Atenção Interdisciplinar em Saúde 2

Samuel Miranda Mattos
Kellen Alves Freire
(Organizadores)

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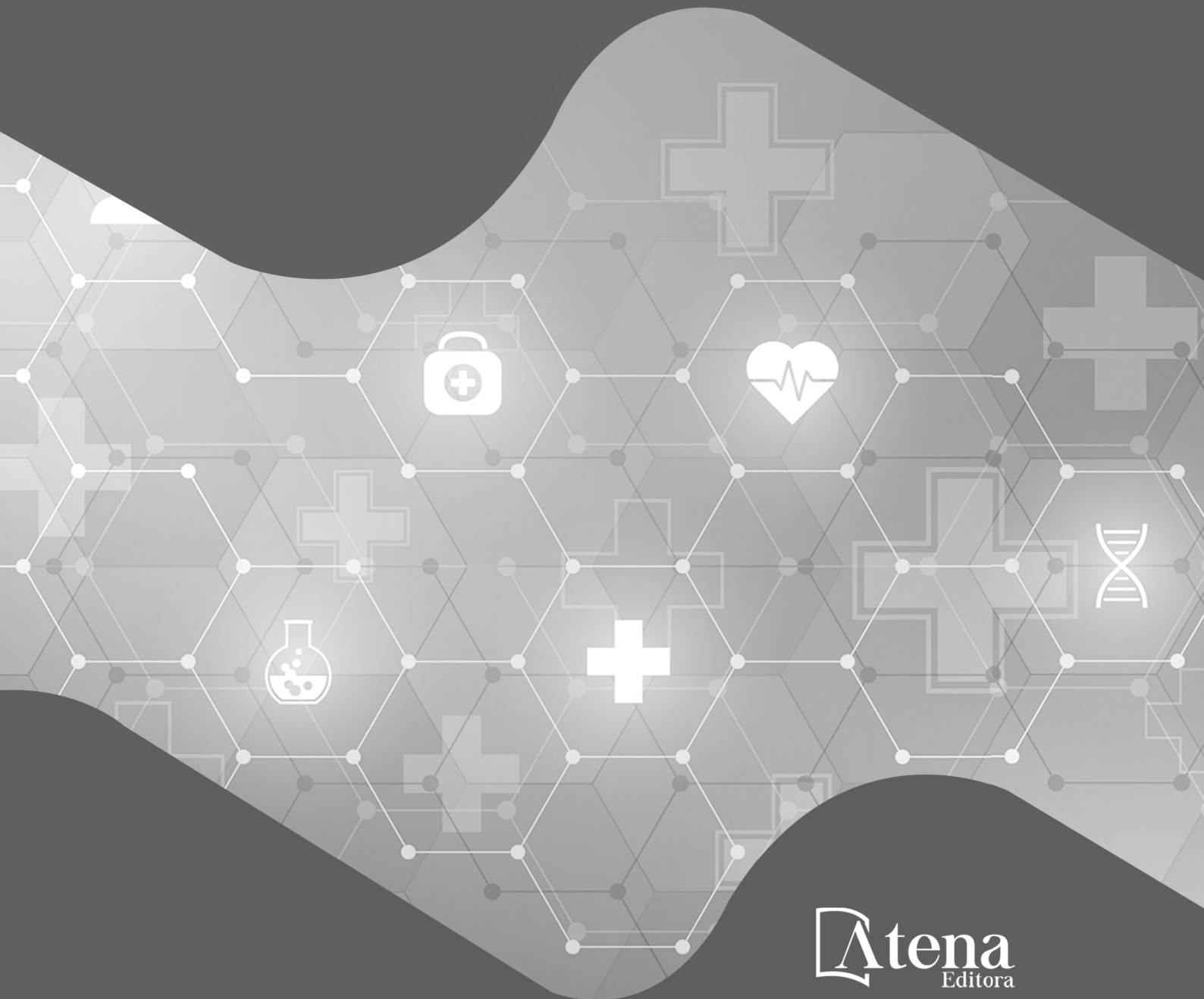

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APRESENTAÇÃO

Constata-se que a interdisciplinaridade profissional reflete diretamente no avanço e melhoria de atendimento na população. Dentro do campo interdisciplinar, encontramos o setor saúde, este que é composto por diversos profissionais que trabalham arduamente para a melhoria dos serviços de saúde, contribuindo na prática clínica e científica.

Acredita-se que registrar e divulgar o modo de trabalho, o conhecimento científico e relatar experiências são estratégias para o aprimoramento do avanço da humanidade.

Sendo assim, nesta coletânea "*Atenção Interdisciplinar em Saúde*", o leitor terá a oportunidade de encontrar trabalhos de pesquisa de caráter nacional e internacionais sobre saúde, produzidos em língua portuguesa, inglesa e espanhola, divididos em quatro volumes.

Destaca-se que o volume I e II tem-se predominantemente pesquisas de revisão de bibliográfica, literatura, integrativa, sistemática e estudo de caso. Já o volume III e IV, encontra-se pesquisas com diferentes desenhos de estudo. Todos os artigos trazem uma ampla visão de diferentes assuntos que transversalizam a saúde.

Acredita-se que o leitor após a leitura desta coletânea estará preparado para lidar com a diversidade de barreiras técnicos/científico no setor saúde. Por fim, convido ao leitor a realizar uma excelente leitura e uma reflexão sobre as temáticas apresentadas, AbraSUS!

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SUMÁRIO

CAPÍTULO 11

MEDICINAL PLANTS FOR HYPERTENSION – AN OVERVIEW OF SYSTEMATIC REVIEWS

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ABSTRACT: Hypertension is a well-known risk factor for cardiovascular disease and mortality. Medicinal plants are the source of many drugs and can possibly offer solutions to antihypertensive therapy. An overview of systematic reviews was undertaken. A sensitive search was conducted in nine databases, including publications published from January 2006 until November 2016. Systematic Reviews (SR) that have studied the effect of medicinal plants in the treatment of hypertensive patients were selected. The outcomes searched were cardiovascular morbimortality, antihypertensive effect, quality of life and collateral effects. SRs were evaluated by AMSTAR. 41 SR were selected. 23 conducted meta-analysis. 51% of SR were assessed as having good quality. Trials included in SRs have short duration, and cardiovascular outcomes could not be investigated. Only one SR evaluated quality of life. There is moderate quality evidence that garlic, green tea, black tea and flaxseed, decrease slightly blood pressure. There are weak evidence that *Hibiscus sabdariffa*, *Nigella sativa,* beetroot, cacao products, grape seed extract, grape juice and *Salvia hispanica* (chia) have a positive effect of reducing slightly blood pressure. Current evidence points to absence of significant effect in blood pressure of *Panax spp.* (ginseng), *Ginkgo biloba*, *Crataegus monogyna* (hawtorn), *Ribes nigrum* and *Pinus pinaster* (*Picnogenol®*). There are no convincing evidence for the use of medicinal plants as a substitute to the usual antihypertensive drugs, however, some of them can be included in dietetic strategies, as complementary management of hypertension.

