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Review

The protective role of curcumin in cardiovascular diseases

Wanwarang Wongcharoen, Arintaya Phrommintikul *

Department of Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

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Abstract

Curcumin (diferuloylmethane) is a polyphenol responsible for the yellow color of the curry spice turmeric. It has been used in a variety of diseases in traditional medicine. Modern scientific research has demonstrated its anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-thrombotic, and cardiovascular protective effects. In this review, we focused mainly on the effects of curcumin on the cardiovascular system. The antioxidant effects of curcumin have been shown to attenuate adriamycin-induced cardiotoxicity and may prevent diabetic cardiovascular complications. The anti-thrombotic, anti-proliferative, and anti-inflammatory effects of curcumin and the effect of curcumin in decreasing the serum cholesterol level may protect against the pathological changes occurring with atherosclerosis. The p300-HAT inhibitory effects of curcumin have been demonstrated to ameliorate the development of cardiac hypertrophy and heart failure in animal models. The inflammatory effects of curcumin may have the possibility of preventing atrial arrhythmias and the possible effect of curcumin for correcting the Ca^{2+} homeostasis may play a role in the prevention of some ventricular arrhythmias. The preclinical studies from animal to clinical data in human are discussed.

Keywords: Curcumin; Herbal medicine; Cardiovascular disease

1. Introduction

Curcumin (diferuloylmethane) is a polyphenol responsible for the yellow color of turmeric, a curry spice. The yellow-pigmented fraction of turmeric contains curcuminoids, which are chemically related to its principal ingredient, curcumin. The major curcuminoids present in turmeric are demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), and the recently identified cyclocurcumin [1]. In traditional Chinese and Indian medicine, curcumin has been used to treat a variety of diseases. A large body of evidence suggests that curcumin has a diverse range of molecular targets, including transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis. As a result, several therapeutic effects of curcumin such as its anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-thrombotic, and cardiovascular protective effects have been demonstrated [2]. A large number of studies have extensively investigated the anti-cancer effects of curcumin in both animal and human subjects. Curcumin has been reported to suppress the carcinogenic activity of a wide variety of carcinogens in cancers of the colon, duodenum, esophagus, stomach, liver, breast, oral cavity, and prostate, as well as leukemia [3]. In addition, previous studies have shown that the anti-inflammatory effects of curcumin may result in the favorable outcomes in the treatment of rheumatoid arthritis, postoperative inflammation and inflammatory bowel disease [4–6]. The anti-oxidant effects of curcumin may also account for early renal graft function [7] and the benefits seen in the treatment of patients with chronic pancreatitis [8]. Furthermore, it has been reported that curcumin may also improve cognitive function in the elderly [9]. At the time of the review, there are several ongoing clinical trials on curcumin in patients with different diseases, including several types of cancer, Alzheimer's disease, epilepsy and psoriasis [2].

* Corresponding author. Tel.: +66 53 946713; fax: +66 53 946715.
E-mail address: apromint@mail.med.cmu.ac.th (A. Phrommintikul).

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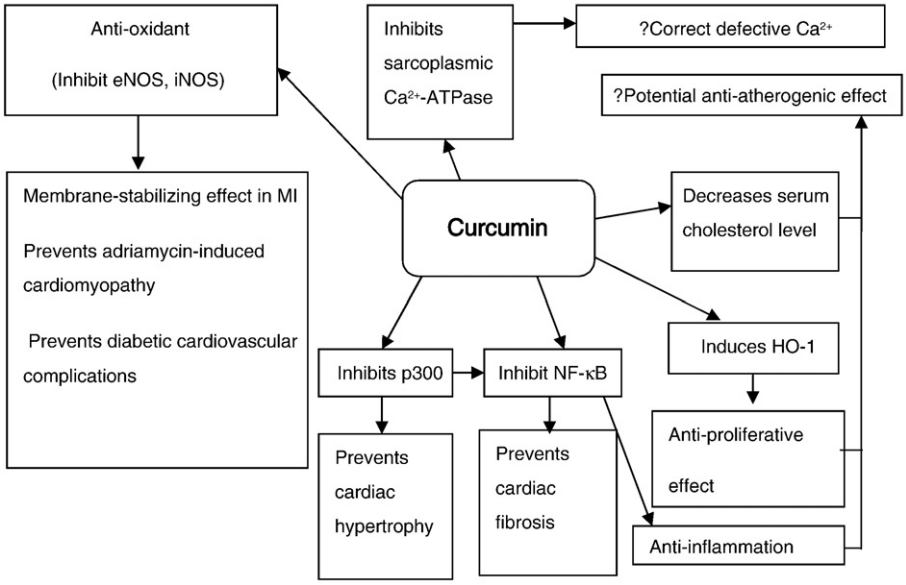

Fig. 1. Diagram showed the potential effect of curcumin on the prevention of cardiovascular diseases.

