Dietary Supplements and Hypertension: Potential Benefits and Precautions

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Dietary supplements (DSs) are used extensively in the general population and many are promoted for the natural treatment and management of hypertension. Patients with hypertension often choose to use these products either in addition to or instead of pharmacologic antihypertensive agents. Because of the frequent use of DS, both consumers and health care providers should be aware of the considerable issues surrounding these products and factors influencing both efficacy and safety. In this review of the many DSs promoted for the management of hypertension, 4 products with evidence of possible benefits (coenzyme Q10, fish oil, garlic, vitamin C) and 4 that were consistently associated with increasing blood pressure were found (ephedra, Siberian ginseng, bitter orange, licorice). The goals and objectives of this review are to discuss the regulation of DS, evaluate the efficacy of particular DS in the treatment of hypertension, and highlight DS that may potentially increase blood pressure. *J Clin Hypertens (Greenwich).* 2012; 14:467–471. ©2012 Wiley Periodicals, Inc.

Dietary supplements (DSs), a type of complementary and alternative medicine (CAM), are used extensively in the general population and many are promoted for the natural treatment and management of hypertension. Although regulations prohibit specific labeling claims for the treatment or prevention of disease, consumers often choose to use these products instead of or in addition to traditional pharmacologic antihypertensive medications and/or lifestyle modification.[1] In a recent national epidemiological survey, 36% of participants with cardiovascular disease used CAM (excluding prayer) in the previous 12 months, with herbal products being the most common therapy.[2]

Because of the frequent uses of DS, both consumers and health care providers should be aware of the many issues surrounding these products and factors influencing both efficacy and safety. Some studies demonstrate possible benefits and efficacy for particular agents in the treatment of hypertension; however, evidence for DS is frequently of limited and meager quality. Considerable issues persist and must be addressed when evaluating products, reviewing literature, and advising consumers.[1,3]

Due to their complexity, botanical DS also have several unique issues in comparison to vitamins, minerals, and other non-plant DS. Plant-based preparations may contain numerous compounds, even hundreds, with a myriad of unknown effects. Manufacturers of botanical supplements often report standardized amounts of active ingredients, although in many cases, the overall constituents and their effects are not actually known. A variety of factors may also alter the quantity and quality of "active ingredient" within the raw material and the finished product, including conditions of plant growth, storage, and the manufacturing process.[1]

A thorough product analysis and review along with accurate labeling are important in determining DS ingredients that could be beneficial or harmful, although uncertainties may still exist. Clinical trials reporting efficacy should also be examined carefully before the results are translated into clinical practice. As with any research, the methods should be evaluated, as well as trial design, number of participants, outcomes, potential biases, and specific factors influencing product formulations. Both consumers and health care providers should be aware of the regulations and manufacturing processes, potential pharmacologic effects, and precautions when selecting and using certain DS. The goal of this review is to discuss the regulation of DS, evaluate the efficacy of particular DSs in the treatment of hypertension, and highlight DSs that may potentially increase blood pressure (BP).

DIETARY SUPPLEMENT REGULATION

The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined DS as "a product taken by mouth that contains a 'dietary ingredient' intended to supplement the diet" and established the authority and limitations of the US Food and Drug Administration (FDA) in this area. Per this act, DSs are classified as foods rather than drugs and may contain vitamins, minerals, herbs or other botanicals, amino acids, and enzymes.[4] Because of this classification, DSs are regulated by the Center for Food Safety and Applied Nutrition (CFSAN) rather than the Center for Drug Evaluation and Research (CDER) and do not require

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FDA approval. However, the FDA does retain the authority to remove products from the market if safety concerns arise.[5] Because DSs are not approved for the treatment of a disease or condition, manufacturers are required to provide the disclaimer "this product is not intended to diagnose, treat, cure, or prevent any disease(s)" on any product claiming to affect normal structure or function in humans.[4] A DS marketed to "promote a healthy mood" would be an example of such, but the product cannot claim to treat depression. DS are also required to have a clear, readable label with a recommended dose and list of ingredients.[6]

In 2007, the FDA established regulations to require current good manufacturing practices (CGMPs) to further address issues of DS quality and safety. In the past, products have been found to be "spiked" or laced with pharmaceuticals, contaminated (microbial, metals, pesticides), or adulterated (intentional or inadvertent) with the wrong plant material.[7–9] The new CGMPs are intended to reduce the incidence of these practices. CGMP regulations mandate that manufacturers have policies to maintain product integrity, prevent contamination and adulteration, and provide accurate labeling and ingredient identification. Product testing is also required to confirm that materials used meet the criteria set by the manufacturer.[3] However, the CGMPs are focused on material procurement, identity, storage, and processing, rather than ingredient safety or efficacy and generally are subject to manufacturer interpretation. The CGMPs do not specify types or methods of product analysis. Hence, a manufacturer may follow the guidelines, but discretion may still result in less-than-adequate testing to ensure product identity or quality.

