

Effects of Bushen-Jiangya granules on blood pressure and pharmacogenomic evaluation in low-to-medium risk hypertension: study protocol for a randomized double-blind controlled trial

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Study protocol

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Abstract

Introduction

Hypertension is one of the most important risk factors for cardiovascular disease, and its treatment and control rates are still low worldwide. The most effective strategy is that patients with hypertension should be diagnosed and treated early. Preliminary studies showed that the Bushen Jiangya granule (BSJY) may suppress ventricular hypertrophy and inflammatory responses, lower blood pressure and protect the target organs of hypertension. We designed a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of BSJY in patients with low-to-medium risk hypertension.

Methods and analysis

This trial is a one-center, randomized, double-blind, placebo-controlled study. A total of 260 participants will be randomized in a 1:1 ratio to an experiment group (BSJY plus amlodipine) and a control group (placebo plus amlodipine). The trial cycle will last 8 weeks. The primary outcome is blood pressure, which is reduced to a threshold set out in Guiding Principles for Clinical Research of New Chinese Medicines. The secondary outcomes include the change in 24-h average systolic and diastolic blood pressure, heart rate variability, pharmacogenomic Evaluation, improvement in TCM Syndrome, serum pro-inflammatory/anti-inflammatory cytokines, etc. between the two groups. Safety in medication will also be evaluated. All the data will be recorded in electronic case report forms and analyzed by SPSS V.22.0.

Ethics and dissemination

This study has been approved by Research Ethics Committee of Guang'anmen Hospital,

China Academy of Chinese Medical Sciences in Beijing, China (No. 2019-186-KY-01). The participants are volunteers, understand the process of this trial and sign an informed consent. The results of this study will be disseminated to the public through peer-reviewed journals and academic conferences.

Discussion

We hypothesize that patients with low-to-medium risk hypertension will benefit from BSJY. If successful, this study will provide evidence-based recommendations for clinicians.

Strengths And Limitations Of This Study

- ▶ This is the first randomized, double-blinded, placebo-controlled clinical trial that exploring the efficacy, safety and pharmacogenomic evaluation of Chinese medicine (BSJY) in treating patients with low-to-medium risk hypertension.
- ▶ Numerous experiments and case study showed that BSJY had good effect on lowering BP and improving quality of life. However, there is a lack of high-quality clinical research on the supposed benefits of BSJY.
- ▶ It should be considered that the complexity of the genetic mechanisms underlying hypertension and the need for much larger sample sizes when looking for genes associated with BP. For BSJY, it can be viewed as a very important environment element to pharmacogenomic evaluation.
- ▶ The Multi-center experiments should be conducted in the future.

Introduction

Hypertension has become one of the most important leading global health challenges as the major risk for stroke, coronary heart disease (including heart attack), renal failure, and heart failure. As of now, the number of hypertensive patients worldwide has increased to 1.1 billion ^[1-2]. According to the 2020 International Society of Hypertension (ISH) Global Hypertension Practice Guidelines, although effective management greatly reduces the risk of cardiovascular events, blood pressure (BP) remains

uncontrolled in many people [3]. This ISH guide is different from the past, mainly in the following three points: 1. Different BP goals: the best standard is that for young and middle-aged people, the target BP should be less than 130/80 mmHg (not less than 120/70 mmHg); 2. The grading of hypertension is simplified, reduced the three stages to the two main ones (stages one, two); 3. Adjust the risk stratification, cancel the very high risk, and merge it into the high risk. BP remains uncontrolled in many people. If the diagnostic criteria for hypertension are moved forward, the BP of more people can be managed, which will help prevent long-term complications and reduce the long-term burden of economic health [4]. Although the new U.S. guidelines advocate the priority lifestyle intervention for the hypertensive population with the new definition, there are big differences in implementation and treatment in China and other Asia counties, and large-scale clinical trials are still needed to determine the ideal antihypertensive treatment, not only for the senior people, but also for the young and middle-aged population [5].

For the treatment of hypertension, five drug classes (β -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, thiazide diuretics and calcium channel blockers) are considered appropriate first-line therapy for HTN [6]. However, the response rates to monotherapy with any given antihypertensive drug are only $\approx 50\%$ [7]. It is said that selection of the initial antihypertensive therapy is essentially by trial and error, therefore the difficulty in determining the most appropriate antihypertensive drug for a specific patient likely contributes to the fact that less than half of the hypertensive patients worldwide currently have their BP controlled [8–10]. Pharmacogenomic evaluation of antihypertensive responses offers the clinical promise of individualization of therapy based on a person's genetic makeup [11]. More than twenty single nucleotide polymorphisms (SNPs) have been associated with BP in genome-wide association studies in Asian [12–13]. The loci/SNPs associated with BP/hypertension are also associated with BP response to antihypertensive drugs [8].