The protective effects of curcumin on the cardiovascular system have been previously described and its use as a therapeutic agent to mitigate cardiovascular disease and other vascular dysfunctions is currently being investigated. This review focuses mainly on the effects of curcumin on the cardiovascular system Fig. 1.

2. Preclinical and clinical studies in animals

2.1. Curcumin and adriamycin-induced cardiotoxicity

Adriamycin is a potent drug for the treatment of a broad spectrum of cancers. However, the cardiotoxicity induced by adriamycin limits its clinical dosage in cancer treatment [10]. It is well established that oxidative stress plays an important role in the mechanism of adriamycin-induced cardiotoxicity while antioxidant compounds have been shown to possess some protective effects [11,12]. A study in rats has shown that adriamycin causes an increased heart rate, ST segment elevation, a decreased myocardial glutathione content and glutathione peroxidase activity, as well as an increased serum lipid peroxide and cardiac catalase activity [13] Curcumin at a dose of 200 mg/kg given 7 days before and 2 days following adriamycin administration significantly prevented those effects induced by adriamycin. The mechanism of the preventive effects of curcumin is unclear and multiple possible mechanisms have been proposed [13]. Firstly, curcumin inhibits lipid peroxidation by scavenging free radicals, leading to a blocking of the lipid chain reaction. This notion was supported by the decrease in the products of lipid metabolism in the curcumin-treated rats shown in the study. Secondly, the increase in the glutathione content observed in the curcumin-treated rats suggested that curcumin, a naturally occurring sulfhydryl group, may help maintain the membrane integrity and promote the non-enzymatic detoxification of hydroxyl radicals and lipid peroxides. Thirdly, curcumin may protect against cardiac injury via a membrane-stabilizing effect, supported by the fact that curcumin prevented the ECG changes induced by adriamycin. Furthermore, in another study phenylbutyrate, a histone acetyltransferases inhibitor, has been shown to have a protective effect against adriamycin-induced cardiac injury, partly due to an increase in the protein level and activity of cardiac manganese superoxide dismutase [14]. Therefore, curcumin which is also a histone acetyltransferases inhibitor may have a similar protective mechanism [15].

2.2. Curcumin and diabetic cardiovascular complications

Increased oxidative stress has been associated with the pathogenesis of chronic diabetic complications, including cardiomyopathy [16]. It has been suggested that the nitric oxide (NO) pathway is involved in augmenting oxidative stress [17]. NO is produced by a set of three nitric oxide synthase (NOS) isozymes: endothelial NOS (eNOS), inducible NOS (iNOS), and neuronal NOS (nNOS). These enzymes convert L-arginine to L-citrulline, leading to the generation of the free radical NO [18]. Many studies have shown that eNOS and iNOS play an essential role in the pathogenesis of cardiovascular complications in diabetes [19]. As curcumin has a striking anti-oxidant property [20] and has been shown to down- regulate NOS and reduce NO oxidation by sequestering the reaction intermediate, nitrogen dioxide, [21] it may have preventive effective on the development of cardiovascular complications in diabetes. Farhangkhoee and coworkers investigated the effects of curcumin on the diabetic-induced changes in the vasoactive factors, including NO in rats [22]. They demonstrated that the myocardial tissue from diabetic rats exhibited increased levels of eNOS and iNOS mRNA as compared to control rats, and curcumin treatment prevented

eNOS and iNOS mRNA upregulation showing a decrease in the oxidative DNA damage. The mechanism of the NOS alteration caused by curcumin involves the activation of the nuclear factor-κB (NF-κB) and activating protein-1 (AP-1). Furthermore, their results showed that curcumin potentiated diabetes-induced ET-1 mRNA levels in the heart but not in the kidneys or retina. It is possible that curcumin has a differential effect on the vasoactive factors representing different molecular aberrations in the target organs of chronic diabetic complications.

