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Herbs Used for the Treatment of Hypertension and their Mechanism of Action

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Abstract There is great interest lately, in the use of herbs for the treatment of hypertension and cardiovascular disease (CVD). Herbs and plants contain many phytochemicals that have been effective in the treatment of CVD and hypertension. Accumulating scientific evidence provides a reason for the use of herbs by health practitioners for treating their patients. The rationale for this expanding use of herbs is the belief of patients in a "holistic medicine" and that herbs are natural, safe, and effective. However, there are reasons of concern with the use of herbs, because they are not regulated or supervised carefully and their use could lead to serious complications or interactions with their combination with traditional medicines. In addition, their use is associated with significant out of pocket expenses, because their use is not compensated by health insurance providers. In this review, we present the scientific evidence for the use of herbs.

Keywords Herbs and hypertension · Herbal effectiveness · Herb safety · Hypertension · Cardiovascular disease · Herb costs

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Introduction

The use of complementary and alternative medicine (CAM) for the treatment of various health conditions that include hypertension, cardiovascular diseases (CVDs), dyslipidemias, and diabetes mellitus is gaining increasing popularity in the USA and worldwide, since a large proportion of patients relies, at least in part, on herbs as a complement to conventional therapy for the primary care of these conditions [1–3]. Over the last decade, the National Health Statistics Reports (NHSR) have shown a steady and substantial increase in the use of CAM and according to NHSR, 4 out of 10 (40%) of US adults interviewed used CAM [1]. This high CAM utilization is fueled by a number of factors like, ease of access, relative affordability, an anecdotal perception of higher safety, and efficacy without any scientific evidence to back up their claims [4•]. Although many herbs have shown promising potential, many of them remain untested and their use is either poorly monitored or not monitored at all, and their interactions, when combined with existing orthodox, pharmaceuticals could lead to serious adverse effects [4•]. Besides the unsure efficacy and safety of herbs, they also result in significant out of pocket expenses, due to the fact that herbs are not covered by health insurance. According to a 2007 estimate by the NHSR, this resulted in $33.9 billion expenses by US adults for purchasing CAM products and visiting CAM practitioners [5•]. Since efficacy and safety continue to be a major issue with the use of herbal remedies, it becomes imperative for the regulatory authorities to put in place appropriate measures for the protection of public health by ensuring that all herbal medicines sold are safe and effective. In order to get a better perspective of the current and overall safety and effectiveness of herbal remedies,

a focused Medline search of the English language literature between 2011 and 2017 was performed, and 34 papers with information on the antihypertensive effectiveness, mechanism of action, and costs of herbal products were selected and will be discussed in this review.

Reasons for Patients of Using CAM for the Treatment of Hypertension

The reasons for using herbs for the treatment of hypertension and other cardiovascular diseases either alone or in combination with conventional drugs are due to several factors. These include their belief in the "holistic concept" of medicine that herbs are effective and safe in contrast to conventional medicines, and they are less expensive than conventional drugs [6–9]. In addition, there is the desire by the patients to have control of their own care due to the perception that CAM is less authoritative and complicated than conventional therapy and is also more compatible with their own religious beliefs and philosophies [9]. It is of interest that the increased desire to use herbal treatment is not a reflection of the economic or educational status of an individual, since the use of CAM is higher among well-educated and wealthier older individuals. Indeed, 70% of the population in developed countries have utilized herbal medicine for the treatment of hypertension and other CVDs [10]. This is not surprising due to the belief that herbs contain thousands of bioactive components that have known therapeutic applications [11]. There is also, a recent interest in adapting the Chinese concept of "holistic regulation" in herbal medicine, in which the organism is considered as a whole, instead of the western medicine's concept, that focuses on a specific disease target and ignores the whole patient [12•]. The concept of holistic and herbal medicine is being widely embraced by many developed countries with CAM now being the mainstream in the UK, the rest of Europe as well as Australia and the USA [4•, 13•, 14]. Because these products are not covered by health insurance, the out of pocket expenses of purchasing CAM products and visiting CAM practitioners are in billions of dollars annually (Table 1).

