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REVIEW

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Exploring the Potential of Lotus Leaf and Its Bioactive Compounds for Anti-obesity Interventions

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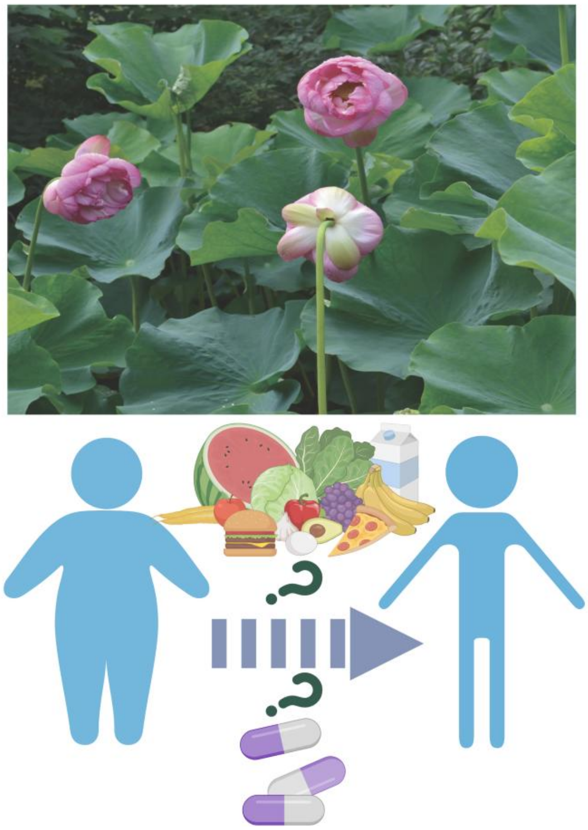
Abstract

The complex syndrome of obesity is a complex syndrome associated with various metabolic disorders, poses significant threats to human health. Many weight loss medications have the potential to rapidly treat obesity, however their toxicity and adverse effects may compromise patients' physiological and psychological well-being. In China, the concept of drug and food homology has been utilized for thousands of years, with lotus leaves serving as a representative example. The lotus leaves have been traditionally used for heat-clearing and lipid-lowering purposes, as well as for cooling the blood and promoting hemostasis, since ancient times. This review represents the first attempt to qualitatively investigate the anti-obesity properties of lotus leaves by integrating gene-disease association databases and drug-target databases for analysis. Additionally, it summarizes the identified monomers in lotus leaves that have been reported to possess functions associated with anti-obesity. The aim of this study is to provide a comprehensive review of the research progress on anti-obesity drugs derived from lotus leaves, and to facilitate further research and development in the field of anti-obesity medication targeting adiposity.

Graphic Abstract



Introduction

Obesity is a kind of heterogeneous syndrome. The occurrence of obesity is associated with a variety of metabolic syndrome, including diabetes, liver steatosis, cardiovascular disease, etc [1,2]. According to the latest data from the Report on the Nutrition and Chronic Diseases Status of Chinese Residents (2020), more than half of Chinese adults are overweight or obese, of which 34.3% are overweight and 16.4% are obese (≥ 18 years of age) [3]. In this nationwide survey, the proportion exceeded 50% for the first time. Obesity is closely related to the development of three high disease (hypertension, hyperlipidemia, hyperglycemia), atherosclerosis and other diseases, as well as the decline of heart function, which seriously threatens human health.

