



# Melatonin and Health: Insights of Melatonin Action, Biological Functions, and Associated Disorders

Sheikh Bilal Ahmad<sup>1</sup> · Aarif Ali<sup>1</sup> · Midhat Bilal<sup>2</sup> · Shahzada Mudasar Rashid<sup>1</sup> · Amir Bashir Wani<sup>3</sup> · Rahil Razak Bhat<sup>1</sup> · Muneeb U. Rehman<sup>4</sup>

Received: 20 November 2022 / Accepted: 26 January 2023 / Published online: 8 February 2023  
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## Abstract

Melatonin is ubiquitous molecule with wide distribution in nature and is produced by many living organisms. In human beings, pineal gland is the major site for melatonin production and to lesser extent by retina, lymphocytes, bone marrow, gastrointestinal tract, and thymus. Melatonin as a neurohormone is released into circulation wherein it penetrates all tissues of the body. Melatonin synthesis and secretion is suppressed by light and enhanced by dark. Melatonin mostly exerts its effect through different pathways with melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) being the predominant type of receptor that are mainly expressed by many mammalian organs. Melatonin helps to regulate sleep patterns and circadian rhythms. In addition, melatonin acts as an antioxidant and scavenges excessive free radicals generated in the body by anti-excitatory and anti-inflammatory properties. A multiple array of other functions are displayed by melatonin that include oncogenic, hypnotic, immune regulation, reproduction, puberty timing, mood disorders, and transplantation. Deficiencies in the production or synthesis of melatonin have been found to be associated with onset of many disorders like breast cancer and neurodegenerative disorders. Melatonin could be used as potential analgesic drug in diseases associated with pain and it has quite promising role there. In the past century, a growing interest has been developed regarding the wide use of melatonin in treating various diseases like inflammatory, gastrointestinal, cancer, mood disorders, and others. Several melatonin agonists have been synthesized and are widely used in disease treatment. In this review, an effort has been made to describe the biochemistry of melatonin along with its therapeutic potential in various diseases of humans.

✉ Sheikh Bilal Ahmad  
sbilal@skuastkashmir.ac.in

Aarif Ali  
draarif31@skuastkashmir.ac.in

Midhat Bilal  
ishraq@skuastkashmir.ac.in

Shahzada Mudasar Rashid  
mudasir@skuastkashmir.ac.in

Amir Bashir Wani  
waniamir1647@skuastkashmir.ac.in

Rahil Razak Bhat  
rahilrazak789@skuastkashmir.ac.in

Muneeb U. Rehman  
mrehman1@ksu.edu.sa

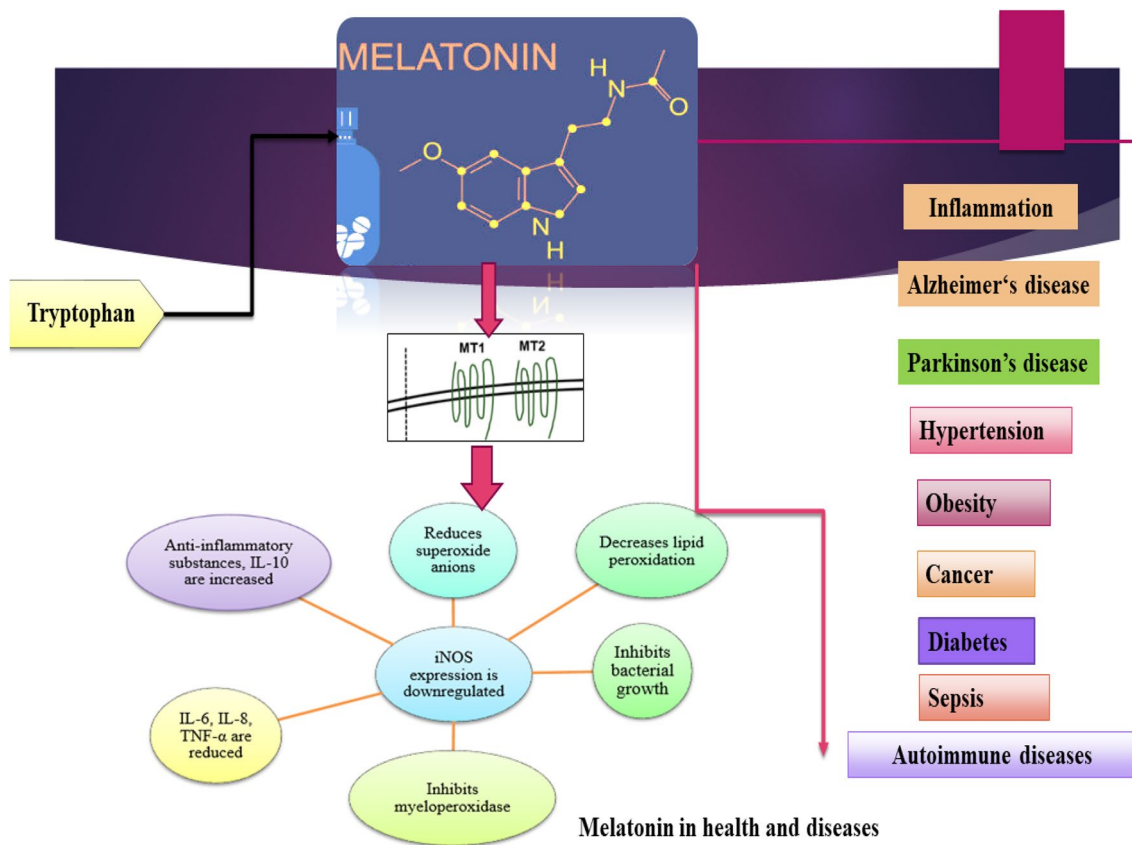
<sup>1</sup> Molecular Biology Lab, Division of Veterinary Biochemistry, F.V.Sc. & A. H. Shuhama, Sher-e-Kashmir University of Agricultural Sciences and Technology-Kashmir, Shalimar, Srinagar 190006, Jammu and Kashmir, India

<sup>2</sup> Division of Forest Biology and Tree Improvement, Faculty of Forestry, Sher-e-Kashmir University of Agricultural Sciences and Technology-Kashmir, Benhama, Ganderbal 191201, Jammu and Kashmir, India

<sup>3</sup> Division of Biotechnology, Sher-e-Kashmir University of Agricultural Sciences and Technology-Kashmir, Srinagar 190006, Jammu and Kashmir, India

<sup>4</sup> Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

## Graphical Abstract



**Keywords** Melatonin · Therapeutic · Antioxidant · Diseases · Agonists

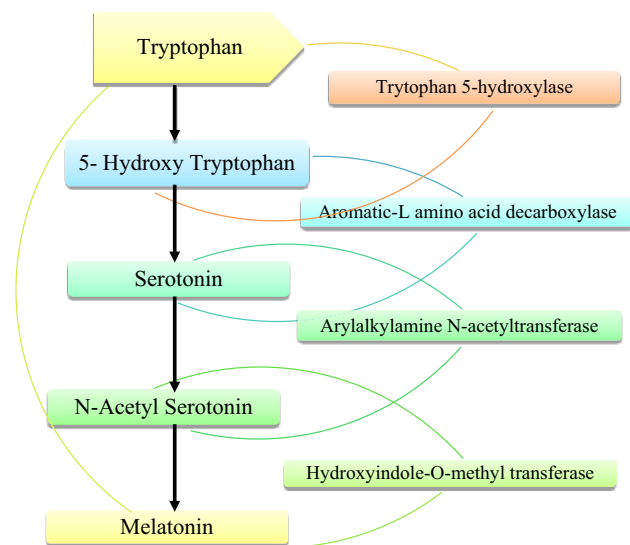
### Abbreviations

ASMT	Acetyl-serotonin-methyltransferase
NAT	<i>N</i> -Acetyltransferase
RZR/ROR	Retinoid-related Orphan nuclear hormone receptor family
GPCR	G-protein coupled receptor
GnRH	Gonadotrophin-releasing hormone
ROS	Reactive oxygen species
SOD	Superoxide dismutase
AD	Alzheimer's disease
A $\beta$	$\beta$ -Amyloid
APP	Amyloid precursor protein
PD	Parkinson's disease
SNC	Substantia nigra pars compacta
T2D	Type 2 diabetes
ZDF	Zucker diabetic fatty
Glut 1 and Glut 2	Glucose transporters
RA	Rheumatoid arthritis
MS	Multiple sclerosis
SLE	Systemic lupus erythematosus
BD	Bipolar disorder

