Review Article

J Babol Univ Med Sci
Vol 19, Issu 1; Jan 2017. P:27-35

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

**E. Habibi (PhD)[1], H. Esmaeeli *[2]**

1.Department of Pharmacognosy, Mazandaran University of Medical Sciences, Sari, I.R.Iran
2.Student Research Committee, Mazandaran University of Medical Sciences, Sari, I.R.Iran

**J Babol Univ Med Sci; 19(1); Jan 2017; PP: 27-35**
**Received: Oct 11th 2016, Revised: Nov 26th 2016, Accepted: Dec 13th 2016.**

## 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-κB, 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.*

**Please cite this article as follows:**

Habibi E, Esmaeeli H. A Review of the Effects of Curcumin on Histone Acetyltransferase Activity in the Prevention of Cardiac Hypertrophy. J Babol Univ Med Sci. 2017;19(1):27-35.

* **Corresponding author: H. Esmaeeli**
**Address:** Student Research Committee, Mazandaran University of Medical Sciences, Sari, I.R.Iran
**Tel:** +98 11 33044864
**E-mail:** esipharm@yahoo.com

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]

## 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).

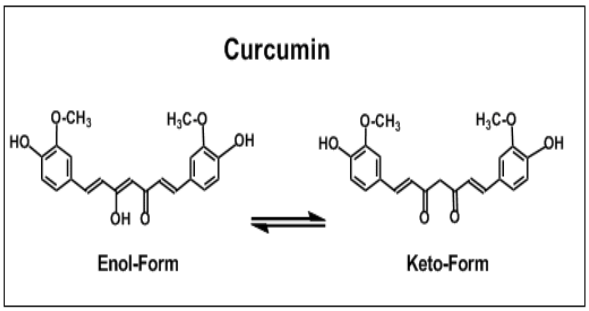


**Figure 1. Structure of curcumin (C21H20O6) that was described for the first time in 1910 by Lampe and Milobedeska (6, 5)**

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 dimethilsulfoxide (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

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]

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) |

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]

**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 µM, 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 µM (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 100µg /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).

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]

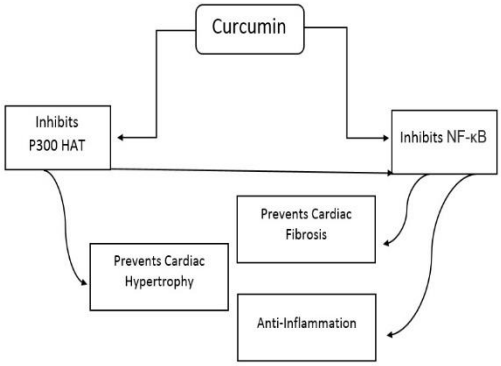


**Figure 2. The role of curcumin in the prevention of cardiac hypertrophy and its associated mechanisms {Wongcharoen and colleagues (21)**

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 de acetylases 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 reduceing 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 the its indiscriminate use is not recommended due to limited bioavailability of curcumin (66).

## Acknowledgments

Thereby, we would like to thank the Department of Science and Technology of Mazandaran University of Medical Sciences for financial support of this research.

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]

## References

1.Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. Life Sci. 2006;78(18):2081-7.

2.Mito S, Watanabe K, Harima M, Thandavarayan RA, Veeraveedu PT, Sukumaran V, et al. Curcumin ameliorates cardiac inflammation in rats with autoimmune myocarditis. Biol Pharm Bull. 2011;34(7):974-9.

3.Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. Trends Pharmacol Sci. 2009;30(2):85-94.

4.Kapakos G, Youreva V, Srivastava AK. Cardiovascular protection by curcumin: molecular aspects.Indian J Blochem Biophosic 2012;49:306-15.

5.Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. Ann New York Acad Sci. 2005;1056(1):206-17.

6.Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003;23(1):363-98.

7.Kiuchi F, Goto Y, Sugimoto N, Akao N, Kondo K, Tsuda Y. Nematocidal activity of turmeric: synergistic action of curcuminoids. Chem Pharm Bull (Tokyo). 1993;41(9):1640-3.

