REVIEW

Beyond conventional therapies: Complementary and alternative medicine in the management of hypertension: An evidence-based review

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Abstract: Hypertension is one of the major causes of morbidity and mortality. Worldwide, Hypertension is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths. This accounts for 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS. This led WHO to set a target of 25% reduction in prevalence by 2025. To reach that, WHO has adopted non-conventional methods for the management of hypertension? Despite worldwide popularity of such non-conventional therapies, only small volume of evidence exists that supports its effectiveness. This review attempted to make a critical appraisal of the evidence, with the aim to (1) describe the therapeutic modalities frequently used, and (2) review the current level of evidence attributable to each modality. Databases from Cochrane Library, MEDLINE, PUBMED, and EMBASE were searched from 2005-2015. A total of 23 publications have been identified and selected. Out of these, 15 systematic reviews and/or meta-analysis of RCTs, 5 RCTs, 1 non-RCT, and 2 observational studies without control. Among those 23 publications, therapeutic modalities identified are: fish oil, qigong, yoga, coenzyme Q10, melatonin, meditation, vitamin D, vitamin C, monounsaturated fatty acids, dietary amino-acids, chiropractic, osteopathy, folate, inorganic nitrate, beetroot juice, beetroot bread, magnesium, and L-arginine. The followings were found to have weak or no evidence: fish oil, yoga, vitamin D, monounsaturated fatty acid, dietary amino-acids, and osteopathy. Those found to have significant reduction in blood pressure are: magnesium, qigong, melatonin, meditation, vitamin C, chiropractic, folate, inorganic nitrate, beetroot juice and L-arginine. Coenzyme Q10on the other hand, showed contradicting results were some studies found weak or no effect on blood pressure while others showed significant blood pressure reduction effect. By virtue of the research designs and methodologies, the evidence contributed from these studies is at level 1. Results from this review suggest that certain non-conventional therapies may be effective in treating hypertension and improving cardiac function and therefore considered as part of an evidence-based approach.

Keywords: Hypertension, non-conventional management, evidence-based therapy.

INTRODUCTION

Hypertension is one of the major causes of morbidity and mortality worldwide. Globally CVD accounts for 17 million deaths annually (WHO, 2013). In 2010, hypertension was ranked as the leading single risk factor for global burden of diseases. Furthermore, hypertension complications accounted for 9.4 million deaths and 7% of the disability-adjusted life years' (DALYs) lost worldwide (Lim *et al*., 2012). The magnitude of hypertension is rising speedily, affecting about 40% of adults aged 25 years and above (WHO, 2011). In May 2013, the World Health Organization (WHO) has endorsed a set of global voluntary targets for non-communicable diseases, and hypertension was targeted for a 25% reduction in the prevalence by 2025 (WHO, 2013b).

The common conventional medications used for treating hypertension are diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, and renin inhibitors. Despite being the most easily controlled risk factor for CVD, hypertension often leads to impaired cardiac function, or hypertensive heart disease. Victor (2012) has postulated that more than one third of hypertensive patients end up with stroke, myocardial infarction, or heart failure even though their blood pressure is under control.

Over the last 20 years, there have been a number of studies on hypertension and cardiac function using complementary and alternative medicine (CAM), or non-conventional therapies. It is not often that the results of CAM therapies contribute to scientific evidence. The bulk of the evidence from CAM is in case reports and case

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series, which occupy the lower strata of evidence contribution. The popularity of CAM has increased over the last two decades. The use of non-conventional therapies among patients with hypertension and its sequel of CVD are prevalent and in many instances provide positive clinically significant effects (Nahas,2008; Houston,2010; Rabito and kaye 2013). Most of the non-conventional therapies come from micronutrients usage. Others include biological-based therapies, mind-body therapies, homoeopathy, qigong, acupuncture, and yoga.

Methodology

Search method

This review attempts to make a critical appraisal of studies from 2005 to early 2015.The aims of this review were:(1) To review the current level of evidence attributed to those non-conventional therapies that are more frequently used in the treatment of hypertension. (2) To describe those therapies that occupies the highest level of evidence deriving from systematic review and meta-analysis. The search methodology for hypertension in literature published in English language, through the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE, PUBMED, and EMBASE databases, was for the period 2005 to January 2015. The following key words, in different combinations, were used: hypertension or high blood pressure with non-conventional therapies, natural therapies, nutrients, micronutrients, vitamins, minerals, amino-acids, coenzyme Q10, ubiquinone, melatonin, herbs, traditional Chinese medicine, acupuncture, qigong, meditation, yoga, and homoeopathy. Only clinical trials on humans and prospective studies were selected as they contribute to higher levels of evidence. Retrospective or animal studies were excluded from this review.

