to weight loss.

The leaves of *Salix matsudana* (family Berberidaceae) are rich in polyphenol compounds that are reported to inhibit intestinal fat absorption and decrease plasma TG in rats. Moreover, 5% polyphenol fractions caused carbohydrate malabsorption by inhibiting α-amylase in the small intestine.[80] Active compounds from the polyphenol fractions of *S. matsudana* leaves that inhibit α-amylase include apigenin-7-*O*-D-glucoside (IC_{50} = 0.20 mg/mL), which significantly reduced weight and parametrial adiposity (both $p < 0.05$) in addition to hepatic TC compared to the HF diet groups.[80,81]

Extracts of *Phaseolus vulgaris* (family Fabaceae) beans have been studied as potential α-amylase inhibitors for controlling food consumption, weight, lipid accumulation, and glycemia.[79] The literature suggests that supplementation of rats with extracts of *P. vulgaris* derivatives may reduce food intake (15%, $p < 0.05$), weight, lipid deposition, and glycemia ($p < 0.05$) compared to the unsupplemented vehicle control rats, and may reduce starch digestion, postprandial plasma hyperglycemia, and insulin.[79,82] In addition, the extracts might increase resistant starch, carbohydrate tolerance, and colorectal bacterial activity,[79] which may be exploited for improving metabolic syndromes.

The flavonoids extracted from *Nelumbo nucifera* leaves inhibited α-amylase and α-glucosidase (IC_{50} = 0.82 and 1.86 mg/mL, respectively).[83] Treatment with *N. nucifera* leaf extract reduced weight gain, parametrial adipose tissue (both $p < 0.01$), and liver TG ($p < 0.05$) in HF diet-induced obese mice, which reduced lipid accumulation in the liver and obesity.[84] Similarly, condensed tannin-rich extracts of the pinhão coat (*Araucaria angustifolia* seeds) inhibited α-amylase by blocking glucose

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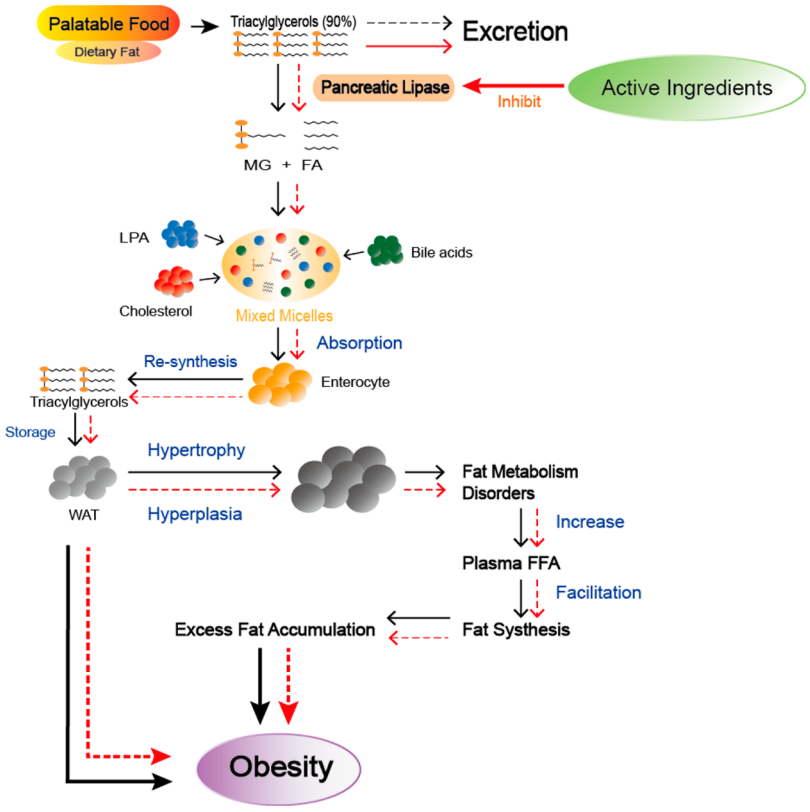

