REVIEW ARTICLE

Coronary Artery Disease And Melatonin: The Mechanisms and Therapeutic Applications

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ABSTRACT

Delaying the formation of atherosclerosis and reducing cardiac ischemia-reperfusion injury remain pressing issues. Melatonin (MLT) possesses anti-inflammatory and antioxidant properties, rendering it a promising candidate for clinical application in coronary artery disease (CAD) patients. While numerous *in vivo* experiments have elucidated the regulatory mechanisms of MLT in animal models and clinical trials have preliminarily demonstrated the excellent therapeutic potential of MLT in CAD, several key questions remain unanswered. In this review, the authors elucidate the mechanisms underlying CAD's occurrence, progression, and prognosis; delineate the pathways through which MLT exerts its effects; and present compelling evidence supporting its efficacy in CAD. In addition, the authors also describe unresolved issues in the treatment of CAD with MLT, thus providing scholars with directions for future research. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of death and morbidity worldwide.[1] In 2019, there were approximately 5.8 million new cases of ischemic heart disease reported in the European Society of Cardiology (ESC) member states;[2] CVD continues to be the leading cause of death in ESC member countries, with ischemic heart disease (IHD) being the most prevalent condition. The occurrence of IHD is primarily due to coronary artery stenosis or obstruction caused by coronary atherosclerosis (CA). Currently, the main treatment options for coronary artery disease (CAD) include drug therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG).

Melatonin (MLT) is a ubiquitous molecule with a simple structure. Its primary function is to regulate behavioral and physiological adaptations in response to the environmental and geophysical day and season;[3] its production decreases with age.[4] Over the past 30 years, numerous studies have consistently demonstrated significantly lower levels of MLT and its metabolites in patients with CAD compared to individuals without CAD.[5-8] Additionally, the level of MLT in the bloodstream is significantly associated with disease severity, and individuals at a higher risk of experiencing myocardial infarction and sudden death tend to exhibit lower MLT levels.[9]

These findings suggest that the level of MLT decreases in CAD patients and progressively declines as the disease develops. Additionally, patients with acute coronary syndrome (ACS) experience increased tissue damage following revascularization, known as ischemia-reperfusion injury (IRI), which typically leads to adverse consequences such as no-reflow phenomenon, myocardial stunning, and arrhythmia events.[10] In recent years, numerous studies have demonstrated that drug therapy can be an effective manner to intervene in IRI.[10-13] Among several drugs, MLT has

garnered increasing attention due to its anti-inflammatory and antioxidant properties. Specifically, MLT can reduce the severity of IRI and inhibit the progression of atherosclerosis and vascular calcification.[14-17]

So far, MLT has shown promising potential in treating CAD in clinical practice. Its effects include delaying the progression of CAD, reducing IRI, and slowing myocardial remodeling. However, research has primarily focused on IRI, and a comprehensive summary of the effects of MLT on CAD is still lacking. Therefore, this review aims to clarify the association between them from the aspects of inflammation, oxidative stress, and activation of signaling pathways. The authors describe the onset, progression, and ischemic injury in CAD and the pathophysiology changes of ischemia-reperfusion (IR). Additionally, the authors discuss MLT's mechanisms, role, and current application in these processes.

FROM CA TO IRI: INFLAMMATION AND OXIDATION

The primary pathological mechanism underlying myocardial ischemic injury involves inadequate blood supply resulting from luminal stenosis following coronary atherosclerosis (CAS), which also includes myocardial ischemia (MI) and hypoxia caused by coronary thrombosis after plaque rupture. Atherosclerosis (AS) is a lipid-induced, multi-focal, sedimentary, and immune-inflammatory disease that affects the middle and large arteries. The involvement of various cells (vascular endothelial cells, smooth muscle cells, inflammatory cells, etc.), activation of pro-inflammatory signaling pathways (NF-κB, JAK-STAT, TLR, and NLRP3, etc.), cytokine/chemokine expression, and oxidative stress are primarily responsible for the progression of the disease.[18-20] There is now substantial experimental and clinical evidence suggesting that inflammation plays a significant role in the pathophysiology of AS and ischemic events.[21]

Reactive Oxygen Species Participate in the Oxidation of Low-Density Lipoprotein

The conversion of low-density lipoprotein (LDL) particles into oxidized low-density lipoprotein (OxLDL) in the subendothelium is closely associated with reactive oxygen species (ROS).[20] Under normal physiological conditions, appropriate levels of ROS play a role in maintaining signaling pathways that regulate processes such as inflammation, cell differentiation, proliferation, and apoptosis. However, ROS production can excessively activate these pathways and contribute to disease progression when it becomes dysregulated.[22] Excessive ROS production can further stimulate ROS generation, leading to oxidative stress and promoting disease progression.[22] In addition to LDL oxidation, ROS can induce oxidative modifications in mitochondrial DNA, consequently leading to endothelial dysfunction and inflammation.

The primary sources of vascular ROS include the mitochondrial electron transport chain (ETC), NADPH oxidase (NOX), xanthine oxidase (XO), and endothelial nitric oxide synthase (eNOS).[23] Numerous studies have demonstrated that increased expression of ETC, NOX, XO, and ROS accumulation caused by these elevated enzymes can promote AS progression.[24-26] However, the role of eNOS in AS remains controversial. A previous study demonstrated that enhanced eNOS activity in Apolipoprotein E-deficient mice exerted beneficial effects in preventing AS,[27] but another study published in the same year arrived at the opposite conclusion.[28] Additionally, studies focused on the relationship between decreased eNOS expression and AS development have also yielded conflicting conclusions.[29,30] The possible reasons for this discrepancy are that the disease stages and vascular endothelial states differed in these studies.

OxLDL is Associated with Inflammation.

OxLDL induces inflammatory responses by modulating both innate and acquired immune responses.[31] In macrophages, OxLDL binds to pattern recognition receptors (PRRs) such as scavengers or toll-like receptors (TLRs), leading to foam cell formation and secretion of inflammatory factors like interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) in an NF-κB-dependent pathway.[32,33] Numerous studies have demonstrated that OxLDL-specific T cells are involved in inflammation related to AS.[33-35]

Additionally, several studies have found that the anti-OxLDL IgG secreted by B cells also contributes to inflammation in AS, while anti-OxLDL IgM exhibited protective effects.[36] Ait-Oufella et al. discovered that after using anti-CD20 to remove mature B cells from circulation in Ldlr -/- and Apoe -/- mice, levels of anti-OxLDL IgG significantly decreased. Still, anti-OxLDL IgM only showed a slight decrease. Furthermore, AS progression was delayed.[36] Kyaw et al. conducted a study transferring IgM-secreting B1a B cells or conventional IgG-secreting B2 B cells to Apoe-/-Rag2-/-Gamma(c)-/- mice, as well as transferring B2 B cells to Apoe-/-μMT-/- mice. They found that transferring B1a B cells resulted in the elimination of AS, whereas transferring B2 B cells led to over 300% increase in lesion size.[37]

Inflammation and Oxidation in Reperfusion

Plaque rupture is a leading cause of coronary thrombosis, which clinically presents as ACS.[38] ACS can lead to ischemic injury and necrosis in the myocardial region controlled by culprit vessels. If coronary artery perfusion is not restored early, it can lead to myocardial remodeling and heart failure, with the most serious complications being non-fatal myocardial infarction and cardiac death.[39] Therefore, it is particularly urgent to perform early vascular reconstruction on culprit vessels.

