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REVIEW ARTICLE

New insights into the role of melatonin in diabetic cardiomyopathy

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Abstract

Diabetic cardiovascular complications and impaired cardiac function are considered to be the main causes of death in diabetic patients worldwide, especially patients with type 2 diabetes mellitus (T2DM). An increasing number of studies have shown that melatonin, as the main product secreted by the pineal gland, plays a vital role in the occurrence and development of diabetes. Melatonin improves myocardial cell metabolism, reduces vascular endothelial cell death, reverses microcirculation disorders, reduces myocardial fibrosis, reduces oxidative and endoplasmic reticulum stress, regulates cell autophagy and apoptosis, and improves mitochondrial function, all of which are the characteristics of diabetic cardiomyopathy (DCM). This review focuses on the role of melatonin in DCM. We also discuss new molecular findings that might facilitate a better understanding of the underlying mechanism. Finally, we propose potential new therapeutic strategies for patients with T2DM.

KEYWORDS
autophagy, diabetic cardiomyopathy, melatonin, mitochondrial function, myocardial fibrosis, myocardial metabolism, oxidative stress

1 | INTRODUCTION

Thirty years ago, the prevalence of diabetic patients was only one-fourth the current prevalence. In fact, the current number of diabetic patients has soared to 1 diabetic patient in every 11 people globally.[1] Moreover, diabetes has become the ninth leading cause of death worldwide. According to statistics from the World Health Organization, as of 2000, the number of diabetes patients worldwide had exceeded 170 million, and it is still increasing at an extremely fast rate. It is predicted that the number of diabetic-related deaths will double between 2000 and 2030.[2] Among diabetic patients, type 2 diabetes mellitus (T2DM) is most common, accounting for approximately 90% of adult patients with diabetes. Unlike type 1 diabetes mellitus (T1DM), which is an autoimmune disease, the

Abbreviations: AGEs, advanced glycation end products; ATF-6, activated transcription factor 6; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; DCM, diabetic cardiomyopathy; DOX, doxorubicin; Drp1, dynamin-related protein 1; EPC, endothelial progenitor cell; ER, endoplasmic reticulum; ET-1, endothelin-1; G6PD, glucose-6-phosphate dehydrogenase; GRP78, glucose-regulated protein 78; GSH, glutathione; GSIS, glucose-stimulated insulin secretion; HO-1, heme oxygenase 1; iNOS, inducible nitric oxide synthase; JAK/STAT, Janus kinase/signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MI/R, myocardial ischemia/reperfusion; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor 3; NR, Nuclear hormone receptor; NR4A1, nuclear receptor subfamily 4, group A, member 1; NRF1, nuclear respiratory factor 1; PKC, protein kinase C; RAGE, receptor for AGE; RORα, related orphan receptor alpha; ROS, reactive oxygen species; SAFE, survivor activating factor enhancement; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; STZ, streptozocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; taVNS, transcutaneous vagus nerve stimulation; TFAM, mitochondrial transcription factor A; TGF-β, transforming growth factor β; TLR4, toll-like receptor 4; TNFα, tumor necrosis factor alpha; UCP, uncoupling protein; UPR, unfolded protein response; WT, wild-type; ZDF, Zucker diabetic fatty.

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pathogenesis underlying T2DM is insulin resistance. Obesity, age, diet, a sedentary lifestyle with little exercise, and environmental factors are all susceptible factors for the onset of T2DM. An elevated blood glucose level and insulin resistance often lead to diabetic complications, including cardiovascular disease, diabetic neuropathy, diabetic retinopathy, and diabetic nephropathy.[3,4]

Diabetic cardiomyopathy (DCM) is a diabetic complication independent of coronary artery disease and hypertension. The basic pathologic changes of DCM include abnormal carbohydrate and fatty acid metabolism, microvascular disease and endothelial dysfunction, myocardial necrosis and fibrosis, excessive cardiomyocyte programmed death, increased oxidative stress, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, insulin resistance, glycotoxicity, and other related pathologic changes in the myocardium.[5-8] These adverse reactions, driven by increased blood glucose, will largely lead to structural remodeling and impaired function of the heart. According to reports, DCM significantly increases the risk of heart failure and can lead to a preserved or reduced ejection fraction.[9] Experiments conducted using a DCM model showed that diastolic dysfunction is more common than systolic dysfunction in T2DM-related cardiomyopathy, whereas the opposite occurs in patients with T1DM.[10] Thus, the different types of diabetes exert different effects on myocardial function.

Melatonin, which is mainly produced in the pineal gland of most mammals, is a hormone that regulates the circadian rhythm. Melatonin can also be synthesized locally in a variety of cells and tissues.[11] Studies have shown that melatonin plays an important role in anti-aging, anti-oxidation, immunomodulation, curing cancer, treatment of cardiovascular disease, and treatment of diabetes and diabetic complications.[12-15] There is also evidence showing the therapeutic effect of melatonin in patients with diabetes-associated cardiac dysfunction. Therefore, in this review we focused on the role of melatonin in the pathogenesis underlying DCM with the aim of collating evidence for this potential medical treatment for DCM (Figure 1).

2 | MELATONIN AND RELATIVE RECEPTORS

2.1 | Melatonin and the nuclear melatonin receptor, retinoic acid–related orphan receptor alpha

Nuclear hormone receptors (NRs) comprise a superfamily of transcription factors. NRs have diverse physiologic functions, including regulation of metabolism and stress responses.[16-18] In addition, NRs are molecular targets for drug therapy, highlighting the potential role in therapeutic intervention. Related orphan receptor alpha (RORα), also known as the nuclear melatonin receptor, is a unique receptor in cardiomyocytes.[19] RORα is involved in the development and regulation of DCM. Zhao et al.[20] reported that RORα deficiency contributes to myocardial apoptosis, autophagy dysfunction, and oxidative stress by disrupting antioxidant gene expression. They observed that in a T1DM mouse model induced by streptozocin (STZ) injection, mice with higher RORα expression due to genetic modification or taking melatonin had improved cardiac function and structure compared with the control group after 8 weeks. This effect, induced by activation of RORα, was attenuated by SR3335, an RORα inhibitor.[20] RORα deficiency can also significantly worsen pathologic myocardial hypertrophy,[21] which is related to a decrease in transactivation of the manganese-dependent superoxide dismutase (SOD) induced by RORα. Defects in intracellular protective signaling is also a feature of heart dysfunction and myocardial damage caused by diabetes. Ischemic preconditioning or ischemic postconditioning are weakened in patients with diabetes.[22,23] He et al.[24] concluded that melatonin prevents myocardial ischemia/reperfusion (MI/R) injury by activation of RORα. These experimental results suggest that

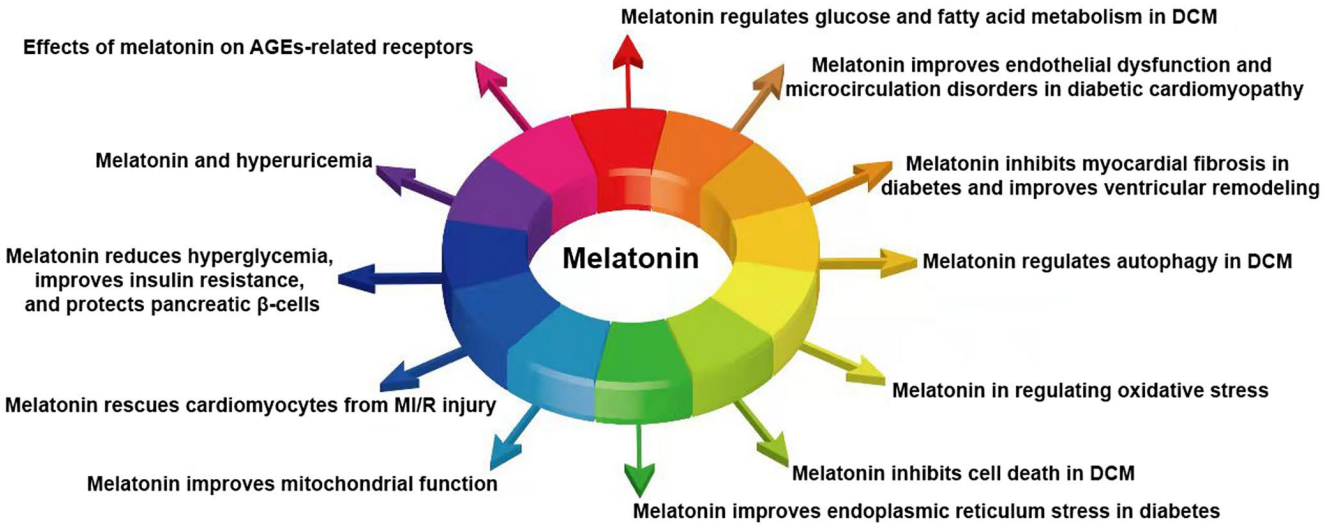

FIGURE 1 The role of melatonin in the treatment of diabetic cardiomyopathy. AGE, advanced glycation end products; DCM, diabetic cardiomyopathy

regulating the nuclear melatonin receptor, RORα, may delay the development of DCM.

