Review

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Traditional Chinese medicine modulates hypothalamic neuropeptides for appetite regulation: A comprehensive review

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SUMMARY: Obesity has emerged as a global health crisis, imposing substantial burdens on both individual well-being and socioeconomic development. The pathogenesis of obesity primarily stems from disrupted energy homeostasis, wherein the hypothalamus plays a pivotal role through its complex neuropeptide networks that regulate appetite and energy balance. Recent advances have highlighted the therapeutic potential of traditional Chinese medicine (TCM) in modulating hypothalamic appetite regulation. This comprehensive review systematically evaluates current evidence from PubMed and China National Knowledge Infrastructure databases, focusing on the mechanisms by which TCM interventions influence hypothalamic neuropeptide signaling pathways. Our analysis reveals that various TCM modalities, including bioactive compounds (*e.g.*, berberine and, evodiamine), herbal formulations (*e.g.*, Pingwei Powder, Fangji Huangqi Decoction), plant extracts (*e.g.*, Cyclocarya paliurus aqueous extract), and Chinese patent medicines (*e.g.*, Danzhi Jiangtang Capsules and Jingui Shenqi Pills), have significant effects on key appetite-regulating pathways. These effects are mediated through modulation of critical neuropeptide systems, particularly AgRP/NPY and POMC/CART neurons, as well as leptin signaling. These findings not only provide mechanistic insights into TCM's anti-obesity effects but also demonstrate the value of integrating traditional medicine with modern pharmacological approaches. The synergistic potential of TCM formulas, when combined with contemporary research methodologies, offers promising avenues for developing novel therapeutic strategies for obesity and related metabolic disorders.

Keywords: obesity, traditional Chinese medicine (TCM), hypothalamic neuropeptides, appetite regulation, energy homeostasis

1. Introduction

Obesity is a significant public health challenge worldwide. The World Obesity Alliance's 2023 World Obesity Map predicts that 1.9 billion people globally will be classified as obese by 2035, leading to an anticipated global economic impact of $4.32 trillion (*1*). Obesity increases the risk of various health issues, including type 2 diabetes, cardiovascular disease, chronic kidney disease, gastrointestinal disorders, nonalcoholic fatty liver disease, cancer, respiratory ailments, dementia, and Alzheimer's disease (*2*).Moreover, for women of childbearing potential, a higher BMI is associated with a reduced likelihood of conception within 3 years following diagnosis (*3*). Consequently, reducing the incidence of obesity is an urgent global health concern.

Genetic and environmental factors promote the development and progression of obesity. Key contributors to the rising prevalence of obesity include changes in social and economic modes of production and lifestyle changes, such as diet, nutrition, and exercise (*4*). A disequilibrium between energy intake and expenditure can lead to metabolic diseases like obesity and diabetes. Eating is the primary source of energy intake in the human body, and the hypothalamus plays a crucial role in regulating eating behaviors and energy balance (*5*). Therefore, controlling appetite and energy intake through hypothalamic mechanisms is essential to combating obesity.

To date, a number of pharmacological agents for weight management, including orlistat, liraglutide, lorcaserin, and diethylpropion, have received regulatory approval (*6,7*). However, the financial burden associated with these medications is substantial, and a growing array of adverse effects has been documented, encompassing cephalalgia, vertigo, asthenia, nausea, xerostomia, insomnia, anxiety, and constipation (*8,9,10*). These limitations necessitate the exploration of alternative therapeutic options, among which traditional Chinese medicine (TCM) holds significant promise.

TCM, with its holistic approach and utilization of natural compounds, offers a complementary perspective on appetite suppression and weight management. Many drugs have demonstrated the ability to regulate appetite and energy metabolism, which is closely related to the function of neuropeptides that modulate appetite in the hypothalamus, such as AgRP/NPY, POMC/CART and leptin (*11*). This paper reviews the effects of TCM monomers, formulas, extracts, single medicines, or Chinese patent medicines on appetite regulation mediated by hypothalamic neuropeptides in order to provide insights to develop traditional prescriptions and improve medicinal preparations. By capitalizing on the strengths of TCM, we can explore new avenues to address the global challenge of obesity and metabolic disorders.

2. Regulatory mechanism of the hypothalamus in feeding and energy consumption

Appetite is not only regulated by the energy steady-state system to meet the body's metabolic needs but is also regulated by the reward system to achieve steady-state regulation. The two systems form a complex neural circuit of mutual projection through various factors to comprehensively regulate appetite. Eating is reliable when most organisms are in a steady-state energy-deficient state but can be observed when energy is not required, and especially in the presence of highly palatable foods (*12,13*). The hypothalamus regulates energy metabolism through various nuclei, including the arcuate nucleus (ARC), ventromedial hypothalamus nucleus (VMH), dorsomedial hypothalamic nucleus (DMH), lateral hypothalamus (LH), parabrachial nucleus (PBN), and paraventricular nucleus (PVN). These nuclei interact through synaptic connections that affect each other while independently regulating energy homeostasis (*14*). In the hypothalamus, there are mainly three types of neural circuits that affect appetite. These circuits have different characteristics that can affect appetite independently and interact with each other, thus forming three pillars of appetite control (*15*) (Figure 1).

2.1. Appetite-regulated neurons predominantly in the ARC region

The first pillar involves the expressing neurons in the hypothalamic ARC, they are primarily involved in food seeking but are less likely to normally drive food consumption. In the ARC, neuropeptide Y (NPY) and agouti-related protein (AgRP), which promote appetite, and pro-opiomelanocortin (POMC), which inhibits feeding, play essential roles in regulating appetite. When the ARC receives, integrates, and evaluates signals from the peripheral circulation, it secretes AgRP/NPY or POMC to the LH and PVN, generating corresponding feedback responses (*16*). During satiety, POMC cleaves to form the α-melanocyte-stimulating hormone (α-MSH), which binds to the melanocortin (MC) 3/4 receptor of POMC, and especially to MC-4R (*17*). This binding promotes the synthesis of PVN, which reduces appetite and enhances energy consumption. Additionally, it stimulates the release of thyrotropin-releasing hormone and corticotropin-releasing hormone to inhibit feeding and increase energy consumption. Conversely, in a hungry state, AgRP/NPY neurons secreted by ARC promote appetite and release NPY and AgRP. NPY directly stimulates food intake by activating the Y1 and Y5 receptors of NPY. The binding of AgRP to MC-3/4R and NPY to NPY-1/5R can antagonize the effects of α-MSH and stimulate food intake (*17*) (Figure 2). Additionally, AgRP/NPY neurons can release the inhibitory

