**Supplementary Table 1** Checklist of Items for Reporting Trials of Chinese Herbal Medicine Formulas*

| Section/Topic | Item Number | Standard CONSORT Checklist Item | Extension for CHM Formulas | Reported on Page Number |
|---|---|---|---|---|
| **Title, abstract, and keywords** | 1a | Identification as a randomized trial in the title | *Statement of whether the trial targets a TCM* Pattern*, a Western medicine–defined disease, or a Western medicine–defined disease with a specific TCM* Pattern*, if applicable* | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts [26, 27]) | *Illustration of the name and form of the formula used, and the TCM* Pattern *applied, if applicable* | 2 |
| | 1c | | *Determination of appropriate keywords, including "Chinese herbal medicine formula" and "randomized controlled trial"* | 2 |
| **Introduction** | | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | *Statement with biomedical science approaches and/or TCM approaches* | 3-4 |
| | 2b | Specific objectives or hypotheses | *Statement of whether the formula targets a Western medicine–defined disease, a TCM* Pattern*, or a Western medicine–defined disease with a specific TCM* Pattern | 4 |

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| **Methods** | | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial), including allocation ratio | | 4-5 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | | N/A |
| Participants | 4a | Eligibility criteria for participants | *Statement of whether participants with a specific TCM* Pattern *were recruited, in terms of 1) diagnostic criteria and 2) inclusion and exclusion criteria. All criteria used should be universally recognized, or reference given to where detailed explanation can be found.* | 5-6, Ref 26 |
| | 4b | Settings and locations where the data were collected | | 4-5 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | *Description(s) for different types of formulas should include the following:*<br>***5a. For fixed CHM formulas***<br>*1. Name, source, and dosage form (e.g., decoctions, granules, powders)*<br>*2. Name, source, processing method, and dosage of each medical substance. Names of substances should be presented in at least 2 languages: Chinese (*Pinyin*), Latin, or English. Names of the parts of the substances* | 6-8, Ref 26, suppl file 1 |

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| | | | *used should be specified.*<br>*3. Authentication method of each ingredient and how, when, where, and by whom it was conducted; statement of whether any voucher specimen was retained, and if so, where they were kept and whether they are accessible*<br>*4. Principles, rationale, and interpretation of forming the formula*<br>*5. Reference(s) as to the efficacy of the formula, if any*<br>*6. Pharmacologic study results of the formula, if any*<br>*7. Production method of the formula, if any*<br>*8. Quality control of each ingredient and of the product of the formula, if any. This would include any quantitative and/or qualitative testing method(s); when, where, how, and by whom these tests were conducted; whether the original data and samples were kept, and, if so, whether they are accessible.*<br>*9. Safety assessment of the formula, including tests for heavy metals and toxic elements, pesticide residues, microbial limit, and acute/chronic toxicity, if any. If yes, it should be stated when, where, how, and by whom these tests were conducted; if the original data and samples were kept; and, if so, whether they are accessible.*<br>*10. Dosage of the formula, and how the dosage was determined* | |

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| | | | *11. Administration route (e.g., oral, external)*<br>***5b. For individualized CHM formulas***<br>*1. See recommendations 5a 1–11*<br>*2. Additional information: how, when, and by whom the formula was modified*<br>***5c. For patent proprietary CHM formulas***<br>*1. Reference to publicly available materials, such as pharmacopeia, for the details about the composition, dosage, efficacy, safety, and quality control of the formula*<br>*2. Illustration of the details of the formula, namely 1) the proprietary product name (i.e., brand name), 2) name of manufacturer, 3) lot number, 4) production date and expiry date, 5) name and percentage of added materials, and 6) whether any additional quality control measures were conducted*<br>*3. Statement of whether the patent proprietary formula used in the trial is for a condition that is identical to the publicly available reference*<br>***5d. Control groups***<br>*Placebo control*<br>*1. Name and amount of each ingredient*<br>*2. Description of the similarity of placebo with the intervention (e.g., color, smell, taste, appearance, packaging)*<br>*3. Quality control and safety assessment, if any* | |

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| | | | *4. Administration route, regimen, and dosage*<br>*5. Production information: where, when, how, and by whom the placebo was produced*<br>*Active control*<br>*1. If a CHM formula was used, see recommendations 5a–5c*<br>*2. If a chemical drug was used, see item 5 of the CONSORT Statement (24)* | |
| Outcomes | 6a | Completely defined, prespecified primary and secondary outcome measures, including how and when they were assessed | *Illustration of outcome measures with* Pattern *in detail* | 8-9 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | | 9 |
| Sample size | 7a | How sample size was determined | | 9-10 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | | N/A |
| Randomization | | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | | 9, Ref 26 |

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| | 8b | Type of randomization; details of any restriction (such as blocking and block size) | | 9, Ref 26 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | | 9, Ref 26 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | | 9, Ref 26 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | | 9, Ref 26 |
| | 11b | If relevant, description of the similarity of interventions | | 9, Ref 26 |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | | 11-12 |

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| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | | 12 |
| **Results** | | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome | | 12-13, Fig. 1 |
| | 13b | For each group, losses and exclusions after randomization, together with reasons | | 12-13, Fig. 1 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | | 12 |
| | 14b | Why the trial ended or was stopped | | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | | Table 1, Suppl Tables 6-7 |
| Numbers analyzed | 16 | For each group, number of participants (denominator) included in each analysis and whether the | | Fig. 1, Suppl Table 5 |

