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Review Article

Protective Effects of Phytochemicals against Cardiac Hypertrophy by Modulating Oxidative Stress and Inflammation: A Review

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ABSTRACT
When heart undergoes increased work load, as a compensatory mechanism size of myocyte increases, this is denoted as cardiac hypertrophy (CH). If this condition is sustained for long term, it may lead to heart failure. Drugs used to treat this condition are associated with adverse drug reactions and there is a need of new drugs to combat hypertrophy. Subsequently, this concern has encouraged interest in the use of natural products, which may be better tolerated. Many studies have investigated the cardioprotective effect of phytochemicals against CH by abrogating oxidative stress and inflammation. This review concisely introduces the role of oxidative stress and inflammation in the progression of CH, and then enlighten the progress of phytochemicals towards its treatment. We highlight the promising applications and mechanisms of action of phytochemicals towards the treatment of CH in both *in vitro* and *in vivo* studies.
Keywords: Cardiac hypertrophy, Cardiac diseases, Oxidative stress, Inflammation, Phytochemicals.

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INTRODUCTION

Cardiovascular diseases (CVD) are leading causes for mortality and morbidity around the world.[1] Cardiac hypertrophy (CH) is increase in the size of myocytes, it is a compensatory mechanism due to mechanical stress and neuro-hormonal stimuli.[2] CH is associated with expression of foetal genes, changes in contractility and metabolism. There are two types of hypertrophies one is physiological hypertrophy, it occurs in conditions like pregnancy, exercise and post-natal hypertrophy, there is a mild increase in the length and width of myocyte as well as cardiac mass. It is not accompanied with fibrosis and cell death. The expression of foetal genes like atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and myosin heavy chain (MHC) is not activated or remains unaffected, this condition is reversible.[3] On the other hand, pathological hypertrophy which is irreversible is upregulation of genes like ANP and BNP. There will be death of cardiomyocytes which further proceeds to cardiac fibrosis, Ventricular dilatation and inability of myocardium to contract are the main features. It is beneficial in the early stages as it meets the demands of the body by increased force of contraction but a prolonged condition of CH leads to heart failure. CH is a risk factor for CVD such as arrythmia, myocardial infarction and heart failure.[4-5]

Modern medicine used in the treatment of CH has associated with severe adverse effects. Now the focus is on alternative medicine which are showing promising activity in the preclinical studies. Natural products are associated with lesser side effects. Phytochemicals are natural bioactives compounds present in fruits, medicinal plants, and aromatic plants, which act as a shield to fight against diseases. The phytochemicals from natural products cover a diverse range of chemical entities such as polyphenols, flavonoids, steroidal saponins, and vitamins. Many phytochemicals have been screened against various animal models of CH, they have showed better results. As per our knowledge this is the first review regarding phytochemicals inhibiting CH, we briefly explained about role of oxidative stress and inflammation in pathogenesis of CH and discussed about recent studies involving phytochemicals and their mechanism of action.

Role of Oxidative Stress in Cardiac Hypertrophy

Numerous studies revealed the role of oxidative damage in the progression of CH.[6-7] The imbalance between oxidants and antioxidants can cause permanent damage to the myocardium and activates many intracellular pathways that plays a major role in the CH.[8] Reactive oxygen species (ROS) are the molecules which are deficient in electrons, they are unstable and highly reactive. They cause damage to lipids, proteins and DNA present in the cell leading to irreversible damage. Some of the radicles which are commonly produced in the biological system includes, superoxide anon, hydroxyl radicle and peroxynitrite anion.[9] Endogenous mechanisms are present to scavenge these free radicals which

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are produced in physiological process. There are two types of anti-oxidants in the body one is enzymatic which includes superoxide dismutase (SOD), glutathione peroxidase (GSHPx), and catalase.[7] Non enzymatic contains glutathione, Vitamin-A, Vitamin-C, flavonoids and polyphenols. Whenever these free radicles overpower antioxidant system this is known as oxidative stress. ROS is known to have role in some redox signalling pathways as well as in defence against some pathogens, the role of antioxidants is not to eliminate free radicals completely but to maintain them in optimum level.[10]