AGENTS WITH POSSIBLE BENEFIT IN HYPERTENSION

Methods

We reviewed studies published in the English language from 1990 to 2009 of DSs claiming to show a benefit in the treatment of hypertension. An initial list of possibly effective agents and studies was obtained from the online reference, Natural Medicine Comprehensive Database. Using PubMed, we searched agents identified from this list and the MeSH terms "hypertension," "human," and "dietary supplement," alone and in combination. Assessment of an adequate antihypertensive effect from the DS was defined as a BP reduction consistent with that achieved from the incorporation of lifestyle modifications. We have previously described this method for comparison, which defines the average BP reduction for systolic BP (SBP) as $\geq$9 mm Hg and/or a diastolic BP (DBP) reduction of $\geq$5 mm Hg. These conservative values are based on the proven efficacy and average BP reduction noted in weight loss, exercise, and diet trials such as the Dietary Approaches to Stop Hypertension (DASH) diet.[10] Only studies of DS meeting these criteria with a statistically significant SBP or DBP reduction were included. Investigations and interventions utilizing dietary sources of supplements or based on diet were not included. Additionally, investigations involving pregnant, pediatric (younger than 18 years), or normotensive individuals were excluded.

A total of 163 articles were identified for review. Of these, 56 were excluded because they did not measure BP and 48 because they included pregnant, pediatric, or normotenisve individuals or a dietary source. Another 47 were excluded because they did not meet the BP reduction criteria. Four DSs were found to have studies meeting these inclusion criteria: coenzyme Q10 (CoQ10), fish oil, garlic, and vitamin C (Table I). Table II provides a summary of the included studies involving these identified DSs that may be effective in the treatment of hypertension.

CoQ10

Singh and associates demonstrated that CoQ10 further reduced both SBP and DBP after 8 weeks when added to conventional antihypertensive agents. Participants with a diagnosis of coronary artery disease and taking antihypertensives for a minimum of 1 year were given CoQ10 or a control (B-complex supplement).[11] Burke and colleagues suggested a benefit of CoQ10 in the treatment of isolated systolic hypertension. The cohort received CoQ10 for 12 weeks or a vitamin E placebo. SBP was reduced by 17.8 mm Hg in the treatment group and 1.7 mm Hg in the placebo group. However, the study failed to achieve the power needed for any definitive correlation and was confounded by concurrent statin therapy.[12] Digiesi and associates administered CoQ10 to patients with essential hypertension for 10 weeks. A statistically significant decrease in both SBP and DBP was noted; however, their study design was not clear. Patients had a 2-week washout period prior to CoQ10 initiation, but it is unclear as to what medications were discontinued.[13] Finally, Langsjoen and colleagues administered CoQ10 to patients with hypertension and taking antihypertensive medications for at least 1 year. CoQ10 doses were adjusted to achieve a serum concentration of $\geq$2.0 μg/mL. Patients were followed for 1 year or longer, with dose adjustments made on a monthly basis if needed. Statistically significant decreases in both SBP and DBP were noted.[14]

TABLE I. Dietary Supplements in Hypertension

Some Evidence of Benefit	Evidence of Harm
Coenzyme Q10	Ephedra
Fish Oil	Bitter Orange
Garlic	Siberian Ginseng
Vitamin C	Licorice

