

# The Mechanism of Traditional Chinese Medicine for the Treatment of Obesity

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**Abstract:** Obesity is the lipid deposition caused by the imbalance between energy intake and consumption caused by a variety of factors. Obesity can lead to multiple systemic complications. At present, the treatment of obesity is mainly lifestyle intervention, drug weight loss, and weight loss surgery, but the curative effect is limited or the side effects are serious. Traditional Chinese medicine plays a unique role in the treatment of obesity. Existing studies have found that traditional Chinese medicine can treat obesity in a variety of ways, such as regulating intestinal microflora, enhancing hormone level, regulating fat metabolism, and so on. In this review, we will introduce and summarize the mechanism of traditional Chinese medicine in the treatment of obesity.

**Keywords:** metabolism, leptin, intestinal microflora, adiponectin

## Introduction

According to the definition of the World Health Organization, overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.<sup>1</sup> The prevalence of obesity among children, adolescents, and adults worldwide is increasing every year.<sup>2-4</sup> According to the World Health Organization, the worldwide population rate of obesity (BMI  $\geq$  30) in 2016 was significantly higher in all countries, especially the Americas, Europe, and Oceania. With the obesity rate in some countries as high as 60.7%, the need for attention to this problem is urgent.

Obesity can lead to injury of multiple biological systems, significantly increasing the risk of metabolism-related diseases, cardiovascular diseases, respiratory diseases, Alzheimer's disease, osteoarthritis, and some cancers,<sup>5-8</sup> and it increases mortality.<sup>9</sup> To date, the main measures for treating obesity are lifestyle management, drugs for lipid reduction (orlistat and lipopeptide), weight loss surgery (Roux-en-Y gastric bypass, sleeve gastrectomy, or adjustable gastric banding) and strategies<sup>6</sup> to reduce food intake and absorption and increase its utilization. However, due to a typical rebound in weight gain, the high risks associated with surgery and other problems, obesity has not been effectively resolved, and there is an urgent need to find a way to reduce the risks and improve patient compliance.

The ancient documentation of traditional Chinese medicine, "Lingshu Jing of the Inner Canon of Huangdi", pointed out that obesity means "people have fat, ointment and meat." It characterizes obesity as a disease mainly based on spleen and kidney deficiency and liver depression, with phlegm, dampness, heat, and blood stasis as the standard manifestations. Traditional Chinese medicine has been used

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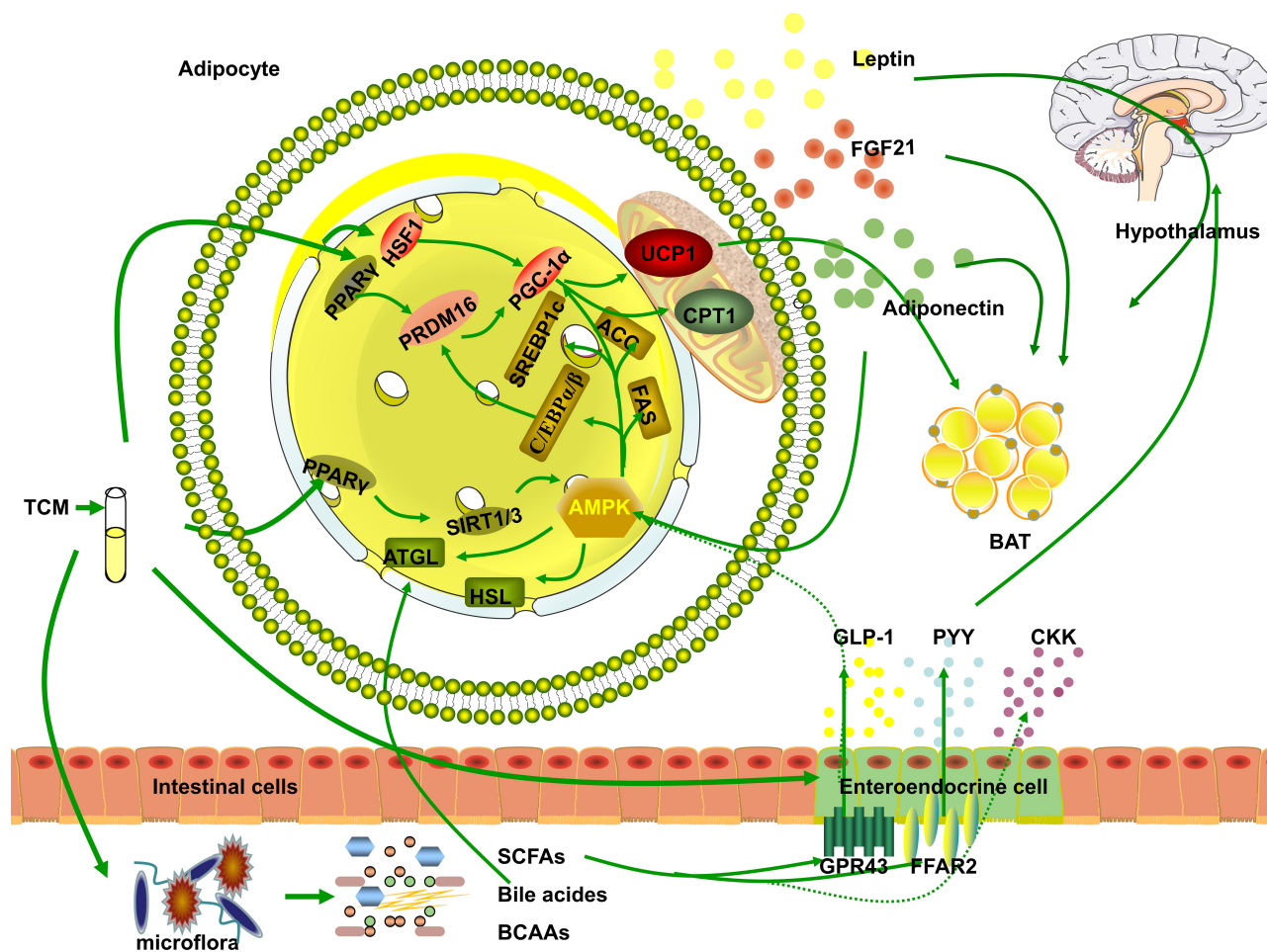
for a long time for treating diseases, playing an important role in the treatment of obesity.<sup>10,11</sup>

