Review

The cardioprotective potential of melatonin on cardiac hypertrophy: A mechanistic overview

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ABSTRACT

Cardiac hypertrophy (CH) is an increment of muscle mass to maintain the heart regular operations. A physiological cardiac hypertrophy due to exercise or other normal physiological process is characterized by normal contractile function and structural framework of heart tissue. In contrast, pathological hypertrophy occurs in response to increased pressure or volume overload from several cardiovascular diseases including hypertension, valvular diseases, cardiac infarction and heart failure. It is of major concern as it is one of the leading causes of death worldwide. Despite much progress in this field there is a scope for understanding of the molecular mechanisms of this condition. In this review, various types of cardiac hypertrophy and their intricate physio-pathological mechanisms have been discussed. In addition, the genetic mutations in sarcomere genes and oxidative stress are also closely linked to hypertrophic cardiomyopathy. Although several drugs against cardiac hypertrophy have been used, it appears that melatonin, due to its high bioavailability and low side effects, is a better candidate than the conventional medicine for treatment of hypertrophic cardiomyopathy. Melatonin, a hormone and a potent antioxidant, is secreted mainly from the pineal gland, but it is also synthesized from different peripheral tissues including the heart. This molecule can regulate a myriad of cellular functions. It can protect against cardiac hypertrophy via reducing oxidative stress, elevating Cu-Mn SOD via controlling several cell signalling pathways of Akt/mTOR, ROR-α and NLRP3 cascades. Melatonin also mitigates cardiac hypertrophy by suppressing pro-inflammatory cytokines including TNF-α and TGF-β and cardiac hypertrophy markers like β-MHC, ANP, BNP, LDH. This review focuses on the molecular mechanisms of cardiac hypertrophy and the defensive role of melatonin on it. We propose melatoninas a propitious adjunct for the treatment of cardiac hypertrophy.

Keywords: Cardiac hypertrophy, oxidative stress, antioxidant, melatonin

1. INTRODUCTION

Cardiovascular diseases (CVDs) are the foremost cause of death worldwide, with approximately 17.9 million fatalities each year (1,2). Cardiac hypertrophy (CH) or dilated

cardiac tissue is a major one of devastating consequences associated with CVDs (3). It brings with several disorders including differential gene expression, discrepancies in metabolism, contractility, and viability of cardiomyocytes (4). CH is frequently associated with hypertension, hypertrophic cardiomyopathy (HCM), valvular disease, congenital heart disease, pressure overload and mutations in sarcomeric and non-sarcomeric genes (5). Physiological and pathological hypertrophies are two different forms as to diagnosis. Their intrinsic pathways and their cardiac behaviour vary significantly; however, both originally arise to maintain homeostasis of heart function (4). Five to ten percent of children and fifty to sixty percent of patients exhibit HCM and its incidence are 1:500 that makes it a cause for concern. In carriers of specific genetic mutations, symptoms typically do not appear until adolescence, but the development of HCM can occur at any age, from infants to the elderly (6-8). Among several molecular cascades involved in the development of CH, oxidative stress is one of the major intermediaries (9). It has been demonstrated that intracellular reactive oxygen species (ROS) generation is involved in CH caused by angiotensin II, endothelin-1, tumour necrosis factor (TNF-alpha), or pulsatile mechanical strain in cultured cardiomyocyte. Antioxidants can suppress ROS formation (10). Although not all hypertensive individuals acquire left ventricular hypertrophy as a result of chronic pressure overload, this condition is linked to several serious cardiovascular risks including atrial fibrillation, diastolic and systolic cardiac failure, and sudden death. Left ventricular hypertrophy can be reversed quickly by anti-hypertension medications including ACE inhibitors or Angiotensin II receptor blockers (11). Oxidative stress suppressors like mdiv-1 (12), resveratrol (11), mitoQ(13), could attenuate hypertrophy in heart.CH was also found to be mitigated by a myosine inhibitor of Mavacamten (14), a Ca^{2+} blocker similar to diltiazem(15) or peptidase inhibitor such asteneligpin (16).However, these drugs have low bioavailability and various side effects including hypotension, dry cough, hyperkalaemia, dry mouth, nausea, constipation (17-19).Therefore, it is urgent to identify medicines with low negative effects on health. Melatonin seems to fit this requirement (19, 20). Melatonin is a ubiquitously presented multifunctional biomolecule (11). In vertebrates, melatonin is not only secreted from pineal gland but also from peripheral tissues and functions in an autocrine and paracrine manner (21). Melatonin has a vital impact on human cardiovascular health and disease (22). It is reported that melatonin could influence the cardiovascular system in both human and rodent by preventing cardiac degeneration caused by ischemia/reperfusion injury, retarding atherosclerosis, alleviating hypertension at night, and decreasing isoproterenol-induced cardiac damage (23-27). Melatonin protects against transverse aortic constriction, CH caused by 3,5,3'-tri-iodo-L-thyronine, and monocrotaline toxicity (28-30). Covid-19 can cause cardiovascular injury leading to mortality; treatment with melatonin can effectively protect against Covid-19 patients (31, 32). In this review, we have summarized the types of CH, their causes and clinical manifestations. The emphasis will be given to pathological CH. The beneficial effects of melatonin against various cardiovascular diseases and protective role against pathological CH via different intrinsic pathways have also been discussed.

2. TYPES OF CH, ETIOLOGY, AND CLINICAL CONSEQUENCES

CH arises as a result of pressure or volume stress, mutations in sarcomeric or different kinds of proteins, or atrophied contractile mass after a previous infarction. Many cardiac illnesses, including ischemia, hypertension, heart failure, and valve disease, are accompanied by hypertrophic expansion (33-35). Normal postnatal development, pregnancy, and exercise result in physiological growth of cardiac tissue whereas the pathological hypertrophy can be a result of conditions mentioned above. Pathological hypertrophy is often linked to degeneration of myocytes and substitution by fibrosis, cardiac disarray, and a higher risk of heart failure and