Figure 1. Main routes of lipid absorption regulated with active ingredients. Dietary fat comprises 90% triacylglycerols (TGs). TGs are hydrolyzed by pancreatic lipase into MGs and FAs that are combined with bile acids, cholesterol, and LPAs to form mixed micelles. Mixed micelles are assimilated into enterocytes, which are where TGs that are finally stored in WAT are resynthesized. Inhibition of pancreatic lipase by active ingredients impedes the hydrolysis of TGs and the formation of mixed micelles. Subsequently, the absorption of mixed micelles and the resynthesis of TGs in enterocytes are reduced, and the TG level in excretion is increased, resulting in the alleviation of fat metabolism disorders and fat accumulation and the improvement of obesity. MG, monoglyceride; FA, fat acid; LPA, lysophosphatidic acid; WAT, white adipose tissues; FFA, free fat acid. Solid arrow, promoting effect; dashed arrow, inhibiting effect; black arrow, normal action; red arrow, action of active ingredients.

absorption derived from starch, which may have anti-obesity actions.[85]

Reduced Formation of WAT. Adipose tissue is a complex organ with a profound influence on physiology and pathophysiology. Adipose tissues can be classified as white (WAT) or brown (BAT).[86] WAT is essential for lipid homeostasis and energy balance by ensuring high-efficiency energy storage and rapid fat mobilization for peripheral demands.[87] WAT is organized into discrete anatomical depots of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) expansion, which contribute to obesity and its complications.[88] WAT expansion occurs with adipocyte hyperplasia or amplification of size (hypertrophy). Hyperplasia of WAT indicates an enhanced de novo formation (adipogenesis), and hypertrophy is tightly linked to adipose dysfunction, which is critical to the development of metabolic syndromes in the obese.[89] Therefore, the strict regulation of WAT development and function may be needed to maintain energy homeostasis, and understanding the mechanisms controlling adipogenesis may help guide obesity treatment.

In contrast, the expansion of BAT or "browning" of WAT, an oxidative anti-lipotoxic process that can decrease deleterious effects and lipid overspill induced by dysfunctional WAT, is thought to be a potential therapeutic target for treating obesity and related metabolic diseases in rodents and humans.[90] Brown adipocytes are highly specialized cells that dissipate stored energy as heat through β-adrenergic receptors.[87] In addition, they also act in this context by stimulating uncoupling protein-1 (UCP-1), a mitochondrial BAT-specific protein that catalyzes proton leak across the inner mitochondrial membrane and uncouples substrate oxidation from adenosine triphosphate (ATP) synthesis.[86] Chronic cold exposure can increase BAT or recruit increased BAT mass in rodents, thereby enhancing thermogenesis. Moreover, UCP1-expressing thermogenic adipocytes have been identified in WAT in the form of WAT browning (beige adipocytes).[91] Beige adipocytes possess low basal UCP1 expression similar to white adipocytes, whereas brown adipocytes respond to cAMP stimulation with high UCP1 expression and respiration rates, which are preferentially impressible by irisin.[92] Facilitating BAT recruitment mass/activity and beige adipocytes to enhance mitochondrial UCP1 expression-mediated thermogenic effects may provide a potential therapeutic strategy for treating obesity.[90] Botanicals that reduce WAT formation and increase BAT and beige adipocytes are summarized in Table 3, and their mechanisms of action in inhibiting adipogenesis are illustrated in Figure 2.

Chitosan oligosaccharides (COS) are derivatives of chitosan (CTS)[93] with 2−10 degrees of polymerization, and through the β-1,4 glycosidic linkage of glucosamine and *N*-acetylglucosamine,[94] they possess anti-obesity and lipid-lowering properties.[95,96] Huang et al.[97] reported that subjects treated with low molecular mass COS (M_w, 1000, 250−1000 mg/kg) showed less weight gain than those treated with high molecular mass COS (M_w, 3000, 250−1000 mg/kg) and orlistat (75 mg/kg).

