Efficacy and safety of *Ginkgo biloba* dropping pills in the treatment of coronary heart disease with stable angina pectoris and depression: study protocol for a randomised, placebo-controlled, parallel-group, double-blind and multicentre clinical trial

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ABSTRACT

**Background**  Coronary heart disease (CHD) with stable angina pectoris is a common cardiovascular disease. It has been reported that 10%–81.4% of these patients suffer from psychological conditions, such as depression, which has been associated with more frequent angina, lower treatment satisfaction and lower perceived quality of life. *Ginkgo biloba* extract (GBE), the raw material of *Ginkgo biloba* dropping pills (GBDPs), is widely used to treat various conditions, including cardiovascular disease, ischaemic cerebrovascular disease, and depression. This clinical trial aimed to examine the efficacy and safety of GBDPs in improving the frequency of angina pectoris and the life quality of patients with stable angina pectoris and depression symptoms.

**Methods**  This randomised, double-blind, placebo-controlled, parallel-group and multicentre clinical trial will be conducted in four medical centres in China. We aim to recruit approximately 72 participants aged 18–75 years with depression and coronary heart disease with stable angina pectoris. Based on conventional drug treatment, participants will be randomly assigned to the treatment group (GBDPs group; n=36) or the control group (placebo group; n=36) at a 1:1 allocation ratio. After randomisation, follow-up will be done at 4 weeks, 8 weeks and 12 weeks (±3 days). Additionally, 30 healthy individuals will be enrolled to investigate the underlying pharmacological mechanisms of the effects of GBE. The primary outcomes will be the Seattle Angina Questionnaire score and the frequency of angina pectoris-related symptoms each week. The secondary outcomes will include the 36-item Short Form Health Survey quality-of-life scale, Hamilton Depression Scale and composite endpoint incidence of major adverse cardiovascular events.

**Ethics and dissemination**  This trial has been approved by the Research Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine, China (approval number: ZYECK [2020]030). Written informed consent will be obtained from all participants. The results of this trial will be publicly shared through academic conferences and peer-reviewed journals. The main limitation of the present study is the small sample study recruited from 4 centres located in southern China. Whether the same effect would be observed in larger sample sizes and other regions remains uncertain.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

- This is the first multicentre randomised controlled trial investigating the effect of *Ginkgo biloba* dropping pills (GBDPs) for treating coronary heart disease with stable angina pectoris and depression.
- Placebo and GBDPs are similar in packaging, appearance, odour and dosage form.
- All patients will fill out the Seattle Angina Questionnaire, and the weekly frequency of angina-related symptoms will be recorded at each follow-up visit. Other measurements and major adverse cardiovascular events will also be observed.
- The main limitation of the present study is the small sample study recruited from 4 centres located in southern China. Whether the same effect would be observed in larger sample sizes and other regions remains uncertain.

INTRODUCTION

Coronary heart disease (CHD) with stable angina pectoris (SAP) is a common cardiovascular disease. Many patients with SAP also develop psychological conditions due to the pain and near-death sensation they experience at the time of onset and the stress induced by factors such as the poor prognosis of CHD.1–4 The most common psychological...
conditions among these patients are anxiety and depression, which can substantially impair the patients’ quality of life. Depressive symptoms have been strongly associated with symptom burden, physical function, disease-specific quality of life and perceived overall health among patients with coronary disease. 