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| | | analysis was by original assigned groups | | |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | | 13-17, Tables 2-3, Fig. 2-5, Suppl Tables 8-10, Supple Fig. 1 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | | 13 |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory | | 13-17, Tables 2-3, Fig. 2-5, Suppl Tables 8-10, Supple Fig. 1 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms [28]) | *(There is no extension for this item)* | 15, Suppl Table 10 |
| **Discussion** | | | | |
| Limitations | 20 | Trial limitations; addressing sources of potential bias; imprecision; and, if | | 21 |

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|---|---|---|---|---|
| | | relevant, multiplicity of analyses | | |
| Generalizability | 21 | Generalizability (external validity, applicability) of the trial findings | *Discussion of how the formula works on different TCM* Patterns *or diseases* | 17-18 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | *Interpretation with TCM theory* | 17-18, 20 |
| **Other information** | | | | |
| Registration | 23 | Registration number and name of trial registry | | 22 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | | 5, Ref 26 |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | | 22 |

*CHM* Chinese herbal medicine, *CONSORT* Consolidated Standards of Reporting Trials, *TCM* traditional Chinese medicine

* The original CONSORT items are provided; elaborations for CHM formulas are in italicized text. We strongly recommend reading this checklist in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all original items of CONSORT Statement.

**Supplementary Table 2** Evaluation of lifestyle modification execution status of participants

| Execution status | Definition |
|---|---|
| 5 | Total calorie of daily diet was approximate 1660kcal in more than 3 days per week.<br>Total exercise time for moderate aerobic sports was above 150mins per week. |
| 4 | Total calorie of daily diet was approximate 1660kcal in 3 days per week.<br>Total exercise time for moderate aerobic sports was 120-150mins per week. |
| 3 | Total calorie of daily diet was approximate 1660kcal in 2 days per week.<br>Total exercise time for moderate aerobic sports was 75-120mins per week. |
| 2 | Total calorie of daily diet was approximate 1660kcal in 1 day per week.<br>Total exercise time for moderate aerobic sports was 35-75mins per week. |
| 1 | Total calorie of daily diet was approximate 1660kcal in less than 1 day per week.<br>Total exercise time for moderate aerobic sports was below 35mins per week. |

**Supplementary Table 3** Primers sequences of 6mA immunoprecipitation real-time qPCR

| RNAs | Primers (5'->3') |
|---|---|
| PPP1R3A | Forward: AGGGTCAGACAGATTCAC<br>Reverse: GGATTCAGTTTGCCAGTA |
| ATG3 | Forward: TCACGGCAACCTCCACCT<br>Reverse: CAAACATGGAGAAACCCT |
| KCNQ1 | Forward: AAATGAGTTAGGGAGG<br>Reverse: AGAGGCACAAAGAGGA |
| INTU | Forward: TTGTGCCGACCTCCTATC<br>Reverse: ATTTGAACCAGAGCGACT |

**Supplementary Table 4** Lifestyle modification execution status of participants who completed the trial and did not violate protocol

| Execution status | SLGZG | LLGZG | Placebo | P value |
|---|---|---|---|---|
| 5 | 31 (43.1%) | 31 (43.7%) | 41 (54.7%) | |
| 4 | 24 (33.3%) | 26 (36.6%) | 22 (29.3%) | |
| 3 | 14 (19.4%) | 9 (12.7%) | 11 (14.7%) | 0.246 |
| 2 | 3 (4.2%) | 5 (7.0%) | 1 (1.3%) | |
| 1 | 0 (0%) | 0 (0%) | 0 (0%) | |

The execution status of lifestyle modification was evaluated based on continuous 5-levels scale. Level "1" meant lifestyle modification requirements were met in less than 1 day per week, namely the worst compliance, while level "5" indicated lifestyle modification requirements were met in more than 4 days per week, namely the best compliance. Data were presented as n (%). *P* values were obtained using Kruskal-Wallis test among three groups. ITT, intention-to-treat; LLGZG, lower dose of Lingguizhugan Decoction; PP, per-protocol; SLGZG, standard dose of Lingguizhugan Decoction.

**Supplementary Table 5** Participants distribution based on BMI

| | Population | Groups | | | P |
|---|---|---|---|---|---|
| | | SLGZG | LLGZG | Placebo | value |
| ITT | Overall | 81 (100%) | 81 (100%) | 81 (100%) | |
| | BMI ≥ 24kg/m$^2$ | 61 (75.3%) | 65 (80.2%) | 57 (70.4%) | 0.346 |
| | BMI < 24kg/m$^2$ | 20 (24.7%) | 16 (19.8%) | 24 (29.6%) | |
| PP | Overall | 72 (100%) | 71 (100%) | 75 (100%) | |
| | BMI ≥ 24kg/m$^2$ | 54 (75.0%) | 57 (80.3%) | 53 (70.7%) | 0.404 |
| | BMI < 24kg/m$^2$ | 18 (25.0%) | 14 (19.7%) | 22 (29.3%) | |

Data were presented as n (%). *P* values were obtained using chi-square test among three groups. BMI, body mass index; ITT, intention-to-treat; LLGZG, lower dose of Lingguizhugan Decoction; PP, per-protocol; SLGZG, standard dose of Lingguizhugan Decoction.