Traditional Chinese medicine (TCM) has long been widely used in hypertension in China. *Huangdi Neijing*, a classic work on TCM classified hypertension as headaches and vertigo. It is an early mention of hypertension occurs in ancient China. Nowadays, numerous studies have demonstrated the biological activity and therapeutic mechanism of TCM in hypertension [14–15]. Bu-Shen-Jiang-Ya granule (BSJY), is composed of eight herbs, Dihuang (Radix Rehmanniae Glutinosae), Shanzhuyu (Corni Fructus), Duzhong (Cortex Eucommiae Ulmoidis), Tianma (Gastrodiae Rhizoma), Sanqi (Notoginseng Radix), Mudanpi (Cortex Radicis Moutan), Shanzha (Crataegi Fructus), and Zexie (Rhizoma Alismatis), which is made from a modification of the classical Chinese herbal formula Liuwei Dihuang pill (table.1). Our previous evidence shows that BSJY has clinically effect on patients suffering from kidney-Yin Deficiency syndrome type hypertension [38–40]. The experimental acute toxicology study showed that the safety of BSJY is reliable [41]. Besides, BSJY reversed hypertensive ventricular hypertrophy by regulating the ERK pathway, and protected the endothelial function by regulating the PI3K/Akt pathway [42]. However, the pharmacogenomic evaluation of antihypertensive responses of BSJY remains unclear. This study is designed to investigate whether BSJY may represent a potential remedy for decreasing BP and slowing disease progression in low-to-medium risk hypertension based on pharmacogenomic evaluation. If positive, this work will be the first one that provide an evidence-based medicine remedy for TCM on treating hypertension by pharmacogenomic evaluation.

Methods And Design

Objectives

Our study aims to assess the clinical effect of BSJY on pharmacogenomics and pro-inflammatory/anti-inflammatory cytokines in patients with low-to-medium risk hypertension, to firstly provide a preliminary pharmacogenomic evaluation of antihypertensive responses in hypertension, and to observe whether TCM plus Western medicine has a better curative effect than Western medicine alone.

Study design

This protocol will be designed as a randomized, placebo-controlled trial. Participants, investigators, and statisticians will be blinded. A total of 260 subjects will be recruited at Guang An Men Hospital of the China Academy of Chinese Medical Sciences in China. The trial will be implemented base on the principles of good clinical practice and reported according to the CONSORT statement [43, 44]. The trial flow diagram is illustrated in Fig. 1. The Standard Protocol Items: Recommendations for Interventional Trials

(SPIRIT) ^[45] Checklist is shown in Additional file 1. This study has been registered at <http://www.chictr.org.cn>. (ChiMCTR1900002876).

Patient and public involvement

This trial was designed to evaluate the effect of BSJY on BP and pharmacogenomic evaluation in low-to-medium risk hypertension. Our previous clinical practice showed that BSJY adding to routine medications may lower BP and improve life quality in essential hypertension patients. The primary and secondary outcome measures used in this trial were considered as important endpoints in clinical practice. However, the participants of this trial were not directly involved in design, recruitment or conduct of the study. After the trial completes, the results of this study will be disseminated to the public through peer-reviewed journals and academic conferences. The burden of intervention will not be assessed by trial participants.

Participants

Inclusion criteria

Stage I or II hypertension with low to medium risk, which is diagnosed according to the Chinese Hypertension Guidelines published in 2018 ^[46]. The BP was continuous or more than 3 times in a non-same day sitting position with systolic BP ≥ 140 mmHg and < 180 mmHg and (or) diastolic BP ≥ 90 mmHg and < 110 mmHg. TCM syndrome is associated with kidney deficiency syndrome; TCM kidney deficiency syndrome is shown in Additional file 2. male or female; Without taking any hypotensive drugs. Aged between 18 and 75 years. The participants are volunteers, understand the process of this trial and sign an informed consent.

Exclusion criteria

Uncooperative. Secondary hypertension (symptomatic hypertension); severe hypertension systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 110 mmHg; severe heart failure; insulin-dependent diabetes; infectious diseases; hyperthyroidism; combined with severe primary diseases including liver, kidney, hematopoietic system, nervous system, mental illness, and malignant tumors; patients participating in other clinical trials; pregnant or breastfeeding women; recent history of trauma.

Withdraw criteria

- (1) Those who are unwilling to continue clinical trials during the research period;
- (2) Those who did not follow the prescribed protocol during the study period;
- (3) Those who have not completed the course of treatment or have incomplete information;
- (4) During the study period, those who applied drugs other than those specified in the study plan that affect the efficacy of observation.

Ethics

The protocol (version 4.0, dated 09 October 2019) was approved by the clinical research ethics committee of Guang An Men Hospital of the China Academy of Chinese Medical Sciences in China (approval 2019-186-KY-01), where the study will take place. It has been registered with the Chinese Clinical Trial Registry (ChiMCTR1900002876), which is listed in the WHO Registry Network. The Declaration of Helsinki and the principles of good clinical practice was complied by this trial ^[47, 48]. The participant must sign an informed consent form before enrollment. Meanwhile, they have right to withdraw from the trial at any time.

Randomization and blinding

The generate random tables were developed with Statistical Analysis System (SAS, Version 9.4) by randomization biostatisticians. All the participants were included in the clinical trial according to the order of random table numbers. The ratio of two groups was 1:1. For blinding, 260 sealed opaque envelopes were used to keep the allocation code for each participant, which were not accessible to the researchers, participants, clinical trial pharmacists, data managers, or statisticians. The BSJY granule was similar to its placebo in each group. The manufacturer, Sichuan Neo-Green Pharmaceutical Technology Development Co., Ltd labeled the random codes on the package according to the principles of GCP.