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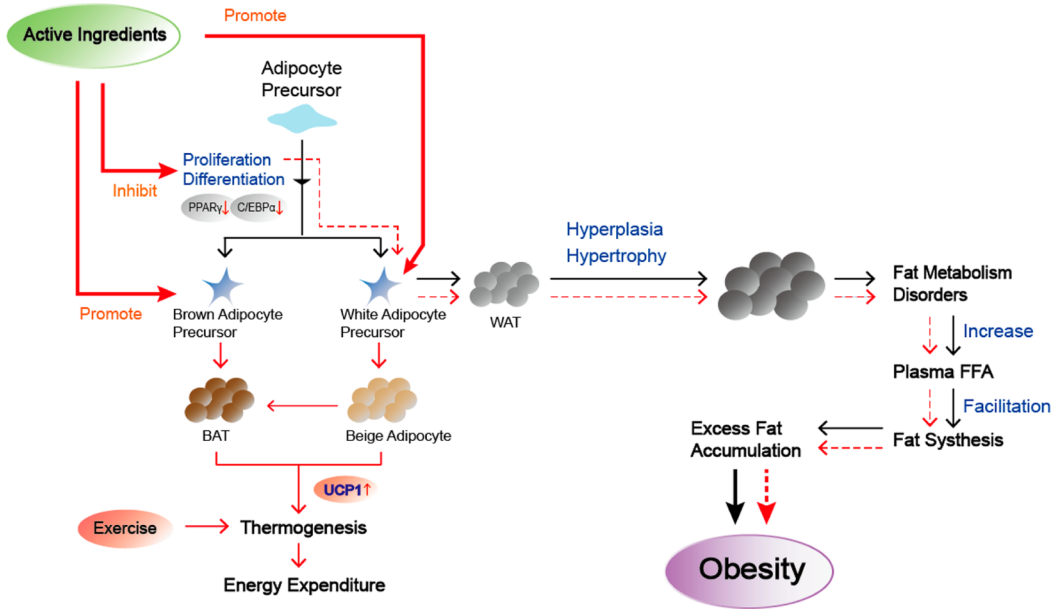

Figure 2. Main routes of anti-adipogenesis and energy expenditure regulated with active ingredients. Adipocyte precursors develop into WAT and BAT via proliferation and differentiation. WAT expansion occurs with adipocyte hyperplasia or amplification of size (hypertrophy). Hyperplasia of WAT indicates an enhanced de novo formation (adipogenesis), and hypertrophy is tightly linked to adipose dysfunction, which is critical to the development of fat metabolism disorders, giving rise to increased plasma FFAs level, the facilitation of fat systhesis, and excess fat accumulation. Suppression of proliferation and differentiation in adipocyte precursors by active ingredients decreases hyperplasia and hypertrophy of adipocytes, elicits WAT reduction and fat metabolism disorders amelioration, and diminishes plasma FFAs and fat systhesis, leading to the alleviation of fat accumulation. Additionally, stimulation of brown adipocyte precursors by active ingredients increases the activation of BAT thermogenesis, resulting in energy expenditure. Moreover, action of active ingredients on white adipocyte precursors induces beige adipocyte formation to activate and recruit BAT. PPARγ, peroxisome proliferator-activated receptor γ; C/EBPα, CCAAT-enhancer binding protein α; BAT, brown adipose tissues; WAT, white adipose tissue; UCP-1, uncoupled protein 1; FFA, free fat acid. Solid arrow, promoting effect; dashed arrow, inhibiting effect; black arrow, normal action; red arrow, action of active ingredients.

Additionally, serum TC ($p < 0.01$), TG ($p < 0.05$), and LDL-C ($p < 0.01$) were diminished and PPARγ, $p < 0.01$) and liver X receptor α (LXRα, $p < 0.01$) mRNA expressions in epididymal adipose tissue were down-regulated in the COS groups. This action was superior to that of orlistat compared to the HF groups, suggesting that low and high molecular mass COS could prevent weight gain and treat obesity and dyslipidemia by inhibiting the differentiation of adipocytes in obese rats with few side effects.[97]

