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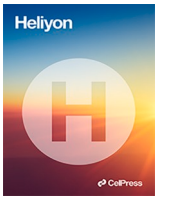

Antihypertensive effect and mechanism of the traditional recipe of medicine food homology (Buyang Huanwu Decoction) in China: Meta analysis and network pharmacological exploration

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ABSTRACT

Background: Hypertension has become a part of the lives of many people worldwide. With the development, an increasing number of people have begun to control their hypertension through products of medicine food homology, such as Buyang Huanwu Decoction (BYHWD). However, there has been no objective review of the regulation of hypertension by BYHWD.
Methods: As of 9 October 2023, this review made a detailed search of nine databases to look for random controlled trials (RCTs) focused on the use of BYHWD for treating hypertension. This was followed by network pharmacological analysis, and molecular docking assessment using AutoDockTools to explore the mode of action.
Results: BYHWD was effective in reducing SBP (MD: 0.767; 95 % CI: 0.629, 0.905; $p = 0.000$), DBP (MD: 0.427; 95 % CI: 0.292, 0.561; $p = 0.000$), 24h SBP (MD: 0.665; 95 % CI: 0.368, 0.962; $p = 0.000$), 24h DBP (MD: 0.547; 95 % CI: 0.318, 0.777; $p = 0.000$), dSBP (MD: 0.625; 95 % CI: 0.395, 0.855; $p = 0.000$), dDBP (MD: 0.632; 95 % CI: 0.401, 0.862; $p = 0.000$), nSBP (MD: 0.859; 95 % CI: 0.340, 1.377; $p = 0.001$), nDBP (MD: 0.704; 95 % CI: 0.297, 1.112; $p = 0.001$), pv (MD: 1.311; 95 % CI: 0.363, 2.259; $p = 0.007$) and NIHSS (MD: 1.149; 95 % CI: 0.100, 2.199; $p = 0.032$), and elevating CER (OR = 2.848; 95 % CI: 1.388, 5.843; $p = 0.004$). However, BYHWD did not significantly reduce HCY, and there was no significant difference in the incidence of AE. In terms of the mechanism of action, the main active ingredient of BYHWD is quercetin, and the core targets are AKT1, MMP9, and others. Molecular docking also showed that quercetin mainly interacts with the amino acid residue CYS-28 of MMP2. Second, the KEGG analysis showed that BYHWD mainly act on HIF-1, Apelin, and cGMP-PKG signalling pathways, and GO analysis showed that it related to the apical part of the cell, circulatory system processes, and nuclear receptor activity. **Conclusion:** BYHWD can lowered blood pressure, reduced plasma viscosity, and restored neurological function with good tolerability, and had no significant effect on HCY levels. This study further demonstrated that quercetin is the main active ingredient of BYHWD that acts via the AKT1 and HIF-1 signalling pathways. These results provide new guidance for people's dietary choices by the general public.

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1. Introduction

Hypertension is a major factor in cardiovascular diseases and is widely distributed in the world. Given the current social trends in food choices, where the general public prefers spicy, oil-rich, and high sugar content foods, the number of patients with hypertension is increasing annually. Nearly 20 million people die annually from cardiovascular diseases. Hypertension accounts for 45 % of all cardiovascular disease-related mortalities [1,2].

Currently, the treatment for hypertension in Western medicine involves lifelong use of oral antihypertensive drugs that can be classified into six categories: diuretics, α-receptor blockers, β-receptor antagonists, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists [3]. However, disadvantages such as poor patient compliance and unclear improvement of symptoms abound. Therefore, methods for controlling blood pressure and improving quality of life are required. Currently, food therapy based on the medicines having food homology has gradually begun to attract the attention of the general public because of advantages like safety, effectiveness and universality. It is easy for people to accept this approach of using food as medicine because the products of medicine food homology can prevent and treat diseases while filling the stomach. This approach is encapsulated in the saying "Food to an empty stomach and medicine to the sick" [4,5]. In fact, the Inner Canon of the Yellow Emperor of Chinathat has a history of more than 2000 years, suggests that medicine and food are interrelated and that diseases should be prevented before they manifest [6]. Through diet therapy, dietary supplements, or medicinal diets, the body can be regulated and human immunity can be improved to prevent diseases [7]. Nowadays, global medical concepts are shifting from treatment to prevention. Increasingly, the products of medicine food homology are gaining popularity [8]. Furthermore, the Chinese Health and Welfare Commission and the General Administration of Market Supervision and Administration of China (2020) jointly issued the "Notice on the Pilot Work on the Management of Nine Substances such as Party Ginseng that are Both Food and Traditional Chinese Medicines according to Tradition", that refers to numerous medicinal foods comprising 84 ingredients including cloves, ginseng, ginseng leaves, ginseng fruit, anise, knife beans, cumin, yam, hawthorn, horse amaranth, umeboshi, papaya, fire flaxseed, yucca, panax ginseng, earth poria, liquorice, dahurica, white fruit, cardamom and angelica, etc [9]. Notably, the combination of Astragalus Membranaceus, Radix Paeonia Rubra, Rhizoma Chuanxiong, Chinese Angelica, Earthworm, Peach Kernel and Safflower formed a new recipe, termed Buyang Huanwu Decoction (BYHWD). The BYHWD was created by Qingren Wang (1768–1831 AD), a doctor of Chinese medicine during the Qing Dynasty, who wrote about it in the book Correction on Errors in Medical Classics. It has the advantages of invigorating qi, replenishing blood, promoting blood circulation, removing blood stasis, and clearing collaterals at five levels. It has been widely used to regulate hypertension and various cardiovascular complications caused by it, and has a history of use of more than 190 years [10]. Several anecdotal cases have described the positive effects of BYHWD on hypertension [11,12]. Moreover, modern pharmacological studies have reported similar results. Recent research has found that the chemical composition of Chinese Angelica includes polysaccharides, saponins, flavonoids, and other substancesthat may lower blood pressure and improve vascular remodelling by regulating protective and pro-apoptotic factors in the emergency recovery system of the human body [13,14]. See Table 1 and Fig. 1 for other ingredients, proportions, and physical photographs of the natural ingredients.

Multiple studies have shown that BYHWD effectively regulates hypertension. However, the sample sizes of existing trials are generally small. In addition, there has been no review of the guidelines for BYHWD as a daily supplement for managing hypertension, and there is also no report of using network pharmacology to probe the mechanism of action of BYHWD that regulates hypertension. This makes it difficult to convince the public that BYHWD is a food-based medicinal product that is significantly effective against hypertension, limiting its use and promotion. In fact, food -based medicines is an effective way of preventing and treating chronic diseases. As complementary and alternative medicines are increasingly being recognised in various countries, natural medicines, represented by food-based and herbal medicines, are also attracting attention. Since these products share the positive characteristics of efficacy and high safety, they can be easily promoted in the community and among family members, and have broad application prospects. BYHWD is a safe and effective alternative to traditional blood pressure medications, and there is a need to promote its use in the treatment of hypertension through the development of evidence-based guidelines. In this study, we comprehensively evaluated the effects and intrinsic mechanisms of BYHWD on hypertension, to facilitate its popularisation as a new food resource. This therapeutic approach, focusing on the use of food-based medicine to treat hypertension may generate a high degree of acceptance in the current environment. For example, the potential ameliorative effect of dietary fiber as a cardioprotective drug in patients diagnosed with cardiovascular disease and hypertension has been suggested [15–17]. This study will benefit the exchange of knowledge about traditional medicine between different countries in the field of food and medicine, and at the same time enhance the scientific recognition of products with medicine food homology in various countries, with a view to laying an important foundation for the development of medicinal food protocols for the treatment of hypertensive diseases [18,19].

Table 1
BYHWD introduction.

English name	Chinese name	Family	Part used	Main Nutrients	Proportion
Astragalus Membranaceus	Huang Qi	Fabaceae	Root	astragalus polysaccharide; quercetin	120
Chinese Angelica	Dang Gui	Apiaceae	Root	ferulic acid; carvacrol	6
Radix Paeonia Rubra	Chi Shao	Paeoniaceae	Root and rhizome	spinasterol; salicylic Acid; benzoic Acid	5
Earthworm	Di Long	Megascolecidae	Dried Body	earthworm protein; tubulin	3
Rhizoma Chuanxiong	Chuan Xiong	Apiaceae	Rhizome	ligustrazine; caffeic acid	3
Safflower	Hong Hua	Zingiberaceae	Flower	quercetin;	3
Peach Kernel	Tao Ren	Rosaceae	Seed	sitosterol alpha1; hederagenin	3

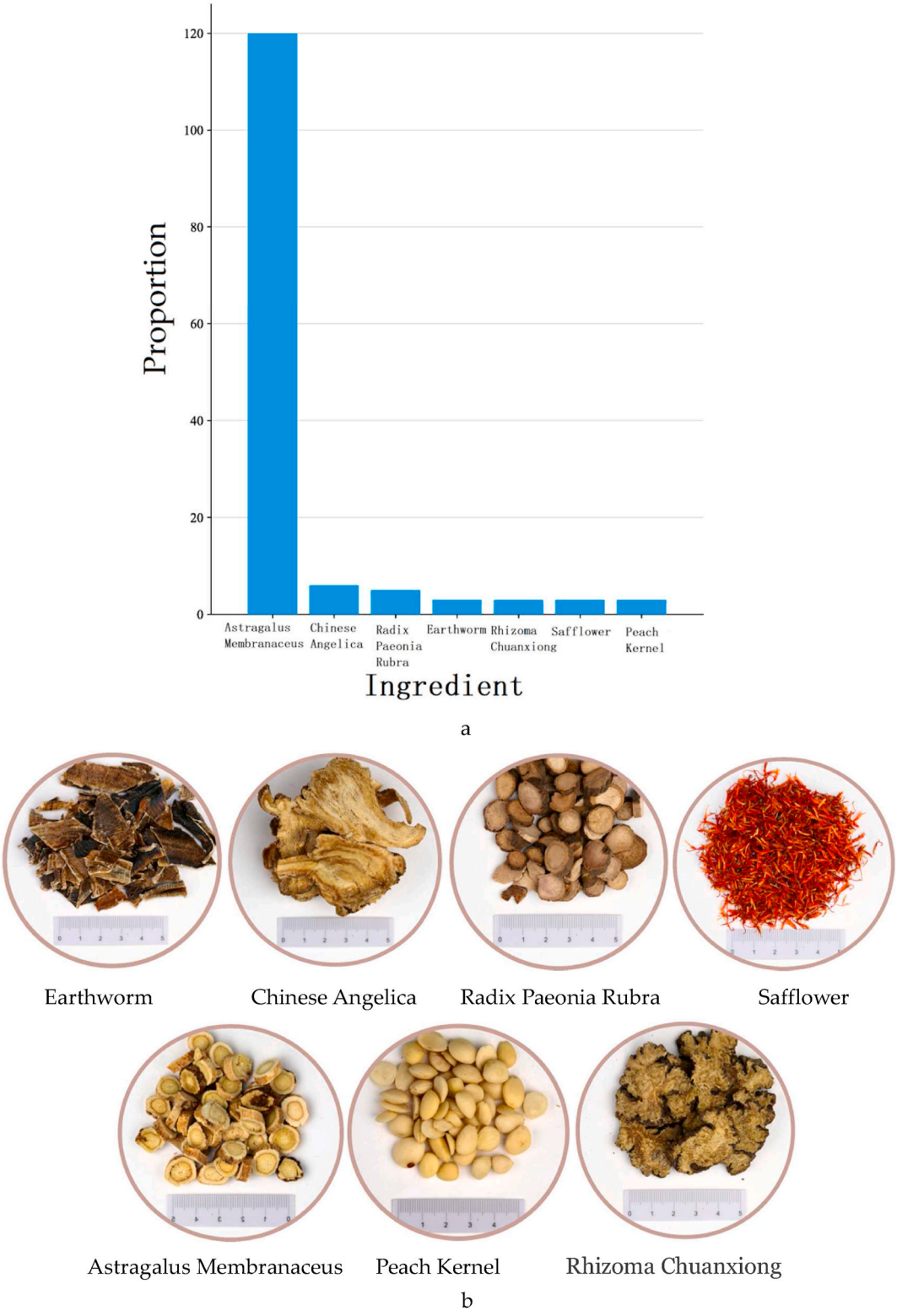


Fig. 1. a. The proportions of **various ingredients in** BYHWD. Earthworm Chinese Angelica Radix Paeonia Rubra Safflower, Astragalus Membranaceus Peach Kernel Rhizoma Chuanxiong, Fig. 1b. **Photographs showing the natural ingredients** of BYHWD.

2. Methods

2.1. Meta-analysis

This meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO) trial registry (CRD42023395845).

2.1.1. Inclusion and exclusion criteria

Inclusion criteria.

