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A Review on Melatonin Effect on Immune System by Aging

[1.]VADAKALURI LEELAVATHI*
Bachelor of pharmacy, Krishna Teja Pharmacy College, chadalawadanagar, renigunta road, Tirupathi, Andhra Pradesh- 516101.
Email id: leelavathiod@gmail.com
[2.]Dr. V. JAYASANKAR REDDY, M. PHARM. Ph D
HOD department of pharmacology
Krishna Teja pharmacy college
[3.] Mrs. K. NANDINI M. PHARM
Assistant professor in Krishna Teja pharmacy College, Chadalawadanagar Renigunta road, Tirupathi, andhrapradesh-516101
[4.]THARIGONDA REDDYRANI
Bachelor of pharmacy, Krishna Teja Pharmacy College, chadalawada Nagar, renigunta road, Tirupathi, Andhra Pradesh- 516101.
[5.]PERMI RAJESWARI
Bachelor of pharmacy, Krishna Teja Pharmacy College, chadalawada Nagar, renigunta road, Tirupathi, Andhra Pradesh-516101
[6.]DASARI SONA SINDHIYA
Bachelor of pharmacy, Krishna Teja Pharmacy College, chadalawada Nagar, renigunta road, Tirupathi, Andhra Pradesh- 516101.

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ABSTRACT
Melatonin, a pineal gland-derived hormone, has Known for its diverse physiological functions, including its potential modulatory effects on the immune system. The aging process is associated with a decline in immune function, commonly referred to as immune senescence, leading to increased susceptibility to infections and a diminished ability to mount an effective immune response. Melatonin, known for its role in regulating circadian rhythms and sleep-wake cycles, has also been recognized as an immunomodulator with anti-inflammatory and antioxidant properties. The hormone's ability to regulate immune cell activity as a therapeutic intervention for immune dysfunction.

KEY WORDS
Melatonin, Immune system, T cells, B cells, Mast cells, Hypomelatoninemia Hypermelatoninemia

I. INTRODUCTION

Melatonin is a ubiquitous molecule being found in almost all living organisms [1]. Melatonin is the main hormone secreted by pineal gland [2]. It is an endogenous neurohormone derived from tryptophan, which is an essential amino acid [3]. Pineal gland melatonin synthesis in mammals is timed by the hypothalamic suprachiasmatic nucleus [SCN master clock][4]. Melatonin secretion enhanced by darkness and inhibited by light [2].

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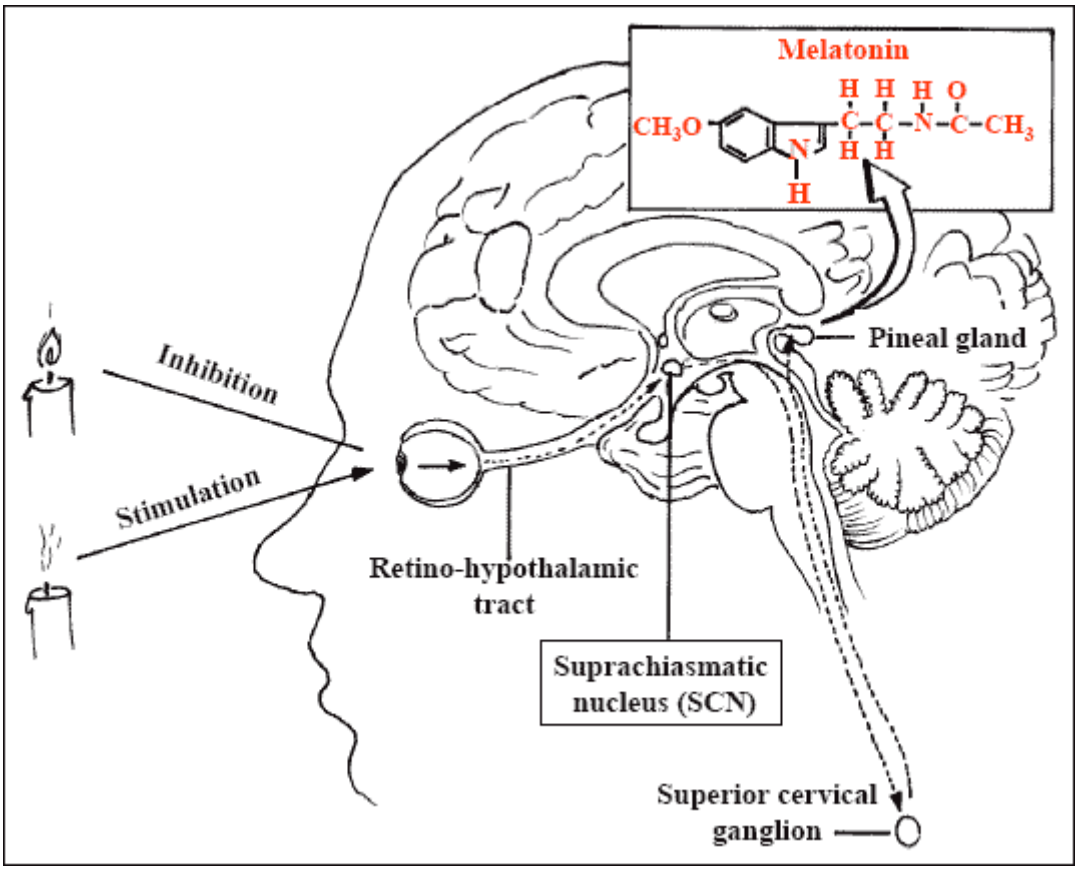
Tryptophan
↓ TPH
5-hydroxytryptophan
↓ AADC
5-hydroxytryptamine (serotonin)
↓ AA-NAT
N-acetylserotonin
↓ HIOMT
N-acetyl-5-methoxytryptamine (melatonin)

