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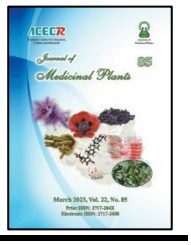

Review Article

Clinical antihypertensive efficacy and safety of Iran plants: a systematic review

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ABSTRACT

Background: Antihypertensive plants are one of the means of hypertension control. **Objective:** To examine the clinical antihypertensive efficacy and safety of the plants found in Iran. **Methods:** PUBMED, MEDLINE, SCOPUS, EMBASE, SCIENCEDIRECT, PROQUEST, OVID, EBSCO, GOOGLE, and GOOGLE SCHOLAR were searched. The PRISMA guideline was observed. The search terms were Iran, Iranian, plant, herb, antihypertensive, hypertension and randomized controlled trial (RCT). English-language articles published until the end of 2022 were included. In-vitro and animal studies, editorials, and reviews were excluded. The methodological quality of the RCTs was evaluated using the JADAD scale. **Results:** Two hundred and eight studies were found. Only 74 of them were eligible. For *Berberis vulgaris* (5 studies), *Nigella sativa* (10 studies), *Allium sativum* (12 studies), *Hibiscus sabdariffa* (11 studies), *Beta vulgaris* L (15 studies), S*olanum lycopersicum* (5 studies), *Cinnamomum verum* (9 studies), *Rhus coriaria* (1 study), *Phyllanthus emblica* (1 study), *Olea europaea* (4 studies), and *Vaccinium arctostaphylos* (3 studies) were found. Most RCTs had high methodological quality and reported efficacy and no side effects. **Conclusion:** While most trials demonstrate antihypertensive efficacy and safety, there are more evidence regarding *Hibiscus sabdariffa*, *Olea europaea*, *Vaccinium arctostaphylos* and *Allium sativum* versus the other plants.

Abbreviations: 2hPPG, 2 hour post-prandial plasma glucose; ABPM, ambulatory blood pressure monitoring; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice a day; BL, base line; BMI, body mass index; BP, blood pressure; BS, blood sugar; BUN, blood urea nitrogen; CBC, complete blood count; CK-MB, creatine kinase-myoglobin binding; Cr, creatinine; CVLT-II, California Verbal Learning Test Second Edition; DBP, diastolic blood pressure; EC, enteric coated; eGFR, estimated glomerular filtration rate; EHTN, essential hypertension; ET, extract; FBS, fasting blood sugar; FID, 4 times a day; HAM, healthy adolescent male; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HDL-C, high density lipoproteins-cholesterol; HR, heart rate; HS, *hibiscus subdariffa*; hs-CRP, high-Sensitivity C-Reactive Protein; LDL, low-density lipoprotein; ICAM-1, intercellular adhesion molecule-1; LDL-C, low density lipoproteins-cholesterol; HTN, hypertension; HCL, hypercholesterolemia; LV, left ventricular; MDA, malondialdehyde; MetS, metabolic syndrome; N/A, not applicable; NS, *nigella sativa*; NS, Not Significant; Po, placebo; RDB, randomized double blind; PAH, Pulmonary arterial hypertension; Pre-DM, pre diabetes mellitus; s-ICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; T2DM, type 2 diabetic mellitus; TID, 3 times a day; SBP, systolic blood pressure; NAFLD, non-alcoholic fatty liver disease; NHV, Normal healthy volunteer; OLE, olive leaf extract; RCT, randomized controlled trial; SBP, systolic blood pressure; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; STAI, State-Trait Anxiety Inventory; TC, total cholesterol; TDS, three times a day; TE, tomato extract; TG, triglycerides; TNF-*α*, tumor necrosis factor alpha; Tsp, tea spoonful; UHTN, uncontrolled hypertension.

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1. Introduction

Hypertension is a prevalent condition categorized into two types: essential hypertension and secondary hypertension. Essential and secondary hypertensions respectively constitute 90-95 % and 5-10 % of the hypertensive cases [1, 2]. Uncontrolled hypertension leads to cardiovascular complications such as stroke, myocardial infarction, nephropathy, and retinopathy. Hypertension is the leading cause of morbidity and mortality. It is usually defined as SBP (systolic blood pressure) ≥ 140 mm Hg and DBP (diastolic BP) ≥ 90 mm Hg [1, 3]. Normal BP is defined as SBP < 120 mm Hg and DBP < 80 mm Hg. Every 20/10 mm Hg increase of BP above 115/75 mm Hg is associated with a doubling of the risk of cardiovascular diseases (CVD). The target of 120/80 mm Hg is more beneficial than the previous goal of 140/90 mm Hg in hypertension control [4]. There are around 1.4 billion hypertensive adults in the world, but the BP of less than 14 % is controlled with antihypertensive pharmacotherapy to a SBP/DBP < 140/90 mm Hg [5, 6]. One of the main causes of inadequate BP control is limited efficacy and safety profiles of the conventional antihypertensive drugs, which necessitates alteration of drug regimen or combination therapy [7, 8]. More than one-half of the patients need two or more antihypertensive drugs to achieve the goal BP [9]. Antihypertensive plants can be used as alternative or complementary therapies to conventional antihypertensive drugs [10]. Some plants found in Iran may have antihypertensive effects. This review aims to evaluate the clinical antihypertensive efficacy and safety of the plants existing in Iran.

2. Materials and Methods

2.1. Method of search and assessment of trial quality

This systematic review was conducted in accordance with the Preferred Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The terms Iran, Iranian, plant, herb, antihypertensive, hypertension, randomized controlled trial (RCT) were searched in the databases PubMed, Medline, Scopus, Embase, ScienceDirect, ProQuest, Ovid, Ebsco, Google, and Google Scholar. References from relevant articles were searched manually. Also, the methodological quality of the trials was evaluated by the JADAD scale as described previously [11].

2.2. Eligibility of the articles

RCTs in the English language studying the antihypertensive efficacy and safety of the plants found in Iran were eligible. The articles published until the end of the year 2022 were included. Reviews, editorials and animal and in vitro studies were excluded.

2.3. Selection of articles

The authors independently screened the retrieved articles and resolved differences through discussion. The titles, abstracts and full texts of the retrieved articles were assessed.

2.4. Collation of data

The process of data collation is depicted in the PRISMA flow diagram (Fig. 1).

