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*Original Article*

# Efficacy evaluation and mechanism exploration of Dachaihu Decoction in treating hyperlipidemia: an integrated network meta-analysis and network pharmacology study

Wenyu Bu, Hanxue Li, Shidian Zhu, Yanzi Liu, Yinghong Xia, Fuming Liu

*Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing 210023, Jiangsu, China*

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**Abstract:** Background: Dachaihu Decoction (DCHD), a traditional herbal formula from Shanghan Lun, has been widely used in the management of hyperlipidemia. However, the comparative efficacy of its modified formulations and their underlying mechanisms remain unclear. This study aimed to evaluate the therapeutic efficacy of DCHD and its modifications and to elucidate the potential mechanisms using integrated analytical strategies. Methods: We conducted a Bayesian network meta-analysis (NMA) of randomized controlled trials (RCTs) systematically retrieved from multiple databases up to May 2024, following the PRISMA-NMA Guidelines. Lipid parameters, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), as well as response rates, were evaluated. In addition, network pharmacology, molecular docking, and molecular dynamics (MD) simulations were performed to further explore the underlying mechanisms. Results: A total of 23 randomized controlled trials (RCTs) involving 1,816 patients were included. The surface under the cumulative ranking curve (SUCRA) analysis indicated that Dachaihu Decoction combined with Shengjiang Powder had the highest efficacy in reducing TC, TG, and LDL-C in patients with hyperlipidemic pancreatitis. However, sensitivity analysis revealed that Dachaihu Decoction alone and in combination with Guizhi Fuling Pill showed more stable efficacy in chronic populations. Network pharmacology identified 69 active components, including quercetin, β-sitosterol, and baicalein, and 305 intersecting targets. Protein-protein interaction (PPI) analysis highlighted TLR4, MMP9, SIRT1, ICAM1, and GSK3B as core targets. KEGG pathway enrichment analysis indicated significant involvement in lipid metabolism and inflammatory pathways. Molecular docking and molecular dynamics simulations revealed that the β-sitosterol-ICAM1 complex exhibited stable conformational stability, with an MM-GBSA binding free energy of -37.09 kcal/mol. Conclusions: Modified DCHD formulations showed therapeutic potential for hyperlipidemia through multi-target and multi-pathway synergistic mechanisms. DCHD combined with Shengjiang Powder appears particularly promising in hyperlipidemic pancreatitis, whereas DCHD alone shows stable efficacy in chronic populations. These findings provide robust evidence supporting the rational clinical application and modern pharmacological interpretation of the classical formula DCHD documented in Shanghan Lun.

**Keywords:** Dachaihu decoction, hyperlipidemia, network meta-analysis, network pharmacology, molecular dynamics simulation

## Introduction

Hyperlipidemia is a chronic metabolic disorder characterized by elevated plasma levels of triglycerides and/or cholesterol and is a major contributor to the development and progression of atherosclerotic cardiovascular disease (ASCVD) [1]. In recent years, lifestyle changes and rising obesity rates have driven a continuous increase in the global prevalence of hyperlipidemia, with an alarming trend toward younger populations [2]. Currently, hyperlipidemia is primarily managed with statins. Although statins are effective at reducing low-density lipoprotein cholesterol (LDL-C), their use in clinical practice is often limited by statin intolerance, which can lead to adverse effects such as myalgia, hepatic dysfunction, and other adverse

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effects [3]. These side effects reduce both therapeutic efficacy and patient adherence. Moreover, even with intensive statin therapy, some patients remain at residual cardiovascular risk, particularly due to elevated triglyceride (TG) levels, which are often difficult to control [4].

Against this background, Traditional Chinese Medicine (TCM) has shown considerable potential for treating hyperlipidemia. Its theoretical framework emphasizes holistic regulation and syndrome differentiation, enabling a "multi-target, multi-pathway" approach [5]. Clinical and experimental studies have demonstrated that TCM can improve lipid profiles, enhance insulin sensitivity, exert anti-inflammatory and antioxidant effects, and is generally well tolerated, supporting its role in personalized treatment [6]. In TCM theory, hyperlipidemia is mainly attributed to stagnation of qi and dysfunction of the liver and gallbladder, leading to the accumulation of phlegm-turbidity, blood stasis, and lipid deposits, particularly in the Yangming system. Dachaihu Decoction (DCHD), originating from the *Treatise on Cold-induced Febrile Diseases*, is a classical formula for the "combined disease of Shaoyang and Yangming". The herbs in DCHD work synergistically to harmonize Shaoyang and unblock Yangming. Both clinical observations and experimental studies indicate that DCHD is effective and safe for the treatment of hyperlipidemia [7, 8]. Despite these findings, two critical gaps remain. First, although several randomized controlled trials (RCTs) have shown that DCHD reduces lipid levels, the comparative effectiveness of its formulations remains unclear, limiting optimal selection of a clinical regimen. Second, the modern pharmacological mechanisms underlying DCHD's effects on hyperlipidemia have not been systematically elucidated. Given the complex, multi-component nature of TCM formulas, understanding the interactions among components, targets, and pathways requires further investigation.

To address these gaps, this study used a network meta-analysis to quantitatively compare the relative efficacy of different modified versions of DCHD, aiming to identify the optimal clinical regimen. Although network meta-analysis (NMA) and molecular docking approaches have previously been applied in TCM research on hyperlipidemia [5], to our knowledge, this is the first study to simultaneously compare different modified DCHD formulations within a single NMA framework. It should be noted that most included trials compared modified DCHD combined with conventional therapy versus conventional therapy alone; therefore, inter-formulation comparisons were largely indirect and based on a shared comparator.

In addition, network pharmacology was used to construct a comprehensive "formula-components-targets-pathways-disease" network, predicting the network's core active components, key targets, and signaling pathways to reveal its mechanism of action. This integrated approach aims to establish a complete evidence chain linking clinical efficacy and biological mechanisms, consequently supporting the precise clinical application and scientific understanding of this classical formula.

## Materials and methods

### *Composition, authentication, and preparation of Dachaihu Decoction*

Dachaihu Decoction (DCHD) is a classical Traditional Chinese Medicine (TCM) formula traditionally prescribed for complex conditions characterized by Shaoyang meridian qi stagnation combined with Yangming fu-organ excess heat. Clinically, this pattern shows as hypochondriac pain and bitter taste in the mouth due to Shaoyang constraint, together with constipation and abdominal distension or discomfort caused by heat accumulation and excess in the Yangming fu-organs. In modern clinical practice, DCHD is commonly used for the treatment of hyperlipidemia presenting with a corresponding TCM pattern of liver qi stagnation accompanied by gastrointestinal excess heat. The standard DCHD formula consists of eight herbs. The botanical origins and medicinal parts of all herbs were authenticated by cross-referencing the World Flora Online database and the Pharmacopoeia of the People's Republic of China (2025 Edition). Representative botanical and pharmacognostic characteristics are shown in **Figure 1**, and the detailed composition and dosage ranges are provided in **Table 1**.

All herbal materials were processed (Pao Zhi) in accordance with the Pharmacopoeia to enhance therapeutic efficacy and reduce poten-

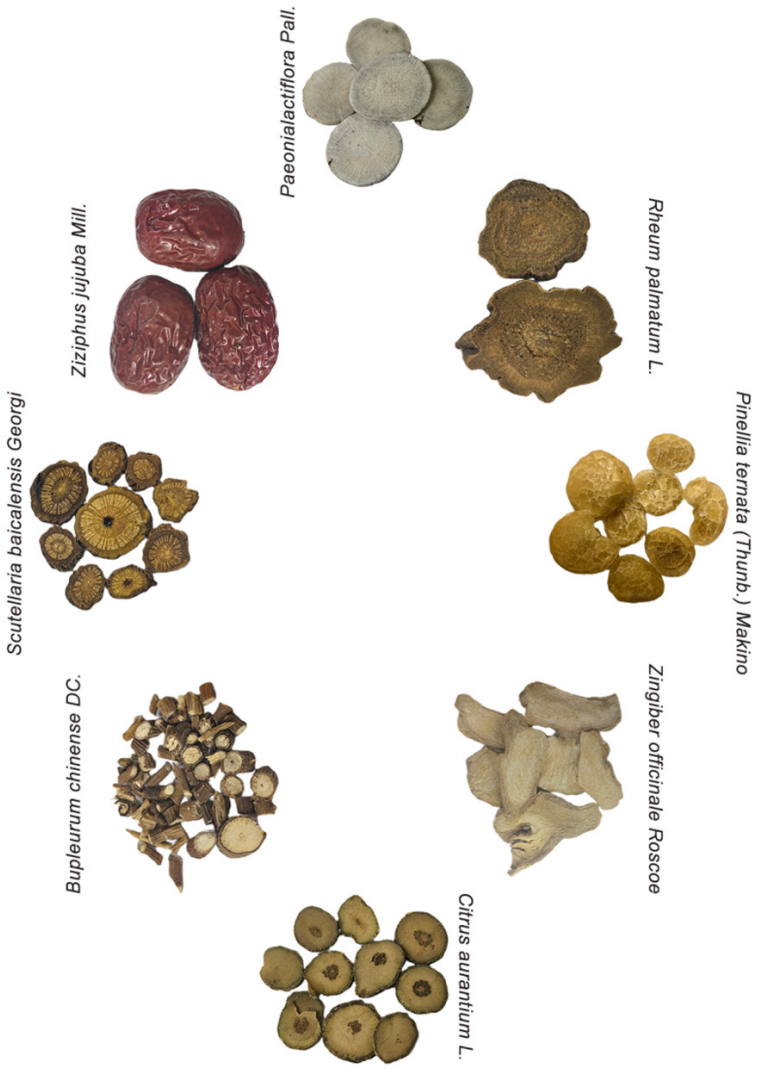



**Figure 1.** Botanical and pharmacognostic characteristics of the eight herbs comprising DCHD.

**Table 1.** Eight botanical drugs comprising DCHD

| Botanical Source (Verified Name) | Medicinal part | Chinese name | Ratio (g) |
|---|---|---|---|
| *Scutellaria baicalensis Georgi* | Root | Huangqin | 3-10 |
| *Ziziphus jujuba Mill.* | Fruit | Dazao | 6-15 |
| *Bupleurum chinense DC.* | Root | Chaihu | 3-10 |
| *Citrus aurantium L.* | Young fruit | Zhishi | 3-10 |
| *Rheum palmatum L.* | Root and Rhizome | Dahuang | 3-15 |
| *Pinellia ternata (Thunb.) Makino* | Tuber | Banxia | 3-9 |
| *Paeonialactiflora Pall.* | Root | Baishao | 6-15 |
| *Zingiber officinale Roscoe* | Rhizome | Shengjiang | 3-10 |

All botanical names and their authorship have been verified and standardized according to the World Flora Online (http://www.worldfloraonline.org).

tial toxicity. For example, *Pinellia ternata (Thunb.) Makino* was ginger-processed to reduce its irritant properties. The decoction was prepared according to standardized procedures described in official pharmacopoeias and relevant clinical trial guidelines. Briefly, the herbs were soaked in water and decocted twice. *Rheum palmatum L.* was added later in the decoction to preserve its heat-sensitive components. The resulting decoctions were then combined, filtered, and concentrated to a final volume of 150-300 mL.

### *Network meta-analysis of DCHD for hyperlipidemia*

#### *Protocol and registration*

The protocol for this systematic review and network meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42024-569042). The review was conducted and reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.3) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The PRISMA 2020 guidelines are provided in Supplementary Material 1. All data were extracted exclusively from published clinical studies.

#### *Search strategy*

A comprehensive literature search was conducted in four English-language electronic databases (PubMed, Web of Science, Cochrane Library, and

Embase) and four Chinese databases (China National Knowledge Infrastructure [CNKI], Wanfang Data, VIP Chinese Science and Technology Journal Database [VIP], and SinoMed). In addition, three clinical trial registries - the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov, and the Chinese Clinical Trial Registry - were searched to identify ongoing or unpublished studies. To assure completeness, reference lists of relevant reviews were manually screened to identify additional eligible studies not captured by the electronic searches. The search covered studies published from database inception to May 2024. The search strategy combined free-text terms and controlled vocabulary, including Medical Subject Headings (MeSH) and Emtree terms, developed based on previously published systematic reviews, clinical practice guidelines, and International Classification of Diseases (ICD) terminology. English search terms included "Dachaihu", "Dachaihu Decoction", "Dachaihu Tang", "Da Chaihu", "Da Chaihu Tang", "Da Chaihu Decoction", "Major Bupleurum Decoction", "Major Bupleurum Tang", "hyperlipemia", "hyperlipidemia", and "dyslipidemia". Corresponding Chinese databases were searched using relevant Chinese terms for Dachaihu Decoction and hyperlipidemia. Detailed search strategies for each database are provided in Supplementary Material 2.

*Inclusion and exclusion criteria*

Studies were included regardless of country or language. Randomized controlled trials (RCTs) published in Chinese or English, or with full texts available through translation, were included. Blinding was not required for inclusion.

Population. Adult patients (≥ 18 years) diagnosed with dyslipidemia, with or without comorbidities conditions (e.g., diabetes mellitus, coronary heart disease, non-alcoholic fatty liver disease, hypothyroidism, severe hepatic or renal dysfunction, or hematological diseases). Pregnant and lactating women were excluded, given the inclusion of *Rheum palmatum* L. in the DCHD formula, which is classified as contraindicated during pregnancy due to its purgative and uterotonic properties. No restrictions were applied regarding sex, geographic region, or ethnicity.

Intervention. Modified DCHD is administered as monotherapy or in combination with conventional therapy. No restrictions were placed on formulation (e.g., decoction, capsule, or granule), dosage, or administration frequency.

Control. Placebo or conventional therapy. Conventional therapy included lipid-lowering pharmacological treatments (e.g., statins) and/or non-pharmacological interventions such as health education, low-fat diet, exercise therapy, and lipid monitoring.

Outcomes. Studies were required to report at least one pre-specified outcome measure.

(1) Primary outcomes. Changes in lipid profile parameters, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

(2) Secondary outcomes. Clinical response rate.

Exclusion criteria. Non-randomized studies (e.g., cohort, case-control, cross-sectional studies), animal experiments, reviews, dissertations, theoretical analyses, case reports, and experience summaries were excluded. For duplicate publications, the study with the most complete dataset was retained. Studies with unavailable full texts or incomplete methodological or outcome data were also excluded.

*Study selection and data extraction*

All retrieved records were imported into EndNote X9 for management. Two investigators (BWY and LHX) independently screened studies according to the predefined inclusion and exclusion criteria. The screening process consisted of three stages: (1) removal of duplicate records; (2) exclusion of clearly irrelevant studies based on titles and abstracts; and (3) full-text assessment of potentially eligible studies to determine final inclusion based on population characteristics, study design, and outcome measures. Any disagreements were resolved through discussion with a third investigator until consensus was reached.

Data extraction was performed independently by the same two investigators using a standardized extraction form. When data were missing or unclear, the corresponding authors were contacted via email for clarification. Extracted

data included both baseline study characteristics and outcome measures.

Baseline characteristics comprised the first author, year of publication, funding source, study location, diagnostic criteria, inclusion and exclusion criteria, study population, sample size, gender distribution, mean age, disease duration, comorbidities, treatment duration, and details of the intervention and control groups. Outcome measures included lipid metabolism indices and clinical response rates.

*Risk of bias assessment*

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias tool (Version 1). This tool evaluates seven domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other sources of bias. Two researchers independently conducted the assessments, and each domain was rated as having a "low risk", "high risk", or "unclear risk" of bias. An "unclear risk" rating was assigned when insufficient information was available to permit a definitive judgment.

Risk of bias figures were generated using Review Manager (RevMan) version 5.3. A risk of bias summary presents the judgments for each bias domain across all included studies, using a color-coded scheme (green for low risk, red for high risk, and yellow for unclear risk). In addition, a risk of bias summary graph was created, where each row represents an included study, each column a bias domain, and symbols ("+" for low risk, "-" for high risk, "?" for unclear risk) indicate the judgment for each study-domain pair.

*Data analysis and statistical methods*

A Bayesian network meta-analysis (NMA) was performed using Markov Chain Monte Carlo (MCMC) simulation implemented through the gemtc package in R, interfaced with JAGS. A random-effects consistency model was fitted for each outcome. Non-informative prior distributions were specified, with $N(0, 10^4)$ for treatment effect parameters and a uniform prior for the between-study standard deviation. Four MCMC chains were run with 50,000 iterations after a burn-in of 20,000 iterations, using a thinning interval of 10. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic ($\hat{R} < 1.05$) and visual inspection of trace plots. Between-study heterogeneity was quantified using a common heterogeneity variance ($\tau^2$) across treatment comparisons. For continuous outcomes (TC, TG, LDL-C, and HDL-C), mean differences (MDs) with 95% credible intervals (CrIs) were calculated. For the dichotomous outcome (clinical response rate), odds ratios (ORs) with 95% CrIs were estimated.

Network inconsistency was assessed using both global and local approaches. Global inconsistency was evaluated using the design-by-treatment interaction model based on a generalized Cochran Q test. Local inconsistency was assessed using the node-splitting method, which separates direct and indirect evidence for each comparison and tests for statistically significant disagreement ($P < 0.05$). Treatment rankings were estimated using the surface under the cumulative ranking curve (SUCRA) derived from posterior probability distributions, ranging from 0% (worst) to 100% (best). Statistical heterogeneity was further quantified using the $I^2$ statistic, with 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Potential publication bias was assessed using comparison-adjusted funnel plots, following the method described by Chaimani et al. [9], with treatments ordered from most to least effective according to SUCRA rankings. An evidence network plot was generated to visualize relationships among interventions, where node size represented sample size and edge width represented the number of direct comparisons.

