Cardiovascular Protection by Curcumin: Molecular Aspects

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Curcumin is the active component in turmeric — a spice that has been extensively used as a culinary agent and a home remedy to prevent and treat many diseases in India and other countries for hundreds of years. However, systematic studies to understand the molecular basis of disease preventing or therapeutic properties of curcumin began to appear in the scientific literature only during the last 40 years. As a result of these studies, substantial evidence has accumulated to suggest that curcumin can affect signaling pathways linked to cellular growth, proliferation, survival, inflammation and transcription. In addition, curcumin has also been shown to exert anti-atherosclerotic, anti-cancer, anti-diabetic, anti-inflammatory and anti-oxidative properties in animal models of various diseases and in human subjects. In this article, we highlight the cardiovascular protective role of curcumin with an emphasis on the molecular basis of this effect.

Keywords: Curcumin, Atherosclerosis, Cardiac hypertrophy, Vascular dysfunction, Signaling pathways, PKB, MAPKs

Introduction

The last decade has witnessed a surge in interest on the use of plant-derived products, also known as phytochemicals or phytoceuticals as preventive and therapeutic agents against a wide range of diseases.

Curcumin

Turmeric contains a wide variety of phytochemicals including curcuminoids, a group of polyphenolic compounds comprising of three bioactive analogs-curcumin (curcumin I), demethoxycurcumin (curcumin II) and bisdemethoxycurcumin (curcumin III)\(^1\) (Fig. 1). They have all been isolated and differ in their methoxy substitution on the aromatic ring. Among these, curcumin is the most active and abundant constituent of turmeric and it is estimated that approximately 2 to 5% of turmeric is composed of...
Curcumin and atherosclerosis

Atherosclerosis is a chronic and progressive disease arising from the inflammatory processes and oxidative stress within the vessel wall. The progression of the disease includes platelet migration and aggregation, perturbation in lipid metabolism and pathologic oxidation that lead to the formation of atherosclerotic lesions. Curcumin has been shown to exhibit anti-atherosclerotic action through protection against inflammation and oxidation, modulation of cholesterol homeostasis and inhibition of platelet aggregation. Studies have reported that curcumin is beneficial in lowering low-density lipoprotein-cholesterol (LDL) and raising high-density lipoprotein-cholesterol (HDL) while reducing lipid peroxidation. Animal studies in high fat-fed atherosclerotic rabbit model have revealed that curcumin effectively inhibits LDL oxidation and decreases cholesterol and triglycerides levels.

In a similar model, curcumin supplementation is also shown to significantly reduce early atherosclerotic lesions in thoracic and abdominal aorta, associated with reduced oxidative stress and decreased lipid peroxidation.

Orally administered curcumin also decreases the formation of atherosclerotic lesions by 20% in apolipoprotein E (apoE) and LDL receptor-double knockout mice model of atherosclerosis, whereas a 50% reduction in atherosclerotic lesions and decreased accumulation of oxidized-LDL-induced cholesterol in cultured vascular smooth muscle cells (VSMC) in apoE knockout mice is observed following curcumin treatment. Curcumin has also proven to be an effective antioxidant through the prevention of oxidation and modification of LDL, and the subsequent restoration of prostacyclin release in human endothelial cells, thereby exerting a protective role in preventing pathological conditions related to oxidative stress and the development of atherosclerosis.

Anti-platelet activities of curcumin has also been documented in several in vitro studies, for example, platelet-activating factor arachidonic acid or adenosine diphosphate induced platelet aggregation is reported to be inhibited by curcumin. Moreover, a recent study showing that curcumin oil-induced antithrombotic action in a mouse model of thrombosis is associated with inhibition of platelet activation, further suggests that anti-platelet properties of curcumin may in part be responsible for some of its anti-atherosclerotic actions. However, additional studies are needed to confirm this.

