Review

# Protective effect of melatonin in atherosclerotic cardiovascular disease: A comprehensive review

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**Running title:** Melatonin protects cardiovascular tissue from atherosclerosis

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## ABSTRACT

Heart failure is characterized by the heart losing its capacity to pump sufficient blood to match the body's demand. It is caused by a variety of cardiovascular impairments. Among them, atherosclerosis is the most common one. Although, a variety of medicines selectively target this pathology, the death rate due to atherosclerosis associated heart disorders remain high. To address this issue, the use of antioxidants combined with conventional therapy to achieve synergistic effects has gained popularity. Melatonin is one of such antioxidants. In addition to its potent antioxidant activity, this molecule acts in harmony to protect the cardiovascular tissue. This review explores the various mechanisms by which melatonin protects the cardiovascular tissue. This information will contribute further insights into the role of melatonin in maintaining cardiovascular homeostasis in normal as well as in pathological conditions. It will also help us to better understand the potential synergistic effects of melatonin with conventional therapy to successfully target the heart failure associated with atherosclerosis.

**Keywords:** melatonin, atherosclerosis, reactive oxygen species (ROS), endothelial cell, smooth muscle cell, antioxidant.

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## 1. INTRODUCTION

Current advances in understanding the risks associated with cardiovascular disease are supposedly extraordinary, considering that the first cohort studies were reported just 6 decades ago (1, 2). Since then, an extensive decline in the age-specific onset of cardiovascular diseases has been observed. Yet, the fatality rate of the disease still looms high, thus affecting millions of people worldwide. According to a recent report, 610,000 people are dying every year in the United States alone due to heart diseases, which can

roughly be summated to one out of every four American deaths (3, 4). Comparable risk assessment has indicated that lifestyle-related behavior and poor lifestyle choices are the foremost reasons for these deaths in the United States and other countries (5).

Many pathological conditions can damage the cardiovascular system; among them, coronary artery disease (CAD) has drawn the attention of researchers. This is mostly because the invasiveness and complications of CAD directly associate with a risk factor, atherosclerosis (6).

Atherosclerosis is a chronic inflammatory condition marked by progressive hardening and narrowing of the blood vessels, due to the interaction of the elements of the arterial wall with modified lipoproteins, T-cells, macrophages, and platelets (7). This interaction, with time, proceeds to plaque formation. The plaques or their ruptures will result in severe consequences that hinder the blood supply to tissues. In addition, hypertension, diabetes *mellitus*, hypercholesterolemia, obesity, and cigarette smoking are the major factors responsible for atherosclerosis. The onset of atherosclerosis is a slow process and occurs silently during a relatively long period of time. Thus, the severity of coronary atherosclerosis is often underestimated under coronary arteriogram evaluation due to the unsubstantial remodeling of vessel walls at the early stage of the disease (8, 9), thus, hindering the diagnosis.

Melatonin is secreted from the pineal gland. It has several functions including maintaining the biological rhythm, modulating the immune system, anti-inflammation, lowering blood pressure, and normalizing lipid profile (10–12). In addition, it is highly efficient in ameliorating oxidative stress (13, 14). Based on these pieces of evidence, it can be hypothesized that melatonin can possibly reverse an atherosclerotic pathology (15). Also, its extremely low toxicity makes it the perfect choice as a therapeutic agent (16, 17).

In this review, we provide an insight on how endogenously produced melatonin protects against atherosclerotic development and whether any further enhancement in protection occurs upon exogenously administered melatonin.

## 2. PATHOGENESIS OF ATHEROSCLEROSIS

Atherosclerosis is an immuno-inflammatory disorder of the vasculature, kindled mainly by lipid malmetabolism and reactive oxygen species (ROS) (18). However, several controllable and uncontrollable risk factors enhance the onset of this disorder (Table 1). Briefly, it is a chronic inflammatory process resulting from the interaction of the cellular elements of the arterial walls with free radicals, modified lipoproteins, monocyte-derived macrophages, and T-cells (7).

**Table 1: Risk factors associated with atherosclerosis.**

| Category | Risk Factors | Effects |
|---|---|---|
| Controllable | Hypercholesterolemia | LDL↑ (19) |
| | | oxLDL↑ (19) |
| | | ROS↑ (20) |
| | Hypertension | Vascular permeability↑ (21) |
| | | LDL↑ (22) |
| | | ROS↑ (23) |
| | | Altered NO synthesis (23) |
| | Diabetes | LDL glycation↑ (24) |
| | | Endothelial dysfunction (25) |
| | | ROS↑ (26) |
| | Obesity | oxLDL↑ (27) |
| | | Free fatty acid↑ (28, 29) |

| | | |
|---|---|---|
| | | Triglycerides↑ (30) |
| | | ROS↑ (31) |
| | Smoking | Vascular inflammation (32) |
| | | Platelet coagulation (33) |
| | | Vascular dysfunction (34) |
| | | Impaired lipid profiles (35) |
| | | ROS↑ (36) |
| Uncontrollable | Age | Cellular senescence (37) |
| | | Vascular aging (37) |
| | | DNA damage (37) |
| | | ROS↑ (37) |
| | Gender | Frequent in males due to the absence of estrogen-mediated cardioprotection (38) |
| | Genetic Factors | Family history (39) |

It is a progressive process causing a variety of cardiovascular diseases (Fig. 1) (40–49) which are the leading cause of death all over the world (50). The common pathology of this process is characterized by focal thickening of the intima in the innermost layer of arteries. The thickenings are asymmetric in nature and are known as atherosclerotic lesions (51). The lesions consist of lipids, cellular debris, immune cells, and connective tissue elements that bring major morphological changes in vascular endothelial cells and smooth muscle cells (8).