KEYWORDS: hypertension, complementary therapies, medicinal plants, overview, systematic review

1 I BACKGROUND

Hypertension is a well-known risk factor for cardiovascular disease. Its prevalence in the population over 25 years is approximately 40%, causing 7.5 million annual deaths, or approximately 12.8% of total mortality.[1] Globally, 51% of stroke (cerebrovascular disease) and 45% of ischemic heart disease deaths are attributable to high Blood Pressure (BP).[2]

Data from the National Health and Nutrition Examination Survey, 2011 – 2012, from United States, showed the difficulty of achieving treatment goals in BP. Only 55% of hypertensive women and 49% of hypertensive men have achieved BP control.[3]

According to World Health Organization 70 to 95% of world population use or have used medicinal plants [4]. This is a widespread practice, widely accepted, that can offer new possibilities in antihypertensive treatment. The potential of medicinal plants as therapeutic agents is well known. 50% of drugs are derived from compounds first identified in plants.[5] Studies *in vitro* and with animal have demonstrated that many plants have potential antihypertensive effects, as some of them are diuretic, have vasodilator action or inhibit the angiotensin converting enzyme.[6]

Because there are a great number of Systematic Reviews (SRs) that study the effect of medicinal plants on BP, it is necessary to systematize information. This paper presents an overview of SRs. An overview is an adequate technology to gather sound information to help clinicians, health managers and policy makers to take decisions. The goal of this overview is to evaluate the available evidence on the effectiveness of the use of medicinal plants in the treatment of arterial hypertension.

2 I METHODS

The methodology used in this research was based on the guidelines from Cochrane collaboration[7] and from the Centre for Reviews and Dissemination`s Guidance for Undertaking Reviews in Health Care, from York University.[8]

We selected SRs that studied the effect of medicinal plants on hypertension. A literature search was conducted in the following databases: Pubmed, Embase, Cochrane, Scopus, ProQuest Dissertations & Theses Global, Lilacs, Scielo, CAPES and Google Scholar, from January 2006 until November 2016. A sensitive search was conducted in order to get as many as possible publications. Additional research was carried out by accessing the references of selected articles. There was no restriction of language. Two reviewers independently accessed eligibility of the studies and disagreement where solved by consensus.

Literature search was individualized for each database. The following descriptors and terms were used: *Hypertension, high blood pressure, antihypertensive, antihypertensive agent, phytotherapy, herb, herbs, herbal, medicinal plant, plant extract, plant preparations, botanicals, systematic, meta-analysis,* and *overview*.

Specialists in herbalism were contacted to suggest plants, which were included in the search strategy: *Allium, Andrographis, Apium, Bidens, Boerhavia, cacao, Camellia, Coix lacryma, Coptis, Coriandrum, Crataegus, Crocus, Cymbopogon, Equisetum, Hibiscus, Nigella, Panax, Petroselinum, Phyllanthus, Plantago, Salvia, Sechium, Taraxacum, Tulbaghia, Zingiber*. In the databases: LILACS, SCIELO and CAPES the search included also terms in Spanish and Portuguese

The inclusion criteria of the SRs were: (1) Being a SR (defined by describing that a search was made in the literature with an explicit and reproducible method, and with explicit inclusion and exclusion criteria); (2) To have studied the effect of medicinal plants in the treatment of hypertensive patients. Exclusion criteria were: (1) To have researched isolated active substances; (2) Research of multiple plants intervention; (3) Not focusing on antihypertensive treatment; (4) No presentation of values of effect in BP; (5) Duplicated data; (6) Review that has been updated.

The following data were extracted: Objectives of the review; Search method; Eligibility criteria; Number of included trials that studied the effect on hypertension with population number and characteristics; Intervention; Controls; Results; Collateral effects; Author's conclusions; limitations of the review and methodological quality. Assessment of the methodological quality of SRs where made with AMSTAR instrument.[9] One reviewer extracted data with a standard form and a second reviewer checked the information. Disagreements where solved by consensus.

In this paper are presented the methodological quality and the characteristics of each SR included, and are described the effects of interventions and collateral effects founded for each studied plant. Meta-analysis of meta-analysis will not be conducted.

3 I RESULTS

The database search identified 1794 articles. After deletion of duplicates 1265 records were selected. These articles were then carefully evaluated by title reading, and the remaining by abstract reading. Articles that were clearly not related to the focus of the research were excluded. 187 articles were selected to be read in full text. Complementary search identified further three articles, being selected in total 41 SRs. The selection process, with causes of exclusion can be seen in Figure 1.

All selected SRs were in English language. All analysis used 95% confidence interval. Description of the included SR are presented in Table 1. Table 2 presents the meta-analysis results.

A growth in the number of SRs studying the effect of medicinal plants on hypertension is observed in recent years. Six reviews were published from 2008 to 2010, eleven reviews from 2011 to 2013 and twenty reviews in the period from 2014 to 2016. Considering the 41 included reviews, 51% were considered of good quality, fulfilling at least 7 of the 11 AMSTAR criteria, but only two met all the criteria[44, 39].

The most prevalent deficiencies were: not to have provided information about *a priori* protocol in 31 articles, not to have provided a list of included and excluded articles in 34 SRs. AMSTAR complete evaluation can be seen in Table 3.

Only one SR reported outcome of Quality of Life[25], two trials were found that reported effect of green tea in quality of life. Significant difference was found only in post-intervention scores on hedonic tone (P = 0.048) in one study, whereas no significant effect on quality of life could be identified in the other trial (P>0.05).

No SRs reported results for cardiovascular outcomes, or death for any cause, possibly because of the short duration of trials. The longest included trials lasted 27 months for ginseng[34], one year for flaxseed[32], 26 weeks for garlic[13] and green/black tea[20], and 18 weeks for cacao[44]. For all other studied plants, the trials lasted less than 18 weeks. At the moment, evidence on the use of medicinal plants for hypertension treatment relies only on the effect in reducing BP.

A summary of results, quality of evidence and collateral effects found is presented in the sequence.

Allium sativum (garlic)

With the exception of the study from Reinhart[11] made in 2008, the recent meta-analysis[13-16] published in 2015 and 2016 point to a significant effect of garlic in reducing SBP between -4.4 mmHg to -9.4 mmHg and DBP by -2.0 mmHg to -6.1 mmHg. Studies lasted from 2 to 26 weeks, short time to verify significant effects on cardiovascular morbimortality.

In two meta-analysis[14,16], the overall methodological quality of included trials was moderate. In three meta-analysis[11, 16, 17] there was no evaluation of trials quality.

The more prominent side effect of garlic treatment are body odor and halitosis.[13, 15-17] In Ried[16] one third of participants complained about odor. These side effects are most prominent with raw garlic and are improved in some odor-free garlic preparations[17]. Smell difficult blinding process. Knox[47] found two trials that studied perception of odor by patients. In one trial, despite using agents designed to lessen the odor and taste, 90% of patients given garlic supplements noticed a garlic smell. In another trial, 77% of patients receiving garlic, correctly guessed that they were taking garlic.

In Rohner[13] three trials reported dropouts in the garlic groups due to adverse events in 5 of 105 individuals. All events were related to gastrointestinal symptoms (bloating, discomfort/mild pain). The use of Garlic in the morning or with food can help with collateral effects.[15]

There are reports of allergic disturbance, including anaphylaxis and of coagulation disturbance with high doses.[17] Garlic can interact synergistically with anticoagulants.[47] The use should be discontinued before surgeries.

Beta vulgaris (beet root)

One small meta-analysis[18] with 15 trials and 254 individuals, mostly healthy young people studied beetroot in hypertension, and found statistical significant reduction of SBP of -4.4 mmHg (-5.9, -2.8) and no effect on DBP.

Three trials included in meta-analysis use not beetroot, but nitrate salts, so indirectness bias is possible. However, subgroup analysis excluding nitrate salts trials showed similar results in SBP reduction of -4.5 mmHg (-6.4, -2.5) and also no statistically significant effect on DBP. Inclusion of studies with acute effect or short-term effect (the longest study lasted two weeks) was another limitation of beetroot meta-analysis. Most of included trials were considered of good methodological quality.