Diabetes can also significantly increase the risk of cardiovascular events.[25] And many evidences indicates that RORα plays an important role in preventing cardiovascular disease in diabetic patients. A number of reports have shown that RORα is distributed on blood vessels, and melatonin can act on these receptors. Specifically, melatonin activates RORα in endothelial cells to produce a vascular protective effect, including a reduction in reactive oxygen species (ROS) production and an increase in NO production.[26] Melatonin can also effectively inhibits the differentiation of macrophages in the atherosclerotic plaque to the pro-inflammatory M1 phenotype by the RORα-dependent AMP kinase (AMPK) α-STATs pathway to improve inflammation in the plaque, stabilize rupture-prone vulnerable plaques, and reduce the risk of cardiovascular events.[27]

2.2 | Melatonin and membranous melatonin receptors

A number of studies have demonstrated that melatonin receptors (MTs) have potential to protect against DCM. There are two melatonin membrane receptors, MT1 and MT2, which are expressed on cardiomyocytes.[19] It has been reported that MT2, but not MT1, is upregulated after melatonin administration and ameliorates myocardial injury and improves cardiac function after MI/R.[28,29] This finding may be because upregulation of MT2 activates the cGMP-PKG signaling pathway, affects the subordinate signaling pathways, inhibits myocardial oxidative stress and nitrification stress induced by MI/R, reduces ER stress and mitochondrial damage, and inhibits cardiomyocyte apoptosis. In another set of experiments, Li et al.[30] reported that melatonin activates the mitogen-activated protein kinase (MAPK)-ERK signaling pathway activated by MTs, then maintains the mitochondrial membrane potential in a model of oxidative stress induced by hydrogen peroxide. This finding indicates that activation of MTs stabilizes mitochondrial function in cardiomyocytes treated with oxidative stress.

There are also MTs expressed in the cardiovascular system, including MT1 and MT2,[31,32] and melatonin has an effect on these MTs. Experiments show that the mRNA for both the MT1 and MT2 was localized in the smooth muscle layer. Melatonin activates MT1 on vascular smooth muscle, which enhances vasoconstriction. Alternatively, melatonin activates the MT2 on vascular smooth muscle, which leads to vasodilation.[33,34]

2.3 | Melatonin acts on the cardiovascular system through nonreceptors or other receptors

Melatonin also affects the cardiovascular system through other receptor or nonreceptor pathways. Melatonin has a role on other receptors in the myocardium, such as activating toll-like receptor 4 (TLR4) and further initiating the survivor activating factor enhancement (SAFE) pathway which is mediated by tumor necrosis factor alpha (TNFα) and signal transducer and activator of transcription 3 (STAT3).[35] TNFα has been shown to protect cardiomyocytes from hypoxic damage (There are also many findings that prove that TNFα increase the damage of cardiomyocytes. It is currently believed that this contradiction may be related to different receptors or concentration differences of TNFα[36]), and this protective effect is speculated to be produced by activating the JAK/STAT pathway.[36] STAT3 is then activated to reduce cardiomyocyte apoptosis during ischemia-reperfusion.

Zhao et al.[37,38] reported that melatonin passes through the cell membrane and activates the large-conductance Ca^{2+}-activated K^{+} channel on smooth muscle cells directly to cause cell membrane hyperpolarization. This process relaxes the artery.

2.4 | Melatonin receptor ligands

Activation of melatonin receptors is involved in multiple cytoprotective pathways; however, in addition to melatonin alone, melatonin receptors also bind to a variety of other ligands. Understanding these ligands may help to understand the prospects of melatonin replacement therapy in the treatment of DCM. The well-known, non-selective MT1-MT2 receptor ligands with agonist properties include ramelteon, agomelatine, and tasimelteon, and these drugs are all MT receptor-selective drugs. In addition, there are many non-selective MT receptor agonists, such as 6-chloromelatonin, 6-hydroxymelatonin, 2-iodomelatonin, and GR 196429.[39] It has been confirmed that by activating the MT receptor, especially MT2, some of the above drugs exert a myocardial protective effect. For example, ramelteon improves the reperfusion injury of cardiomyocytes.[40] The relevant mechanism involves activation of the downstream signaling pathways (Akt and PKG) caused by the activation of MTs, and eventually causes opening of mitochondrial calcium-sensitive potassium channels and release of ROS.[41] Release of ROS to a certain degree is beneficial by inhibiting the opening of mitochondrial permeability transition pores, thereby reducing the influx of cytochrome C into the cytoplasm and preventing the initiation of the cytochrome C-mediated apoptosis program.[42]

3 | MELATONIN REGULATES GLUCOSE AND FATTY ACID METABOLISM IN DCM

Metabolic disorders are distinguishing feature of diabetic patients that mainly manifest as glucose utilization disorders and increased mitochondrial fatty acid intake.[43] Indeed, the main energy substrates of cardiomyocytes are glucose and fatty acids. The ATP production-to-oxygen consumption ratio is lower for fatty acids than glucose (2.33 vs. 2.58) in cardiomyocytes. Therefore, increased fat oxidation and decreased glucose oxidation caused by diabetes will reduce the efficiency of the myocardium.[44]

The main cause of increased fat uptake by cardiomyocytes is the excessive activation of transcription factor peroxisome proliferator-activated receptor-α (PPAR-α), which is regulated by the level of fatty

acids in the myocardium. When the insulin effect is insufficient, body fat synthesis will be weakened, lipolysis will increase, and blood lipids and fatty acids in different tissues will increase. Increased fatty acids in the myocardium, however, will cause increased expression of PPAR-α in the myocardium. PPAR-α regulates a variety of enzymes related to β oxidation in the myocardium,[45] thereby upregulating the utilization of fatty acids and inhibiting the utilization of glucose.[44] At present, there are few studies that have focused on the effect of melatonin on fatty acid metabolism in the myocardium. In an experiment designed to determine whether melatonin affects glucose and lipid metabolism disorders caused by light, the levels of blood glucose, blood lipids, and PPAR-α mRNA expression in guinea pigs were determined when guinea pigs were treated differently.[46] After 10 weeks of feeding, experiments showed that a high-fat diet combined with 24 h light/day (Light, especially night light, will severely inhibit the secretion of melatonin[47]) leads to increased blood glucose and lipids, including total cholesterol and low-density lipoprotein-cholesterol, and a decreased level PPAR-α mRNA in the liver and adipose tissue of guinea pigs; however, melatonin reversed the above findings. Subcutaneous injection of melatonin for 3 weeks increased the level of PPAR-α mRNA and decreased the plasma concentration of lipids and glucose in guinea pigs.[46] In another similar experiment with hamsters, melatonin also increased the expression of PPAR-α in the liver and reduced blood glucose and lipids.[48] The expression of carnitine palmitoyl transferase I in the liver of hamsters was also increased, thus β oxidation in the liver was increased.[48] It seems that melatonin increases the expression of PPAR-α and enhances the utilization of fatty acids by cells, which did not meet our expectations. Indeed, this experiment detected PPAR-α in liver and adipose tissue instead of the myocardium. There is also detection of PPAR-α in the myocardium. Melatonin reduces myocardial PPAR-α mRNA in hyperthyroidism.[49] Thus, melatonin can reduce blood lipids and glucose in guinea pigs with abnormal metabolism, and in theory, either directly or by reducing the concentration of blood lipids to inhibit the activation of myocardial PPAR-α,[50] normalizing myocardial fatty acid metabolism.

Melatonin also has an effect on abnormal glucose metabolism in tissues. For example, existing experiments have confirmed that melatonin increases the activity of glucose-6-phosphate dehydrogenase (G6PD) in red blood cells,[51] which effectively increases NADPH and the synthesis of glutathione. In a STZ-induced diabetic rat model, the activity of hexokinase and G6PD in the rat liver was significantly downregulated; however, whether pre- or post-treated with melatonin, the hexokinase and G6PD in the liver tissues of diabetic rats were effectively restored.[52]

An impaired AKT/glucose transporter 4 (GLUT4) signaling pathway is considered to be the main cause of insufficient heart glucose uptake in diabetic patients.[53] Existing studies have shown that the expression and membrane translocation of GLUT4 is decreased in the myocardium in TM1D and TM2D[54,55]; however, melatonin has a very significant rescue effect on this pathway. Melatonin successfully restores the decrease in GLUT4 mRNA in myocardium caused by hyperthyroidism,[49] and the myocardial glucose uptake rate is consistent with the change in GLUT4 mRNA. Taken together, the use of melatonin is beneficial to the uptake of glucose by cardiomyocytes.

4 | MELATONIN IMPROVES ENDOTHELIAL DYSFUNCTION AND MICROCIRCULATION DISORDERS IN DCM

Endothelial dysfunction in diabetic patients is primarily caused by the reduced release of endothelium-derived relaxing factors or the impairment of NO bioavailability caused by hyperglycemia,[56-58] which is considered to be a cause of various cardiovascular diseases. Both endothelium-dependent and endothelium-independent vasodilatation impairment in the micro- and macro-circulation are associated with diabetes mellitus.[59] Hence, if the impaired endothelium-derived relaxing factors secretory function of endothelial cells can be improved or the response of blood vessels to dilators can be increased, the cardiovascular complications of diabetes may be improved.