Curcumin, the phenolic yellowish pigment from *Curcuma longa* rhizomes, can lower lipids and prevent obesity-associated complications[98] by activating Wnt/β-catenin signaling and suppressing 3T3-L1 adipocyte differentiation.[99] Compared to the mice in the untreated HF diet groups, those supplemented with 500 mg/kg dietary curcumin showed a significant decrease in weight, total body fat, and serum cholesterol (all $p < 0.05$). In vitro, curcumin (5−25 μM) elevated 5′-AMP-activated protein kinase (AMPK) phosphorylation and carnitine palmitoyltransferase-1 expression ($p < 0.05$) but decreased glycerol-3-phosphate acyl transferase-1 expression. These actions reduced fatty acid esterification and enhanced fat oxidation ($p < 0.05$). In addition, curcumin significantly decreased the expression of PPARγ ($p < 0.05$) and CCAAT-enhancer binding protein α (C/EBPα, $p < 0.05$), which are two key transcription factors in adipogenesis, and this effect modified lipid metabolism in adipocytes and inhibited white adipogenesis.[100]

Capsaicin, the major ingredient in *Capsicum annuum*, increases the expression of browning-specific genes in subcutaneous WAT and increases thermogenesis and mitochondrial biogenesis genes in BAT.[101] Suppression of 3T3-L1 pre-adipocyte differentiation into adipocytes was observed in low-dose capsaicin (0.1−1 μM)-treated groups compared to the untreated control pre-adipocyte groups, suggesting an anti-adipogenic effect ($p < 0.05$) through the activation of the transient receptor potential vanilloid type-1 (TRPV-1) channel and induction of a brown-like phenotype.[102] Furthermore, a 0.01% capsaicin diet markedly up-regulated UCP2 and UCP3 ($p < 0.01$ and <0.05, compared to the control and HF diet groups, respectively) expression in mature adipocytes of visceral fat, promoting fat oxidation and energy expenditure.[103] Capsaicin combined with chitosan as a microsphere had additive obesity-reducing effects.[104,105]

Celastrol, from the stem of the roots of *Tripterygium wilfordii*, is a pentacyclic triterpene and a potent anti-obesity agent. Celastrol (0.1 mg/kg) is a leptin sensitizer, which enhanced plasma leptin ($p < 0.001$), decreased appetite ($p < 0.001$), and promoted a 45% weight loss ($p < 0.001$) in diet-induced obese mice by improving leptin sensitivity compared to the untreated vehicle groups.[106] Moreover, thermogenesis (BAT level), white fat remodeling, and mitochondrial function in the fat ($p < 0.01$) and muscle ($p < 0.05$) were improved by celastrol (1 and 3 mg/kg) compared to the HF diet groups.[107] This occurred by the activation of the HSF1-PGC1α transcriptional axis, which increased HSF1 ($p < 0.01$), a temperature sensor regulating energy metabolism, compared to that of the HSF1 knockout groups.[107]

According to reports in the literature, agents derived from black soybeans,[108,109] *Salacia reticulata*,[110−112] and *Wasabia japonica* (wasabi)[113,114] reduce pre-adipocyte differentiation

