

A Review of the Effects of Curcumin on Histone Acetyltransferase Activity in the Prevention of Cardiac Hypertrophy

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ABSTRACT

BACKGROUND AND OBJECTIVE: Curcumin, a natural polyphenolic compound derived from the rhizome of turmeric, has a cardiovascular protective effects. Histone acetyltransferase (HAT) is a consequential enzyme in processes of cardiac hypertrophy (cardiomegaly). According the high prevalence of cardiovascular disease and necessity for prevention, this review had studied the effect of curcumin on the activity of the histone acetyltransferases and cardiac hypertrophy process.

METHODS: In this study, scientific articles indexed in databases "Web of science, Scopus, PubMed, SID, ISI" were studied using key words "Curcumin, Tumeric, Histone Acetyltransferases, Cardiomegaly".

FINDINGS: 66 articles were studied eventually of the 640 articles in the initial search. Cardiac hypertrophy, as one of the most common symptoms of cardiovascular disease, may lead to the heart failure and cardiac arrest. Curcumin plays an important role in the prevention and treatment of cardiac hypertrophy; which inhibits the DNA transcription and myocardial uncontrolled growth by reducing the activity of HAT and GATA4 acetylation. Curcumin acts as a selective histone acetyltransferase inhibitor and reduces the ratio of heart weight to body weigh. In addition, curcumin reduces the activity of NF- κ B, a transcription factor in the pathophysiology of myocardial diseases, and inflammatory biomarkers, including MCP-1, IL-6, IL-1, TNF- α .

CONCLUSION: Although the mechanism of curcumin is not as clear, according to previous studies it can be realized turmeric is associated with the inhibition of histone acetyltransferase activity and prevent cardiac hypertrophy. However, curcumin is not toxic to humans in high doses, but its overuse use is not recommended due to limited bioavailability.

KEY WORDS: *Curcumin, Tumeric, Histone Acetyltransferases, Cardiomegaly.*

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Introduction

Curcumin is a polyphenol with natural origin that is abundantly found in the rhizome of perennial herb – belong to the ginger (Fig 1) (2, 1), generally has been used as a food spice and coloring agent of the cooking for hundreds of years in prevention and treatment of many diseases - particularly inflammatory diseases (3, 4). Curcumin or Diferuloylmethane was isolated in pure form as responsible for the yellow color (*Curcuma longa* L.) (3 and 1) for the first time in 1842 AD by Vogel (6,5).

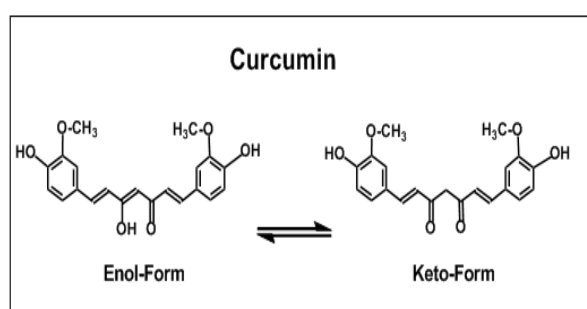


Figure 1. Structure of curcumin (C₂₁H₂₀O₆) that was described for the first time in 1910 by Lampe and Milobedeska (6, 5)

Curcumin is a yellow-orange crystalline powder and insoluble in water (6, 5). Apart from curcumin there are other compounds such as Demethoxy Curcumin, bis demethoxy curcumin and cyclocurcumin in curcumin that are called "curcuminoid" (7). Srinivasan in 1953 separated components of curcumin by chromatography method (8). Curcumin is insoluble in water and ether and soluble in alcohol and dimethylsulfoxide (9).

The increase ten times in the size of the heart from infancy to adulthood as enlarged cell size (not cell division) is called cardiac hypertrophy that not only it is not pathological but it is important for person's life (11, 10). Hemodynamic overload in heart cells also induces hypertrophy that might occur due to myocardial damage, systolic and diastolic dysfunction, heart failure and death (10).

