Electronic Journal of Biotechnology 71 (2024) 1–9

Contents lists available at ScienceDirect

Electronic Journal of Biotechnology

journal homepage: www.elsevier.com/locate/ejbt

Research article

Efficacy of powder of ginsengporia and atractylodis macrocephalae combined with aerobic exercise in the treatment of obese T2DM: A randomized controlled clinical trial ☆

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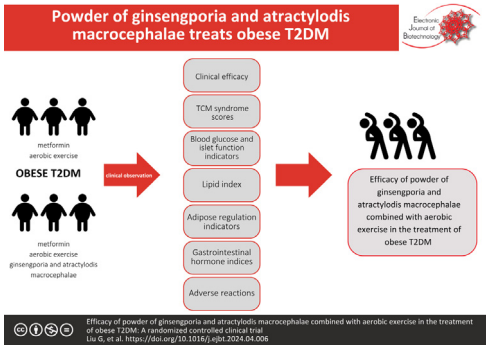
GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 27 November 2023
Accepted 29 April 2024
Available online 6 June 2024

Keywords:
Aerobic exercise
Atractylodis macrocephalae
Chinese medicine
Glucose metabolism
Lipid metabolism
Obese T2DM
Powder of ginsengporia

ABSTRACT

Background: To explore the efficacy of powder of ginsengporia and atractylodis macrocephalae combined with aerobic exercise in the treatment of obese T2DM and its influence on glucose and lipid metabolism indices.

Results: Both groups of patients were given metformin drug treatment. The control group was given aerobic exercise intervention, and the observation group was given ginsengporia and atractylodis macrocephalae on the basis of the control group. The total effective rate of the observation group (95.74%) was higher than that of the control group (82.98%) ($P < 0.05$). After treatment, the main symptoms of the observation group were less ($P < 0.05$), such as thirst and lack of desire to drink, fatigue, loss of appetite, limb numbness and tingling, sticky stool, scanty dark urine, and lower total score. FPG, 2hPG, and HbA1c were lower ($P < 0.05$), FINS, HOMA-IR, and HOMA-β were higher ($P < 0.05$), TG, TC, and LDL-C were lower, and HDL-C levels were higher in the observation group ($P < 0.05$). After treatment, Nesfatin-1 and adiponectin were lower, visfatin and leptin were higher ($P < 0.05$), and GIP and GLP-1 levels were higher in the observation group ($P < 0.05$). No significant difference was found in the incidence of adverse reactions between the two groups ($P > 0.05$).

☆ Audio abstract available in Supplementary material.

Peer review under responsibility of Pontificia Universidad Católica de Valparaíso

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https://doi.org/10.1016/j.ejbt.2024.04.006
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Conclusions: Powder of ginsengporia and atractylodis macrocephalae combined with aerobic exercise is effective in treating obese T2DM, which can alleviate clinical symptoms and the disorder of glucose and lipid metabolism, and improve the islet function and gastrointestinal function.
How to cite: Liu G, Kanti Das S. Efficacy of powder of ginsengporia and atractylodis macrocephalae combined with aerobic exercise in the treatment of obese T2DM: A randomized controlled clinical trial. Electron J Biotechnol 2024;71. https://doi.org/10.1016/j.ejbt.2024.04.006.
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1. Introduction

Diabetes mellitus has a high incidence in China, among which T2DM is the most common. At present, metformin is commonly preferred for treatment, but the clinical efficacy is poor [1]. Obese T2DM patients are in a state of hyperglycemia and hyperlipidemia for a long time, easily causing damage to islet beta cells, increasing insulin resistance, and reducing the efficacy of traditional hypoglycemic drugs. Meanwhile, hyperlipemia can increase the burden on the liver, which is more unfavorable to the regulation of glucose and lipid metabolism. For such patients, daily exercise should be strengthened to reduce body fat [2]. However, it has been reported that Traditional Chinese medicine (TCM) has shown clinical efficacy in the treatment of obese T2DM [3]. TCM believes that obese diabetes is a syndrome of spleen deficiency and dampness, and T2DM is mainly caused by spleen and stomach dysfunction caused by congenital deficiency, unreasonable diet and exercise, emotional disorders, etc. Obesity is a condition of stomach preponderance and spleen weakness, of which the pathological mechanism is deficiency in origin and excess in superficiality. The treatment should focus on invigorating the spleen, removing dampness, and dredging channels [4]. Powder of ginsengporia and atractylodis macrocephalae containing Poria, Atractylodes Macrocephala, Atractylodis Rhizama, Pinellia ternata (Thunb.) Breit., and Alismatis Rhizoma, has the effects of invigorating spleen, removing dampness, reducing blood stasis, and dredging channels, while aerobic exercise can reduce the weight of patients, suggesting that the combined treatment of both can improve clinical efficacy. Based on this, this study was to explore the efficacy of powder of ginsengporia and atractylodis macrocephalae combined with aerobic exercise in the treatment of obese T2DM and its influence on glucose and lipid metabolism.

2. Data and methods

The study was designed as a randomized clinical trial in which subjects are randomly and equally assigned to either an observation or control group. The random number assignment was provided by Dongcheng Hospital of Traditional Chinese Medicine (No. 201911BJ27). Participants in each group received three months of treatment and were followed up after treatment. The flow chart of the study is shown in **Fig. S1**.

