Asemi *et al. Journal of Cardiothoracic Surgery* (2025) 20:194
https://doi.org/10.1186/s13019-025-03423-9

Journal of Cardiothoracic Surgery

REVIEW Open Access

Melatonin as a treatment for atherosclerosis: focus on programmed cell death, inflammation and oxidative stress

Reza Asemi[1], Elham Omidi Najafabadi[2*], Zahra Mahmoudian[3*], Russel J. Reiter[4], Mohammad Ali Mansournia[5] and Zatollah Asemi[6*]

Abstract

Delaying the development of atherosclerosis (AS) and decreasing cardiac ischemia-reperfusion damage remain serious challenges for the medical community. Chronic arterial disease, i.e., AS, is frequently linked to oxidative stress and inflammation as significant contributing causes. AS risk factors, such as hyperlipidemia, high blood pressure, age, hyperglycemia, smoking, high cholesterol, and irregular sleep patterns, can exacerbate AS in the carotid artery and further shrink its lumen. Finding new approaches that support plaque inhibition or stability is an ongoing problem. The last ten years have shown us that melatonin (MLT) affects the cardiovascular system, although its exact mechanisms of action are yet unknown. MLT's direct free radical scavenger activity, its indirect antioxidant qualities, and its anti-inflammatory capabilities all contribute to its atheroprotective effects on several pathogenic signaling pathways. Herein, we examine the evidence showing that MLT treatment has significant protective effects against AS and AS-related cardiovascular diseases. The numerous pieces of the puzzle that have been as for epigenetic and biogenetic targets for prevention and therapy against the atherosclerotic pathogenic processes are identified.

Keywords Melatonin, Atherosclerosis, Apoptosis, Autophagy, Pyroptosis

*Correspondence:
Elham Omidi Najafabadi
dreliomidi@gmail.com
Zahra Mahmoudian
mahsamahmoudian69@yahoo.com
Zatollah Asemi
asemi_r@yahoo.com
[1]Department of Internal Medicine, School of Medicine, Cancer Prevention Research Center, Seyyed Al-Shohada Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Department of Cell Systems and Anatomy, UT Health. Long School of Medicine, San Antonio, TX, USA
[5]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[6]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, Iran

Introduction

The primary cause of cardiovascular disease (CVD) is atherosclerosis (AS), a chronic inflammatory disease of the arterial wall characterized by stenosis, plaque rupture, or occlusion because of thrombosis and platelet aggregation [1, 2]. Age-related illnesses and aging-related aging are associated with disruption of the pathways responsible for programmed cell death (PCD), which is necessary for tissue homeostasis and cell turnover [3, 4]. A multiprotein complex known as the inflammasome mediates pyroptosis, a kind of pro-inflammatory PCD [5, 6]. NOD-like receptor family protein 3 (NLRP3) binds the adaptor protein apoptosis-associated speck-like protein containing in the traditional pyroptosis pathway, which leads to the maturation of interleukin-18 (IL-18) and pro-caspase-1 (IL-1β) and the cleavage of pro-caspase-1 into physiologically active caspase-1 [7, 8]. By activating the NLRP3 inflammasome during AS, a number of detrimental cardiovascular variables can cause inflammation and worsen atheroma development; blocking the inflammasome helps to stabilize the plaque [9, 10]. The PCD processes of pyroptosis and apoptosis are distinguished by caspase dependency, nuclear condensation, and chromatin condensation. The connection between pyroptosis and apoptosis has not been extensively studied, although a number of crucial proteins, including those between FADD and caspase-8 [11], gasdermin D (GSDMD) and caspase-1 [12, 13], and GSDME and caspase-3 [14, 15], are known to mediate between the two types of cell death.

The pineal indoleamine melatonin (MLT), exhibits a circadian rhythm and is more abundantly produced at night. One function of the circadian MLT rhythm is to influence sleep/wake cycle [16, 17]. In addition to MLT production by the pineal gland, the mitochondria of all other organs also likely synthesize MLT [16]. Unlike the pinealocytes, these cells do not release MLT but rather use in intracellularly to protect against oxidative stress, etc. MLT has a variety of metabolic, vasomotor, antioxidant, and anti-inflammatory actions [18]. These cells produce MLT in their mitochondria [17]. This MLT functions locally, without being released or exhibiting a circadian rhythm; its function shields cells from oxidative and inflammatory damage [19]. Through receptor-dependent signaling pathways and chemical interactions with free radicals, MLT provides electrons to neutralize radical products and carries out anti-inflammatory and other antioxidant effects by stimulating antioxidant enzymes [20, 21]. The main MLT receptors include MT1, MT2, MT3, and retinoid-related orphan receptors, which, when activated, influence the heart and blood vessels [22]. MT3 is not a conventional MLT receptor in the strict sense; it is an enzyme called quinone reductase-2. MLT delays the development of AS by preventing low-density lipoprotein (LDL) oxidation [23, 24]. Subsequent investigations have proven MLT's function in AS and highlighted probable molecular pathways in modulating AS. It inhibits endothelial adhesion molecules, reduces the build-up of fat in the artery wall, neutralizes free radicals, decreases lipid peroxidation, improves endogenous cholesterol clearance, and protects mitochondrial electron transport chain function [25, 26]. Additionally, multiple studies have employed MLT to target critical AS signaling pathways and it consistently exhibited the ability to slow AS progression [5, 27, 28]. Also, toll-like receptors, proprotein convertase subtilisin/kexin type 9, NLRP3, Wnt, Notch, and other molecular pathways are among the primary routes by which MLT functions. In the current review, we examine how MLT affects different types of PCD (identify PDC), inflammation and oxidative stress, and how these interactions could be utilized for the prevention as well as treatment of AS.

How endogenous MLT May reduce atherosclerotic risk?

Naturally secreted MLT—produced by the pineal gland in response to the circadian rhythm—may play a role in reducing the risk of atherosclerotic diseases. Several studies have suggested that healthy sleep habits, which support endogenous MLT production, are linked to a lower risk of CVD, including AS. However, while the theory is plausible, more longitudinal and interventional human studies are needed to establish a direct cause-and-effect relationship. MLT is a key regulator of the biological clock and influences cardiovascular function by modulating blood pressure, heart rate, and vascular tone. Studies suggest that disrupted circadian rhythms (such as shift work, late-night exposure to artificial light, and irregular sleep patterns) are associated with increased risk of hypertension, dyslipidemia, and AS [29, 30]. In addition, MLT acts as a powerful antioxidant, scavenging reactive oxygen species (ROS) and reducing oxidative stress, which plays a key role in endothelial dysfunction and AS progression. It also modulates inflammatory pathways, decreasing the levels of pro-inflammatory cytokines, which contribute to vascular damage and plaque formation [31]. Endothelial dysfunction is a hallmark of early AS. MLT enhances nitric oxide production, leading to better vasodilation and reduced vascular stiffness, both of which are protective against AS [32]. In addition, MLT has been shown to reduce sympathetic nervous system activity, which is important because chronic sympathetic overactivation contributes to hypertension, a major risk factor for AS [33].

Several studies support the idea that natural MLT secretion through healthy sleep patterns may reduce the risk of AS [34]. A meta-analysis of 71 studies (with 3.8 million participants) found that sleep duration 7.5 h

per night) was associated with a reduced risk of cardiocerebrovascular disease [35]. Also, a study on shift workers found that disruptions in the sleep-wake cycle led to reduced MLT levels, increased arterial stiffness, and higher risk of subclinical AS [36]. In addition, it was reported that endogenous MLT production via maintaining healthy sleep-wake cycles is an important but often overlooked factor in cardiovascular health [37].

