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RESEARCH ARTICLE

Nutraceuticals with Blood Pressure Lowering Potential: A Summary of Clinically Relevant Information

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Abstract

Nearly half of patients diagnosed with hypertension are unable to keep their blood pressure under control despite pharmacologic intervention, indicating a need for adjunctive anti-hypertensive therapies [1]. Nutraceuticals may be a promising option for intervention due to their ease of implementation and demonstrated efficacy [2-4]. The use of nutraceuticals clinically has thus far been limited by a lack of guidelines, likely stemming from a history of poor regulatory standards that allow supplements to go on the market before rigorous clinical trials are conducted [5]. Recently, research examining nutraceutical use has begun to catch up with the marketplace, which may allow for clinical use of supplements from reputable companies, such as those approved by third party companies such as National Science Foundation (NSF) International [5]. The following review aims to facilitate the translation of research into clinical application by summarizing the current knowledge on nutraceuticals used as anti-hypertensives. Web-based guidelines from the American Association of Family Physicians (AAFP), American Heart Association (AHA), American Stroke Association, American College of Cardiology (ACC), National Center for Complementary and Integrative Health, European Cardiology Society, the Canadian Heart and Stroke Foundation, and the Mayo Clinic were examined. Nutraceuticals recommended by two or more of these organizations were reviewed, including garlic, fish oil, and cocoa. Specific details on dosage, pharmacokinetics, pharmacodynamics, adverse effects, and drug-herb interactions are discussed in order to summarize clinically relevant information.

Keywords

Hypertension, Preventative medicine, Cardiovascular disease, Nutraceuticals, Adjunctive hypertension therapies

Introduction

Cardiovascular Disease is the leading cause of death in the United States, annually claiming over 610,000 lives, and costing 555 billion dollars per in year in healthcare spending (CDC, AHA). This impact is expected to rapidly increase in the next two decades, with some projections indicating that over 45 percent of the US population will suffer from cardiovascular disease (CVD) by 2035 [6]. The most significant pathophysiologic contributor to cardiovascular disease is the development of hypertension, which, according to new guidelines, is defined as having a systolic blood pressure (BP) reading > 120 and/or a diastolic BP reading > 80 mmHg. The lifetime risk of developing hypertension is 90% [2]. Despite anti-hypertensive medications being one of the most commonly prescribed pharmacologic interventions, only about half of patients are able to keep their blood pressure under control [1]. This problem will be considerably amplified in the coming years, as the new 2017 AHA blood pressure guidelines indicate that an additional 31 million US individuals will need treatment, and 29 million patients currently being treated will need to intensify their current treatment regimens [7]. For this reason, there is a significant and growing need for adjunctive and alternative therapies.

There are a number of effective anti-hypertensive dietary interventions, such as the commonly used Dietary Approaches to Stop Hypertension (DASH) diet, which

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advises a high intake of vegetables, fruits, and whole grains, while limiting intake of sweets, sugary beverages, and red meat [8]. The most recent meta-analysis of clinical trials examining the DASH diet demonstrated decreases in systolic BP of 5.2 mmHg and 2.6 mmHg diastolic [9]. These decreases are significant, as a decrease in systolic BP of 5 mmHg is associated with mortality reductions of 14% from stroke, 9% from heart disease, and 7% from all causes [10]. Unfortunately, even though this approach has shown to be beneficial, few patients are able to consistently follow this rigorous diet. In a recent study following 4,386 patients attempting to eat in accordance with the DASH diet, only 22 percent of patients were able to adhere to it [8]. Moreover, compliance has been shown to decrease with time after intervention [11]. Similarly, for patients in programs to support low sodium intake, which alone has been shown to considerably reduce BP, especially in patients who are 'salt sensitive' rather than have essential hypertension, only 20-40% of patients are able to reduce their intake to below the maximum recommended limit [12-14]. In a cross-sectional study examining reasons for non-compliance with the DASH diet, 70% of participants cited personal reasons such as psychological factors, stress, changes in sleep patterns, and difficulty implementing lifestyle changes as the main reasons for not adhering to the recommendations [15].