Intervention

BSJY (production batch number 191201), the placebo for BSJY (production batch number 191201), were produced and packed in a single batch by Sichuan Neo-Green Pharmaceutical Technology Development Co.,

Ltd. (Unified Social Credit Identifier 91510000684559613P). As tested, the drug conformed with the quality specified in the Chinese medicine standards published by the State Food and Drug Administration. Each bag of BSJY granule was 14.91g, and made from 138 g of original drug. The main component of the placebo for BSJY is dextrin and 10% original drug. Amlodipine besylate tablets was bought from Pfizer Co., Ltd. (Unified Social Credit Identifier 912102006048147187)

Endpoint measurements

Primary outcome

BP is reduced to a threshold set out in Guiding Principles for Clinical Research of New Chinese Medicines [49].

Secondary outcomes

1. The change in 24-h average systolic and diastolic BP, 24-h coefficient of BP variability (CV), morning BP, 24-h BP trough/peak ratio (T/P), 24-h BP smoothing index (SI).
2. Heart rate variability, based on routine 24-h BP monitoring.
3. Assessment of any improvement in TCM Syndrome, using TCM Syndrome Integral Scale (Additional file 2).
4. Assessment of any improvement in quality of life, using 36-Item Short Form Health Survey [50, 51]
5. Changes in levels of blood lipids, including total cholesterol, triglycerides, low-density lipoproteins, and high-density lipoprotein.
6. Serum pro-inflammatory/anti-inflammatory cytokines in patients: Changes in serum levels of TNF α , IL2R, IL6, IL8, IL10, IL1 β will be assessed at baseline and treatment endpoint.
7. Pharmacogenomic Evaluation: twenty loci/SNPs associated with BP/hypertension will be assessed at baseline and treatment endpoint.
8. Safety evaluation: routine blood and urine test including levels of creatinine, blood glucose, homocysteine will be assessed at baseline and treatment endpoint.

Data collection and management

The case report form (CRF) will be used for recording the process for each participant. In addition to the enrollment evaluation (-7 ± 0 days), each participant will attend an evaluation visit when allocated and every 2 weeks afterwards during the trial (0 days, 2 weeks, 4 weeks, 6 weeks, and 8 weeks). The assessments including physical examination, improvement in symptoms, compliance with medications, questions about adverse events, will be given to each participant. Blood tests and 24-h BP monitoring will be evaluated only at the enrollment and close-out visits. The schedule of enrolment, interventions, and assessments can be check in table 2. All researchers involved in data entry and data management will sign a confidentiality agreement to prevent data leakage. The personal information of all participants will be carefully protected and the original CRF will be kept for 5 years after the end of the trial.

Adverse events

Any accident, any signs of discomfort, or any disease symptoms, such as severe pain, syncope, hematoma, bleeding, or hypertensive emergencies will be viewed as Adverse events, and will be recorded on the participant's CRF. The research leader, sponsor, and the ethics committee will be contact with in 24h, if the clinical researchers report adverse event. And the ethics committee will recommend relevant treatment.

Statistical analysis

Sample size calculation

The formula used to calculate the sample size is as follows, which is based on superiority clinical trial interval hypothesis test sample size estimation [52]. The sample size was calculated based on expected reduction in reducing of BP. One previous study suggested that the reducing of BP after interventional treatment is 4.5 mmHg, and the BP SD is 10mmHg. Therefore, we assume the reduction of BP as 4.5 mmHg in this study. In the following formula, c is the ratio between two sample cases. $n_1 = n_2$, so $c=1$. σ is the BP SD 10 mmHg and δ is the expected effect BP 4.5 mmHg, so $\sigma=10$, $\delta=4.5$. Given a type I error rate of $\alpha = 0.05$, a power of 90 % (type II error rate of $\beta = 0.1$), so $u_{\alpha}=1.96$, $u_{\beta}=1.282$. $n_1=n_2 \approx 104$, the sample size for one group needs to be 104,

resulting $n=2 \times 104=208$ patients. Considering the maximum possible dropout rate is 20%, a total of 260 patients needs to be allocated to reach the required number of patients for the efficacy analysis.

$$n_1 = \left[\frac{(u_{\alpha} + u_{\beta})\sigma}{\delta} \right]^2 \frac{(1+c)}{c}, \quad n_2 = cn_1$$
$$n_1 = n_2 \approx 104$$

Planned data analysis

The intention-to-treat principle will be used to analyze the efficacy and safety of BSJY. The independent data administrator and the professional statistician will undertake data entry and data management, perform the data analysis respectively. All the efficacy and safety analyses with all randomly assigned participants included will be conducted within the full analysis set (FAS). The per-protocol set (PPS) analysis will also be conducted to compare the results from FAS and PPS. Demographic and laboratory characteristics will be calculated at baseline and after-treatment period for all patients. The statistical analysis will be done at Guang'anmen Hospital, China Academy of Chinese Medical Sciences in Beijing.

For continuous variables with normal distribution, the comparability of the characteristics between the two study groups will be assessed by using t-test. While for the comparison of data with non-normal distribution, the non-parametric Mann-Whitney-Wilcoxon test will be used. Continuous variables will be expressed by mean \pm SD. Specifically, we will assess the paired t-test to compare the difference of the outcome between preintervention and postintervention in each group by using independent t-test. A χ^2 test will be used for categorical variables, while the Fisher exact test will be used when the theoretical frequency is less than 5 in more than 25% of the cells. Categorical variables will be shown as counts and percentages. Whether the hypothesis of superiority is available will be judged by comparing the 95%CI of the difference in intergroup efficacy. All statistical tests are unilateral test, $p < 0.05$ is statistically significant. All statistical analyses will be performed using SPSS V.20.0.