Apoptosis

Apoptosis is a type of programmed cell death important for sustaining cell homeostasis. It is characterized by a systematic, controlled process and is regulated by numerous genes [38]. Cell shrinkage, pseudopodia disappearance, chromatin clumping, nuclear membrane shrinkage, nucleoli breaking, and, at the end, the development of apoptotic bodies are the physical changes that occur during apoptosis. It entails activating genes and regulating them in various ways. Numerous disease processes involving the cardiovascular system, such as atherosclerosis, include apoptosis in macrophages, vascular smooth muscle cells, myeloid, and lymphoid cells [39, 40]. Uncontrolled apoptosis can alter the stability, morphology, and metabolism of the arteries during the course of atherosclerosis. This plays a crucial role in regulating the cytotoxicity of elements of the arterial wall [41, 42]. Apoptosis is initiated by any of the two pathways: the internal or external route. This is decided by the signal that initiates apoptosis. Caspases in the external route are activated and apoptosis is initiated by extracellular signals. Endogenous mechanisms mediate the induction of cysteine aspartate proteases by internal stimuli. These activated caspases induce apoptosis and generate major proteins in cells [43–45] (Fig. 1). Many in vitro and in vivo investigations, along with several trials' clinical trials, have investigated whether the antioxidant activity of

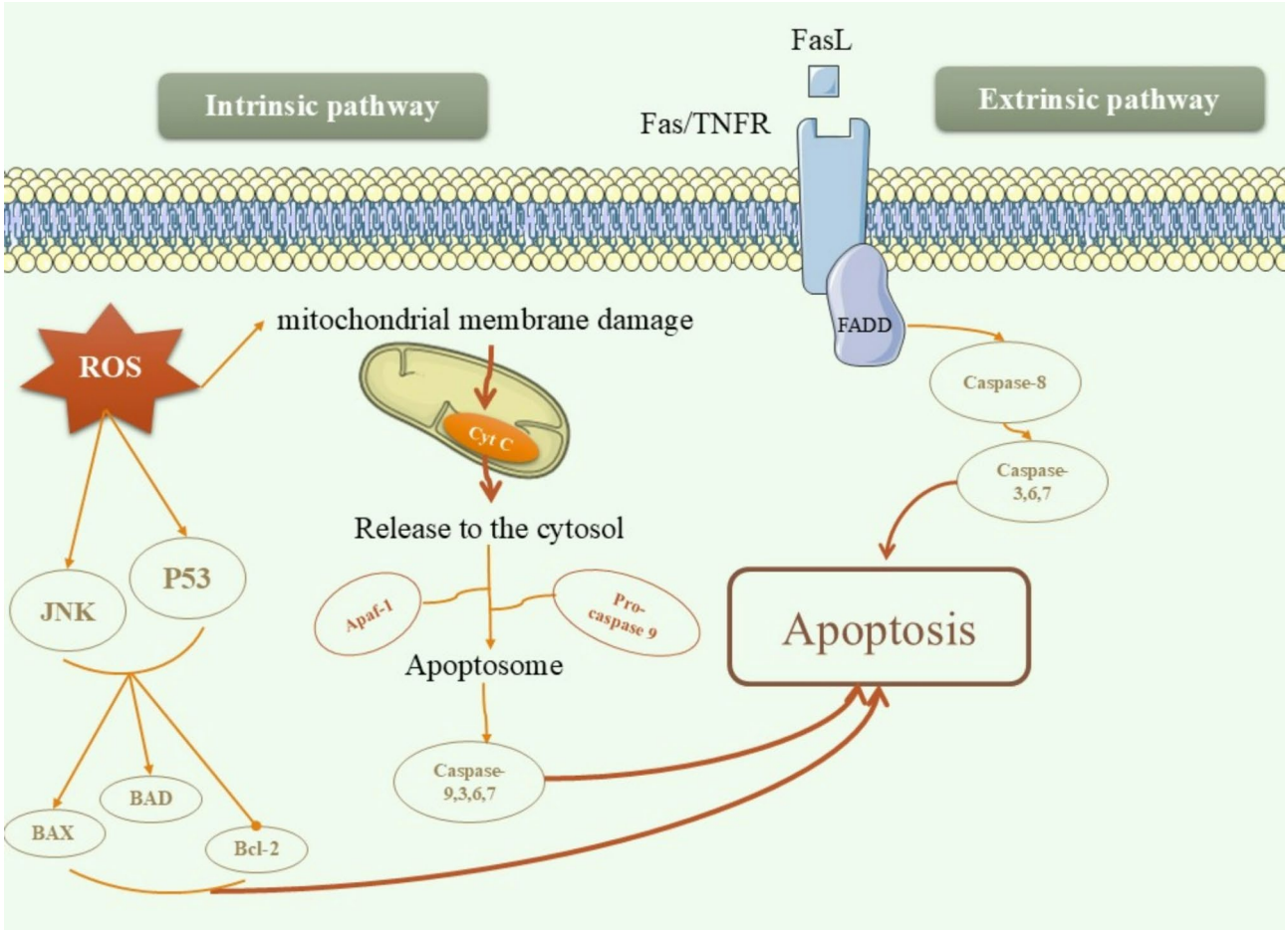

Fig. 1 This figure illustrates the two main apoptotic pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway. The intrinsic pathway is triggered by cellular stress, such as reactive oxygen species (ROS) and DNA damage, which activate p53, JNK, and pro-apoptotic proteins (BAX, BAD) while inhibiting Bcl-2, leading to mitochondrial membrane damage and cytochrome c (Cyt C) release. Cyt C binds Apaf-1, forming the apoptosome, which activates caspase-9 and executioner caspases (caspase-3, -6, -7), inducing apoptosis. The extrinsic pathway is initiated by the binding of Fas ligand (FasL) to Fas/TNFR, recruiting FADD and activating caspase-8, which directly triggers executioner caspases, leading to apoptos
is. Both pathways ultimately result in controlled cell death through caspase activation

MLT has a positive impact on CVD via regulating oxidative stress. Previous studies have shown that MLT favorably reduces apoptosis as well as pyroptosis [5, 46, 47]. The accumulation of ROS leads to cellular damage that can ultimately activate apoptotic pathways. Oxidative stress plays a central role in modulating both the intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways of apoptosis, and its effects are tightly regulated by several key molecular mechanisms. Mitochondria are central to the regulation of apoptosis, and oxidative stress has a profound impact on their integrity. ROS can damage mitochondrial membranes and proteins, leading to mitochondrial dysfunction. One of the earliest events in the intrinsic apoptotic pathway is the loss of mitochondrial membrane potential, which is induced by oxidative stress. This damage triggers the release of pro-apoptotic factors such as cytochrome c from the mitochondrial intermembrane space into the cytosol [48]. In addition, tumor necrosis factor-alpha (TNF-α) and its receptor (TNFR) are upregulated in response to oxidative stress. TNF-α binding to TNFR triggers the recruitment of adapter proteins which activates caspase-8, promoting cell death [49]. Nuclear factor-kappa B (NF-κB) is a redox-sensitive transcription factor that is activated by ROS and plays a critical role in inflammation. NF-κB can promote both cell survival and apoptosis, depending on the context and the type of cellular stress. NF-κB activation leads to the expression of pro-inflammatory cytokines like TNF-α and IL-1β, which, in turn, activate death receptors and amplify apoptotic signals. NF-κB also regulates the expression of pro-apoptotic genes, which links TNF signaling to apoptotic cascades [50].