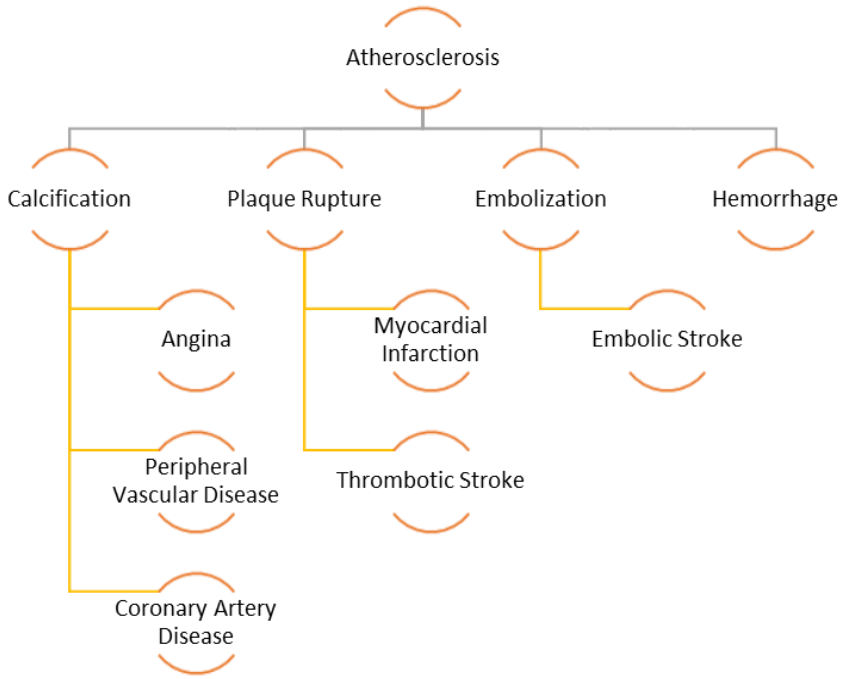


**Fig 1. Clinical manifestations of atherosclerosis.**

### 2.1. Endothelial cells.

The entire circulatory system is lined by the vascular endothelium. The endothelial layer and the extracellular matrix form the tunica intima in coronary arteries. It was originally considered as a simple passive barrier of the arteries, but recently its role has been highlighted to maintain vascular homeostasis. The endothelium is a semipermeable

membrane involved in regulating the transport of macromolecules between the vascular lumen and the vascular smooth muscle cells (52).

**2.1.1. Role of endothelial cells in maintaining vascular homeostasis.**

The endothelium maintains the vascular tone and fibrinolytic properties. This is primarily achieved by the release of several chemical vasoconstrictors and dilators from endothelium (53). Other than vascular tonal regulation, the endothelial cells maintain vascular homeostasis by modulating numerous processes and secreting chemical substances.

**2.1.2. Pathophysiological changes during atherosclerosis.**

Multiple studies have shown a significant association between endothelial dysfunction and strong coronary risk factors like hypercholesterolemia, hypertension, diabetes, smoking, etc. that potentiate in the gradual development of atherosclerosis (53). Apart from these, several other factors can directly link to endothelial cell dysfunction and atherosclerosis.

2.1.2.1. *Enhanced vascular permeability.*

Various pathophysiological stimuli including low shear stress, altered vascular endothelial growth factor (VEGF) expression, increased lipopolysaccharides, ROS, and phospholipid oxidative products can dramatically alter the permeability of vascular endothelium. Inflammatory mediators like thrombin, histamine, and IL-1β can also instigate the opening of intercellular junctions in the endothelium (54, 55) resulting in an enhanced vascular permeability. The destruction of the endothelial glycocalyx is also associated with increased endothelial permeability and vascular responsiveness (56). The thinning of the endothelial glycocalyx in high cholesterol-fed mice further supports an important role of endothelial glycocalyx played in the initiation and progression of atherosclerosis (57).

2.1.2.2. *Low-Density Lipoprotein (LDL) accumulation.*

Induction of enhanced endothelial permeability results in increased infiltration and local accumulation of LDL which is one of the most critical events in the initiation of atherosclerosis (58, 59). Infiltration of LDL and its accumulation in the arterial intima further initiates inflammatory responses in the arterial wall (58, 60). LDL oxidation releases phospholipids that can activate arterial endothelial cells especially at sites of hemodynamic strain (60, 61). Disturbed patterns of hemodynamic flow upregulate the expression of inflammatory genes and increase adhesion molecules in arterial endothelium (51).