In this paper, we selected drugs that have been widely discussed in obesity-related metabolic studies and can be used in clinical practice without obvious toxic and side effects, such as ginsenoside (Ginseng),<sup>12</sup> celastrol (*Tripterygium wilfordii*),<sup>13</sup> berberine (*Coptis chinensis*),<sup>14</sup> curcumin (Turmeric),<sup>15</sup> and the Xiexin<sup>16</sup> and Danggui Buxue decoctions.<sup>17</sup> Considering that different organ tissues may play similar weight-reducing roles under the role of TCM or TCM extracts in the weight-reducing process, we will mainly generalize from the specific mechanisms (regulating fat metabolism, intestinal Microflora, and regulating hormone level, etc.), as shown in Figure 1. In order to clarify the specific mechanism, the mechanism that

plays the same role in different organs will be reflected in the tissue localization in Table 1. Summary of the mechanisms of traditional Chinese medicine and its extracts in the treatment of obesity, specifically as follows.

## Regulate Fat Metabolism

It is well known that excessive energy intake or insufficient energy consumption by the human body can cause mature adipocytes to accumulate lipid and expand. The treatment of obesity can regulate the balance of energy intake and consumption by inhibiting lipid synthesis, promoting lipid decomposition, and/or promoting thermogenic fat activation. Traditional Chinese medicine has been successfully applied to the treatment of obesity in this way.



**Figure 1** Basic Research on TCM in the Treatment of Obesity. The three pathways of TCM in obesity treatment: 1. By affecting the composition of intestinal microflora, regulation of intestinal metabolites (SCFAs, bile acids, and BACC) directly affects the roles of metabolites in obesity or indirectly increases the secretion of hormones by endocrine cells (GLP-1, PYY, and CCK) that regulate the hypothalamus, affect appetite and attenuate obesity. 2. AMPK is activated to regulate lipid metabolism or upregulate BAT-related genes in WAT to promote the browning of WAT and thermogenic fat activation. 3. Directly or indirectly promote fat tissue secretion of leptin, adiponectin, FGF21, GLP-1, and PYY to promote lipid metabolism and/or affect appetite by regulating the hypothalamus.