The anti-pyroptotic and anti-oxidative stress properties of MLT on human THP-1 macrophages exposed to nicotine have been examined. To create a pyroptosis model in vitro, 1 μM nicotine was added to THP-1 macrophages, which were then treated with 30 mM MLT. In vivo, 0.1 mg/mL nicotine solution was given as drinking water to ApoE-/- mice, and 10 mg/kg/day of 1 mg/mL MLT solution was given intragastrically. There were observed alterations in oxidative stress, pyroptosis, and apoptosis. The findings showed that MLT inhibited pyroptosis, which was accompanied by a decrease in the generation of ROS, a reversal of sirtuin 3 activity, and an overexpression of Forkhead box O3. MLT also prevented apoptosis, which was primarily brought on by the interaction of the proteins, caspase-1 and caspase-3 [51] **(**Table 1**).**

Pyroptosis

The first indication of pyroptosis was observed in Salmonella-mediated macrophage death. Subsequently, it cell death known as "PCD", which is dependent on the caspase-1 enzyme and associated with the production of some inflammatory cytokines [52, 53]. Pyroptosis is induced by certain inflammatory substances that cause gastrin to separate and awaken latent cytokines like IL-1 and IL-18. AS and diabetic nephropathy are two diseases that are closely linked to these processes [54, 55]. AS develops more quickly as a result of an increase in vascular wall cell loss [56, 57]. Inflammation is a complex biological response to damaging stimuli. The release of GSDMD, which promotes cell death in the eyelid's pores, causes pyroptosis. NLRP3 inflammatory bodies have been observed to be activated by a range of threats and stimuli [58, 59]. Thus, blocking the activation of NLRP3 inflammatory bodies may reduce pyroptosis and interrupt the development and progression of AS. Pyroptosis is a highly inflammatory form of PCD. Depending on whether it depends on caspase-1, the inflammatory route is categorized as being normal or atypical. Drooping

Table 1 Role of melatonin on programmed cell death, inflammation and oxidative stress

Marker	Disease	MLT dose	Target	Model	Results	Reference
Apoptosis	Atherosclerosis	30 mM	Human THP-1 macrophages	In vitro	Inhibited apoptosis	[51]
Pyroptosis	Atherosclerosis	-	Human umbilical vein endothelial cells	In vitro	Prevented endothelial cell pyroptosis	[61]
Pyroptosis	Atherosclerosis	-	Aortic endothelium	In vitro	Prevents endothelial cell pyroptosis	[5]
Inflammation	Atherosclerosis	20 mg/kg/d	mRNA and protein levels	In vitro	Inhibiting S100a9/NF-κB signaling	[78]
Inflammation	Atherosclerosis	-	THP-1 macrophages	In vivo and in vitro	Downregulating Gal-3 and inhibiting inflammation	[79]
Inflammation	Atherosclerosis	-	mRNA and serum levels	In vitro	Increased expressions of visfatin and STAT-3	[80]
Inflammation	Atherosclerosis	10 mg/kg/day	mRNA and serum levels	In vitro	Reduced expressions of MyD88, TLR4, and NF-κB p65 and increased IκB expression	[27]
Oxidative stress	Atherosclerosis	-	mRNA and serum levels	In vitro	Enhancing antioxidant capacity	[92]
Oxidative stress	Atherosclerosis	-	mRNA and serum levels	In vitro	Enhancing antioxidant capacity	[93]
Oxidative stress	Atherosclerosis	10 mg/kg/day	mRNA and serum levels	In vitro	Enhancing antioxidant capacity	[94]

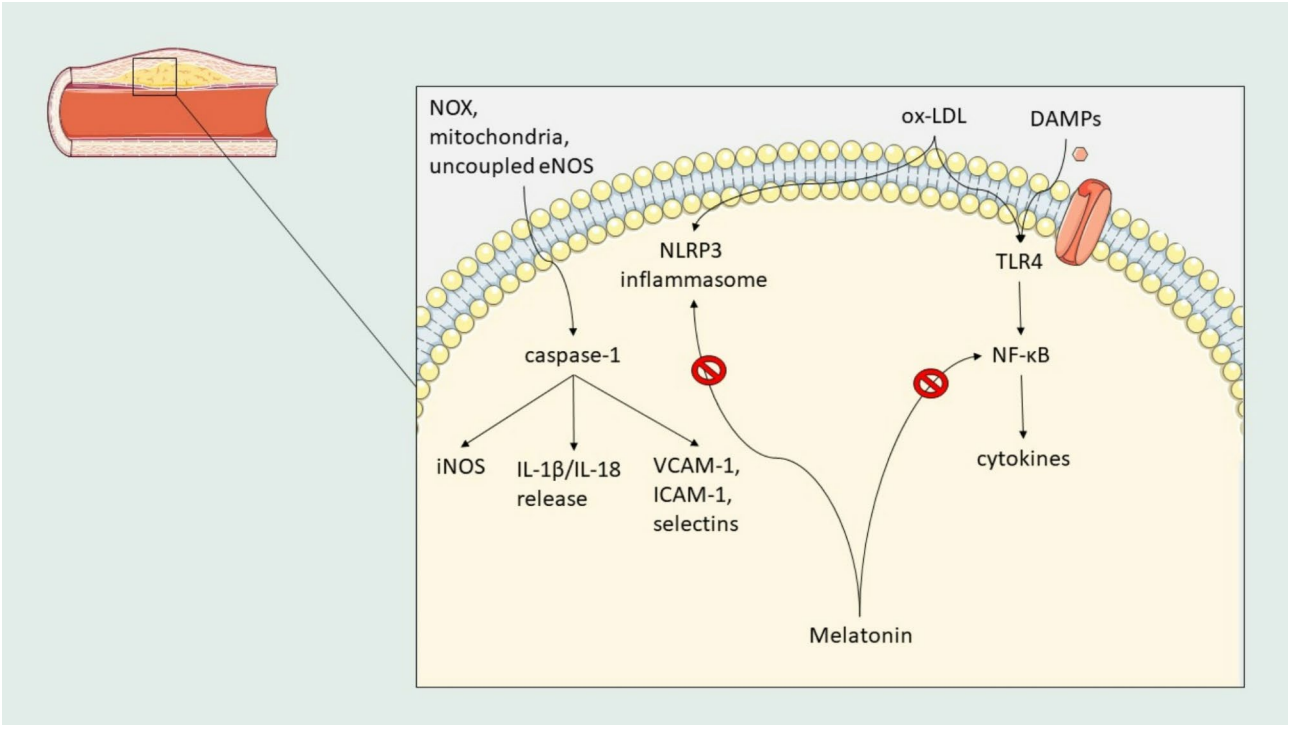

Fig. 2 This figure illustrates the molecular mechanisms linking oxidative stress and inflammation to atherosclerosis, as well as the protective effects of melatonin. Reactive oxygen species (ROS) generated by NADPH oxidase (NOX), mitochondria, and uncoupled endothelial nitric oxide synthase (eNOS) contribute to oxidative stress, leading to the activation of inflammatory pathways. Oxidized low-density lipoprotein (ox-LDL) and damage-associated molecular patterns (DAMPs) activate Toll-like receptor 4 (TLR4), which triggers nuclear factor kappa B (NF-κB) signaling. This results in the transcription of pro-inflammatory cytokines, promoting vascular inflammation and endothelial dysfunction. In parallel, oxidative stress and inflammatory stimuli activate the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, which in turn activates caspase-1, leading to the cleavage and release of pro-inflammatory cytokines interleukin-1 beta (IL-1β) and interleukin-18 (IL-18). Additionally, caspase-1 promotes the expression of inducible nitric oxide synthase (iNOS) and adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and selectins, facilitating immune cell recruitment and plaque progression. Melatonin, a potent antioxidant and anti-inflammatory molecule, inhibits NF-κB activation and NLRP3 inflammasome assembly, thereby reducing cytokine production and endothelial dysfunction. This highlights its potential therapeutic role in mitigating oxidative stress and inflammation in atherosclerosis

is caused by caspase-3 and caspase-8, which reduce GSDMD and GSDME, respectively (Fig. 2). The antipyroptotic effect of MLT is likely be attributed to inhibition of the toll-like receptor 4 (TLR4)/NF-κB signaling pathway [60].