2.1. Clinical data

A total of 94 cases of obese T2DM patients from January 2021 to January 2023 were divided into a control group and an observation group by random number table method, with 47 cases/group. Both groups had no significant difference in clinical data ($P > 0.05$, Table 1).

2.2. Inclusion criteria

① Patients met the diagnostic criteria for T2DM [5]; ② BMI $\geq$ 28 kg/m^2; ③ Male waist circumference $\geq$ 85 cm, female waist circumference $\geq$ 80 cm; ④ Patient met the dialectical standard of spleen deficiency and dampness syndrome, the main symptoms are thirst and lack of desire to drink, fatigue, loss of appetite, and body obesity; the secondary symptoms are limb numbness and tingling, sticky stool, scanty dark urine, reddish or dull tongue, white or greasy fur, and weak or thin pulse.

2.3. Exclusion criteria

① Patients with severe abnormal liver and kidney function; ② Patients with secondary obesity caused by gonadal function decline and hypothyroidism; ③ Patients with a history of weight-reducing or lipid-regulating drugs in the past 6 months; (4) Patients with acute complications of diabetes or infection; ⑤ Patients with a history of drug allergy.

2.4. Methods

Conventional treatment: Both groups were treated with metformin. Patients in the control group were given aerobic exercise training: according to patients' physique, blood glucose, and disease status, aerobic exercise programs were developed on the premise of patient tolerance, including slow walking, shadow boxing, cycling, aerobics, and Baduanjin. According to the patient's own situation, the above exercise methods were selected reasonably. The patients should warm up for 5 to 10 min before each exercise, and each exercise should be 30 min, 1–2 times a day, 5 d a week, and the total exercise time should be $\geq$ 150 min a week. The whole process follows the principle of gradual transition from low intensity to high intensity. Target heart rate was controlled: (220 - age - resting heart rate) $\times$ 60% + resting heart rate. It was necessary to

Table 1
Comparison of clinical data between the two groups.

Items	Observation group	Control group	χ2/t	P
Gender (cases)			0.172	0.678
Male	27	25		
Female	20	22		
Age (years)	53.98 ± 6.75	54.27 ± 5.91	0.222	0.825
Disease course (years)	6.38 ± 1.24	6.43 ± 1.27	0.193	0.847
BMI (kg/m2)	31.05 ± 1.49	30.97 ± 1.51	0.259	0.797
Combined hypertension	9	8	0.072	0.789
Family history of diabetes	5	6	0.103	0.748

adjust the exercise program to fit the patient's needs and to guide the patient to insist on exercising.

The observation group was given powder of ginsengporia and atractylodis macrocephalae on the basis of the control group, and the formula composition was as follows: 20 g each for Poria, Dioscoreae Rhizoma, 15 g each for Codonopsis Radix, Astragali Radix, and Crataegi Fructus, 10 g each for Atractylodes Macrocephala, Atractylodis Rhizama, *Pinellia ternata* (Thunb.) Breit., Alismatis Rhizoma, Citri Reticulatae Pericarpium, and Magnoliae Officinalis Cortex. Astragali Radix increased to 30 g in patients with qi deficiency; 15 g Dolichos lablab L., 6 g Amomi Fructus, and 6 g Alpinia tonkinensis Gagnep were added for those with dampness and loose stool. Lycium-rehmannia pills were given to those with kidney essence deficiency; 15 g Salvia miltiorrhiza Bge., 10 g Carthami Flos, 10 g Chuanxiong Rhizoma, 10 g Radix Padoniae Rubra, 6 g Cinnamomi Ramulus were further given for patients with cardiovascular diseases; In patients with peripheral neuropathy, 10 g Angelicae Sinensis Radix and 10 g Pheretima were added. Herbs were decocted with water and drank twice a day (200 ml). The treatment was continuous for three months.

2.5. Observation indicators

2.5.1. Clinical efficacy

According to the Guideline for Clinical Trials of New Patent Chinese Medicines [6], Nimodipine method was used to calculate the efficacy index: [(pre-treatment score − post-treatment score)/pre-treatment score] × 100%. Clinical recovery: Clinical symptoms and signs disappeared or basically disappeared, and the efficacy index ≥ 95%. Obviously effective: Symptoms and signs were significantly improved, and the efficacy index was 70–94%. Effective: Symptoms and signs were improved, and the efficacy index was 30–69%. Ineffective: Symptoms and signs did not improve significantly, and the efficacy index was < 30%.

2.5.2. TCM syndrome scores

According to the Guideline for Clinical Trials of New Patent Chinese Medicines [6] standard, the symptoms of patients were divided into none, mild, moderate, and severe. The main symptoms of thirst and lack of desire to drink, fatigue, loss of appetite, and body obesity were scored 0, 2, 4, and 6 points according to the severity of symptoms. Limb numbness and tingling, sticky stool, and scanty dark urine were scored 0, 1, 2, and 3 respectively. The higher the score, the more serious the symptoms were.

2.5.3. Blood glucose and islet function indicators

Fasting plasma glucose (FPG), 2-h plasma glucose (2hPG), and HbA1c were detected using a blood glucose monitor (7393, Bayer, Germany), and fasting insulin (FINS) by ELISA. HOMA-IR = FPG (mmol/L) × FINS (ng/ml)/22.5; HOMA-β = 20 × FINS/ (PFG − 3.5)].

2.5.4. Lipid index

TG, TC, HDL-C, and LDL-C were detected using an automatic biochemical analyzer (7600, Hitachi, Japan) and detection kits (Snibe Diagnostic, Shenzhen, China).