2.1.2.3. *Leukocyte trafficking and foam cell formation.*

Hypercholesterolemia-induced expression of vascular cell adhesion molecule 1 (VCAM-1) leads to monocyte and leucocyte adherence on the arterial endothelium. Similarly, chemokines in underlying intima stimulate their migration into subendothelial spaces where the monocytes differentiate into macrophages (62). The macrophages express scavenger receptors that engulf oxidized lipoproteins and become foam cells (63). They also stimulate the release of inflammatory cytokines, enzymes that aid in the destruction of extracellular matrix and ROS, thereby, resulting in inflammation and tissue damage (51, 63). The macrophages further act on neighboring smooth muscle cells and induce their proliferation along with the synthesis of extracellular matrix components leading to the generation of a fibromuscular plaque (55). TGF-β signaling mediated endothelial to the mesenchymal

transformation of cells affect monocyte recruitment within the atherosclerotic niche and has also been identified as a promoting phenomenon in the formation of atherogenic lesions (64).

2.1.2.4. *Disturbances in vascular tone.*

The damaged epithelium results in a disrupted balance between the vasoconstriction and vasodilation, thus, giving rise to a cascade of reactions that exaggerate atherosclerosis (53). A hallmark of endothelial dysfunction is the impairment of NO-mediated endothelium-dependent vasodilation. A decrease in production and activity of NO has been marked as one of the major signs of endothelial dysfunction, thereby, promoting atherosclerosis. An increase in LDL levels decreases the bioavailability of NO produced by the endothelium along with the downregulation of endothelial eNOS (65). Oxidized LDL cholesterol increases caveolin-1 synthesis which inhibits NO production via inactivation of eNOS. Evidence of impaired endothelium-dependent vasodilation has been observed in preclinical and advanced stages of atherosclerosis in humans (66). Thus, decreased production of NO prevents maintenance of vascular homeostasis along with its antioxidant, anti-inflammatory, and antiproliferative properties, thus, promoting atherogenesis (52).

2.1.2.5. *Metabolic alterations.*

Apart from morphological changes in endothelial cells, deregulated endothelial metabolism has also been associated with the accelerated development of atherosclerosis via risk factors like diabetes, obesity, and aging (67, 68). Endothelial cells subject to low shear stress exhibit enhanced expression of glycolytic enzymes along with activation of the proinflammatory pathway (69). Enhanced glycolysis in endothelial cells occurs via NF-κβ-HIF1α dependent axis despite the presence of sufficient oxygen (69, 70). Proinflammatory cytokines increase both uptakes of glucose and glycolysis in endothelial cells which, in turn, upregulate cytokine-induced NF-κβ activation thereby forming a vicious cycle that aggravates the condition thus starving the cell out of glucose (71).

## 2.2. Smooth muscle cells.

The media or the middle layer of the vasculature consists of contractile smooth muscle cells surrounded by small amounts of collagen and other connective tissue components (71). Their main function is to maintain the vascular tone by regulating the compliance and elastic recoil of the arteries based on the hemodynamic changes (72, 73). Almost 75% of their cytoplasm is made up of contractile filaments and their role in contraction is responsible for the modulation of arterial diameter (73).

### 2.2.1. Role of Smooth Muscle cells in maintaining vascular homeostasis.

The smooth muscle functions through an extensive organized structural hierarchy extending over numerous spatial scales to perform various functions at the cell, tissue, and organ levels (74). One of its most important functions is mechanotransduction that regulates the contractility of the cells. The vascular smooth muscle cells are exposed to a number of mechanical stimuli like pulsatile pressure-induced vascular shear strain, transmural pressure, and circumferential wall tension, due to cyclic cardiac pumping (75). This results in cytoskeletal remodeling, alteration in membrane conductance, and activation of biochemical signals that, in turn, regulate functional changes in maintaining the tone of vascular smooth muscle cells (76, 77, 78). The ability of vascular smooth muscle cells to perceive these

mechanical stimuli and respond accordingly, in both healthy and injured states, is critical for maintaining vascular tone (74).

### 2.2.2. Atherosclerosis associated pathophysiological changes.

Vascular smooth muscle cells possess a fully functional and differentiated phenotype in a healthy state. Yet they retain remarkable plasticity. The pathological condition of intimal thickening, a primitive stage of the atherosclerotic lesion, is associated with biochemical and morphological changes in vascular smooth muscle cells and the adjacent extracellular matrices (78).

#### 2.2.2.1. *Phenotypic plasticity.*

The phenotypically altered smooth muscle cells possess features different from that of the normal ones (79). Dysfunctional endothelium and inflammatory cells synthesize proteolytic agents, growth factors, and extracellular matrix proteins which induce the proliferation and migration of smooth muscle cells from the media (80). Thus, the phenotype of the smooth muscle cell changes from contractile to that of a synthetic one (81, 82). The contractile phenotype of smooth muscle cells is found in normally differentiated arteries whereas the synthetic phenotype is more common in the damaged arteries (83). Normal smooth muscle cells in the artery appear spindle-shaped with the classical "hill and valley" pattern of growth while in pathological conditions, an epithelial phenotype with "cobblestone" morphology is frequently observed, accompanied by endothelial damage (84–86). The phenotype switching phenomenon in vascular smooth muscle cells is characterized by a reduction in the expression of contractile proteins and less dense myofilaments than usual (73).