The revascularization techniques commonly employed in clinical practice include thrombolysis, PCI, and CABG. Recent research shows revascularization commonly leads to IRI.[10] IRI accelerates and exacerbates myocardial damage, contradicting the primary objective of vascular recanalization. During myocardial ischemia, organelles generate significant ROS and pro-apoptotic signals, which are pivotal in initiating and

maintaining the inflammatory phase of IRI. Restoration of blood flow may exacerbate tissue damage by reoxygenation, generating additional ROS, and activating complementary pathways. Subsequently, damaged cardiomyocytes and interstitial cells bind to PRRs on parenchymal cells such as cardiac fibroblasts, resident macrophages, and infiltrating leukocytes through danger-associated molecular patterns. NF-κB is a prominent signaling pathway driving the expression of numerous pro-inflammatory genes, instigating and amplifying inflammatory response.[40] Moreover, macrophages play a crucial role in IRI pathogenesis. Functional M1 macrophages promote inflammation development.[41] During myocardial infarction, monocytes are recruited to the infarction site and differentiate into pro-inflammatory M1 macrophages.[42] In cardiomyocytes, mitochondria play a crucial role in IRI pathogenesis. Ischemia and hypoxia-induced perturbation of intracellular milieu disrupt mitochondrial structure and function, impairing the electron transport chain, increasing mitochondrial permeability transition pore (mPTP) opening, and mitophagy induction, culminating in oxidative stress.[43] Upon sudden reperfusion of ischemic cardiomyocytes, ROS concentration significantly increases, leading to pronounced mPTP opening.[44] This event causes an osmotic pressure imbalance across the organelle membrane, resulting in mitochondrial swelling, rupture, and cellular demise.[45] Additionally, inflammasome activation is also associated with IRI. Well-characterized NLRP3 inflammasomes, a type of cytoplasmic PRRs, are predominantly present in leukocyte cytoplasm.[46] Animal studies have demonstrated that inhibiting the NLRP3 receptor could attenuate myocardial cell death and delay myocardial remodeling in a mouse acute myocardial infarction (AMI) model by mediating inflammasome activation.[47]

Inflammation and oxidative stress are pivotal in AS, AMI, and myocardial IRI pathogenesis. Targeted interventions on identified pathways involved in these processes could improve CAD patient prognosis and reduce the incidence of major adverse cardiovascular events. Despite using various drugs like statins, antiplatelet agents, and hypoglycemic medications to mitigate AS progression,[48] current methods may not completely halt its advancement.[49] In recent decades, numerous drugs exhibiting antioxidant and anti-inflammatory properties have been investigated for potential therapeutic benefits in cardiovascular diseases. MLT has emerged as a promising candidate.

Mechanisms of MLT in CAD: Focusing on the Plaque Phase and IR Phase

MLT is an indoleamine synthesized by the pineal gland, exhibiting a circadian rhythm with higher nocturnal levels. Its primary role is regulating sleep patterns.[50-52] MLT exerts diverse anti-inflammatory, antioxidant, metabolic, and vasomotor effects.[53] Some tissues, in addition to the pineal gland, also express key MLT synthesis enzymes, indicating they can independently synthesize MLT.[54] This MLT does not exhibit circadian rhythms and works locally, protecting cells from oxidative and inflammatory damage.[50,51] MLT exerts anti-inflammatory and antioxidant functions through receptor-dependent signaling pathways and chemical reactions with free radicals, providing electrons to neutralize them.[55,56] Receptors for MLT primarily consist of MT1, MT2, MT3, and retinoid-related orphan receptors, which can play a role in the heart and blood vessels upon activation.[55,57] Notably, MT3 is not a true MLT receptor in the strict sense; it is an enzyme called quinone reductase-2.

Protective Role of MLT in AS

Previous studies showed MLT could potentially protect against AS development by inhibiting LDL oxidation.[58] Subsequent studies have demonstrated MLT's role in AS and elucidated potential mechanisms. It can prevent endothelial adhesion molecule formation, decrease arterial wall fat accumulation, neutralize free radicals, lower lipid peroxidation levels, enhance endogenous cholesterol clearance, and safeguard mitochondrial ETC function.[59-61] Additionally, several studies have utilized MLT to target crucial AS signaling pathways and consistently demonstrated notable AS progression reduction.[62-66] The main pathways include toll-like receptors, NOD-like receptor protein 3 (NLRP3), proprotein convertase subtilisin/kexin type 9 (PCSK9), Notch, Wnt, and others.

Hu et al. conducted a study applying MLT in rabbits fed a high-fat diet and discovered MLT can improve vascular endothelial dysfunction, inflammation, and AS by inhibiting the TLR4/NF-κB system.[63] Additionally, a recent study revealed that MLT exerts an anti-atherosclerotic effect by effectively suppressing the S100a9/NF-κB pathway.[64] Zhang et al. conducted a study using ApoE-/- mice fed a high-fat diet as an AS animal model to investigate MLT's effects on arteries.[65] They discovered treating mice with MLT for 12 weeks reduced aortic atherosclerotic plaque development and prevented endothelial pyroptosis by regulating the long non-coding RNA MEG3/miR-223/NLRP3 axis. Ma et al. investigated cigarette smoke extract's (CSE) impact on HepG2 cell PCSK9 and its molecular mechanism regulating low LDL receptor (LDLR).[66] They discovered CSE exposure significantly increased PCSK9 expression and inhibited LDLR expression. Moreover, CSE triggered ROS and NF-κB generation and activation. Remarkably, MLT treatment effectively attenuated CSE's regulatory effects on PCSK9 and LDLR in HepG2 cells by modulating the ROS/NF-κB signaling pathway. Furthermore, Ren et al. discovered MLT can improve oxidative stress injury and apoptosis in diabetic rat aortas induced by streptozotocin by activating the Notch1/Hes1 signaling pathway.[67]

Recently, studies have focused on other pathways to clarify MLT's effects. Having previously identified MLT's role in the TLR pathway, Hu et al. further investigated whether MLT's anti-AS properties were associated with upregulating the anti-inflammatory hepatocyte growth factor/mesenchymal-epithelial transformation factor system, and their findings confirmed this relationship.[68] Additionally, the Wnt signaling pathway has been identified as a critical AS

factor. However, no studies have investigated MLT's impact on AS in the Wnt pathway. Meanwhile, most of the above studies focused on AS rather than CAS. The researchers eagerly anticipate future research to enhance and refine MLT application in cardiovascular health.