Most Commonly Used Herbs for the Treatment of Hypertension and Cardiovascular Diseases

There is a growing interest in the USA for the use of herbal and plant products by health practitioners and pharmacologists for the treatment of CVD and hypertension. Several studies and meta-analyses have demonstrated their BP-lowering effects as well as their tolerance and acceptability by patients [5•, 6–15]. The results from these studies of the most commonly used herbs are listed in Table 2 and will be discussed here.

Table 1 Annual costs of complementary and alternative medicine by 2007 NHSR

Total annual costs of CAM	$33.9 billion
Self-care costs	$22.0 billion (64.8%)
NVNMNP	$14.8 billion (43.7%)
CAM practitioner's fees	$11.9 billion (35.2%)
Yoga, tai chi, and qigong classes	$4.1 billion (12.0%)
Homeopathic medicine	$2.9 billion (8.7%)
Relaxation techniques	$0.2 billion (0.6%)

Table constructed from data from reference 5

CAM complementary alternative medicine, *NVNMNP* non-vitamin non-mineral natural products

Allium sativum (Garlic)

Garlic in different preparations (powder, extract) has been used extensively for thousands of years and by different countries around the world for the treatment of hyperlipidemia, the prevention of CVD, as well as the treatment of hypertension, with good results. The BP-lowering effects of garlic have been reported by several studies and reviews and are listed in Table 2. In a randomized, double-blind, placebo-controlled study, Ried et al. [16] tested the effects of aged garlic in 88 patients with uncontrolled BP to receive either aged garlic extract (1200 mg/day) or placebo. After 12 weeks of follow-up, the BP was significantly reduced with garlic by 11.5 ± 1.9/6.3 ± 1.1 mmHg ($p < 0.001$) compared to placebo. Central hemodynamic measures including central BP, central pulse pressure (PP), pulse wave velocity (PWV), and arterial stiffness tended to improve with garlic compared to placebo. In this study, garlic was effective in significantly lowering the brachial BP and improving central hemodynamics and it was highly tolerated and acceptable by the patients. In a systematic review and meta-analysis, Rohner et al. [17] analyzed the effects of garlic treatment on BP in nine double-blind trials involving 482 patients with hypertension. After a follow-up ranging from 12 to 26 weeks and using different garlic preparations and different doses ranging from 600 to 900 mg/day, the BP was decreased by 12.6/6.2 mmHg on average, which was significantly lower compared to placebo. In another review and meta-analysis, Wang et al. [18] analyzed the results of garlic treatment in 18 randomized trials involving 799 hypertensive and normotensive subjects. After a follow-up ranging from 12 to 24 weeks and different doses of garlic treatment ranging from 300 to 2400 mg/day, the BP was decreased by 4.4/2.7 mmHg in the hypertensive but not in the normotensive subjects and was superior to placebo treatment. However, these studies showed significant heterogeneity in the BP effects of garlic treatment [17, 18]. Regarding the mechanism of the BP-lowering effects of garlic, these have been attributed to a number of active sulfur compounds that have been reported to modulate endothelium-relaxing factors including stimulation of

Table 2 Clinical trials demonstrating the blood pressure-lowering effects of herbs

Herb name	Trial design	Patients no.	Condition status	Dose mg/day	F-U weeks	Effect mmHg	Reference no.
Allium sativum	RTC	88	HTN	1200	12	− 11.5/− 6.3 BP	16
Allium sativum	Rev	482	HTN	600–900	12	− 12.6/− 6.2 BP	17
Allium sativum	Rev	799	HTN	300–2400	12–24	− 4.4/− 2.7 BP	18
Beetroot Juice	RTC	35	HTN	250 ml	4	− 7.7/− 2.4 BP	21
Camelia sinensis	RCT	95	HTN	3 CBT	42	− 2.7/− 2.3 ABP	23
Camelia sinensis	Rev	821	HTN	4–6 CGT	42	− 3.2/− 3.4 BP	24
Coptis chinensis	Rev	228	HTN	600 mg	4–8	− 4.9/− 2.0 BP	25
Crataegus species	RTC	21	HTN	2000–5000 mg	4 days	− 6.9/+ 0.6 ABP	29
Crocus sativus	RTC	30	NTN	400 mg	1	− 11.0 SBP	33
Hibiscus sabdariffa	RTC	193	HTN	250 mg	4	− 17.2/− 12.0 BP	35
Hibiscus sabdariffa	RTC	65	HTN	3 × 240 ml ext	6	− 7.2/− 3.1 BP	36
Nigella sativa	RTC	70	NTN	2.5 ml oil	8	− 10.6/− 9.6 BP	43
Panax (ginseng)	RTC	64	HTN	3000 ext	12	− 17.4/− 7.2 BP	46
Panax (ginseng)	RCO	23	NTN	400	1	− 4.4/− 3.6 BP	47
Panax (ginseng)	RCT	90	HTN	300	8	− 3.1/− 2.3 BP	48
Salviae miltiorrhizae	RTC	55	HTN	2000 ext	12	− 13.9/− 4.0 BP	52

