Chapter 15
Melatonin: A Saga of Health and Longevity

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15.1 Introduction

Melatonin, *N*-acetyl-5-methoxytryptamine, is a hormone synthesized from tryptophan by the neuroendocrine pineal gland originating from the third ventricle of the brain. The secretory activity of the pineal gland is under the control of the biological clock residing in the hypothalamic suprachiasmatic nucleus (SCN). To maintain the diurnal rhythm of melatonin biosynthesis, SCN uses constant stimulatory signals via the paraventricular nucleus (PVN) pathway to pineal in the form of glutamate which is inhibited during the daytime suppressing the melatonin synthesis (Benarroch 2008). The nocturnally elevated levels of melatonin derived from the pineal gland act as an endocrine signal that conveys the circadian information and synchronizes the body's physiology to the changing environmental conditions (Reiter et al. 2014). Interventions like exposure to light at night, shift work, or certain drugs and medications, have been shown to disrupt the circadian system and the hormonal rhythms being governed by light–dark cycles resulting in altered sleep–wake patterns, psychological stress, and impaired physiologic and metabolic control leading to comorbidities like metabolic syndrome, cancer, and Alzheimer's disease (Reiter et al. 2020a, b).

Besides the vertebrate pineal gland, melatonin is ubiquitously expressed in bacteria to plants and other animal phyla and is synthesized as extra-pineal melatonin from various organs of the body (Acuna-Castroviejo et al. 2014). Unlike pineal melatonin, extra-pineal melatonin lacks rhythmicity and has been suggested to perform

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A. Jagota (ed.), *Sleep and Clocks in Aging and Longevity*, Healthy Ageing and Longevity 18, https://doi.org/10.1007/978-3-031-22468-3_15

local cytoprotective functions via autocrine, intracrine, or paracrine signaling mechanisms (Acuna-Castroviejo et al. 2014). Melatonin is a versatile molecule and can exert multifarious effects via receptor depend or independent mechanisms that can be expanded to its anti-tumor, anti-mutagenic, anti-genotoxic, anti-cancer, anti-neurodegenerative, anti-apoptotic, and immunomodulatory and cardioprotective effects. One of the most significant effects of melatonin includes its antioxidant role and free radical scavenging capacity which directly or indirectly also regulates the anti-inflammatory and immunomodulatory potentials of melatonin (Hardeland 2018). The high levels of melatonin found in mitochondria, a site where most of the reactive oxygen species are formed during metabolism, support its cytoprotective merit in terms of preventing molecular damages that otherwise would accumulate and manifest into various pathologic conditions. The further sections of the chapter highlight the protective role of melatonin in the maintenance of cellular homeostasis and survival concerning various aspects of physiology.

15.2 Stress and Melatonin

The environmental conditions majorly influence the physiological activity of animals that are largely exposed to the environment. Moderate to extreme environmental conditions like extreme heat/cold, humidity, rain fall, and pathogenic invasion confront animals with an adversative situation that consequently activates the stress response. The stress response generally occurs to reduce the impact of stress (Charmandari et al. 2005), but under the lack of appropriate responses, this phenomenon costs the fitness and survival of an organism.

Stress is a constellation of actions that acts as a stimulus (stressor) to initiate the stress response in the physiological system (Dhabhar and McEwen 2001). Stress leads to suppression of immune functions and increases susceptibility to various infections (Glaser and Kicolt-Glaser 2005). The stress condition causes homeostatic imbalance by affecting the immune functions like reduction of immune cells activities, the decline in lymphocyte numbers, and proliferative capacity of NK-cells parallelly, with declined antioxidant response that leads to an immunocompromised state (Webster Marketon and Glaser 2008).

Stress condition activates hypothalamic-hypophyseal-adrenal (HPA) axis that modulates the activity of different target genes via glucocorticoids (GC) and GC receptor (GR) mediated actions (Sapolsky et al. 2000). Reports suggest that increased GC and its receptor expression activates immune cell apoptosis and declines antioxidant enzyme activity (Ashwell et al. 2000). The stress increases apoptosis by declining anti-apoptotic protein Bcl-2 and upregulating the level of Bax that ultimately reducing Bcl-2/Bax ratio (Singh and Haldar 2016). GR activation has also been reported to suppress antioxidant response (Kratschmar et al. 2012). The nuclear translocation of GR is precisely regulated by HSP90-based chaperone machinery where HSP90 plays an imperative role in regulating functional activation and inactivation of GR (Grad and Picard 2007).

Melatonin has been suggested to act as a potent anti-stress hormone. It downregulates GC and GR-mediated inhibition of immune responses (Gupta and Haldar 2013; Singh and Haldar 2016). Melatonin seasonal variation influences GR expression in human mononuclear leucocytes and in vitro melatonin treatment relieves the suppressive effect of GR and upregulates antioxidant response via Nrf-2-HO-1-mediated pathways in peripheral blood mononuclear cells (PBMCs) (Kratschmar et al. 2012; Singh and Haldar 2016). Nrf-2-HO-1 pathway upregulates the expression and activity of enzymes like superoxide dismutase (SOD), heme oxygenase-1 (HO-1) and catalase (CAT) to promote antioxidant repertoire (Singh and Haldar 2016). The downregulation of Nrf2 signaling has been suggested to increase apoptosis by influencing apoptotic proteins (Pan et al. 2013). Melatonin positively influences the Bcl-2/Bax ratio that protects the cells from apoptosis and increases the proliferative competency of PBMCs (Singh and Haldar 2016). The melatonin treatments also influence the secretory pattern of different pro- and anti-inflammatory cytokines to modulate the immune responses (Singh and Haldar 2020). Melatonin treatment ameliorates cold stress-induced immune suppression and prevents cellular death via upregulating HSF-1 and HSP-70 (Rastogi and Haldar 2020).

Oxidative and nitrosative stress is the major cause of disrupting various physiological activities like immune regulation. It has also been observed that declining melatonin levels with aging results in an increased level of oxidative and nitrosative stress conditions. The increased stress condition causes a decline in immune responses by inducing apoptosis in immunocompetent tissues and cells. Further, the administration of melatonin ameliorates oxidative and nitrosative stress in aging animals (Vishwas et al. 2013).

Consequences of stress could not be restricted to physiological disturbances rather psychological stress also plays a critical role in inducing the stress response. Our lifestyle has changed drastically in recent decades like shift-work (day-night) and target-oriented tasks that forces the individual to restrain on a chair for a longer period, which could be termed as restraint stress. Such conditions are very common in corporate culture, for the soldiers in barracks, nurses, doctors, etc. This restraint stress leads to psychological stress that adversely affects the health condition. It has been observed that night shift workers are more prone to mental and physiological stress conditions than day shift workers. The shift work disrupts the circadian rhythm resulting in a sleep deficit that compromises the work output and increased chances of accidents (Costa 2010). Melatonin being a potent anti-stress molecule could be used in clinical settings to regularize the endogenous circadian rhythms and its supplementation can be used to counterbalance the psychological and mental stress generated due to restrained conditions and shift work.

15.3 Oxidative Stress and Melatonin

Oxidative stress refers to the condition when body tissues are unable to adequately handle the endogenously generated reactive oxygen and nitrogen-based free radical

species. Oxidative stress is strongly linked to both local and systemic aging, as well as to a variety of health conditions like hyperglycemia, dyslipidemia, age-dependent neurodegeneration, inflammatory disorders, cardiovascular conditions, and so on (Liguori et al. 2018). Though free radicals are generally damaging, a bare minimum quantity of them is essential for the regulation of various cellular signaling mechanisms and maintenance of redox homeostasis. Melatonin is among such endogenous molecules that apart from exhibiting a prodigious functional diversity also makes oxygen metabolically more tolerable for the biological system (Manchester et al. 2015).