Discussion

Hypertension, as one of the most important risk factors for cardiovascular disease, its treatment and control rates are still low worldwide [53]. Better treatment methods with fewer side effects are required, which was the motivation to apply BSJY in this research. In this trial, we will assess the efficacy and safety of BSJY in treating patients with low-to-medium risk hypertension.

According to our previous studies, BSJY can promote the expression of the ERK pathway and inhibit the expression of the TNF- α , MCP-1, IL-6, which would suppress ventricular hypertrophy and inflammatory responses. Furthermore, BSJY may lower BP and protect the target organs of hypertension including heart, kidney by inhibiting TGF- β 1/Smads signaling molecules in spontaneous hypertensive rats [54]. Based on network pharmacology, 93 active ingredients were predicted for BSJY involving 566 core targets, including 50 direct targets, such as epinephrine receptor, adenosine receptor, endothelin receptor, nitric oxide synthase, glucose Kinases, etc.; involved in the regulation of calcium and sodium ion transport, vascular endothelial function, glucose and lipid metabolism and other related biological processes and signaling pathways [55]. A liquid chromatography–mass spectrometry analysis of BSJY also has been conducted to evaluate its chemical components. It mainly contains tartaric acid, gallic acid, gastrodin, catalpol, neochlorogenic acid, 2-[4-(b-D-Glucopyranosyloxy) benzyl] citrate, morroniside, chlorogenic acid, oxypaeoniflorin, cryptochlorogenic acid, loganin, parishin B, pinoresinol di-O-Glc, parishin C, quercetin-3-O-sambubioside, suffruticoside A or B or C or D, galloylpaeoniflorin, iso-Mudanpioside H. However, there is a lack of high-quality clinical research on the supposed benefits of BSJY.

Pharmacogenomic evaluation of antihypertensive responses offers the clinical promise of individualization of therapy based on a person's genetic makeup [11]. It is said that the loci/SNPs associated with BP/hypertension are also associated with BP response to antihypertensive drugs [8]. This is the first paper that researching pharmacogenomic evaluation of antihypertensive responses in TCM. The present study is designed as a double-blind, randomized, placebo-controlled trial that will provide high-powered evidence regarding the efficacy, safety and pharmacogenomic evaluation of BSJY in treating patients with low-to-medium risk hypertension. The progress and quality of the trial will be monitored by a clinical research organization of Guang'anmen Hospital.

There are also some limitations in this study. First, we supposed to test twenty single nucleotide polymorphisms (SNPs) that have been associated with BP in genome-wide association studies in Asian. It is different that significant genetic loci for BP and hypertension reported in genome-wide association studies in Europeans and Asians and Africans. It should be considered that the complexity of the genetic mechanisms underlying hypertension and the need for much larger sample sizes when looking for genes associated with BP. For TCM, it can be viewed as a very important environment element to pharmacogenomic evaluation. Second, our Multi-center experiments will be conducted in China in the future.

Trial Status

Patient recruitment began in November 2019 and was expected to be completed in December 2022. At the time of manuscript submission, 80 patients had been recruited and completed the 9-week follow-up. Currently, we are still recruiting participants. However, no analysis has been conducted since the commencement of the trial. No serious AEs have occurred to date.

References

- [1] Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet*.doi.org/10.1016/S0140-6736(16)31919-5
- [2] Wang C, Yuan Y, Zheng M, et al. Association of Age of Onset of Hypertension With Cardiovascular Diseases and Mortality. *J Am Coll Cardiol*.2020.doi.org/10.1016/j.jacc.2020.04.038
- [3] Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020 Jun;75(6):1334-1357. doi: 10.1161/HYPERTENSIONAHA.120.15026. Epub 2020 May 6. PMID: 32370572.
- [4] Wyss F, Coca A, Lopez-Jaramillo P, Ponte-Negretti C; Task Force for the management of Arterial Hypertension of the Interamerican Society of Cardiology (IASC); Reviewers from European Society of Hypertension (ESH), Latin-American Society of Hypertension (LASH), Spanish Society of Cardiology (SSC). Position statement of the Interamerican Society of Cardiology (IASC) on the current guidelines for the prevention, diagnosis and treatment of arterial hypertension 2017-2020. *Int J Cardiol Hypertens*. 2020 Jul 15;6:100041. doi: 10.1016/j.ijch.2020.100041. PMID: 33447767; PMCID: PMC7803017.
- [5] Luo D, Cheng Y, Zhang H, Ba M, Chen P, Li H, Chen K, Sha W, Zhang C, Chen H. Association between high blood pressure and long term cardiovascular events in young adults: systematic review and meta-analysis. *BMJ*. 2020 Sep 9;370:m3222. doi: 10.1136/bmj.m3222. PMID: 32907799; PMCID: PMC7478061.
- [6] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report.*JAMA*. 2003; 289:2560–2572.
- [7] Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, et al.. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo: The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents.*N Engl J Med*. 1993; 328:914–921.
- [8] Gong Y, McDonough CW, Wang Z, Hou W, Cooper-DeHoff RM, Langae TY, Beitelshes AL, Chapman AB, Gums JG, Bailey KR, Boerwinkle E, Turner ST, Johnson JA. Hypertension susceptibility loci and blood pressure response to antihypertensives: results from the pharmacogenomic evaluation of antihypertensive responses study. *Circ Cardiovasc Genet*. 2012 Dec;5(6):686-91. doi: 10.1161/CIRCGENETICS.112.964080. Epub 2012 Oct 19. PMID: 23087401; PMCID: PMC3529147.
- [9] Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2012 update: a report from the American Heart Association.*Circulation*. 2012; 125:e2–e220.