The most common side effect was red urine and red stools, and no serious collateral effect was found.[18]

Camellia sinensis (black tea, green tea)

Many meta-analysis[19-26] were made to study *C. sinensis*. With the exception of the oldest meta-analysis[48], they all point to a small reduction of BP, with an effect in SBP of -1.5 mmHg to -2.2 mmHg and DBP of -1.0 mmHg to -2.8 mmHg.

Subgroup analysis showed more effect with use for more than 12 weeks[22, 24] with reduction of SBP between -2.6 mmHg to -3.0 mmHg and DBP of -2.2 mmHg to 2.4 mmHg. There is a slightly bigger effect on hypertensive patients[21]. Each 10 mmHg higher baseline BP was associated with a 1 mmHg larger effect.[20]

The BP lowering effects of tea is not influenced by ethnicity, caffeine intake, tea polyphenol doses, health status of participants and study quality.[21] Onakpoya[23] conducted the only SR that study interest conflict, and found that 12 from 18 trials included in meta-analysis were financed by green tea industry or authors were affiliated with green tea manufacturing industries.

Khalesi[21], evaluated the included trials as having good quality. Two SRs[20,] reported that few trials blinded patients, Hartley[19] informed that many studies have unknown risk of bias. Two SRs[24, 26] reported that included trials have low methodological quality and one SR[23] specified allocation concealment risk of bias in included trials.

Green and black tea are widely consumed and considered safe. They are the second most used beverage in the world, only after water.[51] There was reports of constipation, elevated BP, and rash.[23] Controversial information exists on green tea having potential hepatoprotetive or hepatotoxic effect.[23]

Crataegus monogyna (hawthorn)

There was found just one trial, with 36 individuals, that showed no statistically significant effect on BP.[47]

Hawthorn may cause fatigue, nausea, and rashes. Because of the herb's

proposed vasodilatory effects, hawthorn should be used with caution when combined with other vasodilators.[47]

Ginkgo biloba

One SR[27] conducted two meta-analysis. One with 332 individuals, showed a tendency of a slight effect, not statistically significant, in reducing BP. Another meta-analysis with 5 trials and 684 individuals was conducted with dichotomous results (effective or ineffective), compared Ginkgo biloba extract plus conventional antihypertensive against conventional antihypertensive alone. It is the only meta-analysis of our study that analyses dichotomous results. They found that BP is significantly decreased in experimental group at the end of treatment RR: 1.08 (1.02, 1.14); P = 0.01.

All included studies from both meta-analysis have risk of bias. The authors of SR[27] conclude that there is no convincing evidence to support the routine use of Ginkgo Biloba for hypertension.

Few included trials studied collateral effects. One trial reported abdominal discomfort and loss of appetite in 6 cases.[27]

Glycine max (soybean)

A small meta-analysis[49] with 299 individuals showed a tendency, not statistically significant, in reducing BP. The overall methodological quality of included trial were evaluated as low. There was no information about collateral effects.

Hibiscus sabdariffa (roselle)

A small meta-analysis[30] with 370 patients showed that roselle supplements reduce SBP by -7.5 mmHg and DBP by -3.5 mmHg. Results with high heterogeneity (I^2 92% for SBP and 68% for DBP). Four of five included trials have low methodological quality. The longest trial lasted only 6 weeks.

Only one trial informed about occurrence of collateral effects. It reported 28% withdrew related to roselle extract taste.[29]

Linum usitatissimum (flaxseed, linseed)

Meta-analysis results[31, 32] point out a slight effect of flaxseed on SBP of -1.8 mmHg to -2.8 mmHg and DBP of -1.2 mmHg to -2.4 mmHg. In general, there was poor methodological quality in the included trials.

Flaxseed is considered safe. Two studies reported only mild cases of constipation and other minor gastrointestinal problems.[31]

Nigella sativa (nigella)

A meta-analysis[33] with 11 trials and 860 patients found that Nigella reduce SBP by –3.3mmHg, and DBP by –2.8mmHg. Six from eleven of the included trials were considered of having a high or unclear risk of bias. Sahebkar[33] found no serious adverse reactions, and reported only mild nausea in two included trials.

Panax spp. (ginseng)

In the past, there was concern that ginseng would increase BP, but available literature is reassuring. One meta-analysis[38] with 17 trials and 1381 patients demonstrated neutral effect on BP of genus *Panax*. There was low methodologic quality in 47% of the included trials.

The safety profile of ginseng is generally safe.[36-38] In Komishon[38] SR, no side effects have been reported. *P. ginseng* was associated with gastrointestinal problems ranging from stomach discomfort and nausea to vomiting and diarrhea. Also with insomnia, palpitations, headache and mild hepatic dysfunctions.[36, 37] *P. quinquefolium* (american ginseng) was associated with insomnia, headache, chest discomfort, and diarrhea, plus type 2 diabetes mellitus (two cases in 130 individuals).[36, 52]

Pinus pinaster (Picnogenol®)

One SR[39] studied the effects of Picnogenol® (Trademark of *P. pinaster* bark extract). Two small trials (69 individuals in total) showed no reduction of BP. No collateral effect was found in the SR.

Ribes nigrum (blackcurrant)

One trial, with 28 individuals showed no statistically significant effect on BP.[47] There was no information about collateral effects.

Salvia hispanica (chia)

Two SRs[40, 41] included one small trial[53] with *S. hispanica*, with 27 healthy volunteers (20 in the end of the trial). It demonstrated a reduction of SBP of 6.3 ± 4 mmHg ($p < 0.001$).

The historical use of *S. hispanica* suggests that it is safe for consumption by nonallergic individuals, but there are reports of gastrointestinal symptoms and theoretically additive interaction with anticoagulants.[40]

Theobroma cacao (cacao, cocoa, chocolate)

The four meta-analysis[42-44, 48] included in our oveview point to a small effect of cacao on diminishing BP. But not all reviews found statistically significance on the

effect, see Table 2. In Ried's[44] meta-analysis roughly half of the included trials had some methodological issues. In Hooper[43], no included trials were considered at low risk of bias.

Financial bias is possible. In one of the biggest meta-analysis[42], 54% from the included studies had cacao industry funding or the authors were employed by the cacao industry. In Ried's[44] meta-analysis, from 20 trials, 8 had industry funding and 3 had unclear funding source.

Control used in trials were also very heterogeneous. Subgroup analysis showed effect when cacao was controlled with products without flavonoid, SBP effect of -3.70mmHg (-6.02, -1.3) I^2 86% and DBP of -2.71 (-4.26, -1.15) I^2 77%.[44] But no statistical significance is identified when controls have a low flavonoid content. This confounding factor probably lowered the calculated effect of cacao.

Ried[44] reports the number of patients who withdrew treatment because of collateral effects (cacau intervention/ control). As a total of 5% / 1%, with gastrointestinal complaints (n=5/2), distaste of the trial product (n=3/1), headache (n=2/0), and jitteriness (n=1/0). The product with a high theobromine content in one trial had a laxative effect on (n=12/2) patients.

Vitis vinifera (grapes, grape seed extract, wine, grape juice)

A recent meta-analysis[46] with 810 individuals, on grape seed extract effect on BP showed reduction of SBP of -6 mmHg and DBP of -2.8 mmHg. They conducted a limited literature search and not properly evaluate quality of included trials.