sudden death with an increase in heart size (36-38). In physiological hypertrophy, the fibrillar collagen network supports the unification of adjacent myocytes to truncate the length of myocyte for effective ventricular pump performance. Rigidity of ventricles with disruption of the systolic and diastolic phases hampers the electrical coupling of cardiac myocytes. The accumulated extracellular matrix proteins with the reduced capillary density due to type 1 collagen deposition increase the oxygen diffusion distance and lead to myocardial ischemia, and accelerate the transformation from pathological hypertrophy to heart failure (39). Elevated myosin ATPase and enhanced contractility were observed in exercise or thyroid hormone induced physiological hypertrophy, whereas the pathological hypertrophy was seen in renal hypertension or aortic banding disorders (39, 40). Physiological or pathological heart hypertrophies are further classified as concentric or eccentric hypertrophy on the basis of heart shape. Eccentric hypertrophy is defined as an increase in cardiac mass accompanied by enlarged chambers with/out the increased relative wall thickness and the inclusion of sarcomeres in a series causes an increase in myocyte cell length. Concentric hypertrophy is defined as an increase in relative wall thickness and cardiac mass with negligible changes in chamber volume. It is distinguished by insertion of sarcomere in parallel fashion that results in broader myocytes (39, 41). Non-pathological eccentric hypertrophy is characterized by increased ventricular volume and coordinated increase in wall and septal thickness, with equal elongation of the length and breadth of cardiomyocytes, however, pathological eccentric hypertrophy causes ventricular dilatation and selective lengthening of cardiomyocytes. Cardiomyocytes normally expand in thickness rather than length in pathological concentric hypertrophy caused by hypertension or valvular disorders, while activity such as wrestling can generate non-pathological concentric hypertrophy (42-44). Compensatory hypertrophy is caused by pressure overload to improve ejection function by regulating systolic wall stress (45). These beneficial alterations in the myocardium, in terms of the systolic pump capacity of the left ventricle against increasing load, result in unfavourable hemodynamic changes early in the adaptation phase. As a result of these functional cardiac implications of left ventricular hypertrophy, diastolic filling is compromised, and diastolic dimensions are reduced (46). Hypertrophic cardiomyopathy (HCM) is a hereditary ailment of cardiac myocytes, characterized by unexplained CH, a non-dilated left ventricle, and a normal or increasing ejection fraction (47). The preponderance of HCM in the overall adult population has been estimated to be 0.16 - 0.29%. HCM in adults is identified by the presence of a left ventricular end-diastolic wall thickness of more than 13 mm on echocardiography or other imaging methods (38, 48-50). The phenocopy circumstances might cause heart hypertrophy, which constituted for 5 to 10% of clinically confirmed HCM cases in infants (51-54). The most common symptoms of HCM are diastolic ventricular dysfunction, congestion in left ventricular outflow, disparity in myocardial oxygen supply and demand, and cardiac arrhythmias (55). Dilated cardiomyopathy (DCM) is defined as left ventricular or biventricular dilatation and hindered contraction that cannot be explained by aberrant loading circumstances such as hypertension or valvular heart disease or coronary artery disease. DCM can be caused by mutations in numerous genes, including those encoding the structural components of the sarcomere and desmosome. It also occurs due to variety of non-genetic factors, including inflammation of the myocardium caused by an infection (usually viral), side effects of medicines, chemicals, or allergens, as well as systemic endocrine or autoimmune illnesses (56). Left ventricular hypertrophy (LVH) occurs when the left ventricular mass increases, either because of more thickened wall, expansion of the left ventricular chamber, or both (57). In individuals with hypertension, LVH is a reliable predictor of cardiovascular morbidity and mortality (58). Some patients with HCM have an abnormal right ventricular (RV) architecture or function. RV dysfunction in HCM might be primary or secondary with altered cardiomyocyte alignment and the swollen, disoriented, and irregularly shaped cardiomyocytes.

RVH in HCM may be seen in the free wall, inferior septum wall, or ventricle apex. However, a significant majority of individuals exhibited a diffuse pattern, in which hypertrophy was evident in all three segments (59).

3. CH AND ITS PATHOPHYSIOLOGICAL MECHANISMS

CH initiation occurs through various complicated signalling pathways including mitogen-activated protein kinase (MAPK), tyrosine kinase, insulin-like growth factor (IGF), TGF, fibroblast growth factor (FGF), c-Jun N-terminal kinase (JNK), and protein kinase C (PKC). These pathways causevariations of gene expression to produce the phenotypic changes of myocardial hypertrophy (60-62). Development of physiological or pathological CH depends upon the upstream stimulants and cell signalling mechanisms rather than the duration of cardiac stress (63-67). In the heart, the cell development, proliferation, differentiation, apoptosis, contractility, and metabolism are regulated by insulin and insulin-like growth factor 1 (IGF1) (68). The activation of insulin receptor recruits and phosphorylates the adaptor proteins, insulin receptor substrate 1 (IRS1) and IRS2 which in turn trigger PI3K-AKT1 (phosphoinositide 3-kinase-RAC-a serine/threonine-protein kinase) signalling (69). PI3K-AKT1 then, suppresses CCAAT/enhancer binding protein- β (C/EBPβ), a negative regulator of cell proliferations. Theexercise can also activate PI3K-AKT1 pathway to amplify CBP/p300-interacting trans activator 4 (CITED4) and to increase cellular size and number,hence, promoting physiological hypertrophy (70).Physiological hypertrophy due to aerobic exercise results in variable expression of microRNAs (miRNAs) in cardiac tissue (71). Over expression of miRNA-222 in physiological hypertrophy represses p27 (a cell cycle inhibitor gene), Hipk1 and Hipk2 (protein kinase-encoding genes), and Hmbox1 (transcriptional repressor gene), causing accelerated cell expansion and division of cardiomyocytes (72). p38 kinases and JNKs phosphorylate and switch on GATA4-mediated transcription via MEK3/MEK6 and MEK4/MEK7 of MAPK pathway to cause pathophysiological hypertrophy (73). Dephosphorylation of Nuclear factor of activated T cells (NFAT) by calcineurin, a Ca^{2+}-induced serine/threonine protein phosphatase, enhances its translocation to the nucleus where it interacts with transcriptional cofactors such as GATA4 and myocyte-specific enhancer factor 2 A (MEF2A) and upregulating genes linked to hypertrophy. However, neither pregnancy nor exercise induced physiological hypertrophy is conciliated by the calcineurin-NFAT pathway (74). Neuronal transmitters of catecholamines bind to α and β adrenergic receptors, which belong to GPCRs subclass, triggering adenylyl cyclase enzyme to elevate cAMP level. The cytosolic Ca^{2+}can be increased by cAMP which lead to contractile proteins dephosphorylation. Chronic activation of ß-adrenergic receptor by hypertension, MI, and heart failure causes pathological hypertrophy and receptor desensitization, which is controlled by GPCR kinase (GRK)-mediated β-arrestin signalling (75). In addition, the signalling pathways for protein kinase C beta 2 and PI3K-Akt also contribute to physio-pathological cardiac hypertrophy respectively with each other. PI3K can act as an upstream modulator to reverse the pathological cardiac dysfunction caused by over expression of PKCß2 (76).In CH, intensified protein synthesis or reduced protein breakdown occurs with mTORC1 (a serine/threonine kinase) activation.mTORC1 stimulates ribosomal protein synthesis (mRNA translation) by precisely triggering ribosomal protein S6 kinase-ß1 (S6K1) and impeding eIF4E-binding protein 1 (4EBP1), therefore, permits cap-dependent translation by eIF4E without any prohibition, (77-79). Inducing physiological hypertrophy requires only over expression of cardiac-specific polyadenylate-binding protein 1 (PABPC1), which interacts with eIF4G to increase global mRNA translation (77). The role of PABPC1 on the development of pathological hypertrophy requires further investigation (80). In the condition of pressure overload, mTORC2 activation occurs, which prevents cell death by blocking the pro-apoptotic mammalian STE20-like protein kinase (81).Thus, mTORC1 and