3. Results

The results were summarized and presented in the Table.

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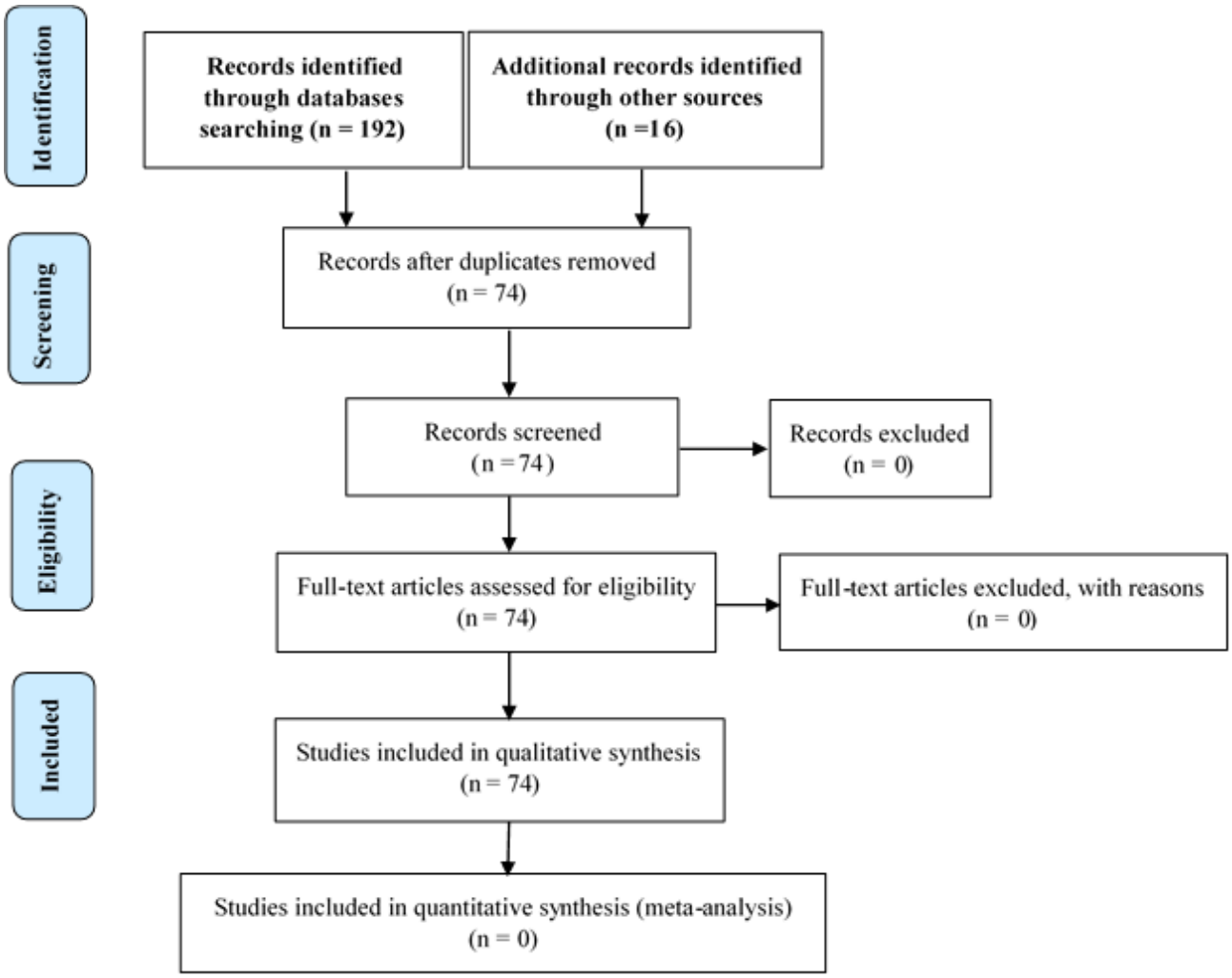

Fig. 1. The PRISMA flow diagram

Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran

Ref	JADAD score (Out of 5)	*Level of evidence/Study design/Participants/Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
			Berberis vulgaris		
12	> 3	I/RCT/57 (19 *B. vulgaris* 1Tsp, 19 2Tsp /19 Po)/T2DM	Group1- n = 19, daily consumption of 1Tsp processed *B. vulgaris* in apple vinegar Group 2- n = 19, daily consumption of 2Tsp processed *B. vulgaris* in apple vinegar Group3- n = 19 with no change in their diet (Po) for 4 weeks	BP and inflammatory markers	NS* SBP/ DBP change compared with Po and BL No adverse effect reported

Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/Study design/Participants/Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
13	> 3	I/RCT/80 (40 *B. vulgaris* and 40 Po)/ NAFLD	Case group- n = 40 Two capsules (750 mg) including *B. vulgaris* extract every day for 3 months Control group n = 40 Po every day for 3 months	BP and weight	↓ SBP/ DBP compared with Po No adverse effect reported
14	> 3	I/RCT/101 (51 *B. vulgaris* 50 Po)/MetS and Aged between 18-65 years	Case group n = 51 receiving a capsule of barberry 600 mg/daily for 6 weeks Control group n = 50 receiving a Po capsule for 6 week s	Anthropometric measurements, BP and FBS	↓ SBP/ DBP compared with Po No adverse effect reported
15	> 3	I/RCT/(23) *B. vulgaris* and 23 Po)/T2DM	Barberry juice group n = 23 who consumed 200 ml of barberry juice daily for 8 weeks Control group n = 23 with no intervention for 8 weeks	BP and biochemical markers	↓ SBP/ DBP compared with BL and ↓ DBP compared with Po No adverse effect reported
16	> 3	I/RCT/80 (40 *B. vulgaris* and 40 Po)/T2DM and Age 20-65 years	Group1- n = 40, 1000mg dry extract (157.3 mg berberine per day) for 6 weeks Group2- n = 40, daily consumption of Po for 6 weeks	Blood glucose and Lipid profile levels	NS* SBP/ DBP change compared with Po and BL No adverse effect reported
			Nigella sativa		
17	> 3	I/RCT/70 (35 NS and 35 Po)/NHV	Group1- n = 35 received 2.5 ml NS oil BID for 3 months Group2- n = 35 received similarly 2.5 ml mineral oil BID for 3 months	SBP/DSB, BMI and blood levels of SGOT, ALT, ALP, Cr and BUN	↓ SBP/ DBP compared with Po and BL No adverse effect reported
18	> 3	I/RCT/20 (10 NS and 10 Po)/stage 1 HTN	NS group n = 10 receiving 1000 mg of powdered NS BID for 50 days Control group n = 10 receiving the same doses of Po for 50 days	SBP/DBP, lipid profile, BS, some anthropometric indicators	↓ SBP/DBP compared with Po. ↓ SBP compared with BL No adverse effect reported
19	< 3	I/NRCT/114/(57 NS and 57 Po)/T2DM	NS group n = 57 receiving 2 g of powdered NS daily for 1 year Control group n= 57 receiving the same doses of Po for 1 year	Lipid levels, BP and HR	↓ SBP/ DBP compared with BL and ↓ DBP compared with Po No adverse effect reported
21	> 3	I/RCT 119/ (36 NS, 39 NS and 33 Po)/Mild HTN	Group1- n = 36, 200 mg NS extract Group2- n = 39, 400 mg NS extract Group3- n = 33 Po for /8 weeks	HTN	↓ SBP, DBP in both groups compared with Po and BL No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/Study design/Participants/Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
22	> 3	I/RCT/73(39 NS and 34 Po)/HCL	Group1- n = 39, 2 g NS powder Group2- n = 34 Po/ 6 weeks	BMI, waist-hip ratio, BP, FBS, serum lipids, and serum ALT and Cr	NS* SBP/DBP change compared with Po and BL No adverse effect reported
23	> 3	I/RCT/39 (19 NS and 20 Po)/obese Men	Group1- n = 19, 1.5 g NS powder Group2- n = 20 Po/ 12 weeks	BW, waist circumference, and BP, serum free testosterone, FBS, TG, HDL-Cholesterol, UA, Cr, SGOT and SGPT, adiponectin, and hs-CRP	↓ SBP compared with BL No adverse effect reported
24	> 3	I/RCT /40 (20 NS and 20 Po)/HAM	Group1- n=20 1g NS powder Group2 n= 20 Po /9 weeks	TC, TG and HDL cholesterol, VLDL, LDL cholesterol, CK-MB; AST, ALT, ALP, Total protein, Albumin, Bilirubin, Cr and BUN	NS* SBP/DBP change compared with Po and BL No adverse effect reported
25	> 3	I/RCT /80 (40 NS and 40 Po)/MetS	Group1- n= 40 NS powder 500mg Control group n= 40 Po /8 weeks Aspirin 150mg once a day was given in both groups.	FBG, PPBG & HbA1C at the beginning of the trial, the once every two weeks during the trial. Venous blood was also collected from each subject before and after the trial	↓ SBP, DBP compared with BL and control group No adverse effect reported
26	> 3	I/RCT /48 (24 NS and 24 Po)/HAM	Group1- n = 24 500 mg NS powder Group2- n = 24 Po /4 weeks	Cognition with CVLT-II, mood with Bond-Lader scale and anxiety with STAI	NS* SBP/DBP change compared with Po and BL No adverse effect reported
			Allium sativum		
27	< 3	I/RCT /20 (In 1 group)/EHTN	Group1- n= 20 Garlic pearls 250mg/day for 2 months	Lipids and lipoprotein subfractions, plasma-ox-LDL, plasma and urinary concentration of 8-iso-$PGF_{2\alpha}$ and the TOS	↓ SBP/DBP compared with BL No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/ Study design/ Participants/ Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
28	> 3	I/RCT /62 (30 garlic 32 Po)/normo-lipidaemic volunteers	Group1- n = 30 Garlic powder (10.8 mg alliin) Group2- n = 32 Po/ 12 weeks	Serum lipids, BP and arterial stiffness	NS* SBP/DBP change compared with Po and BL No adverse effect **reported
29	> 3	I/RCT /47 (24 garlic 23 Po)/mild HTN	Group1- n = 24 Garlic powder 600 mg Group2- n = 23 Po/ 12 weeks	BP and plasma lipids	↓ Supine DBP compared with BL No adverse effect reported
30	> 3	I/RCT /42 (garlic 23 and 19 Po)/normotensives mild HCL men	Group1- n = 23 Garlic powder 600 mg Group2- n = 19 Po/ 12 weeks	TC, LDL, HDL cholesterol	↓ SBP/DBP compared with Po No adverse effect reported
