Effects of Jia Wei Dachaihu-Tang on gut microbiota and inflammatory markers in patients with overweight or obesity: study protocol for a randomized, controlled, double-blinded trial

Yang Gao
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine
https://orcid.org/0000-0002-1190-4561

Peipei Hong
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine

Tingting Liao
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine

Xuke Han
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine

Shan Zhou (zhoushan0611@163.com)
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine

Qiu Chen
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine

Research Article

Keywords: obesity, overweight, gut microbiota, inflammation, Jia Wei Dachaihu-Tang, Traditional Chinese Medicine

Posted Date: October 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-800736/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background

The increasing number of overweight and obesity has posed an enormous hazard to the health of worldwide people, but the present methods for it still exist a few drawbacks, which implied that new effective treatment is urgently needed. Jia Wei Dachaihu-Tang (JWDT), a Chinese herbal medicine formulation wildly used to remedy obesity in clinical practice, has been confirmed its effectiveness and safety in our previous studies. In the study, the impacts of JWDT on gut microbiota and inflammatory markers in patients with overweight or obesity will be further investigated.

Methods/design:

This trial will be a randomized, double-blinded, parallel-group, placebo-controlled single-center trial recruiting 60 participants who are 18 to 80 years of age with a body mass index (BMI) \( \geq 25 \text{ kg/m}^2 \). Participants will be enrolled on a random basis and are equally assigned to either Jia Wei Dachaihu-Tang or placebo for 12 weeks. The primary outcome is the change in BMI during this trial. Secondary outcomes contain changes in waist circumference, waist to hip ratio, blood lipid, insulin resistance index (HOMA-IR), body composition, inflammatory factors, gut microbiome, appetite, etc. Blood and fecal sample collection will be conducted at the baseline and after the 12-week intervention.

Discussion

This study will further testify the therapeutic effect of JWDT in overweight or obesity, and investigate its power on insulin resistance, body composition, gut microbiota, inflammation, appetite, food intake, emotion. Furthermore, investigators attempt to pursue the possible mechanism that JWDT ameliorates overweight and obesity from the perspective of gut microbiota, expecting to provide new targets and directions for the treatment of obesity.

Trial registration:

The protocol has been registered on the Chinese Clinical Trial Registry (ChiCTR2000040889) on 14 December 2020, http://www.chictr.org.cn/abouten.aspx.

Background:

Overweight and obesity, a common chronic condition, characterized by excessive fat accumulation and weight gain. Affected by multiple elements such as modified dietary structure, reduced physical activity, and psychosocial stress, its prevalence has increased at an alarming rate[1, 2]. According to WHO data, the global prevalence of obesity boomed by approximately triple between 1975 and 2016, and, in 2016,
the number of overweight adults in the world reached 1.9 billion, accounting for 39%, among which more than 650 million belongs to obese[3]. Sharp growth rate and severe complications make overweight and obesity an intractable problem, which imposes more financial burdens on the millions of people worldwide and makes them suffer from increased risks of numerous non-communicable diseases. Previous researches demonstrated that overweight and obesity are the major risk factors for diabetes, metabolic syndrome, fatty liver, cardiovascular diseases, tumors, and global leading sources of death and disability[1].

Controlled by multi-factor, the pathological mechanism for overweight or obesity is complex. In addition to simple energy imbalance, obesity has also been linked to insulin resistance, inflammation, oxidative stress, and immunity[4]. The inflammation mediates related insulin resistance which is generally considered as the pivotal pathological mechanism for obesity. Low degree chronic inflammation induced by excess adiposity has been observed in many tissues, especially adipose tissue, liver, pancreas, and skeletal muscle[5]. Several pieces of research suggested that chronic inflammation of metabolic diseases such as obesity and diabetes have an intense correlation with intestinal flora imbalance[6–8]. Reduction of Short-Chain Fatty Acids derived from the gut microbiota may result in inflammation via increasing intestinal permeability[9]. Emerging studies also indicate that inflammation mediated by gut microbes can be caused by enhanced circulating lipopolysaccharide (LPS) levels and altered intestinal barrier[10]. The Gut microbiota may also participate in several human physiopathological activities such as energy consumption, fatty deposits, insulin resistance, immunity, even food intake, and emotion, to some extent which just coincide with the pathogenesis of overweight and obesity[6]. These treatments working by modulating the gut flora, such as probiotics, fecal transplantation, antibiotic therapy, dietary fiber, etc., significantly ameliorate increased weight, insulin resistance, blood lipid metabolism, food intake, and inflammation in obesity[11], which reveal gut microbiota interact with overweight and obesity. However, to date evidence supporting these points mostly comes from animal model trials and only a few from clinical studies, which implies more prospective clinical researches needed to enhance its reliability[12].