[FIGURE 1; SYNTHESIS OF MELATONIN]

The synthesis of melatonin is a multistep process. Firstly, tryptophan is hydroxylated by tryptophan-5-hydroxylase [TPH] to form 5-hydroxytryptophan, which is subsequently decarboxylated to 5-hydroxytryptamine [serotonin] by L-aromatic amino acid decarboxylase [AADC]. Serotonin is N-acetylated by aryl alkylamine N-acetyltransferase [AA-NAT, also called "Time zyme," is the rate-limiting enzyme for melatonin synthesis], to form N-acetyl serotonin, which is converted to N-acetyl-5-methoxytryptamine [melatonin] by N-acetyl serotonin-O-methyltransferase [ASMT, also called hydroxy indole-O-methyltransferase or [HIOMT]. The last step is the rate-limiting step in the biosynthesis of Melatonin [3].



[FIGURE 2; Retino-pineal pathway; noradrenergic fibres originating from superior cervical have their ganglia terminals in the pineal]

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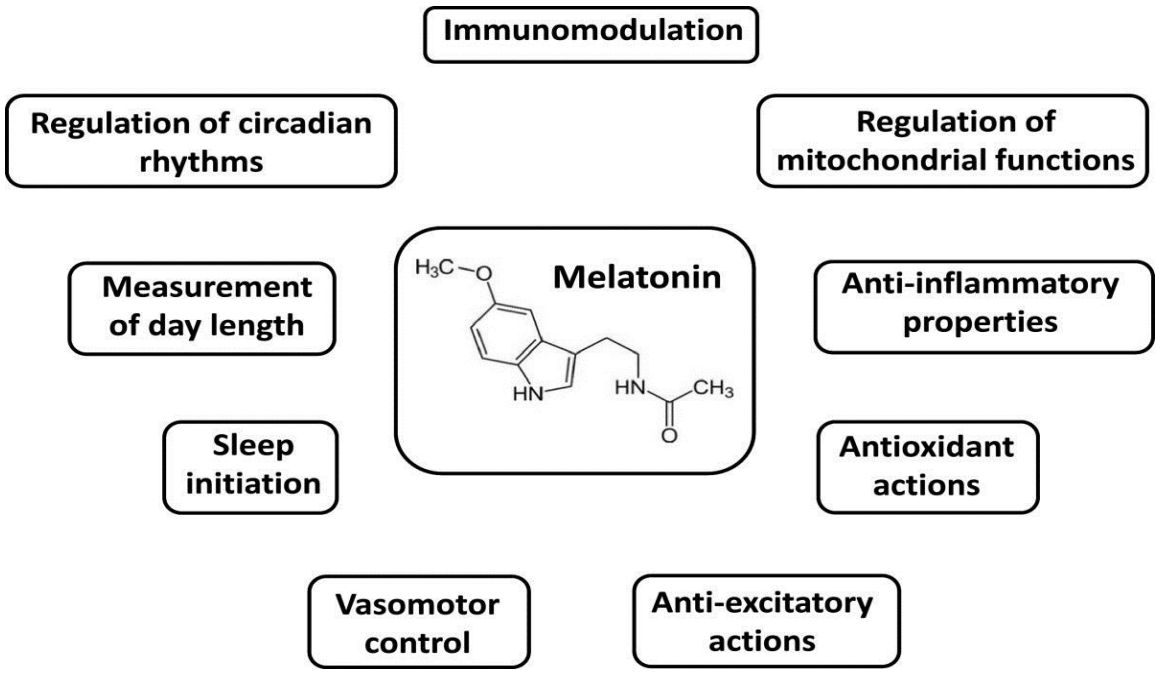
ROLE OF MELATONIN

Melatonin is a natural antioxidant with significant antiaging properties[5].Melatonin has often referred to as a ‘’sleep hormone’’ it plays role in managing sleep wake cycle and circadian rhythm[6].Melatonin regulates various physiologic processes including mood regulation ,anxiety ,sleep , appetite, immune responses and cardiac functions[7].Melatonin provides vital support to the immune system helping coordinate immune responses to defend against a wide variety of threats, including viruses[8].Melatonin may as well be involved in early foetal development, with direct effects on placenta, glial and neuronal development and could play an onto genic role in establishment of diurnal rhythms and synchronization of foetal biological clock[9,10,11].