mTORC2 act antagonistically to each other in pathophysiological hypertrophy (80). Upon pathogenic stimuli, TGFß is increased, which causes cardiac hypertrophy and fibrosis. In response to pressure overload, canonical TGFß-SMAD2/SMAD3 signalling promotes cardiac fibrosis without inducing hypertrophy, whereas non-canonical SMAD-TAK1 (TGFß- activated kinase 1; also known as MAP3K7) signalling in cardiomyocytes promotes pathological hypertrophy and fibrosis (80-83). Patients with pathological hypertrophy and heart failure have higher levels of pro-inflammatory cytokines IL-6, IL-1, and tumour necrosis factor (TNF) in their blood (84, 85). The activation of JNK pathway triggers IL-6 receptor subunit ß (IL-6Rß) which causes pathological hypertrophy in mice (86, 87). The epigenome determines the disease manifestation in individuals with a substantial genetic predisposition to HCM (88). For example, Trimethylation of H3 at K4, K9 or K27 and demethylation of H3 at K9 and K79 are implicated in gene reprogrammed pathological hypertrophy (89). In addition, histone deacetylase 5 (HDAC5) inhibits histone deacetylases 2 (HDAC2). HDAC5 is phosphorylated in response to hypertrophic stress, which activates cardiac tissue. Casein kinase 2a1 (CK2a 1) in nucleus phosphorylates HDAC2, and CBP-associated factor (pCAF) attaches to HDAC2 to cause acetylation. Consequently, HDAC2 activation caused myocardial enlargement. The deacetylases play the important roles in myocardial hypertrophy (90, 91). miRNA levels continuously fluctuate in different stages of HCM. ncRNAs (non coding RNAs) with 22 or less nucleotides comprise miRNA (92). miR-1 and miR-133 are downregulated even before target gene over expression in mice models of HCM (93). A unique miRNA signature, miR-29a, is specifically enhanced in the plasma of patients with obstructive HCM (94). LncRNAs (long non coding RNAs) regulate transcription and post-transcriptional gene expression (95). miR-29a expression in HCM and the levels of lncRNA myocardial infarction associated transcript (MIAT) are inversely correlated. For example, Subjects without fibrosis had higher levels of lncRNA-MIAT and lower levels of miR-29a than those with fibrosis did (96). HCM has been linked to mutations in genes that encode proteins of the cardiomyocyte contractile apparatus, including myosin-binding protein C and beta-myosin heavy chain. Sarcomere gene mutations can affect non-cardiac cells, such as fibroblasts, and stimulate other signalling pathways through transcriptional activation (97). Oxidative stress is one of the foremost molecular mechanisms and the main participants in the development of heart hypertrophy (98). Since cardiac hypertrophy occurs through intricate mechanisms it poses a great challenge in the field of cardiac research to come up with a concrete therapy to these disorders even at present time.

3.1. Contributions of genetic mutations on CH.

HCM is an autosomal dominant and age-relateddisorder. Single mutation in one of the sarcomeric protein genes, for example at thick- or thin-filament genes and *hcm* (99). Approximately 1500 different mutations have been identified in the genes encoding the eight sarcomere proteins beta-myosin heavy chain (*MYH7*), cardiac myosin-binding protein C (*MYPBC3*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), cardiac actin (*ACTC*), alpha-tropomyosin (*TPM1*), essential myosin light chain (*MYL3*), and (*MYL2*) (100, 101). About 50% of HCM cases are caused by mutations in *MYH7* and *MYPBC3*, but fewer than 20% of HCM cases are caused by mutations in *TNNT2*, *TNNI3*, *ACTC*, *TPM1*, *MYL3*, and *MYL2* (102). Mutations at the genes encoding titin (*TTN*), muscle LIM protein (*CSRP*), telethonin *(TCAP*), and myozenin 2 (*MYOZ2*) have also been found in HCM patients (103). *MYH7, MYBPC3, TNNT2, TNNI3,* and *TPM1* are highly restricted and are not very tolerant to missense and loss-of-function (LoF) genetic variations, according to the ExAcdatabase. Since no *LoF* variant was found in the *ACTC1* gene in over 60,000 unrelated people, *ACTC1* is extremely intolerant to missense and *LoF* mutations. *ACTC1* missense and *LoF* mutations commonly result in HCM (or dilated cardiomyopathy) (104). Patients with sporadic HCM and

small families with HCM have a high prevalence of low- to moderate-penetrance genetic variations (105). The *pArg502Trp* mutation in *MYBPC3*, occurring between 1.5 and 3% of HCM patients, is a notable exception (106-108). Except for the mutations in *MYBPC3*, which have a propensity for insertion/deletion and premature truncation alterations because of a frame shift, the majority of the causative mutations in HCM are missense mutations (55, 109, 110). HCM generally occurs in sporadic cases or in small families, which is crucial to the challenge in discovering the remaining responsible genes, commonly referred to as the missing causal genes (103). Large families of autosomal dominant single gene related HCM may be caused by genetic variations with largescale. The co-segregation and linkage analysis have been used to map and identify these mutations. Examples include genetic variations in the *MYH7* and *MYBPC3*. Certain genetic variants induced by genetic and non-genetic factors possess intermediary to large effect sizes and incomplete penetrance. About 5% of HCM patients have digenic (two) or oligogenic (more) casual mutations in the same or different genes. In individuals with these mutations, ventricular hypertrophy appears to be more severe (111). Sequence investigations of titin, a massive Z-disc molecule that extends from the Z-disk to the M-line and covers half of the sarcomere, are restricted to a fraction of its 363 exons and are less studied compared to other mutational screens of other Z-disc proteins. Protein-protein interactions can be remodelled. For instance, modified titin residues of HCM patient's exhibit higher actinin or cardiac ankyrin repeat protein binding affinity (112-114). The cardiomyopathies in patients with incomprehensible LVH and clinical signs unusually are comparable to those typically seen with HCM. But they have different molecular mechanism from HCM. Similar to HCM, LVH is inherited as a dominant trait and is caused by mutations in the gamma subunit of AMP-dependent protein kinase (*PRKAG2*); nevertheless, cardiac histology reveals a notable aggregation of glycogen inside myocytes and the absence of myocyte order. In boys and young male adolescents, mutations in the X-linked lysosome-associated membrane protein 2 (*LAMP2*) gene result in significant ventricular arrhythmias, large LVH, and a swift advancement to cardiac failure. The histopathology of *LAMP 2* mutations exhibit a build-up of autophagic vacuoles with degenerated cellular products (115). A patient suffering from Fabry disease which is brought on by mutations in the alpha-galactosidase gene (*GAA*), located on chromosome X, typically show systemic CH in which myocardial illness overshadows the other subclinical disorders including renal, cutaneous, and neurological symptoms (55). More than 90% of HCM patients exhibit the phenotype by the age of 20 and also exhibit sudden mortality due to the *Arg403Gln* mutation in the heavy chain of cardiac myosin, indicating that the mutation has a high penetrance. By the age of 15 weeks, *Arg403Gln* mutation mice show the characteristic histological abnormalities of HCM such as hypertrophic disorganized myocyte and fibrosis, and by the age of 30 weeks, left ventricular hypertrophy is apparent by echocardiography test (116). The mechanics of cardiac muscle-derived *Arg403Gln* myosin have been studied, and the results showed higher actin-activated ATPase activity, increased force, and sliding of actin filament was also found to be expedited (117). Deregulated secretion of Ca^{2+} from the sarcoplasmic reticulum, and being captured in the mutated sarcomere, is a significant preliminary molecular episode in HCM as implicated by myofibrillar protein extract, immunohistochemistry, and ryanodine receptor phosphorylation found in the *Arg403Gln* mouse model of HCM (55). Mutations in *MYBPC3* and *MYH7* result in aberrant actin-myosin interactions, which reduce sarcomeric forces. Therefore, hypertrophic remodelling is a compensatory response to decreased heart performance. Additionally, mutations may alter the calcium sensitivity of the troponin complex, resulting in a power stroke (118). *MYBPC3* mutation not only causes premature termination of transcription but also destruction of sarcomere proteins via the decay-inducing complex, resulting in lower protein levels by gain of function of non-sense codons (119, 120). *MYBPC3's* exonic CpG methylation level is higher and can result in methylated CpGs