2.3. Curcumin and the membrane-stabilizing effects in myocardial infarctions

It has been shown that a lysosomal alteration may partly account for the myocellular damage during a myocardial infarction. The formation of autophagic vacuoles, the disruption of lysosomes, and the spread of lysosomes throughout the cell have been found in ischemic hearts [23]. The abnormal degradation of the cellular components by lysosomal hydrolases may cause irreversible myocardial necrosis [24]. In experimentally-induced myocardial infarctions, it was reported that a decrease in the lysosomal stability increased the levels of lysosomal enzymes, leading to a change in the metabolism of various connective tissue constituents, such as, glycosaminoglycan, glycoprotein and collagen [25]. An increase in the lysosomal hydrolase activity has also been observed in isoproterenol-induced myocardial infarctions, which may be attributed to the tissue damage of the infarcted myocardium [26]. The stabilization of the membranes of ischemic myocytes, including the lysosomal membranes may potentially protect cells from autolytic and heterolytic damage and may attenuate the tissue damage due to myocardial ischemia. Curcumin has been reported to have a membrane-stabilizing effect [27]. Nirmala and coworkers have studied the effect of curcumin on the change in the lysosomal hydrolase activity in serum and myocardial tissue in isoproterenol-induced myocardial infarctions in rats [28,29]. They found a significant increase in the lysosomal hydrolase activity, including that of β-glucuronidase, β-N-acetylglucosaminidase, cathepsin B, cathepsin D, and acid phosphatase, in serum and myocardial tissue. Curcumin treatment resulted in a decrease in the enzyme activity nearly to the control levels. The histopathologic findings also showed that curcumin treatment decreased the degree of myocardial necrosis in isoproterenol-administered rats. Multiple protective mechanisms of curcumin in the myocardial infarction model have been proposed [29]. Firstly, curcumin may inhibit the release of lysosomal enzymes as well as decrease the activity of the total lysosomal acid hydrolases, leading to an enhancement of the stability of the lysosomes. Secondly, curcumin may release endogenous corticoids which help indirectly in stabilizing the lysosomal membranes [30]. Thirdly, the oxygen free radicals generated during myocardial ischemia, in addition to the direct myocardial damaging effects, may also account for the cardiac damage through the release of lysosomal enzymes; therefore, the antioxidant effect of curcumin by scavenging oxygen free radicals may help preserve cellular viability and secondarily stabilize lysosomes.

2.4. Curcumin and cardiac hypertrophy

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 cardiac myocytes and the whole heart [31]. Sustained pathological hypertrophy is deleterious and may lead to heart failure and death [32]. Hypertrophic stimuli initiate a number of subcellular signaling pathways, which finally reach the nuclei of cardiac myocytes and change the pattern of the gene expression [33]. Transcription factors that mediate these changes include the myocyte enhancing factor-2, [34] serum response factor, [35] AP-1, [36] and a zinc finger protein, GATA-4 [37]. The involvement of multiple transcription factors in the hypertrophic responses suggests that these factors are activated in a coordinated fashion.

Acetylation is emerging as a posttranslational modification that is essential for the regulation of transcription and modifies the transcription factor affinity for binding sites on DNA, stability, and/or nuclear localization, Histone acetylation is one of the key control points for gene regulation in the hypertrophic myocardium [38]. Acetylation of histone tails, mediated by histone acetyltransferases (HATs), confers the accessibility of the DNA template to the transcriptional machinery and is associated with activation of the gene expression [39]. Histone deacetylases (HDACs), on the other hand, catalyze the removal of acetyl groups on aminoterminal lysine residues of histones and, by promoting nucleosomal condensation, act as transcriptional repressors or silencers of genes [39]. The status of histone acetylation is therefore determined by the balanced action of HATs and HDACs. An adenovirus E1A-associated protein, p300, acts as a coactivator of these hypertrophy-responsive transcription factors. In addition, p300 serves as an intrinsic HAT and promotes an active chromatin configuration [40]. The p300 protein can also acetylate certain nonhistone proteins such as DNA-binding transcription factors [40,41]. Several lines of evidence suggest that p300 plays a critical role in the physiological growth and differentiation of cardiac myocytes during development [42]. Mice lacking a functional p300 gene die between days 9 and 11.5 of gestation, exhibiting defects of cardiac muscle differentiation and trabeculation [43]. Recent studies have demonstrated that p300 transcriptional activity is enhanced during agonist-induced cardiac hypertrophy and that subsequent blocking of the p300-HAT activity inhibits the agonist-mediated cardiac growth [44,45]. Moreover, transgenic mice that over-express p300 in the heart develop cardiac hypertrophy and eventual heart failure [42].