In a set of controlled experiments, an animal model of T2DM was used to determine the effect of L-carnitine and melatonin treatment.[60] After melatonin treatment, T2DM mice had better vascular responses to acetylcholine relaxation compared with the untreated diabetic group.[60]

Endothelial progenitor cell (EPC) apoptosis significantly reduces the production of antioxidant NO, the ability to repair vascular endothelium, and affects the function of vascular endothelial cells. This finding may be related to the impaired EPC autophagy mediated by advanced glycation end products (AGEs) in diabetic patients; however, melatonin improves the impaired autophagy flux and protects EPCs from apoptosis in diabetic patients.[61] In addition, melatonin alleviates atherosclerosis by inhibiting the expression of inducible nitric oxide synthase (iNOS),[62] which differs from endothelial (e) and neuronal (n)NOS. Inducible nitric oxide synthase promotes the generation of peroxynitrite, a proatherosclerosis oxidant, and promotes the formation of atherosclerosis.[63]

It is thought that calcium overload is the cause of endothelial cell apoptosis under oxidative stress conditions.[64] One of the main signals of damage is inositol 1,4,5-triphate receptor (IP3R)[65]; however, microvascular endothelial cell oxidative damage is a characteristic of cardiac microvascular reperfusion injury and is closely related to no reflow.[66] Based on the above characteristics, melatonin has been shown to have a good effect in regulating the calcium balance of vascular endothelial cells and preventing endothelial cell apoptosis under conditions of oxidative stress.[67] H_2O_2 treatment simulates a vascular endothelial cell model of oxidative damage in which calcium overload and cell apoptosis were noted. H_2O_2 activates the ER calcium channel receptor, IP3R, which causes cytoplasmic calcium overload, then the calcium enters the mitochondria through a voltage-dependent anion channel (VDAC), leading to mitochondrial calcium overload, impaired mitochondrial membrane potential, and opening of the mitochondrial permeability transition pores. All of these findings are prerequisites of cytochrome c release, which result in cell apoptosis.[68,69] Melatonin has an effect on IP3R and

VDAC. Melatonin inhibits the activation of IP3R and VDAC to alleviate calcium overload in the cytoplasm and mitochondria, and prevents cardiac microvascular endothelial cell death under oxidative stress conditions.

Microcirculation disorders are also an important characteristic of DCM. Focal necrosis of the myocardium due to microcirculation disorders reduces myocardial contractility. The coronary blood flow reserve of diabetic patients is significantly less than healthy people.[70] It has also been shown in animal experiments that the occurrence of diabetes leads to a decrease of arterioles in the heart.[71] The reason for this phenomenon may be partly related to the increased secretion of endothelin-1 (ET-1) which is thought to induce potent vasoconstriction through increasing the expression of protein kinase C (PKC).[72,73] High levels of ET-1 also impair endothelial NO production via an isoform-specific PKC-mediated inhibition of eNOS expression.[74] These changes greatly enhance the contractile function of the vascular endothelium and cause microcirculation disorders. In addition, endothelin also increases the proliferation and migration of vascular smooth muscle cells, which is related to the development of atherosclerosis.[75,76]

The inhibitory effect of melatonin on ET-1 has been demonstrated in several experiments. For example, melatonin inhibits edn-1 mRNA (the first step in ET-1 synthesis) expression in colon cancer by inhibiting edn-1 promoter activity regulated by FoxO1 and nuclear factor kappa B (NF-κB), therefore reducing the production of ET-1.[77] Melatonin also inhibits the concentration of ET-1 in the blood of cigarette smokers,[78] and ET-1 concentration, as well as an increased expression of endothelin receptor mRNA in hepatic ischemia/reperfusion.[79]

5 | MELATONIN INHIBITS MYOCARDIAL FIBROSIS IN DIABETES AND IMPROVES VENTRICULAR REMODELING

Myocardial fibrosis is one of the common complications in patients with diabetes, and is widely observed in patients with type 1 and 2 diabetes[80,81] The occurrence of this complication will largely lead to increased myocardial stiffness and decreased ventricular diastolic function. The causes of myocardial fibrosis include the formation and accumulation of AGEs, activation of the receptor for AGE (RAGE) by AGEs, and stimulation of hyperglycemia. All of this ultimately leads to the proliferation, differentiation, and collagen production of cardiac fibroblasts.[82-84]

Therefore, it is meaningful to discuss whether melatonin can inhibit myocardial fibrosis and reverse the diastolic dysfunction caused by myocardial fibrosis. Transforming growth factor β (TGF-β) is one of the important pathways for regulating tissue fibrosis. The TGF-β pathway not only promotes the occurrence of fibrosis but also inhibits the progress of fibrosis. SMAD proteins are the pivotal intracellular effectors of TGF-β, and multiple subtypes of SMAD proteins have positive effects on the epithelial-myofibroblast transition and collagen expression, such as SMAD2 and SMAD3, whereas some of the subtypes of SMAD proteins have negative effects, such as SMAD7.[85,86] NOD-like receptor 3 (NLRP3)/IL-1β pathway is related to TGF-β/SMAD pathway and located upstream of TGF-β/SMAD pathway. IL-1β is a downstream factor of NLRP3 pathway, and can promote *TGF-β* gene expression.[87] It has been shown that blocking the NLRP3 pathway can reduce myocardial fibrosis.[88] In addition, the NLRP3 protein monomer is involved in fibrosis but is independent of the fibrosis of the inflammation mediated by the NLRP3 complex.[89] At present, there is relevant evidence to provide the anti-fibrosis effect of influencing these signaling pathways to DCM. It was found that tissue growth factor, fibronectin, type I collagen, and type III collagen of diabetic mice induced by STZ was significantly higher than normal mice. The diabetic mice were administered intragastric melatonin for 8 weeks had a significantly lower level of the above data compared with diabetic mice that did not receive melatonin treatment.[90] The subsequent detection of the TGF-β1/SMADS and NLRP3 signaling pathways was also as expected. The levels of TGF-β1, p-SMAD2, p-SMAD3, and NLRP3 inflammasome complexes, as well as the downstream NLRP3 factors, such as IL-1β, IL-18, and cleaved caspase-1 were all increased in the myocardium of diabetic mice, and melatonin treatment significantly reversed these adverse effects by increasing the expression of miR-141 and inhibiting the activity of lncR-MALAT1 (there is a binding site of miR-141 on lncR-MALAT1, and the binding of the former with the latter inhibits the activity of the latter).[90] At the same time, melatonin can significantly improve ventricular dysfunction caused by diabetes. For example, compared with untreated diabetic mice, the mRNA levels of brain natriuretic peptide in the myocardium of diabetic mice treated with melatonin decreased significantly. Echocardiography also showed that the cardiac ejection fraction and fraction shortening of diabetic mice were improved by melatonin.[90] Taken together, the effect of melatonin in improving myocardial fibrosis and inhibiting ventricular remodeling was verified.

6 | MELATONIN REGULATES AUTOPHAGY IN DCM

Autophagy is a process by which cellular organelles are engulfed by double-membraned structures and subsequently targeted for lysosomal degradation.[91] Autophagy can eliminate redundant and structurally damaged cells, and recycle the intracellular substances to maintain the normal physiologic function of cells, so as to adapt to various adverse stimuli.[91] Normal autophagy has an important role in cell function and quality control of protein and organelles.[92] Excessive autophagy can degrade more important components in cells and induce cell apoptosis or death[93]; however, recent findings indicate that abnormal autophagy of cardiomyocytes is related to insulin resistance and T2DM.[94] Thus, autophagy involvement in the pathophysiology underlying DCM might play a key role in the development of T2DM and its complications. Using a murine model, it was shown that myocardial autophagy is elevated in patients with T2DM, but suppressed in patients with T1DM.[95-97] In a study

involving melatonin action in diabetic mice induced by STZ, the protein level of the specific autophagic substrate, sequestosome 1 (p62), was increased in diabetic sg/sg mice (mice expressing inactive RORα),[20] which represents a reduction in autophagy flux. The double membrane-bound autophagic vesicles and phosphorylation levels of AMPK, a positive regulator of autophagy,[98] are decreased in the diabetic hearts of sg/sg mice, while the activity of mammalian target of rapamycin complex, a well-recognized negative regulator of autophagy, is significantly increased. Melatonin used to treat a STZ-induced rat model of T1DM promoted autophagy by inhibiting the mammalian Ste20-like kinase 1 (Mst1), a protein that regulates autophagy,[99] phosphorylation, and activating silent information regulator 3 (SIRT3) expression, as well as reducing the level of mammalian target of rapamycin complex expression.[100-102] Inhibition of Mst1 is effective in improving cardiomyocyte autophagy. Melatonin treatment of Mst1 transgenic (Mst1 Tg) mice increased cardiomyocyte autophagy, reduced apoptosis, and improved mitochondrial function, but had no effect on Mst1 knockout ($Mst1^{-/-}$) mice. In addition to the above, melatonin also increases the ratio of LC3-II to LC3-I (as a marker of autophagy, LC3-II participates in the formation of autophagosomes[103]), but attenuates the level of p62 in the cardiomyocytes and EPCs of diabetic patients,[61,104] indicating the increase in autophagy flux. In H9C2 cells, however, after anoxia/reoxygenation injury treatment, melatonin inhibits excessive mitochondrial autophagy,[105] suggesting that the effect of melatonin on autophagy depends on cell or organelle status. Melatonin or melatonin receptors play an important role in regulating autophagy of cardiomyocytes and EPCs. It is important to note that the level of autophagy needs to be balanced. The current consensus is that acute autophagy induction (e.g., acute myocardial infarction induced by permanent coronary artery occlusion) may be beneficial, while persistent autophagy induction (e.g., failing heart, DCM induced by T2DM, and cardiac anoxia/reoxygenation) may be harmful.[97,106,107] How to determine if the role of autophagy induction in DCM is more beneficial or harmful will require a more specific model.