In humans, a study involving the administration of 500 mg of curcumin for 7 days to 10 healthy volunteers has shown a 29% increase in HDL cholesterol, a 12% decrease in total serum cholesterol and a 33% decrease in serum lipid peroxidases. Administration of curcumin also reduces total and LDL cholesterol levels in patients with acute coronary syndrome. Another study has shown that 10 mg of curcumin given twice daily during 30 days significantly lowers the serum LDL levels and increases the serum HDL levels in healthy patients. The same group reported that 10 mg of curcumin administered twice daily for 15 days significantly lowers plasma fibrinogen levels in humans with atherosclerosis.

Abnormal proliferation of VSMC and mononuclear cells also contributes to the progression of cardiovascular diseases, including atherosclerosis. Curcumin suppresses mitogen-induced proliferation of human blood mononuclear cells and inhibits neutrophil activation and also inhibits serum-induced...
as well as platelet-derived growth factor (PDGF)-dependent proliferation of rabbit VSMC\textsuperscript{18}. VSMC migration and collagen synthesis are also key events involved in the pathological changes occurring with atherosclerosis. Curcumin exhibits potent inhibitory effects on PDGF-induced VSMC proliferation, migration and collagen synthesis\textsuperscript{19}. This inhibitory effect on vascular remodeling is attributable to the attenuation of PDGF-induced activation of platelet-derived growth factor receptor (PDGF-R), extracellular signal-regulated kinases 1 and 2 (ERK1/2) and protein kinase B (PKB) signaling by curcumin in VSMC\textsuperscript{19}.

In an arterial balloon-injury rat model, application of curcumin has been found to significantly inhibit neointima formation, collagen synthesis, cell proliferation and overexpression of PDGF-R\textsuperscript{19}. Curcumin also decreases cholesterol-induced proliferation of aortic rat VSMC and suppresses the phosphorylation of ERK1/2 as well as its translocation to the nucleus\textsuperscript{20}. The vascular anti-proliferative effect of curcumin is also demonstrated through the induction of heme-oxygenase (HO) expression in rat and human VSMC\textsuperscript{21}. Curcumin’s potential role in the prevention of atherosclerosis is further supported through its inhibitory effect on VSMC migration\textsuperscript{22}. This inhibitory effect is associated with decreased reactive oxygen species (ROS) production, suppression of matrix metallopeptidase-9 (MMP-9) activation and protein expression through the downregulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)\textsuperscript{22}. Synthetic curcuminooids have also been shown to exert anti-proliferative effects on cell growth. For example, dehydrozingerone, a biosynthetic structural analogue of curcumin, inhibits PDGF-stimulated VSMC migration, proliferation, collagen synthesis and PDGF/hydrogen peroxide (H\textsubscript{2}O\textsubscript{2})-stimulated phosphorylation of PDGF-R and PKB\textsuperscript{23}. HO-3867, another synthetic curcuminoid, significantly inhibits the proliferation of serum-stimulated VSMC\textsuperscript{24}. Hydrazinocurcumin, yet another synthetic curcumin derivative, potently attenuates the proliferation of bovine aortic endothelial cells\textsuperscript{25}. Since atherosclerosis is a chronic inflammatory disease associated with increased oxidative stress in VSMC, it is possible that the anti-atherogenic effects of curcumin are attributable to its antioxidant and anti-inflammatory properties and its ability to inhibit proliferative and migratory signaling pathways\textsuperscript{22}. This latter ability could also explain some other positive effects of curcumin in heart disease as summarized in the following section.

**Curcumin and cardiac hypertrophy**

The effect of curcumin on cardiac hypertrophy and myocardial ischemia (MI) has been studied in both \textit{in vivo} and \textit{in vitro} models. Cardiac hypertrophy is an adaptive enlargement of the myocardium in response to a variety of stresses, such as an increased workload or myocardial infarction and is characterized by an increase in the size of the individual cardiomyocytes and the whole heart\textsuperscript{26}. Cardiac remodeling plays a critical role in the progression of pathologic cardiac hypertrophy to heart failure and death\textsuperscript{26}. Hypertrophic stimuli initiate several subcellular signaling pathways and these signals reach the nuclei of cardiomyocytes and activate a subset of hypertrophy-responsive transcription factors that change the pattern of the gene expression. Activation of these transcription factors is mediated, in part, through post-transcriptional modifications, such as acetylation by an intrinsic histone acetyltransferase (HAT) p300\textsuperscript{27}.