To evaluate the robustness of the primary findings, sensitivity analyses were performed by: (1) excluding 11 studies involving patients with acute hyperlipidemic pancreatitis, due to their substantially different baseline lipid profiles and clinical context; and (2) excluding the retrospective study [10]. Sensitivity and subgroup analyses were conducted using a frequentist random-effects NMA framework implemented in the netmeta package in R, with between-study heterogeneity estimated using the restricted maximum likelihood (REML) method. Treatment rankings were expressed as

P-scores, the frequentist analogue of SUCRA. Subgroup analyses were performed according to treatment duration (short-term: ≤ 14 days; medium-term: 15 days-2 months; long-term: > 2 months) and primary diagnosis (pure hyperlipidemia, hyperlipidemic pancreatitis, and other comorbidities). When subgroup sample sizes were insufficient for NMA (< 3 studies, < 3 treatments, or disconnected networks), pairwise meta-analysis was conducted instead.

All Bayesian analyses were performed using R (gemtc package) and JAGS, with additional analyses conducted in STATA version 16.0 and R (netmeta and meta packages). Risk-of-bias figures were generated using Review Manager (RevMan) version 5.3. Forest plots were used to display effect estimates, and rankograms were generated to illustrate treatment ranking probabilities. A two-sided *P*-value < 0.05 was considered statistically significant.

*Network pharmacology analysis of DCHD for hyperlipidemia*

*Identification and screening of active compounds in DCHD*

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) was used to retrieve the chemical constituents of the eight herbs comprising Dachaihu Decoction (DCHD). Initial compound screening was conducted based on oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. For the compounds meeting these criteria, isomeric SMILES (or canonical SMILES when isomeric SMILES were unavailable) were obtained from the PubChem database. Subsequently, ADME (absorption, distribution, metabolism, and excretion) evaluation was performed using the SwissADME platform. Compounds meeting at least two "Yes" criteria among the assessed ADME parameters were defined as active compounds. All identified active compounds were compiled and organized in Microsoft Excel for subsequent network pharmacology analysis.

*Prediction of potential targets for DCHD active compounds*

For the active compounds identified in sections 2.3.1, their corresponding isomeric or canonical SMILES strings were individually imported into the SwissTargetPrediction online platform to predict potential protein targets. Predicted targets with a probability > 0 were considered relevant. All predicted target names were subsequently standardized by conversion to official gene symbols using the UniProt database. After removing duplicate entries, a consolidated list of putative therapeutic targets associated with DCHD was obtained.

*Identification of hyperlipidemia-related targets*

The keywords "hyperlipidemia" and "hypertriglyceridemia" were used to search the GeneCards and Online Mendelian Inheritance in Man (OMIM) disease databases. The retrieved gene lists were downloaded, merged, and deduplicated using Microsoft Excel to generate a comprehensive set of hyperlipidemia-related targets.

*Identification of intersecting targets and Venn diagram construction*

The predicted targets of DCHD identified in section 2.3.2 and the hyperlipidemia-related targets obtained in section 2.3.3 were imported into Venny 2.1.0 to identify intersecting targets. A Venn diagram was generated to depict the overlap between DCHD-related targets and hyperlipidemia-associated targets visually.

*Protein-protein interaction (PPI) network construction and core target screening*

The intersecting targets identified in section 2.3.4 or section 2.2.4 were imported into the STRING database to construct a protein-protein interaction (PPI) network. The "Multiple proteins" option was selected, and the organism was restricted to Homo sapiens. Network visualization settings included enabling the 3D bubble layout and hiding disconnected nodes. The resulting PPI network was exported, and the interaction data were downloaded in TSV format. The TSV file was subsequently imported into Cytoscape (version 3.10.2) for further network visualization and topological analysis. Degree centrality values for each node were calculated using the CytoNCA plugin, and node attributes (size, color gradient, and transparency) were mapped proportionally to degree values to identify hub targets. Core targets were further screened using the CentiScaPe 2.2 plugin based on three topological parameters: degree, betweenness centrality, and clo-

seness centrality. A refined PPI network comprising these core targets was then constructed and visualized.

*Construction of the herb-compound-target-pathway-disease network*

Following the identification of intersecting targets in section 2.3.4, the relationships among herbs, active compounds, intersecting targets, pathways, and disease were systematically organized using Microsoft Excel. An integrated multi-layer network was then constructed and visualized in Cytoscape (version 3.10.2). Degree centrality for each node was calculated using the CytoNCA plugin, and visual attributes - including node size, color gradient, and transparency - were mapped proportionally to degree values to facilitate the identification of key herbs, active compounds, and core targets within the network.

*GO functional and KEGG pathway enrichment analysis*

The intersection targets identified in section 2.3.4 or section 2.2.4 were subjected to functional enrichment analysis using the DAVID bioinformatics database, with the species restricted to "Homo sapiens". Gene Ontology (GO) enrichment analysis was conducted across three categories: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF), along with Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. The enrichment results were downloaded and organized in Excel. Terms with a $P$ value < 0.01 were considered statistically significant. For visualization and interpretation, the top 10 enriched terms from each GO category and the top 20 KEGG pathways were selected based on enrichment ranking. These data were subsequently imported into an online bioinformatics plotting platform to generate GO and KEGG enrichment diagrams, which were used to elucidate the key biological functions and signaling pathways potentially involved in the therapeutic effects of DCHD against hyperlipidemia.

*Molecular docking and MD simulation of DCHD for hyperlipidemia*

*Selection of receptors and ligands*

To ensure both biological relevance and network significance, a multi-step screening strategy was used to select receptor proteins for molecular docking. First, the KEGG pathway "Lipid and atherosclerosis", identified in enrichment analysis as the most relevant pathway associated with lipid metabolism, was selected for further investigation. Target genes involved in this pathway were then intersected with the top 10 hub genes obtained from the protein-protein interaction (PPI) network analysis. This integrative approach yielded four key targets-ICAM1, MMP9, TLR4, and GSK3B-which exhibit both pathway relevance and network hub characteristics, making them suitable receptor proteins for subsequent molecular docking and mechanistic exploration. The three-dimensional crystal structures of these target proteins were retrieved from the RCSB Protein Data Bank (PDB) and preprocessed using the Protein Preparation Wizard module in Schrödinger. The standard preparation workflow was followed, including protein preprocessing, assignment, regeneration of native ligand states, optimization of hydrogen-bonding networks, energy minimization, and removal of crystallographic water molecules. For ligand selection, we aimed to integrate evidence from clinical efficacy and network-predicted bioactivity. Based on the network meta-analysis results, DCHD was identified as the optimal formulation for the treatment of hyperlipidemia. Within the constructed "Herb-Active Compound-Intersection Target-Pathway-Disease" network, β-sitosterol and stigmasterol were selected as representative active compounds. These molecules were chosen due to their high frequency of occurrence across the eight constituent herbs of DCHD and their central positions within the network. The two-dimensional structures of both compounds were obtained in SDF format and processed using the LigPrep module in Schrödinger to generate energetically minimized three-dimensional conformations and relevant chiral states for docking analysis.

*Molecular docking*

Potential binding sites of the four target proteins (ICAM1, MMP9, TLR4, and GSK3B) were first predicted using the SiteMap module in Schrödinger. Based on the identified binding pockets, receptor grids were generated using the Receptor Grid Generation module. The prepared ligands, β-sitosterol and stigmasterol, were then docked into the corresponding active sites of each target protein using the Glide

module in extra precision (XP) mode. Docking performance was evaluated using Glide scores, with lower scores indicating more favorable predicted binding interactions. To further refine binding affinity estimation, the Molecular Mechanics/Generalized Born Surface Area (MM-GBSA) approach was applied to the resulting protein-ligand complexes. The calculated MM-GBSA dG_bind values were used as approximations of binding free energy, with more negative values indicating stronger, more stable binding interactions.

*Molecular dynamics simulation*

Molecular dynamics (MD) simulations were conducted using the Desmond module to evaluate the conformational stability and dynamic behavior of the protein-ligand complex under simulated physiological conditions. The complex showing the most favorable MM-GBSA binding free energy was selected for simulation. All systems were parameterized using the OPLS4 force field and solvated in an orthorhombic simulation box with the SPC/E water model. To neutralize the system and mimic physiological ionic strength, $Na^+$ and $Cl^-$ ions were added to a final concentration of 0.150 M. Energy minimization was first performed for 50,000 steps using the steepest-descent algorithm. This was followed by a two-stage equilibration process consisting of 500 ps simulations performed under both the NVT (constant number of particles, volume, and temperature) and NPT (constant number of particles, pressure, and temperature) ensembles, during which positional restraints were applied to heavy atoms. All simulations were carried out at a temperature of 300 K and a pressure of 1 bar. Subsequently, an unrestrained production MD simulation was performed for 100 ns. Trajectory information was analyzed using the Maestro 14.3 software suite to assess structural stability, conformational changes, and key protein-ligand interactions throughout the simulation period.

## Results

*Network meta-analysis findings*

*Literature screening and selection*

A total of 512 records were initially identified from the following databases: PubMed (n = 13), Web of Science (n = 0), Cochrane Library (n = 6), Embase (n = 17), SinoMed (n = 60), China National Knowledge Infrastructure (n = 86), Wanfang (n = 258), and VIP (n = 72). After removing 188 duplicate records using EndNote software, 324 articles remained for title and abstract screening. During screening, case reports, letters, guidelines, responses, conference abstracts, registration records, dissertations, reviews, meta-analyses, and other ineligible publication types were excluded. As a result, 173 full-text articles were assessed for eligibility. Of these, 17 studies were excluded for irrelevant outcomes, and 111 were excluded for ineligible interventions or study populations. Consequently, 23 studies [10-32] met the inclusion criteria and were included in the systematic review and network meta-analysis. The study selection process is summarized in **Figure 2**.

*Characteristics of included studies*

A total of 23 RCTs conducted in China, involving 1816 participants, were included in the final analysis. The studies were published between 2005 and 2023. The enrolled populations were diagnosed with dyslipidemia across various clinical contexts, including hyperlipidemic pancreatitis (11 studies), hyperlipidemia (7 studies), hyperlipidemia with diabetes (2 studies), metabolic syndrome (2 studies), and non-alcoholic fatty liver disease (1 study). In the control groups, interventions consisted primarily of usual care (22 studies), with CA therapy (1 study). The intervention groups received DCHD-based treatments, including DCHD alone (11 studies), DCHD combined with Guizhi Fuling Pill (4 studies), DCHD plus Shengjiang Powder (2 studies), DCHD combined with Dachengqi Decoction (2 studies), DCHD combined with CA therapy (2 studies), DCHD plus Huanglian Wendan Decoction (1 study), and DCHD combined with Erchen Decoction (1 study). Across all included trials, DCHD-based interventions were administered once daily. Detailed baseline characteristics of the included studies are summarized in **Table 2**. Meanwhile, a supplementary table (Table S1) summarizes the baseline levels of TC, TG, LDL-C, and HDL-C across all 23 included studies, stratified by population type.

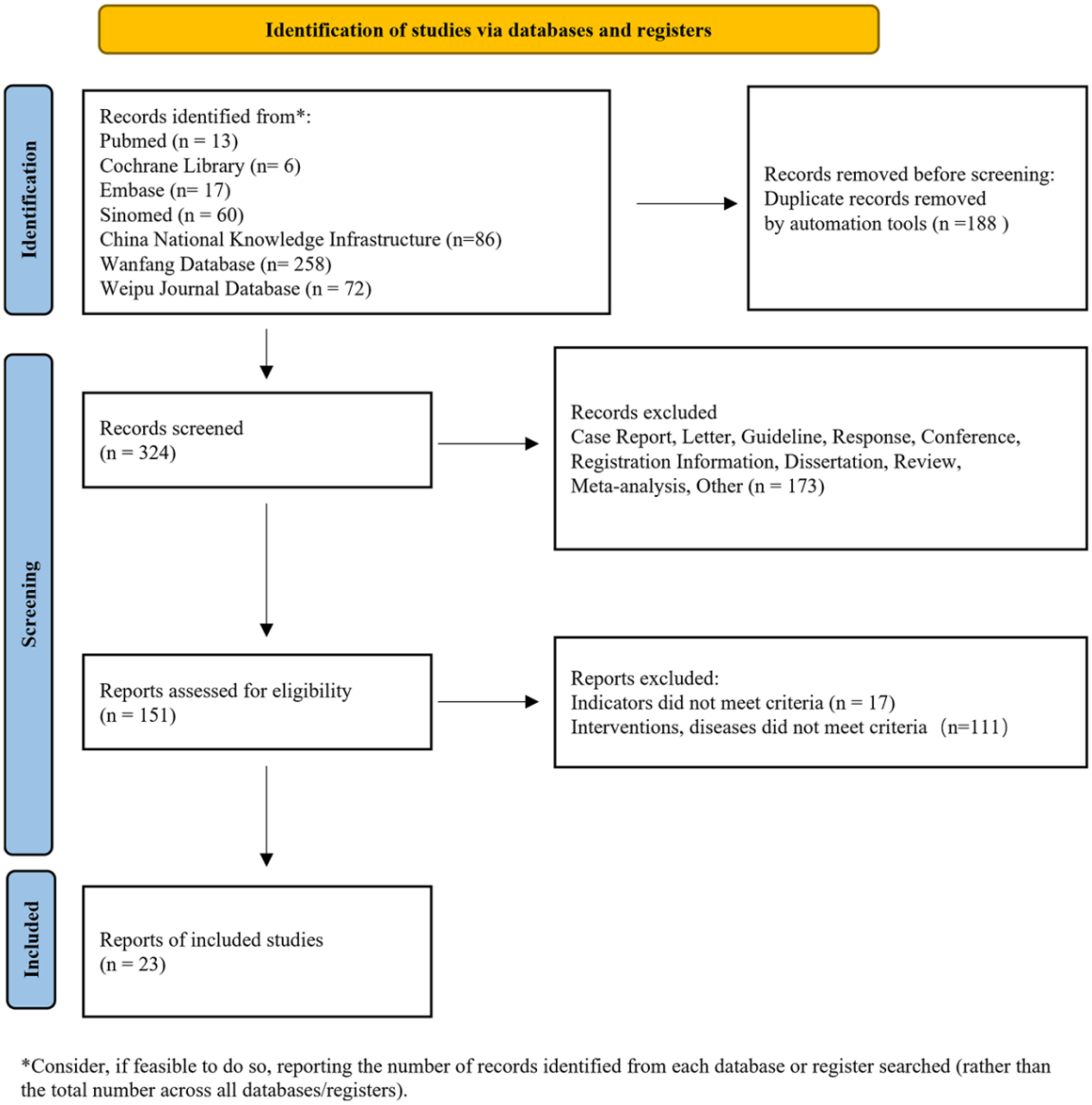



**Figure 2.** Flowchart of the literature screening and selection process.

*Risk of bias and methodological quality*

The risk-of-bias assessment of the 23 included studies is summarized in **Figure 3**. For the domain of random sequence generation, studies that explicitly reported appropriate randomization methods (e.g., random number tables or computer-generated sequences) were rated as low risk, whereas studies that merely stated that participants were "randomly divided" without providing further details were rated as unclear risk.