(1) Study type: Randomised controlled trials (RCTs) of BYHWD on hypertension.
(2) Participant type: Essential hypertension patients, no age, gender, or race restrictions.
(3) Grouping type: The control group was given antihypertensive treatment. The experimental group used BYHWD alone or added BYHWD in addition to the former.
(4) Outcome indicator: The key indicators were systolic blood pressure (SBP), diastolic blood pressure (DBP), and 24-h ambulatory blood pressure (AMBP). Secondary indicators were the clinical efficiency rate (CER), homocysteine (HCY), plasma viscosity (PV), and National Institutes of Health Stroke Scale (NIHSS) scores. Safety was assessed based on adverse events(AEs).

Exclusion criteria.

(1) Studies that did not record blood pressure data.
(2) Subjects with incomplete key baseline data.
(3) Unclear reporting of interventions.

2.1.2. Search strategy

Nine databases were searched by two evaluators (LB and LC): PubMed, Embase, Cochrane Library, Web of Science, MEDLINE Library, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal (VIP), Chinese BioMedical Literature (CBM), and Wanfang. No restrictions were imposed from the construction of the repository until 9 October 2023. We used the following combination of subject words and free words to determine inclusion: (“Hypertension” OR “Hypertensions” OR “Blood Pressure, High” OR “Blood Pressures, High” OR “High Blood Pressure” OR “High Blood Pressures”) and (“buyang huanwu decoction” OR “buyang huanwu tang” OR “buyang huanwu soup” OR “buyang huanwu prescription").

2.1.3. Research screening and data selection

Duplicate studies were removed during further screening by two evaluators (LB and LC) based on the title, abstract, or full text. The following data were then extracted from the included studies: (1) year of publication, first author, and title; (2) sample size, age, sex, and hypertension classification; (3) type, dose, frequency, and duration of the intervention; (4) closing indicators, including SBP, DBP, AMBP, CER, HCY, PV, and NIHSS; (5) AE. Disagreements arising from this process were addressed by a third reviewer (WXD).

2.1.4. Assessment of the risk of bias

Two assessors (LB and LC) used Review Manager 5.4 to assess the level of RCTs adopted. The evaluation programs have seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias [20]. Three levels of each program were “high risk,” “low risk,” and “unclear risk”. And every RCT was also divided into three levels: good (all programs rated as low risk), fair (low risk programs >3) or weak (low risk programs ≤ 3). Disagreements arising from the above process were resolved by the third reviewer (WXD).

2.1.5. Statistical analysis

This analysis was performed using Stata 17.0 software. Continuous outcomes, including SBP, DBP, 24-h AMBP, HCY, PV, and NIHSS scores, were expressed as mean difference (MD) with 95 % confidence intervals (CI). Categorical outcomes, clinical effectiveness rate (CER), and AE were expressed as odds ratios (OR) and 95 % CI. A random-effects model was used when $I^2 \geq 50$ %, whereas a fixed-effects model was used for $I^2 < 50$ %.

2.1.6. Subgroup and Sensitivity Analysis

When $I^2 \geq 50$ %, sensitivity analysis was used to find abnormal tests, and further subgroup analysis was used to find the key causes of high heterogeneity [21].

2.1.7. Trial sequential analysis

Trial sequential analysis (TSA) of SBP, DBP and CER was performed using the TSA 0.9.5.10 software to test for sample size adequacy. The cumulative Z-curve indicates the cumulative sample size of the included studies. When the Z-curve simply crosses a conventional boundary, false positives are obtained. If the Z-curve crosses both the traditional and TSA boundaries, the results are considered reliable. When the Z-curve intersects the required amount of information (RIS) boundary, the number of samples is considered sufficient [22–24].

2.1.8. Publication bias

Egger's statistical test was applied to assess publication bias [25].

2.1.9. Quality of evidence

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method was used by two evaluators (LB and LC) to assess the quality of the evidence. Evidence was classified into four levels based on research limitations, inconsistencies, indirectness, inaccuracies and other factors (e.g., publication bias), and ranged from high, moderate, low, to very low. The initial level of evidence for RCTs was high. Factors that are rated as "serious" or "publication bias suspected" were lowered slightly, and those rated "very serious" or "publication bias strongly suspected" were reduced more significantly. Disagreements arising from the above process were resolved by the third reviewer (WXD).

2.2. Network pharmacology

2.2.1. Gene target (BYHWD - hypertension) screening

The chemical constituents of BYHWD were identified through the Traditional Chinese Medicine Systems Pharmacology (TCMSP), the Encyclopedia of Traditional Chinese Medicine (ETCM) and literature searches for "Huang Qi", "Dang Gui", "Chi Shao", "Di Long", "Chuan Xiong", "Hong Hua" and "Tao Ren". The screening criteria we employed were as follows: Oral bioavailability (OB)$\geq$30 %, and drug likeness (DL) $\geq$0.18. The active chemical constituents identified in this manner were converted into gene targets using the UniProt database. At the same time, by searching the keyword "hypertension" in GeneCards, online Mendelian inheritance in man (OMIM) and Drugbank databases, we obtained disease targets that were then intersected with BYHWD gene targets to obtain drug-disease gene targets [26].

2.2.2. Protein-protein interaction (PPI)

The drug–disease intersection targets were entered into the STRING database for protein interactions using the following screening criteria: the study species was human (Homo sapiens), and the interaction score was 0.900 [27].

2.2.3. Gene ontology (GO) and kyoto encyclopaedia of genes and genomes (KEGG) analysis

The key targets of BYHWD in hypertension were enriched by using the Metascape database [28]. The screening criteria were as

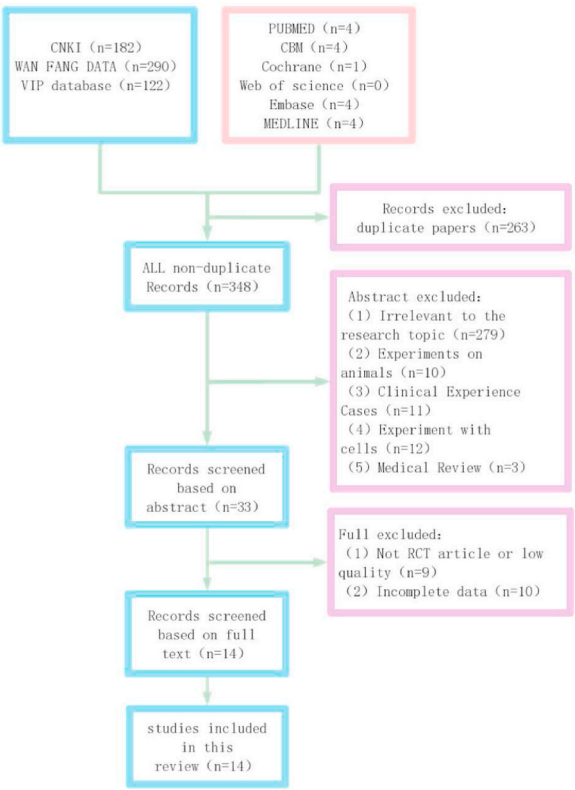


Fig. 2. Flowchart of the study selection process.

Table 2
Characteristics of the included studies.

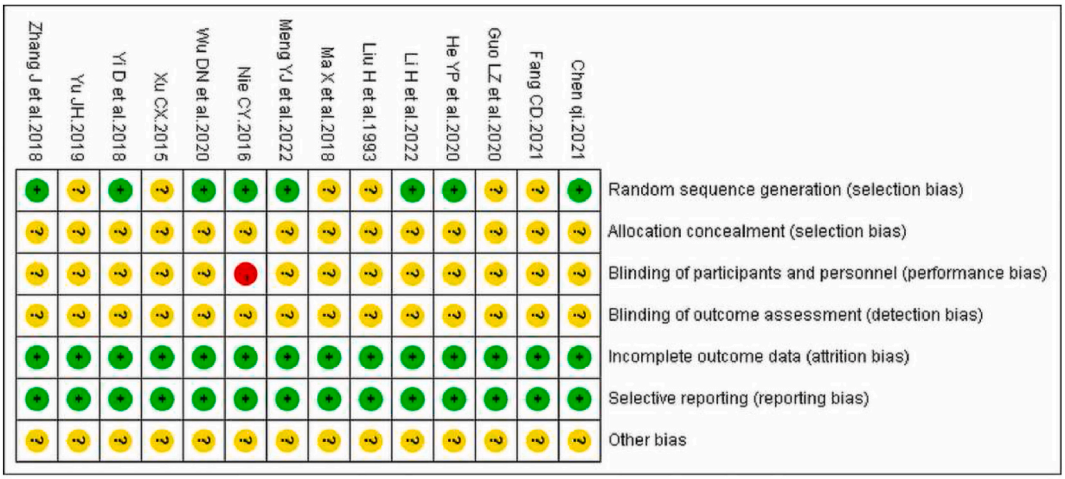
Study (first author et al. year)	sample size (BYHWT/Con)	population	Age (years)	Intervention	Control	Duration	Outcomes
Liu H et al., 1993	50/30	Grade 2or3 hypertension	BYHWD: 62.8 ± 6.9 Con: 63.6 ± 6.3	BYHWD (one dose a day, bid)	Compound Reserpine (one or two pieces at a time, bid or tid)+γ January grass a E pellet (0.9g, tid)	8 weeks	SBP, DBP, PV
Xu CX.2015	32/28	Essential hypertension	BYHWD: 55.81 ± 9.98 Con: 55.36 ± 10.83	BYHWD (one dose a day, bid) + Candesartan tablets (8 mg, qd)	Candesartan tablets (8 mg, qd)	8 weeks	SBP, DBP
Nie CY.2016	42/41	Essential hypertension	BYHWD: 58.9 ± 10.2 Con: 57.8 ± 10.1	BYHWD (one dose a day, bid) + Erbexatan tablets (0.15g, qd)	Erbexatan tablets (0.15g, qd)	3 months	SBP, DBP, CER
Ma X et al., 2018	50/50	Essential hypertension	BYHWD: 56.63 ± 8.95 Con: 54.84 ± 9.22	BYHWD (one dose a day, tid) + Amlodipine benzylate tablets (5 mg, qd)	Amlodipine benzylate tablets (5 mg, qd)	2 weeks	SBP, DBP, CER
Yi D et al., 2018	30/30	Type H hypertension	BYHWD: Con:	BYHWD (one dose a day, tid) + Erbexatan tablets/ Hydrochlorothiazide tablets (150mg/12.5 mg, qd) + Folic acid tablets (5 mg, qd)	Erbexatan tablets/Hydrochlorothiazide tablets (150mg/12.5 mg, qd) + Folic acid tablets (5 mg, qd)	–	SBP, DBP, HCY, CER
Zhang J et al., 2018	50/50	Type H hypertension	BYHWD: 62.51 ± 7.68 Con: 62.85 ± 8.12	BYHWD (one dose a day, bid) + Enalapril Maleate and Folic Acid Tablets (10 mg, qd)	Enalapril Maleate and Folic Acid Tablets (10 mg,qd)	4 weeks	ABPM, HCY, AE
Yu JH.2019	42/42	Essential hypertension	BYHWD: 62.57 ± 5.15 Con: 62.46 ± 5.18	BYHWD (one dose a day, tid) + Amlodipine benzylate tablets (5 mg, qd)	Amlodipine benzylate tablets (5 mg,qd)	2 weeks	SBP, DBP
Guo LZ et al., 2020	60/60	Type H hypertension	BYHWD: 63.25 ± 11.27 Con: 67.57 ± 9.56	BYHWD (one dose three day, bid) + Enalapril Maleate and Folic Acid Tablets (10 mg, qd)	Enalapril Maleate and Folic Acid Tablets (10 mg, qd)	12 months	SBP, DBP, ABPM, HCY, CER
He YP et al., 2020	30/30	Type H hypertension	BYHWD: 55.16 ± 10.33 Con: 54.33 ± 10.70	BYHWD (one dose a day, bid) + Beenapril hydrochloride tablets (10 mg, qd)	Beenapril hydrochloride tablets (10 mg, qd)	3 weeks	SBP, DBP, PV, HCY, NIHSS, AE
Wu DN et al., 2020	43/43	Type H hypertension	BYHWD: 62.4 ± 6.7	BYHWD (one dose a day, bid) + Enalapril Maleate and Folic Acid Tablets (10 mg, qd)	Enalapril Maleate and Folic Acid Tablets (10 mg, qd)	3 months	SBP, DBP, HCY

(*continued on next page*)

Table 2 (*continued*)

Study (first author et al. year)	sample size (BYHWT/Con)	population	Age (years)	Intervention	Control	Duration	Outcomes
			Con: 60.9 ± 7.2				
Chen qi.2021	36/35	Type H hypertension	BYHWD: 62.8 ± 6.5 Con: 62.5 ± 6.8	BYHWD (one dose a day, bid) + Enalapril maleate tablets (10 mg, qd) + Folic acid tablets (1.25 mg, qd)	Enalapril maleate tablets (10 mg, qd) + Folic acid tablets (1.25 mg, qd)	3 months	SBP, DBP, CER
Fang CD.2021	41/43	Essential hypertension	BYHWD: 72.20 ± 3.69 Con: 72.42 ± 3.96	BYHWD (one dose a day, tid) + Amlodipine benzylate tablets (5 mg, qd)	Amlodipine benzylate tablets (5 mg, qd)	4 weeks	ABPM, CER
Li H et al., 2022	49/49	Essential hypertension	BYHWD: Con:	BYHWD (one dose a day) + Beenapril hydrochloride tablets (5–10 mg, qd)	Beenapril hydrochloride tablets (5–10 mg, qd)	12 weeks	SBP, DBP, NIHSS, CER
Meng YJ et al., 2022	50/50	Essential hypertension	BYHWD: 58.11 ± 5.21 Con: 58.89 ± 6.34	BYHWD (one dose a day, bid) + Routine antihypertensive treatment in Western medicine	Routine antihypertensive treatment in Western medicine	3 weeks	SBP, DBP, PV, NIHSS, CER

BYHWD, Buyang Huanwu decoction; Con, control; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring; CER, clinical effectiveness rate; HCY, homocysteine; PV, plasma viscosity; NIHSS, neurological function score; AE, adverse events.