**Table I** Mechanism of TCM in the Treatment of Obesity

TCM	Functions	Genes/Proteins	Tissue Localization	References
Celastrol ( <i>Tripterygium wilfordii</i> )	Promote thermogenic fat activation	HSFI, PGC1 $\alpha$ , UCP1 $\uparrow$	WAT; Muscle	(Ma et al, 2015) <sup>13</sup>
	Enhance leptin sensitivity	STAT3 <sub>Tyr705</sub> , SOCS3 $\uparrow$	Hypothalamic	(Liu et al, 2015) <sup>68</sup>
Capsaicin (Chili pepper)	Promote thermogenic fat activation	TRPV1, PPAR $\gamma$ -PRDM16 $\rightarrow$ PGC1 $\alpha$ -UCP1 $\uparrow$	EAT; SAT; Liver	(Baskaran et al, 2016; Bort et al, 2019) <sup>33,34</sup>
	Up-regulation of GLP-1 and PYY	PYY, GLP-1 $\uparrow$ $\rightarrow$ NPY- and AgRP-expressing neurons $\downarrow$ , POMC- and CART-expressing neurons $\uparrow$ ,	Hypothalamic	(Wang et al, 2020) <sup>46</sup>
	Increase the level of SCFAs	Acetate, propionate $\uparrow$	Intestines	(Wang et al, 2020) <sup>46</sup>
Chrysophanic Acid/ Rhein (Rhubarb)	Promote thermogenic fat activation	Sirt1, Sirt3 $\uparrow$ $\rightarrow$ AMPK $\uparrow$ , UCP1, PGC1 $\alpha$ $\uparrow$	BAT	(Lim et al, 2016) <sup>31</sup>
	Inhibit fat production and accumulation	AMPK $\uparrow$ $\rightarrow$ PPAR $\gamma$ , C/EBP $\alpha$ , GLUT4, Lipin1, AP2 $\downarrow$	Preadipocytes	(Lim et al, 2016) <sup>31</sup>
	Up-regulation of GLP-1	GLP-1 $\uparrow$	Small intestine; Ileum	(Wang et al, 2018) <sup>86</sup>
Resveratrol ( <i>Polygonum cuspidatum</i> )	Inhibit fat production and accumulation	SREBP-1c $\downarrow$	Liver	(Izdebska et al, 2018) <sup>28</sup>
	Regulation of bile acid excretion	CYP7A1 $\uparrow$	Liver; Duodenum; Ileum	(Chambers et al, 2019) <sup>61</sup>
INDUS810 ( <i>Trigonella foenum-graecum</i> (L.))	Inhibit fat production and accumulation	AMPK $\uparrow$ , PPAR $\beta$ , PGC $\beta$ , SIRT1, SIRT3 $\uparrow$	WAT(3T3); Liver	(Cheng et al, 2018) <sup>19</sup>
	Increase lipid decomposition	AMPK, ATGL $\uparrow$	Adipose tissue; Liver	(Cheng et al, 2018) <sup>19</sup>
Tea catechins GT-polyphenols (Green tea)	Increase lipid decomposition	ACO $\uparrow$ ; MCAD $\uparrow$ $\rightarrow$ oxidation of FAs, AMPK $\alpha$ 1 $\uparrow$ $\rightarrow$ PKA-HSL $\uparrow$	Liver; SAT	(Murase et al, 2002; Bolin et al, 2020) <sup>24,79</sup>
	Regulate the level of adiponectin	adiponectin $\uparrow$	WAT; BAT	(Bolin et al, 2020) <sup>79</sup>
Xiexin decoction	Inhibit fat production and accumulation	AMPK $\uparrow$ , SREBPs, ACC, FAS $\downarrow$	Liver	(Xiao et al, 2019) <sup>16</sup>
	Increase the level of SCFAs	ACK, MMD, BUT, BUK $\uparrow$ $\rightarrow$ SCFAs $\uparrow$	Colon	(Xiao et al, 2019) <sup>16</sup>
White tiger plus ginseng decoction	Inhibit fat production and accumulation	AMPK $\uparrow$ , ACC $\downarrow$	Liver	(Liu et al, 2015) <sup>21</sup>
	Increase lipid decomposition	AMPK, ATGL $\uparrow$	Liver	(Liu et al, 2015) <sup>21</sup>
Curcumin (Turmeric)	Promote thermogenic fat activation	FGF21, Cidea, Tmem26, Tbx1, UCP1, PGC-1 $\alpha$ , PRDM16, C/EBP $\beta$ , CPT1, Oxidation of fatty acids $\uparrow$	SAT	(Lone et al, 2016) <sup>30</sup>
	Inhibit fat production and accumulation	p-ACC $\uparrow$ , ACC $\downarrow$	SAT	(Lone et al, 2016) <sup>30</sup>
	Enhance leptin sensitivity	leptin sensitivity $\uparrow$	EAT	(Chang et al, 2018) <sup>72</sup>
	Regulate the level of adiponectin	adiponectin $\uparrow$	EAT	(Chang et al, 2018) <sup>72</sup>

(Continued)

Table I (Continued).

TCM	Functions	Genes/Proteins	Tissue Localization	References
Berberine ( <i>Coptis Chinensis</i> )	Increase the level of SCFAs	Acetate, propionate↑	Colon	(Zhang et al, 2012) <sup>45</sup>
	Increase lipid decomposition	AMPK, ATGL, p-HSL↑	WAT(3T3)	(Jiang et al, 2016) <sup>20</sup>
	Regulation of BCAA	BCKDC↑, BCKDHA, BCKDK↓→ BCAA, valine, leucine, isoleucine↓	Liver; EAT	(Yue et al, 2019) <sup>63</sup>
	Increase the level of SCFAs and GLP-1	SCFAs30, GPR43-GLP-1↑	Colon; Gastrointestinal	(Sun et al, 2018) <sup>14</sup>
Chaihu Shugan Powder	Enhance leptin sensitivity	leptin sensitivity↑	Adipose tissue; Liver	(Jiang et al, 2018) <sup>73</sup>
	Regulate the level of adiponectin	adiponectin↑	Adipose tissue; Liver	(Jiang et al, 2018) <sup>73</sup>