MDD	Major depressive disorder
SAD	Seasonal affective disorder
BZD	Benzodiazepinergic
TNF- $\alpha$	Tumor necrosis factor- $\alpha$
IL-1 $\beta$	Intereukin-1 $\beta$
MT1	Melatonin receptor 1
MT2	Melatonin receptor 2

### Introduction

The word 'melatonin,' comes from a Greek word 'melas meaning dark' and 'tonos meaning hormone of darkness' is a ubiquitous hormone found in all living organisms of animal kingdom. Melatonin (*N*-acetyl-5-methoxytryptamine), an indoleamine, is predominantly secreted and synthesized by the pineal gland through hydroxylation of essential amino acid i.e., tryptophan at carbon 5 forming 5-hydroxytryptophan by tryptophan hydroxylase. Decarboxylation of 5-hydroxytryptophan yields a key neurotransmitter, 5-hydroxytryptamine (serotonin) which on acetylation



**Fig. 1** Pathway of melatonin synthesis in humans

by enzyme arylalkylamine *N*-acetyltransferase produces *N*-acetyl serotonin, the immediate precursor of melatonin. Subsequently, the enzyme acetyl-serotonin-methyltransferase (ASMT) through the process of methylation converts *N*-acetyl serotonin to melatonin (Coon et al. 2001) (Fig. 1). Pineal gland is the principal synthesizer and secretor of melatonin, in addition to many reports indicating the formation of melatonin in very small quantities by other organs namely retina, hardierian gland (Cardinali and Rosner 1971), gastrointestinal tract (Bubenik 2002), and lymphocytes. The traces of melatonin have been significantly identified in different parts of higher plants like fruits, seeds, and leaves (Tan et al. 2016; Reiter et al. 2014). However, the levels in these plant parts are too low for supply to human beings. The wide distribution of melatonin in primitive bacteria depicts ancient origin of the molecule and has been retained from evolution of living creatures (Pshenichnyuk et al. 2017). In bacteria, melatonin has evolved by process of endosymbiosis. Earlier, melatonin was thought to be involved in the photosynthesis and metabolic pathways and free radical detoxification processes (Manchester et al. 2015; Tan et al. 2015). However, during the course of evolution, melatonin diversified and attained a pleiotropic nature showing predominant role not only in resisting oxidative stress but also affecting biological rhythms and reducing inflammatory states (Tan et al. 2010; Tamtaji et al. 2018). Different species have evolved divergent melatonin biosynthetic routes and the genes encoding the enzymes involved in these pathways (Back et al. 2016). The role of melatonin is quite evident from its involvement in multiple biosynthetic metabolic pathways. In unicellular and multicellular organisms, the enzymes involved in biosynthesis of melatonin located in subcellular localization may somehow have been changed

(Lee et al. 2017). The separate subcellular sites of localization for biosynthesis of melatonin may be beneficial for its efficient control (Back et al. 2016; Byeon et al. 2015). The secretion of the melatonin is controlled by enzyme hydroxyindole-*O*-methyltransferase (HIOMT), also referred as acetyl-serotonin-methyltransferase (ASMT) which indirectly is commanded by photoneural system (Jang et al. 2010). Within the parenchymal cells, the presence of many capillaries permit excessive metabolic activity. Because the pineal lacks a blood–brain barrier, it shows resemblance to other periventricular glands like subfornical organ (SFO), median eminence, and subcommissural organ (SCO), which all are produced from ependymal cells in the third ventricle’s roof (Hissa et al. 2008). In living species, a circadian manner of melatonin secretion is observed with highest levels at night with 30–70-fold increase in *N*-acetyltransferase (NAT) enzyme activity. Melatonin production and release peak during the dark hours and fall during the day in all species studied (Binkley et al. 1988; Bolliet et al. 1996). The pineal gland does not store melatonin; however, the gland capacity of synthesis is reflected by its plasma concentration. The pineal gland responds directly to light in early non-mammalian vertebrates, whereas in higher vertebrates, it is no longer sensitive to light. Due to high lipid and water solubility of melatonin, its distribution is facilitated through most cell membranes including the blood–brain barrier (Pardridge and Mietus 1980). When released into circulation, it easily gains entry into different body fluids, cellular compartments, and tissues. Melatonin is mostly synthesized at night with its peak plasma concentration found around 3:00 to 4:00 a.m. Mainly, melatonin in blood is largely bound to albumin (70%) and to orosomucoid or alpha-1-acid glycoprotein to lower extent. The melatonin in circulation can travel to all tissues in the body and easily modulate activity of brain by crossing blood–brain barrier. No or very less melatonin secretion occurs upto 3 months of age. Then, at the age of 3–4 years, the production of melatonin reaches its peak, and by the adult stage, it progressively drops down by 80%. Temporarily, this change has been associated with sexual maturity and not with growing size of body; however, production of constant melatonin during childhood is due to increasing body size (Waldhauser et al. 1993).

### Factors Affecting Melatonin Synthesis

In humans, melatonin synthesis and generation is influenced by many factors as represented in Table 1 (Simonneaux and Ribelayga 2003; Zawilska et al. 2009).

**Table 1** Factors affecting production of melatonin

Factor	Effect on melatonin	Remarks
Light	Suppress	A > 30 lx light intensity in the wavelength of 460–480 nm has found to be more potent
Light	Phase-shift	Light of shorter wavelengths found to be efficacious
Timing of sleep	Phase-shift	Secondarily partial light exposure
Exercise	Increased phase-shift	Vigorous
5-Hydroxytryptamine	increases fluvoxamine	Metabolic effect
β-Adrenoceptor-A	Decreased synthesis	Anti-hypertensive
Chlorpromazine	Increases	Metabolic effect
Benzodiazepines	Changes are variable	–
Ibuprofen, Aspirin	Decreases	–
Alcohol	Decreases	–
Smoking	Possibly changes	–
Caffeine	Increases	–
Oral contraceptives	Increases	–
Testosterone	Decreases	–
Estradiol	Decreases, but not clear yet	–
Menstrual cycle	Changes are inconsistent	–

**Table 2** Amount of melatonin in edible plant and related foods

Plant/Food	Amount	Part/Organ	References
Tomato	3–114 ng/g	Fruit	Iriti et al. (2010), Sturtz et al. (2011)
Strawberry	1–11 ng/g	Fruit	Iriti et al. (2010)
Rice/Barley	300–1000 pg/g	Seed	Hattori et al. (1995)
Corn	14–53 ng/g	Seed	Mena et al. (2012)
Walnuts	3–4 ng/g	Seed	Reiter et al. (2005)
Olive oil	53–119 pg/ml	Seed	de la Puerta et al. (2007)
Black pepper	1093 ng/g	Leaf	Padumanonda et al. (2014)
Curcuma	120 ng/g	Root	Chen et al. (2003)
Coriander	7 ng/g	Seed	Manchester et al. (2000)
Black mustard	129 ng/g	Seed	Manchester et al. (2000)
Almond	39 ng/g	Seed	Manchester et al. (2000)
Cherry	18 ng/g	Fruit	Burkhardt et al. (2001)
Pomegranate	5.5 ng/g	Fruit	Mena et al. (2012)
Fennel	28 ng/g	Seed	Manchester et al. (2000)
White radish	485 ng/g	Bulb	Chen et al. (2003)
Beer	52–170 pg/ml	Fruit	Maldonado et al. (2009)
Wine	50–230 pg/ml	Fruit	Iriti et al. (2010)

## Edible Sources of Melatonin

Melatonin has been notably found in a variety of food items, whether edible plants or plant-based products. The plants and few food entities not only possess melatonin but also its precursor. In plants, melatonin presence is universal; however, the concentrations may vary from picograms to micrograms in plant tissue (Tan et al. 2012). Table 2 shows the amount of melatonin that has been detected by chromatographic and immunological techniques in food and plants.

Melatonin in plants plays an important role in reducing oxidative stress, promotes growth and germination of seeds, improves resistance to stress, stimulates immune system, modulates circadian rhythms, controls closure of stomata on leaves, and antistress agent against drought, toxic chemicals, salinity, heavy metal stress, UV radiation, high and low ambient temperatures, water stress, and light-induced stress. Moreover, melatonin also shows its role in combating biotic stress in plants that includes various properties like antibacterial, antiviral, and antifungal effects.