2.5.5. Adipose regulation indicators

Nesfatin-1, adiponectin, visfatin, and leptin levels were determined by ELISA.

2.5.6. Gastrointestinal hormone indices

Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) levels were measured by Luminex multiple test system (Luminex company, USA) and reagents.

2.5.7. Adverse reactions

The incidence of adverse reactions such as nausea, vomiting, headache, and hypoglycemia was analyzed.

2.6. Statistical analysis

All the data were processed by SPSS 22.0 software, the enumeration data were expressed as % and compared by χ^2 test, and the measurement data were expressed as (±s) after normality test and compared by *t*-test. $P < 0.05$ meant that the difference was statistically significant.

3. Results

3.1. Clinical efficacy and TCM syndrome scores

The number of obviously effective, effective, and ineffective cases in the observation group was 18, 27, and 2, respectively, and 16, 23, and 8, respectively in the control group. The total effective rate of the observation group (95.74%) was higher than that of the control group (82.98%) ($P < 0.05$). There was no significant difference in TCM syndrome scores between the two groups before treatment ($P > 0.05$). After treatment, TCM syndrome scores in both groups were lower than those before treatment, and the main symptoms in the observation group were less than those in the control group ($P < 0.05$), including lack of thirst and desire to drink, fatigue, loss of appetite, limb numbness and tingling, sticky stool, scanty dark urine, and total scores (Table 2).

Table 2
Comparison of TCM syndrome scores before and after treatment between the two groups (scores).

Items	Observation group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
Primary symptoms				
Thirst or no desire to drink	4.16 ± 0.53	1.98 ± 0.25*	4.21 ± 0.45	2.20 ± 0.33*#
Fatigue	4.08 ± 0.46	2.11 ± 0.29*	4.18 ± 0.32	2.35 ± 0.28*#
Loss of appetite	3.85 ± 0.42	1.57 ± 0.27*	3.78 ± 0.45	1.72 ± 0.31*#
Body obesity	4.19 ± 0.83	1.83 ± 0.31*	4.12 ± 0.78	1.90 ± 0.29*
Secondary symptoms				
Limb numbness and tingling	1.85 ± 0.30	1.03 ± 0.21*	1.81 ± 0.24	1.19 ± 0.27*#
Sticky stool	1.79 ± 0.25	1.25 ± 0.28*	1.76 ± 0.28	1.42 ± 0.21*#
Scanty dark urine	1.92 ± 0.27	1.31 ± 0.26*	1.89 ± 0.31	1.58 ± 0.22*#
Total score	21.84 ± 2.73	11.08 ± 2.15*	21.75 ± 2.11	12.36 ± 1.97*#

Note: Compared with the group before treatment; * $P < 0.05$: Compared with the observation group after treatment; # $P < 0.05$.

3.2. Blood glucose indices

Blood glucose indices suggested no significant difference between the two groups before treatment ($P > 0.05$). FPG, 2hPG, and HbA1c in both groups after treatment were lower than those before treatment, and those in the observation group were lower than in the control group ($P < 0.05$, Fig. 1).

3.3. Islet function indices

Islet function indices indicated no significant difference between the two groups before treatment ($P > 0.05$). FINS, HOMA-IR, and HOMA-β in both groups after treatment were higher than before treatment, and higher in the observation group than the control group ($P < 0.05$, Fig. 2).

3.4. Blood lipid indices

Before treatment, there was no significant difference in blood lipid indices between the two groups ($P > 0.05$). TG, TC, and LDL-C in both groups after treatment were lower than before treatment, and lower in the observation group than the control group ($P < 0.05$). HDL-C levels showed the opposite level trend ($P < 0.05$, Fig. 3).

3.5. Adipose-regulating indices

Adipose-regulating indices showed no significant difference between the two groups before treatment ($P > 0.05$). Nesfatin-1 and adiponectin levels in the two groups after treatment were lower while visfatin and leptin were higher than before treatment, and the changes were more obvious in the observation group ($P < 0.05$, Fig. 4).

3.6. Gastrointestinal hormone levels

Before treatment, there was no significant difference in gastrointestinal hormone levels between the two groups ($P > 0.05$). GIP and GLP-1 levels after treatment were higher than before treatment in both groups, especially in the observation group ($P < 0.05$, Fig. 5).