To date, the major strategies for weight loss consist of lifestyle regulation, drugs, and surgery. Lifestyle regulation is generally the preferred treatment, but it’s challenging to maintain over a long time. Else two interventions, which probably lead to side effects and hurt, are lowly accepted. As a result, the population of obesity and relevant complications continues to climb without restriction. Therefore, it’s urgent to seek new rational methods. Traditional Chinese Medicine, with a long history and special superiority, as well as smaller toxic and side effects, may represent a useful strategy for overweight and obesity. In previous studies, Acupuncture, acupoint catgut embedding, TCM prescription all showed significant weight loss effects and safety on obesity[13–15]. Furthermore, TCM prescription has the potential of multi-target treatment, may provide more new targets and directions for the treatment of obesity.

*Jia Wei Dachaihu-Tang*(JWDT), an effective TCM prescription for overweight and obesity, has been proved reliable in pharmacodynamics. It is made up of ten Chinese medicinal herbs: *Bupleuri Radix*(Chaihu), *Scutellaria amoena*(Huangqin), *Rhizoma Pinelliae Praeparata*(Fabanxia), *Ginger*(Shengjiang), *Common Peony*(Baishao), *Poria cocos*(Fuling), *Chinese
**rhubarb**, **Dahuang**, Atractylodes macrocephala (Baizhu), Fructus Ziziphi Jujubae (Dazao), Trifoliate Orange (Zhishi) [16]. Composed on the basic of Dachaihu-Tang, a classic TCM formula from Synopsis of Golden Chamber [17], JWDT additional adds Poria cocos and Atractylodes macrocephala to enhance clinical efficacy. According to statistical analysis, Poria cocos and Atractylodes macrocephala are considered as one of the most frequently used drugs in obesity treatment and are also involved in multiple pathways and targets [18]. The preliminary studies performed with JWDT have validated its benefits in weight regulation, fat metabolism, relieving insulin resistance, and oxidative stress, which indicates it a rational and effective treatment and deserves further study [16].

However, whether JWDT relieves gut microbiota and inflammation in obese patients is still unknown, so, we design a 12-weeks random-control trial to work out the correlation. In our previous study, JWDT has been proved reliable in pharmacodynamics and be an effective Traditional Chinese Medicine prescription for overweight and obesity. This study will be conducted to further verify the therapeutic effect of JWDT in weight or obesity, and investigate its influence on insulin resistance, appetite, food intake, quality of life, gut microbiota, inflammation, etc., what's more, hunt for the potential mechanism that JWDT targets overweight and obesity from the perspective of gut microbiota.

### Methods/design

#### Study design

This trial will be a randomized, double-blinded, parallel-group, placebo-controlled single-center trial. It will be carried out in the Hospital of Chengdu University of Traditional Chinese Medicine. Participants will be outpatients who fulfill the eligibility criteria of the institution. This study will have two arms with a 1:1 allocation ratio to the JWDT treatment group and placebo group. Participants will take either JWDT or the placebo drug for 12 weeks. The study included three stages: 1 week of screening, 12 weeks of treatment, and 4 weeks of follow-up. The study flowchart is presented in Fig. 1, and a detailed schedule of enrolment, interventions, and assessments is given in Fig. 2.

#### Participants

**Inclusion criteria**

1. Over 18 years to under 65 years of age

2. Body mass index with $\geq 25.0 \text{ kg/m}^2$ (overweight/obese) [19]

3. Able and willing to provide informed consent and comply with study procedures

**Exclusion criteria**

1. Patients with the endocrine disease that may affect body weight, such as hypothyroidism, Cushing's syndrome, or those with thyroid-stimulating hormone concentration $< 0.1 \text{ uIU/ml}$ or $> 10.0 \text{ uIU/ml}$
2. Subjects who are already on a diet or undertaking heavy exercise for weight control purposes

3. Subjects who have undergone surgical procedures for weight control

4. Patients with a history of neurological or psychological disease or currently suffering from such diseases (schizophrenia, epilepsy, alcoholism, drug addiction, anorexia, bulimia, etc.)