F-U follow-up, *RTC* randomized controlled trial, *RCO* randomized cross-over trial, *Rev* review and meta-analysis, *HTN* hypertension, *NTN* normotension, *ABP* ambulatory BP, *SBP* systolic BP, *CBT* cups black tea, *CGT* cups green tea, *ext* extract

production of nitric oxide (NO) and hydrogen sulfide (H_2S) with the most important being allicin and its inhibitory effect on the angiotensin converting enzyme (ACE), all of which lead to BP reduction [12•, 19]. Overall, garlic was well tolerated and had a high acceptance rate (93%) among the subjects treated. The only minor adverse effects included mild gastrointestinal problems. The only contraindication to treatment with garlic is patients taking anticoagulants, because it could increase the bleeding risks due to its platelet atiaggregatory effects [20].

Beetroot

Beetroot food supplements have been shown to exert favorable effects on BP. In a randomized, placebo-controlled study, Kapil et al. [21•] investigated the effects of beetroot juice dietary supplement in 68 hypertensive patients, 34 treatment naïve, and 34 treated, ages 18–85 years. The patients were randomized to beetroot juice 250 ml/day ($n = 32$) or placebo (250 ml/day nitrate-free beetroot juice) and were followed for 4 weeks. Beetroot supplementation reduced the clinic BP by 7.7/2.4 mmHg ($p < 0.001$), the mean 24-h ambulatory BP (ABP) by 7.7/4.2 mmHg ($p < 0.0.001$), and the home BP by 8.1/3.8 mmHg ($p < 0.001$). The endothelial function was improved by 20% ($p < 0.001$), and the arterial stiffness (PWV) was reduced by 0.59 m/s ($p < 0.01$). The beetroot supplements were well tolerated, and there was no evidence of tachyphylaxis to treatment. In another randomized placebo-controlled, cross-over study by Bondonno et al. [22], 27 treated hypertensive patients mean age 63.2 years were randomized to treatment with high-nitrate beetroot juice (140 ml/day) or low-nitrate beetroot juice (nitrate depleted juice 140 ml/day) and were followed for 1 week. The high nitrate group had a reduction in home BP of 4.9/3.5 mmHg compared to low-nitrate group BP reduction of 5.4/3.2 mmHg. Similar BP reductions were observed in the 24-h ABP. In this study, there was no difference in BP reduction between the high- and low-nitrate groups in both home and 24-h ABP. The non-significant difference in BP reduction in this study between the high- and low-nitrate group could be attributed to fairly well-controlled BP from the concomitant treatment with 1–3 antihypertensive medications. The antihypertensive effects of beetroot juice have been attributed to the high supply of inorganic nitrates and the generation of endothelial NO from the chemical reduction of inorganic nitrite (NO_2^-).

Camelia sinensis (Tea)

Collectively, the teas (black and green) prepared from *Camellia sinensis* are the most frequently consumed beverages worldwide and are only second to water. Tea has pleiotropic effects that include its anti-inflammatory, antidiabetic, and antihypertensive actions. Although the antihypertensive effects of tea are not well established, several studies have demonstrated significant BP-lowering effects. In a randomized, placebo-controlled trial by Hodgson et al. [23], 95 hypertensive patients aged 35–75 years were randomized to 3 cups/day of leaf black tea containing 429 mg of polyphenols +96 mg caffeine or a placebo matched of caffeine flavor drink. After a follow-up of 6 months, the 24-h ABP was reduced by 2.7/2.3 mmHg in tea consumers compared to placebo consumers ($p < 0.001$). In a review on the