According to the pathogenesis and clinical development process, obesity can be classified as primary obesity, also known as simple obesity; And secondary obesity, also known as symptomatic obesity [4,5]. Among them, simple obesity often arises from an overconsumption of calories. For example, a lack of dietary regulation and the consumption of high-fat or calorie-dense foods can lead to the accumulation of adipose tissue, while excessive eating may also contribute to its development. However, if simple obesity is not addressed with due seriousness, it may progress into secondary obesity. Clinical research primarily focused on secondary obesity which is predominantly related to hormone imbalance. According to literature research, this paper categorized obesity into hyperinsulinemic obesity [6], Cushing syndrome obesity [7], hypothalamic obesity [8], hypothyroid obesity [9], and polycystic ovary syndrome based on their respective pathogenesis and pathogenic sites [10]. Secondary obesity is mainly caused by abnormal endocrine metabolism. Hyperinsulinemic obesity results from excessive insulin secretion in terms of hormone metabolism [11], while Cushing's syndrome-related obesity stems from overproduction of glucocorticoids [12]. Hypothyroidism-induced obesity is linked to the disorder of glucose metabolism [13], and hypothalamic obesity arises due to damage to the satiety and feeding centers, leading to an abundance of glucose-sensing neurons and various neuropeptide receptors in the satiety center [14,15]. These neurons are involved in the regulation of energy balance and the metabolism of substances such as melanin and glutamic acid produced by the central nervous system [16,17]. Additionally, polycystic ovary syndrome is characterized by excessive androgen activity or hyperandrogenism [18,19].

The classification, symptomatology, and underlying mechanisms of obesity are delineated in Table 1. Although diet pills have certain effects on weight loss, prolonged use may result in adverse side effects. Over the past few decades, numerous weight-loss pills have been withdrawn from the market due to their cardiotoxicity. In recent years, although many diet pills have played a certain role in the short-term treatment of obesity, they also exert significant impacts on patients' physical and mental health. For instance, Orlistat Capsules, as a typical weight loss product in the market, prevent fat absorption by inhibiting gut enzymes that absorb fat [20,21]. However, this has been confirmed to cause adverse reactions such as diarrhea, abdominal pain and liver toxicity. A clinical study assessing drug has demonstrated that weight-loss medications, such as Lorcaserin, may elevate the risk of cancer [22,23].

In China, there has been a long-standing belief that food and medicine share the same origin [24,25]. This implies that many foods possess dual properties of both nourishment and healing. The homologous function of medicine and food aligns with the modern concept of nutritional immunology, encompassing four key aspects: 1) balancing the human body and regulating endocrine glands to promote normal endocrine function; 2) providing a natural cleansing effect; 3) supplying vitamins, minerals, and other essential nutrients; and 4) furnishing the immune system with vital nourishment.

According to the principles of traditional Chinese medicine, lotus leaves are characterized as having a flat nature and bitter taste, and they affect the liver, spleen, stomach, and heart meridians. Its effects include clearing summer-heat and dampness, promoting lucid yang energy, cooling blood, and stopping bleeding. In dietary therapies such as winter melon lotus leaf tea, lotus leaf purple cabbage soup, lotus leaf chicken and lotus leaf rice, the small molecules of lotus leaf can effectively penetrate into the food to achieve its desired effect of clearing heat and reducing fat. Lotus leaves are widely distributed in ponds, lakes, and paddy fields throughout North and South China. The phrase "out of the mud and not dyed" is commonly used to praise the lotus, but few know that its true essence lies within the lotus leaf. According to historical records, lotus leaves have been utilized for medicinal purposes in China for over 2,000 years. During the Qin and Han dynasties, they were first employed as a tonic medicine. Meanwhile, lotus leaf is also considered a weight loss aid among the populace. The lipid-lowering effects of lotus leaves have been documented in numerous ancient texts, such as the Compendium of Materia Medica, which states that "lotus leaves generate Yang qi, reduce fat and promote weight loss." In Qing Dynasty's "Materia Medica Truth-seeking" it is noted that "consuming more lotus leaves will lead to slimming and toning," indicating that increased consumption of lotus leaves can result in weight reduction.

The lotus leaf and its derivatives have been documented in contemporary scientific research for their potential to exert anti-obesity effects [26]. Among them, the study revealed that the fermentation supernatant of lotus leaf inhibited adipogenesis in 3T3-L1 preadipocytes induced by a high-fat diet in obese rats, thereby exerting an inhibitory effect on obesity [27]. Additionally, it has been reported that lotus leaf extract exhibits anti-obesity effects in obese mice fed a high-fat diet [28]. Furthermore, the study also investigated the impact and mechanism of ethanol extract from lotus leaf on intestinal microbiome and obesity in rats with a high-fat diet [29].