Regarding allocation concealment, only a small proportion of studies provided sufficient methodological details; therefore, most studies were assessed as unclear risk in this domain. One study was identified as having a retrospective design and was consequently rated as high risk of bias [10]. A sensitivity analysis excluding this study demonstrated no change in treatment rankings across all five outcomes, indicating that its inclusion did not materially influence the overall results. Blinding of participants and personnel was not feasible given the nature of the TCM interventions, resulting in a high risk of performance bias in most trials. In addition, none of the included studies reported prospective trial registration in registries such as ClinicalTrials.gov or the Chinese Clinical Trial

**Table 2.** Basic characteristics of the included studies

| Study | Sample size (I/C) | Sex M/F | | Age (years) | | Intervention measures | Treatment duration | Time point of inclusion | Outcomes |
|---|---|---|---|---|---|---|---|---|---|
| | | I | C | I | C | | | | |
| Chen 2023 [10] | 30/28 | 14/16 | 11/17 | 42.65 ± 7.24 | 43.14 ± 7.56 | DCHD | 2 weeks | After treatment | ② |
| Jiang 2012 [11] | 36/40 | - | - | - | - | DCHD | 6 months | Before treatment, After treatment | ①② |
| Zhang 2019 [12] | 44/44 | 21/23 | 24/20 | 54.8 ± 7.2 | 56.2 ± 6.1 | DCHD guizhi fuling pill | 56 days | Before treatment, After treatment | ①②③ |
| Liu 2017 [13] | 45/45 | 27/18 | 25/20 | 57.7 ± 6.5 | 57.9 ± 6.7 | DCHD guizhi fuling pill | 8 weeks | Before treatment, After treatment | ①②③ |
| Ding 2019 [14] | 60/60 | 0/60 | 0/60 | 43.82 ± 10.61 | 43.80 ± 10.58 | DCHD guizhi fuling pill | 2 months | Before treatment, After treatment | ①②③④ |
| Liu 2016 [15] | 39/37 | 19/20 | 18/19 | 47.18 ± 5.89 | 46.94 ± 6.15 | DCHD guizhi fuling pill | 60 days | Before treatment, After treatment | ①② |
| Yang 2022 [16] | 29/29 | 15/14 | 16/13 | 44.35 ± 3.24 | 45.38 ± 3.54 | DCHD shengjiang powder | - | Before treatment, After treatment | ①②③④ |
| Feng 2022 [17] | 40/40 | 19/21 | 20/20 | 34.4 ± 5.2 | 38.7 ± 3.9 | DCHD shengjiang powder | 7 days | Before treatment, After treatment | ①②③④ |
| Chen 2005 [18] | 32/26 | 18/14 | 15/11 | 58.6 ± 13.1 | 49.6 ± 12.6 | DCHD | 8 weeks | Before treatment, After treatment | ①②③④ |
| Hu 2021 [19] | 31/31 | 18/13 | 20/11 | 61.81 ± 3.35 | 61.32 ± 3.26 | DCHD | 4 weeks | Before treatment, After treatment | ①② |
| Sang 2024 [20] | 30/30 | 19/11 | 18/12 | 68.20 ± 10.70 | 69.10 ± 10.49 | DCHD | 28 days | Before treatment, After treatment | ①②③④ |
| Lei 2018 [21] | 20/20 | 9/11 | 12/8 | 56.5 ± 9.5 | 55 ± 10 | DCHD CA therapy (+Immunotherapy with Ozone-Enriched Blood Transfusion) | 5 days | Before treatment, After treatment | ①② |
| He 2016 [22] | 40/40 | 31/9 | 34/6 | 36.6 ± 13.2 | 35.3 ± 14.2 | DCHD dachengqi decoction | 7 days | Before treatment, After treatment | ①② |
| Liu 2023 [23] | 42/42 | 26/16 | 28/14 | 62.50 ± 10.15 | 62.74 ± 10.21 | DCHD | 3 months | Before treatment, After treatment | ①②③ |
| Liu 2015 [24] | 40/40 | 26/14 | 29/11 | 58.9 | 54.6 | DCHD CA therapy (+ external application of raw rhubarb) | 7 days | After treatment | ② |
| Shi 2017 [25] | 36/36 | 21/15 | 26/10 | 44.23 ± 9.14 | 46.79 ± 8.21 | DCHD | 3 days | After treatment | ② |
| Zhao 2016 [26] | 60/60 | 32/28 | 29/31 | 49.84 ± 4.28 | 53.26 ± 4.15 | DCHD | 12 weeks | Before treatment, After treatment | ①②③④ |
| Zhang 2014 [27] | 43/43 | 29/14 | 31/12 | 48.9 | 50.1 | DCHD erchen decoction | 3 months | After treatment | ②③ |
| Yang 2018 [28] | 30/30 | - | - | - | - | DCHD dachengqi decoction | - | Before treatment, After treatment | ② |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Zhang 2020 [29] | 40/40 | 19/21 | 22/18 | 54.52 ± 5.93 | 53.97 ± 5.89 | DCHD | 8 weeks | Before treatment, After treatment | ①②③ |
| Liu 2014 [30] | 38/30 | - | - | 58.9 | 60.2 | DCHD | 7 days | Before treatment, After treatment | ② |
| Li 2019 [31] | 50/50 | 33/17 | 35/15 | 53.44 ± 1.20 | 54.40 ± 1.25 | DCHD | 7 days | Before treatment, After treatment | ①② |
| Gu 2015 [32] | 60/60 | 29/31 | 28/32 | 48.5 ± 7.7 | 47.6 ± 7.9 | DCHD huanglian wendan decoction | 12 weeks | Before treatment, After treatment | ②④ |

Notes: I, intervention group; C, control group; -, not mentioned; ① TC: total cholesterol. ② TG: triglycerides. ③ LDL-C: low-density lipoprotein cholesterol. ④ HDL-C: high-density lipoprotein cholesterol. ⑤ Efficient.

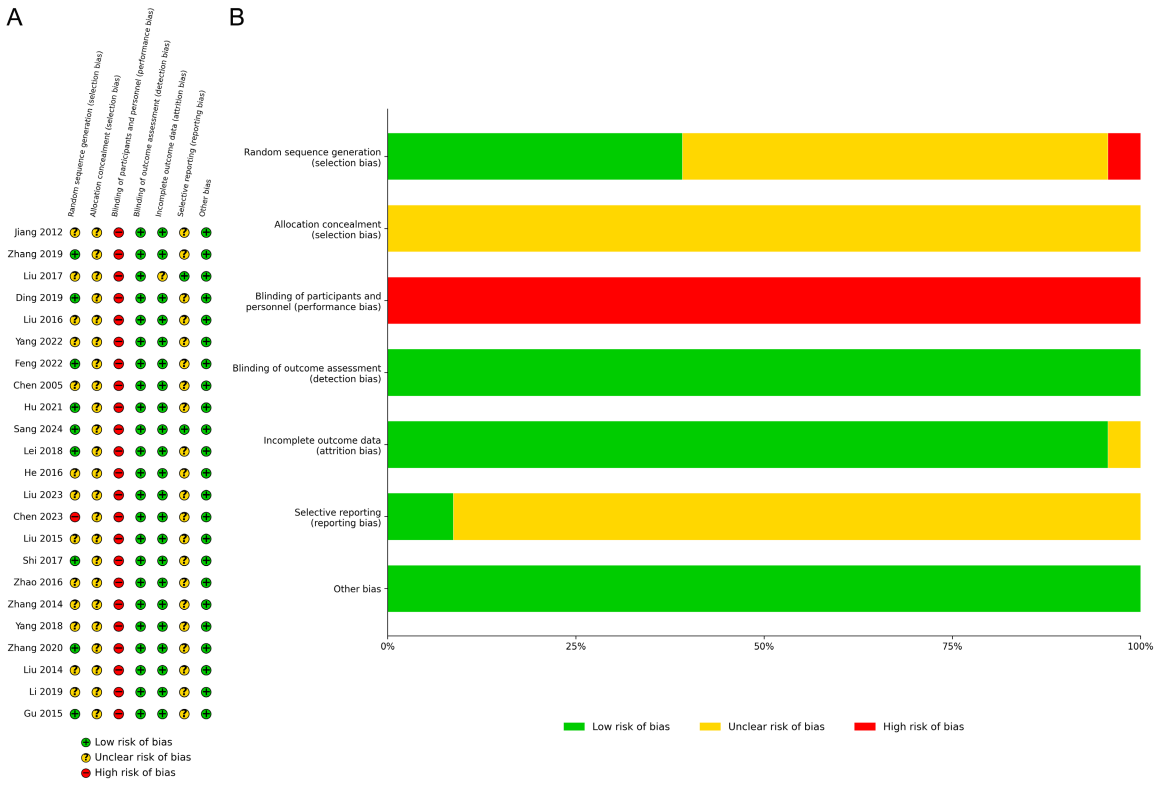



**Figure 3.** Bias and quality assessment of included studies. A. Risk of bias summary; B. Risk of bias graph.

Registry, making it impossible to verify selective outcome reporting. Consequently, the selective reporting domain was assessed as unclear risk for all studies.

Overall, the methodological quality of the included trials should be interpreted with caution, as most were small, single-center randomized controlled trials conducted in China, with limited reporting transparency regarding key methodological procedures.

*Evidence network graphs*

The evidence network graphs for the five outcomes, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and response rate are shown in **Figure 4** and include seven intervention nodes. Each node represents an intervention, with node size proportional to the total sample size. Direct comparisons between interventions are depicted by connecting lines, the thickness of which reflects the number of studies available for each comparison.

*Total cholesterol (TC)*

The TC network included 17 RCTs and 7 interventions. As shown in the forest plot (**Figure 5A**), compared with DCHD alone, both the control group (0.88, 95% CrI: 0.28 to 1.50) and CA therapy (2.60, 95% CrI: 0.71 to 4.50) were associated with significantly higher TC levels. In contrast, compared with the control group, DCHD Shengjiang Powder significantly reduced TC levels (-1.80, 95% CrI: -3.00 to -0.52). The rankogram (**Figure 5B**) showed that CA therapy was the least effective intervention for TC reduction. Based on SUCRA values, DCHD Shengjiang Powder (85.18%), DCHD + CA therapy (78.41%), and DCHD alone (60.06%) ranked as the three most effective interventions for lowering TC.

*Triglycerides (TG)*

The TG network included 22 RCTs and 7 interventions. As shown in the forest plot (**Figure 5C**), compared with DCHD alone, both the control group (0.92, 95% CrI: 0.54 to 1.40) and CA therapy (1.60, 95% CrI: 0.25 to 2.90) were

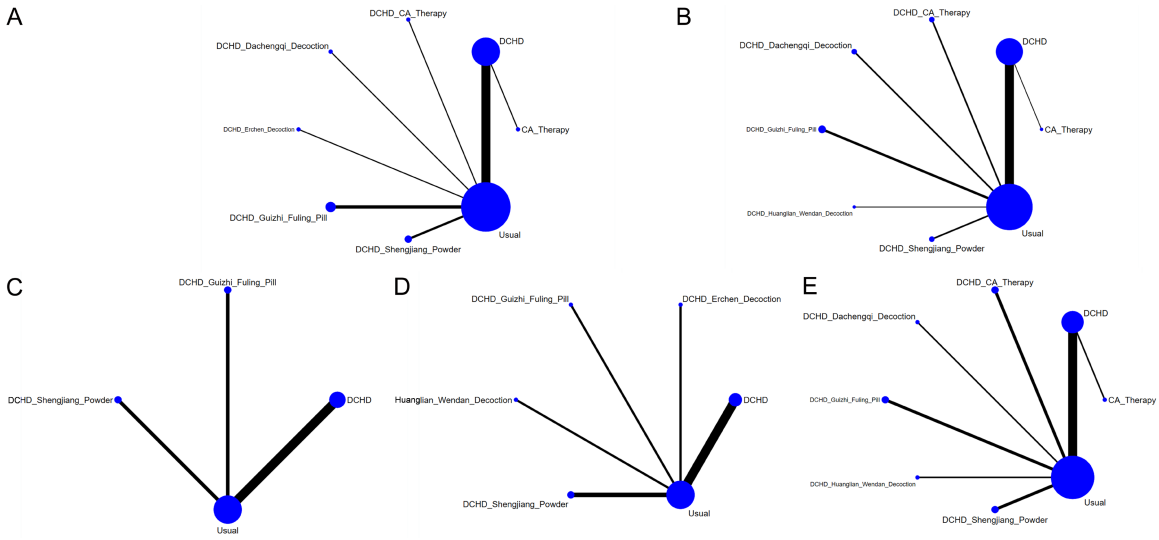



**Figure 4.** Network plots of treatment effects. A. Total cholesterol (TC); B. Triglycerides (TG); C. Low-density lipoprotein cholesterol (LDL-C); D. High-density lipoprotein cholesterol (HDL-C); E. Response rate.

associated with significantly higher TG levels. Compared with the control group, DCHD + CA therapy (-1.30, 95% CrI: -2.60 to -0.04) and DCHD + Dachengqi Decoction (-2.30, 95% CrI: -4.50 to -0.14) significantly reduced TG levels. In contrast, no statistically significant differences were observed for DCHD + Guizhi Fuling Pill (-0.66, 95% CrI: -1.40 to 0.08), DCHD + Huanglian Wendan Decoction (-0.22, 95% CrI: -1.50 to 1.10), or DCHD Shengjiang Powder (-0.93, 95% CrI: -1.90 to 0.09). The rankogram (**Figure 5D**) indicated that DCHD Shengjiang Powder, DCHD + CA therapy, and DCHD alone ranked among the most effective interventions for TG reduction based on SUCRA values.

*Low-density lipoprotein cholesterol (LDL-C)*

The LDL-C network comprised 9 RCTs, including three active interventions (DCHD, DCHD + Guizhi Fuling Pill, and DCHD Shengjiang Powder) and a control group. As shown in the forest plot (**Figure 5E**), both DCHD (-0.65, 95% CrI: -1.30 to -0.01) and DCHD Shengjiang Powder (-1.10, 95% CrI: -2.10 to -0.09) significantly reduced LDL-C levels compared with the control. The rankogram (**Figure 5F**) demonstrated that DCHD Shengjiang Powder had the highest probability of being the most effective intervention for lowering LDL-C (80.60%), followed by DCHD + Guizhi Fuling Pill (67.32%) and DCHD alone (49.44%).

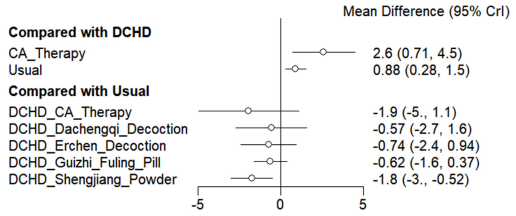
*High-density lipoprotein cholesterol (HDL-C)*

The HDL-C network comprised 9 RCTs. As shown in the rankogram (**Figure 5H**), DCHD Shengjiang Powder had the highest probability of being the most effective intervention for increasing HDL-C levels (78.56%). However, the forest plot (**Figure 5G**) revealed that none of the interventions produced a statistically significant improvement in HDL-C compared with the control group, including DCHD (-0.24, 95% CrI: -1.20 to 0.69), DCHD + Erchen Decoction (-0.45, 95% CrI: -2.30 to 1.40), DCHD + Guizhi Fuling Pill (0.23, 95% CrI: -4.20 to 4.60), DCHD + Huanglian Wendan Decoction (0.09, 95% CrI: -1.80 to 2.00), and DCHD Shengjiang Powder (0.69, 95% CrI: -0.64 to 2.00). Overall, no statistically significant differences in HDL-C levels were observed among the intervention groups.

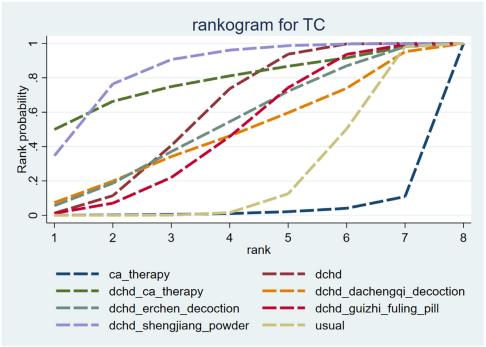
*Clinical response rate*

The response rate network included 15 RCTs. As shown in the forest plot (**Figure 5I**), both CA therapy (0.39, 95% CrI: 0.23 to 0.59) and the control group (0.84, 95% CrI: 0.76 to 0.92) had significantly lower response rates compared with DCHD alone. In contrast, DCHD + CA therapy (1.27, 95% CrI: 1.07 to 1.55), DCHD + Guizhi Fuling Pill (1.15, 95% CrI: 1.00 to 1.33), and DCHD Shengjiang powder (1.30, 95% CrI: 1.08 to 1.60) achieved significantly higher response rates than the control group. According

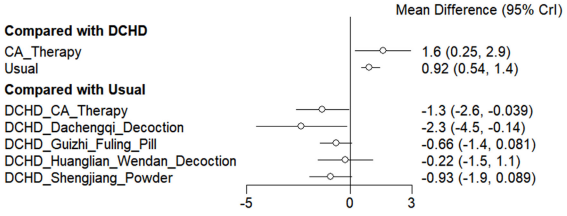
A


Mean Difference (95% CrI)
Compared with DCHD
CA_Therapy
2.6 (0.71, 4.5)
Usual
0.88 (0.28, 1.5)
Compared with Usual
DCHD_CA_Therapy
-1.9 (-5., 1.1)
DCHD_Dachengqi_Decoction
-0.57 (-2.7, 1.6)
DCHD_Erchen_Decoction
-0.74 (-2.4, 0.94)
DCHD_Guizhi_Fuling_Pill
-0.62 (-1.6, 0.37)
DCHD_Shengjiang_Powder
-1.8 (-3., -0.52)
-5
0
5

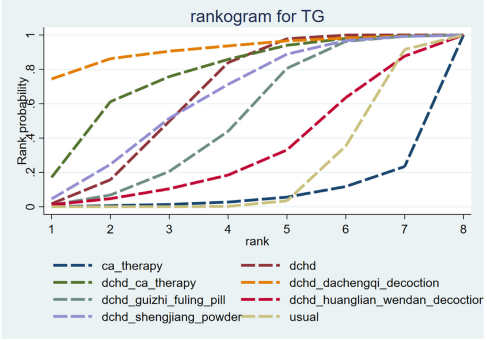
B


rankogram for TC
Rank probability
rank
ca_therapy
dchd
dchd_ca_therapy
dchd_dachengqi_decoction
dchd_erchen_decoction
dchd_guizhi_fuling_pill
dchd_shengjiang_powder
usual

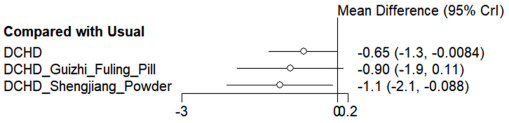
C


Mean Difference (95% CrI)
Compared with DCHD
CA_Therapy
1.6 (0.25, 2.9)
Usual
0.92 (0.54, 1.4)
Compared with Usual
DCHD_CA_Therapy
-1.3 (-2.6, -0.039)
DCHD_Dachengqi_Decoction
-2.3 (-4.5, -0.14)
DCHD_Guizhi_Fuling_Pill
-0.66 (-1.4, 0.081)
DCHD_Huanglian_Wendan_Decoction
-0.22 (-1.5, 1.1)
DCHD_Shengjiang_Powder
-0.93 (-1.9, 0.089)
-5
0
3