**Abbreviations:** ACC, acetyl-CoA carboxylase; ACK, acetate kinase; ACO, acyl-CoA oxidase; AgRP, agouti-related protein; AMPK, AMP-activated protein kinase; AP2, fatty acid-binding protein; ASIV, Astragaloside IV; ATGL, adipose triglyceride lipase; BCAAs, branched chain amino acids; BAS, bile acids; BAT, brown adipose tissues; BCKDC, branched-chain ketoacid dehydrogenase complex; BCKDHA, branched chain keto acid dehydrogenase E1  $\alpha$  subunit; BCKDK, branched-chain  $\beta$ -keto dehydrogenase kinase; BDNF, brain-derived neurotrophic factor; BeAT, beige adipose tissues; BUK, butyrate kinase; BUT, butyryl-CoA:acetate CoA transferase; C/EBP $\alpha/\beta$ , CCAAT/enhancer-binding protein  $\alpha/\beta$ ; Cidea, cell death-inducing DNA fragmentation factor alpha-like effector A; CCK, cholecystokinin; Cox8b, cytochrome c oxidase 8b subunit; GPCR, G protein-coupled receptor; CPT1, carnitine palmitoyltransferase 1; CYP7A1, cytochrome P450 family 7 subfamily A member 1; DGAT1/2, diacylglycerol O-acyltransferase 1/2; DiO2, type II iodothyronine deiodinase; FAT, fatty acid translocase; FFAs, free-fatty-acids; FFAR2, free fatty acid receptor 2; FGF21, fibroblast growth factor 21; FXR, liver farnesol X receptor; GLP-1, glucagon-like peptide 1; GLUT4, glucose transporter type 4; GPR43, G protein-coupled receptor 43; HFD, high-fat diet; HSF1, heat shock transcriptional factor 1; HSL, hormone-sensitive lipase; IWAT, inguinal adipose tissue; JAK2, Janus kinase 2; LEPR, leptin receptor; L-SGgly, low-polar 22 *Siraitia grosvenorii* glycoside; LXR $\alpha$ , liver X receptor alpha; MCAD, medium-chain acyl-CoA dehydrogenase; MMD, methylmalonyl-CoA decarboxylase; mTOR, liver mechanistic target of rapamycin kinase; NPY, neuropeptide Y; NST, nonshivering thermogenesis; PGC1 $\alpha/\beta$ , peroxisome proliferator-activated receptor-gamma coactivator 1 alpha/beta; PPAR $\beta/\gamma$ , peroxisome proliferator-activated receptor beta/gamma; PRDM16, PR domain containing 16; PYY, peptide YY; SCD-1, stearoyl-CoA desaturase-1; SCFAs, short-chain fatty acids; SIRT1/3, sirtuin 1/3; SNS, sympathetic nervous system; SREBP1c, sterol response element-binding protein 1c; STAT3, signal transducer and activator of transcription 3; TAG, triglyceride; Tbx1, T-box transcription factor; TCM, traditional Chinese medicine; TGR5, G protein-coupled bile acid receptor 1; Tmem26, transmembrane protein 26; TRPV1, transient receptor potential cation channel subfamily V member 1; UCPI, mitochondrial uncoupling protein 1; WAT, white adipose tissues.

## Increase Lipid Decomposition

Traditional Chinese medicine can increase the decomposition of lipids to treat obesity through the regulation of AMP-activated protein kinase (AMPK), autonomic nerves, or  $\beta$ -adrenoceptors. After being activated, AMPK can coordinate a variety of metabolic pathways (including liver lipid metabolism), regulate metabolism by phosphorylating key metabolic proteins and transcription factors, promote catabolism and inhibit anabolism.<sup>18</sup> Many traditional Chinese medicines affect lipid synthesis and metabolism by acting on AMPK to induce weight loss. INDUS810 isolated from *Trigonella foenum-graecum* (L.) can activate AMPK to increase lipid degradation in a time-dependent manner.<sup>19</sup> Berberine can upregulate the expression of adipose triglyceride lipase (ATGL) and phosphorylation of hormone-sensitive lipase (p-HSL) through AMPK, thus stimulating basal lipolysis in mature adipocytes.<sup>20</sup> The phosphorylation of AMPK induced by the white tiger plus ginseng decoction promotes the expression of ATGL and lipolysis.<sup>21</sup> The smell of grapefruit oil and its active ingredient limonene affects the

autonomic nervous system and increases fat decomposition through a histamine reaction.<sup>22</sup> The extract of *Nelumbo nucifera* leaves can upregulate the lipolysis of 3T3-L1 adipocytes as mediated by  $\beta$ -adrenoceptors.<sup>23</sup> Long-term use of tea catechins (Green tea) could effectively activate the mRNA expression of acyl-CoA oxidase (ACO) and medium-chain acyl-CoA dehydrogenase (MCAD) in the liver, promote the oxidation of fatty acids, and inhibit the diet-induced obesity.<sup>24</sup>