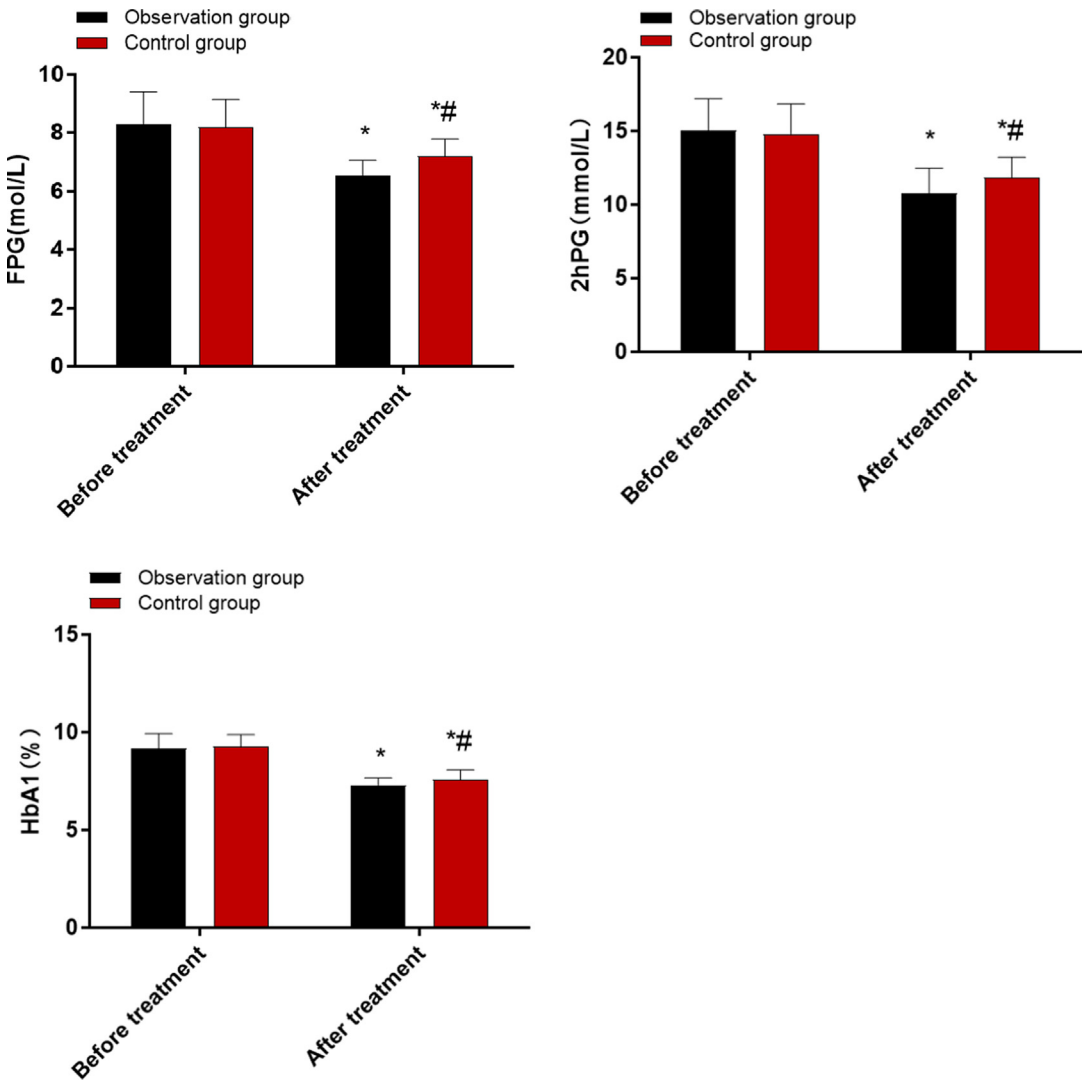

Fig. 1. Blood glucose indices. Note: Compared with the group before treatment, * $P < 0.05$; Compared with the observation group after treatment, # $P < 0.05$.