7 | MELATONIN IN REGULATING OXIDATIVE STRESS

Oxidative stress is caused by the loss of balance between oxidation and antioxidant systems in cells and tissues, which over-produce oxidative-free radicals and ROS.[108,109] The production of ROS in the human body mainly comes from NADPH oxidase, xanthine oxidase/oxidoreductase, the mitochondrial electron transport chain, uncoupled nitric oxide synthase, the arachidonic acid metabolic pathway, and microsomal enzymes.[110] The main ROS in organisms are free radicals, including nitric oxide ($NO^{\bullet}$), superoxide radical anion ($O2^{\bullet-}$), hydroxyl radical ($OH^{\bullet}$), carbonate radical anion ($CO3^{\bullet-}$), nitrogen dioxide ($NO2^{\bullet}$), alkoxyl/alkyl peroxyl ($RO^{\bullet}$/$ROO^{\bullet}$) and non-free radicals, including hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^{-}$)/peroxynitrous acid (ONOOH), and hypochlorous acid (HOCl).[111] A significant increase in oxidative stress and ROS production has been demonstrated in the myocardium of diabetics,[112] and the main site of ROS production is myocardial cells. If the glucose content in the cell increases, the flux of electron transfer donors into the mitochondrial respiratory chain will also increase. Then, the resulting hyperpolarization of the mitochondrial inner membrane potential will inhibit electron transport in complex III and accumulate electrons to ubisemiquinone, therefore generating ROS.[108,113] In contrast, NADPH oxidase produces a huge amount of superoxide $O2^{\bullet-}$.[114] These unstable superoxides will subsequently dismutate to stable H_2O_2. In fact, a large number of NADPH oxidase subtypes (Nox2 and Nox4) are expressed in cardiomyocytes and can be activated by activated PKC, angiotensin receptor AT1, and Ca^{2+}/calmodulin-dependent protein kinase II induced by high glucose.[115-119] The cardiovascular system also contributes to produce ROS in diabetes. Except for the increase in ROS caused by mitochondria and NADPH oxidase similar to cardiomyocytes,[120] hyperglycemia increases the expression of iNOS in vascular endothelium, which will form large quantities of superoxide and NO and further produce strong oxidizing peroxynitrite $ONOO^{-}$.[121,122]

The mechanism underlying subclinical inflammation and oxidative stress is now widely accepted to play an important role in the development of diabetes and its complications.[123] When ROS are excessive, DNA, protein, and lipids will be damaged, and the ROS will participate in various pathologic states in DCM, such as cardiac inflammation, myocardial hypertrophy, apoptosis, fibrosis, vascular endothelial dysfunction, atherosclerosis, and arterial stiffness.[124]

In previous studies, it has been shown that melatonin is an immunomodulator that protects against pathologic inflammation.[125,126] In STZ-induced diabetes animal model experiments, melatonin has been shown to be a strong antioxidant. Melatonin injected intraperitoneally increased the activity of antioxidant enzymes in mice and inhibits the release of superoxide-free radicals.[127] A similar study showed that the increased glycemia, fructosamine, cholesterol, triglycerides, and lipoperoxides caused by STZ induction are reversed by a melatonin injection.[128] Additional experiments directly proved that melatonin effectively reduces inflammation and oxidative stress in mice with T2DM.[129] Using young male Zucker diabetic fatty (ZDF) rats in an experimental model of metabolic syndrome and T2DM, melatonin treatment reduced the levels of interleukin-6, TNFα, C-reactive protein, and plasma lipid peroxidation, a criterion for evaluating oxidative stress in ZDF rats, indicating that melatonin treatment attenuated the inflammatory state and oxidative stress. Melatonin administration also decreased the malondialdehyde (MDA) level, and increased the reduced glutathione (GSH) level and other antioxidant enzymes in the myocardium.[130] Experiments with rabbits yielded similar results.[131] Although early-stage diabetes led to an increase in the serum GSH level in rabbits, prolonged diabetes resulted in a lower serum GSH level and higher serum oxidized glutathione level compared with controls[131]; however, melatonin treatment maintained the level of serum GSH at an elevated level in diabetic rabbits. Clinical trials have generated corresponding evidence for the effect of melatonin on oxidative stress inhibition. In a double-blind trial to study the effects of melatonin on diabetic

patients,[132] the group treated with melatonin had an increased level of GSH and nitric oxide and a decreased level of MDA compared with the placebo-treated group. Together, these data indicate that melatonin plays an important role in improving oxidative stress induced by diabetes.

To date, melatonin has been shown to inhibit oxidative stress via multiple pathways. RORα, as a transcription factor and an important mediator of melatonin-exerted cardioprotection, has strong antioxidant activity in ischemic heart injuries. He et al.[24] assessed the role of RORα in regulating MI/R-induced oxidative/nitrative stress. Specifically, MI/R induced oxidative stress and nitrification stress in wild-type (WT) mice,[24] as evidenced by increased accumulation of ROS and nitrotyrosine. In sg/sg mice, these metabolites were increased compared with WT mice. Moreover, it was shown that RORα deficiency increases NADPH oxidase activity,[133] and increases the level of NADPH oxidase subunit gp91phox as well as iNOS, a proatherogenic enzyme that mediates nitrification stress.[63,121] Melatonin inhibits MI/R-induced myocardial oxidative stress injury by activating RORα.

In addition to the MTs that protect mitochondrial function in the myocardium from oxidative stress via the MAPK-ERK signaling pathway, as previously discussed, activation of melatonin receptors also reduces ROS in cardiomyocytes and reverses the inhibited activity of mitochondrial SOD and other anti-oxidant substances in an oxidative stress model induced by hydrogen peroxide.[30] In the doxorubicin (DOX)-induced oxidative stress model, melatonin also has a therapeutic effect, which may have an enlightening role for melatonin in the treatment of oxidative stress in DCM. Activation of the AMPK signaling pathway, silent information regulator 1 (SIRT1), LKB1, AMPK, and peroxisome proliferator-activated receptor coactivator 1alpha (PGC-1α) have the effect of protecting myocardial function[134,135] (Figure 2). The PGC-1α downstream signaling molecules, including nuclear respiratory factor 1 (NRF1), mitochondrial transcription factor A (TFAM), and uncoupling protein (UCP), plays an important role in mitochondrial energy homeostasis.[136] Melatonin treatment reversed downregulation of the AMPK phosphorylation induced by oxidative stress, thus increasing the expression of PGC-1α in hypoxic and ischemic cardiomyocytes. Compared with the control group, H9C2 cells induced by DOX had lower ROS levels and increased activity of the SOD after melatonin treatment, implying that melatonin alleviates the damage of oxidative stress in cardiomyocytes.[137] Another group used a STZ-induced mouse model of T1DM and reported that melatonin treatment increases the level of PGC-1α, SIRT3, and mitochondrial SOD2 in cardiomyocytes by activating AMPK-PGC-1α-SIRT3 signaling and preserving mitochondrial function, thus significantly improving MI/R injury. It has been reported that activation of SIRT3 prevents myocardial mitochondrial oxidative stress and damage[138,139]; however, these protective effects of melatonin are blunted by compound C (a special AMPK signal blocker).[140] Moreover, nuclear factor erythroid 2-related factor 2 (Nrf2) participates in AMPK-PGC-1α pathway, together forming the PGC-1α/Nrf2 signaling pathway.[141] The activation of Nrf2 has been shown to reduce simulated ischemia reperfusion-induced oxidative stress and apoptosis.[142,143] The related mechanisms may be due to activation of Nrf2, which promotes the expression of anti-oxidative proteins and phase II detoxifying enzymes, including heme oxygenase 1 (HO-1), UCP2, and SOD in cardiomyocytes[144]; however, melatonin also has an effect on the Nrf2 signaling pathway. It has been reported that melatonin pretreatment of H9c2 cells with simulated ischemia reperfusion significantly increases the expression of Nrf2 in the nuclei and whole cells, which reduces ischemia/reperfusion-induced oxidative stress and apoptosis in H9c2 cell compared with controls. In addition, the expression of HO-1, an important target gene of Nrf2, also increased after using melatonin.[145-148] HO-1 has been shown to be an indispensable endogenous protective enzyme in response to inflammation and oxidative stress, and is an important target for the prevention and treatment of a variety of cardiovascular diseases.[149] Therefore, the antioxidative effect of melatonin depends on the activation of the PGC-1α/Nrf2 signaling pathway.