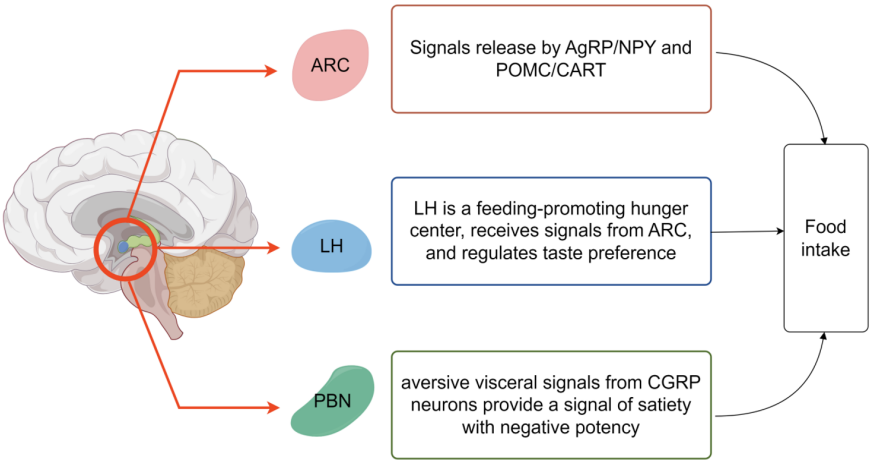

Figure 1. In the hypothalamus, three main types of neural circuits affect appetite, including ARC, LHs, and PBN. The interaction of these three pathways drives the initiation, maintenance, and termination of food consumption. AGRP and POMC neurons receive hunger or satiety signals and transmit them to LHs, which complete feeding behavior that can be counteracted by the loop of PBN^{CGRP}.

neurotransmitter γ-aminobutyric acid, which acts on several neurons that inhibit appetite in the brain (*18*).

Leptin, a hormone secreted by white adipocytes, is regulated by fat content. This hormone is crucial in modulating the AgRP/NPY and POMC/cocaine amphetamine-regulated transcript (CART) neuronal pathways. The primary mechanism involves leptin inhibiting the AgRP/NPY neuronal pathway while stimulating the POMC/CART neuronal pathway (*19*). High levels of leptin act on the hypothalamus through blood circulation and bind to the leptin receptor (OB-R) in the ARC to regulate animal body weight and energy intake. Research has demonstrated that POMC/CART and AgRP/NPY neurons express the OB-Rb receptor, bind leptin to its receptor, and inhibit neuropeptide synthesis and release, thereby reducing appetite (*20*). *In vitro* studies indicate that glucagon-like peptide (GLP-1) directly stimulates POMC/CART neurons and indirectly inhibits the neurotransmission of AgRP/NPY neurons through γ-aminobutyric acid (GABA) -dependent signal transduction pathways, thereby inhibiting appetite and reducing energy intake (*21*).

Central and peripheral serotonin (5-hydroxytryptamine, 5-HT) modulate alimentary signals associated with energy homeostasis. There are at least fourteen 5-HTR subtypes expressed in the hypothalamus that regulate appetite and energy metabolism, such as 5-HT1BR and 5-HT2CR (*22*). 5-HT2CR is distributed in POMC neurons of ARC, while 5-HT1BR is expressed in AgRP/NPY neurons. The combination of 5-HT and 5-HT subtype receptors can regulate the expression of POMC/CART and AgRP/NPY neurons and result in inhibiting appetite and reducing body weight (*23*).

2.2. LH-dominated appetite regulation circuit

The second pillar consists of circuits involving LH (Figure 3). LH is usually a feeding-promoting hunger center that receives both AgRP/NPY and POMC/CART neuronal projections from the arcuate nucleus and into the cerebral system and extracortical areas. It contains neurons that express melanin concentrating hormone (MCH), neurotensin (NT), and orexin. Melanin concentrate and neurotensin are factors that inhibit appetite. MCHs activate downstream G-protein-coupled receptors, including MCHR1 and MCHR2, and regulate food intake, energy balance, and other physiological functions by stimulating MCHR1 and MCHR2 receptors (*24*). Orexin is a factor that promotes appetite. Orexin can be divided into two neuropeptides, orexin A(OXA) and orexin B (OXB), whose common precursor is preorexin secreted by hypothalamic neurons (*25*). Orexin binds to two G-protein-coupled receptors, orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R) (*26*). OXR1 is mainly distributed in areas that control food intake, learning and memory, and reward (*27*).

Orexin-expressing neurons can be widely projected into the ARC (especially NPY neurons), VMH, DMH, PVN, and ventral capsular region (*28*). These neurons receive different inputs from the area of direct self-balance control and the area associated with hedonic or environmental feeding (*29,30*). Other studies have shown that photogenetic activation of LH inhibitory neurons marked by the vesicular GABA transporter leads

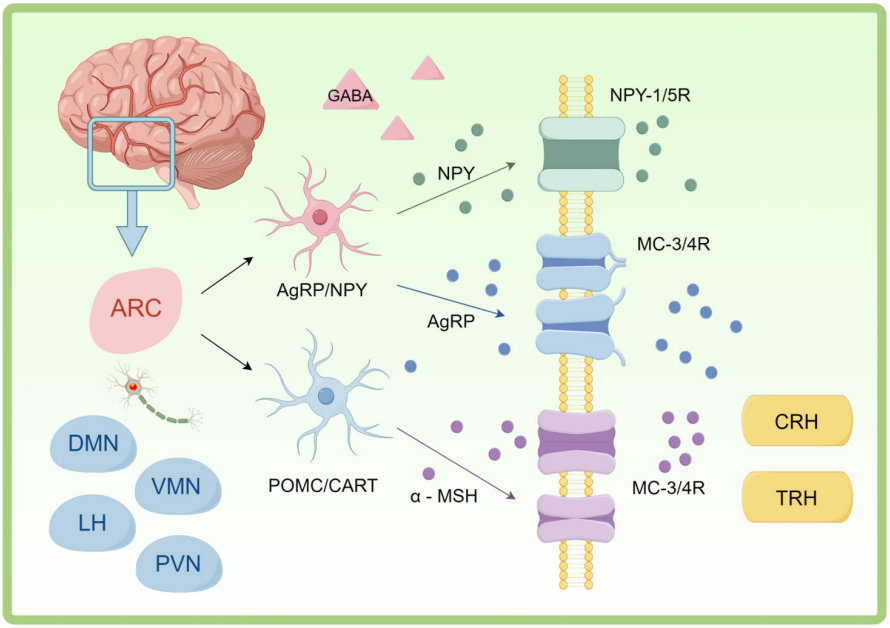

Figure 2. Appetite-regulated neurons predominantly in the ARC region. In the ARC, AgRP/NPY neurons and POMC/CART neurons modulate receptors NPY-1/5R, MC-3R, and MC-4R by releasing neuropeptides such as AgRP, NPY, and α-MSH, thereby influencing appetite regulation and energy expenditure.