Mechanisms of Action of MLT in IRI

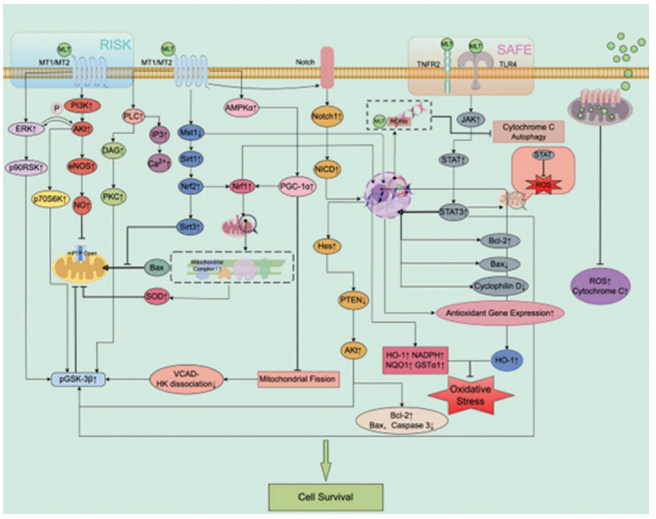
MLT's role and mechanism in animal IRI models have been extensively studied. MLT can effectively enhance cardiomyocyte survival after IR by activating critical signaling pathways like reperfusion injury salvage kinase (RISK), survivor activating factor enhancement (SAFE), Notch, and others[69-73] (Figure 1). MLT acts on G protein-coupled receptors to activate PI3K, which phosphorylates downstream Akt and ERK. Phosphorylated Akt and ERK inhibit mPTP opening, reducing myocardial cell apoptosis after IR.[70] MLT can also activate cGMP and enhance anti-oxidative stress ability through the KG1α-Nrf2/HO-1 pathway.[74] MLT acts on the Toll4 and TNF receptors for the SAFE pathway, leading to JAK phosphorylation. Subsequently, p-JAK phosphorylates STAT. Dimercized STAT translocates into the nucleus to facilitate antioxidant gene expression, thereby reducing oxidative stress and IRI. Meanwhile, STAT inhibits pro-apoptotic protein Bax transfer and enhances anti-apoptotic Bcl2 expression, suppressing mPTP opening and mitigating oxidative stress and IRI.[70,71] For the Notch pathway, MLT activates the Notch/Hes1 pathway and improves Akt function, resulting in reduced pro-apoptotic proteins and increased anti-apoptotic protein production.[72]

Recently, MLT was found to act on other pathways. Zhou et al. found MLT exerts a direct protective effect on cardiac microcirculating endothelial cells against IR injury by inhibiting the mitochondrial fission-VDAC1-HK2-mPTP mitophagy axis, thereby safeguarding cardiomyocytes.[73] Yu et al. showed MLT leads to antioxidant upregulation by activating the SIRT1/FoxO pathway, thereby mitigating oxidative stress.[75] Additionally, by binding to the nuclear RORα receptor or through PKB/Akt, the MLT molecule exerts regulatory effects on genes, which is crucial in inhibiting oxidative stress.[76,77] Due to its lipophilic characteristics, MLT can penetrate mitochondria and exhibit antioxidant properties, reducing oxidative stress and apoptosis potential helping protect mitochondrial function.[78] Furthermore, several MLT receptor agonists, including Ramelteon, Piromelatine, Agomelatine, and other documented MLT receptor agonists like Tasimelteon, have been studied in animal models and shown beneficial effects in safeguarding the heart during IR but have not yet been studied in humans.[79-81] Thus, further investigation into MLT and MT receptor agonist clinical application in coronary heart disease (CHD) patients is needed.

CLINICAL RESEARCH OF MLT ON IR AND AS

As a safe drug, MLT has gained widespread clinical acceptance.[81] Numerous clinical studies have investigated MLT's cardiac effects on IR using various administration methods. Table 1 shows the major clinical research studies.

Figure 1. Melatonin acts on cardiomyocytes during the IR phase by activating multiple pathways.



Note: Melatonin acts on cardiomyocytes during the IR phase by activating multiple pathways: (1) MLT activates PI3K after binding to MT receptor, which activates the RISK pathway, and phosphorylates the ERK and AKt. On one hand, Akt inhibits the opening of mPTP by stimulating eNOS and promoting NO production. Conversely, ERK and AKt activation leads to an upregulation of p90RSK and p70S6K, respectively, resulting in increased phosphorylation of pGSK-3β, which subsequently inhibits mPTP opening. (2) The combination of MLT with TNFR2 and TLR4 triggers JAK phosphorylation, thereby activating the SAFE pathway and subsequently inducing STAT3 activation. Nuclear translocation of STAT3 stimulates the expression of antioxidant and anti-apoptotic genes while suppressing apoptotic gene expression, ultimately mitigating injury and death in cardiomyocytes following IRI. Additionally, STAT inhibits ROS generation within mitochondria, thereby mitigating oxidative stress. Moreover, STAT3 promotes phosphorylation of pGSK-3β and suppresses the opening of mPTP. (3) MLT binds to MT receptor and activates the Notch pathway. Subsequently, NICD increases and acts in the nucleus to increase Hes expression, thereby inhibiting PTEN production and increasing AKt. On the one hand, it regulates genes and reduces cell apoptosis, on the other hand, it increases pGSK-3β and inhibits mPTP opening. (4) MLT also inhibits the opening of mPTP through the PLC/PKC pathway and AMPKα/PGC-1α pathway. Moreover, it increases SOD by augmenting respiratory chain complex levels, thus restraining mPTP opening. Additionally, the Nrf2/Sirt3 pathway suppresses Bax translocation to mitochondria, thereby mitigating cellular damage. (5) Mst1 and Nrf1 translocate into the nucleus to modulate the expression of antioxidant factors, thereby exerting a pivotal role in combating oxidative stress. Moreover, MLT exhibits its inhibitory effect on cytochrome C and autophagy by binding to nuclear RORα receptors. Furthermore, MLT directly penetrate mitochondria and suppress both cytochrome C release and ROS generation. Abbreviation: MLT: melatonin; IR: ischemia-reperfusion; IRI: ischemia-reperfusion injury; RISK: reperfusion injury salvage kinase; SAFE: survivor activating factor enhancement; ROS: reactive oxygen species; mPTP: Reactive oxygen species; eNOS: endothelial nitric oxide synthase; VDAC-HK: voltage-dependent anion channel (VDAC)-hexokinase (HK).