8.Srinivasan K. A chromatographic study of the curcuminoids in Curcuma longa, L. J Pharm pharmacol. 1953;5(1):448-57.

9.Tonnesenn H, Karlsen J. Studies on curcumin and curcuminoids. Zeitschrift für Lebensmittel-Untersuchung und Forschung. 1985;180(5):402-4.

10.Carabello BA. Is Cardiac Hypertrophy Good or Bad?. JACC: Cardiovascular Imaging. 2014;7(11):1081-3.

11.Grossman W. Cardiac hypertrophy: useful adaptation or pathologic process? Am J Med. 1980;69(4):576-84.

12.Sadoshima J-i, Xu Y, Slayter HS, Izumo S. Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. Cell. 1993;75(5):977-84.

13.Ghosh SS, Salloum FN, Abbate A, Krieg R, Sica DA, Gehr TW, et al. Curcumin prevents cardiac remodeling secondary to chronic renal failure through deactivation of hypertrophic signaling in rats. Am J Physiol Heart Circ Physiol. 2010;299(4):975-84.

14.Salvetti M, Muiesan ML, Paini A, Monteduro C, Bonzi B, Galbassini G, et al. Myocardial ultrasound tissue characterization in patients with chronic renal failure. J Am Soc Nephrol. 2007;18(6):1953-8.

15.Frey N, Olson E. Cardiac hypertrophy: the good, the bad, and the ugly. Ann Rev Physiol. 2003;65(1):45-79.

16.Morimoto T, Sunagawa Y, Fujita M, Hasegawa K. Novel heart failure therapy targeting transcriptional pathway in cardiomyocytes by a natural compound, curcumin. Circulat J. 2010;74(6):1059-66.

17.Wei JQ, Shehadeh LA, Mitrani JM, Pessanha M, Slepak TI, Webster KA, et al. Quantitative control of adaptive cardiac hypertrophy by acetyltransferase p300. Circulation. 2008;118(9):934-46.

18.Roth JF, Shikama N, Henzen C, Desbaillets I, Lutz W, Marino S, et al. Differential role of p300 and CBP acetyltransferase during myogenesis: p300 acts upstream of MyoD and Myf5. EMBO J. 2003;22(19):5186-96.

19.Miyamoto S, Kawamura T, Morimoto T, Ono K, Wada H, Kawase Y, et al. Histone acetyltransferase activity of p300 is required for the promotion of left ventricular remodeling after myocardial infarction in adult mice in vivo. Circulation. 2006;113(5):679-90.

20.Aasouri M, Ataee R, Ahmadi AA, Amini A, Moshaei MR. Antioxidant and free radical scavenging activities of curcumin. Asian J Chem. 2013;25(13):7593-5.

21.Wongcharoen W, Phrommintikul A. The protective role of curcumin in cardiovascular diseases. Inter J Cardiol. 2009;133(2):145-51.

22.Epstein J, Sanderson IR, MacDonald TT. Curcumin as a therapeutic agent: the evidence from in vitro, animal and human studies. Brit J Nut. 2010;103(11):1545-57.

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]