**Supplementary Table 6** Baseline characteristics of obese participants (BMI ≥ 24 kg/m$^2$, ITT analysis and PP analysis)

| Characteristic | ITT | | | | PP | | | |
|---|---|---|---|---|---|---|---|---|
| | SLGZG (n = 61) | LLGZG (n = 65) | Placebo (n = 57) | *P* value | SLGZG (n = 54) | LLGZG (n = 57) | Placebo (n = 53) | *P* value |
| Gender, male, *n* (%) | 29 (47.5%) | 23 (35.4%) | 26 (45.6%) | 0.332 | 26 (48.1%) | 18 (31.6% | 24 (45.3%) | 0.165 |
| Age (yr) | 57.11 (12.15) | 59.38 (11.88) | 54.91 (14.84) | 0.262 | 58.00 (11.96) | 59.33 (12.27) | 55.15 (14.81) | 0.371 |
| BMI (kg/m$^2$) | 27.87 (3.01) | 27.67 (2.68) | 27.51 (2.60) | 0.888 | 27.71 (2.85) | 27.80 (2.77) | 27.47 (2.61) | 0.833 |
| HOMA-IR | 3.26 (2.67) | 2.86 (1.40) | 3.35 (2.17) | 0.674 | 3.13 (2.74) | 2.93 (1.45) | 3.20 (1.93) | 0.474 |
| *Lipid metabolism* | | | | | | | | |
| TC (mmol/L) | 4.76 (0.85) | 4.70 (0.76) | 4.70 (0.74) | 0.735 | 4.73 (0.87) | 4.66 (0.75) | 4.71 (0.76) | 0.775 |
| TG (mmol/L) | 2.16 (1.10) | 1.94 (0.93) | 2.35 (1.59) | 0.197 | 2.15 (1.14) | 1.97 (0.96) | 2.34 (1.65) | 0.397 |
| LDL-C (mmol/L) | 3.04 (0.81) | 2.99 (0.76) | 2.95 (0.68) | 0.797 | 3.00 (0.84) | 2.93 (0.74) | 2.94 (0.69) | 0.868 |
| HDL-C (mmol/L) | 1.14 (0.28) | 1.17 (0.28) | 1.11 (0.26) | 0.484 | 1.13 (0.27) | 1.17 (0.28) | 1.12 (0.27) | 0.727 |
| ApoA1 (g/L) | 1.28 (0.21) | 1.28 (0.17) | 1.25 (0.19) | 0.444 | 1.28 (0.18) | 1.28 (0.18) | 1.25 (0.20) | 0.653 |
| ApoB (g/L) | 1.03 (0.22) | 1.02 (0.21) | 1.00 (0.20) | 0.845 | 1.02 (0.23) | 1.00 (0.20) | 1.00 (0.20) | 0.908 |
| *Hepatic function* | | | | | | | | |
| ALT (U/L) | 30.43 (19.74) | 25.37 (19.30) | 30.11 (25.69) | 0.085 | 28.28 (16.94) | 25.56 (18.53) | 30.43 (26.55) | 0.321 |
| AST (U/L) | 22.98 (8.10) | 21.20 (9.40) | 23.18 (13.52) | 0.189 | 22.41 (7.51) | 21.37 (8.96) | 23.26 (13.97) | 0.455 |
| GGT (U/L) | 42.56 (48.45) | 39.22 (50.42) | 42.16 (46.32) | 0.331 | 42.69 (51.18) | 40.56 (53.21) | 42.49 (47.94) | 0.653 |
| ALP (U/L) | 77.02 (20.61) | 80.32 (22.01) | 75.23 (20.74) | 0.372 | 79.59 (20.30) | 81.65 (22.29) | 76.77 (20.36) | 0.420 |
| *Glucose metabolism* | | | | | | | | |
| FPG (mmol/L) | 5.27 (0.67) | 5.33 (0.59) | 5.22 (0.61) | 0.426 | 5.22 (0.62) | 5.37 (0.61) | 5.22 (0.61) | 0.325 |
| FINS (μU/L) | 13.50 (9.85) | 11.94 (5.55) | 14.21 (8.38) | 0.555 | 13.08 (10.19) | 12.22 (5.80) | 13.62 (7.76) | 0.594 |
| HbA1c (%) | 5.76 (0.40) | 5.80 (0.40) | 5.76 (0.46) | 0.722 | 5.76 (0.40) | 5.80 (0.41) | 5.76 (0.47) | 0.693 |
| *Inflammatory biomarkers* | | | | | | | | |

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| CRP (mg/L) | 1.53 (1.26) | 4.11 (16.25) | 2.24 (2.77) | 0.473 | 1.56 (1.32) | 2.23 (3.40) | 2.15 (2.78) | 0.519 |
| WBC counts ($\times 10^9$/L) | 6.29 (1.41) | 6.45 (1.91) | 6.49 (1.43) | 0.617 | 6.27 (2.04) | 6.43 (1.87) | 6.49 (1.48) | 0.645 |

Data were presented as mean (SD). *P* values were obtained using ANOVA, Kruskal-Wallis test or chi-square test. ALP, alkaline phosphatase; ALT, alanine aminotransferase; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; AST, aspartate transaminase; BMI, body mass index; CRP, C-reactive protein; FINS, fasting insulin; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LLGZG, low dose of Lingguizhugan Decoction; PP, per-protocol; SLGZG, standard dose of Lingguizhugan Decoction; TC, total cholesterol; TG, triglycerides