5. Patients with a history or existence of eating disorders such as anorexia nervosa or bulimia nervosa, etc.

6. Patients with experience of medications that could have an effect on weight within last 3 months such as appetite suppressant, laxative, or oral steroid, thyroid hormone, amphetamine, cyproheptadine, phenothiazine, or medications affecting absorption, metabolism, and excretion

7. Subjects who diagnosed with diabetes or other metabolic health disturbances

8. Patients who have used other clinical trial drugs within 3 months

9. Subjects who have had weight changes > 10% of their previous weight within the last 6 months

10. Those whose aspartate transaminase or alanine transaminase exceeds five times the normal upper limit (200 IU/L)

11. Kidney dialysis patients or those with creatinine concentration more than twice the normal upper limit

12. Those who are in seriously unstable medical condition, such as cardiovascular disease, respiratory disease, gastrointestinal disease, hepatobiliary disease, metabolic disease, endocrine disease, renal disease, or problems in the urinary reproductive system and nervous system

13. Those who have had a diagnosis or have been treated for malignant tumors within the last 5 years

14. Women who are pregnant, planning to become pregnant, or lactating, or subjects who do not agree to use effective methods of contraception during the clinical trial (Oral contraceptives are not allowed during the clinical trial.)

15. Receiving medications or supplements that could affect gut microbiota during the last 3 months (examples: antibiotics, probiotics, prebiotics, laxatives, etc.)

**Sample size**

There is no clinical study to evaluate the clinical effect of JWDT on gut microbiota and inflammatory markers in patients with overweight or obesity. Therefore, this study calculated the sample size according to similar studies that had used herbal supplements for weight loss, opinions of medical statistics, and clinical experts[20, 21]. According to the previous studies and assuming an alpha = 0.05 and power = 0.80 (80%) and the standard deviation of 2.2 for body weight, we would need to recruit 24
subjects in each study arm. After considering the dropout rate of approximately 20%, the sample size for each group is 30 participants. Therefore, the total sample size of this trial is 60.

**Randomization and blinding**

The statisticians will use the SAS program to generate random sequences. The subjects of this experiment will be randomly divided into the JWDT group or control group according to the ratio of 1:1. Randomization procedures will be performed at Week 0, using a random number card in an opaque envelope that will not be disclosed until the clinical trial is completely over unless serious adverse events (SAEs) happen. All participants, investigators, and monitors will be blinded. Except for the statisticians in this study, no one would know which random number refers to the treatment group or the placebo group. To evaluate whether the blinding is successful, at the end of the study, all participants will be asked which group they think they are assigned to.

**Intervention**

Participants mixed JWDT or placebo with 150 ml of water until dissolved and drank it 15-20 minutes before three meals three times a day for 12 weeks. These medicines will be distributed monthly. To improve adherence to intervention protocols, the remaining drugs will be asked to return. JWDT and placebo will be prepared by the Pharmacy Department of the Hospital of Chengdu University of Traditional Chinese Medicine in strict accordance with the Chinese Traditional Chinese Medicine Production Guidelines. The composition of JWDT is shown in Table 1. JWDT granules contain JWDT soft extract, lactose hydrate, and corn starch. The placebo contains lactose hydrate, corn starch, and food coloring, and is similar in appearance, shape, weight, taste, and color to JWDT. To evaluate the compliance of the intervention, subjects will be told to carry empty bags of ingested test drugs and remaining drugs. At the end of the study, subjects with drug compliance less than 70% will be eliminated. The research team will contact subjects regularly by telephone or WeChat to improve compliance and check safety.

**Lifestyle changes**

An experienced nutritionist from the Hospital of Chengdu University of traditional Chinese medicine will introduce to all patients participating in the study a diet to lose weight (5% weight loss during the study), suggestions for increasing physical activity (moderate-intensity aerobic exercise, at least three times a week, 30-45 minutes), and lifestyle changes.

**Assessments**

**Anthropometric measurements**

The height and weight will be measured using a height and weight meter when participants wear light clothes and do not wear shoes and socks. Body mass index (BMI) is calculated by dividing weight (kg) by the square of height (m). Waist circumference and hip circumference will be measured according to the
World Health Organization instructions. Anthropometry will be performed by the same person to minimize errors. Then the waist to hip ratio (WHR) will be calculated for each person. Body composition (% fat mass, % fat-free mass, visceral fat (L)) will be measured using a body composition analyzer (DONGHUAYUAN, Body Composition Analyzer, DBA-510).