8 | MELATONIN INHIBITS CELL DEATH IN DCM

In addition to regulating autophagy and relieving oxidative stress, melatonin also reduces cell apoptosis. Programmed cell death usually occurs when the cells are damaged by non-receptor-mediated stimulation and is very common in normal life activities. As an important means for cell renewal, proper apoptosis always maintains the normal vitality of cells.[150,151] Once the intensity of this activity is too high, it will cause the original normal tissue and organ function to decline. Now, it has been proven that increased cell death, including both apoptotic- and necrotic-related cell death, is a frequent characteristic in the myocardium of humans and rodent models with diabetes.[152-155] This type of cell death in T1DM is augmented by RORα deficiency due to a reduction in the anti-apoptotic protein, B-cell lymphoma-2 (Bcl-2), and an increase in the pro-apoptotic protein, Bcl-2-associated X protein (Bax), and cytoplasmic cytochrome c.[20] By feeding melatonin to diabetic rats, Amin et al.[156] effectively reduced cardiomyocyte apoptosis. Amin et al.[156] noted that melatonin enhanced Bcl-2 expression and blocked activation of CD95 and apoptotic proteins (caspases-3, -8, and -9). Serum creatine kinase-MB and lactate dehydrogenase were also significantly improved.[156] All these findings demonstrate the effect of melatonin in improving the diabetic myocardium. In addition, the use of melatonin therapy significantly reduces the level of JNK phosphorylation in the heart, reduces the p53 level, and inhibits cell apoptosis in post-MI diabetic mice.[157]

9 | MELATONIN IMPROVES ER STRESS IN DIABETES

ER stress is characterized by a perturbation in Ca^{2+} or redox balance in the ER, and cause the accumulation of mis- or un-folded proteins,[158,159] which exceed the processing capacity of the ER, resulting in disturbed homeostasis and cell dysfunction. In the early

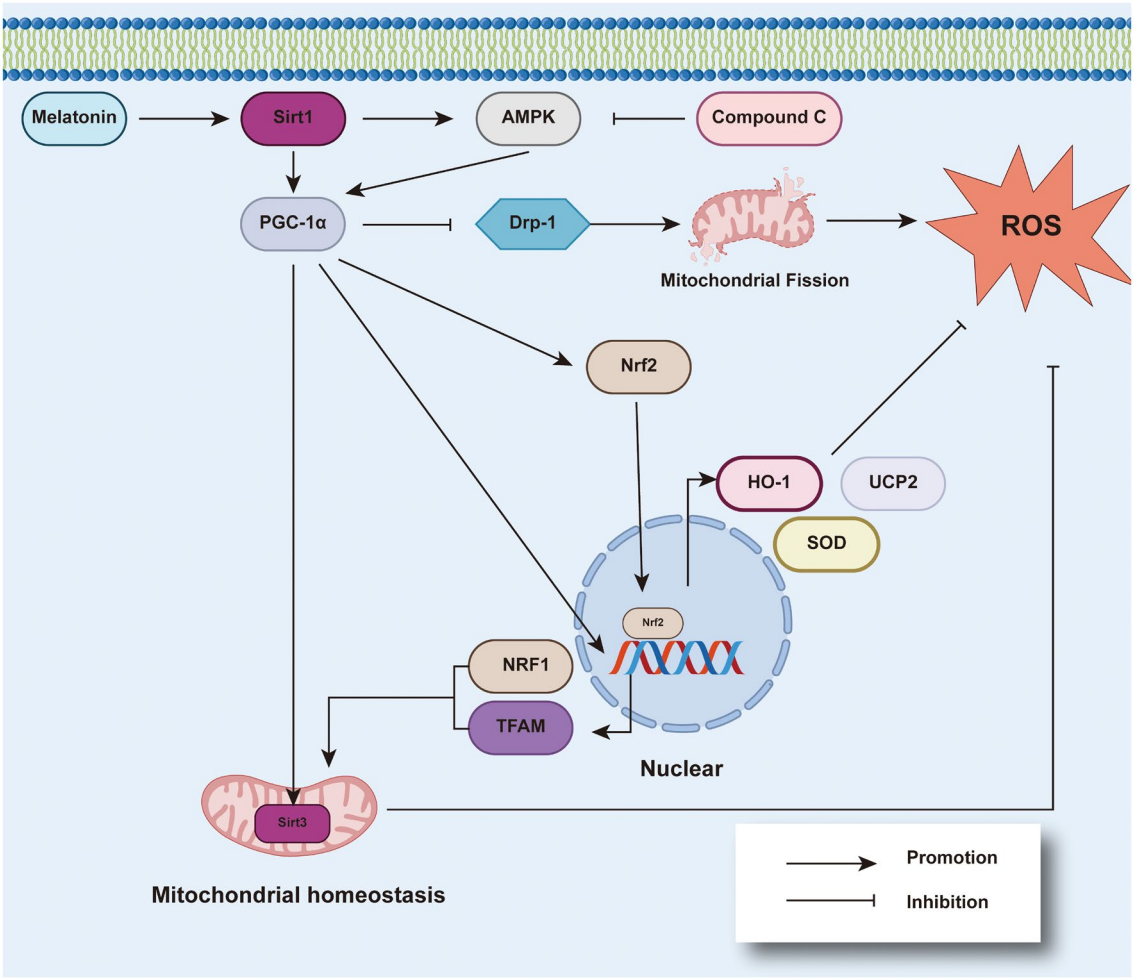

FIGURE 2 Melatonin relieves oxidative stress by activating PGC-1α. Melatonin can activate Sirt1/PGC-1α with or without AMPK activation, which produces anti-oxidative stress effects. This effect is mainly achieved by four pathways. (1) PGC-1α inhibits mitochondrial fission promoted by Drp1, maintaining the stability of mitochondrial structure and function, then reducing the production of ROS. (2) PGC-1α activates Nrf2 and generates a variety of molecules with antioxidant effects, including HO-1, SOD, and UCP2. (3) PGC-1α also helps transcribe NRF1 and TFAM, these two substances are beneficial to mitochondrial copy and biogenesis. (4) PGC-1α activates Sirt3 located on the mitochondria, which helps maintain mitochondrial homeostasis. AMPK, AMP kinase; Drp1, dynamin-related protein 1; HO-1, heme oxygenase 1; NRF1, nuclear respiratory factor 1; PGC-1α, proliferator-activated receptor coactivator 1 alpha; ROS, reactive oxygen species; SIRT1, silent information regulator 1; SOD, superoxide dismutase; TFAM, mitochondrial transcription factor A; UCP, uncoupling protein

stage of ER stress, the unfolded protein response (UPR), a protective mechanism, is initiated to alleviate the protein load by reducing the rate of new protein synthesis and increasing chaperone protein expression, but if this mechanism is inadequate, UPR induces cellular apoptosis and related effects.[160,161] UPR is mediated by three important transducers, including protein kinase RNA-like endoplasmic reticulum kinase (PERK), activated transcription factor 6 (ATF-6), and inositol-requiring protein-1α (IRE1α). Usually, the transducers bind to ER chaperone protein glucose-regulated protein 78 (GRP78), but with the accumulation of unfolded protein in the ER, GRP78 leave the transducers and participate in handling the accumulated protein.[162]

Existing research shows that ER stress is very closely related to diabetes.[163-165] As a cellular function damaged by diabetes, ER stress participates in myocardial infarction, ischemia, pressure overload, DCM, heart failure, and hypertrophy.[166] ER stress is often accompanied by oxidative stress, but ER stress is independent of oxidative stress in diabetes.[167] Indeed, ER stress has been shown to intersect with many different signaling pathways and cause a variety of cell dysfunction complications.

It has been shown that if ER stress persists for a long time, it will lead to cell apoptosis in various ways. Activation of the downstream signaling pathway of PERK, ATF-6 and IRE1α will downregulate the anti-apoptotic protein Bcl-2, and increase the expression of CHOP (As a transcription factor, CHOP can downregulate the expressions of BCL2, BCL-XL, and MCL-1, and upregulate the expression of Bak and Bax[168,169]) and the caspase family of proapoptotic cysteine proteases, including caspase-12, -9, -8, and -3.[170-175] It is also observed that the expression of GRP78, PERK, ATF-6, CHOP, and pro-apoptotic protein BAX, caspase-3 were increased, the anti-apoptotic protein Bcl-2 was decreased in the myocardium of diabetic rats induced by STZ.[176] The percentage of apoptotic myocardial cells was also increased in diabetic rats compared with controls. These

changes are caused, at least in part, by the reduced activation of SIRT1. It has been reported that SIRT1 plays an important role in DCM. Researchers have observed that activation of SIRT1 improves organ and tissue dysfunction induced by hyperglycemia, including cardiomyocyte apoptosis.[177,178] And melatonin can happen to activate SIRT1 (Figure 3). A related study showed that melatonin activates SIRT1, then suppresses PERK/eIF2α/ATF4/CHOP signaling pathway, thereby attenuates ER stress, and eventually protects the function of cardiomyocytes.[179] The increased expression of ATF-6 caused by diabetes in the rat heart is also inhibited by melatonin.[176] In addition to cardiomyocytes, melatonin has a similar effect in osteoblastic cells. Melatonin reduces the expression of P-PERK, P-eIF2α, and P-ATF4, then affects the expression of CHOP and attenuates apoptosis of osteoblastic cells.[180] Taken together, it is evident that melatonin inhibits ER stress, thereby protecting cells from apoptosis. It is noteworthy, however, that melatonin does not significantly reduce the increased expression of IRE1α caused by diabetes.[176] The effect of melatonin in renal tissues is different.[181] Specifically, melatonin restores the level of GRP78, IRE1α, and ATF6 expression, but has no significant effect on the level of PERK expression in diabetic obese rats, indicating that the effect of melatonin on ER stress has tissue or cellular differences.

