Review

Multiple strategies of melatonin protecting against cardiovascular injury related to inflammation: A comprehensive overview

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ABSTRACT

The onset and progression of baneful chronic diseases are often accompanied by a torrent of uncontrolled inflammatory reactions. Although inflammation is a natural response to detect, eliminate, and counterpoise the harmful insults to physiological integrity, a persistent inflammation causes tissue damage or more serious disorders, for example, the atherosclerosis and myocardial infarction. Inflammation often occurs in the cardiovascular system, but are also caused by other disorders including metabolic syndrome, autoimmune diseases, AIDS, and cancer that can affect the cardiac health. To effectively treat heart diseases a potent remedy is necessary which not only suppresses the inflammation but also prevents inflammation-associated cardio-pathogenesis. The ubiquitous antioxidant molecule melatonin has both anti-inflammatory and cardioprotective activities. Melatonin executes its anti-inflammatory activity by its antioxidant function or by targeting multiple intracellular signalling cascades such as modulating cytokine profile, blocking inflammasome activation and apoptosis. Lipid dysregulation and endothelial dysfunction that play a crucial role in the pathogenesis of atherosclerosis, insulin resistance, and diabetes are prevented by melatonin. Attenuation of mitochondrial and ER stress by melatonin is also pertinent to its cardioprotective action. Additionally, melatonin by its immuno-stimulatory activity can suppress inflammaging and immuno-senescence in HIV patients and thereby averts chronic inflammation-induced cardiovascular abnormality in these subjects. Modulation of cytokine profile and decrease in MMP-9 secretion by melatonin is beneficial in autoimmune conditions. In addition to its anti-tumour potency, melatonin can reduce chemotherapy-induced cardio-toxicity in cancer patients. This review, therefore, provides a concise summary of the currently available information appertaining to the roles of melatonin in mitigation of chronic inflammation and its effect on cardiovascular integrity.

Key words: Melatonin, cardiovascular diseases, inflammation, atherosclerosis, myocardial infarction, metabolic syndrome, autoimmune diseases, immunodeficiency, cancer.

1. INTRODUCTION

The internal homeostasis of organisms is frequently threatened by various toxic and pathogenic agents as well as the malfunctions of endogenous molecular processes. These noxious challenges can lead to inevitable tissue injury or even lethal outcome in organisms. Therefore, organisms, in course of evolution, have developed a well-integrated defence machinery that aims to neutralize the injurious stimuli and thereby to restore functional harmony in the affected tissue. A good example is the inflammatory system. Inflammation is a healing process; however, its overreaction can lead to detrimental consequences. In some cases, the latter often outweighs the beneficial effect of this innate immune process (1).

Evidence derived from epidemiological studies indicates that the cardiovascular diseases often emerge ensuing a chronic inflammatory state (2). Various hallmarks of inflammation are often associated with menacing cardiovascular events including atherosclerosis (3), myocardial infarction, and cardiac arrest (4). The aetiology can be explained by the fact that cardiac tissue is enriched with mitochondria which are both a source as well as the victim of oxidative stress. The tremendous metabolic activity of the heart requires a huge oxygen supply yet the relatively low levels of antioxidant capacity make the heart vulnerable to oxidative stress and concomitant inflammatory injury (5). Many chronic disorders including diabetes, obesity, autoimmune diseases, and cancer are associated with sustained low-grade inflammation that adversely affects the cardiovascular system, leading to cardiomyopathies, that originate independent of the traditional cardiovascular risk factors (6).

Animals, especially, mammals, are well equipped to combat the nocuous effect of persistent inflammatory reactions. The cellular antioxidant repertoire represents a checkpoint in the trajectory of inflammation-induced pathologies. This evokes the demand for selecting a suitable antioxidant to target inflammation (7). One such endogenous molecule is melatonin (N-acetyl-5-methoxytryptamine), a potent antioxidant and a powerful anti-inflammatory agent. It protects the cells against uncontrolled inflammation by modulating both pro- and anti-inflammatory processes (8). Cardioprotective actions of this indoleamine are usually mediated by the receptor-independent mechanism, whereby the amphiphilic feature allows it to pass through the biological membrane to achieve on-site protection inside the cells (9). Melatonin also exerts its action on cardiovascular system by interacting with its receptors localized in the cardiac and endothelial cells (10-11). In addition, systemic inflammatory reactions caused by chronic illnesses are efficiently prevented by melatonin, thus arresting the imminent attack on the cardiovascular tissues (12). Melatonin not only inhibits the persistent migration of leukocytes (13) but also suppresses the production of reactive oxygen species (ROS) (14), prevents lipid oxidation and resultant lipotoxicity (15), inhibits inflammasome activation (16), up-regulates the antioxidant, anti-inflammatory (17), and anti-apoptotic genes while minimizing the release of pro-inflammatory cytokines and pro-apoptotic proteins (18). An in-depth description encompassing the modalities of inflammation and the target points of melatonin in various signalling events within the cardiovascular tissue will be discussed in this review.

2. INFLAMMATION AND INFLAMMATORY DISEASES

Inflammation is a pathophysiological response of the body to infection or injury in which the various components of the immune system co-ordinately activate a series of signalling processes and regulate the levels of mediator molecules in the host tissue