*Ginkgo biloba* dropping pills (GBDPs) is a Chinese patent medicine made of *Ginkgo biloba* extract (GBE) and approved for treating cardiovascular and cerebrovascular diseases by the China Food and Drug Administration (China drug approval number: Z 20040071). It is a new type of GBE preparation (full extract) that is prepared by using the extraction method of the pharmacopoeia of the People’s Republic of China (Edition 2015). This method increases their concentrations, achieving a rapid clinical effect, satisfactory efficacy with a small dose, good safety, and good patient compliance in long-term administration. Besides flavonoids, new terpenoids and a lignan have also been recently isolated from *Ginkgo biloba* leaves (GBL). The main ingredient of the GBDPs is ginkgolide. Preliminary studies on the pharmacology of GBE have confirmed that it can reduce oxidative stress and anxiety, promote sedation, regulate blood lipid level and inhibit platelet aggregation. GBE was also found to increase coronary blood flow and alleviate myocardial ischaemia (MI)/reperfusion injury. Moreover, Ge et al showed that ginkgolide B markedly increases the 5-HT content in brain median raphe nuclei and cortex by reducing interleukin 1β production in these tissues, thus reducing the severity of depression in a myocardial infarction mouse model. The clinical studies further demonstrated that GBE could improve coronary blood flow in patients with CHD; however, the efficacy of GBDPs in treating CHD with SAP and depression based on the standard conventional therapy should be further confirmed by high-quality trials and evidence.

The aim of this randomised, parallel, placebo-controlled, double-blind and multicentre clinical trial was to examine the efficacy and safety of GBDPs in improving angina frequency, functional status and disease-specific quality of life and to explore its effects on depressive symptoms and overall health in patients with CHD accompanied by SAP and depression. The results of this trial may provide clinical evidence for treating patients with CHD accompanied by SAP and depression.

**METHODS AND DESIGN**

**Study design**

This randomised, double-blind, placebo-controlled and multicentre clinical trial will be conducted in four medical centres in China, that is, the First Affiliated Hospital of the Guangzhou University of Chinese Medicine, the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Shenzhen Luohu People’s Hospital and Central Hospital of Chancheng District, Foshan. Trained research doctors will introduce the trial information to patients. Approximately 72 participants who meet all the inclusion criteria and none of the exclusion criteria and agree to provide written informed consent will be randomly assigned to the treatment group or the control group in a 1:1 ratio. Based on the standard medical therapy for SAP, participants will be orally administered GBDPs or a placebo (5 pills, 3 times a day) for 12 weeks. Follow-up visits will occur 4 weeks (±3 days), 8 weeks (±3 days) and 12 weeks (±3 days) after randomisation. Meanwhile, 30 healthy individuals will be recruited as another control group to investigate the underlying pharmacological mechanisms of GBE.

The relevant medical data of trial participants will be accurately recorded using an electronic case report form (eCRF) through an electronic data management system (Gooclin). The database will be maintained by the data department of the Data Management and Statistical Analysis Unit, which adopts the standard of the Clinical Data Interchange Standards Consortium to the greatest extent possible.

**Patients and public involvement**

None of the patients will be directly involved in the study’s design, recruitment or conduct. After the trial is completed, the results will be disseminated to the public through academic conferences and peer-reviewed journals. Once the manuscript is published, the results will be briefly summarised in simple language, and all trial participants will be informed through the telephone. The trial participants will not assess the burden of intervention.