## Receptors and Mechanism of Action

Melatonin is a multifaceted hormone exhibiting its effects through endocrine, autocrine, and paracrine modes (Reiter 2003). Its action is facilitated either by receptor binding or acting directly. Within species, the melatonin receptors express considerable variability in density and location (Morgan et al. 1994; Liu et al. 2016). In mammals, melatonin shows its effect by binding to plasma membrane receptors, intracellular proteins like calmodulin or orphan nuclear receptors.

Melatonin also shows interaction with intracellular protein molecules such as calreticulin, calmodulin, and tubulin (Bolliet et al. 1996). Calmodulin is an intracellular secondary messenger. Melatonin directly competes with calcium for binding to calmodulin (Bolliet et al. 1996; Ekmekcioglu 2006) which may also be responsible for anti-proliferative effect observed in cancers. The immunomodulatory effects of melatonin are due to synthesis of IL-2 and IL-6 by mononuclear cells by binding of melatonin to Retinoid-related Orphan nuclear hormone receptor family (RZR/ROR) (Ekmekcioglu 2006).

In animal cells, melatonin mostly exerts its effects through membrane-bound G-protein coupled receptors (GPCR) (Jockers et al. 2016). In mammals, melatonin three designated GPCR are MT1, MT2, MT3 and also one nuclear receptors have been identified (Reppert et al. 1995; Nosjean et al. 2000). The receptors of melatonin are widely distributed and are found in brain, cardiovascular system, aorta, cardiac ventricular wall, cerebral and coronary arteries, gallbladder, liver, retina, parotid gland, appendix, cecum, colon, skin, pancreas, platelets, immune system cells, kidney, brown and white adipocytes, breast and ovarian granulosa cells, epithelial cells of prostate, fetal kidney, and placental myometrium (Uz et al. 2005, Hardeland 2012). In the jejunal and colonic mucosa of the gastrointestinal tract, most of the receptors of melatonin are typically located (Bolliet et al. 1996). Since the melatonin exhibits its action through the involvement of various molecular pathways, the most described pathways involve activation of specific membrane receptors namely ML1 i.e., high affinity and low affinity i.e., ML2 sites (Dubocovich 1995; Morgan et al. 1994). ML1 acts directly on the target cells or via G-protein coupled receptors and contains two sub types MT1 and MT2 (Li et al. 2013), whereas the newly purified ML2 receptors also referred as MT3 protein that belongs to quinone reductases family (Cardinali et al. 1997). On the basis of chromosome location and molecular structure, the receptors of melatonin (MT1 and MT2) are described as distinct subtypes (Reppert et al. 1995; Dubocovich et al. 2003).

## MT1 Receptor

MT1 also known as Mel1a receptor is made up of 351 amino acids and is encoded by chromosome 4 in humans (Li et al. 2013). Mel1a has a wide distribution in pars tuberalis and suprachiasmatic nucleus (SCN) of the hypothalamus the anatomical site of the circadian clock, cortex, thalamus, substantia nigra, cerebellum, nucleus accumbens, and retina (Jockers et al. 2008). The binding of melatonin to these high affinity receptors of GPCR super family in target cells causes inhibition of the adenylate cyclase/cAMP activity and increases phospholipase C/IP<sub>3</sub> action (Ebisawa et al. 1994). MT1 receptors have two subgroups, MT1a and MT2b (Morgan et al. 1994). In cardiac vessels and SCN that express MT1 receptor helps to modulate circadian rhythms (Dubocovich et al. 1998; Liu et al. 1997) and constrict cardiac vessels (Doolen et al. 1998). Apart from these areas, other parts of the brain and peripheral tissues express MT1 (Clemens et al. 2001; Ram et al. 2002).

## MT2 Receptor

It has 363 amino acids and is coded on human chromosome 11 (Li et al. 2013). MT2 receptors, also known as Mel1b receptors, have low affinity and are involved in phosphoinositol hydrolysis (Brzezinski 1997), retinal physiology (Klein 1985), circadian rhythm modulation (Dubocovich et al. 1998), cardiac vessel dilation (Doolen et al. 1998), and inflammatory responses (Lotufo et al. 2001; Li and Witt-Enderby 2000; Masana and Dubocovich 2001; Von Gall et al. 2002). The localization of MT2 receptors is restricted as compared to MT1 and primarily they are found in retina and secondarily in hippocampus, cortex, paraventricular nucleus, and cerebellum (Zawilska et al. 2009; Li and Witt-Enderby 2000; Masana and Dubocovich 2001; Von Gall et al. 2002).

## MT3 Receptor

Initially, MT3 was purified from the kidney of Syrian hamster and showed similar binding profile to MT2 (Dubocovich 1995; Molinari et al. 1996; Nosjean et al. 2000). It was discovered that the MT3 protein is 95% identical to human quinone reductase 2, a detoxifying enzyme (Nosjean et al. 2000). Leukotriene B<sub>4</sub>-induced leukocyte adherence is inhibited and intraocular pressure is reduced when MT3 receptors are activated (Dubocovich et al. 2003).

In addition to this, few properties of melatonin cannot be described by membrane receptors. Another group of receptors known as orphan nuclear hormone receptor superfamily RZR/ROR appears to be the natural ligand



for melatonin. The immunomodulatory properties of melatonin are because of these nuclear bound receptors (Carrillo-Vico et al. 2003).

### Melatonin Actions (Non-receptor Mediated)

Most of the activities of the melatonin are receptor mediated; however, a few occur with the involvement of receptor molecule and thus are non-receptor mediated and the prominent example is the free radical scavenging activity. Melatonin being a strong antioxidant is directly responsible for scavenging of the free radicals and so are its metabolites (Galano et al. 2013). It also activates many scavenging pathways and enhances the antioxidant enzyme activity (Barlow-Walden et al. 1995; Rodriguez et al. 2004). It also binds to the transition metals thus preventing the formation of hydroxyl radicals (Galano et al. 2015). Melatonin being highly concentrated in mitochondria protects proteins, lipids, and DNA from oxidative damage caused by free radicals (Venegas et al. 2012; Garcia et al. 2014). The antioxidant role of melatonin is of paramount importance for mitochondrial activities where free radical production is a natural phenomenon because of cellular respiration (Reiter et al. 2017). Apart from antioxidant role, melatonin plays a prime role not only in regulating respiratory chain complexes I and IV but also prevents the mutation and deletion of mitochondrial DNA (Jou et al. 2002). This action of melatonin results by direct interaction between melatonin and protein. Melatonin plays an antagonist role in protein degradation by its direct interaction with  $\text{Ca}^{2+}$ -calmodulin thereby inhibiting the  $\text{Ca}^{2+}$ /calmodulin-dependant protein kinase II activity and autophosphorylation (Benitez-King et al. 1996). It prevents DNA damage by down regulation of the expression of ATM (a phosphoinositide 3-kinase-related kinase) and histone H2AX phosphorylation process involved in DNA degradation (Majidinia et al. 2017).

### Melatonin and Brain

Melatonin has a diverse role and mostly affects brain. It has role in regulating circadian rhythm, seasonal adaptation, and puberty development pubertal development (Pandi et al. 2008). Melatonin is associated with memory by regulating memory formation by directly affecting hippocampal neurons (Comai and Gobbi 2014). It also controls posture and balance of the body (Pandi et al. 2008). Melatonin has antinociceptive, antidepressant, anxiolytic, and locomotor regulating effects (Uz et al. 2005). Melatonin has neuroprotective, lowering blood pressure, modulating pain, vascular, retinal, osteoblast differentiation, seasonal reproductive,

ovarian physiology, anti-tumor, and antioxidant properties (Li et al. 2013). From hypothalamic neurons, secretion of gonadotrophin-releasing hormone (GnRH) is regulated by melatonin that further affects synthesis of follicle stimulating hormone (FSH) and luteinizing hormone (LH) (Dubocovich et al. 2003). In granulosa cells, the production of progesterone is promoted by melatonin (Dubocovich et al. 2003). Melatonin also inhibits estrogen receptor expression and estrogen activation (Carlberg 2000). Melatonin has been shown very helpful in treating neurological disorders such as Parkinsonism (Gunata et al. 2020), Alzheimer's disease (Vecchierini et al. 2021), brain edema and traumatic brain injury (Dehghan et al. 2013), depression (Grima et al. 2018), cerebral ischemia (Tang et al. 2014), hyperhomocysteinuria (Karolczak and Watala 2021), glioma (Lai et al. 2019), and phenylketonuria (Yano et al. 2016). Melatonin was shown to inhibit amyloidosis (Shukla et al. 2017).