Employ MLT Through Oral Administration

Based on MLT's beneficial effect of inducing nuclear factor-erythroid 2-related factor 2 (Nrf2) activation against oxidative stress, Haghjooy et al. investigated potential protective effects of MLT on IRI during the CABG by activating Nrf2 as a critical transcription factor involved in cellular antioxidant defense.[81] The study revealed patients undergoing CABG receiving 10mg oral MLT starting one

Table 1. Major Randomized Controlled Studies of Clinical Research on the Effects of Melatonin on the Ischemia-Reperfusion Phase

Study (Author) (Year)	Country	Diagnosis	Admin. methods	Grouping dosage, and timing	Surgical approach	Participants (N)	Age (y)	Male (%)	IR duration	Follow-up duration	Outcome measure	Conclusion
Haghjooy 2013	Iran	IHD	Oral admin	10 mg MLT or placebo once daily for 1 month before surgery	CABG	30	59.1 ± 9.4	86.7	NA	45 min	NRF2	Positive effects
Ghaeli 2015	Iran	STEMI	Oral admin	3 mg MLT with usual care or only usual care starting the night after surgery during hospitalization	pPCI	40	58.4 ± 12.2	75.0	NA	6 h	hs-TNT and CK-MB	Positive effects
Dwaich K 2016	Iraq	IHD	Oral admin	10 mg or 20 mg MLT or placebo once daily for 5 days before surgery	CABG	45	52.9 ± 5.3	80.0	NA	1 day	cTn-1, IL-1β, and iNOS	Positive effects
Shafiei E 2018	Iran	IHD	Oral admin	5 mg MLT starting from 24 h before surgery for 3 times and a single dose with 200 cc water 1 hour before surgery; 600 mg NAC for 2 days before surgery for 3 times daily and a single dose in the morning of the surgery; or placebo	CABG	86	60.4 ± 9.4	54.6	NA	After recovery at the ICU	Troponin I, MDA, and TNF-α	Positive effects
Dominguez-Rodriguez A 2017	Spain	STEMI	Injection admin	12 mg MLT or placebo i.v. before surgery and 2 mg MLT or placebo i.c. after surgery	pPCI	125	57.8 ± 9.7	88.8	208.5 ± 71.0 (min)	7 days	LVEF, LVSDV, LVEDV, and total LV mass	Positive effects
Ekeloef S 2017	Denmark	STEMI	Injection admin	1 mg MLT or placebo i.c. as soon as a reperfusion visible and 49 mg MLT or placebo i.v. was started immediately after pPCI	pPCI	48	62.8 ± 12.8	79.2	3.4 ± 0.8 (h)	4 ± 1 days	LVEDV, LVESV, LVEF, Area at risk, Infarct size, and MSI	Positive effects

Abbreviation: IR, ischemia-reperfusion; MLT, melatonin; CABG, coronary artery bypass grafting; NRF2, nuclear erythroid 2-related factor 2; IHD, ischemic heart disease; STEMI, ST-segment elevation myocardial infarction; pPCI, primary percutaneous coronary intervention; i.c., intracoronary injection; i.v., intravenous injection; ICU, intensive care unit; hs-TnT, high-sensitive troponin T; CK-MB, creatinine kinase myocardial band; cTn-I, cardiac troponin I; IL-1β, interleukine-1β; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; MSI, myocardial salvage index.

month before surgery exhibited significantly increased Nrf2 concentration compared to placebo, indicating reduced oxidative stress. However, this study did not assess perioperative differences beyond Nrf2 levels, making myocardial injury level evaluation challenging.

Subsequently, Ghaeli et al. investigated the effect of postoperative oral MLT on hs-TNT and CK-MB in STEMI patients undergoing primary PCI.[82] One group received 3 mg oral MLT nightly after PCI until discharge, while the control group only received usual care during hospitalization. Blood hs-TnT and CK-MB concentrations were measured before and 6 hours after surgery. Results demonstrated MLT administration significantly reduced CK-MB serum levels without significantly changing hs-TnT levels between groups. Therefore, they suggested MLT can serve as adjunctive therapy alongside conventional treatment after initial PCI, leading to reduced cardiovascular events.

In contrast to Ghaeli et al.'s postoperative administration, Dwaich et al. employed preoperative oral MLT to investigate potential cardioprotective effects in CABG patients and the dose-dependent relationship between MLT and cardiac injury reduction extent.[83] Subjects were randomly assigned to receive a placebo, 10 mg/day MLT, or 20 mg/day MLT for 5 days before surgery. Both MLT groups exhibited significantly increased ejection fraction and decreased heart rate compared to controls. Furthermore, plasma cTnI, interleukin-1β, inducible nitric oxide synthase, and caspase-3 levels significantly reduced the MLT groups. Meanwhile, the high-dose group changes were more pronounced than the low-dose group.

Additionally, Shafiei et al. investigated N-acetylcysteine (NAC) and MLT's effects on early reperfusion injury and acute oxidative stress in CABG patients. They measured pre- and post-treatment serum cardiac cTnI, lactate, MDA, and TNF-α levels with oral placebo, MLT, or NAC. Eighty-eight patients were included.[84] After surgery, MLT and NAC groups had significantly lower levels of all four biomarkers versus controls. They also found significant differences in mean ICU stay time between groups. In summary, oral MLT, whether pre- or post-operatively administered, may reduce myocardial injury after PCI and CABG.

Employ MLT Through Injection

Dominguez-Rodriguez et al. explored different MLT administration timing efficacy in STEMI patients using intravenous or intracoronary injection.[85] STEMI patients undergoing primary PCI were randomly assigned to intravenous, intracoronary MLT, or placebo. Time from symptom onset to PCI was divided into tertiles, with subsequent infarct size assessment via magnetic resonance imaging within one week.

Results indicated MLT effectively reduced infarct size when administered within 136 minutes of symptom onset to balloon dilatation, likely due to the absence of oxidative stress at this stage. However, when administered beyond 294 minutes, MLT did not significantly reduce infarct size as irreversible oxidative stress had already occurred. Therefore, early MLT application possesses anti-IRI effects and better protects the heart.

Nevertheless, contrasting Dominguez-Rodriguez, Ekeloef et al. found no association between MLT usage during cardiac reperfusion and myocardial salvage index.[86] Intravenous and intracoronary 50 mg MLT or placebo were initiated at IR onset. However, between groups, no significant myocardial salvage index differences were observed via cardiac magnetic resonance imaging after 4±1 day. MLT did not affect left ventricular function, infarct size, or cardiac biomarkers. Additionally, at 90 days, no discernible difference in clinical event incidence was observed between groups. However, the ischemia to reperfusion duration was approximately 3.1 hours in the MLT group, compared to 3.7 hours in placebo, potentially explaining the

differing conclusions, as irreversible oxidative stress damage may have occurred from the relatively prolonged MI. Integrating both studies, early reperfusion may enhance MLT efficacy in mitigating IRI. Currently, more precise medicine remains paramount, an inevitable and prevailing trend.

