



## Review article

## Recent evidence in support of traditional chinese medicine to restore normal leptin function in simple obesity

Jialin Shao<sup>a</sup>, Chen Li<sup>b</sup>, Litao Bai<sup>c</sup>, Xiaolin Ni<sup>d,e,f</sup>, Shaoqin Ge<sup>a</sup>, Jinghui Zhang<sup>a</sup>, Hanqing Zhao<sup>a,\*</sup><sup>a</sup> College of Traditional Chinese Medicine, Hebei University, Baoding, PR China<sup>b</sup> Institute of Information on Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing, PR China<sup>c</sup> The Second Affiliated Hospital of Chongqing Medical University, Chongqing, PR China<sup>d</sup> The Key Laboratory of Geriatrics, Beijing Institute of Geriatrics, Beijing Hospital, National Center of Gerontology, National Health Commission, Beijing, PR China<sup>e</sup> Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, PR China<sup>f</sup> Graduate School of Chinese Academy of Medical Science and Peking Union Medical College, Beijing, PR China

## ARTICLE INFO

## Keywords:

Obesity  
Leptin resistance  
Network pharmacology  
Chinese herbal compound  
Food intake

## ABSTRACT

Reducing the incidence of obesity is the focus of global attention, and traditional Chinese medicine (TCM) may play an important role in achieving this goal. Numerous studies have shown that most individuals with obesity have leptin resistance, exogenous leptin is ineffective in individuals with obesity, and the effect of leptin decreases with increased serum leptin levels in individuals with obesity. At present, there are many hypotheses regarding the mechanism of leptin resistance, but there is no definite conclusion. TCM has a long history of treating obesity, and single and compound TCM is an effective obesity treatment method. However, TCM's mechanism of action is complex and resists further weight loss drug development. In the last decade, network pharmacology has become an important tool for exploring the mechanism of compound TCMS. In this study, we reviewed the interrelation between TCM obesity treatment and leptin resistance, and network pharmacology studies of TCM intervention in simple obesity revealed that their targets overlap with the leptin pathway. We also summarized TCM pairs that effectively interfere with leptin resistance and their related intervention mechanisms, providing targets for anti-obesity drug development.

## 1. Introduction

The global prevalence of obesity has nearly tripled since 1975 and continues to increase at a pandemic rate (Yanovski et al., 2018; Bentham et al., 2017). The prevalence of overweight, obesity, and abdominal obesity in China has rapidly increased over the past 20 years, along with improvements in living standards (Y.F Wang et al., 2019). Simple obesity is an excess accumulation or abnormal distribution of body fat for which there is no obvious endocrine, metabolic, or other etiology (Zou, 1999). Western anti-obesity drugs have clinical side effects including increased risk of depression, anxiety, stroke, cancer, and other diseases (Cao et al., 2020), and the clinical effect may not be obvious when compared with placebo. Surgical treatment with liposuction or gastrectomy is effective; however, it is invasive, may have sequelae, and may even lead to death. Leptin is a protein encoded by the obesity gene (Zhang et al., 1994), and its anti-obesity effect depends on the reduction of food intake and the

induction of energy expenditure (Pelleymounter et al., 1995). The discovery of leptin has contributed the understanding simple obesity. Statistical analysis of clinical data revealed sex-related differences in leptin levels in those with obesity (Kennedy et al., 1997; Saad et al., 1997), and that most individuals with obesity have hyperleptinemia with reduced leptin sensitivity or leptin resistance. However, the causes of leptin resistance have not yet been clearly described and there are no clear guidelines for its diagnosis and treatment. Traditional Chinese medicine (TCM) has rich experience in the diagnosis of simple obesity and its complications and has good clinical results in the treatment of simple obesity. TCM includes prescriptions, acupuncture, massage, embedding at acupoints, and other methods designed to treat the human body based on syndrome differentiation (Jin et al., 2019). Compared to Western medicine, TCM has fewer side effects, which can greatly reduce the physical and mental pain experienced during treatment. Recent obesity research has focused on network pharmacology to identify ways to

\* Corresponding author.

E-mail address: [zhaohq@hbu.edu.cn](mailto:zhaohq@hbu.edu.cn) (H. Zhao).

increase leptin sensitivity and improve leptin resistance. An analysis of the research results revealed that the pathways and targets of many TCMS with fat-reducing effects overlap with the leptin signaling pathways. Therefore, we reviewed recent studies on the mechanism of leptin resistance and its correlation with simple obesity to provide new ideas for the treatment of simple obesity with TCM and a network pharmacological perspective as the core of the search for possible mechanisms of herbal compound intervention in leptin resistance in simple obesity (Figure 1).

## 2. TCM theory and studies of simple obesity

### 2.1. Etiology and pathogenesis

The earliest understanding of obesity in TCM can be traced back to "Lingshu: Deficiency of Qi," in which obesity includes seven emotions, such as yin and yang imbalance, internal resistance of phlegm, and blood stasis, and emphasizes the status of phlegm, blood stasis, deficiency, and stagnation at the onset of obesity (Lu and Wang, 2006). Zhu Danxi noted that "fat people have more phlegm and dampness. Thin people have less." Zhang Jingyue noted that "fat people have more qi deficiency, more dampness, and more stagnation." Ancient doctors understood that the causes of obesity are both internal and external, such as water, dampness, phlegm, and stasis, which are related to dysfunction of the lungs, spleen, kidneys, and other internal organs, caused by existing deficiencies. The modern understanding of the etiology and pathogenesis of obesity is based on preceding views and includes the involvement of six contributing factors: overeating and lack of movement, abnormal emotions, sexual development factors, fertility factors, genetic factors, and use of tobacco and alcohol (Yin et al., 2016).

### 2.2. Principles of governance

The pathology of obesity can be described by "the original deficiency, the deficiency and the excess, and the interaction of deficiency and excess." The treatment of obesity is primarily based on tonic and relieving methods, such as strengthening the spleen and replenishing qi, stimulating the kidney and qi, warming the spleen and kidney, and promoting diuresis and dampness, dampness and heat release, expectoration, and elimination (Li et al., 2019). Treatment is influenced by Zhu Danxi's concept of "fat people have more phlegm." Modern experimental studies have validated the ancient understanding that phlegm-dampness influences obesity (Gong et al., 2014) and treating phlegm is the basis of obesity treatment (Li and Tang, 2018).

### 2.3. Correlation between phlegm and leptin

The "Lingshu Jing" describes the concept of "blood turbidity" as confusion, or a change in the composition of blood, and chaos, or a disorder in the circulation of blood (Z. Wang et al., 2019). Obesity is often

accompanied by hyperleptinemia, and the syndrome differentiation of obesity in TCM often belongs in the category of "phlegm turbidity" (Song et al., 1995; Wen et al., 2008). A recent study described a leptin conjugate in the serum with a molecular mass of  $450 \times 10^3$  Da, and its reversible combination with leptin weakened the biological activity of leptin (Campfield et al., 2020). A study of the relationship between leptin, hyperlipidemia, phlegm syndrome, and viscera (Hong et al., 2007) confirmed the correlation of leptin with TCM phlegm syndrome differentiation. Relevant animal studies showed that leptin levels are significantly elevated in rats in a phlegm-damp model (Wu et al., 2016). Leptin levels were significantly elevated in hyperlipidemic conditions (Liang et al., 2020; Wang et al., 2014); and relevant clinical experiments demonstrated that people with phlegm-damp accumulation in the body are more likely to develop obesity (Wang et al., 2013). Dampness is also the main pathogenesis of hyperlipidemia (Zhang et al., 2015), and leptin is positively correlated with blood lipid indicators (You et al., 2017). A clinical trial revealed that the symptom scores of the phlegm-dampness obstruction group were positively correlated with leptin by carefully observing patients' symptoms and making symptom scores according to the relevant quantitative tables of phlegm-dampness (Qian, 2018). The treatment of phlegm and dampness in TCM is very characteristic (Zhang et al., 2016, Zhang and Hu, 2016), and the method of strengthening the spleen and resolving phlegm can lead to weight loss and dyslipidemia improvement (Zhang et al., 2015, 2020; Ding et al., 2018), as well as lowering leptin and improving leptin resistance (Jiang, 2020, Zhou, 2017; Liu et al., 2020).

## 3. Modern medicine studies of simple obesity

Simple obesity is a chronic metabolic disease influenced by eating disorders and physical activity in addition to genetic, environmental, and socioeconomic variables (Manna and Jain, 2015). Obesity can be improved through TCM therapy, and the mechanism of TCM intervention in obesity is a popular research topic. We believe that the search for overlapping targets through network pharmacology and related media will facilitate the exploration of TCM mechanisms in the treatment of obesity. Current TCM research on the mechanism of obesity (Table 1) focuses on changes in the intestinal flora (Torres-Fuentes et al., 2017), hormone secretion (Álvarez et al., 2011), expression of adipocyte proinflammatory factors (Maurizi et al., 2017), and obesity-related genes (Fall and Ingelsson, 2014). Chai-Udom et al. (2018) found that hypothalamic injury, which alters the secretion of glucagon-like peptide-1 (GLP-1) participated in the pathogenesis of obesity. Because the mechanism of obesity is extremely complicated and there are countless related media involved, we only selected presently popular research topics to highlight, and there is other content not included in this review. For example, hypothalamic inflammation has been reported to not only cause energy imbalance but also aggravate central insulin resistance and leptin resistance associated with fat accumulation and obesity (You and Shen, 2020). Baldini and Phelan (2019) described the involvement of the

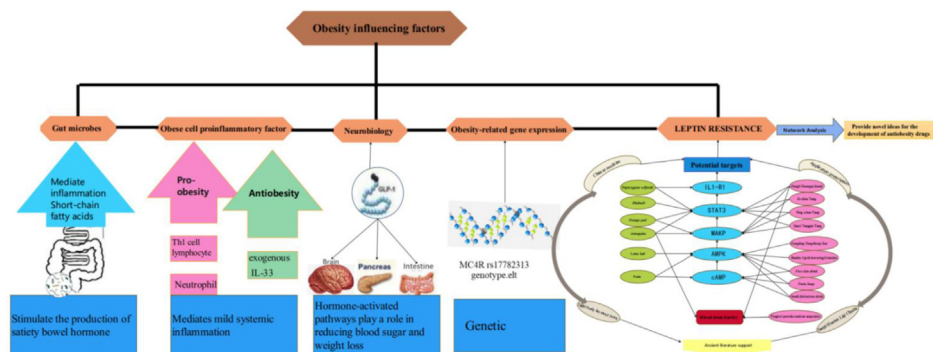


Figure 1. Pathogenesis of simple obesity and potential targets.

**Table 1.** Intervention mechanism of traditional Chinese medicine on obesity.

Factors influencing obesity	Mechanism	Related medium	Chinese medicine	Experiment type	Reference
Regulate fat metabolism	Increases lipid decomposition	MPK SIRT3 autonomic nerves, or β-adrenoceptors.	Trigonella foenum-graecum Rhizoma coptidis Nucifera-leaves Green tea	Animal experiment Human experiment	(Cheng et al., 2018) (Jiang et al., 2016) (Ono Y et al., 2006) (Murase et al., 2002)
	Inhibits fat production and accumulation	Inhibiting the proliferation and differentiation of adipocytes	Carthami Flos Radix Asteris Ganoderma Lucidum Polygona cuspidati -rhizoma Cordyceps militaris Curcumin Rhubarb Trigonella foenum-graecum	Animal experiment Human experiment	(Zhu et al., 2014) (Han et al., 2017) (Chang et al., 2018) (Izdebska et al., 2018) (Tran et al., 2019) (Lone et al., 2016) (Lim et al., 2016) (Cheng et al., 2018)
	Promotes thermogenic fat activation	Heat shock transcriptional factor 1 Receptor-gamma coactivator 1 alpha Mitochondrial uncoupling protein 1	Tripterygium wilfordii Rhubarb Curcuma longa Spatholobi caulis	Animal experiment	(Ma et al. 2015) (Wang et al., 2020) (Wang et al., 2017) (Zhang et al., 2019)
Gut microbes	Increases the level of short-chain fatty acids (SCFA)	Mediate inflammation SCFA	Rhizoma coptidis Chili pepper Ephedra sinica Ginseng	Animal experiment Human experiment	(Zhao. et al., 2018) (Tremaroli et al., 2015) (Visconti et al., 2019) (Trøseid et al., 2013) (Fei and Zhao, 2013)
	Induces a reduction in the number of branched-chain amino acids	CYP7A1 TGR5 BCKDC	Pueraria lobata Scutellaria baicalensis Rhizoma coptidis Luffa cylindrica		(Chambers KF et al., 2019) (Han K et al., 2017) (Yue SJ et al., 2019) (Zhang L et al., 2020)
Regulate hormone level	Enhances leptin sensitivity	Leptin-JAK2-STAT3 signaling and AMPK signaling Brain-derived neurotrophic factor	Tripterygium wilfordii Orange peel Poria Lotus leaf Astragalus Rhubarb Ginseng Curcuma longa	Animal experiment Human experiment	(Fu et al., 2020) (Huang et al., 2019) (Lee et al., 2020) (Li.G et al., 2018) (Li.X et al., 2016) (Meng et al., 2020) (Chen.Y et al., 2003) (Zhou.P et al., 2019) (Chang.C et al., 2018)
	Regulates the level of adiponectin	AMPK, S6K1 PKA-HSL AdipoR1	Pepper Green tea Ginger	Animal experiment Human experiment	(Li et al., 2014) (Bolin et al., 2020) (Liu L et al., 2019)
	Upregulation of GLP-1 and PYY	Glucagon-like peptide 1 (GLP-1) Peptide YY(PYY)	Capsicum annum Rhubarb Salvia miltiorrhiza Rhizoma coptidis	Animal experiment	(Knudsen et al., 2019) (Bays et al., 2017) (Østergaard et al., 2017) (Tamborlane et al., 2019) (Larabee et al. 2020) (Wang Yet al., 2020) (Wang Ret al., 2018) (Tung et al., 2017) (Sun Yet al., 2018)
Obese cell proinflammatory factor	Mediates mild systemic inflammation	Pro-obesity Th1 cell lymphocyte Neutrophil Anti-obesity exogenous IL-33	Rhizoma coptidis Scutellaria baicalensis Siraitia grosvenorii Polygonatum odoratum Lotus seed Radix polygalae Flos lonicera Lotus leaf Fallopia multiflora Pomegranate peel Loquat leaves Flos Caryophylli	Animal experiment Human experiment	(Hamjane et al., 2020) (Brestoff et al., 2015) (Talukdar et al., 2012) (Cohen et al., 2015) (Grill et al. , 2020) (Huang et al., 2019) (Wang et al., 2020) (Song et al. , 2019) (Zhu et al., 2021) (Wang Z.Y., 2019) (Wang et al., 2017) (Wang et al., 2014) (Xiong et al., 2021) (Park et al., 2016) (Fan et al., 2013) (Wang et al., 2018) (Li, 2019)