31	> 3	I/RCT /84 (garlic 30/18/16 and 20 Po)/mild & moderate HTN	One tablet containing 300 mg garlic powder BID, n = 30 or continued to receive a Po of identical appearance, n = 20 Some patients were randomly switched to the open-label branch and received either 2400 mg Allicor daily (2 tablets FID, n = 18 or 900 mg Kwai 1 tablet containing 300 mg TID, n=16/Po 12 weeks	TC, LDL, HDL cholesterol	↓ SBP in 480/960 compared with Po No adverse effect reported
32	> 3	I/RCT/189 (seven groups; A:300, B: 600, C: 900, D: 1200, E: 1500 mg garlic, F: 100 mg atenolol and G: Po n = 27/EHTN	Group A- n = 27, Garlic 300 mg Group B- n = 27, Garlic 600 mg Group C- n = 27, Garlic 900 mg Group D- n = 27, Garlic 1200 mg Group E- n = 27, Garlic 1500 mg Group F- n= 27, Atenolol 100 mg Group G- n = 27 Po/ 24 weeks	BP readings recorded at weeks 0, 12 and 24	↓ SBP, DBP compared with Po
33	> 3	I/RCT /50 (garlic 25 and 25 Po)/UHTN	Group1- n = 25 Garlic extract 960 mg Group2- n = 25 Po/ 12 weeks	SBP and DBP at baseline, 4, 8 and 12 weeks, and change over time	↓ SBP compared with Po No adverse effect reported
34	> 3	I/RCT /37 (garlic 16 and 23 Po)/pre HTN	Group1- n = 16, Garlic powder 600 mg Group2- n = 23 Po/ 12 weeks	BP were recorded at visits 1 and 2. Then all participants were further instructed to self-measure their BP at home during the 2-week interval between clinic visits 2 & 3	↓ SBP, DBP compared with Po No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/ Study design/ Participants/Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
35	> 3	I/RCT /88 (garlic 50 and 38 Po)/UHTN	Group1- n = 50 Aged-garlic extract 1.2 g Group2- n = 38 Po/ 12 weeks	BP, and secondary outcome measures of central-hemodynamics and other cardiovascular markers, including cholesterol, homocysteine, platelet function, and inflammatory markers	↓SBP, DBP compared with Po No adverse effect reported
36	> 3	I/RCT /49 (garlic 23 and 26 Po)/UHTN	Group1- n = 23 Aged-garlic extract 1.2 g Group2- n = 26 Po/ 12 weeks	BP, pulse wave velocity and arterial stiffness, inflammatory markers, and gut microbiota	↓SBP, DBP compared with Po No adverse effect reported
37	> 3	I/RCT /98 (garlic 23 and 26 Po)/ NAFLD	Group1- n = 47 Garlic tablet 400 mg (EC-coated tablet containing 1.5 mg Allicin) BID Group2- n = 51 Po (EC-coated tablet containing 400mg microcrystalline cellulose) BID/ 15 weeks	BP and hs-CRP	↓SBP, DBP compared with Po No adverse effect reported
			Hibiscus sabdariffa		
38	> 3	I/RCT /54 (HS 31 and 23 Po)/moderate EHTN	Group1- n = 31 10g HS (decoction) Group2- n = 23 Po/ 2 weeks	SBP and DBP were measured before and 15 days after the intervention	↓SBP, DBP compared with BL and control groups No adverse effect reported
39	> 3	I/RCT/7 5 (39 HS 36 Po)/ T2DM with mild HTN	Group1- n = 39 10 g HS (decoction) Group2- n = 36 Po/ 4 weeks	tolerability, diastolic reduction > or = 10 mm Hg and, in the experimental group, urinary electrolytes modification	↓SBP, DBP compared with BL and Po groups No adverse effect reported
40	> 3	I/RCT /171 (were in HS and Po)/stage I or II HTN	Group1- n = 86 HS equivalent to 250 mg anthocyanin Control group n = 85 (10mg Lisinopril)/ 4 weeks	Effectiveness (DBP reduction ≥10 mmHg), Safety (absence of pathological modifications in the biochemical tests of hepatic & renal function), Tolerability (absence of intense side effects), effect on serum electrolytes, and ACE activity	↓SBP, DBP compared with BL and Po group No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/Study design/Participants/Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
41	> 3	I/RCT /53 (27 HS 26 Po)/ T2DM with mild HTN	Group1- n = 27 HS 2 g (decoction) Group2- n = 26 Po (black tea)/ 4 weeks	BP was measured on days 0, 15 and 30 of the study	↓SBP compared with BL and Po group No adverse effect reported
42	< 3	I/RCT /20 (10 HS and 10 captopril)/mild HTN	Group1- n = 10 HS extract 1000 mg (250 mg anthocyanin) Control group n = 10, 25 mg Captopril/ 6 weeks	ABPM	↓SBP, DBP compared with BL No adverse effect reported
43	> 3	I/RCT /41 (20 HS 21 Po)/diabetic nephropathy	Group1- n = 20 HS extract 850mg Group2- n = 21 Po/ 8 weeks	BP and Urinary albumin concentration	↓SBP compared with BL No adverse effect reported
44	> 3	I/RCT /65 (35 HS 30 Po)/ pre and mild HTN	Group1- n = 35 HS 3.75g (decoction)/ Group2- n = 30 Po/ 6 weeks	A standardized method was used to measure BP at baseline and weekly intervals	↓SBP compared with Po group No adverse effect reported
45	> 3	I/RCT/36 (19 HS 17 Po) /T2DM with mild HTN	HSE-treated group n = 19 HS extract 900 mg Control group n = 17 Po/ 12 weeks	BMI, body fat, waist-to-hip ratio, and FFA	↓SBP compared with BL and Po group No adverse effect reported
46	> 3	I/RCT/50 (25 HS 25 Po)/mild to moderate HTN	Group1- n = 25 HS 9 g (decoction)/ Group2- n = 25 Po/ 4 weeks	BP, serum, and urine electrolytes were measured at baseline, weekly during treatment and 1 week after withdrawal of treatment	↓SBP, DBP compared with BL and Po group No adverse effect reported
47	> 3	I/RCT/35 (18 HS 17 Po)/MetS	Group1- n = 18 HS extract 500 mg Group2- n = 17 Po/ 4 weeks	SBP and DBP and BMI FBS, Insulin, lipoproteins, TG, hs-CRP, and MDA were determined pre- and post-intervention	↓SBP compared with Po group No adverse effect reported
48	> 3	I/RCT/33 (17 HS 16 Po) /healthy adult	Group1- n = 17 HS extract 450 mg	48	>3