**Supplementary Table 7** Baseline characteristics of lean participants (BMI < 24 kg/m$^2$, ITT analysis and PP analysis)

| Characteristic | ITT | | | | PP | | | |
|---|---|---|---|---|---|---|---|---|
| | SLGZG (n = 20) | LLGZG (n = 16) | Placebo (n = 24) | *P* value | SLGZG (n=18) | LLGZG (n=14) | Placebo (n=22) | *P* value |
| Gender, male, *n* (%) | 5 (25.0%) | 5 (31.3%) | 8 (33.3%) | 0.828 | 5 (27.8%) | 4 (28.6%) | 7 (31.8%) | 0.957 |
| Age (yr) | 56.65 (12.36) | 60.63 (11.22) | 60.83 (10.16) | 0.524 | 58.17 (11.92) | 60.71 (11.74) | 60.82 (10.63) | 0.796 |
| BMI (kg/m$^2$) | 22.59 (1.42) | 22.34 (1.66) | 22.72 (1.24) | 0.743 | 22.75 (1.16) | 22.63 (1.20) | 22.75 (1.25) | 0.844 |
| HOMA-IR | 1.97 (1.21) | 1.92 (1.05) | 2.37 (1.02) | 0.197 | 2.05 (1.23) | 2.07 (0.98) | 2.30 (0.91) | 0.441 |
| *Lipid metabolism* | | | | | | | | |
| TC (mmol/L) | 4.78 (0.76) | 4.82 (1.05) | 4.91 (0.79) | 0.644 | 4.82 (0.79) | 5.05 (0.87) | 4.94 (0.72) | 0.703 |
| TG (mmol/L) | 1.45 (0.57) | 1.96 (0.96) | 1.86 (0.65) | 0.083 | 1.51 (0.56) | 2.10 (0.94) | 1.86 (0.67) | 0.104 |
| LDL-C (mmol/L) | 3.06 (0.58) | 3.10 (0.86) | 3.20 (0.79) | 0.808 | 3.06 (0.61) | 3.27 (0.74) | 3.25 (0.73) | 0.541 |
| HDL-C (mmol/L) | 1.39 (0.38) | 1.25 (0.32) | 1.27 (0.30) | 0.375 | 1.39 (0.40) | 1.26 (0.34) | 1.25 (0.27) | 0.405 |
| ApoA1 (g/L) | 1.40 (0.20) | 1.33 (0.24) | 1.34 (0.21) | 0.485 | 1.41 (0.21) | 1.36 (0.25) | 1.33 (0.21) | 0.522 |
| ApoB (g/L) | 0.99 (0.17) | 1.03 (0.29) | 1.04 (0.20) | 0.710 | 1.00 (0.17) | 1.10 (0.22) | 1.06 (0.18) | 0.309 |
| *Hepatic function* | | | | | | | | |
| ALT (U/L) | 22.10 (12.16) | 20.44 (14.45) | 21.13 (9.76) | 0.915 | 23.06 (12.38) | 21.43 (15.09) | 20.64 (9.42) | 0.818 |
| AST (U/L) | 21.30 (7.62) | 20.44 (9.23) | 20.29 (5.32) | 0.892 | 21.94 (7.63) | 21.21 (9.58) | 20.27 (5.55) | 0.778 |
| GGT (U/L) | 32.35 (28.43) | 47.19 (58.04) | 24.92 (11.09) | 0.733 | 32.89 (29.59) | 52.50 (60.36) | 22.95 (8.58) | 0.196 |
| ALP (U/L) | 73.40 (19.54) | 88.13 (29.33) | 78.75 (22.11) | 0.215 | 74.67 (19.67) | 91.86 (29.47) | 81.59 (19.94) | 0.138 |
| *Glucose metabolism* | | | | | | | | |
| FPG (mmol/L) | 5.10 (0.45) | 5.04 (0.49) | 5.28 (0.70) | 0.541 | 5.14 (0.45) | 5.04 (0.52) | 5.18 (0.57) | 0.719 |
| FINS (μU/L) | 8.59 (4.92) | 8.50 (4.60) | 10.03 (3.76) | 0.446 | 8.94 (4.98) | 9.20 (4.29) | 9.98 (3.74) | 0.733 |
| HbA1c (%) | 5.58 (0.41) | 5.59 (0.46) | 5.75 (0.45) | 0.338 | 5.62 (0.41) | 5.66 (0.43) | 5.74 (0.45) | 0.680 |
| *Inflammatory biomarkers* | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CRP (mg/L) | 0.92 (1.00) | 0.99 (1.16) | 1.25 (1.21) | 0.142 | 0.99 (1.03) | 1.08 (1.21) | 1.28 (1.24) | 0.306 |
| WBC counts ($\times 10^9$/L) | 5.46 (0.92) | 6.08 (1.65) | 6.35 (1.74) | 0.246 | 5.41 (0.92) | 6.19 (1.74) | 6.29 (1.71) | 0.156 |

Data were presented as mean (SD). *P* values were obtained using ANOVA, Kruskal-Wallis test or chi-square test. ALP, alkaline phosphatase; ALT, alanine aminotransferase; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; AST, aspartate transaminase; BMI, body mass index; CRP, C-reactive protein; FINS, fasting insulin; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; ITT, intention-to-treat; LDL-C, low density lipoprotein cholesterol; LLGZG, low dose of Lingguizhugan Decoction; PP, per-protocol; SLGZG, standard dose of Lingguizhugan Decoction; TC, total cholesterol; TG, triglycerides