(continued on next page)

Table 1 (continued)

Factors influencing obesity	Mechanism	Related medium	Chinese medicine	Experiment type	Reference
Obesity-related gene expression	Genetic	Melanocortin-4 receptor rs17782313 genotype		Cross-sectional survey	(Yu et al., 2020) (López-Rodríguez et al., 2020) (Gao et al., 2019)

melanocortin pathway in the development of obesity in mice. During feeding,  $\alpha$ -melanocyte stimulating hormone released by pro-opiomelanocortin (POMC) neurons binds to melanocortin-4 receptors, which then bind to the paraventricular nucleus (PVN) to send out signals to reduce energy intake. Thus, leptin and insulin receptors send signals from POMC neurons to regulate energy intake. Deepening our understanding of the leptin resistance mechanism will open new horizons for the treatment of obesity.

#### 4. Leptin resistance

Leptin is a hormone secreted by white adipocytes, and binding of leptin to its receptor activates a variety of intracellular signal transduction pathways, such as Janus kinase 2 signal transducer and transcription activator 3 (JAK2-STAT3) (Bates et al., 2003; Moon et al., 2015). Leptin receptors are ubiquitous in the body. Consequently, leptin has a wide range of effects (Gu et al., 1999), including reduced food intake and increased energy consumption (Ravussin et al., 2014), blood pressure and heart rate regulation (Marsh et al. (2015); Simonds, Pryor, and Cowley (2017), reduced blood sugar (Anna et al., 2017), improved bone density (Reid et al. 2017), immune regulation, and regulation of reproductive function (Malik, Durairajanayagam, and Singh 2019; Donato et al., 2011). The lateral hypothalamus and ventral medial, dorsal, ventral premastoid, and arcuate nuclei are the primary sites of leptin binding. Activation of these areas leads to changes in cognition, mood, and memory (Swieten et al., 2014). Leptin binding in the metabolic regulation center of the hypothalamus is followed by a reduction in food intake and inhibition of fat synthesis (Qin and Tong, 2010). A slight increase in leptin levels can suppress appetite and induce weight loss; high leptin levels are often accompanied by obesity (Considine et al., 1996, Robert, 1996). Leptin resistance refers to a high level of serum leptin but insensitivity to leptin, which results in the absence of expected weight control and possible development of overweight and obesity (Liu et al., 2018). Hyperleptinemia and leptin resistance coexist, and the restoration of leptin sensitivity requires a reduction in body fat and serum leptin levels (Andreoli et al., 1999). The mechanism underlying leptin resistance has not yet been fully elucidated. Most studies on leptin resistance have evaluated leptin receptor mutations, intravascular defects, and defects in leptin transport, leptin signaling systems, and leptin conversion (Cao et al., 2020). The current results indicate that the expression of suppressor of cytokine signaling 3 (SOCS3) leads to the inhibition of the effects of leptin. The advantages of TCM include its activity against multiple targets for the treatment of leptin resistance, such as the STAT3, adenosine monophosphate activated protein (AMPK), and mitogen-activated protein kinase (MAPK) signaling pathways. As leptin research has intensified recently, more potential targets and signaling pathways have emerged in addition to the classical signaling pathways. An unidentified LepR neuron Sh2b1/SNS/BAT/thermogenic axis was recently identified, and the hypothalamic overexpression of SH2B1 may reportedly prevent high-fat diet-induced obesity (Jiang et al., 2020). Skeletal glucocorticoid signaling determines leptin resistance and obesity in aging mice and regulates NMDARs via Src to modulate  $\beta$ -cell excitability, suggesting that NMDARs may be a potential target to overcome leptin resistance (Henneicke et al., 2020; Cochrane et al., 2020). C1qTNF-related protein 4 reverses leptin resistance by inhibiting

NF- $\kappa$ B-dependent microglial activation and hypothalamic inflammation (Ye et al., 2021).

How leptin enters the central nervous system and crosses the blood-brain barrier (BBB) has also been extensively researched in recent years. Experiments showed that increasing the access of hormones to the brain by managing ciliary neurotrophic factor may overcome obesity-induced leptin resistance (Banks et al., 2021). The ability to exploit neuronal plasticity in brain circuits can enhance leptin sensitivity (Maffei M et al., 2021). At the same time, in addition to enhancing leptin passage at the BBB through drugs, it has been demonstrated that leptin brain entry via a transcytotic LepR-EGFR shuttle controls lipid metabolism and pancreas function (Duquenne et al., 2021). This experiment provides further evidence that leptin can enter the brain through channels other than the BBB, providing a new approach for improving leptin resistance.

Lifestyle changes are also important factors for improving leptin resistance. However, the mechanisms underlying this phenomenon require further exploration. For example, physical exercise is effective in improving leptin resistance and improving leptin resistance through resistance training has been a hot research topic in recent years (Lopes et al., 2020; Rios et al., 2021). In addition, the circadian clock plays an important role in leptin secretion and leptin resistance (Russo et al., 2021; Adhikary et al., 2016). However, disruption of the circadian clock may alter the circadian rhythm and synthesis of leptin and induce leptin resistance; thus, the restoration of the circadian rhythm may be beneficial for improving leptin resistance (Dibner et al., 2015). Leptin resistance induced by a high-fat diet is a temporary phenomenon that occurs only at certain times of the day; therefore, eating during leptin-sensitive periods may be metabolically beneficial (Boucsein et al., 2019).

Simultaneously, the combination of leptin with other obesity-related hotspots has provided new ideas for improving leptin resistance. For instance, the combination of leptin with gut flora has also become a new research top of interest (Al-Muzafar et al., 2017; Ji et al., 2018). Probiotics can reduce circulating leptin levels by altering the gut microbiome. Supplementation with high doses of *Lactobacillus rhamnosus* GG can alleviate leptin resistance in obese mice on a high-fat diet, which may be associated with improved digestive health (Cheng et al., 2020). It is also possible that endoplasmic reticulum stress is reduced by biochanin A to improve leptin resistance (Horiuchi et al., 2021).

#### 5. Mechanisms of TCM interventions to restore leptin sensitivity

##### 5.1. Enhanced activation of AMPK signaling by adiponectin

Yasuo et al. (2001) described the relationship between the effect of Fang Feng Tong Sheng San on weight loss and leptin activity, and Jin et al. (2017) found that it could regulate leptin secretion by fat cells. Leptin and adiponectin (APN) act within the hypothalamus to regulate AMPK activity (Handy et al., 2010, Wu, 2016b), and leptin reduces appetite by inhibiting AMPK activity. In the skeletal muscle and liver, APN phosphorylation activates AMPK, phosphorylates acetyl-CoA carboxylase (ACC), promotes fatty acid oxidation, and reduces fat deposition. Inhibition of the hypothalamic ACC inhibits the mediation of food intake by leptin (Gao et al., 2007). Fang Feng Tong Sheng San activates AMPK signaling by enhancing APN expression (Wu et al., 2016) and activates brown fat metabolism (Xu, 1995), resulting in weight loss.



### 5.2. Increased expression of JAK2 and STAT3

Recent reviews on the use of TCMs have reported that Jianpi Huatan prescriptions are widely used for the treatment of simple obesity (Si et al., 2016; Zhou et al., 2015) considering that obesity is primarily a consequence of phlegm and dampness (Wu et al., 2020). Other reviews (Zhao et al., 2018; Yu et al., 2018) have summarized the evidence that activation of the JAK2-STAT3-Bcl-2 pathway in gastrointestinal mucosal cells is part of the mechanism of strengthening the spleen and resolving phlegm. Sheng et al. (2017) reported that the Jianpi Shugan Jiangzhi decoction significantly reduced serum leptin levels and body weight ( $P < 0.05$ ) in 70 individuals with simple obesity. Wu et al. (2015) found that Jiawei Xiaoyao San, which is used to soothe the liver and invigorate the spleen, significantly improved leptin resistance and hypo-adiponectinemia ( $p < 0.05$ ) in patients with simple fatty liver, liver depression, and spleen deficiency. Kong et al. (2016) reported that the Liujunzi decoction significantly reduced serum leptin, body mass index, and body fat percentage ( $P < 0.01$ ). A study on weight loss and the physiological effects of sibutramine, spleen-invigorating, qi-regulating prescriptions (Citrus reticulata, Radix Aucklandiae, and Citrus aurantium), and Shengqing prescriptions (Bupleurum, Cimicifuga, and Pueraria lobata) demonstrated body weight loss with each treatment. Shengqing was better than sibutramine at increasing leptin levels and reducing body weight and neuropeptide Y (NPY) and suppressor of cytokine signaling-3 (SOCS-3) levels. Shengqing drugs inhibit leptin resistance by reducing the levels of NPY and SOCS-3 and ultimately reducing body weight (Jiang et al., 2014). A study conducted in a mouse model of simple obesity reported that medium- and high-dose Huaji Jianpi decoctions had stronger effects on LEPRb, JAK2, and STAT3 expression than orlistat ( $P < 0.05$ ), which was used as the control drug (Zhu and Zhan, 2019a,b). A 12-week intervention with Jiawei Banxia-baizhu Tianma decoction showed a significant ( $P < 0.05$ ) reduction in body weight and leptin level in obese, hypertensive rats that was centrally regulated by the JAK2-STAT3 pathway (Wu et al., 2016). In a placebo-controlled study, after 6-weeks of gavage administration, the Wendan decoction resulted in a significantly greater weight loss compared with distilled water gavage ( $P < 0.01$ ). The decoction regulated the JAK2-STAT3 signaling pathway, which adjusted the leptin level to achieve the weight loss goal. Dunn et al. (2015) found that knockdown of the expression of SOCS-3 by short interfering RNA led to increased phosphorylation of JAK2 and STAT3 and increased leptin sensitivity.

### 5.3. Passage of leptin through the BBB

Treatment with pingwei powder and ear acupoints reduced body weight and body fat percentage in a group of 64 individuals with simple obesity. Serum NPY and leptin levels were also reduced (Deng et al., 2018). In obesity, Fangji Huangqi treatment improved leptin sensitivity (Liu et al., 2016). A water extract of Scutellaria baicalensis Georgi significantly increased leptin levels in the rat hypothalamus and decreased leptin levels in the peripheral blood. A decrease in blood leptin suggested that Astragalus root increased the transport of leptin across the BBB, thereby inhibiting obesity (Yang et al., 2008). The blood leptin concentration is three times higher in people with obesity than in lean people, but the leptin concentration in the cerebrospinal fluid of people with obesity is only 30% of that of lean people (Caro et al., 1996). In people with obesity and hyperleptinemia, leptin levels are much lower in the hypothalamus than in the serum, which is consistent with the lack of transport across the BBB. Tracking the transport of fluorescently labeled leptin demonstrated that the choroid plexus plays a key role in transporting leptin to the cerebrospinal fluid, leading to a significant difference in leptin levels between obese and lean mice (Harrison et al., 2018). The coexistence of hyperleptinemia and low leptin concentrations in the cerebrospinal fluid of individuals with obesity may result from a lack of transport across the blood-cerebrospinal fluid barrier. Further research is needed to improve leptin transport into the cerebrospinal fluid.