**Blood pressure**

Blood pressure (BP) will be measured with a portable electronic sphygmomanometer after each subject rest for at least 10-15 minutes. Three measurements will be taken to calculate an average at each visit.

**Health-related quality of life (HRQoL) questionnaire**

HRQoL was examined using the Short Form Health Survey Questionnaire (SF-36) which is a widely used and self-administered health questionnaire[22, 23]. The SF-36 contains 36 items, measuring 8 HRQoL areas, divided into physical (function, role restriction, physical, pain, general health) and mental health (vitality, social function, role restriction-emotion, and emotional/mental health) (Additional file 1)[24]. Each item is scored as 0–100 where higher scores indicate better HRQoL. The score for each subscale is then generated by averaging all items for that subscale.

**Assessments of appetite and food intake**

Subjects will record weekly subjective appetite scores at home using a validated 100 mm VAS[25, 26]. And we'll set up the problem according to the method Raylene A Reimer provides. Subjective appetite scores using VAS will be collected immediately before and after meals[27]. At weeks 0 and 12, investigators will assess current individual food and nutrient intakes. Participants will be asked to write down the food and beverage consumed in the past three days through the energy intake record sheet.

**Blood testing**

Blood index collection will be collected from subjects who have been fasted for 12 hours at baseline and at the end of the trial. The blood test will include blood lipid(total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)), fasting insulin, fasting plasma glucose, and inflammatory factors (hs-CRP, TNF-α, and IL-6). Studies have shown that these inflammatory factors have a significant correlation with obesity[28, 29]. Besides, HOMA insulin resistance index (HOMA-IR) will be calculated as [Plasma glucose (GLU, mmol/L) * serum insulin (mIU/L)] / 22.5.

**Gut microbiome analysis**

Fecal samples will be collected at baseline and the end of the trial. Subjects will be provided with a set of fecal collection tools and guidance on proper fecal collection methods. One teaspoon of feces will be placed in a pre-labeled sterile cone tube, placed in a biohazard bag, and frozen until the visit. participants will bring frozen samples to the laboratory within 48 hours, and then the samples will be stored in a...
laboratory refrigerator -80°C until analysis. The microbial community will be evaluated by 16S rRNA sequencing analysis. The relative abundance of bacterial taxa in each sample will be obtained and significant differences between JWDT and placebo groups will be evaluated.

**Safety assessment**

The subjects will be asked if they had any physical discomfort at each interview and their blood pressure, heart rate and body temperature will be measured. If adverse events (AEs) occur, a safety assessment will be conducted and recorded on the case report form (CRF). Researchers will follow up with all participants who report AEs, and if necessary, perform additional blood tests on the subjects to assess the cause of the AE and its possible relationship with interventions. During the study period, subjects who meet the exclusion criteria will be withdrawn from the study to ensure their safety.

**Outcomes**

The primary outcome is the mean change of BMI during this trial. Secondary outcomes contain changes in waist circumference, waist to hip ratio, blood lipid, insulin resistance index (HOMA-IR), appetite, food intake, body composition, inflammatory factors, and the gut microbiome from baseline to the end of 12 weeks after JWDT or placebo. Safety outcomes will be evaluated through the frequency of adverse events.

**Monitoring**

Major investigators will receive rigorous training before recruiting, and the overall process will carry out under the guidance and monitoring of the Medical ethics committee of the Hospital of Chengdu University of Traditional Chinese Medicine. Investigators will strictly follow the protocol and record the case report form (CRF) accurately. Withdrawal or cancellation of visits is also required on the case report form. The Medical ethics committee will regularly review the CRF, examine the inclusion, exclusion, and exit criteria, and ensure that the CRF information is consistent with the information in the source medical record.