Britto[50] describes one small trial controlled with placebo that investigated grape juice, on 40 hypertensive men with reduction of SBP of –7.2 mmHg and DBP of –6.2 mm Hg.[54]

Hooper[49] studied the effect of grapes and wine in BP in a meta-analysis with 138 individuals and found no difference on BP. There were overall low quality of included trials.

No SRs collect information on collateral effects of *Vitis vinifera* products.

4 I DISCUSSION

It is widely accepted that small decreases in BP will result in a positive impact on public health. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, a 5 mmHg reduction of SBP in population would result in a 14% overall reduction in mortality due to strokes, a 9% reduction in mortality due to Cardiovascular Health diseases, and a 7% decrease in all-cause mortality.[55] This effect of 5mmHg reduction in BP is similar to the effect found for some of the plants here studied.

The meta-analysis on tea effect (*Camellia sinensis)*, point to a humble effect

in hypertensive patients, around -2.6 mmHg to -3 mmHg reduction of SBP, what is expected to bring a small reduction in mortality. The longest trial lasted only 26 weeks, probably not enough to identify long-term cardiovascular outcomes. Indeed, a big cohort study in Japan[51] with 40.530 participants observed that Green tea consumption is associated with reduced mortality due to all causes and due to cardiovascular disease.

As a rule, clinical trial made with medicinal plants used multiple formulations and doses. As an example, Wang SR[14] included studies that used garlic powder in doses ranging from 300 to 2.400mg/day or aged garlic extract in doses between 960 to 2.400mg/day. So it is especially difficult to recommend doses with the available evidence. More research is needed before doses of medicinal plants can be stated for hypertension.

Control used in researches were also very heterogeneous. This was particularly relevant with *Theobroma cacao* studies, were some trials used controls with low flavonoid content and others flavonoid free controls. Subgroup analysis showed effect only with flavonoid free controls.[44] Future trials should use preferentially flavonoid free controls. This phenomenon raises an interesting question. Do cacao flavonoids have a maximum effective antihypertensive dose? Is just a small dose of cacao flavonoids enough for the effect of lowering BP?

The studied plants showed very few collateral effects, and all listed plants are considered generally safe. But clinical trials have the power to detect only frequent collateral effects, and not all SRs report information about collateral effects. Rare adverse effects are better known by case-control studies.

Our results have some limitations. Despite our efforts in conducting a sensitive search, is always possible that we have missed important SRs. We also did not include SRs published before 2006. Even so, it is likely that some medicinal plants with effect on hypertension were not been listed because they have not been studied by any SR.

Having defined in the selection criteria to exclude association of plants, excluded many SRs of Traditional Chinese Medicine for hypertension. Fortunately, Xinke[56] made recently a consistent overview on Chinese Herbal Medicine for hypertension treatment that fulfills this gap.

The option for choosing a sensitive inclusion criteria, resulted in a big number of SRs that has low methodological quality. Also, it is important to emphasize that most of the trials included in the SRs were not considered to have low risk of bias. It is very important that researchers should follow publication guidelines, so that their work will contribute to build solid evidence.

We hope that these limitations will decrease in the near future, with the continuous process of systematization of scientific evidence. Is our wish that this overview will go on, through a periodically updating process.

5 I CONCLUSIONS

Nowadays existing evidence on the use of medicinal plants for hypertension treatment relies only on BP effect, and not on cardiovascular outcomes. So, there are no convincing evidence for the use of medicinal plants as a substitute to the usual antihypertensive drugs. As most of the studied plants are very safe and widely used by the population, they can be considered to be included as a complementary dietetic strategy for the global management of hypertension.

We have moderate confidence that the regular use of garlic, green tea, black tea and flaxseed, decrease slightly BP, and it sounds reasonable to advice their regular use to hypertensive patients who appreciate them.

There are weak evidence from meta-analysis that *Hibiscus sabdariffa*, *Nigella sativa,* beetroot, cacao products and grape seed extract have a positive effect of reducing slightly BP. Small trials indicate a possible antihypertensive effect of grape juice and *Salvia hispanica* (chia).

Current evidence points to no significant effect in BP of *Panax spp.* (ginseng), *Ginkgo biloba*, *Crataegus monogyna* (hawtorn)*, Ribes nigrum* and *Pinus pinaster* (*Picnogenol®*).

Evidence on medicinal plants are of limited quality, but growing fast. We expect an increase of the evidence available in the following years. More clinical trials and SRs with good methodological criteria are welcome to raise the quality of evidence.

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7 I CONFLICT OF INTEREST

The authors declare no conflict of interest.

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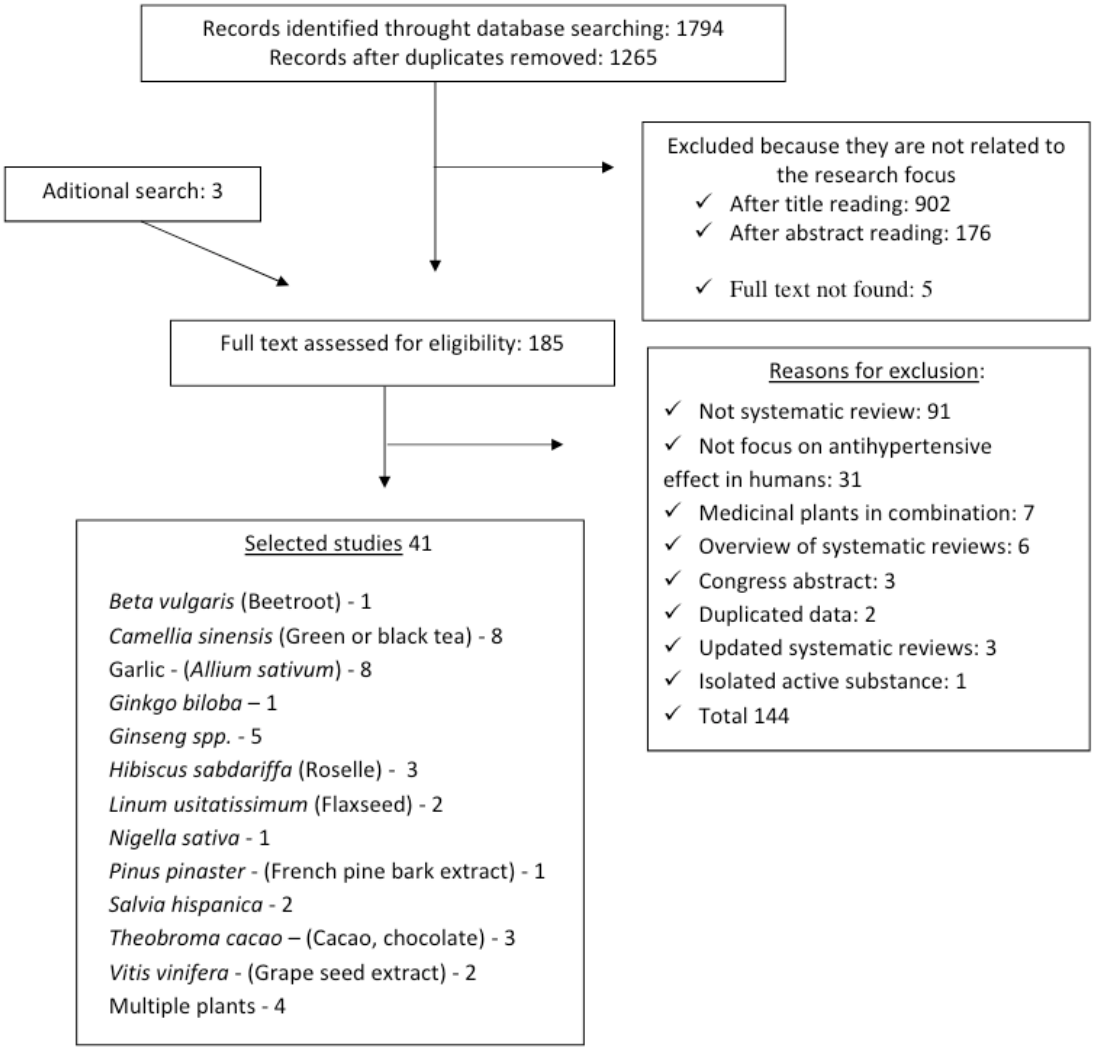