### Antioxidant, Anti-inflammatory, and Neuroprotective Role of Melatonin

In the humans, there is a high consumption of oxygen in the brain i.e., 20% and this increased consumption causes oxidative stress and generates toxic free radical molecules in the body. These high reactive molecules damage DNA, proteins, and cell membrane (Gupta et al. 2003). The presence of considerable amount fat in membrane and myelin sheaths enhances the damage by free radicals thus creating an imbalance between oxidants and antioxidants (Skaper et al. 1999). The damage by reactive oxygen species (ROS) results in compromised blood–brain barrier and enhanced expression of excitatory neurotransmitter glutamate to extracellular space thereby triggers the depolarization (Gilman et al. 1993). The ROS also results in the alteration of gene expression, initiate apoptotic cascade, and decreased neuron viability (Gilgun-Sherki et al. 2002). Melatonin scavenges free radicals endogenously through its role as an antioxidant (Tordjman et al. 2017). The intake of melatonin supplementation enhances the superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity (Mayo et al. 2002). Thus, melatonin exerts its neuroprotective potential through its antioxidant power. The onset of stroke results in the massive destruction of cells with enhanced production of ROS and inflammation. The neuron survival is dependent on active energy metabolism hence, any obstruction in the cerebral flow of blood, restricted glucose and oxygen supply results in ischemic stroke that can have catastrophic implication on neurons (Flynn et al. 2008). In case of glucose and oxygen scarcity, the cell survival is compromised through many pathways. In particular, the function of ATP-dependent  $\text{Na}^+/\text{K}^+$ -ATPase is compromised which results in the intracellular accumulation of  $\text{Na}^+$  resulting in anoxic depolarization and activation of voltage-gated calcium channels and reduction

in  $\text{Na}^{2+}/\text{Ca}^{2+}$  exchange, the disturbance results in the intracellular accumulation of  $\text{Ca}^{2+}$  which initiates cell injury (Stys 1998). Melatonin a potential antioxidant protects from ischemic injury (Watson et al. 2016; Wu et al. 2017).

The administration of melatonin in animal models with induced stroke results in the reduction of cerebral infarction (Sinha et al. 2001; Pei et al. 2003). Melatonin imparts a protective ability in gray and white matter, diminishes the inflammatory cascade and permeability of blood–brain (Chen et al. 2006; Lee et al. 2007). Melatonin injection attenuates oxidative brain injury in rat models (Ersahin et al. 2009; Wu et al. 2017). Melatonin also helps in  $\text{Ca}^{2+}$  homeostasis and reduction in extracellular glutamate levels by preventing its release into oxygen glucose-deprived rat model of ischemia (Patiño et al. 2016). In rat models with induced injury to brain, melatonin showed anti-inflammatory properties as it reduces the movement of macrophages/monocytes and neutrophils in circulation to the damaged area (Lee et al. 2007). Paredes et al. (2015) reported that intake of melatonin resulted in the significant decrease of interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), BAD, and BAX in the ischemic area of both hippocampus and cortex compared to non-administration group.

Alzheimer's disease (AD) is an age-related disorder that results by the deposition of toxic proteins  $\beta$ -amyloid (A $\beta$ ) and neurofibrillary tangles (NFTs) in memory-related areas resulting in progressive cognitive behavior decline (Ittner and Gotz 2011; He et al. 2010). Neuronal loss and oxidative stress are triggered by the deposition of harmful protein molecules (Sultana and Butterfield 2010; Jeong 2017). Oxidative stress resulting due to accumulation of A $\beta$  generated free radicals, membrane dysfunction, and inflammation and thereby plays a critical role in the onset of AD (Prasad 2017; Nesi et al. 2017). A recent study has reported antiamyloidogenic melatonin action on AD (Shukla et al. 2017). Melatonin also halts the synthesis of amyloid precursor protein (APP) which in turn disrupts the A $\beta$  formation (Lahiri 1999). The long-time administration of melatonin is known to prevent the accumulation of A $\beta$  in hippocampus and cortex in transgenic mice (Olcese et al. 2009). In AD, melatonin acts

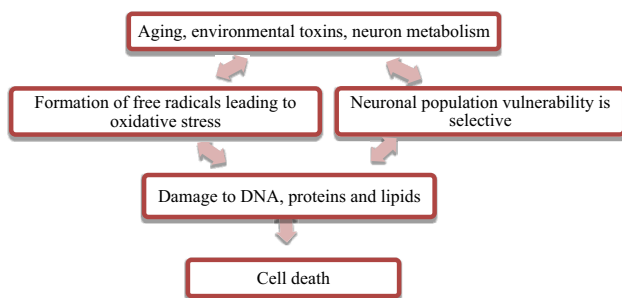
as a strong antioxidant as it diminishes A $\beta$ -facilitated oxidative stress and lipid peroxidation (Daniels et al. 1998; Shukla et al. 2017). It has been reported that melatonin maintains the level of certain antioxidants like catalase, GPx, and SOD in the cortex of AD transgenic mice (Olcese et al. 2009).

Millions of people are suffering from Parkinson's disease (PD) worldwide (Elbaz and Moisan 2008; Wirdefeldt et al. 2011). PD is a neurodegenerative disease with multiple etiological factors associated with the onset of PD such as genetics, age, smoking, dairy products consumption, and exposure to manganese and lead (Elbaz and Moisan 2008; Hughes et al. 2017; Ma et al. 2017). In substantia nigra pars compacta (SNc), there is dopaminergic neuronal loss in PD, thus resulting in striatal dopamine depletion which ultimately causes disturbance of the smooth coordinated muscle resulting in rigidity, tremor, bradykinesia, and postural problems (Tansey et al. 2007; Maguire-Zeiss and Federoff 2010). A number of reports have demonstrated the age-related PD is accompanied with oxidative pressure (Padurariu et al. 2013). In the onset of PD, free radicals are the initiating factors. The integral features of this disease are insomnia and depression in PD, and disturbances in sleep are related to psychiatric signs and decline in cognitive feature. The various factors that cause PD are shown in Fig. 2.

In the striatum and hippocampus, melatonin administration prevents peroxidation of lipids thereby arresting the neuronal death in an MPTP-induced PD model (Antolin et al. 2002). In animal models induced with PD, melatonin regulates the antioxidant enzyme activity of SOD and catalase in the nigrostriatal pathway in 6-OHDA. Therefore, it can be seen that melatonin exhibits its neuroprotective properties through its antioxidant and anti-inflammatory actions.

## Melatonin and Hypertension

Hypertension is more frequently observed in obese individuals in comparison to lean cases, and melatonin's role in modulating and regulating blood pressure seems an interesting subject for researchers from many years (Poirier et al. 2006; Qin et al. 2013; Cook et al. 2011). In mammals, melatonin regulates heart rate and arterial blood pressure (BP) (Simko and Pechanova 2009; Reiter et al. 2010) as the receptors for melatonin are identified in heart and different arterial beds (Capsoni et al. 1994; Krause et al. 1995; Pang et al. 1993, 1996). Subjects with hypertension exhibit disturbed day–night rhythms with changes in sympathetic and parasympathetic cardiac tone (Nakano et al. 2001). Individuals suffering from coronary heart ailment an outcome of the hypertension show reduced melatonin levels during the night hours (Brugger et al. 1995). Similarly, pinealectomy in rats has been reported to result in hypertension, and administration of endogenous melatonin has inhibited the increase in



**Fig. 2** Factors responsible for Parkinson's disorder

BP in pinealectomised rats (Simko and Paulis 2007). There is strong evidence that people with hypertension during day hours have disordered circadian rhythms (Simko and Paulis 2007). From pineal gland, the melatonin secretion is controlled by SCN (Buijs et al. 2003), melatonin through its high affinity receptors sends feed back to SCN there by controls its own production and other circadian rhythms (Amaral and Cipolla-Neto 2018). Night hour's melatonin secretion directly boosts circadian rhythms through the principal pacemaker and has a critical role in improving the day–night rhythms (Cipolla-Neto and Amaral 2018) and BP (Scheer et al. 2004). Grossman et al. (2006) reported that administration of melatonin (2 mg for 4 weeks) at bed time reduced the nocturnal systolic and diastolic BP. There are a number of ways by which melatonin exerts its influence on BP. ROS and reactive nitrogen species (RNS) have significant role in the occurrence of hypertension (Anwar et al. 2001; Pechanova et al. 2006), while antioxidants diminish the hypertensive effects of ROS and NOS. The melatonin is reported to reduce BP by lowering the intracellular superoxide anion content, malondialdehyde, NF- $\kappa$ B expression, and enhancing GPx activity (Girouard et al. 2004; Nava et al. 2003; Paulis 2006). In young women patients with hypertension, lower levels of nocturnal melatonin were considered as risk factor in hypertension development (Forman et al. 2010). In hypertensive patients, impairment in secretion of melatonin resulted in decrease of nocturnal levels of melatonin (Zeman et al. 2005). As a result of these findings, melatonin is a potent therapeutic molecule in non-dipper patients or cases with hypertensive heart disease or nocturnal hypertension (Reiter et al. 2010). The intake of melatonin in individuals with nocturnal hypertension reduced systolic and diastolic blood pressure (Grossman et al. 2011).