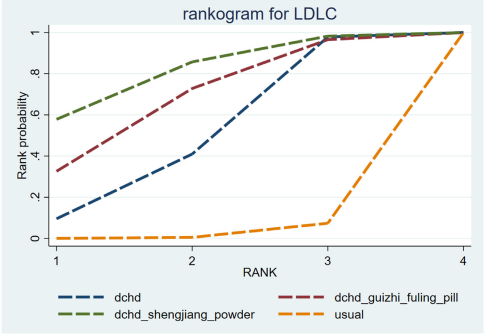
D


rankogram for TG
Rank probability
rank
ca_therapy
dchd
dchd_ca_therapy
dchd_dachengqi_decoction
dchd_guizhi_fuling_pill
dchd_huanglian_wendan_decoction
dchd_shengjiang_powder
usual

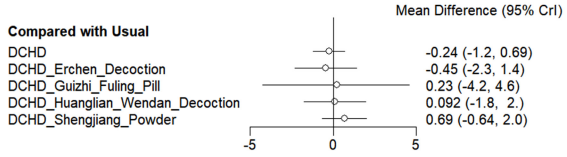
E


Mean Difference (95% CrI)
Compared with Usual
DCHD
-0.65 (-1.3, -0.0084)
DCHD_Guizhi_Fuling_Pill
-0.90 (-1.9, 0.11)
DCHD_Shengjiang_Powder
-1.1 (-2.1, -0.088)
-3
0
0.2

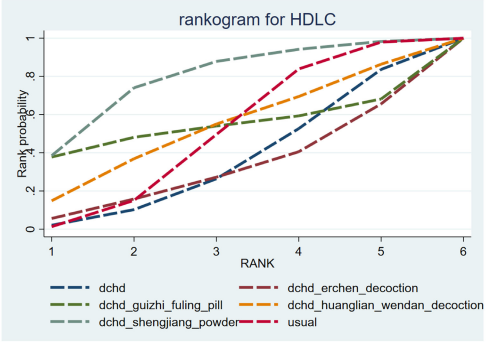
F


rankogram for LDLC
Rank probability
RANK
dchd
dchd_guizhi_fuling_pill
dchd_shengjiang_powder
usual

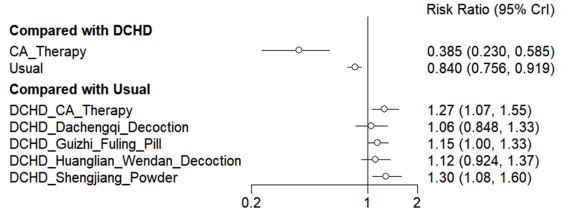
G


Mean Difference (95% CrI)
Compared with Usual
DCHD
-0.24 (-1.2, 0.69)
DCHD_Erchen_Decoction
-0.45 (-2.3, 1.4)
DCHD_Guizhi_Fuling_Pill
0.23 (-4.2, 4.6)
DCHD_Huanglian_Wendan_Decoction
0.092 (-1.8, 2.)
DCHD_Shengjiang_Powder
0.69 (-0.64, 2.0)
-5
0
5

H


rankogram for HDLC
Rank probability
RANK
dchd
dchd_erchen_decoction
dchd_guizhi_fuling_pill
dchd_huanglian_wendan_decoction
dchd_shengjiang_powder
usual

I


Risk Ratio (95% CrI)
Compared with DCHD
CA_Therapy
0.385 (0.230, 0.585)
Usual
0.840 (0.756, 0.919)
Compared with Usual
DCHD_CA_Therapy
1.27 (1.07, 1.55)
DCHD_Dachengqi_Decoction
1.06 (0.848, 1.33)
DCHD_Guizhi_Fuling_Pill
1.15 (1.00, 1.33)
DCHD_Huanglian_Wendan_Decoction
1.12 (0.924, 1.37)
DCHD_Shengjiang_Powder
1.30 (1.08, 1.60)
0.2
1
2

J

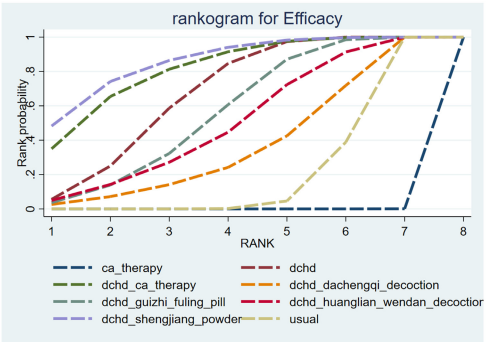

rankogram for Efficacy
Rank probability
RANK
ca_therapy
dchd
dchd_ca_therapy
dchd_dachengqi_decoction
dchd_guizhi_fuling_pill
dchd_huanglian_wendan_decoction
dchd_shengjiang_powder
usual

**Figure 5.** Forest plots and rankograms of clinical outcomes. A. Forest plot of TC; B. Rankogram of TC; C. Forest plot of TG; D. Rankogram of TG; E. Forest plot of LDL-C; F. Rankogram of LDL-C; G. Forest plot of HDL-C; H. Rankogram of HDL-C; I. Forest plot of response rate; J. Rankogram of response rate.

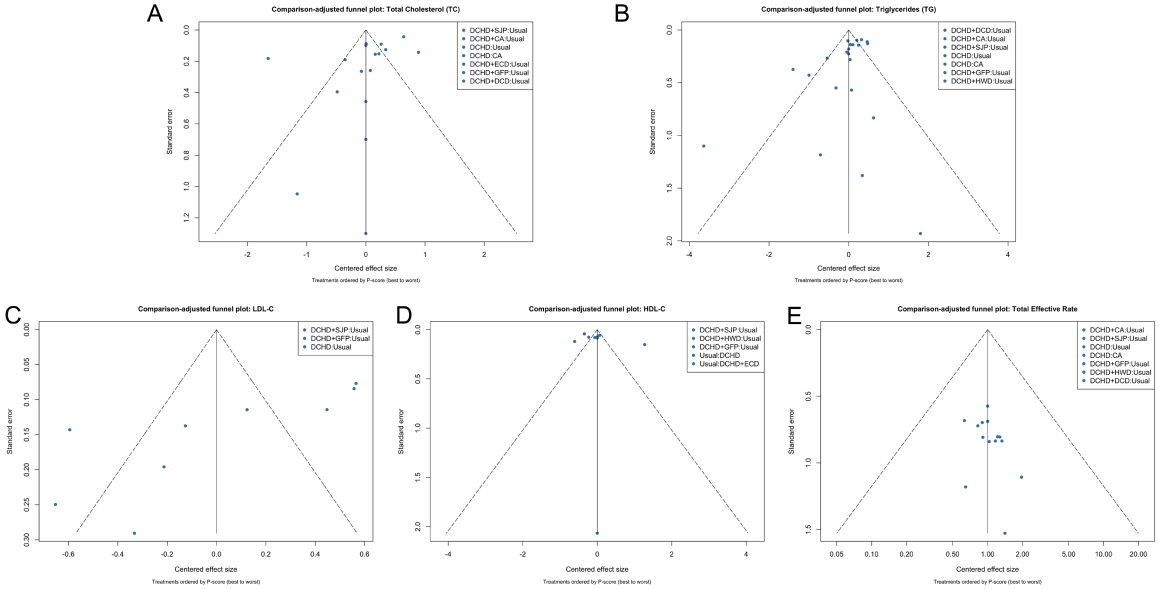



**Figure 6.** Comparison-adjusted funnel plots for publication bias assessment. A. TC; B. TG; C. LDL-C; D. HDL-C; E. Response rate. Treatments are ordered from most to least effective based on SUCRA values. Asymmetry in the funnel plot may indicate small-study effects or publication bias.

to the rankogram (**Figure 5J**), DCHD Shengjiang Powder (85.85%), DCHD + CA therapy (81.51%), and DCHD alone (67.33%) were ranked as the three most effective interventions for improving response rate.

*Assessment of publication bias*

Potential publication bias was assessed using comparison-adjusted funnel plots, with treatments ordered from most to least effective based on SUCRA rankings, as recommended for network meta-analysis [9]. Comparison-adjusted funnel plots were generated for TC, TG, LDL-C, HDL-C, and response rate (**Figure 6**). Visual inspection indicated broadly symmetric distributions for most outcomes; however, the relatively small number of studies in certain treatment comparisons limits the interpretability of these plots. It is important to note that all 23 included studies were published in Chinese-language journals, raising the possibility of language and regional publication bias. Previous evidence suggests that clinical trials of TCM conducted in China frequently report positive findings, and the lack of unpublished or negative studies may inflate pooled effect estimates and influence treatment rankings. This concern is further addressed in the limitations section.

*Sensitivity and subgroup analyses*

To explore the robustness of the primary findings and address potential clinical heterogeneity, we conducted a series of sensitivity and subgroup analyses, including exclusion of pancreatitis studies, exclusion of a retrospective study, stratification by treatment duration, and subgroup analysis by primary diagnosis. Detailed results are provided in Tables S2, S3 and Figures S1, S2, S3, S4, S5.

*Sensitivity analysis excluding acute pancreatitis studies:* To address heterogeneity introduced by acute hyperlipidemic pancreatitis, we excluded all 11 pancreatitis-related studies and re-ran the network meta-analysis using a frequentist random-effects NMA (netmeta package). This exclusion removed three treatment nodes (DCHD Shengjiang powder, DCHD combined with CA therapy, and DCHD com-

bined with Dachengqi Decoction) from the network, as evidence for these formulations was derived exclusively from pancreatitis trials. The remaining treatments formed a connected network, including DCHD alone, DCHD combined with Guizhi Fuling Pill, DCHD combined with Erchen Decoction, DCHD combined with Huanglian Wendan Decoction, CA therapy, and conventional treatment.

The relative efficacy rankings remained largely stable for DCHD alone and DCHD combined with Guizhi Fuling Pill, indicating that these treatments demonstrated consistent benefits in non-pancreatitis populations. Full P-score rankings are presented in Table S2 and Figure S1.

*Sensitivity analysis excluding the retrospective study:* Excluding the single retrospective study [10] did not change the overall treatment rankings for any outcomes. P-scores showed negligible variation, confirming the robustness of the primary analysis.

*Subgroup analysis by treatment duration:* Studies were stratified into short-term (≤ 14 days), medium-term (15 days-2 months), and long-term (> 2 months). The short-term subgroup included mostly pancreatitis studies, with NMA feasible for TC, TG, and response rate. Results closely mirrored the pancreatitis subgroup, with DCHD combined with CA therapy and DCHD combined with Dachengqi Decoction ranking highest for key outcomes.

Medium-term studies, representing primarily chronic hyperlipidemia, showed DCHD alone consistently ranking highest across TC, TG, and LDL-C, followed by DCHD combined with Guizhi Fuling Pill. The single long-term study (6 months) was described narratively [11]. These findings reinforce that short-term studies are largely pancreatitis-focused, while longer-term studies reflect chronic hyperlipidemia management. Detailed rankings are presented in Figure S2.

*Subgroup analysis by primary diagnosis:* Subgroup NMAs were performed for three population types: pure hyperlipidemia (7 studies), pancreatitis (11 studies), and other comorbidities (5 studies; diabetes, metabolic syndrome, NAFLD).

(1) In pure hyperlipidemia, DCHD alone consistently ranked highest for TC, TG, LDL-C, and response rate, while DCHD combined with Guizhi Fuling Pill ranked second; HDL-C showed comparable effects between conventional treatment and DCHD+GFP.

(2) In pancreatitis, DCHD Shengjiang Powder, DCHD combined with Dachengqi Decoction, and DCHD combined with CA therapy ranked highest for TC, TG, and response rate, respectively. Pairwise analyses were used for outcomes with insufficient network connectivity (HDL-C, LDL-C).

(3) In other comorbidities, DCHD+Erchen Decoction ranked highest for TC, DCHD alone for TG and response rate, and DCHD + Huanglian Wendan Decoction for HDL-C.

These analyses highlight that treatment efficacy differs across patient populations, emphasizing the importance of distinguishing pancreatitis-specific evidence from chronic hyperlipidemia outcomes. Full results are reported in Table S3 and Figures S3, S4, S5.

*Network pharmacology analysis*

*Active components of DCHD and their predicted targets*

The chemical constituents of the eight herbs comprising DCHD were retrieved and screened using the TCMSP database and the SwissADME platform. A total of 69 active components meeting the screening criteria were identified. Potential protein targets corresponding to these components were subsequently predicted using the PubChem database and the SwissTargetPrediction platform. All target proteins were standardized to official gene symbols using the UniProt database. After removing duplicates, 738 unique targets associated with the active components of DCHD were obtained. Detailed information on the 69 active components is provided in **Table 3**.

*Hyperlipidemia-related targets*

Hyperlipidemia-associated targets were identified by searching the GeneCards and OMIM disease databases using the keyword “hyperlipidemia”. A total of 3,501 and 205 target genes were retrieved from GeneCards and OMIM, respectively. After merging the two datasets and removing duplicate entries, 3,520 unique hyperlipidemia-related targets were obtained.

**Table 3.** Active components of DCHD (n = 69)

| Traditional Chinese Medicine | Mol ID | Molecule Name | MW | OB | DL |
|---|---|---|---|---|---|
| *Scutellaria baicalensis Georgi* (Huangqin) | MOL001689 | acacetin | 284.28 | 34.97 | 0.24 |
| | MOL000173 | wogonin | 284.28 | 30.68 | 0.23 |
| | MOL000228 | (2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one | 270.3 | 55.23 | 0.2 |
| | MOL002908 | 5,8,2'-Trihydroxy-7-methoxyflavone | 300.28 | 37.01 | 0.27 |
| | MOL002909 | 5,7,2,5-tetrahydroxy-8,6-dimethoxyflavone | 376.34 | 33.82 | 0.45 |
| | MOL002910 | Carthamidin | 288.27 | 41.15 | 0.24 |
| | MOL002915 | Salvigenin | 328.34 | 49.07 | 0.33 |
| | MOL002917 | 5,2',6'-Trihydroxy-7,8-dimethoxyflavone | 330.31 | 45.05 | 0.33 |
| | MOL002925 | 5,7,2',6'-Tetrahydroxyflavone | 286.25 | 37.01 | 0.24 |
| | MOL002926 | dihydrooroxylin A | 286.3 | 38.72 | 0.23 |
| | MOL002927 | Skullcapflavone II | 374.37 | 69.51 | 0.44 |
| | MOL002928 | oroxylin a | 284.28 | 41.37 | 0.23 |
| | MOL002932 | Panicolin | 314.31 | 76.26 | 0.29 |
| | MOL002933 | 5,7,4'-Trihydroxy-8-methoxyflavone | 300.28 | 36.56 | 0.27 |
| | MOL002934 | NEOBAICALEIN | 374.37 | 104.34 | 0.44 |
| | MOL002937 | DIHYDROOROXYLIN | 286.3 | 66.06 | 0.23 |
| | MOL000525 | Norwogonin | 270.25 | 39.4 | 0.21 |
| | MOL000552 | 5,2'-Dihydroxy-6,7,8-trimethoxyflavone | 344.34 | 31.71 | 0.35 |
| | MOL001458 | coptisine | 320.34 | 30.67 | 0.86 |
| | MOL002879 | Diop | 390.62 | 43.59 | 0.39 |
| | MOL002897 | epiberberine | 336.39 | 43.09 | 0.78 |
| | MOL008206 | Moslosooflavone | 298.31 | 44.09 | 0.25 |
| | MOL012245 | 5,7,4'-trihydroxy-6-methoxyflavanone | 302.3 | 36.63 | 0.27 |
| | MOL012246 | 5,7,4'-trihydroxy-8-methoxyflavanone | 302.3 | 74.24 | 0.26 |
| | MOL012266 | rivularin | 344.34 | 37.94 | 0.37 |
| *Ziziphus jujuba Mill.* (Dazao) | MOL012921 | stepharine | 297.38 | 31.54 | 0.33 |
| | MOL012976 | coumestrol | 268.23 | 32.48 | 0.33 |
| | MOL012992 | Mauritine D | 342.46 | 89.12 | 0.45 |
| | MOL001454 | berberine | 336.39 | 36.86 | 0.77 |
| | MOL001522 | (S)-Coclaurine | 285.37 | 42.35 | 0.23 |
| | MOL004350 | Ruvoside | 390.57 | 36.12 | 0.75 |
| | MOL000627 | Stepholidine | 327.41 | 33.1 | 0.54 |
| | MOL007213 | Nuciferin | 295.41 | 34.43 | 0.4 |
| | MOL000787 | Fumarine | 353.4 | 59.26 | 0.82 |
| | MOL002773 | beta-carotene | 536.96 | 37.18 | 0.58 |
| *Bupleurum chinense DC.* (Chaihu) | MOL000354 | isorhamnetin | 316.28 | 49.6 | 0.3 |
| | MOL004598 | 3,5,6,7-tetramethoxy-2-(3,4,5-trimethoxyphenyl) chromone | 432.46 | 31.97 | 0.59 |
| | MOL004609 | Areapillin | 360.34 | 48.96 | 0.41 |
| | MOL013187 | Cubebin | 356.4 | 57.12 | 0.63 |
| | MOL004653 | (+)-Anomalin | 426.5 | 46.05 | 0.65 |
| | MOL004718 | α-spinasterol | 412.77 | 42.97 | 0.75 |
| | MOL000490 | petunidin | 317.29 | 30.04 | 0.3 |
| *Citrus aurantium L.* (Zhishi) | MOL013277 | Isosinensetin | 372.4 | 51.15 | 0.44 |
| | MOL013279 | 5,7,4'-Trimethylapigenin | 312.34 | 39.83 | 0.29 |
| | MOL013430 | Prangenin | 286.3 | 43.59 | 0.29 |
| | MOL013435 | poncimarin | 330.41 | 63.62 | 0.34 |
| | MOL013436 | isoponcimarin | 330.41 | 63.27 | 0.31 |
| | MOL013437 | 6-Methoxy aurapten | 328.44 | 31.23 | 0.3 |
| | MOL001803 | Sinensetin | 372.4 | 50.55 | 0.44 |
| | MOL001941 | Ammidin | 270.3 | 34.54 | 0.22 |