While diet modification has proven to be difficult for patients to maintain, it may still be beneficial for physicians to recommend incorporating specific foods, or bioactive compounds that make diets, such as the DASH diet, effective. Bioactive components of food are known as "nutraceuticals", which can be defined as food or a part of a food that provides medical or health benefits, including the prevention and/or treatment of a disease [4]. Use of nutraceutical supplements may be a manageable initial step, or effective adjunctive therapy for patients. In a recent cross-sectional study including 343 patients with cardiovascular disease, 82.5% of patients had used nutraceuticals for a variety of health conditions [16]. According to a recent review, there are several dietary components with pharmacologically active properties that have repeatedly demonstrated reductions in blood pressure that are comparable to the entirety of the DASH diet [17]. These nutraceuticals included Coenzyme Q10, fish oil, garlic, vitamin C, and L-arginine.

Despite the potential role for nutraceuticals as adjunctive therapies for hypertension, implementation into clinical practice is uncommon as there is a lack of guidelines for their use [18,19], as well as a lack of dialog about nutraceuticals between patients and physicians [16,20,21]. This likely stems from a history of poor regulatory standards for supplement use. Manufacturers, rather than the FDA, have had the responsibility for ensuring the efficacy of their products since the signing of the Dietary Supplement Health and Education Act in 1994 [5]. This has allowed for products to be placed on the market without prior clinical trial testing. Recently, research regarding the potential uses of nutraceuticals in clinical trials has begun to catch up to the market place, which may allow for the clinical use of nutraceuticals from reputable companies [22]. Well respected nutraceutical companies are certified as having "good manufacturing products" by third party companies such as the Natural Products Association (NPA, formerly NNFA) and NSF International, which includes toxicology testing, testing for potential contaminants, and testing to verify products correspond to their label [5].

The following review aims to aid in the translation of research into application by summarizing the current knowledge on nutraceuticals used as anti-hypertensive therapies. Web- based guidelines from the American Association of Family Physicians, American Heart Association, American Stroke Association, American College of Cardiology, National Center for Complementary and Integrative Health, European Cardiology Society, the Canadian Heart and Stroke Foundation, and the Mayo Clinic were consulted. Nutraceuticals recommended by two or more of these institutions were reviewed, and include garlic, fish oil, and Cocoa. Co-enzyme Q10 was recommended by multiple organizations, but ultimately was not included in this review because the most rigorous meta-analysis of its' use found no effect on blood pressure [23]. Further, the minerals potassium and magnesium were recommended by multiple organizations but not included due to their mineral status. Information regarding nutraceuticals recommended by at least one organization, and information regarding minerals, are included in Table 1. PubMed, Micromedex, Lexicomp, and the Natural Medicines Comprehensive Database were used to collect relevant articles. Only randomized control trials on human subjects lasting more than our weeks were included in the written portion of this review, however shorter duration studies are included in Table 1. What is currently known about dosage, pharmacokinetics, pharmacodynamics, adverse effects, and drug- herb interactions are discussed in order to summarize clinically relevant information.

Garlic

Dosage and meta-analyses: A meta-analysis of trials evaluating the efficacy of garlic in the treatment of high blood pressure has shown that garlic decreases systolic blood pressure (SBP) by 6.7 mmHg and diastolic blood pressure (DBP) by 4.8 mmHg at doses higher than 300 mg/day for greater than 12 weeks [24]. A separate meta-analysis of trials including only hypertensive patients found a drop of 8.4 ± 2.8 mmHg for SBP and 7.3 ± 1.5 mmHg for DBP ($p < 0.001$) at a dose of 600 or more mg/d for 12-24 weeks [25]. Further analysis from this group determined that the blood pressure lowering effects are additive when combined with the use of anti-hypertensive drugs [26]. All meta-analyses on garlic thus far have used supplements ranging from 300 mg/d

Table 1: Review of anti-hypertensive nutraceuticals.