[FIGURE 3; MELATONIN FUNCTIONS]

MELATONIN LEVELS IN BODY

Pineal melatonin levels vary widely based on your age and sex. New born babies don’t produce their own melatonin before birth they can receive through placenta and after birth, they can receive through breast milk. Melatonin cycle appears when they are2 to 3 months old.

Melatonin levels then continue to increase as your child ages, reaching peak levels right before puberty. Once puberty hits, there’s a steady decrease in melatonin levels until it evens out in the late teens. In all ages after puberty, melatonin levels are higher in women and people assigned female at birth [AFAB] than in men and people assigned male at birth [AMAB].

Melatonin levels are then stable until around age 40, followed by a decline as you continue to age. In people who are over 90 years old, melatonin levels are less than 20% of young adult levels.

Different factors cause the decline in age-related melatonin production, including calcification of your pineal gland, which is very common, and issues with light detection due to eye conditions, such as cataracts.

Melatonin hormonal dysfunction can be classified as hypomelatoninnemia and hyper melatonin nemia.

International Journal of Humanities Social Science and Management (IJHSSM)
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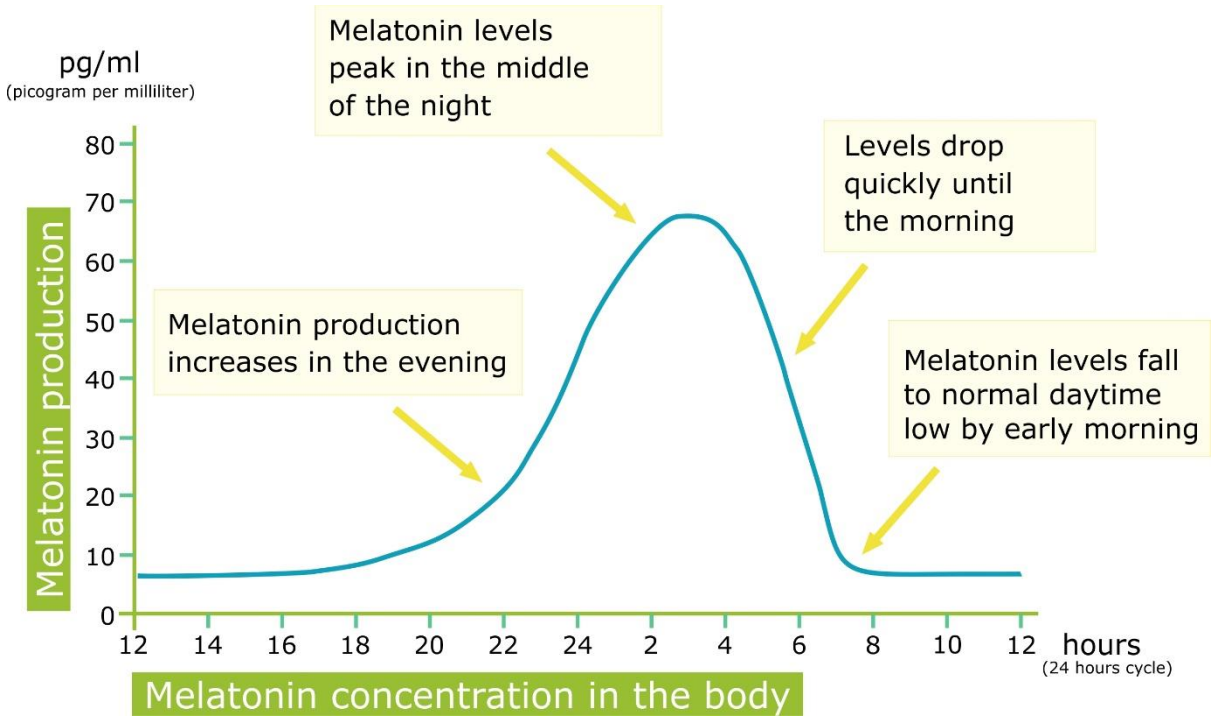

[FIGURE 4; MELATONIN PRODUCTION IN 24 HOUR CYCLE]

HYPERMELATONINEMIA; Hyperproduction of pineal melatonin

Naturally occurring hypermelatoninemia is rare the medical conditions associated with it include;

- Hypogonadotropic hypogonadism
- Anorexia Nervosa
- Polycystic ovarian syndrome
- Spontaneous hypothermia hyperhidrosis
- Rabson Mendenhall syndrome [6]

HYPOMELATONINEMIA; Decreased melatonin nocturnal peak value when compared to what is expected for the age and sex paired population.