Figure 1. Selection process

Article	Plant	AMSTAR	Type of subjects	Databases searched	Objective	Outcomes	Interest conflict
Pittler, 2007 [10]	*Allium sativum* (Garlic)	1	?	Amed, Cochrane, Embase, Medline, NMCD, NS	Update and assess the clinical evidence based on rigorous trials of the effectiveness of garlic	All health outcomes	Not described

Reinhart, 2008 [11]	*Allium sativum* (Garlic)	4	HT, NHT	Cinahl, Cochrane, Medline	To examine the effect of garlic on BP in patients with and without elevated SBP	Variation in SBP and DBP	Industry funding could not be ruled out in clinical trials. Authors of SR don´t declare IC
Stabler, 2012 [12]	*Allium sativum* (Garlic)	9	HT	Agricola, AMED, BIOSIS, CAB, FSTA, CINAHL, Cochrane, Embase, IPA, LILACS, MEDLINE, ProQuest, SCIRUS and Web of Science	To determine whether the use of garlic as monotherapy, in HT, lowers the risk of cardiovascular morbidity and mortality compared to placebo	All case mortality, cardiovascular events, cerebrovascular events, variation in BP, collateral effects	Do not evaluate IC in included trials. Authors of SR declare no IC
Rohner, 2015 [13]	*Allium sativum* (Garlic)	8	HT	Cochrane, Embase, PUBMED, Web of Science	To evaluate the effect of garlic on BP in individuals with HT	Variation in BP, any other clinical outcome, collateral effect	2 trials with possible IC, 3 without information. Authors of SR declare no IC
Wang, 2015 [14]	*Allium sativum* (Garlic)	7	HT, NHT	MEDLINE, COCHRANE, PUBMED	To update the evidence on the association between garlic intake and BP, and (2) to examine this association according to dosage and duration	Variation in BP	Do not evaluate IC in included trials. Authors of SR declare no IC
Xiong, 2015 [15]	*Allium sativum* (Garlic)	8	HT	COCHRANE, CCTR EMBASE, ICTR PUBMED	To investigate the current evidence of garlic for the treatment of HT	Mortality or cardiovascular events. Variation in BP	Do not evaluate IC in included trials. Authors of SR declare no IC
Ried, 2016 [16]	*Allium sativum* (Garlic)	1	HT, NHT	MEDLINE	To updated a previous meta-analysis on the effect of garlic on BP and reviewed the effect of garlic on cholesterol and immunity	Variation in BP and lipids	Do not evaluate IC in included trials. Authors of SR declare no IC
Varshney, 2016 [17]	*Allium sativum* (Garlic)	2	?	PUBMED	To summarize the evidence for the use of garlic in hypertension, total cholesterol, C-reactive protein, pulse wave velocity, coronary artery calcium and side effects	Variation in BP, lipids, aortic stiffness	Do not evaluate IC in included trials. Authors of SR declare no IC
Siervo, 2013 [18]	*Beta vulgaris* (Beet root)	9	Healthy, HT, DM2	EMBASE, PUBMED, SCOPUS	Investigate the efficacy of inorganic nitrate and beetroot supplementation on BP in humans	Variation in BP, changes in nitrate and nitrite concentrations in biological fluids	6 Trials with IC and 6 trials did not mention IC. Authors of SR declare no IC
Hartley, 2013 [19]	*Camellia sinensis* (Black tea, green tea)	10	Healthy, OBESITY HT, DM, CVR	COCHRANE, CTG, DARE EMBASE, Google Scholar, HEED, HTA MEDLINE, MRCT, OpenGrey	To determine the effects of green and black tea on the primary prevention of cardiovascular heart disease	Cardiovascular clinical events, all-cause mortality and major cardiovascular risk factors, including variations in BP	Do not evaluate IC in included trials. Authors of SR declare no IC
Greyling, 2014 [20]	*Camellia sinensis* (Black tea)	5	Healthy, CHD, HT, HLD	Biosis, Chemical abstracts, Embase Medline	To investigate the effects of black tea consumption on BP	Variation in BP	Do not evaluate IC in included trials. The authors have IC
Khalesi, 2014 [21]	*Camellia sinensis* (green tea)	6	S, OBESITY, OVERWEIGHT, DM, HT, MS	COCHRANE ProQuest, PUBMED, SCOPUS	To examine the effect of green tea consumption on BP.	Variation in BP, lipids, glucose, body mass index	Do not evaluate IC in included trials. Authors of SR declare no IC
Liu, 2014 [22]	*Camellia sinensis* (Black tea, green tea)	8	NHT, Healthy, CAD, HT, CVR, DM, OVERWEIGHT, OBESITY	COCHRANE, EMBASE, PUBMED	To determine the acute and chronic effects of tea intake on BP	Variation in BP	Do not evaluate IC in included trials. Authors of SR declare no IC

Onakpoya, 2014 [23]	*Camellia sinensis* (green tea)	9	HLD, OBESITY, OVERWEIGHT, HT, Healthy, DM, CHD	AMED, CINAHL, COCHRANE, EMBASE, MEDLINE	To evaluate the evidence for or against the effectiveness of green tea on BP and lipid parameters	Variation in BP and lipids	From 18 included trials, 8 were financed by green tea industry and 4 studies, authors were affiliated with green tea manufacturing industries. Authors of SR declare no IC
Peng, 2014 [24]	*Camellia sinensis* (green tea)	6	HT, PRE-HT, OBESITY, OVERWEIGHT, DM	COCHRANE, EMBASE, PUBMED	To quantitatively evaluate the effects of green tea on BP control	Variation in BP	Not described
Li, 2015 [25]	*Camellia sinensis* (green tea)	9	OVERWEIGHT, OBESITY, DM	COCHRANE, CTG EMBASE, MEDLINE	To assess the effect of green tea supplementation compared to placebo on the change in BP among overweight and obese adults. Also to determine the effect on quality of life, adverse events and treatment discontinuation rates	Variation in BP, quality of life, adverse effects and discontinuation rates	Do not evaluate IC in included trials. Authors of SR declare no IC
Yarmolinsky, 2015 [26]	*Camellia sinensis* (Black tea, green tea)	7	HT, PRE-HT, Healthy, OBESITY, DM	COCHRANE, CTG, EMBASE, EMBASE, PUBMED, Web of Science	To evaluate the effects of tea on BP in hypertensive or pre-HT	Variation in BP	Not described
Xiong, 2014 [27]	*Ginkgo biloba*	8	HT	COCHRANE, EMBASE, PUBMED, 4 chinese databases	To critically assess the current clinical evidence of efficacy and safety of *Ginkgo biloba* extract to HT	Variation in BP	Do not evaluate IC in included trials. Authors of SR declare no IC
Ngamjarus, 2010 [28]	*Hibiscus sabdariffa* (Roselle)	6	None trials included	ACMD, AGRICOLA AMED, BIOSIS CINAHL COCHRANE, DARE, EMBASE, FSTA, IBID, IPA, ISI, MEDLINE, openSIGLE	To explore the effect of Roselle on BP in hypertensive adult patients.	Variation in BP, pulse pressure and hearth rate. Withdrawals due to adverse effects	No trials included
Wahabi, 2010 [29]	*Hibiscus sabdariffa* (Roselle)	6	HT e PRE-HT	CINAHL, COCHRANE, CTG, EMBASE, MEDLINE, Google	To determine the effectiveness and safety of Hibiscus sabdariffa in the treatment of patients with pre-HT or HT	Variation in BP	Not described
Serban, 2015 [30]	*Hibiscus sabdariffa* (Roselle)	7	HT, NHT, DM, MS	COCHRANE, EMBASE, MEDLINE, SCOPUS	To investigate the impact of Roselle supplementation on BP	Variation in BP	Do not evaluate IC in included trials. Authors of SR declare no IC
Khalesi, 2015 [31]	*Linum usitatissimum* (Flaxseed, linseed)	7	Healthy, DM, MS, HLD, peripheral artery disease	CINAHL, COCHRANE, PUBMED	To provide information on effective interventions that involve dietary flaxseed consumption, including appropriate duration and flaxseed consumption type, to provide BP and health benefits	Variation in BP	Not described
Ursoniu, 2015 [32]	*Linum usitatissimum* (Flaxseed, linseed)	5	Healthy, DM2, CVR, peripheral artery disease, HLD, Overweight, teenagers, MS	COCHRANE, EMBASE, SCOPUS, PUBMED	To assess efficacy of flaxseed on BP reduction	Variation in BP	Do not evaluate IC in included trials. Authors of SR declare no IC