An investigation of MLT's anti-pyroptotic properties and possible mechanisms in atherosclerotic endothelium has been published. The findings demonstrated that MLT decreased the expression of pyroptosis-related genes in human umbilical vein endothelial cells treated with oxidized LDL (ox-LDL), like caspase-1, NLRP3, and IL-1β. In addition, MLT decreased pyroptosis, lowered ubiquinol-cytochrome c reductase core protein 1 (UQCRC1) methylation, and increased the expression of ten-eleven translocation 2. MLT's up-regulation of UQCRC1 enhanced mitochondrial activity, which prevented endothelial cell pyroptosis and oxidative stress [61]. To clarify the possible processes and explore the antipyroptotic effects of MLT in atherosclerotic endothelium have also been examined. ApoE-/-mice given a high-fat diet (HFD) served as an animal model for AS in this investigation. The findings showed that a 12-week intragastric dose of MLT significantly decreased the amount of atherosclerotic plaque in the aorta. In the aortic endothelium of MLT-treated rats, MLT also reduced the expression of genes linked to pyroptosis, such as NLRP3, ASC, GSDMD N-termini, cleaved caspase1, NF-κB/GSDMD, IL-18, and IL-1β. Human aortic endothelial cells (HAECs) treated with ox-LDL likewise showed consistent antipyroptotic effects. Furthermore, in HAECs, lncRNA MEG3 improved pyroptosis. Moreover, miR-223 knockdown prevented MLT antipyroptotic effects in HAECs treated with ox-LDL [5].

Inflammatory markers

Inflammation plays a critical role in the development of the atherosclerotic process (the initial formation and development of plaques in the arteries) as well as its course (the progression and outcomes of the disease). The main causes of endothelial damage, aberrant blood

lipid levels, and hemodynamic stress in the early stages of AS are as follows [62]. AS is also characterized by the accumulation of lipids in macrophages, which easily initiates the activation of an inflammasome, a multiprotein complex [63, 64]. NLRP3 inflammasome is the most well-researched regulator linked to the pathophysiology of CVD among the many inflammasomes. Important NLRP3 components are expressed at higher levels in human atherosclerotic lesions, and studies have demonstrated that blocking the NLRP3 inflammasome significantly slows the advancement of AS [65]. The creation of secondary inflammatory mediators such as IL-6 is triggered by the pro-inflammatory response, which is mostly dependent on the local production of IL-1β. Due to its many inflammatory effects on smooth muscle cells, macrophages, and vascular endothelial cells, IL-1β plays a major role in AS and its consequences. For example, IL-1β stimulates the generation of platelet-derived growth factors via autocrine processes and increases adhesion molecules in human endothelial cells, both of which can promote the proliferation of smooth muscle cells. Moreover, this cytokine stimulates innate immunity-related cells, especially macrophages [66, 67]. MLT has significant anti-inflammatory properties. COX-2 and iNOS have a tight relationship with inflammation and the generation of inflammatory cytokines [68]. The release of NK-κB bound to the inhibitor IκB [69, 70] and the translocation of dimerized NK-κB to the nucleus are caused by phosphorylation of NK-κB, which in turn promotes the production of inflammatory genes, including inflammatory cytokines [71]. This is a crucial mechanism that controls inflammatory reactions and promotes the production of COX-2 and iNOS [72, 73]. The NF-κB pathway primarily controlled the production of iNOS and COX-2, and this route was strongly linked to myocardial dysfunction [74]. MLT suppresses the production of COX-2 and iNOS [75, 76]. This also reduces inflammatory responses and lessens tissue damage by blocking the NF-κB pathway [77].

A recent study assessed the efficacy of MLT as a treatment for AS. For 12 weeks, MLT (20 mg/kg/day) was given intraperitoneally to mice lacking in apolipoprotein E (ApoE-/-) in an AS model produced by a HFD. In ApoE-/-mice with HFD-induced AS, MLT therapy significantly reduced atherosclerotic lesions, produced stable phenotypic sclerotic plaques, prevented macrophage infiltration, and reduced the release of pro-inflammatory cytokines. Notably, S100a9 was found to be a key mediator in the protective effects of MLT by combining IPA and DIA-based quantitative proteomics. Furthermore, MLT dramatically reduced the mRNA and protein levels of HFD-induced S100a9 expression. The NF-κB signaling pathway was strongly activated and the antagonistic impact of MLT on HFD-induced vascular inflammation during atherogenesis was considerably eliminated when S100a9 was overexpressed. By blocking S100a9/NF-κB signaling, MLT has a strong antiatherogenic impact [78]. Also, MLT slows the course of AS by downregulating Gal-3 to improve autophagy and reduce inflammation. As a result, it used THP-1 macrophages and ApoE-/- mice given a HFD for both in vitro and in vivo studies. The differentially expressed genes (DEGs) downregulated by MLT were enriched in immune-related processes, according to smart-seq of AS plaque macrophages. Additionally, MLT-treated HFD-fed ApoE-/- mice and THP-1 macrophages showed lower levels of proinflammatory factors, which further supported the changes in the inflammatory status. Additionally, the upstream target genes of the smart-seq DEGs were discovered using the transcriptome-based multiscale network pharmacology platform (TMNP), with Gal-3 demonstrating a high score. MLT therapy resulted in downregulation of Gal-3 both in vivo and in vitro. Moreover, the TMNP method's anticipated target gene enrichment showed that autophagy had a significant impact on the DEGs. The majority of proteins linked to the inflammatory response were downregulated by MLT and Gal-3 knockdown, which may have improved autophagy. Mechanistically, MLT suppressed Gal-3, which decreased NF-κB pathway activity and increased transcription factor EB's nuclear localization. Conversely, elevated Gal-3 secretion impeded autophagy by binding to CD98 and activating the PI3K/AKT pathway [79].

An objective of a recent investigation was to examine how MLT affected the expressions of dimethylarginine dimethylaminohydrolase (DDAH), visfatin, vaspin, and signal transducer and activator of transcription-3 (STAT-3) to assess endothelial function and inflammation in the hypercholesterolemic rats. Five groups of rats were created: (1) control, (2) hypercholesterolemia, (3) MLT administered simultaneously with cholesterol diet, (4) MLT administered just for the final two weeks and fed with cholesterol diet, and (5) atorvastatin administered only for the final two weeks and fed with cholesterol diet. Hypercholesterolemic diets caused a reduction in the expression of the vaspin and DDAH proteins, despite an increase in the expression of STAT-3, visfatin, and ADMA levels. It was shown that MLT returned all the parameters to their typical signaling levels [80]. The potential for MLT to reduce inflammation, VED, and AS in HFD rabbits by inhibiting the TLR4/NF-κB pathway has been examined. The diets that the rabbits were given over a period of 12 weeks were standard (control group), high-cholesterol (AS group), or high-cholesterol with 10 mg/kg/day MLT. Following treatment, the AS group of rabbits had considerably higher blood lipid and inflammatory indicators from a HFD than from the control group. Furthermore, a HFD increased the intima/media

thickness ratio, caused VED, and typical atherosclerotic plaque development. These effects were greatly mitigated by MLT administration. Further histological and immunoblot analyses revealed that a HFD increased the expression of TLR4, IκB and myeloid differentiation main response protein, but lowered the expression of TLR4. By comparison, MLT treatment enhanced IκB expression while decreasing the levels of MyD88, TLR4, and NF-κB p65. Additionally, in HFD rabbits, MLT reduced inflammation, lipid metabolism, and VED while slowing the development of AS [27].

