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used to reduce weight have associated side effects5 and specifically, fenfluramine,6 rimonabant, and sibutramine7 were withdrawn from the market because of dangerous side effects.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-OBESETY 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-HT2C-receptor agonist, and its characteristic minimal activity at both the 5-HT2A and 5-HT2B 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 inhibitor23 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
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 FDA in 1997, was used as an anti-obesity drug because of the 5-HT-NE re-uptake inhibitor, sibutramine, approved by the FDA in 1997, was used as an anti-obesity drug because of its combination with 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 neuropyschosis because of the buuponrop combination 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 aid40 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-OBESEITY 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 adipocytes42 (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 lipase44 because reduced fat absorption can improve diabetes45 and, therefore, may be an option for weight loss treatment. As a pancreatic lipase inhibitor, orlistat, with a median inhibitory concentration (IC50) 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

<table>
<thead>
<tr>
<th>Table 1. Current Situation of Anti-obesity Drugs Based on Mechanisms</th>
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<tbody>
<tr>
<td><strong>mechanism</strong></td>
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<tr>
<td>signal transduction</td>
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</table>

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 | obinutuzumab | <5 | adverse cardiovascular effects | phase II |
| NA agent and anti-epileptic drug | phentermine with topiramate | 9–10 | parasthesia, constipation, dysgeusia, dizziness, insomnia, psychosis, and tardosegitogenity | 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 neuropyschosis | approved in 2014 |
| 5-HT/DA/NA re-uptake inhibitor | tesofensine | 9–11 | increased heart rate and blood pressure | phase III |

“Sources: Rodgers et al;14 Adan;162 Shin and Gadde;170 Solas et al;171 Wong.163”