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/Study design/Participants/Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
			Beta vulgaris		
49	N/A	47 intervention (n = 650) and 43 control (n = 598) groups.	2-56 days, 70-500 ml/d Beetroot juice supplemented	SBP, DBP	↓ SBP, DBP in nitrate-rich compared with control groups No adverse effect reported
50	> 3	I/RCT/ 12 (5 male, 7 female)/healthy older adults	3 h after ingestion 140 ml of nitrate-rich/ 140 ml nitrate-depleted beetroot juice	BP, blood coagulation, vascular inflammation markers, plasma nitrate and nitrite before, and 3 h and 6 h after ingestion	↓ SBP, DBP in nitrate-rich compared with BL No adverse effect reported
51	3	I/RCT/24 in either group/mild HTN	Group1- n = 24 250 ml Raw beetroot juice Group2- n = 24 250 g Cooked beetroot juice/ 2 weeks	SBP, DBP, FMD and TNF-α	↓ SBP, DBP compared with BL in both groups No adverse effect reported
52	> 3	I/RCT/40 (20 nitrate-rich and 20 nitrate-depleted beetroot juice)/ HTN pregnant women	Group1- n = 20 beetroot juice 70 ml Group2- n =20 nitrate-depleted beetroot juice 70ml/ 8 day	BP, cardiovascular function and utero-placental blood flow	No overall reduction in BP in the nitrate-treated group; however there was a highly significant correlation between changes in plasma nitrite concentrations and changes in DBP in the nitrate-treated arm only
53	> 3	I/RCT/18 cross-over/untreated HTN	Group-1 n = 18 consumed randomly, a nitrate-rich (8.1 mmol-BRJ nitrate) and a nitrate-depleted (BRJ placebo) BRJ	Participants performed submaximal isometric handgrip with beat-by-beat monitoring of hemodynamics and cBRS. AMBP assessment followed.	Office/ambulatory BP were lower following BRJnitrate vs BRJpo No adverse effect reported
54	< 3	II/RCT/30 (10 in each group)/ healthy non-smoking men and women, aged 55–70 years, with a BMI between 25 and 40 kg/m2	Group1- n = 10 beetroot juice Group2- n = 10 r isometric handgrip exercise Group3- n=10 control/7 days	Clinic and 24-h ABP, peripheral arterial function quantified by pulse wave velocity and arterial volume distensibility were assessed before and after intervention.	No change in SBP and DBP No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/ Study design/ Participants/ Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
55	> 3	I/RCT/14/ non-hypertensive obese individuals	Fourteen were randomly assigned to 3 experimental sessions: 1) Beetroot juice with exercise (BJE, 200 ml with ≈ 800 mg nitrate and 40 minutes of moderate-intensity aerobic exercise at an intensity of 50% of the heart rate reserve), 2) fruit soda with exercise (FSE, 200ml of a low-nitrate drink and the same exercise session) and 3) control (CON, 200ml of water, an insignificant nitrate drink without exercise).	Subjects were instructed to shower after each experimental session. ABMP device was fitted on their non-dominant arm. They were fitted with the ABPM device ~60 minutes after the experimental sessions and had it removed on the following day. The device was programmed to measure BP every 15 minutes while the subject was awake and every 30 minutes during their periods of sleep	NS* changes were observed for ambulatory DBP No adverse effect reported
56	< 3	II/RCT/21 (10 & 11) subjects completing the study	56	< 3	II/RCT/21 (10 & 11) subjects completing the study
51	< 3	II/RCT/24 twelve raw beet juice and 12 cooked beet/ HTN	24 hypertensive subjects aged 25-68 years	51	< 3
57	< 3	I/RCT/ 15 / patients with PAH	Group 1- n=15 The patients received nitrate-rich beetroot juice (~16 mmol nitrate per day) and Po in 2 treatment periods of 7 days each.	The primary outcome: change in peak oxygen consumption (VO2 peak) and VO2 at the anaerobic threshold. The secondary outcome: changes in; the 6-minute walking test, WHO-functional class, right and left ventricular function, right and left atrial/ventricular dimensions, systolic pulmonary artery pressure, exhaled NO, systemic BP, N-terminal pro-brain natriuretic peptide, biochemical variables involved in the NO system, a range of standard variables obtained from the ergo-spirometry PAH	SBP and DBP did not differ between interventions No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/ Study design/ Participants/ Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
58	> 3	I/RCT/64 NHV	Group1- n = 32 receive daily dietary supplementation with dietary nitrate (250 ml daily, as beetroot juice) Group2- n = 32 Po (250 ml daily, as nitrate-free beetroot juice)/ 4 weeks	ABP, BP, and HR	Robust BP lowering No adverse effect reported
59	> 3	I/RCT/ 47 middle-aged and older participants	Group1- n = 16 Combined intervention (high-nitrate beetroot juice and folic acid) Group2- n = 16 Single intervention (high-nitrate beetroot juice and Po) Group3- n = 15 control (nitrate-depleted beetroot juice and Po)/ 60 days	Clinic and 24-h ambulatory BP and measurements of compliance in plasma (nitrate and folate concentrations) and saliva (nitrate and nitrite) were obtained at baseline, 30 d, and 60 d	↓ BP No adverse effect reported
60	> 3	I/RCT/ 87/ patients with/at risk of T2DM	Group1- n = 27 Doxazocin + Po juice Group2- n = 16 Doxazocin + Active beetroot juice Group3- n = 20 Spironolactone + Po juice Group4- n = 24 Spironolactone + Active beetroot juice/3 and 6 months	Haemodynamic parameters, Echocardiographic morphological Parameters, and Echocardiographic Systo-Diastolic function	BP did not differ between the juices, or between the drugs. However, 6 months' dietary nitrate decreased LV volumes ~5% No adverse effect reported
61	> 3	I/RCT/ 87/ UHTN	Group1- n = 20 (13 + 7) 7-d, double-blind, randomized, Po - controlled, cross-over trial to assess the effect of dietary nitrate. Subjects were tested on three separate occasions – baseline (day 1), midpoint (day 8) and endpoint (day 15) – before and after each intervention period	On all 3 testing days (days 1, 8 and 15) in an identical manner and at the same time of day, non-fasting blood was drawn and subjects were fitted with an ABPM for 24 h	It is noteworthy that BP values decreased after Po, as well as after NO_3^- No adverse effect reported
62	> 3	I/RCT/27/HTN men and women	Group1 – n = 27 The effect of 1-week intake of nitrate-rich beetroot juice was compared with 1-week intake of nitrate-depleted beetroot juice (Po)	The primary outcome was BP assessed by measuring home BP during the intervention and 24-h AMBP on day 7 of the intervention. Other outcomes included nitrate metabolism assessed by measuring nitrate and nitrite in plasma, saliva, and urine	An increase in dietary nitrate intake may not be an effective short-term approach to further lower BP in treated hypertensive subjects No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/ Study design/ Participants/ Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
			Solanumly copersicum		
63	< 3	I/RCT/31/grade-1 HTN	Group1-n=31 Po period/ 4 weeks The same group (Group1) n =31 TE 250mg/ 8 weeks	SBP, DBP	↓SBP, DBP in TE group compared with BL No adverse effect reported
64	> 3	I/RCT/25 pre-HTN 15 TE, 11 dark chocolate, 10 Po	Group1- n= 11 Fifty grams daily dose of dark chocolate with 70% cocoa containing 750mg polyphenols Group2- n= 15 Were allocated one tomato extract capsule containing 15mg lycopene per day, and Control group n= 10 received 1 placebo capsule daily/ Over 8 weeks followed by a 4-week washout period.	Median BP, weight, and abdominal circumference	No change in SBP and DBP No adverse effect reported
65	> 3	I/RCT /50 (26 TE, 24 Po)/uncontrolled HTN	Group1- n= 26 TE 250mg (15 mg lycopene) Group2- n=24 Po/ 6 weeks	Plasma concentrations of lycopene, nitrite and nitrate	↓SBP, DBP in TE group compared with BL No adverse effect reported
66	> 3	I/RCT/126 (41 lycopen 6 mg; 37 lycopen 15 mg; 38 Po)/NHV	Group1- n= 41 Lycopen 6 mg Group2- n= 37 Lycopen 15 mg Group3- n= 38 Po/ 8 weeks	hs-CRP, SBP, sICAM-1 and sVCAM-1 β-carotene and LDL	↓SBP in 15 mg Lycopen group with BL No adverse effect reported
67	> 3	I/RCT /24 in either group/Mild HTN	Group1- n= 24 Synthetic lycopene 15mg Group2- n=24 Po/ 8 weeks	BP	↓SBP compared with control groups No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/ Study design/ Participants/ Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
			Cinnamomum verum		
68	> 3	I/RCT /22 (12 in cinnamon 10 in Po)/Pre-DM	Group1- n = 12 Cinnamon extract 250 mg TID Group2- n = 10 Po/ 12 Weeks	FBG, SBP, and Body composition	↓ SBP No change in DBP No adverse effect reported
69	> 3	I/RCT /58 (30 in cinnamon 28 in Po)/T2DM	Group1- n = 30 Cinnamon 2g daily Group2- n = 28 Po/ 12 Weeks	FBG, SBP, DBP, HbA1c	↓ SBP, DBP compared with Po No adverse effect reported
70	> 3	I/RCT/59 (29 in cinnamon 30 in Po)/T2DM	Group1- n = 29 Cinnamon extract 400 mg TID Group2- n = 30 Po/ 12 Weeks	BP, HbA1c, FBG, lipid profile, physical examination, and Blood and Urine chemistry	↓ SBP ↓DBP compared with Po and BL No adverse effect reported
71	> 3	I/RCT /37 T2DM 19 in cinnamon 18 in Po	Group1- n = 19; 2 capsule each contain 500 mg Cinnamon powder TID (3g daily) Group2- n = 18 Po/ 8 weeks	Weight, height, body fat mass, SBP and DBP	No change in SBP and DBP No adverse effect reported
72	> 3	I/RCT/ 135 (63 in cinnamon 72 in Po)/Hyperglycemic individual	Group1- n = 63 Cinnamon extract 250 mg BID Group2- n=72 Po/ 8 Weeks	FBG, SBP and DBP, serum lipids, and Fructosamine.	No change in SBP and DBP No adverse effect reported
73	> 3	I/RCT /79 (40 cinnamon/39 P)/T2DM	Group1- n = 40 Cinnamon 3g daily + Black tea Control group n =39 Po + Black tea/ 8 Weeks	ICAM-1, SBP, DBP and Anthropometric measures	No change in SBP and DBP No adverse effect reported
74	> 3	I/RCT /99 (49 cinnamon/50 Po)/T2DM	Group1- n = 49 Cinnamon extract 500 mg TID Group2- n = 50 Po/ 8 Weeks	Glucose, TG, HDL-C levels, TG/HDL-C ratio, BP, and eGFR	↓ SBP ↓DBP compared with Po and BL No adverse effect reported
75	> 3	I/RCT /116 (58 cinnamon/58 Po (/MetS	Group1- n = 58 Cinnamon powder 3g daily Control group n = 58 Po/ 16 Weeks	Body composition, BP and Metabolic parameters	↓ SBP ↓DBP compared with Po and BL No adverse effect reported
76	> 3	I/RCT /36 (18 in cinnamon 18 in Po)/RA women	Group1- n = 18 Cinnamon capsule 500 mg FID Control group n = 18 Po/ 8 Weeks	FBS, lipid profile, liver enzymes, serum levels of CRP, TNF-α, ESR, BP, and Clinical symptoms	↓ SBP ↓DBP compared with Po and BL No adverse effect reported