Oxidative stress

LDL particle buildup is the first step in the development of an atherosclerotic plaque [81, 82]. Ox-LDL builds up in artery wall and increases the expression of cell adhesion molecules on endothelial cells, including vascular cell adhesion molecule-1 (VCAM-1). Inflammatory signaling triggers antioxidant-inhibitory pathways, including a redox-sensitive activation of NF-κB, which in turn drives endothelial VCAM-1 expression [83, 84]. ROS contribute to AS in a number of ways. In addition to producing oxidized lipoproteins, ROS also interact with endogenous vasoactive mediators in endothelial cells and directly damage cellular and nuclear membranes [85, 86]. Among the enzymes that make up the oxidant system are lipoxygenases, NADPH oxidases (NOX), uncoupled eNOS, xanthine oxidase, and mitochondrial respiratory chain enzymes. Superoxide dismutase (SOD), glutathione peroxidases, catalase, peroxiredoxins, paraoxonases, the thioredoxin system, and other enzymes are components of the antioxidant system. Furthermore, O2 – is produced by uncoupled eNOS, exacerbating vascular oxidative stress. L-arginine or tetrahydrobiopterin deficits, hyperglycemia, ox-LDL, and eNOS S-glutathionylation are the primary causes of eNOS uncoupling [87]. The literature has thoroughly detailed the antioxidant capacity of MLT [88]. This molecule can function directly as an antioxidant by scavenging free radicals, or indirectly as an antioxidant by inhibiting pro-oxidant enzymes and activating antioxidant enzymes [89]. Additionally, MLT prevents metal-induced oxidation by forming chelates with certain transition metals, which suppresses processes like lipid peroxidation [89].Moreover, MLT activates many enzymes that catalyze antioxidant reactions and eradicate free radicals. MLT can increase the production and activity of enzymes including SOD, catalase, glutathione peroxidase, and glutathione reductase by attaching to the MT1 and MT2 receptors. MLT suppresses lipoxygenase activity in terms of blocking pro-oxidant enzymes [90, 91].

The effects of MLT on Lp-PLA2 expression during the atherosclerotic process and to determine the underlying processes have been investigated. After feeding a HFD to ApoE-/-mice in vivo, either with or without MLT treatment, the plaque area and collagen content were measured. The treatment of MLT dramatically slowed the growth of atherosclerotic plaque. The MLT group's atherosclerotic root macrophages had considerably higher levels of glutathione peroxidase 4 (GPX4) and SLC7A11 than did the HF diet groups. In vitro, MLT increased antioxidant capacity, decreased lipid peroxidation, and suppressed Lp-PLA2 expression in macrophages via activating the nuclear factor-E2-related Factor 2 (NRF2)/SLC7A11/GPX4 signaling pathway. Additionally, MLT used ferrostatin-1 and/or erastin to counteract the ferroptosis caused by ox-LDL. Additionally, in ML385-treated macrophages and in ApoE-/- mice treated with AAV-sh-NRF2, the protective effects of MLT on Lp-PLA2 expression, antioxidant capacity, lipid peroxidation, and ferroptosis were diminished. MLT inhibited macrophage ferroptosis and slightly activated the NRF2 pathway, which lowered Lp-PLA2 expression and AS processes [92]. Based on vascular Doppler ultrasonography, ApoE-/-mice exposed to PM2.5 had decreased aortic flexibility. Blood biochemical and pathological analysis revealed that PM2.5 exposure resulted in dyslipidemia, oxidative damage to the aorta, and an increase in the area of atherosclerotic plaque; however, administration of MLT effectively mitigated the effects of PM2.5 on macrophage M1 polarization and AS in mice. Mitochondria and NOX2 are two important sources of ROS generation triggered by PM2.5. By blocking NOX2-mediated crosstalk of the Keap1/Nrf2/NF-κB and TLR4/TRAF6/NF-κB signaling pathways, the concurrent use of two ROS-specific inhibitors and MLT significantly restored PM2.5-triggered macrophage M1 polarization and foam cell production [93].

The function of cyclophilin A (CyPA) in the early stages of AS and looked at the antioxidant qualities of MLT's potential atheroprotective effects has been assessed. MLT was administered to APOE null mice at 6 and 15 weeks of age at a dosage of either 0.1 mg/kg/day or 10 mg/kg/day. The study examined rolling mononuclear cell expression and histological changes in endothelial and vascular smooth muscle cells throughout the early stages of AS development. The results showed that, promoting vascular smooth muscle cell movement and inflammatory cell extravasation in a time-dependent manner, CyPA expression increased and may affect inflammatory cell adhesion and IL-6 production. Additionally, MLT was found to have an indirect atheroprotective impact on vascular damage [94].

Conclusions

MLT is an effective therapeutic drug that has a broad variety of actions on many organs and disorders, some of which are mediated by receptors and others of which

are receptor independent. It's interesting to note that this drug frequently has opposite effects on healthy and diseased cells since it encourages apoptosis in certain cells while preventing it in others. The optimal development of numerous organs depends on highly conserved processes called PCDs, with disruption of these systems occurring in a number disorder. By controlling their signaling pathways, MLT affects PCD, inflammation, and oxidative stress. Depending on the pathogenic condition of the cell, MLT either increases or decreases these processes. Due to their involvement in a number of illnesses, such as cancer, cardiovascular disorders, and AS, PCDs are a subject of many ongoing studies. To determine how altering these processes might be advantageous to an organism, it is necessary to comprehend how they are modulated. This faces a number of difficulties, one of which to closely define if normal or diseased cells are being examined. Given that MLT may modify these processes in both diseased and normal cells by different means, it would be helpful to define how MLT mediates its effects on oxidative stress, inflammation, and PDCs. Moreover, a few frequently overlooked factors such the best dosage, distribution strategies, and long-term safety, should be taken into account. Despite the promising anti-atherosclerotic effects of MLT observed in various preclinical studies, there are several reasons why MLT is not widely used as a medication to prevent AS in clinical practice. Although MLT has shown anti-inflammatory, antioxidant, and vasoprotective effects in animal models, human clinical trials are limited. Most studies on MLT's effects on AS have been conducted in preclinical models (such as mice or rats), and while these results are encouraging, translating these findings into humans has proven to be challenging. The exact dose and timing of MLT administration, as well as the long-term effects, are not yet fully understood in the context of AS prevention in humans. Also, MLT's effects on AS may not be consistent across different populations. Variability in genetic factors, age, lifestyle, and underlying comorbidities (such as diabetes or hypertension) can influence how MLT impacts cardiovascular health. For example, some individuals may not experience the same level of benefit from MLT supplementation due to differences in MLT receptor expression, metabolism, or circadian rhythm disturbances. While MLT is generally regarded as safe when used for short durations (such as for sleep disorders), its long-term safety for cardiovascular health has not been sufficiently established. Prolonged use of MLT may cause side effects like drowsiness, headaches, and hormonal imbalances (since it regulates the sleep-wake cycle and is involved in other hormonal pathways). There are also concerns about its potential interactions with other medications, such as anticoagulants, antihypertensives, or immunosuppressants. These safety concerns need further investigation, especially in patients with pre-existing cardiovascular conditions. In addition, there are already well-established and widely used treatments for the prevention and management of AS, such as statins, ACE inhibitors, antiplatelet therapy, and lifestyle modifications (e.g., diet, exercise). These therapies have been extensively studied and have clear guidelines for use in clinical practice. In contrast, MLT lacks the same level of evidence for effectiveness, making it a less attractive option for clinicians. Furthermore, MLT is classified as a supplement rather than a pharmaceutical drug in many countries, meaning it does not undergo the same rigorous regulatory approval process as prescription medications. As a result, its use in clinical settings, especially for conditions like AS, is limited to off-label or alternative therapies.