**Data collection and management**

All related sources will be collected according to standard procedure, which contains demographic data, anthropometric measurements dates, laboratory results, informed consent, questionnaires. Enrolled participants will be required to complete the designed questionnaires and anthropometric measurements at every visit. Laboratory examination will be performed on day 0 and week 12 of the trial. All required dates will be accurately recorded in case report form (CFR) in compliance with this study protocol by two independent investigators, and then this collected information will be entered into the computer again. To protect the confidentiality, paper and electronic materials will be maintained in locked cabinets and electronic folders respectively. The final dataset of the clinical trial will be accessible to all authors, and the results will be published in a peer-reviewed journal.
Statistical analysis

The statistical analysis of the data of this subject will be completed using SPSS 22. Whether the data is normally distributed will be tested using Kolmogorov-Smirnov. Log transformation will be conducted for the non-normally distributed data. Independent t-test or Wilcoxon rank-sum test will be used for continuous variables between the intervention group and control group, and the chi-square test or Fisher's exact test will be used for categorical variables. In this analysis, the baseline values of outcome variables and potential confounding variables between the two groups will be adjusted to avoid the potential risk of bias and to detect independent results. P <0.05 will be considered significant.

Discussion

Obesity is an intractable problem that poses a major threat to global human health both physical and mental. Studies demonstrated obesity contributes to greater risks for diabetes, hypertension, cardiovascular diseases, even death and disability, and also impairs one's cognitive competence and emotion, resulting in Alzheimer's disease and anxiety[30–32]. However, present treatments cannot achieve the desired effect, and a new strategy for weight loss is needed.

In the early stage of the study, the effectiveness and safety of JWDT have been verified. In the present study, it will be confirmed again by measuring BMI, WC, blood lipid, and body composition. Further, its impact on gut microbiota, inflammation, food intake, emotion, and insulin resistance will be investigated, moreover, we try to explore its mechanism from the point of gut flora.

Low-grade inflammation and insulin resistance, as the major pathological mechanism of obesity, are found to be closely linked to impaired intestinal flora in emerging researches[33]. Gut microbiota hydrolyzes the fiber into short-chain fatty acids, which destroy the intestinal barrier and reduce intestinal permeability, resulting in systemic low-grade inflammation and further aggravating insulin resistance[9]. Results of our study may help to work out the impacts of JWDT on gut microbiota, insulin resistance, and inflammation, additional, the correlation of the three will be analyzed.

Interacting with the brain through a variety of pathways such as nerve, metabolism, endocrine, and immunity, gut microbiota involves in the regulation of food intake, emotion, and cognitive ability[34]. Therefore, we assume that JWDT may take effect on obesity by reducing food intake and relieving negative emotions via regulating gut microbiota.

Traditional Chinese medicine, with a history of several thousand years in clinical practice, is feasible and trustworthy. The 12-weeks randomized controlled clinical study conducted with JWDT in overweight or obesity will observe many novel features and be the first to research the related mechanism through gut microbiota. Further, the results of our study will add more evidence to enhance the correlation between gut microbiota and obesity in humans not animals, and provide new targets and directions for the treatment of obesity.
But, some limitations of this study should be also mentioned. Restricted by clinical practice, we only permit 60 patients to carry out a 12-week trial. In the study, we just observe the species abundance and proportion of gut microbiota by 16sRNA, don’t detect related derivatives such as short-chain fatty acids. Furthermore, the observation index of food intake is assessed depending on a daily diet chart recorded by these participants themselves, which may result in a deviation between collected data and the actual situation.

**Trial Status**

The most recent version of the protocol is version 1.0 (10 October 2020), and this was approved by the Medical ethics committee of the Hospital of Chengdu University of Traditional Chinese Medicine. Recruitment will begin in January 2021 and complete in January 2022.

**Abbreviations**

AEs: adverse events  
BMI: Body mass index  
CRF: case report form  
JWDT: Jia Wei Dachaihu-Tang  
HDL-C: high-density lipoprotein cholesterol  
HRQoL: Health-related quality of life  
hs-CRP: hypersensitive C-reactive protein  
LDL-C: low-density lipoprotein cholesterol  
IL-6: interleukin 6  
SAEs: serious adverse events  
Sf-36: The Short Form Health Survey Questionnaire  
TCM: Traditional Chinese medicine  
TNF-α: tumor necrosis facto α  
WHR: waist to hip ratio  

**Declarations**
Acknowledgments

The authors express their gratitude to all subjects who will participate in this clinical trial.

Author contributions

YG, PH, and QC contributed to the design of the study protocol. TL was involved in designing the statistical methods used in the study and calculated the sample size. GY, PH, XH, SZ, and CC participated in the project development and collected the outcome data. YG, PH, and TL prepared the initial draft of the manuscript. XH, SZ, and PH will be involved in data management and statistical analysis. QC is the project leader. All authors were responsible for drafting the manuscript and approved the final version.