Hypertrophy of the heart or skeletal muscle is a fundamental adaptive process in response to mechanical load (12). Cardiac hypertrophy is one of the most common abnormality of heart leading to

death. Heart response against both internal and external triggers imposed-up biomechanical stresses. Although hypertrophy is essentially a compensatory mechanism, but may be harmful in the long time (16, 15).

Histone acetyltransferase enzymes are (HAT = Histone AcetylTransferase) included p300, (CREBbinding protein) CBP (17). P300 plays an important role in the process of cardiac hypertrophy (18) as induction of acetylation in some transcription factors such as GATA-4 by p300 provides evidence (19). Since cardiovascular disease and cardiac hypertrophy is one of the most common diseases as well as curcumin is known as one of the most common available spices, in this study will consider detailed mechanisms of curcumin effects on the progress of cardiomegaly or cardiac hypertrophy.

Methods

In this review article as a narrative review electronic resources such as valid scientific articles indexed in databases "Web of science, Scopus, PubMed, SID, ISI" in 1953 and 2016 were considered to investigate the effect of curcumin on activity of histone acetyltransferase enzyme to prevent from cardiac hypertrophy and the results were carefully evaluated. The search was done using the keywords Curcumin, Tumeric, Histone Acetyltransferases, and Cardiomegaly as well as search in Iranian databases was performed by keywords curcumin, turmeric, Histone Acetyltransferases, cardiac hypertrophy and obtained article were studied reviewed.

Results

640 related articles were extracted in the initial evaluation, of total about 66 articles were selected. In many studies anti-inflammatory effects (13), antioxidants (20), anti-carcinogenic, anti-thrombotic and cardiovascular protective properties of curcumin were studied (21). Curcumin in traditional medicine in Asia and Africa have been used in the treatment of diseases more than 4,000 years old (22). Previous

studies focused on the pharmacological effects of curcumin on neurodegenerative disorder (24,23), cardiovascular disease (25), diabetes (26), allergies (27), inflammatory diseases (28), renal ischemia (29), psoriasis (30), AIDS (31) and cancer (32).

Study of Khopde and colleagues showed that curcumin in term of antioxidant is at least 10 times more active than antioxidants such as vitamin E (33). Aggarwal and colleagues also indicated inhibitory effects of curcumin in hemoglobin oxidation and lipid peroxidation (6).

Two years later, in another study, Aggarwal and colleagues have demonstrated that curcumin is effective against atherosclerosis and myocardial infarction (34), probably by preventing LDL oxidation, inhibition of platelet aggregation and by reducing development of myocardial infarction(5). Curcumin by blocking the transformation, angiogenesis and metastasis inhibits carcinogenesis and prevents from skin carcinogenesis, the front of the stomach, colon and liver in mice (5).

Nowadays the curcumin is used as an antioxidant in combination with radiation or chemotherapy (36, 35). According to the study of Yang et al curcumin by suppressing oxidative damage, inflammation and accumulation of amyloid was effective in Alzheimer's disease (37). Mohanty and colleagues in a study considered the effects of cardio protective effects of curcumin on the toxicity of doxorubicin (DOX) in rats and the obtained results indicated that a significant reduction of the cardio toxic effects of doxorubicin. Curcumin also increases levels of glutathione (GSH) in

myocardial tissue and prevents the production of antioxidant (38). Recent studies have shown that curcumin prevents from virus differentiation by inhibiting in vitro HIV-Tat protein acetylation and thus curcumin can be used in AIDS treatment protocol (39). In another study it was shown that curcumin has a destructive effect on malaria parasite through in vitro production of ROS and down regulating the activity of the PfGCN5 HAT (40).

In a study on salt-sensitive rats, a significant improvements in systolic function was observed in the group of rats that received curcumin for 7 weeks. The amount of acetylation GATA4 leading to increased blood pressure, significantly decreased (41). Sunagawa et al study on rats suggests that curcumin get beneficial effects on left ventricular systolic function before myocardial infarction (42).