Melatonin probably evolved to neutralize the toxic oxygen derivatives in photosynthetic bacteria around 3.0–2.5 billion years ago (Tan et al. 2013). During evolution, the original antioxidant function of melatonin was topped up with a variety of other new roles some of which includes immunomodulation, geroprotection, oncostatic, and chronobiotic function (Reiter et al. 2016). Melatonin manifests its antioxidant actions either by direct detoxification of reactive oxygen and nitrogen species or indirectly by stimulating the antioxidant enzymes while suppressing the activity of pro-oxidant enzymes. Accordingly, melatonin could be metabolized in a variety of ways, including enzymatic, pseudo-enzymatic, and non-enzymatic free radical interactive processes (Reiter et al. 2016; Hardeland 2017). The uniqueness of melatonin lies in the fact that generations of metabolites, produced from melatonin also act as effective antioxidants thereby establishing a radical scavenging cascade reaction (Tan et al. 2000). Melatonin and its metabolite N1-Acetyl-5-methoxykynuramine (AMK), scavenges oxidizing free radicals and singlet oxygen, downregulates iNOS and nNOS, as well as cyclooxygenase-2(COX-2) (Mayo et al. 2005). Both AMK and melatonin are known to prevent the collapse of mitochondrial membrane potential and reduce electron leakage through the respiratory chain thereby avoiding the generation of superoxide anions (Hardeland 2017). The melatonin-mediated avoidance of radical formation seems to be a more significant chronobiological function in terms of maintaining low levels of oxidative damage during peak metabolic activity (Hardeland 2008).

Compared to classical antioxidants, melatonin was found to be four times more effective in scavenging ABTS [2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid)] cation radical and unlike other antioxidants, exhibited synergistic actions when used in combination with other antioxidant molecules like vitamin C, E, and glutathione (Tan et al. 2013). The free radical quenching property of melatonin is superior to that of glutathione against the hydroxyl radical (OH), whereas its activity against the peroxyl radical (ROO) involves single electron or hydrogen atom transfer for the creation of radical adducts (Galano et al. 2018). Apart from scavenging free radicals, melatonin can also interact with non-radical oxidants such as hydrogen peroxide (H_2O_2), singlet oxygen ($1O_2$), and peroxynitrite ($ONOO^-$) (Reiter et al. 2016). Melatonin was also found to stimulate antioxidative enzymes including CuZnSOD, MnSOD, catalase, glutathione peroxidase, and glutathione reductase while down regulating the pro-oxidant enzymes viz. nitric oxide synthases, lipoxygenases (LOX), and also regulating the activity of quinone reductase 2 (Boutin and Ferry 2019). Melatonin is also known to inhibit the activity and expression of

myeloperoxidase and eosinophil peroxidase. In addition to its role in alleviating oxidative stress directly or indirectly, melatonin is also involved in the chelation of transition metal ions involved in Fenton or Haber–Weiss reactions thereby reducing the incidence of oxidative stress by preventing the formation of toxic hydroxyl radical (Romero et al. 2014).

Subcellular concentrations of melatonin were found to be the order of magnitude higher than the concentration of melatonin present in blood suggesting its cytoprotective role (Acuña-Castroviejo et al. 2014). Unusually, higher concentrations of melatonin found in mitochondria suggest that these organelles apart from sequestering melatonin can also synthesize melatonin, implying that melatonin gains rapid access to the source where bulk free radicals are being produced (Suofu et al. 2017). In mitochondria, melatonin upregulates the activity of superoxide dismutase-2 (SOD2), by inducing sirtuin 3 (SIRT3), which deacetylates SOD2 rendering it active (Reiter et al. 2018). Forkhead box 03 (FOXO3a) is a direct target of SIRT3 which is also involved in melatonin's action against oxidative damages (Kumar et al. 2021). The antioxidant actions of melatonin on radical detoxification can also be mediated by Keap1-Nrf2-ARE (antioxidant response element) promoter located upstream of superoxide dismutase and glutathione peroxidase (Manchester et al. 2015; Yu et al. 2017) reported that melatonin activates AMPK-PGC-1α-SIRT3 signaling and increases SOD2, NRF1 and mitochondrial transcription factor A (TFAM) expression to protect the heart from the hypoxia and reoxygenation-induced (ischemia/reperfusion) oxidative damages. A recent report has demonstrated that melatonin improves cardiac capacity in the myocardial infarction rat model through the Sirt6-dependent antioxidant pathway (Wang et al. 2022). Melatonin also inhibits heamin-induced oxidative stress, ferroptosis, and platelet activation reducing the risk of thrombotic complications (NaveenKumar et al. 2019). Administration of melatonin in preterm neonates has been shown to inhibit free radical-mediated tissue destruction and prevent lung injury in neonates thereby protecting the high-risk newborns (Marseglia et al. 2021). Supplementation of pharmacological levels of melatonin (3 mg) has been reported to protect critically ill patients from oxidative injuries (Mistraletti et al. 2017).

Besides being potent antioxidant melatonin also acts as a conditional pro-oxidant. A higher concentration of melatonin (10 μM–1 mM) has been found to increase markers of oxidative stress and show moderate cytotoxicity (Büyükavci et al. 2006; Clapp-Lilly et al. 2001). However, the pro-oxidant effects of melatonin are mostly demonstrated in cancer cell lines and tumor cells which are either mediated by calmodulin-dependent PLA2 (phospholipase A2) activation and production of free radicals or via electron transport chain mediated free radical generation in mitochondria (Zhang and Zhang 2014).

15.4 Melatonin in Immunomodulation

Melatonin acts as a primary mediator of diurnal rhythmicity observed in the physiological functions including immunity. Almost every aspect of the innate or adaptive immune mechanism including the trafficking of immune cells, inflammatory processes, response to infection, chemokine and cytokine expression, and the activation of immune cell signaling exhibits diurnal variation (Man et al. 2016). This inherent rhythmicity in immune cell functions relies on neural and hormonal signals generated by the central clock, residing in the hypothalamic suprachiasmatic nucleus, in the form of glucocorticoid and melatonin (Córdoba-Moreno et al. 2020). Pineal ablation or other experimental approaches that inhibit melatonin synthesis (e.g., exposure to constant illumination, pineal denervation) depresses both cellular and humoral immunity that can be partly counteracted by exogenous melatonin administration (Luo et al. 2020). The night shift work in humans has also been shown to disrupt the relative phase of the rhythms of cytokine secretion and alter immune cell counts (Cuesta et al. 2016) thereby enhancing the risk of infections, exaggerated inflammation, and increased incidence of autoimmune disorders, cancer and cardiometabolic diseases (Morris et al. 2016). The disrupted sleep–wake pattern has been reported to suppress the magnitude of antibody response following vaccination while adequate sleep and time of vaccination can effectively improve antibody generation (Schmitz et al. 2022) suggesting the involvement of rhythmic melatonin levels in mechanisms related to an antibody response. Studies suggest that melatonin supplementation in a time-dependent manner or otherwise can promote antibody response either by enhancing antigen presentation to immunocompetent cells or by modulating the production of cytokines that regulate the cellular events critical for antibody generation (Cernysiov et al. 2010).