Nuclear acetylation by p300-HAT is a critical event during cell hypertrophy. Activation of p300-HAT is not only required for pathological myocyte growth but also for normal myocardial development and differentiation. p300-HAT also induces the expression of genes encoding atrial natriuretic factor (ANF), endothelin-1 (ET-1) and β-myosin heavy chain (β-MHC), which are well established markers of myocardial cell hypertrophy\textsuperscript{28,29}. Curcumin is reported to be an inhibitor of p300-HAT and is found to repress p300-HAT-induced hypertrophic responses in cultured neonatal cardiomyocytes, including the expression of both ANF and β-MHC genes\textsuperscript{31}. It also inhibits the p300-HAT activity and thereby prevents the development of heart failure in two different heart failure models \textit{in vivo}-hypertensive salt-sensitive Dahl rats and in a surgically-induced rat model of myocardial infarction\textsuperscript{11}.

Systemic inflammation with overexpression of local inflammatory cytokines including tumor necrosis factor-α (TNF-α) has also been suggested to contribute to cardiac remodeling and heart failure\textsuperscript{32,33}. Consistent with this, the improvement in left ventricular function by curcumin in a pressure
overload rabbit model of heart failure is associated with suppression of cardiac TNF-α expression and the inhibition of myocardial collagen remodeling. In a renal failure model of cardiac hypertrophy, curcumin treatment significantly improves cardiac remodeling as judged by a lowered left ventricular (LV) mass and decreased LV dilatation. This improvement is associated with attenuation of several components of pro-hypertrophic signaling pathways, such as glycogen synthase kinase-3 (GSK-3)/beta catenin, calcineurin/nuclear factor of activated T-cells (NFAT), PKB and ERK1/2. Curcumin treatment is also shown to decrease infarct size in cardiac ischemia/reperfusion injury model through the activation of phosphoryl-insositol-3 kinase (PI3K)/PKB/GSK-3-dependent pro-survival pathways and inactivation of toll-like receptor 2 (TLR-2) and p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun N-terminal kinase (JNK).

As previously mentioned curcumin also behaves as an antioxidant and inhibits lipid peroxidation and DNA damage. Consistent with this, cardioprotective effect of orally administered curcumin in isoproterenol-induced model of myocardial injury is reported to be associated with enhanced levels and activities of antioxidant enzymes. Similarly, a reduction in lipid peroxidation and catalase activity, as well as an increase in the activity of glutathione peroxidase (GPx) and reduced glutathione (GSH) levels have been observed in a rat model of adriamycin-induced cardiotoxicity following curcumin administration.

Cardiac hypertrophy in response to angiotensin II (Ang II) is initiated though activation of its receptors, which results in a marked increase in oxidative stress via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and NF-κB activation. NF-κB regulates the transcription of a host of pro-inflammatory, pro-oxidant and pro-growth genes in response to Ang II. Freund et al. demonstrated a role of NF-κB in Ang II-mediated cardiac hypertrophy in vivo.

Curcumin treatment attenuates Ang II-mediated ROS generation, expression of NADPH oxidase and NF-κB in cardiomyocytes. Lectin-type oxidized LDL receptor 1 (LOX-1) upregulation has a central role in cardiomyocyte hypertrophy response to Ang II. Curcumin reduces the Ang II-mediated upregulation of angiotensin II type 1 receptor (AT1R) and LOX-1 expression and activation which translates into a strong inhibition of redox signaling, resulting in a marked inhibition of cardiomyocyte growth. It may thus be suggested that the ability of curcumin to reduce oxidative stress and attenuate pro-hypertrophic and pro-inflammatory responses may play an important role in reducing cardio-toxicity and hypertrophy in various experimental models.

