



The vasodilatory effects of medicinal herbs on the cardiovascular system: A systematic review

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ABSTRACT

Vasodilators are drugs that induce or start the widening of blood vessels and are commonly applied to treat disorders with irregularly high blood pressure, including hypertension, congestive heart failure, and angina. The present study aims to systematically review the studies on the vasodilation effects of medicinal herbs. The study was done according to the 06- Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-Analysis Facility (SyRF) database. Various English databases, such as Scopus, PubMed, Web of Science, EMBASE, and Google Scholar, were used to find publications about the vasodilation effects of medicinal herbs with no date limitation. The searched terms and keywords were: “medicinal herbs”, “medicinal plants”, “vasodilator”, “vasorelaxant”, “hypertension”, “high blood pressure”, “vasodilation”, “extract”, “essential oil”. Out of 1820 papers (up to 2020), 31 papers meeting the inclusion criteria were reviewed. The most important medicinal plants with vasodilation/vasorelaxant activity belonged to the family Asteraceae (19.4%) followed by Zingiberaceae (9.7%). Aerial parts (30.5%), leaves (30.5%), followed by roots (11.1%) were the most common parts used in the studies. Ethanolic (33.3%), aqueous (22.2%), methanolic (19.4%), and hydroalcoholic (8.3%) methods were the most frequently used extracting methods. Herbal essential oils (13.9%) have also been commonly used. The results of the current review study revealed that the plant vasodilatory agents were might be used as an alternative and complementary source to treat hypertension as they had lower important toxicity. Nevertheless, more investigations, particularly clinical trials, are needed to clear this suggestion.

Implication for health policy/practice/research/medical education:

This review presents a detailed insight into the effective medicinal herbs on vasodilation and presents a list of medicinal plants for the treatment of hypertension, congestive heart failure, and angina, which might be used to prepare new agents.

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Introduction

Vasodilatation is well-known as one of the main therapeutic strategies to treat some cardiovascular diseases with high blood pressure (1,2). Vasodilators are drugs that induce or start the widening of blood vessels, which are commonly applied to treat disorders with irregularly high blood pressure, including hypertension, congestive heart failure, and angina (3-5).

At present, there are many agents that have been shown

to have vasodilation effects by various mechanisms, such as inhibiting angiotensin-converting enzyme (ACE), blocking calcium channels, opening potassium channel, or inhibiting cGMP-specific 3',5'-cyclic phosphodiesterase (PDE5) (6,7). However, despite the potential effects of the existing vasodilators, recent studies have indicated some limitations of these drugs, including drug resistance, drug dependence, reducing the systemic vascular resistance through renal retention of sodium and water, orthostatic

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hypotension and syncope upon standing, increasing the heart rate and inotropy (8,9). Therefore, the development and discovery of novel agents as blood vessel dilators are promising among researchers.

Medicinal plants have always been used by humans throughout history. The use of plants, plant materials, plant compounds has been introduced as herbal medicine all over the world (10,11). On the other hand, the return to nature and the reuse of drugs of plant and natural origin takes place in a situation where today's man has faced the side effects of these drugs. Scientific research has proven the effectiveness and safety of some complementary medicine methods, including herbs, in the treatment of some diseases (12,13). The present study aims to systematically review the studies on the vasodilation effects of some medicinal herbs.

Methods

Search strategy

This study was done according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (14) and registered in the CAMARADES-NC3Rs Preclinical SyRF database. Various English databases, such as Scopus, PubMed, Web of Science, EMBASE, and Google Scholar, were used to find publications about the vasodilation effects of medicinal herbs up to 2020. The searched words and terms

were: “medicinal herbs”, “medicinal plants”, “vasodilator”, “vasorelaxant”, “hypertension”, “high blood pressure”, “vasodilation”, “extract”, “essential oil” (Figure 1).

