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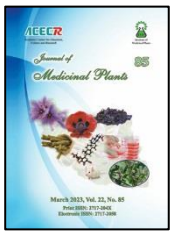

**Review Article**

# 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-$\alpha$, 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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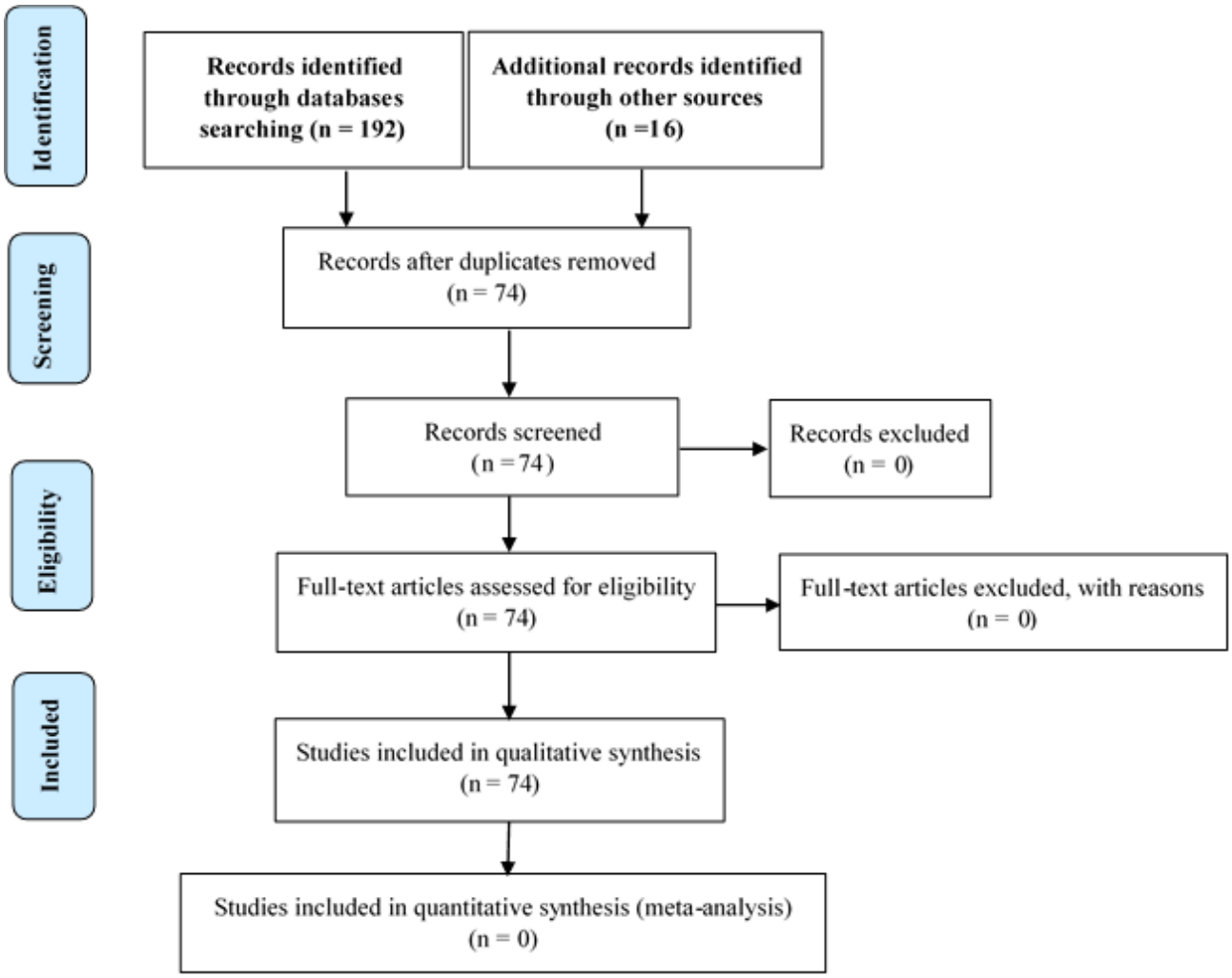


**Fig. 1.** The PRISMA flow diagram

**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<br>Group 2- n = 19, daily consumption of 2Tsp processed *B. vulgaris* in apple vinegar<br>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<br>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 |
|---|---|---|---|---|---|
| 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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|---|---|---|---|---|---|
| 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)<br>Group2- n = 32 Po/ 12 weeks | Serum lipids, BP and arterial stiffness | NS* SBP/DBP change compared with Po and BL<br>No adverse effect **reported |
| 29 | > 3 | I/RCT /47 (24 garlic 23 Po)/mild HTN | Group1- n = 24 Garlic powder 600 mg<br>Group2- n = 23 Po/ 12 weeks | BP and plasma lipids | ↓ Supine DBP compared with BL<br>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<br>Group2- n = 19 Po/ 12 weeks | TC, LDL, HDL cholesterol | ↓ SBP/DBP compared with Po<br>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<br>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<br>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<br>Group B- n = 27, Garlic 600 mg<br>Group C- n = 27, Garlic 900 mg<br>Group D- n = 27, Garlic 1200 mg<br>Group E- n = 27, Garlic 1500 mg<br>Group F- n= 27, Atenolol 100 mg<br>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<br>Group2- n = 25 Po/ 12 weeks | SBP and DBP at baseline, 4, 8 and 12 weeks, and change over time | ↓ SBP compared with Po<br>No adverse effect reported |
| 34 | > 3 | I/RCT /37 (garlic 16 and 23 Po)/pre HTN | Group1- n = 16, Garlic powder 600 mg<br>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<br>No adverse effect reported |