**Supplementary Table 8** Comparison of treatment effect of changes in BMI, lipid metabolism and glucose metabolism from baseline to 12 weeks (PP analysis)

| Variable | Population | Groups | | | 3 groups |
|---|---|---|---|---|---|
| | | SLGZG | LLGZG | Placebo | P value |
| BMI ($kg/m^2$) | Overall | 0.32 (0.55) | 0.15 (0.99) | 0.16 (0.87) | 0.732 |
| | BMI ≥ 24 $kg/m^2$ | 0.41 (0.56) | 0.07 (0.98) | 0.20 (0.95) | 0.241 |
| | BMI < 24 $kg/m^2$ | 0.08 (0.43) | 0.49 (1.01) | 0.05 (0.65) | 0.270 |
| *Lipid metabolism* | | | | | |
| TC (mmol/L) | Overall | 0.21 (0.67) | 0.15 (0.73) | 0.15 (0.60) | 0.816 |
| | BMI ≥ 24 $kg/m^2$ | 0.34 (0.60) | 0.19 (0.66) | 0.11 (0.64) | 0.363 |
| | BMI < 24 $kg/m^2$ | -0.18 (0.74) | -0.02 (0.96) | 0.25 (0.48) | 0.177 |
| TG (mmol/L) | Overall | -0.03 (1.09) | -0.20 (0.61) | -0.30 (1.11) | 0.299 |
| | BMI ≥ 24 $kg/m^2$ | -0.01 (1.23) | -0.18 (0.63) | -0.37 (1.25) | 0.198 |
| | BMI < 24 $kg/m^2$ | -0.09 (0.50) | -0.30 (0.49) | -0.14 (0.65) | 0.843 |
| LDL-C (mmol/L) | Overall | 0.20 (0.69) | 0.20 (0.73) | 0.18 (0.53) | 0.816 |
| | BMI ≥ 24 $kg/m^2$ | 0.30 (0.64) | 0.24 (0.64) | 0.19 (0.56) | 0.941 |
| | BMI < 24 $kg/m^2$ | -0.09 (0.77) | 0.07 (1.05) | 0.17 (0.45) | 0.569 |
| HDL-C (mmol/L) | Overall | 0.09 (0.16) | 0.05 (0.15) | 0.09 (0.17) | 0.330 |
| | BMI ≥ 24 $kg/m^2$ | 0.10 (0.17) | 0.06 (0.13) | 0.08 (0.16) | 0.508 |
| | BMI < 24 $kg/m^2$ | 0.05 (0.14) | 0.02 (0.22) | 0.10 (0.18) | 0.335 |
| ApoA1 (g/L) | Overall | 0.11 (0.11) | 0.08 (0.12) | 0.09 (0.14) | 0.355 |
| | BMI ≥ 24 $kg/m^2$ | 0.12 (0.12) | 0.09 (0.11) | 0.09 (0.13) | 0.456 |
| | BMI < 24 $kg/m^2$ | 0.09 (0.09) | 0.02 (0.13) | 0.11 (0.16) | 0.103 |
| ApoB (g/L) | Overall | 0.04 (0.19) | 0.04 (0.21) | 0.04 (0.15) | 0.996 |
| | BMI ≥ 24 $kg/m^2$ | 0.07 (0.18) | 0.04 (0.19) | 0.04 (0.16) | 0.728 |

| | | | | | |
|---|---|---|---|---|---|
| | BMI < 24 kg/m$^2$ | -0.04 (0.20) | 0.03 (0.29) | 0.03 (0.14) | 0.502 |
| *Glucose metabolism* | | | | | |
| | Overall | 0.05 (0.55) | -0.01 (0.56) | 0.14 (0.44) | 0.313 |
| FPG (mmol/L) | BMI ≥ 24 kg/m$^2$ | 0.05 (0.57) | -0.03 (0.54) | 0.14 (0.43) | 0.367 |
| | BMI < 24 kg/m$^2$ | 0.08 (0.50) | 0.06 (0.63) | 0.13 (0.47) | 0.905 |
| | Overall | -0.40 (7.24) | -0.97 (4.38) | 0.33 (5.02) | 0.135 |
| FINS (μU/L) | BMI ≥ 24 kg/m$^2$ | -1.15 (7.35) | -1.35 (4.64) | 0.92 (5.39) | 0.011 |
| | BMI < 24 kg/m$^2$ | 1.87 (6.58) | 0.58 (2.70) | -1.08 (3.70) | 0.236 |
| | Overall | 0.03 (0.18) | 0.00 (0.24) | 0.09 (0.22) | 0.010 |
| HbA1c (%) | BMI ≥ 24 kg/m$^2$ | 0.04 (0.16) | -0.02 (0.23) | 0.06 (0.23) | 0.050 |
| | BMI < 24 kg/m$^2$ | -0.02 (0.21) | 0.06 (0.26) | 0.15 (0.19) | 0.025 |

Data were presented as mean (SD). *P* values were obtained using ANOVA or Kruskal-Wallis test. ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; AST, aspartate transaminase; BMI, body mass index; FINS, fasting insulin; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LLGZG, low dose of Lingguizhugan Decoction; PP, per-protocol; SLGZG, standard dose of Lingguizhugan Decoction; TC, total cholesterol; TG, triglyceride