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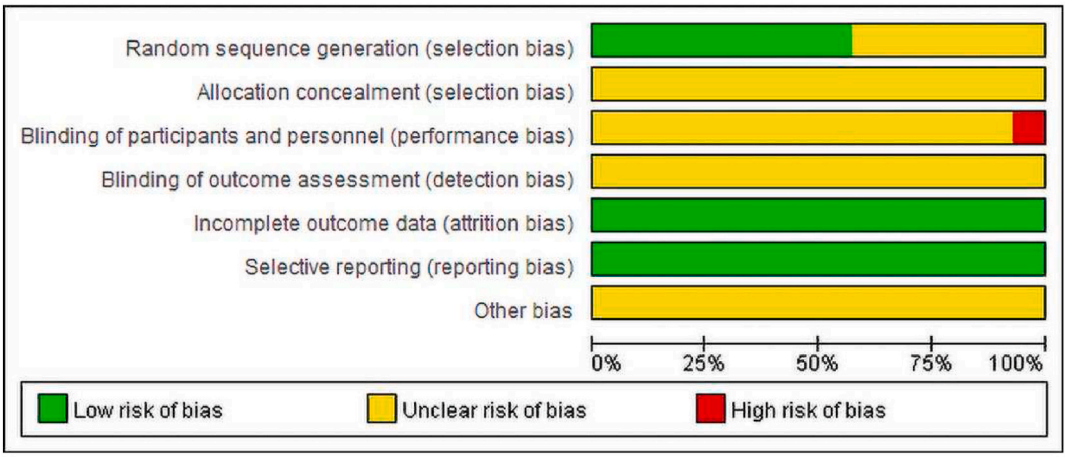

b

Fig. 3. a Overall Risk of Bias, Fig. 3 b. Risk of Bias Bar Chart.

follows: human (H. sapiens), followed by personalised analysis. Data were screened based on the enrichment analysis results at $P < 0.05$ [29].

2.2.4. Active ingredient target network

The active ingredients previously identified in BYHWD were integrated with their corresponding targets into an Excel file and then imported into Cytoscape 3.7.2 software (http://www.cytoscape.org) to generate a network diagram of BYHWD compound-target interactions.

2.2.5. Molecular docking validation

Selected core target protein PDB files were downloaded from the RSCB PDB database [30]. The PyMOL software was used to dehydrate and remove organic matter from the core target protein. Next, PDB files of key compounds were obtained from PubChem and PyMOL. Finally, Autodock was used to dock each active compound with a protein target and scores were derived.

3. Results

3.1. Meta-analysis

3.1.1. Study selection

A total of 611 potentially relevant articles were initially identified (PubMed, 4; CBM, 4; Cochrane Library, 1; Web of Science, 0; Embase, 4; MEDLINE, 4; CNKI, 182; Wanfang, 290; and VIP, 122), and 263 duplicate publications were removed. Of the remaining 348

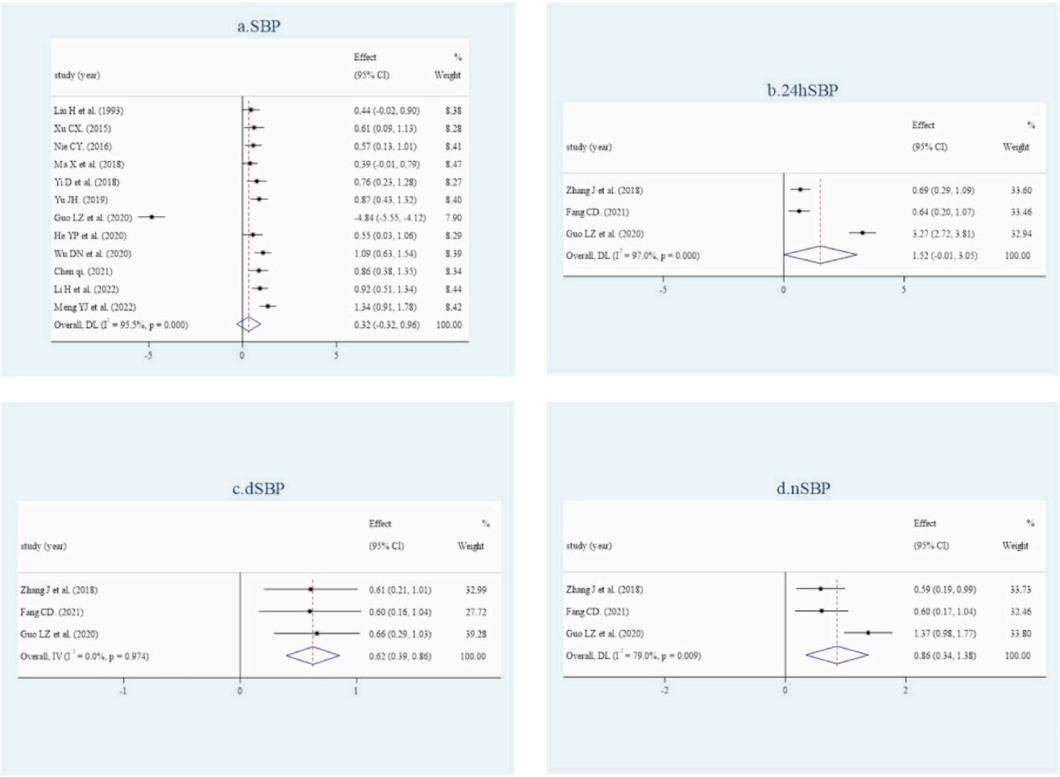

Fig. 4. Forest plot meta-Aanalysis results for SBP.

articles, 315 were excluded on the basis of their titles and abstracts. Subsequently, 33 articles were further evaluated based on the full text, and 19 were excluded for the following reasons: non-RCTs (n = 9) and no hypertension data (n = 10). Finally, 14 RCTs were included in the quantitative analysis (Fig. 2).

3.1.2. Characteristics of the included studies

The 14 RCTs [31–44] included in this meta-analysis were published between 1993 and 2023 and involved 1186 patients with an average age of 43.63–76.38 years, including 675 men and 511 women. One RCT compared the efficacy of BYHWD with that of antihypertensive drugs alone. Thirteen RCTs compared BYHWD efficacy in combination with antihypertensive drugs or antihypertensive drugs alone. Twelve RCTs involving 1,002 patients reported SBP and DBP data. Three RCTs involving 304 patients reported 24-h AMBP data; eight RCTs involving 716 patients reported CER values; five RCTs involving 426 patients reported HCY levels; three RCTs involving 240 patients reported PV data; three RCTs involving 258 patients reported NIHSS scores; and two RCTs involving seven patients reported AE data (Table 2).

3.1.3. Risk of bias assessment

The generation of randomised sequences was reported in detail in eight of 14 RCTs, seven of which used the randomised number table method and one used the randomised touch ball method. Two RCTs reported the number of dropouts and the exact reason for dropping out patients. Finally, all 14 RCTs were rated as poor quality (Fig. 3a and 3b).

3.1.4. Meta-analysis

3.1.4.1. SBP. Twelve RCTs involving 1,002 cases compared the efficacy of BYHWD alone or that in combination with antihypertensive drugs and antihypertensive drugs alone on SBP. Heterogeneity tests showed significant heterogeneity (Cochrane Q test = 245.33, $p = 0.000$, $I^2 = 95.5$ %); therefore, a random effects model was used. The results showed that there was no significant difference between the experimental and control groups in regulating SBP (MD: 0.321; 95 % CI: 0.321, 0.964; $p = 0.327$) (Fig. 4a).

3.1.4.2. 24h SBP. Three RCTs comprising 304 patients compared the efficacy of BYHWD combined with antihypertensive drugs and antihypertensive drugs alone on 24h SBP. The heterogeneity test showed high heterogeneity (Cochrane Q test = 66.66, $p = 0.000$, $I^2 = 97.0$ %); therefore, a random effects model was used. The results showed no significant difference between the experimental and control groups in the regulating of 24h SBP (MD: 1.520; 95 % CI: 0.011, 3.052; $p = 0.052$) (Fig. 4b).

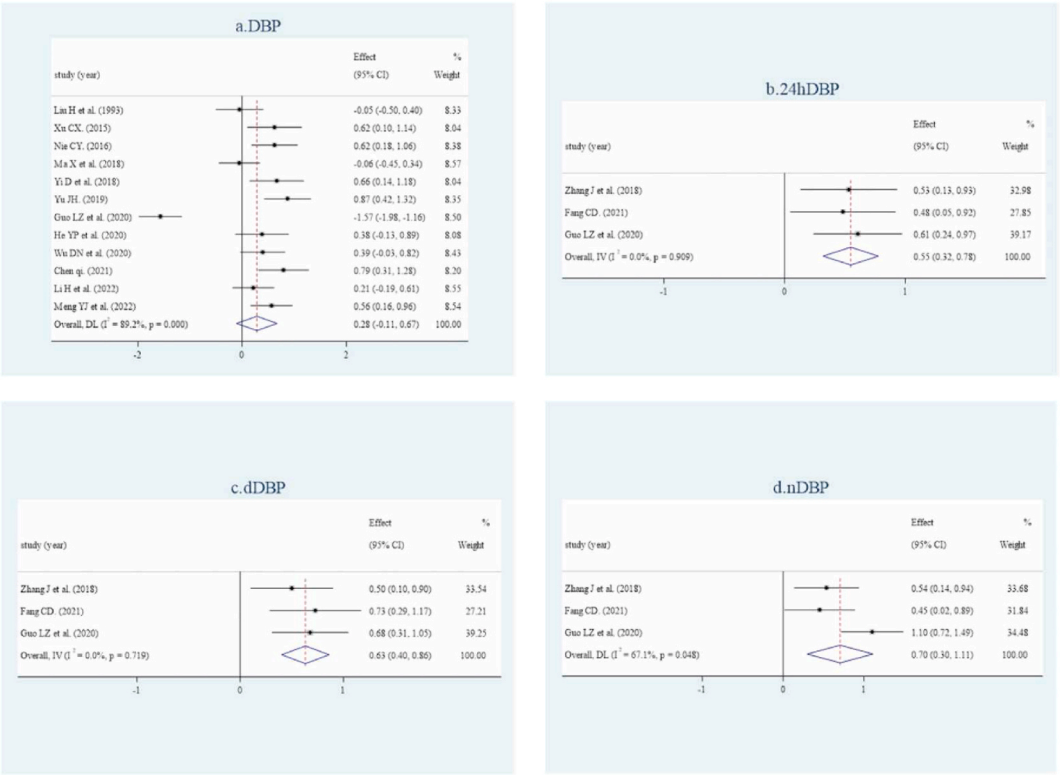

Fig. 5. Forest plot meta-analysis results for DBP.

3.1.4.3. dSBP. Three RCTs involving 304 patients compared the efficacy of BYHWD in combination with antihypertensive drugs and antihypertensive drugs alone on dSBP. Heterogeneity tests showed no heterogeneity (Cochrane Q test = 0.05, $p = 0.974$, $I^2 = 0.00$ %); therefore, a fixed-effects model was used. The results showed that dSBP was significantly reduced in the experimental compared to the control group (MD: 0.625; 95 % CI: 0.395–0.855; $p = 0.000$) (Fig. 4c).

3.1.4.4. nSBP. Three RCTs involving 304 patients compared the efficacy of BYHWD combined with antihypertensive drugs and antihypertensive drugs alone on 24h SBP. Heterogeneity tests showed significant heterogeneity (Cochrane Q test = 9.51, $p = 0.009$, $I^2 = 79.0$ %); therefore, a random effects model was applied. The results showed that the experimental group did better (MD: 0.859; 95 % CI: 0.340, 1.377; $p = 0.001$) (Fig. 4d).