effects of black and green tea on BP reduction, Hartley et al. [24] analyzed the results of 11 randomized control trials (RCTs), seven with green tea and four with black tea, involving 821 participants. After a mean follow-up of 6 months, the black tea reduced the BP by 1.85/1.27 mmHg, whereas the green tea reduced it by 3.18/3.42 mmHg. The treatment was well tolerated, and there were no major adverse events related to treatment. Regarding the BP-lowering effects of tea, there are several potential mechanisms to account for this. Its major effect is due to the flavonoids (catechins) content of tea. Flavonoids stimulate NO production and reduce the plasma concentrations of endothelin-1. These actions lead to reduction of vascular tone causing vasodilation and reduction in peripheral vascular resistance and BP. Another possible mechanism could be through weight reduction. It has been shown that flavonoids, which are the same in green and black tea together with caffeine, could reduce abdominal fat resulting in weight loss.

Coptis chinensis (Berberine)

Coptis chinensis and its natural alkaloid berberine have been used for centuries by Chinese and Ayurvedic medicine. Its activity in carbohydrate metabolism, endothelial function, the cardiovascular system, and hypertension have generated considerable interest in the Western countries in the last decade. Berberine is mainly used for the treatment of diabetes mellitus, CVD, and hypertension [25, 26]. Regarding the antihypertensive effects of berberine, a review and meta-analysis by Lan et al. [25] of 27 RCTs involving 2569 patients with different conditions including hypertension, berberine extract demonstrated significant BP-lowering effects. Of the 27 studies, two involved in 228 hypertensive patients. These patients were randomized to active treatment with berberine 0.6 g/day + background antihypertensive therapy (n = 116) or to control group with background antihypertensive therapy only (n = 112). Berberine added to background therapy reduced the BP by 4.91/2.00 mmHg compared to control group. The hypotensive effects of berberine were attributed to increased generation of NO through stimulation of NO synthase (eNOS) and the decreased catecholamine levels leading to peripheral vasodilation and decrease in BP. In addition to BP-lowering, berberine exerts significant antidiabetic effects including reduction of body weight [26]. Additional hypotensive mechanisms have been attributed to increased levels of prostaglandin I_2 (PGI_2), opening the K_{ATP} and blocking the $^{i}Ca^{2+}$ voltage gated channels, thus blocking the Ca^{2+} cell influx [15•].

Crataegus Species (Hawthorns)

Hawthorns (hawberry, thorn apple) are shrubs that comprise almost 300 species and have been used for centuries in traditional medicine for the treatment of CVDs [27]. Treatment of hypertensive patients with hawthorn extracts resulted in modest decreases of BP. In an older study by Walker et al. [28], hawthorn extras of 500 and 600 mg/day decreased significantly only the diastolic BP (DBP) by 13.1 mmHg. However, a recent study by Asher et al. [29] used hawthorn extracts of 1000, 1500, and 2500 mg twice daily in a four-period cross-over study in 21 mildly hypertensive subjects mean age 51 years to investigate its effects on BP-lowering and in flow-mediated vasodilation. In this study, there was no change from baseline in ABP or in flow-mediated vasodilation by hawthorn extracts. The actual changes in baseline ABP were − 8.2/+ 1.2, − 6.9/+ 0.2, and − 6.8/+ 0.7 with placebo and − 6.9/+ 0.2, − 6.8/+ 0.7, and − 5.8/+ 0.7 mmHg for the hawthorn extracts 1000, 1500, and 2500 mg twice daily, respectively (p = ns). Some of hawthorn's individual constituents (procyanidins and flavonoids) have been shown to increase NO levels and to improve endothelial function, which could indicate that hawthorn extracts have BP-lowering effects. More studies are needed to demonstrate whether hawthorn extras can be used for the treatment of hypertension. When the participants of this study were asked whether they would use hawthorn extracts for the treatment of their BP, 66.6% said they would use it alone and 90.5% said they would use it in combination with other antihypertensive drugs.