Melatonin exerts stimulatory effects on the cellular and humoral immune responses during immunocompromised states or under basal conditions. An early report from Maestroni and colleagues (1986) suggested that the night-time peak of plasma melatonin attenuates propranolol-induced cellular and humoral immunosuppression in mice. Several other reports from various groups also suggested the melatonin-mediated antagonism of steroid and age-dependent immunosuppressed conditions (Akbulut et al. 2001; Gupta and Haldar 2013). The functional spectrum of immunomodulation by melatonin is highly complex and involves various cytokines. Melatonin generally increases B-cell proliferation and the Th1 cytokines (IL-2 and IFN-γ) and decreased Th2 cytokines such as IL-10 production in aged mice. Pinealectomy-induced disruption in nocturnal melatonin rhythm was shown to polarize thymic Th1/Th2 cells toward Th2 type response which was reversed following melatonin treatment (Kelestimur et al. 2006). Melatonin modulates immune response by inhibiting the activation of inflammatory processes and regulating the proliferation and activity of immune-competent cells (Carrillo-Vico et al. 2013; Tarocco et al. 2019). In vitro treatment of melatonin increases splenic and thymic lymphocyte proliferation along with $CD4^+$ expression on the splenic cells (Kim et al. 2000; Gupta and Haldar 2013). Melatonin supplementation

increases peripheral levels of Th1, Th2, and Th17-related cytokines in pinealectomized mice and activates T- and B-cell signaling (Luo et al. 2020). Melatonin is also involved in T-cell development in the thymus. The T-cell-mediated immune responses protect mammals from cancer, infections, and various inflammatory and autoimmune diseases (Ren et al. 2017). Melatonin enhances Ki67 and Bcl-2 expression in antigen-specific T-cells suggesting its involvement in T-cell proliferation (Yoo et al. 2016). The most detailed studies have focused on the Th pathway where melatonin increases the number of Th ($CD4^+$) lymphocytes (Lissoni et al. 1995) and restores impaired Th-cell activity in immunosuppressed mice, and augments humoral response (Fraschini et al. 1998; Akbulut et al. 2001).

15.4.1 Melatonin and Immune Cells

Melatonin influences the activity of different armaments of the immune system like neutrophils (NaveenKumar et al. 2020), macrophages (Xia et al. 2019), T-cells (Ren et al. 2017), dendritic cells, and natural killer cells NK-cells (Calvo et al. 2013) thus, playing an important role in modulating innate immune responses. A close association between night-time melatonin peak and proliferation of granulocyte and macrophage progenitor cells has been reported (Haldar et al. 1992; Guerrero and Reiter 2002). Melatonin also stimulates bone marrow and spleen-mediated production of monocytes (Currier et al. 2000). Monocytes serve two important functions, secretion of cytokines and production of reactive oxygen species (ROS) critical for monocyte functioning. Melatonin activates human monocytes to secrete IL-1, IL-6, and IL-12, thereby activating and inducing cytotoxicity in monocytes. Melatonin prevents ultraviolet irradiation-induced apoptosis by inhibiting the intrinsic pathway at the mitochondrial level in monocytic cell line U937 (Luchetti et al. 2009). Macrophages are a group of highly diversified and plastic cells derived mainly from circulating monocytes, except for the tissue-resident macrophages which are known by various names in different tissues. Macrophages express the major histocompatibility complex class I and II by the virtue of which macrophage acts as antigen-presenting cells (APCs) that display antigens to and activate T lymphocytes. Melatonin supplementation enhances the expression of major histocompatibility complex class II (MHC-II) in antigen-presenting cells and peritoneal macrophages (Luo et al. 2020) and augments the secretion of IL-1, IL-6, TNF-α, and M-CSF (Guerrero and Reiter 2002). One of the aspects of macrophage function is related to its phagocytic activity. The nocturnal circulatory levels of melatonin enhance the phagocytic activity of peritoneal macrophages and testicular macrophages (Pawlak et al. 2005; Sanchez et al. 2008). Melatonin influences anti-inflammatory (M2) polarization in macrophages by inhibiting nitric oxide (NO) production and inhibiting the expression of NF-kB and cyclooxygenase-2 (COX-2) and promotes NF-E2-related factor 2 (Nrf2) and haemoxygenase1 HO-1(Aparicio-Soto et al. 2014; Singh and Haldar 2016).

Dendritic cells are specialized APCs that link innate and adaptive immunity and are extensively found in the primary and secondary lymphoid organs except for bone marrow. A very recent study demonstrates that melatonin exerts a stimulatory effect on dendritic cell numbers and its secretory activity which may be correlated to increased immunity (Abd-Elhafeez et al. 2021). In vitro treatment of melatonin enhanced the intensity of oxidative burst in neutrophils but inhibited metalloprotease activity thereby inhibiting L-selectin cleavage (Recchioni et al. 1998). Exposure to constant light has been shown to decrease the phagocytic activity of the neutrophils which was regained following melatonin supplementation suggesting the involvement of melatonin in the maintenance of neutrophil-mediated phagocytosis (Hriscu 2005). Natural killer (NK) cells are the third-largest subset of the lymphocytes that possess the ability to kill or eliminate without undergoing clonal expansion and differentiation. Different studies suggest that melatonin in conjunction with IL-2 increases the number of NK-cells (Currier et al. 2000). Pinealectomized mice have been reported to show diminished NK-cell activity which was resumed following melatonin administration (Del Gobbo et al. 1989). The melatonin-mediated increase in NK-cell number and activity has been attributed to increased T-helper cell cytokines IL-2, IL-6, IL-12, and IFN-γ (Lissoni et al. 1998; Currier et al. 2000).

15.4.2 Immunocompetent Cells and Melatonin Receptors

Most of the immunoenhancing effects of melatonin on immune cells are either mediated by membrane-bound MT1 and MT2 melatonin receptors belonging to GPCR super family (Carrillo-Vico et al. 2013; Gupta and Haldar 2013) or through nuclear receptors belonging to RZR/ROR subfamily (Lardone et al. 2011; Gupta et al. 2015). Apart from canonical receptors many of the actions of melatonin are receptor-independent viz. scavenging of free radicals; interaction with cytosolic proteins and enzymes like calmodulin, calreticulin, metalloproteinase-9 (MMP-9), and quinone reductase 2 (Liu et al. 2019a, b). Lymphocytes, monocytes, and other immune cells widely express melatonin membrane receptors, and their expression depends on the maturation, physiological status, and age of the immune cells (Ahmad and Halder 2012; Carrillo-Vico et al. 2013). Studies by Drazen and colleagues (2001) indicated that melatonin receptor subtype MT2 is involved in melatonin-induced enhancement of cell-mediated and humoral function in mice. However, a report from our lab suggested the involvement of MT1 receptor in mediating the immunomodulatory roles of melatonin in a tropical seasonal breeder, *Funambulus pennanti* (Ahmad and Halder 2012; Gupta and Haldar 2013). Apart from expressing melatonin receptors, immunocompetent cells like monocytes, macrophages, neutrophils, mast cells, and lymphocytes including B and T-cells have been reported to express the biosynthetic machinery for the synthesis of melatonin (Maldonado et al. 2010; Carrillo-Vico et al. 2013; Calvo et al. 2013; Yoo et al. 2016). The melatonin derived from the immune cells through paracrine, autocrine, or intracrine mechanisms plays an important role

in the maintenance of cellular physiology and serves cytoprotective functions there by regulating the immune mechanisms.