#### 2.2.2.2. *Proliferation and migration.*

Epithelioid smooth muscle cells have greater proliferative potential than spindle-shaped ones (83). Following massive endothelial injury, the smooth muscle cells proliferate first in the media continuing in the intima and this proliferation has been identified as a key requisite process in the development of atherosclerosis (87). The intact endothelium is a potent inhibitor of smooth muscle cell proliferation further supports the argument mentioned above (87). PDGF is one of the main mitogens responsible for the growth, proliferation, and migration of the smooth muscle cells. When the PDGFR-β pathway is inhibited, it significantly suppresses fibrous cap formation (88). A known fact for phenotype switching of vascular smooth muscle cells is KLF4 dependent and its expression is also induced by PDGF to cause the phenotypic switching (73).

#### 2.2.2.3. *Expression of various cellular markers related to atherosclerosis.*

One of the most striking features observed in smooth muscle cells present in atherosclerotic plaques is their ability to express cell markers such as in macrophages. Cells expressing both α-SMA and CD68 have been isolated from atherosclerotic intima (89). Fisher's study has also linked cholesterol loading with the expression of macrophage markers CD68 and Mac2 in cultured smooth muscle cells (90). Apart from macrophage markers, markers of mesenchymal stem cells and myofibroblasts have also been identified in smooth muscle cells (91). Vascular smooth muscle cells are a source of the various phenotypes of cells that make up the atherosclerotic plaque, at all stages of atherosclerosis. This includes

foam cells, mesenchymal-stem-cell-like cells, extracellular matrix-producing cells of the fibrous cap, and macrophage-like cells (73).

2.2.2.4. *Interaction with immune cells*.

Another important feature of smooth muscle cells is their potential to acquire markers of inflammatory cells and release cytokines including IL-1β, TNF-α, MCP-1, and IL-6. The TNF-α and IL-1β, in turn, stimulate the expression of other inflammatory molecules like (I-CAM)-1 and (VCAM)-1 and release of MMP-9 which relates to the vulnerability of plaques, in smooth muscle cells (92, 93). ICAM-1 upregulation has also been reported on smooth muscle cell surfaces found in atherosclerotic plaques and they have an important role in promoting the adhesion of macrophages, monocytes, and T-cells (94). Additional factors already present in atherosclerotic plaques include angiotensin-II, oxidized phospholipids, oxLDL, and toll-like receptor ligands which further initiate NF-κβ and RAGE pathway mediated inflammation in smooth muscle cells (95, 96).

2.2.2.5. *Foam cell formation.*

The formation of foam cells, a crucial event in both early and advanced stages of atherosclerosis, is aided by the expression of scavenger receptors in smooth muscle cells followed by the uptake of lipoproteins by macrophages (96). Uptake of aggregated LDL by smooth muscle cells through LDL receptor-related protein-1 has also been reportedly involved in foam cell formation (97). Lipid loading by smooth muscle cells plays an important role in impairing their ability to assemble fibrillar extracellular matrix which might contribute to decreasing plaque stability (94, 99).

2.2.2.6. *Biochemical changes.*

Alongside morphological changes, metabolic changes in vascular smooth muscle cells also emerge as an important aspect in the development of atherosclerosis. It has been seen that mitochondria in vascular smooth muscle cells significantly decrease glucose oxidation and instead, increase the rate of fatty acid oxidation during their phenotypic switching suggesting that vascular smooth muscle cells promote the synthesis of DNA and other molecules required for proliferation by redirecting the use of glucose and it's metabolites (100, 101).

## 3. ROLE OF ROS IN ATHEROSCLEROSIS

Extensive studies in human and animal models indicate well-choreographed synchrony between the levels of intracellular ROS and antioxidant enzymes (Figure 2). Thus, very high levels of oxidative stress result from an increased production of ROS and a simultaneous decrease in antioxidant reserve. This, in turn, plays an important role in the pathogenesis of atherosclerosis through endothelial dysfunction (101, 102). Hydroxyl radicals, superoxide anions, and hydrogen peroxide can damage the DNA, membrane lipids, and proteins of the cells. This results in the disruption of the normal functioning of the cell (103). Mitochondrial oxidative damage can also contribute to several intracellular pathological conditions that might lead to cardiovascular diseases.

Cardiovascular risk factors like hypertension, hypercholesterolemia and diabetes dramatically increase ROS levels in the vascular walls causing an imbalance between the

activities of pro-oxidative enzymes such as NADPH oxidase (NOX), xanthine oxidase (XO) and antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase (8, 105–107). During the pathogenesis of atherosclerosis, ROS is generated mainly by the upregulation of enzymes like NOX, XO and uncoupling of eNOS (108). In addition, NOX activation in the vasculature is greatly associated with angiotensin II-induced hypertension, hypercholesterolemia and diabetes which are potential risk factors for the development of atherosclerosis (106, 107, 109, 110). Interestingly, NOX is considered to be the initiating factor for mitochondrial dysfunction ahead of other ROS generating enzymes and this suggests that superoxide generated from NOX activates XO and uncoupling of eNOS (110). XO has also been associated with the production of endothelial superoxide ions in experimental models of hypercholesterolemia along with activation of NOX (111).