### 5.4. Inhibiting IKK $\beta$ /NF- $\kappa$ B mediated inflammatory reaction and preventing leptin resistance

Hypothalamic leptin resistance is mainly attributed to the direct effects of hypothalamic inflammation and the indirect effects of peripheral inflammation. Chronic hypertrophic disease leads to activation of the IKK $\beta$ /NF- $\kappa$ B pathway and production of proinflammatory cytokines in peripheral adipose tissue. In turn, the production of proinflammatory cytokines cross back over the BBB, activating hypothalamic IKK $\beta$ /NF- $\kappa$ B, resulting in a chronic inflammatory response. Chronic hypothalamic IKK $\beta$ /NF- $\kappa$ B activation leads to selective leptin resistance through upregulation of SOCS3 and PTP1B production. As negative regulators of leptin signaling, both SOCS3 and PTP1B induce central leptin resistance by disrupting the phosphorylation of JAK2-STAT3 (de Git and Adan, 2015; Mark, 2013; Wang et al., 2012). In contrast, studies have shown that nicotine-induced activation of  $\alpha$ 7nAChR significantly alleviates peripheral inflammation by blocking the IKK $\beta$ /NF- $\kappa$ B pathway and contributes to improving leptin resistance in obese rats (Wang et al., 2011). However, due to the negative effects of nicotine, it is not a suitable agent for alleviating metabolic inflammation. Therefore, alternatives to activate the  $\alpha$ 7nAChR should be explored. Astragaloside IV (As IV) is a major bioactive compound derived from Astragalus membranaceus. It crosses the BBB and is detected in the brain parenchyma. At the same time, As IV prevents obesity by inhibiting IKK $\beta$ /NF- $\kappa$ B-mediated inflammatory responses and suppressing leptin resistance, and these results are associated with upregulation of  $\alpha$ 7nAChR expression (Chen et al., 2006; Wu et al., 2016).

### 5.5. Leptin-brain-derived neurotrophic factor pathway

Leptin is unusual in that it is the only peptide hormone whose primary site of action is the brain (Friedman and Halaas, 1998; Cohen et al., 2001). In the adult brain, brain-derived neurotrophic factor (BDNF) is the most abundant and widely distributed neurotrophic factor (Kolbeck et al., 1999; Patapoutian et al., 2001). Wang et al. (2020) described a direct role for BDNF + neurons in the PVN of the hypothalamus, where leptin controls the neural architecture of adipose organs by regulating BDNF-expressing neurons in the hypothalamic paraventricular nucleus, thereby facilitating lipolysis and utilization. Ginseng is a traditional Chinese herb, and ginsenoside Rb1 is one of the main bioactive saponins in ginseng, which has the effect of "lightning the body and prolonging life" according to "Shen Nong's Materia Medica." Recent pharmacological studies revealed that ginsenoside Rb1 increases the expression of leptin-induced BDNF, promotes leptin-BDNF axon growth and synapse formation, and contributes to weight loss by improving leptin sensitivity, which can reverse leptin resistance (Wu et al., 2018; Zhou et al., 2019).

## 6. Treatment of leptin resistance with Chinese herbal compounds

### 6.1. Potential targets of TCM for leptin resistance

Network pharmacology analysis found many TCMs described in ancient books as having "lightweight" effects that overlap with leptin signaling pathways and targets. In addition, we appended the more interesting molecules in the current study to the names of the herbal medicines (Table 2).

### 6.2. Compatibility of TCM with leptin resistance

Experimental research showed that herbal medicines and their extracts can reduce body weight by lowering the leptin levels in the body. Herbal and TCM formulas contain numerous active molecules. Essentially, they are a type of cocktail therapy. The interactions between herbs and TCM formulas are complex, and compounding links single herbs to compound prescriptions, which is required for the drugs to be fully effective and for the disease to be treated more effectively. It is common

**Table 2.** Similarities between the action pathways of Chinese herbal medicines and leptin pathways and targets.

Chinese medicine	Mode of action	Target/medium	Ancient literature support	Application prescription	Animal/human experiment	Type	References
Tripterygium wilfordii (Celastrol)	1. Improves leptin sensitivity 2. Inhibits adipocyte differentiation 3. Promotes body fat metabolism 4. Improves endoplasmic reticulum stress to increase leptin sensitivity	STAT3 Interleukin 1 Receptor 1	\	\	\	In vitro	(Fu et al., 2020) (Hu. et al., 2018) (Feng et al., 2019) (Crunkhorn et al., 2016) (Zhang et al., 2019) (Hou et al., 2020) (Abu-Bakar et al., 2020) (Sait et al., 2019) (De et al., 2020)
Orange peel (Tangeretin)	1. cAMP and PI3K-Akt autophagy signaling pathways are involved in leptin signaling 2. Rich digestive system related pathways	STAT3 MAKP	"Materia Medica Annotation" "Light body for many years"	Er Chen Tang Ping Chen Tang Sanzi Yangqin Tang	\	In vitro	(Lin.Y et al., 2018) (Liu.W et al., 2012) (Huang et al., 2019)
Poria (Pachymaran)	cAMP, AMPK pathway overlap with leptin action pathway cAMP	AMPK cAMP	"Shen Nong's Materia Medica" Do not starve and prolong the year	Five skin drink Poria Soup Small distinction drink	YES	In vitro	(Zhang.X et al., 2019)(Huang et al., 2020)
Lotus leaf (Nuciferin)	Regulates PPAR-γ and leptin levels	AMPK	"Syndrome and Treatment" "The lotus leaf gray suit is thin"..."	Shanhe Lipid-lowering Granules	YES	In vitro	(Liu et al., 2018) (Huang.J., 2007) (Li.M., 2017) (Sun.C,2014)(Li, 2018)
Astragalus (Astragaloside IV)	1. Inhibits activation of STAT3 and MAPK pathways 2. Inhibits the production of SOCS-3 3. Inhibits the proinflammatory response mediated by IKKβ/NF-kB in the hypothalamus and peripheral adipose tissue 4. Up-regulates the expression of LepR mRNA in the hypothalamus and phosphorylation of p-STAT3 5. Improves the transport rate of leptin through the blood-brain barrier	STAT3 MAPK	Long muscle, strong physique but deficiency of Qi, excess in shape but deficiency in Qi	Fangji Huangqi Decoction	YES	In vitro	(Li.X et al., 2016) (Ma et al., 2018) (Meng et al., 2020) (Song.Q. et al., 2015) (Jiang P. et al., 2018)
Rhubarb (Chrysophanic-Acid/Rhein)	Inhibition of C/EBPα mRNA expression further reduces leptin expression	STAT3	"Shen Nong's Materia Medica"	Xiaochengqi Tiaowei Chengqi Decoction Long-term use of single-flavored rhubarb	YES	In vitro	(Chen.Y et al., 2003)
Ginseng (Ginsenoside -Rb1)	1. Reverses central leptin resistance 2. Increases leptin-JAK2-STAT3 signaling 3. Induces expression of BDNF	STAT3 BDNF	"Shen Nong's Materia Medica" "Light body for many years"	Baihu-Xiexin Decoction	YES	In vitro	(Wu.Y et al., 2018) (Zhou.P et al., 2019)
Curcumin (Turmeric)	Improves the sensitivity to leptin by improving the hypoxic state of cells	STAT3	\	\	YES	In vitro	(Chang.C et al., 2018)

to use two or three herbs in a compound (Lu and Zheng, 2020). This is an important feature of TCM in the treatment of obesity. It embodies the characteristics of special diseases that match the special prescription of TCM.

A study on the frequency of use of TCM prescriptions for the treatment of obesity revealed a number of highly correlated combinations of two to three herbs with similar efficacy, such as Pinellia ternata and poria or Pinellia ternata and orange peel, which eliminate phlegm and strengthen the spleen, or Salvia miltiorrhiza and Fructus crataegi, which invigorate blood circulation to eliminate blood stasis. In TCM, this special form of use is called a *drug pair* (in this context, the application of two herbs in pairs to enhance their effectiveness).

**6.2.1. Pinellia ternate, poria, and orange peel**

As mentioned above, phlegm-dampness is one of the main pathogenic factors of obesity, and leptin levels have a strong positive correlation with phlegm-dampness. According to TCM theory, "the spleen is the

source of phlegm." Spleen deficiency cannot metabolize water and dampness; and thus, water, dampness, phlegm, and lipids accumulate in the body. Common symptoms in this group of patients include body obesity, fat accumulation in the abdomen, chest tightness, excessive phlegm, ease of sleepiness, and preference for greasy high-calorie food, fatter tongue, and white, and greasy tongue coating. Therefore, it is often treated with Pinellia ternata, poria, and orange peel, which have the effect of eliminating phlegm and strengthening the spleen (Liu, 2020a). The representative compounds to deal with these symptoms include Er Chen Tang, Wen Dan Tang, and Cang Fu Dao Tan Tang, which include Pinellia ternata and poria. Pinellia ternata and orange peel are used more frequently.

Er Chen Tang was first published in the "Prescriptions of Peaceful Benevolent Dispensary Volume IV" during the Song Dynasty. This formula consists of a combination of Pinellia ternata, orange peel, poria, licorice, and ginger. In recent years, basic experiments and clinical studies revealed that Erchen decoction and its modified formula, mainly

comprising these herbs, regulate glucose and lipid metabolism through various mechanisms, such as regulating lipid metabolism-related signaling pathways (Shao et al., 2020; Ding et al., 2017) and hormone levels, including leptin levels (Lee et al., 2020; Wang et al., 2017). These drugs were studied through network pharmacology, and their key targets were closely related to those of obesity (Zhu et al. 2022).

The Erchen decoction is probably derived from the Wendan decoction (Jin et al., 2021). The Wendan decoction is comprised of the following herbs: Pinellia, Zhuru, Citrus aurantium, orange peel, poria, and licorice. This small complex prescription reduced serum leptin levels and body weight in obese rats and decreased leptin mRNA expression in the hypothalamus, suggesting that the small complex prescription of Pinellia, orange peel, and poria can effectively reduce leptin levels in the body and decrease leptin resistance, ultimately leading to weight loss (Liu et al., 2020, Yu et al., 2019).

Cang Fu DaoTan Tang is a new compound formula based on Er Chen Tang. It is based on the main components of the Erchen decoction, Pinellia, orange peel, and poria, with the addition of Cyperirrhizoma, Arisaemacum Bile, Aurantii fructus, Chuanxiong rhizoma, Medical talc powder, and Massa medicata fermentata to reduce weight by lowering the leptin levels (Wang, 2018). This proves that the drug compatibility of orange peel and poria could effectively regulate the level of leptin in the body, thus showing good results in the treatment of obesity.

### 6.2.2. *Fructus crataegi, lotus leaf, and astragalus*

An analysis of the literature related to the laws of TCM in the treatment of simple obesity shows that simple obesity is not only closely related to phlegm and dampness, but also that qi stagnation and blood stasis are causative factors for a large proportion of the disease (Si et al., 2016). Meanwhile, the top three biased physiques in individuals with obesity were phlegm-dampness, damp-heat, and blood stasis. In particular, the proportion of blood stasis evidence tended to increase with the prolongation of the disease, which is consistent with the view that blood stasis is seen more often in chronic diseases in TCM. With the prolongation of the disease, qi deficiency and blood stasis or phlegm and blood stasis were inevitable results of pathological development (Yu.C et al., 2018). Individuals with obesity often have the following symptoms: lack of luster and dullness on the face; rough brown skin, often with hyperpigmentation; purple spots on the skin; dry lips; and slight bruising of the tongue or petechiae. In addition, they often feel weak and depressed.

Many studies demonstrated that prescriptions with activated blood circulation have significant effects in modulating serum leptin levels (Yue et al., 2016; Chang et al., 2016). Fructus crataegi and Astragalus significantly reduced inflammation levels and improved glycolipid metabolism (Gong et al., 2021) and preparations, such as the lotus leaf tables (comprising lotus leaf, Salvia miltiorrhiza, and Fructus crataegi), He Qi powder (comprising lotus leaf, Astragalus, and Polygonum multiflorum), and other preparations with lotus leaf as the main ingredient have good lipid-regulating effects (Qiao et al., 2018). However, if we combined TCMs eliminating phlegm and strengthening the spleen with TCMs promoting blood circulation to remove blood stasis, the combined prescriptions were significantly more effective than the single drug (Yang et al., 2015), suggesting that there may be synergistic effects between both types of medicines. It is suggested that the compatibility of medicines, such as Pinellia and orange peel with Fructus crataegi and lotus, is important for the prevention and treatment of obesity and related diseases.