Causes of hypomelatoninemia can be primary or secondary. Primary causes are factors that directly affect your pineal gland, and secondary developed as a consequence of primary event, such as systemic disease [e.g.; hyperglycaemia] or environmental factor [e.g.; light at night][1].

Secondary causes are

- Shift work
- Aging
- Neurodegenerative diseases such as Alzheimer's disease and Parkinson disease [6]

Melatonin release rate is 29mg per day, especially starts on between 9.00pm and 10.00 pm. On between 2.00 am and 4.00 am level reaches to peak and by 7.00 am it starts to decrease, concentration during night can rise to 10 times compared to the day time [12].

MECHANISM OF ACTION

Melatonin has endocrine, autocrine and paracrine actions and some of these are receptor mediated while others are direct [13]. The most common melatonin receptors are MT1, MT2 and MT3 membrane receptors which are member of G protein -coupled receptor family [12]. As for its amphiphilicity melatonin is able to cross the cell, organelles, nuclear membranes and directly interact with intra cellular with intracellular molecules called non-receptor mediated actions. In addition to that melatonin also presents receptor mediated actions that result from the interaction of this hormone with both membrane and nuclear receptors [4].

Melatonin acts through different molecular pathways. The best characterized pathway is the activation of two types of membrane specific receptors: high affinity ML1 sites and low affinity ML2 sites [14,15]. The activation of ML1 receptors [16], which are G protein-coupled receptors leads to an inhibition of the adenylate cyclase in target cells. The activation of ML2 receptors, currently called MT3, leads to phospho-inanities hydrolysis. MT3 is expressed in various brain areas and has been shown to be the enzyme quinone reductase 2[17] Two sub-types of the ML1 receptor have been described [18], Mel1a and Mel1b. Mel1a [or MT1] is encoded in human chromosome #4 [4q35.1] and consists of 351 amino

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acids. Mel1a is widely distributed in the *par's tuber Alis* of the anterior pituitary and the SCN of the hypothalamus [which is the anatomic site of the circadian clock], and also in the cortex, thalamus, substantia nigra, nucleus acumens, amygdala, hippocampus, cerebellum, cornea and retina [19]. Mel1b [or MT2] is encoded in human chromosome #11 [11q21-q22] and consists of 363 amino acids. Mel1b is distributed mainly in the retina and secondarily in the hippocampus, cortex, paraventricular nucleus, and cerebellum [20]. Melatonin has also an intracellular action by binding, on the one hand, to cytosolic calmodulin,[21] and on the other hand, to two receptors of the Z retinoid nuclear receptors family [22].