in an attempt to ameliorate tissue damage (1, 19). The non-immune and immune cells express surface receptors known as pattern recognition receptors (PRR) that have affinity for foreign agents as well as damaged self-substances such as mitochondrial DNA, cardiolipin and other structures released by the injured cells. PRR recognize the pathogens and damaged self-molecules via their pathogen associated molecular patterns (PAMP) and danger associated molecular patterns (DAMP), respectively (20, 21). Their interactions activate a series of signalling events known as inflammatory responses. Toll-like receptors (TLR) are among the most conserved and well explored member of the PRR family and are known to trigger intracellular pathways that activate a range of transcription factors such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), mitogen-activated protein kinase (MAPK) and interferon regulatory factor 3 (IRF-3) (22-24). These transcription factors translocate into the nucleus to mediate gene expression of a set of pro-inflammatory and anti-inflammatory cytokines and chemokines. Tumour Necrosis Factor alpha (TNF-α) and Interleukin-1 beta subtype (IL-1β) are the first pro-inflammatory molecule to be secreted which perpetuates the molecular cascade of inflammatory reactions resulting in activation of transcription factors and generation of other cytokines and proteins that control apoptosis (25). Other important pro-inflammatory markers including IL-1α, IL-6, IL-8, macrophage inflammatory protein 1-α (MIP-1α), interferons (IFN), colony stimulating factors and transforming growth factors (TGF) (26-27) are also recruited during inflammation. However, inflammatory mechanism is not solely characterized by the release of pro-inflammatory cytokines, rather anti-inflammatory molecules have a vital role in dampening of aggressive immune reactions. An impairment in the anti-inflammatory response locally may culminate in a pernicious inflammatory state at the systemic level which may have detrimental results such as multi-organ dysfunction syndrome, septic shock, and mortality (25). In addition, inflammation associated oxidative stress can also activate NFκB, MAPK and JAK-STAT (Janus Kinase-Signal Transducer and Activator of Transcription) pathways to generate inflammatory cytokines and chemokines that make the situation worse (28). Trauma and oxidative stress increase the activity of some proinflammatory enzymes such as nitric oxide synthase, xanthine oxidase, cyclooxygenase, lipoxygenase, and NADH/NADPH oxidases (19, 29). All these events pave the way for the development of a plethora of inflammatory diseases such as autoimmune conditions, Acquired Immune Deficiency Syndrome (AIDS), metabolic syndrome and cancer which will be discussed below in detail.

2.1. Inflammatory autoimmune disorders.

Autoimmune diseases involve a broad range of inflammatory conditions that arise due to a breach in immune tolerance leading to ignition of immune response against self-molecules, a condition that is either limited to a specific organ or evolves a systemic disorder (30). Interestingly, basal level of auto-reactivity of the T and B cells to self-antigens is not considered as a pathological sign and is indispensable for the survival of mature T cells in the peripheral blood. However, the decreased threshold of the activation of lymphocytes at the genetic level evokes immune reactivity against self-molecules (31). Additionally, external factors such as infection, certain xenobiotics and trauma may also induce or exacerbate autoimmune response (30). A current evidence has documented that a dysregulated inflammatory state may be associated with the pathogenesis of autoimmune disorders (32). The common autoimmune diseases characterized by chronic inflammation include rheumatoid arthritis, systemic lupus

erythematosus, systemic sclerosis, type-1 diabetes, psoriasis, inflammatory bowel disease and autoimmune thyroid conditions.

2.2. Human Immunodeficiency Virus (HIV) infection and AIDS.

Human Immunodeficiency Virus infection and AIDS is manifested by persistent immune activation that result in chronic inflammatory status allowing continuous viral replication, gradual cell death, loss of immune function and inflammation-associated degenerative diseases (33, 34). Although the emergence of combinational anti-retroviral therapy has reduced AIDS-related mortality, yet prolonged viral suppressive treatment escalates the risk of non-AIDS-related morbidity including cardiovascular pathogenicity (35-36).

HIV antigens interact with $CD4^+$ and $CD8^+$ lymphocytes leading to profuse secretion of pro-inflammatory cytokines and chemotactic agents including IL-1β, IL-6, TNF-α, IFN-α, MIP-1α, chemokine ligands (CXCL-9, CXCL-10 and CCL-2), and cell adhesion molecules (CAM) such as ICAM and VCAM. This results in excessive activation of T cells, their decreased half-lives, exhaustion of T cells during viral encounter and apoptosis-mediated depletion of T cell pool (37-40). Further, with the progressive viremia, the optimally functional B cells, dendritic cells, and natural killer (NK) cells are compromised resulting in utmost immune system imbalance and premature immuno-senescence (41).

2.3. Metabolic syndrome.

The World Health Organization (WHO) has proposed that metabolic syndrome comprises of multiple clinical features with insulin resistance and/or diabetes *mellitus* being the hallmark disorder along with at least two of the following abnormalities which include hypertension, abnormal plasma lipid profile, abdominal obesity and increased urinary albumin excretion (42). Manifestation of insulin resistance in adipocytes abolishes the antilipolytic action of insulin, thereby increases circulating free fatty acids (FFA) which further amplifies insulin resistance in adipose tissue (43). Additionally, plasma FFA has deleterious impact on insulin homeostasis due to lipotoxicity-mediated pancreatic beta cell destruction (44).

The cardiovascular component of metabolic syndrome has its pathogenetic basis in the chronic inflammatory mechanisms that are instigated by insulin resistance (45). The adipose tissues are responsible for the up-regulation of pro-inflammatory pathways by secretion of inflammation promoting adipokines such as chemerin and leptin along with the release of other pro-inflammatory mediators including IL-8, monocyte chemotactic protein (MCP)-1, and C-reactive protein (CRP)(46-47). Besides, adipose tissue resident macrophages also release inflammatory molecules viz., TNF-α which phosphorylates and inactivates insulin receptor in both smooth muscle cells and adipocytes contributing to elevated FFA release into the circulatory pool (48). TNF-α is responsible for down-regulation of adiponectin, an anti-inflammatory molecule produced by adipocytes that enhance insulin sensitivity (48, 49). Additionally, IL-6 secreted by the immune cells and adipose tissue up-regulates the production of fibrinogen and CRP in the liver (49,50). Increased circulatory fibrinogen concentration is associated with prothrombotic condition in patients with metabolic syndrome (49).