**Study population**

**Inclusion criteria**

1. Age 18–75 years, either sex.
2. A clear understanding of the study and voluntary participation in the study, as confirmed by signature on the informed consent form.
3. Diagnosis of CHD based on at least one of the following criteria: (a) a clear history of myocardial infarction; (b) acceptance of treatment by coronary artery revascularisation; (c) coronary radiography or coronary angiography results showing stenosis of at least one coronary artery and lumen stenosis ≥50% and (d) cardiac MRI, radionuclide myocardial perfusion imaging or cardiac colour Doppler imaging confirming CHD with MI.
4. Diagnosis of SAP.
5. Prior treatment of SAP according to the clinical guidelines with stability achieved for at least 4 weeks.
6. Meeting the diagnostic criteria for a depressive episode provided in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) issued by the WHO.
7. No consumption of any food that impacts the intestinal flora, such as foods containing probiotics (such as yoghurt) or drugs (such as antibiotics) within 7 days (table 1).
Table 1 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>▶ Age 18–75 years, either sex</td>
<td>▶ The presence of acute myocardial events, unstable angina pectoris or severe heart failure; serious arrhythmia; severe or poorly controlled hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg); sitting blood pressure and systolic blood pressure ≤85 mm Hg or symptomatic hypotension; severe primary diseases such as liver, kidney and haematopoietic system; or serious diseases affecting survival (such as a tumour, and so on)</td>
</tr>
<tr>
<td>▶ A clear understanding of the study and voluntary participation in the study, as confirmed by signature on the informed consent form</td>
<td>▶ Serious suicidal tendencies; HAMD item 3 score ≥3, bipolar disorder depressive episode in patients with epilepsy history or depression secondary to other mental or physical diseases, alcohol and drug dependence within 1 year</td>
</tr>
<tr>
<td>▶ Diagnosis of CHD based on at least one of the following criteria:</td>
<td>▶ Abnormal liver and kidney function (ALT and/or AST &gt;3 times the normal upper limit and/or Cr &gt;2 times the normal upper limit)</td>
</tr>
<tr>
<td>1. A clear history of myocardial infarction</td>
<td>▶ Current use of anti-anxiety drugs</td>
</tr>
<tr>
<td>2. Acceptance of treatment by coronary artery revascularisation</td>
<td>▶ Pregnancy, lactation, plan to become pregnant or any non-use of effective contraceptive measures among women of childbearing age</td>
</tr>
<tr>
<td>3. (Coronary radiography or coronary angiography results show stenosis of at least 1 coronary artery and artery lumen stenosis ≥50%)</td>
<td>▶ Participation in a clinical trial of another new drug within 30 days prior to screening</td>
</tr>
<tr>
<td>4. Cardiac MRI, radionuclide myocardial perfusion imaging or cardiac colour Doppler imaging confirming CHD with MI</td>
<td>▶ Other conditions that researchers believe make the individual unsuitable to participate in the study</td>
</tr>
<tr>
<td>▶ Diagnosis of SAP</td>
<td>▶ Allergy to any ingredient of GBDPs</td>
</tr>
<tr>
<td>▶ Prior treatment of SAP according to the clinical guidelines with stability achieved for at least 4 weeks</td>
<td></td>
</tr>
<tr>
<td>▶ Meeting the diagnostic criteria for a depressive episode provided in the ICD-10 issued by the WHO</td>
<td></td>
</tr>
<tr>
<td>▶ No consumption of any food that impacts the intestinal flora, such as foods containing probiotics (e.g., yoghurt) or drugs (e.g., antibiotics) within 7 days</td>
<td></td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, coronary heart disease; Cr, creatinine; GBDPs, Ginkgo biloba dropping pills; HAMD, Hamilton Depression Scale; ICD-10, International Statistical Classification of Diseases and Related Health Problems; MI, myocardial ischaemia; SAP, stable angina pectoris.

Exclusion criteria

1. The presence of acute myocardial events, unstable angina pectoris or severe heart failure; serious arrhythmia; severe or poorly controlled hypertension (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg); sitting blood pressure and systolic blood pressure ≤85 mm Hg or symptomatic hypotension; severe primary diseases such as liver, kidney and haematopoietic system; or serious diseases affecting survival (such as a tumour, and so on).

2. Serious suicidal tendencies; Hamilton Depression Scale (HAMD) item 3 score ≥3, bipolar disorder depressive episode in patients with epilepsy history or depression secondary to other mental or physical diseases, alcohol and drug dependence within 1 year.

3. Abnormal liver and kidney function (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 times the upper normal limit and/or creatinine (Cr) >2 times the normal upper limit).


5. Pregnancy, lactation, plan to become pregnant or any non-use of effective contraceptive measures among women of childbearing age.

6. Participation in a clinical trial of another new drug within 30 days prior to screening.

7. Other conditions that researchers believe make individuals unsuitable to participate in the study.

8. Allergy to any ingredient of GBDPs (table 1)

Withdrawal criteria

1. Refusal to continue the trial.

2. Refusal to use the test drugs, complete testing and participate in follow-up.

3. Occurrence of some complications, serious adverse events (SAEs) except major adverse cardiovascular events (MACEs) or special physiological changes, and conditions making the continuation of the study participation inappropriate.