Sahebkar, 2016 [33]	*Nigella sativa*	7	HT, HLD, OBESITY, H, MS	COCHRANE, MEDLINE, PUBMED, SCOPUS, WEB OF , SCHOLLAR GOOGLE	To quantify the effect of *N. sativa* on BP both in NHP and HP participants.	Variation in BP	Do not evaluate IC in included trials. Authors of SR declare no IC
Buettner, 2006 [34]	*Panax spp.* (Ginseng)	6	HT, CVD, DM, Healthy	AMED, BIOSIS, CAB, COCHRANE, EMBASE, MEDLINE	To examine the evidence for the efficacy of ginseng on cardiovascular risk factors, including BP, lipid profiles, and blood glucose	Variation in BP, glucose and lipids	Not described
Hur, 2010 [35]	*Panax spp.* (Ginseng)	6	HT	CINAHL, CNKI, COCHRANE, EMBAE, MEDLINE, PsyInfo, 6 Korean medical databases, Chinese medical database and 3 Japanese electronic databases	To investigate the effectiveness of ginseng in treating hypertension.	Variation in BP	Three of the included trias were financed by ginseng companies. Authors of SR declare no IC
Lee, 2011 [36]	*Panax spp.* (Ginseng)	5	HT	CINAHL, COCHRANE, EMBASE MEDLINE, 5 Korean medical databases and 4 chinese medical databases	To evaluate the available evidence from randomized clinical trials of the clinical efficacy and safety of ginseng	Any kind of health outcome	Not described
Shergis, 2013 [37]	*Panax ginseng* (Ginseng)	6	H, HT	CINAHL, COCHRANE, MEDLINE, PsychINFO	To evaluated if P. ginseng is an effective and safe treatment in any kind of disease	Any kind of health outcome	7 from 65 studies were sponsored by industry. Authors of SR declare no IC
Komishon, 2016 [38]	*Panax spp..* (Ginseng)	8	HT, H, DM, MS, OBESITY	CINAHL, COCHRANE, EMBASE, MEDLINE	To assess whether ginseng has an effect on BP.	Variation in BP	Do not evaluate IC in included trials. Some authors declare IC
Schoonees, 2012 [39]	*Pinus pinaster* (Picnogenol®)	11	HT	COCHRANE, EMBASE, ICTRP, MEDLINE, CTG, CCT	To assess the efficacy and safety of Pycnogenol® for the treatment of chronic disorders	Any outcome related to cronic disease	One study with IC and the other did not declare source of funding. Authors of SR declare no IC
Ulbricht, 2009 [40]	*Salvia hispanica* (Chia)	4	DM	AMED, CANCERLIT, CINAHL, CISCOM, COCHRANE, EMBASE, HerbMed, IPA, MEDLINE, NAPRALERT	To evaluate the scientific evidence on chia including history, folkloric precedent, expert opinion, pharmacology, dosing, interactions, adverse effects, and toxicology	All kinds of outcomes related to humans	Not described
Ferreira, 2015 [41]	*Salvia hispanica* (Chia)	6	DM	COCHRANE, LILACS, MEDLINE, SCIELO, SCOPUS, WEB OF SCIENCE	To systematize the findings of studies assessing the effect the consumption of chia seed in the prevention/control of cardiovascular risk factors in humans	Variation in BP, lipid profile, glucose, body mass, inflammatory markers, eicosapentoic acid and alpha-linoleic acid	The study included was considered of low financial bias risk. Authors of SR declare no IC

Shrime, 2011 [42]	*Theobroma cacao*	7	Healthy, HT, CHD, DM, OVERWEIGHT, HLD	COCHRANE, CTG, EMBASE, MEDLINE	To evaluate the effect of flavonoid rich cocoa on cardiovascular risk factors and to assess a dose-response relationship	BP, pulse, lipid levels, Body mass index, C-reactive protein, flow-mediated vascular dilation, fasting glucose, fasting, insulin, serum isoprostane, and insulin sensitivity/resistance indices	54% of all included studies had cocoa industry funding or authors were employed by cocoa industry. Authors of SR declare no IC
Hooper, 2012 [43]	*Theobroma cacao*	10	OVERWEIGHT, HT, Healthy, PRE-HT	COCHRANE EMBASE, MEDLINE	To systematically review the effects of chocolate, cocoa, and flavan-3-ols on major cardiovascular risk factors	Variation in BP, lipids, glucose, insulin, Glycosylated hemoglobin, flow mediated dilatation and C-reactive protein	From the total of 42 SR, 28 receive industry funding and 6 were unclear about funding. Authors of SR declare no IC
Ried, 2012 [44]	*Theobroma cacao*	11	HT, PRE-HT, NHT	COCHRANE, DARE, EMBASE, FSTA, MEDLINE, international trials registries	To determine the effect of flavonoid rich chocolate or cocoa products on BP in people with or without HT	Variation in BP	8 trials with industry funding and 3 trials without information on funding. Authors of SR had governmental funding
Feringa, 2011 [45]	*Vitis vinifera* (Grape seed extract)	7	HT, smoker, CVR, MS, Healthy	AGRICOLA, COCHRANE, MEDLINE, SCOPUS	To assess the effect of grape seed extract on changes in BP, heart rate, lipid levels, and C-reactive protein, levels	Variation in BP, heart rate, lipid levels and C-reactive protein	Do not evaluate IC in included trials. Authors of SR declare no IC
Zhang, 2016 [46]	*Vitis vinifera* (Grape seed extract)	4	Healthy, HT, PRE-HT, MS	EMBASE, PUBMED	To systematically evaluate the impact of grape seed extract treatment on the changes of BP by meta-analyzing available randomized controlled trials	Variation in BP	Do not evaluate IC in included trials. Authors of SR declare no IC
Knox, 2007 [47]	*Ribes nigrum, Allium sativum*, *Crataegus monogyna*	3	?	COCHRANE, MEDLINE, ProQuest	To systematically review the dietary supplements available for the prevention and treatment of CHD	Variation in BP or in lipids. Cardiovascular events	Not described
Taubert, 2007 [48]	*Theobroma cacao*, *Camellia sinensis*	8	Cacau: Healthy, HT; Tea: NHT, H, HT, CAD, DM, HLD	COCHRANE, EMBASE, MEDLINE, SCI, SCOPUS	To determine changes in BP due to the intake of cocoa products or black and green tea	Variation in BP	Cacau studies: no CI. Tea studies: CI in 2 studies. Authors of SR declare no IC
Hooper, 2008 [49]	*VItis vinifera (wine or grapes), Camellia sinensis), Theobroma cacao, Glycine max* (Soybean)	6	?	COCHRANE, MEDLINE, EMBASE	To systematically review the effectiveness of different flavonoid subclasses and flavonoid-rich food sources on cardiovascular disease and risk factors	Variation in BP, in lipids and flow mediated dilatation. Cardiovascular events	More than 50% of the studies on soy, or wine/grapes had potential IC. Authors of SR declare no IC
Britto, 2013 [50]	*Vitis vinifera (grape juice), Salvia hispanica (chia), Allium sativum (garlic)*	1	HT, PRE-HT, DM, HLD	MEDLINE, PUBMED	To update of the evidence about effectiveness of isolated nutrients extracted from food, nutritional supplements, and novel foods proposed to have the capacity to reduce BP in HT, HLP, DM, and obese patients	Variation in BP	Not described