15.4.3 Anti-inflammatory Potential of Melatonin

Melatonin apart from promoting an effective immune response restrains the persistent inflammatory events which can cause tissue damage. However, melatonin does not act as a blunt anti-inflammatory agent, it rather modulates the immune response in a complex manner such that the body is protected from chronic and deleterious effects of inflammatory response. The antioxidant and anti-inflammatory actions of melatonin are of great importance for the maintenance of health and longevity. Melatonin has been reported to reduce symptoms of "inflammaging" (low-grade inflammatory processes during the progression of aging) in the senescence-accelerated aging mice model and counteracts the low-grade brain inflammation (Hardeland et al. 2015). The amyloid-beta (Aβ) peptide, a central player in the pathogenesis of Alzheimer's disease, acts synergistically with pro-inflammatory cytokines to promote astrocyte and microglia activation (LaRocca et al. 2021). The release of pro-inflammatory mediators is not restricted to microglia, even neurons respond to Aβ peptide by upregulating the expression of cytokines like tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and T-cell and monocyte chemo attractant factor (CX3CL1) (Hanzel et al. 2014). Melatonin has been reported to show anti-amyloidgenic effect and promote Aβ clearance and suppress pro-inflammatory mediators (Hardeland 2018). Melatonin administration in an experimental model of inflammation has also been shown to reduce pro-inflammatory cytokines like TNF-α and IL-1β while enhancing the levels of anti-inflammatory cytokines IL-4 (Carrasco et al. 2013). Melatonin supplementation inhibits transcriptional activation of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX) and suppresses the expression of inflammatory mediators like leukotrienes, chemokines, and adhesion molecules (Deng et al. 2006; Liu et al. 2017). Melatonin-mediated reduction of inflammatory reaction involves degradation of IκBα thereby retarding the nuclear translocation and transcriptional activation of pro-inflammatory factor NF-κB (Li et al. 2005). To exhibit its anti-inflammatory actions, melatonin activates SIRT1 leading to upregulation of Nrf2 and downregulation of NF-κB (Negi et al. 2011; El-Bakry et al. 2018). The functional association between SIRT1 and melatonin seems to be overlapping as SIRT1 is known to enhance the circadian amplitude of SCN that may influence melatonin rhythm and SIRT1 and melatonin perform similar actions (Chang and Guarente 2013; Hardeland 2018). Likewise, inhibiting NF-κB melatonin is also reported to prevent gasdermin D (GSDMD) inducing pyroptosis in adipose tissue (Liu et al. 2017).

NLRP3 inflammasome activation and induction of inflammatory caspases can be induced by a variety of signals under different conditions. Melatonin has been reported to downregulate NLRP3 and inhibit inflammasome activation via a mitophagy-mediated reduction in levels of ROS (Cao et al. 2017; Liu et al. 2017). Melatonin has been reported to reduce lipopolysaccharide (LPS) induced

inflammation thereby preventing NLRP inflammasome formation in adipocytes by downregulating genes involved in inflammasome assembly, i.e., NLRP3, ASC, caspase-1, and IL-1β. Activation of TLR-4 (toll-like receptor4) is another pro-inflammatory pathway being targeted by melatonin. In lipopolysaccharide (LPS)-stimulated macrophages RAW264.7, melatonin downregulated interferon (IFN)-regulated factor-3 (IRF3), which was involved in TLR-4-mediated TRIF-dependent signaling thereby suppressing the expression of pro-inflammatory cytokines viz. TNF-α, IL-1β, IL-6, and IL-8 (Xia et al. 2012). Modulation of the mTOR (mechanistic target of rapamycin) pathway by melatonin has also been shown to manifest its anti-inflammatory effects. Melatonin inhibits mTOR expression thereby interrupting the mTOR signaling and activation of pro-inflammatory cytokines in the hippocampus in an experimental model of isoflurane-induced cognitive impairment (Yuan et al. 2019). Melatonin prevents ethanol-induced activation of mTOR, AMP-activated protein kinases (AMPK), mitogen-activated protein kinase (MAPK), and nuclear factor of activated T-cells (NFATc-1) pathway thereby alleviating the senescence-like phenotype and osteoclast activity in human periodontal ligament and cementoblasts cells via inhibition of PIN1 pathway (Bae et al. 2018). Anti-inflammatory properties of melatonin have also been extensively studied in sepsis. In experimental models of sepsis, melatonin has been shown to improve survival and prevent multiorgan failure through the restoration of redox homeostasis via regulation of ETC function, inhibition of iNOS expression and nitric oxide synthesis, and reducing cytokine production (Colunga Biancatelli et al. 2020). Furthermore, the overproduction of reactive oxygen species contributes significantly to the inflammatory process via the activation of pro-oxidant genes that eventually results in the activation of pro-inflammatory markers. Melatonin by its antioxidant properties counteracts inflammatory processes via direct or indirect purging of free radicals.

15.5 Melatonin and Metabolic Health

The earliest reference regarding the relationship between pineal neurohormone melatonin and energy metabolism was given by a Romanian group describing pineal peptide "pinealin" as being similar to insulin in its anabolic, hypoglycemic and anti-cholesterinemic effects (Milcu and Milcu 1958). Pinealin was reported to improve glucose tolerance, while pinealectomy was shown to inhibit insulin secretion and impair glucose tolerance (Diaz and Blázquez 1986). However, several contrasting reports were also published regarding the role of melatonin in the regulation of glucose metabolism (Bailey et al. 1974; Neacşu 1988). In recent decades, various experimental studies have recognized the involvement of melatonin in metabolic processes and regulation of energy balance in terms of food intake, energy storage, and energy expenditure (Cipolla-Neto et al. 2014). Melatonin dictates the daily rhythm of metabolic hormones like leptin, ghrelin, resistin, and adiponectin to modulate nutrient utilization and storage thereby synchronizing these metabolic rhythms to the environmental light–dark cycle to ensure metabolic homeostasis (Chakir et al.

2015; Challet 2015). Disruption of these functional metabolic rhythms, as in the case of shift workers, can lead to the development of obesity and metabolic syndrome. Melatonin supplementation has been reported to suppress body weight gain and reduce adiposity (She et al. 2009; Nduhirabandi et al. 2011). The reversal of body weight gain following melatonin supplementation was independent of food intake suggesting an increase in the energy expenditure mechanisms (Wolden-Hanson et al. 2000) while the rats with ablated pineal gland developed adiposity (Alonso-Vale et al. 2004). The development of adiposity was probably due to the induction of leptin resistance which was likely to affect the ability of leptin to influence body weight, food intake, and hypothalamic centers regulating satiety (Buonfiglio et al. 2018), suggesting the protective role of melatonin against leptin resistance during the obesity (Suriagandhi and Nachiappan 2022). Melatonin administration has also been shown to retard the body weight gain and restore insulin sensitivity in animal models of diet-induced obesity (DIO) (Sartori et al. 2009). Recent studies carried out in melatonin receptor MT1 knock-out (KO) mice suggest that melatonin through MT1R signaling exerts its protective effect on metabolic responses in the case of DIO. Thus, MT1R can be one of the important therapeutic targets for counteracting obesity (Owino et al. 2019).