deamination，thus，causes familial HCM. The carcinogens like benzo (a) pyrenediol and acrolein also can bind to methylated CpG sites resulting in a common HCM mutation due to G-to-T transversion. The genetic instability caused by the methylation of the cardiac troponin T CpG islands further leads to the deamination of this area, a mutation that subsequently predispose to HCM (121, 122). Thus, the mutations of cardiac genes are intricately linked to various cell signalling pathways involved in several pathogenesis of cardiac hypertrophy and various genetic aberrations lead to distinct genotypic and phenotypic heart hypertrophy. Identification of HCM at the molecular level makes the gene specific therapeutic intervention possible and can more effectively treat CH.

3.2. Oxidative stressas a key player in CH.

A major cause of heart hypertrophy is oxidative stress (123). This disorder has been associated with ROS and reactive nitrogen species (RNS) including peroxynitrite (ONOO–), hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH^{\cdot-}$), and superoxide anion ($O_2^{\cdot-}$). In addition to the ER, peroxisomes and NADH oxidases, mitochondria are the main source of ROS production (124-127). H_2O_2 and O_2^- are mainly produced at the NADH site of complex I and Q cycle of complex III during oxidative phosphorylation in mitochondria (128). Mn-SOD in cardiac mitochondria takes major responsibility to detoxify $O_2^{\cdot-}$. The mitochondrial Mn-SOD-deficient mice have the high chance to develop cardiomyopathy (129). Enhanced ROS production can activate mitochondrial permeability transition pore (MPTP) and lead to mitochondrial dysfunction and cell death (130). As mentioned above, complex, I and complex III of the mitochondria asthe major ROSsource in the cardiac tissue (131-133). The increased activity of complex I in HCM patients has been linked to increased ROS production, elevated levels of ATP and antioxidant enzymes as the compensating mechanism (134). CH has been linked to anomalies in mitochondrial ion equilibrium. Overexpression of transient receptor potential channel canonical 3 (TRPC3) in cardiac mitochondria occurs in the case of excessive salt consumption, which in turn elevates calcium absorption and ROS generation. Reduced ATP synthesis with lowering complex I and II activityoccur in the pathological heart hypertrophy (135). Endonuclease G (ENDOG), which is a mitochondrial nuclease, regulates the Akt/GSK3ß and class-II HDAC signalling cascades, promotes ROS production and cell enlargement and it is a determinant of CH (136). Ca^{2+} reabsorption by the sarcoplasmic reticulum is altered due to dysfunction in sarcoplasmic reticulum ATPase 2a (SERCA2a) activity, resulting in slowed kinetic Ca^{2+} decay in the sarcoplasm and impaired relaxation of the cardiac fibre during diastole. The sarcolemma Na^+/Ca^{2+} exchanger is up-regulated to compensate for this deficiency, thereby increasing the cytosolic Na^+ concentration in the sarcoplasm. The dysfunction of SERCA2a activity deceleratesthe kinetic Ca^{2+}dynamics in the sarcoplasmic reticulum, and hence impedes cardiac fibre relaxation in the diastolic phase, thereby increasing the sarcolemma Na^+/Ca^{2+} exchanger not only to compensate for the insufficiency but also to increase sarcoplasmic Na^+ concentration. Variation in the generation of ROS and energy in the mitochondria occurs because of the change in the equilibrium of Na^+ concentration via Na^+/Ca^{2+}, leading to an energetic deficit and NADPH-induced oxidative stress. Thus, oxidative stress generated by the mitochondria in cardiac tissue has been linked to the pathophysiology of RVH and HF (137-139). In *TIMP50* KO mice, the ASK1/Jnk/p38 MAPK axis was elevated with the reduced activities of SOD, catalase, and complexes I, II, and IV of the electron transport chain. These alterations lead to oxidative stress and CHwith increased cardiomyocytes size and fibrosis in the TIM50 deficient mice (140). The NADPH oxidase (Nox) also catalyses the formation of O_2^- by reducing oxygen in the cardiovascular cells (141, 142). Several factors including cyclic stretch, AngII, α-adrenergic agonists, endothelin-1, and TNF-α, can greatly increase NADPH oxidase activity and intracellular ROS.

The increased ROS suppress endothelium nitric oxide production leading to LV diastolic dysfunction (143). Therefore, *Nox2*$^{-/-}$ mice were safeguarded from pressure overload cardiac dysfunction (144). Increased activity of NOX2 down-regulates PPARα-target genes including medium-chain acyl-CoA dehydrogenase and carnitine palmitoyl transferase I, resulting in decreased mitochondrial membrane potential, elevated levels of ROS and calcium, as well as reduced mitochondrial activity and ATP synthesis, thereby aggravating cardiac remodelling and systolic function (145, 146). Increased NOX4 level causes nuclear export of HDAC 4 (Histone deacetylase 4) whichis a critical inhibitor of CH; thus, promote hypertrophy while angiotensin II stimulation increases NOX4 level (17). Transgenic *NOX5* overexpressed mice had significantly increased hypertrophy, fibrosis and contractile dysfunction, indicating the critical role of NOX5 on hypertrophy (147). The over expression of human LOX (copper-dependent amine oxidase that regulates matrix remodelling) in mice not only increased hearthypertrophy but also cardiac malfunction due to increased fibrosis caused by excessive inflammation and formation of ROS. Mechanistically, inflammation and ROS accelerated the activity of p38 MAPK while inhibited AMP-activated protein kinase (AMPK) (148). On other hand, ROS is the regulator of autophagy, and its deregulation cause CH. However, it remains debatable whether defective or overactive autophagy is the primary mechanism of CH progression (149, 150). For example, retardation of autophagy occurs via oxidative stress mediated p38 MAPK and JNK signalling, and blocking these pathways restores autophagy and averts CH (151). By specifically targeting the ubiquitination and degradation of the important autophagy regulator LC3, ectopic expression of CDC20 exacerbates the hypertrophic response and promotes CH (152). Therefore, autophagy appears to be both upstream and downstream of oxidative stress-mediated CH, which is plausible given that its dysregulation may result in the build-up of faulty cellular components that may cause a stressful cellular environment (150). A higher level of the ubiquitin E3 ligase TRAF6 was in the presence of CH of both human and mouse. ROS produced during the progression of hypertrophy promoted its auto-ubiquitination and the formation of TRAF6-TAK1 association that was essential for cardiac remodelling (153). It is reported that loss of function of RNF5 (Ring-finger protein) which is an E3 ubiquitin ligase aggravates CH by stimulating NF-kβ signalling and reactivation of fatal gene expression. Furthermore, RNF5 interacts with another protein known as stimulator of interferon genes (STING), which is involved in inflammation and immune responses by stimulating secretion as well as degradation of type 1 interferon via K48-linked polyubiquitination, thereby, reducing CH (154). Nuclear export of FOXO3a (Fork head box O3) led to the elevation of REG-γ (a member of 11 S proteasome and cause degradation of proteins via 20S proteasome) which in turn reduces Mn-SOD and increases ROS leading to CH (155, 156). It has been discovered that the persistent overexpression of the mouse Hsp22 small heat shock protein increases ROS generation, and CH and senescence, ultimately the reduced lifespan. Inflammation, which may cause right ventricular dysfunction and RVH, is another significant component of CH (157). Inflammation increases expression of cytokines, chemokines, and transcription factors such as IL-1, IL-6, tumour necrosis factor (TNF-alpha), MCP-1, and NF-kB (158). The oxidative stress, inflammation, and cardiovascular disease are associated to the Toll-like receptor 4 (TLR4) signalling; TLR4 signalling can cause ROS generation, inflammation, and CD68+ macrophage infiltration, which led to a hypertrophic heart response, fibrosis, and cardiac dysfunction. TLR4 antagonist can minimise these events (159, 160). Nrf2 deficiency promotes oxidative stress, fibrosis, and cardiac malfunction leading to CH via IL-6/STAT3 pathway (161).Inflammatory mediators known as adipokines have been linked to CHsince the cardiomyocyte-specific adipokine, CTRP3 was elevated in the patients and cardiac hypertrophic mouse model. The rise of CTRP3 was caused by ROS and CTRP3 overexpression worsened CH via PKA /TAK1/JNK cascade while CTRP3 deficiency reduced the hypertrophic