Insulin resistance has an important effect on DCM.[182] Reversing insulin resistance may help treat DCM. According to some reports, inhibition of ER stress alleviates insulin resistance,[183,184] which may be one of the mechanisms by which melatonin restores insulin sensitivity. The Akt protein is an important downstream signaling molecule for insulin. ER stress reduces phosphorylated Akt in a severity-dependent manner.[185] After skeletal muscle cells are exposed to insulin, tunicamycin, an ER stress activator, causes ER stress, inhibits Akt phosphorylation, and stimulates PERK phosphorylation; however, melatonin reverses the changes induced by tunicamycin. The phosphorylation of Akt was increased and the phosphorylation of PERK was decreased by melatonin pretreatment in this ER stress model.[186] Therefore, insulin resistance caused by inhibition of Akt phosphorylation is restored, in part, because of the alleviation of ER stress by melatonin.

Melatonin attenuates ER stress in hepatocytes by regulating microRNA,[187] but there are no studies regarding the effect on the myocardium. Therefore, a study to determine if melatonin regulates ER stress in the myocardium via microRNA is warranted.

10 | MELATONIN IMPROVES MITOCHONDRIAL FUNCTION

In skeletal muscle cells of diabetic patients, increased fatty acid uptake promotes mitochondrial fission and the damage of electron transport chain activity, leading to impaired mitochondrial function.[188] A previous study confirmed that this kind of damage can be suppressed by metformin.[189] In recent years, it was shown that melatonin also has a similar effect in cardiomyocytes.[190] Specifically, SIRT1 is the target of melatonin, and activation of SIRT1 activates PGC-1α, then inhibits dynamin-related protein 1 (Drp1)-mediated mitochondrial fission and reduces the level of superoxide produced by mitochondria[190] (Figure 2). Hyperglycemia increased Drp1 protein expression in H9c2 cells, causing mitochondria to become spherical and shorter, indicating mitochondrial fragmentation; however, hyperglycemia-induced mitochondrial fragmentation was attenuated after melatonin treatment.[190] Moreover, melatonin treatment reduced mitochondria-derived superoxide production induced by hyperglycemia in cells.[190]

Activation of nuclear receptor subfamily 4, group A, member 1 (NR4A1) is also a potential target of melatonin in the treatment of DCM. It has been reported that NR4A1 contributes to cardiomyocyte injury in cardiac microvascular ischemia/reperfusion by fatal mitochondrial fission.[191] Increased NR4A1 expression activated serine/threonine kinase casein kinase 2α, which promotes phosphorylation of mitochondrial fission factor, enhances translocation of Drp1 to the mitochondria, thus leading to fatal mitochondrial fission. Other studies have confirmed this finding.[192,193] Indeed, it is possible that NR4A1 upregulation activates the DNA-PKcs/p53 pathway, increases Drp1 expression in cells and translocation to mitochondria, and inhibits Bnip3-required mitophagy, thereby aggravating mitochondrial fission and impairing mitochondrial homeostasis. Melatonin inhibits upregulation of NR4A1 to inhibit mitochondrial fission in the liver.[194] Nevertheless, direct clinical evidence is needed to confirm that melatonin also protects the myocardium by inhibiting NR4A1 in diabetes.

Melatonin also improves the activity of some enzymes and mitochondrial complexes in mitochondria.[195] The activity of citrate synthase and mitochondrial complexes I, III, and IV are reduced in the hepatic mitochondria of ZDF rats. Treatment with melatonin improves the activity of these important enzymes and complexes, especially complex IV. Melatonin increases the intermediate product of the tricarboxylic acid cycle in the mitochondria of an insulin resistance skeletal muscle cell model induced by palmitic acid.[196] The content of alpha-ketoglutarate, citrate, and malate was decreased in this insulin resistance model; however, melatonin treatment reversed this change, improved the content of the three substances to a normal level, and improved mitochondrial function.[196] Notably, in normal cells, melatonin treatment only increases citrate content, but not alpha-ketoglutarate and malate content. Thus, the effect of melatonin increasing the alpha-ketoglutarate and malate content appears to be limited to cells in special states, such as insulin resistance.

Moreover, melatonin improves mitochondrial function and content in intramuscular pre-adipocytes by increasing the gene expression of mitochondrial biogenesis.[197] After melatonin administration, the intracellular ATP generation in porcine intramuscular adipocytes is increased and the expression of mitochondrial-related genes, including *PGC-1α*, *TFAM*, *carnitine palmitoyl transferase-1β*, and the thermogenesis gene is upregulated. Furthermore, the mitochondrial copy is also increased in intramuscular adipocytes.

Melatonin has a clear protective effect on cardiomyocyte mitochondrial dysfunction when the myocardium has an ischemia/reperfusion injury.[198] After melatonin pre-treatment of rats with ischemia/reperfusion injury, mitochondrial SOD activity is

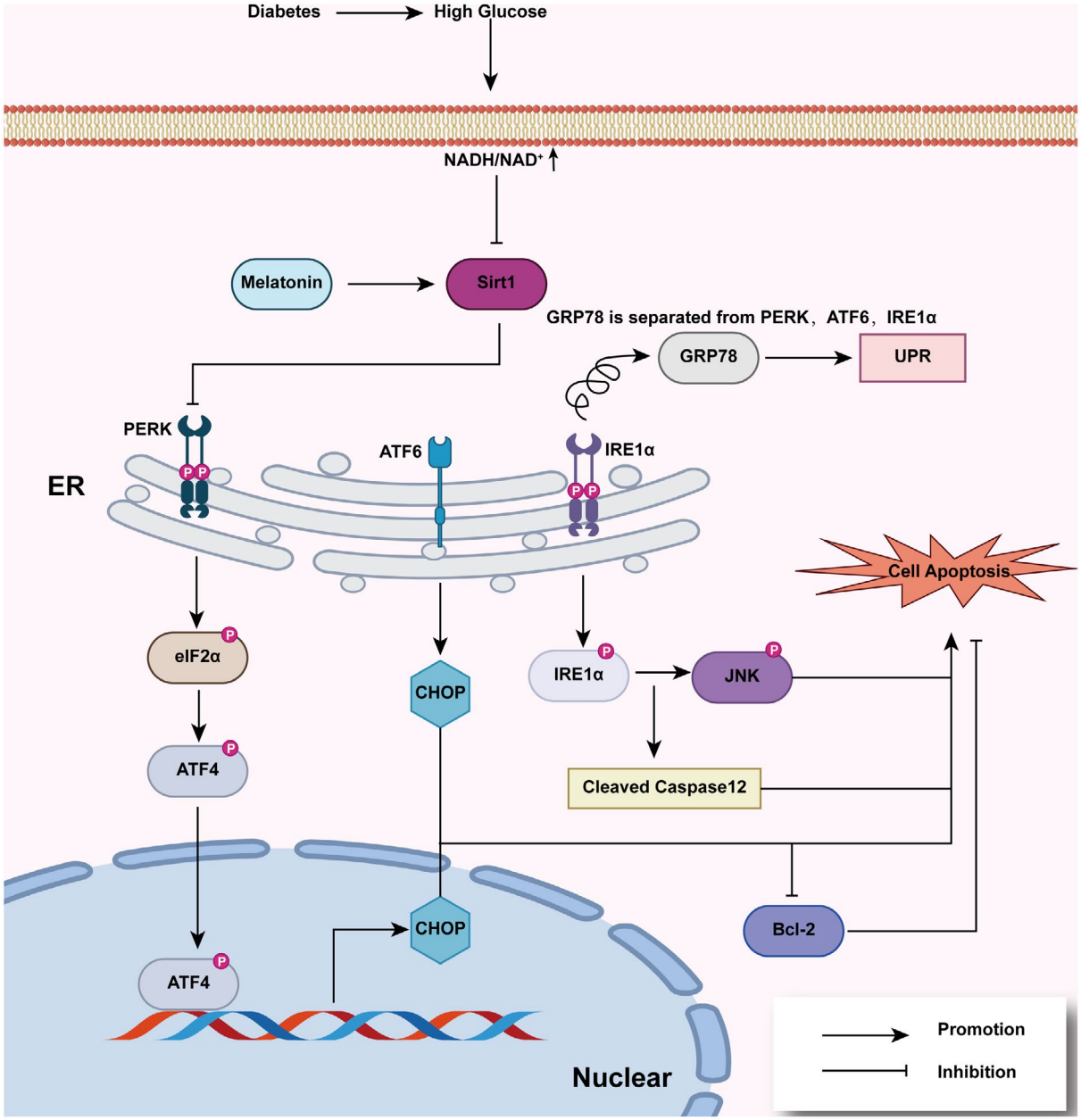

FIGURE 3 The inhibitory of melatonin on endoplasmic reticulum (ER) stress. When ER stress occurs, GRP78 is separated from PERK, ATF6, and IRE1α, which activates three signal pathways and leads to increased levels of downstream molecules, including p-elf2α, p-ATF4, CHOP, p-IRE1α, p-JNK, and cleaved caspase 12, which eventually leads to cell apoptosis. Melatonin activates Sirt1, which is inhibited by hyperglycemia in cardiomyocytes, and inhibits the PERK-p-elf2α-ATF4-CHOP signaling pathway, thus reducing ER stress and reducing cardiomyocyte apoptosis in diabetic patients. ATF-6, activated transcription factor 6; IRE1α, inositol-requiring protein-1α; PERK, protein kinase RNA-like endoplasmic reticulum kinase

increased and mitochondrial H_2O_2 and MDA are decreased, indicating that melatonin functions to preserve mitochondrial redox potential.