Furthermore, melatonin supplementation has been shown to limit hypertrophic obesity and decrease the density of crown-like structures in adipose tissues thereby improving the inflammatory profile of the adipocytes in high-fat diet-induced model of obesity (de Farias et al. 2019a, b). Melatonin supplementation prevents morphological alterations in adipocytes, inhibits inflammatory cell infiltration, and attenuates the pro-inflammatory adipokines expression (Farias et al. 2019a, b), reducing the inflammatory response and improving the sensitivity of peripheral organs to insulin and leptin signals for better glycemic control (Favero et al. 2015; Oliveira et al. 2018). Melatonin promotes lipolysis in adipocytes and upregulates the expression of perilipin 1 (PLIN1) and enzymes like hormone-sensitive lipase (HSL), adipocyte triglyceride lipase (ATGL) via activation of MT2R signaling (Yang et al. 2017). Melatonin-mediated reduction of body weight gain may be associated with role in energy expenditure. In Zücker diabetic fatty rats, melatonin treatment induces browning of inguinal fat pads and increases brown adipose tissues (BAT) weight and expression of uncoupling protein 1 (UCP1), associated with energy expenditure through non-shivering thermogenesis (Fernández Vázquez et al. 2018). Melatonin reduces ectopic deposition of fat in muscles and promotes intramuscular thermogenesis by enhancing mitochondrial biogenesis and mitochondrial respiration (Liu et al. 2019a, b). Melatonin was shown to inhibit high-fat diet-induced oxidative damage to the liver and reverse the loss of mitochondrial membrane potential, prevented mitochondrial fission, and was shown to restore mitophagy to improve hepatocyte function in non-alcoholic fatty liver disease (NAFLD) (Zhou et al. 2018). In an experimental model of NAFLD and hyperlipidemia, melatonin decreases the activity of the hepatic lipogenic enzymes and enhances the expression of hepatic carnitine palmitoyltransferase-1 (Ou et al. 2019). Ablation of the pineal gland induces nocturnal hepatic glucose production and increases gluconeogenesis due

to activation of unfolded protein response (UPR) mediated by activating transcription factor 6 (ATF6) (Nogueira et al. 2011). Melatonin reduces the expression of fetuin-A (FETUA) and α2-HS-glycoprotein gene (AHSG), hepatokines involved in insulin resistance, and alleviates hepatic steatosis (Heo et al. 2018). Recent studies suggest that the impact of melatonin on the metabolic outcomes is also mediated by alterations in gut microbiota. Melatonin treatment has been shown to change the composition of gut microbiota in high-fat-fed mice (Xu et al. 2017). Melatonin supplementation decreased Firmicutes to Bacteroidetes ratio and increased Akkermansia while normalizing the diversity of gut microbes thereby inhibiting low-grade meta-inflammation and body weight gain (Yin et al. 2018).

15.5.1 Melatonin in the Protection of Cardiovascular Health

The favorable effect of melatonin on serum cholesterol and lipid profile forms the very basis for its cardioprotective role in the metabolic disorders. Several experimental studies have shown that melatonin reduces the number and area of atheromatous plaques thus being effective in the treatment of atherosclerosis (Rodella et al. 2013). Melatonin has been shown to retard the progression of atherosclerosis and stabilize the rupture-prone plaques (Ding et al. 2019). Melatonin has been shown to improve the characteristic features of diabetic cardiomyopathy including reduced myocardial fibrosis, vascular endothelial cell death, oxidative, and endoplasmic reticulum stress and improves microcirculation and mitochondrial function (Huang et al. 2022). Melatonin by the virtue of its anti-inflammatory actions protects against obesity and ischemic stroke (Yawoot et al. 2021). Diminished levels of melatonin and its metabolite, 6-sulphatoxymelatonin, have been reported in various cardiovascular conditions like myocardial infarction, coronary heart disease, and nocturnal hypertension (Dominguez-Rodriguez et al. 2016; Baker and Kimpinski 2018). Exogenous melatonin supplementation has been found to exert a protective effect against ischemia–reperfusion injury in diabetic rats (Yu et al. 2017), increased heart rate (Simko et al. 2016), and postural tachycardia (Green et al. 2014). The melatonin-mediated cardioprotective mechanisms mainly includes its antioxidative and anti-inflammatory effects with activation of Nrf2, reperfusion injury salvage kinase (RISK), and survivor activating factor enhancement (SAFE) mediated pathways, and nitric oxide signaling (Song et al. 2020). Melatonin prevents arrhythmogenic remodeling of cardiac tissue and reduces fibrosis and apoptosis in rat hearts (Prado et al. 2018). Melatonin protects against oxidized low-density lipoprotein-(ox-LDL-)induced endothelial cell damage and mitochondrial dysfunction and prevents endothelial cell pyroptosis (Zhang et al. 2018; Li et al. 2021). Melatonin via activation of nuclear receptor retinoic acid-related orphan receptor-α prevents endothelial dysfunction in systemic lupus erythematosus (Huang et al. 2022). It has been suggested that melatonin, through breast milk during the early days in neonates influences body weight in the later part of life, limits the development of comorbid obesity

and promotes optimal conditions for the development of the cardiovascular system in infants (Gombert and Codoñer-Franch 2021).

15.5.2 Melatonin and Diabetic Nephropathy

Various experimental models of chronic kidney disease suggest positive effects of melatonin in lowering blood pressure (BP) and normalization of diurnal rhythms in non-dipper to dipper type of BP variations highlighting its reno-protective role (Simko et al. 2016). Common features of diabetic nephropathy include enlarged nephrons, hypertrophied mesangial cells resulting in glomerulosclerosis, and hyperfiltration (Bherwani et al. 2016). Apart from ROS, several other factors are involved in the progression of chronic kidney disease related to diabetes like dyslipidemia, inflammatory cytokine production, pro-fibrotic signaling, and connective tissue growth (Pourhanifeh et al. 2020). Melatonin treatment during diabetic nephropathy showed beneficial effects on glycemic control, high-density lipoprotein-cholesterol (HDL-C), and total antioxidant capacity of the blood serum (Satari et al. 2021). Melatonin showed a synergistic effect when used with folic acid and significantly decreased the plasma levels of urea, uric acid, creatinine, TNF-α, IL-6, cholesterol, triglycerides, and low-density lipoprotein (LDL) along with renal malondialdehyde (MDA) and nitric oxide in the kidney of diabetic rats (Ebaid et al. 2020). Melatonin reverses the effect of oxidative stress-induced renal tubular damage and reduces the level of *N*-acetyl-β-D-glucosaminidase and albumin in the urine of diabetic rats (Oktem et al. 2006). Melatonin when used with rowatinex showed the most potent effects against the streptozotocin-induced diabetic nephropathy (Motawi et al. 2019). Melatonin activates SIRT1/Nrf2/HO-1 signaling pathway to protect from oxidative injury induced by acute kidney ischemia/reperfusion (Shi et al. 2019). Melatonin inhibits the accumulation of advanced glycation products (AGEs) and transforming growth factor-β (TGF-β) and attenuates the activation of the renin-angiotensin system to protect against kidney damage induced by diabetes (Guo et al. 2021). Most of the evidence suggests that melatonin can contribute beyond its well-known antioxidant and anti-inflammatory activity to reverse the kidney damage induced by diabetes, however, further studies are required to get better insights into the reno-protective mechanisms of melatonin.

15.6 Bone Health (Osteoporosis and Osteoarthritis) and Melatonin

Bone is a dynamic organ in which remodeling occurs throughout life. The remodeling process involves the initiation of bone resorption by osteoclasts, the transition from

resorption to new bone formation, and bone formation by osteoblasts (Florencio-Silva et al. 2015). There exists a fine balance between the osteoclast-mediated bone resorption and osteoblast-mediated bone formation throughout life. Bone remodeling is crucial for fracture healing, and repair of microscopic cracks as well for regulating skeletal calcium homeostasis. Osteoblasts under the influence of bone morphogenetic proteins (BMPs), wingless (WNTs), and runt-related transcription factor (RunX2) get differentiated from the mesenchymal stem cells. RunX2 upregulates the osteoblast-specific genes such as collagen type II (ColII), alkaline phosphatase (ALP), bone sialoprotein (BSP), bone Gla (gamma carboxy glutamic acid rich) protein (BGLP), and osteocalcin (OCN) (Florencio-Silva et al. 2015). Nowadays, a huge population beyond the age of 40 years is affected with bone diseases due to lifestyle changes. Osteoarthritis and osteoporosis are the two most common diseases that are seen in aged people and are the cause of major disabilities worldwide (Cui et al. 2020).