## Inhibit Fat Production and Accumulation

Obesity can lead to adipocyte proliferation and hypertrophy and thus can also play a role in weight loss by inhibiting the proliferation and differentiation of adipocytes. Hydroxy safflower yellow pigment (HSYA), the extract of *Carthamus tinctorius*, can inhibit the proliferation of 3T3-L1 preadipocytes in a time- and concentration-dependent manner.<sup>25</sup> The ethanol extract of *Aster yomena* (EEAY) exerts its anti-adipogenic effect by inhibiting or delaying the differentiation of 3T3-L1 preadipocytes and the expression of adipogenic factors (peroxisome proliferator-activated receptor gamma

(PPAR $\gamma$ ), CCAAT/enhancer-binding protein  $\alpha/\beta$  (C/EBP $\alpha/\beta$ ) and sterol response element-binding protein 1c (SREBP1c), inhibiting the de novo synthesis of lipids and the differentiation of adipocytes.<sup>26</sup> The water extract from *Ganoderma lucidum* mycelia can reduce the expression of adipogenic genes and the level of serum free-fatty-acids (FFAs) in a dose-dependent manner in mice fed a high-fat diet (HFD).<sup>27</sup> Resveratrol (*Polygonum cuspidatum*) and the extract from fermented *Cordyceps militaris* decrease the expression and activity of SREBP-1c and decrease fat synthesis.<sup>28,29</sup> Curcumin increases the phosphorylation of acetyl-CoA carboxylase (p-ACC) and decreases the rate-limiting enzyme acetyl-CoA carboxylase (ACC) of fatty acid synthesis, which inhibits lipogenesis.<sup>30</sup> Traditional Chinese medicine can also inhibit lipid synthesis and metabolism by activating AMPK. Chrysophanic acid (rhubarb) can reduce weight by activating AMPK to inhibit lipid accumulation and the expression of adipogenic factors (PPAR $\gamma$  and C/EBP $\alpha$ , glucose transporter type 4 (GLUT4), lipin 1 and adipocyte fatty acid-binding protein (AP2)) in 3T3-L1 adipocytes.<sup>31</sup> INDUS810 can reduce the content of intracellular triglycerides after adipocyte differentiation, reduce lipid accumulation during lipid differentiation in an AMPK-dependent manner, and increase the expression of peroxisome proliferator-activated receptor beta (PPAR $\beta$ ), peroxisome proliferator-activated receptor-gamma coactivator 1 beta (PGC1 $\beta$ ), sirtuin 1 (SIRT1) and SIRT3.<sup>19</sup> Babaodan can downregulate the expression of lipid synthesis genes (*SREBP-1c*, *ACC*, *stearoyl-CoA desaturase-1 (SCD-1)*, *liver X receptor alpha (LXR $\alpha$ )*, and *FAT/CD36*) by activating AMPK.<sup>32</sup> The Xiexin decoction can also upregulate AMPK, inhibit SREBPs, downregulate the expression of ACC and fatty acid synthase (FAS), and reduce fat production.<sup>16</sup> The white tiger plus ginseng decoction can induce the activation of AMPK, inhibit the expression of ACC, and reduce the synthesis and accumulation of lipids.<sup>21</sup>

## Promote Thermogenic Fat Activation

Traditional Chinese medicine can promote the browning of white adipose tissue (WAT) by upregulating the expression of brown adipose tissue (BAT)-related genes in white adipose tissue or activating BAT heat generation to increase energy consumption and weight loss. Celastrol can induce the browning of inguinal adipose tissue (IWAT), upregulate heat shock transcriptional factor 1 (HSF1) expression, increase peroxisome proliferator-activated receptor-gamma coactivator 1 alpha/mitochondrial uncoupling protein 1 (PGC1 $\alpha$ /UCP1) expression,

