Published in final edited form as:
Cardiovasc Ther. 2010 August ; 28(4): e20–e32. doi:10.1111/j.1755-5922.2010.00137.x.

Natural Antioxidants and Hypertension: Promise and Challenges

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Abstract

Hypertension reigns as a leading cause of cardiovascular morbidity and mortality worldwide. Excessive reactive oxygen species (ROS) has emerged as a central common pathway by which disparate influences may induce and exacerbate hypertension. Potential sources of excessive ROS in hypertension include NADPH oxidase, mitochondria, xanthine oxidase, endothelium-derived NO synthase (eNOS), cyclooxygenase 1 and 2, cytochrome P450 epoxygenase and transition metals. While a significant body of epidemiological and clinical data suggests that antioxidant rich diets reduce blood pressure and cardiovascular risk, randomized trials and population studies using natural antioxidants have yielded disappointing results. The reasons behind this lack of efficacy are not completely clear, but likely include a combination of 1) ineffective dosing regimens 2) the potential pro-oxidant capacity of some of these agents 3) selection of subjects less likely to benefit from antioxidant therapy (too healthy or too sick), 4) inefficiency of non-specific quenching of prevalent ROS versus prevention of excessive ROS production. Commonly used antioxidants include Vitamins A, C and E, L-arginine, flavanoids, and mitochondria targeted agents, Coenzyme Q10, acetyl-L-carnitine and alpha-lipoic acid. Various reasons, including incomplete knowledge of the mechanisms of action of these agents, lack of target specificity, and potential inter-individual differences in therapeutic efficacy preclude us from recommending any specific natural antioxidant for antihypertensive therapy at this time. This review focuses on recent literature regarding above mentioned issues evaluating naturally occurring antioxidants with respect to their impact on hypertension.

Keywords

Hypertension; Antioxidants; Oxidative Stress

Introduction

Hypertension (HTN) is the most important cardiovascular risk factor worldwide, contributing to half of prevalent coronary heart disease and approximately two thirds of prevalent cerebrovascular disease burdens.1 While a multitude of genetic and environmental factors contribute to this complex disease, excessive reactive oxygen species have emerged as a central common pathway by which disparate influences may induce and exacerbate hypertension.2 Further, a significant body of epidemiological3 and clinical trial data4, 5 suggest that diets known to contain significant concentrations of naturally occurring antioxidants appear to reduce blood pressure and may reduce cardiovascular risk.

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Conflicts of Interest: None

In light of these data, there is significant interest in identifying key, naturally-occurring antioxidants to both prevent and treat hypertension. This reviewl focuses on the recent literature evaluating naturally occurring antioxidants with respect to their impact on hypertension.

Role of Oxidative Stress in the Pathogenesis of Hypertension

Reactive oxygen species (ROS) are generated by multiple cellular sources, including NADPH oxidase, mitochondria, xanthine oxidase, uncoupled endothelium-derived NO synthase, cycloxygenase, and lipoxygenase (Table 1).[6, 7] The dominant initial ROS species produced by these sources is superoxide (O_2^-). Superoxide is short-lived molecule that can subsequently undergo enzymatic dismutation to hydrogen peroxide. Superoxide can oxidize proteins and lipids, or react with endothelium-derived nitric oxide (NO) to create the reactive nitrogen species peroxynitrite. Peroxynitrite and other reactive nitrogen species can subsequently oxidize proteins, lipids, and critical enzymatic cofactors that may further increase oxidative stress.[8, 9] Hydrogen peroxide produced by enzymatic dismutation of O_2^- can be further convert to highly reactive hydroxyl radical (via Fenton chemistry) that can cause DNA damage.[10] The balance between superoxide production and consumption likely keeps the concentration of O_2^- in the picomolar range and hydrogen peroxide in the nanomolar range.[11] These homeostatic levels of reactive oxygen species appear to be important in normal cellular signaling[12–14] and normal reactions to stressors.[15, 16]

While multiple diverse factors likely contribute to the development of hypertension, the pathogenesis of this disease appears related, at least in part, to the development of a state of excessive oxidative stress. Local excessive superoxide production in the kidneys, CNS, and vasculature, along with inflammatory activation, are central findings in hypertension models.[17,18] Animal studies demonstrate the development of hypertension with associated increases in oxidative stress and impaired vasodilation in rats exposed to a high-salt and oxidant containing diet.[19] Further, infusion of superoxide dismutase lowers oxidative stress and blood pressure in these animal models.[20–22] Divergent animal models of hypertension, including spontaneous hypertension,[23] salt-sensitive hypertension,[24,25] renovascular hypertension,[26,27] and obesity-related hypertension[28] are all associated with excessive oxidative stress. These data suggest, regardless of etiology, excessive ROS is a common factor in the pathogenesis and morbidity of hypertension.