- [10] Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet*. 1999; 353:2008–2013.
- [11] Gong Y, McDonough CW, Wang Z, Hou W, Cooper-DeHoff RM, Langaee TY, Beitelshes AL, Chapman AB, Gums JG, Bailey KR, Boerwinkle E, Turner ST, Johnson JA. Hypertension susceptibility loci and blood pressure response to antihypertensives: results from the pharmacogenomic evaluation of antihypertensive responses study. *Circ Cardiovasc Genet*. 2012; 5:686–691.
- [12] Kato N, Takeuchi F, Tabara Y, Kelly TN, Go MJ, Sim X, et al. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. *Nat Genet*. 2011 Jun;43(6):531–8.
- [13] Lu X, Wang L, Lin X, Huang J, Charles Gu C, He M, et al. Genome-wide association study in Chinese identifies novel loci for blood pressure and hypertension. *Hum Mol Genet*. 2015 Feb;24(3):865–74.
- [14] Wang Jie, Xingjiang Xiong, Evidence-based chinese medicine for hypertension, Evidence-based complementary and alternative medicine: eCAM. 2013 (2013), 978398.
- [15] Xingjiang Xiong, Xiaochen Yang, Wei Liu, Fuyong Chu, Pengqian Wang, Jie Wang, Trends in the treatment of hypertension from the perspective of traditional Chinese medicine, Evidence-based complementary alternative medicine: eCAM. 2013, 275279.
- [16] Li-fang Luo, Wei-hua Wu, Ying-jun Zhou, Jin Yan, Guo-ping Yang, Dongsheng Ouyang, Antihypertensive effect of *Eucommia ulmoides* Oliv, extracts in spontaneously hypertensive rats, *J. Ethnopharmacol*. 129 (2) (2010) 238–243.
- [17] Yansheng Yao, Yanbing Wang, Yibo Zhang, Chang Liu, Klotho ameliorates oxidized low-density lipoprotein (ox-LDL)-induced oxidative stress via regulating LOX-1 and PI3K/Akt/eNOS pathways, *Lipids Health Dis*. 16 (2017) 77.
- [18] Kai He, Xuegang Li, Xin Chen, Xiaoli Ye, Jing Huang, Yanan Jin, Panpan Li, Yafei Deng, Qing Jin, Qing Shi, Hejing Shu, Evaluation of antidiabetic potential of selected traditional Chinese medicines in STZ-induced diabetic mice, *J. Ethnopharmacol*. 137 (3) (2011) 1135–1142.
- [19] Xinxin Dai, Shulan Su, Hongdie Cai, Dandan Wei, Hui Yan, Tianyao Zheng, Zhenhua Zhu, Er-Xin Shang, Sheng Guo, Dawei Qian, Jin-Ao Duan, Protective effects of total glycoside from *Rehmannia glutinosa* leaves on diabetic nephropathy rats via regulating the metabolic profiling and modulating the TGF- β 1 and wnt/ β -Catenin signaling pathway, *Front. Pharmacol*. 9 (2018) 1012.
- [20] Lei Ren, Yapei Xu, Guijun Qin, Cong Liu, Shoujun Wang, Effects of water extracts of *Rehmannia glutinosa* on antioxidant system of Nrf2 in paraquat-induced insulin resistance diabetic rat model, *Exp. Ther. Med*. 14 (6) (2017) 5847–5850.
- [21] X. Duan, W. Wang, X. Liu, H. Yan, R. Dai, Q. Lin, Neuroprotective effect of ethyl acetate extract from *Gastrodia elata* against transient focal cerebral ischemia in rats induced by middle cerebral artery occlusion, *J. Tradit. Chin. Med*. 35 (6) (2015) 671–678.
- [22] Min Chul Kho, Yun Jung Lee, Jeong Dan Cha, Kyung Min Choi, Dae Gill Kang, Sub Lee Ho, *Gastrodia elata* ameliorates high-fructose diet-induced lipid metabolism and endothelial dysfunction, Evidence-based complementary alternative medicine: eCAM. 2014 (2014), 101624.
- [23] Yuan Liu, Jialiang Gao, Min Peng, Hongyan Meng, Hongbo Ma, Pingping Cai, Yuan Xu, Qiong Zhao, Guomin Si, A review on central nervous system effects of *Gastrodin*, *Front. Pharmacol*. 2 (9) (2018) 24.
- [24] Hye-Lin Kim, Yong-Deok Jeon, Jinbong Park, Hong-Kun Rim, Mi-Young Jeong, Hara Lim, Seong-Gyu Ko, Hyeung-Jin Jang, Byung-Cheol Lee, Kyung-Tae Lee, Kang-Min Lee, Hyejung Lee, Sung-Hoon Kim, Su-Jin Kim, Seung-Heon Hong, JaeYoung Um, *Corni fructus* containing formulation attenuates weight gain in mice with diet-induced obesity and regulates adipogenesis through AMPK, *Evid. Complement. Alternat. Med*. 2013 (2013), 423741.