2.4. Cancer.

Chronic inflammation often associates to carcinogenesis of the inflamed tissue. The immuno-pathogenic facets of cancer progression are often observed from the biopsiesthat display a panoply of inflammatory cells in the tumour microenvironment (51). The mechanistic nexus between inflammation and cancer can be explained by two pathways— the intrinsic and the extrinsic pathways. Several mutational events engendering the activation of oncogenes, deactivation of tumour-suppressor genes, and initiate the intrinsic pathway leading to neoplastic growth and associated inflammatory changes, even in cases without any history of inflammatory disorders (52). On the other hand, extrinsic pathway operates when carcinogenesis is attributable to a pre-existing inflammatory condition. However, both the pathways are connected to a common inflammatory mechanism that involves activation of NFκB, JAK-STAT, and HIF-1α (Hypoxia-inducible factor 1α)-mediated cytokine and chemokine production (52). One crucial chemokine molecule secreted by the neoplastic tissue is the MCP which plays a significant role in attracting monocytes that transform into tumour associated macrophages (TAM) (53). Although TAM may exhibit mild anti-malignant effect by inducing IL-12, IL-2 expression and consequent natural killer cell activation, it also involves in tumour growth and metastasis which makes TAM a major culprit in cancer progression (54, 55). Experimentally, TAM have been demonstrated to produce several pro-angiogenic growth factors such as transforming growth factor-β (TGF-β), epidermal growth factor, platelet derived growth factor, vascular endothelial growth factors and their receptors along with the production of several extracellular proteases and pro-inflammatory cytokines including IL-1, IL-6, and TNF-α (56, 57). In addition to macrophages, other immune cells including neutrophils, eosinophils, mast cells, and T lymphocytes produce chemotactic molecules, pro-angiogenic factors, and matrix degrading proteases that augment neoplastic development (53).

3. HEART AND THE VASCULAR SYSTEM AS VICTIMS OF CHRONIC INFLAMMATION

Inflammation significantly contributes to the pathogenesis of atherosclerosis and other cardiovascular morbidity. Orchestration of a number of inflammatory signalling pathways forms a crucial link between atheroma formation and associated cardiovascular complications including myocardial infarction. The notion regarding the involvement of inflammatory mediators in atherogenesis is strengthened by the observation that LDL lowering drugs seem inefficient in fully impeding the atherosclerotic process (3). Additionally, therapeutic interventions targeting inflammation have shown outstanding improvement in the prognosis of patients suffering from arteriosclerotic heart disease (3). Atherogenic diet which causes lipotoxicity in the arterial tissue is considered to be an initial step in the development of atherogenic plaque. The lipids accumulating in the arterial wall are prone to pro-oxidation due to the fact that the arterial intima isa shield to the direct exposure to blood antioxidants (58). These oxidized lipoproteins are trapped locally and phospholipids are responsible for NFκB-mediated transcription of VCAM-1 in the endothelial cells (58-61). Circulating monocytes attach to the VCAMs on the surface of the endothelial cells undergoing diapedeses along the gradient of chemokine MCP-1 (3, 62). Lymphocytes also penetrate in the sub-endothelial area in response to lymphocyte specific chemo-attractants [interferon-γ (IFN-γ)-inducible chemokines of the CXC family] (63). Monocytes assembling within the tunica intima constitute the

tissue macrophages which then engulf the oxidized lipoprotein to form arterial foam cells. These foam cells release free radicals and cytokines that augment the pro-inflammatory response (3, 62). The lymphocytes interact with oxidized lipoproteins and heat shock proteins to produce cytokines that facilitate activation of other cells including foam cells (62). Consequently, matrix metalloproteinases (MMPs) are released from the foam cells. MMPs break down extracellular matrix proteins and weaken the fibrous covering around the plaque; thus, lead to vascular rupture. When the plaque splits open the tissue factor (factor-III) released by plaque resident leukocytes is exposed to blood to form thrombosis with the dying macrophages to constitute the central necrotic core of the atheroma (3, 62).

An atherosclerotic lesion formed in the coronary artery can often result in arterial occlusion and the consequent ischemic cardiac injury. Acute myocardial ischaemia, infarction and reperfusion injury involve the activation of innate and adaptive immune responses that promote oxidative stress, inflammation, apoptosis, and transient or permanent loss of cardiac function (64, 65). Recruitment of inflammatory factors is indispensable at the onset of acute cardiac infarction. These factors can aid in the removal of dead cells and cellular debris from the site of infarction (66, 67). The necrotic cardiomyocytes, fibroblasts, interstitial cells and the endothelial cells trigger innate immune response by releasing damaged DNA, proteins, and lipids. These substances are then recognized as DAMP by the TLR receptors expressed by cardiomyocytes, endothelial cells, and the immune cells (68). This culminates in the activation of NFκB signalling and upregulation of several other cytokine and chemokine molecules (69,70). The chemotactic signals contribute to the directed migration of leukocytes to the site of infarction. DAMPS can further activate the complement cascade and inflammasomes in the infarct area (70, 71). This triggers the release of pro-inflammatory cytokines including IL-1, IL-6 and IL-18 and instigates pyroptosis of cardiomyocytes (70). Further, ROS generated from dysfunctional mitochondria of the infarct zone exacerbates the inflammatory process through activation of complement pathway and secretion of chemokines and cell adhesion molecules (68).

Strong evidence has demonstrated that chronic inflammation, such as rheumatoid arthritis, is associated with carotid arteriosclerosis, and increased risk of myocardial infarction and strokes even in patients without conventional cardiovascular risk factors (72-74). Several inflammatory cytokines including IL-1β, IL-6, IL-7, and TNF-α are hallmarks of atherosclerotic conditions to be detected in the plasma of animals with rheumatoid arthritis (75, 76). Activation of inflammatory cascades which contributes to the immuno-pathogenesis of systemic lupus erythematosus also promotes cardiovascular complications including dyslipidaemia and atherosclerosis, peripheral arterial occlusion, coronary artery disease, and stroke (77-79). Cardiac dysfunction with impaired ventricular contractility and altered diastolic function along with greater incidence of myocardial infarction have been observed in systemic sclerosis patients (80). Inflammatory bowel disease (IBD) which includes two chronic inflammatory conditions of the gut— Crohn's disease and ulcerative colitis can predispose individuals to atherosclerotic cardiovascular disease (ASCVD) (81, 82). Clinical markers of IBD including CRP, IL-1, TNF-α, anti-neutrophil cytoplasmic antibodies, IgM and IgG antibodies, and vascular endothelial growth factors attribute to leukocyte migration, ROS generation, and endothelial injury, all contribute to atherogenic cardiomyopathies (83). Cardiovascular component of metabolic syndrome is often caused by inflammation and neuro-hormonal misbalance (49). Increased serum CRP and IL-6 cytokine levels observed in metabolic syndrome is correlated with ASCVD