In this study we compared the effects of curcumin alone and curcumin combined with enalapril as well. In table 1 all studies on the effect of curcumin on cardiac hypertrophy in recent years were listed.

Mechanisms of cardiac hypertrophy: the glycogen synthase kinase 3 beta / beta -Katenin and calcineurin / Nfat pathways are known as mechanisms of cardiac hypertrophy. Studies have shown that stimulators of hypertrophy leads to phosphorylation (inactivation) glycogen synthase kinase - 3 beta by (Akt) cAMP - dependent kinase. Active glycogen synthase kinase 3 beta is dephosphorylated and inhibits transcription regulators such as beta-catenin and NFAT and prevents growth of hypertrophic cardiac myocytes (13).

Table 1. The effect of curcumin on cardiac hypertrophy

Type of sample	Dose	Effects	Reference
Mice	oral 75mg/kg	GATA4 acetylation by inhibition of p300-HAT, block of phenylephrine-induced hypertrophy	(43)
Rats	oral 50mg/kg	destruction of p300/GATA4 Complex and suppression of the hypertrophic response	(44)
Mice	Intraperitoneal 100µg/kg	Reducing the activity of p300-HAT, inhibiting the hypertrophy induced by lipopolysaccharide	(45)

The relation of cardiac hypertrophy with histone acetyltransferase enzyme: cardiac hypertrophy is the adaptive thickening of heart muscle or myocardium that may lead to heart failure, sudden death or heart failure in a long time (43, 15). HAT is an enzyme that can convert lysine residue in histones to N- acetyl lysine by transferring an acetyl group from acetyl-CoA group that ultimately leads to the expression of most genes (46). Histone acetylation is one of the key checkpoints for gene regulation in cells susceptible to hypertrophic myocardium (43). This is done by the HAT enzymes. In contrast, the histone de acetylases enzyme (HDACs) removes acetyl groups from lysine in N-terminal amino acid on the histones. The level acetylation of histone is measured by checking the balance between the histone acetyltransferase enzymes and histone de acetylase (46, 43).

The effects of curcumin on histone acetyltransferase enzyme: curcumin inhibits histone acetyltransferase enzyme that increases cardiac hypertrophy and heart failure, and prevents from hypertrophy (47, 43). Furthermore, curcumin protects heart from ischemia / reperfusion damages (49, 48, 4). P300 is a necessary HAT for growth of cardiac myocytes that modulate chromatin and transcription factors and increases the activity of associated genes (50, 17). Curcumin in cells leads to proteasome-dependent P300 degradation, which inhibits the activity of HAT and prevents from P300 function in H3 histone and p53 as a substrate by enzyme. Thus, curcumin acts as a selective inhibitor of the HAT enzyme (47). Curcumin prevent from excessive weight of heart that body weight with this mechanism (2).

Several natural analogues of curcumin have been identified from different plant sources. paradol, Garsinol, Kasomonin, Galanal and Isoeugenol ... are analog compounds of curcumin that like curcumin are derived from plant roots. Some of these analogues are stronger and others act weaker than curcumin. (5) For example, garsinol is stronger in inhibition of cancer cell (51) and Isoeugenol is weaker than curcumin (52). In the first phase of human clinical trials it was shown that even by taking curcumin 8 mg/day do not occur side effects (53).

Discussion

Curcumin is a polyphenol with low molecular weight and, was used as a natural compound in the treatment of many diseases, particularly cardiovascular disease and cancer (54, 1) and inhibits cardiac hypertrophy regulated by HAT enzymes particularly p300 (41). Since overexpressing of P300 gene leads to hypertrophy and heart failure in transgenic mice (19), it is expected that HAT play a vital role in responding to stimuli inducing cardiac hypertrophy. Based on Histone acetylation evidence or some transcription factors is associated with cardiac hypertrophy (16).

Curcumin by inhibiting HAT function prevents from DNA replication and uncontrolled growth of myocardial cells (43) and prevents from cardiac hypertrophy. In addition, curcumin as an inhibitor of this enzyme plays a potential role in cancer treatment (56 and 55). Inhibitory properties of curcumin on myocardial hypertrophy, according to a decrease in gene expression of BNP as a diagnostic marker of heart cells hypertrophy has been proven (57).