Uncoupled eNOS reduces the bioavailability of NO in endothelium thereby, disturbing its normal functions that include vasodilation, inhibition of smooth muscle proliferation, platelet adhesion and aggregation, expression of proinflammatory genes and prevention of LDL conversion to oxLDL (112). The oxLDL is then engulfed by the macrophages which transform into foam cells (102). The oxLDL also participates in NO inactivation leading to further endothelial dysfunction and an increase of adhesion molecules (102). ROS is the major etiology for the initiation and development of atherosclerosis (113). ROS can also activate MAP kinase to stimulate the proliferation of smooth muscle cells and fibroblast migration, both of which contribute to the process of atherogenesis (114, 115).

Similarly, ROS also regulates the expression of proinflammatory genes directly or indirectly that release MCP-1, VCAM-1, ICAM-1, and E-Selectin (8, 116). These molecules act in the early stages of atherosclerosis by inducing endothelial-leukocyte interaction (115). The manifestations of the altered redox state upregulate gene expression of these inflammatory molecules and redox-sensitive transcription factors such as NF-κβ (8, 117). This, in turn, triggers proliferative signals in vascular smooth muscle and induces their migration (113). The related pathways have been illustrated in figure 2.

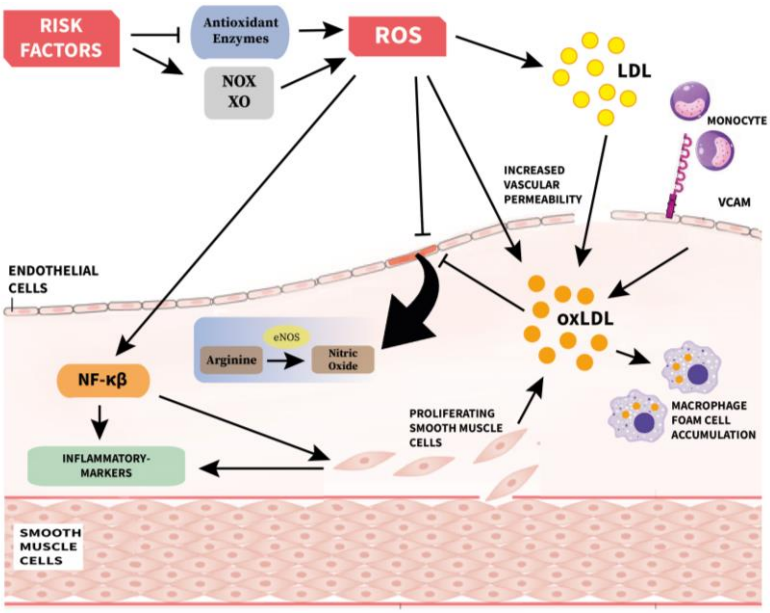


**Fig 2: Pathogenesis of Atherosclerosis.**

*The risk factors enhance the level of ROS which in turn oxidize LDL to form oxLDL. oxLDL contacts with immune cells and smooth muscle cells to give rise to foam cells. ROS also uncouples eNOS which results in reduced NO secretion.*

## 4. CURRENT CLINICAL INTERVENTION FOR ATHEROSCLEROSIS

Presently, a number of medications are broadly used for treating atherosclerosis. Epidemiological studies have identified several factors including hypertension, hypercholesterolemia, diabetes, and smoking as the risk factors of atherosclerosis (117). Thus targeting these risk factors has become the popular approach for drug development against atherosclerosis (118).

It is difficult to detect atherosclerosis in its early stages. The diagnosis of atherosclerosis mainly depends on its clinical manifestations of coronary artery disease or myocardial ischemia (119). Currently, there are no direct anti-atherosclerotic medicines available (120). The reason is that the exact mechanisms for its formation are still uncertain and hence, the pinpointed therapeutic targets have not been made possible.

The current medicines used for atherosclerotic patients are expensive and have severe side effects. These shortcomings limit their indications and also their use in the early stages of this disease. Table 2 lists some of those drugs commonly used for targeting the risk factors of atherosclerosis.