Nutraceutical & Recommending Organizations	Meta-analysis & number of randomized controlled trials included	BP lowering effects (mmHg)	Dosage & Length of Time
Garlic *AAFP / NCCIH/ Mayo Clinic/ AAC/ Canadian Heart and Stroke Foundation*	Ried [25]; Meta-analysis of 20 RCT's	SBP = -7.6 ± 2.2; p < 0.001 DBP = -6.1 ± 1.3; p < 0.001	600 + mg 12-24 weeks
	Xiong, et al. [24]; Meta-analysis of 7 RCT''s	SBP = -6.7 (-12.4, -0.9); p = 0.02 DBP = -4.8 (-6.6, -2.9); p < 0.00001	300 + mg 12 weeks
	Ried, et al. [110]; Meta-analysis of 11 RCT's	SBP = - 8.4 ± 2.8; p < 0.001 DBP = -7.3 ± 1.5; p < 0.001	600 + mg 12-24 weeks
	Reinhart, et al. [109]; Meta-analysis of 10 RCT's	SBP = -16 (-6.2, -26.5) p<.010 DBP = -9.3 (-5.3, -13.3) p < 0.10	600 + mg > 2 weeks
Magnesium *AAFP / Mayo Clinic/ AHA / ASA/ Canadian Heart and Stroke Foundation*	Dibaba et al. [111]; Meta-analysis of 11 RCT's	SBP = -4.2 (-0.4, -0.03) SMD = -0.20 DBP = -0.3; (-0.5, -0.03) SMD = -0.27	380 mg/d 3 months
	Zhang, et al. [112]; Meta-analysis of 34 RCT's	SBP = -2.0 (-0.4, -3.6); p < 0.05 DBP = -1.8 (-0.7, -2.8); p < 0.05	365-450 mg/d 1-6 months
	Kass, et al. [113]; Meta-analysis of 22 RCT's Jee, et al. [114]; Meta-analysis of 20 RCT's	SBP = reported range of -3 to -4 DBP = reported range of -2 to -3 SBP = -4.3 (-6.3, -2.2); p < 0.001 DBP = -2.3 (-4.9 ,0.0); p = 0.09	Mean of 410 mg/d 3-24 weeks 10-40 mmol/day 3-24 weeks
Omega 3- fatty acids (fish oil) *AAFP / Mayo Clinic/ ASA/ Canadian Heart and Stroke Foundation*	Geleijnse et al. [115]; Meta-analysis of 36 RCT's	SBP = -2.1 (-1.0, -3.2); p < 0.01 DBP = -1.6 (-1.0, -2.2); p < 0.01	3.7 g/d (median dose) > 2 weeks
	Appel, et al. [13]; Meta-analysis of 17 RCT's	SBP = -5.5 (-8.1, -2.9); p < 0.001 DBP = -3.5 (-5.0, -2.1); p < 0.001	3 g/d median of 6 weeks
	Morris, et al. [116]; Meta-analysis of 31 RCT's	Dose-response effect of -0.66/-0.35 mmHg/g omega-3 fatty acids	3-24 weeks
Coenzyme Q10 *AAFP / Mayo Clinic/ Canadian Heart and Stroke Foundation*	Ho, et al. [23]; Meta-analysis of 3 RCT's	SBP = -3.68 (-8.86, 1.49); not significant DBP = 2.04 (-4.86, 0.810; not significant)	100-120 mg/d > 3 weeks
	Rosenfeldt, et al. [117]; Meta-analysis of 12 RCT's	SBP = -16.6 (-12.6, -20.6); p < 0.001 DBP = -8.2 (-6.2, -10.2); p < 0.001	76-360 mg/d 8-12 weeks