Roles and Interactions of Sources of Oxidative Stress in Hypertension

As delineated in Table 1, multiple diverse sources of reactive oxygen species generation are relevant to the pathogenesis of hypertension. The prominent role of excessive superoxide produced by NADPH oxidase under angiotensin II stimulation in the development of hypertension has recently been extensively reviewed.[17] Interestingly, data emerging over the past several years indicate that hypertension-related excessive ROS levels are most likely secondary to regulatory interactions between the major sources of ROS themselves involving ROS in the signaling process.

Mitochondria produce excessive ROS in the setting of spontaneous hypertension[29,30] as well as in hypertensive states characterized by salt-sensitivity and elevated endothelial-1 levels.[31] Mitochondria may produce superoxide through multiple mechanisms, including the electron transport chain complexes (I, II, and III), monoamine oxidase A and B, and Krebs cycle enzymes.[32] Interestingly, extensive regulatory crosstalk between NADPH oxidase and mitochondria appears to modulate superoxide production from both sources.[33,34] For example, over-expression of thioredoxin-2, an important mitochondrial-based antioxidant thiol, reduces angiotensin II-induced hypertension[35] and lowers basal blood pressure in transgenic mice over-expressing thioredoxin.[36]

NADPH oxidase and mitochondria also interact with endothelium-derived NO synthase (eNOS) through ROS production, modulating overall NO bioavailability and superoxide production from eNOS. eNOS has been localized to the outer mitochondrial membrane in endothelial cells.37 Beyond quenching NO through direct reaction to create peroxynitrite, superoxide from NADPH oxidase or mitochondria can oxidize tetrahydrobiopterin (BH_4), a necessary eNOS cofactor, leading to eNOS uncoupling and superoxide production from eNOS. 38 Further, uncoupling of eNOS leads to reduced NO bioavailability and excessive mitochondrial ROS production. 39

Xanthine oxidase, which generates superoxide by converting hypoxanthine to xanthine, is upregulated by NADPH oxidase under oscillatory shear conditions.40 Xanthine oxidase may also contribute to excessive ROS production in salt-sensitive hypertension, although its relative contribution compared to mitochondria and NADPH oxidase remains to be fully elucidated.41 Prior work also demonstrates potential roles for lipoxygenase, cycloxygenase, cytochrome P450 epoxygenase, and transitional metals in overall cellular superoxide production, but further study is necessary to better delineate the roles of these sources of ROS in hypertension.

While the causal intrinsic and extrinsic factors governing the development of hypertension are very likely multi-factorial, genetic polymorphisms associated with sources of oxidative stress in hypertension may modulate an individual's potential for elevated ROS and the development of hypertension under genetic and environmental influences.42–50 Overall, while there may be a hierarchy of the relative contributions of each ROS source in hypertension, the measured combined local concentrations of superoxide and peroxynitrite most likely reflect a combination of genetic susceptibility, coordinated ROS generation from multiple sources, local environmental influences on sources of ROS production, and overall intrinsic anti-oxidant defense mechanisms.51

Selecting Natural Antioxidants to Treat Hypertension

Randomized trials employing non-pharmacological dietary interventions emphasizing fruits, vegetables, whole grains, and nuts have shown impressive blood pressure lowering results in both hypertensive and normotensive subjects.52–54 Similar interventions demonstrated to reduce cardiovascular morbidity and mortality continue to maintain interest in the potential of isolating specific compounds enriched in these diets that may be responsible for the overall dietary benefits.55