| | | | | | |
|---|---|---|---|---|---|
| *Rheum palmatum L.* (Dahuang) | MOL002235 | EUPATIN | 360.34 | 50.8 | 0.4 |
| | MOL002268 | rhein | 284.23 | 47.06 | 0.27 |
| | MOL002281 | Toralactone | 272.27 | 46.46 | 0.23 |
| | MOL002297 | Daucosterol | 386.73 | 35.88 | 0.7 |
| | MOL000096 | (-)-catechin | 290.29 | 49.67 | 0.24 |
| *Pinellia ternata (Thunb.) Makino* (Banxia) | MOL001755 | 24-Ethylcholest-4-en-3-one | 412.77 | 36.08 | 0.75 |
| | MOL002670 | Cavidine | 353.45 | 35.64 | 0.8 |
| *Paeonialactiflora Pall.* (Baishao) | MOL001918 | paeoniflorgenone | 318.35 | 87.59 | 0.36 |
| | MOL001919 | (3S,5R,8R,9R,10S,14S)-3,17-dihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9-hexahydro-1H-cyclopenta[a]phenanthrene-15,16-dione | 358.52 | 43.55 | 0.53 |
| *Zingiber officinale Roscoe* (Shengjiang) | MOL001771 | poriferast-5-en-3beta-ol | 414.79 | 36.91 | 0.75 |
| | MOL008698 | Dihydrocapsaicin | 307.48 | 47.07 | 0.19 |
| *Scutellaria baicalensis Georgi Citrus aurantium L.* | MOL002914 | Eriodyctiol (flavanone) | 288.27 | 41.35 | 0.24 |
| *Scutellaria baicalensis Georgi Ziziphus jujuba Mill. Bupleurum chinense DC. Pinellia ternata (Thunb.) Makino Zingiber officinale Roscoe* | MOL000449 | Stigmasterol | 412.77 | 43.83 | 0.76 |
| *Bupleurum chinense DC. Pinellia ternata (Thunb.) Makino* | MOL000422 | kaempferol | 286.25 | 41.88 | 0.24 |
| *Scutellaria baicalensis Georgi Paeonialactiflora Pall.* | MOL000359 | sitosterol | 414.79 | 36.91 | 0.75 |
| *Scutellaria baicalensis Georgi Pinellia ternata (Thunb.) Makino* | MOL002714 | baicalein | 270.25 | 33.52 | 0.21 |
| *Scutellaria baicalensis Georgi Ziziphus jujuba Mill. Rheum palmatum L. Pinellia ternata (Thunb.) Makino, Paeonialactiflora Pall. Zingiber officinale Roscoe* | MOL000358 | beta-sitosterol | 414.79 | 36.91 | 0.75 |
| *Ziziphus jujuba Mill. Paeonialactiflora Pall.* | MOL000211 | Mairin | 456.78 | 55.37 | 0.77 |
| *Ziziphus jujuba Mill. Bupleurum chinense DC.* | MOL000098 | quercetin | 302.25 | 46.43 | 0.27 |

*Intersection targets of DCHD and hyperlipidemia*

The target sets identified in Section 3.2.1 (DCHD-related targets) and Section 3.2.2 (hyperlipidemia-related targets) were intersected using the Venny 2.1.0 online tool. This analysis yielded 305 common targets. The overlap between the two target sets is illustrated by a Venn diagram (**Figure 7A**), indicating 305 potential targets through which DCHD may exert therapeutic effects in hyperlipidemia.

*Protein-protein interaction (PPI) network construction and core target identification*

A PPI network was constructed based on the 305 intersecting targets using the STRING database. The interaction data (TSV format) were imported into Cytoscape 3.10.2 for visualization and network analysis, and Degree centrality for each node was calculated using the CytoNCA plugin. In the PPI network (**Figure 7B**), node size, color intensity, and transparency are proportional to the corresponding Degree values. Core targets were further screened using the CentiScaPe 2.2 plugin based on three topological parameters (Degree, Betweenness, and Closeness), with threshold values of 37.02, 328.62, and 0.0016, respectively. This analysis yielded a core network comprising 40 targets, among which TLR4, MMP9, SIRT1, ICAM1, and GSK3B showed high degrees and strong network connectivity.

*Herb-active component-intersection target-pathway-disease network*

The files network.xlsx and type.xlsx, containing information on herb names, active compo-

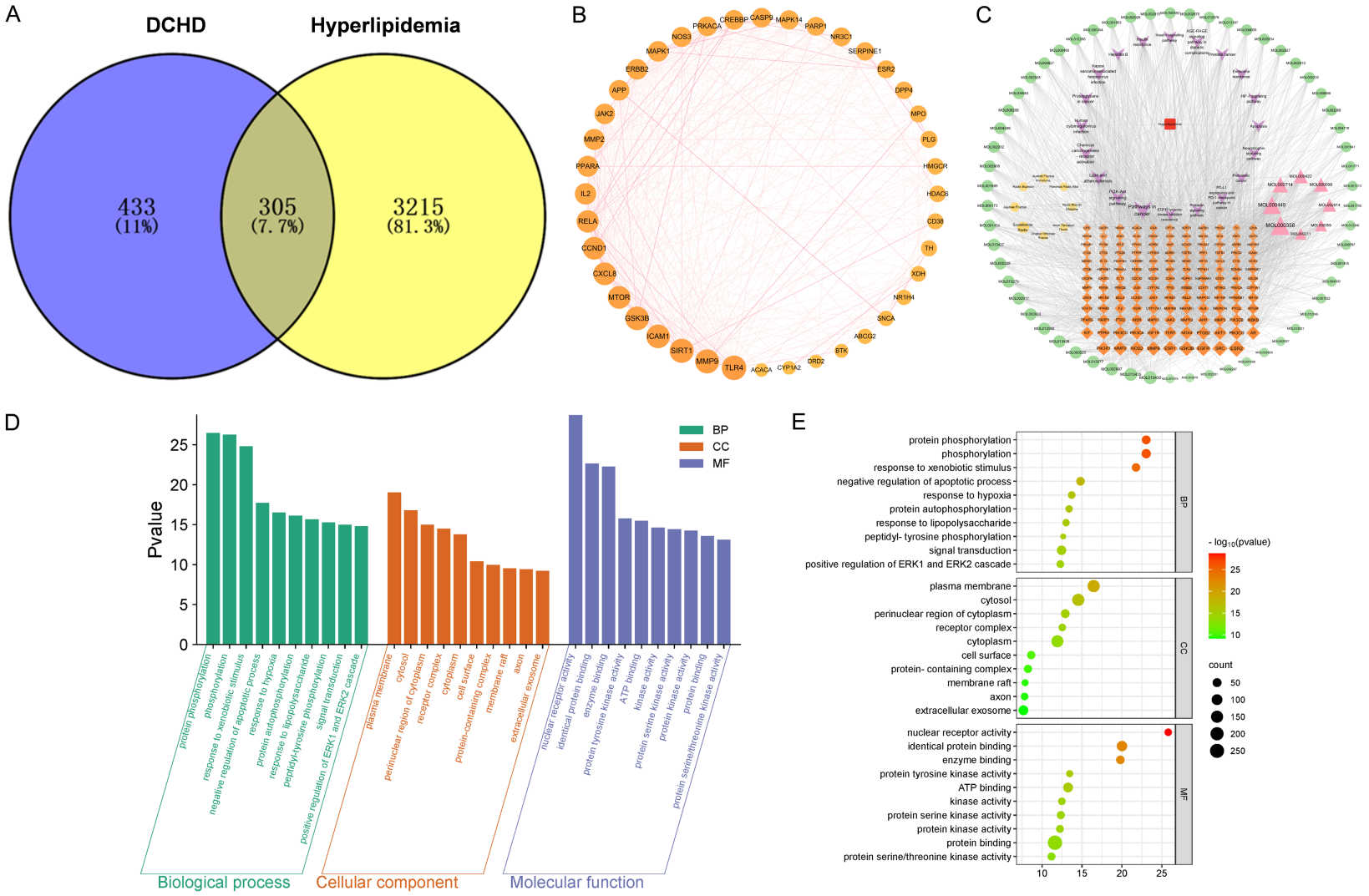



**Figure 7.** Network pharmacology-based analysis of GP and AS. A. Venn diagram showing intersecting targets between DCHD and hyperlipidemia; B. Protein-protein interaction (PPI) network of core targets; C. Herb-active compound-target-pathway-disease network; D. Gene Ontology (GO) enrichment analysis; E. KEGG pathway enrichment analysis.

nents, intersection target genes, and pathways, were imported into Cytoscape 3.10.2 to construct an integrated herb-active component-target-pathway-disease network (**Figure 7C**). The CytoNCA plugin was again used to calculate Degree centrality, with visual node attributes scaled accordingly. Light yellow hexagons represent the eight herbs comprising DCHD, green circles represent their corresponding active components, and pink triangles denote active components shared by multiple herbs. Orange squares indicate intersection targets common to the drug, disease, and pathways, purple V-shaped nodes represent signaling pathways, and red squares represent the disease.

*GO functional and KEGG pathway enrichment analysis*

The 305 intersecting targets were submitted to the DAVID database for Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. In total, 1,420 enriched terms were identified, including 899 biological process (BP) terms, 115 cellular component (CC) terms, 224 molecular function (MF) terms, and 182 KEGG pathways. The top 10 significantly enriched terms ($P < 0.01$) from each GO category (BP, CC, and MF) and the top 30 significantly enriched KEGG pathways ($P < 0.01$) were selected for visualization using the SRplot platform. The GO enrichment results (**Figure 7D**) showed that the most significantly enriched BP terms included protein phosphorylation, response to xenobiotic stimulus, and negative regulation of apoptotic process. The major CC terms were plasma membrane, cytosol, perinuclear region of cytoplasm, and receptor complex. The predominant MF terms included nuclear receptor activity, identical protein binding, enzyme binding, and protein tyrosine kinase activity. KEGG pathway enrichment analysis (**Figure 7E**) revealed that the intersecting targets were mainly involved in pathways such as pathways in cancer, lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, insulin resistance, and prostate cancer. These enriched pathways suggest potential biological processes through which DCHD may exert therapeutic effects in hyperlipidemia.

*Molecular docking and molecular dynamics simulations confirm stable interactions of DCHD core components with key targets*

To validate the network pharmacology predictions at the molecular level and provide structural evidence for key targets, molecular docking and molecular dynamics (MD) simulations were performed. This approach aimed to computationally assess the binding modes and dynamic interactions between core active components and the key target. The targets were obtained by intersecting genes from the KEGG pathway most relevant to lipid metabolism ("Lipid and atherosclerosis") with the top 10 hub genes from the PPI network, yielding four core targets: ICAM1, MMP9, TLR4, and GSK3B, each exhibiting both pathway relevance and network centrality. High-resolution crystal structures of these proteins (Homo sapiens) were obtained from the RCSB Protein Data Bank (PDB IDs: ICAM1-1IAM, MMP9-4XCT, TLR4-2Z62, GSK3B-7SXJ Chain A). Based on network meta-analysis results identifying DCHD Shengjiang Powder as the optimal formulation and component-sharing analysis, two representative ligands, beta-sitosterol and stigmasterol, were selected for docking studies.

Molecular docking results indicated favorable binding between the core active components and key targets. As shown in **Table 4**, based on combined XP docking scores and MM-GBSA binding free energy analysis, the binding between beta-sitosterol and ICAM1 was the most stable, with a docking score of -2.072 and an MM-GBSA binding free energy of -37.09 kcal/mol, outperforming other combinations. Visualization of the binding mode (**Figure 8A**) revealed that beta-sitosterol fit precisely into ICAM1's active pocket. The interaction was primarily stabilized by hydrophobic contacts with residues PRO115, ALA114, VAL82, and TRP84, and a key hydrogen bond with ASP60 (**Figure 8B**). The beta-sitosterol-ICAM1 complex was subjected to a 100 ns MD simulation to evaluate dynamic stability. The root mean square deviation (RMSD) reached equilibrium within 20 ns and remained stable for the remaining simulation time (**Figure 8C**), indicating a stable binding conformation. Root mean square fluctuation (RMSF) analysis showed increased flexibility in residues 35-50 and 65-75, suggesting local conformational adjustments upon

**Table 4.** Molecular docking results based on XP scoring and MM-GBSA binding free energy analysis

| Compound | Target | XP Gscore | MM-GBSA dG Bind (kcal/mol) |
|---|---|---|---|
| beta-sitosterol | ICAM1 | -2.072 | -37.09 |
| Stigmasterol | | -0.545 | -26.91 |
| beta-sitosterol | MMP9 | -1.159 | -37.25 |
| Stigmasterol | | -1.856 | -33.74 |
| beta-sitosterol | TLR4 | -2.127 | -16.42 |
| Stigmasterol | | -1.975 | -13.12 |
| beta-sitosterol | GSK3B | -2.410 | -32.84 |
| Stigmasterol | | -3.387 | -23.04 |

ligand binding (**Figure 8D**). Non-bonded interaction analysis identified residues contributing to complex stability. Interaction frequency mapping (**Figure 8E**) showed that SER5, PRO6, SER7, LYS8, VAL9, and LEU18 maintained frequent contacts with beta-sitosterol (represented by darker orange). A detailed interaction diagram (**Figure 8F**) further highlights water-bridge and ionic interactions involving SER7 (8%) and LYS8 (6%), forming a dynamic yet robust binding network.

Overall, MD simulation results indicate that the beta-sitosterol-ICAM1 complex maintains excellent dynamic stability with minimal structural fluctuations. The stable network of hydrophobic and water-mediated interactions provides a structural basis supporting the relevance of ICAM1 as a core target identified by network pharmacology.

## Discussion

This study provides a comprehensive investigation of DCHD in the treatment of hyperlipidemia by integrating evidence from network meta-analysis and network pharmacology, thereby linking clinical efficacy with underlying systems-level mechanisms. The network meta-analysis results indicate that DCHD-based herbal interventions show favorable overall performance in regulating lipid metabolism, with different modified formulations demonstrating distinct therapeutic characteristics. Concurrently, network pharmacology elucidates a synergistic "multi-component, multi-target, multi-pathway" mode of action, offering a robust scientific rationale for the observed clinical benefits. As a representative formula for harmonizing Shaoyang and unblocking Yangming, DCHD consists of herbs with complementary and coordinated actions. *Bupleurum chinense DC*. and *Scutellaria baicalensis Georgi* function to soothe the liver and clear constrained heat. Modern pharmacological studies indicate that *saikosaponin D*, a major active constituent of *Bupleurum chinense DC*., activates PPARα to induce INSIG1/2 expression, thereby inhibiting SREBP1c-dependent lipogenesis and promoting its degradation, ultimately improving lipid homeostasis [33]. Baicalein, a key active component of *Scutellaria baicalensis Georgi*, has been shown to upregulate ABCA1 and ABCG1 expression via the PPARγ/LXRα signaling pathway, thereby promoting cholesterol efflux, inhibiting lipid accumulation, and reducing pro-inflammatory cytokine release [34]. *Radix Rhei Et Rhizoma* and *Citrus aurantium L*. act to purge the fu-organs and eliminate turbidity. Emodin, a major active component of *Radix Rhei Et Rhizoma*, improves serum lipid profiles by reducing TC and LDL-C, inhibiting lipid accumulation, reversing hepatic steatosis, and ameliorating glucose tolerance and islet function in obese mice [35]. Naringin, a flavonoid derived from *Citrus aurantium L*., enhances cholesterol clearance and lipid metabolism by upregulating hepatic LDLR and p-AMPKα expression while suppressing SREBP1, SREBP2, and PCSK9 levels [36]. Clinical evidence further indicates that naringin supplementation improves metabolic and lipid parameters in obese and hypercholesterolemic individuals, reflected by reductions in body weight, TC, TG, and LDL-C, along with increases in HDL-C and adiponectin levels [37]. *Pinellia ternata (Thunb.) Makino* and *Zingiber officinale Roscoe* resolve phlegm and harmonize the stomach. Studies revealed that aqueous extracts of *Pinellia ternata* improve lipid profiles and suppress inflammation by activating the PI3K/Akt-eNOS/VEGF axis and increasing circulating endothelial progenitor cells [38]. 6-Gingerol, a major bioactive compound of *Zingiber officinale* Roscoe, effectively reverses high-fat diet-induced obesity by inhibiting adipocyte hypertrophy and hyperplasia, blocking the TLR3/IL-6/JAK1/STAT3 inflammatory axis, and restoring AKT/INSR/IRS-1 insulin signaling, thereby alleviating hepatic metabolic inflammation and insulin resistance [39]. *Paeonia lacti-*