- [25] Dongying Wang, Chenxi Li, Wenchang Fan, Tao Yi, Anchi Wei, Yuxiang Ma, Hypoglycemic and hypolipidemic effects of a polysaccharide from *Fructus Corni* in streptozotocin-induced diabetic rats, *Int. J. Biol. Macromol.* 133 (2019) 420–427.
- [26] Chien-Chih Chen, Chia-Yun Hsu, Chin-Ying Chen, Hui-Kang Liu, *Fructus Corni* suppresses hepatic gluconeogenesis related gene transcription, enhances glucose responsiveness of pancreatic beta-cells, and prevents toxin induced beta-cell death, *J. Ethnopharmacol.* 117 (3) (2008) 483–490.
- [27] Dawei Gao, Qingwang Li, Zhengrong Gao, Lixin Wang, Antidiabetic effects of *Corni Fructus* extract in streptozotocin-induced diabetic rats, *Yonsei Med. J.* 53 (4) (2012) 691–700.
- [28] Chan Hum Park, Jeong Sook Noh, Jong Cheol Park, Takako Yokozawa, Beneficial effect of 7-O-Galloyl-D-sedoheptulose, a polyphenol isolated from *corni fructus*, against diabetes-induced alterations in kidney and adipose tissue of type 2 diabetic db/db mice, *Evidence-based complementary alternative medicine: eCAM.* 2013 (2013), 736856.
- [29] Thi Ha Do, Trinh Nam Trung, Tran Thi Hien, Trong Tuan Dao, Namhui Yim, Tran Minh Ngoc, Oh Won Keun, Kih Wan Bae, Selected compounds derived from *Moutan Cortex* stimulated glucose uptake and glycogen synthesis via AMPK activation in human HepG2 cells, *J. Ethnopharmacol.* 131 (2) (2010) 417–424.
- [30] Juan Chen, Xue-Feng Hou, Gang Wang, Qing-Xiang Zhong, Ying Liu, Hui-Hui Qiu, Nan Yang, Jun-Fei Gu, Chun-Fei Wang, Li Zhang, Jie Song, Lu-Qi Huang, XiaoBin Jia, Ming-Hua Zhang, Liang Feng, Terpene glycoside component from *Moutan Cortex* ameliorates diabetic nephropathy by regulating endoplasmic reticulum stress-related inflammatory responses, *J. Ethnopharmacol.* 193 (2016) 433–444.
- [31] Hong Dan, Juan Wu, Min Peng, Xuefeng Hu, Chengwu Song, Zhiwen Zhou, Shanggong Yu, Nianbai Fang, Hypolipidemic effects of *Alismatis rhizome* on lipid profile in mice fed high-fat diet, *Saudi Med. J.* 32 (7) (2011) 701–707.
- [32] X. Zhou, Q. Ren, B. Wang, G. Fang, Y. Ling, X. Li, *Alisol a 24-Acetate* isolated from the *alismatis rhizoma* improves hepatic lipid deposition in hyperlipidemic mice by ABCA1/ABCG1 pathway, *J Nanosci Nanotechnol.* 19 (9) (2019) 5496–5502.
- [33] Chiakang Ho, Ya Gao, Danning Zheng, Yanjun Liu, Shengzhou Shan, Bin Fang, Yixuan Zhao, Dingzhong Song, Yifan Zhang, Qingfeng Li, *Alisol A* attenuates highfat-diet-induced obesity and metabolic disorders via the AMPK/ACC/SREBP-1c pathway, *J. Cell. Mol. Med.* 23 (8) (2019) 5108–5118.
- [34] Y.B. Chen, Y.H. Dong, Clinical effect and pharmacological analysis of *panax notoginseng* saponins in the treatment of hyperlipidemia, *China Med Pharm.* 6 (139) (2006) 51–53.
- [35] D.U. Xue-Jun, Yan Lei, Jing Yang, Effects of *Radix ginseng* and *Radix notoginseng* formula on expressions of vascular endothelial growth factor receptor-2 and hypoxia-inducible factor-1alpha in ischemic myocardium of rats with acute myocardial infarction, *Zhong Xi Yi Jie He Xue Bao* 8 (6) (2010) 548-553.
- [36] Long-Tao Liu, Guang-Juan Zheng, Wen-Gao Zhang, Gang Guo, Min Wu, Clinical study on treatment of carotid atherosclerosis with extraction of *polygoni cuspidati rhizoma et Radix and crataegi fructus*: a randomized controlled trial, *Zhongguo Zhong Yao Za Zhi* 39 (6) (2014) 1115-1119.
- [37] E. Dalli, E. Colomer, M.C. Tormos, J. Cosin-Sales, J. Milara, E. Esteban, G. Saez, *Crataegus laevigata* decreases neutrophil elastase and has hypolipidemic effect: a randomized, double-blind, placebo- controlled trial, *Phytomedicine* 18 (2011) 769–775.
- [38] X.C. Yang, X.J. Xiong, J. Wang, Clinical observation of 108 cases of primary hypertension treated with *bu shen jiang ya* therapy, *World J. Integr. Traditional Western Med.* 10 (2014) 1083–1087.
- [39] Wang Jie, Xingjiang Xiong, Current situation and perspectives of clinical study in integrative medicine in china, *Evidence-based complementary alternative medicine: eCAM.* 2012 (2012), 268542.