Acknowledgements
NA.

Author contributions
Reza Asemi, Elham Omidi Najafabadi, Zahra Mahmoudian, Russel J.Reiter, Mohammad Ali Mansournia, Zatollah Asemi contributed in data collection and manuscript drafting. All authors approved the final version for submission. All authors reviewed the manuscript."

Funding
NA.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
NA.

Consent for publication
NA.

Competing interests
The authors declare no competing interests.

Received: 6 December 2024 / Accepted: 6 April 2025
Published online: 12 April 2025

References

1. Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X et al. Research progress on the relationship between atherosclerosis and inflammation. Biomolecules. 2018;8.
2. Chistiakov DA, Melnichenko AA, Grechko AV, Myasoedova VA, Orekhov AN. Potential of anti-inflammatory agents for treatment of atherosclerosis. Exp Mol Pathol. 2018;104:114–24.
3. Li M, Wang ZW, Fang LJ, Cheng SQ, Wang X, Liu NF. Programmed cell death in atherosclerosis and vascular calcification. Cell Death Dis. 2022;13:467.
4. Zhang C, Liu N. Ferroptosis, necroptosis, and pyroptosis in the occurrence and development of ovarian cancer. Front Immunol. 2022;13:920059.
5. Zhang Y, Liu X, Bai X, Lin Y, Li Z, Fu J et al. Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis. J Pineal Res. 2018;64.
6. Wu X, Zhang H, Qi W, Zhang Y, Li J, Li Z, et al. Nicotine promotes atherosclerosis via ROS-NLRP3-mediated endothelial cell pyroptosis. Cell Death Dis. 2018;9:171.