Potassium *Mayo Clinic/ Canadian Heart and Stroke Foundation*	Filppilini et al. [118]; Meta-analysis of 18 RCT's	SBP = -4.5 (-3.1, -5.9); p < 0.001 DBP = -2.9 (-1.1, 4.8); not significant	> 90 mmol/day > 4 weeks
	Whelton et al. [119]; Meta-analysis of 33 RCT's	SBP = -3.1 (-1.9, -4.3); p < 0.001 DBP = -1.9 (-0.5, -3.4); p < 0.001	60-200 mmol/day 5 weeks (median)
	Cappuccio et al. [120]; Meta-analysis of 13 RCT's	SBP = -11.9 (-10.5, -13.3); p < 0.05 DBP = -5.4 (-4.4, -6.4); p < 0.01	96 mmol/d (median) > 4 weeks
Cocoa *AAFP / Mayo Clinic / NCCIH*	Desch, et al. [121]; Meta-analysis of 10 RCT's	SBP = -4.5 (-5.9, -3.2); p > 0.001 DBP = -2.5 (-3.9, -1.2); p < 0.001	5-174 mg/d 2-18 weeks
	Ried, et al. [26] Meta-analysis of 13 RCT's	SBP = -3.2 ± 1.9 p = 0.001 DBP = -2.0 ± 1.3 p = 0.003	30-1000 mg/day > 2 weeks
	Ried, et al. [25] Meta-analysis of 40 RCT's	SBP = -1.7 (-3.09, -0.43); p = 0.009 DBP = -1.7 (-2.57, 0.94); p < 0.001	670 mg/day (average) 2-18 weeks
	Hooper [101] Meta-analysis of 42 RCT''s	SBP = -1.6 (-2.77, -0.42) MAP = -1.6 (-3.27, -0.01)	50-100 mg 2-18 weeks
	Egan, et al. [122]; Meta-analysis of 5 RCT''s	SBP = -4.7 p = 0.002 DBP = -2.8 p = 0.006	11-100 g/day > 4 days
	Taubert, et al. [83] Meta-analysis of 5 RCT's	SBP = -4.7 (-7.6, -1.8); p = 0.002 DBP = -2.8 (-4.8, -0.8); p = 0.006	46-105 mg/day > 2 weeks
Vitamin C *AAFP*	Juraschek, et al. [123]; Meta-analysis of 15 RCT's	SBP = -4.8 p = 0.01 DBP = -1.7 p = 0.17	500 mg/d 8 weeks (median)
	McRae [124]; Meta-analysis of 13 RCT's	SBP = -3.9 (-3.6, -0.3); p = 0.04 DBP = -2.1 (-3.1 ,1.1); not significant	500 mg/d 6 weeks (mean)
Flaxseed *NCCIH*	Ursonui [125]; Meta-analysis of 15 RCT's	SBP = -2.8 (-5.3, -0.3); p = 0.027 DBP = -2.4 (-3.8, -0.99); p = 0.001	Powder 28 g-60 g/d OR oil containing 1.2 g-15 g ALA/day OR derived lignin complex 360 mg-600 mg/day. 4 weeks-12 months
	Khalesi, et al. [126]; Meta-analysis of 11 RCT's	SBP = -1.7 (-3.5, 0.09); p = 0.04 DBP = -1.6 (-2.6, 0.5); p = 0.003	30-50 mg/day whole seed flaxseed OR 360-600 mg/day flaxseed lignin 12 weeks- 6 months

