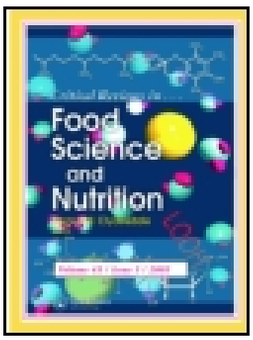

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The Emerging Role of Curcumin for Improving Vascular Dysfunction: A Review

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ABSTRACT

Curcumin, when administered in a bioavailable form, has potential to influence vascular health of various populations, leading to decreases in cardiovascular disease risk. Clinical intervention studies with curcumin have demonstrated significant improvements in endothelial function, arterial compliance, arterial stiffness, and other measures of vascular hemodynamics in young, middle-aged, old, post-menopausal, healthy, diabetic, and obese individuals. Mechanistically, curcumin is believed to improve vascular function through its effects on inflammation, oxidative stress, nitric oxide bioavailability, and structural proteins of the artery. Current data give support for curcumin to be administered for improvements in vascular health to individuals that may or may not be at risk for cardiovascular disease. This review briefly summarizes the techniques used for the establishment of vascular health and overviews the literature investigating the role of curcumin in the improvement of vascular health.

KEYWORDS

Turmeric, endothelial function, oxidative stress, inflammation, bioavailability, arterial stiffness

INTRODUCTION

Curcumin [1,7-bis-(4-hydroxy-3-methoxy- phenyl)-1,6-heptadiene-3,5-dione] is a naturally occurring polyphenol and the active constituent found in the spice turmeric, from the *Curcuma longa* plant. Turmeric contains three curcuminoid compounds (curcumin, demethoxycurcumin, and bisdemethoxycurcumin), of which curcumin is the primary fraction (Julie and Jurenka 2009). Comprising merely 3.14% of pure turmeric, curcumin accounts for the vibrant yellow color of the spice (Tayyem et al. 2006). Historically, the countries of China and India have used turmeric as an herbal remedy to treat sickness and disease (Wongcharoen and Phrommintikul 2009). More recently, scientific evidence has supported the therapeutic use of curcumin in chronic inflammatory diseases, neurodegenerative diseases, cardiovascular diseases, arthritic diseases, and cancer, to name a few (Aggarwal and Harikumar 2009). Nevertheless, while curcumin has favorable therapeutic effects, unformulated curcumin has poor bioavailability in humans, attributed to poor absorption, rapid metabolism, and rapid elimination (Aggarwal and Harikumar 2009). Therefore, multifarious modifications of curcumin, including administration as nanoparticles (Sasaki et al. 2011, Bisht et al. 2007), encapsulation in a liposomal delivery system (Li, Braiteh, and Kurzrock 2005), combination of a lipidated nanoparticle formulation (Gota et al. 2010), creation of curcumin-phospholipid complexes (Maiti et al. 2007), and co-administration with adjuvants piperine and soluble fiber from fenugreek (Shoba et al. 1998, Krishnakumar et al. 2012), have been created to enhance absorption. Curcumin is well-tolerated and is considered non-toxic in humans up to 12 g/day, but some gastrointestinal distress has been reported at the higher doses in a few individuals (Lao et al. 2006, Sharma et al. 2001, Dhillon et

al. 2008). The various formulations of curcumin are currently being studied for the multi-faceted effects they can produce throughout the body.

An emerging area of research with regard to the therapeutic use of curcumin is for the improvement of vascular dysfunction, which is implicated in a reduced risk for cardiovascular disease (CVD). CVD is an important global health concern, as CVD accounts for more deaths than any other cause in the United States and worldwide (World Health Organization 2016, Murphy, Xu, and Kochanek 2013). By the year 2030, it has been projected that 40.5% of individuals in the United States will have CVD, amounting to an estimated $818 billion in direct medical costs and $276 billion in indirect costs (Heidenreich et al. 2011). Therefore, the need for both preventive and intervention strategies, outside of traditional pharmacological approaches that are costly and often lead to further complications, is paramount for slowing the progression and reversing the advancement of CVD.

There is a growing interest in using natural, cost-effective strategies, such as curcumin, to reduce vascular disease. A primary concern in the development of CVD is the age-associated deterioration of the arterial system, characterized by both arterial stiffening and endothelial dysfunction of large arteries, which include the aorta and carotid artery (Scuteri et al. 2005). Encompassed in this age-related decline in arterial dysfunction are alterations in cardiovascular hemodynamics, specifically an increase in blood pressure (BP) (Lakatta and Levy 2003, Franklin et al. 1997). In particular, measures of arterial stiffness have great predictive power in determining future incident hypertension, cardiovascular events, cardiovascular mortality, and all-cause mortality (Vlachopoulos, Aznaouridis, and Stefanadis 2010, Vlachopoulos et al. 2010, Störk et al. 2004). Additionally, measures of endothelial dysfunction, which serve as early

indicators of atherosclerosis, are predictive of incident and recurrent cardiovascular events (Yeboah et al. 2009, Rubinshtein et al. 2010). Also valuable in the prediction of cardiovascular events are longitudinal changes in BP, which serve as indirect measures of fluctuations in hemodynamic patterns associated with aging; however, these measures of BP can be an indication of the aforementioned large artery stiffness, or they could accelerate the progression of it (Franklin et al. 1997, Franklin et al. 2001). Accordingly, curcumin is being investigated for its ability to attenuate arterial stiffening, endothelial dysfunction, and hypertension as indicators of decreased CVD risk in multiple populations. The purpose of this review is to: 1) briefly review the techniques used for determination of vascular health, and 2) examine the current literature that considers the role of curcumin to improve vascular function.

II. ARTERIAL STIFFNESS: PROGNOSTIC VALUE

Large artery stiffness, specifically of the aorta, regulates the ability of the arteries to expand and recoil throughout the cardiac cycle and has an integral role in the determination of overall cardiovascular health (Vlachopoulos, Aznaouridis, and Stefanadis 2010, Ben-Shlomo et al. 2014, Mitchell et al. 2010). Briefly, when the left ventricle of the heart contracts, blood is ejected from the heart into the ascending aorta. This causes the aorta to expand, and a pulse pressure wave is sent to the peripheral arteries and arterioles (O'Rourke et al. 1968). In young, healthy adults, the aorta is elastic and compliant in nature, and the pulse pressure wave travels at a relatively slow rate (Scuteri et al. 2005, Reference Values for Arterial Stiffness' Collaboration 2010). In contrast, as arteries stiffen with advancing age or disease, the pulse pressure wave will travel at an increased velocity (Scuteri et al. 2005, Reference Values for Arterial Stiffness' Collaboration 2010). Thus, in young, healthy individuals, the aorta is elastic and compliant, rendering it

capable of buffering pulsations efficiently and effortlessly (Benetos et al. 1993). With age, or various other factors including disease status or obesity, the elastic nature of the aorta decreases with the increased workload placed on it due to its proximity to the heart, causing a progressive stiffening (O'Rourke and Hashimoto 2007). The stiffening process occurs through structural and functional changes of the artery from complex interactions as a result of increased collagen content, decreased elastin content, greater advanced glycation end-products, augmented inflammatory activity, amplified matrix metalloproteinase activity, and increased reactive oxygen species (Díez 2007, Fleenor and Berrones 2015, Zieman, Melenovsky, and Kass 2005).

There are various methods to assess aortic stiffness, which are summarized in Table 1 along with the methods for determination of vascular endothelial function and hemodynamics. A primary method is the 'gold standard' carotid-femoral pulse wave velocity (cfPWV) (Laurent et al. 2006). With this method, determination of the velocity of the pulse pressure wave occurs by measuring the pulse wave velocity from the carotid to femoral artery, and is a simple calculation of distance over time (reported in meters per second). The calculated cfPWV is an important risk factor, independent of conventional risk factors, in determining cardiovascular events (Mattace-Raso et al. 2006, Vlachopoulos, Aznaouridis, and Stefanadis 2010, Mitchell et al. 2010). In fact, an increase in cfPWV of 1.0 m/s amplifies risk for cardiovascular events by 14% and risk for cardiovascular mortality by 15% (Vlachopoulos, Aznaouridis, and Stefanadis 2010).