**Curcumin and hypertension**

The effect of curcumin on hypertension has not been explored in detail, yet a recent in vivo study has revealed for the first time that curcumin attenuates the development of hypertension in Nω-nitro-L-arginine methyl ester (L-NAME)-induced hypertensive rats. In these studies, curcumin treatment suppresses blood pressure elevation, decreases vascular resistance and restores vascular responsiveness in hypertensive rats, without affecting these parameters in normotensive animals. This beneficial effect is accompanied with an increase in endothelial nitric oxide synthase (eNOS) expression and (GSH) levels and a decrease in oxidative stress.

Curcumin is also shown to induce vasorelaxation in isolated porcine coronary arteries through its antioxidant capacity to promote nitric oxide (NO) release. Moreover, curcumin supplementation is shown to significantly attenuate mean arterial blood pressure in streptozotocin-induced diabetic rats. In humans, oral turmeric supplementation is reported to decrease systolic blood pressure in patients with kidney disease- lupus nephritis. However, in a renal failure rat model of cardiac hypertrophy, curcumin treatment was unable to decrease the nephrectomy-induced increase in systolic blood pressure. Thus, more studies are needed to further examine the antihypertensive effects of curcumin.

**Curcumin and diabetic cardiovascular complications**

A pilot study done in 1972 reported that curcumin lowered blood sugar levels in human diabetic subjects. Since then, several reports have documented this response in animal models of diabetes and insulin resistance. For example, curcumin is shown to significantly decrease hyperglycemia in streptozotocin-induced diabetic rat and KK-Ay mice which are well established models of type 1 and type 2 diabetes, respectively. In addition, the reduction of hyperglycemia by curcumin in diabetic models is also associated with an increase in NO bioavailability due to changes...
in NOS levels in cardiac tissues from diabetic animals\textsuperscript{55}, suggesting a role of curcumin in reducing cardiomyopathy and improving endothelial dysfunction associated with diabetes\textsuperscript{55}.

Diabetic cardiomyopathy eventually leads to heart failure\textsuperscript{56}. Transcriptional co-activator p300-HAT and its interaction with myocyte enhancer factor-2 (MEF2) play a role in diabetes-induced cardiomyocyte hypertrophy. Curcumin treatment prevents diabetes-induced upregulation of these transcripts, suggesting a protective role of this pathway in glucose-induced cardiomyocyte hypertrophy in diabetes\textsuperscript{57}. NF-κB, early growth response protein-1 (Egr-1) and TNF-α have been closely linked with the induction of insulin resistance and curcumin treatment is found to downregulate their expression, activation or function\textsuperscript{58-63}, suggesting their putative role in overcoming insulin resistance in animal models of diabetes\textsuperscript{64-66}. Curcumin supplementation is also associated with lowered plasma levels of TNF-α, interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) in streptozotocin-diabetic rats and in high glucose treated monocytes\textsuperscript{67}. Recently, attenuation in diabetes-induced endothelial dysfunction in streptozotocin-induced diabetic rats through decreased protein kinase C (PKC) expression and decreased ROS production has also been demonstrated\textsuperscript{69}.

Consistent with the studies in animal models, a randomized 8-weeks study performed on 72 patients with type 2 diabetes has shown an improvement in endothelial function and significant reductions in the levels of malondialdehyde, ET-1, IL-6 and TNF-α in subjects receiving 150 mg of curcumin twice daily\textsuperscript{68}. It thus appears that the ability of curcumin to decrease hyperglycemia, oxidative stress and to inhibit some signaling pathways implicated in inducing the inflammatory responses may contribute to its cardiovascular protective properties in diabetes.