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<table>
<thead>
<tr>
<th>primary source (species)</th>
<th>active compounds</th>
<th>parts used</th>
<th>IC\textsubscript{50} value</th>
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<th>suitable dosage</th>
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</thead>
<tbody>
<tr>
<td><strong>pancreatic lipase inhibitors</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Platycodon grandiflorum (Campanulaceae)</td>
<td>platycodins</td>
<td>roots</td>
<td>20 mg/mL</td>
<td>hamsters</td>
<td>0.3−0.5% platycodin in aqueous extract of platycodi radix per day</td>
<td>4 weeks</td>
<td>46−48</td>
</tr>
<tr>
<td>Acanthopanax sessiliflorus (Araliaceae)</td>
<td>sessiloside, chis anoside, isochis anoside</td>
<td>leaves</td>
<td>0.36, 0.75, 4.0 mg/mL</td>
<td>mice</td>
<td>5% aqueous extract of platycodi radix in high-fat diet per day (570 mg/kg/day)</td>
<td>5 weeks</td>
<td>49, 50</td>
</tr>
<tr>
<td>Acanthopanax senticosus (Araliaceae)</td>
<td>silphioside F, copteroside B</td>
<td>fruits</td>
<td>0.22, 0.25 mM</td>
<td>mice</td>
<td>500 mg/kg/day A. senticosus extract</td>
<td>12 weeks</td>
<td>51, 52</td>
</tr>
<tr>
<td>Alpinia officinarum (Zingiberaceae)</td>
<td>3-methyl ethergalangin, 5-hydroxy-7-(49-hydroxy-39-methoxyphenyl)-1-phenyl-3-heptanone</td>
<td>rhizome</td>
<td>1.30, 1.50 mg/mL</td>
<td>rats</td>
<td>3−5% (weight/diet weight, w/w) powdered A. officinarum ethanolic extract in high-fat diet per day</td>
<td>6 weeks</td>
<td>53−55</td>
</tr>
<tr>
<td>Clusia nemorosa (Clusiaceae)</td>
<td>betulinic acid (BA)</td>
<td>barks</td>
<td>21.1 μM</td>
<td>cell lines</td>
<td>1.5−100 μM BA</td>
<td>4 h</td>
<td>56, 57</td>
</tr>
<tr>
<td>Gardenia jasminoides (Rubiaceae)</td>
<td>crocin, crocetin</td>
<td>fruits</td>
<td>2.10, 2.60 mg/mL</td>
<td>mice</td>
<td>50 mg/kg/day crocin, crocetin</td>
<td>5 weeks</td>
<td>58, 59</td>
</tr>
<tr>
<td>Panax ginseng (Araliaceae)</td>
<td>ginsenoside Rg3, ginsenoside Rh2, protopanaxadiol saponins, protopanaxatriol saponins</td>
<td>roots, berries</td>
<td>ginseng saponin, 0.5 mg/mL</td>
<td>mice</td>
<td>3% (w/w) ginseng saponin extract in high-fat diet per day</td>
<td>3 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Panax quinquefolium (Araliaceae)</td>
<td>ginsenosides Rb1, Rb2, and Rc</td>
<td>stems, leaves</td>
<td>0.50 mg/mL</td>
<td>mice, rats</td>
<td>1000 mg/kg/day crude saponins</td>
<td>8 weeks</td>
<td>61</td>
</tr>
<tr>
<td>Panax japonicus (Araliaceae)</td>
<td>chikusetsusaponins III and IV</td>
<td>0.25, 0.50 mg/mL</td>
<td>mice</td>
<td>1−3% total chikusetsusaponins in high-fat diet per day</td>
<td>9 weeks</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Aesculus turbinata (Hippocastanaceae)</td>
<td>escins Ib and Ia</td>
<td>seeds</td>
<td>m0.50 g/mL</td>
<td>mice</td>
<td>2% total escins in high-fat diet per day</td>
<td>11 weeks</td>
<td>63, 64</td>
</tr>
<tr>
<td>green tea</td>
<td>(-)-epigallocatechin gallate</td>
<td>leaves</td>
<td>18 ± 0.57 μM</td>
<td>mice</td>
<td>10−30 mg/mL in drinking water</td>
<td>3 h</td>
<td>65</td>
</tr>
<tr>
<td>gomchui tea</td>
<td>di-O-cafeoylquinic acid</td>
<td>leaves</td>
<td>12.7−40.4 μM</td>
<td>vitro</td>
<td>10−30 mg/mL in drinking water</td>
<td>3 h</td>
<td>65</td>
</tr>
<tr>
<td>oolong tea</td>
<td>oolonghomobisflavan A, oolonghomobisflavan B, oolongtheanin-3′-O-gallate</td>
<td>leaves</td>
<td>0.048, 0.108, 0.068 μM</td>
<td>vitro</td>
<td>6.67 mg/mL in drinking water</td>
<td>3 h</td>
<td>65</td>
</tr>
<tr>
<td>Eisenia bicyclis</td>
<td>7-phloroeckol, fucofuroeckol A</td>
<td>leaves</td>
<td>12.7 ± 1.0, 37.2 ± 2.3 μM</td>
<td>vitro</td>
<td>unclear</td>
<td>unclear</td>
<td>67</td>
</tr>
<tr>
<td>Glycyrrhiza uralensis (Leguminosae)</td>
<td>licochalcone A</td>
<td>roots</td>
<td>103.4 μM</td>
<td>vitro</td>
<td>unclear</td>
<td>unclear</td>
<td>68</td>
</tr>
<tr>
<td>Acacia mearnsii (Acacia)</td>
<td>acacia polyphenol (AP)</td>
<td>barks</td>
<td>0.95 mg/mL</td>
<td>mice</td>
<td>250−1000 mg/kg/day API, 2.5−5% AP in high-fat diet per day</td>
<td>7 weeks</td>
<td>69, 70</td>
</tr>
<tr>
<td>Actinidia arguta (Actinidiaceae)</td>
<td>ursolic acid</td>
<td>roots</td>
<td>51.21 μM</td>
<td>rats</td>
<td>50−100 mg/kg/day ursolic acid</td>
<td>4 h</td>
<td>71</td>
</tr>
<tr>
<td>Rosmarinus officinalis (Lamiaceae)</td>
<td>carnosic acid, carnosol</td>
<td>leaves</td>
<td>36, 13 μM</td>
<td>rats</td>
<td>20 mg/kg/day carnosic acid, 200 mg/kg/day R. officinalis extract</td>
<td>65 days</td>
<td>72</td>
</tr>
<tr>
<td>Salvia officinalis (Lamiaceae)</td>
<td>carnosic acid, carnosol</td>
<td>leaves</td>
<td>36, 13 μM</td>
<td>mice</td>
<td>5−20 mg/kg/day carnosic acid</td>
<td>14 days</td>
<td>73</td>
</tr>
<tr>
<td>Sapindus rarak (Sapindaceae)</td>
<td>rarasaponins I and II, rarasoside A</td>
<td>pericarps</td>
<td>131, 172, 151 μM</td>
<td>vitro</td>
<td>unclear</td>
<td>unclear</td>
<td>74</td>
</tr>
<tr>
<td>Ginkgo biloba (Ginkgoaceae)</td>
<td>ginkgolide A and B, bilobalide</td>
<td>leaves</td>
<td>22.9, 900, 60.1 μg/mL</td>
<td>molecular modeling</td>
<td>1.56−100 μg/mL G. biloba extract</td>
<td>unclear</td>
<td>75</td>
</tr>
<tr>
<td>Calotropis procera (Asclepiadaceae)</td>
<td>2,4-bis(1,1-dimethylethyl) ester, 1,2-benzenedi-carboxylic acid, bis(2-methylpropyl) ester</td>
<td>roots</td>
<td>purified diterpenoid fraction, 9.47 μg/mL</td>
<td>vitro</td>
<td>unclear</td>
<td>unclear</td>
<td>76</td>
</tr>
<tr>
<td>Dioscorea nipponica (Dioscoreaceae)</td>
<td>dioscin, diosgenin</td>
<td>roots, rhizomes</td>
<td>20.0, 280 μg/mL</td>
<td>mice</td>
<td>100 mg/kg/day dioscin and diosgenin</td>
<td>8 weeks</td>
<td>77</td>
</tr>
</tbody>
</table>