- [40] Jie Wang, Xingjiang Xiong, Wei Liu, Traditional chinese medicine syndromes for essential hypertension: a literature analysis of 13,272 patients, Evidence-based complementary and alternative medicine, eCAM 2014 (2014), 418206.
- [41] W. Liu, J. Wang, X.J. Xiong, X.C. Yang, Experimental study of bu shen jiang ya decoction on acute toxicology, Beijing J Tredit Chin Med. 32 (2013) 647–649.
- [42] Xingjiang Xiong, Xiaochen Yang, Lian Duan, Wei Liu, Yun Zhang, Yongmei Liu, Pengqian Wang, Shengjie Li, Xiaoke Li, Traditional Chinese medicine suppresses left ventricular hypertrophy by targeting extracellular signal-regulated kinases signaling pathway in spontaneously hypertensive rats, Sci. Rep. 7 (2017) 42965.
- [43] Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010;63(8):e1–e37.
- [44] Boutron I, Altman DG, Moher D, et al. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. Ann Intern Med. 2017;167(1):40–47.
- [45] Chan A W, Tetzlaff J M, Gøtzsche P C, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials[J]. BMJ. 2013;346:e7586.
- [46] Liu J. Highlights of the 2018 Chinese hypertension guidelines. Clin Hypertens. 2020 May 1;26:8. doi: 10.1186/s40885-020-00141-3. PMID: 32377372; PMCID: PMC7193361.
- [47] World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ. 2001;79(4):373–4.
- [48] Switula D. Principles of good clinical practice (GCP) in clinical research. Sci Eng Ethics. 2000;6(1):71–77.
- [49] Zheng XY. Guiding Principles for Clinical Research of New Chinese Medicines. China Medical Science and Technology Press. 2002; 4:73–77.
- [50] Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
- [51] Insana SP, Hall M, Buysse DJ, Germain A. Validation of the Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder (PSQI-A) in U.S. male military veterans. J Trauma Stress. 2013;26(2):192–200.
- [52] Wan X, Zh L, Liu JP. Estimation of sample size in clinical studies: (1) clinical trials. Journal of Traditional Chinese Medicine 2017; 48:504–7.
- [53] Ventura HO, Taler SJ, Strobeck JE. Hypertension as a hemodynamic disease: the role of impedance cardiography in diagnostic, prognostic, and therapeutic decision making. Am J Hypertens. 2005;18(2 Pt 2):26S–43S.
- [54] Liu W, Li Y, Xiong X, Chen Y, Qiao L, Wang J, Su X, Chu F, Liu H. Traditional Chinese medicine protects against hypertensive kidney injury in Dahl salt-sensitive rats by targeting transforming growth factor- β signaling pathway. Biomed Pharmacother. 2020 Nov;131:110746. doi: 10.1016/j.biopha.2020.110746. Epub 2020 Sep 17. PMID: 33152915.
- [55] Yang Xiao-chen, Zhang Yun, Liu Yongmei, Wang Jie. Explore mechanism of Bushen Jiangya Decoction for hypertension based on network pharmacology. Chinses Journal of Integrative Medicine on Cardio-cerebrovascular disease. 2021, 19 (2): 197-205.

Declarations

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Author Contributions

Xiaochen Yang and Xingjiang Xiong contributed equally to this work. Xiaochen Yang drafted the protocol. Xingjiang Xiong, Yun Zhang and Yongmei Liu revised the protocol. Hongzheng Li, Kuiwu Yao and Jie Wang recruited the patients. All of the authors participated in the design and read and approved the final manuscript.

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Ethics declarations

Ethics approval

The Ethics Committee of Guang An Men Hospital of the China Academy of Chinese Medical Science has approved this trial for the participating centers (No. 2019-186-KY-01) and an informed consent form must be obtained before randomization.

Consent for publication

All participants have provided consent to share their individual medical information.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 2. Schedule of data collection

Item	Process	Run-in period	Run-in period	Pre-treatment	Treatment period			
					2W	4W	6W	8W
	Time point	-7 day	1day	0day				
Baseline information								
	Informed consent	√						
	Eligibility screen			√				
	Medical history	√						
	Allocation	√						
Effectiveness observation								
	Blood pressure	√		√	√	√	√	√
	24-h blood pressure			√				√
	pro-inflammatory/anti-inflammatory cytokines			√				√
	improvement in TCM Syndrome			√	√	√	√	√
	improvement in quality of life			√				√
	Pharmacogenomic Evaluation			√				√
Safety observation								
	Physical exam		√					√
	Blood pressure		√					√
	Routine Blood test		√					√
	Routine urine test		√					√
	Liver and kidney function		√					√
	Adverse event				√	√	√	√
Other work								
	CRF audit							√