Crocus sativus (Saffron)

Saffron is a stemless herb indigenous to Southwest Asia, Spain, Greece, and Marocco and has been used over 4000 years for the treatment of various medical conditions including hypertension [30]. Saffron contains several ingredients that include crocin, picrocrocin, safranal, and crocetin, flavonoids, and anthocyanins, which exhibit different mechanisms of action including antihypertensive and vasodilatory effects [30]. Several experimental studies have shown significant antihypertensive and vasodilatory effects of saffron ingredients [31, 32]. Also, a randomized, placebo-controlled study in 30 volunteers demonstrated significant BP-lowering effects of *Crocus sativus* [33]. The subjects were divided in three groups, ten each and were followed for 1 week. Group 1 received placebo, and groups 2 and 3 received 200 and 400 mg tablets, respectively. The 400-mg dose of the herb resulted in significant reduction in systolic BP (SBP) and mean arterial pressure by 11 and 5 mmHg, respectively. The herb was well tolerated, and no adverse effects were noted. The mechanism of action of *C. sativus* for its antihypertensive and vasodilatory effects is possibly mediated through blockade of Ca^{2+} channels, opening of potassium channels, and antagonism of the β-adrenoceptors.

Hibiscus sabdariffa (Roselle)

Hibiscus, widely known as roselle, is a popular folk medicine used for fever, hypertension, and other conditions. Roselle's BP-lowering effects have been studied in both animals [34]

and man [35, 36]. In a randomized, double-blind trial by Herrera-Arellano et al. [35], 193 patients ages 25–61 years with stage I or II hypertension were randomized to treatment with *Hibiscus sandariffa* 250 mg/day (n = 100) or lisinopril 10 mg/day (n = 93) and followed for 4 weeks. *H. sabdariffa* decreased the BP by 17.2/12 mmHg, and 65.12% achieved BP control. There were no significant clinical or metabolic adverse effects noted, and the drug was tolerated by 100% of patients. In another randomized, double-blind, placebo-controlled trial by McKay et al. [36], 65 treatment naive prehypertensive and mildly hypertensive subjects ages 30–70 years were randomized to 3 servings/day of 240 ml *H. sabdariffa* or placebo and were followed for 6 weeks. *H. sabdariffa* lowered the SBP by 7.2 mmHg vs placebo—1.3 mmHg (p = 0.030), but not the DBP compared to placebo. Participants with higher baseline BPs showed greater reductions in BP. No adverse clinical or metabolic effects were noted. This showed that hibiscus tea incorporated into the diet could lower the BP of hypertensive subjects. The antihypertensive effects of *H. sabdariffa* have been attributed to increased production of NO, inhibition of Ca^{2+} channels, and the opening of K_{ATP} channels [37–39].

Nigella sativa (Black Cumin, Seed of Blessing)

Nigella sativa has been used for centuries by different countries (Europe, Middle East, Africa, and South and Southwest Asia) for different ailments including diabetes, gastrointestinal diseases, and hypertension [40]. *N. sativa* and its most active product thymoquinone have been reported by several studies to lower BP in humans as well as in different animal models of hypertension [41–43]. In a randomized, placebo-controlled clinical trial, Fallah Huseini et al. [43] tested the BP-lowering effects of *N. sativa* seed oil in 70 healthy volunteers ages 34–63 years. The subjects were randomized to receive 2.5 ml seed oil or placebo twice daily for 8 weeks. *N. sativa* seed oil decreased the SBP by 10.6 mmHg (p < 0.002) and the DBP by 9.6 mmHg (p < 0.04). The results of this recent study agree with the results of an older study in mild hypertensive patients. In this study, *N. sativa* seed extract 100 and 200 ml twice daily for 8 weeks reduced the BP by 2.2/2.0 mmHg [44]. In addition to BP-lowering, *N. sativa* reduced total and LDL cholesterol. The antihypertensive effects of *Nigella sativa* have been attributed to its vasorelaxant effects by blocking voltage-gated Ca^{2+} channels and reducing oxidative stress [41, 42].