### 6.2.3. *Tripterygium wilfordii and licorice*

As mentioned above, Tripterygium wilfordii was improved leptin resistance in the treatment of obesity, whereas a simple modification of glycyrrhiza acid (a compound related to licorice) leads to GA-02, which plays a role in obesity treatment by reactivating leptin signaling and reducing systemic inflammation, especially in the hypothalamus (Zhou et al., 2018). It is considered a celastrol mimic with anti-obesity

druggability, and the combination of licorice and Tripterygium wilfordii is worth exploring as a classical drug pair (Liang and Zhang, 2019).

As a traditional Chinese herb, Tripterygium wilfordii is the root of Tripterygium wilfordii Hook. The earliest account of its medicinal uses is in "Dian Nan Ben Cao" (Yunnan Materia Medica) in 1476. It eliminates wind and dampness, dredges the collaterals to stop pain, promotes blood circulation, and relieves edema. Celastrol is a pentacyclic triterpenoid isolated from the root of Tripterygium wilfordii and is also one of the main active ingredients of Tripterygium wilfordii (Li et al., 2019). In 2015 (Bray, 2015; Greenhill, 2015; Liu et al., 2015), reports determined that Tripterygium wilfordii achieved weight loss by regulating leptin levels and increasing leptin sensitivity. Since then, due to the great potential of TCM in effecting weight loss, many teams have actively researched the involvement of leptin in the regulation of lipid metabolism. In clinical practice, the key to the application of this herb is ensuring its efficacy while minimizing its toxic side effects (Hou et al., 2020). Herbalists can reduce toxicity by combining different drugs. We reduced drug toxicity through the combination of TCMs, which fully reflects the essence of TCM philosophy of "treatment based on syndrome differentiation." According to the literature, the combination of Tripterygium wilfordii with drugs such as licorice, Astragalus, Paeoniae radix Alba, and Rehmannia glutinosa increases the effectiveness of detoxification.

According to Chinese medical texts, licorice has the property of "detoxifying all poisons," and leigongteng and licorice are commonly combined in TCM. As an important herbal medicine, licorice makes up 80% of the Chinese herbal formulas and has a good safety profile. It is widely grown and readily available at low cost (Hayashi et al., 2003).

The combination of Tripterygium wilfordii and licorice is a classic drug combination, and the combination of Tripterygium wilfordii with licorice or licorice and Tripterygium wilfordii reduced toxic side effects, regulated disorders of glucose and lipid metabolism, and enhanced the efficacy of weight reduction. At the same time, the potentiation effect of combining licorice and Tripterygium wilfordii is related to the dosage of licorice used, while the specific mechanism of enhancing weight reduction efficacy may be related to the following two aspects. The combination of glycyrrhiza acid and tretinoin may increase weight loss through anti-inflammatory, antioxidant and anti-apoptotic pathways. However, regulating the glycerophospholipid metabolic pathway improves disorders of lipid metabolism. Exploring the mechanism of action of this drug combination using metabolomics revealed that glycerophospholipid metabolism has the greatest variability and effect on all metabolic pathways. Meanwhile, some experiments used the classical Drosophila model to explore the efficacy of Tripterygium wilfordii combined with licorice on improving disorders of glucolipid metabolism using a high-glucose and high-fat model. Ultimately, Tripterygium wilfordii and licorice had synergistic efficacy in improving glucolipid metabolism disorders. These experiments suggest that the combination of licorice and Tripterygium wilfordii may reduce weight by modulating key targets in the glycerophospholipid metabolic pathway, influencing the metabolic pathway, and modifying the disorder of lipid metabolism.

## 7. Safety of TCM

In recent years, with the renewed public interest and transformed medical paradigms, the efficacy of TCM in preventing and treating diseases has been recognized and accepted by the international community. With the growing acceptance of complementary and alternative medicines in Western countries, natural medicines used as both food and medicine, as represented by TCM, are gradually gaining attention. In China, there is a long custom of medicine and food being homologous, and "Huangdi Neijing" records the theory that food is used to regulate the state of the body, and that the essence of *the homology of medicine and food* (which means medicine and food in the same source) is edible Chinese medicinal materials. Because of its dual use as medicine and food, it has

been used in medical and health care as diet therapy and medicinal meals. The TCMs mentioned above are mostly used as medicinal and food substances as teas, staple foods, and soups in the daily diet. These include drinking green tea; brewing herbs, such as *Fructus crataegi*, lotus leaves, and *Siraitia grosvenorii*, to make drinks; making poria into cakes; and cooking *Coicis semen* porridge. At the same time, East Asia has a consensus linking medicine and food from the same source, while in the developed regions of Europe and the United States there is a high need for additional health supplements. We have witnessed the application of TCM expanded to include dietary supplement.

At present, the application of molecules and single Chinese herbs is supported by modern pharmacological studies. However, there is little pharmacological research on herbal medicines as a unit. Compatibility of herbal medicines is integral as herbal medicines are combined into prescriptions according to certain rules. Compatibility of traditional Chinese herb medicine is a popular topic in the field of TCM today. We found that research on compatibility is mainly based on TCM theories, and modern scientific methods used to demonstrate the mechanism of compatibility are inadequate. The substances produced by the combination of some single herbs are difficult to fully elucidate by modern medicine, and their related mechanisms of action still need to be further explored. Most current studies focus on drug combinations with similar potency, and lack in-depth exploration of the compatibility of drugs with large differences in potency. We suggest that it is essential to strengthen the research on these two aspects, which will strongly support researching TCM intervention to treat leptin resistance.

## 8. Conclusion and outlook

In summary, TCM has a long history of treating obesity and has certain curative effects. TCM has recognized the pathogenic factors of obesity since the Yellow Emperor's Internal Classic period and has provided treatment protocols and prescriptions. Later generations gradually evolved classical TCM compound prescriptions, and this study focuses on summarizing the relationship between TCM for the treatment of obesity and leptin resistance. TCM differs from the single-target mechanisms of chemical drugs and has the advantages of targeting multiple pathways for therapy. The targets of the classical drugs and compound formulas summarized in this paper overlap not only with the targets of obesity but also with leptin signaling pathways. The variations in targets suggest that herbal medicines are great potential treatments for leptin resistance and weight loss drug development.

However, many problems remain, such as the unknown pathogenesis of obesity and the complex and confusing specific components and mechanisms of action of herbal medicines. Current research is focused on the composition and mechanism of action of single herbs, but less research is done on herbal compounding and there is limited clinical translation. Therefore, we believe that exploring the secrets of TCM intervention in obesity and leptin resistance should focus more on TCM compounding and should elucidate its effective mechanism of action. Drug experiments should be combined with clinical trials, and the characteristics of certain combinations of drugs with obvious efficacy be specifically analyzed. This will be not only beneficial to the study of the mechanism of action of TCM compounding, but also significantly impact the research and development of new TCM drugs. We believe that with the continuous development of basic medicine, big data, artificial intelligence, and clinical research, the specific mechanisms of TCM intervention in obesity will be further explored, and the treatment of obesity, leptin resistance, and its complications will enter a new era.

## Declarations

### Author contribution statement

Jialin Shao; Chen Li, Litao Bai, Xiaolin Ni: Wrote the paper; Analyzed and interpreted the data.

Shaoqin Ge: Conceived and designed the experiments.

Jinghui Zhang: Analyzed and interpreted the data.

Hanqing Zhao: Conceived and designed the experiments; Wrote the paper.

### Funding statement

This work was supported by the Science and Technology Research Key Project of Higher Education Department of Hebei Province (No. ZD2020101). Shaoqin Ge was supported by NHC Key Laboratory of Family Planning and Healthy, Hebei Key Laboratory of Reproductive Medicine, Hebei Research Institute for Family Planning Science and Technology Open Project (No. SZ-202003).

### Data availability statement

No data was used for the research described in the article.

### Declaration of interests statement

The authors declare no conflict of interest.

### Additional information

No additional information is available for this paper.

## References

- Abu-Bakar, M.H., Shariff, K.A., Tan, J.S., Lee, L.K., 2020 Sep 15. Celastrol attenuates inflammatory responses in adipose tissues and improves skeletal muscle mitochondrial functions in high fat diet-induced obese rats via upregulation of AMPK/SIRT1 signaling pathways. *Eur. J. Pharmacol.* 883, 173371. Epub 2020 Jul 24. PMID: 32712089.
- Adhikary, N., Shrestha, S.L., Sun, J.Z., 2016 Jul 19. Metabolic disturbances: role of the circadian timing system and sleep. *Diabetol. Int.* 8 (1), 14–22. PMID: 30603302; PMCID: PMC6224937.
- Al-Muzafar, H.M., Amin, K.A., 2017 Jan 13. Probiotic mixture improves fatty liver disease by virtue of its action on lipid profiles, leptin, and inflammatory biomarkers. *BMC Compl. Alternative Med.* 17 (1), 43. PMID: 28086768; PMCID: PMC5237220.
- Álvarez-Castro, Paula, Sangiao-Alvarellos, Susana, Brandón-Sandá, Iria, Córdido, Fernando, 2011. Funcion endocrina en La obesidad. *Endocrinol. Nutr.* 58 (8), 422–432.
- Andreoli, M.F., Andreoli, María F., Donato Jr., Jose, Cakir, Isin, Perello, Mario, 1999. Leptin resensitisation : a reversion of leptin-resistant states. *J. Endocrinol.* 241.
- Anna, M.D., Ursula, H Neumann, Glavas, Maria M., Kieffer, Timothy J., 2017. The glucoregulatory actions of leptin. *Mol. Metabol.* 1–14.
- Baldini, Giulia, Phelan, Kevin D., 2019. The melanocortin pathway and control of appetite-progress and therapeutic Implications. *Banks WA. Leptin and the blood-brain barrier: curiosities and controversies*, 2021 Sep 23 *Compr. Physiol.* 11 (4), 2351–2369. PMID: 34558673.
- Bates, Sarah H., Walter, H Stearns, Trevor, A Dundon, Banks, Alexander S., Hugh, J Lavery, Asma, K Haq, Myers Jr., Martin G., 2003. STAT3 signalling is required for leptin regulation of energy balance but not reproduction. *Nature* 421 (February).
- Bays, Harold, Pi-Sunyer, Xavier, Uddén Hemmingsson, Joanna, Claudius, Birgitte, Jensen, Christine B., Van Gaal, Luc, 2017. Liraglutide 3.0 Mg for weight management: weight-loss dependent and independent effects. *Curr. Med. Res. Opin.* 33 (2), 225–229.
- Bentham, James, Di Cesare, Mariachiara, Bilano, Ver, Bixby, Honor, Zhou, Bin, Stevens, Gretchen A., Riley, Leanne M., et al., 2017. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 390 (10113), 2627–2642.
- Bolin, A.P., Sousa-Filho, C.P.B., Marinovic, M.P., Rodrigues, A.C., Otton, R., 2020. Polyphenol-rich green tea extract induces thermogenesis in mice by a mechanism dependent on adiponectin signaling. *J. Nutr. Biochem.* 78, 108322.
- Boucein, A., Rizwan, M.Z., Tups, A., 2019 Nov. Hypothalamic leptin sensitivity and health benefits of time-restricted feeding are dependent on the time of day in male mice. *FASEB J.* 33 (11), 12175–12187. Epub 2019 Jul 31. PMID: 31366239; PMCID: PMC6902664.
- Brestoff, Jonathan R., Kim, Brian S., Saenz, Steven A., Stine, Rachel R., Monticelli, Laurel A., Sonnenberg, Gregory F., Thome, Joseph J., et al., 2015. Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature* 519 (7542), 242–246.
- Campfield Arthur, L, Françoise Smith, J, Guisez, Yves, Devos, Rene, Paul, Burn, 2020. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 269 (5223), 546–549. Published by : American