Funding

This study is supported by three fund projects: Medical Service and Guarantee Capacity Improvement Subsidy Funds (Major and difficult diseases) CYW2019079), Science and technology development fund project of Hospital of Chengdu University of Traditional Chinese Medicine (18PY24 / Y2018024). These projects do not play a role in the design, conduct, or data analysis of the present study or in the decision to submit the manuscript for publication.

Availability of data and materials

The final dataset of the clinical trial will be accessible to all authors.

Ethics approval and consent to participate

Ethics approval for this trial protocol has been obtained from the Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (number: 2020SL-013, version 1.0). All participants will be provided with sufficient time to consider whether to enter the trial or not. The investigators and research assistants must obtain the written informed consent from each participant before randomization. The study will be conducted following the ethical principles of the Declaration of Helsinki (2013 version). It has been registered on the Chinese Clinical Trial Registry (ChiCTR2000040889) on 14 December 2020.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

References
1. Haslam DW, James WP. Obesity Lancet. 2005;366(9492):1197–209.
2. Lu J, Bi Y, Ning G. Curbing the obesity epidemic in China. Lancet Diabetes Endocrinol. 2016;4(6):470–1.
3. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019;92:6–10.
4. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016;8(1):42.
5. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest. 2017;127(1):1–4.
6. Gérard P. Gut microbiota and obesity. Cell Mol Life Sci. 2016;73(1):147–62.
7. Bajzer M, Seeley RJ. Physiology: obesity and gut flora. Nature. 2006;444(7122):1009–10.
8. Ley RE, Turnbaugh PJ, Klein S, Gordon JJ. Microbial ecology: human gut microbes associated with obesity. Nature. 2006;444(7122):1022–3.
9. Saad MJ, Santos A, Prada PO. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. Physiology (Bethesda). 2016;31(4):283–93.
10. Maruvada P, Leone V, Kaplan LM, Chang EB. The Human Microbiome and Obesity: Moving beyond Associations. Cell Host Microbe. 2017;22(5):589–99.
11. Seganfresco FB, Blume CA, Moehlecke M, Giongo A, Casagrande DS, Spolidoro JVN, Padoin AV, Schaan BD, Mottin CC. Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. Obes Rev. 2017;18(8):832–51.
12. Meijnikman AS, Gerdes VE, Nieuwdorp M, Herrema H. Evaluating Causality of Gut Microbiota in Obesity and Diabetes in Humans. Endocr Rev. 2018;39(2):133–53.
13. Sui Y, Zhao HL, Wong VC, Brown N, Li XL, Kwan AK, Hui HL, Ziea ET, Chan JC. A systematic review on use of Chinese medicine and acupuncture for treatment of obesity. Obes Rev. 2012;13(5):409–30.
14. Guo T, Ren Y, Kou J, Shi J, Tianxiao S, Liang F. Acupoint Catgut Embedding for Obesity: Systematic Review and Meta-Analysis. Evid Based Complement Alternat Med. 2015;2015:401914.
15. Zhang RQ, Tan J, Li FY, Ma YH, Han LX, Yang XL. Acupuncture for the treatment of obesity in adults: a systematic review and meta-analysis. Postgrad Med J. 2017;93(1106):743–51.
16. Zhu YX, Gao Y, Zhou S, Zhao Z, Chen Q. Observation on the curative effect of Jia Wei Dachaihu-Tang in treating simple obesity with liver-Qi and Spleen deficiency and heat knot type. Electronic Journal of Clinical Medicine. 2017;4(90):17679–81.
17. Hussain A, Yadav MK, Bose S, Wang JH, Lim D, Song YK, et al. Daesiho-Tang Is an Effective Herbal Formulation in Attenuation of Obesity in Mice through Alteration of Gene Expression and Modulation of Intestinal Microbiota. PLoS One. 2016;11(11):e0165483.
18. Lyu RY, Zheng SQ. [A study of the medication rule for obesity and its potential role based on data mining and network pharmacology]. Journal of Tianjin University of Traditional Chinese Medicine. 2020;39(1):103–10.
19. Templeman I, Thompson D, Gonzalez J, Walhin JP, Reeves S, Rogers PJ, et al. Intermittent fasting, energy balance and associated health outcomes in adults: study protocol for a randomised controlled trial. Trials. 2018;19(1):86.