A recent study showed that melatonin is able to relieve ER dysfunction and mitochondrial calcium overload associated with mitochondrial dysfunction. Excessive production of mitochondrial ROS leads to peroxidation of ER-related proteins and causes ER dysfunction. Then, the ER releases calcium into the cytoplasm, causing mitochondrial calcium overload in the cell, which in turn affects mitochondrial membrane potential and function.[64,67,199] Zhou et al.[200] reported that inhibition of spleen tyrosine kinase (Syk) by melatonin promotes cardiomyocyte survival by reducing mitochondria and ER-related apoptosis. When activated by hyperglycemia, Syk weakens the expression of mitochondrial complex I, thereby increasing the production of ROS, resulting in peroxidation of sarcoplasmic reticulum Ca^{2+} ATPase (SERCA). Then, the ability of SERCA to transport calcium back to ER is impaired, which leads to cytoplasmic calcium overload. Eventually, mitochondrial dysfunction, ER

dysfunction, and cardiomyocyte apoptosis occur[200]; however, melatonin supplementation delays or even reverses these alterations by regulating the Syk/COX-I/SERCA signaling pathway.[200]

11 | MELATONIN RESCUES CARDIOMYOCYTES FROM MI/R INJURY

Clinical evidence has shown that compared with non-diabetic patients, diabetic patients with acute myocardial infarction have a larger infarct size after reperfusion therapy.[201,202] Similarly, the infarct size decreases after acute myocardial infarction in the short term, but always increases the infarct size with time in STZ-induced diabetic mice compared with normal mice,[203,204] indicating that diabetes causes a deficiency in cardiomyocyte protective function. An earlier study showed that melatonin has a protective effect on MI/R.[205] Sahna et al.[206] verified that melatonin helps reduce the infarct size induced by MI/R. Sahna et al.[206] observed that melatonin treatment in diabetic mice reversed the increased level of MDA and decreased the GSH level caused by MI/R. The specific signaling pathway involving cardiomyocyte protection in MI/R has been studied in other experiments. For example, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway has been confirmed to play an important role in cardiomyocyte protection during MI/R.[207] There is evidence that melatonin activates the JAK/STAT signaling pathway in MI/R to produce cardiomyocyte protection.[198,208] In these experiments, melatonin pre-treatment of the heart led to increased levels of p-STAT3 and p-JAK2 expression, which increased the level of Bcl-2 expression and decreased the levels of Bax, caspase-3, and C-caspase-3 expression after MI/R administration.[198,208] Eventually, the infarct size and cell apoptosis were reduced.[198,208] These effects are inhibited by the JAK2/STAT3 inhibitor, AG490. Yet, is activation of the JAK2/STAT3 signaling pathway always beneficial to cells and tissues? Does melatonin always activate the JAK2/STAT3 signaling pathway? Part of the existing evidence indicates that excessive activation of the JAK2/STAT3 signaling pathway has a damaging effect on cardiomyocytes and endothelial cells. For example, the JAK2/STAT3 signaling pathway is activated by H_2O_2 in endothelial cells, but the expression of caspase-3 and Bax is also increased, the expression of Bcl-2 is decreased, and melatonin reverses these changes.[209] Similarly, in septic myocardium, activation of the JAK2/STAT3 signaling pathway aggravates myocardial damage, which is attenuated by melatonin via inhibition of the JAK2/STAT3 signaling pathway.[210] In summary, although the effects of melatonin on the JAK2/STAT3 signaling pathway are different under specific circumstances, the main effects are to protect cells.

SIRT3-dependent regulation is also a significant method in cardiomyocyte protection during MI/R. Zhai et al.[211] reported that compared with the sham operation group, MI/R caused a decrease in LVEF and LVFS in the IR group, which was reversed by melatonin treatment (20 mg/kg intraperitoneally 10 min before reperfusion). In the same experiments, melatonin also significantly reduced the infarct size and the level of serum lactate dehydrogenase after MI/R administration.[211] Related mechanisms may involve melatonin-induced increased SIRT3 expression, resulting in activation of SOD2 and glutathione peroxidase (an important peroxide decomposing enzyme), upregulating the expression of Bcl-2 and Nrf2, and downregulating the expression of Bax, caspase-3, and gp91phox.

Moreover, reducing SIRT1 is another reason of worsening myocardial MI/R injury.[179,212] In the T2DM model, melatonin reduced the apoptosis of cardiomyocytes by increasing the expression of SIRT1 that was inhibited by diabetes, increased LVEF and LVFS, and improved cardiac function after MI/R, which is related to the inhibition of the PERK-eIF2α-ATF4-CHOP signaling pathway by melatonin. This protective effect was suppressed by SIRT1 inhibition, which confirmed that melatonin relieves ER stress via the SIRT1 signaling pathway.

In addition, MT2 receptor-dependent cGMP-PKGIα signaling is another signaling pathway in which melatonin protects cardiomyocytes from I/R injury.[29] It has been reported that Nrf2-HO-1 and MAPK signaling, two key downstream targets of cGMP-PKG signaling in the MI/R injured diabetic heart, have changed. Specifically, Nrf2/HO-1 signaling is decreased, while the phosphorylation levels of ERK, JNK and p38 MAPK (three MAPK signal molecules) is increased; however, melatonin has a role in protecting cardiomyocytes in diabetics during ischemia/reperfusion via cGMP-PKG signal by acting on the MT2 receptor. Melatonin enhances cGMP-PKG signaling, upregulates Nrf2/HO-1 signaling, downregulates MAPK pathway (mainly reduces p-JNK/JNK and p-p38 MAPK/p38 MAPK level, but increases p-ERK/ERK level), and eventually reduces myocardial apoptosis.

In addition to the protective effect of melatonin on MI/R injury, melatonin can also directly promote myocardial proliferation of an infarction injury.[213] MicroRNA can be used as a target for melatonin to combat ischemic injury of cardiomyocytes. For example, inhibiting the expression of miR-143-3p, melatonin increases the protein expression of Yap and Ctnnd1, and eventually enhances cardiomyocyte proliferation in MI neonatal mice; however, this effect is limited to the neonatal heart. Furthermore, both MT1 and MT2 siRNA inhibit these alterations, indicating that the miR-143-3p/Yap/Ctnnd1 signaling pathway may be mediated by the MT receptors.

12 | MELATONIN REDUCES HYPERGLYCEMIA, IMPROVES INSULIN RESISTANCE, AND PROTECTS PANCREATIC β-CELLS

Hyperglycemia, hyperinsulinemia, and insulin resistance are risk factors for the development of DCM. The resulting series of abnormal reactions, such as metabolism, inflammation, and stress, lead to cardiac tissue interstitial fibrosis, cardiac stiffness/diastolic dysfunction, and later, systolic dysfunction.[6] Therefore, controlling the blood glucose level and improving insulin resistance are important measures in the treatment of DCM.

A recent clinic trial confirmed that melatonin reduces the fasting plasma glucose level and increases insulin sensitivity in diabetic

hemodialysis patients after 12 weeks of treatment.[214] In animal experiments involving male Wistar rats with T2DM, the blood glucose level and insulin resistance were determined after 15 days of melatonin treatment.[215] It was found that the serum glucose level was significantly improved and insulin resistance was reduced.[215] In addition to melatonin injection, stimulating the vagus nerve to secrete melatonin effectively controls the blood glucose level.[216] Transcutaneous vagus nerve stimulation (taVNS) triggers extrapineal melatonin secretion in ZDF rats. Furthermore, once daily taVNS for 7 days reduces the glucose concentration to a normal level, and 5 consecutive weeks of taVNS maintains normal plasma glycosylated hemoglobin, thus verifying the ability of melatonin to lower and maintain the elevated blood glucose level.