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| 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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| 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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|---|---|---|---|---|---|
| | | | ***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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|---|---|---|---|---|---|
| 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<br>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.<br>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<br>No adverse effect reported |



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| 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<br>The same group (Group1) n =31 TE 250mg/ 8 weeks | SBP, DBP | ↓SBP, DBP in TE group compared with BL<br>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<br>Group2- n= 15 Were allocated one tomato extract capsule containing 15mg lycopene per day, and<br>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<br>No adverse effect reported |
| 65 | > 3 | I/RCT /50 (26 TE, 24 Po)/uncontrolled HTN | Group1- n= 26 TE 250mg (15 mg lycopene)<br>Group2- n=24 Po/ 6 weeks | Plasma concentrations of lycopene, nitrite and nitrate | ↓SBP, DBP in TE group compared with BL<br>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<br>Group2- n= 37 Lycopen 15 mg<br>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<br>No adverse effect reported |
| 67 | > 3 | I/RCT /24 in either group/Mild HTN | Group1- n= 24 Synthetic lycopene 15mg<br>Group2- n=24 Po/ 8 weeks | BP | ↓SBP compared with control groups<br>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<br>Group2- n = 10 Po/ 12 Weeks | FBG, SBP, and Body composition | ↓ SBP No change in DBP<br>No adverse effect reported |
| 69 | > 3 | I/RCT /58 (30 in cinnamon 28 in Po)/T2DM | Group1- n = 30 Cinnamon 2g daily<br>Group2- n = 28 Po/ 12 Weeks | FBG, SBP, DBP, HbA1c | ↓ SBP, DBP compared with Po<br>No adverse effect reported |
| 70 | > 3 | I/RCT/59 (29 in cinnamon 30 in Po)/T2DM | Group1- n = 29 Cinnamon extract 400 mg TID<br>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<br>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)<br>Group2- n = 18 Po/ 8 weeks | Weight, height, body fat mass, SBP and DBP | No change in SBP and DBP<br>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<br>Group2- n=72 Po/ 8 Weeks | FBG, SBP and DBP, serum lipids, and Fructosamine. | No change in SBP and DBP<br>No adverse effect reported |
| 73 | > 3 | I/RCT /79 (40 cinnamon/39 P)/T2DM | Group1- n = 40 Cinnamon 3g daily + Black tea<br>Control group n =39 Po + Black tea/ 8 Weeks | ICAM-1, SBP, DBP and Anthropometric measures | No change in SBP and DBP<br>No adverse effect reported |
| 74 | > 3 | I/RCT /99 (49 cinnamon/50 Po)/T2DM | Group1- n = 49 Cinnamon extract 500 mg TID<br>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<br>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<br>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<br>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<br>No adverse effect reported |



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| 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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| 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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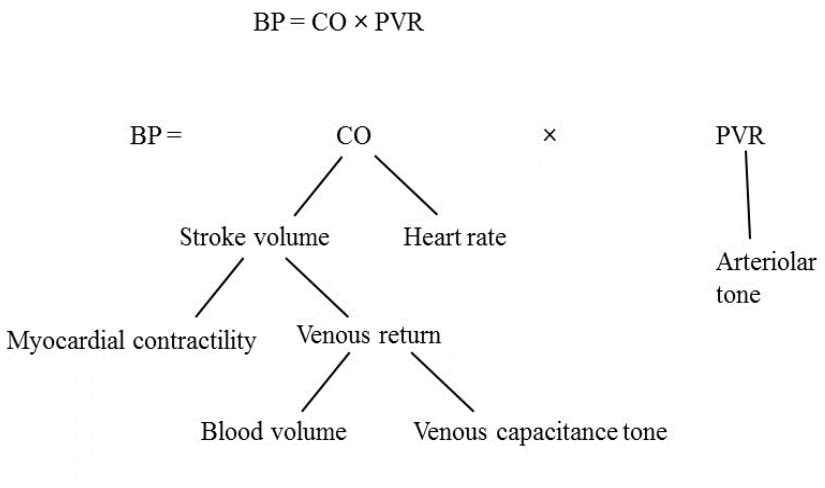


**Fig. 2.** A schema on the hemodynamic factors involved in blood pressure regulation and hypertension.

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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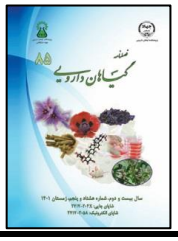

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مقاله مروری

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

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**اطلاعات مقاله**

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طب مکمل
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**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، کرآتینین؛ 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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