Another common method for measuring aortic stiffness is through pulse wave analysis, where the radial pressure wave is measured, and a validated generalized transfer function indirectly generates the aortic pressure waveform (Sharman et al. 2006). Following this determination of the aortic pressure waveform, aortic BP and augmentation index (AIx) are

derived and used to classify aortic stiffness. AIx is a measure of systemic arterial stiffness that has prognostic value in determining cardiovascular events and all-cause mortality (Vlachopoulos et al. 2010). This measure is often expressed with a standardized heart rate of 75 (AIx_{75}), as AIx is influenced by heart rate (Wilkinson et al. 2000).

In addition to aortic stiffness, stiffening of the carotid artery also predicts cardiovascular mortality risk (Störk et al. 2004). Carotid stiffness is commonly measured by determining the β-stiffness index. Often used synonymously with arterial stiffness, compliance of an artery is defined as the absolute change in diameter given a certain amount of pressure (O'Rourke et al. 2002). Determination of the β-stiffness index, therefore, occurs through measurement of carotid BP via a non-invasive tonometer in relation to measurement of the diameter of the artery via ultrasound imaging (Akazawa et al. 2013). Nevertheless, carotid arterial compliance determined with the β-stiffness index is not the most sensitive indicator of large artery stiffness and has not been shown to provide the same prognostic assessment as aortic stiffness measures via cfPWV (Oliver and Webb 2003).

While the aorta and carotid artery are commonly used as measures of central arterial stiffness, the composite measure of both peripheral and central arterial stiffness, brachial-ankle pulse wave velocity (baPWV), is also used in the determination of vascular health (Yamashina et al. 2003). Measurement of baPWV occurs at the brachial and dorsalis pedis arteries by way of a volume-plethysmographic apparatus, which produces the phonocardiogram, electrocardiogram, pulse pressure waveform, and the blood pressure at the respective arteries. Then, the pressure waveforms from both arterial sites are used to quantify baPWV, which is the distance the pulse wave travels from one site to the next divided by the time taken to travel that distance. This

measure is an independent predictor of atherosclerotic cardiovascular risk and severity of atherosclerotic vascular damage (Yamashina et al. 2003). Furthermore, baPWV is strongly associated with 'gold standard' cfPWV (Tanaka et al. 2009).

III. VASCULAR ENDOTHELIAL FUNCTION

In addition to arterial stiffness, vascular endothelial function gives indication of another important aspect of arterial health. The endothelium forms the inner layer of blood vessels and allows them to efficiently respond to changes in the vasculature, such as BP, shear stress, hormonal stimuli (e.g. noradrenaline, serotonin), and chemical stimuli (e.g. acetylcholine, bradykinin) (Endemann and Schiffrin 2004, Cocks and Angus 1983). Vascular homeostasis at the level of the endothelium is maintained through changes in relaxing and contracting factors, and most notably nitric oxide (NO) (Anderson 2006). NO is not only a potent vasodilator of the endothelium, but it is also a messenger, mediator, and regulator of cell function (Kuo and Schroeder 1995). Additionally, NO bioavailability is essential in vascular health (Joannides et al. 1995). Therefore, proper functioning of the endothelium plays a critical role in vascular health through regulation of vascular tone, inflammatory response, coagulation, and thrombocyte adhesion (Landmesser and Drexler 2005).

Flow-mediated dilation (FMD), a measure of macrovascular function, has been regarded as the non-invasive gold standard (Kobayashi et al. 2004), as it is the most well-studied method with the greatest potential for clinical application (Faulx, Wright, and Hoit 2003). However, the level of technical training required by the investigator for measuring FMD limits its clinical applicability and reproducibility (Corretti et al. 2002). The measurement of FMD occurs by occlusion of the brachial artery with a sphygmomanometer and subsequent release, resulting in

reactive hyperemia ensued by endothelium-dependent vasodilation (Corretti et al. 2002). Ultrasound images are captured of the brachial artery before and after hyperemia to determine percentage of vasodilation. The degree of vasodilation produced by the brachial artery is, in part, indicative of NO bioavailability (Joannides et al. 1995).

Another method used to assess endothelial function is peripheral arterial tonometry by means of finger probe plethysmography, an assessment of microvascular function, to calculate a reactive hyperemia index (RHI). Similarly to FMD, occlusion of the brachial artery is incited with a sphygmomanometer, followed by a releasing of the cuff, leading to reactive hyperemia. Via plethysmography, finger probes measure pulse volume amplitude to detect abnormalities in hyperemic response (Rubinshtein et al. 2010). Post-occlusion pulse wave amplitude data are compared to pre-occlusion data and normalized to the control arm to compute the RHI. Unlike FMD, this technique measures microvascular function, is operator-independent, and is highly reproducible. The values determines by RHI, however, may not be as predictive of cardiovascular health for every population as those determined by FMD (Rubinshtein et al. 2010).

An alternative measure used in the determination of endothelial function is the assessment of the reflective index, a parameter derived from the analysis of the pulse wave reflections, following a salbutamol challenge test (Usharani et al. 2008). Similar to RHI, the reflective index measure incorporates finger probe plethysmography and is a determinant of microvascular function. However, vascular reactivity is determined in this method following inhalation of salbutamol, a bronchodilator. Digital volume pulse is used to determine change in response from baseline to

post-inhalation of salbutamol, and the reflective index is generated as a measure of endothelial function (Chowienczyk et al. 1999).

A final, invasive measure for assessing microvascular endothelial function is through forearm blood flow (FBF) with strain-gauge venous occlusion plethysmography (Dietz et al. 1994). With this technique, cuffs are placed on the wrists and upper arm to occlude blood flow, while the strain gauge remains on the forearm for determination of FBF. The wrist cuff remains inflated throughout the measurement while the upper arm cuff cycles pressure. Meanwhile, incremental acetylcholine is infused into the brachial artery to assess FBF (FBF_{ACh}) in the determination of endothelium-dependent dilation (Kaplon et al. 2016). Endothelium-independent dilation can also be measured, where incremental sodium nitroprusside is infused into the brachial artery to determine the contribution of smooth muscle relaxation in FBF measures. This determination of FBF has, likewise, been considered a gold standard, but the invasive nature of this protocol often makes this technique less practical in a clinical setting (Wilkinson and Webb 2001). Taken together, these measures of endothelial function can reveal additional information about vascular health.

IV. ADDITIONAL MEASURES OF VASCULAR HEMODYNAMICS

Vascular hemodynamics are complicated to quantify, and the aforementioned measures help in quantification, but hemodynamic changes are also inferred through longitudinal changes in BP components (Franklin et al. 1997). In particular, useful measures in this quantification include traditional BP measures taken at the brachial artery, including both systolic and diastolic BP (bSBP and bDBP, respectively). Derived from these measures, pressure is often assessed by the steady component, mean arterial pressure (bMAP), and the pulsatile component, pulse pressure

(bPP) (Nichols, O'Rourke, and Vlachopoulos 2011). Whereas MAP is heavily influenced by cardiac output and vascular resistance, PP is influenced more so by left ventricular ejection, large artery stiffness, early pulse wave reflection, and heart rate (Franklin et al. 1997). Therefore, PP has also proven useful as a surrogate measure of arterial stiffness (Laurent et al. 2006). However, measures of aortic pulse pressure have shown greater prognostic insight compared with bPP (Laurent et al. 2006). Furthermore, it has been shown that central measures of BP and associated components at the aorta or carotid artery provide more useful predictive information regarding CVD risk than peripheral measures taken from the brachial artery (Laurent et al. 2006); therefore, central measures of SBP, DBP, PP, and MAP taken at the aorta (aSBP, aDBP, aPP, and aMAP) and carotid artery (cSBP, cDBP, cPP, and cMAP) have also been used in the quantification of changing hemodynamic patterns.