4. Poor compliance, defined as the use of <80% of the prescribed amount of drug, except for the occurrence of endpoint events or endpoint indicators of this trial, or >120% of the prescribed amount.

5. Use of prohibited drugs or other treatments specified in the scheme.

6. Unblinding during the trial for various reasons.

Recruitment

The recruitment of participants began in May 2020 and is expected to finish in May 2022. The research assistants will manage recruitment, and doctors will diagnose the participants. The study information will be publicised through the placement of posters in the hospitals, after which the recruitment will proceed according to the following steps:
1. Identification of those who are interested in participating.
2. A brief introduction is given to potential participants.
3. Preliminary physical examination of potential participants.
4. Collection of written informed consent (online supplemental appendices) from eligible individuals;
5. Further screening of eligible patients.
6. Random group allocation of eligible patients.

Randomisation

The central block randomisation method will be used for randomised allocation. A statistician from a third-party statistical unit (Guangzhou Jeeor Medical Research Co.) will generate the randomisation sequences using SAS V.9.4.

The predetermined values of parameters, such as block length and seed number, will be recorded in a random number table to strengthen the internal validity of the design. Each sequential number will correspond to a sealed opaque envelope containing the information of the randomisation group, according to a previously prepared randomised list of numbers, thus guaranteeing concealment. The patients who meet the inclusion criteria will be assigned in a successive order according to the corresponding random numbers from small to large extracted in the order of their enrolment.

Blinding

This study will be a double-blind, placebo-controlled design study. The sponsors will produce, package and provide the experimental drugs following the double-blind principle. The drug and control solution will be prepared by blinded editors who will not be involved in any other aspect of this project. Neither participants nor the treating medical team (ie, responsible nurses and physicians) will know the group allocation, nor will they be able to identify the treatment. Also, no member of the study team and extended staff, except for pharmacists and biostatisticians, will have access to the randomisation scheme during the study. In this experiment, emergency envelopes will be available for unblinding. In the case of a SAE or other emergencies, the researchers will consult the principal investigator (PI) and open the emergency envelope with the signature of the PI. Within 24 hours after unblinding, the researcher will inform the clinical research team leader and relevant personnel to explain the cause for unblinding. The blinding work will be recorded and signed by all the researchers responsible for the blinding. After sub-packaging, the blinding code will be sealed and kept by the applicant and PIs of the medical centres.

Interventions

After ensuring that all the participants were stable for at least 4 weeks, they will receive standard medical therapy for SAP following clinical guidelines. Standard conventional therapy includes: (a) antiplatelet agents: aspirin (75–100mg, once per day) or clopidogrel (75mg, once per day, mainly for patients with a history of percutaneous coronary intervention or patients with contraindications to aspirin); (b) β-blockers: metoprolol extended-release tablets (50–200mg, once per day) or analogous agents; (c) lipid-lowering agents (statins): atorvastatin, rosuvastatin, etc; (d) angiotensin-converting enzyme inhibitors are recommended for patients at high risk of combined diabetes, heart failure or left ventricular systolic insufficiency (eg, captopril 12.5–50mg, three times per day, or perindopril 4–8mg, once per day) and (e) nitrates: sublingual (0.5–0.6mg, no more than 3 consecutive doses, each 5 min apart) or aerosol (0.4mg, no more than 1.2mg in 15 min) nitroglycerine should only be used to relieve symptoms of angina pectoris. Long-acting nitrates (eg, isosorbide mononitrate 40–60mg, once per day) are suitable for chronic long-term treatment. This treatment will remain unchanged during the trial unless patients experience clinically meaningful or SAEs.

Before the trial treatment, the following parameters will be recorded: a detailed medical history, clinical symptoms of SAP, vital signs, laboratory test results, ECG changes, the 36-item Short Form Health Survey (SF-36) results and the Seattle Angina Questionnaire (SAQ) scale score. During the trial, different groups will receive the following treatments.