DOI: 10.1021/acs.jafc.6b04468
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. 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. In addition, Han et al. suggested that the study group treated with 5% platycodi radix aqueous extract (570 mg/kg) showed a reduction in final parametrical 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. 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 sifphioside 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. According to Cha et al., 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 ethergalanigin 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). 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.

Betulinic acid (BA), a pentacyclic triterpenic acid, is widely distributed in various plants such as *Clusia nemorosa* (family Clusiaceae). The anti-obesity effect of BA has been investigated with respect to the inhibition of pancreatic lipase and amylase. 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 2. continued**

<table>
<thead>
<tr>
<th>primary source (species)</th>
<th>active compounds</th>
<th>parts used</th>
<th>suitable dosage</th>
<th>model</th>
<th>IC$_{50}$ value</th>
<th>duration</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cudrania tricuspidata</em></td>
<td>cudraflavone C</td>
<td>leaves</td>
<td>9.91 μg/mL</td>
<td>rats</td>
<td>50−200 mg/kg/day C. tricuspidata extract</td>
<td>4 h</td>
<td>78</td>
</tr>
<tr>
<td><em>Salix matsudana</em></td>
<td>apigenin-7-D-glucoside</td>
<td>leaves</td>
<td>0.20 mg/mL</td>
<td>mice</td>
<td>20−5% polyphenols of <em>S. matsudana</em> leaves in high-fat diet</td>
<td>9 weeks</td>
<td>80, 81</td>
</tr>
<tr>
<td><em>Phaseolus vulgaris</em></td>
<td>phytohemagglutinin</td>
<td>beans</td>
<td>unclear</td>
<td>rats</td>
<td>50−250 mg/kg/day P. vulgaris extract</td>
<td>22 days</td>
<td>79, 82</td>
</tr>
<tr>
<td><em>Nelumbo nucifera</em></td>
<td>phenolic compounds</td>
<td>leaves</td>
<td>0.820 mg/mL</td>
<td>mice, rats, mice, rats, mice, rats</td>
<td>1.22 g/kg/day N. nucifera extract</td>
<td>6 weeks</td>
<td>83, 84</td>
</tr>
<tr>
<td><em>Araucaria angustifolia</em></td>
<td>pinha o coat tannin</td>
<td>seeds</td>
<td>unclear</td>
<td>mice</td>
<td>250−500 mg/kg/day pinha o coat tannin</td>
<td>6 h</td>
<td>85</td>
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### Table 3. Active Ingredients for Anti-obesity Effect Based on Adipose Tissues and Appetite Regulation