phenotype (162). Hence, it can be stated that oxidative stress mediated CH occurs through different biomolecular pathways.

4. CONVENTIONAL THERAPEUTIC APPROACHES AND MEDICATIONS FOR MANAGEMENT OF CH

Although, hypertrophic cardiomyopathy (HCM) is the most prevalent inherited heart condition, it lacks specific therapy. These unspecific medicines including disopyramide, non-dihydropyridine calcium channel blockers, or ß-adrenergic receptor blockers, are used to attune diverse downstream molecules that are altered in hypertrophic hearts. These are implemented in the treatment of HCM according to guidelines and are typically given to individuals who have developed symptomatic outflow obstruction (163). The most commonly prescribed medication for HCM is β-blockers, which have preference for non-vasodilating medications. These β-blockers including atenolol, nadolol, bisoprolol, and metoprolol are the first-line treatment for LVOT (left ventricular outflow tract) (164). By inhibiting L-type calcium channels and hence lowering excess calcium, non-dihydropyridine CCBs (calcium channel blockers) are also used in CH (165). Mavacamten is a pioneering, highly selective calcium channel blocker similar to diltiazem and verapamil. It helps in the retrieval of calcium cycling myosin inhibitor that drastically decreases ATPase activity in mouse cardiac myofibrils and isolated bovine myosin S1 in a dose-dependent manner (IC50 = 0.3 M), demonstrating its ability to directly interact with myosin (15). In a mouse HCM model, mavacamten treatment reduced hypercontractility, ventricular hypertrophy, fibrotic response, and cardiomyocyte disorder (15). Teneligliptin, a dipeptidyl peptidase inhibitor abated the CH by upregulation of NOX4 mRNA, 4-hydoxynonenal and HDAC4 export via elevating GLP-1 level (17). The beneficial effects of metformin on CH are due toimprove fatty acid oxidation, decrease oxidative stress, and normalize the AMPK and mTOR signalling pathways; thus, its treatment significantly lowers LV mass index, LV mass, systolic blood pressure, body weight, and oxidative stress and LVH in patients with coronary artery disease (30). Allyl methyl sulphide, a novel sulphur metabolite of garlic, reduces cardiac hypertrophy and fibrosis by lowering oxidative stress, apoptosis, and stabilizing extracellular matrix components via Na+ /K+-ATPase activation (166). Mdivi-1, aDrp1 inhibitor, can reduce LVH, fibrosis, and ROS generation viasuppressing the expression of calcineurin and CaMKII, therefore, reducing hypertensive CH (167). Elevated ROS, NOX4 expression, endoplasmic reticulum stress markers (BiP and CHOP), and autophagy markers (LC-3 II/I and beclin-1) promote cellular hypertrophy through an endoplasmic reticulum stress-autophagy route (168). The epigenetic regulator, BRD4, is upregulated in cardiomyocytes with angiotensin II treatment, leading to enhanced ROS production, thus, BRD4 suppression reduces cell growth, blocks TGFß1/SMAD signalling pathways, and reduces inflammation and oxidative stress by inhibiting NF-κBbut enhancing Nrf2/HO-1 signallings (169). Resveratrol, a polyphenol, retains systolic function and normal LV volume in hypertrophic heart via improving mitochondrial respiration as well as lowering ROS levels and myocardial oxidative stress (12). Emerging evidence also indicates that lncRNAs participate in mitochondrial metabolism (lnc-Plscr4), intracellular calcium management (lnc-TINCR) and sarcomere function (Lnc-Mhrt). Thus, lncRNAs may exhibit therapeutical use to stop or reverse heart hypertrophy (170). Notwithstanding, the increasing circulating miR-1 and miR-133 levels in asymptomatic patients might be the biomarkers in the early identification of HCM in the future (171). The transfer of selective high-density lipoprotein-raising human apolipoprotein A-I gene can reduce pathological cardiac remodelling, nitro-oxidative stress, and apoptosis while increasing myocardial capillary density and enhancing cardiac function, suggesting that gene therapy may also be a good strategy to prevent the development of CH caused by pressure overload (172).

For example, that the *MYBPC3* mutant hotspots, such as exon 25, which contains 11% hotspots, is AAV-mediated exon skipping with anti-sense nucleotides or CRISPR/Cas9 has been used in correct cardiac hypertrophy (173,174). The phase 2 trial of SERCA2a gene therapy has shown that AAV1-mediated gene transfer is safe and feasible in humans, but has not demonstrated beneficial outcomes in this cohort, despite the fact that AAV9 has proven to be the most effective for cardiac gene transfer after various trials in mouse and large animal models (175-177).