15.6.1 Osteoporosis and Melatonin

According to the studies conducted among Indian women beyond the age of 50 years, 46 million women have osteoporosis (Pal et al. 2016). Osteoporosis is chronic, an asymptomatic skeletal disorder that increases the fragility and high risk of fracture specifically hip, spine, and wrist. It is a slow progressing, silent disease that does not display any symptoms till bones fracture. Osteoporosis is a condition that appears when there is a reduction in bone volume and bone mass. Studies suggest that osteoporosis patients have an imbalance between osteoblast differentiation and osteoclast production (Hart et al. 2020). Bone modeling is either formation of bone by osteoblasts or the resorption of bone by osteoclasts where these activities occur in sequentially coupled manner. The primary function of bone modeling is to increase bone mass and maintain or alter bone shape (Cui et al. 2020). Osteoclasts cells degrade bone by generating free radicals, such as superoxide and hydroxyl anions (Florencio-Silva et al. 2015) and melatonin inhibits the osteoclast activity by scavenging the free radicals (Munmun and Witt-Enderby 2021). Melatonin also inhibits bone resorption by inducing osteoprotegerin (OPG). OPG retards the interaction between receptor activator NF-κB (RANK) and receptor activator NF-κB ligand (RANKL) by binding to RANKL thereby inhibiting the bone loss (Wada et al. 2006). On the other hand, it is noted that melatonin stimulates osteoblasts to counterbalance bone loss (Sethi et al. 2010).

Melatonin via binding to its MT2 receptor on mesenchymal cells influences the osteogenesis by the formation of osteoblasts (Sethi et al. 2010). It induces osteoblast differentiation through ERK1/2-MAPK signaling pathway and expresses differentiation markers like alkaline phosphatase (ALP). Melatonin also induces osteoblast differentiation by influencing BMP-2 and Runx2, p38, and ERK1/2 signaling (Sethi et al. 2010). Therefore, melatonin prevents bone degradation and promotes bone formation via its receptor-dependent and independent mechanisms. As discussed previously, melatonin alleviates the glucocorticoid-mediated stress

condition. Reports also suggest that for the treatment of a variety of inflammatory condition and autoimmune disorders glucocorticoid-based medicines are being used that causes a significant decrease in bone mass and increased risk of fracture. Melatonin may impair osteoclast activity by its free radical scavenging and antioxidant property. Melatonin also has been suggested to induce osteoblast differentiation and proliferation (Li et al. 2019).

Melatonin could be a potential treatment for osteoporosis. Melatonin resists bone loss *by* eliminating the free radicals required for osteoclast activity. Reports also suggested that melatonin and combined fluid shear stress (FSS) enhances ERK/Akt/mTOR signaling in preosteoclasts, which activates the anabolic effect for the preservation of cell structure and function against osteoporosis (Kim et al. 2018). Increased bone resorption and low bone mass are accompanied by oxidative stress (Domazetovic et al. 2017). Osteoclast degrade bone by generating free radicals like hydrogen peroxide, superoxides, and hydroxyl ions (Florencio-Silva et al. 2015). Other experimental evidence suggest that melatonin increases short-term bone formation and improves the alveolar bone loss and fracture healing in a diabetic mouse model by reducing the oxidative load (Kose et al. 2016). Melatonin downregulates the iNOS expression to reverse the changes associated with osteoporosis in the ovariectomized rats (Oktem et al. 2006).

15.6.2 Melatonin and Osteoarthritis

Osteoarthritis (OA) is a chronic disability characterized by progressive degeneration of articular cartilage (AC), which covers the ends of long bones (Xia et al. 2014). More than 60% of the population above the age of 65 years suffers from this disease. The increasing number of incidences causes a massive loss in workplace productivity. This disease is ranked as the 15th major cause of years lived with disability (Bitton 2009). The most striking and unfortunate part of osteoarthritis is that at present there is "no disease-modifying therapy" available to deal with it. Osteoarthritis is considered a multi-factorial disease of the whole synovial joint. The onset and progression of osteoarthritis are being studied for last three decades and observed that there are multiple factors involved in this disease like age-associated inflammation, cellular senescence, mitochondrial dysfunction, oxidative load, genetic factors, mechanical insult, trauma, obesity, and low-grade inflammation (Loeser et al. 2016). With accumulating evidence, it is suggested that at present there is only palliative care being provided to intervene in the disease, but unfortunately, these treatments do not stop the progression of the disease and ultimately the joint fails, that is being replaced with a prosthesis (joint replacement), however, there is a limitation as well, i.e., limited shelf-life of the prosthetic joints (Steinhaus et al. 2017). This disease causes a huge economic burden to the family as well as the country (Bitton 2009).

The only cells present in articular cartilage are chondrocytes that secret extra cellular matrix containing collagen type II and proteoglycans. The quality of articular cartilage is maintained by the fine balance between the anabolic and catabolic

activity of chondrocytes. The declined proliferative capacity of chondrocytes leads to a significant reduction in extracellular matrix production that ultimately compromises the quality of articular cartilage (Hou et al. 2018). It is well documented that melatonin concentration declines with aging and that disrupts the tuning of oxidant and antioxidant balance in the physiological system. This leads to increased inflammation that might be involved in the progression of the declined anabolic function of chondrocytes and downregulates matrix synthesis that ultimately leading to reduced quality of articular cartilage and onset of osteoarthritis (Karasek and Reiter 2002).

The cellular death of chondrocytes and loss of ECM leads to compromised quality of articular cartilage. The ECM contains collagen type II (ColII) which is a key feature of articular cartilage (Taniguchi et al. 2009). During osteoarthritis matrix, metalloproteinases (MMPs) are produced by hypertrophic chondrocytes. MMP-13 is responsible for the degradation of collagen type II, aggrecan and fibronectin. Another enzyme a disintegrin and metalloproteinase with thrombospondin motifs, ADAMTS4 and ADAMTS5, cleave aggrecan that also promotes articular cartilage degradation (Neuhold et al. 2001; Song et al. 2007). Experimentally, it was observed that melatonin restores the major component of articular cartilage, collagen type II, through the downregulation of MMP-13, pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, ADAMTSs, and catalytic transcription factors such as NF-κB in case of osteoarthritis (Zhang et al. 2019). Increased inflammatory cytokines generate NO by the chondrocytes and catabolic enzymes that cause progressive articular degeneration (Loeser et al. 2012). ROS are primary factor involved in the development of osteoarthritis. Mitochondrial dysfunction in osteoarthritic chondrocytes causes oxidative stress by increasing generation of ROS and RNS that inhibits ECM synthesis from chondrocytes (Lepetsos and Papavassiliou 2016). Further, the increased oxidative stress accelerates catabolism and initiates chondrocyte death, destroying articular cartilage and disturbs chondrocyte homeostasis (Lepetsos and Papavassiliou 2016).