<table>
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<th>parts used</th>
<th>molecular pathways</th>
<th>model</th>
<th>suitable dosage</th>
<th>duration</th>
<th>refs</th>
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<tr>
<td>reduce white adipose formation</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>crab and shrimp shells</td>
<td>chitosan oligosaccharides (COS)</td>
<td>shells</td>
<td>decreases the mRNA expression of PPARγ, LXRα (both ( p &lt; 0.01 )), inhibits the differentiation of adipocytes</td>
<td>rats</td>
<td>250–1000 mg/kg/day</td>
<td>6 weeks</td>
<td>93–97</td>
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<tr>
<td>Curcuma longa (Zingiberaceae)</td>
<td>curcumin</td>
<td>rhizomes</td>
<td>activates Wnt/β-catenin signaling and AMPK phosphorylation, increases carnitine palmitoyltransferase-1 expression (( p &lt; 0.05 )), decreases glyceraldehyde-3-phosphate acyltransferase-1, PPARα and C/EBPβ (all ( p &lt; 0.05 )) expression, suppresses 3T3-L1 adipocyte differentiation</td>
<td>cell lines</td>
<td>5–25 μM curcumin</td>
<td>24 h</td>
<td>98–100</td>
</tr>
<tr>
<td>black soybeans (Leguminosae)</td>
<td>anthocyanins (cyanidine-3-O-glucoside, delphinidin-3-O-glucoside, petunidin-3-O-glucoside)</td>
<td>seeds</td>
<td>suppresses 3T3-L1 cell differentiation and lipid accumulation, decreases the expression of LXRα, PPARγ, C/EBPδ, and SREBP-1c (all ( p &lt; 0.01 ))</td>
<td>cell lines</td>
<td>10–50 μg/mL anthocyanins</td>
<td>24 h</td>
<td>108, 109</td>
</tr>
<tr>
<td>Salacia reticulata (Celastraceae)</td>
<td>mangiferin (−)epicatechin, (−)-epigallocatechin</td>
<td>roots, stems</td>
<td>represses fat accumulation, reduces the size of weight adipocytes (( p &lt; 0.05 )), decreases PPARα, C/EBPβ expression and glycerol-3-phosphate dehydrogenase (all ( p &lt; 0.05 )), suppresses adipocyte differentiation</td>
<td>cell lines</td>
<td>10–100 μg/mL S. reticulata extract</td>
<td>96 h</td>
<td>110–112</td>
</tr>
<tr>
<td>Wasabia japonica (Cruciferae)</td>
<td>hot water extract</td>
<td>leaves, rhizomes</td>
<td>suppresses 3T3-L1 pre-adipocyte differentiation, decreases the regulation of PPARα, SREBP-1c, fatty acid synthase, C/EBPβ and adipocyte fatty acid binding protein 2 (all ( p &lt; 0.05 ))</td>
<td>cell lines</td>
<td>0.1–1 μM vitamin A</td>
<td>8 days</td>
<td>115</td>
</tr>
<tr>
<td>Vitex vinifera (Vitaceae)</td>
<td>vitisin A</td>
<td>seeds</td>
<td>represses pre-adipocyte proliferation and differentiation via p21- and Rb-dependent cell cycle arrest, decreases lipid content (( p &lt; 0.01 ))</td>
<td>cell lines</td>
<td>5–10 μg/mL carnosic acid</td>
<td>5 days</td>
<td>116, 117</td>
</tr>
<tr>
<td>Rosmarinus officinalis (Lamiaceae)</td>
<td>carnosic acid, carnosol</td>
<td>leaves</td>
<td>induces phase II enzymes, stimulates the metabolism of glutathione (GSH, ( p &lt; 0.01 )), inhibits the PPARα, fatty acid binding protein-4 expression (FABP4) (both ( p &lt; 0.01 )), suppresses 3T3-L1 adipocyte differentiation</td>
<td>cell lines</td>
<td>1–3 mg/kg/day P. grandiflorum extract</td>
<td>7 weeks</td>
<td>118</td>
</tr>
<tr>
<td>Platycodon grandiflorum (Campanulaceae)</td>
<td>platycodins</td>
<td>roots</td>
<td>inhibits 3T3-L1 pre-adipocyte differentiation and reduces fat accumulation (( p &lt; 0.05 )), decreases the size of subcutaneous adipocytes (( p &lt; 0.05 ))</td>
<td>rats</td>
<td>150 mg/kg/day</td>
<td>2 weeks</td>
<td>106, 107</td>
</tr>
<tr>
<td>increase brown adipose tissue (increase thermogenesis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsicum annuum (Solanaceae)</td>
<td>capsaicin</td>
<td>fruits</td>
<td>increases the expression of browning-specific genes in subcutaneous white adipose, up-regulates UCP1 and UCP3 (( p &lt; 0.01 ) and ( &lt;0.05 ), compared to the control and HF diet groups, respectively) (thermogenesis) expression, suppresses the differentiation of 3T3-L1 pre-adipocytes (( p &lt; 0.05 ))</td>
<td>cell lines</td>
<td>0.1–1 μM capsaicin</td>
<td>24 h</td>
<td>101–105</td>
</tr>
<tr>
<td>Tripterygium Wilfordii (Celastraceae)</td>
<td>celastrol</td>
<td>roots</td>
<td>thermogenesis, increases plasma leptin (( p &lt; 0.001 )), activates the HSF1-PGC1α transcriptional axis (( p &lt; 0.01 ))</td>
<td>mice</td>
<td>1–3 mg/kg/day</td>
<td>2 weeks</td>
<td>106, 107</td>
</tr>
<tr>
<td>appetite suppression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcinia Cambogia (Guttiferae)</td>
<td>(−)-hydroxycitric acid (HCA)</td>
<td>fruits</td>
<td>suppresses the ATP-citrate lyase, increases satiety, decreases ([1^1]{H})-S-HT uptake by 20% (( p &lt; 0.01 )), enhances the release of neurotransmitter</td>
<td>rats</td>
<td>300 μM HCA extract</td>