## Melatonin and Diabetes

Diabetes mellitus (DM) is a disorder of carbohydrate metabolism that is associated with elevated glucose levels in blood and defects in secretion and action of insulin (Ali et al. 2017a, b; Bhat et al. 2017). Melatonin has gained its importance because of its role in sleep and circadian regulation. However, during recent past, it has gained importance for its role in glucose tolerance and type 2 diabetes (T2D) risk or treatment. This is due to partial discovery of T2D risk variants in MTNR1B and partially negative impact of disturbed circadian rhythms on glucose metabolism (Mason et al. 2020). The disturbance in circadian rhythm has been reported to result in metabolic syndrome including obesity and diabetes (Pulimeno et al. 2013). There are many reports about the role of melatonin in insulin secretion and glucose homeostasis. A diminished level of melatonin has been reported in patients with T2D (Prokopenko et al. 2009). A study conducted on

the role of melatonin glucose homeostasis in young Zucker diabetic fatty (ZDF) rats, an experiment model of metabolic syndrome and T2D revealed that oral administration of melatonin results in anti-hyperglycemic effect in young ZDF rats through improvement in  $\beta$ -cell function (Agil et al. 2012). Studies have revealed that deficiency of melatonin receptor has a direct bearing on levels of pancreatic islet hormones and glucose transporters (Glut 1 and Glut 2) (Bazwinsky-Wutschke et al. 2014). The relation between melatonin and T2D on the basis of a finding that secretion of insulin is inversely proportional to concentration of melatonin in plasma (Peschke et al. 2013). Subduing the secretion of melatonin as a result of nocturnal light exposure could be vital parameter in onset of T2D (Fonken and Nelson 2014). A large number of literature suggest a correlation between disturbed sleep orders and decreased glucose tolerance and T2D (Donga et al. 2010; Yaggi et al. 2006). A study reported by Hajam et al. (2022) has reported the therapeutic efficacy of coadministration of insulin and melatonin rat models with diabetes-induced renal injury. The outcome of the study reported has revealed that the combination of insulin and melatonin may be quite effective to treat renal alterations caused by diabetes as confirmed by sera biochemical parameters, anti-inflammatory molecules in serum, and histoarchitecture changes in kidney (Hajam et al. 2022). The melatonin administration modulates the synthesis of insulin in the pancreatic  $\beta$ -cells as well as enhancing the optimistic insulin effect (Hajam and Rai 2019).

## Melatonin and Cancer

During the last century, different reports have assessed the oncostatic properties of melatonin against various malignancies like colorectal, breast cancer, prostate cancer, leukemia, pancreatic cancer, and melanoma (Foon 1989). These studies provided a promising result in the breast cancer cells that express estrogen receptors. Cancer accounts for the most number of deaths globally after cardiovascular diseases (Ferlay et al. 2012; Fitzmaurice et al. 2015). Statistically lung cancer results in most number of deaths in both sexes, while prostate cancer figures top in male deaths and breast cancer among female deaths (Ferlay et al. 2012; Fan et al. 2015; Torre et al. 2016; James et al. 2017). The availability of data of neoplastic diseases upto now clearly suggests the progression of human cancers not only depends disease biological characteristics like mutation, overexpression of genes, grading, histology, but also on immunobiological response of patient that includes immune and endocrine system status as well (Foon 1989). Similarly, the malfunctioning of the immune system does not rely on immune cells activity but also on modulation of neuroendocrine physiology, that is primarily influenced by pineal system. The pineal gland exerts anti-tumor anti-proliferative functions



through secretion of peptide hormones and various anticancer indole molecules and mostly widely the melatonin hormone (Brzezinski 1997). Prior to the characterization of pineal gland hormones, it was known that the onset of tumor and dissemination was due to pinealectomy (Buswell 1975). The associations between melatonin and cancer have been studied from many decades and a large number of epidemiological studies favor the protective potential of melatonin against cancer (Nooshinfar et al. 2017; Li et al. 2017). Different research studies have reported other than melatonin, many anticancer hormones may be produced by pineal gland (Anisomov et al. 2001). Various studies have demonstrated the preventive role of melatonin in different type of cancers (Cos and Sanchez-Barcelo 2000; Wang et al. 2012; Kanishi et al. 2000; Subramanian et al. 2007). An important property of melatonin that makes it helpful in combating the tumor is its ability to diminish neoplastic amplification with cytostatic and cytotoxic actions (Martin et al. 2007; Liu et al. 2016). Several other studies reported the protective role of melatonin against mammary cancer (Kosar et al. 2016; Gatti et al. 2017). A decrease in circulating melatonin has been reported to be associated with increased prevalence of mammary tumors through carcinogen 7,12-dimethylbenz(a)-anthracene (DMBA) the treatment with melatonin minimizes the incidence (Chu et al. 2018). Melatonin in combination with retinoic acid on MCF-7 hormone-dependant breast cancer cells has completely blocked the cell growth and reduced the cell number by activation of apoptosis (Margheri et al. 2012). Other researchers have reported that melatonin suppresses the progress of tumor through its ability to inhibit the differentiation of cell cycle (Sánchez-Sánchez et al. 2011; Cabrera et al. 2010; Martin et al. 2007).

## Melatonin and Obesity

There is substantial evidence connecting impaired circadian clock and obesity development. Despite the fact that the causal association between obesity and chronodisruption is bi-directional (Bray and Young 2012), melatonin and its agonists administration have proven to be effective in circadian rhythm resetting (Zawilska et al. 2009) and correcting disorders associated to obesity (Cardinali et al. 2011; She et al. 2009; Oxenkrug and Summergrad 2010). Furthermore, obesity is linked to a variety of comorbidities like sleeping disorders and melatonin or other medications have shown to be effective (Cardinali et al. 2011). Melatonin is hypothesized to play a role in energy metabolism and body weight management. In the body of seasonal animals, melatonin's involvement in modulating metabolism and fat mass was first studied and established (Bartness and Wade 1985), and it was connected to its activity as a seasonal and circadian rhythm regulator (Arendt 2006). Depending on the animal species, any rise in

circulation melatonin levels owing to photoperiodic variations or exogenous melatonin injection was eventually related with a loss or increase in body fat mass in these seasonal animals (Bartness and Wade 1985). Exposure to long photoperiod conditions of obese Zucker rats resulted in increased body weight as compared to short photoperiod exposed animals (Larkin et al. 1991). In accord, the elimination of the pineal gland decreased levels of melatonin in circulation and in obese rats elevated body weight as compared to healthy rats after 3 weeks (Prunet-Marcassus et al. 2003). In normal rats when postoperative duration was increased to 2 months, they gained weight in both the body and the heart (Kurcer et al. 2006). Melatonin (30 mg/kg/day, i.p. 1 h before lights-out) could prevent these pinealectomy-induced changes for 3 weeks (Prunet-Marcassus et al. 2003). The same researchers found that melatonin given in the same way could minimize body weight gain caused by a high-fat meal while having no effect on overall food intake (Prunet-Marcassus et al. 2003). Obesity-induced dyslipidemia symptoms have been demonstrated to be improved by melatonin. This was first noticed in non-obese hypercholesterolemia rats (Hussain 2007), and later validated in different obesity-induced rat models (Agil et al. 2012). Melatonin performs its diverse functions via receptor-mediated or non-receptor-mediated routes, as previously indicated (Venegas et al. 2012). The therapeutic potency of melatonin in treatment and prevention of obesity has been well summarized with high efficacy results in animal models (Barrenetxe et al. 2004; Shieh et al. 2009).