23.Smith DG, Cappai R, Barnham KJ. The redox chemistry of the Alzheimer's disease amyloid β peptide. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2007;1768(8):1976-90.
24.Ataie A, Sabetkasaei M, Haghparast A, Moghaddam AH, Ataee R, Moghaddam SN. Curcumin exerts neuroprotective effects against homocysteine intracerebroventricular injection-induced cognitive impairment and oxidative stress in rat brain. J Med Food. 2010;13(4):821-6.
25.Hansson GK, Robertson A-KL, Söderberg-Nauclér C. Inflammation and atherosclerosis. Ann Rev Pathol Mech Dis. 2006;1:297-329.
26.Pillarisetti S, Saxena U. Role of oxidative stress and inflammation in the origin of Type 2 diabetes-a paradigm shift. Exp Opin Therap Target. 2004;8(5):401-8.
27.South E, Exon J, Hendrix K. Dietary curcumin enhances antibody response in rats. Immunopharmacol Immunotoxicol. 1997;19(1):105-19.
28.Li L, Aggarwal BB, Shishodia S, Abbruzzese J, Kurzrock R. Nuclear factor-kappaB and IkappaB kinase are constitutively active in human pancreatic cells, and their down-regulation by curcumin (diferuloylmethane) is associated with the suppression of proliferation and the induction of apoptosis. Cancer. 2004;101(10):2351-62.
29.Shoskes DA. Effect of bioflavonoids quercetin and curcumin on ischemic renal injury: a new class of renoprotective agents. Transplantation. 1998;66(2):147-52.
30.Vamvouris T, Hadi S. A review of the treatment of psoriasis with infliximab. Rev Recent Clin Trials. 2006;1(3):201-5.
31.Vlietinck AJ, De Bruyne T, Apers S, Pieters LA. Plant-derived leading compounds for chemotherapy of human immunodeficiency virus (HIV) infection. Planta Med. 1998;64(2):97-109.
32.Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. Cancer letters. 2008;267(1):133-64.
33.Khopde SM, Priyadarsini KI, Venkatesan P, Rao M. Free radical scavenging ability and antioxidant efficiency of curcumin and its substituted analogue. Biophysical Chem. 1999;80(2):85-91.
34.Aggarwal BB, Kumar A, Aggarwal MS, Shishodia S. Curcumin derived from turmeric (Curcuma longa): a spice for all seasons. Phytopharm Cancer Chemoprev. 2005;23:351-87.
35.Bengmark S. Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases. JPEN J Parenter Enteral Nutr. 2006;30(1):45-51.
36.Hosseinimehr SJ. A review of preventive and therapeutic effects of curcumin in patients with cancer. J Clin Excell. 2014;2(2):50-63.
37.Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, et al. Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biolog Chem. 2005;280(7):5892-901.
38.Mohanty I, Singh Arya D, Dinda A, Joshi S, Talwar KK, Gupta SK. Protective effects of Curcuma longa on ischemia-reperfusion induced myocardial injuries and their mechanisms. Life Sci. 2004;75(14):1701-11.
39.Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Siddappa NB, Ranga U, et al. Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. J Biol Chem. 2004;279(49):51163-71.
40.Cui L, Miao J, Cui L. Cytotoxic effect of curcumin on malaria parasite Plasmodium falciparum: inhibition of histone acetylation and generation of reactive oxygen species. Antimicrob Agent Chem. 2007;51(2):488-94.
41.Morimoto T, Sunagawa Y, Kawamura T, Takaya T, Wada H, Nagasawa A, et al. The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J Clin Invest. 2008;118(3):868-78.

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]

42.Sunagawa Y, Morimoto T, Wada H, Takaya T, Katanasaka Y, Kawamura T, et al. A natural p300-specific histone acetyltransferase inhibitor, curcumin, in addition to angiotensin-converting enzyme inhibitor, exerts beneficial effects on left ventricular systolic function after myocardial infarction in rats. Circulat J. 2011;75(9):2151-9.

43.Li H-L, Liu C, de Couto G, Ouzounian M, Sun M, Wang A-B, et al. Curcumin prevents and reverses murine cardiac hypertrophy. J Clin Invest. 2008;118(3):879.

44.Morimoto T, Sunagawa Y, Kawamura T, Takaya T, Wada H, Nagasawa A, et al. The dietary compound curcumin inhibits p300 histone acetyltransferase activity and prevents heart failure in rats. J clin Invest. 2008;118(3):868-78.

45.Chowdhury R, Nimmanapalli R, Graham T, Reddy G. Curcumin attenuation of lipopolysaccharide induced cardiac hypertrophy in rodents. ISRN inflammation. 2013;2013. Article ID 539305, 8 pages. http://dx.doi.org/10.1155/2013/539305

46.Clayton AL, Hazzalin CA, Mahadevan LC. Enhanced histone acetylation and transcription: a dynamic perspective. Molecular Cell. 2006;23(3):289-96.

47.Marcu MG, Jung Y-J, Lee S, Chung E-J, Lee M-J, Trepel J, et al. Curcumin is an inhibitor of p300 histone acetylatransferase. Med Chem. 2006;2(2):169-74.

48.Srivastava R, Dikshit M, Srimal R, Dhawan B. Anti-thrombotic effect of curcumin. Thromb Res. 1985;40(3):413-7.