Quality assessment and article selection

Initially, the publications were imported to the EndNote X9 software based on the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE); whereas the duplicate papers were omitted. Then, three independent authors tested the titles and abstracts of the papers, and the relevant publications were included for further analysis. The same authors carefully analyzed the publications, and the suitable papers with acceptable inclusion criteria were selected. Any disagreement between the authors were resolved through the corresponding author

Inclusion and exclusion criteria

All papers evaluating the vasodilation effects of medicinal plants were included, whereas the studies with only abstract, inadequate information, failure to match methods with results, and inappropriate interpretation of the results were excluded (Figure 1).

Data extraction

The independent researchers extracted data, including the name of plant, plant family, the part used, type of extraction, concentration, and important results.

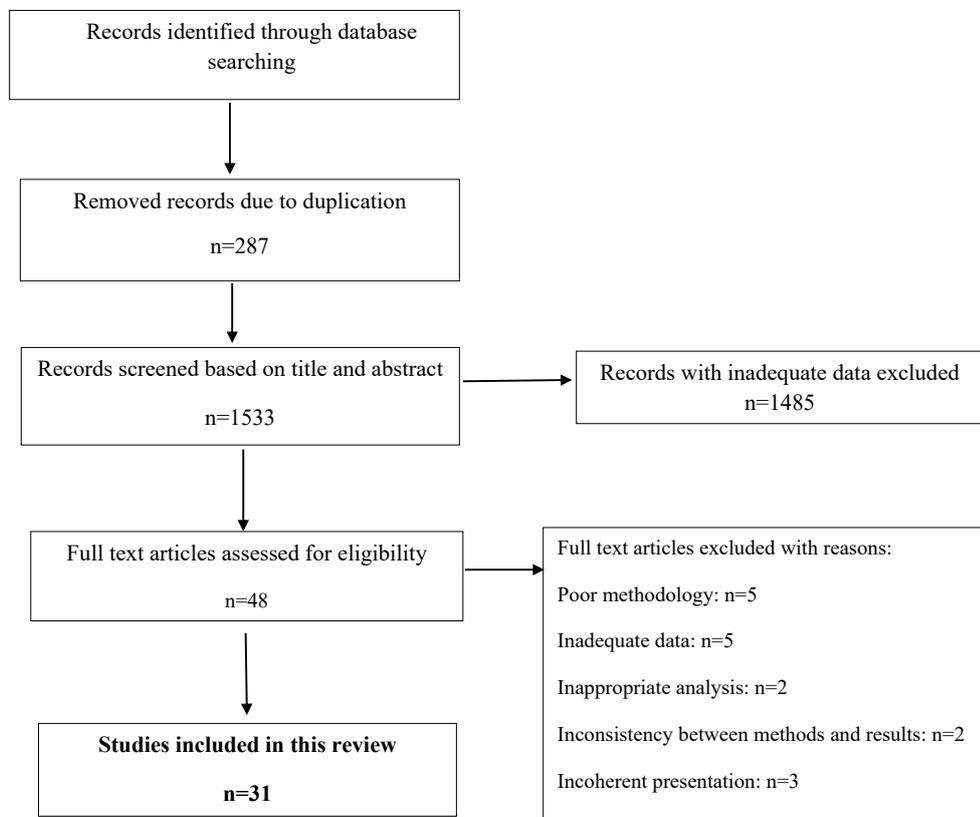


Figure 1. Flowchart describing the study design process.