1. Treatment group (n=36): based on conventional drug treatment, the patients in the experimental group will be orally given GBDPs (63mg/pill), 5 pills each time, 3 times a day for 12 weeks.
2. Control group (n=36): based on conventional drug treatment, the patients in the control group will be orally given the mimetic drug for GBDPs (63mg/pill), 5 pills each time, 3 times a day for 12 weeks.

During the trial, participants will be allowed to use medications for treating underlying diseases, such as diabetes mellitus and hypertension, whereas all anti-anxiety drugs (whether traditional Chinese medicine or Western medicine) will be prohibited. In addition, throughout the study, the participants will be asked to avoid any food or drug that may significantly impact intestinal flora (including probiotics, antibiotics or yoghurt). Finally, in order to ensure good compliance, the researchers will patiently explain to patients the trial’s significance and the importance of taking medication on time. Patients will be required to record medication taking in the Medication Diary Card and return unused medication and its packaging at each follow-up visit. (figure 1 and table 2).

Outcome measurements

Primary outcomes

1. SAQ score: the scores will be obtained for 19 questions of the 11 items of the scale, and the total scores will be calculated separately for the 11 items. The scores will then be converted into standard points according to the following formula:

\[
\text{Standard score} = \left( \frac{\text{actual score of the dimension} - \text{the lowest score of the dimension}}{\text{(highest score of the dimension} - \text{the lowest score of the dimension})} \right) \times 100.
\]

A higher score indicates a better quality of life and body function. The scores obtained before treatment,
Figure 1  Flow diagram. Flow chart of the study procedure. GBDPs, *Ginkgo biloba* dropping pills; SAP, stable angina pectoris; SAQ, Seattle Angina Questionnaire.
2. Frequency of angina pectoris-related symptoms each week: a questionnaire survey will be used to judge whether patients are experiencing angina pectoris and record the frequency of angina pectoris symptoms. The frequency of such symptoms before treatment, during the follow-up and after treatment will be compared within and between groups.

Secondary outcomes
1. SF-36: the 36 items of the SF-36 quality-of-life scale will be categorized into 8 dimensions. According to the influence degree of each item on the quality of life, a corresponding weight will be given, and each dimension will be converted into 100 points. A higher score will indicate better functional status and higher quality of life. The scores for each dimension and the total physical and psychological well-being before and after treatment will be compared within and between groups.

Table 2  Study schedule of assessments

<table>
<thead>
<tr>
<th>Visit cycle</th>
<th>Screening</th>
<th>Enrollment</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Out of group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit cycle</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Number of eCRF records</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Time point</td>
<td>–4 weeks</td>
<td>0 weeks</td>
<td>4 weeks</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

1. The window period of all visits is ±3 days.
2. If AEs, drop-out cases or drug combinations occur, they should be recorded at any time, and the AEs should be followed up.
3. The endpoint setting refers to the endpoint specified in this protocol.

*Record once before enrollment and once a week after enrollment.

AEs, adverse events; cTnl, cardiac troponin I; ECG, electrocardiogram; eCRF, electronic case report form; HAMD-17, Hamilton Depression Scale-17 item; MACEs, major adverse cardiovascular events; PI, principal investigator; SAQ, Seattle Angina Questionnaire; SF-36, 36-item Short Form Health Survey.
to define an effective treatment. The differences in scores before and after treatment and the effective rate will be compared within and between groups.

3. Composite endpoint incidence of MACEs: the incidence of MACEs, including cardiovascular death, non-fatal myocardial infarction and revascularisation, will be recorded. The incidence of MACEs during the trial will be compared within and between groups.

**Monitoring**

The Data and Safety Monitoring Boards monitors will supervise the trial process. When visiting, the monitors will check the accuracy and completeness of the records and documents to guarantee the rights and interests of the participants and ensure that the implementation complies with the approved protocol, GCP and relevant regulations. Also, the monitors will review the records and eCRF of each participant completing the trial and fill in the monitoring report. Interim analyses will be conducted to monitor the data and progress of the trial.