and increase thermogenic function and energy consumption.<sup>13</sup> Capsaicin (chili pepper) can induce the browning of WAT by activating transient receptor potential cation channel subfamily V member 1 (TRPV1) channels.<sup>33,34</sup> Chrysophanic acid increases the expression of the thermogenic genes *UCP1* and *PGC1 $\alpha$*  by upregulating SIRT1 and SIRT3, activating AMPK and promoting thermogenesis.<sup>31</sup> Jiang Gui Fang (JG) increases the expression of BAT markers (PPAR $\gamma$ , PGC1 $\alpha$ , and UCP1), activates interscapular brown adipose tissue through the PPAR $\gamma$ /SIRT1-PGC1 $\alpha$  pathway, and induces IWAT browning.<sup>35</sup> The Danggui Buxue decoction (DBT1155) can activate the Ca<sup>2+</sup>-AMPK signaling pathway in a time-dependent manner to trigger WAT browning in adipocytes and increase the expression of BAT markers in a dose-dependent manner.<sup>17</sup> Curcumin can significantly upregulate the expression of BAT-specific genes (*fibroblast growth factor 21 (FGF21)*, *cell death-inducing DNA fragmentation factor alpha-like effector A (Cidea)*, *transmembrane protein 26 (Tmem26)*, *T-box transcription factor (Tbx1)*) and proteins (UCP1, PGC1 $\alpha$  and PR domain containing 16 (PRDM16)) to drive BAT thermogenesis. Curcumin can also increase carnitine palmitoyltransferase I (CPT1) to increase the activity of mitochondria in brown adipocytes and enhance the oxidation of fatty acids.<sup>30</sup> The water extract from *Caulis Spatholobi* (WECS) can promote whole-body energy metabolism by increasing the oxygen consumption of HFD mice and increasing the levels of BAT febrile genes (*UCP1*, *PRDM16*, and *PGC1 $\alpha$*  and *medium-chain acyl-CoA dehydrogenase (MCAD)*) mRNA.<sup>36</sup> *Withania somnifera* extract (WSE) increases oxygen consumption and enhances the expression of BAT genes, including *UCP1*, *PGC1 $\alpha$* , *type II iodothyronine deiodinase (DiO2)* and *cytochrome c oxidase 8b subunit (Cox8b)*, and promotes the browning of subcutaneous adipose tissue in mice fed a high-fat diet.<sup>37</sup>

## Regulate Intestinal Microflora

Intestinal microflora can affect host energy metabolism, the immune system and the inflammatory response, and changes to its structure and function can promote obesity. By changing the abundance and constituent ratio of intestinal microorganisms, traditional Chinese medicine can increase the proportion and content of short-chain fatty acids (SCFAs), regulate the levels of bile acids, choline, amino acids, and other metabolites, thus playing a role in improving obesity.

## Increase the Level of SCFAs

SCFAs produced by intestinal microorganisms can activate G protein-coupled receptor 43 (GPR43) to inhibit insulin signal transduction in adipocytes, thereby inhibiting fat accumulation in adipose tissue and promoting unbound lipid metabolism in other tissues.<sup>38</sup> Acetate, propionate, and butyrate account for 83% of human intestinal SCFAs.<sup>39</sup> Acetate can activate AMPK to increase the indexes related to lipid catabolism, reduce abdominal lipids, and protect the liver and abdomen from lipid accumulation.<sup>40</sup> Butyrate can reduce the accumulation of fat in the liver, reduce metabolism and mitochondrial efficiency, and counteract obesity.<sup>41</sup> Propionic acid, similar to butyric acid, induces weight loss by adjusting the energy balance.<sup>42–44</sup>

Berberine and capsaicin can improve obesity by increasing acetic acid and propionic acid levels.<sup>45,46</sup> Chinese cannabis can increase acetate levels to reduce visceral fat and induce weight loss.<sup>47</sup> Protopanaxatriol saponins (PPTs) can increase the levels of SCFAs and their receptors to ameliorate obesity.<sup>48</sup> Inulin can increase SCFAs in the colon and thus affect appetite and the secretion of peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) to regulate obesity-related metabolism.<sup>49</sup> Homogenized polysaccharide S-3-1 from the Sijunzi decoction can improve the production of intestinal microbiota-derived SCFAs, regulate energy metabolism, and attenuate dyslipidemia induced by a high-fat diet in obese rats.<sup>50</sup> The Xiexin decoction reduces weight by increasing the level and activity of key enzyme mRNAs involved in SCFA synthesis (acetate kinase (ACK), methylmalonyl-CoA decarboxylase (MMD), butyryl-CoA: acetate CoA transferase (BUT) and butyrate kinase (BUK)) and increasing the abundance of intestinal microflora.<sup>16</sup>

## Regulate the Levels of Bile Acids and Other Metabolites

There is a two-way interaction between bile acid and intestinal microbial composition.<sup>51</sup> Bile acid can change the bacterial community structure, affect host metabolism,<sup>52</sup> regulate liver lipid, glucose and energy balance, and maintain metabolic balance.<sup>53</sup> Bile acid can also induce WAT browning by activating G protein-coupled bile acid receptor 1 (TGR5)<sup>54</sup> or directly or indirectly affect glucose metabolism and insulin signal transduction through lipid emulsification, affecting the cell membrane and inducing ectopic functions and receptors (such as liver farnesol X receptor (FXR) and G protein-coupled receptor (GPCR)).<sup>55</sup> Choline can stimulate the lipolysis of triglyceride (TAG) in

adipocytes and liver through specific lipases (ATGL, lipoprotein lipase (LPL) and HSL), inhibit the formation of TAG through diacylglycerol O-acyltransferase 1/2 (DGAT1/2), activate liver AMPK and mitochondrial fatty acid oxidation gene PPAR $\alpha$ , and reduce fatty acid synthesis genes *SREBP1*, *SCD1* and *FAS* to reduce hepatic steatosis.<sup>56,57</sup> It was found that inducing a reduction in the number of branched-chain amino acids (BCAAs) leads to rapid body weight and fat weight loss.<sup>58</sup> BCAAs can inhibit lipid production and autophagy by activating the liver mechanistic target of rapamycin kinase (mTOR) and reduce HFD-induced body weight.<sup>59</sup>