V. THE POTENTIAL OF CURCUMIN IN HUMAN INTERVENTION STUDIES

Table 2 presents the human intervention studies to date that have examined the effects of curcumin on vascular health. In these studies, interventions range from four weeks to six months duration. The most significant findings include: 1) improvements in endothelial function as measured by FMD (Akazawa et al. 2012, Oliver et al. 2016, Santos-Parker et al. 2017), FBF_{Ach} (Santos-Parker et al. 2017), and reflective index (Usharani et al. 2008); 2) improvements in arterial stiffness as measured by cfPWV (Campbell et al. 2017), baPWV (Chuengsamarn et al. 2014), and the β-stiffness index (Akazawa et al. 2013); and 3) longitudinal improvements in vascular hemodynamic measure bPP (Campbell et al. 2017). Additionally, when combined with exercise, curcumin also improved AIx_{75} and hemodynamic measures, aSBP and bSBP (Sugawara et al. 2012). Curcumin dosage ranged from 50 mg to 5 g per day, with the lowest

dosage conferring benefits for vascular health at 150 mg curcumin (Akazawa et al. 2012). All of the studies were randomized controlled trials (Akazawa et al. 2013, 2012, Sugawara et al. 2012, Campbell et al. 2017, Usharani et al. 2008, Oliver et al. 2016, Nieman et al. 2012, Santos-Parker et al. 2017), while one contained a cross-over design (Nieman et al. 2012). Curcumin was shown to be efficacious with regard to at least one aspect of vascular health in various populations, including post-menopausal women (Akazawa et al. 2012), Type II diabetics (Usharani et al. 2008, Chuengsamarn et al. 2014), young adults (Oliver et al. 2016), middle-aged and older adults (Santos-Parker et al. 2017), and in a subset of obese men with greater baseline stiffness (Campbell et al. 2017). While the majority of these studies used curcumin formulations previously demonstrated to be bioavailable to humans (Akazawa et al. 2013, 2012, Dhindsa et al. 2008, Campbell et al. 2017, Oliver et al. 2016, Santos-Parker et al. 2017), a few of the formulations did not have previous reports validating bioavailability (Nieman et al. 2012, Usharani et al. 2008, Chuengsamarn et al. 2014). In a study using whole turmeric as an intervention for improving vascular function in middle-aged and older obese women, it is probable that the curcumin within the turmeric was not bioavailable; therefore, the efficacy of curcumin in this population is not known and should be evaluated using a bioavailable formulation (Nieman et al. 2012). Considering the mounting evidence from these preliminary findings in clinical trials, curcumin shows great potential to improve vascular health.

Nevertheless, caution should be taken in interpreting these results from clinical trials. The only study showing improvements in the ‘gold standard’ arterial stiffness marker, cfPWV, did not find a systematic amelioration in arterial stiffness; instead, a reduction in cfPWV dependent on initial baseline stiffness measures was reported (Campbell et al. 2017). Additionally, the

sample sizes for the studies considering curcumin and vascular function may not be adequately powered to determine significance. In the studies presented in this review, sample sizes per group range from 10 to 107 individuals. Additional larger-scale clinical trials are warranted to determine the potential of bioavailable formulations of curcumin on the various facets of vascular health.

Despite the potential of curcumin to influence vascular health, mechanistic insight is more sparing through studies in humans. In young, obese men, however, a trending increase in anti-inflammatory cytokines, interleukin (IL)-10 and IL-13, was reported with concomitant reductions in bPP and cfPWV, respectively (Campbell et al. 2017). In Type II diabetics, inflammatory cytokines, TNF-α and IL-6, and an oxidative stress marker, malondialdehyde, were measured. Curcumin treatment significantly reduced each of these parameters, and the authors suggest that improvements in inflammation and oxidative stress were responsible for the amelioration of endothelial dysfunction occurring in type II diabetics (Usharani et al. 2008). Furthermore, in middle-aged and older adults, improvements in endothelial function were explained by enhanced NO bioavailability, as determined by resistance artery nitric oxide-mediated endothelium-dependent dysfunction with or without a nitric oxide synthase inhibitor (L-NMMA), and reduced oxidative stress, as measured by oxidative stress-mediated suppression of endothelium-dependent dysfunction with or without the antioxidant vitamin C (Santos-Parker et al. 2017). Therefore, current human studies showing improvements in vascular health with curcumin point to inflammation and oxidative stress as potential contributors, but these findings have yet to be corroborated. Currently, there are limited studies showing mechanistic insight for curcumin’s improvement to vascular health in humans.

VI. ANIMAL INTERVENTION STUDIES: WHAT CAN THEY TELL US?

Animal studies with curcumin as an intervention can give further insight on the mechanisms that underlie improvements in vascular health. Rodent studies have shown curcumin ameliorates arterial stiffness in aged mice (Fleenor et al. 2013) and hypertensive rats (Nakmareong et al. 2012), and protects against cadmium-induced arterial stiffening in rats (Sangartit et al. 2014). In aged mice, four weeks of curcumin-supplemented chow was sufficient to improve arterial stiffness, as measured by aortic pulse wave velocity, and NO-mediated endothelial dysfunction, as determined by changes in luminal diameter of the carotid artery in response to acetylcholine, to levels that were not significantly different from young mice (Fleenor et al. 2013). Mechanistically, curcumin also normalized arterial collagen and advanced glycation end-products, reduced oxidative stress, and improved NO bioavailability associated with aging (Fleenor et al. 2013). Hypertensive rats intragastrically administered two weeks of tetrahydrocurcumin, a metabolite of curcumin, saw improvements in blood pressure and aortic stiffness (Nakmareong et al. 2012). These effects of tetrahydrocurcumin were associated with reduced oxidative stress through suppression of the free radical, superoxide (O_2), formation and enhanced blood antioxidant (glutathione); elevated endothelial nitric oxide synthase (eNOS) expression; and elevated plasma nitrate/nitrite expression. Therefore, the authors suggest the improvements in blood pressure and aortic stiffness are due to the antioxidant properties of tetrahydrocurcumin, which increased NO bioavailability (Nakmareong et al. 2012). A final study conducted in mice with cadmium-induced hypertension revealed that eight weeks of intragastrically co-administered tetrahydrocurcumin protected mice against hypertension, arterial stiffness, and vascular remodeling (Sangartit et al. 2014). Tetrahydrocurcumin was suggested to

exert its effects through downregulation of inducible nitric oxide synthase (iNOS) expression, upregulation of eNOS, decreases in nitrate/nitrite urinary levels, decreases in oxidative stress, enhancements in antioxidant (glutathione) levels, and normalization of structural arterial proteins (collagen and elastin). Thus, the authors suggest tetrahydrocurcumin reduces cadmium-associated hypertension through its antioxidant and chelating properties, indicated by its ability to influence vascular response and decrease the negative effects of cadmium exposure (Sangartit et al. 2014). Therefore, multiple studies indicate curcumin attenuates arterial stiffness by enhancing the antioxidant defense system, ameliorating structural proteins of the artery, and improving NO bioavailability.

Beyond the studies providing mechanistic insight for improvements in arterial stiffness, several animal studies offer further insight on the mechanisms that underlie amelioration of endothelial dysfunction. In diabetic rats, six weeks of high (300 mg/kg/day) and low (30 mg/kg/day) dose administration of curcumin via oral feeding ameliorated endothelial dysfunction, as measured by vasodilatory responses to acetylcholine, and hyperglycemia, as measured by plasma glucose levels (Rungseesantivanon et al. 2010). The antioxidant capacity of curcumin was associated with the attenuation of endothelial dysfunction, as measured by decreased O_2 production, which was believed to occur through the inhibition of vascular protein kinase C (PKC) observed in this study (Rungseesantivanon et al. 2010). However, there was not a significant difference in the vascular benefits of curcumin between the high and low dose. Furthermore, in hypertensive rats, six weeks of low (50 mg/kg/day) and high (100 mg/kg/day)

dose curcumin treatment by gavage improved endothelial dysfunction, as measured by vasodilatory responses in isolated aortic rings, and blood pressure (Boonla et al. 2014). Greater

improvements were seen with the high dose, and the mechanisms associated with improvements in endothelial function included changes in structural proteins of the arterial wall (collagen and elastin), increased NO bioavailability, improved antioxidative response, reduced plasma angiotensin converting enzyme levels, and attenuated matrix metalloproteinases (MMP-2 and MMP-9) (Boonla et al. 2014). Similarly to studies involving arterial stiffness, the beneficial effects of curcumin on endothelial dysfunction in rodents are reported to occur through enhanced antioxidative response, improved NO bioavailability, and structural modifications in the arterial wall. Concomitant with changes in arterial stiffness and endothelial dysfunction, blood pressure is often improved in rodents when curcumin is administered (Nakmareong et al. 2012, Sangartit et al. 2014, Boonla et al. 2014).