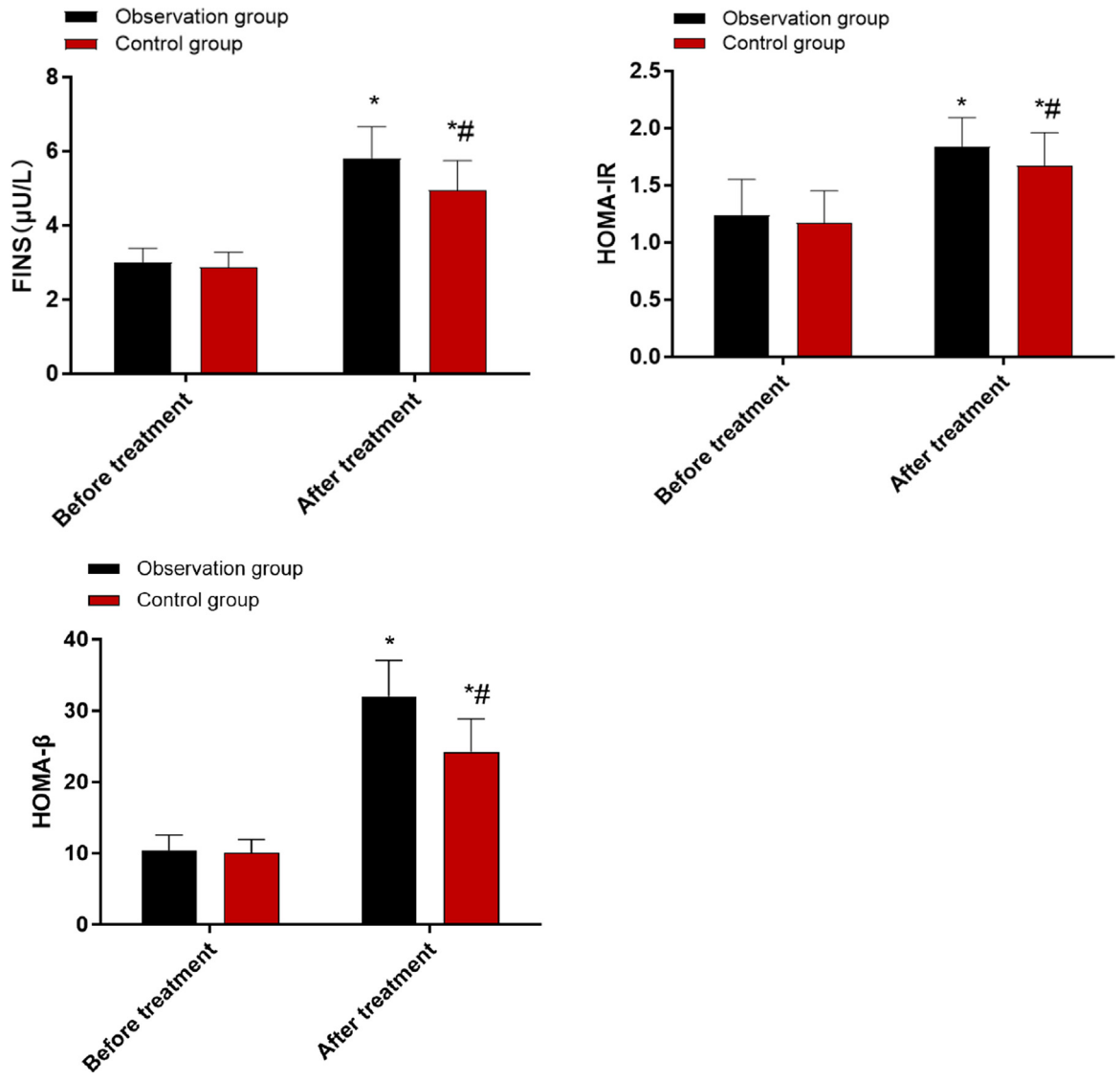

Fig. 2. Islet function indices. Note: Compared with the group before treatment, * $P < 0.05$; Compared with the observation group after treatment, # $P < 0.05$.

3.7. Adverse reactions

There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$, Table 3).

4. Discussion

Obese patients have a higher risk of developing T2DM. Patients with obesity who eat foods high in calories and fats and exercise insufficiently tend to overload pancreatic β cells. This leads to reduced insulin production, glucose accumulation in liver cells, and glucose uptake in muscle cells, culminating in higher blood glucose levels [7]. Patients with T2DM who are obese and have an inadequate diet have blocked qi in the spleen and stomach, preventing normal water and nutrient exchange. The qi is damaged by lying for a long time, while the muscles are overburdened by sitting. A lack of exercise results in stagnation of zang-fu qi and dampness, phlegm, turbidity, and fat, resulting in heat-syndromes and Yin injury manifested in obesity. The spleen is the source of qi and blood and is responsible for the transportation and transformation of nutrient substances. Individuals lacking dietary control and consuming fatty foods find that spleen deficiency disrupts water absorption and transfer, affecting water metabolism. This leads to frequent urination, polydipsia, diabetes, and various metabolic issues, culminating in pathological dampness in the spleen and the development of spleen deficiency dampness syndrome [8,9]. Despite many advances in the management of diabetic patients, the quest for safe and effective antidiabetic drugs continues. In addition, the quest for herbs with potential anti-obesity properties has attracted the attention of researchers [10,11,12]. Dioscoreae Rhizoma, Codonopsis Radix, Astragali Radix, and Atractylodes Macrocephala in powder of ginsengporia and atractylodis macrocephalae can generate Yang qi of the spleen and stomach, which have the function of ascending clear qi, descending turbid substance, and transporting body fluid. Poria can dip dampness, reduce turbidity, and purify deficient fire; Crataegi Fructus can invigorate the stomach and promote the circulation of qi; Atractylodis Rhizama can eliminate dampness and reduce turbidity and dampness to dredge Middle Jiao; Pinellia ternata (Thunb.) Breit can eliminate dampness and phlegm; Alismatis Rhizoma can remove dampness and promote diuresis; Citri Reticulatae Pericarpium regulates qi circulation and invigorates spleen, eliminates dampness, and resolves phlegm; Magnoliae Officinalis Cortex promotes qi circulation to remove dampness. The combina-