(84). Besides dyslipidaemia, insulin resistance can induce hypertension by increasing serum viscosity, circulatory fibrinogen concentration and angiotensin-II production (49). Angiotensin-II has been demonstrated to augment NOX-mediated free radical generation leading to NFκB activation, platelet aggregation, endothelial dysfunction and oxidation of LDL, thereby mediating initiation and exacerbation of ASCVD (49, 85). Other chronic inflammatory diseases including cancer (86) and AIDS (87) have also been found to promote progressive atherosclerotic event and adverse cardiovascular co-morbidity.

4. THE BUILT-IN DEFENCE STRATEGIES AGAINST CHRONIC INFLAMMATION

A loss of control over progressive inflammation is potentially inimical to the systemic homeostasis. A concatenation of inflammatory events that if not resolved will gradually progress towards a chronic inflammation with irreversible organ damage (88). Fortunately, our body has developed self-limiting mechanism to curb its progress with endogenous anti-inflammatory molecules and immuno-resolvents (89, 90). From the histological perspective, an inflammation resolution phase commences from the point of extreme neutrophil invasion in the inflammatory zone and continues until all the infiltrates being eliminated from this area (90). This is achieved by the accumulated leukocytes undergoing apoptotic elimination or phagocytosis or flushing away through systemic recirculation (90). The synthesis of pro-inflammatory molecules such as cytokines, prostaglandins, leukotrienes, CAM are down-regulated and their catabolic degradation promotes resolution process (90, 91).

Several natural molecules are actively produced in aiding termination of inflammation at the induction of resolution phase. These include the resolvins, lipoxins, protectins and maresins (92). Resolvins are endogenously synthesized lipid pro-resolutive mediators derived from dietary ω-3 fatty acids— eicosapentaenoic and docosahexaenoic acids (93). The pro-resolutive activity of resolvins are attributable to their ability to inhibit neutrophils, monocytes, and dendritic cell migration and down-regulation of IL-1β, TNF-α, P-selectin, and VEGF gene expression (91-94). Resolvins also enhance tissue repair and regeneration after the termination of inflammation (91). Unlike resolvins, lipoxins are synthesized from the non-dietary endogenous fatty acid— arachidonic acid (95). Lipoxins potentially inhibits neutrophil mobilization and promote recruitment of non-inflammatory macrophages that are important for phagocytosis of apoptotic neutrophil and other cellular debris (a process called efferocytosis) (96). Another vital lipid immuno-resolvent is protectin which besides promoting efferocytosis and preventing polymorphonuclear neutrophil infiltration, checks T cell recruitment and stimulates their apoptosis via TNF-α and IFN-γ signalling mechanism (91).

5. MELATONIN AS AN ANTI-INFLAMMATORY AGENT

Melatonin is a phylogenetically old molecule, first discovered in the bovine pineal gland, chemically identified as N-acetyl-5-methoxytryptamine (97-98). From bacteria to the most advanced species, *Homo sapiens*, melatonin's omnipresence has intrigued the scientific world to investigate its biological functions across the species. The free radical scavenging activity of melatonin is considered to be its most ancient function that has probably made this tryptophan derivative a life sustaining molecule in most of the organisms (99). The other functions of melatonin including regulation of

circadian rhythm (9, 14, 100), stimulation of antioxidant enzymes (101-102), participation in immuno-regulation (103) and maintenance of metabolic homeostasis of cells are acquired during evolution. The immuno-modulatory action of melatonin encompasses both pro-inflammatory and anti-inflammatory mechanisms (104). The pro-inflammatory property is known to play a significant role in coping with pathogenic insult, while the anti-inflammatory function is the most crucial for tissue injury prevention and recuperation.

Free radical production and inflammation are reciprocally connected process . The antioxidative and ROS scavenging property of melatonin is, therefore, critical to the anti-inflammatory activity (13, 17, 105). Melatonin directly protects the proteins, lipids, and nucleic acids from oxidative injury and also stimulates the gene expression and activities of the antioxidant enzymes to restore cell's innate ability to suppress oxidative stress (14-15, 106). The progression of inflammation is always accompanied by acute ROS production that potentiate pathogen induced tissue damage (107). For instance, in one hand, the infiltrated neutrophils trigger NADPH oxidase (NOX)-induced superoxide generation known as "respiratory burst" to kill pathogens. On the other hand, this process damages the host tissues by extensive oxidative stress (108). Melatonin can proficiently suppress NOX-mediated uncontrolled oxidative burst by the phagocytes and microglial cells; therefore, prevents an impending aggressive and chronic inflammatory state (104). ROS facilitates the intercellular communications of endothelial cells by decreasing occludin expression (109). Adhesion molecules including selectins (E- selectin and P- selectin) and cell adhesion molecules (VCAM and ICAM) expression on the vascular endothelial cells are modulated by free radicals which enhance leukocyte transmigration to the site of inflammation, a process that is attenuated by superoxide dismutase (SOD) activation (110-111), while melatonin stimulates SOD activity in tissues (112). Additionally, melatonin limits adhesion molecule expression on activated endothelial cells; thus, it prevents sustained immune cell recruitment and reduces the inflammation (13).

ROS, pathogenic substances like lipopolysaccharides (LPS), and certain inflammatory mediators activate NFκB, which in turn, stimulates the expression of genes of pro-inflammatory cytokines as well as proinflammatory enzymes, viz., cycloxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (113-116). Melatonin suppresses the NFκB activation; therefore, downregulates pro-inflammatory gene expression and their downstream signalling (104). For example, in LPS challenged murine cells, the NFκB-upregulated iNOS and/or COX expression was significantly attenuated by melatonin (13). In SAMP8 mice melatonin suppresses NFκB activity and reduces hepatic inflammation (117). Suppression of NFκB to inhibit inflammatory damages by melatonin in ischaemia/reperfusion injury (118-120), exercise stress (121-122), Alzheimer's disease (123), pulmonary inflammation (124), IBD (125), diabetic conditions (126), and cancer (127) has been well documented.