While these animal models provide insight into the mechanisms underlying the improvements seen in human studies, it is not yet known whether the mechanisms found in animal models are similar to those in humans. Additionally, while curcumin has significant effects on the structural components of the arterial wall (namely collagen and elastin) of mice after as little as four weeks (Fleenor et al. 2013), it is unlikely that these same improvements would occur as readily in humans. Furthermore, it has been suggested that these changes in humans following twelve weeks of intervention occur through functional rather than structural changes in the artery (Campbell et al. 2017). Due to an inability to study these structures in humans in vivo, further work needs to be done to see if long-term improvements in humans occur after curcumin intervention, which could suggest that curcumin is able to alter the structural properties of the arteries. Also, longer intervention periods are needed to examine long-term efficacy and safety, and to gain mechanistic insight in various populations.

VII. IN VITRO CELL STUDIES: MECHANISTIC INSIGHT

The anti-inflammatory properties of curcumin have largely not been assessed in rodent models of vascular dysfunction. In vitro studies, however, have examined the effects of curcumin on endothelial inflammation. In human umbilical vein endothelial cells, curcumin inhibited Nuclear Factor-κB (NFκB) signaling, decreasing pro-inflammatory cytokine expression; reduced the production of reactive oxygen species; and suppressed signaling via mitogen-activated protein kinases (MAPK) and signal transducer and activator of transcription (STAT)-3 (Kim et al. 2007). Another study using human umbilical vein endothelial cells suggested curcumin exerts anti-inflammatory effects on high mobility group box (HMGB) 1 protein through down-regulation of toll-like receptors (TLR)-2 and -4 (Kim, Lee, and Bae 2011). Therefore, these in vitro studies give support for the findings in clinical trials indicating the anti-inflammatory properties of curcumin contribute to the attenuation of vascular dysfunction.

VIII. DOSAGE AND BIOAVAILABILITY

The necessary dosage to see improvements in vascular function is currently unknown. Various formulations of curcumin have been developed due to the poor bioavailability in humans (Gupta, Patchva, and Aggarwal 2013). Nonetheless, studies have not been conducted to test the lowest effective dose. Currently, the lowest effective dose producing vascular benefits is 150 mg of curcumin (Akazawa et al. 2012); however, this dosage might be specific to the formulation, which has been reported to increase bioavailability 27.3-fold compared with unformulated curcumin (Sasaki et al. 2011). Further clinical trials need to be conducted to determine the lowest effective dose, which is likely to be different among various clinical populations. Furthermore, it has not yet been determined whether curcumin found within the spice turmeric, when used in

daily food preparation, could be efficacious in producing these same beneficial effects. It is likely, however, that turmeric would need to be combined with an adjuvant, such as piperine from black pepper, to increase bioavailability in daily food usage.

IX. CONCLUSION

In conclusion, curcumin could help improve the vascular health of various individuals including arterial stiffness, vascular endothelial dysfunction, and hemodynamic parameters. However, larger scale clinical trials using gold standard methodology for measures of vascular health are needed to corroborate the preliminary findings from small scale randomized clinical trials in several populations of interest. While minimal mechanistic insight is available through clinical trials, increased anti-inflammatory cytokines, decreased oxidative stress, and improved NO bioavailability have been implicated. Animal and cell studies have added mechanistic insight for changes in curcumin-mediated improvements in vascular health, giving support for curcumin to attenuate vascular dysfunction via modulation of inflammation, reduce oxidative stress, improve NO bioavailability, and alter structural proteins of the arterial wall. The proposed beneficial effects of curcumin to promote vascular health from human, animal, and cell studies are summarized in Figure 1. These findings have yet to be substantiated in clinical trials, and further study is warranted. Curcumin shows promise as a potential cost-effective, natural strategy to help eliminate some of the burden imposed by increased CVD risk, but additional study needs to be done to validate the findings in this emerging area of research.

Disclosures

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XI. REFERENCES

Aggarwal, Bharat B, and Kuzhuvelil B Harikumar. 2009. "Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases." *The International Journal of Biochemistry & Cell Biology* 41 (1):40-59.

Akazawa, Nobuhiko, Youngju Choi, Asako Miyaki, Yoko Tanabe, Jun Sugawara, Ryuichi Ajisaka, and Seiji Maeda. 2012. "Curcumin ingestion and exercise training improve vascular endothelial function in postmenopausal women." *Nutrition Research* 32 (10):795-799.

Akazawa, Nobuhiko, Youngju Choi, Asako Miyaki, Yoko Tanabe, Jun Sugawara, Ryuichi Ajisaka, and Seiji Maeda. 2013. "Effects of curcumin intake and aerobic exercise training on arterial compliance in postmenopausal women." *Artery Research* 7 (1):67-72.

Anderson, Todd J. 2006. "Arterial stiffness or endothelial dysfunction as a surrogate marker of vascular risk." *Canadian Journal Of Cardiology* 22:72B-80B.

Ben-Shlomo, Yoav, Melissa Spears, Chris Boustred, Margaret May, Simon G Anderson, Emelia J Benjamin, Pierre Boutouyrie, James Cameron, Chen-Huan Chen, and J Kennedy Cruickshank. 2014. "Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects." *Journal of the American College of Cardiology* 63 (7):636-646.

Benetos, A, S Laurent, AP Hoeks, PH Boutouyrie, and ME Safar. 1993. "Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries." *Arteriosclerosis, Thrombosis, And Vascular Biology* 13 (1):90-97.

Bisht, Savita, Georg Feldmann, Sheetal Soni, Rajani Ravi, Collins Karikar, Amarnath Maitra, and Anirban Maitra. 2007. “Polymeric nanoparticle-encapsulated curcumin (” nanocurcumin“): a novel strategy for human cancer therapy.” *Journal of nanobiotechnology* 5 (1):1.

Boonla, Orachorn, Upa Kukongviriyapan, Poungrat Pakdeechote, Veerapol Kukongviriyapan, Patchareewan Pannangpetch, Parichat Prachaney, and Stephen E Greenwald. 2014. “Curcumin improves endothelial dysfunction and vascular remodeling in 2K-1C hypertensive rats by raising nitric oxide availability and reducing oxidative stress.” *Nitric Oxide* 42:44-53.

Campbell, Marilyn S., Adam J. Berrones, I. M. Krishnakumar, Richard J. Charnigo, Philip M. Westgate, and Bradley S. Fleenor. 2017. “Responsiveness to curcumin intervention is associated with reduced aortic stiffness in young, obese men with higher initial stiffness.” *Journal of Functional Foods* 29:154-160. doi: http://dx.doi.org/10.1016/j.jff.2016.12.013.

Chowienczyk, Philip J, Ronan P Kelly, Helen MacCallum, Sandrine C Millasseau, Tomas LG Andersson, Raymond G Gosling, James M Ritter, and Erik E Änggård. 1999. “Photoplethysmographic assessment of pulse wave reflection: blunted response to endothelium-dependent beta2-adrenergic vasodilation in type II diabetes mellitus.” *Journal of the American College of Cardiology* 34 (7):2007-2014.

Chuengsamarn, Somlak, Suthee Rattanamongkolgul, Benjaluck Phonrat, Rungsunn Tungtrongchitr, and Siwanon Jirawatnotai. 2014. “Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial.” *The Journal of nutritional biochemistry* 25 (2):144-150.

Cocks, TM, and JA Angus. 1983. "Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin."

Corretti, Mary C, Todd J Anderson, Emelia J Benjamin, David Celermajer, Francois Charbonneau, Mark A Creager, John Deanfield, Helmut Drexler, Marie Gerhard-Herman, and David Herrington. 2002. "Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force." *Journal of the American College of Cardiology* 39 (2):257-265.

Cortez-Cooper, Miriam Y, James A Supak, and Hirofumi Tanaka. 2003. "A new device for automatic measurements of arterial stiffness and ankle-brachial index." *The American journal of cardiology* 91 (12):1519-1522.

Dhillon, Navneet, Bharat B Aggarwal, Robert A Newman, Robert A Wolff, Ajaikumar B Kunnumakkara, James L Abbruzzese, Chaan S Ng, Vladimir Badmaev, and Razelle Kurzrock. 2008. "Phase II trial of curcumin in patients with advanced pancreatic cancer." *Clinical Cancer Research* 14 (14):4491-4499.

Dhindsa, Mandeep, Shawn M Sommerlad, Allison E DeVan, Jill N Barnes, Jun Sugawara, Obdulia Ley, and Hirofumi Tanaka. 2008. "Interrelationships among noninvasive measures of postischemic macro-and microvascular reactivity." *Journal of Applied Physiology* 105 (2):427-432.