Green/Black tea *NCCIH*	Houston M [3] Meta-analysis of 25 RCT's	SBP = -1.8 (-2.4, -1.1) p < 0.01 DBP = - 1.4 (-2.2, -0.6) p < 0.01	100 mg-1200 mg extract with polyphenols 2-24 weeks
	Peng, et al. [127]; Meta-analysis of 13 RCT's	SBP = -1.9 (-2.9, -1.0); p < 0.001 DBP = -1.9 (-3.2, -0.7); p = 0.002	< 585 mg/d 2-24 wks
	Taubert, et al. [83]; Meta-analysis of 5 RCT's	SBP = -0.4 (-1.3, -2.2); p = 0.63 DBP = -0.6 (-1.5, -0.4); p = 0.38	900 + mL/d tea Mean 4 weeks
Probiotics *NCCIH*	Khalesi, et al. [135]; Meta-analysis of 9 RCT's	SBP = -3.6 (-6.5, -0.7); p < 0.01 DBP = -2.4 (-2.4, -0.9); p < 0.01	> 10 Colony-forming units > 8 weeks
	Dong, et al. [128]; Meta-analysis of 14 RCT's	SBP = -3.0 (-4.6, 5.6); p < 0.05 DBP = 1.1 (-2.1 to -0.1); p < 0.05	100-450 ml/d 4-24 weeks
Herb Roselle *NCCIH*	Walton, et al. [129]; Analysis of 10 RCT's	SBP = reported range of -6.3 to -31.9 DBP = reported range of -1.1 to -19.7	9.62 mg/d 4 + weeks
L-arginine *Mayo Clinic*	McRae [130]; Review of 7 meta-analyses	SBP = reported range of -2.2 to -5.4 DBP = reported range of -2.7 to -3.1	8-11 g/d 12-24 wks
	Dong [131]; Meta-analysis of 11 RCT's	SBP = -5.3 (-8.5, -2.3); p = 0.001 DBP = -2.7 (-3.7, -1.5); p < 0.001	4-24 g/d > 4 weeks
Calcium *Mayo Clinic*	Van Mierlo, et al. [132]; Meta-analysis of 40 RCT's	SBP = -1.9 (-2.9, -0.8); p < 0.05 DB = 0.99 (-1.6, -0.4); p < 0.05	1200 mg (mean) > 2 wks
	Allender [133]; Meta-analysis 21 RCT's	SBP = -0.9 (-1.7, -0.05); p < 0.05 DBP = -0.2 (-0.7, 0.4) p < 0.05	0.5 g to 2 g 8 weeks (median)
Folic acid *Mayo*	McRae [134]; Meta-analysis of 12 RCT's	SBP = -2.0 (-3.6, -0.4); p = 0.04 DBP = -0.01 (- 0.1, 1.1); not significant	500 + mg/d 2-16 weeks

Parentheses indicate 95% confidence intervals. SBP indicates systolic blood pressure in mmHg. DBP indicates diastolic blood pressure in mmHg. MAP indicates mean arterial pressure, in mmHg. SMD indicates standard mean difference.

to 900 mg/d. An overview of meta-analyses pertaining to the use of garlic as an anti-hypertensive agent can be seen in Table 1.

Pharmacology: The active components in garlic are allicin, flavonoids and sulfur-containing proteins. The most active compound, allicin, has been demonstrated to have anti-TNF-alpha properties, and therefore anti-inflammatory effects, in human studies [27]. In murine studies, allicin has been shown to have Angiotensin Converting Enzyme (ACE) inhibitory activities, as well as calcium channel blocking activity [28,29]. Sulfur-containing proteins in garlic have been shown to reduce catecholamine sensitivity in humans [30]. In murine studies, the sulfur-containing proteins of garlic have additionally been shown to replenish endothelial glutathione, thereby preventing oxidized LDL-induced

injury [31]. Finally, the flavonoids in garlic reduce oxidative damage, thereby improving arterial compliance, as demonstrated in human studies [29].

Pharmacokinetics: Garlic is rapidly absorbed through mucous membranes and skin, and subsequently metabolized by both the liver and kidney [32-34]. Murine studies suggest that the maximal concentrations of the active component allicin occurs approximately 30 minutes after oral ingestion [35]. Excretion of garlic follows zero order kinetics [36], with the active products having a half-life of approximately 6-hours [37]. Excretion of garlic is primarily via urine, but it also contributes slightly to bile [38].