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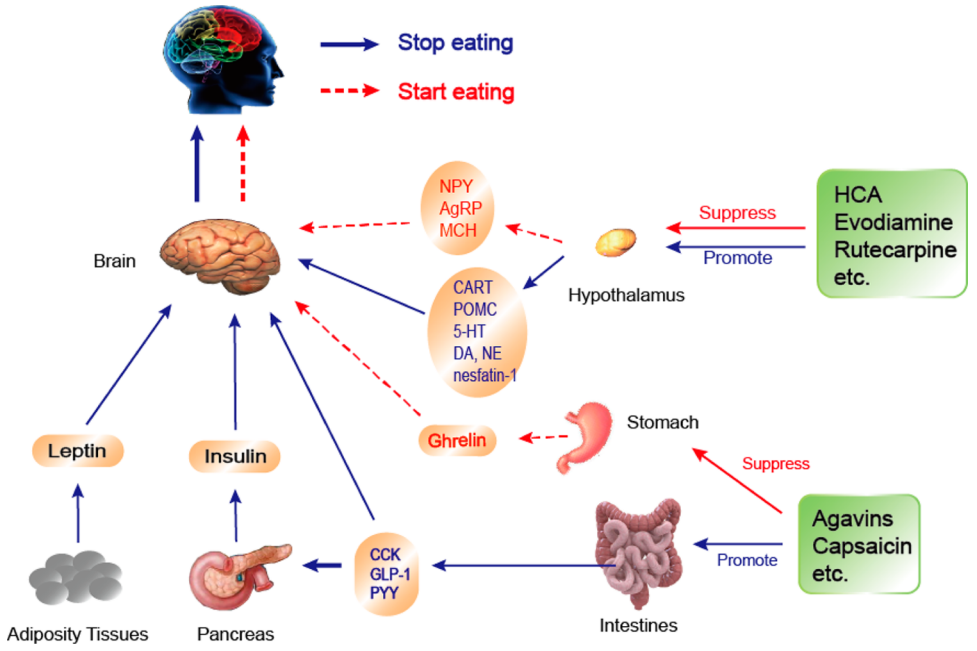

Figure 3. Role of major hormones adjusted with active ingredients in appetite regulation. Activation of anorexigenic peptides and suppression of orexigenic peptides by active ingredients in hypothalamus increase the release of CART, POMC, 5-HT, DA, NE, and nesfatin-1 and decrease NPY, AgRP, and MCH levels, resulting in the satiety (stop eating) increase and food intake (start eating) reduction. Additionally, the appetite regulation of active ingredients on the gastrointestinal tract decreases ghrelin in stomach and increases intestinal CCK, GLP-1, and PYY levels, which promote the pancreas to release insulin. Moreover, leptin released from adipose tissues also affects the brain to regulate appetite. NPY, neuropeptide Y; AgRP, agouti-related protein; MCH, melanin-concentrating hormone. Anorexigenic peptides: CART, cocaine- and amphetamine-regulated transcript; POMC, pro-opiomelanocortin; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY. Solid arrow, promoting effect; dashed arrow, inhibiting effect; red arrow, orexigenic pathway; blue arrow, anorexigenic pathway.

and suppress fat accumulation. The potential molecular pathways mediating these effects are shown in Table 3. In addition, some plants that contain vitisin A,[115] carnosic acid, and carnosol,[116,117] as well as *Platycodon grandiflorum* extract[118] allegedly reduce white adipogenesis (Table 3). Notably, carnosic acid and carnosol are suggested neurotoxins owing to the presence of α-thujone.[119]

Appetite Regulation. The disequilibrium between energy intake and expenditure is proposed as the cause of obesity. Therefore, drugs to decrease energy intake or increase energy expenditure or both without adverse effects are currently of interest because energy intake is highly variable and energy expenditure is modulated chiefly by physical exercise.[120] Sibutramine and fenfluramine reduce food intake and increase satiety by acting on 5-HT/NE neural pathways and the 5-HT receptor, respectively; however, because of their side effects, they were withdrawn from the market.[14] Therefore, researchers are studying natural products (Table 3) as alternative sources of weight loss agents, and the mechanisms of action of some active ingredients for appetite regulation are shown in Figure 3.

The hypothalamus arcuate nucleus (ARC) and brainstem facilitate the regulation of appetite through numerous signaling pathways, and this area contributes to balancing energy and glucose. The complicated central and peripheral neuroendocrine signaling pathways include approximately 40 orexigenic and anorexigenic hormones, neuropeptides, enzymes, and other chemical signaling molecules and their receptors, and these positively or negatively respond to appetite and satiety.[121] Neuropeptide (NPY), agouti-related peptide (AgRP), and melanin-concentrating hormone (MCH) are orexigenic signaling molecules, whereas proopiomelanocortin (POCM), cocaine, amphetamine-regulated transcript (CART), nesfatin-1, 5-HT (5-HT_{1B} and 5-HT_{2C}), DA, and NE are anorexigenic mediators in the hypothalamus.[121] NPY and AgRP expression is up-regulated by fasting and suppressed by leptin, a peptide produced in adipose tissues. Leptin increases following overfeeding and decreases with starvation. In contrast, leptin stimulates POCM and CART neurons, and POCM expression is reduced via fasting.[122] In addition, nesfatin-1, a novel anorectic peptide, is an amino-terminal fragment of NEFA/nucleobindin2 (NUCB2), and starvation weakens its expression in the hypothalamic paraventricular nucleus.[123]