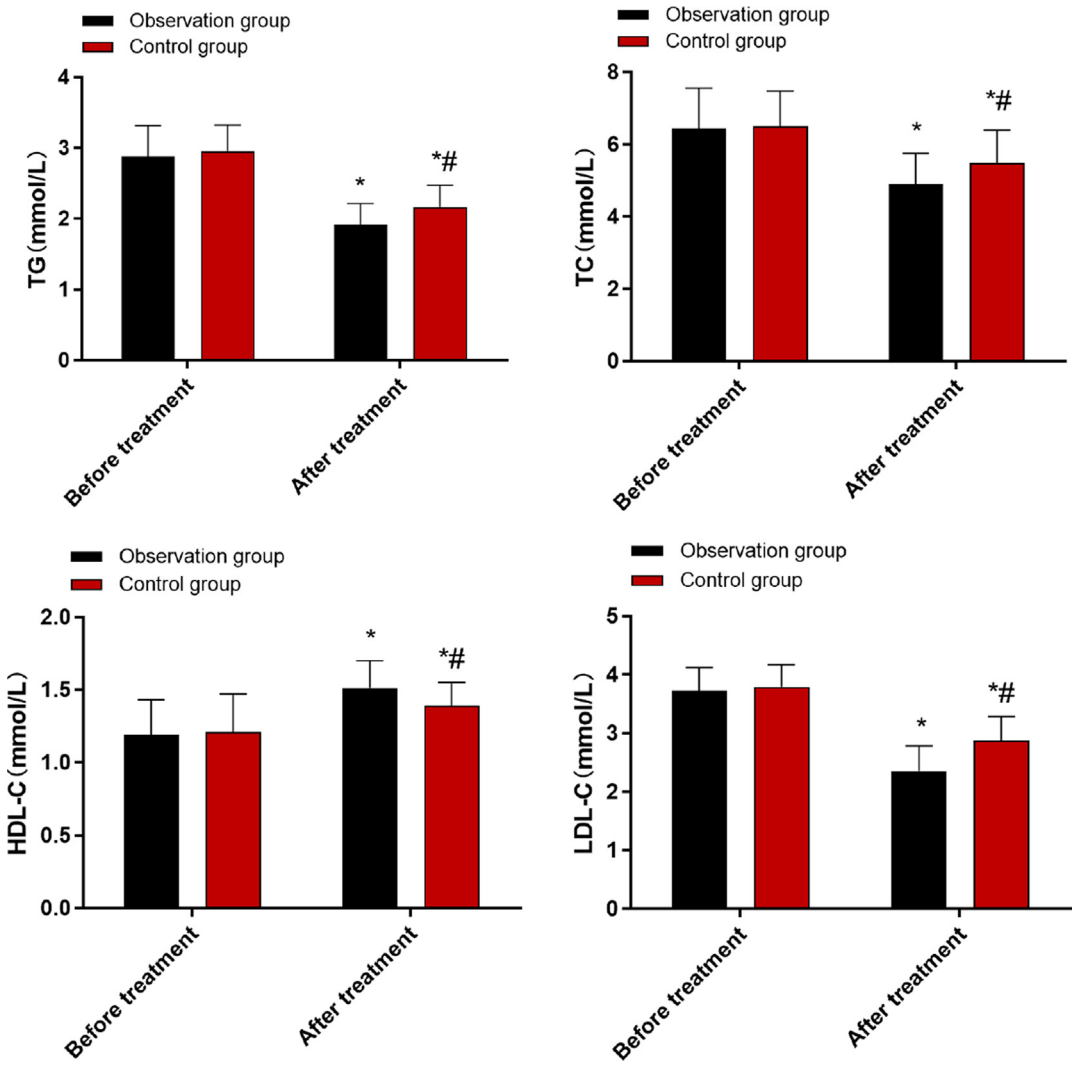

Fig. 3. Blood lipid indices. Note: Compared with the group before treatment, * $P < 0.05$; Compared with the observation group after treatment, # $P < 0.05$.

tion of all kinds of herbs can tonify qi and invigorate spleen, eliminate dampness and reduce turbidity, making vigorous qi in the spleen and finally promoting the body's dampness transport, relieving symptoms, and reducing blood glucose [13,14]. In this study, FPG, 2hPG, and HbA1c in the observation group were lower than those in the control group after treatment, while FINS levels, HOMA-IR, and HOMA-β were higher, suggesting that combined treatment can reduce blood glucose levels and improve islet function. The reason is that Codonopsis Radix, Poria, Astragali Radix, Puerariae Lobatae Radix, and Crataegi Fructus have the effect of lowering blood glucose. Codonopsis polysaccharide can regulate blood lipid metabolism, inhibit glycoconogenesis, and increase liver glycogen content and serum insulin level to lower blood glucose. Pachyman in Poria can reduce blood glucose and body weight. Astragalus polysaccharide and Astragaloside in Astragali Radix and Puerariae Lobatae Radix have hypoglycemic effects, and puerarin can improve insulin resistance and reduce serum total cholesterol and low-density lipoprotein to lower lipid and glucose [15,16]. The results of this study showed that the total effective rate of the observation group was higher than that of the control group. After treatment, the main symptoms of thirst and lack of desire to drink, fatigue, and loss of appetite, and secondary symptoms including limb numbness and tingling, greasy stool, scanty dark urine, and total scores were lower than those of the control group, suggesting that powder of ginsengporia and atractylodis macrocephalae combined with aerobic exercise has higher efficacy in the treatment of obese T2DM and can alleviate clinical symptoms. Consistent with previous research results [17], the main reason is that combined treatment can help to regulate blood glucose, harmonize spleen-stomach, remove internal heat, and thus improve the symptoms of fatigue, abdominal distension and overeating.

Adipose tissue serves as the body's cholesterol reservoir, storing/consuming energy and secreting hormones. It can secrete a variety of fat hormones. Fat hormones are closely related to endocrine, nervous, and cardiovascular systems of the body. Abnormal secretion of fat hormone is causal for insulin resistance and can induce T2DM [18]. Nesfatin 1 can not only control appetite, improve the distribution of white adipose tissue but improve the sensitivity of peripheral tissue to insulin and avoid the damage of islet beta cells. Adiponectin can induce tyrosine phosphorylation of insulin receptors in lipid skeletal muscle and improve insulin sensitivity. Visfatin has an insulin-like effect and can induce glucose transport in adipocytes. Leptin can destroy the normal adipose-leptin-islet pulse feedback mechanism and cause hyperinsulinemia [19]. The decrease in serum leptin and leptin levels and the increase in serum lipocalin levels may be attributed to the improvement in glycemic status and IR, lipid profile, and the