Melatonin reduces the pro-inflammatory cytokines, TNF-α, IFN-γ and IL-12, but increases anti-inflammatory cytokine IL-10 in LPS stimulated mice (17). Similar results have been observed in animals exposed to heat stress or ageing, where IL-10 protein expression was restored by melatonin administration (128-131). In senescent animals, melatonin minimizes expressions of pro-inflammatory cytokines— IL-1β, IL-6 and TNF-α (129-130). Melatonin also normalizes the cytokine profiles in animals subjected to strenuous exercise (121, 122) and chemical injury (132-134). It also attenuates NLRP3 inflammasome activation and apoptosis (18).

6. ROLE OF MELATONIN AS AN EFFICIENT CARDIOPROTECTIVE MOLECULE

Melatonin has profound beneficial effects on cardiovascular disorders. Myriad of molecular mechanisms have been proposed for its cardioprotective effect. One of them is the regulation of Sirtuin 1 (SIRT1), an NAD+ dependent class III histone deacetylase and a sensor for metabolic and inflammatory stress (135). Under oxidative stress, SIRT1 deacetylates a transcription factor called Forkhead Box-O (FOXO) and triggers the transcription of its target genes of anti-oxidant enzymes (catalase and SOD), anti-apoptotic factors, and proteins that control the cell cycle (136). SIRT-1 activation is essential for cell survival and stress resistance; however, it is often down-regulated in many cardiac disorders including age-related cardiac abnormalities and ischaemia/reperfusion (I/R)-induced cardiac injuries (137). In I/R injury, melatonin upregulates SIRT1 expression and consequently reduces malondialdehyde concentration, superoxide formation and NOX, caspase-3, and BAX protein expression while increasing Bcl-2 production (135). SIRT1 expression is up-regulated by melatonin in rats treated with high fat diet and streptozotocin or subjected to I/R stress (138).

In addition to SIRT1, the Notch/Hes/PI3K/Akt signalling pathway is also involved in myocardial remodelling, regeneration and restoration. Notch-1 is critical for cellular communication and is responsible for cell proliferation, differentiation, and survival (139). Upon ligand-receptor interaction, Notch intracellular domain (NICD) is split apart from the receptor by the action of γ-secretase, and is translocated to the nucleus to induce the transcription of hairy and enhancer of split-1 (HES1) mRNA (140). Protein kinase-B (also known as Akt) is an efficient suppressor of cell death and it is activated upon docking at phosphoinositides, phosphorylated by phosphoinositide 3-kinase (PI3K). This PI3K/Akt signalling is inhibited by phosphatase and tensin homolog (PTEN), and HES1 protein is known to abolish such pathway (141). Melatonin stimulates Notch1, NICD, and HES1 production, while inhibits PTEN expression. Notch/HES1/Akt signalling up-regulates anti-apoptotic BCL-2 gene and decreases the expression of pro-apoptotic genes such as caspase-3 and BAX and this pathway is enhanced by melatonin (142). Under a stressful condition such as ischaemia, the Notch signalling serves as a cardioprotective response and melatonin enhances this signalling pathway potentiating a protective mechanism (142).

Endoplasmic reticulum (ER) stress response is implicated in functional impairment of cardiac tissue. Defective protein folding and disrupted calcium homeostasis can culminate in ER stress which is characterized by aggregation of scrambled proteins. This activates the “unfolded protein response” (UPR) with resultant protein kinase RNA-like ER kinase (PERK)-mediated phosphorylation of eukaryotic initiation factor-2α (eIF2α). eIF2α, then, facilitates translocation of active transcription factor-4 (ATF4) into the nucleus to trigger transcription of mRNAs associated with autophagy and apoptosis (143). Melatonin attenuates PERK/eIF2α/ATF4 signalling-stimulated myocardial ER stress in I/R injury, possibly by the activation of pro-survival mechanisms—reperfusion injury salvage kinase (RISK) pathway and survivor activating factor enhancement (SAFE) pathway (144). Hypoxia-induced I/R damage can result in disruption of calcium homeostasis in cardiomyocyte sarcoplasmic reticulum. Melatonin efficiently extenuates I/R-induced calcium imbalance by regulating the calcium-handling proteins— sarco/endoplasmic reticulum calcium ATPase (SERCA) and sodium calcium exchanger (NCX), and enzymes such as endothelial nitric oxide synthase and calcium/calmodulin-dependent protein kinase II

(CaMKII) (145). The cardioprotective effects of melatonin is also confirmed by another way, i.e., melatonin deficiency. Ganglionectomy which causes melatonin deficiency and diminishes the expressions of melatonin receptors and SERCA pump in cardiomyocytes, has been found to augment ventricular tachycardia in rat heart subjected to I/R injury (146).

Melatonin exerts its anti-hypertensive effect by receptor-mediated activation of the anterior hypothalamic area, vascular smooth muscle relaxation, antioxidant action , and lowering the blood catecholamine (147). Melatonin regulates vascular integrity by restoring a normal mitochondrial function, modulating mitochondrial dynamics through mitofusin-2 and inhibition of mitochondrial permeability transition pore (mPTP) opening (148).

Obesity and insulin resistance are common risk factors for cardiovascular conditions. A negative correlation has been observed between serum melatonin and obesity (149). In fact, melatonin can mimic the actions of insulin and leptin in regulation of energy homeostasis via a common signalling mechanism involving PI3K and STAT-3 (149). In diabetic rats, melatonin supplementation dose-dependently raised circulatory adiponectin levels, decreased glucose intolerance and enhanced insulin sensitivity (150). Besides, melatonin can prevent platelet aggregation, curbs plasma level of cholesterol, decreases endothelial permeability and attenuates inflammatory reactions, thereby impeding atherosclerotic cardiovascular disorder (151).