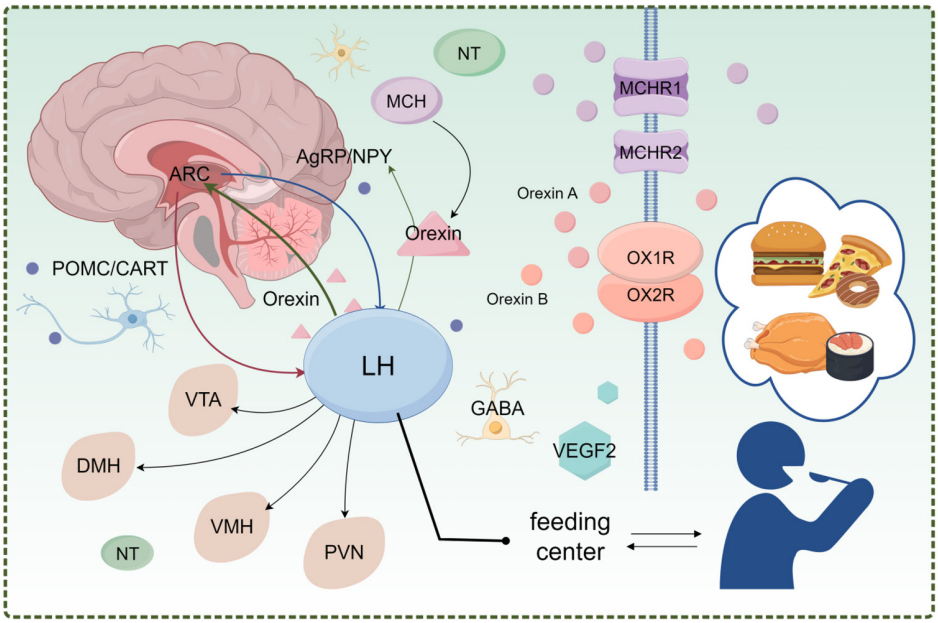

Figure 3. LH-dominated appetite regulation circuit. LH receives signals from AgRP/NPY and POMC/CART neuronal expression in ARCs and influences food intake by releasing MCHs, NTs, and orexin, while projecting signals into areas such as ARCs, DMHs, VMHs, and PVNs.

to feeding, and these manoeuvres are also beneficial (*31*). In contrast, activation of excitatory LH neurons expressing vesicular glutamate transporter type 2 inhibits feeding and leads to avoidance responses, while photoinhibition of these neurons is rewarding and leads to food consumption (*32*).

In most studies, evoked feeding was strongly associated with the reward characteristics of LH stimulation. LH neurons, for example, display different patterns of activity, including multiple stages of searching for and consuming food. LH activity regulates the hedonic quality of taste stimuli, suggesting the role of LH in the formation and maintenance of taste preference and aversion (*33,34,35*). In addition, taste sensory information enters the brain through the nucleus of the solitary tract (NTS) and reaches the LH through the PBN (*36*). This sensitivity to food palatability, coupled with exacerbated LH disturbance, suggests a role for the LH in promoting the consumption of palatable foods (*37*).

2.3. Mechanism of calcitonin gene-related peptide (CGRP) neurons in PBN

The third pillar consists mainly of CGRP neurons in the PBN. NTS is the main entry point for visceral, taste, hormone, and metabolic information into the brain, and PBN is the link between taste and visceral sensory information. These neurons effectively inhibit feeding when PBN is activated, but they do not increase food intake when inhibited. Studies have shown that activation of PBN neurons is associated with nausea (*38*), hormones causing satiety(*39,40*), and gastric dilatation-mediated visceral aversion (*41,42*).

CGRP neurons mediate the physiological effects of satiety, unlike PBN neurons that mediate the transmission of taste information (*43*), whose photogenetic activation strongly reduces food intake. PBN^{CGRP} neurons receive projections from excitatory Vglut 2-expressing neurons from NTS (*44,45*). When PBN^{CGRP} neurons are activated by signals associated with food intake, they provide a signal of satiety. Moreover, inhibition of PBN^{CGRP} neurons increases the duration of a meal without increasing total food consumption (*46*). As a result, the number of rounds of food consumption decreases over a fixed period of time, while the amount of food consumed increases within a round.

3. Effect of TCM on related factors in the hypothalamus

3.1. Effects of Chinese medicine monomers

The role of Chinese medicine monomers in the regulation of hypothalamic appetite is reported to be mainly in the neuropeptides AGRP/NPY and POMC/CART and leptin in ARCs. The following studies illustrate the effects of Chinese herbal monomers in this process (Figure 4 and Table 1).

Berberine in isoquinoline alkaloids is one of the main effective components of *Coptis chinensis* (Huanglian). According to TCM theory, *Coptis chinensis* Franch has effects of regulating the spleen and stomach, clearing heat and drying dampness, and eliminating fire and removing toxic substances, so it is one of the common TCMs used to treat obesity and diabetes. Modern studies have proven that berberine has a variety of