Adverse effects: Reported effects of oral garlic in clinical trials include malodorous breath, body odor, nausea, vomiting, flatulence, and weight loss [26,39,40]. Furthermore, excretion of garlic may cause polyuria or dysuria in some individuals [41,42]. Oral garlic has been demonstrated to increase fibrinolytic activity and platelet dysfunction in several case studies, and therefore discontinuation at least 10 days prior to surgery is recommended [43,44]. Finally, topical garlic has been reported to induce contact dermatitis and allergic reactions [45-47].

Herb-drug interactions: Garlic has been shown to have antiplatelet activity, and can increase prothrombin time, therefore it theoretically may enhance the effect of anticoagulants or antiplatelet drugs and should be used with caution in combination with drugs such as aspirin, clopidogrel, enoxaparin, and warfarin [43,48,49]. Garlic has also been shown to lower blood glucose levels in both healthy and diabetic individuals. As such, it should initially be monitored when used concurrently with anti-diabetic agents, as dose adjustments may be necessary due to the risk of hypoglycemia [50,51]. The metabolism of garlic appears to alter the cytochrome P450 system, specifically by inhibiting the CYP2E1 enzyme [52]. Therefore, patients taking other drugs metabolized by this system, which includes acetaminophen, chlorzoxazone, ethanol, theophylline, enflurane, halothane, isoflurane and methoxyflurane, should not use garlic as a supplement [53]. Garlic's' alteration of the cytochrome P450 system may also include induction of the enzyme CYP34A, which may increase the metabolism of the antiretroviral agents atazanavir and saquinavir [54,55]. Finally, data suggests that garlic may inhibit the absorption of Isoniazid across the intestinal mucosa, however the exact mechanism of the interaction is unknown [56].

Rigor of the included meta-analyses: The meta-analyses reviewed all show similar trends; reduced SBP ranging from 6 to 8 mmHg and DBP lowered by 4 to 7 mmHg, with more significant reductions when analyzing only hypertensive individuals. All trials had dosages ranging from 300-600 mg/d. The 2016 meta-analysis by Reid included only double-blind, randomized control trials with either parallel or crossover designs. This review assessed the quality of included trials with the help of two reviewers, using the Cochrane Collaboration guidelines [25]. Similarly, Xiong, et al. [24] in 2015 used Cochrane guidelines, and utilized Cochrane software Revman 5.2 to assess quality.

Fish oil

Dosage and meta-analyses: A meta-analysis of fish oil supplementation specifically in untreated hypertensive individuals found a SBP reduction of 5.5, and a DBP reduction of 3.5 mmHg at a dose of 3 g/day for a median of 6 weeks [13]. A separate review using a meta-regression analysis to determine the dose-relationship between fish oil and BP found that supplementation decreased SBP by an average of 2.5 and DBP by 1.5 mmHg independent of dose above 3 g/d for supplementation longer than an 8 week period [58]. This is supported by the observation that higher doses result in the same blood concentration achieved at a supplementation of 3 g/day [59]. This data indicates that fish oil supplementation at 3 g/d may have some benefits, but benefits do not increase with higher dosages. Further, there is evidence that some of the antihypertensive benefits of fish oil come specifically from the active component docosahexaenoic acid, and when this compound is taken in isolation, a dosage of 2 g/d produces a drop in BP over a six week period [4,60]. An overview of the meta-analyses reviewed is presented in Table 1.

Pharmacology: Omega-3 fatty acids contained in fish oil, eicosapentoic acid and docosahexanoic acid, exert a variety of effects on the vasculature. Both murine and human studies have demonstrated that omega-3 fatty acids are able to directly modulate intracellular calcium concentration, resulting in a dilatory effect on vascular smooth muscle [61,62]. Moreover, these molecules have been demonstrated to enhance the generation and bio-availability of the endothelium derived relaxant factor, nitric oxide, by upregulating endothelial nitric oxide synthase, eNOS in both murine and human studies [63]. Finally, the antioxidant properties of these molecules decrease endothelial oxidative stress, slowing atherosclerosis, and preventing vascular inflammatory cascades [64]. These combined effects result in increased arterial compliance in both small and large arteries [61].