<td>14 days</td>
<td>131–134</td>
</tr>
<tr>
<td>Eruca sativa (Rutaceae)</td>
<td>evodiamine, rutecarpine</td>
<td>fruits</td>
<td>decreases the mRNA expression of NPY (( p &lt; 0.05 )) and AgRP (( p &lt; 0.01 )), decrease the protein expression of NPY peptide (( p &lt; 0.001 )), enhance leptin level (( p &lt; 0.001 )), decrease blood cholesterol, nonfasting glucose level</td>
<td>rats</td>
<td>40 mg/kg/day evodiamine</td>
<td>25 days</td>
<td>135, 136</td>
</tr>
<tr>
<td>Agave angustifolia and Agave potatorum (Agavaceae)</td>
<td>agavins</td>
<td>leaves</td>
<td>increases anorexigenic GLP-1 (AASDP, 40.93%; APSDP, 93%, respectively, ( p &lt; 0.05 )) and decreases the orexigenic ghrelin (AASDP, 16%; APSDP, 38%, respectively, ( p &lt; 0.05 ))</td>
<td>cell lines</td>
<td>10–100 μM agavins in diet</td>
<td>5 days</td>
<td>137, 138</td>
</tr>
<tr>
<td>Catha edulis (thea-cea)</td>
<td>cathinone</td>
<td>leaves</td>
<td>increases satiety, reduces the sense of hungry (( p &lt; 0.05 ))</td>
<td>humans</td>
<td>unclear</td>
<td>180 min</td>
<td>139, 140</td>
</tr>
<tr>
<td>Capsicum annuum (Solanaceae)</td>
<td>capsaicin and capsaite</td>
<td>fruits</td>
<td>increases the level of GLP-1 (( p &lt; 0.05 )), tended to decrease ghrelin content (( p = 0.07 ))</td>
<td>humans</td>
<td>unclear</td>
<td>180 min</td>
<td>141, 142</td>
</tr>
<tr>
<td>Griffonia simplicifolia (Leguminosae)</td>
<td>5-hydroxtryptophan</td>
<td>seeds</td>
<td>increases satiety, lowers food intake</td>
<td>humans</td>
<td>unclear</td>
<td>4 weeks</td>
<td>143</td>
</tr>
<tr>
<td>primary source</td>
<td>active compounds</td>
<td>parts used</td>
<td>molecular pathways</td>
<td>model</td>
<td>suitable dosage</td>
<td>duration</td>
<td>ref(s)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------------</td>
<td>------------</td>
<td>------------------------------------------------------------------------------------</td>
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<td>--------</td>
</tr>
<tr>
<td>Panax ginseng (Araliaceae)</td>
<td>ginseng crude saponins</td>
<td>roots, berries</td>
<td>decreases the NPY expression and leptin level (both $p &lt; 0.05$), increases the level of CCK</td>
<td>rats</td>
<td>200 mg/kg/day</td>
<td>3 weeks</td>
<td>144, 145</td>
</tr>
<tr>
<td></td>
<td>protopanaxadiol, protopanaxatriol triol</td>
<td></td>
<td></td>
<td></td>
<td>100 mg/kg/day G. octoba extract</td>
<td>4 weeks</td>
<td>146, 147</td>
</tr>
<tr>
<td>Gymnema sylvestre (Asclepiadaceae)</td>
<td>gymnemic acids</td>
<td>leaves</td>
<td>prevents sugar molecular absorption, reduces food intake (27−54%, $p &lt; 0.001$)</td>
<td>mice</td>
<td>200−1000 mg/kg/day</td>
<td>7−14 h</td>
<td>149</td>
</tr>
<tr>
<td>Phaseolus vulgaris (Fabaceae)</td>
<td>phytohemagglutinin</td>
<td>beans</td>
<td>inhibits ghrelin secretion ($p &lt; 0.05$), reduces food intake, increases satiety sensations</td>
<td>humans</td>
<td>unclear</td>
<td>120 min</td>
<td></td>
</tr>
<tr>
<td>Benincasa hispida (Cucurbitaceae)</td>
<td>methanol extract</td>
<td>fruits</td>
<td>stimulates central nervous system, reduces food intake (25−54%, $p &lt; 0.001$)</td>
<td>mice</td>
<td>100−7 mg/day S. matsudana extract</td>
<td>4 weeks</td>
<td>146, 147</td>
</tr>
<tr>
<td>Crocin and crocetin</td>
<td></td>
<td></td>
<td>inhibit cyclical adenosine monophosphate (cAMP)-dependent phosphodiesterase ($p &lt; 0.01$), and it may accelerate lipid mobilization by increasing lipolysis in adipose tissues.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The active ingredients of Panax ginseng, Panax quinquefolium, Aesculus turbinata, green tea, gomchui, and oolong teas, Glycyrhiza uralensis, Acacia mearnsii, Rosmarinus officinalis, Salvia officinalis, Sapindus rarak, Ginkgo biloba, Calotropis procera, Dioscorea nipponica, and Cudrania tricuspidata 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.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**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. 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 $\alpha$-amylase in the small intestine. Active compounds from the polyphenol fractions of S. matsudana leaves that inhibit $\alpha$-amylase include apigenin-7-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. Extracts of Phaseolus vulgaris (family Fabaceae) beans have been studied as potential $\alpha$-amylase inhibitors for controlling food consumption, weight, lipid accumulation, and glycemia. 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. In addition, the extracts might increase resistant starch, carbohydrate tolerance, and colorectal bacterial activity, which may be exploited for improving metabolic syndromes.