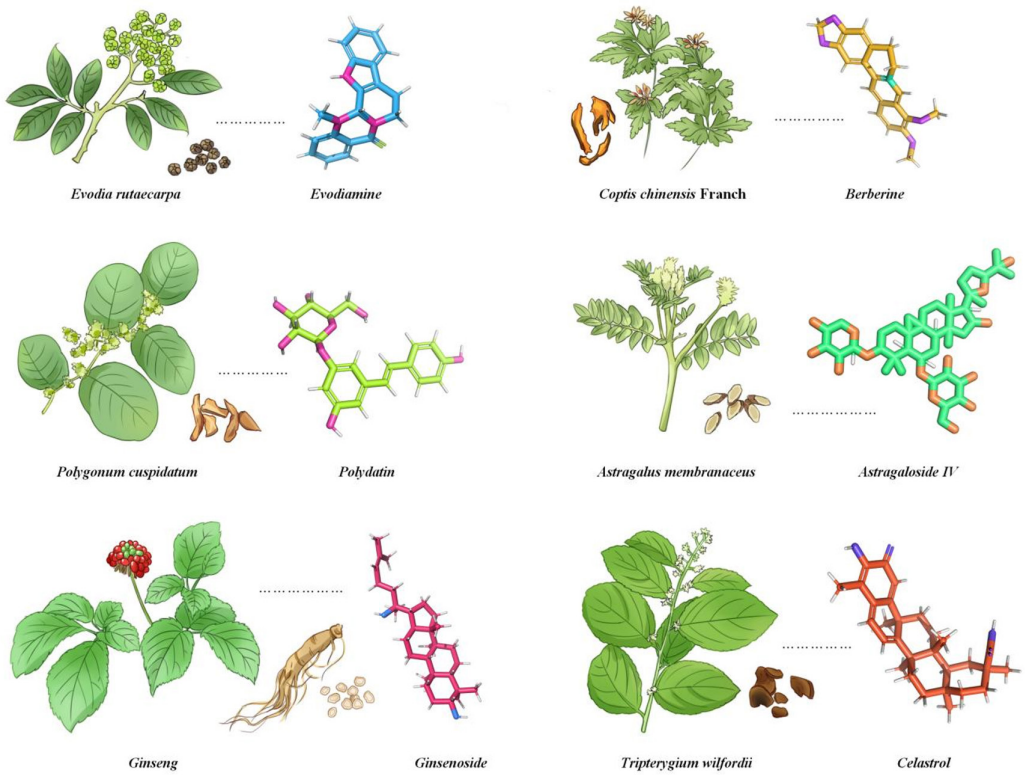

Figure 4. Several monomeric compounds derived from Chinese herbal medicines possess appetite-regulating effects. (A) *Evodia rutaecarpa* herbal plant and its processed slices; (B) 3D structural diagram of evodiamine; (C) *Coptis chinensis* herbal plant and its processed slices; (D) 3D structural diagram of berberine; (E) *Polygonum cuspidatum* herbal plant and its processed slices; (F) 3D structural diagram of polydatin; (G) *Astragalus membranaceus* herbal plant and its processed slices; (H) 3D structural diagram of astragaloside IV; (I) *Ginseng* herbal plant and its processed slices; (J) 3D structural diagram of ginsenoside; (K) *Tripterygium wilfordii* herbal plant and its processed slices; (L) 3D structural diagram of celastrol. (Note: The Chinese herbal medicine illustrations and sliced herbs were modified and illustrated by the author based on reference images online. Image sources: https://weibo.com; https://www.163.com; https://mp.weixin.qq.com; https://baike.baidu.com; http://www.dajiazhongyi.com/drug.php; The 3D structural information on the compounds was obtained from the PubChem database, and the molecular models were rendered using the software PyMOL).

biological activities, including antioxidative action, anti-inflammatory action, anti-cancer action, immune regulation, and antibacterial activity (*47*). It can reduce blood glucose and blood lipids and inhibit lipid production (*48*). Park *et al*. demonstrated that berberine can reduce food intake, body weight, fat content, serum leptin, and glucose levels in mice fed a high-fat diet (*49*). The food intake of mice injected with NPY increased, compared to those injected with artificial cerebrospinal fluid, and the food intake of mice injected with berberine decreased significantly, while the serum glucose level in mice treated with NPY and berberine was significantly lower than that in mice injected with NPY.

Evodiamine is a tryptamine indole alkaloid and the principal bioactive compound in *Evodia rutaecarpa* (Wuzhuyu). Contemporary pharmacological studies have demonstrated that this compound has antineoplastic, cardioprotective, anti-ulcerative, antimicrobial, anti-inflammatory, and analgesic properties (*50*). A study has revealed that evodiamine exhibits a previously unidentified capacity to suppress adipogenesis through a mechanism involving the activation of ERK/MAPK signaling pathways, which subsequently down-regulated the expression of adipogenic transcription factors and attenuated insulin-mediated Akt signaling (*51*). Shi *et al*. examined the impact of evodiamine on dietary consumption, body mass, and the levels of mRNA and peptide expression of appetite-regulating neuropeptides within the hypothalamus of male rats (*52*). Their findings demonstrated that intragastric administration of evodiamine at a dose of 40 mg/kg resulted in reduced food consumption and attenuated a body weight increase post-onset in rats. This was accompanied by elevated circulating leptin levels and a reduction in NPY and AgRP mRNA and peptide levels within the ARC. However, there were no significant alterations in the hypothalamic levels of POMC, CART, MCH, and MC4. Conversely, a lower dose of evodiamine (4 mg/kg) proved ineffective.

Astragaloside IV is one of the main components of *Astragalus membranaceus* (Huangqi) extract, which has many characteristics such as antioxidative action, anti-inflammatory action, and anti-apoptotic action. Thus far, numerous studies in cellular and animal models have shown that astragaloside IV is effective at protecting the cardiovascular system, lungs, kidneys, and the brain

Table 1. Several Chinese medicine monomers regulating appetite *via* the hypothalamus

Monomers	Source of Chinese herbal medicine	Animals	Intervention	Functional mechanism	Ref.
Berberine	*Coptis chinensis* (Huanglian)	Mice fed a high-fat diet	Intra-3rd ventricular microinjections	Decreases NPY levels	(*49*)
Evodiamine	*Evodia rutaecarpa* (Wuzhuyu)	Male rats	Intragastric administration	Decreases AgRP/NPY mRNA levels and peptide expression	(*52*)
Astragaloside IV	*Astragalus membranaceus* (Huangqi)	Fat-fed rats	Oral gavage	Increases p-STAT3, LepRb and POMC, decreases p-PI3K, SOCS3 and PTP1B	(*55*)
Ginsenosides	*Ginseng* (Renshen)	High fat diet induced obese mice	Intraperitoneal injection	Lowers leptin levels	(*59*)
Celastrol	*Tripterygium wilfordii* (Leigongteng)	Diet-induced obese mice	Intraperitoneal injection	Enhances leptin sensitivity, suppresses PERK activity, increases phosphorylated STAT3 expression	(*62,63*)
Polydatin	*Polygonum cuspidatum* (Huzhang)	High-fat diet-induced obese mice	Oral gavage	Upregulates leptin levels	(*67*)

(*53,54*). Jiang *et al*. found that astragaloside IV reduced leptin resistance in fat-fed rats by increasing p-signal transducer and activator of transcription 3 (STAT3), LepRb mRNA, and POMC mRNA and decreasing p-PI3K, suppressor of cytokine signaling (SOCS3), and protein tyrosine phosphatase-1B (PTP1B) mRNA in the hypothalamus (*55*). STAT3 modulates the suppression of AGRP/NPY neuronal activity and the facilitation of POMC/CART neuronal activation through its interaction with leptin and OB-R (*56*). Concurrently, the inhibition of SOCS3 and PTP1B expression augments STAT3 phosphorylation, thereby amplifying leptin signal transduction and ultimately having an anorexigenic effect (*57*). This pharmacological effect helps astragaloside IV prevent body weight gain and fat accumulation in rats with obesity induced by a high-fat diet, it alleviates metabolic disorders, and it reduces blood pressure and heart rate as well as noradrenaline levels in blood and kidney tissues.