Studies of gel assay of HAT show that curcumin with an IC₅₀ 25 μ M, strongly inhibits histone acetylation on third histone (H3) and fourth histone (H4) by CBP P300 takes. But other factors associated with changes in activity of CBP P300 does not cause even at concentrations of curcumin 100 μ M (41), indicating the specificity of curcumin for this type of enzymes (58). Since cardiac hypertrophy induced by lipopolysaccharide in mice mediated by blocking of HAT- P300 activity were returned through curcumin 100 μ g /kg treatment (45), demonstrating that curcumin has a great potential in the treatment of cardiomegaly.

Curcumin has an interoperability function of HAT on lysine on another set of enzymes called histone acetylases (59). At least 18 histone de acetylases enzymes have been identified in human (60). The interesting issue is that the performance of some of these enzymes particularly HDACII are inhibited by curcumin and suppresses myocytes growth (63-61). From 33 carboxylic acid derived compounds, curcumin with concentrations of 50 to 500 micro-molar known as the most effective HDAC inhibitor (64).

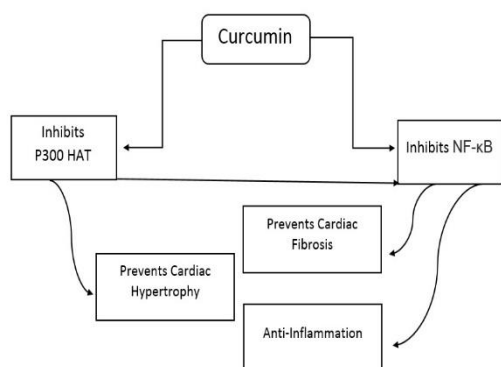


Figure 2. The role of curcumin in the prevention of cardiac hypertrophy and its associated mechanisms {Wongcharoen and colleagues (21)}

This challenging paradox that HDAC and HAT inhibitors, despite the interoperability function also have the same pharmacological effect, is likely justified to modulate gene expression and transcription. Stimulation of some histone deacetylases enzymes by curcumin created a huge challenge to the validity of this mechanism (64). However, previous studies indicated the balance between the activities of two types of HDAC and HAT enzymes (17).

Other mechanisms suggest associated with cardiac hypertrophy inhibition that inhibiting the activity of inflammatory markers is one of them (43). NF-κB plays a key role in cardiac disorders (65, 49) and curcumin by reducing the activity of NF-κB and inflammatory markers, including MCP-1, IL-6, IL-1 and TNF-α inhibits the cardiac hypertrophy (43). Curcumin applies anti-inflammatory effects by down regulation of the NF-κB transcription factor, some

enzymes (cyclooxygenase-2 and 5-lipoxygenase) and cytokines (IL-1, IL-6 and TNF) (32, 13). In addition, lipid peroxidation by curcumin could suppress the inflammation in the body (5). The important point is that these two mechanisms as mutual (Fig 2) are connected and indicating that the HAT enzyme is associated with activity of inflammatory markers and indicate that the effect of this enzyme is in cardiac fibrosis and inflammation (21).

The mechanism of action of curcumin as an inhibitor of cardiomegaly still is not entirely clear. One of the most reliable mechanisms mentioned in this regard is inhibition of histone acetyltransferase enzyme. HAT- P300 can be considered as a therapeutic target in reducing the prevalence of cardiac hypertrophy. Therefore, based on mentioned evidence and the relevant mechanisms, curcumin plays an important role in the prevention of cardiac hypertrophy and heart failure reduction. Curcumin is the active ingredient of turmeric that is an inexpensive and safe material and is a raw drug (16) that has many health benefits that by inhibition of HAT prevents from cardiac hypertrophy and heart failure. Although it is not toxic in high dosage (22), but its indiscriminate use is not recommended due to limited bioavailability of curcumin (66).

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