The flavonoids extracted from Nelumbo nucifera leaves inhibited $\alpha$-amylase and $\alpha$-glucosidase (IC$_{50}$ = 0.82 and 1.86 mg/mL, respectively). 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. Similarly, condensed tannin-rich extracts of the pinhoã coat (Araracuara angustifolia seeds) inhibited $\alpha$-amylase by blocking glucose absorption. The active compounds of S. matsudana and N. nucifera were studied for their potential in controlling diabetes.

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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). WAT is essential for lipid homeostasis and energy balance by ensuring high-efficiency energy storage and rapid fat mobilization for peripheral demands. 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. 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. 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. Brown adipocytes are highly specialized cells that dissipate stored energy as heat through β-adrenergic receptors. 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. 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). 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 impressive by irisin. 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. 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.
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 synthesis, 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 alleviation, and diminishes plasma FFAs and fat synthesis, 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.27

Curcumin, the phenolic yellowish pigment from Curcuma longa rhizomes, can lower lipids and prevent obesity-associated complications98 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 S′-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 annum, 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

Celastril, from the stem of the roots of Tripterygium wilfordii, is a pentacyclic triterpene and a potent anti-obesity agent. Celastril (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 celastril (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,106,109 Salacia reticulata,110–112 and Wasabia japonica (wasabi)113,114 reduce pre-adipocyte differentiation...
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 extract118 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. 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, and amphetamine-regulated transcript (CART), nesfatin-1, 5-HT (5-HT1B and 5-HT2C), DA, and NE are anorexigenic mediators in the hypothalamus.122 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 (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), CCK, and GLP-1.127 PYY3–36 regulates the neural activity of the...
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.\textsuperscript{128} CCK stimulates gallbladder contraction and pancreatic and gastric secretions, which ultimately slow energy intake.\textsuperscript{129} Intracerebroventricular and peripheral supplementation of the incretin GLP-1 potently stimulates insulin release and decreases food intake, and suppresses appetite, respectively.\textsuperscript{130} Therefore, anorexigenic hormones may be effective strategies for managing obesity.