- Association for the Advancement of Science Stable URL. <https://www.Jstor.Org/Stable/2887670>. JSTOR Is a Not-for-Profit Se.
- Cao, J.M., Li, H., Meng, Y.P., Cheng, S.S., Bai, Z.Y., Song, J.G., 2020. Research and application progress of commonly used weight-loss drugs. *Forum Prevent. Med.* 5, 396–400.
- Caro, José F., Kolaczynski, Jerzy W., Nycze, Mark R., Ohanesian, Joanna P., Opentanova, Irina, Goldman, Warren H., Lynn, Richard B., Pei-li, Z., Sinha, Madhur K., Considine, Robert V., 1996. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. *Lancet* 348, 159–161.
- Chai-udom, Rapeepun, Aroonparkmongkol, Suphab, Sahakitrungruang, Taninee, 2018. Metabolic features and changes in glucose-induced serum glucagon-like peptide-1 levels in children with hypothalamic obesity. *J. Pediatr. Endocrinol. Metab.* 1–7.
- Chambers, K.F., Day, P.E., Aboufarrag, H.T., Kroon, P.A., 2019. Polyphenol effects on cholesterol metabolism via bile acid biosynthesis, CYP7A1: a review. *Nutrients* 11, 11.
- Chang, Z.L., 2016. Effect of guizhi fuling pills on serum leptin, vascular endothelial growth factor, interleukin-8 and ovarian function in patients with endometriosis. *Modern J. Integr. Tradit. Chin. West. Med.* 25 (35), 3915–3917.
- Chang, C.J., Lu, C.C., Lin, C.S., et al., 2018. Antrodia cinnamomea reduces obesity and modulates the gut microbiota in high-fat diet-fed mice. *Int. J. Obes.* 42 (2), 231–243.
- Chen, Y., Qu, X.Y., Jin, H.M., Zhang, G.P., Jiao, D.H., 2003. Effects of compound rhubarb preparations on leptin and C/EBP $\alpha$  in fat cells of obese rats. *Chin. J. Basic Med. Trad. Chin. Med.* (4), 27–31.
- Cheng, Y.C., Liu, J.R., 2020 Aug 24. Effect of *Lactobacillus rhamnosus* GG on energy metabolism, leptin resistance, and gut microbiota in mice with diet-induced obesity. *Nutrients* 12 (9), 2557. PMID: 32846917; PMCID: PMC7551584.
- Cheng, C.Y., Yang, A.J., Ekambaranello, P., Huang, K.C., Lin, W.W., 2018. Antiobesity action of INDUS810, a natural compound from *Trigonella foenum-graecum*: AMPK-dependent lipolysis effect in adipocytes. *Obes. Res. Clin. Pract.* 12 (6), 562–569.
- Cochrane, V.A., Wu, Y., Yang, Z., ElSheikh, A., Dunford, J., Kievit, P., Fortin, D.A., Shyng, S.L., 2020 Dec 11. Leptin modulates pancreatic  $\beta$ -cell membrane potential through Src kinase-mediated phosphorylation of NMDA receptors. *J. Biol. Chem.* 295 (50), 17281–17297. Epub 2020 Oct 9. PMID: 33037073; PMCID: PMC7863909.
- Cohen, E.Suzanne., Scott, Ian.C., Majithiya, Jayesh.B., Rapley, Laura, Kemp, Benjamin.P., England, Elizabeth, Gareth Rees, D., et al., 2015. Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation. *Nat. Commun.* 6, 1–10.
- Considine, R.V., et al., 1996. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N. Engl. J. Med.* 334 (5), 292–295.
- Crunkhorn, S., 2016. Metabolic disease: leptin sensitizer reverses obesity. *Nat. Rev. Drug Discov.* 15 (9), 601.
- De Angelis, M., Schriever, S.C., Kyriakou, E., Sattler, M., Messias, A.C., Schramm, K.W., Pfluger, P.T., 2020 Jun. Detection and quantification of the anti-obesity drug celastrol in murine liver and brain. *Neurochem. Int.* 136, 104713. Epub 2020 Mar 6.
- de Git, K.C., Adan, R.A., 2015 Mar. Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation. *Obes. Res.* 16 (3), 207–224. Epub 2015 Jan 14.
- Deng, C., Zhang, Y., Cen, M., Cai, J.Z., Lai, Y.X., Yang, Z.M., 2018. The clinical effect of Pingwei San combined with ear points on simple obesity and its effect on serum NPY and Leptin. *Guangzhou Med. J.* 3, 19–22.
- Dibner, C., Gachon, F., 2015 Sep 1. Circadian dysfunction and obesity: is leptin the missing link? *Cell Metabol.* 22 (3), 359–360.
- Ding, S.S., Kang, J., Zhang, L.Y., 2017. Effect of Erchen Decoction on the expression of Cav-1 and PI3K/AKT in mice with lipid metabolism disorders. *Chin. J. Trad. Chin. Med.* 32 (1), 242–244.
- Ding, S., Kang, J., Tong, L., Lin, Y., Liao, L., Gao, B., 2018 Oct 8. Erchen decoction ameliorates lipid metabolism by the regulation of the protein CAV-1 and the receptors VLDLR, LDLR, ABCA1, and SRB1 in a high-fat diet rat model. *Evid. Based Compl. Alternat. Med.* 2018, 5309490.
- Donato Jr., José, Roberta, Renata, M Cravo, Carol, Frazão, 2011. Hypothalamic sites of leptin action linking metabolism and reproduction. *Neuroendocrinology* 9077, 9–18.
- Dunn, Sarah L., Bjo, Marie, Bates, Sarah H., Chen, Zhibin, Seifert, Matthew, Myers, Martin G., 2015. Feedback inhibition of leptin receptor/Jak2 signaling via tyr 1138 of the leptin receptor and suppressor of cytokine signaling 3. *Mol. Endocrinol.* 19 (October), 925–938.
- Duquenne, M., Folgueira, C., Bourouh, C., Millet, M., Silva, A., Clasadonte, J., Imbernon, M., Fernadois, D., Martínez-Corral, I., Kusumakshi, S., Caron, E., Rasika, S., Deliglia, E., Jouy, N., Oishi, A., Mazonne, M., Trinquet, E., Tavernier, J., Kim, Y.B., Ory, S., Jockers, R., Schwanager, M., Boehm, U., Nogueiras, R., Annicotte, J.S., Gasman, S., Dam, J., Prévot, V., 2021 Aug. Leptin brain entry via a tanyctytic LepR-EGFR shuttle controls lipid metabolism and pancreas function. *Nat. Metab.* 3 (8), 1071–1090.
- Fall, Tove, Ingelsson, Erik, 2014. Genome-wide association studies of obesity and metabolic syndrome. *Mol. Cell. Endocrinol.* 382 (1), 740–757.
- Fan, H., Wu, D., Tian, W., et al., 2013. Inhibitory effects of tannic acid on fatty acid synthase and 3T3-L1 preadipocyte. *Biochim. Biophys. Acta* 1831 (7), 1260–1266.
- Fei, Na, Zhao, Liping, 2013. An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice. *ISME J.* 7 (4), 880–884.
- Feng, Xudong, Guan, Dongxian, Auen, Thomas, Choi, Jae Won, Andrés Salazar Hernández, Mario, Lee, Jaemin, Chun, Hyonho, et al., 2019. IL1R1 is required for celastrol's leptin-sensitization and antiobesity effects. *Nat. Med.* 25 (4), 575–582.
- Fu, J.M., Zhou, Y., Zhang, T.T., 2020. Research progress of tripterygium in the treatment of obesity. *Chin. Pharmaceut. J.* 55 (4), 293–297.
- Gao, Su, Kinzig, Kimberly P., Aja, Susan, Scott, Karen A., Keung, Wendy, Kelly, Sandra, Ken Strynadka, et al., 2007. Leptin activates hypothalamic acetyl-CoA carboxylase to inhibit food intake. *Proc. Natl. Acad. Sci. Unit. States Am.* 104 (44), 17358–17363.
- Gao, Luying, Wang, Linjie, Yang, Hongbo, Pan, Hui, Gong, Fengying, Zhu, Huijuan, 2019. MC4R single nucleotide polymorphisms were associated with metabolically healthy and unhealthy obesity in Chinese northern han populations. *Int. J. Endocrinol.* 2019.
- Gong, Y., H., 2021. Effect of Preventive Administration of Astragalus-Hawthorn on Polycystic Ovary Syndrome in Rats Induced by High-Fat Diet. Shanxi University of Traditional Chinese Medicine.
- Gong, Y., Shi, X.L., Niu, J.J., et al., 2014. Pathogenesis of hypothalamic inflammation and obesity. *J. Liaoning Univ. Trad. Chin. Med.* (7), 85–88.
- Grill, Harvey J., 2020. A role for GLP-1 in treating hyperphagia and obesity. *Endocrinology* 161 (8), bqaa093.
- Gu, W.Q., Chen, M.D., Tang, J.F., Li, F.Y., Chen, C.R., Luo, M., Chen, J.L., Xu, M.Y., 1999. The relationship between serum leptin level and obesity in Chinese. *Chin. J. Endocrinol. Metabol.* 1, 18–21.
- Hamjane, Nadia, Benyahya, Fatiha, Ghailani Nourouti, Naima, Bennani Mechita, Mohcine, Barakat, Amina, 2020. Cardiovascular diseases and metabolic abnormalities associated with obesity: what is the role of inflammatory responses? A systematic review. *Microvasc. Res.* 131, 104023.
- Han, K., Bose, S., Wang, J.H., et al., 2017. In vivo therapeutic effect of combi nation treatment with metformin and *Scutellaria baicalensis* on maintaining bile acid homeostasis. *PLoS One* 12 (9), e0182467.
- Han, M.H., Jeong, J.S., Jeong, J.W., et al., 2017. Ethanol extracts of *Aster yomena* (Kitam.) Honda inhibit adipogenesis through the activation of the AMPK signaling pathway in 3T3-L1 preadipocytes. *Drug Discov. Ther.* 11 (5), 281–287.
- Handy, Jeffrey A., Saxena, Neeraj K., Fu, Pingping, Lin, Songbai, Jamie, E Mells, Gupta, Nitika A., Anania, Frank A., 2010. *Cell. Biochem. Biophys.* 1207 (October 2009), 1195–1207.
- Harrison, Luke, Schriever, Sonja C., Feuchtinger, Annette, Kyriakou, Eleni, Baumann, Peter, Pfuhlmann, Katrin, Messias, Ana C., Walch, Axel, Tschöp, Matthias H., Paul, T.P., 2018. Fluorescent blood – brain barrier tracing shows intact leptin transport in obese mice. *Int. J. Obes.* 43 (6), 1305–1318.
- Henneicke, H., Kim, S., Swarbrick, M.M., Li, J., Gasparini, S.J., Thai, J., Foong, D., Cavanagh, L.L., Fong-Yee, C., Karsten, E., Lin, R.C.Y., Cooper, M.S., Zhou, H., Seibel, M.J., 2020 Dec. Skeletal glucocorticoid signalling determines leptin resistance and obesity in aging mice. *Mol. Metabol.* 42, 101098.
- Hong, M.G., Zhang, Y.F., Leng, J.H., Chen, J., Wang, L.J., 2007. Study on the correlation between leptin and phlegm and viscera of hyperlipidemia. *China J. Trad. Chin. Med. Sci. Technol.* 3, 147–148.
- Horiuchi, K., Tsuchio, K., Matsushima, G., Thon, M., Hosoi, T., Ozawa, K., 2021 Aug 11. The possible role of biochanin A in ameliorating endoplasmic reticulum stress-induced leptin resistance. *Neuroreport* 32 (12), 983–987.
- Hou, W., Liu, B., Xu, H., 2020 Mar 1. Celastrol: progresses in structure-modifications, structure-activity relationships, pharmacology and toxicology. *Eur. J. Med. Chem.* 189, 112081.
- Hu, W.Y., 2018. Study on the Therapeutic Effect and Mechanism of Tripterygium Wilfordii on Obesity in Rats. Nanjing Medical University.
- Huang, J., 2007. Effects of Shanhe Jiangzhi Granules on Leptin and Adiponectin in Diet-Induced Obesity Rats. Jinan University.
- Huang, J., Hu, W., Lin, X.D., 2019. The effect of berberine on the intestinal flora of obese mice and its mechanism. *Genom. Appl. Biol.* 38 (2), 810–814.
- Huang, X.F., Yu, G.Z., Tong, J.J., 2019. Analysis of the pharmacological mechanism of tangerine peel based on network pharmacology. *Chin. Patent Med.* 12, 3038–3045.
- Huang, Y.L., Xu, Y.J., Feng, G.F., Huang, B.Q., Yang, Y., Deng, Y.J., 2020. Effects of Shenlingbaizhu Powder on mTORC1/STAT3 signaling pathway in Kupffer cells of rats with non-alcoholic fatty liver disease induced by high-fat diet. *Hebei Trad. Chin. Med.* 42 (1), 89–95 back cover 3.
- Izdebska, M., Herbet, M., Gawrońska-Grzywacz, M., et al., 2018. Resveratrol limits lipogenesis and enhance mitochondrial activity in HepG2 cells. *J. Pharm. Pharmaceut. Sci.* 21 (1), 504–515.
- Ji, Y., Park, S., Park, H., Hwang, E., Shin, H., Pot, B., Holzapfel, W.H., 2018 Apr 10. Modulation of active gut microbiota by *Lactobacillus rhamnosus* GG in a diet induced obesity murine model. *Front. Microbiol.* 9, 710.
- Jiang, P., Song, Q.L., 2014. The effect of Shengqing traditional Chinese medicine on diet-induced leptin resistance in obese rats. *China J. Inform. Trad. Chin. Med.* 8, 60–63.
- Jiang, D., Wang, D., Zhuang, X., et al., 2016. Berberine increases adipose triglyceride lipase in 3T3-L1 adipocytes through the AMPK pathway. *Lipids Health Dis.* 15 (1), 214.
- Jiang, P., Ma, D., Wang, X., et al., 2018. Astragaloside IV prevents obesity-associated hypertension by improving pro-inflammatory reaction and leptin resistance. *Mol. Cell.* 41 (3), 244–255.
- Jin, J., Chen, X., 2021. Research progress in the main treatments of Wendan Decoction prescriptions. *Chin. Patent Med.* 1–6.
- Jin, X., Hou, R.F., Tao, F., Lu, H., 2017. The research progress of Fangfeng Tongsheng Powder in regulating body weight and body fat. *World J. Integr. Trad. Chin. West. Med.* 12 (10), 1472–1476.
- Jin, Y.T., Wang, L.H., Chen, X., Huang, W., Song, A.Q., Hu, F., Cheng, Y., Zhou, Z.Y., 2019. Analysis of the current status of the use of curative effect standards in randomized controlled trials of Chinese medicine for simple obesity. *Chin. J. Trad. Chin. Med.* 3, 606–610.
- Kennedy, Adele, Gettys, Thomas W., Watson, Patricia, Wallace, Penny, Ganaway, Elizabeth, Pan, Qin, Timothy Garvey, W., 1997. The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. *J. Clin. Endocrinol. Metab.* 82 (4), 1293–1300.
- Knudsen, Lotte Bjerre, Lau, Jesper, 2019. The discovery and development of liraglutide and semaglutide. *Front. Endocrinol.* 10 (12), 10–155.