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/ Study design/ Participants/ Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
			Rhus coriaria		
77	> 3	I/RCT /80/HTN	Group1- n = 40 received *R. Coriaria* capsules (500mg BID) and captopril (25mg daily) Group2- n = 40 Po capsules (500mg starch BID) and captopril (25mg daily)/ 8 weeks	BP and BMI	↓ SBP ↓DBP compared with Po and BL No adverse effect reported
			Olea europaea		
78	> 3	I/RCT/64 (32 in OLE 32 Po)/mild to moderate HTN	Group1- n = 32 OLE 500mg Group2- n = 32 Po/ 8 Weeks	Risk factors of atherosclerosis and co-morbid medical conditions, SBP, DBP, and HR	↓SBP in OLE group compared with Po and BL. ↓DBP compared with Po No adverse effect reported
79	< 3	I/RCT /40 monozygotic twins/ borderline HTN	Group1- n = 10; 500 Olive leaf extract Control group1- n = 10; No medication but advice on how HTN be ameliorated by an adequate lifestyle Group2- n = 10; 500 Olive leaf extract Control group2- n = 10; No medication but advice on how HTN be ameliorated by an adequate lifestyle/ 8 Weeks	Body weight, HR, BP, glucose and lipids	↓SBP, DBP in 1000 mg OLE group compared with BL No adverse effect reported
80	> 3	I/RCT /148 stage-1 HTN/ 72 olive leaf extract 76 captopril	Group1- n = 72; 500 mg Olive leaf extract BID Control group n = 76 /12.5 mg captopril BID/ 8 Weeks	SBP/DBP	↓SBP, DBP in 1000 mg OLE group and 25 mg Captopril compared with BL No adverse effect reported
81	< 3	II/Non-controlled, non-randomized pilot study/663/T2DM and pre T2DM with Grade 1 HTN	100 mg/d of Oleuropein and 20 mg/d of Hydroxytyrosol BID	SBP/DBP	↓SBP, DBP in TE group compared with BL No adverse effect reported
			Vaccinium arctostaphylos		
82	> 3	I/RCT /100 50 *Vaccinium arctostaphylos*/50 Po)/ HTN, T2DM with hyperlipidemia	Group1- n = 50 *Vaccinium arctostaphylos* leaf extract 350 mg TID Control group n = 50 Po/ 2 Months	BP, FG, 2hPPG, HbA1c, TC, LDL-C, TG, HDL-C, SGOT, SGPT and Cr	↓SBP, DBP in leaf extract group compared with Po and BL No adverse effect reported
83	> 3	I/RCT /39 (in one group)/ T2DM with HTN	Group1- n = 39; 1, 2, 3 and 4 weeks Decoction of 7 g *V. arctostaphylos* oral solution	FBS and BP	↓SBP, DBP compared with BL Not reported any harmful effect