Employ MLT Through Oral Administration Combined with Injections

Previous research has shown that oral or injection MLT administration reduces IRI. However, few clinical studies have used combined administration in CAD patients. Gögenur et al. investigated perioperative MLT treatment effects on perioperative IRI, clinical cardiac morbidity, and ischemic events in elective abdominal aortic aneurysm repair.[87] They administered 50 mg intravenous MLT within 2 hours of surgery, followed by 10 mg oral MLT nightly for 3 days after. Blood samples were collected up to 96 hours post-reperfusion, and Holter monitoring assessed postoperative cardiac morbidity. Results demonstrated perioperative MLT significantly reduced clinical heart disease incidence, myocardial injury marker levels, and MI occurrence.[88] Although fewer abnormal ECG ST-segment changes occurred in the MLT versus control group, this difference was not statistically significant. In summary, perioperatively administered oral and intravenous MLT could reduce IRI extent and effectively decrease clinical heart disease incidence and cardiac ischemic events after abdominal aortic aneurysm repair. The authors hypothesize that combined oral and intravenous MLT could also reduce IRI in CAD patients, but there is currently minimal research comparing the efficacy of different administration methods. Further research is imperative to determine optimal preoperative, postoperative, or perioperative administration and oral versus intravenous versus combined MLT.

Furthermore, MLT administration timing plays a crucial role, with efficacy influenced by timing. A secondary study evaluating MLT administration efficacy and optimal route and timing found intravenous and intracoronary MLT improved left ventricular ejection fraction within 3.5 hours of MI to reperfusion.[88] Infarct size reduction was observed within 2.5 hours, with these positive effects absent beyond 3.5 hours. Based on these conclusions, MLT injection treatment in early MI stages is suggested. However, due to limited clinical studies, accurately defining these stages remains uncertain, necessitating further research to determine the optimal administration route and deadline.

As previously stated, animal experiments have shown that MLT can improve atherosclerosis through receptor-mediated and non-receptor pathways. However, published clinical studies investigating MLT treatment for AS and the potential to delay CAS progression are currently lacking. However, Zaslavskaia et al. found adding MLT to conventional treatment produced significant anti-ischemic and anti-anginal effects in CHD patients, suggesting MLT may have a clinical role in controlling CAS progression.[89] Therefore, more human RCTs are crucial to provide insights into disease progression, treatment efficacy, hospitalization outcomes, and long-term prognosis.

SUMMARY

Melatonin, a well-established sleep regulator, has been scientifically proven to possess antioxidant and anti-inflammatory properties and the ability to safeguard the cardiovascular system through various mechanisms. Although substantial research has yielded valuable insights into oxidative stress and inflammation mechanisms in CAD, further comprehensive investigation and existing knowledge refinement are warranted. Currently, there is a limited number of published clinical studies on MLT treatment for coronary atherosclerosis and IRI. However, overall findings demonstrate positive results, encouraging further exploring MLT as an adjunctive CAD therapy and offering hope in reducing arteriosclerotic cardiovascular disease incidence and improving prognosis. Additionally, numerous studies have investigated MT receptor application. The primary challenge is determining optimal timing, route, and dosage, necessitating extensive clinical studies to obtain robust evidence. In the future, these drugs are anticipated to be recommended as standard adjunctive CHD treatment options in guidelines.

ETHICAL COMPLIANCE

Not applicable.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

R.-Q.Y.: Funding acquisition, Supervision, Writing - review and editing; Z.-Z.L. and R.-X.C.: Writing - original draft; P.Y., D.-J.Z., J.Z., and X.L.: Supervision, Visualization, Writing- review and editing. ZL and RC share first authorship.

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REFERENCES

1. Latif R, Mumtaz S, Al Sheikh MH, Chathoth S, Al Naimi SN; Effects of Turmeric on Cardiovascular Risk Factors, Mental Health, and Serum Homocysteine in Overweight, Obese Females. *Altern Ther Health M*. 2021;27(114-119
2. Timmis A, Vardas P, Townsend N, et al; Atlas Writing Group, European Society of Cardiology. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J*. 2022;43(8):716-799. doi:10.1093/eurheartj/ehab892
3. Zhang N, Zhang K, Xu X, Hu J, Wang X, Meng X. Correlation between troponin T and N-Terminal brain natriuretic peptide levels and cardiac structure and function and cardiovascular disease in elderly maintenance hemodialysis patients. *Cell Mol Biol (Noisy-le-grand)*. 2022;68(7):117-122. doi:10.14715/cmb/2022.68.7.19
4. Reiter RJ, Richardson BA, Johnson LY, Ferguson BN, Dinh DT. Pineal melatonin rhythm: reduction in aging Syrian hamsters. *Science*. 1980;210(4476):1372-1373. doi:10.1126/science.7434032
5. Moon C, Benson CJ, Albashayreh A, Perkhounkova Y, Burgess HJ. Sleep, circadian rhythm characteristics, and melatonin levels in later life adults with and without coronary artery disease. *J Clin Sleep Med*. 2023;19(2):283-292. doi:10.5664/jcsm.10308
6. Yaprak M, Altun A, Vardar A, Aktoz M, Ciftci S, Ozbay G. Decreased nocturnal synthesis of melatonin in patients with coronary artery disease. *Int J Cardiol*. 2003;89(1):103-107. doi:10.1016/S0167-5273(02)00461-8
7. Sakotnik A, Liebmann PM, Stoschitzky K, et al. Decreased melatonin synthesis in patients with coronary artery disease. *Eur Heart J*. 1999;20(18):1314-1317. doi:10.1053/euhj.1999.1527
8. Girotti L, Lago M, Ianovsky O, et al. Low urinary 6-sulphatoxymelatonin levels in patients with coronary artery disease. *J Pineal Res*. 2000;29(3):138-142. doi:10.1034/j.1600-079X.2000.290302.x
9. Dominguez-Rodriguez A, Abreu-Gonzalez P, Sanchez-Sanchez JJ, Kaski JC, Reiter RJ. Melatonin and circadian biology in human cardiovascular disease. *J Pineal Res*. 2010;49(1):14-22. doi:10.1111/j.1600-079X.2010.00773.x
10. Wang F, Gao Q, Yang J, et al. Artemisinin suppresses myocardial ischemia-reperfusion injury via NLRP3 inflammasome mechanism. *Mol Cell Biochem*. 2020;474(1-2):171-180. doi:10.1007/s11010-020-03842-3
11. Zhang XJ, Liu X, Hu M, et al. Pharmacological inhibition of arachidonate 12-lipoxygenase ameliorates myocardial ischemia-reperfusion injury in multiple species. *Cell Metab*. 2021;33(10):2059-2075.e10. doi:10.1016/j.cmet.2021.08.014
12. Jiang W, Zhang Y, Zhang W, et al. Hirsutine ameliorates myocardial ischemia-reperfusion injury through improving mitochondrial function via CaMKII pathway. *Clin Exp Hypertens*. 2023;45(1):2192444. doi:10.1080/10641963.2023.2192444
13. Singhanat K, Apaijai N, Jaiwongkam T, Kerdphoo S, Chattipakorn SC, Chattipakorn N. Melatonin as a therapy in cardiac ischemia-reperfusion injury: potential mechanisms by which MT2 activation mediates cardioprotection. *J Adv Res*. 2020;29:33-44. doi:10.1016/j.jare.2020.09.007
14. Zhen G, Liang W, Jia H, Zheng X. Melatonin relieves sepsis-induced myocardial injury via regulating JAK2/STAT3 signaling pathway. *Minerva Med*. 2022;113(6):983-989. doi:10.23736/S0026-4806.20.06626-4