Therefore, in order to facilitate more profound and comprehensive investigation and exploration into the anti-obesity potential of lotus leaf, as well as to further enhance its clinical applicability, it is imperative to conduct a meticulous review and synthesis of its chemical composition and pharmacological activity, thereby establishing a solid foundation for subsequent in-depth research and practical implementation.

Table 1 Types of obesity are classified based on various neuroendocrine and metabolic disorders.

Classification		Characteristics	Mechanism
Isolated obesity	Not related to endocrine system diseases	The body fat is evenly distributed	Excessive-intake;no organic disease
Secondary obesity	Hyperinsulinemic obesity	Abominal obesity	Iinsulin overproduction
	Cushing syndrome obesity	Centripetal obesity	Excess glucocorticoids secretion
	Hypothalamic obesity	A strong appetite	Disorder of melanin-concentrating hormone metabolism
	Hypothyroid obesity	Reduced systemic metabolism	Disorder of glucose metabolism
	Polycystic ovary syndrome	Abominal obesity	Excessive androgen secretion

The correlation between identified monomeric drug targets in lotus leaves and their potential role in treating obesity

We employed the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database and analysis platform to explore the chemical composition of lotus leaf [30,31]. The database revealed that 105 active ingredients have been isolated and identified in the previous researches, and subsequently, we conducted Gene Ontology (GO) analysis on the reported target genes of these compounds. The screening threshold was set at false discovery rate (FDR)<0.05, and the analysis revealed that the top 20 biological processes were primarily associated with responses to oxygen levels, carboxylic acid and organic acid biosynthesis, as well as lipid localization. The results of the GO analysis are presented in Figure 1A.

Moreover, we have identified 52 compounds out of the 105 active ingredients that exhibit an oral bioavailability (OB) greater than 20% according to the TCMSP database. We then determined the pharmacodynamic targets of these monomers and utilized disease-related databases such as GeneCards, DisGeNet, DISEASE, and OMIM to extract genes associated with obesity [32]. The extracted disease-related genes were integrated with drug targets for further analysis. The analytical procedure is illustrated in Figure 1B.

The monomer component of lotus leaf (OB>20%, based on the screening criteria established in previous research [33]) targets are 80% related to obesity, as shown in Figure 1C, indicating its potential anti-obesity function. Further investigation into the underlying mechanisms and development of health products holds significant research value.

The monomeric constituents of lotus leaf associated with obesity have been documented

Based on the ranking of oral availability of monomer components in lotus leaves, we conducted a literature review and summarized the reported active ingredients for anti-obesity related diseases with an OB greater than 20%. Furthermore, based on the classification of different types of compounds, we present our findings as follows:

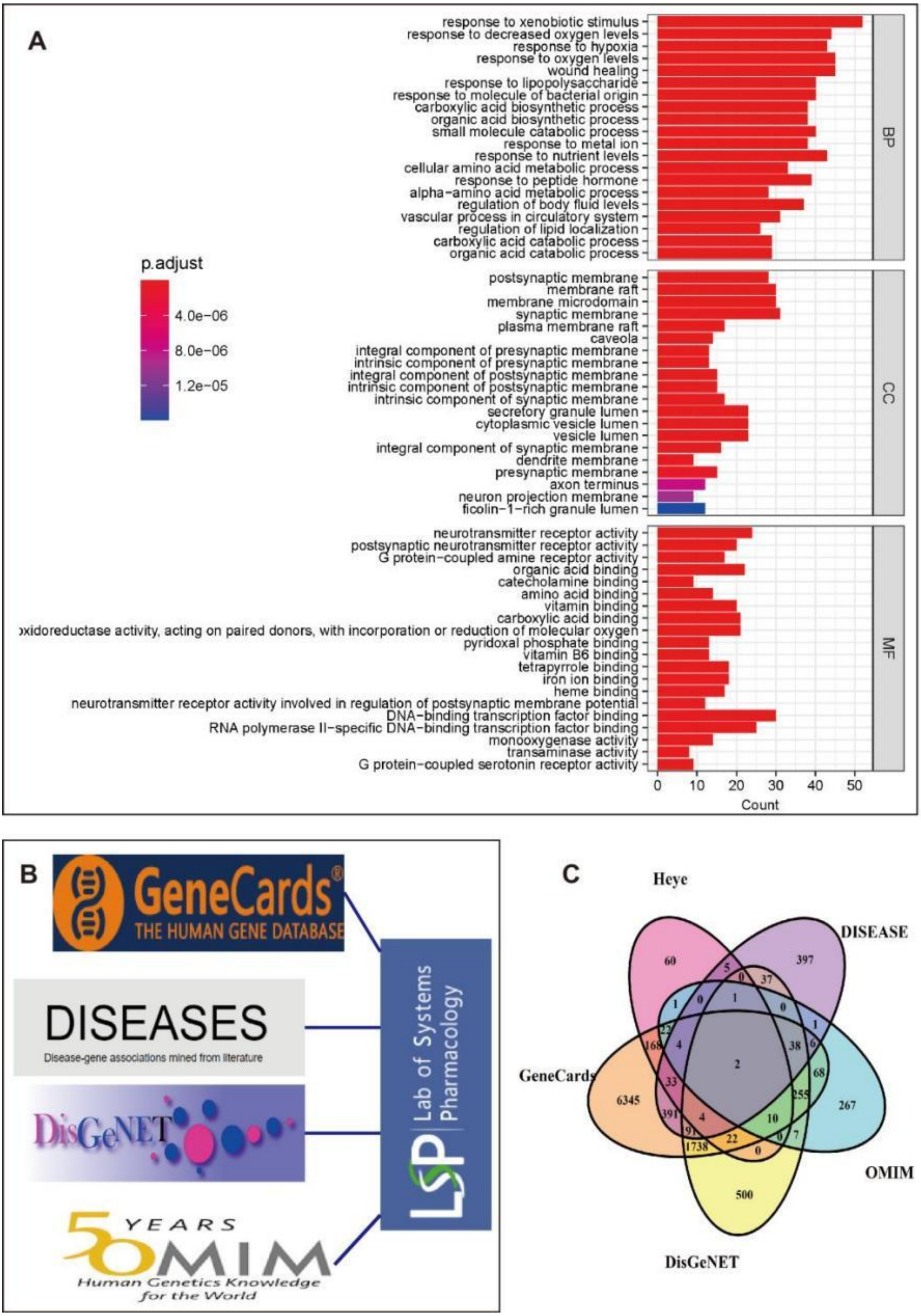


Figure 1 Integration of disease databases was conducted to analyze the correlation between drug targets of lotus leaf components with oral availability greater than 20% and obesity. **A.** Performing GO-analysis to predict the molecular functions of putative targets of lotus leaf components. **B.** The utilized databases for integrated analysis were presented. **C.** The Venn diagram demonstrated the results obtained from panel A.

Flavonoids

Flavonoids, existing in the form of flavonoid glycosides and aglycones, are a significant class of secondary metabolites in plants. They can be found in various plant species such as fruits, vegetables, legumes, and tea. Research has shown that low-density lipoprotein is detrimental to human health and may lead to coronary heart disease [34,35]. Flavonoids have been shown to inhibit the production of harmful low-density lipoprotein and reduce the formation of blood clots, leading to a lower mortality rate from coronary heart disease in individuals with high flavonoid intake [36-38]. Additionally, research suggests that the flavonoid components may effectively reduce the risk of cancers, cardiovascular diseases, gynecological disorders, metabolic disorders, musculoskeletal conditions, endocrine dysfunctions, neurological disorders, and renal complications, particularly in perimenopausal women [39].