5. CARDIOPROTECTIVE EFFICACY OF MELATONIN IN PATHOLOGICAL CONDITIONS OF HEART

Melatonin (N-acetyl-5-methoxytryptamine) is a tryptophan derivative. Although it is mostly generated in the pineal gland but it is also secreted by other peripheral organs including heart. After its synthesis, the pineal melatonin is instantly released into the circulatory system andother body fluids, including the cerebrospinal fluid. It has a variety of physiological effects such as modulating sleep awake patterns, scavenging free radicals, enhancing immunity, and preventing of biomolecules from oxidation (178, 179). Melatonin not only has anti-cancer, anti-microbial, anti-inflammatory properties but also have beneficial effects on periodontal, cerebrovascular, neurodegenerative and cardiovascular diseases (180). Angiotensin II, epinephrine, and doxorubicin can injury heart, whereas melatonin has the capacity to reduce their side effects. Additionally, it guards against aortic constriction and sepsis-induced myocardial damage as well as hypertrophy (181). Melatonin protects against various heart injuries including arrhythmia by regulating oxidative stress or through activation of G-protein coupled membrane receptors (GPRCs), tumour necrosis factor receptors (TNFR), toll-like receptors (TLRs), and nuclear retinoic acid receptor-related orphan receptors (RORs) (182-187). The anti-adrenergic effect of melatonin is mediated by a number of signalling molecules, including adenylate cyclase, phospholipase C, protein kinase C (PKC), guanylate cyclase, potassium channels, calcium channels, and phospholipase A2. (188-190). Melatonin receptors (MTRs) are promising targets for the treatment of cardiovascular diseases (CVDs) since they are expressed in the ventricles, aorta, coronary arteries, and endothelial cells of the cardiovascular system and exhibit a crucial function in attenuating heart failure and cardiomyopathy due to myocardial infarction (191). The MT1 and MT2 receptors are present in human coronary arteries (192, 193). Melatonin binding to MT2 receptors of endothelial cells promotes nitric oxide production. The nitric oxide stimulates theactivity of soluble guanylate cyclase in smooth muscle cells, leading to an increase in cGMP levels and vasodilation (194). The MT3 receptor is a QR2 (quinone oxidoreductase 2) cytosolic enzymeand exerts its antioxidant activity via a receptor-independent mechanism (195). SOD, glutathione peroxidase (GPx), and nuclear factor-erythroid-2 (NF-E2)-related factor 2 (Nrf2) are antioxidant enzymes. However, they also can stimulate the production of melatonin to further strengthen the antioxidant activities (196). Luzindole, a non-specific melatonin receptor antagonist, reverses the cardioprotective effects of melatonin, strongly suggesting the importance of MT1 and MT2 receptors in this process (197, 198). Suppression of MT3 by prazosin also partially reduces protective effects of melatoninon infarcts (199).The two members of the sirtuin (silent mating type information regulation 2 homolog) family, Sirtuin 1 (SIRT1) and Sirtuin 3 (SIRT3), are highly conserved NAD^+-dependent deacetylases that activate catabolic whileinhibit anabolic processes, thereby regulating energy equilibrium in cells (200). Melatonin can trigger SIRT1 and SIRT3 signallingthat are dramaticallyreducedunder heart ischemia/reperfusion (I/R) conditions, and hence prevent I/R damage (201, 202). Melatonin therapy also increased the expression of the anti-apoptotic protein Bcl-2 in adipose-derived mesenchymal stem cells in a mouse model of heart infarction and decreased the expression of acetylated pro-apoptotic

proteins such as FoxO1, p53, NF-κB, and Bax (185). Melatonin exhibits its antioxidant property not only in cell membrane but also in cytosol due to its hydrophilicand lipophilic nature (203). The oligopeptide transporters PEPT1/2 (SLC15A1/2) and GLUT transporter/solute carrier family 2A (GLUT/SLC2A10) influence the transportation of melatonin into mitochondria (204, 205). The high level of mitochondrial melatonin maintains the energy metabolism and structure, stabilization of the mitochondrial membrane potential in cardiomyocytes (206). Doxorubicin (Dox) is a frequently prescribed anthracycline-class anticancer medication that has been widely used for the treatment of both hematologic and solid cancers (207); however, it also can damage LV, if melatonin was co treatment with Dox this combination decreased ROS production and prevented apoptosis by increasing MMP levels in cardiomyocytes (208). The Hippo signalling pathway, which has an impact on cardiac functions, includes a downstream component, Yes-associated protein (YAP) (209), which was found to be upregulated by melatonin in cardiac muscle cells in which it was knocked down by siRNA and thus, reduced the cardiotoxicity caused by Dox (208). The septic cardiomyopathy is a serious medical issue with poor prognosissince the mortality is approaching 30% among elderly and has few effective medications available (210). Melatonin treatment can reduce septic cardiomyopathy by targeting ER-mitochondrial interactions and the ERK-BAP31 axis (211). Melatonin may prevent atherosclerosis caused by cigarette smoke via the Nrf2/ROS/NLRP3 axis (212). Melatonin therapy significantly decreased infarction, increased cardiac function, blood flow, and normalized microcirculation perfusion. The molecular mechanisms are that melatonin inhibits the activation of PINK1/Parkin-mediated mitophagy by blocking MPTP opening, tightening the coupling of HK2 to the mitochondria, and reducing VDAC1 oligomerization (213). Melatonin infusion enhanced left ventricular ejection fraction and left ventricle fractional shortening, while decreasing left ventricular end-diastolic volume, norepinephrine levels, NOX2, NOX4, IL-1 beta, the amount of ROS, and NF-κB activity. It also increased IL-10 and SOD levels. Melatonin infusion reduces sympathetic nerveactivity and myocardial IRI (212). Melatonin blocked H_2O_2 dependent down-regulation of lncRNA H19 and miR-675 in progenitor cells. Therefore, melatonin therapy inhibited the H19/miR-675/USP10 pathway from causing premature senescence of progenitor cells (214). Melatonin has been shown to inhibit calmodulin, which interacts with ACE2 by decreasing ectodomain shedding, a critical infectious mechanism in SARS-COVID19 (32). Melatonin inhibits AMPK2-dependent mitochondrial damage to provide protection against doxorubicin-induced cardio toxicity (215). As melatonin is affordable and safe molecule more thorough clinical trials should be conducted to determine its effectiveness in treating a range of cardiovascular diseases (187). Melatonin has little serious acute and chronic side effects compared to some other therapeutic drugs, such as benzodiazepines, opioids, non-steroidal anti-inflammatory drugs, and glucocorticoids. Besides, melatonin does not cause any addiction (216). Thus, melatonin is considered as a drug of choice for heart disease.

6. POTENTIAL AMELIORATIVE PROFICIENCY OF MELATONIN AGAINST CH

CH, a compensatory reaction to cardiomyopathy, if not controlled, it eventuallywill lead to heart failure (217). The *in vitro* (neonatal rat cardiomyocyte culture) and *in vivo* (C57BL/6 mice) studies showed that melatonin treatment amends CH induced by transverse aortic constriction or by Angiotensin II administration, respectively, by stimulating PGC-1 β (28). The two isoforms of myosin heavy chain (MHC), α-MHC and β- MHC are differentially expressed in the foetal and adult stages of hypothyroidism, pathological hypertrophy, and cardiac failure conditions. In adult individuals, the normal expression pattern of α-MHC and β-MHC is reversed in the CH, resulting in the increased β-MHC and downregulation of α-