3.1.4.5. DBP. Twelve RCTs involving 1,002 cases compared the efficacy of BYHWD alone or that in combination with antihypertensive drugs and antihypertensive drugs alone on DBP. Heterogeneity tests showed significant heterogeneity (Cochrane Q test = 102.15, $p = 0.000$, $I^2 = 89.2$ %); therefore, a random effects model was used. The results showed that there was no significant difference between the experimental and control groups in the regulation of DBP (MD: 0.280; 95 % CI: 0.112, 0.671; $p = 0.161$) (Fig. 5a).

3.1.4.6. 24h DBP. Three RCTs involving 304 patients compared the efficacy of BYHWD in combination with antihypertensive drugs and antihypertensive drugs alone on 24h DBP. Heterogeneity tests showed no heterogeneity (Cochrane Q test = 0.19, $p = 0.909$, $I^2 = 0.0$ %); therefore, a fixed-effects model was used. The results showed that the experimental group did better (MD: 0.547; 95 % CI: 0.318, 0.777; $p = 0.000$) (Fig. 5b).

3.1.4.7. dDBP. Three RCTs involving 304 patients compared the efficacy of BYHWD in combination with antihypertensive drugs and antihypertensive drugs alone on dDBP. Heterogeneity tests showed no heterogeneity (Cochrane Q test = 0.66, p = 0.719, $I^2 = 0.00$ %); therefore, a fixed-effects model was used. The results showed that dDBP was significantly reduced in the experimental group compared to the control group (MD: 0.632; 95 % CI: 0.401, 0.862; p = 0.000) (Fig. 5c).

3.1.4.8. nDBP. Three RCTs involving 304 patients compared the efficacy of BYHWD in combination with antihypertensive drugs and antihypertensive drugs alone on nDBP. Heterogeneity tests showed significant heterogeneity (Cochrane Q test = 6.07, p = 0.048, $I^2 = 67.1$ %); therefore, a random effects model was used. The results showed that nDBP was significantly reduced in the experimental group compared to the control group (MD: 0.704; 95 % CI: 0.297, 1.112; p = 0.001) (Fig. 5d).

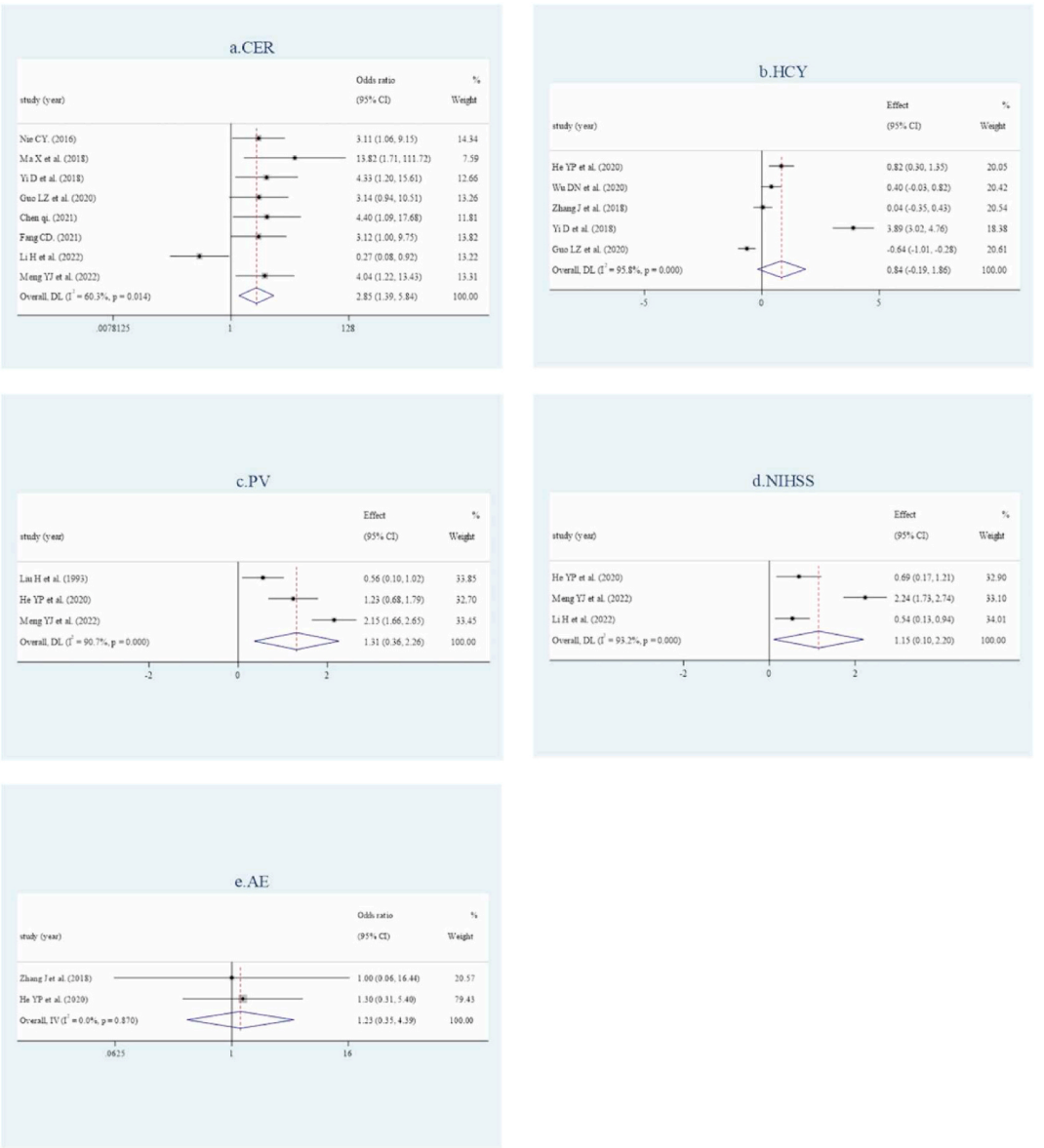

Fig. 6. Forest plot meta-analysis results for CER, HCY, PV, NIHSS, and AE.

3.1.4.9. CER. Eight RCTs involving 716 patients compared the clinical effectiveness of BYHWD combined with antihypertensive drugs and antihypertensive drugs alone for the treatment of hypertension. Heterogeneity tests showed significant heterogeneity (Cochrane Q test = 17.64, p = 0.014, I^2 = 60.3 %); therefore, a random effects model was used. The results showed that the CER of the experimental group was significantly higher than that of the control group (OR = 2.848; 95 % CI: 1.388, 5.843; p = 0.004) (Fig. 6a).

3.1.4.10. HCY. Five RCTs involving 426 patients compared the efficacy of BYHWD in combination with antihypertensive drugs and antihypertensive drugs alone in regulating HCY levels. Heterogeneity tests showed high heterogeneity (Cochrane Q test = 96.04, p = 0.000, I^2 = 95.8 %); therefore, a random effects model was used. The results showed no significant difference between the experimental and control groups in the regulation of HCY levels (MD: 0.837; 95 % CI: 0.190, 1.863; p = 0.110) (Fig. 6b).

3.1.4.11. PV. Three RCTs involving 240 patients compared the efficacy of BYHWD alone or in combination with antihypertensive drugs and antihypertensive drugs alone on PV. Heterogeneity tests showed high heterogeneity (Cochrane Q test = 21.43, p = 0.000, I^2 = 90.7 %); therefore, a random effects model was applied. The results showed that the experimental group did better (MD: 1.311; 95 % CI: 0.363, 2.259; p = 0.007) (Fig. 6c).

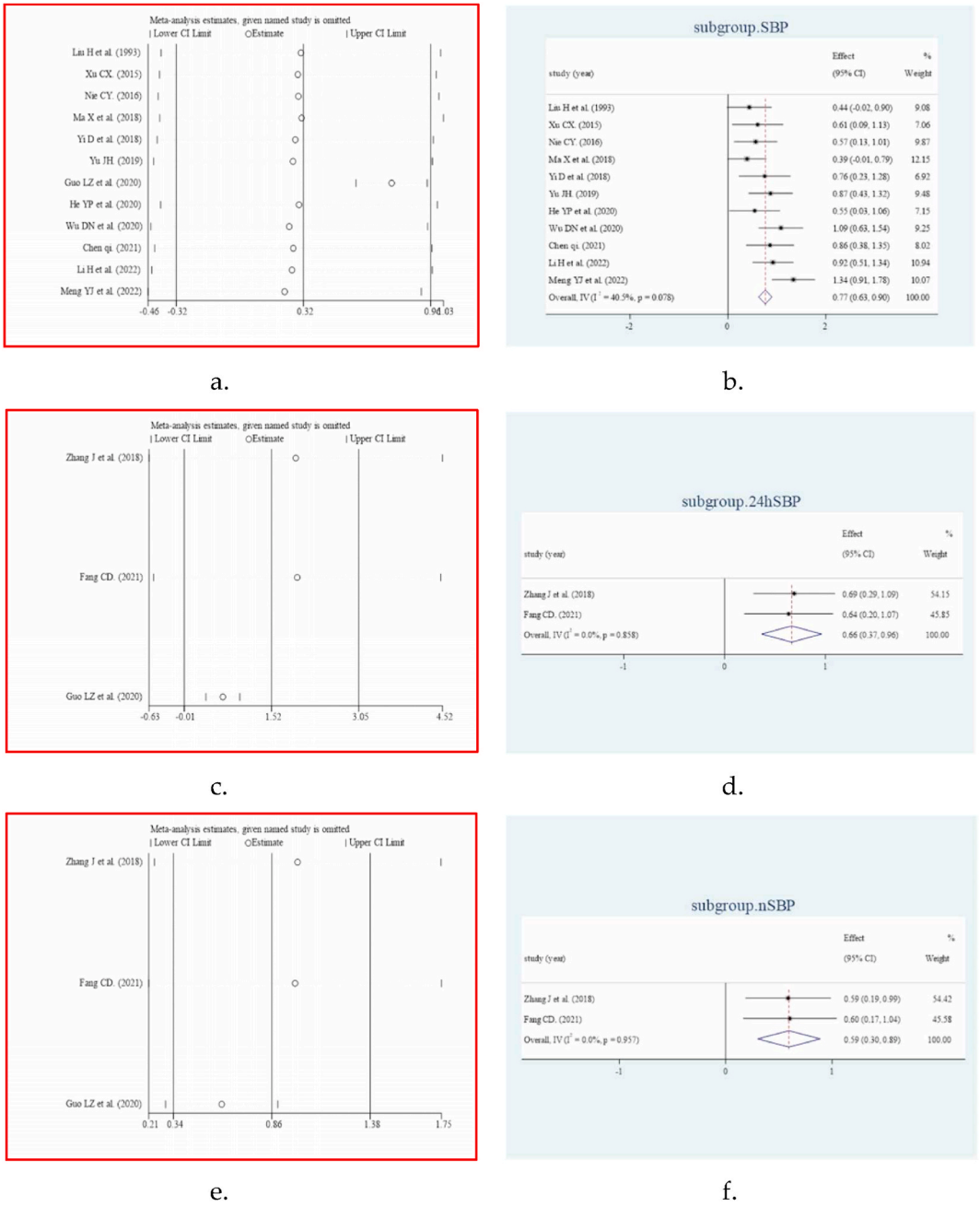

Fig. 7. Subgroup and sensitivity analysis of SBP.

Table 3
Subgroup and sensitivity analysis of SBP.

	Item	Group	No. o studies	No. of participants	MD	95 % CI	P (effect)	Q	I^2	P (het)
Treatment duration	SBP	<12 months	11	882	0.767	[0.629, 0.905]	0.000	16.82	40.5 %	0.078
		≥12 months	1	120	–	–	–	–	–	–
Treatment duration	24h SBP	<12 months	2	184	0.665	[0.368, 0.962]	0.000	0.03	0.00 %	0.858
		≥12 months	1	120	–	–	–	–	–	–
Treatment duration	nSBP	<12 months	2	184	0.595	[0.299, 0.890]	0.000	0.00	0.00 %	0.957
		≥12 months	1	120	–	–	–	–	–	–

SBP was analyzed according to different criteria of treatment duration. P (effect) evaluated the overall effect; I^2 and P (het) were calculated to assess heterogeneity.