7. MELATONIN SHIELDS THE CARDIOVASCULAR SYSTEM AGAINST INFLAMMATORY DISEASE-MEDIATED ADVERSE REACTIONS

The potent anti-inflammatory and cardioprotective properties of melatonin contribute to its efficiency in alleviating cardiovascular disease associated with inflammation.

7.1. Melatonin in atherosclerotic cardiovascular disease.

Aggregation of oxidized phospholipids and low-density lipoproteins in the arterial intima instigates NFκB-induced expression of CAMs in endothelial cells. This is a primary step in atherogenesis. This process promotes leukocyte recruitment and their trans-endothelial migration as mentioned previously. All these events can be minimized by melatonin. In addition, melatonin down-regulates the TLR4/myeloid differentiation primary response protein (MyD88)/NFκB signalling event, further strengthening its anti-inflammatory function (152). The oxidized LDL acts as a ligand for endothelial TLR4, melatonin reduces this ligand of TLR4. The atherosclerosis related serum high density lipoprotein, triglycerides, TNF-α, IL-6, high-sensitivity C-reactive protein were all reduced by melatonin along with the reduction in foam cell count (152). Melatonin stimulates SIRT3/FOXO3/Parkin system-induced suppression of NLRP3 inflammasome, thus minimizing atherosclerotic progression (153). MMP is an important factor that is responsible for the rupture of atheromatous plaque and exacerbation of atherosclerotic condition. The MMP9 activity is inhibited by melatonin that docks at the active site of the enzyme (154).

7.2. Melatonin and myocardial infarction.

Ischaemia/reperfusion injury and myocardial infarction are manifested by aggressive inflammatory reactions that can cause severe consequences, even mortality

(155). In a murine model, administration of melatonin prior to ischaemic insult attenuates TLR4 pathways by the activation of SAFE mechanism (156). Besides, melatonin-mediated regulation of several intracellular signalling cascades such as MAPK and JAK-STAT pathways, as well as SIRT1/FOXO1, Notch/Hes/PI3K/Akt/SIRT3, AMP-dependent protein kinase (AMPK)/peroxisome proliferator-activated receptor γ co-activator 1α (PGC1α)/SIRT3 and AMPK/Protein kinase G-1α (PKG1α)/NF-E2-related factor2 (Nrf2) axes have been implicated in defending against inflammatory responses during myocardial infarction (155, 157). Due to the lipophilic property, melatonin easily reaches cytosol and activates SIRT1, SIRT3 and Nrf2 to exert its anti-inflammatory activity (155). When melatonin is used as adjunctive therapy with primary percutaneous coronary intervention (pPCI) in acute myocardial infarction patients with ST-segment elevation, it significantly improves the efficacy of pPCI and leads to the reduction of infarct size (158,159). Although both melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) are found in the mammalian heart, cardioprotective action of melatonin in I/R injury is primarily mediated by the MT2 (160). Further, melatonin administration into hypothalamic paraventricular nucleus (PVN) has resulted in reduced level of free radicals, improvement of antioxidant activity, increase in IL-10 and decrease in NF-κB and IL-1βlevels in PVN, all these are beneficial in ameliorating inflammatory cardiac damage induced by myocardial I/R injury (161).

7.3. Melatonin in diabetic cardiomyopathy.

Type-II diabetes *mellitus* is considered to be an independent hazard to coronary heart disease and myocardial infarction (162). c-Jun NH2-terminal kinase (JNK) is one of the components of MAPK pathway to involve in post-ischaemic injury in diabetic mice model. Melatonin abrogates JNK/p53 signal-induced cardiac fibrosis and apoptosis of cardiomyocytes caused by high lipid/high glucose and hypoxic assaults (163). Melatonin was able to inhibit mitochondrial and ER stress-induced cardiac cell death in diabetes by preventing the activation of tyrosine-protein kinase or Syk, thereby, improving mitochondrial complex I activity, and repressing ROS generation, pro-inflammatory cytokine (TNF-α, TGF-β, and IL-6) release, SERCA peroxidation, and release of pro-apoptotic caspase-9 and caspase-12 (164). Melatonin treatment has further shown an enhancement of SOD, glutathione peroxidase, catalase activities and decrease in expression of mammalian target of rapamycin (mTOR) protein in diabetic heart. mTOR is known to be involved in the pathogenesis of type-II diabetes-induced cardiac disorders (165). Additionally, in hyperglycaemic conditions, melatonin attenuates cardiac NLRP3 inflammasome activation and the concomitant rise in inflammatory cytokines— IL-18 and IL-1β driven by procaspase-1 cleavage, thus preventing inflammation-mediated diabetic cardiomyopathy (166). Activated NLRP3 participates in TGF-β/Smad signalling pathway in cardiac fibroblasts and consequently increases the synthesis of extracellular matrix proteins that paves the way for cardiac fibrosis. Melatonin effectively prevents such fibrotic changes in cardiac tissue by inhibiting the TGF-β/Smad pathway activation (166).

7.4. Melatonin in chronic autoimmune disease-induced cardiovascular diseases.

Several autoimmune diseases entail common inflammatory mechanisms which often cause cardiovascular disorders. Chronic inflammatory autoimmune conditions can predispose patients towards lethal cardio-pathogenic alterations even in absence of