In humans, it was observed that during osteoarthritis, the expression of endoplasmic reticulum (ER) stress associated downstream molecular players are positively correlated with cartilage degeneration (Rellmann et al. 2021). Articular cartilage being a hypocellular and avascular tissue is always at a risk of hypoxic and catabolic stress that may lead to activation of ER stress that contributes to cartilage degeneration via chondrocyte apoptosis. The expressions of phosphorylated protein kinase R like endoplasmic reticulum kinase (pPERK), ubiquitin (Ub), C/EBP Homologous Protein (CHOP), and phosphorylated c Jun N-terminus kinase (pJNK) are positively associated with the number of caspase-3 positive chondrocytes in in vivo and in vitro conditions (Takada et al. 2011; Price et al. 2010). ER stress induced by tunicamycin increased CHOP expression and reduced X-box binding protein 1 (XBP-1) mRNA splicing in high concentrations results in extensive apoptosis (Takada et al. 2011). Several studies show the induction of CHOP happens earlier than anti-apoptotic BiP, and this rapid upregulation of CHOP contributes to chondrocyte death (Price et al. 2010). Advanced glycation products (AGEs) induce ER stress in chondrocytes by specific receptors for AGE (RAGE), and activation of RAGE engages critical signaling pathways. In human chondrocytes, AGEs induce

ER stress and stimulate the expression of cyclooxygenase-2 (COX-2) and PGE2 through eIF2α, p38-MAPK, and NF-κB pathways (Oakes and Papa 2015). Melatonin treatment inhibits ER stress by attenuating ER stress mediators. Melatonin also mitigates glucose regulated protein 78 (GRP78) upregulation, phosphorylation of pulmonary eIF2a, cleaved activating transcription factor 6 (ATF6) elevation, and repressed inositol requiring enzyme 1a (IRE1a) phosphorylation and activation of XBP-1 and JNK, two downstream targets of the IRE1 pathway (Zhao et al. 2014).

Chondrocyte apoptosis and decline in autophagy results in reduced cellularity in the superficial zone of articular cartilage (Zhao et al. 2019). Melatonin performs its chondroprotective role via SIRT1 signaling and reverses the detrimental effect of sirtinol that blocks the activity of SIRT1 (Coryell et al. 2021). In chondrocytes, SIRT1 exerts an anti-apoptotic effect by regulating gene expression of the transcription factors RelA/p65 and p53 (Yeung et al. 2004). Melatonin via SIRT1 pathway protects chondrocytes against ROS-dependent p38 kinase activation and suppression of chondrocyte apoptosis (Lu et al. 2021). Melatonin induces autophagy to prevent extracellular matrix (ECM) degeneration via NF-κB pathway to ameliorate apoptosis and calcification by SIRT1-mediated autophagy. Melatonin increases SOX9 levels to promote chondrogenesis under inflammatory conditions induced by IL-1β. It also blocks the other mediators of inflammation including iNOS and COX-2, at transcriptional and translational level and also inhibit the secretion of TNF-α, IL-1β, and IL-8 from chondrocytes in in vitro condition (Hosseinzadeh et al. 2016).

Under osmotic stress, SIRT1 induces nuclear factor of activated T-cell (NFAT5) expression (Johnson et al. 2014), that acts on a specific set of targets, including TNF-α, IL-6, nitric oxide synthase 2, and MMP-13 in a spatio-temporal manner (Yoon et al. 2011). Melatonin decreases SIRT1-dependent NFAT5 expression in chondrocytes treated with IL-1β and its supplementation significantly reduces TNF-α, IL-1β, prostaglandin E2 (PGE2) in chondrocytes showing its suppressive effect on inflammation (Guo et al. 2017). Therefore, it can be suggested that melatonin exerts its effects in osteoporosis as well as different stages of osteoarthritis. Moreover, melatonin has therapeutic potential for bone regeneration and may also act as a potent therapeutic drug in osteoarthritis to prevent the exacerbation of articular cartilage damages.

15.7 Life Span Extending Benefits of Melatonin

Healthy aging and longevity have been one of the greatest pursuits of mankind. An unending search for an agent that could increase health expectancy and decrease the burden of age-related degenerative diseases has brought melatonin into focus. The declining nocturnal peak of melatonin in elderly associated melatonin to aging (Karasek and Reiter 2002; Tozawa et al. 2003) and based on this background melatonin supplementation was hypothesized to promote healthy aging and prolong life span (Anisimov et al. 2003). Unlike pineal melatonin, aging promotes the expression of enzymes related to melatonin biosynthesis in metabolically active tissues like

liver, intestine, and kidney. This locally produced, extra pineal melatonin activates antioxidant repertoire thereby defending these organs against age induced oxidative damages (Popović et al. 2018). Although scientists always remained doubtful regarding the clinical utility of melatonin, however, previous studies have reported the antioxidant, analgesic, anti-stress, and chronobiotic benefits of melatonin supplementation in counteracting age-related diseases and enhancing life span (Marseglia et al. 2015; Anghel et al. 2022). Initial studies demonstrated that pineal gland ablation induced senescence was reversed following melatonin supplementation in rats (Dilman et al. 1979; Armstrong and Redman 1991). Pineal of young animals when grafted into old animals delayed the development of senescence-like phenotype and prolonged the life span of old animals (Pierpaoli and Regelson 1994). Even lower dose of melatonin was shown to reduce the tumor incidence, especially the mammary carcinomas, thereby influencing the life span of the animal (Anisimov et al. 2003).

The prolongation of life span by melatonin has mostly been implied in terms of its immunomodulatory, antioxidant, and anti-stress properties. A recent study suggests that melatonin prolonged the life span of animals independent of the age at which the melatonin supplementation was started (Damiani et al. 2020). Melatonin supplementation effectively reduces age-dependent DNA damages exhibiting anti-genotoxic and anti-mutagenic potential thereby maintaining the genomic integrity (Damiani et al. 2020). Telomeres are considered as the guardian of genome stability and oxidative stress has been shown to negatively impact telomere length and promote its attrition, a hallmark of aging (Gavia-García et al. 2021). Reports suggest that melatonin facilitates telomere elongation probably through stimulation of telomerase activity, thus preventing age-related degenerative conditions in vascular endothelial and retinal pigment epithelial cells (Rastmanesh 2011; Xie et al. 2021). Melatonin interacts with numerous DNA repair and DNA damage response processes (Liu et al. 2013) and induces phosphorylation of p53 (Ser-15), a critical mediator of DNA protective effects of melatonin, responsible for regulation of cell survival, proliferation, and prevention of cancer (Santoro et al. 2012). Apart from enabling molecular defense mechanisms to prevent DNA damages melatonin also offers on-site protection to DNA through scavenging locally generated free radicals (Galano et al. 2018). Evidences indicate that there exists a direct connection between telomere attrition and mitochondrial dysfunction (Passos et al. 2007). Moreover, an aging axis has been proposed that links compromised genomic integrity to altered mitochondrial biogenesis and function via p53-mediated suppression of PGC1α and PGC1β (Sahin and DePinho 2012).