Level of evidence

There are basically four levels of evidence widely accepted in the scientific and healthcare field. Adapting from the Oxford Centre for Evidence-Based Medicine and United States Agency for Healthcare Policy and Research, the four levels of evidence are:

Level-1: Randomized controlled trials - includes quasi-randomized processes.
Level-2: Non-randomized trials - prospective studies with predetermined eligibility criteria and outcome measures.
Level-3: Observational studies with controls – retro-spective, interrupted time series, case-controlled studies, cohort studies with controls, and researches that include adjustment for confounding factors.
Level-4: Observational studies without controls - cohort studies, case series, case reports, and expert opinions.

With this categorization, however, not all levels of evidence are of equal value. It should not be misunderstood that those studies categorized at the lower levels are not important. All levels of evidence are important and each has its own value.

RESULTS

Evidence-based review

Searches from 2005 to January 2015 revealed a total of 23 publications on the topic of interest. Of the 23 publications, 15 were systematic reviews and/or meta-analysis, 5 RCTs, 1 non-RCT and 2 observational studies without control table1 summarizes all studies selected (table 1).

From the 23 publications, non-conventional therapeutic modalities identified were: fish oil, qigong, yoga, coenzyme Q10, melatonin, transcendental meditation, vitamin D, vitamin C, monounsaturated fatty acids, dietary amino-acids, chiropractic, osteopathy, folate, inorganic nitrate, beetroot juice, beetroot bread, magnesium, and L-arginine. The followings were found to have a weak or no evidence: fish oil, yoga, vitamin D, monounsaturated fatty acid, dietary amino-acids, and osteopathy. Those found to have significant reduction in blood pressure are: magnesium, qigong, melatonin, meditation, vitamin C, chiropractic, folate, inorganic nitrate, beetroot juice, L-arginine and coenzyme Q10. By virtue of the research designs and methodologies, the evidence contributed from these studies is at level 1. Table 2 summarizes the strength of the evidence supporting the non-conventional approaches to the lowering of blood pressure (table 2)

Evidence from systematic reviews and meta-analysis of RCTs supports the blood pressure lowering of qigong, melatonin, meditation, vitamin C, inorganic nitrate, beetroot juice and beetroot bread, L-arginine, and coenzyme Q10. Evidence from an RCT each also supports blood pressure lowering by chiropractic and folate.

DISCUSSION

Qigong

Qigong (also known as *yang sheng*) is an ancient Chinese energy medicine that stimulates the flow of *qi*, or life energy through a group of postures, movements, breathing patterns, and meditation. it is claimed that the healthy flow of *qi* throughout the body has healing effect against cardiovascular diseases (Sancier and Holman, 2004). Even though 3 systematic reviews on the effects of qigong on hypertension showed some encouraging results for lowering blood pressure, the conclusiveness of the evidence has several short comings. Chief among these lies in the methodological quality of the studies, where the risk of bias is generally high. Furthermore, for causal relationship the mechanism of action must be well explained, and this is lacking in the studies of qigong and hypertension. More rigorous trial designs are warranted to confirm these results (Lee *et al.*, 2007; Guo X *et al*., 2008; Xiong X *et al*., 2015).

Table 1A: Summary of the studies with systematic review and/or meta-analysis of RCTs