49.Yeh C-H, Chen T-P, Wu Y-C, Lin Y-M, Lin PJ. Inhibition of NFκB Activation with Curcumin Attenuates Plasma Inflammatory Cytokines Surge and Cardiomyocytic Apoptosis Following Cardiac Ischemia/Reperfusion 1. J Surg Res. 2005;125(1):109-16.

50.Yanazume T, Hasegawa K, Morimoto T, Kawamura T, Wada H, Matsumori A, et al. Cardiac p300 is involved in myocyte growth with decompensated heart failure. Molecular Cellul Biol. 2003;23(10):3593-606.

51.Pan M-H, Chang W-L, Lin-Shiau S-Y, Ho C-T, Lin J-K. Induction of apoptosis by garcinol and curcumin through cytochrome c release and activation of caspases in human leukemia HL-60 cells. J Agricult Food Chem. 2001;49(3):1464-74.

52.Fujisawa S1, Atsumi T, Ishihara M, Kadoma Y. Cytotoxicity, ROS-generation activity and radical-scavenging activity of curcumin and related compounds. Anticancer Res. 2004;24(2):563-70.

53.Cheng A-L, Hsu C-H, Lin J-K, Hsu M-M, Ho Y-F, Shen T-S, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2000;21(4):2895-900.

54.Miquel J, Bernd A, Sempere J, Dıaz-Alperi J, Ramırez A. The curcuma antioxidants: pharmacological effects and prospects for future clinical use. A review. Arc Gerontol Geriat. 2002;34(1):37-46.

55.Eliseeva ED, Valkov V, Jung M, Jung MO. Characterization of novel inhibitors of histone acetyltransferases. Mol Cancer Ther. 2007;6(9):2391-8.

56.Lee Y-H, Hong SW, Jun W, Cho HY, Kim H-C, Jung MG, et al. Anti-histone acetyltransferase activity from allspice extracts inhibits androgen receptor-dependent prostate cancer cell growth. Biosci Biotechnol Biochem. 2007;71(11):2712-9.

57.Gardner DG. Natriuretic peptides: markers or modulators of cardiac hypertrophy?. Trend Endocrinol Metabol. 2003;14(9):411-6.

58.Fu S, Kurzrock R. Development of curcumin as an epigenetic agent. Cancer. 2010;116(20):4670-6.

59.Boyanapalli SS, Kong A-NT. "Curcumin, the king of spices": epigenetic regulatory mechanisms in the prevention of cancer, neurological, and inflammatory diseases. Current Pharmacol Rep. 2015;1(2):129-39.

60.Xu W, Parmigiani R, Marks P. Histone deacetylase inhibitors: molecular mechanisms of action. Oncogene. 2007;26(37):5541-52.

61.Backs J, Olson EN. Control of cardiac growth by histone acetylation/deacetylation. Circulation Res. 2006;98(1):15-24.

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]

62.Zhang CL, McKinsey TA, Chang S, Antos CL, Hill JA, Olson EN. Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy. Cell. 2002;110(4):479-88.
63.Antos CL, McKinsey TA, Dreitz M, Hollingsworth LM, Zhang C-L, Schreiber K, et al. Dose-dependent blockade to cardiomyocyte hypertrophy by histone deacetylase inhibitors. J Biologic Chem. 2003;278(31):28930-7.
64.Bora-Tatar G, Dayangaç-Erden D, Demir AS, Dalkara S, Yelekçi K, Erdem-Yurter H. Molecular modifications on carboxylic acid derivatives as potent histone deacetylase inhibitors: Activity and docking studies. Bioorg Med Chem. 2009;17(14):5219-28.
65.Valen G, Yan ZQ, Hansson GK. Nuclear factor kappa-B and the heart. J Am Coll Cardiol. 2001;38(2):307-14.
66.Kalani A, Kamat PK, Kalani K, Tyagi N. Epigenetic impact of curcumin on stroke prevention. Metab Brain Dis. 2015;30(2):427-35.

[ DOR: 20.1001.1.15614107.1395.19.1.4.1 ]
[ DOI: 10.22088/jbums.19.1.27 ]