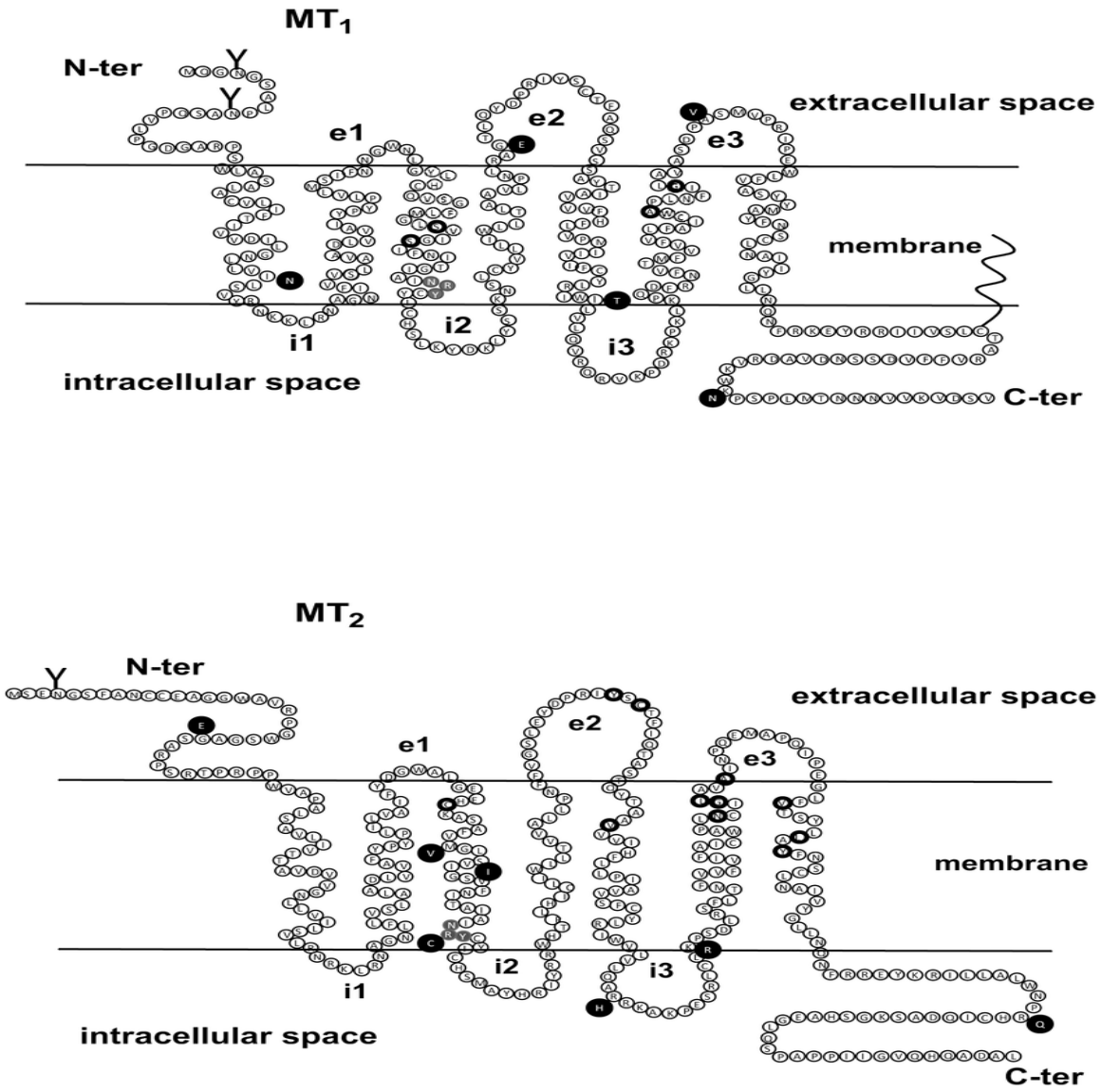

FIGURE 5; Topology of MT1 and MT2 receptors. The amino acid sequence of MT1 [A] and MT2 [B] receptors are shown and amino acids identified in receptor variants are highlighted in black. Amino acids known to be involved in 125I-MLT binding are circled in black. The NRY motif is highlighted in grey [C-Ter, carboxyl terminal domain; e1, e2, e3, extracellular loops 1–3; i1, i2, i3, intracellular loops 1–3; N-Ter, amino terminal domain]

International Journal of Humanities Social Science and Management (IJHSSM)
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DISTRIBUTION AND FUNCTION OF MELATONIN ON IMMUNE SYSTEM

Receptor Type	Distribution	Function	Signaling Pathway
MT1	Human peripheral blood mononuclear cells	Regulation of interleukin-2 production Cytoskeletal actin rearrangement CD25+ expression Regulation of interleukin-2 production	Inhibition of cAMP accumulation Inhibition of T-mitogen dependent proliferation Counteraction of prostaglandin EP3 receptor induced Ca^{2+} influx
	Jurkat cells	Regulation of interleukin-2 production	
	Human T cells	Regulation of interleukin-2 and interleukin-2 receptor (CD25) production	Inhibition of forskolin-stimulated cyclic AMP (cAMP) production, cyclic GMP (cGMP) production and diacylglycerol (DAG) production
	Human monocytes		
	Mouse peritoneal macrophages		Pertussis toxin-sensitive G protein inhibition of adenylyl cyclase
	Rat B cells and T cells		
	Rat spleen and thymus	Maturation of secondary immune response	
	Mouse splenocytes	Increase of proliferation	
MT2	Rat leukocytes	Inhibition of motility (rolling)	
	Chick spleen	Regulation of splenocyte proliferation	
	Jurkat cells	Regulation of of interleukin-2 production	
	Human T cells	Regulation of interleukin-2 and interleukin-2 receptor (CD25) production	cAMP—dependent signaling
	Human peripheral blood mononuclear cells	Modulation of cell life/death balance of human leucocytes	Inhibition of TNF-α Activation of ERK signaling
MT1/MT2	U937 cells	Prevention of apoptosis induced by ultraviolet irradiation	Activation of extracellular signal-regulated protein kinase (ERK) and mitogen-activated protein kinase (MAPK) pathway

* empty columns indicate lack of information.