- Kong, Y.Q., Wang, Y.Z., 2016. Effect of Liujunzi decoction on serum leptin and chemerin in simple obese women. *China J. Trad. Chin. Med. Technol.* 5, 521–523.
- Larabee, Chelsea.M., Oliver, C. Neely., Domingos, Ana I., 2020. Obesity: a neuroimmunometabolic perspective. *Nat. Rev. Endocrinol.* 16 (1), 30–43.
- Lee, S.M., Jueun, L., Kang, E.J., 2020. Lipidomic analysis reveals therapeutic effects of Yijin-Tang on high-fat/high-cholesterol diet-induced obese mice. *Phytomedicine* 74, 152936.
- Li, L.R., 2017. Study on the changes in the content of characteristic components of Leigongteng in combination with *Glycyrrhiza glabra*, *Paeonia lactiflora* and *Lycopodium officinale* in detoxification herbs. *Tianjin Tianjin Beichen Distr. Hosp. Trad. Chin. Med.* 12–12.
- Li, G., 2018. AMPK activation-mediated lotus leaf alkaloids intervention in lipotoxicity. In: *Proceedings of the 8th Pan-Bohai Sea Biochemistry and Molecular Biology Academic Exchange Conference.*
- Li, Z.W., 2019. Identification and Characterization of Active Ingredients that Inhibit Fatty Acid Synthase Expression and Obesity in Clove. Jiangnan University, Wuxi.
- Li, C.D., Tang, H.Z., 2018. Treating obesity from phlegm and dampness. *Guangxi Med. Sci.* 40 (23), 2829–2831.
- Li, X., Choi, Y., Yanakawa, Y., Park, T., 2014. Piperonal prevents high-fat diet-induced hepatic steatosis and insulin resistance in mice via activation of adiponectin/AMPK pathway. *Int. J. Obes. (Lond)* 38 (1), 140–147.
- Li, X., Zhang, J.Q., Wang, X., Jiang, P., 2016. Effects of Astragalus on fat accumulation and leptin resistance in diet-induced obese rats. *Chin. J. Trad. Chin. Med.* 31 (3), 833–837.
- Li, H., Lin, Y.X., Ni, Q., Ma, L.R., 2019. Thoughts and methods of comprehensive diagnosis and treatment of simple obesity in traditional Chinese medicine. *J. Pract. Trad. Chin. Inter. Med.* 11, 105–108.
- Li, H.Z., Liu, B., Shu, H., 2019. Systematic evaluation of the toxicity-reducing effects of Leigongteng with *Glycyrrhiza glabra* in animal experiments. *Chin. J. Trad. Chin. Med.* 44 (16), 3512–3519.
- Li, H.Z., Liu, B., Shu, H.Y., Yuan, R.L., Ji, X.Y., Hu, H., Meng, X., Liu, Y.Q., Shi, N.N., Wang, P., Lyu, C., 2019. Toxicity-reducing effect of compatibility of Tripterygium and licorice in animals: systematic review. *Zhongguo Zhongyao Zazhi* 44 (16), 3512–3519. Chinese. PMID: 31602916.
- Liang, S.H., Zhang, X.J., 2019. Study on the efficacy and toxicity reduction of Leigongtang *Glycyrrhiza glabra* pairing to improve disorders of glucolipid metabolism based on *Drosophila* biological model. *J. Pharmaceut. Forum* 40 (6), 3–6.
- Liang, X., Wang, Q., Jiang, Z., Li, Z., Zhang, M., Yang, P., Wang, X., Wang, Y., Qin, Y., Li, T., Zhang, T., Wang, Y., Sun, J., Li, Y., Luo, H., Li, L., 2020 Aug. Clinical research linking Traditional Chinese Medicine constitution types with diseases: a literature review of 1639 observational studies. *J. Tradit. Chin. Med.* 40 (4), 690–702.
- Lim, H., Park, J., Kim, H.L., et al., 2016. Chrysophanic acid suppresses adipogenesis and induces thermogenesis by activating AMP-activated protein kinase alpha in vivo and in vitro. *Front. Pharmacol.* 7, 476.
- Lin, Y.Y., Xiong, Y.T., 2018. The effect of mixed decoction of eucommia, hawthorn and tangerine peel on weight loss and lipid reduction in nutritionally obese rats. *China Contemp. Med.* 25 (17), 20–23.
- Liu, Y.R., 2020. Effect of Intervention of Dyslipidemia with Spleen Strengthening and Expectorant Method on Intestinal Flora, Leptin and Lipocalin. Liaoning University of Traditional Chinese Medicine.
- Liu, W.Z., Lu, H.J., Ye, X.C., Huang, J., Wang, L.F., Liu, Yanwen., 2012. Study on the lipid-lowering and weight-reducing effects of the compound tangerine peel composition. *China Pharm.* 19, 1744–1746.
- Liu, J., Lee, J., Salazar Hernandez, M.A., Mazitschek, R., Ozcan, U., 2015. Treatment of obesity with celastrol. *Cell* 161 (5), 999–1011.
- Liu, X.Q., Jin, X., Hou, R.F., Tao, F., Lu, H., 2016. Re-evaluation of the weight loss effect of Fangji Huangqi Decoction from the obesity phenotype system. *World J. Integr. Trad. Chin. West. Med.* 11, 1610–1614.
- Liu, S.Y., Qi, A.R., Luo, D.G., et al., 2018. Advances in the study of reproductive toxicity and co-administration reduction of Leigongteng preparations. *Chin. J. Trad. Chin. Med. Inform.* 25 (4), 133435.
- Liu, J.R., Yang, Xiaoning, Yu, Siwang, Zheng, Ruimao, 2018. The Leptin Resistance, pp. 145–163.
- Liu, L., Yao, L., Wang, S., et al., 2019. 6-Gingerol improves ectopic lipid accumulation, mitochondrial dysfunction, and insulin resistance in skeletal muscle of ageing rats: dual stimulation of the AMPK/PGC-1alpha signaling pathway via plasma adiponectin and muscular AdipoR1. *Mol. Nutr. Food Res.* 63 (6), e1800649.
- Liu, C., Zuo, Z.Y., Wang, B.Z., Liu, C.H., Yao, F.Y., 2020. Effects of Jiawei wendan decoction on LEP, ACC and MCA in female nutritional obesity rats. *Chin. J. Experi. Formul.* 26 (1), 87–91.
- Lone, J., Choi, J.H., Kim, S.W., Yun, J.W., 2016. Curcumin induces brown fat-like phenotype in 3T3-L1 and primary white adipocytes. *JNB (J. Nutr. Biochem.)* 27, 193–202.
- Lopes, L.M.P., de Oliveira, E.C., Becker, L.K., Costa, G.P., Pinto, K.M.C., Talvani, A., Carraro, J.C.C., Coelho, D.B., 2020 Sep 4. Resistance training associated with dietetic advice reduces inflammatory biomarkers in the elderly. *BioMed Res. Int.* 2020, 7351716.
- López-Rodríguez, Guadalupe, Estrada-Neria, Alin, Suárez-Diéguez, Teodoro, Elizabeth Tejero, M., Carlos Fernández, Juan, Galván, Marcos, 2020. Common polymorphisms in MC4R and FTO genes are associated with BMI and metabolic indicators in Mexican children: differences by sex and genetic ancestry. *Gene* 754, 144840.
- Lu, S.J., Wang, F.F., 2006. Obesity and its etiology and pathogenesis. *Chin. J. Basic Med. Trad. Chin. Med.* 12 (3), 215–216.
- Lu, R.Y., Zheng, S.Q., 2020. Analysis of obesity medication rules and potential effects based on data mining and network pharmacology. *J. Tianjin Univ. Trad. Chin. Med.* 1, 103–110.
- Ma, D.F., 2018. Pre- and post-control Study of Shugan Yunpi Decoction in the Treatment of Obesity-Related Hypertension and the Mechanism of Action of Astragaloside IV. Shandong University of Traditional Chinese Medicine, pp. 1–129.
- Maffei, M., Giordano, A., 2021 Apr 6. Leptin, the brain and energy homeostasis: from an apparently simple to a highly complex neuronal system. *Rev. Endocr. Metab. Disord.* Epub ahead of print.
- Malik, Ifrah Alam, Durairajanayagam, Damayanthi, Jeet Singh, Harbindar, 2019. Leptin and its actions on reproduction in males. *Asian J. Androl.* 296–299. May 2018.
- Manna, Prasenjit, Jain, Sushil K., 2015. Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies. *Metab. Syndr. Relat. Disord.* 13 (10), 423–444.
- Mark, A.L., 2013 Sep 15. Selective leptin resistance revisited. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 305 (6), R566–R581. Epub 2013 Jul 24.
- Marsh, Ainsley J., Fontes, Marco A.P., Killinger, Suzanne, Dorota, B Pawlak, Polson, Jaimie W., Dampney, Roger A.L., 2015. Cardiovascular responses evoked by leptin acting on neurons in the ventromedial and dorsomedial hypothalamus. *Hypertension* 42.
- Maurizi, G., Della Guardia, L., Maurizi, A., Poloni, A., 2017. Adipocytes properties and stromal cell with immune system in obesity-related inflammation. *J. Cell. Physiol.* 233 (1), 88–97.
- Meng, X.Y., Qu, C., Yang, Y.F., Shi, Y., 2020. Based on network pharmacology to explore the mechanism of Astragalus-Salvia on the treatment of diabetic nephropathy. *Chin. J. Trad. Chin. Med.* 8, 39–42+260.
- Moon, Hyun-seuk, Huh, Joo Young, Dincer, Fadime, Schneider, Benjamin E., Hasselgren, Per-olfo, Mantzoros, Christos S., 2015. Identification and saturable nature of signaling pathways induced by metreleptin in humans: comparative evaluation of in vivo, ex vivo, and in vitro administration. *44 (March)*, 828–839.
- Murase, T., Nagasawa, A., Suzuki, J., Hase, T., Tokimitsu, I., 2002. Beneficial effects of tea catechins on diet-induced obesity: stimulation of lipid catabolism in the liver. *Int. J. Obes. Relat. Metab. Disord.* 26 (11), 1459–1464.
- Ono, Y., Hattori, E., Fukaya, Y., Imai, S., Ohizumi, Y., 2006. Anti-obesity effect of *Nelumbo nucifera* leaves extract in mice and rats. *J. Ethnopharmacol.* 106 (2), 238–244.
- Østergaard, Lauge, Seerup Frandsen, Christian, Fremming Dejgaard, Thomas, Madsbad, Sten, 2017. Fixed-ratio combination therapy with GLP-1 receptor agonist liraglutide and insulin degludec in people with type 2 diabetes. *Expet Rev. Clin. Pharmacol.* 10 (6), 621–632.
- Park, S.Y., Jin, M.L., Chae, S.Y., et al., 2016. Novel compound from *Polygonum multiflorum* inhibits inflammatory response in LPS-stimulated microglia by upregulating AMPK/Nrf2 pathways. *Neurochem. Int.* 100, 21–29.
- Pelleymounter, Mary Ann, Jane Cullen, Mary, Baker, Mary Beth, Hecht, Randy, Winters, Dwight, Boone, Thomas, Collins, Frank, 1995. Effects of the obese gene product on body weight regulation in Ob/Ob mice. *Science* 269 (5223), 540–543.
- Qian, L., 2018. Study on the Correlation between TCM Evidence Types and Serum Leptin and Apolipoprotein AI in Dyslipidemic Patients. Beijing University of Traditional Chinese Medicine.
- Qiao, Y., Zhang, J.C., Ma, L.L., et al., 2018. Meta-analysis of the intervention effect of traditional Chinese medicine lotus leaf preparation on lipid metabolism. *J. Integr. Trad. Chin. West. Med. Cardio-Cerebrovasc. Dise.* 16 (1), 5–11.
- Qin, P.J., Tong, X.L., 2010. Research progress on the leptin resistance mechanism of obesity. *Med. Rev.* 16 (5), 662.
- Ravussin, Y., Leduc, C.A., Watanabe, K., Mueller, B.R., Skowronski, A., Rosenbaum, M., Leibel, R.L., 2014. Effects of chronic leptin infusion on subsequent body weight and composition in mice: can body weight set point be reset? *Mol. Metabol.* 1–9.
- Reid, Ian R., Baldock, Paul A., Cornish, Jillian, 2017. Effects of leptin on the skeleton. *Endocr. Rev.* 938–959.
- Robert, V., et al., 1996. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N. Engl. J. Med.* 292–295.
- Rios, I.N.M.S., Lamarca, F., Vieira, F.T., de Melo, H.A.B., Magalhães, K.G., de Carvalho, K.M.B., Pizato, N., 2021 Aug. The positive impact of resistance training on muscle mass and serum leptin levels in patients 2-7 Years post-roux-en-Y gastric bypass: a controlled clinical trial. *Obes. Surg.* 31 (8), 3758–3767. Epub 2021 May 26.
- Russo, B., Menduni, M., Borboni, P., Picconi, F., Frontoni, S., 2021 May 14. Autonomic nervous system in obesity and insulin-resistance-the complex interplay between leptin and central nervous system. *Int. J. Mol. Sci.* 22 (10), 5187.
- Saad, Mohammed, F., Damani, Sidhdharth, Gingerich, Ronald L., Riad-gabriel, Maggy G., Khan, Arshad, Boyadjian, Rima, Jinagouda, Sujata D., et al., 1997. Sexual dimorphism in plasma. *Leptin Concentr.* 82 (2), 579–584.
- Saito, K., Davis, K.C., Morgan, D.A., Toth, B.A., Jiang, J., Singh, U., Berglund, E.D., Grobe, J.L., Rahmouni, K., Cui, H., 2019 Jun. Celastrol reduces obesity in MC4R deficiency and stimulates sympathetic nerve activity affecting metabolic and cardiovascular functions. *Diabetes* 68 (6), 1210–1220.
- Shao, Y.F., Zhang, P., Hu, Y.J., 2020. Effects of different phlegm-resolving methods on the expression of PPAR $\gamma$  gene in liver tissue of lipid metabolism in C57BL/6 mice with high-fat diet. *Lishizhen Med. Mater. Res.* 31 (4), 793–796.
- Sheng, Z.Y., Hu, Y.H., Liu, J., Ying, R.J., Shen, J., 2017. Clinical efficacy of Jianpi Shugan Jiangzhi Decoction in the treatment of simple obesity and its influence on leptin and adiponectin. *World Chin. Med.* 12 (3), 587–590.
- Si, F.G., Chen, R., Si, J.Q., Si, F.C., 2016. Analysis of obesity syndromes and prescriptions in traditional Chinese medicine. *Henan J. Trad. Chin. Med.* 11, 2032–2035.
- Simonds, Stephanie E., Pryor, Jack T., Cowley, Michael A., 2017. Does leptin cause an increase in blood pressure in animals and humans? *Curr. Opin. Nephrol. Hypertens.* 26 (1), 20–25.
- Song, X.W., 2019. Preventive Mechanism of Mogroside on Obese Mice Induced by High-Fat Diet. Tianjin University of Commerce, Tianjin.