Recent evidences found that two enzyme systems namely NADPH oxidases (Nox) and xanthine oxidases plays a major role in the progression of oxidative stress (Figure 1) in myocardium.[7,11] Nox is a multi-enzyme subunit, it generates superoxide radicle, there are several isoforms of Nox, out of these Nox2 and Nox4 are mainly present in the myocardium.[12] Studies proved that activity of these enzymes increased during cardiac hypertrophy.[13] Xanthine oxidases are known to generate free radicles, febuxostat an inhibitor of xanthine oxidase inhibited cardiac hypertrophy.[14]

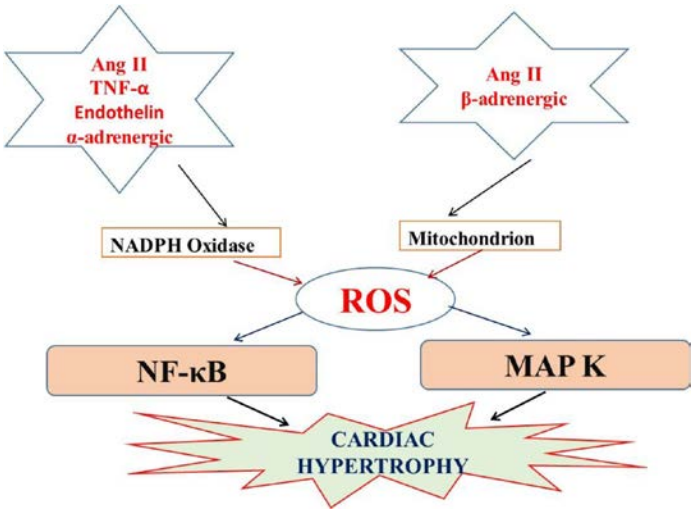


Figure 1: Represents the role of various stimuli that can generate ROS and role of ROS to cause CH.

NF-KB SIGNALLING PATHWAY

Nuclear factor kappa B (NF-κB) is a vital transcription factor that is included in immune and inflammatory responses.[15] It increases the expression of proteins like several cytokines, major histocompatibility complex (MHC) and several adhesion proteins for neutrophil adhesion and activity.[16] NF-κB is present in almost all the cells, in the cell it is actually present in inactive form, which gets activated by external signals. It is sequestered in the cytoplasm by proteins named IκB. Whenever there is a stimuli from immune cells like tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), IκB gets ubiquitinized and degrades in the cytoplasm then NF-κB translocate in to the nucleus and augment target genes.[15] NF-κB transcription factor has most important role in the pathogenesis of cardiac disorders like ischemic heart diseases, cardiac hypertrophy, acute coronary syndrome and atherosclerosis. Several studies have proved that inhibiting NF-κB resulted in attenuating of CH.[17] It is known to increase the expression of genes which causes CH.[18] Purcell demonstrated that NF-kB activation is essential and ample to produce a hypertrophic response through the G-Proteins binding to isolated cardiomyocyte receptors.[19] Higuchi and colleagues have showed that hypertrophy in cardiomyocytes in culture by TNF-α requires the activation of NF-kB and blockade of NF-κB activation inhibited myocardial hypertrophy without worsening cardiac function.[20] Apart from this many Phytochemicals are known to protect myocardium by various stimuli by blocking NF-kB pathway.[21]

MAPK Signalling Pathway

Mitogen activated protein (MAP) kinase pathway is extremely conserved signal transduction pathway which connects several extracellular signals to a series of intracellular functions comprising cell differentiation, cell division and cell death.[22] MAPK signalling pathways involves an order of sequentially functioning kinases that eventually result in the dual phosphorylation and activation of ERKs, c-Jun N-terminal kinases (JNKs) and p38.[23] This signalling cascade is generally activated by stimuli such as stretch and through receptors like G-Protein coupled receptors (GPCR) and tyrosine kinase receptors (fibroblast growth factor receptors and transforming growth factor receptors.[24] Activated ERK, p38 and JNKs individually phosphorylate numerous intracellular targets, together with abundant transcription factors that persuade the activation of gene expression leading to cardiac hypertrophy.[25]