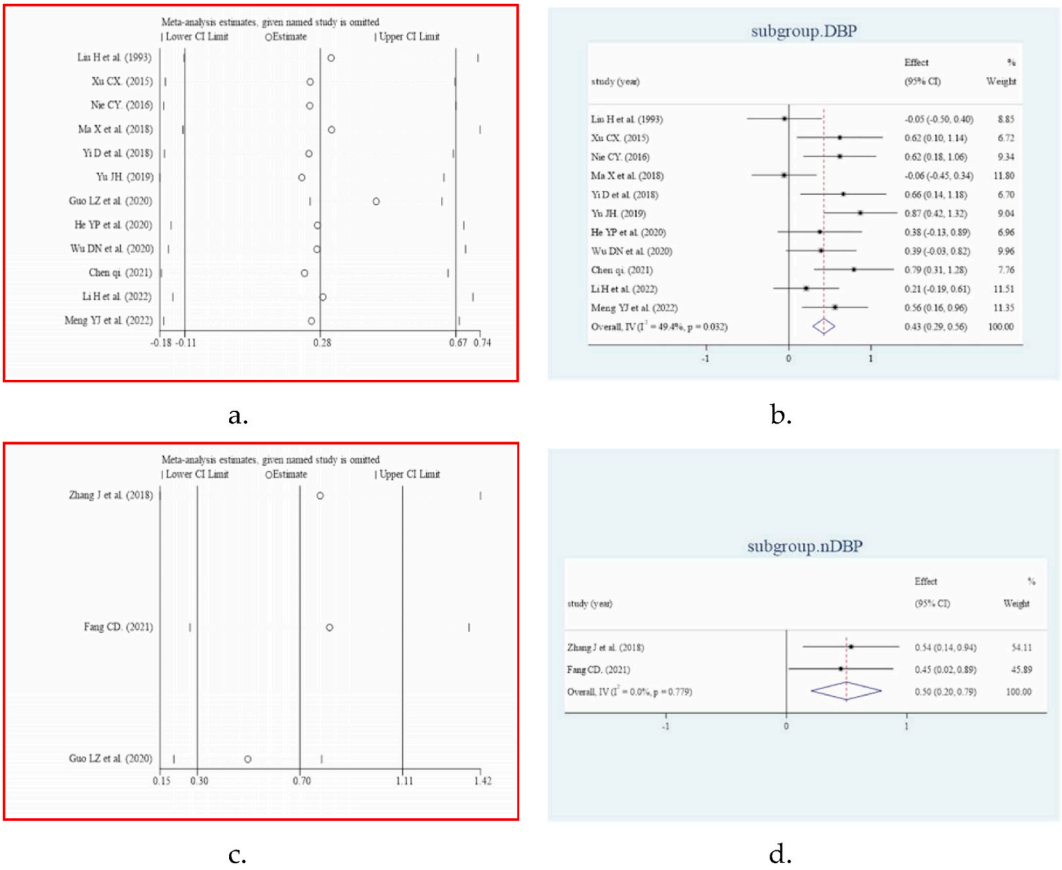

Fig. 8. Subgroup and sensitivity analysis for DBP

Table 4
Subgroup and sensitivity analysis of DBP.

	Item	Group	No. of studies	No. of participants	MD	95 % CI	P (effect)	Q	I^2	P (het)
Treatment duration	DBP	<12 months	11	882	0.427	[0.292, 0.561]	0.000	19.76	49.4 %	0.032
		≥12 months	1	120	–	–	–	–	–	–
Treatment duration	nDBP	<12 months	2	184	0.497	[0.204, 0.791]	0.001	0.08	0.00 %	0.779
		≥12 months	1	120	–	–	–	–	–	–

DBP was analyzed according to different criteria of treatment duration. P (effect) evaluated the overall effect; I^2 and P (het) were calculated to assess heterogeneity.

3.1.4.12. NIHSS. Three RCTs involving 240 patients compared the efficacy of BYHWD alone or that in combination with antihypertensive drugs and antihypertensive drugs alone on NIHSS. Heterogeneity tests showed high heterogeneity (Cochrane Q test = 21.43, p = 0.000, I^2 = 90.7 %); therefore, a random effects model was used. The results showed that the experimental group did better (MD: 1.311; 95 % CI: 0.363, 2.259; p = 0.007) (Fig. 6d).

3.1.4.13. AE. Two RCTs reported AEs, and the difference in the incidence of AEs between the two groups was not statistically significant (OR = 1.232; 95 % CI: 0.346–4.385; p = 0.748) or heterogeneous (Cochrane Q test = 0.03, p = 0.870, I^2 = 0 %) (Fig. 6e). Adverse reactions were generally mild and included dizziness, nausea and constipation.

3.1.5. Subgroup and Sensitivity Analysis

Subgroup and sensitivity analysis suggested that long intervention times and inconsistent doses of antihypertensive drugs may be the potential causes of heterogeneity.

3.1.5.1. SBP. One study was the main source of heterogeneity in the sensitivity analysis [37] (Fig. 7a). One study [37] had a treatment duration of 12 months, and the remaining studies had treatment duration of 2 weeks–3 months. Subgroup analysis differentiated by

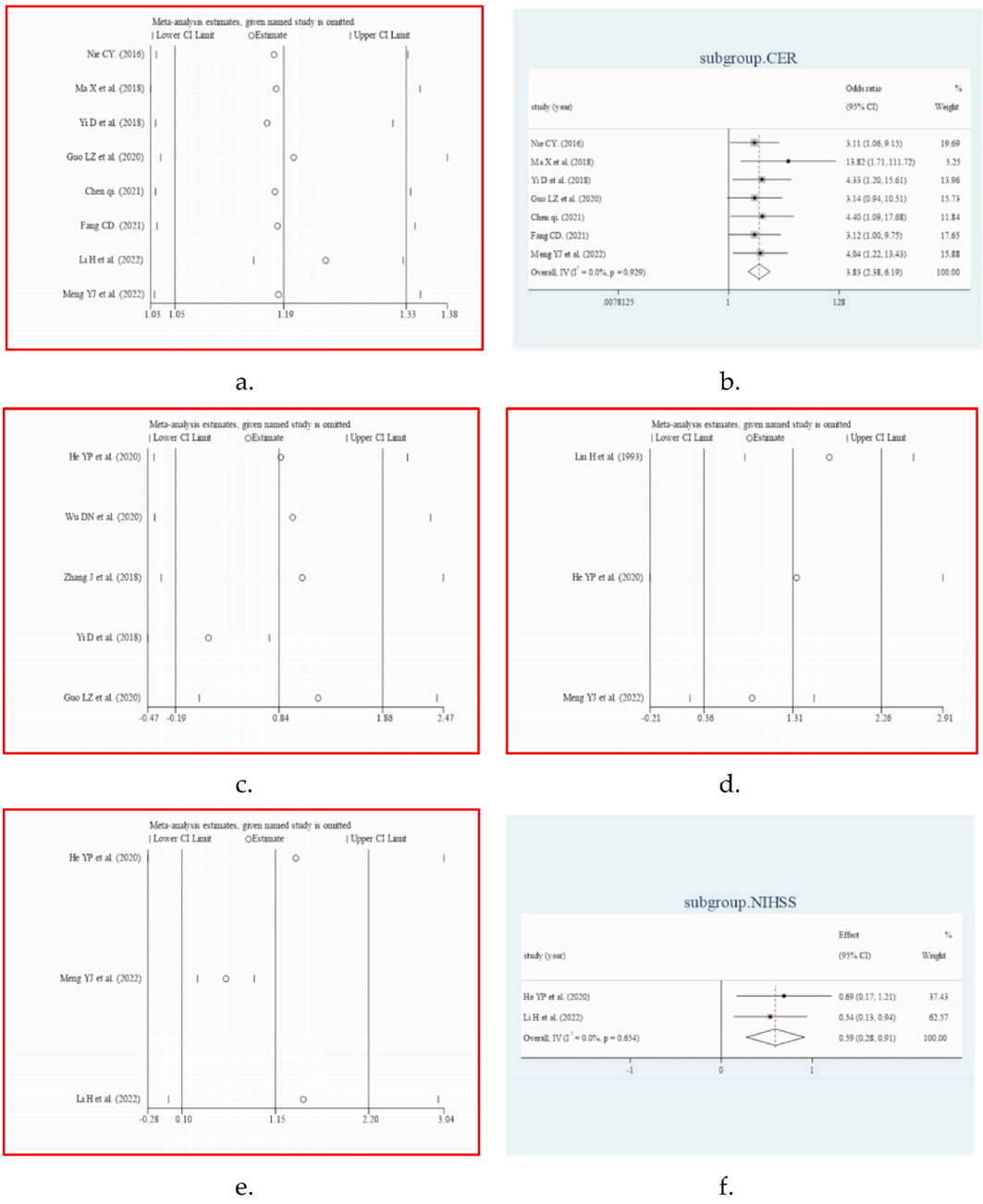

Fig. 9. Subgroup and sensitivity analysis for CER, HCY, PV, NIHSS.

Table 5
Subgroup and sensitivity analysis of CER, NIHSS.

	Item	Group	No. of studies	No. of participants	MD/OR	95 % CI	P (effect)	Q	I^2	P (het)
Uniform dose	CER	Uniform	7	618	1.237	[1.150, 1.330]	0.000	2.47	0.00 %	0.872
		Not uniform	1	98	–	–	–	–	–	–
–	NIHSS	–	2	158	0.594	[0.275, 0.913]	0.000	0.20	0.00 %	0.654
		–	1	100	–	–	–	–	–	–

CER were analyzed according to whether the dose was strictly uniform. P (effect) evaluated the overall effect; I^2 and P (het) were calculated to assess heterogeneity.

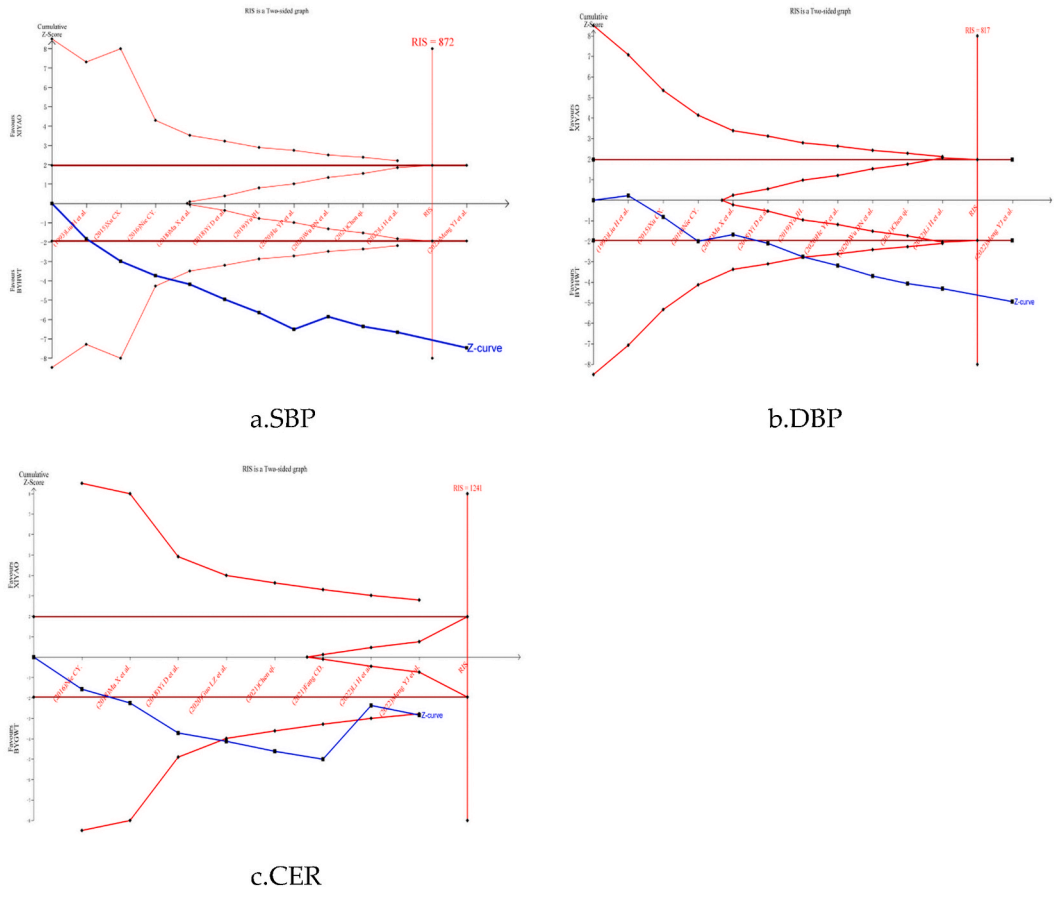

Fig. 10. TSA

treatment duration showed low heterogeneity (Cochrane Q test = 16.82, $p = 0.078$, $I^2 = 40.5$ %); therefore, a fixed-effects model was used. The results showed that SBP was significantly lower in the experimental compared to the control group (MD: 0.767; 95 % CI: 0.629, 0.905; $p = 0.000$) (Fig. 7b, Table 3).

3.1.5.2. 24h SBP. One study was the main source of heterogeneity in the sensitivity analysis was from one study [37] (Fig. 7c). One study [37] had a treatment duration of 12 months, and the remaining studies administered treatment for 4 weeks. Subgroup analysis differentiated by treatment duration showed no heterogeneity (Cochrane Q test = 0.03, $p = 0.858$, $I^2 = 0.00$ %); therefore, a fixed-effects model was used. The results showed that the experimental group did better (MD: 0.665; 95 % CI: 0.368, 0.962; $p = 0.000$) (Fig. 7d, Table 3).