7. Qian Z, Zhao Y, Wan C, Deng Y, Zhuang Y, Xu Y, et al. Pyroptosis in the initiation and progression of atherosclerosis. Front Pharmacol. 2021;12:652963.
8. Liu X, Luo P, Zhang W, Zhang S, Yang S, Hong F. Roles of pyroptosis in atherosclerosis pathogenesis. Biomed Pharmacother. 2023;166:115369.
9. Liu Y, Li C, Yin H, Zhang X, Li Y. NLRP3 inflammasome: A potential alternative therapy target for atherosclerosis. Evid Based Complement Alternat Med. 2020;2020:1561342.
10. Aghelan Z, Pashaee S, Abtahi SH, Karima S, Khazaie H, Ezati M, et al. Natural immunosuppressants as a treatment for chronic insomnia targeting the inflammatory response induced by NLRP3/caspase-1/IL-1β axis activation: A scooping review. J Neuroimmune Pharmacology: Official J Soc NeuroImmune Pharmacol. 2023;18:294–309.
11. Tourneur L, Chiocchia G. FADD: a regulator of life and death. Trends Immunol. 2010;31:260–9.
12. Tsuchiya K, Nakajima S, Hosojima S, Thi Nguyen D, Hattori T, Manh Le T, et al. Caspase-1 initiates apoptosis in the absence of gasdermin D. Nat Commun. 2019;10:2091.
13. Mahib MR, Hosojima S, Kushiyama H, Kinoshita T, Shiroishi T, Suda T, et al. Caspase-7 mediates caspase-1-induced apoptosis independently of bid. Microbiol Immunol. 2020;64:143–52.
14. Rogers C, Fernandes-Alnemri T, Mayes L, Alnemri D, Cingolani G, Alnemri ES. Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death. Nat Commun. 2017;8:14128.
15. Heilig R, Dilucca M, Boucher D, Chen KW, Hancz D, Demarco B et al. Caspase-1 cleaves bid to release mitochondrial SMAC and drive secondary necrosis in the absence of GSDMD. Life Sci Alliance. 2020;3.
16. Acuña-Castroviejo D, Escames G, Venegas C, Díaz-Casado ME, Lima-Cabello E, López LC, et al. Extrapineal melatonin: sources, regulation, and potential functions. Cell Mol Life Sci. 2014;71:2997–3025.
17. Reiter RJ, Sharma R, Tan DX, Chuffa LGA, da Silva DGH, Slominski AT, et al. Dual sources of melatonin and evidence for different primary functions. Front Endocrinol (Lausanne). 2024;15:1414463.
18. Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin–a pleiotropic, orchestrating regulator molecule. Prog Neurobiol. 2011;93:350–84.
19. Venegas C, García JA, Escames G, Ortiz F, López A, Doerrier C, et al. Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. J Pineal Res. 2012;52:217–27.
20. Galano A, Reiter RJ. Melatonin and its metabolites vs oxidative stress: from individual actions to collective protection. J Pineal Res. 2018;65:e12514.
21. Tan DX, Reiter RJ, Manchester LC, Yan MT, El-Sawi M, Sainz RM, et al. Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger. Curr Top Med Chem. 2002;2:181–97.
22. Ma H, Kang J, Fan W, He H, Huang F. ROR: nuclear receptor for melatonin or not?? Molecules. 2021;26.
23. Seegar H, Mueck AO, Lippert TH. Effect of melatonin and metabolites on copper-mediated oxidation of flow density lipoprotein. Br J Clin Pharmacol. 1997;44:283–4.
24. Walters-Laporte E, Furman C, Fouquet S, Martin-Nizard F, Lestavel S, Gozzo A, et al. A high concentration of melatonin inhibits in vitro LDL peroxidation but not oxidized LDL toxicity toward cultured endothelial cells. J Cardiovasc Pharmacol. 1998;32:582–92.
25. Reiter RJ, Tan DX, Paredes SD, Fuentes-Broto L. Beneficial effects of melatonin in cardiovascular disease. Ann Med. 2010;42:276–85.
26. Reiter RJ, Tan DX, Pappolla MA. Melatonin relieves the neural oxidative burden that contributes to dementias. Ann N Y Acad Sci. 2004;1035:179–96.
27. Hu ZP, Fang XL, Fang N, Wang XB, Qian HY, Cao Z, 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;55:388–98.
28. Yang S, Li R, Tang L, Qu X, Ge G, Ma J, et al. TLR4-mediated anti-atherosclerosis mechanisms of angiotensin-converting enzyme inhibitor–fosinopril. Cell Immunol. 2013;285:38–41.
29. Alaasam VJ, Liu X, Niu Y, Habibian JS, Pieraut S, Ferguson BS et al. Effects of dim artificial light at night on locomotor activity, cardiovascular physiology, and circadian clock genes in a diurnal songbird. Environmental pollution (Barking, Essex: 1987). 2021;282:117036.
30. Portaluppi F. The circadian organization of the cardiovascular system in health and disease. Indian J Exp Biol. 2014;52:395–8.
31. Maldonado M, Romero-Aibar J, Calvo J. The melatonin contained in beer can provide health benefits, due to its antioxidant, anti-inflammatory and Immunomodulatory properties. J Sci Food Agric. 2023;103:3738–47.
32. Luo Z, Tang YY, Zhou L. Melatonin as an adjunctive therapy in cardiovascular disease management. Sci Prog. 2024;107:368504241299993.
33. Vajdi M, Moeinolsadat S, Noshadi N, Pourteymour Fard Tabrizi F, Khajeh M, Abbasalizad-Farhangi M, et al. Effect of melatonin supplementation on body composition and blood pressure in adults: A systematic review and Dose-Response meta-analysis of randomized controlled trial. Heliyon. 2024;10:e34604.
34. Reiter RJ, Sharma R, Romero A, Simko F, Dominguez-Rodriguez A, Cardinali DP. Melatonin stabilizes atherosclerotic plaques: an association that should be clinically exploited. Front Med. 2024;11:1487971.
35. Huang YM, Xia W, Ge YJ, Hou JH, Tan L, Xu W, et al. Sleep duration and risk of cardio-cerebrovascular disease: A dose-response meta-analysis of cohort studies comprising 3.8 million participants. Front Cardiovasc Med. 2022;9:907990.
36. Torquati L, Mielke GI, Brown WJ, Kolbe-Alexander T. Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose-response relationship. Scand J Work Environ Health. 2018;44:229–38.
37. Reiter RJ, Sharma R, Chuffa LGA, Simko F, Dominguez-Rodriguez A. Mitochondrial Melatonin: Beneficial Effects in Protecting against Heart Failure. Life (Basel, Switzerland). 2024;14.
38. Wang Z, Chen X, Liu N, Shi Y, Liu Y, Ouyang L, et al. A nuclear long Non-Coding RNA LINC00618 accelerates ferroptosis in a manner dependent upon apoptosis. Mol Therapy: J Am Soc Gene Therapy. 2021;29:263–74.
39. Tabas I. Apoptosis and efferocytosis in mouse models of atherosclerosis. Curr Drug Targets. 2007;8:1288–96.
40. Lv JJ, Wang H, Zhang C, Zhang TJ, Wei HL, Liu ZK, et al. CD147 sparks atherosclerosis by driving M1 phenotype and impairing efferocytosis. Circ Res. 2024;134:165–85.
41. Simion V, Zhou H, Haemmig S, Pierce JB, Mendes S, Tesmenitsky Y, et al. A macrophage-specific LncRNA regulates apoptosis and atherosclerosis by tethering HuR in the nucleus. Nat Commun. 2020;11:6135.
42. Cynn E, Li DY, O'Reilly ME, Wang Y, Bashore AC, Jha A, et al. Human macrophage long intergenic noncoding RNA, SIMALR, suppresses inflammatory macrophage apoptosis via NTN1 (Netrin-1). Arterioscler Thromb Vasc Biol. 2023;43:286–99.
43. Dong Y, Chen H, Gao J, Liu Y, Li J, Wang J. Molecular machinery and interplay of apoptosis and autophagy in coronary heart disease. J Mol Cell Cardiol. 2019;136:27–41.
44. Grossini E, Caimmi PP, Platini F, Molinari C, Uberti F, Cattaneo M, et al. Modulation of programmed forms of cell death by intracoronary Levosimendan during regional myocardial ischemia in anesthetized pigs. Cardiovasc Drugs Ther. 2010;24:5–15.
45. Hamacher-Brady A, Brady NR, Gottlieb RA. The interplay between pro-death and pro-survival signaling pathways in myocardial ischemia/reperfusion injury: apoptosis Meets autophagy. Cardiovasc Drugs Ther. 2006;20:445–62.
46. Rafiyian M, Reiter RJ, Rasooli Manesh SM, Asemi R, Sharifi M, Mohammadi S, et al. Programmed cell death and melatonin: A comprehensive review. Funct Integr Genom. 2024;24:169.
47. He R, Cui M, Lin H, Zhao L, Wang J, Chen S, et al. Melatonin resists oxidative stress-induced apoptosis in nucleus pulposus cells. Life Sci. 2018;199:122–30.
48. Green DR, Kroemer G. The pathophysiology of mitochondrial cell death. Science. 2004;305:626–9.
49. Redza-Dutordoir M, Averill-Bates DA. Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys Acta. 2016;1863:2977–92.
50. Trombetti S, Cesaro E, Catapano R, Sessa R, Lo Bianco A, Izzo P et al. Oxidative stress and ROS-Mediated signaling in leukemia: novel promising perspectives to eradicate chemoresistant cells in myeloid leukemia. Int J Mol Sci. 2021;22.
51. Cong L, Liu X, Bai Y, Qin Q, Zhao L, Shi Y, et al. Melatonin alleviates pyroptosis by regulating the SIRT3/FOXO3α/ROS axis and interacting with apoptosis in atherosclerosis progression. Biol Res. 2023;56:62.
52. Jia C, Chen H, Zhang J, Zhou K, Zhuge Y, Niu C, et al. Role of pyroptosis in cardiovascular diseases. Int Immunopharmacol. 2019;67:311–8.
53. Wang Q, Wu J, Zeng Y, Chen K, Wang C, Yang S, et al. Pyroptosis: A pro-inflammatory type of cell death in cardiovascular disease. Clin Chim Acta. 2020;510:62–72.
54. Zhang Z, Zhang H, Li D, Zhou X, Qin Q, Zhang Q. Caspase-3-mediated GSDME induced pyroptosis in breast cancer cells through the ROS/JNK signalling pathway. J Cell Mol Med. 2021;25:8159–68.