Furthermore, numerous individuals with obesity have high leptin levels and are resistant to its effect on metabolism,[124] so targeting the leptin pathway for treating obesity may not be feasible. However, short-term signals from the gastrointestinal tract are crucial to appetite regulation and may be a more desirable target for obesity treatments. These signals that sense starvation before a meal and postprandial satiety are not considered primarily controlled by leptin.[125] The gastrointestinal tract is the largest endocrine organ and releases more than 20 diverse peptide hormones to regulate physiological processes, and they are especially sensitive to the nutritional status of the gut and, thus, influence the regulation of appetite[125] (Figure 3). Ghrelin, an appetite-stimulating peptide hormone, consists of 28 amino acids and is secreted from the stomach into the circulation.[126] Ghrelin is enhanced by fasting and is a confirmed orexigenic substance because central or peripheral supplementation of acylated ghrelin stimulates food intake and leads to weight gain.[125] Moreover, several desired models of anorexigenic signals are produced in the gastrointestinal tract such as those involving the peptide tyrosine−tyrosine (peptide YY, $PYY)_{3-36}$, CCK, and GLP-1.[127] PYY_{3-36} regulates the neural activity of the

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corticolimbic and higher cortical areas and homeostatic brain regions, which alter neural activity in the caudolateral orbital frontal cortex to control food intake during high plasma PYY phases, whereas hypothalamic activation predicts feeding behavior during low PYY.[128] CKK stimulates gallbladder contraction and pancreatic and gastric secretions, which ultimately slow energy intake.[129] Intracerebroventricular and peripheral supplementation of the incretin GLP-1 potently stimulates insulin release and decreases food intake, and suppresses appetite, respectively.[130] Therefore, anorexigenic hormones may be effective strategies for managing obesity.

(−)-Hydroxycitric acid (HCA) is a major active ingredient of *Garcinia cambogia* extract[131] and has been identified as a valid competitive inhibitor of extramitochondrial ATP-citrate lyase, which transforms excess glucose into fat. HCA diverts fatty acids and carbohydrates for conversion to hepatic glycogen by suppressing ATP-citrate lyase, which is followed by satiety signaling to the brain with curbed appetite.[132] Reportedly, 300 μM HCA suppressed [^{3}H]-5-HT uptake by 20% ($p < 0.01$) at 90 min, and enhanced neurotransmitter release, which controls appetite in the rat brain cortex.[133] To date, no significant toxicity or adverse effects have been reported in experimental animals and humans after *G. cambogia* treatment.[134]

Evodiamine and rutecarpine are alkaloidal components isolated from the fruit of *Evodia rutaecarpa*. Compared to the untreated control groups, intragastric administration of evodiamine (40 mg/kg) lowered food intake and weight gain (each $p < 0.01$) by down-regulating orexigenic NPY ($p < 0.05$) and AgRP ($p < 0.01$) mRNA expression and NPY peptide protein ($p < 0.01$) expression in the ARC and enhancing leptin ($p < 0.01$).[135] Similarly, treatment with rutecarpine (20 and 100 mg/kg) inhibited appetite (43.5 and 65.2%, $p < 0.05$ and $p < 0.01$, respectively) compared to that of the HF diet groups and decreased the levels of blood cholesterol and nonfasting glucose compared to those of the control groups. In addition, rutecarpine (10 and 100 μM) suppressed the expression of NPY and AgRP (each $p < 0.001$) mRNA in the ARC and some related neuropeptides in mouse N29-4 hypothalamic cells.[136]