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Melatonin is a derivative of tryptophan. It binds to melatonin receptor type 1A, which then acts on adenylate cyclase and the inhibition of a cAMP signal transduction pathway. Melatonin not only inhibits adenylate cyclase, but it also activates phospholipase C. This potentiates the release of arachidonate. By binding to melatonin receptors 1 and 2, the downstream signalling cascades have various effects in the body. The melatonin receptors are G protein-coupled receptors and are expressed in various tissues of the body. There are two subtypes of the receptor in humans, melatonin receptor 1 [MT1] and melatonin receptor 2 [MT2]. Melatonin and melatonin receptor agonists, on market or in clinical trials, all bind to and activate both receptor types. The binding of the agonists to the receptors has been investigated for over two decades or since 1986. It is somewhat known, but still not fully understood. When melatonin receptor agonists bind to and activate their receptors it causes numerous physiological processes. MT1 receptors are expressed in many regions of the central nervous system [CNS]: suprachiasmatic nucleus of the hypothalamus [SNC], hippocampus, substantia nigra, cerebellum, central dopaminergic pathways, ventral tegmental area and nucleus acumens. MT1 is also expressed in the retina, ovary, testis, mammary gland, coronary circulation and aorta, gallbladder, liver, kidney, skin and the immune system. MT2 receptors are expressed mainly in the CNS, also in the lung, cardiac, coronary and aortic tissue, myometrium and granulosa cells, immune cells, duodenum and adipocytes. The binding of melatonin-to-melatonin receptors activates a few signalling pathways. MT1 receptor activation inhibits the adenylyl cyclase and its inhibition causes a rippling effect of non-activation; starting with decreasing formation of cyclic adenosine monophosphate [cAMP], and then progressing to less protein kinase A PKA activity, which in turn hinders the phosphorylation of cAMP responsive element-binding protein [CREB binding protein into P-CREB]. MT1 receptors also activate phospholipase C [PLC], affect ion channels and regulate ion flux inside the cell. The binding of melatonin to MT2 receptors inhibits adenylyl cyclase which decreases the formation of cAMP.[4] As well it hinders guanylyl cyclase and therefore the forming of cyclic guanosine monophosphate [CGMP]. Binding to MT2 receptors probably affects PLC which increases protein kinase C [PKC] activity. Activation of the receptor can lead to ion flux inside the cell [23].

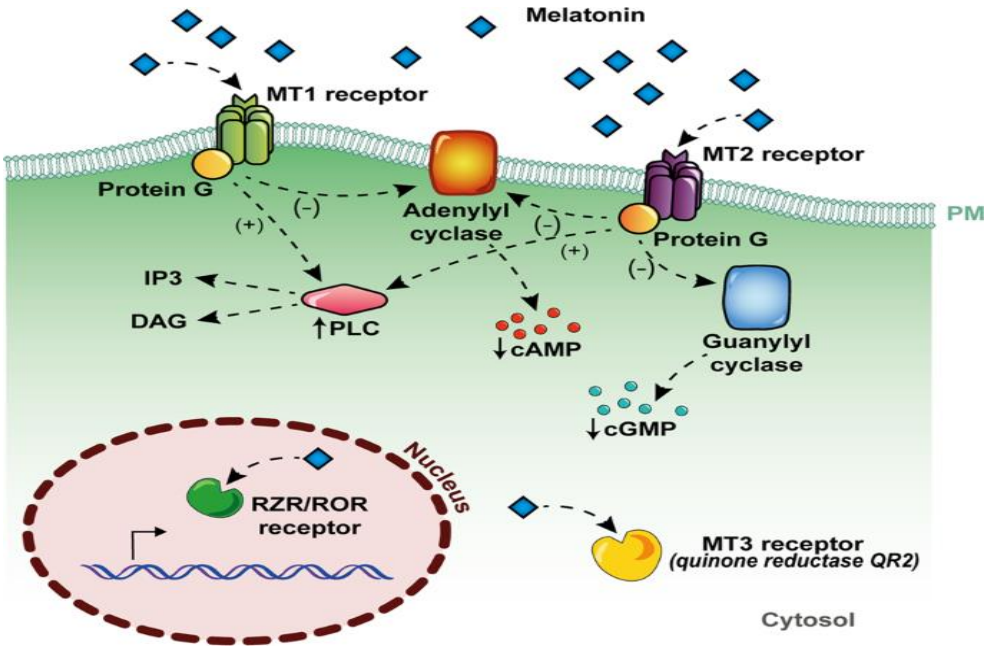

FIGURE 6; Melatonin can exert its effects by acting through receptor-independent mechanisms, which involve the direct interaction of melatonin and other molecules, and they are mainly related to its antioxidant and radical scavenging action [a]. As any other hormone, melatonin can also act through specific cellular receptors, by membrane melatonin receptors, called MT1 and MT2, which are seven transmembrane-spanning proteins belonging to the G-protein-coupled receptor [GPCR] superfamily, by the cytosolic enzyme QR2 [also called MT3], or through the nuclear receptors RZR/ROR [b][24].