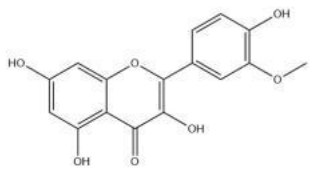
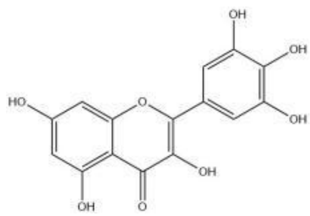
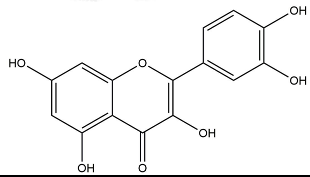
The ingredients of reported flavonoids associated with obesity in lotus leaf are presented in Table 2.

Isorhamnetin

Isorhamnetin is a flavonoid compound found in fruits and herbs, specifically as one of the components in lotus leaves. With an oral bioavailability of 49.6%, it has been shown to possess various functions such as reducing blood pressure, lowering blood lipids, decreasing blood viscosity, enhancing vascular elasticity, and exhibiting anti-atherosclerotic properties [40,41]. It can be considered a potent agent against cardiovascular and cerebrovascular diseases.

The research has demonstrated that isohamnetin can upregulate the NHR-49/PPARα pathway, which plays a crucial role in enhancing fat oxidation and reducing body fat [36,42,43]. Moreover, isorhamnetin has been found to exert its anti-inflammatory and glucose-lowering effects by modulating AMPK-GLUT4 signaling pathway in a high-fat drink induced type 2 diabetes mouse model [43,44].

Table 2 Main flavonoids with Anti-obesity activity in Folium Nelumbinis.

Chemical structure	Compound's name	Oral availability (%)	Tested animals	Molecular mechanism
	Isorhamnetin	49.5	Caenorhabditis elegans; High-fat diet-induced mice	NHR-49/PPARα -dependent pathway ; Activation of the AMPK-GLUT4 pathway
	Myricetin	13.75	High choline-fed mice ; rats	Activation of PI3K/AKT signaling pathway
	Quercetin	46.43	Wistar Rats with Diet-Induced Obesity	Inhibiting the pro-inflammatory molecules

Myricetin

Myricetin, a bioflavonoid primarily extracted from bayberry, has an oral availability of 13.75%. Numerous studies have demonstrated its various cardiovascular pharmacological effects such as anti-thrombosis, anti-myocardial ischemia, and improvement of microcirculation [45,46]. In addition, it exhibits a diverse range of pharmacological effects such as hypoglycemic, antioxidant, hepatoprotective and choleretic activities [47].

Furthermore, in the LDL oxidation experiment, myricetin was found to inhibit LDL oxidation [48]. Myricetin not only possesses pharmacological properties including anti-inflammatory, antitumor, antimutagenic and cariostatic effects as well as antioxidative and free radical scavenging activities but also exerts its maximum effect through glucose inhibition [49,50]. In vitro studies have demonstrated that myricetin reduces blood glucose levels by increasing myocyte uptake and glycogen synthesis [51,52]. The anti-obesity mechanism of Myricetin exerts has been reported to involve the upregulation of SIRT3 in adipose tissue, thereby exerting its anti-obesity effects [53]. However, the precise mechanism of action remains to be elucidated. In summary, myricetin has been shown to inhibit glucose uptake into cultured rat adipocytes.

Quercetin

Quercetin, contained in lotus leaves, exhibited an oral availability of 46.43%. In obese Wistar Rats fed with a high-fat diet and treated with quercetin, total RNA was extracted from the epididymal adipose tissue. The results showed that rats treated with quercetin lost 31% of their body weight compared to the obese control group [54]. Quercetin was also found to suppress the expression of pro-inflammatory cytokines including IL-6, IL-1β, IL-18, Lep, HiF-1α and NF-kB while leaving Socs1 and Socs3 unaffected [55]. These findings suggest that quercetin may modulate the obesity-associated inflammatory response by downregulating pro-inflammatory gene expression and altering signaling pathways.