MHC (218). Melatonin increased the expression of α-MHC while decreasing the expression of β-MHC at both mRNA and protein levels in CH (28). Comparison to vitamin E melatonin is more effective in repressing the elevation in lipid peroxidation and hydroxyl radical formation and boosting Cu-ZSOD in CH rat model induced by 3,5,3'-tri-iodo-L-thyronine, T3 (29). Additionally, melatonin treatment completely reversed the negative effects of T3-induced ventricular hypertrophy (29). Yeung *et al.* (219) observed that heart weight/body weight ratio, left ventricular weight/right ventricular weight and septum ratio were significantly reduced following melatonin treatment in chronic hypoxia-induced rat CH. Melatonin treatment reduced LDH levels and chronic Ca^{2+} overload and hence, provided cardio-protection against remodelling and CH caused by chronic partial oxygen deprivation in rats. Ca^{2+} is one of the factors which controls the expression and activity of PGC1α at the transcriptional level. Ca^{2+} activates the Can A (calcineurin A) which in turn interacts with myocyte enhancer factors 2C and 2D (MEF2C and MEF2D) respectively causing dimerization and translocation to the nucleus. MEF2C and MEF2D bind with binding sites on the promoter region of PGC-1 α and lead to the synthesis of PGC1α. PGC1α binds with its cofactors such as PPAR alpha (Peroxisome Proliferator-Activated receptors) or ERR α (Estrogen Related Receptor alpha) and activates them in the cardiac tissue thereby, upregulating enzymes of Beta oxidation of fatty acids (FAO) and oxidative phosphorylation enzymes (OXPHOS) in mitochondria. In pathological CH and heart failure, the expression of PGC-1α as well as its downstream elements of the PPARs and ERRs were all downregulated (220). MICU1 (Mitochondrial Ca^{2+} uniporter 1) is an inner mitochondrial channel protein and regulates the entry of Ca^{2+} into the mitochondria thereby, preventing Ca^{2+} overload in mitochondria and hence, inhibiting ROS generation (221). The MICU1Ag-II-knock down induced CH both *in vivo* and *in vitro* conditions was aggravated due to a significant increase in ROS levels, altered mitochondrial morphology, and suppressed mitochondrial function. Melatonin reduced all the aforementioned abnormality in WT but not in NMVMs or MICU-knockdown animals. Melatonin binds with PGC1α and stimulates the expression of M1CU1 which reduces ROS generation and decreases the expression of cardiac damage markers such as ANP (Atrial Natriuretic Peptide), BNP (Brain Natriuretic Peptide) and B-MHC (β-Myosin Heavy Chain) and hence ameliorate Ag-II induced ventricular hypertrophy (222). The positive effects of melatonin may bedue to the trans- activation of MnSOD caused by ROR-α binding to its response element in its promoter region. Long-term use of melatonin also reduces CH, promotes cardiac contractile function, and survival rates by turning on PGC1ß and stifling oxidative stress in the presence of pressure (28). Monocrotaline injection to Long Evans rats can induces pulmonary hypertension, RV hypertrophy by the increased interstitial fibrosis, and plasma oxidative stress, while co-treated with melatonin prevents this pulmonary hypertension (223). Autophagy is a cellular process in degrading the damaged organelles and misfolded proteins and retrieving the essential components initiated by Atgs (autophagy related genes) via lysosomal-dependent degradation pathway (224). Although autophagy is a normal cellular process but excessive autophagy leads to CH.In physiological hypertrophy autophagy is precisely regulated with matching the enhanced energy efficiency whereas in pathological hypertrophy, autophagy is over activated (224). It has been found that transverse aortic constriction in mice not only causes the over expression of Atg5 and Atg16 mRNAs but also upregulates the LC-3 II and beclin-1 at the protein level thus aggravating CH through PKC and ERK1/2 signalling cascade (225).In the transfection with adenovirus carrying cardiac-specific Atg5 animal model (under the cTNT promoter Ad-cTNT-Atg5) melatonin not only mitigated CH instigated by TAC and repaired cardiac function. These were indicated by a decreased HW/BW ratio, cell cross-sectional area, fibrosis, the transcription rate of ANP, BNP, and ß-MHC, and improved LVEF and LVFS but also prevented apoptosis and balanced autophagy; however, LY294002 (antagonist of Akt) upregulated Atg5 in cardiac tissue neutralized these

effects. Melatonin has restrained Atg5-dependent autophagy by reducing LC3II/LC3I ratio, the Atg5 protein level and LC3B puncta and increasing p62 (also known as SQSTM1/Sequestosome-1 protein, ubiquitin binding protein) and promoting the Akt/mTOR pathway and thus, reduced pressure overload-induced CH (226). Melatonin inhibits apoptosis and rescues contractile cardiomyocytes in the left ventricular myocardium from hypertrophy in ovariectomized rats with HF (227). Melatonin binds to the retinoid-related orphan receptor in the heart, inhibiting the downstream target, mammalian STE20-like kinase 1, which has anti-apoptotic and pro-autophagic effects, improving cardiac tolerance in high-glucose conditions, and thus attenuating cardiac fibrosis and hypertrophy in diabetic cardiomyopathy (228). Dominguez-Rodriguez *et al.* (30) reported that reduced melatonin levels in serum during daytime were found in 16 patients with hypertensive cardiomyopathy who developed heart failure. Thus, the declining levels of melatonin have been found to be a potent predictor of heart failure in hypertensive cardiomyopathy patients. Tissue-specific delivery of melatonin (20 mg melatonin/2 ml dichloromethane CH2Cl2) using a nanoplatform of CHP (Cardiac Homing Peptide, containing CSTSMLKAC) and SPIONs (Supramagnetic Iron Oxide Nanoparticles), known as CHP-mel@SPIONs, to hypertrophic heart tissue under an external magnetic field could ameliorate pressure overload-induced CH caused by TAC, as it decreased HW/BW, LW/BW, LVPWs, LVPWd, IVSd, and IVSs compared with the untreated TAC rats. Additionally, the mRNA levels of different cardiac fibrosis markers, such as collagen 1, collagen 3, TGF-β1 and Smad 3, β-MHC, and ANP mRNA levels were significantly lower in the CHP-mel@SPIO-treated groups than in the TAC groups (229). Melatonin inhibited the expression of CH markers such as ANP, BNP, -MHC, -MHC, SERCA-2a, and myocardial fibrosis indicators (Collagen I and Collagen III) in PM2.5-exposed mice. Melatonin substantially reduced mitochondrial oxidative damage and modulating SIRT3-mediated SOD_2 deacetylation and hence reversed the CH and fibrosis induced by PM2.5 (230). LPS stimulates the pro-inflammatory cytokine TNF-α secretion and elevated Ca^{2+} levels by increasing CaMKII and CaN which in turn brought on hypertrophic heart whereas melatonin downregulated the levels of TNF-α and increasing CaMKII and CaN and reverted Ca^{2+}equilibrium thus recovered the cardiac tissue from hypertrophy (231). Melatonin treatment in ROR-α deficient C57BL/6J neonatal mouse cardiomyocytes promoted the binding of ROR-α to its response element situated in RORE site in the 5′ - upstream regions (−1065 bp to −1059 bp) of the promoter region of MnSOD and therefore, increased the expression of MnSOD and attenuating oxidative stress in TAC orAgII mediated pathological CH but did not have effect in swimming mediated physiological hypertrophy (232). Melatonin consumption decreases CH, inflammatory cell infiltration, and NLRP3 levels in leptin-deficient obese mice via triggering the metabolic regulators of SIRT1, Nrf2, and AMPK (233). Thus, the protective role of melatonin against CH is evident from the above-mentioned signalling pathways (Figure 1), however, there still exists a gap in finding the mechanistic role of melatonin against CH which needs further investigation.