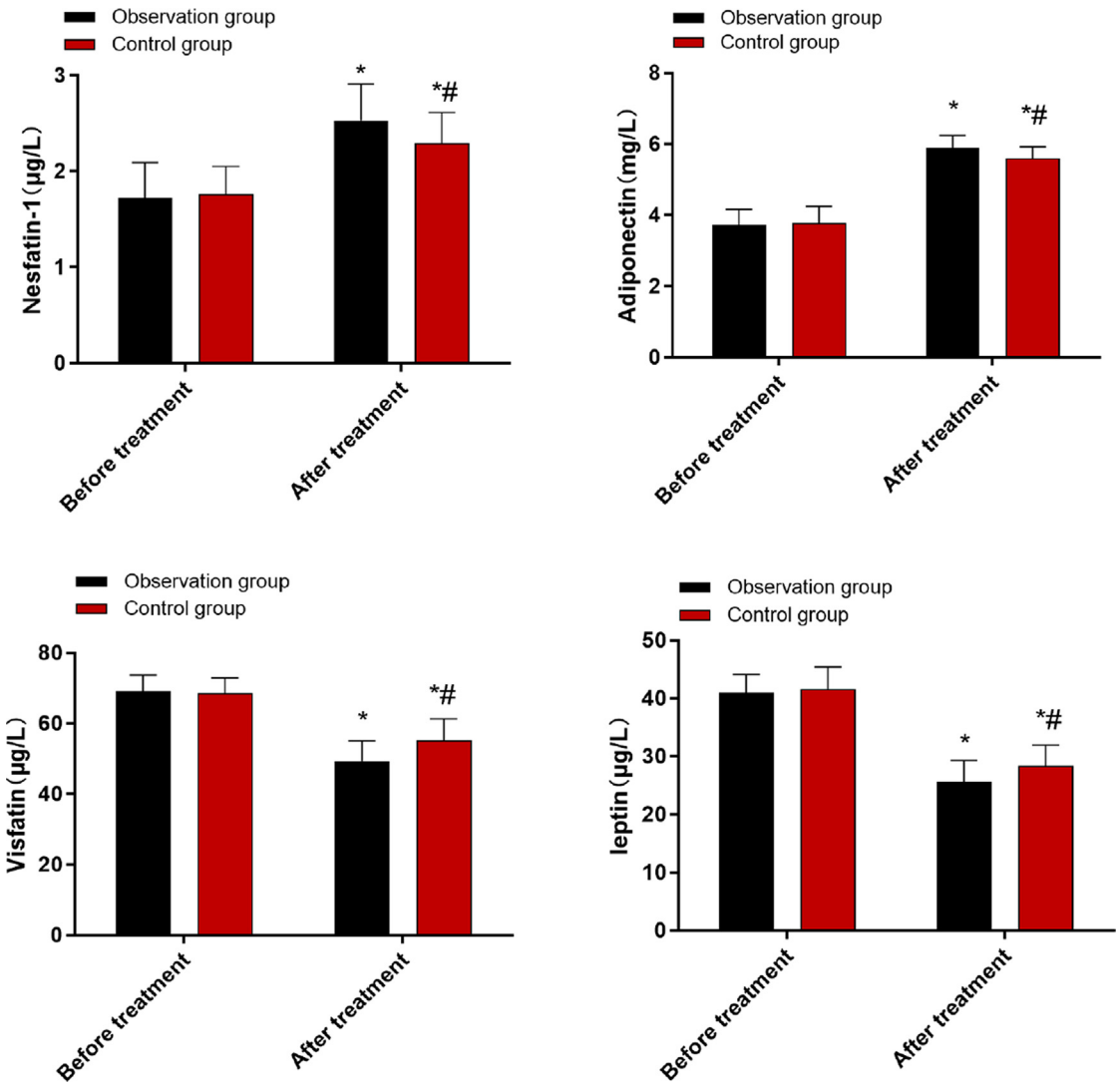

Fig. 4. Adipose-regulating indices. Note: Compared with the group before treatment, * $P < 0.05$; Compared with the observation group after treatment, # $P < 0.05$.

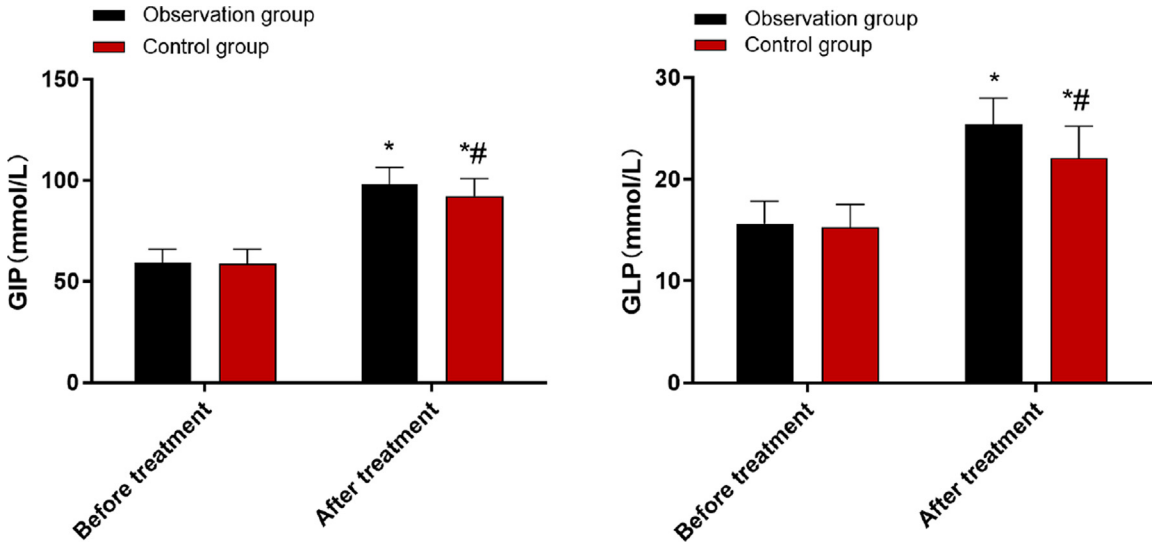

Fig. 5. Gastrointestinal hormone levels. Note: Compared with the group before treatment, * $P < 0.05$; Compared with the observation group after treatment, # $P < 0.05$.