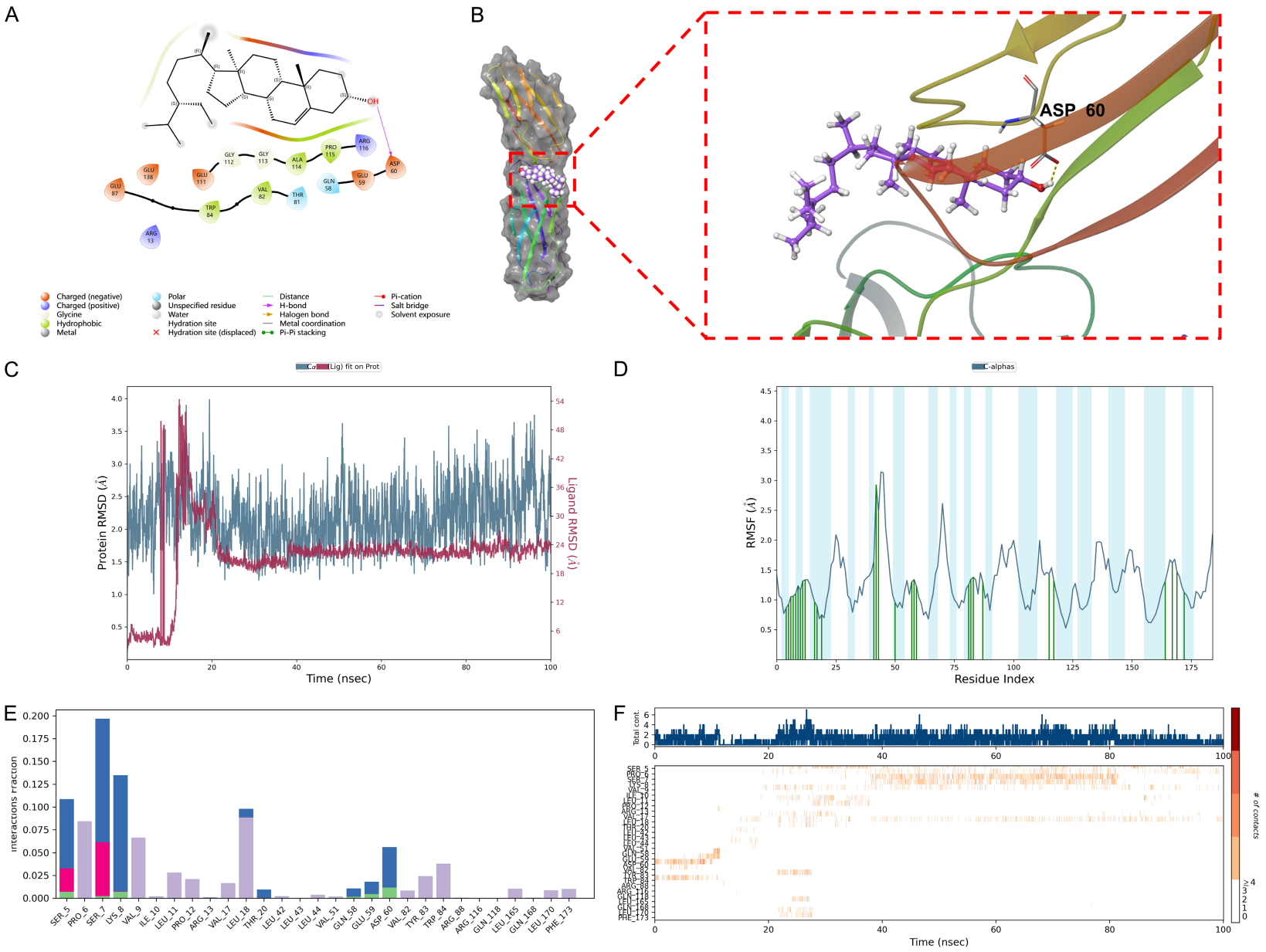



**Figure 8.** Molecular docking and molecular dynamics (MD) simulation of beta-sitosterol with ICAM1. A. Two-dimensional interaction diagram; B. Three-dimensional binding mode; C. Root mean square deviation (RMSD) of the complex; D. Root mean square fluctuation (RMSF) of ICAM1 residues; E. Protein-ligand interaction profile; F. Time-dependent interaction map between beta-sitosterol and ICAM1 residues.

*flora Pall*. nourishes blood and softens the liver, while *Ziziphus jujuba Mill*. harmonizes the middle. The hepatoprotective effects of *Paeonia lactiflora Pall.* against $H_2O_2$-induced oxidative damage in HepG2 cells have been attributed to its potent free radical-scavenging activity [40]. Polyphenols derived from *Ziziphus jujuba peel* also exhibit significant anti-inflammatory and antioxidant properties [40]. Collectively, DCHD achieves multidirectional regulation through the combined actions of soothing the liver, purging the fu-organs, and resolving phlegm, thereby fulfilling the therapeutic principle of harmonizing Shaoyang and unblocking Yangming. From a modern pharmacological perspective, DCHD has also been shown to ameliorate intestinal dysbiosis and serum metabolic dysfunction in non-alcoholic fatty liver disease, while modulating arachidonic acid, glycine/serine/threonine, and glycerophospholipid metabolic pathways [8].

Integrated network meta-analysis results further demonstrate that DCHD and its modified formulations are significantly superior to conventional therapies in reducing TC, TG, and LDL-C, as well as in improving the overall clinical "response rate". Importantly, this study quantitatively ranked the efficacy of different interventions. In the primary Bayesian analysis, including all 23 studies, DCHD Shengjiang Powder consistently ranked among the top interventions, with SUCRA values of 85.18% for TC, 62.41% for TG, 78.56% for HDL-C, 80.60% for LDL-C, and 85.85% for response rate. However, sensitivity analysis excluding the 11 acute hyperlipidemic pancreatitis studies revealed that the evidence supporting DCHD Shengjiang Powder, DCHD combined with Dachengqi Decoction, and DCHD combined with CA therapy was derived exclusively from pancreatitis trials. After exclusion, these three formulations were completely removed from the network for most outcomes. In the non-pancreatitis population, DCHD alone emerged as the top-ranked treatment for TC (*P*-score = 0.7874) and TG (*P*-score = 0.8905), while DCHD combined with Guizhi Fuling Pill ranked first for LDL-C (*P*-score = 0.8403) and response rate (*P*-score = 0.8145), suggesting that these formulations may represent optimal choices for chronic hyperlipidemia management. Population subgroup analysis of the pure hyperlipidemia cohort (7 studies) corroborated these findings, with DCHD alone ranking first for TC (*P*-score = 0.8841), TG (0.8588), LDL-C (0.7886), and response rate (0.7836). DCHD Guizhi Fuling Pill and DCHD Dachengqi Decoction exhibited specific advantages in improving blood stasis patterns and vigorously purging heat accumulation, respectively. These findings provide high-level evidence supporting the TCM principles of "treatment based on syndrome differentiation" and "formula matching the pattern", thereby offering guidance for individualized clinical prescription selection. Network pharmacology results further elucidated the complex mechanisms underlying the therapeutic effects of DCHD. A total of 69 core active components were identified, among which quercetin, kaempferol, beta-sitosterol, and baicalein have been widely reported to possess anti-inflammatory, antioxidant, and lipid-regulating activities [41-44]. PPI network analysis highlighted TLR4, MMP9, SIRT1, ICAM1, and GSK3B as core targets involved in lipid homeostasis, inflammatory regulation, extracellular matrix remodeling, and insulin signal transduction [45-48]. KEGG enrichment analysis further revealed significant involvement of pathways such as "Lipid and atherosclerosis", "Insulin resistance", and the "AGE-RAGE signaling pathway in diabetic complications". Collectively, these findings suggest that DCHD exerts therapeutic effects by inhibiting vascular inflammation and endothelial activation via targets such as TLR4 and ICAM1, improving metabolic disturbances and insulin sensitivity through SIRT1 and GSK3B, and modulating atherosclerotic plaque stability through targets including MMP9. By coordinating the regulation of inflammation, immunity, vascular function, and metabolism, DCHD contributes to the restoration of systemic lipid homeostasis and overall clinical improvement.

The major strength of this study lies in its integrative strategy, which establishes logical coherence between clinical evidence and biological prediction. Molecular docking results showed that the core active components beta-sitosterol and stigmasterol formed stable docking conformations with key targets, including ICAM1, MMP9, TLR4, and GSK3B. Among these, beta-sitosterol showed a particularly strong binding affinity for ICAM1, suggesting its potential role as an essential effector molecule. These results provide initial validation of

the component-target interactions predicted by network pharmacology at a static structural level. Furthermore, MD simulation analysis confirmed that beta-sitosterol forms a dynamically stable complex with ICAM1, extending the network pharmacology predictions into a dynamic, atomistic context.

Notably, the favorable efficacy of DCHD Shengjiang Powder in the primary analysis should be interpreted within the context of the acute pancreatitis treatment setting, as the evidence supporting this formulation was derived entirely from studies enrolling patients with acute hyperlipidemic pancreatitis. These patients present with markedly elevated baseline triglyceride levels and acute inflammatory status, differing fundamentally from chronic hyperlipidemia. Nevertheless, this formulation contains *Zingiber officinale Roscoe*, which is rich in phytosterols, including beta-sitosterol. *Zingiber officinale Roscoe* has been reported to possess antioxidant, anti-inflammatory, glucose- and lipid-lowering, and neuroprotective properties [49]. Recent studies further indicate that oral *Zingiber officinale* nanoparticles preserve insulin sensitivity under high-fat diet conditions by inhibiting AKT1-mediated Foxa2 phosphorylation and inactivation, thereby reshaping the intestinal epithelial exosomal profile [50]. These evidence provides molecular-level support for the observed efficacy of this formulation in the pancreatitis population, particularly in patients with elevated TC accompanied by insulin resistance. For patients with markedly elevated TG levels, DCHD dachengqi decoction, which contains herbs such as *Rheum palmatum L.* and is rich in compounds like emodin and quercetin, was predicted to strongly regulate targets including PPARG and AKT1, offering a mechanistic explanation for its potent purgative action and triglyceride-lowering effects. In the primary analysis, DCHD combined with Dachengqi Decoction ranked first for TG reduction (SUCRA = 91.31%), and this advantage was confirmed in the pancreatitis subgroup analysis (*P*-score = 0.7840). Similarly, the highly efficacious DCHD Guizhi Fuling Pill embodies the TCM principle of simultaneously treating phlegm and blood stasis. Network enrichment analysis linked its activity to pathways such as "Pathways in cancer" and "Apoptosis", suggesting that, beyond lipid regulation, its blood-activating components may confer vascular protection by modulating endothelial and smooth muscle cell proliferation and apoptosis, thereby inhibiting atherosclerotic plaque formation and progression [51, 52]. Importantly, DCHD combined with Guizhi Fuling Pill demonstrated consistent efficacy across both pancreatitis and non-pancreatitis populations, ranking first or second for LDL-C and response rate in multiple sensitivity and subgroup analyses, supporting its broad applicability in clinical practice.

Overall, the synergistic, multi-target, and multi-pathway characteristics of DCHD reflect the core concept of holistic regulation in TCM compound prescriptions and help explain why single-target therapies often fail to achieve the comprehensive therapeutic outcomes observed with multi-component herbal formulations.

Several important limitations should be acknowledged. First, the evidence supporting several highly ranked formulations, including DCHD Shengjiang Powder (SUCRA 80.60-85.85%), DCHD combined with Dachengqi Decoction (SUCRA 91.31% for TG), and DCHD combined with CA therapy (SUCRA 78.41-81.51%), was derived exclusively from studies enrolling patients with acute hyperlipidemic pancreatitis. These patients present with markedly elevated baseline triglyceride levels, acute inflammatory status, and short treatment durations (≤ 14 days), which differ fundamentally from chronic hyperlipidemia management. Sensitivity analysis excluding these 11 pancreatitis studies revealed that these three formulations were completely removed from the network, and treatment rankings shifted substantially, with DCHD alone (*P*-score = 0.79-0.89) and DCHD combined with Guizhi Fuling Pill (*P*-score = 0.65-0.84) emerging as the most effective interventions in non-pancreatitis populations. Therefore, the favorable rankings of DCHD Shengjiang Powder in the primary analysis should be interpreted in the context of pancreatitis treatment rather than generalized to chronic hyperlipidemia.

Second, all 23 included studies were published in Chinese-language journals, which raises concerns regarding language and regional publication bias. Previous reports have indicated that clinical trials of TCM conducted in China frequently report positive findings. The lack of unpublished or negative studies may therefore lead to an overestimation of treatment effects

and influence treatment rankings. The exclusively Chinese-language evidence base also limits the generalizability of these findings.

Third, the methodological quality of the included trials was generally limited. Most studies were small, single-center RCTs with inadequate reporting of randomization methods and allocation concealment. None of the studies had pre-registered protocols, precluding assessment of selective reporting. These limitations are characteristic of the Chinese TCM clinical trial literature and reduce the certainty of the evidence.

Fourth, the relative efficacy rankings among different DCHD modifications are predominantly derived from indirect comparisons through the common comparator (conventional therapy), as direct head-to-head trials among modifications were not available. Readers should interpret the SUCRA rankings with this limitation in mind. Additionally, the sensitivity and subgroup analyses were conducted using a frequentist framework (*P*-scores via netmeta) rather than the Bayesian framework (SUCRA via gemtc) used in the primary analysis. While both approaches yielded consistent directional conclusions, minor numerical differences between SUCRA and *P*-score values should be expected and do not reflect inconsistency in the findings.

## Conclusion

This network meta-analysis indicates that modified DCHD formulations are effective herbal therapies for the treatment of hyperlipidemia. In the overall analysis, including all 23 studies, DCHD Shengjiang Powder achieved the highest efficacy rankings (SUCRA 80.60-85.85%); however, sensitivity analysis revealed that this evidence was derived exclusively from acute hyperlipidemic pancreatitis studies. In non-pancreatitis populations with chronic hyperlipidemia, DCHD alone and DCHD combined with Guizhi Fuling Pill demonstrated stable and favorable efficacy for lipid parameter improvement. Network pharmacology analysis further suggests that the therapeutic effects of DCHD are mediated through the regulation of core targets, including TLR4, MMP9, SIRT1, ICAM1, and GSK3B, as well as the modulation of key signaling pathways such as “Lipid and atherosclerosis”, “Insulin resistance”, and the “AGE-RAGE signaling pathway in diabetic complications”. Moreover, molecular docking and MD simulations provide atomic-level evidence supporting these predictions, demonstrating that the core active component beta-sitosterol forms a stable complex with the key target ICAM1. This computational validation provides preliminary dynamic insights into binding modes and stability, complementing the static “component-target” relationships identified by network pharmacology.

Collectively, this study suggests a coherent analytical framework spanning clinical efficacy, systems-level prediction, and structural mechanistic validation. By bridging macroscopic clinical outcomes with microscopic systems biology and molecular insights, the present work provides supportive evidence for the therapeutic potential and scientific basis of DCHD in the management of hyperlipidemia. Future research should prioritize well-designed, large-scale, multi-center RCTs specifically enrolling patients with chronic hyperlipidemia, and direct head-to-head trials comparing different DCHD modifications are warranted to strengthen the evidence base.

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## Disclosure of conflict of interest

None.

## Abbreviations

ASCVD, atherosclerotic cardiovascular disease; BP, biological process; CC, cellular component; CrI, credibility intervals; DCHD, Dachaihu decoction; GO, Gene Ontology; HDL-C, high-density lipoprotein cholesterol; INSIG1/2, Insulin-Induced Gene 1/2; KEGG, Kyoto Encyclopedia of Genes and Genomes; LDL-C, low-density lipoprotein cholesterol; LXRα, Liver X receptors alpha; MD, molecular dynamics; MF, molecular function; NMA, network meta-analysis; OR, odds ratio; PCSK9, Proprotein Convertase

Subtilisin/Kexin Type 9; PPARα, Peroxisome proliferator-activated receptor alpha; PPI, protein-protein interaction; PROSPERO, Register of Systematic Reviews; RCTs, randomized controlled trials; RMSD, root mean square deviation; RMSF, root mean square fluctuation; SREBP1c, Sterol Regulatory Element Binding Protein-1c; SUCRA, surface under the cumulative ranking curve; TC, total cholesterol; TCM, Traditional Chinese Medicine; TCMSP, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; TG, triglycerides.