The dietary components in these studies are high in compounds known to have antioxidant properties leading many to ascribe the benefits of these diets to their increased content of natural antioxidants. However, prior randomized trials and population studies in healthy populations and patients at high risk for cardiovascular events that have employed combinations of some of these natural antioxidants as dietary supplements have, for the most part, shown disappointing results,56–60 61–63 The reasons behind these disappointing results are not completely clear, but likely include a combination of 1) ineffective dosing and dosing regimens 2) the potential pro-oxidant capacity and other potentially deleterious effects of these some of these compounds under certain conditions,64, 65 3) selection of subjects less likely to benefit from antioxidant therapy (too healthy or too sick). Populations at intermediate cardiovascular risk may be better suitable to see effects of antioxidants in shorter term studies.66 4) inefficiency of non-specific quenching of prevalent ROS versus prevention of excessive ROS production.67, 68

When considering antioxidant therapy for hypertension, lessons from prior disappointing attempts to reduce blood pressure and cardiovascular risk with antioxidant therapy should be considered. The profile of an ideal agent is outlined in Table 2. The importance of patient

selection is being increasingly recognized in light of emerging data suggesting that antioxidant supplementation in healthy subjects may blunt the protective benefits of aerobic exercise training, suggesting ROS generation can be beneficial under certain circumstances. 69

Anti-Hypertensive Profile of Common Natural Antioxidants

Antioxidant Vitamins

Vitamin A Precursors and Derivatives—Vitamin A precursors and derivatives are retinoids that consist of a beta-ionone ring attached to an isoprenoid carbon chain. Foods high in vitamin A include liver, sweet potato, carrot, pumpkin, and broccoli leaf. Initial interest in vitamin A-related compounds focused primarily on beta-carotene, given initial promising epidemiological data with respect to its cardioprotective effects and some correlation with higher plasma levels to lower blood pressure in men.70 However, concerns about beta-carotene's pro-oxidative potential came to light with a report suggesting adverse mitochondrial effects of beta-carotene cleavage products.71 Further, adverse mortality data with respect to beta-carotene has limited interest in this compound as an effective antihypertensive agent.72

Recently, interest in vitamin A derivatives has turned to lycopene, itself a potent antioxidant, 73 found concentrated in tomatoes. One small study has shown a reduction in blood pressure with a tomato-extract based intervention (containing a combination of potential anti-oxidant compounds including lycopene) in patients with stage I hypertension, 74 although second study showed no effect in pre-hypertensive patients. 75

Ascorbic Acid (Vitamin C)—L-ascorbic acid is a six-carbon lactone and, for humans, is an essential nutrient. In Western diets, commonly consumed foods that contain high levels of ascorbic acid include broccoli, lemons, limes, oranges, and strawberries. Toxicity potential of this compound is low, although an increased risk of oxalate renal calculi may exist at higher doses (exceeding 2 grams/day) 76

The initial purported mechanisms for the potential benefits of ascorbate supplementation were centered on quenching of single-electron free radicals. Subsequent research has demonstrated that the plasma concentrations of ascorbate required for this mechanism to be physiologically relevant are not attainable by oral supplementation.77 However, vitamin C can concentrate in local tissues to levels an order of magnitude higher than that of plasma. At this leve, ascobate may to effectively compete for superoxide and reduce thiols.78, 79 Recent data also suggest potential suppressive effects of ascorbate on NADPH oxidase activity.80, 81 Ascorbate appears to have limited pro-oxidant ability.82

Ascorbate's anti-hypertensive efficacy has been evaluated in multiple small studies. Many, 83–86 but not all,87 show modest reductions in blood pressure in both normotensive and hypertensive populations. These data also suggest that supplementation has limited effect on systemic antioxidant markers85 and little additional blood pressure benefits are seen beyond the 500 mg daily dose. Large scale randomized trial data specific to ascorbate supplementation and its effects on hypertension are currently lacking. Data from Heart Protection Study (HPS) suggest no significant mortality from supplementation with 250mg/day of ascorbate supplementation.57 However, the relatively low dose of ascorbate, use of combination therapy, and high-risk patient population studied in HPS leave unanswered the key questions of appropriate dosing and target.

α-Tocopherol (Vitamin E)—Vitamin E is a generic term for a group of compounds classified as tocopherols and tocotrienols.88 While there are four isomers in each class of

Vitamin E compounds, the overwhelming majority of the active form is α-tocopherol.89 Dietary sources high in vitamin E include avocados, asparagus, vegetable oils, nuts, and leafy green vegetables.