Ginsenosides, which are extracted from ginseng (Renshen) with anti-obesity properties, have the ability to modulate metabolic processes and appetite regulation in murine models. A comprehensive review of previous *in vitro* and *in vivo* studies has indicated that ginseng and its ginsenosides enhance energy expenditure by activating the AMPK pathway and concurrently diminishing energy intake (*58*). Yao *et al*. demonstrated that ginsenosides inhibit ERS and regulate the phosphorylation of GT1-7 cells, a mouse hypothalamic gonadotropin-releasing hormone neuronal cell line, and STAT3 in the hypothalamus to reduce body weight and improve hepatic steatosis in mice with obesity induced by a high-fat diet (*59*). In that study, ginsenosides inhibited appetite, reduced body weight, visceral fat, body fat content, and blood glucose and leptin levels and improved glucose tolerance and blood lipids in obese mice.

Celastrol is the most promising compound in *Tripterygium wilfordii* (Leigongteng) and has therapeutic effects on inflammatory diseases, cancer, neurodegenerative diseases, and other conditions such as diabetes, obesity, atherosclerosis, and hearing loss (*60*). A study has reported that celastrol can reduce weight by regulating leptin sensitivity, energy metabolism, inflammation, lipid metabolism, and even intestinal microbiota (*61*). Liu *et al*. demonstrated that celastrol mitigated ERS in the hypothalamus through the suppression of PERK activity, thereby increasing phosphorylated STAT3 expression and subsequently reducing food intake in mice (*62*). This indicates that celastrol enhances leptin sensitivity, curtails energy expenditure, and induces weight loss in mice with obesity induced by a high-leptin diet. However, the compound showed no efficacy in ob/ob and db/db mouse models, implying that celastrol functions as a leptin sensitizer. Similarly, Feng *et al*. demonstrated that celastrol can enhance the sensitivity of leptin through interleukin-1 receptor 1 to inhibit appetite and weight loss (*63*). In

addition, the effect of celastrol has been found to be associated with the absence of PERK in arcuate nuclei POMC neurons, but specific mechanisms and PERK in other regions are still being examined (*64*).

Polydatin, one of the primary active components of *Polygonum cuspidatum* (Huzhang), has been shown in modern pharmacological studies to possess a broad spectrum of biological activities. These activities include the regulation of inflammation, oxidative stress, and apoptosis in key signaling pathways. Polydatin has demonstrated efficacy against cancer, against microbes, and providing protection for various systems, impacting the cardiovascular, nervous, endocrine, digestive, renal, and respiratory systems, as well as offering benefits for rheumatoid diseases, the skeletal system, and female health (*65*). *Polygonum cuspidatum* itself exhibits pharmacological properties such as dispelling dampness, alleviating jaundice, clearing heat, reducing toxins, activating blood, and removing stasis (*66*). Zheng *et al*. investigated the effects of polydatin on body weight control, glucose and lipid metabolism regulation, and combating inflammation in a mouse model of obesity induced by a high-fat diet (*67*). Polydatin reduced the weight of obese mice, regulated blood lipid levels, and significantly upregulated the expression of leptin mRNA and protein in the adipose tissue of obese mice.

3.2. Effects of TCM formulas

The absorption and metabolism of Chinese herbal decoctions and granules can also affect the hypothalamus (Table 2). They also play a role in regulating appetite by influencing AgRP/NPY, POMC/CART, leptin, and related factors.

Deng *et al*. conducted a clinical study on patients with simple obesity in which they were given Pingwei Powder, a combination of stir-fried *Rhizoma Atractylodis* (12 g), ginger-prepared *Cortex Magnoliae Officinalis* (9 g), *Pericarpium Citri Reticulatae* (6 g), and *Radix Glycyrrhizae Preparata* (3 g), and underwent ear acupoint treatment (*68*). This treatment resulted in a significant reduction in serum leptin and NPY levels.

Similarly, Li *et al*. treated simple obesity with Fangji Huangqi Decoction (*Fourstamen Stephania Root* 15 g, *Glycyrrhiza uralensis* 6 g, *Atractylodes macrocephala Koidz* 15 g, and *Astragalus membranaceus* 15 g) combined with abdominal massage (*69*). Although the drugs used differed from Pingwei Powder, the clinical trends were consistent. Fangji Huangqi Decoction can increase adiponectin levels, increase insulin hypersensitivity, enhance the inhibitory effect of insulin glycogen, and reduce blood lipid synthesis.

In a clinical trial, Jin *et al*. used Lianzhu Xiaoke Recipe containing *Coptis chinensis* Franch (30 g), parched *Rhizoma Atractylodis* (12 g), *Fructus Aurantii Immaturus* (10 g), *Cimicifugae* (10 g), *Pericarpium Citri Reticulatae* (12 g), parched *Rhizoma Pinelliae* (10 g), *Crataegus pinnatifida* Bunge (30 g), *Massa Medicata Fermentata* (10 g), *Rhizoma Alismatis* (30 g), *Poria* (15 g), *Bombyx Batryticatus* (10 g), *Hirudo* (3 g), *Rhizoma Zingiberis* (10 g), *Jujubae Fructus* (10 g), and *Glycyrrhiza uralensis* (6 g) to treat patients with obesity and type II diabetes, with metformin hydrochloride as a comparison (*70*). The experimental data revealed a significant decrease in serum leptin and SOCS3 levels in the Chinese medicine group, In contrast, the difference in NPY levels before and after treatment was not statistically significant. The researchers concluded that the mechanisms of action of Lianzhu Xiaoke Decoction and metformin may be inconsistent and that further research is needed.

Bai *et al*. found that POMC expression in the hypothalamus of obese mice treated with Jiangtang No. 3 recipe (JTSHF) — a formulation consisting of *Ginseng*, *Bupleurum*, *Radix Paeoniae Rubra*, *Poria*, and 10 other traditional Chinese herbs in a 1:1:3:1 ratio of free decoction granules — was slightly higher than that in the model group Additionally, AgRP levels decreased significantly, indicating that this recipe may help reduce food intake, lower body weight, and enhance glucose and lipid metabolism by influencing the expression of neuronal proteins associated with the hypothalamic feeding center (*71*). At the genus level, JTSHF increases the relative abundance of Bacteroides, Prevoda, and Bacteroides in the intestinal microflora and reduces the genera Clostridium, Lactobacillus, and Oscillibacter. JTSHF increased the content of short-chain fatty acids, increased the expression of GPR43/41, increased the expression of POMC, and decreased the expression of AgRP and NPY in the hypothalamus (*72*). Serum GLP-1 increased and ghrelin decreased after JTSHF intervention. Therefore, the authors believe that JTSHF plays an anti-diabetic role by affecting the composition, relative abundance and metabolites of intestinal flora, regulating a variety of intestinal brain peptides, affecting the feeding center of hypothalamus, and improving glycolipid metabolism.