**Address correspondence to:** Fuming Liu, Affiliated Hospital of Nanjing University of Chinese Medicine, Jiangsu Province Hospital of Chinese Medicine, Nanjing 210023, Jiangsu, China. E-mail: doctor.liufuming@outlook.com

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**Table S1.** Baseline TC, TG, LDL-C and HDL-C levels for all 23 studies

| Study | TC (mmol/L) | | TG (mmol/L) | | LDL-C (mmol/L) | | HDL-C (mmol/L) | |
|---|---|---|---|---|---|---|---|---|
| | I | C | I | C | I | C | I | C |
| Chen 2023 [10] | - | - | 2.77 ± 0.54 | 2.74 ± 0.56 | - | - | - | - |
| Jiang 2012 [11] | 10.5 ± 2.5 | 10.4 ± 1.9 | 3.6 ± 1.1 | 4.0 ± 1.1 | - | - | - | - |
| Zhang 2019 [12] | 1.2 ± 0.1 | 1.2 ± 0.2 | 1.6 ± 1.1 | 1.5 ± 1.8 | 4.1 ± 1.1 | 4.0 ± 1.5 | - | - |
| Liu 2017 [13] | 1.2 ± 0.3 | 1.2 ± 0.6 | 1.6 ± 0.7 | 1.5 ± 0.8 | 3.9 ± 0.6 | 3.8 ± 0.5 | - | - |
| Ding 2019 [14] | 6.35 ± 0.74 | 6.30 ± 0.77 | 3.14 ± 0.55 | 3.21 ± 0.57 | 0.72 ± 0.08 | 0.75 ± 0.09 | 4.24 ± 0.45 | 4.26 ± 0.49 |
| Liu 2016 [15] | 7.18 ± 1.35 | 7.27 ± 1.35 | 3.77 ± 1.25 | 3.70 ± 1.36 | - | - | - | - |
| Yang 2022 [16] | 6.78 ± 1.21 | 6.81 ± 1.03 | 3.18 ± 0.36 | 3.19 ± 0.43 | 3.79 ± 0.36 | 3.80 ± 0.54 | 1.18 ± 0.23 | 1.19 ± 0.35 |
| Feng 2022 [17] | 6.89 ± 1.37 | 6.92 ± 1.30 | 9.34 ± 2.69 | 9.29 ± 2.72 | 4.17 ± 0.68 | 4.05 ± 0.73 | 1.18 ± 0.19 | 1.21 ± 0.23 |
| Chen 2005 [18] | 6.58 ± 0.67 | 6.46 ± 0.56 | 2.79 ± 0.48 | 2.83 ± 0.46 | 4.43 ± 0.56 | 4.83 ± 0.40 | 1.10 ± 0.26 | 1.06 ± 0.31 |
| Hu 2021 [19] | 7.67 ± 4.55 | 7.60 ± 4.47 | 7.24 ± 2.05 | 7.24 ± 0.31 | - | - | - | - |
| Sang 2024 [20] | 8.32 ± 0.77 | 8.27 ± 0.70 | 3.08 ± 0.75 | 3.26 ± 0.23 | 4.63 ± 1.25 | 4.07 ± 1.34 | 0.91 ± 0.31 | 0.94 ± 0.26 |
| Lei 2018 [21] | 7.68 ± 4.56 | 7.59 ± 4.48 | 7.25 ± 2.04 | 7.26 ± 0.29 | - | - | - | - |
| He 2016 [22] | 8.02 ± 3.34 | 8.59 ± 2.97 | 20.04 ± 6.24 | 18.99 ± 5.88 | - | - | - | - |
| Liu 2023 [23] | 1.23 ± 0.22 | 1.25 ± 0.24 | 1.64 ± 0.52 | 1.60 ± 0.51 | 4.15 ± 1.02 | 4.08 ± 1.05 | - | - |
| Liu 2015 [24] | - | - | 9.91 ± 3.90 | 10.06 ± 4.28 | - | - | - | - |
| Shi 2017 [25] | | | 21.45 ± 4.71 | 20.11 ± 5. 95 | | | | |
| Zhao 2016 [26] | 5.12 ± 0.82 | 5.43 ± 0.96 | 3.38 ±1.33 | 2.46 ± 1.04 | 3.16 ± 0.49 | 2.82 ± 0.41 | 0.93 ± 0.21 | 1.16 ± 0.25 |
| Zhang 2014 [27] | - | - | 3.98 ± 0.3 | 3.71 ± 0.2 | 3.87 ± 0.2 | 3.65 ± 0.5 | - | - |
| Yang 2018 [28] | - | - | 17.1 ± 8.2 | 16.6 ± 7.8 | - | - | - | - |
| Zhang 2020 [29] | 1.19 ± 0.28 | 1.23 ± 0.59 | 1.58 ± 0.69 | 1.51 ± 0.76 | 3.88 ± 0.57 | 3.78 ± 0.47 | - | - |
| Liu 2014 [30] | - | - | 10.95 ± 5.90 | 11.36 ± 6.28 | - | - | - | - |
| Li 2019 [31] | 7.70 ± 1.00 | 7.60 ± 1.11 | 19.33 ± 2.00 | 19.20 ± 2.11 | - | - | - | - |
| Gu 2015 [32] | - | - | 2.47 ± 1.12 | 2.58 ± 1.16 | - | - | 1.23 ± 0.31 | 1.21 ± 0.36 |

Notes: I, intervention group; C, control group; -, not mentioned; TC, Total Cholesterol; TG, Triglycerides; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol.

**Table S2.** Impact of excluding 11 acute pancreatitis studies on treatment rankings

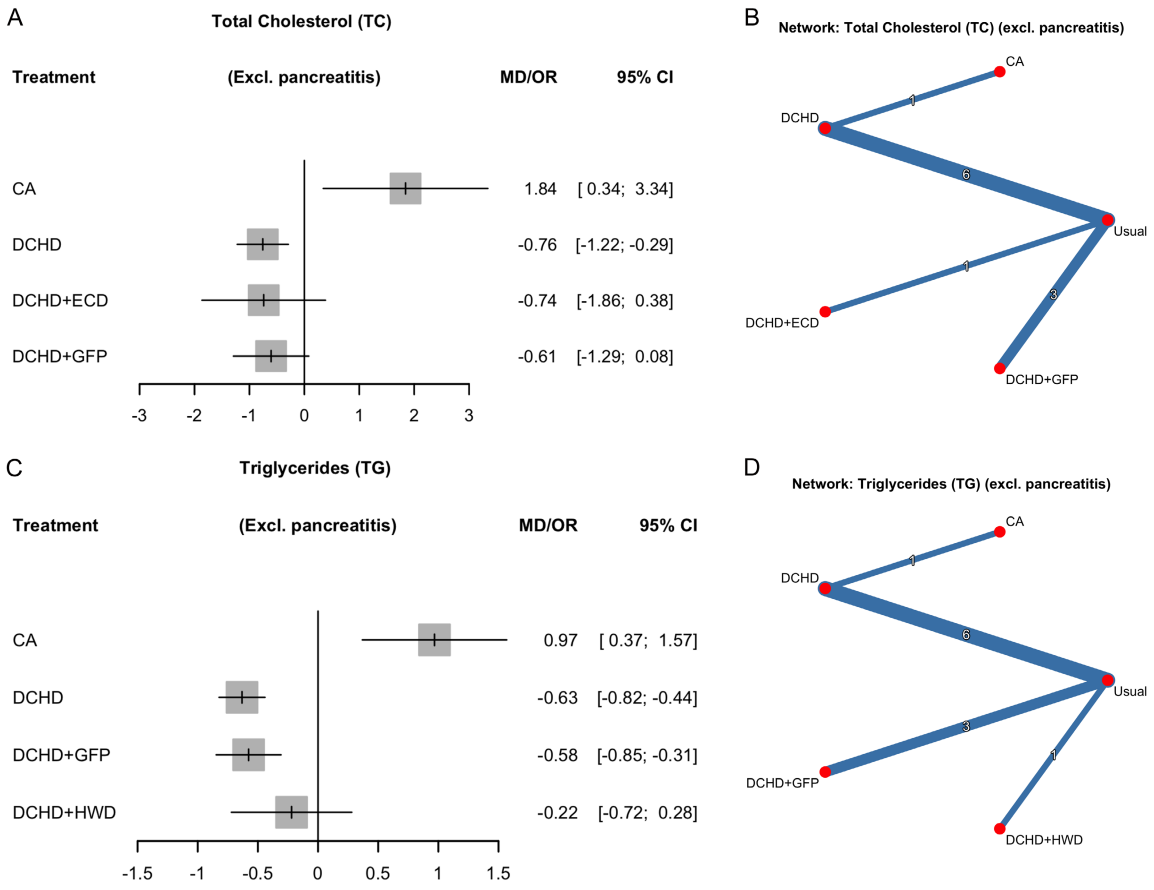
| Outcome | Original (studies/trts) | After exclusion (studies/trts) | Treatments removed | Rank #1 change (P-score) |
|---|---|---|---|---|
| TC | 17/8 | 11/5 | SJP, CA combo, Dachengqi | SJP (SUCRA 85.18%) → DCHD (0.7874) |
| TG | 22/8 | 11/5 | SJP, CA combo, Dachengqi | Dachengqi (91.31%) → DCHD (0.8905) |
| HDL-C | 9/6 | 7/5 | SJP | SJP (78.56%) → HWD (0.6307) |
| LDL-C | 9/4 | 7/3 | SJP | SJP (80.60%) → GFP (0.8403) |
| Response | 15/8 | 6/5 | SJP, CA combo, Dachengqi | CA combo (81.51%) → GFP (0.8145) |

Notes: SJP, DCHD Shengjiang Powder; HWD, Huanglian Wendan Decoction. Critical finding: The evidence supporting DCHD Shengjiang Powder, DCHD + Dachengqi Decoction, and DCHD + CA therapy was derived exclusively from pancreatitis trials. After exclusion, these formulations were completely removed from the network. DCHD alone (P-score 0.79-0.89) and DCHD + Guizhi Fuling Pill (0.65-0.84) showed stable efficacy in non-pancreatitis populations.

**Table S3.** P-score rankings in the pure hyperlipidemia subgroup (DCHD, DCHD+GFP, Usual)

| Outcome | Rank 1 (P-score) | Rank 2 (P-score) | Rank 3 (P-score) |
|---|---|---|---|
| TC | DCHD (0.8841) | GFP (0.5868) | Usual (0.0291) |
| TG | DCHD (0.8588) | GFP (0.6412) | Usual (0.0000) |
| HDL-C | Usual (0.5947) | GFP (0.5745) | DCHD (0.3308) |
| LDL-C | DCHD (0.7886) | GFP (0.6936) | Usual (0.0179) |
| Response | DCHD (0.7836) | GFP (0.7008) | Usual (0.0156) |

In the pancreatitis subgroup (11 studies), DCHD Shengjiang Powder ranked first for TC (P-score = 0.8421), DCHD + Dachengqi Decoction for TG (0.7840), and DCHD + CA therapy for response rate (0.8124). In the other comorbidities subgroup (5 studies), DCHD + Erchen Decoction ranked first for TC (0.9081), DCHD alone for TG (0.9301) and response rate (0.8513).



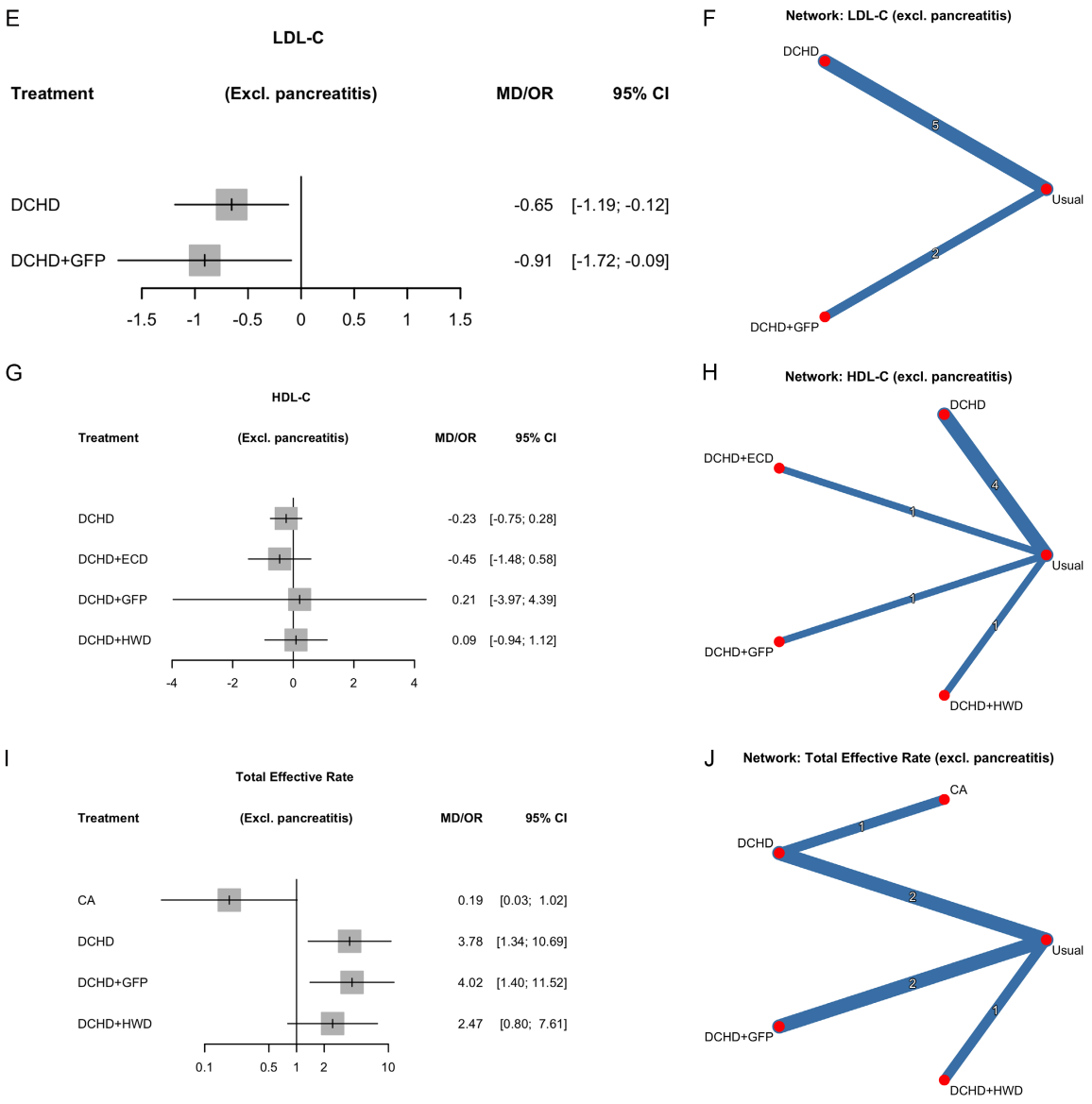



**Figure S1.** Sensitivity analysis excluding acute pancreatitis studies. A. Forest plot of TC; B. Network plot of TC; C. Forest plot of TG; D. Network plot of TG; E. Forest plot of LDL-C; F. Network plot of LDL-C; G. Forest plot of HDL-C; H. Network plot of HDL-C; I. Forest plot of total effective rate; J. Network plot of total effective rate.

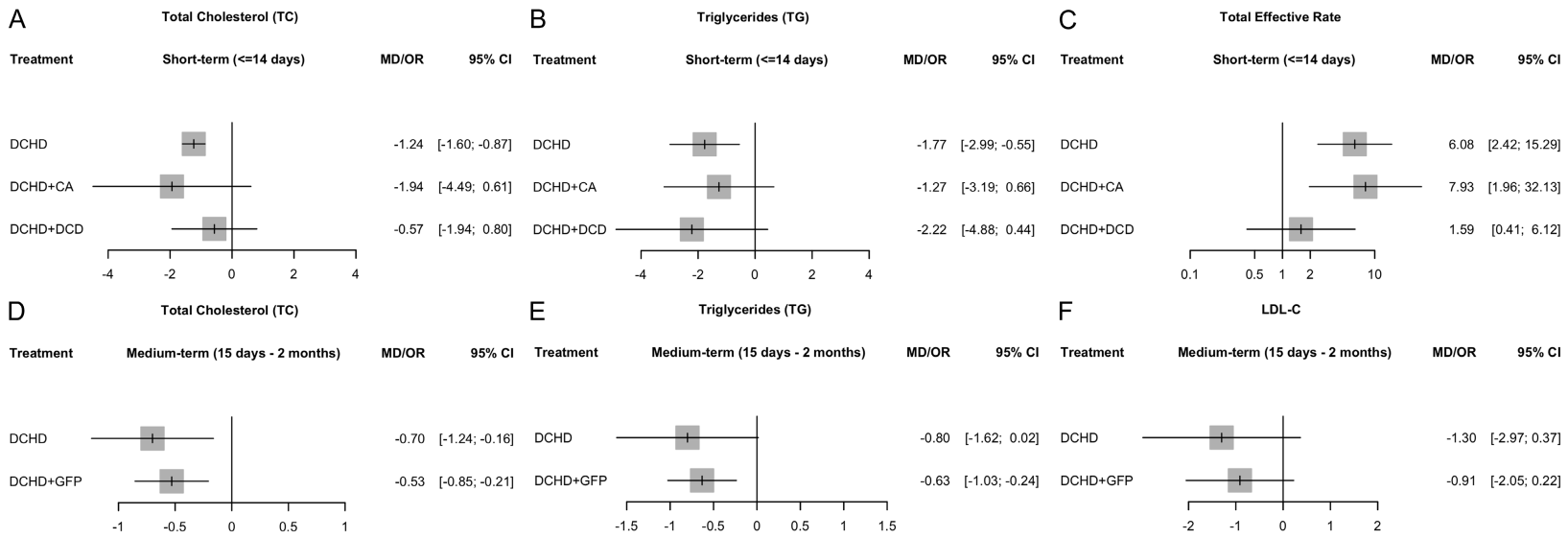
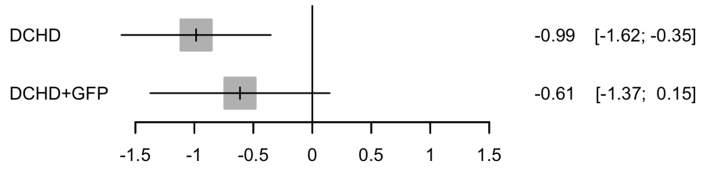
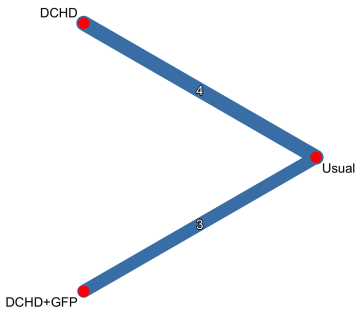



**Figure S2.** Subgroup analysis by treatment duration. A. Forest plot of the short-term subgroup analysis for TC; B. Forest plot of the short-term subgroup analysis for TG; C. Forest plot of the short-term subgroup analysis for total effective rate; D. Forest plot of the medium-term subgroup analysis for TC; E. Forest plot of the medium-term subgroup analysis for TG; F. Forest plot of the medium-term subgroup analysis for LDL-C.