- Song, J.N., Liu, D.Y., Niu, X.H., Jin, H., Li, A.H., 1995. Experimental study on the relationship between hyperlipidemia and phlegm in traditional Chinese medicine. *Chin. J. Basic Med. Trad. Chin. Med.* 1, 49–51.
- Song, Q.L., Jiang, P., Zhang, J.Q., Lin, H.Q., Jiang, Y.H., Li, X., 2015. Regulating effects of spleen-tonifying and spleen-enhancing drugs on diet-induced leptin resistance in obese rats. *Lishizhen Med. Mater. Med. Res.* 1, 1–3.
- Sun, C.G., 2014. On the weight loss and lipid-lowering effects of lotus leaves. *Clin. Res. Trad. Chin. Med.* 6 (3), 100–102.
- Sun, Y., Jin, C., Zhang, X., Jia, W., Le, J., Ye, J., 2018. Restoration of GLP-1 secretion by Berberine is associated with protection of colon enterocytes from mitochondrial overheating in diet-induced obese mice. *Nutr. Diabetes* 8 (1), 53.
- Swieten, M.M.H., Van, R., Pandit, Adan, R.A.H., Van Der Plasse, G., 2014. The neuroanatomical function of leptin in the hypothalamus. *J. Chem. Neuroanat.*
- Talukdar, Saswata, Oh, Da Young, Bandyopadhyay, Gautam, Li, Dongmei, Xu, Jianfeng, McNelis, Joanne, Lu, Min, et al., 2012. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. *Nat. Med.* 18 (9), 1407–1412.
- Tamborlane, William V., Barrientos-Pérez, Margarita, Fainberg, Udi, Frimer-Larsen, Helle, Hafez, Mona, Hale, Paula M., Jalaludin, Muhammad Y., et al., 2019. Liraglutide in children and adolescents with type 2 diabetes. *N. Engl. J. Med.* 381 (7), 637–646.
- Torres-fuentes, Cristina, Schellekens, Harriët, Dinan, Timothy G., Cryan, John F., 2017. Review the microbiota – gut – brain Axis in obesity. *Lancet* 2 (10), 747–756.
- Tran, N.K.S., Kim, G.T., Park, S.H., Lee, D., Shim, S.M., Park, T.S., 2019. Fermented cordyceps militaris extract prevents hepatosteatosis and adipocyte hypertrophy in high fat diet-fed mice. *Nutrients* 11, 5.
- Tremaroli, Valentina, Karlsson, Fredrik, Werling, Malin, Marcus, Ståhlman, Kovatcheva-Datchary, Petia, Olbers, Torsten, Fändriks, Lars, Carel, W., Le Roux, Nielsen, Jens, Bäckhed, Fredrik, 2015. Roux-En-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. *Cell Metabol.* 22 (2), 228–238.
- Trøseid, Marius, Nestvold, Torunn K., Rudi, Knut, Thoresen, Hanne, Nielsen, Erik W., Lappgård, Knut T., 2013. Plasma lipopolysaccharide is closely associated with glycemic control and abdominal obesity: evidence from bariatric surgery. *Diabetes Care* 36 (11), 3627–3632.
- Tung, N.H., Nakajima, K., Uto, T., et al., 2017. Bioactive triterpenes from the root of *Salvia miltiorrhiza bunge*. *Phytother. Res.* 31 (9), 1457–1460.
- Visconti, Alessia, Caroline, Li, Le Roy, Rosa, Fabio, Rossi, Niccolò, Martin, Tiphaine C., Mohney, Robert P., Li, Weizhong, et al., 2019. Interplay between the human gut microbiome and host metabolism. *Nat. Commun.* 10 (1).
- Wang, X.Y., 2018. Effect of modified cangfudaotan decoction on sex hormone level and conception rate in patients with obese polycystic ovary syndrome. *Jilin J. Trad. Chin. Med.* 38 (4), 421–425.
- Wang, X.L., 2019. Turbidity" and "blood turbidity. *Tianjin Trad. Chin. Med.* 9, 833–838.
- Wang, Z.Y., 2019. Study on the Effect and Mechanism of lotus Seed Combined with Phenol on Lipid Metabolism of 3T3-L1 Cells and Obese Mice [D]. Fujian Agriculture and Forestry University, Fuzhou.
- Wang, X., Yang, Z., Xue, B., Shi, H., 2011 Mar. Activation of the cholinergic antiinflammatory pathway ameliorates obesity-induced inflammation and insulin resistance. *Endocrinology* 152 (3), 836–846.
- Wang, X., Ge, A., Cheng, M., Guo, F., Zhao, M., Zhou, X., Liu, L., Yang, N., 2012. Increased hypothalamic inflammation associated with the susceptibility to obesity in rats exposed to high-fat diet. *Exp. Diabetes Res.* 2012, 847246.
- Wang, J., Wang, Q., Li, L., Li, Y., Zhang, H., Zheng, L., Yang, L., Zheng, Y., Yang, Y., Peng, G., Zhang, Y., Han, Y., 2013. Phlegm-dampness constitution: genomics, susceptibility, adjustment and treatment with traditional Chinese medicine. *Am. J. Chin. Med.* 41 (2), 253–262.
- Wang, J.H., Bose, S., Kim, G.C., Hong, S.U., Kim, J.H., Kim, J.E., Kim, H., 2014 Jan 24. Flos *Lonicera* ameliorates obesity and associated endotoxemia in rats through modulation of gut permeability and intestinal microbiota. *PLoS One* 9 (1), e86117.
- Wang, C.C., Yen, J.H., Cheng, Y., et al., 2017a. Polygal tenuifolia extract inhibits lipid accumulation in 3T3 - L1 adipocytes and high - fat diet - induced obese mouse model and affects hepatic transcriptome and gut micro- biota profiles. *Food Nutr. Res.* 61 (1), 40–43.
- Wang, R., Zang, P., Chen, J., et al., 2018. Gut microbiota play an essential role in the antidiabetic effects of rhein. *Evid. Based Compl. Alternat. Med.* 2018, 6093282.
- Wang, X.T., Gong, Y., Zhou, B., et al., 2018. Ursolic acid ameliorates oxidative stress, inflammation and fibrosis in diabetic cardiomyopathy rats. *Biomed. Pharmacother.* 97, 1461–1467.
- Wang, Y., Wang, C., Wang, S.h., Li, X.J., 2018. Analyze the prescription of traditional Chinese medicine for weight loss from the perspective of patent literature. *J. Tradit. Chin. Med.* 46 (6), 83–88.
- Wang, Y.F., Sun, M.X., Xue, H., et al., 2019. Interpretation of "the blue book of obesity prevention and control in China" and recommendations for obesity prevention and control measures in China. *China J. Prevent. Med.* 53 (9), 875–883.
- Wang, Z., do Carmo, J.M., da Silva, A.A., Bailey, K.C., Aberdein, N., Moak, S.P., Hall, J.E., et al., 2019. Role of SOCS3 in POMC neurons in metabolic and cardiovascular regulation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 316 (4), R338–R351.
- Wang, Y., Tang, C., Tang, Y., Yin, H., Liu, X., 2020. Capsaicin has an anti-obesity effect through alterations in gut microbiota populations and short-chain fatty acid concentrations. *Food Nutr. Res.* 64.
- Wang, Z.Y., Jiang, Z.Y., Xiao, P.T., et al., 2020. The mechanisms of baicalin ameliorate obesity and hyperlipidemia through a network pharmacology approach. *Eur. J. Pharmacol.* (prep).
- Wang, J.H., Kim, B.S., Han, K., Kim, H., 2017. Ephedra-treated donor-derived gut microbiota transplantation ameliorates high fat diet-induced obesity in rats. *Int. J. Environ. Res. Publ. Health* 14, 6.
- Wang, D.J., Li, L.K., Zhang, H., 2017. Effect of Jiawei erchen decoction on polycystic ovarian changes, endocrine and metabolism in patients with polycystic ovary syndrome of kidney deficiency and phlegm-dampness type. *Chinese Journal of Experimental Traditional Chinese Medicine* 23 (24), 190–195.
- Wen, L., Liu, S.L., Mei, G.Q., 2008. Study on the distribution of TCM clinical syndromes and the law of syndrome differentiation of hyperlipidemia. *Chin. J. Basic Med. Trad. Chin. Med.* 3, 220–221.
- Wu, S., 2016. Based on the Leptin-Mediated Hypothalamic JAK2/STAT3 Pathway to Explore the Mechanism of Jiawei Banxiaibaizhu Tianma Decoction to Improve Obesity Hypertension. Shandong University of Traditional Chinese Medicine.
- Wu, W.M., 2016. Observation of the Clinical Efficacy of Fangfengtongsheng Pills in the Treatment of Simple Obesity and its Influence on LP and APN. Heilongjiang University of Traditional Chinese Medicine.
- Wu, J.Y., Zhou, J.W., Gao, M., Tang, L.M., 2015. Effect of Shugan Jianpi Xiezhuo Recipe on serum adiponectin and leptin in patients with non-alcoholic fatty liver. *Zhejiang J. Trad. Chin. Med.* 6, 399–400.
- Wu, H., Gao, Y., Shi, H.L., Qin, L.Y., Huang, F., Lan, Y.Y., Zhang, B.B., Hu, Z.B., Wu, X.J., 2016a. Astragaloside IV improves lipid metabolism in obese mice by alleviation of leptin resistance and regulation of thermogenic network. *Sci. Rep.* 6, 30190. PMID: 27444146; PMCID: PMC4957129.
- Wu, S., Jiang, Y.H., Yang, C.H., Meng, X.Q., Hao, D., Qi, Y.Z., 2016b. Establishment and evaluation of hypertensive rat model with excessive accumulation of phlegm-dampness syndrome. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 36 (2), 222–228. Chinese. PMID: 27079001.
- Wu, Y., Huang, X.-F., Bell, C., Yu, Y.Y., 2018. Ginsenoside Rb1 improves leptin sensitivity in the prefrontal cortex in obese mice. *CNS Neurosci. Ther.* 24 (2), 98–107.
- Wu, N., Mao, X.K., Xu, K., Yu, N., Liu, Z.Y., 2020. Based on network pharmacology and molecular docking to study the molecular mechanism of Jianpi Huazhuo Tiaozi granules in the treatment of non-alcoholic fatty liver. *Chin. J. Trad. Chin. Med.* 1, 261–262, 57–60.
- Xiong, W.T., Liao, J.B., Yang, Z.X., Wang, H.W., 2021. Effects of lotus leafine on intestinal flora and chronic inflammation in obese model mice. *China J. Chin. Mater. Med.* 46 (8), 2104–2111.
- Xu, R.T., 1995. Basic research on the weight loss effect of Fangfeng Tongsheng Powder: the activation of brown adipose tissue in obese mice. *Foreign Med. (Trad. Chin. Med. Vol.)* 3, 33–34.
- Yang, J.R., 2008. Intervention study of Astragalus on obesity caused by arcuate nucleus damage in rats. *Tianjin Trad. Chin. Med.* 3, 239–240.
- Yang, S.Q., Chen, G.H., Deng, W., 2015. Effects of Xuefu Zhuyu and Erchen Decoction on the content of visceral fat and other adipokines in obese rats. *J. Beijing Univ. Trad. Chin. Med.* 38 (2), 104–110.
- Yanovski, Jack A., 2018. Obesity: trends in underweight and obesity - scale of the problem. *Nat. Rev. Endocrinol.* 157.
- Yasuo, Morimoto, Michiko, Sakada, Ohno, Akiko, et al., 2001. The effect of the body fat accumulation of furutsu load latto and fangfeng tongsheng san. *J. Japan. Pharmacol.* 117 (1), 77–86.
- Ye, L., Jia, G., Li, Y., Wang, Y., Chen, H., Yu, L., Wu, D., 2021 Jul 18. C1q/TNF-related protein 4 restores leptin sensitivity by downregulating NF-κB signaling and microglial activation. *J. Neuroinflamm.* 18 (1), 159. PMID: 34275474; PMCID: PMC8286609.
- Yin, Y., Liu, Z., C., Xu, B., Lu, S.F., 2016. Analysis of 1528 cases of obesity complicated by hyperlipidemia in TCM syndromes and etiology and pathogenesis. *Lishizhen Med. Mater. Med.* 27 (11), 2673–2675.
- You, H., Zhang, T., Feng, W., Gai, Y., 2017 Sep 11. Association of TCM body constitution with insulin resistance and risk of diabetes in impaired glucose regulation patients. *BMC Compl. Alternative Med.* 17 (1), 459.
- You, H., Lin, Z.W., Qu, S., 2020. The regulation and mechanism of hypothalamic inflammation on obesity. *Chin. J. Endocrinol. Metabol.* (2), 165–169.
- Yu, C., Shen, B., Xu, S.W., Xu, L.L., Qi, L.Y., Wang, Y.W., Xu, Y.P., 2018a. Investigation and analysis of traditional Chinese medicine constitution of 175 patients with simple obesity in Pinggu District, Beijing. *Guangming Trad. Chin. Med.* 33 (8), 1068–1070.
- Yu, T.T., Wang, J.X., Zheng, S.X., Hu, S.L., Bao, C.G., Shan, D.H., 2018b. To explore the biological mechanism of the method of strengthening the spleen and resolving phlegm based on the JAK2/STAT3 pathway of small intestinal mucosal cells. *Liaoning J. Trad. Chin. Med.* 9, 1805–1808.
- Yu, S.R., Bai, Y., Wang, H.B., Shu, Q., Yao, Q., Zhou, L., Wang, P., Cheng, S.M., Jian, H., 2019. Effects of Wendan Decoction on the expression of serum leptin and hypothalamic STAT3 and SOCS3 in obese rats. *J. Tradit. Chin. Med.* 60 (3), 232–236.
- Yu, Keping, Li, Li, Zhang, Lan, Guo, Li, Wang, Chengjian, 2020. Association between MC4R Rs17782313 genotype and obesity: a meta-analysis. *Gene* 733 (312).
- Yue, J., Chang, Y.Q., Lin, M.L., Zheng, T.Z., 2016. The effect of Danshen on ovarietomized obese rats. *J. Tradit. Chin. Med.* 29 (4), 63–66.
- Yue, S.J., Liu, J., Wang, A.T., et al., 2019. Berberine alleviates insulin resistance by reducing peripheral branched-chain amino acids. *Am. J. Physiol. Endocrinol. Metab.* 316 (1), 73–85.
- Zhang, Z., Hu, J., 2016. Recent advances and perspective of studies on phlegm syndrome in Chinese medicine. *Evid. Based Compl. Alternat. Med.* 2016, 6463270.
- Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., Friedman, J.M., 1994. Positional cloning of the mouse obese gene and its human homologue. *Nature* 372 (12), 425–432.
- Zhang, L., Zhang, Q., You, Y., Zhou, M.X., Wang, L.H., Chen, H.B., Yan, X.Z., Liu, X.Z., Liu, W.H., 2015 Jul. Investigation of evolution rules of phlegm and blood stasis syndrome in hyperlipidemia and ath- erosclerosis by NMR-based metabolic profiling and metabolonomic approaches. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 35 (7), 823–833.
- Zhang, Y.P., Yang, Q.H., Deng, Y.J., Han, L., Jin, L., Kong, Y.L., He, Y.F., Liang, Y.J., 2016. Effects of Shenlingbaizhu Powder on the ultrastructure of liver tissue and AMPKα