Many studies proved that the hyper activation of MAPKs (Figure 1) lead to pathological hypertrophy.[26] In transgenic mice that over activated ERK in the myocardial tissue developed unchanging pathological hypertrophy with a unvarying profile of an increased heart-to body weight ratio of approximately 25–30%. It also the increased transcription activity of NFAT (nuclear factor for activated transcription) indicating the cross talk between MAPK and calcineurin–NFAT pathway (another signal transduction pathway in CH). Buena *et al.* have described that expression of physiological levels of MAPK phosphatases obstructed the activation of p38 kinase and further inhibited cardiac hypertrophy caused by administration of catecholamines and aortic banding.[27] p38 MAPK and JNKs are well considered and have been described to be significant for the induction of hypertrophic responses comprising specific gene expression and upsurge in protein synthesis.[26] The c-jun NH2-terminal Kinases (JNKs) and p38 kinases function as specific transducers of stress response, thus they are also considered as stress-activated protein kinases (SAPK). JNK activity is precisely upregulated in response to pressure overload, while p38 activity is noticeably increased in heart exposed to volume overload. Buena *et al.* have described that expression of physiological levels of MAPK phosphatases obstructed the activation of p38 kinase and further inhibited cardiac hypertrophy induced by infusion of catecholamines and aortic banding.[27]

Role of Inflammation

The hallmark of CH is prolonged and consistent inflammation. Infiltration of immune cells like macrophages and neutrophils secrete pro-inflammatory cytokines and activates nuclear factor kappa B (NF-kB).[28-29] Inflammatory signalling mediators produced in the course of cardiac injury can induce hypertrophy and fibrosis.[30] Cardiomyocytes as well as non-cardiomyocytes secrete and retort to several cytokines, but then again the responses are intricate, the concentration of Pro-inflammatory cytokines in heart failure patients correlate with the severity of disease.[31] Studies have proved that expression of TNF-α in the myocytes causes cardiac hypertrophy and fibrosis leading to cardiac dysfunction and infusion of TNF-α causes cardiac hypertrophy.[32] Drugs targeting TNF-α are also helpful in animal models, but to a slighter scope. Mice deficient in IL-1β had protective effect in pressure overload induced CH signifying that IL-1β has an aggravating role in hypertrophic remodelling. It is also showed that IL-1β injections in mice induced cardiac dysfunction. Antagonizing the effects of IL-1β in patients suffering from heart failure in early stages has showed beneficial effect.[3] Anakinra, an antagonist of IL-1 receptor had augmented oxygen intake and exercise performance in patients.[33] IL-6 has detrimental

effect on heart. Infusion of IL-6 resulted in cardiac hypertrophy, fibrosis, and diastolic dysfunction. Studies also showed that genetic omission of IL-6 has revealed to decrease cardiac damage and to reduce angiotensin II–induced cardiac hypertrophy ad fibrosis. IL-6 knockout has also been shown to inhibit noradrenaline-induced hypertrophy and remodelling.[3,34]

Current Pharmacological Therapeutics Targeting Cardiac Hypertrophy

Treatment options for cardiac hypertrophy include physical activity (exercise), pharmacological treatment and surgery. The general aim of the treatment is to decrease the possibility of hospitalization and premature death due to heart failure.[35] Drug treatment is commonly attainable, mostly due to its lesser price. Here, we review existing pharmacological therapy usually recommended to patients with cardiac hypertrophy and their mechanism of action.

ACE Inhibitors

ACE (Angiotensin converting enzyme) inhibitors are one of the widely used drugs in the treatment of hypertension, cardiac hypertrophy and heart failure. These drugs are considered as cornerstone in the treatment of cardiac diseases.[36] They inhibit the formation of ang11 (angiotensin 11), thereby blocking signalling through AT_1 (Angiotensin 1 receptors). They promote excretion of salt and water and decreases blood pressure, they also promote the relaxation of blood vessels leading to decrease in peripheral vascular resistance and decreasing load on the heart. Moreover, treatment with ACE inhibitors decreases the risk of MI and also reduces the chances of developing symptoms of heart failure in patients with left ventricular dysfunction.[37]

Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARB) are antagonists at AT_1 receptors and show similar therapeutic benefits like ACE inhibitors. These drugs are used in patients who are intolerant to ACE inhibitors because they produce severe dry cough as a adverse effect.[38] These drugs in targets both neuro-hormonal systems by inhibiting degradation of peptides (e.g., natriuretic, bradykinin, adrenomedullin) that facilitate advantageous cardiac and renal effects that are compromised in CH and HF, while alongside antagonizing the AT1 receptor. ARB causes regression of hypertrophy and are more effective in reducing left ventricular (LV) mass than ACE inhibitors. There is synergistic effect when ARB and ACE are used in combination but with incidence of increased side effects.[39]