Curcumin has been reported to be an inhibitor of p300-HAT, [15] therefore, it may possess an effect in the prevention of cardiac hypertrophy and heart failure [46,47]. Morimoto and coworkers have examined these effects in two different heart failure models; hypertensive heart disease in salt-sensitive Dahl rats and surgically induced myocardial infarction in rats [47]. In salt-sensitive hypertensive Dahl rats, after the administration of curcumin for 7 weeks, a significant and beneficial preservation of the systolic function in the curcumin-treated group was observed. In addition, the acetylation of GATA4 that normally accompanies hypertension was reduced by curcumin. Consistently, in surgically-induced myocardial infarction rats, the systolic function was improved in the curcumin-treated group, and the hypertrophy of the noninfarcted myocardium (which is thought to contribute to adverse remodeling) was reduced. Similar to those results observed by Morimoto's group, Li and coworkers showed that rodents treated with oral curcumin were markedly resistant to cardiac hypertrophy produced by banding of the aorta and the progression of heart failure was reduced [46]. The beneficial effects of curcumin were observed even when treatment was initiated 2 weeks after the induction of a pressure overload. As inflammation plays an important role in the development of cardiac hypertrophy and heart failure, Li and coworkers also studied the anti-inflammatory effects of curcumin. They found that curcumin decreased the NF-κB activation and inflammatory markers, including MCP-1, IL-6, IL-1, and TNF-α mRNA and protein expression induced by aortic banding. Furthermore, the p300 overexpression significantly reversed the curcumin-induced inhibitory effects on inflammation. As a result, the authors pointed out that curcumin blocks NF-κB signaling and NF-κB-dependent inflammatory responses through the disruption of the p300-HAT activity. Based on these observations, curcumin, a p300-HAT inhibitor, may serve as a promising therapeutic agent in heart failure in humans.

Furthermore, the inhibitory effects of curcumin on the NF-κB activation have been confirmed in a study in rabbits undergoing cardiopulmonary bypass [48]. Cardiac global ischemic and reperfusion injury with cardioplegia occurring during cardiopulmonary bypass activate the pro-inflammatory cytokines and cause apoptosis of cardiac myocytes and myocardial injury. Curcumin administered 2 h before cardiopulmonary bypass has been shown to ameliorate the surge of pro-inflammatory cytokines during CPB and decrease the occurrence of cardiomyocytic apoptosis after global cardiac ischemia/reperfusion injury.

2.5. Curcumin and the anti-inflammatory effects

Curcumin is a highly pleiotropic molecule that interacts physically with its numerous targets. As a result, curcumin exerts its anti-inflammatory effects via several mechanisms, i.e. curcumin down regulates the nuclear factor-κB (NF-κB), resulting in a decrease in the expression of tumor necrotic factor- α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) [2]. In addition, curcumin inhibits the independent mitogen-activated protein kinase (MAPK) pathways which are the pathways activated by most inflammatory stimuli [49]. The inflammatory process plays a crucial role in the pathogenesis of many cardiovascular disorders, such as, atherosclerotic process, acute coronary syndrome, [50] and atrial arrhythmias [51]. Therefore, the anti-inflammatory effects of curcumin may prevent these diseases. However, these therapeutic effects of curcumin have yet to be studied.

2.6. Curcumin and anti-proliferative effect

Heme oxygenase-1 (HO-1) is a widely distributed enzyme in mammalian tissues and its main function is associated with the degradation of heme to iron, carbon monoxide (CO), and biliverdin, the last being converted to bilirubin by the cytosolic enzyme biliverdin reductase. It is well-established that the HO-1 possesses important antioxidant and anti-inflammatory functions and acts in concert with other pivotal enzymes in the maintenance of cellular homeostasis [52]. Substantial evidence indicates that HO-1 is also a down-regulator of growth in vascular smooth muscle cells. Induction of HO-1 by chemical inducers results in the reduction of atherosclerotic lesions in LDL-receptor knockout mice and prevents transplant arteriosclerosis in mouse cardiac allografts [53,54].

It has been shown that curcumin has an ability to induce HO-1 expression, presumably through the activation of Nrf2-dependent antioxidant response element (ARE) in various cells of the cardiovascular system (such as vascular endothelial cells, vascular smooth muscle cells and human aortic smooth muscle cells) [55,56]. There is evidence that the anti-proliferative effect of curcumin is considerably linked to its ability to induce HO-1 expression [56].