Authors	Year	Subjects	Research Design	Intervention	Main outcome
Campbell *et al*.	2013	17 RCTs. n = 1,524	Systematic review and meta-analysis of RCTs	Fish oil	8 studies: significant lowering of SBP and DBP. 9 studies: non-significant.
Guo *et al*.	2008	9 RCTs. n = 908	Meta-analysis of RCTs	Qigong	Significant lowering of SBP and DBP compared with controls with no treatment.
Xiong*et al*.	2015	20 RCTs. n = 2,349	Systematic review and meta-analysis of RCTs.	Qigong	Significant lowering of SBP and DBP.
Tyagi & Cohen *et al*.	2014	120 studies. n = 6,693	Systematic review of clinical studies.	Yoga	Lowers normotension and hypertension.
Posadzki *et al*.	2014	17 studies	Systematic review of randomized clinical trials.	Yoga	Treatment of hypertension is encouraging, but inconclusive.
Cramer *et al*.	2014	7 RCTs. n = 452	Systematic review and meta-analysis of RCTs	Yoga	No evidence found for effect on blood pressure.
Hagins *et al*	2013	17 studies.	Systematic review and meta-analysis of RCTs and non-RCTs.	Yoga	Modest, but significant lowering of blood pressure.
Rosenfeldt *et al.*	2007	3 RCTs and 1 cross-over trial. n = 138	Meta-analysis of clinical trials.	Coenzyme Q10	Significant lowering of SBP and DBP.
Grossman *et al.*	2011	7 RCTs. n = 221	Meta-analysis of RCTs	Melatonin	Controlled release melatonin associated with significant lowering of SBP and DBP.
Anderson *et al.*	2008	9 RCTs. n = 711	Meta-analysis of RCTs.	Meditation	Significant lowering of SBP and DBP.
Witham *et al.*	2009	11 RCTs. n = 716	Systematic review and meta-analysis of RCTs	Vitamin D	Weak evidence to support small effect on blood pressure.
Juraschek *et al.*	2012	29 RCTs. n = 1,332	Systematic review and meta-analysis of RCTs	Vitamin C	Significant lowering of SBP and DBP in short term trials.
Siervo *et al.*	2013	16 RCTs. n = 254	Systematic review and meta-analysis of RCTs	Inorganic nitrate and beet root juice	Significant lowering of SBP.
Dickinson *et al.*	2006	12 studies. n = 545	Systematic review of RCTs	Magnesium	Significant lowering of DBP, but not SBP. Weak causal relationship.
Dong *et al.*	2011	11 RCTs. n = 387	Meta-analysis of RCTs	L-arginine	Significant lowering of both SBP and DBP.

BP – blood pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; RCTs – Randomized Clinical Trials; n – number of subjects enrolled in the study.

Table 1B: Summary of the studies with RCT

Authors	Year	Subjects	Research Design	Intervention	Main outcome
Bakris *et al.*	2007	n = 50	RCT	Chiropractic	Significant lowering of SBP and DBP.
Cagnacci *et al*.	2009	n = 30	RCT	Folate	Significant lowering of nocturnal SBP, DBP, and mean BP.
Coles & Clifton	2012	n = 30	RCT	Beetroot juice	Significant lowering of SBP in men.
Hobbs *et al*.	2013	n = 23	RCT	Beetroot bread	Significant lowering of DBP.
Guerrero-Romero & Rodriguez-Moran	2009	n = 82	RCT	Magnesium	Significant lowering of SBP and DBP in diabetic hypertensive adults.

BP – blood pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; RCTs – Randomized Clinical Trials; n – number of subjects enrolled in the study.

Table 1C: Summary of the study with non-RCT

Authors	Year	Subjects	Research design	Intervention	Main outcome
Cerritelli *et al*	2011	N = 63	Non-randomized controlled trial	Osteopathy	Significantly associated with improvement in SBP, but not DBP.

BP – blood pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; RCTs – Randomized Clinical Trials; N – number of subjects enrolled in the study.

Table 1D: Summary of observational studies.

Authors	Year	Subjects	Research design	Intervention	Main outcome
Miura *et al*	2013	N= 4,680	Cross-sectional epidemiological study	Monounsaturated fatty acids	Significant relationship in lowering blood pressure.
Kuil *et al*	2013	N= 3,086	Cohort cross-sectional study	Dietary amino-acids	No association for glutamic acid, arginine, lysine, and cysteine with lowering blood pressure.

BP – blood pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; RCTs – Randomized Clinical Trials; n – number of subjects enrolled in the study.

Table 2: Summary of evidence for non-conventional approaches on hypertension

Intervention	Number of literature	Level of evidence	Evidence
Fish oil	1	1	Systematic review and meta-analysis of 17 RCTs. Mixed results. Weak evidence.
Qigong	2	1	Systematic review and meta-analysis of 20 RCTs. Significant lowering of SBP and DBP.
Yoga	4	1	Systematic review and meta-analysis of 7 RCTs. No evidence found to support lowering of BP.
Coenzyme Q10	1	1	Meta-analysis of 3 RCTs and 1 crossover trial. Significant lowering of SBP and DBP.
Melatonin	1	1	Meta-analysis of 7 RCTs. Significant lowering of SBP and DBP.
Transcendental meditation	1	1	Meta-analysis of 9 RCTs. Significant lowering of SBP and DBP.
Vitamin D	1	1	Systematic review and meta-analysis of 11 RCTs. Mixed results. Weak evidence.
Vitamin C	1	1	Systematic review and meta-analysis of 29 RCTs. Significant lowering of SBP and DBP in short term trials.
Monounsaturated fatty acids	1	4	Observational epidemiological study. Positive correlation in lowering BP.
Folate	1	1	1 RCT. Significant lowering of SBP and DBP.
Inorganic nitrate, beetroot juice, and beetroot bread	3	1	Systematic review and meta-analysis of 16 RCTs, and 2 RCTs. Significant lowering of SBP and DBP.
Magnesium	2	1	Systematic review of 12 RCTs. Mixed results. Weak evidence.
L-arginine	1	1	Meta-analysis of 11 RCTs. Significant lowering of SBP and DBP.
Dietary amino-acids	1	4	Observational cohort study. No association with lowering BP.
Chiropractic	1	1	1 RCT. Significant lowering of SBP and DBP.
Osteopathy	1	2	1 non-RCT. Significant association with lowering SBP, but not DBP. Weak evidence.