Dietz, Niki M, Juanita M Rivera, Scott E Eggener, Robert T Fix, David O Warner, and Michael J Joyner. 1994. "Nitric oxide contributes to the rise in forearm blood flow during mental stress in humans." *The Journal of physiology* 480 (Pt 2):361.

Díez, Javier. 2007. "Arterial stiffness and extracellular matrix." *Adv Cardiol* 44:76-95.

Endemann, Dierk H, and Ernesto L Schiffrin. 2004. "Endothelial dysfunction." *Journal Of The American Society Of Nephrology* 15 (8):1983-1992.

Faulx, Michael D, Andrew T Wright, and Brian D Hoit. 2003. "Detection of endothelial dysfunction with brachial artery ultrasound scanning." *American heart journal* 145 (6):943-951.

Fleenor, Bradley S, and Adam J Berrones. 2015. "Mechanisms of Arterial Stiffness." In *Arterial Stiffness*, 15-26. Springer.

Fleenor, Bradley S, Amy L Sindler, Natasha K Marvi, Kate L Howell, Melanie L Zigler, Mutsuko Yoshizawa, and Douglas R Seals. 2013. "Curcumin ameliorates arterial dysfunction and oxidative stress with aging." *Experimental Gerontology* 48 (2):269-276.

Franklin, Stanley S, William Gustin, Nathan D Wong, Martin G Larson, Michael A Weber, William B Kannel, and Daniel Levy. 1997. "Hemodynamic patterns of age-related changes in blood pressure The Framingham Heart Study." *Circulation* 96 (1):308-315.

Franklin, Stanley S, Martin G Larson, Shehzad A Khan, Nathan D Wong, Eric P Leip, William B Kannel, and Daniel Levy. 2001. "Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study." *Circulation* 103 (9):1245-1249.

Gota, Vikram S, Girish B Maru, Tejal G Soni, Tejal R Gandhi, Nitin Kochar, and Manish G Agarwal. 2010. "Safety and pharmacokinetics of a solid lipid curcumin particle formulation in osteosarcoma patients and healthy volunteers." *Journal of agricultural and food chemistry* 58 (4):2095-2099.

Gupta, Subash C, Sridevi Patchva, and Bharat B Aggarwal. 2013. "Therapeutic roles of curcumin: lessons learned from clinical trials." *The AAPS Journal* 15 (1):195-218.

Heidenreich, Paul A, Justin G Trogdon, Olga A Khavjou, Javed Butler, Kathleen Dracup, Michael D Ezekowitz, Eric Andrew Finkelstein, Yuling Hong, S Claiborne Johnston, and Amit Khera. 2011. "Forecasting the future of cardiovascular disease in the United States a policy statement from the American heart association." *Circulation* 123 (8):933-944.

Heitzer, Thomas, Seppo Ylä-Herttuala, Jukka Luoma, Sabine Kurz, Thomas Münzel, Hanjörg Just, Manfred Olschewski, and Helmut Drexler. 1996. "Cigarette smoking potentiates endothelial dysfunction of forearm resistance vessels in patients with hypercholesterolemia." *Circulation* 93 (7):1346-1353.

Hirai, Tadakazu, Shigetake Sasayama, Takeshi Kawasaki, and Shinichi Yagi. 1989. "Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis." *Circulation* 80 (1):78-86.

Joannides, Robinson, Walter E Haefeli, Lilly Linder, Vincent Richard, El Hassan Bakkali, Christian Thuillez, and Thomas F Lüscher. 1995. "Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo." *Circulation* 91 (5):1314-1319.

Julie, S, and MT Jurenka. 2009. "Anti-inflammatory properties of curcumin, a major constituent." *Alternative Medicine Review* 14 (2).

Kaplon, Rachelle E, Sierra D Hill, Nina Z Bispham, Jessica R Santos-Parker, Molly J Nowlan, Laura L Snyder, Michel Chonchol, Thomas J LaRocca, Matthew B McQueen, and

Douglas R Seals. 2016. “Oral trehalose supplementation improves resistance artery endothelial function in healthy middle-aged and older adults.” *Aging* 8 (5).

Kim, Dong-Chan, Wonhwa Lee, and Jong-Sup Bae. 2011. “Vascular anti-inflammatory effects of curcumin on HMGB1-mediated responses in vitro.” *Inflammation Research* 60 (12):1161-1168.

Kim, Yong Sook, Youngkeun Ahn, Moon Hwa Hong, Soo Yeon Joo, Kye Hun Kim, Il Suk Sohn, Hyung Wook Park, Young Joon Hong, Ju Han Kim, and Weon Kim. 2007. “Curcumin attenuates inflammatory responses of TNF-α-stimulated human endothelial cells.” *Journal of cardiovascular pharmacology* 50 (1):41-49.

Kobayashi, Kumiko, Masahiro Akishita, Wei Yu, Masayoshi Hashimoto, Mitsuo Ohni, and Kenji Toba. 2004. “Interrelationship between non-invasive measurements of atherosclerosis: flow-mediated dilation of brachial artery, carotid intima-media thickness and pulse wave velocity.” *Atherosclerosis* 173 (1):13-18.

Krishnakumar, IM, Abhilash Ravi, Dinesh Kumar, Ramadasan Kuttan, and Balu Maliakel. 2012. “An enhanced bioavailable formulation of curcumin using fenugreek-derived soluble dietary fibre.” *Journal of Functional Foods* 4 (1):348-357.

Kuo, Paul C, and Rebecca A Schroeder. 1995. “The emerging multifaceted roles of nitric oxide.” *Annals of surgery* 221 (3):220.

Lakatta, Edward G, and Daniel Levy. 2003. “Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises part I: aging arteries: a ”set up" for vascular disease." *Circulation* 107 (1):139-146.

Landmesser, Ulf, and Helmut Drexler. 2005. "The clinical significance of endothelial dysfunction." *Current Opinion In Cardiology* 20 (6):547-551.

Lao, Christopher D, Mack T Ruffin, Daniel Normolle, Dennis D Heath, Sandra I Murray, Joanne M Bailey, Martha E Boggs, James Crowell, Cheryl L Rock, and Dean E Brenner. 2006. "Dose escalation of a curcuminoid formulation." *Bmc Complementary And Alternative Medicine* 6 (1):10.

Laurent, Stephane, John Cockcroft, Luc Van Bortel, Pierre Boutouyrie, Cristina Giannattasio, Daniel Hayoz, Bruno Pannier, Charalambos Vlachopoulos, Ian Wilkinson, and Harry Struijker-Boudier. 2006. "Expert consensus document on arterial stiffness: methodological issues and clinical applications." *European Heart Journal* 27 (21):2588-2605.

Li, Lan, Fadi S Braiteh, and Razelle Kurzrock. 2005. "Liposome-encapsulated curcumin." *Cancer* 104 (6):1322-1331.

Maiti, Kuntal, Kakali Mukherjee, Arunava Gantait, Bishnu Pada Saha, and Pulok K Mukherjee. 2007. "Curcumin--phospholipid complex: preparation, therapeutic evaluation and pharmacokinetic study in rats." *International journal of pharmaceutics* 330 (1):155-163.

Mattace-Raso, Francesco US, Tischa JM van der Cammen, Albert Hofman, Nicole M van Popele, Michiel L Bos, Maarten ADH Schalekamp, Roland Asmar, Robert S Reneman, Arnold PG Hoeks, and Monique MB Breteler. 2006. "Arterial stiffness and risk of coronary heart disease and stroke the rotterdam study." *Circulation* 113 (5):657-663.

McCrea, Cindy E, Ann C Skulas-Ray, Mosuk Chow, and Sheila G West. 2012. "Test--retest reliability of pulse amplitude tonometry measures of vascular endothelial function: implications for clinical trial design." *Vascular Medicine* 17 (1):29-36.

McEniery, Carmel M, John R Cockcroft, Mary J Roman, Stanley S Franklin, and Ian B Wilkinson. 2014. "Central blood pressure: current evidence and clinical importance." *European heart journal* 35 (26):1719-1725.

McVeigh, GE, GM Brennan, GD Johnston, BJ McDermott, LT McGrath, WR Henry, JW Andrews, and JR Hayes. 1992. "Impaired endothelium-dependent and independent vasodilation in patients with type 2 (non-insulin-dependent) diabetes mellitus." *Diabetologia* 35 (8):771-776.