Panax (Ginseng)

Panax species have been used in folk medicine for centuries in Asian countries and lately in the USA, European, and other countries for various ailments that include CVD and hypertension [45]. Heterogenous triterpenoid saponins and steroid glycosides are the main active components of ginseng that mediate its antihypertensive and cardiovascular effects [45]. Regarding its antihypertensive effects, several clinical trials have shown a significant BP-lowering effect compared to placebo. In a randomized, double-blind, placebo-controlled study, Mucalo et al. [46] investigated the effects of American ginseng (AG) on arterial stiffness and BP reduction in 64 diabetic hypertensive patients mean age 63 ± 9.3 years. The patients were randomized to AG extract 3 g/day or placebo and were followed for 12 weeks. AG reduced the BP by 17.4/7.2 mmHg (p = 0.0001), the augmentation index (AIx) by 4.5% (p < 0.041), and the PP by 6.4 mmHg (p < 0.018). In another similar randomized, double-blind, cross-over study, Jovanovski et al. [47] studied the effects of Korean red ginseng (Rg3-KRG) on arterial stiffness and BP in 23 normotensive subjects mean age 25 ± 2 years. The subjects were randomized to either 400 mg Rg3-KRG extract or 400 mg wheat bran on two separate visits with a 7-day washout period. AIx and central BP were measured by applanation tonometry. Compared to control, Rg3-KRG produced significant reductions in AIx by 4.3 ± 8.9% (p < 0.03), central SBP by 5.0 ± 7.9 mmHg (p = 0.01), central DBP by 3.9 ± 6.6 mmHg (p = 0.01), and brachial BP by 4.4 ± 10.0/3.6 ± 6.4 mmHg (p < 0.05), 3 h after intervention compared to control. Yet, in another study, the effects on BP of *Panax ginseng* extract (Ginseol K-g1) were studied by Rhee et al. [48], in 90 subjects mean age 55.2 ± 11.8 years with BPs ranging from 120 to 159/80–99 mmHg. The subjects were divided into three groups. Group-1 (placebo), group-2 (100 mg K-g1), and group 3 (300 mg K-g1) and were followed for 8 weeks. At week 4, the levels of seated SBP (sSBP) and seated DBP (sDBP) were decreased from baseline by 3.1/2.3 mmHg only with the high dose (300 mg) of K-g1 (p < 0.05). However, at week 8, the differences between the groups were no longer different. There were no significant clinical or metabolic adverse events noted. Regarding the BP-lowering effects of *P. ginseng*, these have been attributed to its vascular effects mediated by dramatic increase in eNOS expression and increased production of NO in addition to blockade of Ca^{2+}-gated channels [46, 48].

Salviae miltiorrhizae (Chinese Sage)

Salviae miltiorrhizae, known as Danshen or red Chinese sage, is one of the oldest and most frequently consumed Chinese herbs and is commonly used for the treatment of CVDs [49]. Its antihypertensive effects have been mostly studied in animals where it has been shown to exert a significant BP-lowering effect [50, 51]. So far, there is only one study published in human subjects regarding the antihypertensive effects of *S. miltiorrhizae* by Yang et al. [52]. In this study, 55 Taiwanese patients with uncontrolled mild to moderate hypertension with current conventional treatment ages 18–80 years

were randomized to either to Danshen extract capsules 1000 mg twice daily (n = 30) or placebo capsules (n = 25) and were followed for 12 weeks. The seating BPs prior to randomization were 153.1 ± 9.4/85.6 ± 10.8 in the Danshen group and 157.3 ± 17.5/87.8 ± 8.7 mmHg in the placebo group. After 12 weeks of treatment, the SBP was reduced by 13.9 mmHg with Danshen vs 4.2 mmHg with placebo (p = 0.005) and the DBP was reduced by 4.0 mmHg with Danshen vs 3.2 mmHg for placebo, respectively (p = ns). The drug was well tolerated, and there were no adverse interactions with the other antihypertensive drugs. The antihypertensive mechanism of Danshen is mediated though vasodilatation by the increased generation of NO and its antioxidant, anti-proliferative, and anti-inflammatory effects [50–52].

Herbs with Possible Antihypertensive Effects in Human Subjects

There are several herbs with possible antihypertensive properties from animal studies, but without confirmation of these actions by clinical trials with human subjects.

Andrographis paniculata (King of Bitter)

Andrographis paniculata is a plant commonly known as the "King of bitter" and has been used by Asian traditional medicine for the treatment of the common cold, CVD, and hypertension [15•]. Several labdane-type diterpenoid compounds have been identified in *A. paniculata* extracts with potential antihypertensive effects, due to increase in NO release and the inhibitory effects on ACE and reactive oxygen species (ROS) in SHR [53].