Vitamin E is a potent antioxidant that inhibits LDL and membrane phospholipid oxidation. 90 Interestingly, inflammatory cells and neurons have binding proteins for α-tocopherol, the actions of which may include inhibition of NADPH oxidase, lipoxygenase, and cyclo-oxygenase, actions which may lower oxidative stress.91 However, studies demonstrating vitamin E's pro-oxidant capacity under certain cellular conditions suggest that local condition may influence the vitamin E's redox activity.65

Initial excitement for vitamin E supplementation was based on the reduction of cardiovascular events seen in the CHAOS study.60 However, follow-up studies have been largely disappointing.92–94 While one small study that used vitamin E in combination with zinc, vitamin C, and beta-carotene showed a modest, significant reduction in blood pressure over 8 weeks of therapy,95 other small studies96, 97 show either no effect or a pressor effect from vitamin E supplementation. Further, the more definitive HOPE trial, failed to show blood pressure or mortality benefit for patients at high risk for cardiovascular disease. 92

L-Arginine

L-arginine is an amino acid and the main substrate for the production of NO from eNOS in a reaction that is dependent on tetrahydrobiopterin.98 Potential dietary sources include milk products, beef, wheat germ, nuts, and soybeans. Reduced levels of tetrahydrobiopterin leads to uncoupling of reduced NADPH oxidation and NO synthesis, with oxygen as terminal electron acceptor instead of L-arginine, resulting in the generation of superoxide by eNOS. 99–101 Low cellular levels of L-arginine have been demonstrated in human hypertension, 102, 103 While L-arginine deficiency itself does not appears to lead to uncoupling of eNOS, 104 low levels of L-arginine may lead to reduced levels of bioavailable NO which could contribute to hypertension. Thus, L-arginine supplementation could theoretically reduce blood pressure by allowing for restoration of normal NO bioavailability, perhaps overcoming overall L-arginine deficiency as well as more successfully competing fo the eNOS active site with circulating asymmetric dimet hylarginine, a circulating competitor of L-arginine that may be increased in the setting of hypertension.105

This concept is supported by studies demonstrating the anti-hypertensive effect of L-arginine supplementation in salt-sensitive rats,106 healthy human subjects,107 hypertensive diabetics,108 patients with chronic kidney disease,109 and diabetic patients in combination with N-acetylcysteine, a precursor of glutathione.108 L-arginine's anti-hypertensive response may be mediated in part by its suppressive effects on angiotensin II and endothelin-1, and its potentiating effects on insulin.110

However, recent concerns about potential deleterious increases in homocysteine in the setting of L-arginine supplementation have been raised.111 The majority of L-arginine is processed into creatine, which leads increased homocysteine levels.112 Homocysteine can increase oxidative stress.113 A recent study confirms this mechanism is relevant to L-arginine metabolism in humans,114 suggesting a potential mechanism for neutralizing the eNOS-related anti-oxidant effects of L-arginine.

Flavonoids

Flavonoids are polyphenolic compounds commonly found in concentrated amounts in multiple fruits, vegetables, and beverages, including apples, berries, grapes, onions, pomegranate, red wine, tea, cocoa, and dark chocolate. The exact structure and composition

of the flavonoid compounds varies between food sources, and flavonoid content can be altered based on the manner of food preparation.115 Interest in flavonoids as antioxidant therapy for cardiovascular disease originates from epidemiological data suggesting improved cardiovascular outcomes in individuals with high intake of food and beverages with high flavonoid content115, 116 as well as cellular work suggesting a strong anti-oxidant effect of these compounds.117–120

However, the limited oral bioavailability of flavonoids suggests cell signaling mechanisms, rather than free radical quenching activity, is more likely to be root of sustained cardiovascular benefits from flavonoids.120 This concept is consistent with studies demonstrating that flavonoids can inhibit NADPH oxidase through ACE inhibition,121, 122 increase eNOS-specific NO production through the estrogen receptor,123 and alter COX-2 expression.124 Studies investigating the anti-hypertensive effects of flavonoids are inconclusive. While multiple small studies of short duration dark chocolate therapy have demonstrated blood pressure lowering effects in hypertensives,125–128 studies in normotensive and pre-hypertensive individuals have demonstrated no benefit.75, 129 Further, tea intake may, at least temporarily, increase blood pressure in certain populations.130, 131 The specific flavonoids and combination of flavonoids that exert the largest beneficial effects remain unknown.