**Table 2: Conventional medicines for targeting risk factors of atherosclerosis.**

| Drug Type | Group | Drug Name | Chemical Nature | Route of Administr-ation | Half Life | Side Effects |
|---|---|---|---|---|---|---|
| **Anti-platelet** | N/A | Aspirin | acetylsalicylic acid | Oral, Intravenous (IV) | 20 minutes | gastric ulcers, renal failure, haemorrhagic stroke, impaired platelet function |
| | | Ticlopidine | thienopyridine | Oral, IV | 20-50 hours | gastrointestinal complaints, skin rash, nausea, diarrhea, agranulocytosis |
| | | Clopidogrel | thienopyridine | Oral | 6 hours | purpura, thrombocytopenia |
| | | Abciximab | monoclonal antibody | Intracoronary, IV | 10-30 minutes | haemorrhage, thrombocytopenia, constipation, ileus, arrhythmia |
| **Anti-coagulant** | N/A | Heparin | glycosaminoglycan | IV, Subcutaneous | 60-90 minutes | bleeding, haematuria, thrombocytopaenia, transient and reversible alopecia, osteoporosis |
| | | Warfarin | coumarin derivative | Oral, IV | 20-60 hours | alopecia, dermatitis, diarrhea |
| | | Edoxaban | monocarboxylic acid amide | Oral, IV | 10-14 hours | gastrointestinal haemorrhage |
| **Blood Pressure Regulator** | Beta Blocker | Atenolol | ethanolamine | Oral, IV | 6-9 hours | bradycardia, diarrhea, dizziness, constipation, confusion, dyspnea, headache, heart failure |
| | | Metoprolol | propanolamine | Oral, IV | 3-4 hours | fatigue, dizziness, headache |
| | | Propranolol | propanolamine | Oral, IV | 3-6 hours | bradycardia, gastrointestinal issues, abdominal pain, nausea, erectile dysfunction, wheezing |
| | | Carvedilol | carbazole and propanol derivative | Oral, IV | 7-10 hours | allergy, chest pain, discomfort, tightness, or heaviness, dizziness |
| | Calcium channel blockers | Verapimil | phenyl alkylamine | Oral,IV | 3-5 hours | gingival hyperplasia , constipation, peripheral edema, hypotension , fatigue |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Nifedipine | dihydropyridine | Oral, IV | 1.7 hours | flushing, peripheral edema, dizziness, headache |
| | | Diltiazem | benzothiazepine | Oral, IV | 3.2 hours | edema, bradycardia, dizziness, headache |
| | | Amlodipine | dihydropyridine | Oral | 40-60 hours | oedema, flushing, muscle cramps, frequency of micturition/nocturia, coughing, impotence, asthma, epistaxis |
| | ACE inhibitor | Captopril | l-proline derivative | Oral, IV | 2 hours | skin rash, fever, loss of taste |
| | | Enalapril | dicarboxylic acid monoester | Oral, IV | 2-6 hours | hypotension, azotemia, cough, fatigue |
| | | Lisinopril | peptide derivative | Oral, IV | 12.6 hours | dizziness, headache, cough, hypotension and diarrhea |
| | Nitrates | Nitroglycer-ine | nitroglycerol | Oral, IV | 2-3 minutes | headaches, tachycardia, nausea, vomiting, apprehension, restlessnes |
| | | Isosorbide dinitrate | Nitrate ester and glucitol derivative | Oral, IV | 48-55 minutes | headache, reflex tachycardia , orthostatic hypotension , hypotension. |
| **Lipid Regulator** | Statins | Lovastatin | hexahydronaphthalene | Oral | 1.1-1.7 hours | liver damage, muscle pain, tenderness, or weakness, kidney problems |
| | | Atorvastatin | dihydroxy monocarboxylic acid | Oral | 14 hours | arthralgia, dyspepsia, diarrhea, nausea, nasopharyngitis, insomnia, urinary tract infection |
| | | Simvastatin | hexahydronaphthalene | Oral | 1-2 hours | muscle ache , gastrointestinal symptoms |
| | | Pravastatin | carboxylic ester | Oral | 1.8 hour | nausea, vomiting, dizziness, myalgia, headache, constipation, diarrhea, abdominal pain |
| | Fibric acid derivatives | Clofibrate | ethyl ester of clofibric acid | Oral | 15 hours | headache, muscle aches and gastrointestinal upset |
| | | Gemfibrozil | carboxylic acid | Oral | 1.5 hours | hepatic or severe renal dysfunction, cholelithiasis |
| | | Bezafibrate | monocarboxylic acid amide | Oral | 2 hours | gastrointestinal disturbances, with cutaneous reactions and central nervous system effects |
| | | Fenofibrate | chlorbenzophenone | Oral | 30 hours | myalgia, hepatitis, rashes,cholelithiasis, rhabdomyolysis |
| **Endothel-ium protective** | $I_f$ inhibitor | Ivabradine | benzazepine | Oral | 6 hours | bradycardia, hypertension, atrial fibrillation |
| | Angiote-nsin receptor blocker | Candesartan | Benzimidazolecarbo-xylic acid | Oral, IV | 9 hours | hypotension, abnormal renal function, and hyperkalemia, headache, back pain |
| | | Valsartan | monocarboxylic acid amide | Oral, IV | 9.5 hours | dizziness, headache , migraine , epistaxis, fatigue, rash, joint stiffness, muscle cramps |
| | | Losartan | biphenyltetrazole | Oral, IV | 1.5-2 hours | cough, fatigue, hypoglycemia, anemia, urinary tract infection (UTI), chest pain, |
| | Phosphodiester- | Sildenafil | pyrazolopyrimidinone derivative | Oral, IV | 3-5 hours | flushing , headache, nasal |

| | | | | | |
|---|---|---|---|---|---|
| ase-5-inhibitor | | | | | congestion, heartburn |
| | Vardenafil | sulfonamide | Oral, IV | > 4 hours | headache, flushing |
| | Tadalafil | pyrazinopyridoindole | Oral | 17.5 hours | muscle and back pain, dyspepsia, headache |

## 5. MELATONIN: THE BIOLOGICAL MARVEL

Melatonin (N-acetyl-5-methoxytryptamine), a highly conserved molecule with pleiotropic bioactivities, is well known for its potent antioxidant capability (121-123). Its actions are mediated through both receptor-dependent and receptor-independent mechanisms in organisms (124, 125). Some of the main functions of melatonin include maintaining the circadian rhythm, cytoprotection, immune-stimulation, etc. (125–127). Studies have identified melatonin as a potential free radical scavenger and its roles in improving various pathophysiological conditions associated with oxidative stress, such as cardiovascular and neurodegenerative diseases (128–130). Moreover, it can cross all physiological barriers including blood brain barrier (BBB) to every part of the body and executes its protective role. (125, 131) which will be discussed later.