- phosphorylation in NAFLD rats induced by high-fat diet. *Pharmacol. Clin. Chin. Med.* 1, 6–10.
- Zhang, C., Liu, J., He, X., et al., 2019. *Caulis spatholobi* ameliorates obesity through activating Brown adipose tissue and modulating the composition of gut microbiota. *Int. J. Mol. Sci.* 20, 20.
- Zhang, M., Zhao, J., Deng, J., Duan, Z., Zhu, C., Fan, D., 2019. The protective effect of protopanaxatriol-type saponin on intestinal health in antibiotic-treated mice. *Food Funct.* 10 (7), 4124–4133.
- Zhang, T., Zhao, Q., Xiao, X., Yang, R., Hu, D., Zhu, X., Gonzalez, F.J., Li, F., 2019 Mar 1. Modulation of lipid metabolism by celastrol. *J. Proteome Res.* 18 (3), 1133–1144.
- Zhang, X.Z., Bai, X.G., Dai, Y.N., Ren, Y.Z., Huang, J.J., Wang, D., Wang, Y., He, Y.Y., 2019. Analysis of the mechanism of action of "Atractylodes-Poria" based on network pharmacology. *Clin. Med. Res. Prac.* 15, 1–3+7.
- Zhang, M., Shao, Y., Gao, B., Chen, J., Zhang, P., Hu, Y., Ding, S., 2020 Mar 10. Erchen decoction mitigates lipid metabolism disorder by the regulation of PPAR $\gamma$  and LPL gene in a high-fat diet C57bl/6 mice model. *Evid. Based Compl. Alternat. Med.* 2020, 9102475.
- Zhao, F., Liu, W.J., Chen, W.R., Zhao, J.R., Wang, S.Y., Shan, D.H., 2018. Study on the mechanism of the method of invigorating the spleen and eliminating phlegm based on the JAK2/STAT3 pathway of colonic mucosa. *China J. Trad. Chin. Med. Pharm.* 6, 1411–1413.
- Zhou, H., 2017. Study on the Mechanism of Regulating Lipid Metabolism and Leptin Resistance in Simple Obese Rats by Warming the Kidney, Strengthening the Spleen and Resolving Phlegm. Hubei University of Traditional Chinese Medicine.
- Zhou, H.M., Xiang, N., Hu, X., 2015. Analysis of clinical syndromes and treatment of simple obesity with traditional Chinese medicine based on CNKI in the past 10 years. *Hubei J. Trad. Chin. Med.* 9, 69–71.
- Zhou, X.P., Feng, Z., Zhou, L.L., 2018. Exploring the compounding and toxicity reduction of Leigongteng based on the theory of "heterogeneous phase control". *Chin. Med. Miscell. J. Trad. Chin. Med.* 59 (9), 725–727. +732.
- Zhou, P., Xie, W., He, S., et al., 2019. Ginsenoside Rb1 as an anti-diabetic agent and its underlying mechanism analysis. *Cells* 8 (3), 204.
- Zhu, B.R., Zhan, L.B., 2019a. Exploring the material basis and mechanism of Erchen Decoction for preventing and treating obesity based on the integrated pharmacology platform of Chinese medicine. *Chin. Pharmaceut. J.* 7, 536–541.
- Zhu, B.R., Zhan, L.B., 2019b. Based on the integrated pharmacology platform of traditional Chinese medicine to explore the material basis and mechanism of the prevention and treatment of obesity by Erchen Decoction. *Chin. Pharmaceut. J.* 7, 536–541.
- Zhu, Q., Li, G., i, X., Zeng, L., et al., 2022. Effects of Polygonatum odoratum polysaccharides on obesity and non-alcoholic fatty liver in rats induced by high-fat diet. *Chin. Patent Med.* 1–6.
- Zhu, H.-J., Wang, L.-J., Wang, X.-Q., et al., 2014. Hormone-sensitive lipase is involved in the action of hydroxysafflor yellow A (HYSA) inhibiting adipogenesis of 3T3-L1 cells. *Fitoterapia* 93, 182–188.
- Zou, D.J., 1999. *Practical Clinical Obesity*, first ed. China Medical Science and Technology Press, Beijing, p. 71.
- Banks, W.A., 2021. Leptin and the Blood-Brain Barrier: Curiosities and Controversies. *Compr. Physiol.* 11 (4), 2351–2369.
- Bray, N., 2015. Obesity: Reversing resistance to leptin in obesity. *Nat. Rev. Drug Discov.* 14 (7), 458–459.
- Chen, N., Zhang, Q., Du, Y., et al., 2006. Pharmacokinetics and tissue distribution of astragaloside IV in rats. *Chinese J. Bioprocess Eng.* 67–72.
- Cohen, B., Barkan, D., Levy, Y., et al., 2001. Leptin induces angiopoietin-2 expression in adipose tissues. *J. Biol. Chem.* 276 (11), 7697–7700.
- Friedman, J.M., Halaas, J.L., 1998. Leptin and the regulation of body weight in mammals. *Nature* 395 (6704), 763–770.
- Greenhill, C., 2015. Celastrol identified as a leptin sensitizer and potential novel treatment for obesity. *Nat. Rev. Endocrinol.* 11 (8), 444.
- Han, M.H., Jeong, J.S., Jeong, J.W., et al., 2017. Ethanol extracts of *Aster yomena* (Kitam.) Honda inhibit adipogenesis through the activation of the AMPK signaling pathway in 3T3-L1 preadipocytes. *Drug Discov. Ther.* 11 (5), 281–287.
- Hayashi, H., Hattori, S., Inoue, K., Sarsenbaev, K., Ito, M., Honda, G., 2003. Field survey of *Glycyrrhiza* plants in Central Asia (1). Characterization of *G. uralensis*, *G. glabra* and the putative intermediate collected in Kazakhstan. *Biol. Pharm. Bull.* 26 (6), 867–871.
- Jiang, D.N., et al., 2020. Evaluation of the efficacy of cupping in the treatment of overweight obese patients with phlegm-damp constitution and the effect on serum leptin. *Zhejiang J. Trad. Chinese Med.* 55 (01), 31–32.
- Jiang, N., Su, H., Wu, X., Shen, H., Kim, M.H., Li, Y., Myers Jr., M.G., Owyang, C., Rui, L., 2020. Leptin receptor-expressing neuron Sh2b1 supports sympathetic nervous system and protects against obesity and metabolic disease. *Nat. Commun.* 11 (1), 1517.
- Kolbeck, R., Bartke, Eberle, W., Barde, Y.A., 1999. Brain-derived neurotrophic factor levels in the nervous system of wild-type and neurotrophin gene mutant mice. *J. Neurochem.* 72 (5), 1930–1938.
- Ma, X., Xu, L., Alberobello, A.T., 2015. Celastrol protects against obesity and metabolic dysfunction through activation of a HSF1-PGC1  $\alpha$  transcriptional axis. *Cell Metab.* 22 (4), 695–708.
- Patapoutian, A., Reichardt, L.F., 2001. Trk receptors: mediators of neurotrophin action. *Curr. Opin. Neurobiol.* 11 (3), 272–280.
- Zhu, Q., Li, G.X., Zeng, L., Wu, S.Q., 2021. Effects of polysaccharides of yucca on high-fat diet-induced obesity and nonalcoholic fatty liver in rats. *Chinese Patent Med.* 43 (06), 1612–1617.