conventional cardiovascular risk factors (74, 78, 80, 82). Although the reports regarding effects of melatonin on autoimmune inflammation are not consistent, its potential beneficial effects in this condition have drawn a great attention recently. For example, recent evidence has demonstrated that melatonin down-regulates MMP9 activity, as well as IL-1β and TNF-α expressions in the synovial fibroblasts of patients with rheumatoid arthritis (RA) (167). Melatonin also stimulates microRNA (miR-3150a-3p) to produce anti-apoptotic action in RA patients (167,168). Both systemic lupus erythematosus (SLE) and systemic sclerosis (SS) kindle pro-inflammatory responses leading to atherogenesis and myocardial infarction (79,80), which can be targeted by melatonin (152,153, 155). The potency of melatonin in the regulation of lipid homeostasis and suppression of inflammatory pathways allows it to be a suitable candidate adjuvant to conventional therapies for cardiovascular co-morbidities in patients with systemic autoimmune conditions. Mechanistically, melatonin can switch T-helper 1(TH1) cell subset towards T-helper 2(TH2) and minimizes pro-inflammatory cytokine release, thereby ameliorating the severity of autoimmune diabetes (170). The anti-inflammatory, antioxidant, and anti-apoptotic effects of melatonin are also observed in patients with inflammatory bowel disease (IBD). Rise in circulatory TNF-α and CRP levels in IBD promotes atherogenesis (83). Melatonin significantly reduces TNF-α production in animal model of colitis and reinstate the CRP levels to its physiological range in patients with IBD (171,172), further suggesting melatonin's beneficial role in ulcerative colitis, thus, melatonin has the potential to retard IBD-associated cardiomyopathy.

7.5. Effects of melatonin on immunodeficiency-mediated impaired cardiac homeostasis.

Many studies have demonstrated an association between chronic HIV infection and thickening of the carotid artery wall (173), myocardial inflammation (174), and coronary atherosclerosis (87). The morbidity and mortality related to cardiovascular diseases are higher in HIV infected patients compared to the controls. The patients are often manifested by sustained T-cell activation, persistently escalated circulatory cytokines, gradual deterioration in immune system function, chronic inflammation, viral co-infection secondary to HIV, and adverse effects of long-term combinational anti-retroviral therapy (41). Incidence of acute myocardial infarction and stroke in patients suffering from AIDS have raised serious concern. In this regard, the anti-inflammatory and immuno-stimulatory functions of melatonin could be beneficial. Further, Highly Active Antiretroviral Therapy (HAART) used for HIV treatment has been reported to induce metabolic syndrome, which is a potent risk factor for cardiovascular diseases (175). In a recent study, it has been reported that melatonin administration for a month, in HIV patients receiving HAART, reduced blood glucose level by 23%. Additionally, hypercholesterolaemia and high plasma triglycerides in patients subjected to HAART were efficiently alleviated by melatonin treatment (176).

7.6. Melatonin protects the cardiac function in cancer patients.

Several *in vivo* and in *vitro* investigations have revealed the potent oncostatic effect of melatonin (177). The fundamental mechanisms governing such anti-cancer activities of melatonin involve its antioxidant and anti-inflammatory properties. In addition, the regulation of genomic instability, modulation of tumour metabolism, induction of cancer cell apoptosis, inhibition of angiogenesis as well as epithelial-to-

mesenchymal transition further strengthen the anticancer effects of melatonin (178). Melatonin efficiently shields the DNA against damage and mutagenesis by stimulating the activities of cellular antioxidant molecules, inhibiting the pro-oxidant enzymes and maintaining proper functioning of mitochondrial electron transport chain (177). Melatonin improves rectification of faulty DNA replication in colon cancer (HCT-15) and breast cancer (MCF-7) cell lines (179). DNA distortion caused by UV (180), ionizing radiation (181), nucleotoxic agents such as hydrogen peroxide (182), formaldehyde (183), bisphenol A (184) and phenytoin sodium (185) has also been prevented by melatonin treatment. It is suggested that high nocturnal melatonin concentration is responsible for maintaining non-malignant phenotype in cancer cells by melatonin's ability to regulate pyruvate dehydrogenase complex/pyruvate dehydrogenase kinase axis (186). Further, melatonin halts cancer development and aggression by attenuating NFκB activation (187), destabilizing hypoxia inducible factors (188), repressing cyclins and cyclin dependent kinases (189), stimulating the expressions of tumour suppressor genes (viz., BRCA and p53) (190), promoting apoptosis (191) and impeding PI3K/Akt/mTOR cascade (192).

Besides the direct damaging consequences of the disease itself, the side-effects caused by chemotherapy, which is by far the mainstream treatment for cancer is a big concern. Many of these conventional chemotherapeutic agents evoke toxic reactions that actuate a secondary malignancy as well as adversely affect the vital organs and systems including the cardiovascular system (5). One such popular anticancer drug is doxorubicin, which has been reported to impart potent cardiotoxic effects by increasing the oxidative burden in heart tissue (193). Doxorubicin-induced cardiomyocyte injury, marked by altered electrophysiological property and increased circulating cardiac damage markers, is efficiently prevented by melatonin (194). The defensive mechanism of melatonin against doxorubicin-mediated myocardial damage includes a reduction in lipid oxidation, enhancement of antioxidant activities, preservation of mitochondrial integrity, prevention of DNA fragmentation and apoptosis in cardiomyocytes, modulation of serum lipid profiles and increase in cardioprotective zinc levels in plasma (5). Similar results have been obtained in cardiotoxicity caused by epirubicin, where melatonin co-administration was found to mitigate epirubicin-induced nitrosative stress in the heart (195). Trastuzumab, used as a part of adjuvant therapy in various neoplastic conditions, has noxious impact on the cardiac tissue health (196). Melatonin administration in rats significantly lowers trastuzumab-mediated oxidative stress and cardiac injury biomarkers to their basal levels (197). Taking these together, it can be concluded that melatonin plays a vital role in restoring cardiac homeostasis by ameliorating oxidative stress and inflammatory damage that occur as a ramification of cancer pathogenesis and the toxicity caused by various radio- and chemotherapeutic interventions.