Results

Out of 1820 papers, 48 papers were assessed for eligibility. While 17 papers (9 *in vivo* and 8 *in vitro* studies) were excluded from the study, 31 papers, which met the inclusion criteria were selected for discussion. Thirty-one plant species belonging to 33 genera and 27 families had vasodilation/vasorelaxant activity (Table 1) with various mechanisms (Figure 2). Among 31 selected papers, 16 papers (51.6%) were evaluated the vasodilation/vasorelaxant activity of medicinal herbs *in vivo*, whereas 15 papers (48.4%) were assessed the vasodilation/vasorelaxant activity of medicinal herbs *in vitro*. The most widely used medicinal plants with vasodilation/vasorelaxant activity belonged to the family Asteraceae (19.4%) followed by Zingiberaceae (9.7%). Aerial parts (85.8%) such as leaves (30.5%), followed by ground parts (14.2%) such as root (11.1%) were the most common parts used in the studies. The findings of the present review showed that ethanolic extract (33.3%), followed by aqueous extract (22.2%) and methanolic extract (19.4%) were considered as the desired approaches of herbal extraction, whereas the essential oil (13.9%) and hydroalcoholic extract (8.3%) were the second most used herbal extractions.

Discussion

According to the WHO reports, herbal medicines and their derivatives because of low or no industrial handling and toxicity have been extensively used to treat various diseases such as diabetes, cancer, cardiovascular, and gastrointestinal problems, by local or regional healing methods in developed and developing countries (10,11). Reviews have previously demonstrated that the biological activities and treating properties of medicinal plants are due to the secondary metabolites existing in plants making them a reliable source for providing of new agents (12,13).

Flavonoids are considered one of the key secondary metabolites of plants, which have numerous pharmacological and therapeutics properties in the cardiovascular system, including vasodilation, antiatherogenic, antihypertensive, antioxidant, and antiplatelet properties (46,47). These compounds show their vasodilation and antihypertensive effects through inhibiting tyrosine kinase Pyk2 as the main enzyme to regulate calcium channels, activation of the cAMP/protein kinase A cascade, modulating the renin-angiotensin-aldosterone system, adapting the contraction of vessels of smooth muscles, activating the potassium channels, and decreasing calcium ions in cells by delaying voltage-gated calcium channels, etc (48).

Other important compounds in plants, which have exhibited considerable vasodilation and antihypertensive effects, are phenolic compounds (49, 50). Studies have reported that polyphenols display their effects through some mechanisms such as increasing endothelium-derived nitric oxide bioactivity, suppression of smooth

muscle activation, regulating calcium channels, etc (51,52).

Terpenes are well-known as the key herbal compounds with a broad spectrum of pharmacological and therapeutic activities, including antihypertensive and vasodilation properties (53). Reviews demonstrated that these secondary metabolites act through a direct effect on vascular smooth muscle, an effect on the peripheral vascular resistance, no release of NO, activating the NO-cGMP pathway, and inhibition of Ca²⁺ influx, etc (54).

The present review showed that aerial parts, especially the leaves, were the most common parts of medicinal plants used for their vasodilatory activities. Reviews have demonstrated that leaves are well-known as the favored part of plants for therapeutics aims due to having a high percentage of bioactive composites; and convenience in harvesting without any damage to the herb (55-58).

We found that ethanolic extract, aqueous extract, and methanolic extract were the most used plant formulations. A previous study revealed that the general use of these extracts represents the role of solvents in the extraction of potential bioactive components from different plants and various parts of these herbs (59). The adverse side effects of herbal medicines are linked to a number of factors, including the toxicity of main constituents, lack of suitable manufacturing techniques, and consequently, heavy metals or microbes contaminations, and side effects on consumers, which are dependent on age, genetic and the underlying diseases of them (60-62). Today, exposure of a plant extracts in humans can be evaluated by detecting the increasing effects and doses that cause toxicity, such as carcinogenic, mutagenic, and teratogenic problems (63). A number of toxicity tests are necessary to assess the level of damages triggered by herbal extracts and their derivatives (63). In all *in vivo* studies, including in the present review, the used doses of medicinal herbs for evaluation of their vasodilation/vasorelaxation activities were based on the reliable toxicity tests such as acute toxicity, sub-chronic toxicity, the fixed-dose procedure indicating that these medicinal herbs in used doses have no significant toxicity in tested animals.