Yang *et al*. reported that Wendan Decoction, consisting of *Citri Reticulatae Pericarpium* (10 g), *Pinelliae Rhizoma* (10 g), *Poria* (10 g), *Glycyrrhizae Radix Et Rhizoma* (3 g), *Caulis Bambusae in Taenia* (10 g), *Aurantii Fructus Immaturus* (10 g), *Zingiberis Rhizoma Recens* (5 slices), and *Jujubae Fructus*, effectively reduced body weight in obese rats on a high-fat diet, significantly improved the expression of leptin receptors and POMC mRNA in the hypothalamus, and reduced the level of leptin and OB-R in peripheral blood while reducing body weight (*73*).

Some medicines can also increase appetite-promoting factors. For example, Wang *et al*. observed changes in feeding behavior, body mass, Ob-R, AgRP, and NPY in rats with chronic restraint stress, revealing a possible mechanism of decreased food consumption and slow growth of body mass in rats with chronic stress.

Table 2. Several Chinese medicine formulas regulating appetite *via* the hypothalamus

Compound	Constituents	Efficacy	Sample type	Functional mechanisms	Ref.
Pingwei Powder	*Rhizoma Atractylodis*, ginger-prepared *Cortex Magnoliae Officinalis*, *Pericarpium Citri Reticulatae* , and *Radix Glycyrrhizae Preparata*	Decreases body weight, BMI, and body fat percentage	Simple obese patients	Reduces serum leptin and NPY levels	(*68*)
Fangji Huangqi Decoction	*Fourstamen Stephania Root*, *Glycyrrhiza uralensis*, *Atractylodes macrocephala Koidz*, and *Astragalus membranaceus*	Decreases body weight while enhancing blood glucose, lipid, and blood pressure levels	Simple obese patients	Reduces serum leptin and NPY levels, increases adiponectin levels	(*69*)
Lianzhu Xiaoke recipe	*Coptis chinensis Franch*, *parched Rhizoma Atractylodis*, *Fructus Aurantii Immaturus*, *Cimicifugae*, *Pericarpium Citri Reticulatae*, *parched Rhizoma Pinelliae*, *Crataegus pinnatifida Bunge*, *Massa Medicata Fermentata*, *Rhizoma Alismatis*, *Poria*, *Bombyx Batryticatus*, *Hirudo*, *Rhizoma Zingiberis*, *Jujubae Fructus*, *and Glycyrrhiza uralensis*	Lowers blood glucose, blood lipids, and fasting insulin levels, increases serum GLP-1 levels, and improves carotid atherosclerotic plaques	Obese patients with type 2 diabetes	Reduces serum leptin and SOCS-3 levels	(*70*)
Jiangtang No. 3 recipe	*Panax ginseng* C.A.Mey, *Radix bupleuri* , *Rehmannia glutinosa* (Gaertn.) DC. , *Salvia miltiorrhiza Bunge*, *Coptis chinensis Franch*	Lowers fasting and postprandial blood glucose levels and improves lipid levels	Mice with type 2 diabetes fed a high-fat diet	Reduces AgRP levels, increases POMC levels	(*71,72*)
Wendan Decoction	*Citri Reticulatae Pericarpium*, *Pinelliae Rhizoma*, *Poria*, *Glycyrrhizae Radix Et Rhizoma*, *Caulis Bambusae in Taenia*, *Aurantii Fructus Immaturus*, *Zingiberis Rhizoma Recens*, and *Jujubae Fructus*	Inhibits obesity	High fat diet induced obese rats	Improves the expression of POMC, reduces the level of leptin and OB-R in peripheral blood	(*73*)
Xiaoyao Powder	*Bupleurum*, *Angelica sinensis*, *Radix Paeoniae Alba*, *Rhizoma Atractylodis Macrocephalae*, *Radix Glycyrrhizae*, *Rhizoma Zingiberis Recens*, *Herba Menthae*	Improves stress resistance and appetite	Rats after chronic immobilization stress	Reduces Ob-R levels in ARCs, and increases AgRP and NPY levels	(*74*)
Liujunzi Decoction	*Radix Ginseng*, *Rhizoma Atractylodis Macrocephalae*, *Poria*, *Radix Glycyrrhizae*, *Pericarpium Citri Reticulatae*, and *Rhizoma Pinelliae*	Ameliorates cisplatin-induced injuries in the gastric antrum, liver, and ileum, and alleviates chemotherapy-induced anorexia	Rats with anorexia	Decreases serum leptin levels, down-regulates CART and POMC, up-regulates NPY and AGRP	(*75*)

Concurrently, Xiaoyao Powder (*Bupleurum*, *Angelica sinensis*, *Radix Paeoniae Alba*, *Rhizoma Atractylodis Macrocephalae*, *Radix Glycyrrhizae*, *Rhizoma Zingiberis Recens*, *Herba Menthae*) was selected as the intervention drug (*74*). The results indicated that Xiaoyao Powder effectively alleviated the symptoms of decreased appetite and reduced body weight under chronic restraint stress. This may be related to the inhibition of Ob-R protein and gene expression in ARCs and the upregulation of AgRP and NPY protein and gene expression.

In the treatment of different diseases, formulas affect the appetite-regulating neuropeptides of the hypothalamus differently. Liujunzi Decoction originates from the Medical Biography in the Ming dynasty and consists of six types of herbal medicines such as *Radix Ginseng*, *Rhizoma Atractylodis Macrocephalae*, *Poria*, *Radix Glycyrrhizae*, *Pericarpium Citri Reticulatae*, and *Rhizoma Pinelliae*. It benefits qi and invigorates the spleen and dries dampness to eliminate phlegm. Dai *et al*. created a rat model of anorexia by intraperitoneal injection of cisplatin to evaluate the efficacy of Liujunzi Decoction (*75*). Results showed that Liujunzi Decoction alleviated injury to the gastric antrum, liver, and ileum induced by cisplatin, decreased the serum leptin level, and also decreased the levels of ghrelin, IL-6 and growth differentiation factor 15. In the antrum and hypothalamus, Liujunzi Decoction inhibited cisplatin-induced activation of the JAK-STAT signaling pathway, resulting in down-regulation of transcription levels of the downstream anorexia-related neuropeptides CART, POMC, and TRH and up-regulation of expression of the hypothalamic appetite-related peptides NPY and AGRP.

3.3. Effects of a single medicine or extract

There are two types of Chinese medicine extracts and a type of lyophilized powder that can regulate appetite-related neuropeptides. These are *Cyclocarya paliurus* (Qingqianliu) aqueous extract, *Ginkgo biloba* (Yinxing) extract, and Ziziphi Spinosae Semen freeze-dried powder (Table 3).