Polyphenols extracted from puerarin (*Pueraria lobata*), resveratrol, and quercetin can mediate cholesterol efflux and intestinal microbial changes, thereby regulating bile acid excretion and reducing fat production.<sup>60,61</sup> *Scutellaria baicalensis* can increase the expression of the rate-limiting enzyme cytochrome P450 family 7 subfamily A member 1 (CYP7A1) in the bile acid biosynthesis pathway, and CYP7A1 can prevent the obesity induced by a high-fat diet (the exact mechanism is not clear).<sup>62</sup> Clove, allspice, and aromatic ginger extracts can induce TGR5-mediated BAS weight loss effects. Berberine affects the composition of intestinal microorganisms, activates multienzyme branched-chain ketoacid dehydrogenase complex (BCKDC) to promote BCAAs metabolism in the liver and IWAT of mice fed a HFD, and reduces the number of valine, leucine, isoleucine, and BCAAs during fasting by inhibiting the phosphorylation of branched-chain keto acid dehydrogenase E1  $\alpha$  subunit (BCKDHA) and multienzyme branched-chain  $\beta$ -keto dehydrogenase kinase (BCKDK), leading to bodyweight loss.<sup>63</sup> *Luffa cylindrica* (L.) inhibits bacterial BCAAs biosynthesis, reduces BCAAs, and ameliorates BCAAs dysfunction, thus reducing obesity.<sup>64</sup>

## Regulate Hormone Level

Endocrine cells can play roles in environmental balance and neuroendocrine function by secreting circulating hormones such as leptin, insulin, GLP1, PYY, cholecystokinin (CCK) and the hunger hormone, which can affect human eating behavior and signal satiety, playing a role in weight loss.<sup>65</sup> Adipocytes can secrete adiponectin, leptin, and resistin. The most fruitful results in traditional Chinese medicine research on the regulation of hormone-induced weight loss were obtained from studies on leptin and adiponectin.

## Enhance Leptin Sensitivity

Leptin and its receptor (LEPR) are closely related to the regulation of energy uptake and consumption by the central nervous system.<sup>66</sup> Leptin secreted by WAT can act on leptin-sensitive neurons in hypothalamic nuclei and regulate the lipid decomposition of WAT, nonshivering thermogenesis (NST) of BAT, lipid decomposition of beige adipose tissues (BeAT) and NST in brown adipose tissue through the sympathetic nervous system (SNS).<sup>67</sup> Increasing leptin-LEPR signaling and/or that of other neural pathways that activate leptin regulation can ameliorate obesity. Celastrol can inhibit food intake by increasing leptin sensitivity until body weight returns to normal.<sup>68</sup> Astragaloside IV (ASIV) may improve the central leptin sensitivity of obese mice by upregulating the expression of LEPR mRNA and phosphorylation of signal transducer and activator of transcription 3 (p-STAT3) in the hypothalamus.<sup>69</sup> Ginsenoside Rb1 increases leptin-JAK2-STAT3 signaling and leptin-induced expression of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex of obese mice, promotes leptin-BDNF-axonal growth and synaptogenesis, and plays a role in weight loss by improving leptin sensitivity.<sup>70</sup> It can reverse central leptin resistance.<sup>70,71</sup> Curcumin can improve the sensitivity to leptin by improving the hypoxic state of cells.<sup>72</sup> Chaihu Shugan powder and the Linggui Zhugan decoction decrease the level of leptin and ameliorate obesity.<sup>73,74</sup>