## Melatonin and Autoimmunity

Multiple studies have linked onset of immune-compromised diseases like rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE) with exogenous and endogenous production of melatonin despite the scarcity of data on the relationship of melatonin to other autoimmune diseases. In this regard, psoriatic patients have shown to have disturbances in secretion of circadian melatonin (Mozzanica et al. 1988). In individuals with autoimmune hearing loss, melatonin inhibits proliferation of lymphocytes induced by type II collagen (Lopez-Gonzalez et al. 1997) and protects against idiopathic membranous nephropathy in an experimental model (Wu et al. 2012). Globally, 1% of the population is affected by Rheumatoid arthritis (RA) and the effects of melatonin on this autoimmune disorder appear to be debatable (McInnes and Schett 2011). RA is a progressively inflammatory disease that severely affects joints thereby leading to severe disability (Ali et al. 2017a, b). Several studies using experimental arthritis models suggest melatonin (endogenous and exogenous) has a negative effect. As a result, animals kept in constant darkness develop severe

form of collagen-induced arthritis with increased titers of sera anti-collagen antibodies in comparison to animals living in constant light. Pinealectomy was used to counteract the effect of constant darkness (Hansson et al. 1993). Furthermore, a severe type of arthritis was developed in mice placed under constant light and immunized with type II collagen, whereas melatonin administration at disease onset (days 30–39) had no effect on the clinical signs of the disease (Hansson et al. 1992). In an adjuvant-induced arthritis model, a preventive and/or therapeutic therapy with the indoleamine lowers hind paw swelling in a comparable fashion to indomethacin (Chen and Wei 2002) in comparison to studies that showed the harmful effect of melatonin. Enhanced RA incidence and severity have been linked to higher latitudes, suggesting that increased melatonin production during long winter nights may be linked to RA. The development of RA is inversely related to UV-B exposure as these rays tend to decrease melatonin synthesis from pineal gland (Arkema et al. 2013). In individuals with RA, levels of nocturnal melatonin were higher in patients from Europe as compared to people from Italy (Cutolo et al. 2005). In early morning, the symptoms of RA get worsen (Cutolo and Masi 2005). Different studies have reported that individuals with RA had raised levels of sera melatonin in early morning in comparison to healthy individuals (Cutolo et al. 2005; Sulli et al. 2002). In individuals with RA, melatonin levels were significantly reduced in plasma (West and Oosthuizen 1992). In RA-cultured synovial macrophages, the sites for binding of melatonin molecule had higher affinity and intake of melatonin increased levels of NO and IL-12, respectively (Maestroni et al. 2002; Cutolo et al. 1999). The melatonin levels were higher synovial fluid of individuals with RA (Maestroni et al. 2002).

In young adults, Multiple sclerosis (MS) is the most prevalent neurological disorder with global incidence of 1.1–2.5 million cases and an increased worldwide incidence in middle-aged women. It is a neurodegenerative disease that is caused by an immunological response to myelin (Lassmann and Horsen 2011). Even though etiology of MS is still unknown, one of the environmental elements that appears to be involved is latitude, as the disease's incidence in northern countries increases (Kurtzke 1977). Because the incidence decreases in hilly areas compared to nearby lower areas (Kurtzke 1967), this has been linked to a reduction in sunshine exposure (van der Mei et al. 2003). Lately, shift work at an early age has been linked to an elevated risk of MS, with a positive association between MS risk and shift work length (Hedstrom et al. 2011). Melatonin and a MT6 circadian rhythms are both disrupted in MS patients. Melatonin had an inverted circadian rhythm in a large percentage of patients with worsened MS (Sandyk and Awerbuch 1992).

Systemic lupus erythematosus (SLE) is a complex autoimmune condition with an estimated incidence of 20–150 cases per 100,000 individuals and 1–10 new cases per 100,000 individuals yearly. In blood and tissues, the formation of immune complexes causes substantial tissular damage which is a prominent feature of SLE (Tsokos 2011). In the case of melatonin and lupus, a circadian rhythm uncoupling has been seen in lupus-prone mice (Lechner et al. 2000).

In mouse models of SLE, melatonin therapy has inconsistent effects, depending on the various criteria such as the administration timing and animal sex. Morning melatonin administration improved survival in lupus-prone mice, but the benefit was not replicated with evening treatment (Lenz et al. 1995). In kidney of female mice, melatonin supplementation effectively reduced vascular lesions and inflammatory infiltration, decreasing anti-collagen II and antidsDNA autoantibody titers, lowering production of pro-inflammatory cytokine, and increasing anti-inflammatory cytokine generation both in animals prone to lupus (Jimenez-Caliani et al. 2006) and in pristane-induced lupus (Zhou et al. 2010). Melatonin had little impact or aggravated the condition in male lupus-prone mice (Jimenez-Caliani et al. 2006).

## Melatonin and Sepsis

Primarily sepsis is a microbial infection that causes systemic inflammation in the host body. Generally, microbial pathogens like bacteria, viruses, fungi, and other parasites (Annane et al. 2005; Calandra and Cohen 2005) cause it. It has been found that gram-negative bacteria possess lipopolysaccharide (LPS) in their cell wall that is ultimately been found to be responsible for sepsis initiation (Sriskandan and Cohen 1995). LPS causes significant induction of gene and expression of inflammatory molecules such as cytokines, chemokines, iNOS, and heat shock proteins by activating intracellular signaling pathways such as nuclear factor  $\kappa$ B (Victor et al. 2004; Tsiotou et al. 2005). The natural balance

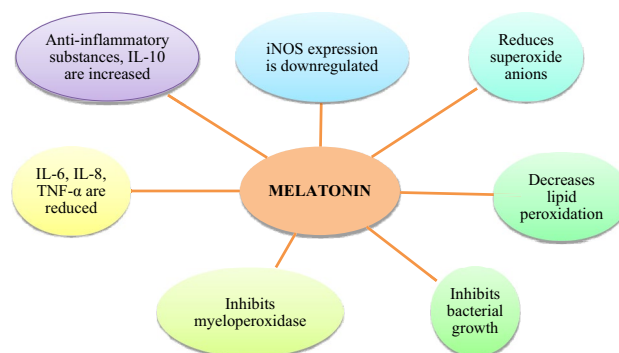


Fig. 3 Melatonin and its beneficial effects in sepsis

between pro-inflammatory and anti-inflammatory mediators is broken during sepsis, resulting in the release of several inflammatory mediators (Pinsky 2001). In early phase of sepsis, soluble inflammatory molecules such as IL-1 and TNF- $\alpha$  are released. IL-1 causes ROS generation and protease stimulation, whereas cell activation is caused by TNF- $\alpha$ . In the onset of sepsis, mediators such as interferons and interleukins are involved. In both humans and animal models, melatonin supplementation has been effective in treating septic shock. The beneficial characteristics of melatonin in sepsis and bacterial infections are shown in Fig. 3.

## Melatonin and Malaria

Malaria is one of the severe protozoal diseases that affects about 200 million people worldwide and kills over one million people each year (Sato 2021). Apart from *Plasmodium falciparum*, which in humans commonly causes malaria, a more known virulent parasite is *Plasmodium knowlesi* that rapidly spread not only in Malaysia but also throughout the world (White 2008; Yusof et al. 2014; Singh and Daneshvar 2013). In the past, a global malaria eradication initiative involving insecticide spraying yielded positive results. Malaria infections have been successfully eradicated thanks to potent antimalarial drugs, but with the increased drug resistance there is a reemergence of drug-resistant-associated malaria. Melatonin works as a trigger for *Plasmodium falciparum* growth and development, according to recent discoveries in malarial parasite genetic investigations (Mallaupoma et al. 2022). The same might be true for

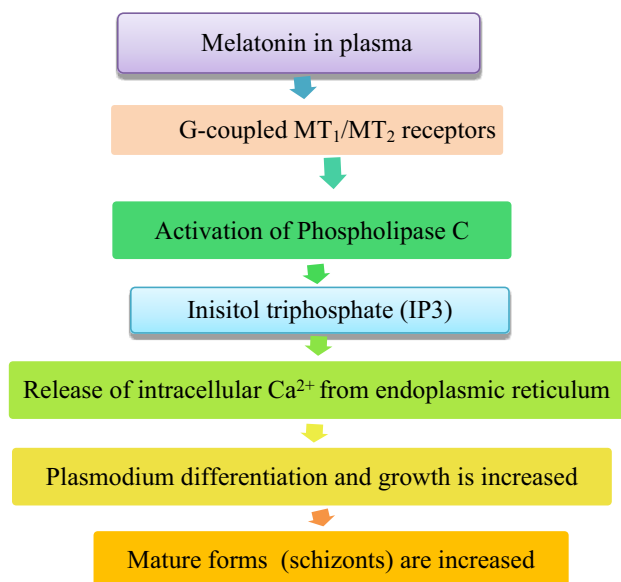
*Plasmodium knowlesi*. As a result, therapeutic strategies that successfully inhibit melatonin action on species of *Plasmodium* throughout the night involve therapy of bright light or blocking receptors of melatonin can be regarded as viable options for eradicating malaria in humans. The therapeutic implication of melatonin on *Plasmodium falciparum* cell cycle is represented in Fig. 4.