Cyclocarya paliurus (Batalin) Iljinskaja, an indigenous and rare monocotyledonous species from Southern China, is renowned for its extensive traditional medicinal properties. These include clearing heat, detoxification, increasing saliva production, quenching thirst, anti-inflammatory action, insecticidal action, dispelling wind, and relieving itchiness. Additionally, it demonstrates efficacy in the prevention and management of diabetes, hypertension, hyperlipidemia, dizziness, and edema as well as in reducing cholesterol and modulating immune system functions (*76*). To reduce obesity, *Cyclocarya paliurus* ethanol leaf extracts primarily alleviate glucose metabolism disorders by reducing glucose absorption, modulating lipid profiles, regulating the insulin signaling pathway, decreasing β-cell apoptosis, enhancing insulin synthesis and secretion, altering

Table 3. Several Chinese medicines or extracts regulating appetite *via* the hypothalamus

Medicine or extract	Efficacy	Animals	Functional mechanism	Ref.
Cyclocarya paliurus aqueous extract	Clears heat, detoxifies, increases saliva production, quenches thirst, anti-inflammatory action, *etc.*	Obese rats with metabolic syndrome	Upregulates POMC, downregulates NPY	(*79*)
Ginkgo biloba extract	Promotes blood circulation and dispels blood stasis, removes turbidity and reduces blood fat	Diet induced obese rats	Decreases the activity of 5-HT transporter, upregulates 5-HT2C serotonin receptor, POMC, and CART	(*81-83*)
Ziziphi Spinosae Semen freeze-dried powder	Nourishes the heart and tonifies the liver, calms the heart and tranquilizes the mind	Rats under 24 h continuous darkness	Increases leptin and POMC levels, decreases NPY levels	(*85*)

the composition of the gut microbiota, and inhibiting α-glucosidase activity (*77*). In rats with diabetes induced by a high-fat diet and streptozotocin, both the ethanol and aqueous extracts of *Cyclocarya paliurus* demonstrated comparable antihyperglycemic, antihyperlipidemic, and antioxidant properties, with no significant differences observed between the two extracts (*78*). Xu *et al*. used Cg-Leprcp/NDmcr SHR/cp rats as an obesity and metabolic syndrome model to investigate the effects of *Cyclocarya paliurus* aqueous extract (CPAE) (*79*). Their findings indicated that CPAE administration significantly decreased food consumption, body weight, organ weight, adiposity, and BMI in SHR/cp rats. Additionally, CPAE treatment resulted in a reduction in fasting blood glucose, fasting serum insulin, HOMA-IR, serum free fatty acids, serum malondialdehyde, serum superoxide dismutase, and serum total glutathione levels. Moreover, CPAE markedly increased the phosphorylation levels of InsR, IRS1, PI3Kp85, Akt, and FoXO1, and upregulated the protein expression of POMC in the hypothalamus while significantly downregulating NPY expression.

Ginkgo biloba has demonstrated effects both centrally and peripherally, influencing the electrochemical, physiological, neurological, and vascular systems in animal models (*80*). *Ginkgo biloba* extract (GBE), derived from the desiccated foliage of the plant, is regarded as one of the most effective extracts for therapeutic applications. In a pilot study, Banin *et al*. established that GBE markedly diminished food consumption and body fat accumulation while averting diet-induced hyperglycemia and dyslipidemia in obese rats. On this basis, the ovaries of female rats were removed to simulate menopause, and GBE was given by gavage for 14 days (*81*). Banin *et al*. showed that GBE decreased the activity of 5-HT transporter, increase the local concentration of 5-HT, and improved appetite and alleviated obesity caused by an estrogen deficiency in climacteric rats (*82*). A separate study indicated that a single oral administration of GBE significantly upregulated the hypothalamic gene expression of anorexigenic mediators in male rats, such as the 5-HT2C serotonin receptor and the neuropeptides POMC and CART, while there were no observable changes in the expression of orexigenic mediators (*83*).

Ziziphi Spinosae Semen has the effects of alleviating anxiety, tranquillizing and hypnosis, preventing depression, and preventing convulsions (*84*). Chinese medicine theory holds that *Ziziphi Spinosae Semen* has the effects of tonifying the liver and calming the heart, and arresting sweating and promoting the production of bodily fluids. It can be used to treat insomnia due to deficiency and restlessness, palpitations, body deficiencies and sweating, and thirst due to disturbed bodily fluids. Xu *et al*. reported that the lyophilized powder of *Ziziphi Spinosae Semen* increased the levels of leptin and POMC in the hypothalamus of rats and decreased the levels of NPY so as to correct the disturbance of awakening from sleep and an abnormal rate of energy metabolism caused by 24 h of darkness (*85*).

3.4. Effects of Chinese patent medicines

Three other Chinese patent medicines have also been shown to regulate appetite *via* the hypothalamus, and their mechanisms of action are reported in the following studies (Table 4). These studies suggest that these medicines influence the hypothalamic pathways by modulating neuropeptide expression and other signaling pathway activity.

Danzhi Jiangtang capsules, consisting of *Radix Pseudostellariae*, *Radix Rehmanniae*, *Semen Cuscutae*, *Cortex Moutan*, and *Hirudo*, are traditionally used to enhance qi, nourish yin, and promote blood circulation. Bi *et al*. found that Danzhi Jiangtang Capsules can promote the secretion of α-MSH and inhibit AgRP secretion in the hypothalamus (*86*). These capsules can improve the feeding behavior of mice, reduce their body weight, alleviate obesity, and lower the risk of diabetes. Their clinical study also showed that Danzhi Jiangtang Capsules can improve the polyfeeding behavior of diabetes patients and that they have the effects of reducing body weight, regulating blood lipids, and reducing BMI.

Jingui Shenqi pills (JSPs) were initially documented in the classical medical text Essentials from the Golden Cabinet (Jīn Guì Yào Lüè). The formulation includes *Radix Rehmanniae*, *Rhizoma Dioscoreae*, *Fructus Corni*, *Poria*, *Cortex Moutan*, *Rhizoma Alismatis*, *Ramulus Cinnamomi*, and *Radix Aconiti Lateralis Preparata*. Zhang *et al*. evaluated the function of JSPs in mice with type 2 diabetes (*87*). Results indicated that JSPs effectively inhibited appetite and led to a steady decline in body weight, fasting blood glucose, and oral glucose tolerance in diabetic mice. In addition, JSPs result in increased dendritic length and branching, which protects hypothalamic neurons and synaptic structures. The expression and activation of POMC increased significantly, while the expression and activation of AgRP decreased when primary hypothalamic neurons were treated with 10% JSPs-rich serum, and these effects may be related to the regulation of PI3K.