Apium graveolens (Celery)

Apium graveolens has been shown to significantly decrease the BP in deoxycorticosterone acetate-induced hypertension in rats as well as in SHR [54]. The antihypertensive effect is attributed to inhibition of intracellular Ca^{2+} influx through voltage-gated calcium channels.

Bidens pilosa (Blackjack)

Bidens pilosa belongs to the family of Asteraceae and has been shown to exhibit antihypertensive effects in different hypertensive rat models [55]. *B. pilosa* is an easy to grow herb that is widely distributed throughout the world as rich source of food and medicine for animals and humans. However, its effects and side effects have not been studied in human subjects [55].

Coreandrum sativum (Cilantro, Coriander)

Coriandrum sativum is being used in several countries as a culinary ingredient as well as traditional medicine for the treatment of CVDs and gastrointestinal ailments [15•]. So far, there have not been any clinical trials for the treatment of hypertension. In animal studies, *C. sativum* has produced a dose-dependent reduction in SBP and DBP in normotensive Sprague-Dawley rats [56]. Its antihypertensive effects have been attributed to its vasodilatory and antioxidant properties.

Cymbopogon citrate (Lemongrass)

Lemongrass has been used widely by traditional medicine in several countries including Brazil, China, and Southern Asia for the treatment of hypertension due to its active vasodilating ingredient citral [56]. Lemon grass has been shown to reduce BP in an experimental hypertensive rat model [57], but not in human subjects. The BP-lowering effects of lemongrass have been attributed to its vasorelaxant and antioxidant properties [57].

Besides these herbs, there are also several other herbal medicines used primarily by the traditional Chinese medicine for the treatment of hypertension and cardiovascular diseases in man recently published in English in a review by Hao P. et al. [58]. However, the original publications are all in Chinese.

Mechanisms of Action of Antihypertensive Herbs

In order to understand the antihypertensive action of herbs, it is necessary to examine their effect on the various factors or processes that are involved in the development and maintenance of hypertension. These factors include the role of vascular smooth muscle cells, the role of endothelial cells, the role of ROS, and the role of hormones endothelin-1 and angiotensin II (Ang II). The mechanisms of action of the main herbs used for the treatment of hypertension are summarized in Table 3 and will be discussed here.

The Role of Vascular Smooth Cells

The vascular smooth muscle cell participation in the development of hypertension is through their increased growth and encroachment on vascular lumen leading to increase in peripheral vascular resistance [59]. This process is generated through the interaction of various modulating factors that either stimulate or inhibit vascular smooth muscle cell (VSMC) growth. The most important factors that are involved in the vascular remodeling are platelet-derived growth factor (PDGF), the fibroblast growth factor (FGF), the endothelin-1, the Ang II, and the Ca^{2+}-calmodulin interaction, which controls the

Table 3 Summary of mechanisms of action of the main antihypertensive herbs

Herb	Mechanisms of action
Allium sativum	Vasodilation from increased of NO and H_2S levels. Blockade of ACE
Beetroot	Vasodilation from increased levels of NO from inorganic NO_2^-
Camelia sinensis	Vasodilation from increased levels of NO from flavonoids contained in Camelia. Reduction of endothelin-1
Coptis chinensis	Increased levels of NO, PGI_2, blocking Ca^{2+} voltage channels, opening K_{ATP} channels, and decreasing catecholamine levels
Crataegus species	Vasodilation from increased production of NO from procyanidins and flavonoids contained in Crataegus species
Crocus sativus	Vasodilation from crocin, picrocrocin, safranal, crocetin, flavonoids, and anthrocyanins contained in *Crocus sativus*
Hibbiscus sabdariffa	Vasodilation from increased production of NO, blockade of Ca^{2+} voltage channels, and opening of K_{ATP} channels
Nigella sativa	Vasodilation through blockade of Ca_{2+} voltage channels and reduction of oxidative stress
Panax ginseng	Vasodilation from increased production of NO and blockade of Ca_{2+} voltage channels
Salviae miltiorrhizae	Vasodilation from increased production of NO and from antiproliferative, antioxidant, and anti-inflammatory effects

NO nitric oxide, *H_2S* hydrogen sulfide, *ACE* angiotensin converting enzyme, *NO_2^-* inorganic nitrite, *PGI_2* prostaglandin I_2

vascular tone through the cross-bridge cycling of the contractile proteins actin and myosin [59–62]. Several herbs discussed in this review interfere with the action of these factors and decrease the BP.