**Supplementary Table 9** Comparison of treatment effect of changes in questionnaires scores from baseline to 12 weeks (ITT analysis)

| Scale, mean (SD) | | Groups | | | 3 groups | SLGZG vs Placebo | LLGZG vs Placebo | SLGZG vs LLGZG |
|---|---|---|---|---|---|---|---|---|
| | | SLGZG | LLGZG | Placebo | P value | P value | P value | P value |
| SF-36 Physical function | Week 0 | 86.73 (18.00) | 87.72 (17.52) | 87.28 (14.06) | | | | |
| | Week 12 | 88.58 (18.71) | 87.84 (14.58) | 91.17 (11.44) | 0.285 | / | / | / |
| | P value | 0.204 | 0.849 | 0.011 | | | | |
| SF-36 Role-physical | Week 0 | 85.19 (28.44) | 82.10 (35.19) | 89.20 (25.90) | | | | |
| | Week 12 | 87.35 (31.90) | 91.67 (26.22) | 93.83 (22.20) | 0.788 | / | / | / |
| | P value | 0.436 | 0.011 | 0.078 | | | | |
| SF-36 Bodily pain | Week 0 | 74.46 (24.07) | 78.54 (21.62) | 75.11 (21.80) | | | | |
| | Week 12 | 76.04 (26.21) | 75.98 (24.76) | 78.57 (23.27) | 0.089 | / | / | / |
| | P value | 0.710 | 0.288 | 0.206 | | | | |
| SF-36 General health | Week 0 | 66.74 (21.38) | 66.04 (21.26) | 60.85 (19.20) | | | | |
| | Week 12 | 70.84 (20.97) | 67.32 (18.50) | 68.40 (19.77) | 0.115 | / | / | / |
| | P value | 0.060 | 0.747 | 0.003 | | | | |
| SF-36 Vitality | Week 0 | 27.96 (19.51) | 32.78 (17.45) | 26.73 (18.08) | | | | |
| | Week 12 | 31.30 (18.99) | 34.14 (16.62) | 34.81 (17.58) | 0.023 | 0.118 | 0.028 | 1.000 |
| | P value | 0.223 | 0.555 | <0.001 | | | | |
| SF-36 Social functioning | Week 0 | 85.49 (20.49) | 87.50 (19.26) | 84.57 (19.29) | | | | |
| | Week 12 | 87.35 (31.90) | 88.12 (18.64) | 85.97 (19.60) | 0.877 | / | / | / |
| | P value | 0.374 | 0.849 | 0.486 | | | | |
| SF-36 Role-emotional | Week 0 | 90.53 (26.48) | 83.95 (32.96) | 90.95 (24.16) | | | | |
| | Week 12 | 93.83 (21.80) | 90.95 (27.39) | 92.18 (22.53) | 0.549 | / | / | / |
| | P value | 0.390 | 0.058 | 0.776 | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SF-36 Mental health | Week 0 | 75.21 (19.82) | 77.88 (19.90) | 74.07 (18.85) | | | | |
| | Week 12 | 80.10 (15.63) | 79.11 (17.45) | 80.54 (16.91) | 0.094 | / | / | / |
| | P value | 0.029 | 0.645 | 0.003 | | | | |
| SAS | Week 0 | 44.14 (6.32) | 45.54 (5.75) | 45.51 (6.38) | | | | |
| | Week 12 | 44.07 (5.21) | 44.72 (5.80) | 44.51 (4.77) | 0.658 | / | / | / |
| | P value | 0.709 | 0.131 | 0.195 | | | | |
| SDS | Week 0 | 55.49 (9.08) | 55.91 (6.44) | 56.46 (7.61) | | | | |
| | Week 12 | 58.28 (7.59) | 54.94 (11.50) | 56.88 (7.06) | 0.063 | / | / | / |
| | P value | 0.005 | 0.716 | 0.869 | | | | |
| Spleen-yang deficiency pattern scale | Week 0 | 35.15 (10.92) | 34.68 (9.97) | 33.80 (12.12) | | | | |
| | Week 12 | 17.98 (10.61) | 21.12 (12.03) | 25.14 (9.60) | <0.001 | <0.001 | 0.003 | 0.169 |
| | P value | <0.001 | <0.001 | <0.001 | | | | |