Table 1 Components and dose of BSJY

Chinese name	English name	Latin name	Origin	Main ingredients	Main Pharmacological effects	Raw drug weight (g)	Granule weight (g)
Duzhong	Eucommia Bark	Cortex Eucommiae Ulmoidis	The bark of Cortex Eucommiae Ulmoidis	Quercetin; Mairin; beta-sitosterol; kaempferol; Erythraline; Eucommin A; (-)-Tabernemontanine; Cyclopamine; GBGB; Helenalin	Lowering BP [16]; reversing hypertensive vascular remodeling and hypertensive cardiac remodeling [17]; improving insulin resistance and lowering blood glucose [18];	10	0.48
Dihuang	Rehmannia	Radix Rehmanniae Glutinosae	The root of Radix Rehmanniae Glutinosae	EIC; sitosterol; Stigmasterol; aegnetic acid; jioglutin D; Rehmaglutin B	Lowering BP and improving insulin resistance [19] glucose metabolism, lipid metabolism, [20];	25	3.57
Tianma	Gastrodia	Gastrodiae Rhizoma	The tuber of Gastrodiae Rhizoma	Daucosterol; citronellal; dauricine; gastrodin; p-hydroxybenzaldehyde; p-hydroxybenzyl alcohol; 4-hydroxybenzylamine; suchilactone; suffruticoside a; sucrose; vanillin; vanillin acetate	impairing vascular endothelial function [21]; Lowering BP [22]; improving lipid metabolism and insulin resistance [23];	20	1.82
Wuzhuyu	Cornus Fruit	Corni Fructus	The fruit of Corni Fructus	beta-sitosterol; sitosterol; Stigmasterol; Mandenol; Ethyl linolenate; poriferast-5-en-3beta-ol; Ethyl oleate (NF); Leucanthoside; Hydroxygenkwanin; Telocinobufagin; gemin D; Tetrahydroalstonine	Regulating adipogenesis [24]; Lowering blood glucose and insulin resistance [25]; improving lipid metabolism [26]; protecting vascular endothelial cell [27], and protecting target organs and tissue related to diabetic damage [28];	10	1.43
Mudanpi	Cortex of the Peony Tree Rote	Cortex Radicis Moutan	The root and bark of Cortex Radicis Moutan	Quercetin; Mairin; sitosterol; kaempferol	increasing the arterial blood flow, and improving glucose metabolism [29]; Lowering BP and heart rate [30];	10	0.91
Zexie	Alisma	Rhizoma Alismatis	The rhizome of Rhizoma Alismatis	Sitosterol; Alisol B; Alisol B monoacetate; alisol,b,23-acetate; alisol B; alisol C; alisol C monoacetate; 1-Monolinolein	Lowering blood glucose [31]; improving Hepatic lipid deposition [32]; Improving lipid metabolism [33];	30	2.73
Sanqi	Notoginseng	Notoginseng	The root of	Quercetin; beta-	Protecting the	3	1.5

	Root	Radix	Notoginseng Radix	sitosterol; Stigmasterol; Mandenol; DFV; ginsenoside rh2; ginsenoside f2	vascular endothelium [34]; improving myocardial ischemia [35];		
Shanzha	Crataegus Fruit	Crataegi Fructus	The fruit of Crataegi	Quercetin; isorhamnetin; sitosterol; kaempferol; Stigmasterol	Promoting anti-atherosclerosis [36]; improving vascular endothelial dysfunction [37];	30	4.29

Figures

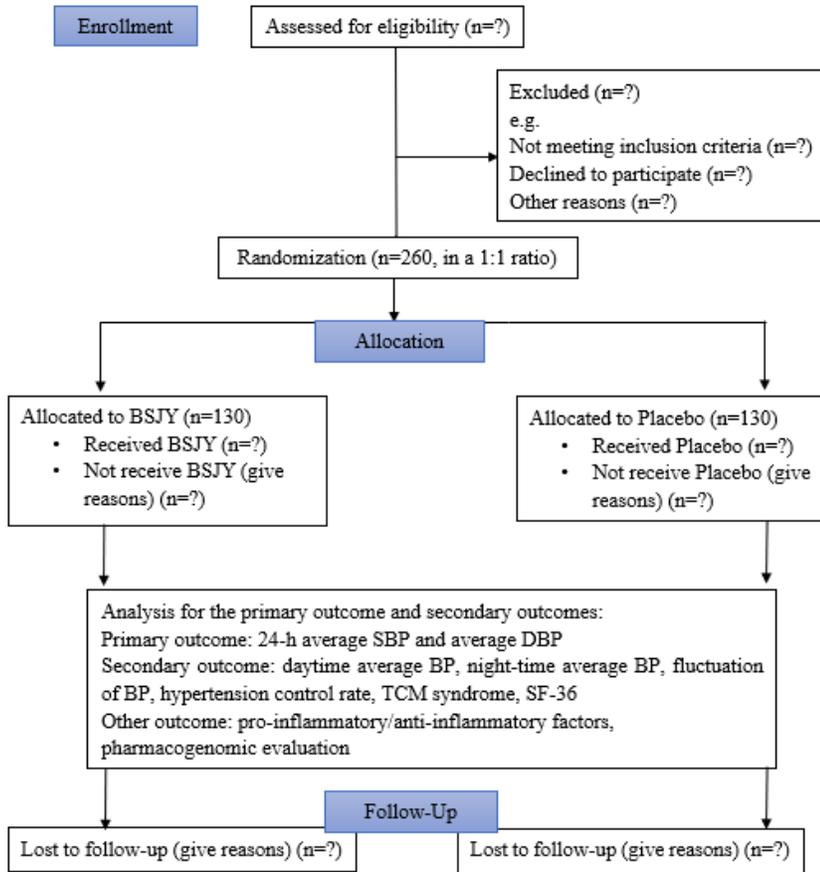


Figure 1

CONSORT flow diagram for BSJY clinical trial. BSJY, Bushen Jiangya granules.

Supplementary Files

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