Organic acids

Organic acids are nutritional components that exist in plants and are widely distributed in the fruits, leaves, and roots of Chinese herbs. Lotus leaves contain a plethora of organic acids. Natural organic acids, such as malic acid, can enhance human metabolism and effectively prevent obesity while playing a role in weight loss [56]. Catechuic acid has pharmacological effects including anti-tumor and anti-oxidation properties [57,58]. The abundance of organic acids found in lotus leaf confirms its efficacy in treating obesity to some extent.

Myristic acid

Myristic acid is a saturated fatty acid with therapeutic potential in traditional Chinese medicine, where it is used to promote digestion [59]. As a warm drug, its oral bioavailability has been determined to be 21.18%. Recent studies have demonstrated the efficacy of myristic acid in managing type-2 diabetes [60]. The Nagoya-Shibata-Yasuda (NSY) mice were selected as the model for Type-2 diabetes in this study, and were treated with 300mg/kg myristic acid or control agents through oral administration every other day [61]. Glucose and insulin tolerance tests were conducted at different time points, revealing that NSY male mice exhibited higher glucose tolerance levels than the control group, while their insulin-responsive blood sugar levels were lower. Meanwhile, myristic acid also decreased the body weight gain of NSY mice, indicating a strong correlation between myristic acid and insulin-obesity. However, several studies have demonstrated that myristic acid, a type of saturated fatty acid (SFA), is considered detrimental to human health as it can exacerbate adipose inflammation and systemic insulin resistance induced by a high-fat diet [62]. Therefore, further research is necessary to fully comprehend the underlying molecular mechanisms involved.

Palmitic acid

Palmitic acid, a saturated fatty acid found in various plants and animals, has an oral bioavailability of 19.31%. Studies have demonstrated that a diet high in Palmitic acid can induce elevated insulin levels in rats [63]. Furthermore, it has been discovered that palmitic acid down-regulates miR-221 expression levels, which reduces glucose uptake by HepG2 cells and inhibits the PI3K/AKT signaling pathway through binding with PI3K mRNA. Ultimately, this may prevent and treat insulin resistance induced by Palmitic acid.

Citric acid

Citric acid is a natural antiseptic and food additive with an oral bioavailability of 56.22%. Appropriate consumption of citric acid can stimulate appetite, enhance gastric juice secretion, alleviate indigestion symptoms, and improve body metabolism [64,65]. Recent experimental research has demonstrated that a mixture containing citric acid can effectively treat and prevent non-insulin dependent diabetes in mice [66]. Furthermore, it has been reported that soluble dietary fiber polyglucose [67], which also contains citric acid, may be utilized to manage and prevent obesity in HFD-fed mice. These studies have exhibited the capacity of citric acid to reduce weight levels, fasting blood glucose levels, and adipose tissue accumulation. Overall, these findings suggest that citric acid exerts a significant impact on lipid metabolism to some extent, and further investigation is warranted to elucidate the underlying molecular mechanisms.

Gallic acid

Gallic acid is widely distributed in various plants, such as swamp mahogany and dogwood. It can also be naturally extracted from sources like pomegranate, tea leaves, lotus leaves, among others. Modern pharmacological research has revealed that gallic acid exhibits multiple functions including anti-inflammatory, antioxidant, and antibacterial properties [68,69]. Recent research has demonstrated that intraperitoneal administration of gallic acid in mice with diet-induced obesity can significantly enhance their glucose tolerance and lipid metabolism [70]. Moreover, gallic acid also exhibits a certain effect on ameliorating fatty liver degeneration in mice [71]. These findings suggest that lotus leaf-derived gallic acid may hold potential therapeutic benefits for high blood glucose-dependent obesity.

The ingredients of reported Organic acids associated with obesity in lotus leaf are presented in Table 3.