Endothelial Cells

The endothelial cells play a significant role in many aspects of cardiovascular homeostasis, since endothelial cell function is regulated by a variety of receptors. These receptors induce the release of vasoactive substances that regulate the vascular tone and smooth muscle cell function like the vasodilators, NO, prostaglandin I_2 (PGI_2), and endothelial-derived hyperpolarizing factor, as well as the vsosoconstrictors, endothelin-1, thromboxane, and PDGF [63]. When there is an imbalance between these vasoactive agents, an increased production of ROS may result, leading to endothelial dysfunction and eventually, the development of hypertension [64]. However, endothelial dysfunction can be reversed by several herbal remedies discussed in this review, accounting for their antihypertensive properties.

Reactive Oxygen Species

Clinical evidence indicates that increased generation of ROS by different pathologic states has been shown to play a significant role in the pathogenesis of atherosclerosis, hypertension, and other vascular complications through oxygen reactive radicals like, hydrogen peroxide (H_2O_2), and superoxide (O_2^-) and hydroxyl (OH^-) anions [64]. ROS regulate many cellular processes in the vasculature such as cell growth, contraction/dilation, and other processes important in maintaining vascular tone and integrity [65, 66]. Several herbs listed in this review have been shown to modify ROS and decrease the BP.

The Role of the Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) plays a very important role in the regulation of BP, mostly through the generation of Ang II by the conversion of Ang I to Ang II by the ACE. Ang II generation causes vascular remodeling and peripheral vasoconstriction leading to increase in systemic vascular resistance through stimulation of the AT1 receptor. In addition, Ang II stimulates the release of aldosterone from the adrenal glands leading to plasma volume expansion through salt and water retention adding to its hypertensive effects. Several herbs discussed in this review have been shown to interfere with the action of ACE and the generation of Ang II [59].

Discussion and Conclusion

The data presented in this review indicate that herbs are fairly safe and effective in inducing moderate reductions in BP either alone or in combination with current antihypertensive drugs and are becoming part of evidence-based medicine for the treatment of hypertension. Their pharmacological actions appear to favorably mediate several parameters implicated in the pathogenesis of hypertension through their action on vascular smooth muscle cells, endothelial cells, ROS, and inhibition of RAAS. The use of herbal medicines continues to increase in popularity, and the past decade has witnessed a tremendous surge in the acceptance and public interest in natural therapies in both the developing and the developed countries. The World Health Organization (WHO) estimates that as many as 5.6 billion people (80%) of the world population are using herbal medicines for primary health care [4•]. However, as the global use of herbal medicinal products continues to grow and many new products are introduced into the market, public health issues surrounding their safety are

becoming a concern. It should be stated at this juncture that approximately 30,000 herbal and food supplements are being sold in the USA with additional 1000 new supplements introduced every year [67]. The problem with herbs in contrast to traditional medicines is that they are not regulated and monitored by the Food and Drug Administration (FDA). In addition, most herbal products lack suitable quality controls, inadequate labeling, and absence of patient information [68•]. They also could be contaminated by heavy metals or be adulterated with pharmaceuticals and prohibited animal and plant ingredients [69]. The WHO is developing programs regarding regulation of marketing of herbs and training workshops for health practitioners regarding the effects and side effects of herbs, since the great majority of health practitioners lack complete knowledge about medicinal herbs [70]. Indeed, the lack of sufficient clinical trials constitutes a significant limitation on their use at present. In this respect, it is important to note that there can be interactions of herbs with existing antihypertensive and other drugs that can lead to serious adverse events and therefore their administration should be closely monitored [4•, 5, 20]. Another problem with the use of CAM is the out of pocket expenses, which are considerable (Table 1), since these products are not approved by the FDA and therefore not covered by the health insurance providers for the time being.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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