**Sample size calculation**

To the best of our knowledge, there are no previous studies on treating SAP with depressive symptoms in CHD with GBDPs. As suggested in previous studies on GBDPs and similar proprietary Chinese medicines for CHD, the sample size was estimated, and the improvement of weekly angina attack frequency was taken as the main effect index according to the statistical requirements. We assumed the mean difference of 2.7, with a pooled SD of 3.8 for each group, \( \alpha = 0.05 \) (the significant level), and \( \beta = 0.2 \) (power of 0.8), the sample size in the test and control groups will be estimated to be 32 (1:1 sample size ratio) for 64 cases. In addition, a potential dropout rate of 10% will be considered, requiring a sample of 72 cases.

**SAFETY ASSESSMENT**

AEs refer to adverse medical events that occur after study participants receive a drug or study treatment; these events do not necessarily have a causal relationship with the treatment administration. In order to observe and record the possible AEs, vital signs (ie, body temperature, heart rate, respiration rate and blood pressure) will be measured at each follow-up visit (four times in total). Also, blood analysis (ie, red blood cell count, white blood cell count, neutrophil percentage, lymphocyte percentage, platelet count and haemoglobin level), troponin I, liver function (ie, ALT, AST, gamma-glutamyltransferase, total bilirubin, direct bilirubin and indirect bilirubin), renal function (ie, urea and Cr) and ECG will be evaluated at admission and the end of the treatment.

Death, any life-threatening and significant damage to organ function, prolonged hospitalisation and so forth are defined as SAEs. Cardiovascular death, non-fatal myocardial infarction and revascularisation are endpoints of this study; hence, they will not be reported as SAEs (and described in the study history). Adverse reactions/events associated with the GBDPs include dizziness, fatigue, facial flushing, dry throat, sweating, chest tightness, rapid heartbeat, bloated stomach, stomach pain, nausea, vomiting and similar. The researchers will explain these to the participants and ask them to truthfully report the changes in their condition after taking the drug while avoiding leading questions. We will especially focus on observing AEs or unexpected side effects while also observing the curative effect. All AEs, whether related to the study drugs or not, will be recorded in detail on the CRFs.

If an AE or adverse reaction should occur in the trial, the researchers will take necessary measures to ensure the participant’s safety, record the event and determine whether the trial needs to be terminated at that time. If an SAE occurs, the participant will be withdrawn from the clinical trial, and appropriate measures will be taken to immediately treat the participant. SAEs will also be reported to Wanbangde Pharmaceutical Group Co., and the Medical Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine within 24 hours. Additionally, the investigator will complete the SAE report form, including signing and dating the report. The date, time, event and person to whom it is being reported will be documented in the source material. The investigator will immediately notify other participating centres and researchers involved in this trial and ensure that the reporting procedures required by all laws and regulations are met.

**STATISTICAL ANALYSIS**

**Statistical analysis method**

The full-analysis set (FAS) will include the participants who have used the study drugs at least once and have post-medication evaluation data. The primary efficacy analysis will be conducted on FAS according to the intention-to-treat principle and on a per-protocol set. The last observation will impute the missing data for the efficacy of the FAS carried forward method. The participants with any safety records will be included in the safety analysis. To reduce confounders’ influence, analysis of covariance (ANCOVA) will be applied, using the baseline, each group and each centre as covariate factors. The baseline data for each group, including demographic and clinical characteristics, will be tabulated. All continuous variables will be presented as the number of cases, mean and SD, or median with range. The categorical variables will be described as the number of cases and proportions in each category. The t-test, analysis of variance or non-parametric statistical methods will be used for analysing quantitative outcomes. The \( \chi^2 \) test, Fisher’s exact probability method and Wilcoxon rank-sum test will be used for analysing categorical or ordinal data. All statistical tests will be two-sided, with the significance level set at 0.05. A \( P \) value of <0.05 will indicate a statistically significant difference. SAS V.9.4 statistical software will be used for all the statistical
analysis. Also, only the steering group will have access to the full trial dataset.