Alkaloids

The lotus leaf contains a variety of alkaloids, including nuciferin, papaverine, methylaconitine, and malic acid as well as some tannins. The reduction of lipid levels and blood pressure has been documented in numerous studies.

Nuciferine

Nuciferine, the primary lipid-lowering active compound in lotus leaves, which has been reported that an active ingredient derived from lotus leaf has the potential to be used as a treatment for obesity and obesity-related diseases [72], exhibits an oral bioavailability of 34.43%.

The previous study has demonstrated that Nuciferine modulates the gut microbiota and confers protection against obesity in rats fed a high-fat diet [42]. Its anti-inflammatory properties have been attributed to its ability to inhibit p38 MAPK/ATF2 signaling pathway stimulated by Lipopolysaccharide [73].

Armepavine

Lotus leaves are abundant in Armepavine, exhibiting an oral utilization rate of 69.31%. Prior research has demonstrated that Armepavine not only possesses anti-inflammatory properties on human peripheral blood Monocyte and immunosuppressive effects on T lymphocytes and lupus nephritis mice, but also exhibits hypolipidemic effects [74,75]. In articles related to these studies, researches employed total cholesterol (TC) and total triglycerides (TG) as evaluation parameters, utilizing a hyperlipidemia model to assess the efficacy of Jiang-zhi-ning, a weight loss product containing an effective extract. The results indicated that Armepavine was one of five active components found in Jiang-zhi-ning through an "active contribution study," which preliminarily demonstrated its ability to reduce blood lipids [74,76].

The ingredients of reported alkaloids associated with obesity in lotus leaf are presented in Table 4.

Table 3 Main Organic acids with Anti-obesity activity in Folium Nelumbinis.

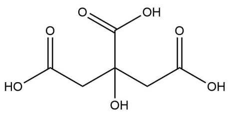
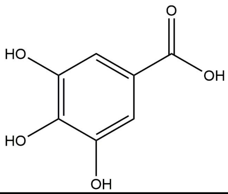
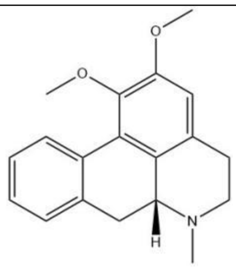
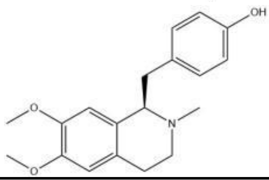
Chemical structure	Compound's name	Oral availability (%)	Tested animals	Molecular mechanism
	Myristic acid	21.18	Nagoya-Shibata-Yasuda mouse model	NA
	Palmitic acid	19.31	Sirt3-MKO mice	PI3K/AKT/GLUT4 Pathway
	Citric acid	56.22	HFD-fed mice	NA
	Gallic acid	31.69	HFD-fed mice	NA

Table 4 Main Alkaloids with Anti-obesity activity in Folium Nelumbinis.

Chemical structure	Compound's name	Oral availability (%)	Tested animals	Molecular mechanism
	Nuciferine	34.43	NA	Inhibiting the NF-κB and p38 MAPK/ATF2 signaling pathways
	Armepavine	69.31	NA	NA

Discussion

Obesity is a type of non-communicable disease that has become the leading cause of mortality, posing a significant threat to human health. In terms of physical consequences, obesity can lead to complications such as hyperlipidemia, coronary heart disease, cardiomyopathy, hematangiosis and even cancer. In terms of psychology, adolescents who suffer from obesity-induced physical limitations or difficulties are vulnerable to bullying and aggression from their peers, leading to social disengagement and feelings of self-deprecation. In severe cases, this may even result in the development of autism spectrum disorder. Even for adults, the dilemma caused by obesity in terms of job opportunities loss, family and economy can lead to psychological distress, ultimately resulting in resentment towards society and posing a danger to both oneself and others.