There are also drugs in Chinese patent medicines that promote appetite. Child compound Endothelium corneum, consisting of *Endothelium Corneum Gigeriae Galli* and *Massa Medicata Fermentata*, has the effects of invigorating the spleen, stimulating appetite, promoting digestion, and removing food stagnancy. In functional dyspepsia, child compound Endothelium corneum has been shown to inhibit the hyperactive POMC/Stat3/Akt pathway in the rat hypothalamus and enhance gastrointestinal motility by rebalancing the homeostasis of the brain-intestine-microbiota axis in rats (*88*).

Table 4. Several Chinese patent medicines regulating appetite *via* the hypothalamus

Chinese patent medicine	Constituents	Efficacy	Animals	Functional mechanisms	Ref.
Danzhi Jiangtang Capsules	*Radix Pseudostellariae*, *Radix Rehmanniae*, *Semen Cuscutae*, *Cortex Moutan*, and *Hirudo*	Nourishes Yin and moistens dryness, promotes blood circulation and dispels blood stasis	Male db/db mice	Promotes the secretion of α-MSH and inhibit AgRP secretion	(*86*)
Jingui Shenqi pills	*Radix Rehmanniae*, *Rhizoma Dioscoreae*, *Fructus Corni*, *Poria*, *Cortex Moutan*, *Rhizoma Alismatis*, *Ramulus Cinnamomi*, and *Radix Aconiti Lateralis Preparata*	Warms and tonifies kidney-yang, dissipates QI and promotes water circulation	Mice with type 2 diabetes	Increases POMC, decreases AgRP	(*87*)
Child compound Endothelium corneum	*Endothelium Corneum Gigeriae Galli* and *Massa Medicata Fermentata*	Invigorates the spleen and stimulates appetite, promotes digestion and removes food stagnancy	Rats with functional dyspepsia	Increases NPY	(*88*)

4. Discussion and prospects

In modern medicine, factors like genetics, lifestyle, diet, and pathology affect drug outcomes, underscoring the need for individualized treatments. Chinese medicine formulas, with their complex components and multi-target mechanisms, offer unique therapeutic effects under various individual- and disease-related conditions, in contrast to modern drugs with a single target. This highlights TCM's advantage in maintaining internal balance and its flexibility in appetite regulation. Most appetite-suppressing medicines in TCM function by invigorating the spleen, removing dampness, promoting blood circulation, and regulating qi, aligning with the "spleen-main movement" theory. These medicines act through various mechanisms, affecting appetite and demonstrating TCM's multi-level approach to hypothalamus regulation. For instance, Xiaoyao Powder targets the liver and spleen simultaneously, achieving a balance through overall regulation rather than focusing on a single organ or pathway. TCM's adaptability shows its potential in comprehensive appetite regulation.

Several monomeric components from TCM have been shown to regulate appetite. While studies on these monomers help explain TCM mechanisms, their clinical effects often differ from those of single or combined herbal formulations. TCM formulas contain diverse chemical components targeting multiple pathways, helping to balance various organs. TCM can also affect the expression of neuropeptides related to the regulation of the appetite of the hypothalamus through a variety of signaling pathways, such as the PI3K/Akt signalin pathway, the autophagy pathway regulated by AMPK, and the PERK-mediated endoplasmic reticulum stress in the hypothalamus. Different TCM formulations can exhibit similar mechanisms, and the same drug's efficacy may vary with different formulas and diseases. Exploring the synergistic effects of these formulas could reveal their overall benefits. In order to identify more cost-effective pharmaceutical ingredients, the focus of future research can be gradually extended to the interaction of neuropeptides with downstream pathways. Exploring the synergistic effects of these pathways might reveal novel therapeutic strategies for metabolic disorders. Integrating TCM with modern pharmacology could potentially optimize treatment efficacy and minimize adverse effects, offering holistic approaches to appetite regulation.

Drug toxicity to the liver and kidneys must be considered. For instance, further studies on evodiamine have revealed its potential liver, heart, and kidney toxicity, which is dose- and time-dependent (*50*). This indicates that future research should carefully consider the dosage and timing of new drugs. TCM formulas can reduce toxicity and enhance efficacy, making them potentially more suitable for long-term use. However, TCM formulas are complex, with numerous interactions

among different herbs. Thus, studying the mechanisms of TCM's toxic adverse effects and understanding these interactions at a molecular level is crucial. By integrating traditional practices with modern pharmacology, toxic components and their pathways can be identified, improving the safety of long-term TCM use and reducing adverse reactions, thus maximizing the benefits of Chinese medicine.

In addition, improving oral bioavailability is a significant challenge in the development of new drugs from TCM monomers. Berberine, despite its wide array of pharmacological activities, has low bioavailability due to poor solubility, low permeability, P-glycoprotein efflux, and hepatic and intestinal metabolism. Long-term oral administration of berberine may also alter gut flora and affect other physiological functions, limiting its clinical use (*48*). Previous studies orally administered TCM formulas, extracts, and patent medicines, but monomers were given both orally and *via* injection. To provide convenient long-term treatment, enhancing oral bioavailability is crucial for TCM research and application. Modern drug development emphasizes drug efficacy and safety; improving bioavailability can impact treatment outcomes and enable more scientific evaluations of TCM's efficacy and toxicity, facilitating new drug development and promoting TCM in the global market.

According to current research, appetite-regulating mechanisms of the hypothalamus have not been fully elucidated, and especially their role in LH and PBN. A few studies have clearly shown that the mechanism of appetite control is related to the regulation of orexin and its receptors, MCHs, and CGRP neurons, but the potential role of TCMs in affecting that mechanism cannot be denied. Further investigation into how TCMs influence these neural circuits could unveil novel pathways for appetite regulation. Of course, we cannot ignore other biological processes involved in weight reduction, such as crocin, which inhibits obesity by inhibiting adipocyte differentiation and promoting lipolysis (*89*). This discussion with the nervous system will help us better understand the role of TCM in it.

Therefore, extensive research is essential to exploring the mechanisms of action of TCM, given its multi-target and multi-pathway nature. The primary objective is translating basic research into clinical use to identify compounds with improved efficacy, safety, and fewer adverse reactions. Moreover, research and development should focus on creating a wide range of adaptable, highly cost-effective, and user-friendly formulations to provide new avenues for preventing and treating obesity.

5. Conclusions

TCMs may affect appetite mechanisms in the hypothalamus, helping to control appetite, reduce body weight, and improve metabolic outcomes. Using ancient remedies in conjunction with modern scientific understanding, TCM can help to develop new, more effective treatments for obesity. Integrating traditional and modern medicine provides a fresh perspective on treating metabolic disorders, where long-term therapeutic options remain limited. This synergy between ancient wisdom and contemporary science can foster innovative therapeutic strategies, potentially unlocking novel pathways for metabolic regulation. Exploring these integrative approaches might also reveal previously untapped mechanisms, enhancing our ability to combat obesity and related metabolic diseases more effectively.

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