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Table 1. Summary of the clinical trials conducted on hypertensive patients to evaluate antihypertensive efficacy and safety of plants found in Iran (Continued)

Ref	JADAD score (Out of 5)	*Level of evidence/ Study design/ Participants/ Inclusion criteria	Intervention/Control group	Outcome measure	Results / Safety
84	> 3	I/RCT/100 (50 *Vaccinium arctostaphylos*/50 Po)/HTN	Extract group n = 50 One extract capsule TID alongside the standard anti-hypertensive treatments for 3 months Po group n = 50 One Po capsule TID alongside the standard anti-hypertensive treatments for 3 months	SBP, DBP, BMI, and waist circumference CBC, blood levels of AST, ALT, ALP, BUN, and Cr	↓ SBP, ↓ DBP compared with Po No adverse effect reported
			Phyllanthus emblica		
85	> 3	I/RCT/81 (*Ph.. emblica* group n = 41 and Po group n = 40)/uncontrolled HTN	EO and Po groups took 500 mg extract and Po respectively TDS after meal with standard anti-hypertensives for 8 weeks	SBP, DBP	↓ SBP/DBP compared with Po. No adverse effect reported

4. Discussion

Hypertension is the leading cause of cardiovascular morbidity and mortality. It causes 9.4 million deaths annually in the world. The global prevalence of hypertension will increase 30 % by the year 2025. Effective treatment of hypertension is a major development in medicine. Development of numerous antihypertensive drugs have extended life expectancy and reduced complications of hypertension. Medicinal plants are considered as one of the modalities for the treatment of hypertension [5]. In this systematic review, the antihypertensive efficacy and safety of the plants found in Iran as evaluated in randomized controlled trials were examined. Most clinical trials as cited in the Table had Jadad scores larger than 3, showing high methodological quality. Virtually all the medicinal plants listed in the Table were able to reduce SBP and DBP. *Hibiscus sabdariffa* was able to reduce SBP and DBP in all studies. Although, the number of studies on *Olea europaea*, *Rhus coriaria*, and *Vaccinium arctostaphylos* was small, but they showed antihypertensive efficacy. The results of studies of other plants were not as consistent as studies of these plants; i.e., the results of some studies showed antihypertensive efficacy, while some other studies did not show efficacy in lowering BP. Among these studies, most studies on *Allium sativum* exhibited antihypertensive efficacy. The studies on *Cinnamomum verum* did not show consistent results. One study concluded that it was able to lower only SBP. *Beta vulgaris* and *Solanum lycopersicum* had conflicting effects on hypertension. No adverse effect was reported in virtually all clinical trials.

Systemic reflexes, namely the baroreceptor neural reflex and the renin-angiotensin-aldosterone hormonal response, control the BP. The reflexes regulate BP via action on the hemodynamic factors. As such, BP equals cardiac output (CO) multiplied by peripheral vascular resistance (PVR). In turn, CO and PVR can be subdivided into their determinants (Fig. 2) [86, 87]:

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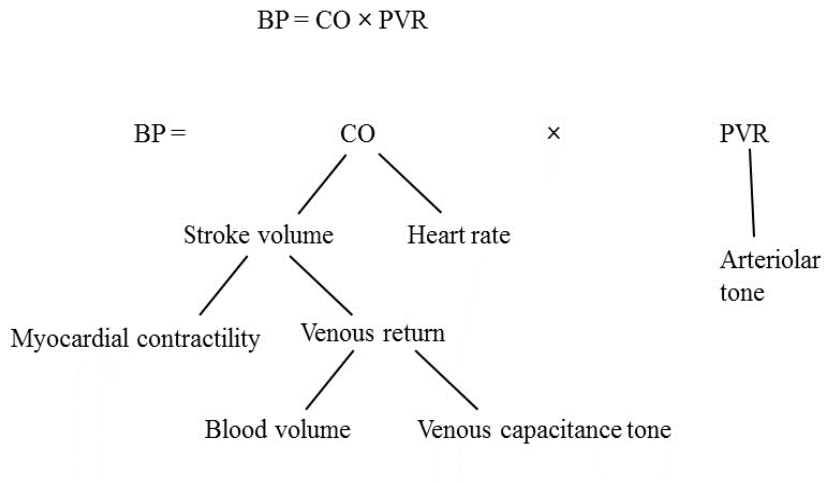

Fig. 2. A schema on the hemodynamic factors involved in blood pressure regulation and hypertension.

BP is a function of peripheral vascular resistance and cardiac output. Hypertension can be depicted in terms of its cardiovascular hemodynamics (Fig. 2). Increased vascular resistance or cardiac output raise BP and cause hypertension. Therefore, antihypertensive plants lower BP by decreasing vascular resistance or/and cardiac output through various mechanisms [86, 87]. Delineation of the mechanisms and sites of antihypertensive action of plants is important for optimal use of plants, for understanding the pathophysiology of hypertension and for development of new drugs [86, 87].

This systematic review suggests that limited clinical trials have been conducted on the antihypertensive efficacy and safety of most plants. There are more clinical evidence regarding the antihypertensive efficacy and safety of *Hibiscus sabdariffa*, *Olea europaea*, *vaccinium arctostaphylos* and *Allium sativum* versus the other plants. These plants seem to have efficacy and safety for the treatment of hypertension.

5. Conclusion

Most clinical trials evaluating the antihypertensive effects of the plants had high methodological quality. Most clinical trials demonstrated antihypertensive efficacy and no adverse effect was reported for virtually all plants. Most clinical trials show promising antihypertensive efficacy and safety of the plants. There are more clinical evidence denoting antihypertensive efficacy and safety of *Hibiscus sabdariffa*, *Olea europaea*, *vaccinium arctostaphylos* and *Allium sativum* compared with the other plants.