Based on the aforementioned negative effects of obesity, weight loss is imperative for all individuals and a variety of weight loss medications have been developed in the past. These weight loss medications contain fenfluramine, a catecholamine, as well as naltrexone, an opioid antagonist, and serotonin receptor agonists that aim to promote weight loss by activating metabolism, suppressing hyperactive appetite, and reducing fat absorption in the gastrointestinal tract. While drugs that have appetite suppression functions are commonly used to treat obesity caused by bulimia, their significant impact on vice function means they should not be prescribed for the general population.For instance, the administration of fenfluramine may readily induce insomnia, thirst, and constipation, while that of naltrexone may easily lead to nausea, vomiting, and headache.

The use of drugs and food in traditional Chinese medicine has a long history, as recorded in Huangdi's Inner Classic [77,78]: "Food is used to satisfy hunger, while medicine is used to treat illness." In the earliest pharmacology monograph, Shennong's Herbal Classic, many common foods were classified as top-grade medicines, indicating that there is no clear boundary between food and medicine. A substance with the same origin as medicine and food possesses the essence of edible Chinese medicinal materials, exhibiting dual functionality in both medicine and cuisine. Its primary function is that of a food rather than a drug.They are primarily reinforcing drugs that serve the functions of recuperation, rehabilitation, and healthcare. These drugs are commonly used in healthcare as part of food therapy, dietary supplementation, and herbal cuisine. According to traditional Chinese medicine, obesity is closely related to one's innate constitution and dietary habits. Patients with this condition tend to be sedentary and averse to physical exercise. The therapy methods utilize the principles of tonifying deficiencies and draining excesses, as well as promoting qi and eliminating phlegm, dissolving water, eliminating fu-organs, removing blood stasis, etc., based on syndrome differentiation and treatment [79,80]. Ultimately, these methods regulate the deficiency of Zang-fu Qi blood Yin and Yang. As previously mentioned in both theoretical and practical experiences of Chinese medicine, the utilization of medicinal and dietary sources from the same origin is recommended for preventing and treating obesity.

The lotus leaf possesses primary functions such as heat-clearing, promoting defecation, strengthening the spleen, and enhancing Yang energy. Furthermore, it has a history of thousands of years in China as an effective aid for weight loss, representing the harmonious integration of medicine and food. In this study, we utilized multiple databases to integrate and analyze the targets of lotus leaf associated with obesity-related targets, ensuring that approximately 80% of the identified targets in lotus leaf are related to obesity. This finding confirms the traditional usage experience of lotus leaf for weight loss in China over many years. Next, we conducted an analysis and ranking of the active components in lotus leaf based on their oral bioavailability, and combined this with a thorough literature search to summarize the reported active components with anti-obesity properties.

Through our research on the aforementioned components, we have discovered numerous compounds with superior anti-obesity properties. For instance, certain alkaloids possess a clear anti-obesity function, while flavonoids and organic acids have also been reported to exhibit such effects. However, the molecular mechanisms underlying these active weight loss components remain unclear, and there are still numerous bioactive components that have yet to be explored, as is the case with other Chinese medicines [81,82]. The field of Chinese herbal medicine offers a wide range of research opportunities, providing valuable inspiration for future studies. Thorough investigation will be necessary for future research.

Conclusion and prospect

The lotus leaf, a renowned traditional Chinese medicine, has been extensively researched in recent decades due to its multifaceted biological activities, particularly its anti-obesity potential. It contains several exceptional monomers and extracts that demonstrate significant anti-obesity effects. However, the majority of existing research on its mechanism of action lacks systematic approaches such as multi-omics investigations, impeding its widespread application and promotion in this field. The present paper provides the first review of the anti-obesity effect of lotus leaf monomer component, which holds significant reference value for further exploration into healthy dietary practices.

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Conflicts of Interest

The authors declare that they have no competing interests.

Author Contributions

Yuwei Liu: Conceptualization, Methodology, Lei Chen, Xinyi Zhang:Writing - Original draft and Editing. Yuwei Liu and Wei Zhang, Writing - Reviewing and Editing. Yuwei Liu and Wei Zhang: Supervision.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

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Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

Supplementary Materials

Not applicable

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