Mitchell, Gary F, Shih-Jen Hwang, Ramachandran S Vasan, Martin G Larson, Michael J Pencina, Naomi M Hamburg, Joseph A Vita, Daniel Levy, and Emelia J Benjamin. 2010. "Arterial stiffness and cardiovascular events the Framingham Heart Study." *Circulation* 121 (4):505-511.

Murphy, Sherry L, Jiaquan Xu, and Kenneth D Kochanek. 2013. "Deaths: final data for 2010." *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 61 (4):1-117.

Nakmareong, Saowanee, Upa Kukongviriyapan, Poungrat Pakdeechote, Veerapol Kukongviriyapan, Bunkerd Kongyingyoes, Wanida Donpunha, Parichat Prachaney, and Chada Phisalaphong. 2012. "Tetrahydrocurcumin alleviates hypertension, aortic stiffening and oxidative stress in rats with nitric oxide deficiency." *Hypertension Research* 35 (4):418-425.

Nichols, Wilmer, Michael O'Rourke, and Charalambos Vlachopoulos. 2011. *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*: CRC Press.

Nieman, David C, Lynn Cialdella-Kam, Amy M Knab, and R Andrew Shanely. 2012. "Influence of red pepper spice and turmeric on inflammation and oxidative stress biomarkers in overweight females: A metabolomics approach." *Plant foods for human nutrition* 67 (4):415-421.

O'Brien, Eoin, Roland Asmar, Lawrie Beilin, Yutaka Imai, Giuseppe Mancia, Thomas Mengden, Martin Myers, Paul Padfield, Paolo Palatini, and Gianfranco Parati. 2005. "Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement." *Journal of hypertension* 23 (4):697-701.

O'Rourke, Michael F, James V Blazek, Charles L Morreels, and L Jerome Krovetz. 1968. "Pressure wave transmission along the human aorta." *Circulation research* 23 (4):567-579.

O'Rourke, Michael F, Alfredo Pauca, and Xiong-Jing Jiang. 2001. "Pulse wave analysis." *British Journal Of Clinical Pharmacology* 51 (6):507-522.

O'Rourke, Michael F, and Junichiro Hashimoto. 2007. "Mechanical factors in arterial aging: a clinical perspective." *Journal Of The American College Of Cardiology* 50 (1):1-13.

O'Rourke, Michael F, Jan A Staessen, Charalambos Vlachopoulos, and Daniel Duprez. 2002. "Clinical applications of arterial stiffness; definitions and reference values." *American Journal Of Hypertension* 15 (5):426-444.

Oliver, James J, and David J Webb. 2003. "Noninvasive assessment of arterial stiffness and risk of atherosclerotic events." *Arteriosclerosis, Thrombosis, And Vascular Biology* 23 (4):554-566.

Oliver, Jonathan M, Lee Stoner, David S Rowlands, Aaron R Caldwell, Elizabeth Sanders, Andreas Kreutzer, Joel B Mitchell, Martin Purpura, and Ralf Jäger. 2016. "Novel Form of Curcumin Improves Endothelial Function in Young, Healthy Individuals: A Double-Blind Placebo Controlled Study." *Journal of Nutrition and Metabolism* 2016.

Pauca, Alfredo L, Michael F O'Rourke, and Neal D Kon. 2001. "Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform." *Hypertension* 38 (4):932-937.

Rambaran, Curtis, Benyu Jiang, James M Ritter, Ajay Shah, Lalit Kalra, and Philip J Chowienczyk. 2008. "Assessment of endothelial function: comparison of the pulse wave response to β2-adrenoceptor stimulation with flow mediated dilatation." *British journal of clinical pharmacology* 65 (2):238-243.

Reference Values for Arterial Stiffness' Collaboration. 2010. "Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'." *European Heart Journal* 31 (19):2338-2350.

Rubinshtein, Ronen, Jeffrey T. Kuvin, Morgan Soffler, Ryan J. Lennon, Shahar Lavi, Rebecca E. Nelson, Geralyn M. Pumper, Lilach O. Lerman, and Amir Lerman. 2010. "Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events." *European Heart Journal* 31 (9):1142-1148. doi: 10.1093/eurheartj/ehq010.

Rungseesantivanon, Sirada, Naris Thenchaisri, Preecha Ruangvejvorachai, and Suthiluk Patumraj. 2010. "Curcumin supplementation could improve diabetes-induced endothelial dysfunction associated with decreased vascular superoxide production and PKC inhibition." *BMC complementary and alternative medicine* 10 (1):1.

Sangartit, Weerapon, Upa Kukongviriyapan, Wanida Donpunha, Poungrat Pakdeechote, Veerapol Kukongviriyapan, Praphassorn Surawattanawan, and Stephen E Greenwald. 2014. "Tetrahydrocurcumin protects against cadmium-induced hypertension, raised arterial stiffness and vascular remodeling in mice." *PloS one* 9 (12):e114908.

Santos-Parker, JR, TR Strahler, CJ Bassett, NZ Bispham, MB Chonchol, and DR Seals. 2017. "Curcumin supplementation improves vascular endothelial function in healthy middle-aged and older adults by increasing nitric oxide bioavailability and reducing oxidative stress." *Aging*.

Sasaki, Hiroki, Yoichi Sunagawa, Kenji Takahashi, Atsushi Imaizumi, Hiroyuki Fukuda, Tadashi Hashimoto, Hiromichi Wada, Yasufumi Katanasaka, Hideaki Kakeya, and Masatoshi Fujita. 2011. "Innovative preparation of curcumin for improved oral bioavailability." *Biological and Pharmaceutical Bulletin* 34 (5):660-665.

Scuteri, Angelo, Samer S Najjar, Christopher H Morrell, and Edward G Lakatta. 2005. "The metabolic syndrome in older individuals: Prevalence and prediction of cardiovascular events the cardiovascular health study." *Diabetes Care* 28 (4):882-887.

Sesso, Howard D, Meir J Stampfer, Bernard Rosner, Charles H Hennekens, J Michael Gaziano, JoAnn E Manson, and Robert J Glynn. 2000. "Systolic and diastolic blood pressure, pulse

pressure, and mean arterial pressure as predictors of cardiovascular disease risk in men." *Hypertension* 36 (5):801-807.

Sharma, Ricky A, Heather R McLelland, Kirsti A Hill, Christopher R Ireson, Stephanie A Euden, Margaret M Manson, Munir Pirmohamed, Lawrence J Marnett, Andreas J Gescher, and William P Steward. 2001. "Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer." *Clinical Cancer Research* 7 (7):1894-1900.

Sharman, James E, Richard Lim, Ahmad M Qasem, Jeff S Coombes, Malcolm I Burgess, Jeff Franco, Paul Garrahy, Ian B Wilkinson, and Thomas H Marwick. 2006. "Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise." *Hypertension* 47 (6):1203-1208.

Shoba, Guido, David Joy, Thangam Joseph, M Majeed, R_ Rajendran, and PSSR Srinivas. 1998. "Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers." *Planta medica* 64 (04):353-356.

Störk, Stefan, Annewieke W van den Beld, Clemens von Schacky, Christiane E Angermann, Steven WJ Lamberts, Diederick E Grobbee, and Michiel L Bots. 2004. "Carotid artery plaque burden, stiffness, and mortality risk in elderly men a prospective, population-based cohort study." *Circulation* 110 (3):344-348.

Sugawara, Jun, Nobuhiko Akazawa, Asako Miyaki, Youngju Choi, Yoko Tanabe, Tomoko Imai, and Seiji Maeda. 2012. "Effect of endurance exercise training and curcumin intake on central arterial hemodynamics in postmenopausal women: pilot study." *American Journal of Hypertension* 25 (6):651-656.

Tanaka, Hirofumi, Masanori Munakata, Yuhei Kawano, Mitsuru Ohishi, Tetsuo Shoji, Jun Sugawara, Hirofumi Tomiyama, Akira Yamashina, Hisayo Yasuda, and Toshitami Sawayama. 2009. "Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness." *Journal of hypertension* 27 (10):2022-2027.

Tayyem, Reema F, Dennis D Heath, Wael K Al-Delaimy, and Cheryl L Rock. 2006. "Curcumin content of turmeric and curry powders." *Nutrition And Cancer* 55 (2):126-131.

Thijssen, Dick HJ, Mark A Black, Kyra E Pyke, Jaume Padilla, Greg Atkinson, Ryan A Harris, Beth Parker, Michael E Widlansky, Michael E Tschakovsky, and Daniel J Green. 2011. "Assessment of flow-mediated dilation in humans: a methodological and physiological guideline." *American Journal of Physiology-Heart and Circulatory Physiology* 300 (1):H2-H12.