Mitochondria-Related Anti-Oxidants

Coenzyme Q10 (CoQ)—CoQ (2, 3 dimethoxy-5 meth-6-decaprenyl benzoquinone) is derived from mevalonic acid and phenylalanine, and can be supplemented by oral intake. This compound is a key component of the electron transport chain, accepting electrons from Complexes I and II and the glyceraldehyde-3-phosphate shuttle. CoQ levels have been shown to be lower in older adults known to have a greater prevalence of hypertension.132 The mechanism of action of CoQ is not likely to be secondary to a superoxide scavenger effect given CoQ's hydrophobic properties. CoQ may reduce mitochondrial superoxide production by increasing the efficiency of electron transfer from Complexes I and II down the mitochondrial electron transport chain.133 Coenzyme Q may also exert an antioxidant effect by reducing lipid peroxidation at the level of the plasma membrane.134

Early data from non-controlled studies in human hypertension demonstrate reductions in blood pressure with CoQ supplementation.135, 136 Further, small randomized studies using a CoQ dose of 100–120mg daily have demonstrated significant reductions in blood pressure with minimal side effects in patient with Stage II hypertension.137–140 Interestingly, a new, mitochondrial-targeted formulation of CoQ has demonstrated anti-hypertensive efficacy in a rat model.141

Acetyl-L-Carnitine (ALCAR) and α-Lipoic Acid (LA)—LA is a dithiol compound synthesized from octanoic acid in mitochondria. The *in vivo* and *in vitro* effects of LA have been thoroughly reviewed elsewhere.142, 143 LA has moderate oral bioavailability.144. While LA is a potent *in vitro* antioxidant, the limited plasma concentrations achievable with supplementation and rapid clearance of LA suggest free radical scavenger and anti-oxidant recycling activity are unlikely to be the primary *in vivo* activity of LA. Participation in mitochondrial-associated metabolic pathways, in cell signaling that may improve coupling of eNOS, and anti-inflammatory actions are among the potential beneficial effects of LA supplementation.142, 145 Work in a diabetic rat and multiple different hypertensive rat models has shown the potential for LA supplementation to reduce blood pressure.146–149

ALCAR (acetylated L-carnitine) is a key compound in the transport of fatty acids into mitochondria for beta-oxidation. The antioxidant mechanism of ALCAR supplementation appears to be secondary to reductions in mitochondrial ROS production in synergy with

concomitant LA therapy.150 The exact intra-mitochondrial mechanism ALCAR's effects are not clear, and prior work in older rats demonstrates ALCAR potential to be pro-oxidative when used alone.151 Further data suggest ALCAR may be of particular benefit in diabetics with hypertension secondary to their low carnitine levels152 and elevated circulating free fatty acid levels.153, 154

Human data with respect to the anti-hypertensive effects of these compounds is limited to two small studies which have shown some promising results. Consistent with animal data, combined ALCAR and LA therapy reduced systolic blood pressure in coronary artery disease patients with hypertension and/or metabolic syndrome at the time of enrollment.155 Also consistent with prior cell culture and animal work, 32 type 2 diabetic subjects supplemented with 2 grams/day of acetyl-L-carnitine showed significantly lowered blood pressure and improved insulin sensitivity.156

Other Potential Natural Antioxidant Agents

Garlic,157 glutamate,158 N-acetylcysteine,159 sour milk,160, 161 and vitamin D162, 163 all have shown anti-hypertensive effects through anti-oxidant mechanisms that may involve inhibition of sources of excessive ROS. Further work remains to be done to establish the mechanisms and efficacy of these interventions.