\textit{(-)-Hydroxycitric acid} (HCA) is a major active ingredient of \textit{Garcinia cambogia} extract\textsuperscript{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.\textsuperscript{132} Reportedly, 300 μM HCA suppressed \textsuperscript{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.\textsuperscript{133} To date, no significant toxicity or adverse effects have been reported in experimental animals and humans after \textit{G. cambogia} treatment.\textsuperscript{134}

Evodiamine and rutecarpine are alkaloidal components isolated from the fruit of \textit{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).\textsuperscript{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.\textsuperscript{136}

Agavins (10% in the diet) with a short degree of polymerization (SDP) are from \textit{Agave angustifolia} (AASDP) and \textit{Agave potatorum} (APSDP). The anorexigenic GLP-1 was elevated after treatment with AASDP (40.93%, p < 0.05) and APSDP (93%, p < 0.05).\textsuperscript{137} In addition, the orexigenic ghrelin was decreased (AASDP and APSDP, 16 and 58%, 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).\textsuperscript{137,138}

Cathinone is an amphetamine-like compound that suppresses appetite and is found in the young leaves of \textit{Catha edulis} (Khat).\textsuperscript{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).\textsuperscript{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\textsuperscript{141} derived from \textit{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.\textsuperscript{142} Additionally, 5-hydroxy-L-tryptophan (5-HTP) from \textit{Griffonia simplicifolia},\textsuperscript{143} ginseng crude saponins (protopanaxadiol and protopanaxatriol) from \textit{P. ginseng},\textsuperscript{144,145} gymnemic acids from \textit{Gymnema sylvestre},\textsuperscript{146,147} and the extracts of \textit{P. vulgaris}\textsuperscript{148} as well as \textit{Benincasa hispida}\textsuperscript{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.\textsuperscript{150} Recently, an association between intestinal microbiota and obesity has gained attention because microbiota regulates the energy balance and metabolic functions of the host.\textsuperscript{150–152} As such, gut flora are a promising strategy for anti-obesity interventions.

\textit{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.\textsuperscript{153} The polyphenolic resveratrol reversed the increase in the Firmicutes/Bacteroidetes ratios and \textit{Enterococcus faecalis} counts and improved \textit{Lactobacillus} and \textit{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.\textsuperscript{154} Furthermore, MDG-1, an ophiopogon polysaccharide, and Rhizoma Atractylodis Macrocephalae regulate gut microbiota composition and theoretically contribute to weight loss.\textsuperscript{155,156}

In contrast, adipocyte apoptosis and fecal fat excretion increased on supplementation with dietary calcium,\textsuperscript{157} which may be promising for weight loss.\textsuperscript{158} The aqueous extract of \textit{Poncirus trifoliata} suppressed body weight gain likely by accelerating the intestinal transit, increasing excretion, and decreasing nutrient absorption without interfering with pancreatic lipase.\textsuperscript{159} Polyphenols and polysaccharides in black tea may reduce body, visceral fat, and adipocyte size by elevating fecal fatty acid and improving serum biochemistry.\textsuperscript{158} Moreover, fecal excretion of nutrients can be increased by using gallocate tea catechins, which repressed gut nutrient absorption and, therefore, may be relevant to body fat reduction and a possible obesity treatment.\textsuperscript{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.\textsuperscript{162} However, poor tolerability and low compliance owing to associated side effects restrict their potential widespread use.\textsuperscript{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
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, capsaicin 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%. However, it is suggested to be neurotoxic because of the presence of α-thujone, 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, hyperlipidemia, and hypercholesterolemia. In addition, over the past decade, our research group has formulated CTS into microspheres and nanoparticles because of CTS’s insolubility. Additionally, CTS and COS target adipogenesis suppression by down-regulating the related adipogenesis genes, such as PPARα. 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. 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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