7. CONCLUSION AND FUTURE PROSPECTS

Cardiovascular diseases are widely spreading disorders with continuously increased risk of death due to CH and other cardiovascular symptoms. These disorders are not just confined to aged people but also to younger adults and adolescents. Genetic mutations and oxidative stress mediated CH get accentuated due to the changing lifestyles, workload and food habits across the world. In addition, the side effects of long-term applications of therapeutic drugs for treating various genetic and lethal diseases including diabetes, cancer and neurodegenerative disorders also damage cardiovascular system and develop co-morbidities of the CH eventuating into death. On the other hand, melatonin being a multifunctional molecule with almost

negligible adverse effects, has gained the interests of researchers and clinicians to use it as an effective drug against different illnesses including CH.However, dose optimisation and supplementation of melatonin through several routes in humans need further investigation. Although melatonin has been reported to enhance GLUT-4 expression, thepossible role of melatonin in MEF2-driven restoration of GLUT-4 expression in T3-induced CH can be studied further. Moreover, the identification of downstreamsignalling molecules that participates in melatonin-mediated upregulation of PGC1-MICU1signalling needs to be investigated. The detailed molecular mechanism by which melatoninattenuates TNF-α and increases CamKII and CaN to ameliorate LPS-induced CH is not well elucidated. Additionally, a lack of understanding of the modulatory effect of melatonin on non-coding RNAs and their suppressive action on NRLP3 inflammasome activation in CH warrants further studies. Nevertheless, further elucidation of mechanistic cascades and meticulous studies are required to unravel the underlying mechanisms by which melatonin interacts with the other signalling molecules at the posttranscriptional and posttranslational levels so that it can be used as adjunct for treating CH.

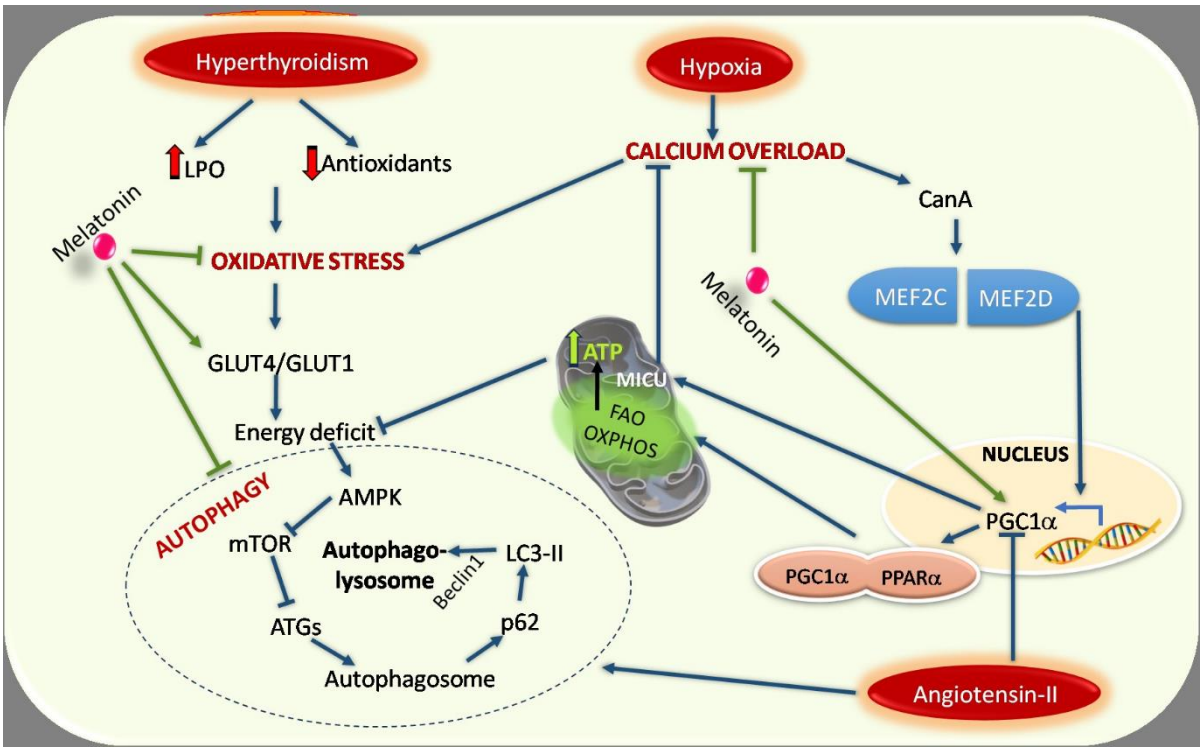

Fig.1. Schematic representation of cardioprotective role of melatonin against CH and its signalling pathways.

LPO: Lipid Peroxidation; GLUT4- Glucose transporter protein type-4;GLUT1- Glucose transporter protein type-1; AMPK- Adenosine monophosphate-activated protein kinase; mTOR-mammalian of Target of Rapamycin; LC3-II- Microtubule-associated protein 1A/1B-light chain 3 phosphatidylethanolamine conjugates; p62- p62/SQSTM1- Sequestosome-1; ATP-Adenosine Tri Phosphate; MICU-Mitochondrial Ca^{2+}uniporter-β-oxidation of fatty acids; OXPHOS-Oxidative Phosphorylation; Can A-Calcineurin A;MEF2C-Myocyte Enhancer Factors 2C; MEF2D-Myocyte Enhancer Factors 2D; PGC-1α-Peroxisome proliferator-activated receptor-gamma coactivator; PARα-Peroxisome proliferator-activated receptor alpha.

ABBREVIATIONS

HCM-Hypertrophic cardiomyopathy
MT-Melatonin
NLRP3-NLR family Pyrin domain containing 3
SOD-Superoxide Oxide Dismutase
GPx- Glutathione peroxidase
ROS- Reactive oxygen species
ERK-Extracellular signal-regulated kinase
ASK1-Apoptosis signal-regulating kinase 1
Jnk-Janus Kinase
Akt-Akt serine/threonine kinase
MAPK-Mitogen-activated protein kinase
BAP3-B cell receptor associated protein 3
STAT 3-Signal transducer and activator of transcription 3
TIMP50-tissue inhibitor of matrix metalloproteinases 50
TRAF6-Tumour necrosis factor receptor (TNFR)-associated factor 6
TAK1-Transforming growth factor β-activated kinase 1
HK2-Hexokinase 2
cGMP- cyclic Guanosine 3',5'-cyclic monophosphate
CAMKII- Calcium–calmodulin (CaM)-dependent protein kinase II
CaN-Calcineurin
CTRP3- C1q/tumour necrosis factor (TNF)–related protein-3
GLP-1-Glucagon like peptide 1
GLUT 4-Glucose transporter protein type-4
MMP-Matrix Metalloprotease
MPTP- Mitochondrial permeability transition pore
MCP-1- Monocyte Chemoattractant Protein 1
VDAC1-Voltage dependent anion channel 1
LPS-Lipopolysaccharide
IL-Interleukin
TNF-α-Tumour Necrosis Factor-α
ATG-Autophagy related gen
LC 3-Microtubule-associated protein 1A/1B-light chain 3
LC 3-I cytosolic form of LC 3
LC 3-II- LC 3-phosphatidylethanolamine conjugate

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AUTHORSHIP

The concept of the review article was developed by Prof. DB, Dr. AC and SS. RK contributed in drafting the manuscript and edited it. SS also prepared the figure and edited the

manuscript. Prof. DB and Dr. AC also revised the manuscript critically and finally approved it.

CONFLICTS OF INTERESTS

The authors declare that they do not have any conflict of interests.

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