It has been reported that treatment with melatonin combined with proper exercise contributes to the expression of *PGC1α*, *NRF-1*, *NRF-2*, *TFAM*, and *GLUT4* gene in the myocardium of T2DM rats.[217] Melatonin and exercise increase mitochondrial biogenesis, alleviates insulin resistance, improves glucose metabolism and mitochondrial function, and the uptake and utilization of glucose by myocardial cells.[217] For other ways to treat insulin resistance, melatonin also plays a role. Akt at Ser473 is a downstream protein in insulin signaling, which can activate GLUT4, thereby promoting glucose transport.[218] In an insulin resistance model induced by palmitic acid, the level of Akt phosphorylation was decreased by palmitic acid treatment in rat skeletal muscle cells, which causes insulin resistance. When melatonin is used in insulin resistance cells, the level of Akt phosphorylation is increased, insulin resistance is alleviated, and glucose uptake is restored.[196]

In contrast, hyperglycemia leads to oxidative stress, reduced production of insulin, ER stress independent of oxidative stress, and death of pancreatic β cells.[167,219,220] As in other cells, glucotoxicity significantly stimulates ROS generation in a rat pancreatic β-cell line (INS-1 cells) with increased phosphorylation of proapoptotic factors (p38-MAPK and JNK) and an increased level of cleaved caspase-3, indicating an increased apoptosis of INS-1 cells. Hyperglycemia also upregulates the expression of ER stress-related genes and reduces glucose-stimulated insulin secretion (GSIS).[221] The activities of SOD, glutathione, and catalase decreased significantly in INS-1 cells treated with high glucose, but melatonin reversed these changes. Melatonin reduces oxidative stress injury in INS-1 cells exposed to high glucose levels, but does not have a significant effect on the levels of ER stress-related gene expression (*ATF4*, *CHOP*, and *GRP78*) or the impaired GSIS in INS-1 cells.[221] This finding suggested that the decreased viability of INS-1 cells is due oxidative stress, while the attenuated GSIS is due to ER stress. The final conclusion is that melatonin can effectively alleviate the oxidative stress of pancreatic β cells, but cannot effectively improve GSIS.

13 | MELATONIN AND HYPERURICEMIA

Hyperuricemia is an independent risk factor for T2DM. In the early stage of impaired glucose metabolism, uric acid levels increase. In diabetic patients, hyperuricemia is associated with micro- and macro-vascular complications.[222,223] In contrast, the increase in uric acid levels also increases the risk of atrial fibrillation and conduction block in patients with T2DM.[224,225] In fact, obese patients with elevated uric acid levels have more severe insulin resistance and oxidative stress than patients with normal uric acid levels, and this relationship is closely related to the occurrence and development of DCM.[226] Xanthine oxidoreductase catalyzes hypoxanthine to uric acid, accompanied by the production of ROS.[227] Although uric acid is the main antioxidant in plasma, uric acid is a pro-oxidant in cells and has a contributory role in the pathogenesis of various cardiovascular diseases.[228] Uric acid also has a toxic effect on vascular endothelial function, which may underlie the cause of cardiovascular disease.[229] Specifically, uric acid inhibits NO production in a dose-dependent fashion and causes vascular endothelial dysfunction. Moreover, high serum uric acid levels are often associated with cardiovascular disease, such as coronary artery disease and hypertension.[230] Therefore, corollary studies involving the effect of melatonin on serum uric acid are warranted. A clinical study showed a significant negative correlation between the levels of endogenous melatonin and uric acid in healthy young males.[231] Another clinical study showed that endogenous melatonin may impact cardiovascular disease risk.[232] Use of exogenous melatonin might decrease the serum uric acid level, and may even reduce the risk of cardiovascular disease. Direct evidence has shown that melatonin decreases plasma uric acid levels and counteracts changes in the plasma LDL-c, triglycerides, and cholesterol levels in rats with metabolic syndrome.[233]

14 | EFFECTS OF MELATONIN ON AGE-RELATED RECEPTORS

AGEs are complex compounds with crosslinks. Unlike enzymatic glycosylation of proteins, AGEs are produced by glycated proteins undergoing a series of non-enzymatic chemical rearrangements. The accumulation of AGEs increase in hyperglycemic states.[234,235] AGEs lead to reduced collagen degradation and increased fibrosis with increased myocardial stiffness and impaired cardiac relaxation,[236] which is related to the phenomenon of collagen cross-linking in collagen resistant to hydrolytic turnover.[237] AGEs contribute to an increase in ROS during production of AGEs and activation of RAGE, leading to complications of diabetes.[109,238] Furthermore, AGEs activate TLR4[239] and RAGE increases the expression of myeloid differentiation factor 88 (MyD88) and NF-κB activity, causing overstimulation of the immune system and hyperinflammation.[240] The excessive expression of TLR4 enhances formation of foam cells and increased MCP-1 and IL-8 in monocytes, leading to atherosclerosis.[241,242] By activating P38, one of the MAPK pathways, AGEs increase EPC apoptosis and decrease the production of NO.[243] Therefore, determining if melatonin has a role in the production of AGEs or AGE-related receptors and signaling pathways has become a new research direction in the treatment of DCM.

According to related studies, melatonin has an effect on inhibiting the damage caused by AGEs related receptors. Melatonin treatment significantly reduced the RAGE overexpression and the levels of p-IKKβ and

NF-κB expression in D-galactose-treated mice nervous system.[244] Other studies have also focused on the effect of melatonin on AGEs and related receptors. Specifically, the injection of melatonin significantly inhibits the overexpression of AGEs and TRL4. P38, c-Jun N-terminal kinases phosphorylation, MyD88, as well as NF-κB translocation, are also suppressed by melatonin. And early growth response protein 1, messenger RNA of macrophage inflammatory protein 2 are increased by melatonin. These findings suggest that melatonin prevents liver fibrosis by inhibiting necroptosis-associated inflammatory signaling.[245,246] However, as mentioned above, melatonin also has an activating effect on TLR4, and it can even rescue cardiomyocytes through the SAFE pathway.[35] So, which aspect is the main role? Are different effects related to tissue specificity? These questions still need a lot of experimental data to solve.

15 | DISCUSSION

Globally, the main cause of non-infectious deaths is heart disease, ranking first among all non-infectious diseases. The prevalence of heart disease is on the rise in both developed and developing countries,[247] and diabetic patients with insulin resistance are at greater risk of heart disease. It has been confirmed that diabetes has a significant effect on heart function and the cardiovascular system. Compared with healthy patients, the risk of sudden cardiac death in diabetic patients is increased 2- to 10-fold.[248] There are many reasons for this phenomenon, such as diastolic dysfunction, heart failure, increased sympathetic tone, and inflammation.[249] Melatonin has many advantages in improving diabetes-related cardiac complications. Melatonin is mainly secreted by the pineal gland, as well as other tissues, and it acts on many tissues and organs. In the heart, melatonin is effective against diabetes-induced cell apoptosis, excessive oxidative stress, ER stress, insulin resistance, sympathetic hypertonia, morbid cardiac microcirculation, and MI/R. In addition, melatonin also has a protective effect on the pancreatic β-cell, which maintains insulin secretion and promotes normal blood glucose levels, thus slowing down the progression of diabetes and its complications.

In most animal experiments that this article refers to, melatonin was used by intraperitoneal injection. This method of use maximizes the utilization of melatonin, but the current use of melatonin in the market is mainly oral. According to some reports, oral melatonin has approximately 3% bioavailability compared with intravenous injection,[250] but there are reports that this value is 9%–33%.[251] Although it is accompanied by huge experimental data and individual differences in these two reports, it is undeniable that the bioavailability of oral melatonin is very low. The reason for this finding is largely due to hepatic first pass effect.[252]

In addition to the exogenous administration method of directly supplementing melatonin, we may be able to find some ways to increase the production of endogenous melatonin. It would be great if these methods can also be used to treat diabetes and cardiomyopathy. So, what is the effect of traditional medicines for the treatment of diabetes and heart failure on the melatonin signal? Angiotensin receptor antagonists and β-receptor blockers are first-line drugs for the treatment of heart failure. In principle, noradrenergic stimulation and angiotensin can increase the secretion of melatonin.[253,254] Related experiments are indeed disappointing. Stoschitzky et al. proved in a set of clinical trials that β-blockers decrease melatonin release via specific inhibition of adrenergic beta1-receptors.[255] Baltatu et al. proved in animal experiments that using losartan to block the angiotensin AT1-receptor significantly reduces the content of melatonin in the rat pineal gland.[254] As one of the core drugs for diabetes treatment, insulin potentiates norepinephrine-mediated melatonin synthesis in cultured rat pineal glands through post-transcriptional mechanisms.[256] In addition, there are also drugs that increase the secretion of melatonin, but are not related to traditional diabetes and heart failure treatments. For example, 5-hydroxytryptamine, as the precursor of the melatonin precursor N-acetylserotonin, increases melatonin secretion evoked by submaximal norepinephrine.[257] Corticosterone potentiates noradrenaline-induced melatonin production through glucocorticoid receptor inhibition of NFkappaB nuclear translocation.[258] Thyroxine T3 can increase the melatonin levels in pineal under light conditions.[259] From this perspective, if it is necessary to show the beneficial effects of melatonin in the treatment of diabetic myocardium, then appropriate supplementation of exogenous melatonin or stimulation of endogenous melatonin production is of clinical value.

Due to the many benefits of melatonin, current research involving melatonin in the treatment of DCM is a dynamic field. In some ways, melatonin can be considered as a new treatment for DCM. In this regard, we look forward to the effective use of melatonin in the treatment of all diabetes-related diseases and the research and development of new therapeutic mechanisms of melatonin.

16 | NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS guide to PHARMACOLOGY,[260] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/2020.[261,262]

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DISCLOSURE

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Keming Huang and Xianling Luo conceived, designed, and planned the study. All authors collected and read the literature. Keming Huang drafted the manuscript. Jian Feng revised the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

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