20. Han K, Kwon O, Park HJ, Jung SY, Yang C, Son CG. Effect of Daesiho-tang on obesity with non-alcoholic fatty liver disease: a study protocol for a randomised, double-blind, placebo-controlled pilot trial. Trials. 2020;21(1):128.

21. Coffey CS, Steiner D, Baker BA, Allison DB. A randomized double-blind placebo-controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment. Int J Obes Relat Metab Disord. 2004;28(11):1411–9.

22. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473–83.

23. Karlsen TI, Tveitå EK, Natvig GK, Tonstad S, Hjelmesæth J. Validity of the SF-36 in patients with morbid obesity. Obes Facts. 2011;4(5):346–51.

24. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988;26(7):724–35.

25. Stubbs RJ, Hughes DA, Johnstone AM, Rowley E, Reid C, Elia M, et al. The use of visual analogue scales to assess motivation to eat in human subjects: a review of their reliability and validity with an evaluation of new hand-held computerized systems for temporal tracking of appetite ratings. Br J Nutr. 2000;84(4):405–15.

26. Blundell J, de Graaf C, Hulshof T, Jebb S, Livingstone B, Lluch A, et al. Appetite control: methodological aspects of the evaluation of foods. Obes Rev. 2010;11(3):251–70.

27. Lambert JE, Parnell JA, Han J, Sturzenegger T, Paul HA, Vogel HJ, et al. Evaluation of yellow pea fibre supplementation on weight loss and the gut microbiota: a randomized controlled trial. BMC Gastroenterol. 2014;14:69.

28. Kopf JC, Suhr MJ, Clarke J, Eyun SI, Riethoven JM, Ramer-Tait AE, et al. Role of whole grains versus fruits and vegetables in reducing subclinical inflammation and promoting gastrointestinal health in individuals affected by overweight and obesity: a randomized controlled trial. Nutr J. 2018;17(1):72.

29. Daneshi-Maskooni M, Keshavarz SA, Qorbani M, Mansouri S, Alavian SM, Badri-Fariman M, et al. Green cardamom increases Sirtuin-1 and reduces inflammation in overweight or obese patients with non-alcoholic fatty liver disease: a double-blind randomized placebo-controlled clinical trial. Nutr Metab (Lond). 2018;15:63.

30. Veronese N, Facchini S, Stubbs B, Luchini C, Solmi M, Manzato E, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2017;72:87–94.

31. Jais A, Brüning JC. Hypothalamic inflammation in obesity and metabolic disease. J Clin Invest. 2017;127(1):24–32.
32. Tan BL, Norhaizan ME. Effect of High-Fat Diets on Oxidative Stress, Cellular Inflammatory Response and Cognitive Function. Nutrients. 2019;11(11):2579.

33. Barazzoni R, Gortan Cappellari G, Ragni M, Nisoli E. Insulin resistance in obesity: an overview of fundamental alterations. Eat Weight Disord. 2018;23(2):149–57.

34. Torres-Fuentes C, Schellekens H, Dinan TG, Cryan JF. The microbiota-gut-brain axis in obesity. Lancet Gastroenterol Hepatol. 2017;2(10):747–56.

Tables

Table 1 Constituents contained in a daily dose of Jia Wei Dachaihu-tang soft extract

| Ingredients                | Latin Name                          | Content(g) |
|----------------------------|-------------------------------------|------------|
| Bupleuri Radix Chaihu      | Bupleurum chinense                  | 2.5        |
| Scutellaria amoena (Huangqin) | Scutellariae Radix                  | 1.0        |
| Rhizoma Pinellinae Praeparata Fabanxia | Arum Ternatum Thunb | 1.6        |
| Ginger Shengjiang          | Zingiber Officinale Roscoe         | 5.0        |
| Common Peony Baishao       | Paeoniae radix alba                 | 1.0        |
| Poria cocos Fuling         | Poria cocos (Schw.) Wolf            | 1.5        |
| Chinese rhubarb Dahuang    | Radix Rhei Et Rhizome               | 2.0        |
| Atractylodes macrocephala  | Atractylodes Macrocephala Koidz     | 2.5        |
| Fructus Ziziphi Jujubae    | Jujubae Fructus                     | 0.6        |
| Trifoliate Orange Zhishi   | Aurantii Fructus Immaturus          | 2.5        |

Figures
Figure 1

Study flowchart
# Figure 2

Schedule of enrolment, interventions and assessments

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• Additionalfile1.docx
• Additionalfile2.docx