15. Wang Z, Gao Z, Zheng Y, et al. Melatonin inhibits atherosclerosis progression via galectin-3 downregulation to enhance autophagy and inhibit inflammation. *J Pineal Res*. 2023;74(3):e12855. doi:10.1111/jpi.12855
16. Xu F, Zhong JY, Lin X, et al. Melatonin alleviates vascular calcification and ageing through exosomal miR-204/miR-211 cluster in a paracrine manner. *J Pineal Res*. 2020;68(3):e12631. doi:10.1111/jpi.12631
17. Dominguez-Rodriguez A, Abreu-Gonzalez P, Reiter RJ. Clinical aspects of melatonin in the acute coronary syndrome. *Curr Vasc Pharmacol*. 2009;7(3):367-373. doi:10.2174/157016109788340749
18. Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*. 2006;47(8)(suppl):C7-C12. doi:10.1016/j.jacc.2005.09.068
19. Förstermann U, Xia N, Li H. Li. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. *Circ Res*. 2017;120(4):713-735. doi:10.1161/CIRCRESAHA.116.309326
20. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative stress in atherosclerosis. *Curr Atheroscler Rep*. 2017;19(11):42. doi:10.1007/s11883-017-0678-6
21. Libby P, Hansson GK. From focal lipid storage to systemic inflammation: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74(12):1594-1607. doi:10.1016/j.jacc.2019.07.061
22. Yang S, Lian G. ROS and diseases: role in metabolism and energy supply. *Mol Cell Biochem*. 2020;467(1-2):1-12. doi:10.1007/s11010-019-03667-9
23. Batty M, Bennett MR, Yu E. The role of oxidative stress in atherosclerosis. *Cells*. 2022;11(23):3843. doi:10.3390/cells11233843
24. Li X, Fang P, Mai J, Choi ET, Wang H, Yang XF. Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. *J Hematol Oncol*. 2013;6(1):19. doi:10.1186/1756-8722-6-19
25. Sorescu D, Weiss D, Lassègue B, et al. Superoxide production and expression of nox family proteins in human atherosclerosis. *Circulation*. 2002;105(12):1429-1435. doi:10.1161/01.CIR.0000012917.74432.66
26. Battelli MG, Polito L, Bolognesi A. Xanthine oxidoreductase in atherosclerosis pathogenesis: not only oxidative stress. *Atherosclerosis*. 2014;237(2):562-567. doi:10.1016/j.atherosclerosis.2014.10.006
27. van Haperen R, de Waard M, van Deel E, et al. Reduction of blood pressure, plasma cholesterol, and atherosclerosis by elevated endothelial nitric oxide. *J Biol Chem*. 2002;277(50):48803-48807. doi:10.1074/jbc.M209477200
28. Ozaki M, Kawashima S, Yamashita T, et al. Overexpression of endothelial nitric oxide synthase accelerates atherosclerotic lesion formation in apoE-deficient mice. *J Clin Invest*. 2002;110(3):331-340. doi:10.1172/JCI0215215
29. Knowles JW, Reddick RL, Jennette JC, Shesely EG, Smithies O, Maeda N. Enhanced atherosclerosis and kidney dysfunction in eNOS(-/-)Apoe(-/-) mice are ameliorated by enalapril treatment. *J Clin Invest*. 2000;105(4):451-458. doi:10.1172/JCI8376
30. Shi Y, Baker JE, Zhang C, Tweddell JS, Su J, Pritchard KA Jr. Chronic hypoxia increases endothelial nitric oxide synthase generation of nitric oxide by increasing heat shock protein 90 association and serine phosphorylation. *Circ Res*. 2002;91(4):300-306. doi:10.1161/01.RES.0000031799.12850.1E
31. Rhoads JP, Major AS. How oxidized low-density lipoprotein activates inflammatory responses. *Crit Rev Immunol*. 2018;38(4):333-342. doi:10.1615/CritRevImmunol.2018026483
32. Chávez-Sánchez L, Madrid-Miller A, Chávez-Rueda K, Legorreta-Haquet MV, Tesoro-Cruz E, Blanco-Favela F. Activation of TLR2 and TLR4 by minimally modified low-density lipoprotein in human macrophages and monocytes triggers the inflammatory response. *Hum Immunol*. 2010;71(8):737-744. doi:10.1016/j.humimm.2010.05.005
33. Nagy L, Tontonoz P, Alvarez JG, Chen H, Evans RM. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARgamma. *Cell*. 1998;93(2):229-240. doi:10.1016/S0092-8674(00)81574-3
34. Dansky HM, Charlton SA, Harper MM, Smith JDT. T and B lymphocytes play a minor role in atherosclerotic plaque formation in the apolipoprotein E-deficient mouse. *Proc Natl Acad Sci USA*. 1997;94(9):4642-4646. doi:10.1073/pnas.94.9.4642
35. Zhou X, Nicoletti A, Elhage R, Hansson GK. Transfer of CD4(+) T cells aggravates atherosclerosis in immunodeficient apolipoprotein E knockout mice. *Circulation*. 2000;102(24):2919-2922. doi:10.1161/01.CIR.102.24.2919
36. Ait-Oufella H, Herbin O, Bouaziz JD, et al. B cell depletion reduces the development of atherosclerosis in mice. *J Exp Med*. 2010;207(8):1579-1587. doi:10.1084/jem.20100155
37. Kyaw T, Tay C, Khan A, et al. Conventional B2 B cell depletion ameliorates whereas its adoptive transfer aggravates atherosclerosis. *J Immunol*. 2010;185(7):4410-4419. doi:10.4049/jimmunol.1000033
38. Schaar JA, Muller JE, Falk E, et al. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *Eur Heart J*. 2004;25(12):1077-1082. doi:10.1016/j.ehj.2004.01.002
39. Stone PH, Libby P, Boden WE. Fundamental pathobiology of coronary atherosclerosis and clinical implications for chronic ischemic heart disease management-the plaque hypothesis: a narrative review. *JAMA Cardiol*. 2023;8(2):192-201. doi:10.1001/jamacardio.2022.3926
40. Algoet M, Janssens S, Himmelreich U, et al. Myocardial ischemia-reperfusion injury and the influence of inflammation. *Trends Cardiovasc Med*. 2023;33(6):357-366. doi:10.1016/j.tcm.2022.02.005
41. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat Immunol*. 2010;11(10):889-896. doi:10.1038/ni.1937
42. Peet C, Ivetic A, Bromage DI, Shah AM. Cardiac monocytes and macrophages after myocardial infarction. *Cardiovasc Res*. 2020;116(6):1101-1112. doi:10.1093/cvr/cvz336
43. Braunersreuther V, Jaquet V. Reactive oxygen species in myocardial reperfusion injury: from physiopathology to therapeutic approaches. *Curr Pharm Biotechnol*. 2012;13(1):97-114. doi:10.2174/138920112798868782
44. Robin E, Guzy RD, Loor G, et al. Oxidant stress during simulated ischemia primes cardiomyocytes for cell death during reperfusion. *J Biol Chem*. 2007;282(26):19133-19143. doi:10.1074/jbc.M701917200
45. Heusch G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat Rev Cardiol*. 2020;17(12):773-789. doi:10.1038/s41569-020-0403-y
46. Martínez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. *Atherosclerosis*. 2018;269:262-271. doi:10.1016/j.atherosclerosis.2017.12.027
47. Mezzaroma E, Toldo S, Farkas D, et al. The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. *Proc Natl Acad Sci USA*. 2011;108(49):19725-19730. doi:10.1073/pnas.1108586108
48. Zhang Y, Koradia A, Kamato D, Popat A, Little PJ, Ta HT. Treatment of atherosclerotic plaque: perspectives on theranostics. *J Pharm Pharmacol*. 2019;71(7):1029-1043. doi:10.1111/jphp.13092
49. Favero G, Rodella LF, Reiter RJ, Rezzani R. Melatonin and its atheroprotective effects: a review. *Mol Cell Endocrinol*. 2014;382(2):926-937. doi:10.1016/j.mce.2013.11.016
50. Acuña-Castroviejo D, Escames G, Venegas C, et al. Extrapineal melatonin: sources, regulation, and potential functions. *Cell Mol Life Sci*. 2014;71(16):2997-3025. doi:10.1007/s00018-014-1579-2
51. Venegas C, García JA, Escames G, et al. Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. *J Pineal Res*. 2012;52(2):217-227. doi:10.1111/j.1600-079X.2011.00931.x
52. Zawilska JB, Skene DJ, Arendt J. Physiology and pharmacology of melatonin in relation to biological rhythms. *Pharmacol Rep*. 2009;61(3):383-410. doi:10.1016/S1734-1140(09)70081-7
53. Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin--a pleiotropic, orchestrating regulator molecule. *Prog Neurobiol*. 2011;93(3):350-384. doi:10.1016/j.pneurobio.2010.12.004
54. Stefulj J, Hörtner M, Ghosh M, et al. Gene expression of the key enzymes of melatonin synthesis in extrapineal tissues of the rat. *J Pineal Res*. 2001;30(4):243-247. doi:10.1034/j.1600-079X.2001.300408.x
55. Paulis L, Simko F, Laudon M. Cardiovascular effects of melatonin receptor agonists. *Expert Opin Investig Drugs*. 2012;21(11):1661-1678. doi:10.1517/13543784.2012.714771
56. Galano A, Reiter RJ. Melatonin and its metabolites vs oxidative stress: from individual actions to collective protection. *J Pineal Res*. 2018;65(1):e12514. doi:10.1111/jpi.12514
57. Ma H, Kang J, Fan W, He H, Huang F. ROR: nuclear receptor for melatonin or not? *Molecules*. 2021;26(9):2693. doi:10.3390/molecules26092693
58. Seegar H, Mueck AO, Lippert TH. Effect of melatonin and metabolites on copper-mediated oxidation of flow density lipoprotein. *Br J Clin Pharmacol*. 1997;44(3):283-284. doi:10.1046/j.1365-2125.1997.00648.x
59. Pita ML, Hoyos M, Martin-Lacave I, Osuna C, Fernández-Santos JM, Guerrero JM. Long-term melatonin administration increases polyunsaturated fatty acid percentage in plasma lipids of hypercholesterolemic rats. *J Pineal Res*. 2002;32(3):179-186. doi:10.1034/j.1600-079x.2002.1o851.x
60. Reiter RJ, Tan DX, Paredes SD, Fuentes-Broto L. Beneficial effects of melatonin in cardiovascular disease. *Ann Med*. 2010;42(4):276-285. doi:10.3109/07853890903485748
61. Rodella LF, Favero G, Foglio E, et al. Vascular endothelial cells and dysfunctions: role of melatonin. *Front Biosci (Elite Ed)*. 2013;5(1):119-129. doi:10.2741/E601
62. Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ, Han M. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. *Signal Transduct Target Ther*. 2022;7(1):131. doi:10.1038/s41392-022-00955-7
63. Hu ZP, Fang XL, Fang N, et al. Melatonin ameliorates vascular endothelial dysfunction, inflammation, and atherosclerosis by suppressing the TLR4/NF-κB system in high-fat-fed rabbits. *J Pineal Res*. 2013;55(4):388-398. doi:10.1111/jpi.12085
64. Chen L, Wang X, Liu C, et al. Melatonin ameliorates atherosclerosis by suppressing S100a9-mediated vascular inflammation. *Eur J Pharmacol*. 2023;957:175965. doi:10.1016/j.ejphar.2023.175965
65. Zhang Y, Liu X, Bai X, et al. Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis. *J Pineal Res*. 2018;64(2):e12449. doi:10.1111/jpi.12449
66. Ma B, Wang X, Zhang R, et al. Cigarette smoke extract stimulates $PCSK_9$ production in $HepG_2$ cells via ROS/NFκB signaling. *Mol Med Rep*. 2021;23(5):331. doi:10.3892/mmr.2021.11970
67. Ren BC, Zhang W, Zhang W, Ma JX, Pei F, Li BY. Melatonin attenuates aortic oxidative stress injury and apoptosis in STZ-diabetes rats by Notch1/Hes1 pathway. *J Steroid Biochem Mol Biol*. 2021;212:105948. doi:10.1016/j.jsbmb.2021.105948
68. Hu ZP, Fang XL, Sheng B, Guo Y, Yu YQ. Melatonin inhibits macrophage infiltration and promotes plaque stabilization by upregulating anti-inflammatory HGF/c-Met system in the atherosclerotic rabbit: USPIO-enhanced MRI assessment. *Vascul Pharmacol*. 2020;127:106659. doi:10.1016/j.vph.2020.106659