International Journal of Humanities Social Science and Management (IJHSSM)
Volume 4, Issue 1, Jan.-Feb., 2024, pp: 974-985 www.ijhssm.org

MELATONIN EFFECT ON IMMUNE SYSTEM:

In recent years much attention has been devoted to the possible interaction between melatonin and the immune system [5]. Melatonin has significant immunomodulatory roles in immunocompromised states. In 1986, Mastroeni et al. first showed that inhibition of melatonin synthesis causes inhibition of cellular and humoral responses in mice. Mice kept under constant light or receiving injections of beta-adrenergic blockers [propranolol] to inhibit melatonin synthesis, exhibited an inability to mount a primary antibody response to sheep red blood cells [SRBC], a decreased cellularity in thymus and spleen and a depressed autologous mixed lymphocyte reaction; all these were reversed by melatonin administration at the late afternoon [25]. Late afternoon injection of melatonin increases both the primary and secondary antibody responses to SRBC][26]. Indeed, the immunoenhancing effect of melatonin was evident only when melatonin was administered in the afternoon or in the presence of T-dependent antigenic stimulation. Since melatonin was ineffective in vitro, Mastroeni and co-workers concluded that it exerts its immunostimulant effect through other neuroendocrine mechanisms in antigen-activated cells [27]. Hamsters exposed to short photoperiods had increased spleen weight and number of splenic lymphocytes and macrophages [28]. A key finding-albeit in young adult humans – with respect to the interplay of melatonin and the immune system, was the observation that the nocturnal rise of blood melatonin in humans correlated with the increase of thymic production of peptides like thymosin-1 alpha and thymine [29].

MELATONIN AND T CELLS

T cells, in addition to have membrane and nuclear melatonin receptors, also have 4 enzymes that needed for melatonin synthesis [aromatic L-amino acid decarboxylase, arylalkyl amine N-acetyltransferase, N□acetyl serotonin methyltransferase, tryptophan hydroxylase] and they can synthesize high amount of melatonin. In committed studies were reported that findings related to melatonin signalisation in the course of T cells development, activation, differentiation and memory [30]. Melatonin stimulates naive T cells differentiation to CD4[+] Th cells (31). It was also decreasing interferon-gamma [IFN-γ] and interleukin-2 [IL-2] production. In contrast to increase IL-4 and IL-10 production. This situation shows that melatonin takes role in immune regulation by suppressing Th1 activity and increasing Th2 cell performance [32]. It was showed that melatonin can be an immune system improving pharmacological agent in older people that has weak immune system by especially increasing CD4[+] T cells function [33]. Studies represented that melatonin increases Treg count without changing amount of them in normal physiologic circumstance in rats which have experimental autoimmune encephalitis. However, as in inflammation, instead of immunosuppression melatonin can decrease Treg amount. Melatonin also effects Ki-67 and Bcl-2 genes amplitude, which is antigen specific T cells differentiation marker protein and which is important for long time protection of Tm cells, respectively [34].

MELATONIN AND B CELLS

It has been reported that melatonin application increases antigen presentation by spleen macrophages and antibody response of B cells against to antigens [32]. Melatonin increases IL-4 release from Th2 cells, in contrast, it inhibits IL-2 and IFN-γ release from Th1 cells. Melatonin is increased IL-4 release stimulated by leads to improvement of transmitted signals to B cells and by this way it leads to increased IgG1 production [35]. Also, there are studies report that melatonin prevention from apoptosis during B lymphocytes formation in rat bone marrow [36].

MELATONIN AND NK [NATURAL KILLER] CELLS

Melatonin and NK (Natural killer) Cells Melatonin is generally a strong immune regulator that increases NK cells cytotoxicity. In a part of melatonin effectivity against to cancer, mediation of increased Knell cytotoxicity is thought [37]. Possible reason for increased NK cells lytic effect is amplified IL-2 production by Th cells [38].

MELATONIN AND MAST CELLS

During inflammatory process, NF-dB [nuclear factor kappa B] pathway that activated by mast cells stimulates melatonin synthesis by arylalkyl amine Acetyltransferase [AA-NAT] enzyme. Mast cells that carry MT1 and MT2 receptors [39], structurally can synthesize endogen melatonin [34]. Melatonin binding to MT1 and MT2 receptors and it leads to inhibition of NF-dB activation and by decreasing IL-6, IL-13 and tumour necrosis factor-alpha [TNF-α] cytokines level it negatively regulates mast cell activation, proliferation and differentiation [40]. In a study was committed in 2019 it was observed that melatonin treatment in

International Journal of Humanities Social Science and Management (IJHSSM)
Volume 4, Issue 1, Jan.-Feb., 2024, pp: 974-985 www.ijhssm.org

animals which are under the effect of influenza A virus, increased survival rate by significantly decrease TNF-α, Il-6 and IFN-γ expression [41].