2.7. Curcumin and calcium homeostasis

Curcumin inhibits the ATPase activity of the Ca^{2+}-ATPase of the skeletal muscle and cardiac sarcoplasmic reticulum (SR), which plays an important role in filling the storage of intracellular Ca^{2+} in skeletal and cardiac muscles. The stored Ca^{2+} is released into the cytosol to produce a contractile activation and in turn is taken up again to allow relaxation [57]. Logan-Smith et al has reported that curcumin at a concentration between 1 and 10 μM increases Ca^{2+}transport by up to 20%, whereas higher curcumin concentrations inhibit the transport [58]. Moreover, the ATPase activity is slightly increased by 1–3 μM of curcumin but inhibited by higher curcumin concentrations. These findings have been confirmed by those from Sumbilla and coworkers [59]. They demonstrated that the Ca^{2+} transport and its slippage could be improved by curcumin in the cardiac as well as skeletal SR, raising the possibility of a pharmacological intervention to correct the defective Ca^{2+} homeostasis.

3. Preclinical and clinical studies in humans

A large body of evidence showed that curcumin possessed a variety of beneficial activities. Many clinical trials have been conducted in patients with cancer, rheumatoid arthritis, cystic fibrosis, inflammatory bowel disease, psoriasis, pancreatitis, and other disorders [2,60]. However, very few have been conducted in patients with cardiovascular disorders.

3.1. Curcumin and serum cholesterol and lipid peroxides

Previous studies have demonstrated the effects of curcumin on the serum cholesterol and lipid peroxide levels [61,62]. A significant 33% decrease in the serum lipid peroxides, 29% increase in the serum HDL cholesterol, and a nearly 12% decrease in the total serum cholesterol were observed in 10 healthy volunteers after the administration of 500 mg of curcumin daily for 7 days [62].Similarly, another study showed that 10 mg of curcumin given twice a day for 28 days significantly lowered the serum LDL levels and increased the serum HDL levels in patients with atherosclerosis [61]. Since the abnormal lipid metabolism principally contributes to the pathogenesis of atherosclerosis, these observations suggest the potentially protective role of curcumin in atherosclerotic diseases.

3.2. Curcumin and vascular smooth muscle cell proliferation

Huang and coworkers have studied the effect of curcumin on the proliferative responses of blood mononuclear cells and vascular smooth muscle cells in humans [63]. They reported that curcumin inhibited the proliferative responses to phytohemagglutinin in a dose-dependent manner and a mixed lymphocyte reaction had an inhibitory effect on the platelet-derived growth factor-stimulated proliferation. Since the proliferation of vascular smooth muscle cells and mononuclear cells plays an important role in the atherosclerotic process, curcumin may be useful as a new template for the development of better remedies for the prevention of atherosclerotic diseases and vascular restenosis.

4. Conclusions

The therapeutic effects of curcumin have been extensively investigated, particularly in the treatment of cancer and anti-inflammatory diseases [2,60]. In addition, curcumin is well tolerated when taken at doses as high as 12 g/day and has low toxicity and low cost [64]. However, very little is known regarding the effect of curcumin on the cardiovascular diseases. There is growing evidence that curcumin has a potential role in the protection against many cardiovascular diseases. The antioxidant effects of curcumin have been shown to attenuate adriamycin-induced cardiotoxicity [13] and may prevent diabetic cardiovascular complications [14]. The anti-thrombotic, [65] anti-proliferative, [63] and anti-inflammatory effects of curcumin and the effect of curcumin in decreasing the serum cholesterol level may protect against the pathological changes seen in atherosclerosis [61,62]. The p300-HAT inhibitory effects of curcumin have been demonstrated to ameliorate the development of cardiac hypertrophy and heart failure in animal models [46,47]. Curcumin, as a potent inducer of HO-1, has been shown to exert anti-proliferative effect [56]. Furthermore, the anti-inflammatory effects of curcumin may prevent atrial arrhythmias [51] and the possible effect of curcumin on correcting the Ca^{2+} homeostasis may play a role in the prevention of some ventricular arrhythmias [66]. Currently, there are several ongoing trials on the preventive effects of curcumin on various cancers, but none are focused on cardiovascular diseases [2]. More extensive research regarding the effect of curcumin on the cardiovascular diseases in both animals and humans are warranted.

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