Agavins (10% in the diet) with a short degree of polymerization (SDP) are from *Agave angustifolia* (AASDP) and *Agave potatorum* (APSDP). The anorexigenic GLP-1 was elevated after treatment with AASDP (40.93%, $p < 0.05$) and APSDP (93%, $p < 0.05$).[139] In addition, the orexigenic ghrelin was decreased (AASDP and APSDP, 16 and 38%, respectively, $p < 0.05$) compared to the SDP, indicating that agavins reduce food intake ($p < 0.05$) and increase weight loss by 30% ($p < 0.05$).[137,138]

Cathinone is an amphetamine-like compound that suppresses appetite and is found in the young leaves of *Catha edulis* (Khat).[139] Compared to the control groups, the group that chewed khat showed significantly enhanced plasma cathinone, which is negatively correlated with hunger and positively correlated with fullness and reduces subjective feelings of hunger ($p < 0.05$).[140] The abuse potential and sympathomimetic effects including increased blood pressure and heart rate have made cathinone available by prescription only in certain countries where it is legally restricted.

Capsaicin and capsiate[141] derived from *C. annuum* also curbed appetite. A meal with capsaicin increased GLP-1 ($p < 0.05$) and tended to diminish ghrelin ($p = 0.07$) compared to the levels of the control groups, suggesting that capsaicin reduces appetite.[142] Additionally, 5-hydroxy-L-tryptophan (5-HTP) from *Griffonia simplicifolia*,[143] ginseng crude saponins (protopanaxadiol and protopanaxatriol) from *P. ginseng*,[144,145] gymnemic acids from *Gymnema sylvestre*,[146,147] and the extracts of *P. vulgaris*[148] as well as *Benincasa hispida*[149] regulate appetite (Table 3) and may be promising sources of potential agents for treating obesity.

MISCELLANEOUS

Several other mechanisms have been shown to modulate obesity and its related complications. The microflora, which grow mutually within the human host, are stably colonized and contribute to controlling the physiological state by protecting against invading pathogens and contributing to digestion and absorption of nutrients in gut.[150] Recently, an association between intestinal microbiota and obesity has gained attention because microbiota regulates the energy balance and metabolic functions of the host.[150−152] As such, gut flora are a promising strategy for anti-obesity interventions.

Ganoderma lucidum, a medicinal mushroom with abundant high molecular weight polysaccharides (>300 kDa), reduced the ratio of Firmicutes/Bacteroidetes and endotoxin-bearing Proteobacteria, which lowered metabolic endotoxemia without injuring the integrity of the intestinal barrier, leading to decreased body weight and plasma glucose levels.[153] The polyphenolic resveratrol reversed the increase in the Firmicutes/Bacteroidetes ratios and *Enterococcus faecalis* counts and improved *Lactobacillus* and *Bifidobacterium* growth. This action ameliorated the intestinal microbiota dysbiosis, metabolic disorders, and obesity by inhibiting the fasting-induced adipogenic factor (Fiaf) signaling pathway and modulating the composition of the intestinal microbes.[154] Furthermore, MDG-1, an ophiopogon polysaccharide, and Rhizoma Atractylodis Macrocephalae regulate gut microbiota composition and theoretically contribute to weight loss.[155,156]

In contrast, adipocyte apoptosis and fecal fat excretion increased on supplementation with dietary calcium,[157] which may be promising for weight loss.[158] The aqueous extract of *Poncirus trifoliata* suppressed body weight gain likely by accelerating the intestinal transit, increasing excretion, and decreasing nutrient absorption without interfering with pancreatic lipase.[159] Polyphenols and polysaccharides in black tea may reduce body, visceral fat, and adipocyte size by elevating fecal fatty acid and improving serum biochemistry.[160] Moreover, fecal excretion of nutrients can be increased by using gallate tea catechins, which repressed gut nutrient absorption and, therefore, may be relevant to body fat reduction and a possible obesity treatment.[161]

CONCLUSION

Obesity is hazardous to human health and has far-reaching consequences, such as T2D, CVD, dyslipidemia, cerebrovascular incidents, and sleep apnea. Presently, only orlistat, lorcaserin, and the fixed-dose combination of phentermine and topiramate are available for treating obesity.[162] However, poor tolerability and low compliance owing to associated side effects restrict their potential widespread use.[163] Therefore, the development of additional drugs from natural products is currently arousing considerable interest because they most likely have fewer side effects.