Tomiyama, Hirofumi, Akira Yamashina, Tomio Arai, Kenichi Hirose, Yutaka Koji, Taishiro Chikamori, Saburoh Hori, Yoshio Yamamoto, Nobutaka Doba, and Shigeaki Hinohara. 2003. "Influences of age and gender on results of noninvasive brachial--ankle pulse wave velocity measurement---a survey of 12 517 subjects." *Atherosclerosis* 166 (2):303-309.

Usharani, P, AA Mateen, MUR Naidu, YSN Raju, and Naval Chandra. 2008. "Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus." *Drugs in R & D* 9 (4):243-250.

Van Bortel, Luc M, Daniel Duprez, Mirian J Starmans-Kool, Michel E Safar, Christina Giannattasio, John Cockcroft, Daniel R Kaiser, and Christian Thuillez. 2002. "Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures." *American Journal Of Hypertension* 15 (5):445-452.

Van Bortel, Luc M, Stephane Laurent, Pierre Boutouyrie, Phil Chowienczyk, JK Cruickshank, Tine De Backer, Jan Filipovsky, Sofie Huybrechts, Francesco US Mattace-Raso, and Athanase D Protogerou. 2012. "Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity." *Journal of hypertension* 30 (3):445-448.

Vlachopoulos, Charalambos, Konstantinos Aznaouridis, Michael F O'Rourke, Michel E Safar, Katerina Baou, and Christodoulos Stefanadis. 2010. "Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis." *European Heart Journal* 31 (15):1865-1871.

Vlachopoulos, Charalambos, Konstantinos Aznaouridis, and Christodoulos Stefanadis. 2010. "Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis." *Journal of the American College of Cardiology* 55 (13):1318-1327.

Wilkinson, Ian B, Helen MacCallum, Laura Flint, John R Cockcroft, David E Newby, and David J Webb. 2000. "The influence of heart rate on augmentation index and central arterial pressure in humans." *The Journal of physiology* 525 (1):263-270.

Wilkinson, Ian B, and David J Webb. 2001. "Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications." *British journal of clinical pharmacology* 52 (6):631-646.

Wongcharoen, Wanwarang, and Arintaya Phrommintikul. 2009. "The protective role of curcumin in cardiovascular diseases." *International Journal Of Cardiology* 133 (2):145-151.

World Health Organization. 2016. “The Top 10 Causes Of Death. Web. Accessed: 11 Feb. 2016..”

Yamashina, Akira, Hirofumi TOMIYAMA, Kazuhiro TAKEDA, Hideichi TSUDA, ARAI Tomio, Kenichi HIROSE, KOJI Yutaka, and Yoshio YAMAMOTO. 2002. “Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement.” *Hypertension research* 25 (3):359-364.

Yamashina, Akira, Hirofumi Tomiyama, Arai Tomio, Ken-ichi Hirose, Koji Yutaka, Yoji Hirayama, and Yoshio Yamamoto. 2003. “Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk.” *Hypertension Research* 26 (8):615-622.

Yeboah, Joseph, Aaron R Folsom, Gregory L Burke, Craig Johnson, Joseph F Polak, Wendy Post, Joao A Lima, John R Crouse, and David M Herrington. 2009. “Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study the multi-ethnic study of atherosclerosis.” *Circulation* 120 (6):502-509.

Zieman, Susan J, Vojtech Melenovsky, and David A Kass. 2005. “Mechanisms, pathophysiology, and therapy of arterial stiffness.” *Arteriosclerosis, thrombosis, and vascular biology* 25 (5):932-943.

Table 1: Techniques used for the determination of vascular health

Primary determinant of measure	Technique	Brief explanation	Additional Resources
Arterial stiffness	Carotid-femoral pulse wave velocity (cfPWV)	The transmission of the pulse wave is determined via applanation tonometry between the carotid and femoral arteries, and cfPWV = distance travelled/transmission time of the pulse wave.	(Van Bortel et al. 2002), (Van Bortel et al. 2012)
	Augmentation index (AIx) and augmentation index corrected for a heart rate of 75 (AIx_{75})	Applanation tonometry is used to determine the pulse waveform at the radial artery, and a generalized transfer function is employed to project a central waveform. From this, the augmentation index is determined as (aAP/aPP)*100. aAP = aSBP -- pressure at the first inflection point on the central waveform; aPP = aSBP - aDBP	(Wilkinson et al. 2000), (O'Rourke, Pauca, and Jiang 2001), (Vlachopoulos et al. 2010)
	B-stiffness index	Carotid arterial compliance is measured with simultaneous use of ultrasound and an applanation tonometer, and is calculated as (diameter/pressure).	(Cortez-Cooper, Supak, and Tanaka 2003), (Hirai et al. 1989)
	Brachial-ankle pulse wave velocity (baPWV)	Recordings of the pulse wave are collected at the brachial and dorsalis pedis arteries via a volume-plethysmographic apparatus, and baPWV = distance travelled/transmission time of the pulse wave.	(Yamashina et al. 2002), (Tomiyama et al. 2003), (Yamashina et al. 2003)
Vascular endothelial function	Flow mediated dilation (FMD)	Ischemia of the brachial artery is incited with a sphygmomanometer, and ultrasound is employed to determine the responsive change is diameter of the brachial artery.	(Thijssen et al. 2011), (Corretti et al. 2002)
	Reactive hyperemia index (RHI) via peripheral arterial tonometry (PAT)	A sphygmomanometer is used to occlude the brachial artery, and finger probe plethysmography is used to determine the responsiveness of the resulting pulse waves. The RHI is calculated by comparing the post-occlusion pulse wave to the pre-occlusion pulse wave and dividing by the same measures of the non-occluded arm.	(Rubinshtein et al. 2010), (McCrea et al. 2012)
	Reflective index	A vasodilator is administered, and finger probe plethysmography is used to determine the response of the pulse wave to the vasodilator.	(Chowienczyk et al. 1999), (Rambaran et al. 2008)
	Forearm blood flow response to acetylcholine (FBF_{Ach})	Cuffs are used at the wrists and upper arm for occlusion, and the vasodilator acetylcholine is infused into the brachial artery. Strain-gauge venous occlusion plethysmography measures forearm blood flow in response to acetylcholine.	(Heitzer et al. 1996), (McVeigh et al. 1992)
Other hemodynamic measures	Brachial blood pressure measurements and associated components (bSBP, bDBP, bPP, and bMAP)	bSBP and bDBP are assessed at the brachial artery with a sphygmomanometer, and then bPP and bMAP are calculated from them. bMAP = (2*bDBP + bSBP)/3; bPP = bSBP - bDBP	(Sesso et al. 2000), (O'Brien et al. 2005), (Laurent et al. 2006)

	Aortic blood pressure measurements and associated components (aSBP, aDBP, aPP, and aMAP)	aSBP and aDBP are derived from measuring the pulse waveform of the radial artery with applanation tonometry and applying a generalized transfer function to derive the waveform of the aorta, and then aPP and aMAP are calculated from them. aMAP = (2*aDBP + aSBP)/3; aPP = aSBP - aDBP	(Pauca, O'Rourke, and Kon 2001), (Vlachopoulos et al. 2010), (McEniery et al. 2014)
	Carotid blood pressure measurements and associated components (cSBP, cDBP, cPP, and cMAP)	cSBP and cDBP are derived from directly measuring the pulse waveform of the carotid artery with applanation tonometry, and then cPP and cMAP are calculated from them. cMAP = (2*cDBP + cSBPc/3; cPP = cSBP - cDBP	(McEniery et al. 2014), (Laurent et al. 2006)

aAP = aortic augmentation pressure; aDBP = aortic diastolic blood pressure; AIx = augmentation index; AIx_{75} = augmentation index corrected for a heart rate of 75; aMAP = aortic mean arterial pressure; aPP = aortic pulse pressure; aSBP = aortic systolic blood pressure; baPWV = brachial-ankle pulse wave velocity; bDBP = brachial diastolic blood pressure; bMAP = brachial mean arterial pressure; bPP = brachial pulse pressure; bSBP = brachial systolic blood pressure; cDBP = carotid diastolic blood pressure; cfPWV = carotid-femoral pulse wave velocity; cMAP = carotid mean arterial pressure; cPP = carotid pulse pressure; cSBP = carotid systolic blood pressure; FBF_{Ach} = forearm blood flow responses to acetylcholine; FMD = flow-mediated dilation; PAT = peripheral arterial tonometry; RHI = reactive hyperemia index