3.1.5.3. nSBP. One study was the main source of heterogeneity in the sensitivity analysis was one study [37] (Fig. 7e). One study [37] had a treatment duration of 12 months, and the remaining [37]studies administered treatment for 4 weeks. Subgroup analysis differentiated by treatment duration showed no heterogeneity (Cochrane Q test = 0.00, $p = 0.957$, $I^2 = 0.00$ %); therefore, a fixed-effects model was used. The results showed that the experimental group did better (MD: 0.595; 95 % CI: 0.299, 0.890; $p = 0.000$) (Fig. 7f, Table 3).

3.1.5.4. DBP. One study was the main source of heterogeneity in the sensitivity analysis was one study [37] (Fig. 8a). One study [37] had a treatment duration of 12 months, whereas the remaining studies had a treatment duration of 2 weeks–3 months. Subgroup analysis differentiated by treatment duration showed low heterogeneity (Cochrane Q test = 19.76, $p = 0.032$, $I^2 = 49.4$ %); therefore, a fixed-effects model was used. The results showed that DBP was significantly reduced in the experimental compared to the control group (MD: 0.427; 95 % CI: 0.292, 0.561; $p = 0.000$) (Fig. 8b, Table 4).

3.1.5.5. nDBP. One study was the main source of heterogeneity in the sensitivity analysis was one study [37] (Fig. 8c). One study [37] administered treatment for 12 months, and the remaining studies administered treatment for 4 weeks. Subgroup analysis differentiated by treatment duration showed no heterogeneity (Cochrane Q test = 0.08, $p = 0.779$, $I^2 = 0.00$ %); therefore, a fixed-effects model was

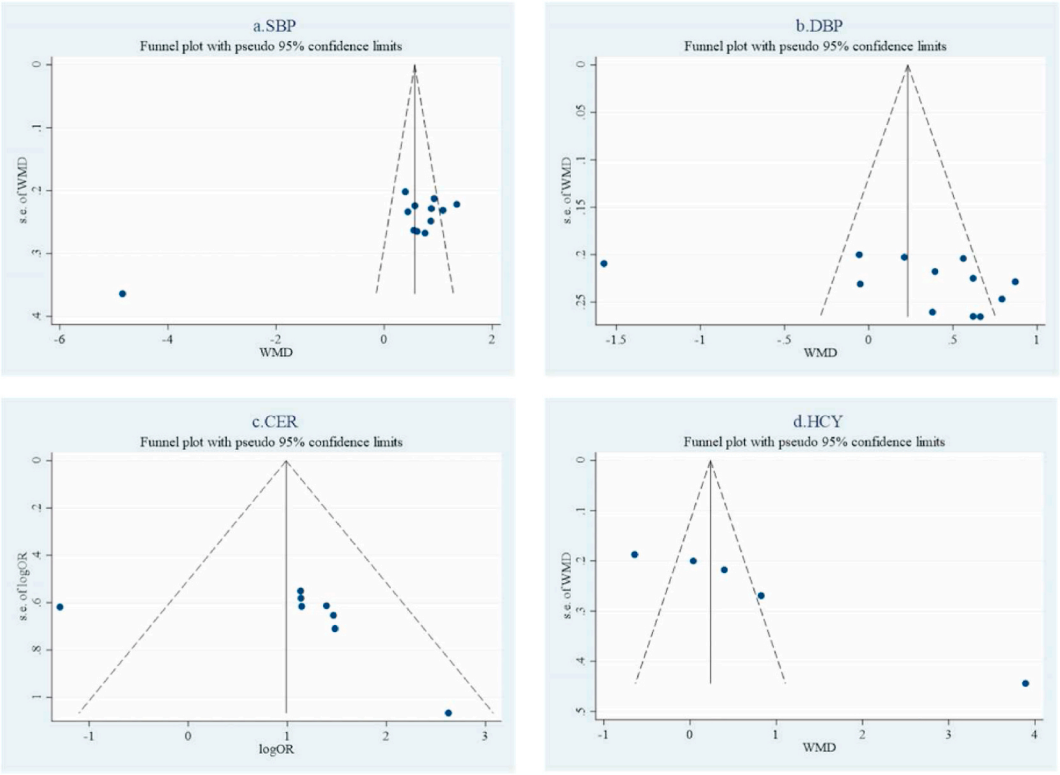

Fig. 11. Publication bias analysis.

used. The results showed that the experimental group did better (MD: 0.497; 95 % CI: 0.204, 0.791; $p = 0.001$) (Fig. 8d, Table 4).

3.1.5.6. CER. One study was the main source of heterogeneity in the sensitivity analysis [[41] (Fig. 9a). One study [41] administered basal medication given in the range of 5–10 mg, depending on blood pressure, and the remaining studies administered uniform doses of basal medication. Subgroup analysis differentiated by whether the dosing was strictly uniform showed no heterogeneity (Cochrane Q test = 2.47, $p = 0.872$, $I^2 = 0.00$ %); therefore, a fixed-effects model was used. The results showed that the CER of the experimental group was significantly higher than that of the control group (OR = 1.237; 95 % CI: 1.150, 1.330; $p = 0.000$) (Fig. 9b, Table 5).

3.1.5.7. HCY. One study was the main source of heterogeneity in the sensitivity analysis [35] (Fig. 9c), but there was also some heterogeneity among the other studies. Heterogeneity did not decrease significantly when studies were excluded individually excluded.

3.1.5.8. PV. One study was the main source of heterogeneity in the sensitivity analysis [42] (Fig. 9d); however there was also high heterogeneity among the other studies.

3.1.5.9. NIHSS. One study was the main source of heterogeneity in the sensitivity analysis [42] (Fig. 9e); however the reason for this remains unclear. When this study was excluded from the subgroup analysis, the results showed no heterogeneity (Cochrane Q test = 0.20, $p = 0.654$, $I^2 = 0.00$ %). Therefore, we used a fixed-effects model in this sensitivity analysis. The results showed that the experimental group did better (MD: 0.594; 95 % CI: 0.275–0.913; $p = 0.000$) (Fig. 9f, Table 5).

3.1.6. TSA

One study [37] was significantly heterogeneous, and this severely affected the accuracy of the SBP and DBP outcomes. Therefore, TSA was performed after excluding this study, as shown in Fig. 10a and b. The Z-curve crossed the conventional boundary, TSA and RIS, revealing that the observation group performed better than the control group, and that the results were reliable. In addition, the Z-curve crossed the conventional boundary, intersecting the TSA but not crossing the RIS, suggesting that the observation group was more effective in terms of CER values than the control group (Fig. 10c). However, further validation through additional trials is required to reach statistically significant conclusions.

Table 6
Grading the **level of** evidence profiles.

	Certaintyassessment							Noofpatients		Effect		Certainty	Importance
Outcomes	No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BYHWD	Control	Relative (95 % CI)	Absolute (95 % CI)		
SBP	12	randomized trials	serious▲	serious	not serious	not serious	publication bias suspected	514	488		MD:0.321 95 % CI: 0.321,0.964	⨁◯◯◯VERY LOW	CRITICAL
24h SBP	3	randomized trials	serious▲	serious	not serious	not serious	none	151	153		MD:1.520 lower 95 % CI: 0.011,3.052	⨁⨁◯◯LOW	CRITICAL
dSBP	3	randomized trials	serious▲	serious	not serious	not serious	none	151	153		MD:0.625 95 % CI:0.395,0.855	⨁⨁◯◯LOW	CRITICAL
nSBP	3	randomized trials	serious▲	serious	not serious	not serious	none	151	153		MD:0.859 95 % CI:0.340,1.377	⨁⨁◯◯LOW	CRITICAL
DBP	12	randomized trials	serious▲	serious	not serious	not serious	none	514	488		MD:0.280 95 % CI: 0.112,0.671	⨁⨁◯◯LOW	CRITICAL
24h DBP	3	randomized trials	serious▲	serious	not serious	not serious	none	151	153		MD:0.547 95 % CI:0.318,0.777	⨁⨁◯◯LOW	CRITICAL
dDBP	3	randomized trials	serious▲	serious	not serious	not serious	none	151	153		MD:0.632 95 % CI:0.401,0.862	⨁⨁◯◯LOW	CRITICAL
nDBP	3	randomized trials	serious▲	serious	not serious	not serious	none	151	153		MD:0.704 95 % CI:0.297,1.112	⨁⨁◯◯LOW	CRITICAL
CER	8	randomized trials	serious▲	serious	not serious	not serious	none	319/358 (89.11 %)	270/358 (75.42 %)	OR = 2.848 95 % CI:1.388,5.843	OR = 2.848 95 % CI:1.388,5.843	⨁⨁◯◯LOW	IMPORTANT
HCY	5	randomized trials	serious▲	serious	not serious	not serious	publication bias suspected	213	213		MD:0.837 95%CI: 0.190,1.863	⨁◯◯◯VERY LOW	IMPORTANT
PV	3	randomized trials	serious▲	serious	not serious	not serious	none	130	110		MD:1.311 95% CI:0.363,2.259	⨁⨁◯◯LOW	IMPORTANT
NIHSS	3	randomized trials	serious▲	serious	not serious	not serious	none	129	129		MD:1.149 95 % CI:0.100,2.199	⨁⨁◯◯LOW	IMPORTANT
AE	2	randomized trials	serious▲	not serious	not serious	not serious	none	6/80 (7.5 %)	5/80 (6.25 %)	OR = 1.232 95 % CI:0.346,4.385	OR = 1.232 95 % CI:0.346,4.385	⨁⨁⨁◯Moderate	IMPORTANT

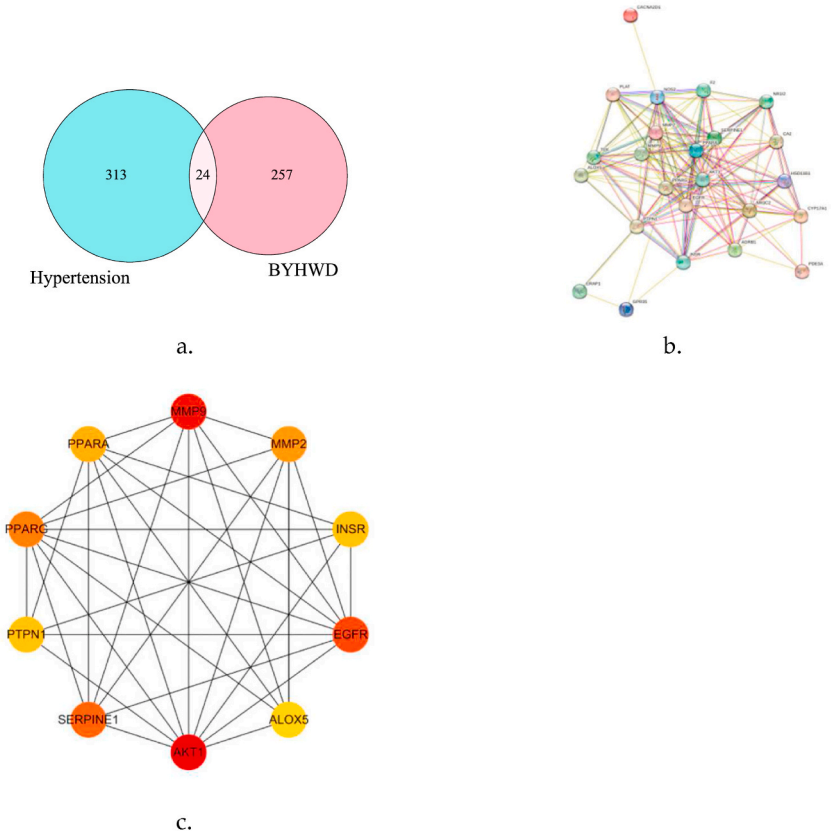

Fig. 12. Key gene target screening and protein interaction analysis.

Table 7
BYHWD-hypertension key gene targets.