### 5.1. Cardioprotective effects of melatonin.

In cardiovascular diseases, melatonin exerts numerous protective effects mediated by its free radical scavenging activity. These include improvement of endothelial cell function, upregulation of the antioxidant defense, modulating LDL clearance, inhibition of LDL oxidation, and reduction in the formation of endothelium-derived adhesion molecules. Vascular endothelial dysfunction is characterized by an imbalance between vascular contraction and relaxation accompanied by inflammation. All of these are identified as the initiating factors of atherosclerosis (132). Melatonin exhibits a dual effect on the vasculature contractibility mediated by its receptors. MT1 receptor activation promotes vasoconstriction while MT2 activation induces vasodilation. The synchronization of both receptors maintains vascular homeostasis (133). The protective effects of melatonin on cardiovascular diseases have been well documented (134).

## 6. ATHEROSCLEROSIS AND MELATONIN

Recently, the protective effects of melatonin in cardiovascular diseases have gained a lot of popularity. The anti-atherosclerotic effect of melatonin is also investigated and several pathways are involved.

### 6.1. Antioxidant and ROS scavenging activity.

Many studies have proved the free radical scavenging activity of melatonin. By scavenging the most toxic $OH^{\cdot}$, melatonin reduces oxLDL induced downregulation of NOS expression in human endothelial cells (129). Although melatonin has shown regulatory effects on NOX activation (a key enzyme involved in ROS generation) in glial cells, its role in controlling NOX activation in the pathogenesis of atherosclerosis remains yet to be studied but can be predicted (135). It is clear that melatonin reduces LDL levels and inhibits their conversion to oxLDL by scavenging free radicals (136).

### 6.2. Anti-inflammatory pathway.

One of the major pathways by which melatonin displays its cardio-protective activities is its anti-inflammatory activity. Via this activity, melatonin suppresses the NF-κβ system which in turn downregulates the expression of IL-1, IL-6, IL-12 which are powerful proinflammatory cytokines (137). Similarly, upregulated VCAM-1, an inflammatory atherosclerotic marker in both smooth muscle cells and endothelial cells is also inhibited by melatonin via a sharp decline in p38 phosphorylation (138).

### 6.3. Structural armament.

An increase in endothelial permeability is also a hallmark of vascular endothelial damage. Melatonin ameliorates this damage by inhibition of endothelial interaction with neutrophils to protect the endothelial cells (139). In hypercholesterolemic states, the increased expression of MLCK actively phosphorylates the actin attached to junctional and adapter proteins leading to hyperpermeability in vascular endothelium; on the contrary, melatonin suppresses this reaction (140). Similarly, melatonin inhibits monocyte adhesion on vascular walls to reduce their damage (138).

### 6.4. Sestrin2 mediated pathway.

A recent study has shown that melatonin inhibits the excessive proliferation of vascular smooth muscle cells by upregulating a stress-inducible protein, Sestrin2 (141). Sestrin2 ameliorates oxidative stress, insulin resistance, and accumulation of fat, thereby reducing the effects of the risk factors which accelerate atherosclerotic progression (142). Sestrin2 also promotes mitochondrial biogenesis and mitohormesis (141, 143). This implies that melatonin plays important role in the recovery of tissue oxidative injury by its direct and indirect activities. Potentially protective mechanisms of melatonin on atherosclerosis are illustrated in figure 3.