β-Blockers

Beta blockers have anti hypertrophic effects and strongly reduce mortality in heart failure. These drugs have negative chronotropic effect (decreases heart rate) and negative ionotropic effect (decreases force of contraction), thus letting the ventricles to fill more efficiently and increases contraction of the heart, and also by reducing blood pressure by vasodilation.[40] However decrease in CH is significantly a lesser amount than compared with ARB and ACE inhibitors.[35]

Aldosterone Receptor Blockers

Aldosterone receptor stimulation in the myocardium leads to CH by promoting inflammation and fibrosis.[41] It also increases the retention of salt and water in the body which creates burden on the failing heart. Thus, aldosterone receptor antagonist in the heart signifies a striking therapeutic choice for the treatments of CH. They are prescribed along with Beta blockers and ARB.[42]

Diuretics

Diuretics continue to be main element of drug treatment in both hypertrophy and Heart failure; however, diuretics are combined with β-blocker, ACE inhibitor to relieve symptoms.[35] Diuretics show beneficial effect during fluid retention and cause rapid relief of breathing problems, morbidity and mortality rate due to diuretics is still unknown. Usual side effects related with diuretics consist of electrolyte disturbances and syncope, adverse effects also depend on the type of diuretics that are used for example loop diuretics may cause hearing problems.[43]

Phytochemicals against Cardiac Hypertrophy

Astragaloside IV

Zhang *et al.* reported the potential therapeutic efficiency of astragaloside IV (AS IV) against ISO induced cardiac hypertrophy in rats. They evaluated hypertrophic markers such as HW/BW ratio, ANP and BNP through RT-PCR, which showed dose dependent decrease in these markers compared to ISO group. To investigate the molecular mechanism for the protective effect of ASIV, they studied the quantification of NF-κB and PGC-1α (Peroxisome proliferator-activated receptor-γ coactivator 1 α) proteins through western blot. Irregular production of NF-κB and PGC-1α are linked with imbalances in metabolism in cardiac tissue. Results indicated that ASIV attenuated the activation of NF-κB and increased the activation of PGC-1α and conferred the cardioprotective activity.[44]

Gallic Acid

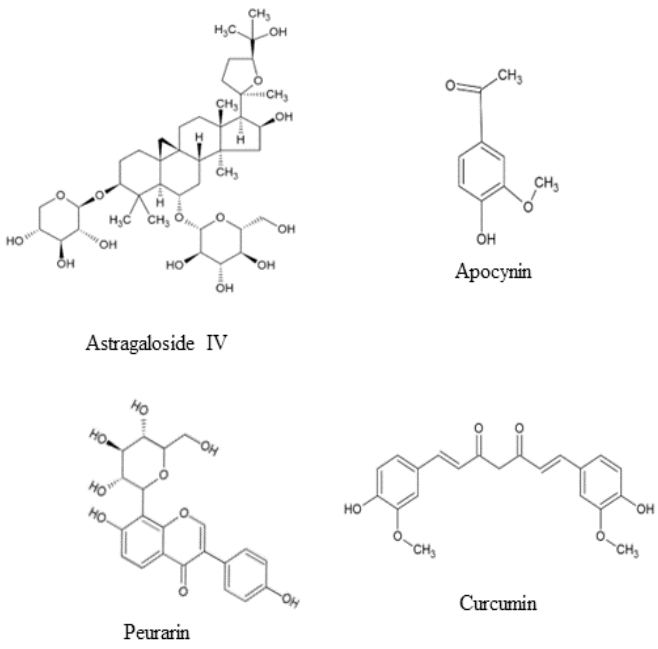
Ryu *et al.* reported the protective effect of Gallic acid against cardiac hypertrophy and fibrosis induced by ISO in mice. In this study pre-treatment with Gallic acid inhibited concentric cardiac hypertrophy. It decreased the induction of ANP, BNP, and beta-myosin heavy chain *in vitro* and *in vivo*. Additionally, it attenuated fibrosis by inhibiting synthesis of collagen. Gallic decreased the activation of MAPK (ERK and JNK). It decreased the expression of phosphorylated Smad 3 binding to the promoter region in the DNA therefore decreasing the production of collagen from cardiac fibroblasts.[45]