## Regulate the Level of Adiponectin

Adiponectin can reduce lipid accumulation in adipose tissue by activating the adiponectin-adenylate protein kinase pathway<sup>75,76</sup> or activate BAT thermogenesis to regulate energy consumption.<sup>77</sup> Piperonal (pepper) inhibits de novo adipogenesis in mice by increasing the level of circulating adiponectin mRNA, increasing the level of AMPK phosphorylation and S6K1 phosphorylation, and reducing the expression of SREBP1c and adipogenesis-related mRNAs.<sup>78</sup> Green tea (GT), which is rich in polyphenols, promotes BAT heat production by increasing adiponectin levels and activates AMPK $\alpha$ 1 to promote lipid decomposition through PKA-HSL.<sup>79</sup> 6-Gingerol can relieve ectopic lipid accumulation in the skeletal muscle of aging rats by increasing the level of adiponectin and its receptor, activating AdipoR1, and downstream AMPK/PGC1 $\alpha$  signaling.<sup>80</sup> Hugaqingzhi tablets (HQTs) can increase adiponectin levels, activate AMPK and PPAR $\alpha$  pathways to inhibit SREBP-1 in the liver and de novo fat

production, promote  $\beta$ -oxidation of fatty acids, and decrease cellular lipid levels.<sup>81</sup> Sheng Jiang San (SJP) increases the level of serum adiponectin and inhibits the activation of inflammatory bodies and lipid accumulation through the adiponectin-AMPK pathway.<sup>82</sup> Chaihu Shugan powder also reduces lipid synthesis by increasing the level of adiponectin.<sup>73</sup>

## Regulate the Levels of Other Hormones

Among gastrointestinal hormones, GLP-1 and PYY are peripheral hormones associated with anorexia that can increase satiety, while ghrelin can induce hunger.<sup>83</sup> Capsaicin can promote intestinal epithelial cells to secrete PYY and GLP-1, which inhibit the expression of neuropeptide Y (NPY) and agouti-related protein (AgRP), and activate neurons expressing POMC and CART in the hypothalamic ARC, thus reducing food intake.<sup>46</sup> Geniposide can ameliorate obesity by activating GLP-1 to activate AMPK $\alpha$  and Sirt1 in vivo (and in vitro).<sup>84</sup> Low-polar 22 *Siraitia grosvenorii* glycoside (L-SGgly) plays a role by increasing the level of serum GLP-1 in rats.<sup>85</sup> Rhein increases plasma activity and the level of GLP-1, regulating appetite.<sup>86</sup> A dietary supplement consisting of lemon fruit combined with hibiscus polyphenol extract increases the level of GLP-1 and decreases the level of ghrelin.<sup>87</sup> The triterpenoids in *Salvia miltiorrhiza* may lead to weight loss by inhibiting the activity of ghrelin.<sup>88,89</sup> Also, some traditional Chinese medicines can increase the production of gastrointestinal hormones (PYY, GLP-1, CCK, and ghrelin) through SCFAs and play a role in weight loss. Inulin increases the concentration of intestinal hormones and the level of SCFAs by increasing the density of specific intestinal endocrine cells in the colon and regulates the secretion of PYY and GLP-1, respectively, by free fatty acid receptor 2 (FFAR2)-dependent and independent mechanisms.<sup>49</sup> Berberine can induce the expression and secretion of GLP-1 by upregulating SCFAs30 and stimulating GPR43, which can lead to weight loss.<sup>14</sup>

## Discussion

We mainly explain the mechanism of weight loss of TCM according to the above three points, but the mechanism targeting muscle, liver and pancreas is not clear. These tissues play an important role in the metabolism of the human body. For example, insulin, a hormone secreted by pancreatic cells, can increase fat production during hyperinsulinemia. Therefore, in the early stage of increased insulin secretion, properly reducing the level of insulin

can improve insulin sensitivity and achieve the purpose of weight loss.<sup>90</sup> In addition, some studies have suggested that resveratrol<sup>91</sup> can improve mitochondrial dysfunction, increase muscle content, reduce fat and lose weight. But it is not clear whether these herbs first improve obesity and then improve the metabolism of these tissues, or whether they first improve the metabolism of these tissues and then improve obesity.

A large number of studies in vitro and animal experiments have shown that TCM has the potential of multi-target treatment for obesity (Table 1). And in clinical treatment, traditional Chinese medicine physicians use TCM to prove its role in the treatment of obesity. In addition, the theory of food and drug homology made TCM, or named nutraceutical,<sup>92</sup> an unrelated food drug derived from food that is believed to have physiological benefits and to improve chronic disease, more acceptable. This type of nutraceutical has great potential to be applied to human weight loss.

However, in clinical use, a combination of multiple drugs is often selected according to patients' personal conditions. The synergistic relationship<sup>93</sup> among these drugs is complex, and the sample drug may have multiple action targets. Therefore, under the uncertain circumstances of the interaction between these drugs, the specific mechanism of single drugs, and the individual differences in the human body, it is still a very difficult and significant task to study the optimal dose, dose-effect relationship, half-life, and the treatment of related adverse reactions that can be used in clinical practice.

As obesity and obesity-related metabolic diseases are often multi-gene variation, multi-target disturbance and multi-disease related, it is not realistic to treat obesity in a single way, while TCM's multi-target, synergistic effect between drugs, small toxic and side effects, and easy to obtain from nature will become its advantages in treating obesity.

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## Disclosure

The authors declare that they have no conflicts of interest regarding this work or the publication of this article.

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