## Melatonin in Vaccination

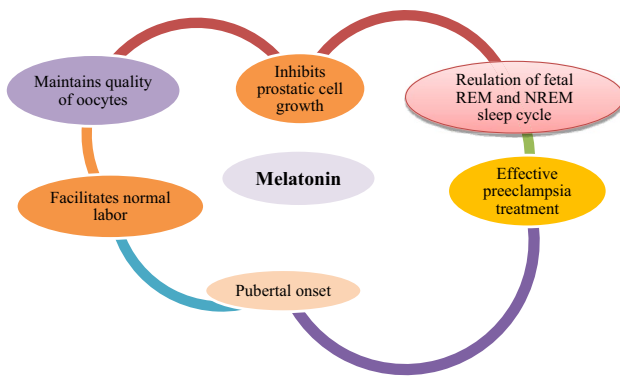
Vaccines are a significant effort to develop immunity to a specific disease and a growing attention toward enhancing the efficiency of preexisting vaccines. Vaccination's immune-promoting efficacy is defined by antigenic part and appropriate adjuvants that are efficient in generating and supporting an effective immune response to pathogenic pathogens. Some in vivo research have looked into using melatonin as a vaccine agent, based on its immunoregulatory qualities. In sheep, lameness (Katz et al. 1991) is caused by *Dichelobacter nodosus* (Regodón et al. 2005) and the administration of melatonin enhanced humoral response in vaccinated sheep. The melatonin administered via injections or implants also increased response of platelets to thrombin stimulation thus improving aggregation rate, percentage, and lag time (Regodón et al. 2012). In sheep's vaccinated with *Clostridium perfringens* type D, the administration of melatonin evoked beneficial immune response (Regodón et al. 2012). Interestingly, it was also found that immunization time also plays a vital part in imparting beneficial effects of melatonin as highest concentration of sera antibodies was found after vaccination prepartum. In vaccine development against prostate cancer, the potential use of melatonin has been described; however, no data have been published till now (Connor 2008). Melatonin significantly improved the vaccine effectiveness of cercarial and soluble worm antigens, and also elevated GSH levels (Soliman et al. 2008). In the vaccination development against Alzheimer's disease, melatonin use as an adjuvant has proved quite effective.

## Melatonin and Reproduction

Melatonin is a potential molecule with wide variety of physiological properties and is known to affect reproductive status in different species (Thiéblot and Le Bars 1955). Before the discovery of melatonin, a study by Huebner in 1898 reported that the tumor of pineal gland in humans affected pubertal development and suggested that some molecule of pineal lineage influences reproductive function. Many researchers have investigated the relationship between the pineal and reproductive state in a number of species as a result of this finding, but few have been successful in proving a functional



**Fig. 4** Graphical overview representing melatonin's effect on life cycle of Plasmodium



**Fig. 5** Melatonin and its effects on reproductive status

relationship (Thiéblot and Le Bars 1955). A study reported that in female rats that were administered with exogenous melatonin reduced ovarian weight (Wurtman et al. 1963). Ever since, there has been a plethora of evidence suggesting that reproductive function in numerous species is influenced by the pineal gland, via melatonin (Reiter 1993). There is substantial evidence that the photoperiod-mediated frequency of melatonin secretion has a direct impact on reproductive capacity. Melatonin's key physiological purpose is to describe the daily light/dark (LD) cycle. The potential impact of melatonin on reproductive functions is shown in Fig. 5.

## Melatonin in Mood Disorders

The role of melatonin has been found in the development of various mood disorders such as bipolar disorder (BD), major depressive disorder (MDD), and seasonal affective disorder (SAD). The major abnormalities associated with BD patients are the disturbances in sleep especially reduced sleep during night and abnormal circadian rhythms (Harvey 2008; Mansour et al. 2005). In individuals affected with BD, a marked decrease in secretion of melatonin is seen in depressed stage, and with symptoms remission, it was restored to normal. In individuals with MDD disturbances like wakefulness in early morning hours, mood, alertness, and fatigue during day time are more commonly known. The individuals with MDD have increased levels of melatonin in their body, and a phase wise shift of this hormone is considered as the utmost clinical feature of this disorder. In SAD, patients during winter season experience depression episodes and euthymia in summer time. The seasonal variations of melatonin are found in SAD individuals. In the pathogenesis of mood disorders, most of the patients suffer from disturbances in circadian rhythms and sleep. In individuals with several mood disorders, altered melatonin levels cause abnormalities in the biological clock functioning

located in suprachiasmatic nuclei of anterior hypothalamus. Hence, treatment procedures should be developed on using antidepressant medications that can restore circadian clock functioning, and in this context, Agomelatine has been found to be quite effective as an antidepressant drug. Agomelatine is a chemically synthesized naphthalenic compound that primarily acts on MT1 and MT2 receptors. The half-life of this drug is higher than melatonin and is primarily metabolized in the liver via CYP isoenzymes (CYP1A1, CYP1A2, and CYP2C9). Agomelatine shows no significant affinity against receptors of adrenergic, dopaminergic, muscarinic, and histaminergic. In the treatment of mood disorders, Agomelatine is quite useful as it resynchronizes abnormal circadian rhythms and disturbed patterns of sleep (Kennedy et al. 2011). In addition to antidepressant property of Agomelatine, no adverse effects like disturbances in sleep patterns, discontinuation of medications, and sexual dysfunction were not found. Agomelatine has also found to be quite efficient in treating obsessive compulsive disorders (Fornaro 2011). In recent times, a number of research studies have reported that Agomelatine shows good clinical efficacy, safety, and tolerability (Rouillon 2006; Kennedy and Rizvi 2010).

## Melatonin in Transplantation

The role of melatonin has also been found in prolonged survival of graft as beneficial in animal models. In a rat model with cardiac transplant, melatonin (200 mg/kg) was found to inhibit allograft immune response as it reduced proliferation of lymphocytes thus stopping rejection and increasing survival of graft (Jung et al. 2004). Simultaneously, after prolonged ischemia in lungs with reperfusion injury similar effects were observed (Inci et al. 2002). In non-obese diabetic mice, high administration of melatonin predominantly enhanced survival of islet graft as it inhibited T cell proliferation and increased IL-10 cell population (Lin et al. 2009). In a rat model with ovary transplantation, the melatonin administration depicted immunosuppressive property (Sapmaz et al. 2003). A comparable research study of ovarian grafts in humans treated with melatonin showed reduced apoptosis (Friedman et al. 2012). In ischemia–reperfusion injured animal models, protective effects of melatonin administration have been reported (Fildes et al. 2009). The intake of melatonin caused reduction in apoptotic cells, oxidative molecules, recruitment of neutrophils, and also raised GSH (Baykara et al. 2009).