Author contributions

SK conceived the title of study. HFH, BF and SK searched for the clinical trials, and wrote the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

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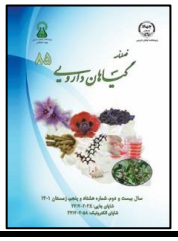

مقاله مروری

اثربخشی و ایمنی بالینی ضد پرفشاری خون گیاهان ایران: یک مرور نظام‌مند

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اطلاعات مقاله

گل‌واژگان:
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پرفشاری خون
فشار خون
گیاه
طب مکمل
طب جایگزین

چکیده

مقدمه: استفاده از گیاهان ضدپرفشاری خون یکی از راه‌های کنترل پرفشاری خون است. **هدف:** بررسی اثربخشی و ایمنی بالینی ضدپرفشاری خون گیاهانی که در ایران یافت می شوند. **روش بررسی:** PUBMED، MEDLINE، SCOPUS، EMBASE، SCIENCE DIRECT، PROQUEST، OVID، EBSCO، Google و Google Scholar مورد جستجو قرار گرفت و از راهنمای PRISMA تبعیت شد. کلمات مورد جستجو عبارت بودند از Iranian، plant، herb، antihypertensive، hypertension و randomized controlled trial. مقالات زبان انگلیسی که تا آخر ۲۰۲۲ چاپ شده استفاده شد. مطالعات برون تنی و حیوانی، مقالات سردبیر و مروری استفاده نشد. کیفیت روش شناختی مطالعات با استفاده از مقیاس JADAD ارزیابی شد. **نتایج:** دویست و هشت مطالعه یافت شد. فقط ۷۴ مطالعه واجد شرایط بود. برای زرشک (*Berberis vulgaris*) (۵ مطالعه)، سیاهدانه (*Nigella sativa*) (۱۰ مطالعه)، سیر (*Allium sativum*) (۱۲ مطالعه)، چای ترش (*Hibiscus sabdariffa*) (۱۱ مطالعه)، چغندر (*Beta vulgaris*) (۱۵ مطالعه)، گوجه فرنگی (*Solanum lycopersicum*) (۵ مطالعه)، دارچین (*Cinnamomum verum*) (۹ مطالعه)، سماق (*Rhus coriaria*) (۱ مطالعه)، آمله (*Phyllanthus emblica*) (۱ مطالعه)، زیتون (*Olea europaea*) (۴ مطالعه) و قره قاط (*Vaccinium arctostaphylos*) (۳ مطالعه) یافت شد. اکثر مطالعات کیفیت روش شناختی بالا داشتند و اثربخشی بدون عوارض جانبی گزارش کردند. **نتیجه‌گیری:** درحالی‌که، اکثر مطالعات اثربخشی و ایمنی ضدپرفشاری خون نشان می‌دهند، شواهد بیشتری در رابطه با چای ترش، زیتون، قره‌قاط و سیر در مقایسه با سایر گیاهان وجود دارد.

مخففها: 2hPPG، گلوکز پلاسما ۲ ساعت بعد غذا؛ ABPM، پایش فشار خون در حالت حرکت؛ ALP، آلکالین فسفاتاز؛ ALT، آلانین آمینوترانسفراز؛ AST، آسپارتات آمینوترانسفراز؛ BID، دو بار در روز؛ BL، شروع مطالعه؛ BMI، شاخص توده بدنی؛ BP، فشار خون؛ BS، قند خون؛ BUN، نیتروژن اوره خون؛ CBC، شمارش کامل خون؛ CK-MB، اتصال کراتین کیناز-میوگلوبین؛ Cr، کراتینین؛ CVLT-II، چاپ دوم آزمایش یادگیری کلامی کالیفرنیا؛ DBP، فشار خون دیاستولی؛ EC، باز شونده در روده؛ eGFR، سرعت تخمینی فیلتراسیون گلومرولی؛ EHTN، پرفشار خون ضروری؛ ET، عصاره؛ FBS، قند خون ناشتا؛ FID، روزی ۴ بار؛ HAM، نوجوان مذکر سالم؛ HbA1c، هموگلوبین گلیکوزیله؛ HDL، لیپوپروتئین با چگالی بالا؛ HDL-C، لیپوپروتئین-کلسترول با چگالی بالا؛ HR، سرعت ضربان قلب؛ HS، چای ترش؛ hs-CRP، پروتئین واکنش دهنده-C با حساسیت بالا؛ LDL، لیپوپروتئین با چگالی پایین؛ ICAM-1، مولکول چسبندگی بین سلولی-۱؛ LDL-C، لیپوپروتئین-کلسترول با چگالی پایین؛ HTN، پرفشاری خون؛ HCL، کلسترل خون بالا؛ LV، بطن چپ؛ MDA، مالون دی الدئید؛ MetS، سندرم متابولیک؛ N/A، شامل نمیشود؛ NS، سیاهدانه؛ NS، غیرمعنیدار؛ Po، دارونما؛ RDB، تصادفی شده دوسوبیخبر؛ PAH، پرفشاری خون شریان ریوی؛ Pre-DM، پیش دیابت شیرین؛ s-ICAM-1، مولکول چسبندگی بین سلولی-۱ محلول؛ sVCAM-1، مولکول چسبندگی سلول رگی-۱ محلول؛ T2DM، دیابت شیرین نوع ۲؛ TID، ۳ بار در روز؛ SBP، فشار خون سیستولی؛ NAFLD، بیماری کبد چرب غیرالکلی؛ NHV، داوطلب سالم طبیعی؛ OLE، عصاره برگ زیتون؛ RCT، کارآزمایی کنترل و تصادفی شده؛ SBP، فشار خون سیستولی؛ SGOT، گلوتامیک اکسالواستیک ترانسامیناز سرم؛ STAI، پرسشنامه اضطراب حالت-صفت؛ TC، کلسترل تام؛ TDS، سه بار در روز؛ TE، عصاره گوجه فرنگی؛ TG، تری گلیسریدها؛ TNF-α، عامل نکروز تومور آلفا؛ Tsp، قاشق چایخوری؛ UHTN، پرفشاری خون کنترل نشده.

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