15.7.1 Melatonin and Mitochondrial Health

Longevity is intimately related to mitochondrial function, while mitochondrial malfunction has been associated with a plethora of diseases collectively called as “mitochondrial diseases,” e.g., neurodegenerative disorders, cardiomyopathy, diabetes mellitus, and cancer. The connection between these diseased states and

mitochondria lies in the higher rate of accumulation of mutation in mitochondrial DNA (mtDNA), expansion of mutated mtDNA and age-related deterioration of the organelle-specific quality control mechanisms (Lionaki et al. 2022). In this context, the regulation of mitochondrial function by melatonin can be one of the mechanisms through which melatonin might promote health and longevity. Mitochondria, in fact, happens to be the most prominent target organelle for melatonin's pleotropic actions (Reiter et al. 2017). Mitochondria not only synthesize melatonin but also accumulate and metabolize melatonin (Reiter et al. 2021; He et al. 2016). Melatonin preserves mitochondrial function by retarding free radical generation at the level of electron transport chain, a process known as radical avoidance (Hardeland 2009). Melatonin stimulates ATP production without altering ATP synthase activity and ROS generation which is critical for prevention of various pathophysiological conditions related to mitochondrial diseases (Reiter et al. 2020a, b; Jauhari et al. 2020). Melatonin maintains mitochondrial membrane potential and prevents opening of the mitochondrial permeability transition pore (mPTP) (Petrosillo et al. 2009). Melatonin has also been demonstrated to prevent oxidation of cardiolipin, a phospholipid located at the inner mitochondrial membrane, thereby preventing cytochrome c release and subsequent activation of apoptotic pathway (Petrosillo et al. 2009). Melatonin by modulating mitochondrial dynamics (mitochondrial fission and fusion) has been shown to regulate redox homeostasis and bioenergetics (Paradies et al. 2010; Tan et al. 2016). Thus, melatonin supplementation can prove to be an effective therapeutic strategy against oxidative stress and age-induced mitochondrial dysfunction that could jeopardize cell survival and health.

15.7.2 Melatonin, Circadian Rhythm and Health

Rhythmicity in the biological clock-controlled functions is also related to well-being of the organism and is among one of the aspects of melatonin physiology that may extend life span (Acosta-Rodríguez et al. 2021). Lack of rhythmicity results in loss of the adaptive ability and impairs the capacity of tissue regeneration (Acosta-Rodríguez et al. 2021; Paatela et al. 2019). Aging results in diminished amplitude of the circadian pacemaker as evident from the decreased melatonin secretion. The loss in circadian amplitude can lead to internal temporal disorder which may act as a prelude for diseased state that may manifest in the form of temporal crises related to sleep–wake cycle, cardiovascular activity, intestinal motility, asthma, and allergic attacks (Froy 2011). Exogenous melatonin supplementation feedback on the circadian pacemaker system to enhance the amplitude of circulatory melatonin thereby retarding the symptoms of aging and increase life span (Armstrong and Redman 1991). Evidence suggests that disruption of circadian system with advancing age is partly due to loss of sensitivity of the suprachiasmatic nucleus (SCN), to the entrainment signals (Chang and Guarente 2013). Inability to adapt to the entrainment signals affects the endogenous periodicity tau (τ), by either shortening it or making it longer than 24 h (h). A positive association between tau close to 24 h and survival have been

suggested (Wyse et al. 2010). Indeed, it was shown that hamsters carrying 20 h period mutation tau, exhibit reduced longevity (Hurd and Ralph 1998). In another study, chronic disruption of circadian pacemaker by continuous reversal of light–dark cycle reduced the life span of cardiomyopathic hamsters (Penev et al. 1998). In fact, aged animals show higher mortality due to phase shifts induced by changing light–dark cycle while, fetal SCN implants in aged animals were shown to restore the higher amplitude rhythms and promote longevity (Davidson et al. 2006; Hurd and Ralph 1998). Thus, impaired circadian rhythmicity is associated with increased morbidity reduced life span, while melatonin supplementation may reset circadian rhythms and restore the pacemaker's amplitude thereby promoting survival.

15.8 Phytomelatonin: A Natural Nutraceutical for Health

D. van Tassel and O'Neill (1993) for the first time identified the endogenous melatonin in higher plants. The presence of melatonin in the Convolvulaceae ivy (morning glory: *Pharbitis nil*, syn. *Ipomoea nil*) and in tomato fruits (*Solanum lycopersicum*) was detected by radioimmunoassay (RIA) and gas chromatography-mass spectrometry (GC–MS), although the results were unpublished until 1995 (D. van Tassel et al. 1995). This melatonin identified in plants was named "phytomelatonin." In due course of time presence of melatonin was identified in coffee beans in 1970, it was isolated as a by-product during the processing of coffee beans (Tan et al. 2012). Since then, a variety of plant species were analyzed and it has been observed that different cereals and medicinal herbs contain a high concentration of melatonin (Hattori et al. 1995; Hardeland and Pandi-Perumal 2005). Surprisingly, the existence of melatonin was also noted in the edible plants and vegetables as well (Hattori et al. 1995; Reiter et al. 2007; Manchester et al. 2000). The presence of melatonin in plants modulates a range of physiological functions like flowering, fruit ripening, stress responses, morphogenesis, and photoprotection and antioxidant response (Arnao 2014).

The consumption of melatonin-rich plant products has been shown to influence the endogenous melatonin concentration (Reiter et al. 2005; Dragsted et al. 1993). Cheap and easily available economical cereals like corn (*Zea mays*) consumption have been shown to increase the endogenous melatonin concentration and improve the antioxidant enzymes status and proliferative potency of peripheral blood mononuclear cells (PBMCs) (Singh and Haldar 2017). The increase in endogenous melatonin concentration could be due to the high tryptophan content (32 mg/100 g of corn seeds) in corn seeds (www.ogtr.gov.au). The pineal gland has a high affinity for uptake of circulatory tryptophan for the synthesis of serotonin and melatonin (Paredes et al. 2009). Epidemiologic evidence suggests that the intake of vegetable has beneficial effects in protecting against cancer and cardiovascular diseases (Riboli and Norat 2003; Bazzano et al. 2003). Multiple studies have identified the beneficial effect of consuming vegetables which might be related to the presence of melatonin with other phytochemicals (Dragsted et al. 1993; Bazzano et al. 2003). The consumption of phytomelatonin-containing nuts like walnut (Reiter et al. 2005) and fermented

products like beer (Maldonado et al. 2009) has also been reported to increase the endogenous melatonin concentration and antioxidant capacity of the serum.

Although the content of melatonin in plant-based supplements is lower compared to exogenous sources containing chemically synthesized melatonin. However, phytomelatonin supplementation even at a low dose could improve circulatory melatonin levels up to 40 times within 5 min (Van Der Helm Vam Mil et al. 2003). Consumption of phytomelatonin-rich Japanese vegetables like sweet corn, bitter gourd, Japanese radish sprout, shimeji mushroom, and shiitake mushroom increases the endogenous melatonin concentration that has been suggested to protect from cancer and cardiovascular diseases (Oba et al. 2008).

Melatonin has a huge number of beneficial effects like antioxidant, anti-stress, oncostatic, and immunomodulatory impact but its supplementation is either subcutaneous or oral in the form of tables available over the counter. However, the general psychology of taking any medicine should be discouraged, and the general practice of preferring some dietary remedies be considered. Accounting for these concerns it is advocated to add phytomelatonin-rich plant products in our daily diet that may help to maintain the endogenous melatonin concentration in healthy and aged populations as well as in immunosuppressed individuals undergoing various treatment regimens.

The addition of phytomelatonin as a nutraceutical might be a promising non-invasive approach to improve health. Phytomelatonin supplementation might help protect against different bacterial and viral infections and can reduce low-grade inflammation thereby protecting against various age-associated cardiovascular diseases and skeletal complications. Therefore, it is suggested that naturally available resources rich in melatonin and other antioxidants should be included in our diet. This warrants further investigation that whether the consumption of phytomelatonin-rich food products could counterbalance the side effects of different drugs like glucocorticoid-based therapy, chemotherapy, etc., being used routinely in various clinical settings.

Acknowledgments The authors gratefully acknowledge the financial support provided in form of Start-up research grant by the University Grants Commission (UGC), New Delhi and Institute of Eminence (IoE), Banaras Hindu University, Varanasi, India.

Compliance with Ethical Standards: This article reviewed the published literature available in the domain with proper citations to the work of the original authors. This article does not contain any studies with human participants performed by any of the authors.

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