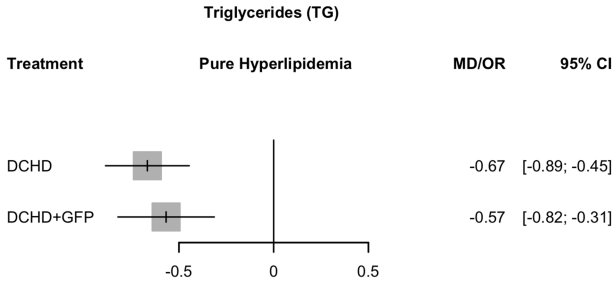
A


Total Cholesterol (TC)
Treatment
Pure Hyperlipidemia
MD/OR
95% CI
DCHD
DCHD+GFP
-0.99 [-1.62; -0.35]
-0.61 [-1.37; 0.15]
-1.5 -1 -0.5 0 0.5 1 1.5

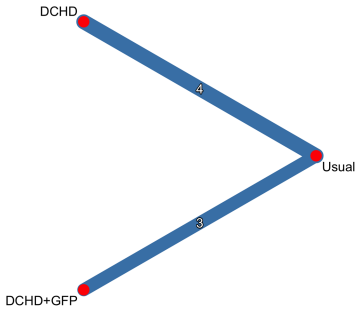
B


Network: TC - Pure Hyperlipidemia
DCHD
Usual
DCHD+GFP
4
3

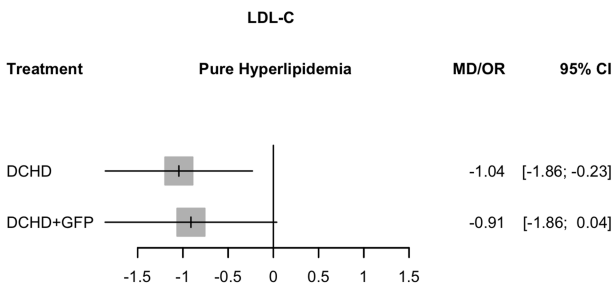
C


Triglycerides (TG)
Treatment
Pure Hyperlipidemia
MD/OR
95% CI
DCHD
DCHD+GFP
-0.67 [-0.89; -0.45]
-0.57 [-0.82; -0.31]
-0.5 0 0.5

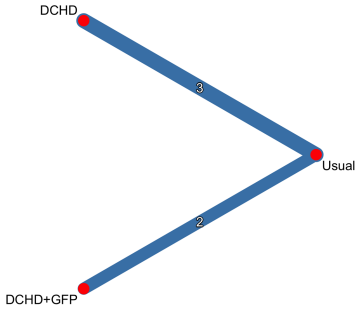
D


Network: TG - Pure Hyperlipidemia
DCHD
Usual
DCHD+GFP
4
3

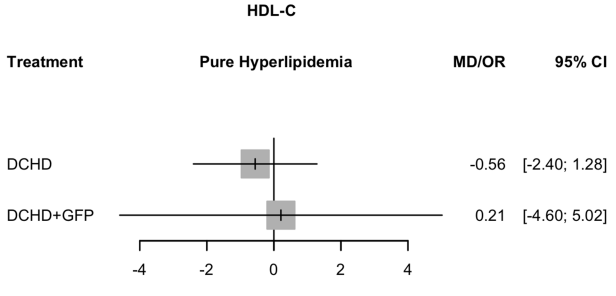
E


LDL-C
Treatment
Pure Hyperlipidemia
MD/OR
95% CI
DCHD
DCHD+GFP
-1.04 [-1.86; -0.23]
-0.91 [-1.86; 0.04]
-1.5 -1 -0.5 0 0.5 1 1.5

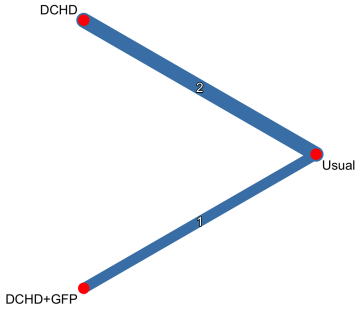
F


Network: LDLC - Pure Hyperlipidemia
DCHD
Usual
DCHD+GFP
3
2

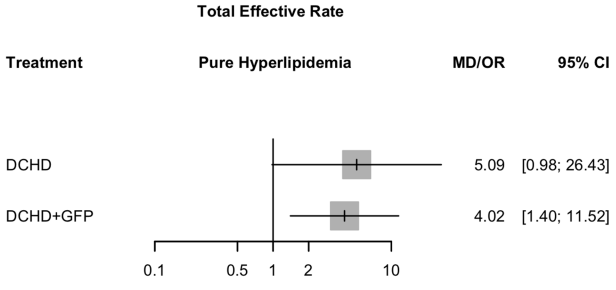
G


HDL-C
Treatment
Pure Hyperlipidemia
MD/OR
95% CI
DCHD
DCHD+GFP
-0.56 [-2.40; 1.28]
0.21 [-4.60; 5.02]
-4 -2 0 2 4

H


Network: HDLC - Pure Hyperlipidemia
DCHD
Usual
DCHD+GFP
2
1

I


Total Effective Rate
Treatment
Pure Hyperlipidemia
MD/OR
95% CI
DCHD
DCHD+GFP
5.09 [0.98; 26.43]
4.02 [1.40; 11.52]
0.1 0.5 1 2 10

J

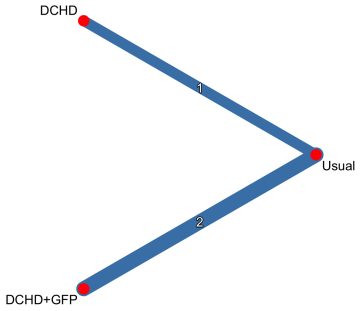
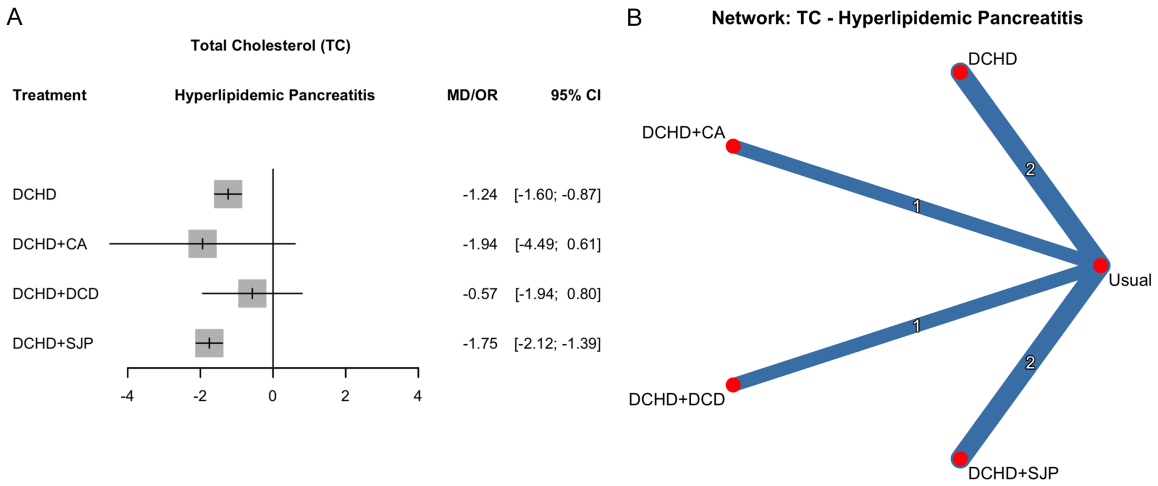
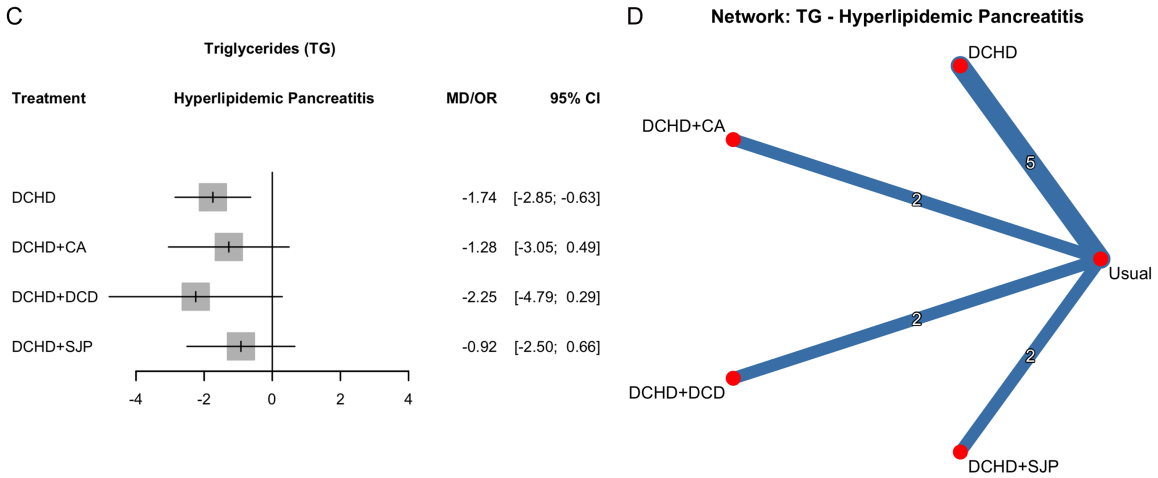

Network: Response - Pure Hyperlipidemia
DCHD
Usual
DCHD+GFP
1
2

**Figure S3.** Pure hyperlipidemia subgroup analysis. A. Forest plot of TC; B. Network plot of TC; C. Forest plot of TG; D. Network plot of TG; E. Forest plot of LDL-C; F. Network plot of LDL-C; G. Forest plot of HDL-C; H. Network plot of HDL-C; I. Forest plot of total effective rate; J. Network plot of total effective rate.



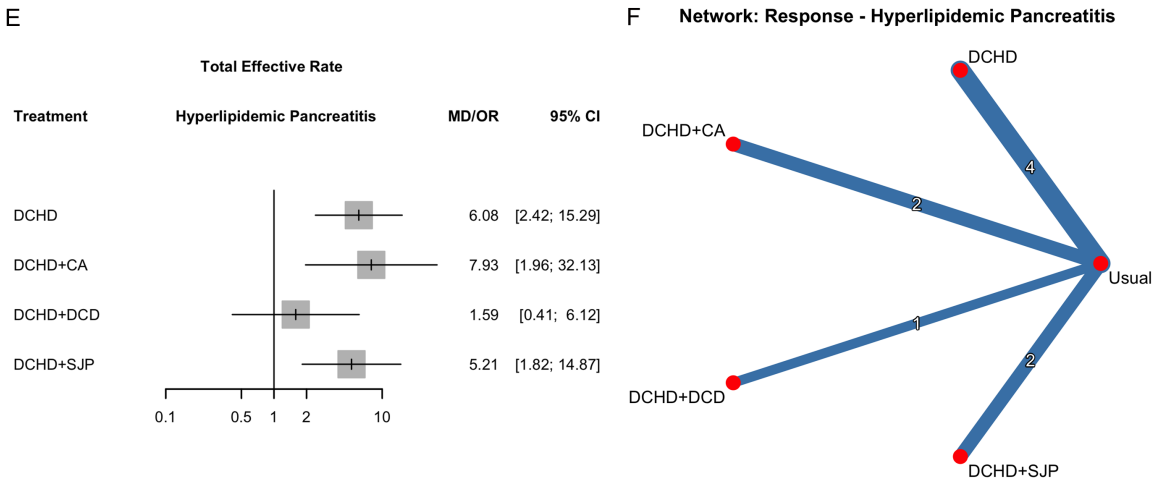




**Figure S4.** Pancreatitis subgroup analysis. A. Forest plot of TC; B. Network plot of TC; C. Forest plot of TG; D. Network plot of TG; E. Forest plot of total effective rate; F. Network plot of total effective rate.

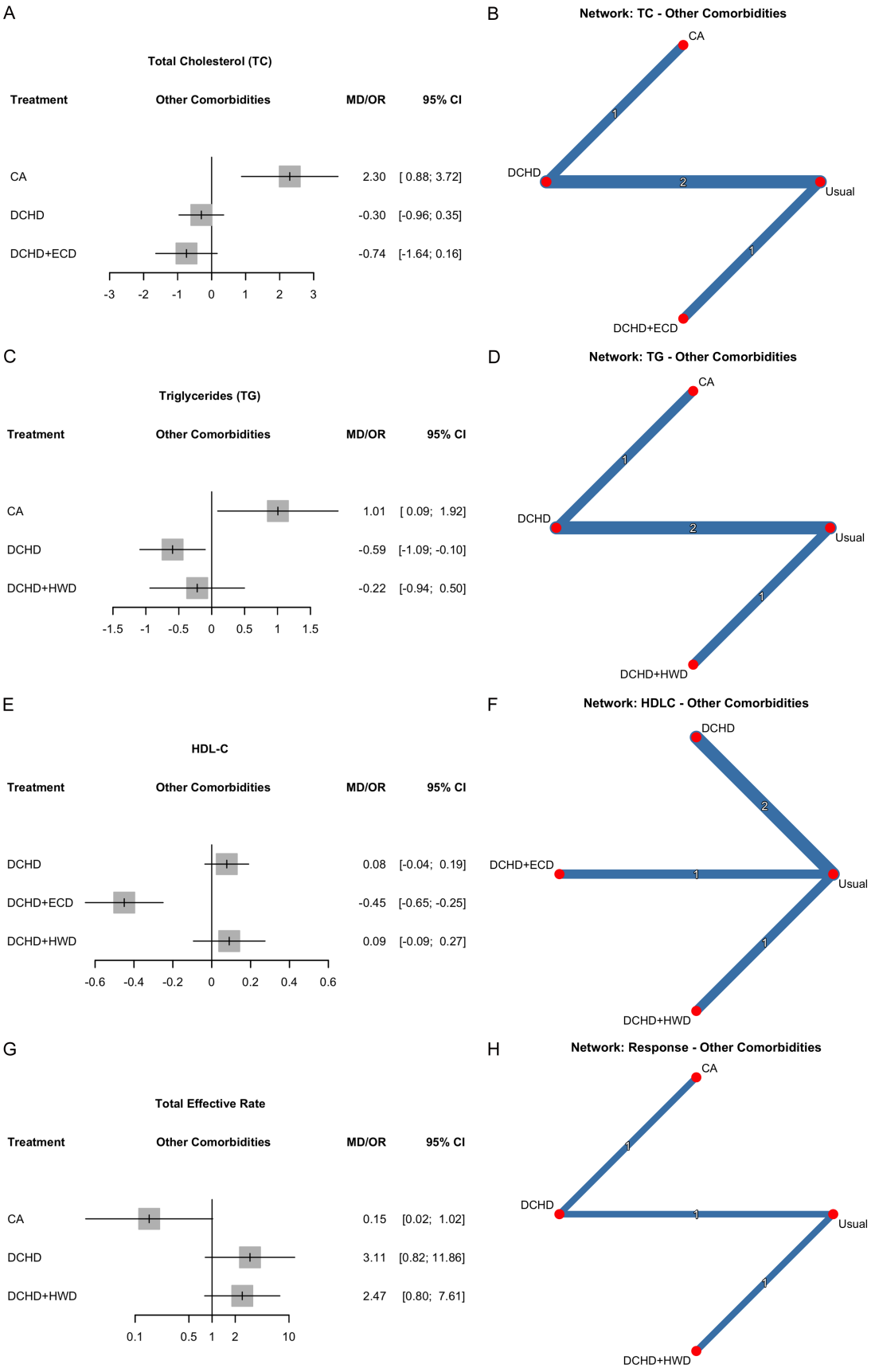



**Figure S5.** Other comorbidities subgroup analysis. A. Forest plot of TC; B. Network plot of TC; C. Forest plot of TG; D. Network plot of TG; E. Forest plot of HDL-C; F. Network plot of HDL-C; G. Forest plot of total effective rate; H. Network plot of total effective rate.