BP: Blood pressure, CHD: Coronary Hearth Disease, CVR: Cardiovascular risk, DM: Diabetes mellitus (not especified), DM2: Diabetes mellitus type 2, HLD: Hyperlipidemic, HT: Hypertension, IC: Interest conflict, MS: Metabolic syndrome, NHT: Not Hypertensive, PHT: Pre-hypertension, SR: Systematic review

DATABASES ACMD: Allied and Complementary Medicine Database, CCT: current controlled trials, Cochrane: Cochrane library, CCTR: Chinese Clinical Trial Register, CINAHL: Cumulative Index to Nursing and Allied Health Literature, CTG: Clinical trials.gov, DARE: Database of Abstracts of Reviews of Effects, FSTA: Food Science and Technology Abstracts, HEED: Health Economics Evaluations Database, HTA: Health Technology Assessment Database, IBID: International Bibliographic Information on Dietary Supplements, ICTR: International clinical trial registry by U.S. National Institutes of Health, ICTRP: The WHO International Clinical Trials Registry platform, IPA: Global Health International Pharmaceutical Abstracts, ISI: ISI Web of Knowledge, NS: Natural Standard, NMCD: Natural Medicine Comprehensive Database, MRCT: MetaRegister of controlled trials, ProQuest: ProQuest Dissertations and Theses

Article	Plant	AMSTAR	Duration of trials	Number of studies related to hypertension/ number of patients	Effect in SBP (mmHg)	Effect in DBP (mmHg)
Reinhart, 2008 [11]	*Allium sativum* (Garlic)	4	?	7/262 (Subgroup – non-HT patients)	-0.5 (-2.1, 3.1) $I^2 < 25\%$	0.9 (-0.9, 2.7) $I^2 < 25\%$
			?	3/139 (Subgroup – HT patients)	-16.33 (-26.45, -6.22) $I^2 < 25\%$	-9.28 (-13.30, -5.25) $I^2 < 25\%$
Rohner, 2015 [13]	*Allium sativum* (Garlic)	8	8 to 26 weeks	9/482	-9.36 (-12.77, -5.95) I^2 67%	-3.82 (-6.69, -0.96) I^2 80%
Wang, 2015 [14]	*Allium sativum* (Garlic)	7	2 to 24 weeks	18/799	-3.75 (-5.04, -2.45) I^2 30,7%	- 3.39 (-4.14, -2.65) I^2 67%
				4/165 (Subgroup HT patients)	-4.40(- 7.37, - 1.42) I^2 0%	-2.02 (-4.17, 0.13) I^2 32,3%
Xiong, 2015 [15]	*Allium sativum* (Garlic)	8	8 to 12 weeks	3/125	-6.71 (-12.44, -0.99) I^2 95%	-4.79 (- 6.60, -2.99) I^2 54%
Ried, 2016 [16]	*Allium sativum* (Garlic)	1	12 to 24 weeks	19/908	-5.07 (-7.30, -2.85) I^2 71%	-2.48 (-4.07, -0.89) I^2 72%
				10/468 (Subgroup HT patients)	- 8.35 (-10.58, -6.11) I^2 48%	-6.08 (-7.33, -4.83) I^2 65%
Siervo, 2013 [18]	*Beta vulgaris* (Beet root)	9	Immediate effect to 2 weeks	15/254 (Beet root and nitrate salts)	-4.4 (-5.9, -2.8) I^2 66%	-1.1(-2.2, 0.1) I^2 45%
				12/? (Subgroup – only Beetroot, without nitrate salts)	-4.5 (-6.4, -2.5) I^2 73.7	-0.9 (-2.3, 0.5) I^2 58,8%
Hartley, 2013 [19]	*Camellia sinensis* (Black tea, green tea)	10	3 months to 6 months	4/290	-2.25 (-3.39, -1.11) I^2 0%	-2.81 (-3.77, -1.86) I^2 41%
Greyling, 2014 [20]	*Camellia sinensis* (Black tea)	5	1 to 26 weeks	11/378	-1.8 (-2.8, -0.7) I^2 35%	-1,3 (-1.8, -0.8) I^2 20%
Khalesi, 2014 [21]	*Camellia sinensis* (Black tea, green tea)	6	3 to 16 weeks	13/1040	-2.05 (-3.06, -1.05) I^2 0%	-1.71 (-2.86, -0.56) I^2 52%
				8/? (Subgroup HT patients)	-2.13(-3.23, -1.03)	-2.69 (-3.59, -1.78)
Liu, 2014 [22]	*Camellia sinensis* (Black tea, green tea)	8	1 to 24 weeks	25/1476	-1.75 (-2.41, -1.15) I^2 17.4%	-1,42 (-2.20, -0.63) I^2 52.5%