8. SUMMARY AND CONCLUSION

Inflammation is considered to be both a saviour and a noxious process depending on the severity and perpetuity of the inflammatory reactions. Melatonin, a regulator of inflammatory reaction, acts via multiple signalling mechanisms to countervail this double-edged sword of inflammation. Since oxidative stress is an integral part of inflammatory process, the antioxidant function of melatonin plays a key role in impeding the overaction of the inflammatory response in many conditions. Melatonin suppresses the excessive production of chemokines and pro-inflammatory cytokines including TNF-α, IFN-γ, IL-1β, IL-6, IL-12 and IL-18 and stimulates the production of

anti-inflammatory IL-10. In addition, melatonin decreases the expression and activities of the proinflammatory enzymes— iNOS and COX-2 and inhibits the excessive migration of immune cells to the inflammatory site by suppressing the expression of selectins and CAM in vascular endothelial cells. Specific to the myocardial tissue, melatonin modulates various molecular pathways, including the Sirtuin and Notch-mediated signalling, thus, attenuating the adverse inflammatory reaction triggered by ischemic episode. Modulation of inflammasome activation, AMPK/PGC-1α or AMPK/PKG-1α, MAPK, JAK-STAT, SAFE and RISK pathways, maintenance of calcium balance, and restoration of a healthy lipid profile confers the protective effects of melatonin against atherosclerosis, myocardial infarction and diabetic cardiomyopathy. Melatonin protects the cardiac tissue during chronic systemic and organ-specific autoimmune conditions like systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, type-1 diabetes and inflammatory bowel disease. These mechanisms are illustrated in Figure 1.

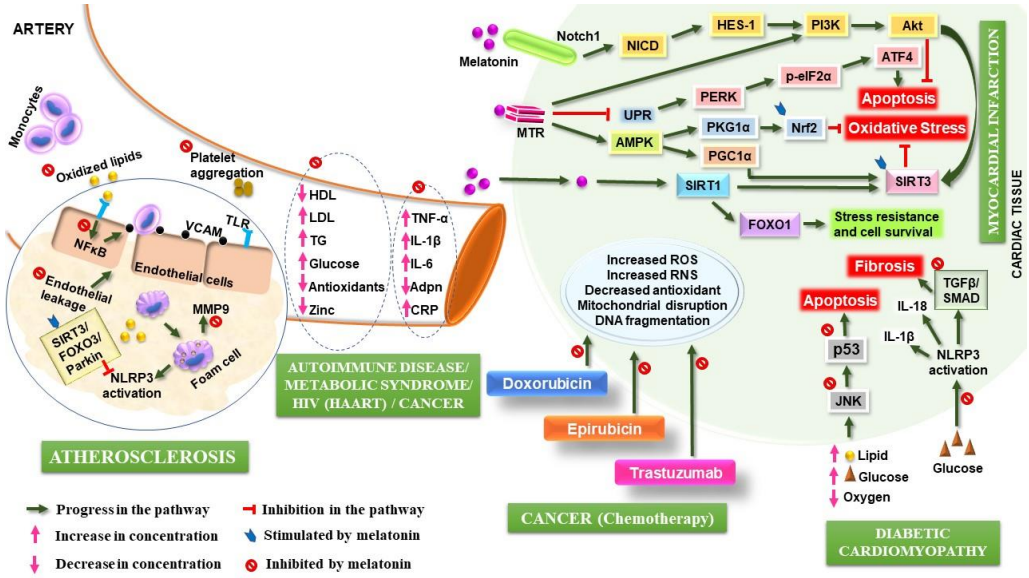

Fig. 1. Protective mechanisms of melatonin against inflammatory disease-mediated cardiovascular complications.

During atherosclerosis, oxididized LDL acts as a ligand for endothelial TLRs to activate NFκB that stimulates VCAM expression in endothelial cells. Circulating monocytes adheres to the endothelial cells and increased endothelial leakage (permeability) allows their diapedesis. Within the arterial intima, monocytes are converted into tissue macrophages and by accumulating fat particles they form foam cells. Inflammatory reactions activated by foam cells and the mechanism by which melatonin prevents such responses are described in the figure. Amelioration of altered plasma composition during inflammatory conditions such as autoimmune disease, metabolic syndrome, HIV infection treated with HAART and cancer with chemotherapeutic intervention have been demonstrated. Myocardial infarction: Melatonin modulates the signaling pathways in myocardial infarction- prevents oxidative stress and apoptosis; promotes stress resistance and cell survival. Cancer (Chemotherapy): Prevention of cardiotoxic effects of doxorubicin, epirubicin and trastuzumab by melatonin has been shown. Diabetic cardiomyopathy: Attenuation of high fat, high glucose and hypoxia-induced proinflammatory pathways by melatonin in diabetic heart tissue has been demonstrated in the figure. Adpn- Adiponectin; AMPK- AMP-dependent protein kinase; ATF4- Activating transcription factor-4; CRP- C-

reactive protein; FOXO1- Forkhead Box O-1; HDL- High density lipoprotein; HES1- Hairy and enhancer of split-1; IL- Interleukin; JNK- c-Jun NH2-terminal kinase; LDL- Low density lipoprotein; MMP9- Matrix metalloproteinase-9; MTR- Melatonin receptor; NFκB- Nuclear factor kappa-light-chain-enhancer of activated B cells; NICD1- Notch intracellular domain-1; NLRP3- NLR family, pyrin domain containing-3; Nrf2- NF-E2-related factor2; p-eIF2α- eukaryotic initiation factor-2α (phosphorylated); PERK- Protein kinase RNA-like endoplasmic reticulum kinase; PGC1α- Peroxisome proliferator-activated receptor γ co-activator 1α; PI3K- Phosphoinositide 3-kinase; PKG1α- Protein kinase G-1α; ROS- Reactive oxygen species; SIRT- Sirtuin; TG- Triglycerides; TGFβ- Transforming growth factor-β; TLR- Toll-like receptor; TNF-α- Tumor necrosis factor-α; UPR- Unfolded protein response; VCAM- Vascular cell adhesion molecule.

Undoubtedly, melatonin is a strong suppressor of excessive inflammatory reaction bestowed with versatile cardioprotective benefits. Thus, melatonin can emanate as a potent therapeutic solution for inflammatory conditions with cardiovascular pathogenicity.

AUTHORSHIP

The concept of the review article was developed by Dr. DB, Dr. AC and SS. Moreover, SS contributed in drafting the manuscript, prepared the figures, and edited it. Dr. DB and Dr. AC also revised the manuscript critically and finally approved it.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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