Table 2: Summary of clinical trials investigating the role of curcumin in vascular health

Reference	Location	Treatment used (dosage per day)	No. of subjects	Population of interest	Treatment duration	Primary outcome(s)	Primary finding(s)
(Usharani et al. 2008)	Nizam's Institute of Medical Sciences, India	I: NCB-02 (600 mg curcumin)	Treatment I: 23	Type II diabetics	8 weeks	Reflective index, markers for inflammation and oxidative stress	Reflective index improved with treatments I and II
		II: Atorvastatin (10 mg)	Treatment II: 23				Reductions in IL-6, TNF-α
			Control: 21				
(Akazawa et al. 2012)	University of Tsukuba, Japan	I: Theracurmin® (150 mg curcumin)	Treatment I: 11	Post-menopausal women	8 weeks	FMD	FMD improved with treatments I and II
		II: Exercise (Aerobic exercise >3 days/week for 30-60 min/day)	Treatment II: 11				
			Control: 10				
(Nieman et al. 2012)	Appalachian State University, United States	I: Turmeric (~112 mg curcumin)	Treatment I: 31	Middle-aged and older obese women	4 weeks	Markers for inflammation and oxidative stress, AIx_{75}	Markers for inflammation and oxidative stress did not change with treatments I or II
		II: Red pepper spice (1000 mg)	Treatment II: 30				AIx_{75} did not change with treatments I or II
			Control: 61‡				
(Sugawara et al. 2012)	National Institute of Advanced Industrial Science and Technology, Japan	I: Theracurmin® (150 mg curcumin)	Treatment I: 11	Post-menopausal women	8 weeks	bBP, aBP, AIx_{75}	bSBP improved in treatments II and III
		II: Exercise (Aerobic exercise 3-6 days/week for 25-45 min/day) + placebo	Treatment II: 11				aSBP improved in treatment III
		III: Exercise (Aerobic exercise 3-6 days/week for 25-45 min/day) +	Treatment III: 12				AIx_{75} improved in treatment III
			Control: 11				

		Theracurmin®					
(Akazawa et al. 2013)	University of Tsukuba, Japan	I: Theracurmin® (150 mg curcumin)	Treatment I: 12	Post-menopausal women	8 weeks	β-stiffness index	β-stiffness index improved in treatments II and II
		II: Exercise (Aerobic exercise >3 days/week for 30-60 min/day) + placebo	Treatment II: 13				
		III: Exercise (Aerobic exercise >3 days/week for 30-60 min/day) + Theracurmin® (150 mg curcumin)	Treatment III: 14				
			Control: 12				
(Chuengsamarn et al. 2014)	Srinakharinwirot University, Thailand	Ethanol-extracted curcumin (1500 mg curcumin)	Treatment: 107	Type II diabetics	3 months	baPWV	baPWV was improved with treatment
			Control: 106				
(Santos-Parker et al. 2017)	University of Colorado, Boulder, United States	Longvida® (2000 mg curcumin)	Treatment: 20	Middle aged and older adults	12 weeks	FMD, FBFach	FMD and FBF_{Ach} improved with treatment
			Control: 19				
(Oliver et al. 2016)	Texas Christian University, United States	I: CurcuWIN® (50 mg curcumin)	Treatment I: 19	Young, healthy adults	8 weeks	FMD	FMD improved with treatment II
		II: CurcuWIN® (200 mg curcumin)	Treatment II: 19				
			Control: 21				
(Campbell et al. 2017)	University of Kentucky, United States	CurQfen® (158 mg curcumin)	Treatment: 11	Young, obese men	12 weeks	cfPWV, bBP, markers for inflammation	Men with higher cfPWV saw reductions in cfPWV with treatment
			Control: 11				Overall reduction in bPP
							Trending increase in IL-10 and IL-13
							No overall differences in

							cfPWV with treatment

ǂ Cross-over study; aBP = aortic blood pressure; AIx_{75} = augmentation index corrected for a heart rate of 75; aSBP = aortic systolic blood pressure; bBP = brachial blood pressure; bPP = brachial pulse pressure; bSBP = brachial systolic blood pressure; cfPWV = carotid-femoral pulse wave velocity; FBF_{Ach} = forearm blood flow responses to acetylcholine; FMD = flow-mediated dilation; IL = interleukin; RHI = reactive hyperemia index; TNF = tumor necrosis factor

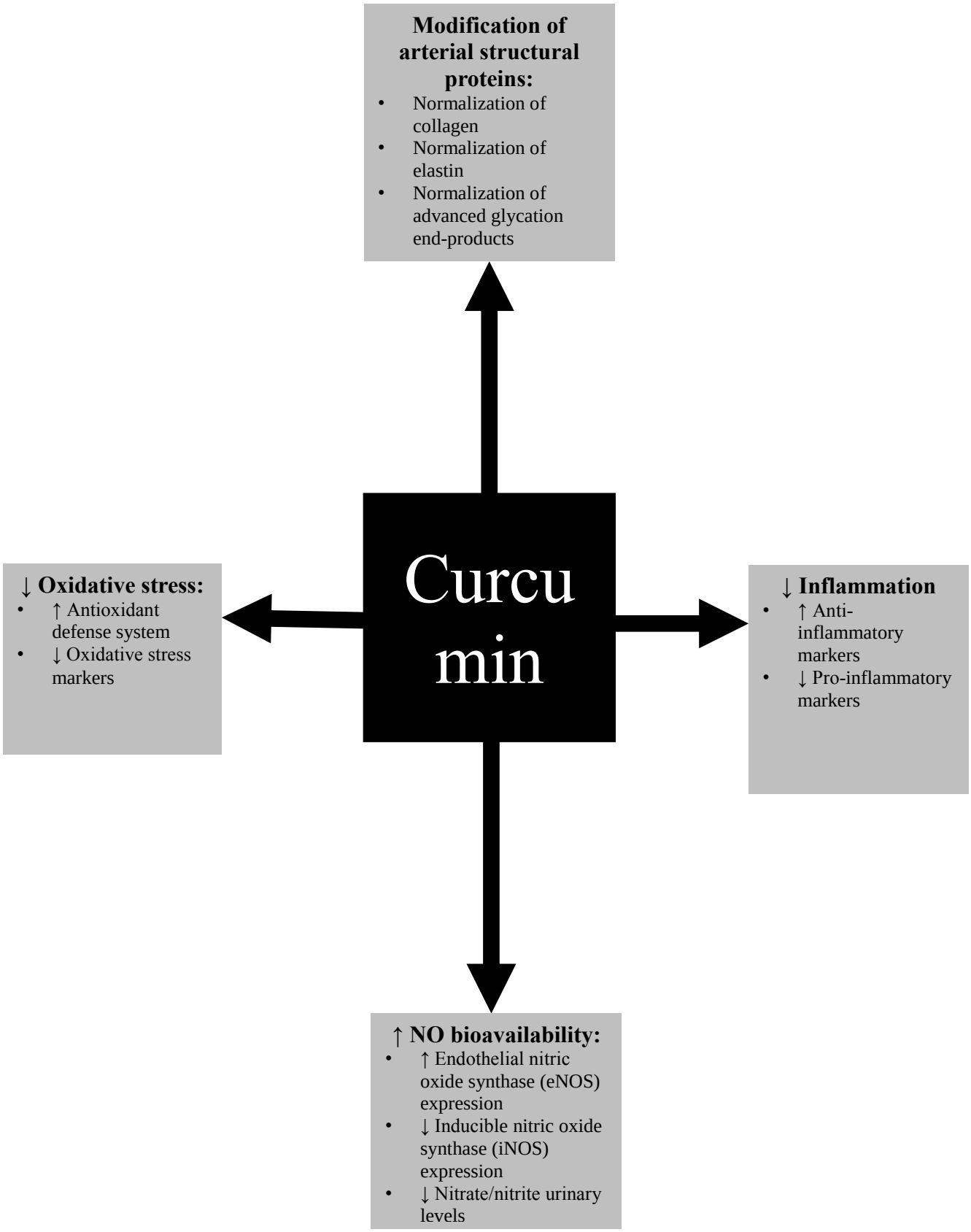

Figure 1: Proposed mechanisms by which curcumin improves vascular dysfunction