TABLE II. Reviewed Trials of Dietary Supplements in Hypertension

Author, Year	Study Design	Participants, No.[a]	Product	Dose	BP Change in Intervention Group, mm Hg		Product Analysis
					SBP	DBP	
Singh et al,[11] 1999	DB, PC, RCT	59	CoQ10	60 mg twice daily	16	9	Not noted
Burke et al,[12] 2001	DB, PC, RCT	80	CoQ10	60 mg twice daily	17.8	2.6	Not noted
Digiesi et al, [13] 1994	Open-label	26	CoQ10	50 mg twice daily	17.8	10	Not noted
Langsjoen et al,[14] 1994	Open-label	109	CoQ10	Average dose of 225 mg/d	12	9	Not noted
Prisco et al,[15] 1998	DB, PC, RCT in parallel	32	Fish oil	Fish oil 2.04 g EPA and 1.4 g DHA	6	5	Not noted
Yosefy et al,[16] 1999	Two open-label trials	Nondiabetic: 20 Diabetic: 19	Fish oil	Fish oil 2700 mg EPA and 1800 mg DHA/d divided TID	Nondiabetic: 12.7 Diabetic: 15.7	7.9 7.6	Not noted
Auer et al,[17] 1990	DB, PC, RCT	47	Garlic powder	200 mg TID	19	9	Not noted
Vorberg and Schneider,[18] 1990	DB, PC, RCT	40	Garlic powder	900 mg/d	9[b]	6.5[b]	Not noted
Duffy et al,[23] 1999	DB, PC, RCT	39	Ascorbic acid	2 g load then 500 mg/d	13	NS	Not noted
Sato et al,[24] 2006	Open-label	24	Ascorbic acid	200 mg TID	20	NS	Not noted

Abbreviations: CoQ10, coenzyme Q-10; DBP, diastolic blood pressure; DB, double-blind; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; NS, no significant change; PC, placebo-controlled; R, randomized controlled trial; SBP, systolic blood pressure; TID, 3 times a day. [a]Only included those who completed the investigations. [b]Noted changes in SBP or DBP are from the meta-analysis.

Fish Oil

In a parallel designed trial of normotensive and hypertensive men, participants were randomized to receive either fish oil (eicosapentaenoic acid, docosahexaenoic acid) or placebo for 4 months followed by a 2-month washout period and reassessment. No significant BP change was noted in either group of normotensive participants. In the fish oil hypertensive group, average SBP decreased by 6 mm Hg and DBP by 5 mm Hg during the treatment period and then returned to baseline after the 2-month washout.[15] Yosefy and colleagues examined the effects of fish oil in obese, hypertensive, and dyslipidemic participants with and without diabetes over 13 weeks. Participants also started the American Heart Association Step I diet. Both groups had statistically significant reductions in both SBP and DBP.[16]

Garlic

In a 12-week trial, Auer and colleagues[17] demonstrated statistically significant reductions in both supine and standing SBP and DBP with garlic supplementation. Vorberg and associates compared garlic with placebo in a 16-week trial. They graphically reported a statistically significant decrease in SBP and DBP; however, they failed to provide clear documentation of the amount of change or their methods, including the "washout period."[18]

Despite a long history of use, the efficacy of garlic in hypertension is still debated. Several reviews and meta-analyses have documented somewhat conflicting results regarding its use.[19–22] Many of the concerns are the same as with other DSs: product inconsistencies, lack of standardization, variable formulations, and questionable study design and quality. Given the wide variation of products used and other limitations of the existing evidence, it is difficult to make a definitive recommendation for the use of garlic in the treatment of hypertension.

Vitamin C

Duffy and colleagues demonstrated a lowering of SBP when vitamin C was added to concurrent antihypertensive medications. Participants received either placebo or a one-time loading dose of 2 g of ascorbic acid followed by 500 mg daily for 1 month. The ascorbic acid group had a significant 13-mm Hg reduction in SBP, but not DBP.[23] Additionally, Sato and colleagues demonstrated a statistically significant reduction in SBP in elderly patients (65 years and older) with drug refractory hypertension compared with younger adults (younger than 65 years) who failed to show a significant BP reduction. After receiving 200 mg of ascorbic acid 3 times daily for 6 months, the mean 24-hour ambulatory SBP decreased by approximately 20 mm Hg.[24] These findings are of interest, although the limited data prevents global recommendations on the efficacy of vitamin C in the treatment of hypertension.

SUPPLEMENTS WITH POTENTIAL TO INCREASE BP

Some DSs can potentially increase BP or exacerbate hypertension. Due to "historical use," consumers often infer that these products are safe and harmless. However, many herbals previously used in other forms, a diluted tea for example, may now be available as concentrated and potent extract formulations and thus

potentially more harmful. Four products have consistent documentation for increasing BP: ephedra, bitter orange, ginseng, and licorice (Table I).