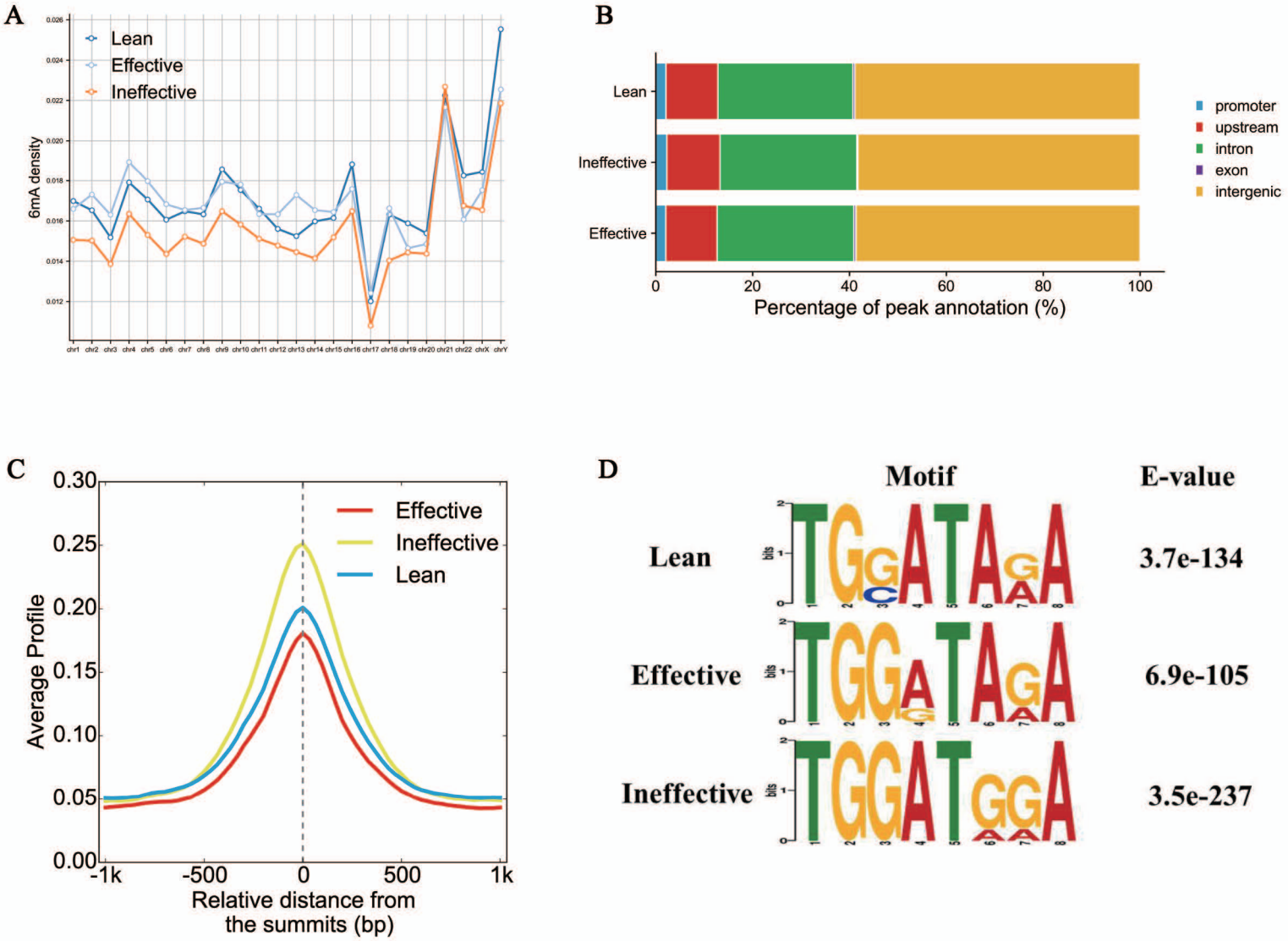
*P* values within group were obtained using paired t-test. *P* values among three groups were obtained using ANOVA or Kruskal-Wallis test. *P* values between different groups were obtained from post hoc pairwise multiple comparisons with Bonferroni-adjusted. LLGZG, low dose of Lingguizhugan Decoction; SAS, self-rating anxiety scale; SD, standard deviation; SDS, self-rating depressive scale; SF-36, 36-item short form survey; SLGZG, standard dose of Lingguizhugan Decoction

**Supplementary Table 10** Comparison of treatment effect toward the change of hepatic function and inflammatory biomarkers from baseline to 12 weeks

| Variables | | Population | Groups | | | 3 groups |
|---|---|---|---|---|---|---|
| | | | SLGZG | LLGZG | Placebo | P value |
| *Hepatic function* | | | | | | |
| ALT (U/L) | ITT | Overall | -0.06 (8.66) | -1.91 (12.71) | 1.67 (16.32) | 0.902 |
| | | BMI ≥ 24 kg/m$^2$ | 0.69 (9.39) | -2.72 (13.74) | 2.35 (19.07) | 0.485 |
| | | BMI < 24 kg/m$^2$ | -2.35 (5.47) | 1.38 (6.47) | 0.04 (6.07) | 0.099 |
| | PP | Overall | -0.49 (8.54) | -2.15 (13.55) | 1.37 (16.24) | 0.918 |
| | | BMI ≥ 24 kg/m$^2$ | 0.22 (9.23) | -3.07 (14.63) | 1.64 (19.06) | 0.563 |
| | | BMI < 24 kg/m$^2$ | -2.61 (5.72) | 1.57 (6.93) | 0.73 (5.39) | 0.069 |
| AST (U/L) | ITT | Overall | 0.11 (5.72) | -0.81 (7.29) | 1.05 (11.41) | 0.577 |
| | | BMI ≥ 24 kg/m$^2$ | 0.39 (6.18) | -0.89 (7.95) | 1.39 (13.57) | 0.519 |
| | | BMI < 24 kg/m$^2$ | -0.75 (4.02) | -0.50 (3.67) | 0.25 (1.92) | 0.567 |
| | PP | Overall | 0.07 (6.00) | -0.83 (7.78) | 0.61 (11.31) | 0.800 |
| | | BMI ≥ 24 kg/m$^2$ | 0.37 (6.48) | -0.89 (8.49) | 0.74 (13.44) | 0.740 |
| | | BMI < 24 kg/m$^2$ | -0.83 (4.25) | -0.57 (3.94) | 0.32 (1.99) | 0.537 |
| GGT (U/L) | ITT | Overall | -3.15 (17.71) | -10.75 (41.16) | -0.35 (30.83) | 0.149 |
| | | BMI ≥ 24 kg/m$^2$ | -2.64 (18.86) | -11.12 (44.66) | 0.53 (36.65) | 0.121 |
| | | BMI < 24 kg/m$^2$ | -4.7 (13.9) | -9.25 (22.85) | -2.42 (5.34) | 0.901 |
| | PP | Overall | -3.74 (18.44) | -11.72 (43.55) | -0.71 (31.84) | 0.103 |
| | | BMI ≥ 24 kg/m$^2$ | -3.24 (19.65) | -12.00 (47.27) | -0.17 (37.84) | 0.067 |
| | | BMI < 24 kg/m$^2$ | -5.22 (14.59) | -10.57 (24.24) | -2.00 (4.94) | 0.728 |
| ALP (U/L) | ITT | Overall | 0.06 (8.60) | -0.34 (10.86) | -0.84 (10.93) | 0.388 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | BMI ≥ 24 kg/m$^2$ | -0.36 (8.30) | -0.97 (9.45) | -1.74 (11.56) | 0.854 |
| | | BMI < 24 kg/m$^2$ | 1.35 (9.56) | 2.19 (15.46) | 1.29 (9.14) | 0.323 |
| | | Overall | -0.21 (9.03) | -0.43 (11.59) | -1.13 (11.21) | 0.462 |
| | PP | BMI ≥ 24 kg/m$^2$ | -0.78 (8.67) | -1.16 (10.07) | -2.25 (11.75) | 0.337 |
| | | BMI < 24 kg/m$^2$ | 1.50 (10.10) | 2.50 (16.58) | 1.54 (9.51) | 0.966 |
| *Inflammatory biomarkers* | | | | | | |
| | | Overall | 0.06 (1.19) | -1.04 (15.21) | -0.27 (3.44) | 0.141 |
| | ITT | BMI ≥ 24 kg/m$^2$ | 0.19 (1.34) | -1.87 (16.42) | -0.48 (3.51) | 0.079 |
| | | BMI < 24 kg/m$^2$ | -0.22 (0.48) | 2.28 (8.32) | 0.24 (3.28) | 0.783 |
| CRP (mg/L) | | Overall | 0.07 (1.25) | 0.59 (6.06) | -0.25 (3.49) | 0.122 |
| | PP | BMI ≥ 24 kg/m$^2$ | 0.18 (1.41) | 0.10 (5.13) | -0.48 (3.52) | 0.049 |
| | | BMI < 24 kg/m$^2$ | -0.24 (0.50) | 2.61 (8.88) | 0.30 (3.43) | 0.742 |
| | | Overall | 0.26 (1.14) | -0.19 (1.29) | 0.07 (1.32) | 0.057 |
| | ITT | BMI ≥ 24 kg/m$^2$ | 0.25 (1.25) | -0.25 (1.35) | 0.04 (1.25) | 0.083 |
| | | BMI < 24 kg/m$^2$ | 0.28 (0.72) | 0.08 (0.97) | 0.13 (1.50) | 0.857 |
| WBC counts, (×10$^9$/L) | | Overall | 0.26 (1.18) | -0.19 (1.33) | 0.11 (1.34) | 0.071 |
| | PP | BMI ≥ 24 kg/m$^2$ | 0.24 (1.30) | -0.26 (1.39) | 0.05 (1.30) | 0.109 |
| | | BMI < 24 kg/m$^2$ | 0.31 (0.75) | 0.09 (1.04) | 0.24 (1.47) | 0.865 |