As described in this review, studies of numerous active ingredients from natural products have been gradually accumulating information from animal experiments to the level of cell lines, proteins, and genes. These studies have

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shown the mechanisms of action of natural products and contributed to promoting interest in the development of anti-obesity agents. Some specific plants have been shown to act via more than one mechanism or signal pathway, such as *P. grandiflorum*, *P. ginseng*, *C. annuum*, and *R. officinalis*. The active ingredients, capsiate and curcumin, are often incorporated as edible components for daily consumption in the diet. Carnosic acid (5 μg/mL) from *R. officinalis* showed an anti-adipogenic effect and decreased the viability of adipocytes by 8%.[116,117] However, it is suggested to be neurotoxic because of the presence of α-thujone,[119] and, therefore, more caution should be exercised when using such agents. Cathinone from *C. edulis* significantly curbed the appetite ($p < 0.05$) in humans, but its abuse potential and sympathomimetic effects (blood pressure and heart rate elevation) have caused it to be available only by prescription in certain countries where it is legally restricted.

CTS and COS are active compounds, mainly isolated from crab and shrimp shells, with few adverse effects, which were studied for the treatment of obesity,[97,105] hyperlipidemia,[164,165] and hypercholesterolemia.[166] In addition, over the past decade, our research group has formulated CTS into microspheres[93,104,167] and nanoparticles[164,166,168,169] because of CTS's insolubility. Additionally, CTS and COS target adipogenesis suppression by down-regulating the related adipogenesis genes, such as PPARγ.[97] The synergistic effect of treatment with CTS and capsaicin (CCMSs) would be preferable to that of orlistat for anti-obesity treatment by up-regulating UCP2 mRNA expression and increasing thermogenesis.[106] This is because the CCMSs-treated groups showed a better suppression of body weight gain, body mass index, and body fat than the orlistat-treated group did. Furthermore, studies investigating the possibility that CTS and COS act through the leptin signal pathway to ameliorate leptin resistance and improve obesity and its related complications are currently underway.

However, the studies of active ingredients with anti-obesity properties are fraught with numerous problems. First, the mechanisms of action of most of these active ingredients are undefined and, therefore, in-depth explorations should continue. Moreover, the development of diverse active ingredients, which are supposed to be incorporated into pharmacological and toxicological research studies as well as clinical studies of their efficacy, is challenging. However, the reasonable and effective compatibility of these active ingredients makes them preferable for use in treating the perplexity of obesity. Last but not least, most of the plants we evaluated have not been investigated clinically in humans, although they are currently sold in the form of supplements. Only a few compounds have moved into clinical trials, but none have reached the final stage for ratification because the transferability of most of the study data on dosage and active ingredients in animal models to humans is questionable. In addition, for safety reasons, low concentrations or doses of active compounds used in the cell culture and animal models should be accorded priority over high doses in determining the effective dosage. Generally, more studies of natural products in healthy volunteers are needed to determine the safety and efficacy of these potential anti-obesity drugs.

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Notes

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ABBREVIATIONS USED

5-HT, 5-hydroxytryptamine; CB1, cannabinoid 1; GLP-1, glucagon-like peptide-1; CNS, central nervous system; FDA, U.S. Food and Drug Administration; NPY, neuropeptide Y; PYY, peptide YY; NE/NA, norepinephrine/noradrenaline; DA, dopamine; HF, high fat; WAT, white adipose tissue; BAT, brown adipose tissue; UCP, uncoupling protein; PPARγ, peroxisome proliferator-activated receptor γ; C/EBPα, CCAAT-enhancer binding protein α; HSF1, heat shock factor 1; PGC1α, peroxisome proliferator-activated receptor γ coactivator-1α; SREBP-1c, sterol-regulatory-element-binding protein-1c; ATP, adenosine triphosphate

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