Pharmacokinetics: The omega-3 fatty acids in fish oil are easily absorbed as ethyl-esters or triglycerides [65]. Their absorption appears to decrease the absorption of omega-6 fatty acids, which have inflammatory, vasoconstrictor, and thrombo-genic effects [66,67]. They are then metabolized in the liver and redistributed widely throughout the body, resulting in increased levels of omega-3 fatty acids in the serum, plasma, myocardium, and adipose tissue [68,69].

Adverse effects: Fish oil is generally well-tolerated at doses of 3-4 grams/day or less, however halitosis, heartburn, dyspepsia, nausea, loose stools, and rash

have been reported in clinical trials, with increased incidence at higher doses [70,71]. The gastrointestinal upset occurring with supplementation occurs in about 1.5% of patients, and nausea occurs in about 5% of patients [72]. Taking supplements with meals or freezing prior to ingestion seems to decrease these side effects for some patients [73]. Interestingly, supplementation can increase LDL cholesterol levels in some patients, however this increase does not seem to increase the development of atherosclerosis [74]. There is some evidence that fish oil at doses greater than 3 g/day may adversely affect immune function by suppressing B-cell and T-cell function and reducing the production of cytokines, therefore caution should be taken with immunocompromised patients [75,76].

Herb-drug interactions: While fish oil is not a potent inhibitor of platelet function, concomitant use of fish oil may enhance the effects of anti-coagulants or anti-platelet drugs, therefore this combination should be closely monitored [77-80]. In addition, some evidence suggests that oral contraceptives, such as ethinyl estradiol, levonorgesterol, and norethindrone may interfere with fish oil's BP lowering affects [81]. Finally, fish oil may reduce vitamin E levels, though the mechanism is unknown [76].

Rigor of the included meta-analyses: The review by Appel included 6 un-blinded trials, and two trials in which participants were not randomly allocated to treatment or control. The review by Houston in 2010 does not comment on exclusion criteria [61]. The review by Campbell, et al. included only randomized, double blind, cross-over trials with a washout period and paired analysis, and also assessed quality of blinding, randomization, concealment, and loss to follow-up [58]. This review is therefore the most rigorous of trials, and notably correlates with the least significant effect on blood pressure, a SBP/DBP reduction of 2.5/1.5 mmHg.

Cocoa

Dosage: The most recent meta-analysis of cocoa's effect on hypertension contained 35 randomized controlled trials and found that cocoa reduces blood pressure by 1.8 (-3.1, -0.4; $p = 0.009$) mmHg diastolic and 1.8 (-2.57, -0.94; $p < 0.001$) mmHg systolic in normotensive individuals at an average dose of 670 mg/day for an average of 5.5 weeks [82]. Cocoa appears to have the largest effect on pre-hypertensive, or Stage I hypertensive individuals. In a meta-analysis of 5 studies with pre-hypertensive (Stage I hypertensive) individuals had a systolic drop of 4.7 mmHg (-7.6, -1.8; $p = 0.002$) and a diastolic drop of 2.8 mmHg (-4.8, -0.8 mmHg; $p = 0.006$) at a dose of 50-100 mg/day for a median duration of 4 weeks [83]. An overview of meta-analyses pertaining to cocoa, including several others not mentioned above is presented in Table 1.

Pharmacology: Cocoa has diuretic, cardiac stimulant, and peripheral (endothelium mediated) dilatory effects in humans. The stimulant effects come from the compound theobromine, a methyl-xanthine found in cocoa [84]. Dilatory effects also stem from flavonols in cocoa, which increase nitric oxide synthesis and exert anti-oxidant effects [85,86]. This can specifically be attributed to the pro-cyanidin oligomers in flavonols, which increase nitric oxide bioactivity in humans [87]. Additionally, epicatechin and catechin produced by flavonols exert anti-platlet effects by reducing glycoprotein IIb/IIIa expression [88].