69. Yang Y, Duan W, Jin Z, et al. JAK2/STAT3 activation by melatonin attenuates the mitochondrial oxidative damage induced by myocardial ischemia/reperfusion injury. *J Pineal Res*. 2013;55(3):275-286. doi:10.1111/jpi.12070
70. Yu L, Li B, Zhang M, et al. Melatonin reduces PERK-***eIF2α***-ATF4-mediated endoplasmic reticulum stress during myocardial ischemia-reperfusion injury: role of RISK and SAFE pathways interaction. *Apoptosis*. 2016;21(7):809-824. doi:10.1007/s10495-016-1246-1
71. Nduhirabandi F, Lamont K, Albertyn Z, Opie LH, Lecour S. Role of toll-like receptor 4 in melatonin-induced cardioprotection. *J Pineal Res*. 2016;60(1):39-47. doi:10.1111/jpi.12286
72. Yu L, Liang H, Lu Z, et al. Membrane receptor-dependent Notch1/Hes1 activation by melatonin protects against myocardial ischemia-reperfusion injury: in vivo and in vitro studies. *J Pineal Res*. 2015;59(4):420-433. doi:10.1111/jpi.12272
73. Zhou H, Zhang Y, Hu S, et al. Melatonin protects cardiac microvasculature against ischemia/reperfusion injury via suppression of mitochondrial fission-VDAC1-HK2-mPTP-mitophagy axis. *J Pineal Res*. 2017;63(1):e12413. doi:10.1111/jpi.12413
74. Yu LM, Di WC, Dong X, et al. Melatonin protects diabetic heart against ischemia-reperfusion injury, role of membrane receptor-dependent cGMP-PKG activation. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864(2):563-578. doi:10.1016/j.bbadis.2017.11.023
75. Yu L, Sun Y, Cheng L, et al. Melatonin receptor-mediated protection against myocardial ischemia/reperfusion injury: role of SIRT1. *J Pineal Res*. 2014;57(2):228-238. doi:10.1111/jpi.12161
76. He B, Zhao Y, Xu L, et al. The nuclear melatonin receptor RORα is a novel endogenous defender against myocardial ischemia/reperfusion injury. *J Pineal Res*. 2016;60(3):313-326. doi:10.1111/jpi.12312
77. Nduhirabandi F, Du Toit EF, Blackhurst D, Marais D, Lochner A. Chronic melatonin consumption prevents obesity-related metabolic abnormalities and protects the heart against myocardial ischemia and reperfusion injury in a prediabetic model of diet-induced obesity. *J Pineal Res*. 2011;50(2):171-182. doi:10.1111/j.1600-079X.2010.00826.x
78. Reiter RJ, Paredes SD, Manchester LC, Tan DX. Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. *Crit Rev Biochem Mol Biol*. 2009;44(4):175-200. doi:10.1080/10409230903044914
79. Stroethoff M, Behmenburg F, Spittler K, et al. Activation of melatonin receptors by ramelteon induces cardioprotection by postconditioning in the rat heart. *Anesth Analg*. 2018;126(6):2112-2115. doi:10.1213/ANE.0000000000002625
80. Yu J, Wei J, Ji L, Hong X. Exploration on mechanism of a new type of melatonin receptor agonist Neu-p11 in hypoxia-reoxygenation injury of myocardial cells. *Cell Biochem Biophys*. 2014;70(2):999-1003. doi:10.1007/s12013-014-0009-2
81. Jia P, Liu C, Wu N, Jia D, Sun Y. Agomelatine protects against myocardial ischemia reperfusion injury by inhibiting mitochondrial permeability transition pore opening. *Am J Transl Res*. 2018;10(5):1310-1323.
82. Ghaeli P, Vejdani S, Ariamanesh A, Hajhossein Talasaz A. Effect of melatonin on cardiac injury after primary percutaneous coronary intervention: a randomized controlled trial. *Iran J Pharm Res*. 2015;14(3):851-855.
83. Dwaich KH, Al-Amran FG, Al-Sheibani BI, Al-Aubaidy HA. Melatonin effects on myocardial ischemia-reperfusion injury: Impact on the outcome in patients undergoing coronary artery bypass grafting surgery. *Int J Cardiol*. 2016;221(977-986. doi:10.1016/j.ijcard.2016.07.108
84. Shafiei E, Bahtoei M, Raj P, et al. Effects of N-acetyl cysteine and melatonin on early reperfusion injury in patients undergoing coronary artery bypass grafting: A randomized, open-labeled, placebo-controlled trial. *Medicine (Baltimore)*. 2018;97(30):e11383. doi:10.1097/MD.0000000000011383
85. Dominguez-Rodriguez A, Abreu-Gonzalez P, de la Torre-Hernandez JM, et al; MARIA Investigators. Usefulness of early treatment with melatonin to reduce infarct size in patients with st-segment elevation myocardial infarction receiving percutaneous coronary intervention (from the melatonin adjunct in the acute myocardial infarction treated with angioplasty trial). *Am J Cardiol*. 2017;120(4):522-526. doi:10.1016/j.amjcard.2017.05.018
86. Ekeloef S, Halladin N, Fonnes S, et al. Effect of intracoronary and intravenous melatonin on myocardial salvage index in patients with st-elevation myocardial infarction: a randomized placebo controlled trial. *J Cardiovasc Transl Res*. 2017;10(5-6):470-479. doi:10.1007/s12265-017-9768-7
87. Gögenur I, Kücükakin B, Panduro Jensen L, Reiter RJ, Rosenberg J. Melatonin reduces cardiac morbidity and markers of myocardial ischemia after elective abdominal aortic aneurism repair: a randomized, placebo-controlled, clinical trial. *J Pineal Res*. 2014;57(1):10-15. doi:10.1111/jpi.12138
88. Lv T, Yan J, Lou Y, et al. Evaluation of melatonin therapy in patients with myocardial ischemia-reperfusion injury: a systematic review and meta-analysis. *Oxid Med Cell Longev*. 2022;2022:4610522. doi:10.1155/2022/4610522
89. Zaslavskaia RM, Shcherban' EA, Lilitsa GV, Logvinenko SI. [Melatonin in the combined treatment of cardiovascular diseases]. *Klin Med (Mosk)*. 2010;88(3):26-30.