Apocynin

Saleem *et al.* has reported the beneficial effect of Apocynin on ISO induced cardiac hypertrophy. This study assessed the effects of apocynin (Apo), on the generation of ROS and the advancement into cardiac hypertrophy in male Wistar rats. It is noticeable from the parameters like HW/BW ratio, HW/ TL ratio, expression of hypertrophic genes, echocardiography, and histopathological observations induced by ISO were attenuated by Apo. ISO treatment increased the expression of subunits of Nox, which is responsible for production of ROS. Administration of ISO also caused a reduction in reduced glutathione concentration that was reinstated by Apo. RT-PCR studies showed that expression of fibrotic genes like ANP, BNP and β-MHC by Iso was either partly or completely inhibited by Apo. Activation of key signalling kinases such as, Erk,, Akt by ISO was also attenuated by Apo treatment.[46]

Puerarin

Yuan *et al.* investigated the effect of Puerarin against pressure overload-induced cardiac hypertrophy. They performed Aortic banding (AB) to induce cardiac hypertrophy in mice. The degree of cardiac hypertrophy was assessed by histological and molecular studies of cardiac tissues. Apoptosis in myocytes was evaluated by quantifying Bax and Bcl-2 proteins and TUNEL staining, where Puerarin decreased the cardiomyocyte apoptosis compared to AB group. ANP and BNP levels are also decreased in treatment group in comparison with AB group. Further they performed western blot analyses to explore the molecular



Structures of phytochemicals represented in the manuscript.

pathway for its mechanism of action which revealed blockade of PI3K/Akt and JNK signalling imparts a key role in retarding the development of pressure overload in the aortic banding mice model.[47]

Curcumin

Liu *et al.* reported the cardioprotective activity of curcumin in murine model of cardiac hypertrophy. The present study was intended to elaborate the effect of curcumin on inhibition of ISO induced cardiac hypertrophy and fibrosis in rat. RT -PCR was performed to study biomarkers of CH, Results showed that curcumin at the dose of 200mg/kg efficiently abridged hypertrophic and fibrotic markers in the heart tissues from ISO treated rats. Curcumin treatment decreased the deposition of collagen which is evident from masons trichome staining. Molecular mechanism revealed that the protective action is by inhibiting autophagy by activating m-TOR pathway.[48]

Chrysophanol

Yuan *et al.* studied the activity of Chrysophanol a natural anthraquinone compound present in Chinese plant Rheum officinale. They performed ISO treatment on primary cardiomyocytes from heart tissue and treated with Chrysophanol which showed decreased cell surface area and decreased expression of CH biomarkers like ANP, BNP and β-MHC. To additional validation, activity of chrysophanol on hypertrophy was studied on SD rats with ISO administration. Furthermore, the morphometric studies showed that the cardiac tissue of ISO-treated rats compared with control group developed hypertrophic alterations. An increased cross- sectional area of myocytes was too showed by HE staining. Administration of ISO caused the increase in HW/BW ratio. Treatment with Chrysophanol inhibited ISO induced pathological changes and expression of cardiac foetal genes like ANP, BNP and β-MHC. Western blot analysis conformed that inhibition of ISO induced JAK and STAT3 activation in both cardiomyocytes and rats is responsible for protective action of Chrysophanol.[49]

Baicalein

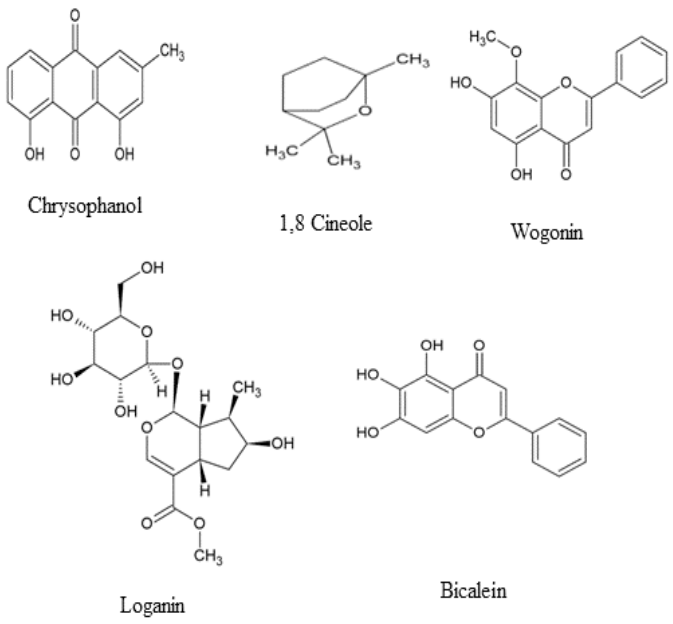
Baicalein was investigated against cardiac hypertrophy *in vivo* and *in vitro*. Cardiac hypertrophy was induced in mice by administration of ISO at 30mg/kg for 15 days. Mice were injected with baicalein (25mg/kg) on 3rd, 6th, 9th, 12th, and 15th days. ISO-induced cardiac hypertrophy by promoting the transcriptional activity of FOXO3a. FOXO3a transactivates the antioxidation gene catalase to inhibit ROS bursts, while the autophagy-associated gene FUNDC1 is also transactivated to activate impaired autophagy, which might provide a potential therapeutic strategy for cardiac hypertrophy.[50]