Melatonin

Melatonin, a derivative of the amino acid, tryptophan, is a hormone secreted by the pineal gland. Known for its role as an antioxidant (Hardeland 2005; Poeggeler *et al*., 1993), melatonin plays an important role in the circadian rhythm and the regulation of sleep cycles (Scheer F *et al*., 2004). In most hypertensive cases, the high blood pressure phenomenon can be explained from the oxidative stress theory. Excessive oxidation from oxygen free radicals leads to endothelial dysfunction and eventual constriction of blood vessels. The majority of people have fluctuating blood pressure in a 24-hour period, which is highest in the day and lowest at night, called the nocturnal dip. This nocturnal dipping is a natural phenomenon and non-dipping has been associated with increased frequency of hypertension and cardiovascular disease (Ingelsson E *et al*., 2006). On the basis of its antioxidant and regulatory role of circadian rhythm, melatonin may have a role in

Table 3: Summary of CAM intervention on blood pressure lowering

No evidence	Weak evidence	Significant evidence
1. Yoga	1. Fish oil	1. Qigong
2. Dietary amino-acids	2. Vitamin D	2. Coenzyme Q10
	3. Monounsaturated fatty acids	3. Melatonin
	4. Magnesium	4. Transcendental meditation
	5. Osteopathy	5. Vitamin C
		6. Folate
		7. Inorganic nitrate
		8. Beetroot
		9. L-arginine
		10. Chiropractic

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regulating nocturnal blood pressure. The meta-analysis of RCTs by Grossman and colleagues concluded that with controlled-release melatonin, nocturnal blood pressure was significantly reduced (Grossman E *et al*., 2011). Larger trials with longer duration are required to determine long-term beneficial effects of melatonin. Standardization of dose and frequency of treatment is also needed.

Transcendental meditation

Transcendental meditation (TM) is a specific form of mantra meditation that is aimed to bring the mind into a state of pure consciousness. This means the mind is 'transcended' into a state of perfect rest, stillness, and absence of mental boundaries. It also means the psychosomatic mode comes to a state of total relaxation and free from stress. Relaxation is an antagonist to stress. If what is claimed about TM is true, therefore the achievement of total relaxation through TM may have an effect on blood pressure through the neuro-hormonal pathway. The study of Anderson and colleagues using meta-analysis of 9 RCTs concluded that TM has the potential to lower blood pressure and is clinically significant. Of the 9 RCTs studied, only 3 were of high quality (Anderson J *et al*., 2008). More studies in a larger population are warranted to further determine the positive effect of TM on hypertension.

Vitamin C

There are multiple known physiological functions of vitamin C (ascorbic acid) in the human body. Perhaps those functions that play a direct or indirect role on hypertension are the antioxidant role of scavenging superoxide anion, the improvement of endothelial vasomotor dysfunction, as well as diuresis. However, the efficiency of ascorbic acid in its scavenging role is dose dependent. Sherman and colleagues has shown that it is necessary to maintain a high or pharmacological dose for ascorbic acid to achieve the result of reversing endothelial dysfunction (Sherman D *et al*., 2000). The systematic review and meta-analysis of 29 RCTs by Juraschek and colleagues concluded that in short-term trials, vitamin C supplementation lowers both systolic and diastolic blood pressure. The median dose used was 500 mg/day, while the median duration of study in the 29 RCTs was 8 weeks (Juraschek S *et al*., 2012). Long-term trials on the effects of vitamin C supplementation on blood pressure will ensure its efficacy potential.

Inorganic nitrate, beetroot juice, and beetroot bread

According to European food safety authority (EFSA), Both beetroot juice and beetroot bread have high content of inorganic nitrate, ranging from 110 to 3670 mg of nitrate/kg, and a median concentration of 1,100 mg/kg. The blood pressure lowering effects of inorganic nitrate may derive from the generation of NO which affects the endothelium and causes arteriodilation (Kelm M, 1999; Siervo M *et al*., 2011). Reduced NO bioavailability may lead to endothelial dysfunction resulting in higher risk of hypertension as well as cardiovascular diseases (Avogaro A *et al*., 2008; Siervo *et al*., 2011b). Systematic review and meta-analysis of 16 RCTs concluded that inorganic nitrate and beetroot juice supplementation were associated with a significant reduction of systolic blood pressure (Siervo *et al*., 2013). Long-term studies on the efficacy of inorganic nitrate and beetroot juice supplementation, together with assessment of safety and tolerance holds promise.