Conclusions and Future Directions

A summary of our findings with respect to the above interventions is contained in Table 3. Critical evaluation of the these data reveal several issues and limitations related to our current knowledge of natural antioxidant compounds and their potential anti-hypertensive efficacy that obviate our ability to recommend any individual agent at this time (Table 4). First, the majority of these agents have been discovered to have potential mechanisms of action that were initially unanticipated, including the potential for deleterious, pro-oxidative effects. A greater understanding of the mechanisms of action of the above agents may allow providers to better target therapies to appropriate populations. Second, while interventions such as tomato extract and dark chocolate may hold promise, the identity of the compounds or mix of compounds responsible for the antihypertensive effects of these interventions remain unknown and need to be identified before lycopene or individual flavonoid compounds can be recommended as supplements for anti-hypertensive therapy. Third, small, single center trials often enrolling less than 100 subjects comprise the majority of studies found related to novel antioxidant therapy for hypertension, leaving open concerns with respect to publication bias. In addition, the vast majority of these studies made no systemic measurements of total antioxidant capacity, making to determine whether changes in anti-oxidant capacity accompanied the observed reductions in blood pressure. With the exception of Vitamins A and E (which cannot be recommended at this time), data from larger randomized clinical trials aimed at blood pressure lowering and optimally also measuring cardiovascular endpoints and antioxidant effects would help more clearly distinguish which of the above agents, if any, may be reasonable to recommend to as anti-hypertensive agents as well as help determine if antioxidant actions may be responsible for any ameliorative effects. Thus, despite some interesting findings, the recommendations of the American Heart Association of a dietary strategy rich in fruits and vegetables appears to continue to be the best strategy for non-pharmacological therapy in hypertension.164 Further work is clearly necessary in order to more clearly identify which natural antioxidants have efficacy and their mechanisms of action.

How did you gather, select and analyze the info you considered in your review?

Literature search was conducted by both authors independently using Medline (1966-present) and Cochrane database of systematic reviews. References from the extracted papers, reviews and meta analyses were also consulted to complete the database. About 150 high quality studies specifically focusing on redox physiology and pathophysiology in hypertension, as well as anti-oxidant therapy for hypertension were selected by the authors and analyzed for this review.

What is the take home message?

Reactive oxygen species play a central role in the pathogenesis of hypertension and its vascular complications. While there are several promising anti-oxidants being tested, current data do not support the use of individual compounds or combinations of supplemental antioxidants for the treatment of hypertension at this time. Further work is necessary to identify which natural antioxidants are efficacious in hypertension. Pending future discoveries in this area, the American Heart Association's recommendation of a diet rich in fruits and vegetables remains to be the best "natural antioxidant" strategy for non-pharmacological therapy in hypertension.

Acknowledgments

Dr. Widlansky is supported by 1K23HL089326. Dr. Kizhakekuttu is supported by a Ruth L. Kirschstein NIH T32 training grant (HL007792-15).

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Table 1

Potential Sources of Excessive Reactive Oxygen Species in Hypertension

• NADPH Oxidase
• Mitochondria
• Xanthine Oxidase
• Endothelium-Derived NO Synthase (eNOS)
• Cycloxygenase 1 and 2
• Cytochrome P450 epoxygenase
• Transition Metals (e.g. Iron)

Table 2

Optimal Profile of Natural Antioxidant Agent for Anti-Hypertensive Therapy

- Good oral bioavailability
- Patient-friendly dosing regimen (once or twice daily dosing)
- Concentrates locally in relevant tissues (kidney, brain, and/or vasculature)
- Limited potential for pro-oxidative role and secondary cell signaling that may limit effectiveness
- Inhibits the production of ROS rather quenching ROS post-production.
- Good safety profile with limited side effects
- Efficacious for hypertension originating from disparate etiologies
- No adverse interactions with the metabolism of potential concomitant anti-hypertensive pharmacological therapy
- Has pleiotropic effects that go beyond blood pressure lowering and translate into prevention of/ reversal of/ slower progression of end organ damage

Table 3

Profiles of Commonly Used Natural Antioxidants for Hypertension

Supplement	Antioxidant Capacity?	Pro-oxidant Capacity	Lowers BP in small clinical trials	Lowers BP in large randomized controlled studies
Vitamin A				
Beta-carotone	+	+	−	−
Lycopene (tomato extract)	+	?	+	?
Vitamin C	+	−	+	?
Vitamin E	+	+	+/−	−
L-Arginine	+	+	+	?
Flavonoid Containing food/beverages	+	?	+/−(positive for dark chocolate, negative for tea)	?
Acetyl-L-Carnitine	?	+/−	+	?
α-**Lipoic Acid**	+	−	+ (in combination with ALCAR)	?

Table 4

Current Limitations Precluding Recommendation of Specific Natural Antioxidant Supplements for Hypertension

• Incomplete knowledge of the mechanism(s) of action of these agents
• Lack of target specificity of these agents
• Lack of large, randomized control trials to determine true anti-hypertensive efficacy for many of these agents
• Lack of data on “hard” outcome (e.g. death, cardiovascular events)
• Potential differences in therapeutic efficacy in different hypertensive populations