Wogonin

Wogonin (Wog) is obtained from the root of *Scutellaria baicalensis*. Wog was evaluated against AngII induced hypertrophy in H9C2 cells. Wog treatment decreased the AngII induced hypertrophy and inhibited the ROS generation. SOD and MDA concentration were measured, Wog increased the level of SOD and decreased the levels of MDA. RT-PCR revealed that mRNA levels of anti-oxidants like Nrf-2, HO-1 and NOQ1 are increased in treatment with Wog. Transverse aortic constriction (TAC) was performed in C57BL/6 mice to develop CH. Wog treatment reversed the irregularities in hear functions which was evident by echocardiography. Histopathological studies also showed wog reversed CH. Protective effect of Wog is mediated by modulating Keap-1/Nrf-2 pathway.[51]

1, 8-cineole

Wang *et al.* studied the effect of 1,8-CIN against ISO induced cardiac hypertrophy in H9C2 cells and rats. In H9C2 cells 1,8-CIN decreased apoptosis induced by ISO, which was evident by flow cytometric analysis and TUNEL assay. Subcutaneous injection of ISO increased cardiac hypertrophy, fibrosis and death of cardiomyocyte. Treatment with 1, 8-CIN attenuated cardiomyocyte death and reduced cardiac hypertrophy, fibrosis and apoptosis. Authors observed that miR-206-3p was upregulated after ISO treatment, which was responsible for accumulation of misfolded proteins leading to endoplasmic reticulum (ER) stress in heart tissue. 1, 8-CIN inhibited the expression of miR-206-3p and showed cardioprotective effect.[52]



Structures of phytochemicals represented in the manuscript.

Loganin

Loganin a glycoside extracted from Cornus officinalis, was investigated on Ang II–induced cardiac hypertrophy in mice and H9C2 cells. Loganin diminished the Ang II–induced protein upregulation of ANP, BNP, and β-MHC in H9C2 cells. Furthermore, in mice loganin attenuated cardiac fibrosis by decreasing pro-inflammatory cytokine secretion, and subduing the phosphorylation of critical proteins such as JAK2, STAT3, p65, and IκBα. Study also proved the non-toxic effects of loganin on other organs like heat liver and kidney.[53]

CONCLUSION

Numerous studies have proved oxidative stress as a significant facilitator of cardiac hypertrophy and constantly, aiming at oxidative stress has been shown to abrogate hypertrophic response. Phytochemicals have showed protective effect by inhibiting oxidative stress and inflammation in preclinical studies. Further studies have to be conducted to find their toxicity profiles and these compounds are to be taken into clinical settings to study their prophylactic as well as therapeutic effect.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

ABBREVIATIONS

CH: cardiac hypertrophy; **CVD:** Cardiovascular diseases; **ANP:** atrial natriuretic peptide; **BNP:** brain natriuretic peptide; **MHC:** myosin heavy chain; **ROS:** Reactive oxygen species; **SOD:** superoxide dismutase; **GSHPx:** glutathione peroxidase; **NF-κB:** Nuclear factor kappa B; **MHC:** major histocompatibility complex; **TNF-α:** tumor necrosis factor-α; **IL-1:** interleukin-1; **MAPK:** Mitogen activated protein kinase; **JNK:** c-Jun N-terminal kinases; **NFAT:** nuclear factor for activated transcription; **ACE:** Angiotensin converting enzyme; **ARB:** Angiotensin receptor blockers; **PGC-1α:** Peroxisome proliferator-activated receptor-γ coactivator 1 α.

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