**Anti-inflammatory properties of curcumin**

Several studies have demonstrated that curcumin is able to modulate the production of various inflammatory cytokines, thereby exhibiting potent anti-inflammatory activity. It has been shown to downregulate NF-κB, a transcription factor that plays a critical role in the induction of many pro-inflammatory mediators involved in chronic and acute inflammatory diseases and various cancers\textsuperscript{69}. Singh and Aggarwal\textsuperscript{69} were the first to demonstrate that curcumin suppressed NF-κB activation induced by different inflammatory stimuli, resulting in the suppression of NF-κB-dependent gene products that mediate proliferation, invasion and angiogenesis\textsuperscript{56}. The downregulation of NF-κB by curcumin results in a decrease in the expression of TNF-α, interleukin-1 (IL-1) and IL-6\textsuperscript{59}. Therefore, inhibition of pro-inflammatory cytokine production by regulation of transcription factors, such as NF-κB may be a potential mechanism for controlling inflammatory responses. In addition, curcumin has been reported to inhibit the activities of cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) enzymes that are involved in generating lipid mediators implicated in inducing the inflammation via arachidonic acid metabolism\textsuperscript{71}.

The nuclear transcription factor Egr-1 which regulates the transcription of several genes involved in inflammation, differentiation, growth and development and wound healing\textsuperscript{72} is also a target of curcumin\textsuperscript{58,59}. Curcumin has been shown to suppress the induction of Egr-1 in endothelial cells, fibroblasts and VSMC\textsuperscript{58,59}. A potential role of Egr-1 in mediating inflammatory response has also been suggested\textsuperscript{73}. Thus, curcumin-induced inhibition of Egr-1 may also participate in mediating the anti-inflammatory effects of curcumin.

Curcumin also downregulates MAPK pathways, which are activated by many inflammatory stimuli\textsuperscript{74}. It can contribute to the protection against the adverse vascular effects of the pro-inflammatory response through the suppression of TNF-α-stimulated ROS generation, monocyte adhesion, phosphorylation of JNK and p38 MAPK and signal transducer and activator of transcription 3 (STAT-3) in endothelial cells\textsuperscript{74}. In vitro studies are somewhat contradictory since other investigators have paradoxically shown an activation of MAPK by curcumin\textsuperscript{75,76}. The mechanism is unexplained, nevertheless in both cases, its final effects appear to be anti-inflammatory\textsuperscript{77,78}. Since a dysregulated inflammatory response has been implicated in the pathogenesis of cardiovascular diseases, it is possible that the ability of curcumin to serve as an attenuator of inflammatory pathway may be one of the mechanisms for its cardioprotective effects.

**Antioxidant activity of curcumin**

Oxidative stress, associated with overproduction of ROS, plays a major role in the pathogenesis of various diseases, including cardiovascular diseases\textsuperscript{79}. Curcumin has been shown to be a potent scavenger of a variety of ROS\textsuperscript{80} including O\textsuperscript{2-}, OH\textsuperscript{-}, nitrogen dioxide radicals\textsuperscript{83} and non-free radical species, such
as \( \text{H}_2\text{O}_2 \). It has also been shown to enhance the activity of antioxidant enzymes and to counteract the activity of ROS generating enzymes. Sreejayan and Rao first claimed that the presence of phenolic groups in the structure of curcumin (Fig. 1) was fundamental in its ability to eliminate ROS. Recently, it has been shown that phenolic and methoxy groups on the phenyl ring and 1,3-diketone system are important structural features that contribute to the antioxidant effects. A role of the H-atom donation from the phenolic group is also shown to be critical for the strong antioxidant and ROS scavenging properties of curcumin.

Thus, by its ability to scavenge various types of ROS, curcumin can decrease oxidative damage of proteins, lipids and DNA as reported in multiple studies. Curcumin is also shown to augment the activities of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, GSH, glutathione S-transferase (GST) and GPx. Since increased oxidative stress is associated with various cardiovascular diseases and ROS are also known to induce pro-inflammatory responses, the inhibitory effect of curcumin on ROS generation coupled with its anti-inflammatory properties may contribute towards its protective role in cardiovascular disease.