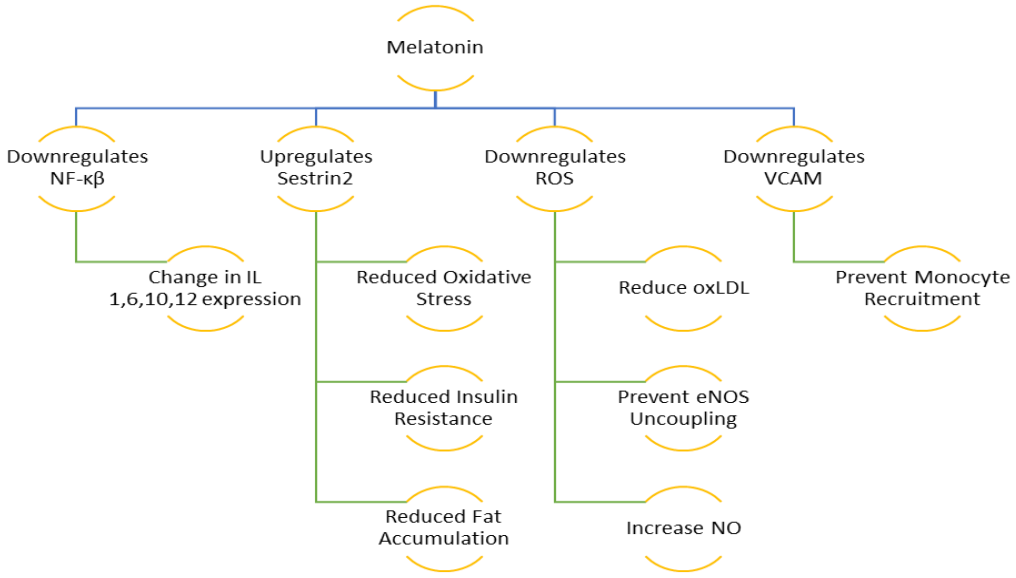


**Fig 3. Roles of melatonin in ameliorating the process of atherosclerosis.**

## 7. FUTURE PERSPECTIVE

Due to the extensive investigations in the field, researchers have successfully gained some insights into the cardiovascular disorders associated with atherosclerosis. The focuses are the

etiology of the disease and its effective therapies. The outcomes are full of challenges. This encourages researchers to identify more cost-effective and scalable interventions to target atherosclerosis and its associated heart diseases.

In the past 5-10 years many studies have indicated that melatonin has a profound role in altering the etiology of atherosclerosis among patients with different ages. Being an endogenously produced molecule, melatonin has a very high safe margin and low toxicity for patients. Thus melatonin shines bright as a potential candidate in curbing down atherosclerosis and thus preventing further damage to the heart. Studies have uncovered that melatonin level declines in patients with atherosclerosis and heart diseases (136). This strengthens the argument of melatonin's role in atherosclerosis. Accordingly, more studies involving melatonin in combination with conventional drugs or alone might bring out many breakthroughs in the treatment of atherosclerosis and its associated manifestations.

As mentioned above, melatonin is capable of upregulating stress-inducible protein, Sestrin2. This protein plays an active role in mitogenesis and mitohormesis. Mitochondria are also a key player in the etiology of atherosclerosis. Interestingly, melatonin is synthesized in mitochondria and many of its functions are also mediated by mitochondria (144). Upregulation of Sestrin2 is one of the examples of melatonin's activity on mitochondria. Extensive studies on the regulatory mechanisms of melatonin on mitochondria might reveal its beneficial effects even on the early stages of atherosclerosis. Hence, the principle of Sestrin2 mediated mitochondrial biogenesis and mitohormesis promoted by melatonin deserves to be studied more thoroughly.

## 8. CONCLUDING REMARKS

As highlighted in this review, atherosclerosis is a serious vascular infirmity that can cause fatal heart diseases if not intervened in time. In this review, we have focused on the different aspects of atherosclerosis, its etiology, and progression with potential molecular mechanisms of this disease. Further, we have also discussed how melatonin as a naturally occurring antioxidant takes part in healing the damaged vascular tissues caused by atherosclerosis. In short, the paper is a gist of how the body fights off the vascular anomalies caused by multiple lifestyle-related stressors. Also, how we can enhance the body's natural healing process by reinforcing with a platoon of external melatonin to ensure a quicker and smoother recovery. Thus, we suggest that melatonin can be an inexpensive and well-tolerated treatment for atherosclerosis.

## AUTHOR'S CONTRIBUTION

Dr. AC and Dr. DB contributed to the conception, critically corrected and approved the manuscript. MD contributed to the conception, preparation, drafting and editing the manuscript. RM contributed to editing the manuscript and preparing the tables and figures.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

| | |
|---|---|
| CAD: | Coronary Artery Disease |
| CD68: | Cluster of Differentiation 68 |
| eNOS: | Endothelial Nitric Oxide Synthase |
| HIF1α: | Hypoxia Inducible Factor 1α |
| I-CAM: | Intercellular Adhesion Molecule 1 |
| IL-1β: | Interleukin 1β |
| KLF4: | Krüppel like Factor 4 |
| LDL: | Low Density Lipoprotein |
| MCP-1: | Monocyte Chemotactic Protein |
| MLCK: | Myosin Light Chain Kinase |
| MMP-9: | Matrix Metalloproteinase |
| NF-κβ: | Nuclear Factor -κβ |
| NO: | Nitric Oxide |
| NOX: | NADPH Oxidase |
| OH*: | Hydroxyl Radical |
| oxLDL: | Oxidized Low-Density Lipoprotein |
| PDGF: | Platelet Derived Growth Factor |
| PDGFR-β: | Platelet-Derived Growth Factor Receptor β |
| RAGE: | Receptor for Advanced Glycation in Products |
| ROS: | Reactive Oxygen Species |
| TGF-β: | Transforming Growth Factor β |
| TNF-α: | Tumor Necrosis Factor- α |
| VCAM-1: | Vascular Cell Adhesion Molecule |
| VEGF: | Vascular Endothelial Growth Factor |
| XO: | Xanthine Oxidase |
| α-SMA: | α-Smooth Muscle Actin |

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