55. Zheng X, Zhong T, Ma Y, Wan X, Qin A, Yao B, et al. Bnip3 mediates doxorubicin-induced cardiomyocyte pyroptosis via caspase-3/GSDME. Life Sci. 2020;242:117186.
56. Chen LD, Zhu WT, Cheng YY, Li ZH, Chen YQ, Yuan ZW, et al. T-cell death-associated gene 8 accelerates atherosclerosis by promoting vascular smooth muscle cell proliferation and migration. Atherosclerosis. 2020;297:64–73.
57. Niu X, Pi SL, Baral S, Xia YP, He QW, Li YN, et al. P2Y(12) promotes migration of vascular smooth muscle cells through Cofilin dephosphorylation during atherogenesis. Arterioscler Thromb Vasc Biol. 2017;37:515–24.
58. Tang Y, Wa Q, Peng L, Zheng Y, Chen J, Chen X, et al. Salvianolic acid B suppresses ER Stress-Induced NLRP3 inflammasome and pyroptosis via the AMPK/FoxO4 and Syndecan-4/Rac1 signaling pathways in human endothelial progenitor cells. Oxid Med Cell Longev. 2022;2022:8332825.
59. Zhang L, Yuan M, Zhang L, Wu B, Sun X. Adiponectin alleviates NLRP3-inflammasome-mediated pyroptosis of aortic endothelial cells by inhibiting FoxO4 in arteriosclerosis. Biochem Biophys Res Commun. 2019;514:266–72.
60. Wen L, Wang M, Luo P, Meng X, Zhao M. Melatonin exerts cardioprotective effects by inhibiting NLRP3 Inflammasome-Induced pyroptosis in mice following myocardial infarction. Oxid Med Cell Longev. 2021;2021:5387799.
61. Zeng J, Tao J, Xia L, Zeng Z, Chen J, Wang Z, et al. Melatonin inhibits vascular endothelial cell pyroptosis by improving mitochondrial function via up-regulation and demethylation of UQCRC1. Biochem Cell Biol. 2021;99:339–47.
62. Della Corte V, Todaro F, Cataldi M, Tuttolomondo A. Atherosclerosis and its related laboratory biomarkers. Int J Mol Sci. 2023;24.
63. Abderrazak A, Syrovets T, Couchie D, El Hadri K, Friguet B, Simmet T, et al. NLRP3 inflammasome: from a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases. Redox Biol. 2015;4:296–307.
64. Lorey MB, Öörni K, Kovanen PT. Modified lipoproteins induce arterial wall inflammation during atherogenesis. Front Cardiovasc Med. 2022;9:841545.
65. Rajamäki K, Mäyränpää MI, Risco A, Tuimala J, Nurmi K, Cuenda A, et al. p38δ MAPK: A novel regulator of NLRP3 inflammasome activation with increased expression in coronary atherogenesis. Arterioscler Thromb Vasc Biol. 2016;36:1937–46.
66. Libby P, Warner SJ, Friedman GB. Interleukin 1: a mitogen for human vascular smooth muscle cells that induces the release of growth-inhibitory prostanoids. J Clin Invest. 1988;81:487–98.
67. Jones SA. Directing transition from innate to acquired immunity: defining a role for IL-6. J Immunol. 2005;175:3463–8.
68. You R, Long W, Lai Z, Sha L, Wu K, Yu X, et al. Discovery of a potential anti-inflammatory agent: 3-oxo-29-noroleana-1,9(11),12-trien-2,20-dicarbonitrile. J Med Chem. 2013;56:1984–95.
69. de Martin R, Vanhove B, Cheng Q, Hofer E, Csizmadia V, Winkler H, et al. Cytokine-inducible expression in endothelial cells of an I kappa B alpha-like gene is regulated by NF kappa B. EMBO J. 1993;12:2773–9.
70. Read MA, Whitley MZ, Williams AJ, Collins T. NF-kappa B and I kappa B alpha: an inducible regulatory system in endothelial activation. J Exp Med. 1994;179:503–12.
71. Kregel KC, Zhang HJ. An integrated view of oxidative stress in aging: basic mechanisms, functional effects, and pathological considerations. Am J Physiol Regul Integr Comp Physiol. 2007;292:R18–36.
72. Lou T, Jiang W, Xu D, Chen T, Fu Y. Inhibitory effects of Polydatin on Lipopolysaccharide-Stimulated RAW 264.7 cells. Inflammation. 2015;38:1213–20.
73. Lee WS, Shin JS, Jang DS, Lee KT. Cnidilide, an alkylphthalide isolated from the roots of Cnidium officinale, suppresses LPS-induced NO, PGE(2), IL-1β, IL-6 and TNF-α production by AP-1 and NF-κB inactivation in RAW 264.7 macrophages. Int Immunopharmacol. 2016;40:146–55.
74. Yang P, Han Y, Gui L, Sun J, Chen YL, Song R, et al. Gastrodin Attenuation of the inflammatory response in H9c2 cardiomyocytes involves Inhibition of NF-κB and MAPKs activation via the phosphatidylinositol 3-kinase signaling. Biochem Pharmacol. 2013;85:1124–33.
75. Hsu JT, Le PH, Lin CJ, Chen TH, Kuo CJ, Chiang KC, et al. Mechanism of salutary effects of melatonin-mediated liver protection after trauma-hemorrhage: p38 MAPK-dependent iNOS/HIF-1α pathway. Am J Physiol Gastrointest Liver Physiol. 2017;312:G427–33.
76. Hsu JT, Kuo CJ, Chen TH, Wang F, Lin CJ, Yeh TS, et al. Melatonin prevents hemorrhagic shock-induced liver injury in rats through an Akt-dependent HO-1 pathway. J Pineal Res. 2012;53:410–6.
77. Liu Z, Gan L, Xu Y, Luo D, Ren Q, Wu S et al. Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-κB/GSDMD signal in mice adipose tissue. J Pineal Res. 2017;63.
78. Chen L, Wang X, Liu C, Deng P, Pan L, Yang L, et al. Melatonin ameliorates atherosclerosis by suppressing S100a9-mediated vascular inflammation. Eur J Pharmacol. 2023;957:175965.
79. Wang Z, Gao Z, Zheng Y, Kou J, Song D, Yu X, et al. Melatonin inhibits atherosclerosis progression via galectin-3 downregulation to enhance autophagy and inhibit inflammation. J Pineal Res. 2023;74:e12855.
80. Sezgin D, Aslan G, Sahin K, Tuzcu M, İlhan N, Sahna E. The effects of melatonin against atherosclerosis-induced endothelial dysfunction and inflammation in hypercholesterolemic rats. Arch Physiol Biochem. 2023;129:476–83.
81. El Hadri K, Smith R, Duplus E, El Amri C, Inflammation. Oxidative stress, senescence in atherosclerosis: Thioredoxine-1 as an emerging therapeutic target. Int J Mol Sci. 2021;23.
82. Adameova A, Xu YJ, Duhamel TA, Tappia PS, Shan L, Dhalla NS. Anti-atherosclerotic molecules targeting oxidative stress and inflammation. Curr Pharm Des. 2009;15:3094–107.
83. Poznyak AV, Grechko AV, Orekhova VA, Chegodaev YS, Wu WK, Orekhov AN. Oxidative stress and antioxidants in atherosclerosis development and treatment. Biology. 2020;9.
84. Wassmann S, Wassmann K, Nickenig G. Modulation of oxidant and antioxidant enzyme expression and function in vascular cells. Hypertension. 2004;44:381–6.
85. Najafi M, Roustazadeh A, Alipoor B, Ox -LDL, Particles. Modified components, cellular uptake, biological roles and clinical assessments. Cardiovasc Hematol Disord Drug Targets. 2011;11:119–28.
86. Nakajima K, Nakano T, Tanaka A. The oxidative modification hypothesis of atherosclerosis: the comparison of atherogenic effects on oxidized LDL and remnant lipoproteins in plasma. Clin Chim Acta. 2006;367:36–47.
87. Marchio P, Guerra-Ojeda S, Vila JM, Aldasoro M, Victor VM, Mauricio MD. Targeting early atherosclerosis: A focus on oxidative stress and inflammation. Oxid Med Cell Longev. 2019;2019:8563845.
88. Zang LY, Cosma G, Gardner H, Vallyathan V. Scavenging of reactive oxygen species by melatonin. Biochim Biophys Acta. 1998;1425:469–77.
89. Kopustinskiene DM, Bernatoniene J. Molecular mechanisms of Melatonin-Mediated cell protection and signaling in health and disease. Pharmaceutics. 2021;13.
90. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res. 2016;61:253–78.
91. Chitimus DM, Popescu MR, Voiculescu SE, Panaitescu AM, Pavel B, Zagrean L et al. Melatonin's Impact on Antioxidative and Anti-Inflammatory Reprogramming in Homeostasis and Disease. Biomolecules. 2020;10.
92. Tao Y, Zhao Q, Lu C, Yong W, Xu M, Wang Z, et al. Melatonin suppresses atherosclerosis by ferroptosis Inhibition via activating NRF2 pathway. Faseb J. 2024;38:e23678.
93. Liu J, Sun Q, Sun M, Lin L, Ren X, Li T, et al. Melatonin alleviates PM(2.5)-triggered macrophage M1 polarization and atherosclerosis via regulating NOX2-mediated oxidative stress homeostasis. Free Radic Biol Med. 2022;181:166–79.
94. Rezzani R, Favero G, Stacchiotti A, Rodella LF. Endothelial and vascular smooth muscle cell dysfunction mediated by cyclophylin A and the atheroprotective effects of melatonin. Life Sci. 2013;92:875–82.

Publisher's note