Pharmacokinetics: Cocoa polyphenols are absorbed in the small intestine [89,90]. Flavonols and pro-cyanidins are produced from cocoa by the microbiome of the colon, and reach maximum plasma concentrations two hours after ingestion [85,89,91-93]. These byproducts are conjugated by the liver and excreted in the urine proportional to intake [94,95]. Two to three percent of cocoa by weight contains the methyl-xanthine theobromine [96].

Adverse effects: Cocoa is generally well-tolerated, however it may rarely cause allergic skin reactions, shakiness, diuresis, increased heart rate, and headaches [97,98]. Gastrointestinal side effects include nausea, abdominal discomfort, borborygmi, and flatus, and are mostly associated with dairy contained in some cocoa products [84,99]. Cocoa consumption may also provoke symptoms of gastroesophageal reflux disease (GERD) [100]. Due to its frequent consumption with sugar, there may also be concern for weight gain and increased risk of dental carries [101,102].

Herb-drug interaction: Due to the byproduct epicatechins' ability to block platelet glycoprotein IIb/IIIa, cocoa has anti-platelet effects, and should therefore be used with caution in combination with anti-platelets and anti-coagulants [103]. Cocoa has hyperglycemic effects, and may therefore interfere with diabetic control [102]. Theoretically, the methyl-xanthine caffeine-like properties of cocoa may slow clozapine metabolism by also being degraded by cytochrome P450 enzyme 1A2 (CYP1A2) [104,105]. Methyl-xanthine derivatives in high quantities may also inhibit dipyridamole vasodilation, and could therefore interfere with drug-induced stress tests [106,107].

Rigor of the included meta-analyses: The meta-analysis by Taubert, et al. in 2007 was statistically rigorous; 2 authors reviewed each of the studies, their methodologic quality was acceptable (Jadad scale score of 8-10 out of 13), a funnel plot showed no publication bias, sensitivity analysis identified 1 study with undue influence, and Cochrane Q testing uncovered some inter-study heterogeneity [83]. All included studies were randomized controlled trials. This analysis importantly found blood pressure reductions that were larger than in other included meta-analyses. The review by Ried, et al. in 2010 [82] did not exclude any study on the basis of

quality, resulting in 5/13 double-blind studies included, however all trials had a control group [82].

Conclusion

Due to the increasing prevalence of hypertension, and the inability of nearly half of patients to consistently control their BP, there is a need for safe and effective adjunctive therapies [1]. Nutraceuticals may be an effective additive or primary intervention, due to their relative ease of implementation. This review identified 3 commonly used dietary supplements (garlic, fish oil, and cocoa) that have blood pressure lowering potential, and provided practical information that practitioners may use to guide which of these supplements may be appropriate for their individual patients. Based on his review, garlic appears to have the largest impact on resting blood pressure. The meta-analyses available report average reductions in SBP e with from 6 to 8 mmHg and DBP from 4 to 7 mmHg, at a dosage of 300-600 mg/d. A review of the fish oil literature revealed one rigorous meta-analysis containing only randomized, double-blind, controlled trials (58). This meta-analysis identified a modest, but significant effect of fish oil (3 g/d); average reductions were 2.6 mmHg for SBP and 1.5 mmHg for DBP [58]. The most rigorous meta-analysis of 5 studies evaluating cocoa supplementation reported average reductions in SBP of 4.7 mmHg (-7.6, -1.8; p = 0.002) and DBP of 2.8 mmHg (-4.8, -0.8; p = 0.006.) in Stage-I hypertensive individuals at a dose of 46-105 mg/d for a median of 4 weeks [83].

This guide may by used for practitioners to inform decisions regarding anti-hypertensive nutraceutical use tailored toward the individual, by taking into consideration efficacy, adverse effects and drug-herb interactions. Future work should continue to investigate the long term effects of these and other BP lowering nutraceuticals. Pharmaco-economic analysis of this approach is also needed. For a summary of the information presented in this article, and brief additional information regarding other potential antihypertensive nutraceuticals, see table 1 (Table 1).

Disclosure of Interest

The authors report no conflict of interest.

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