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

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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 widely 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 Pinellinae Praeparata*(Fabanxia), *Ginger*(Shengjiang), *Common Peony*(Baishao), *Poria cocos*(Fuling), *Chinese*

rhubarb 大黄, *Atractylodes macrocephala* (Baizhu), *Fructus Ziziphi Jujubae* (Dazao), *Trifoliate Orange* (Zhishi) [16]. Composed on the basis of Dachaihu-Tang, a classic TCM formula from Synopsis of Golden Chamber [17], JWDT additionally 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 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 $[\text{Plasma glucose (GLU, mmol/L)} * \text{serum insulin (mIU/L)}] / 22.5$.

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, additionally, 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 factor α

WHR: waist to hip ratio

Declarations

Acknowledgments

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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.

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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

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Tables

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

Ingredients	Latin Name	Content(g)
Bupleuri Radix柴胡	Bupleurum chinense	2.5
Scutellaria amoena(Huangqin)	Scutellariae Radix	1.0
Rhizoma Pinellinae Praeparata法半夏	Arum Ternatum Thunb	1.6
Ginger姜	Zingiber Officinale Roscoe	5.0
Common Peony白芍	Paeoniae radix alba	1.0
Poria cocos(Fuling)	Poria cocos (Schw.) Wolf	1.5
Chinese rhubarb大黄	Radix Rhei Et Rhizome	2.0
Atractylodes macrocephala(Baizhu)	Atractylodes Macrocephala Koidz	2.5
Fructus Ziziphi Jujubae(大枣)	Jujubae Fructus	0.6
Trifoliate Orange(枳实)	Aurantii Fructus Immaturus	2.5

Figures

Figure 1

Study flowchart

	STUDY PERIOD					
	Enrolment	Allocation	Treatment period			Follow up
TIMEPOINT	-1 Week	Week 0	Week4	Week 8	Week12	Week16
ENROLMENT:						
Eligibility screen	x					
Informed consent	x					
Random Allocation		x				
INTERVENTION:						
JWDT		◆—————◆				
Placebo		◆—————◆				
ASSESSMENTS:						
Demographic characteristic	x					
Anthropometric measurements	x	x	x	x	x	x
Blood pressure	x	x	x	x	x	x
HRQoL questionnaire		x			x	
Assessments of appetite		x			x	
Blood testing		x			x	
Gut microbiome analysis		x			x	
Blind assessment					x	
Safety assessment			x	x	x	x

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](#)