Ordinal	Gene symbol	Importance
1	AKT1	Critical
2	MMP9	Critical
3	EGFR	Critical
4	PPARG	Critical
5	SERPINE1	Critical
6	PTPN1	Critical
7	PPARA	Critical
8	MMP2	Critical
9	INSR	Critical
10	ALOX5	Critical
11	NR3C2	Important
12	NOS2	Important
13	CACNA2D1	Important
14	TEK	Important
15	PLAT	Important
16	GPR35	Important
17	CA2	Important
18	ERAP1	Important
19	CYP17A1	Important
20	ADRB1	Important
21	F2	Important
22	HSD11B1	Important
23	NR1I2	Important
24	PDE3A	Important

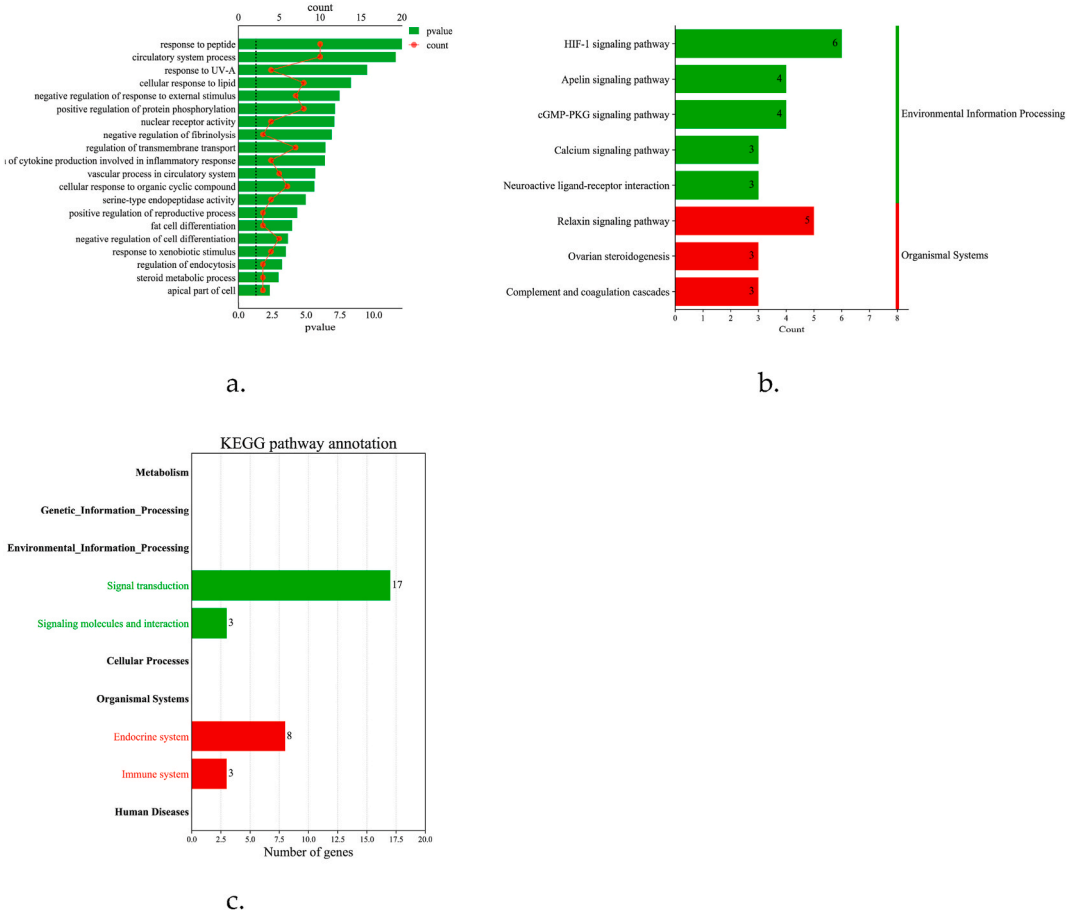

Fig. 13. GO and KEGG enrichment analysis.

3.1.7. Publication bias

Funnel plots and statistical tests showed no publication bias in these RCTs in terms of DBP (Egger's test, $p = 0.194$) or CER (Egger's test, $p = 0.364$). However, there was significant publication bias in terms of SBP (Egger's test, $p = 0.005$) and HCY (Egger's test, $p = 0.005$) (Fig. 11a–d).

3.1.8. Quality of evidence

The quality of evidence for AE was rated as "moderate"; it was "low" for 24 h SBP, dSBP, nSBP, DBP, 24 h DBP, dDBP, nDBP, CER, PV, and NIHSS; it was "very low" for SBP and HCY (Table 6).

BYHWD: Buyang Huanwu decoction; SBP: systolic blood pressure; 24 h SBP: 24-h systolic blood pressure; dSBP: daytime systolic blood pressure; nSBP: nighttime systolic blood pressure; DBP: diastolic blood pressure; 24 h DBP: 24-h diastolic blood pressure; dDBP: daytime diastolic blood pressure; nDBP: nighttime diastolic blood pressure; CER: clinical effectiveness rate; HCY: homocysteine; PV: plasma viscosity; NIHSS: neurological function score; AE: adverse effect.

▲.Poor methodological quality.

3.2. Network pharmacology

3.2.1. Key gene targets screening and protein interactions analysis

The intersection of 281 targets for BYHWD and 337 targets for hypertension revealed 24 key repeat targets (Fig. 12a and Table 7). PPI of key targets was conducted using the STRING database; 24 nodes with 147 edges were obtained, with an average node degree of 12.2, p < 1.0e-16 that was statistically significant. The STRING database analysis was carried out by linking each protein to the association degree, with each circular node representing a protein, the associated nodes connected to each other by connecting lines, and the straight lines of different colours representing different types of actions in different modes of action [45]. The top ten nodes were

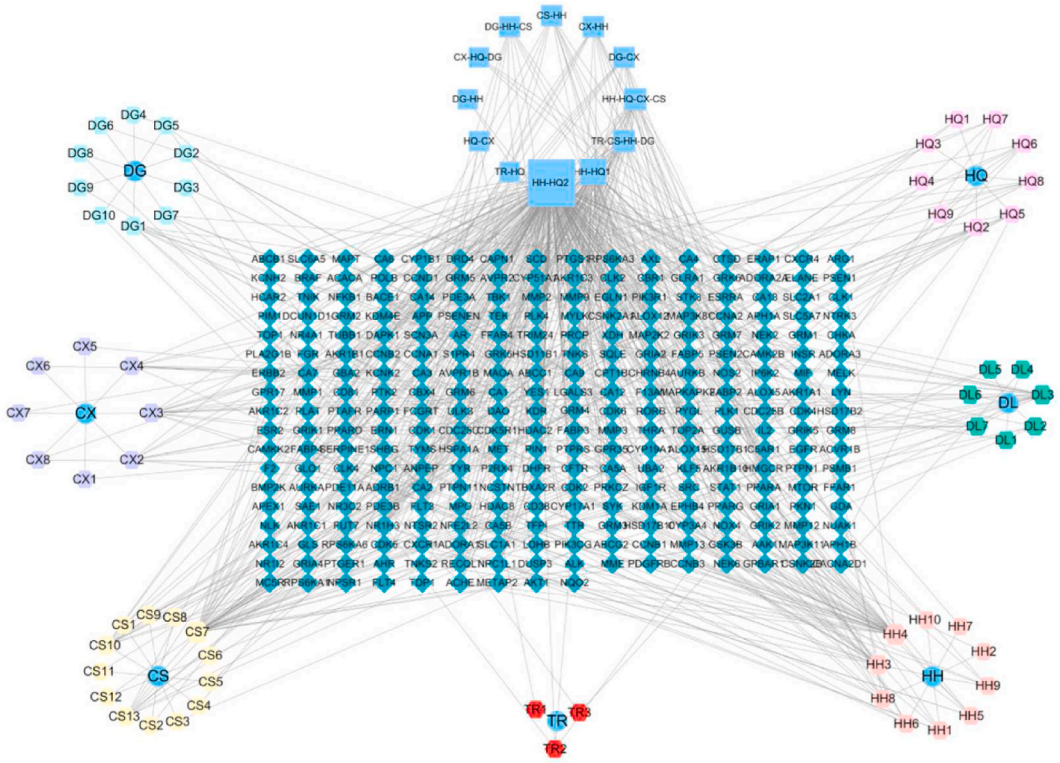

Fig. 14. Effective Active Compound-Target Network of BYHWD Drawing note.

Table 8
Molecular docking results of core targets and leading active ingredients.

Active ingredient	Target protein	Protein data bank ID	Score (kcal · mol-1)
quercetin	AKT1	3mvh	−2.37
quercetin	MMP9	4h1q	−2.65
quercetin	EGFR	1m14	−2.36
quercetin	PPARG	6md0	−1.77
quercetin	SERPINE1	4dte	−1.20
quercetin	PTPN1	1q6n	−1.46
quercetin	PPARA	5hyk	−1.83
quercetin	MMP2	1ks0	−3.38
quercetin	INSR	2hr7	−1.71
quercetin	ALOX5	3v98	−2.36

AKT1, MMP9, EGFR, PPARG, SERPINE1, PTPN1, PPARA, MMP2, INSR, and ALOX5, and these are presumed to be the key regulators of hypertension and play important roles in BYHWD treatment (Fig. 12b, 12c and Table 7).

3.2.2. Go and KEGG analysis

Using the Metascape platform, GO functional analysis was carried out to enrich cross targets from three aspects, namely molecular function, biological process and cell composition. The top 20 sites with the highest enrichment values were identified (Fig. 13a). The top eight signalling pathways and their classifications were obtained using KEGG pathway analysis(Fig. 13b and 13c).

3.2.3. Active ingredient prediction target network

BYHWD displays a good antihypertensive effect through a variety of active ingredients and targets. The network diagram shown below reveals the mechanism of its action (Fig. 14). The larger the graph, the more likely it is that a compound is a key compound. The results showed that compound HH-HQ2(quercetin) had the highest number of targets, and this value was much higher than that of the

second compound, HH-HQ1(kaempferol), suggesting that quercetin may be the key active ingredient in BYHWD intervention in hypertension.

Code	Compound	Code	Compound	Code	Compound
DG1	Ferulic acid	TR2	campesterol	HH8	Linolenic Acid
DG2	Umbelliferone	TR3	hederagenin	HH9	Stearic Acid
DG3	Scopoletin	DL1	Tubulin	HH10	4-dione
DG4	Carvacrol	DL2	xanthine	HQ1	4-Hydroxycoumarin
DG5	Anisic Acid	DL3	Glutamic acid	HQ2	Cetylic Acid
DG6	Succinic Acid	DL4	phenylalanine	HQ3	3-Hydroxycoumarin
DG7	Phenol	DL5	Cholesterol	HQ4	Folic Acid
DG8	Guaiacol	DL6	Platelet activating factor	HQ5	Astramembrannin Ii
DG9	Nicotinic Acid	DL7	Heptadecanoic acid	HQ6	Mairin
DG10	P-Cresol	CX1	FA	HQ7	phenanthren-3-ol
CS1	Spinasterol	CX2	3-O-trans ferulylquinic acid	HQ8	isorhamnetin
CS2	stigmast-7-en-3-ol	CX3	Caffeic Acid	HQ9	formononetin
CS3	campest-5-en-3beta-ol	CX4	3,4-Dihydroxybenzoic Acid	CX-HH	Linoleic Acid
CS4	campest-5-en-4beta-ol	CX5	Butylphthalide	HQ-CX	Folic Acid
CS5	campest-5-en-5beta-ol	CX6	3-Butyl-Phthalide	DG-CX	Palmitic Acid
CS6	campest-5-en-6beta-ol	CX7	Chrysophanol	CS-HH	baicalein
CS7	ellagic acid	CX8	Neochlorogenic acid	HH-HQ1	kaempferol
CS8	Benzoic Acid	HH1	poriferast-5-en-3beta-ol	HH-HQ2	quercetin
CS9	Salicylic Acid	HH2	6-Hydroxykaempferol	DG-HH	Myristic Acid
CS10	Gallic Acid	HH3	quercetagetin	TR-HQ	hederagenin
CS11	Progallin A	HH4	luteolin	CX-HQ-DG	Choline
CS12	Methylgallate	HH5	Sitosterol	DG–HH–CS	Stigmasterol
CS13	naringenin	HH6	Hexadecanoic Acid	HH-HQ-CX-CS	sitosterol
TR1	Sitosterol alpha1	HH7	Lauric Acid	TR–CS–HH-DG	beta-sitosterol

3.2.4. Molecular docking validation

The docking of quercetin with the above 10 proteins that are targets of BYHWD was carried out. The lower the docking score, the more stable the binding. The core active compound quercetin in BYHWD had an average docking score of −2.11 kcal · mol-1 with the key target protein (MMP2), indicating that quercetin has a high binding affinity to this protein (Table 8). MMP2 binds quercetin stably with a docking score of −3.38 kcal · mol-1 that is mainly mediated by the amino acid CYS - 28 at the active site (Fig. 15).

4. Discussion

Fourteen RCTs involving 1,186 subjects were included in this meta-analysis. The results showed that BYHWD improved blood pressure, CER, PV, and NIHSS scores, with no obvious AEs. In addition, patients who received the BYHWD intervention did not exhibit a higher incidence of AEs. However, BYHWD had no significant effect on the SBP, 24 h SBP, DBP, or HCY levels.