Limitations

The main limitations of the present study are the lack of phytochemical analysis on most plants to identify the main components of the plant, the lack of basic vasodilation mechanisms of some plants, and the lack of clinical studies.

Conclusion

Recently, numerous studies have been carried out on the antihypertensive and vasodilation effects of herbal extracts and essential oils alone or in combination with existing drugs. The results revealed that the herbal vasodilatory agents might be used as an alternative and complementary

Table 1. List of included papers related to the vasodilation effects of medicinal herbs

| Plant | Family | Part of used | Extraction | Concentration | Rout of administration | Results | Ref. |
|----------------------------------|----------------|--------------|----------------------------|--------------------------------|------------------------|---|------|
| <i>Acorus calamus</i> | Acoraceae | Rhizomes | Aqueous-methanolic extract | 0.01–10 mg/mL | - | Extract showed the coronary vasodilator effect primarily through endothelial-derived hyperpolarizing factor | 39 |
| <i>Alpinia purpurata</i> | Zingiberaceae | Leaves | Hydroalcoholic extract | 1, 3, 6, 10, 30, 60, and 90 µg | - | The hydroalcoholic extract showed the vasodilator effects in vitro | 41 |
| <i>Alpinia zerumbet</i> | Zingiberaceae | Leaves | Hydroalcoholic extract | 1, 3, 6, 10, 30, 60, and 90 µg | - | The hydroalcoholic extract showed the vasodilator effects in vitro | 41 |
| <i>Artemisia annua</i> | Asteraceae | Aerial parts | Aqueous extract | 100 mg/kg | Oral | Extract showed the vasodilator effect through inhibition of prostaglandin generation both indirectly and directly | 45 |
| <i>Artemisia campestris</i> | Asteraceae | Aerial part | Essential oil | 0.5, 1, 1.5, and 2 mg/kg | Oral | The essential oil showed vasorelaxation via inhibition of L-type Ca ²⁺ channels and the activation of SERCA pumps of reticulum plasma | 43 |
| <i>Borago officinalis</i> | Boraginaceae | Leaves | Aqueous extract | 0.5-10 mg/kg | - | Through Ca ²⁺ antagonist mechanism showed vasodilator and antihypertensive effects | 21 |
| <i>Calea glomerata</i> | Compositae | Aerial parts | Ethanol extracts | 5, 10, 20, 50, and 100 mg/kg | Oral | Extract showed the vasodilator effect through blocking properties on Ca ²⁺ influx through voltage-dependent calcium channels | 44 |
| <i>Calicotome villosa</i> | Fabaceae | Flowers | Methanol extract | 2.5 mg/kg | Oral | Showed the vascular relaxation mediated partially through nitric oxide release | 30 |
| <i>Citrus aurantium</i> | Rutaceae | Aerial parts | Essential oil | 0.05-02% | - | Results showed the endothelial component of neroli-induced vasodilation is partly mediated by the NO-sGC pathway | 38 |
| <i>Cocos nucifera</i> | Arecaceae | Fruit | Ethanol extract | 0.25–2 mg/mL | - | Through nitric oxide production in a concentration and endothelium-dependent manner demonstrated the vasorelaxant and antihypertensive effects of CNE | 18 |
| <i>Coscinium fenestratum</i> | Menispermaceae | Leaves | Aqueous extract | 0.2 mL/100 g | - | Reduced nitric oxide synthase, and subsequently decreased the vasorelaxant action | 31 |
| <i>Croton schiedeanus</i> | Euphorbiaceae | Aerial parts | Ethanol extracts | 5, 10, 20, 50, and 100 mg/kg | Oral | Extract showed the vasodilator effect through blocking properties on Ca ²⁺ influx through voltage-dependent calcium channels | 44 |
| <i>Curatella Americana</i> | Dilleniaceae | Aerial parts | Ethanol extracts | 5, 10, 20, 50, and 100 mg/kg | Oral | Extract showed the vasodilator effect through blocking properties on Ca ²⁺ influx through voltage-dependent calcium channels | 44 |
| <i>Fructus Alpiniae Zerumbet</i> | Zingiberaceae | Leaves | Essential oil | 1.14–72.96 µg/mL | - | Showed the vasodilation effect through the endothelium and concentration, and the mechanism involvement of NOS-cGMP system. | 33 |
| <i>Geum japonicum</i> | Rosaceae | Leaves | Ethanol extract | 1–100 µg/mL | - | Findings suggested the vasorelaxant and hypotensive effects of <i>G. japonicum</i> , mediated via endogenous NO and subsequent cGMP formation. | 23 |
| <i>Guazuma ulmifolia</i> | Malvaceae | Bark | Hexan extract | 10 mg/kg | - | Reduced the contraction induced by norepinephrine through vascular endothelium removal or L-NAME pretreatment | 19 |
| <i>Jasminum sambac</i> | Oleaceae | Flowers | Ethanol extract | 0.5 mL/mouse | Oral | Showed the vasodilation effect through vessel muscarinic receptors or by causing the release of nitric oxide | 34 |
| <i>Jatropha gossypifolia</i> | Euphorbiaceae | Leaves | Ethanol extract | 125 or 250 mg/kg | Oral | Extract showed the vasorelaxant activity on rat mesenteric rings precontracted with norepinephrine or Ca ²⁺ | 25 |