			Subgroup > 12 weeks	9/? (Subgroup > 12 weeks of intervention)	-2.57(-3.48, -1.65) I^2 0%	-2.15(-2.98, -1.32) I^2 43.3%
Onakpoya, 2014 [23]	*Camellia sinensis* (Green tea)	9	2 to 24 weeks	18/1342	-1.94 (-2.95, -0.93) I^2 8%	-0.98 (-2.14, 0.18) I^2 62%
Peng, 2014 [24]	*Camellia sinensis* (Green tea)	6	3 to 12 weeks	13/1367	-1.98 (-2.94, -1.01) I^2 0%	-1.92 (-3.17, -0.68) I^2 54%
				3/? (Subgroup HT patients)	-3.56 (-5.65, -1.47) I^2 16.2%	-4.3 (-5.99, -2.60) I^2 0%
			Subgroup > 12 weeks	8/? Subgroup > 12 weeks of intervention	-2.98 (-4.21, -1.74) I^2 0%	-2.43 (-3.54, -1.32) I^2 17.2
Li, 2015 [25]	*Camellia sinensis* (Green tea)	9	3 to 16 weeks	14/971	-1.42 (–2.47, –0.36) I^2 52%	-1,25 (-2.32, -0.19) I^2 74%
Yarmolinsky, 2015 [26]	*Camellia sinensis* (Black tea, green tea)	7	8 to 12 weeks	10/834	-2.36 (-4.2, -0.52) I^2 0%	-1.77 (-3.03, -0.52) I^2 0%
Xiong, 2014 [27]	*Ginkgo biloba*	8	8 weeks to 6 months	3/332	-4.37 (-11.20, 2.45) I^2 88%	-3.09 (-6.50, 0.33) I^2 73%
			6 months	5/684 (Meta-analysis with dichotomous results: effective x ineffective)	RR: 1.08 (1.02, 1.14); P = 0.01 (favors *G. biloba* intervention)	
Serban, 2015 [30]	*Hibiscus sabdariffa* (Roselle)	7	15 days to 6 weeks	5/370	-7.58 (-9.69, -5.46) I^2 92%	-3.53 (5.16, -1.89) I^2 68%
Khalesi, 2015 [31]	*Linum usitatissimum* (Flaxseed, linseed)	7	3 to 48 weeks	11/1004	-1.77 (-3.34, -0.09) I^2 0%	-1.16 (-2.64, -0.52) I^2 0%
Ursoniu, 2015 [32]	*Linum usitatissimum* (Flaxseed, linseed)	5	4 weeks to 12 months	15/1302	-2.85 (-5.37, -0.33)	-2.39 (-3.78, -0.99)
Sahebkar, 2016 [33]	*Nigella sativa*	7	4 to 12 weeks	11/860	–3.26 (–5.10, –1.42) I^2 59%	–2.80 (–4.28, -1.32) I^2 60%
Komishon, 2016 [38]	*Panax sp.* (Ginseng)	8	4 to 16 weeks	17/1381	-0.38 (-1.86, 1.11)	0.17 (-1.8, 2.76)
Shrime, 2011 [42]	*Theobroma cacao*	7	14 to 126 days	20/914	-1.63 (-3.12, 0.13) I^2 82,7%	Values not informed, reported as nonsignificant
Hooper, 2012 [43]	*Theobroma cacao*	10		22/950	-1.50 (-3.43, 0.43)	-1.60 (-2.77, -0.43) I^2 52%
Ried, 2012 [44]	*Theobroma cacao*	11	1 to 18 weeks	20/856	-2.77(-4.71, -0.82) I^2 93%	-2.20 (-3.46, -0.93) I^2 70%
				7/297 (Subgroup HT patients)	-3.99 (-7.02, -0.97) I^2 91%	-2.11 (-3.35, -0.86) I^2 53%
Feringa, 2011 [45]	*Vitis vinifera*	7	2 to 12 weeks	5/228	-1.54 (-2.85, -0.22) I^2 11%	-0.65 (-1.67, 0.36) I^2 0%
Zhang, 2016 [46]	*Vitis vinifera* (Grape seed extract)	4	2 to 16 weeks	16/810	-6.08 (-10.74, -1.49) I^2 94%	-2,80 (-4.42, -1.19) I^2 62.4%
Taubert, 2007 [48]	*Theobroma cacao*	8	Cacau: 14 days	5/173	-4.7 (-7.6, -1.8) I^2 87.6%	-2.8 (-4.8, -0.8) I^2 87.6%
	Camellia sinensis		Tea: 7 days to 2 months	5/334	-0.4 (-1.3, 2.2) I^2 0%	-0,6 (-1.5, 0.4) I^2 0%
Hooper, 2008 [49]	*Glycine max* (Soybean)	6	Not described	Soybeans 5/299	-5.76 (-12.29, 0.77)	-4.04 (-8.30, 0.22)

Vittis vinifera (wine, grapes)	Not described	Wine and grapes 3/162	0,59 (-0.88, 2.06)	-0,38 (-0.71, 1.47)

Table 2. Meta-analysis results. Effect on blood pressure and I^2 (variance). All results with 95% confidence interval

DBP: Diastolic blood pressure, HT: Hypertension, SBP: Systolic blood pressure

Autor / year	1	2	3	4	5	6	7	8	9	10	11	Total
Pittler, 2007	-	-	+	-	-	-	-	-	-	-	-	1
Reinhart, 2008	-	+	+	-	-	-	-	-	+	+	-	4
Stabler, 2012	+	+	+	-	+	+	+	+	+	+	-	9
Rohner, 2015	-	+	+	-	-	+	+	+	+	+	+	8
Wang, 2015	-	+	+	-	-	+	+	+	+	+	-	7
Xiong, 2015	-	+	+	+	-	+	+	+	+	+	-	8
Ried, 2016	-	-	-	-	-	-	-	-	+	-	-	1
Varshney, 2016	-	+	-	-	-	+	-	-	-	-	-	2
Siervo, 2013	+	+	+	-	-	+	+	+	+	+	+	9
Hartley, 2013	+	+	+	+	+	+	+	+	+	+	-	10
Greyling, 2014	-	-	-	-	-	+	+	+	+	+	-	5
Khalesi, 2014	-	+	+	-	-	+	+	+	+	-	-	6
Liu, 2014	-	+	+	+	-	+	+	+	+	+	-	8
Onakpoya, 2014	-	+	+	+	-	+	+	+	+	+	+	9
Peng, 2014	-	-	+	-	-	+	+	+	+	+	-	6
Li, 2015	+	+	+	+	-	+	+	+	+	+	-	9
Yarmolinsky, 2015	-	-	+	+	-	+	+	+	+	+	-	7
Xiong, 2014	-	+	+	+	-	+	+	+	+	+	-	8
Ngamjarus, 2010	+	+	+	+	+						+	6
Wahabi, 2010	-	+	+	-	+	-	+	+	+		-	6
Serban, 2015	-	+	+	-	-	+	+	+	+	+	-	7
Khalesi, 2015	+	+	+	-	-	+	+	+	+	-	-	7
Ursoniu, 2016	-	-	+	-	-	+	+	-	+	+	-	5
Sahebkar, 2016	-	+	+	-	-	+	+	+	+	+	-	7
Buettner, 2006	-	-	+	+	-	-	+	+	+	+	-	6
Hur, 2010	-	+	+	-	-	-	+	+	+		+	6

Table 3. AMSTAR – QUESTIONNAIRE

Autor/year	1	2	3	4	5	6	7	8	9	10	11	Total
Lee, 2011	-	+	+	+	-	-	+	+	-		-	5
Shergis, 2013	-	+	+	-	-	-	+	+	+		+	6
Komishon , 2016	+	+	+	-	-	+	+	+	+	+	-	8
Schoonees, 2012	+	+	+	+	+	+	+	+	+	+	+	11
Ulbricht, 2009	-	+	+	+	-	+	-	-			-	4
Ferreira, 2015	-	+	+	-	-	+	+	+			+	6
Shrime, 2011	-	+	+	-	-	+	+	-	+	+	+	7
Hooper, 2012	+	+	+	-	+	+	+	+	+	+	+	10
Ried, 2012	+	+	+	+	+	+	+	+	+	+	+	11
Feringa, 2011	-	+	+	-	-	+	+	+	+	+	-	7
Zhang, 2016	-	+	-	-	-	+	-	-	+	+	-	4
Knox, 2007	-	-	+	-	-	-	+	+			-	3
Taubert, 2007	-	+	+	-	-	+	+	+	+	+	+	8
Hooper, 2008	-	+	+	-	-	-	-	+	+	+	+	6
Brito, 2013	-	+	-	-	-	-	-	-			-	1

Table 3. AMSTAR - QUESTIONNAIRE

Yes: +, No: - , Not applicable: Field left in blank

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest included?

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