L-arginine

There are two possible pathways for the synthesis of NO: the enzymatic and the non-enzymatic pathways. The non-enzymatic pathway involves the reduction of nitrate to nitrite and finally to NO. This requires the help of acidification process and low pH of biological tissues (Lundberg J *et al*., 2009; Zweier J *et al*., 1999). The enzymatic pathway, or the classical L-arginine NO synthase pathway, is dependent on the endothelium for its synthesis. The loss of NO bioactivity is an important feature of endothelial dysfunction in hypertension. Therefore, supplementing a substrate to enhance nitric oxide production may be a rational treatment approach. L-arginine serves as the principal substrate for vascular NO production. The endothelial isoform of the NO synthase uses L-arginine as precursor to release NO in the endothelium. This is crucial for the control of vascular

tone, smooth muscle cells, platelet aggregation, and inflammation (Umans and R Levi, 1995). Dong and colleagues' meta-analysis of 11 RCTs concluded that L-arginine supplementation significantly lowers systolic and diastolic blood pressure (Dong J *et al*., 2011). Large scale and longer-term trials are needed to confirm its blood pressure lowering effect as well as safety and possible pro-oxidative effect.

Coenzyme Q10

Coenzyme Q10, also known as ubiquinone because of its ubiquitous distribution in nature, is a fat-soluble molecule obtained through tissue synthesis, which acts as an electron carrier in mitochondria and as a coenzyme for mitochondrial enzymes (Langsjoen P *et al*., 1985). The bioenergetics and antioxidant properties of coenzyme Q10 make it unique. Studies suggest that coenzyme Q10 deficiency may be associated with different cardiovascular conditions such as ischemic heart disease and heart failure (Langsjoen *et al*., 1985b). It also has potential to lower blood pressure (Burke B *et al*., 2001; Rosenfeldt *et al*., 2007). The mechanistic pathway which coenzyme Q10 might work is an antioxidant effect acting directly on vascular endothelium for vasodilation or by reducing super oxide synthesis (McCarty M, 1999). Another possible mechanism is the anti-atherogenic effects as a modulator of beta-integrins levels on the surface of blood monocytes (Quinzii *et al*., 2007; Turunen M *et al*., 2002). Rosenfeldt and colleagues' meta-analysis of 3 RCTs, 1 crossover trial, and 8 observational studies concluded that coenzyme Q10 supplementation significantly lowers both systolic and diastolic blood pressure (Rosenfeldt *et al*., 2007). However, the methodological qualities of those studies were low and open to several types of bias. Better-designed studies over longer period are warranted to confirm the efficacy of coenzyme Q10.

Yoga

Regarding the effect of yogaon blood pressure, mixed types of results were observed. Some studies found that Yoga had a significant lowering effect on both SBP as well as DBP (Xiong *et al.*, 2015; Tyagi & Cohen 2014; Hagins *et al*., 2013). Others concluded that the complementary role of yoga in treating hypertension is encouraging, but inconclusive (Posadzki *et al*., 2014). On the other hand, another study revealed no evidence that Yoga has any effect on blood pressure (Cramer *et al*., 2014).

The result of this review on the effects of CAM therapies on hypertension has shown that there is a current surge of potential evidence in its complementary role in the treatment of hypertension. This is in comparison to a previous review in 2008 on the effects of CAM therapies on hypertension (Nahas, 2008). Their role may be both in reductions in blood pressure and/or reducing target organ damage. The type of evidence provided by CAM intervention on blood pressure lowering is summarized in table 3.

CONCLUSION

All the therapies discussed in this review, particularly qigong, melatonin, transcendental meditation, vitamin C, inorganic nitrate, beetroot, L-arginine and coenzyme Q10; have the potential to reduce blood pressure, improve cardiac function and cardiovascular health, decrease the need for antihypertensive medications, and reduce morbidity and mortality. The economic cost of managing hypertension may be considerably reduced. This review also points to an integrative approach of conventional pharmacological treatment along with non-conventional therapies as the way forward for the treatment and management of hypertension. This is also in line with the aspiration of WHO to reduce the prevalence of hypertension by 25%, by 2025.

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