Table 1. Continued

| Plant | Family | Part of used | Extraction | Concentration | Rout of administration | Results | Ref. |
|--------------------------------|----------------|------------------|--------------------------------------|----------------------------------|------------------------|---|------|
| <i>Laelia anceps</i> | Orchidaceae | Root | Methanolic extract | 100 mg/kg | Oral | Induced vasorelaxant and antihypertensive effects by blockade of Ca ²⁺ channels | 17 |
| <i>Laelia autumnalis</i> | Orchidaceae | Root | Methanolic extract | 15, 46, 150, 300, and 1500 µg/mL | - | Induced relaxation in rat aortic rings through an endothelium-independent pathway, involving blockade of Ca ²⁺ channels and a possible cGMP enhanced concentrations and also caused an antihypertensive effect | 15 |
| <i>Lippia alba</i> | Verbenaceae | Aerial parts | Ethanollic extracts | 5, 10, 20, 50, and 100 mg/kg | Oral | Extract showed the vasodilator effect through blocking properties on Ca ²⁺ influx through voltage-dependent calcium channels | 44 |
| <i>Loranthus ferrugineus</i> | Loranthaceae | Leaves | Methanol extract | 0.01 µM | - | Demonstrated its vascular effect by reversible noncompetitive antagonism of norepinephrine-induced vasoconstriction | 22 |
| <i>Lupinus amandus</i> | Fabaceae | Aerial parts | Ethanollic extracts | 5, 10, 20, 50, and 100 mg/kg | Oral | Extract showed the vasodilator effect through blocking properties on Ca ²⁺ influx through voltage-dependent calcium channels | 44 |
| <i>Mammea atricana</i> | Calophyllaceae | Stem bark | Methanol /methylene chloride extract | 200 mg/(kg) | Oral | Had a beneficial effect in patients with NO deficiency by improving their endothelium-dependent vasorelaxation | 29 |
| <i>Myrtus communis</i> | Myrtaceae | Aerial parts | Methanol extract | 0.01-5 mg/ml | - | Revealed the vasodilator effects through a possible calcium channel blocking activity | 37 |
| <i>Nigella sativa</i> | Ranunculaceae | Seed | Essential Oil | 10-100 µg/mL | - | Essential oil showed the vasodilatory effects through blockade of both voltage-sensitive and receptor-operated calcium channels | 40 |
| <i>Ocimum basilicum</i> | Lamiaceae | Aerial parts | Aqueous- methanolic extract | 3.0-10.0 mg/mL | - | Showed the vasodilation effect through Ca ²⁺ channel blocking activities | 35 |
| <i>Passiflora Edulis rind</i> | Passifloraceae | Leaves | Methanol extract | 10 and 50 mg/kg | Oral | The antihypertensive effect of the extract in SHR's might be due mostly to the GABA-induced antihypertensive effect and partially to the vasodilatory effect of polyphenols including luteolin | 27 |
| <i>Pectis brevipedunculata</i> | Asteraceae | Aerial parts | Essential oil | 1-10 mM | - | Showed the vasorelaxation of thoracic aorta by affecting the NO/cyclic GMP pathway and reduced the calcium influx by the blockade of voltage-dependent L-type Ca ²⁺ channels | 36 |
| <i>Raphanus sativus</i> | Brassicaceae | Seed | Aqueous extract | 0.03–3.0 mg/mL | Oral | Showed the antihypertensive and vasodilation effects mediated through activation of muscarinic receptors | 32 |
| <i>Saururus chinensis</i> | Saururaceae | Root | Ethanollic extract | 10, 30, and 100 mg/kg | Oral | Showed the antihypertensive effect through its direct vasorelaxant properties and negative inotropic actions | 28 |
| <i>Sclerocarya birrea</i> | Anacardiaceae | Stem-bark | Ethanollic extract | 60, 120, and 240 mg/kg | Oral | Extract had reno- and cardio-protective effects in diabetes mellitus | 24 |
| <i>Senecio nutans</i> | Asteraceae | Branches, leaves | Hydroalcoholic extract | 1-4 µg/mL | - | Extract showed the vasodilator effect through endothelium-dependent (NO) and or independent, and may involve a modulation of the calcium channels. | 42 |
| <i>Tanacetum vulgare</i> | Asteraceae | Leaves | Aqueous extract | 800 µg/mL | - | The aqueous extract of Tanacetum possesses NO-mediated and NO-independent vasorelaxing properties in vitro | 20 |
| <i>Tribulus terrestris</i> | Zygophyllaceae | Fruits | Aqueous extract | A single daily dose of 10 mg/kg | Oral | Significantly reduced the systolic blood pressure; whereas reduced the ACE activity significantly lower than that of hypertensive rats | 16 |
| <i>Ulmus macrocarpa</i> | Ulmaceae | Root bark | Ethanollic extract | 100 mg/kg | Oral | Showed the vasorelaxant and antioxidant properties probably through to reduce elevated blood pressure | 26 |