The effectiveness of BYHWD in regulating hypertension was reported in all RCTs included in this study. In terms of SBP, 24 h SBP, nSBP, DBP, and nDBP, sensitivity analyses revealed that heterogeneity came mainly from one study [37]. Subgroup analyses differentiated by duration of treatment showed that BYHWD alone or in combination with antihypertensive agents compared to antihypertensive agents alone reduced SBP, 24 h SBP, nSBP, DBP, and nDBP by 0.767, 0.665, 0.595, 0.427 and 0.497 mmHg, respectively, with statistically significant differences, along with significantly lower heterogeneity. Thus, the source of heterogeneity may be the length of the intervention time; taking too long may result in negative results for SBP, 24 h SBP, and DBP. In terms of the CER, the

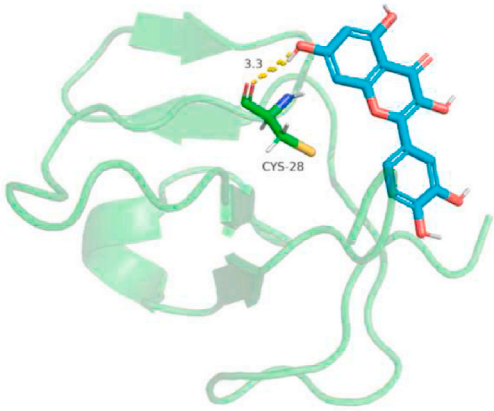

Fig. 15. Schematic showing the docking of MMP2 and Quercetin.

sensitivity analysis attributed the heterogeneity to one study [41]. Subgroup analysis differentiated by whether the dose used was strictly uniform showed significantly lower heterogeneity (Cochrane Q test = 2.47, $p = 0.872$, $I^2 = 0.0$ %) based on significantly higher CER (OR = 1.237) of BYHWD in combination with antihypertensive drugs for hypertension therapy compared with antihypertensive drugs alone. Thus, we concluded that the source of heterogeneity may be whether the dose was strictly uniform. Notably, the most prominent heterogeneity in sensitivity analysis was in one study [35], but the heterogeneity did not decrease after the elimination of each trial, and the HCY levels were not significantly improved by BYHWD. For PV indicators, the most prominent heterogeneity in sensitivity analysis was in one study [42], but the heterogeneity did not decrease after the elimination of each trial. For NIHSS indicators, the most prominent heterogeneity in sensitivity analysis was in one study [42], and after its exclusion, NIHSS scores for BYHWD combined with antihypertensive drugs compared to antihypertensive drugs alone were significantly lower (0.594) based on zero heterogeneity (Cochrane Q test = 0.20, $p = 0.654$, $I^2 = 0.0$ %). Thus, using BYHWD as a medicinal porridge to be taken alone or in combination with anti-hypertensive drugs may be a new direction for healthcare choices in the future for patients with hypertension who are not sensitive to anti-hypertensive drug therapy. Moreover, those who cannot tolerate conventional anti-hypertensive drugs or prefer dietary therapy may benefit significantly. In addition, many studies have reported that BYHWD has a marked interventional effect on hypertension-induced stroke. Hypertension and PV abnormalities can trigger the formation of atherosclerotic plaques that are the pathological basis of brain infarction episodes [46–48]. Similarly, our meta-analysis found that BYHWD significantly reduced PV and NIHSS scores, consistent with a previous study [49] showing that BYHWD has a preventive as well as controlling effect on cerebral infarction while lowering blood pressure. Therefore, BYHWD may come to be the first-choice treatment option for the simultaneous reduction of blood pressure and the risk of cerebral infarction in patients with hypertension and abnormal PV. BYHWD also has certain advantages in the treatment of cerebral haemorrhage caused by hypertension. Hypertensive cerebral haemorrhage is mainly due to high blood pressure and other factors affecting the small cerebral arteries that form a small aneurysm or entrapment artery, that ruptures and bleeds in the case of strenuous activities or emotional excitement. Previous meta-analysis results have shown [50] that BYHWD can reduce NIHSS scores and improve neurological functionthat is consistent with our meta-analysis results, confirming the efficacy of BYHWD in treating hypertensive complications and providing ideas for the clinical use of TCM in prevention and treatment.

Both the BYHWD-treated and control groups demonstrated good tolerability. Two of the 14 RCTs documented mild AEs in 11 patients.

The concept of medicine food homology has a long history of use in China [51]. Recently, food products with medicinal properties have attracted increasing attention. These products have great potential for applications in medicine, food, and healthcare products [52]. Importantly, people have attached greater importance to physical health that has been accompanied by the availability of an increasing number of products with medicine food homology. Many of these enter the lives of people incrementally in the form of tea, porridge, soup, and healthy meals. In TCM theory, food is conceptualised in terms of both nutrition and function, and can be used to treat diseases [53]. In terms of hypertension control, the traditional Chinese medicine diet is based on a light diet, a balance between the “hot” and “cold” nature of food, the harmony of the five tastes of food, and the consistency of dietary intake for treating different health conditions [54]. Studies have shown that medicinal foods can enhance sleep quality, improve energy and stamina, and effectively relieve symptoms such as dizziness and lightheadedness in patients with high blood pressure [55]. Therefore, as a traditional dietary therapy with a long history, BYHWD can be included in the daily diet to prevent and control hypertension and stroke, and improve the well-being of hypertensive patients.

The interactions between products of medicine food homology and the human body is a complex system involving multiple molecular targets and mechanisms. Therefore, it is difficult to elucidate specific components and mechanisms of action [56]. Cyberpharmacology is an emerging discipline based on systems biology theory that involves systematically and comprehensively deciphering the associations between the products of medicine food homology, targets, and diseasess [57].

First, the central targets have been identified by using the PPI network. AKT1, MMP9, EGFR, PPARG, SERPINE1, PTPN1, PPARA, MMP2, INSR, and ALOX5 may play critical roles in the antihypertensive effect of BYHWD. In the early stages of hypertensive cardiac fibrotic disease, AKT1 activity increases in cardiac tissue, that may mediate the inflammatory response by promoting macrophage-induced fibroblast trans-differentiation that contributes to hypertension-induced myocardial fibrosis [58]. MMP-9, as a major degrading enzyme of the ECM, directly affects vascular smooth muscle cell morphology and function by regulating the synthesis and degradation of matrix collagen components and is an important marker of hypertension [59]. *Trans*-activation of EGFR can cause the release of inflammatory mediators and affect vascular metabolism, thereby, participating in the development of hypertension [60]. Interactions between four positive association loci of PPARG and AGTR1 genes had significant effects on essential hypertension [61].

Furthermore, the biological processes and signalling pathways involved in 24 intersection targets were analysed using enrichment analysis. Multiple canonical biological processes were found to be closely associated with hypertension, such as “apical part of cell,” “circulatory system process,” “response to UV-A,” “nuclear receptor activity,” and “apical part of cell.” The KEGG enrichment analysis revealed that the signalling pathways that play crucial roles in BYHWD include “HIF-1,” “Apelin,” “cGMP-PKG,” “Calcium,” “Neuroactive ligand-receptor interaction,” “Complement and coagulation cascades,” “Relaxin,” and “Ovarian steroidogenesis.” One study showed that HIF1-α is involved in cellular metabolic processes [62], leading to the abnormal expression of genes related to blood viscosity [63] and regulation of vascular endothelial function [64], and that the above processes may be involved in the development of hypertension. Apelin may regulate hypertension through a combination of inflammatory factors, micronutrients and oxidative stress pathways [65]. Abnormal regulation of the NO-cGMP-PKG axis can cause inflammation, thrombosis, and pulmonary vasoconstriction, ultimately leading to hypertension [66]. Excessive, calcium intake can regulate blood pressure by affecting the renin-angiotensin-aldosterone system (RAAS) [67]. Relaxin inhibits vasoconstrictive substances such as ET-1 and Ang II, while increasing vascular endothelial MMP activity that produces vasodilatory effects by degrading ET-1 released from endothelial cells, activating endothelin B-type receptors, and inducing the endothelial release of NO [68]. Relaxin may also improve

hypertension-induced endothelial dysfunction by increasing NO-dependent relaxation and decreasing endothelium-dependent contractions [69]. In conclusion, the potential mechanism of BYHWD regulation of hypertension may be a multi-targeted and multi-pathway mode of action.

Third, the results of the BYHWD active ingredient prediction target network showed that HH-HQ2 (quercetin) was connected to more targets than the other compounds. It is a compound found in safflower and astragalus. These results are similar to those reported in a previous study where quercetin combined with conventional blood pressure medications significantly reduced NO, IL-1, and lipid levels, thereby reducing the risk of hypertension [70]. Several studies have revealed that quercetin exhibits free radical-scavenging properties [71,72]; therefore, it is a well-established antioxidant that can potentially be used for the prevention and treatment of cardiovascular diseases. Quercetin was shown to improve SBP and DBP in seven clinical trials (587 patients) [73–79] in a meta-analysis [80]. The results of that review are consistent with those of the present study. Subsequently, molecular docking of quercetin with each of the top 10 key targets of BYHWD for the regulation of hypertension showed that quercetin interacted mainly with the amino acid residues of CYS - 28 at the active site of MMP2.

These results suggest that quercetin is one of the most important components of BYHWD. AKT1 is centrally located in the PPI network. KEGG analysis showed that the "HIF-1 pathway" had the largest number of BYHWD targets. Based on the above experimental results, we speculate that AKT1 may be a critical core targets and that the HIF-1 pathway may be a crucial signalling pathway through which BYHWD exerts its effects on hypertension. BYHWD has a clear curative effect in the treatment of hypertension, has important applications value in medicine, food, and health products and has great potential for development and utilisation. In the future, it will be necessary to further increase the publicity of products of medicine food homology in the treatment of hypertension worldwide, pay attention to the popularisation of personal health, and strive to develop products of medicine food homology.

The strengths of this study are as follows. Only RCTs related to BYHWD for hypertension have been previously conducted, and no systematic meta-analysis or network pharmacology exploration has been performed. This systematic review incorporated RCTs and multiple outcome details from a library built to date and provided a more comprehensive assessment of BYHWD treatment for patients with hypertension, further increasing the range of food treatments for hypertension, and providing new ideas for hypertension treatment. Subgroup and sensitivity analyses revealed that studies with long treatment durations and without strict uniformity of dosing may have partially contributed to heterogeneity. In addition, no systematic review has been conducted on TSA; therefore, the reliability and stability of the results obtained are unknown. Based on TSA results, this study showed that in terms of SBP and DBP, the sample size was sufficient, and the results were reliable. In terms of CER, BYHWD had a positive effect, but more trials are needed in the future to further validate of the results. In addition, network pharmacology and molecular docking were carried out by combining traditional medicine with modern bioinformatics, to explore the mechanism of action of BYHWD on hypertension, interpreting the material basis, multi-target, multi-level mechanism of action, and safety of medicinal foods and traditional Chinese medicines. Our meta-analysis will provide a reference for further research, with a view to providing new guidelines for dietary choices in daily life. However, this meta-analysis has some limitations. First, most RCTs provided little information on allocation concealment or blinding, resulting in a low level of evidence. Second, the included RCTs varied in the types of conditioning used. The associated confounding factors were not completely eliminated. Finally, every RCT was conducted in China; therefore generalising the results to other geographic regions requires thorough consideration.

An increasing number of high-quality RCTs have recently emerged showing that some herbs of medicine food homology, such as Astragalus and Radix Codonopsis, have anti-hypertensive effects with a good safety profile [81,82]. These studies provide a paradigm for future studies to investigating the efficacy and safety of BYHWD and other herbal products of homologous origin or traditional medicines for hypertension. First, rigorous design and manipulation are important. Second, well-designed RCTs with adequate sample sizes should be conducted in accordance with the Consolidated Standards for Reporting Trials (CONSORT) guidelines [83]. Finally, the level of evidence for the effect of BYHWD on cardiovascular events in patients with hypertension is relatively low. Therefore, the efficacy and safety of BYHWD in the treatment of hypertension need to be further validated through long-term intervention and follow-up in large-scale, multi-centre, high-quality RCTs. To further optimise the compatibility and dosage of BYHWD, we explored the potential synergistic effect of BYHWD with conventional antihypertensive drugs and developed an innovative administration method and treatment plan. Simultaneously, the micro-mechanism was studied using a multi-dimensional combination of network pharmacology, molecular docking, metabolomics technology and proteomics.

5. Conclusions

This systematic evaluation and meta-analysis of 14 RCTs showed that BYHWD lowered blood pressure (SBP, DBP, 24h SBP, 24h DBP, dSBP, dDBP, nSBP, and nDBP), modulated PV, and restored neurological function but did not show a significant effect on HCY. BYHWD was well-tolerated and safe. Additionally, the network pharmacology results suggested that quercetin may be the dominant active compound in BYHWD. AKT1 plays a potential regulatory role through HIF-1 signalling pathway and may be the key target of BYHWD in the regulation of hypertension. Therefore, BYHWD can be considered as a new resource of medicine food homology to be widely used in the prevention and control of hypertension in daily life.

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Data availability statement

Raw data is available upon request, as detailed in the attached file excel sheet.

Ethics declarations

Review and approval by an ethics committee was not needed for this study because it was conducted on the basis of RCTs that have already received ethical approval. And informed consent was not required for this study because it was conducted on the basis of RCTs where informed consent was obtained.

CRediT authorship contribution statement

Bo Li: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Chang Lu:** Writing – original draft, Investigation, Data curation, Conceptualization. **Yibo Liu:** Supervision. **Xiaodong Wang:** Validation. **Haiqi Fu:** Formal analysis. **Changyi Li:** Software. **Mingjuan Sun:** Data curation. **Yajun Zhang:** Funding acquisition. **Minhui Li:** Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yajun Zhang reports financial support was provided by Inner Mongolia Medical University. Yajun Zhang reports a relationship with Inner Mongolia Medical University that includes: employment. No other influencing factors. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23474.

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