The sympathomimetic agent, ephedra, is one of the oldest medicinal botanical products available with a 5 million–year history of use.[25] Ephedra metabolites (ephedrine and pseudoephedrine) cause cardiac effects, peripheral vasoconstriction, bronchodilation, and central nervous system stimulation.[26] Several case reports document the occurrence of adverse cardiovascular effects and even fatalities with the use of ephedra as a weight loss product. Hypertension is cited as the most common adverse effect related to ephedra; however, palpitations, tachycardia, stroke, and seizures are also frequently reported.[27] The increasing number of reported adverse events caused the FDA to ban sales of ephedra-containing products in the United States in 2004.[28]

Bitter orange is a botanical product that is often used for weight loss and dyspepsia. Synephrine and octopamine, similar to phenylephrine and ephedra, are the predominant ingredients and are thought to be the cause of BP increases.[29] BP increases occur in healthy people and may be related to dose.[30,31]

Siberian ginseng has been used for centuries, traditionally as an immune-enhancing agent. With eleutherosides as the active components, it has also gained popularity for regulating BP, treating cold symptoms, and improving athletic performance. However, caution is advised because it has been documented to cause hypertension, tachycardia, and palpitations.[32]

Licorice is an herbal product used mainly for gastrointestinal conditions. Glycyrrhizic acid, an active compound found in some licorice preparations, is responsible for creating mineralocorticoid excess syndrome and possibly subsequent hypertension. Individuals with preexisting hypertension and heart disease are more sensitive to this effect.[33]

DISCUSSION

Four DSs have some evidence to support potential efficacy in the treatment and management of hypertension. Based on our review criteria, the conservative limits set for BP reduction, and publication limited to the English language, we may have eliminated studies with clinically meaningful results. Evidence for the benefits of a much smaller reduction in BP is clearly significant population-wide. Our purpose was to identify DSs that are at least as effective as standard lifestyle approaches in lowering BP and managing hypertension. All of these DSs may be advertised "to promote a healthy cardiovascular system" and may be used by consumers in addition to or in place of prescription antihypertensives. However, the paucity of evidence for efficacy and safety surrounding these supplements should be considered. No DS have proven efficacy in BP lowering or morbidity or mortality benefits compared with available antihypertensive drugs.

Health care providers must thoroughly evaluate any publication for biases. Historically, articles on DS have been published without adequate discussion of these issues. Adequate product description is lacking in many clinical trials and case reports utilizing DS. As identified in Table II, none of the investigations acknowledge or identify independent evaluations of product content or quality. When information describing and supporting product quality, including the analysis of active ingredients, lot numbers, and storage conditions, is not clearly outlined, the results and conclusions cannot be generally accepted or adopted into clinical practice.[1] Even when DSs are evaluated in a well-designed trial with few limitations, the results cannot be readily extrapolated to other DS products, as is often done with pharmaceutical research due to the inherent uncertainties about active compounds and product inconsistencies. Clearly sample size is another flaw often observed in research involving DS (Table II). For a pharmaceutical manufacturer to seek FDA approval for an antihypertensive agent, significant information regarding safety and efficacy must be submitted. DSs are not required to meet this same standard despite often being touted as "alternatives" or "compliments" to medicines with proven safety and efficacy.

Despite the concerns and limitations of available evidence, the use of DSs is unlikely to diminish. Many Americans are passionate about their use of DSs. Health care providers must be aware of and acknowledge supplement use among their patients and be able to discuss issues related to these products. Consumers must be reminded that DSs are not always safe and, in most cases, they should not be consumed without the supervision of a health care provider. By communicating openly about DSs, providers can help improve patient understanding of the appropriate use of these products compared with pharmacologic treatments and issues involving safety and efficacy. Additionally, the CGMP regulations will help protect consumers from adulteration and misbranding of DS products.

CONCLUSIONS

This review provides an overview of DSs that may have potential for benefit or harm in the management of hypertension and describes some of the issues surrounding the use of DSs in the United States. While there may be a role for particular DSs in the treatment and management of hypertension, the need clearly remains for the development of standardized products and well-designed studies to better define the effectiveness, safety, and clinical implications compared with existing pharmacologic treatments. By increasing consumer and health care provider knowledge and awareness of the issues surrounding the use of DSs, we can further ensure the safety and appropriate use of DSs in individuals and throughout the population.

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