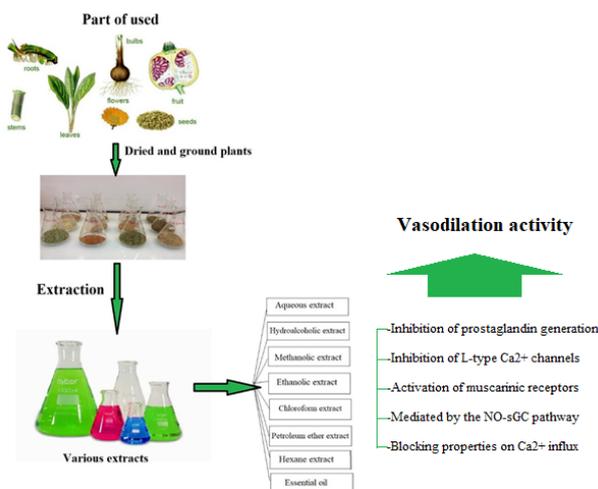


Figure 2. Schematic figure medicinal herbs and their extracts used for vasodilation activity.

source to treat hypertension as had lower important toxicities. Nevertheless, more investigations, especially clinical trials, are needed to clear this suggestion.

Authors' contributions

AA, AK, NB, MA and NM reviewed and contributed to data collection and preparation of the manuscript. The first draft was prepared by AA, and NM. All authors read the final version and confirmed it for publication.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication and etc.) have been completely observed by the authors.

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