ANTIOXIDANT EFFECT

Though sleep regulation by administration of melatonin was known in early 1960s [37], melatonin's anti-oxidant ability was not discovered until many decades later. The first experiments with plausible confirmation melatonińs antioxidant properties were described in the 1990s. Surprisingly, the studies showed the superiority of melatonin antioxidant capacity when compared with standard endogenous antioxidants present in the same molar concentration. Namely, melatonin was proved to be more potent than vitamin E, ascorbic acid, and glutathione [43,44]. Compared to standard hydrophilic antioxidants, melatonin can simply cross the blood brain barrier but remains partially soluble in water [45]. Melatonin acts as a terminal [or suicidal in some sources] antioxidant. It has quite high antioxidant potency when compared with the other indoles [46]. The des-ignition terminal antioxidant for melatonin indicates that melatonin is oxidized into products such as 6-hydroxymelatonin ,3-hydroxymelatonin and N-acetyl-N-formyl 5-methoxykynurenamine [47]. The products of oxidation cannot simply be converted to melatonin by oxidation of a substrate. It is unlike the other endogenous antioxidants that can act as pro-oxidants once oxidized. The superiority of melatonin as an antioxidant when compared with the other low molecular weight antioxidants can likely be explained by two reasons. Firstly, melatonin can inhibit enzymes producing reactive oxy-gen [e.g., quinone oxidoreductase]and nitrogen species [e.g., NOS], as mentioned previously. Secondly, melatonin works through other stoichiometry than the other anti-oxidants. It is believed that one molecule of melatonin can scavenge at least 10 reactive oxygen or nitrogen species [48]. In addition to those effects, melatonin has been proposed to regulate enzymes that participate in fighting with oxidative stress the so-called high molecular weight antioxidants [49,50]

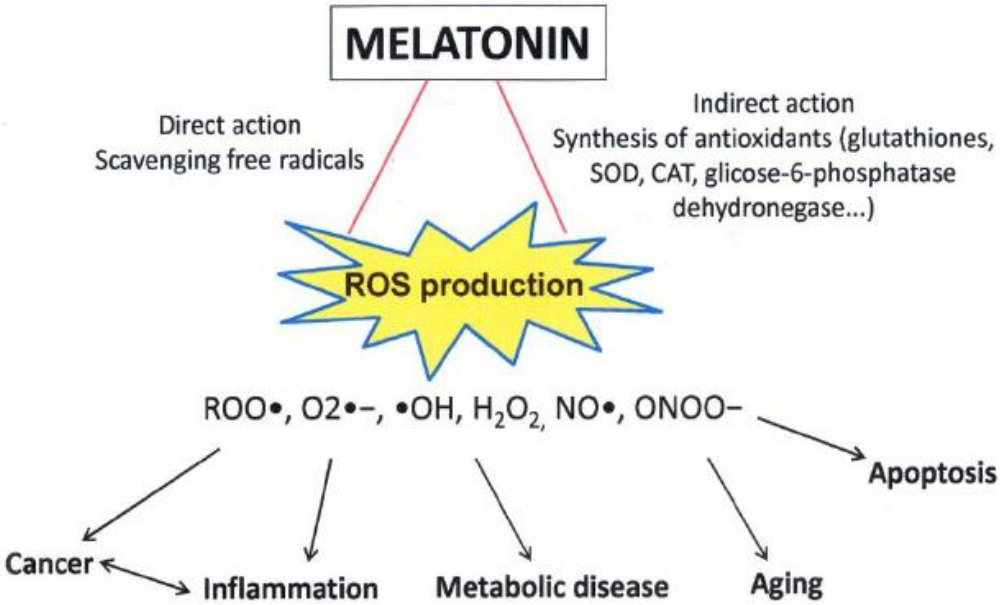

FIGURE 7; Melatonin' actions as natural antioxidant on ROS generation and potential applications in some human diseases. SOD: superoxide dismutase, CAT: catalase, ROS: reactive oxygen species, ROO•: lipid hydroperoxide, O2•−: superoxide anion, •OH: hydroxyl radical, H 2 O 2: hydrogen peroxide, NO•: nitric oxide, ONOO−: nitrite peroxide.

II. CONCLUSION

Melatonin takes major role in maintain of circadian rhythm and also has a strong antioxidant role. It has a strong immune-modulatory function on immune system by directly different receptors mediated mechanisms or it created by indirect effects. As result of having beneficial effects on T lymphocytes, B lymphocytes, NK cells and macrophages', melatonin is necessary for physiological functions' stabilisation especially in immune system. As we've explored throughout this presentation, melatonin, primarily known for its involvement in regulating sleep-wake cycles, also exhibits significant effects on the immune system. The key takeaways include Melatonin plays a multifaceted role in immune function, acting as both an antioxidant and an immune modulator. Its ability to regulate inflammatory responses and protect against oxidative stress positions it as a crucial player in maintaining immune balance.

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