**Curcumin bioavailability, metabolism, biotransformation and pharmacokinetics**

The bioavailability of curcumin is limited by a number of factors, which may be an obstacle to its utility as a therapeutic agent. Poor gastrointestinal absorption, water insolubility and molecular instability have led to the notion that curcumin exhibits poor systemic bioavailability. In order to enhance its bioavailability, co-administration of curcumin with piperine or its complexation with phospholipids, liposomes and micelles has been proposed. Adjuvant co-administration prevents its rapid metabolism by interfering with enzymes that catalyze the metabolism of curcumin, while liposomes, micelles and phospholipid complexes can reduce the hydrophobicity of curcumin and increase the permeability of membrane barriers. Other strategies include use of more potent synthetic curcumin analogues, such as dehydrozingerone and HO-3867, as well as employing nanoparticle technology to enhance easier penetration through membrane barriers.

Data on the pharmacokinetics, metabolites and systemic bioavailability of orally administrated curcumin in humans obtained from trials mainly conducted on cancer patients have shown that after oral administration of curcumin, no curcumin excretion is detected and that serum concentration peaks observed at one to two hours are undetectable at twelve hours. However, most curcumin conjugates produced by in vivo human metabolism are detectable in plasma at greater concentrations than free curcumin with a peak after four hours of dosing. Although it has not yet been established if these metabolites are as active as curcumin, tetrahydrocurcumin, a reduced metabolite of curcumin appears to be biologically active in some systems.

An important feature of curcumin is that despite being consumed daily for centuries, it has not been shown to cause any toxicity. Clinical trials have shown that it is well-tolerated, even at high doses, where it appears non-toxic to animals or humans. In human trials, only minor side effects of curcumin, namely diarrhea, have been reported. These trials, however, have examined the short-term outcome. There is some evidence that long-term high-dose curcumin administration in rodents can be tumourigenic. Also, some reports suggest that at higher concentrations curcumin might exhibit pro-oxidant properties. Therefore, a more thorough evaluation of its potential side effects when used at high concentrations for chronic treatments is essential. Moreover, efforts should also be directed towards developing more potent curcumin analogues and curcumin conjugates with better solubility and intestinal absorption.

**Conclusions**

As exemplified in this article, curcumin has been shown to exert beneficial effects in several models of cardiovascular disease, including atherosclerosis, cardiac hypertrophy, hypertension and ischemia/reperfusion. Increased oxidative stress and an upregulation of inflammatory response appears to be an important feature of cardiovascular disease, and studies using isolated cells or animal models have demonstrated a reduction in both of these parameters subsequent to curcumin treatment. The mechanism by which curcumin reduces oxidative stress includes a reduction in superoxide generation, increase in catalase activity and reduction in NADPH oxidase activity. By reducing oxidative stress, curcumin can...
also enhance NO bioavailability and improve endothelial functions. It inhibits the inflammatory response by suppression of NF-κB activation and reduction in the gene expression of inflammatory cytokines, such as TNF-α, IL-1 and IL-6. It also targets multiple signaling systems, such as growth factor receptors, non-receptor and receptor tyrosine kinases, a series of serine/threonine kinase, such as PKB, PKC and MAP kinases, histone acetylases/deacyetylases, transcription factors that play an important role in regulating cardiovascular homeostasis. In many cardiac pathologies, the expression or activity of these signaling components is altered and curcumin has been shown to fully or partially restore these alterations (Fig. 2). With regards to human therapy, although several clinical trials mainly targeted at cancer treatments are currently in progress, the efficacy of curcumin to treat cardiovascular disease in humans has not been evaluated. However, further studies, in animal models of cardiac disease are warranted before undertaking any long-term human studies.

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