**Enrollment and case completion**

The completion of the trial will be described, and a specific list of all lost cases will be generated. In addition, the distribution of cases, including the number of screening cases, the number of enrolled cases, the distribution of cases in each analytical data set, the cases not included in each data set and so on, will also be listed.

**Safety analysis**

1. AEs and adverse reactions: all AEs and adverse reactions will be recorded. This analysis will be performed by using the $\chi^2$ test or Fisher’s exact test to compare the incidence of AEs (reactions) among groups.

2. Positive and abnormal changes in laboratory test results: a change frequency table will be made, reflecting the changes in laboratory indicators from normal to abnormal before and after treatment. The changes in laboratory monitoring indicators from normal to abnormal or exacerbation of abnormal values will be precisely recorded.

3. The vital signs at each visit will be statistically described as mean with SD values, number of cases or range values.

**ETHICS AND DISSEMINATION**

The trial will comply with the Declaration of Helsinki. This study has been approved by the ethics committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine (approval number: ZYVEC[2020]030), the Ethics Committee of the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (approval number: KYH2020004), the Ethics Committee of Shenzhen Luohu District People’s Hospital (approval number: 2020-LHQRMY-GCPLL-010) and the Ethics Committee of Foshan Chancheng Central Hospital (approval number: CYIRB2020130PJ20200817). If the protocol should be revised during the trial, it will have to be approved by the ethics committee before implementation. The results of this trial will be shared publicly through academic conferences and peer-reviewed journals.

**DISCUSSION**

This randomised, placebo-controlled, parallel-group, double-blind and multicentre trial mainly aims to explore the efficacy, safety and possible pharmacological mechanism of GBE for improving the frequency of angina pectoris and the life quality of patients with SAP and depression symptoms. GBE is one of the most popular and best-selling herbal medicinal products worldwide. Drugs extracted from GBL have been widely used to treat various conditions, including cognitive impairment, Alzheimer’s disease, glaucoma and retinal diseases, cardiovascular disease, ischaemic cerebrovascular disease, depression and others. To the best of our knowledge, this is the first clinical study that focused on GBE’s efficacy in patients with depression and CHD.

Previous research suggests that patients with CHD commonly experience depression symptoms, which in turn have been associated with increased symptom burden, physical limitation, mortality, healthcare expenditures, and reduced treatment satisfaction and quality of life. Therefore, treatments for these conditions are of utmost importance, and reducing the frequency of angina and improving the quality of life in patients with SAP and depression are of great significance for their prognosis.

GBDs is a post-marketing drug used to treat CHD, SAP and cerebral infarction. In addition, GBE has a good anti-depressant effect. According to previous studies, GBE causes vasodilation through endothelium-derived nitric oxide mechanism and increases coronary flow in animal models. Also, previous research has shown that GBE leads to a good augmentation of venlafaxine in treating post-stroke depression. Therefore, GBDs could be used as a potential treatment for depression with CHD.

However, the number of participants included in this trial is relatively small. Therefore, a larger-scale study is needed to further verify our conclusions. Also, this study did not include the interaction testing between GBDPs and routine medication, which should be addressed by future studies with larger sample sizes. Finally, participants were from four centres, all located in southern China, which might limit the applicability of our results.

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**Contributors**

TW, SL and ZL contributed equally to the work. ZY and WL have written the study protocol. TW, SL, ZL and WL have developed the original study design. QL, HT, YN, ST, TX, SX, XH, XD, YT, HL and YH have been involved in the revision of the study design and contributed in the review process of the protocol manuscript. WL and QL were jointly responsible for collecting data and administrating study participants. ZY has provided methodological guidance on research statistics, is the principal investigator and responsible for the funding and overall management of the trial.

**Disclaimer**

The funders have no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Supplemental material**

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REFERENCES


33 Chatterjee SS, Gabard B. Studies on mechanism of action of an extract of Ginkgo biloba, a drug used for treatment of ischemic vascular diseases. Naunyn Schmiedebergs Arch Pharmacol 1982;321:207.