Data were presented as mean (SD). *P* values were obtained using ANOVA or Kruskal-Wallis test. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CRP, C-reactive protein; GGT, gamma-glutamyl transpeptidase; ITT, intention-to-treat; LLGZG, lower dose of Lingguizhugan Decoction; PP, per-protocol; SLGZG, standard dose of Lingguizhugan Decoction; WBC, white blood cell




**Supplementary Fig. 1.** Distribution profiles of DNA m6A modification among the three groups. The (A) distribution of DNA m6A peaks on chromosomes, and (B) percentage of peak annotation, (C) the location of DNA m6A near transcription start site, (D) the motif of DNA m6A among three groups.

**Supplementary File 1** Authentication of LGZG granules

1. Character of granules of four ingredients

| Ingredient | Standard | Result |
|---|---|---|
| ***Poria*** | Off-white to greyish white granules, slight scent, bland flavour | Conformed |
| ***Ramulus Cinnamomi*** | Brown to brownish red granules, aromatic and special scent, sweet flavour with slight spicy | Conformed |
| ***Rhizoma Atractylodis Macrocephalae*** | Pale yellow to brownish yellow granules, faint scent, sweet flavour with slight spicy | Conformed |
| ***Radix Glycyrrhizae*** | Yellow to brownish yellow granules, slight scent, sweet and special flavour | Conformed |

2. Physicochemical properties of granules of four ingredients

| Ingredient | Thin layer chromatography | Particle size[a] | Water content[b] | Dissolubility |
|---|---|---|---|---|
| ***Poria*** | Conformed | 2% | 4.5% | Conformed |
| ***Ramulus Cinnamomi*** | Conformed | 3% | 2.7% | Conformed |
| ***Rhizoma Atractylodis Macrocephalae*** | Conformed | 1% | 1.2% | Conformed |
| ***Radix Glycyrrhizae*** | Conformed | 2% | 5.2% | Conformed |

[a] The percentage indicates the sum total of granules which could not pass sifter size one and granules which could pass sifter size five. The quality requirement is ≤ 15%.

[b] The quality requirement is ≤ 8%.

3. Microbial limit tests of granules of four ingredients

| Ingredient | Total aerobic count[a] | Mold and yeast count[b] | Escherichia coli[c] |
|---|---|---|---|
| ***Poria*** | < 10 CFU/g | < 10 CFU/g | Not detectable |
| ***Ramulus Cinnamomi*** | 15 CFU/g | < 10 CFU/g | Not detectable |
| ***Rhizoma Atractylodis Macrocephalae*** | 820 CFU/g | 10 CFU/g | Not detectable |
| ***Radix Glycyrrhizae*** | 50 CFU/g | < 20 CFU/g | Not detectable |

CFU, colony-forming units

[a] The quality requirement is ≤ 1000 CFU/g.

[b] The quality requirement is ≤ 100 CFU/g.

[c] The quality requirement is “not detectable”.