## Melatonin and Other Infections

During past century, melatonin has been considered as a significant antibiotic, anti-parasitic, and antiviral entity (Bagnaresi et al. 2012). The protective role of melatonin has been found against Venezuelan equine encephalomyelitis virus (VEEV) that causes viral infections (Montiel et al. 2015). From 1920 to 1970, the outbreaks of this viral infection occurred in northern part of South America wherein thousands of people, donkeys, and horses were affected (Bowen and Calisher 1976). This infection also resurfaced in 1995 and caused mortality in the affected area (Weaver et al. 1996). This infection caused excitation and hypermotility, subsequently followed by hypomotility, coma, paralysis, and death. In mice, a series of experimental studies with the infected virus were carried out and after melatonin administration the disease onset was delayed with reduced mortality rate as the viral load decreased in brain and blood (Bonilla et al. 1997). In immunocompetent mice, VEEV levels were reduced in brain by melatonin treatment as compared to immunodepressed mice, proposing that for depicting antiviral activity melatonin requires immune system integrity (Bonilla et al. 2001). In encephalitis, a disease caused by pathogenic encephalomyocarditis virus (EMCV), the melatonin supplementation in mice prevented paralysis and death in rodents infected with EMCV sublethal doses (Wongchitrat et al. 2010). A study reported that Semliki forest virus (SFV)-infected mice had defects in central nervous system and causes death, the administration of melatonin decreased viremia, delayed disease onset, and reduced mortality (Carrillo-Vico et al. 2013). In various developed models of bacterial infections, melatonin seems to have a potent role in scavenging of toxic free radicals and also antioxidant properties (Manchester et al. 2015). In *M. tuberculosis*, few studies have reported seasonality in infection cases which peaks at start of summer and end of winter season (Liao et al. 2019). All of the seasonality changes have been reported, and few researchers have proposed that annual variations in the melatonin concentrations cause seasonal variations in the immune system (Ozkank et al. 2012). The melatonin supplementation has found to be quite efficient in treating parasitic infections.

## Melatonin and Pain

The potential damage to a tissue causes pain that is an unpleasant sensory feeling. The perception of pain mechanism is a multifactorial event consisting of biochemical, neurophysiological, humoral, and psychological parameters (Shavali et al. 2005). During tissue damage, a range of inflammatory molecules such as cytokines, prostaglandins,

TNF- $\alpha$ , bradykinin, and leukotrienes are released into the blood circulation. These inflammatory substances act either directly or release agents that act on receptors that promote excitability of neurons involved in pathways of pain transmission (Meyer 2006). To control and manage, pain is a subject of great concern and interest and various drugs are possibly used for this purpose. Most of the drugs used whether non-steroidal anti-inflammatory drugs or aspirin show their effect by inhibiting cyclooxygenases (Fokunang et al. 2018). In humans and rodents, pain perceptions with diurnal variations have been described (Tappe-Theodor and Kuner 2014). It has been found that during dark phase, individuals experienced less pain, whereas in healthy human cases, prolonged delay in pain levels was reported (Tappe-Theodor and Kuner 2014). This phenomenon was possibly attributed to elevated levels of melatonin at night, and with this observation, a number of experimental designs and models were developed. The antinociceptive property of melatonin as reported by early studies demonstrates the involvement of benzodiazepinergic (BZD) and opiate pathways. Besides these, melatonin influences its effects via neurotransmitter systems and associated receptor sites sigma system, BZD, adrenergic, serotonergic, glutamatergic, dopaminergic, and directly via MT1/MT2 receptors (Mantovani et al. 2006). Antinociceptive property is also exerted by nitric oxide molecule interacting via cyclooxygenase (COX) and NMDA receptors (Cury et al. 2011).

## Melatonin and Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 20% of women at reproductive age (Shaikh et al. 2014). PCOS occurs due to the interaction of various environmental and genetic factors. The clinical features associated with PCOS are hyperandrogenism, anovulatory infertility, menstrual irregularity, and obesity and due to these complaints women often seek treatment. Despite the recent developments made in the understanding and treatment procedures over the years, many questions still remain unanswered; however, changing lifestyle including weight loss and nutritional counseling are included in treatment plan. The oocytes, follicular cells, and cytotrophoblasts are some of the sites of melatonin production in the female reproductive system. The receptors of melatonin in the ovary and intra-follicular fluid maintain the secretion of sex steroid at various phases of follicular maturation. During the follicular maturation, melatonin protects the ovarian follicles as it is a strong antioxidant and scavenges free radicals effectively. In the female reproductive physiology, the melatonin effects are mediated via the receptors located in ovarian, hypothalamic, and pituitary sites (Reiter et al.



2009). Melatonin has been known to protect oocytes and developing fetus from oxidative stress (Tan et al. 2003). In women affected with PCOS, the levels of melatonin have been measured by various studies to know about its role in pathogenesis (Luboshitzky et al. 2003, 2004). Some research studies have suggested that the administration of exogenous melatonin improves glucose hemostasis and endothelial vascular function in experimental animal models (Pai and Majumdar 2014). In PCOS individuals, the melatonin intake imparts protective features against reproductive and metabolic abnormalities.

## Melatonin Agonists

As melatonin hormone possesses various beneficial properties as a result of which many agonists of it have been synthesized. In numerous pathologies, a combination of melatonin with other drugs has proven to be quite useful. The therapeutic potential of melatonin molecule is limited because of its short half-life in circulation. Some of the agonists of melatonin are depicted below.

### Agomelatine

It is synthetic and effectively potential agonist of MT1/MT2 receptors. A > 100 fold selectivity is shown by Agomelatine to MT1/MT2 receptors. The half-life of Agomelatine is higher (2 h) as compared to melatonin. In more than 40 countries of the world, this drug is available now in the market and is mostly used for treatment of adult depression (Fornaro 2011; Carney and Shelton 2011). In patients with depressive disorders, this drug relieves symptoms and restores circadian rhythms. Even though the clinical aim of this drug was to target moderate to severe depression, however, this agonist of melatonin has been found to be quite effective in treating GAD, SAD, and BD (da Rocha and Correa 2011). The chronobiotic and sleep inducing effects of Agomelatine are due to its melatonergic receptors located in SCN. In all the research studies conducted so far, Agomelatine has shown good safety and tolerability.

### Tasimelteon

A non-selective agonist of MT1/MT2 receptor family is Tasimelteon drug. This drug has successfully passed Phase III trials where it was found quite effective in improving maintenance and onset of sleep with minimal side effects (Arendt and Rajaratnam 2008).

### Ramelteon

In 2005, FDA approved this drug for treating sleep disorders, insomnia, and other alterations in sleep (Cajochen 2005). This drug is quite selective agonist with high affinity (3–16 times than melatonin) for receptors of MT1/MT2 (Kato et al. 2005). In patients of insomnia with different age groups (18–83 years), this drug was found to elevate total sleep duration in affected individuals (Greenblatt et al. 2007). Furthermore, this drug showed no affinity to MT3, dopamine, benzodiazepine, opiate, and serotonin receptors (Zammit et al. 2009). In the circulation, the half-life of Ramelteon is much longer (1–2 h) than melatonin. In the gastrointestinal tract, about 84% of Ramelteon is quickly absorbed.

### Piromelatine

This drug is agonist of  $5^{HT}_{1A}$ ,  $5^{HT}_{1D}$ , and  $5^{HT}_{2B}$  and is still under development with studies in rodent animal models. This drug has completed Phase II study and its target includes treatment of insomnia, anxiolytic, and antidepressant effects.

## Conclusion

Melatonin is a ubiquitous molecule with wide distribution in nature and is synthesized by animals, humans, plants, fungi, and unicellular organisms. Biologically melatonin mostly acts through G-protein-coupled receptors located in the plasma membrane with  $MT_1$  and  $MT_2$  being the two functional receptors. All mammals express these in different organs of the body including the humans. A wide range of functions is displayed by melatonin like immune regulating, antioxidant, reproduction, puberty timing, hypnotic, oncostatic, mood, behavior, pain and chronobiotic. Deficiencies in the production of melatonin or impaired receptor expression have been linked to various anomalies like obesity, breast cancer, neurological disorders, diabetes, hypertension, prostate cancer, autoimmune disorders, mood disorders, and transplantation. The involvement of melatonin molecule in chronic insomnia and sleep disorders has been found. In decreasing oxidative damage, melatonin function seems to be quite vital. To prevent and treat various disorders, the administration of exogenous melatonin has been used by many clinical trials. Many melatonin agonists have been synthesized and developed with the aim to treat various disorders. A novel clinical area has been formed with the development of new melatonin agonists as they possess better pharmacokinetics. Thus, melatonin is a quite important hormonal molecule in the biological living world.

**Acknowledgements** The corresponding author acknowledges all the authors for their contribution.

**Author Contributions** AA, SBA, MB, MUR, ABW, SMR, and RRB contributed in the writing, editing, preparation of tables/figures, and drafting of the manuscript. All authors confirmed the final version for submission.

**Funding** No source of funding is associated with this article.

**Data Availability** All the data generated have been presented in this article.

## Declarations

**Competing Interests** All the authors declare no competing interests.

**Ethical Approval** Not applicable.

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