Table 3
Comparison of the incidence of adverse reactions between the two groups (e.g., %).

Groups	n	Nausea and vomiting	Headache	Hypoglycemia	Total incidence rate
Observation group	47	0	1	0	2.13
Control group	47	1	1	1	6.38
χ^2					1.044
P					0.307

decrease in BMI [20]. In this study, it was found that Nesfatin-1, adiponectin, TG, TC, and LDL-C in the observation group after treatment were lower than those in the control group, while visfatin, leptin, and HDL-C were higher, indicating that combined treatment can improve the body's lipid metabolism function.

Spleen deficiency is the key pathogenesis of T2DM. Spleen deficiency promotes blood stasis and phlegm turbidity, stopping water transportation, and eventually causing spleen deficiency and dampness. Obese T2DM patients tend to develop gastrointestinal dysfunction [21]. GIP is synthesized and released by K cells of the proximal small intestine. When nutrients reach the small intestine, GIP secretion will increase significantly and stimulate the secretion of insulin by islet beta cells. GLP-1 is synthesized by L cells of the distal ileum and colon, and plasma insulin concentration is increased after ingestion. GIP and GLP-1 secretion is decreased during insulin resistance, which further explains the correlation between diabetes mellitus and gastrointestinal function. Powder of ginsengporia and atractylodis macrocephalae is widely found in "Taiping Huimin Hejiju Fang", which is a common prescription for supplementing Qi and invigorating spleen in clinical practice. The combination of Codonopsis Radix and Atractylodes Macrocephala is essential for supplementing Qi and invigorating spleen, and the combination of Poria and Atractylodes Macrocephala is essential for removing dampness and invigorating spleen. The combination of the three herbs can make the spleen qi full, which has the power of removing dampness and turbidity and invigorating spleen [22]. In this study, GIP and GLP-1 levels in the observation group were higher than those in the control group after treatment, indicating that combined treatment could improve gastrointestinal function, which was mainly related to the effects of Codonopsis Radix, Poria, Astragali Radix, Puerariae Lobatae Radix, and Atractylodes Macrocephala in powder of ginsengporia and atractylodis macrocephalae, which could lower blood glucose and invigorate spleen, nourish stomach, and benefit qi. Astragali Radix, Codonopsis Radix, and Atractylodes Macrocephala in powder of ginsengporia and atractylodis macrocephalae can tonify qi, nourish stomach, invigorate spleen, and eliminate dampness; Pinellia ternata (Thunb.) Breit. and Citri Reticulatae Pericarpium regulate qi circulation, eliminate dampness, and relieve phlegm; Puerariae Lobatae Radix has the effect of clearing heat and promoting fluid; Astragalus membranaceus is a commonly used prescription for tonifying and generating qi; Crataegi Fructus and Glycyrrhizae Radix Et Rhizoma have the effect of clearing stagnation and harmonizing stomach; The combined use of the above prescriptions can give full play to the effects of tonifying qi, invigorating spleen, removing stasis, and eliminating phlegm.

The combination of powder of ginsengporia and atractylodis macrocephalae and aerobic exercise can effectively down-regulate FPG, 2hPG, HbA1c, TG, TC, LDL-C, Nesfatin-1, and lipocalin levels, and up-regulate FINS, HOMA-IR, HOMA-β, HDL-C, endolipids, leptin, GIP, and GLP-1 levels. However, each individual responds differently to medication and exercise, which may affect the effectiveness of treatment. Moreover, the dosage of herbal medications and the intensity, frequency and duration of aerobic exercise should be individualized to ensure optimal efficacy and safety. Although 94 patients were included in this study, the sample size was still small and the follow-up period was short, which could not provide an accurate and comprehensive evaluation of the therapeutic effect and prognosis of T2DM. Therefore, in order to properly assess the effectiveness of powder of ginsengporia and atractylodis macrocephalae combined with aerobic exercise in obese T2DM, future systematic evaluations based on more rigorously designed randomized trials are necessary.

In summary, powder of ginsengporia and atractylodis macrocephalae combined with aerobic exercise has a high curative effect in the treatment of obese T2DM, which can alleviate clinical symptoms and glucose and lipid metabolism disorders, and improve islet function and gastrointestinal function.

Ethical approval

The present study was approved by the Ethics Committee of Dongcheng Hospital of Traditional Chinese Medicine (No. 201911BJ27), and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Not applicable.

Conflict of interest

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

GuoXiang Liu: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Sreemoy Kanti Das:** Writing – review & editing, Visualization, Validation, Supervision, Software, Investigation, Data curation.

Supplementary material

https://doi.org/10.1016/j.ejbt.2024.04.006.

Data availability

Data will be made available on request.

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