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REVIEW OF PROTECTIVE EFFECTS OF MELATONIN ON NEUROLOGICAL DISORDERS AND OXIDATIVE STRESS

REVISÃO DOS EFEITOS PROTETORES DA MELATONINA SOBRE TRANSTORNOS NEUROLÓGICOS E ESTRESSE OXIDATIVO

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Abstract: Melatonin (MLT) is a neuro-hormone produced and secreted by the pineal gland and other organs/tissues of mammalian animals. It has been stated that MLT regulates the circadian rhythm in vertebrates, besides acting as antioxidant and anti-inflammatory substance in the nervous system. Since oxidative stress is linked to different neurological disorders, it is essential to study the protective effects of MLT on nervous system. Therefore, this review aimed to highlight relevant information regarding the benefits of MLT in the protection of neurological disorders and oxidative stress. For that, it was conducted an integrative literature review of scientific articles published in the last decade, using English descriptors and databases available online, such as Medline, PubMed, and Science Direct. The results here summarized from the analysis of the articles pointed out in different ways the protective effects of MLT in several nervous system regions of laboratory models of mammalian animals through its antioxidant and inflammatory properties, as well as the formation of its secondary metabolites. MLT is capable of scavenging free radicals, which contributes to ameliorate the oxidative stress condition generated in the neurological disorders generally promoted by sleep deprivation, hypobaric hypoxia, and ischemia reperfusion. In short, the information highlighted in this review reaffirms MLT as a promising potential substance used in the treatment of neurological disturbances, including neurodegenerative diseases. It is expected that further clinical and laboratory studies, especially conducted in human beings, can fully enable the use of this neuro-hormone by clarifying in details the mechanisms by which it acts on the nervous system to protect it from neurological disorders and oxidative stress.

Keywords: Melatonin. Neurological Disorders. Oxidative Stress.

Resumo**:** A melatonina (MLT) é um neuro-hormônio produzido e secretado pela glândula pineal e por outros órgãos/tecidos de animais mamíferos. Foi relatado que a MLT regula o ritmo circadiano em vertebrados, além de atuar como antioxidante e anti-inflamatório no sistema nervoso. Uma vez que o estresse oxidativo está ligado a diferentes distúrbios neurológicos, é essencial estudar os efeitos protetores da MLT no sistema nervoso. Portanto, esta revisão teve como objetivo destacar informações relevantes sobre os benefícios da MLT na proteção de distúrbios neurológicos e estresse oxidativo. Para tanto, foi realizada uma revisão integrativa da literatura de artigos científicos publicados na última década, utilizando descritores em inglês e bases de dados disponíveis online, como Medline, PubMed e Science Direct. Os resultados aqui sumarizados a partir da análise dos artigos apontaram de diferentes formas os efeitos protetores da MLT em várias regiões do sistema nervoso de modelos laboratoriais de animais mamíferos por meio de suas propriedades antioxidantes e inflamatórias, bem como a formação de seus metabólitos secundários. A MLT é capaz de eliminar os radicais livres, o que contribui para melhorar a condição de estresse oxidativo gerado nos distúrbios neurológicos geralmente promovidos pela privação do sono, hipóxia hipobárica e isquemia reperfusão. Em suma, as informações destacadas nesta revisão

reafirmam a MLT como uma substância potencial promissora usada no tratamento de distúrbios neurológicos, incluindo doenças neurodegenerativas. Espera-se que novos estudos clínicos e laboratoriais, principalmente realizados em seres humanos, possam viabilizar plenamente o uso desse neuro-hormônio, esclarecendo em detalhes os mecanismos pelos quais ele atua no sistema nervoso para protegê-lo de distúrbios neurológicos e do estresse oxidativo.

Palavras-chave: Melatonina. Distúrbios Neurológicos. Estresse Oxidativo.

1. Introduction

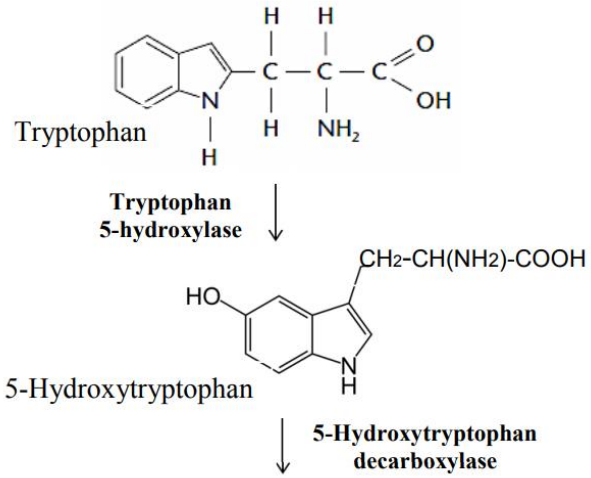
Melatonin (MLT) (or N-acetyl-5-methoxytryptamine) is a neuro-hormone presented in the chemical group of indolamines, secreted mainly by the pineal gland of mammalian animals (CARRASCAL et al., 2018), but secreted in smaller quantity by the retina (CHEN et al., 2016), bones, skin, platelets (BALI et al., 2016), bile, thymus, spleen, testis and ovaries (ROCHA et al., 2011; ASGHARI et al., 2016). In addition, other organs and tissues can release MLT at lower concentrations, such as, the extra orbital lacrimal gland, the gastrointestinal tract (KIM; LEE; LEE, 2014), as well as the brain, the marrowbone and the respiratory epithelium (DZIEGIEL; OKOLOW-PODHORSHA; ZABEL, 2018).

Historically, MLT was discovered in 1958 by the dermatologist Aaron Lerner and collaborators (LERNER et al., 1958), and it received this name due to its ability to contract the melanocytes of frog's melanophores, resulting in skin lightening in these animals (CLAUSTRAT; BRUN; CHAZOT, 2015). Based on this discovery, it was announced a new field of research in reproductive physiology and its relevant implications for the mechanisms of the circadian cycle (REITER et al., 2009).

Currently, it is known that light is characterized as the main environmental factor involved in the MLT biosynthesis regulation in the nervous system by mediating the regular information of the circadian cycle (HADUCH et al., 2016; ZHANG et al., 2017; GUNATA; PARLAKPINAR; ACET, 2020). During the day light, the suprachiasmatic nucleus is active and, due to its GABAergic inhibitory action on the paraventricular nucleus, there is no noradrenergic stimulation of the pineal gland (COOMANS; RAMKISOENSING; MEIJER, 2015). On the other hand, during the night time, the suprachiasmatic nucleus is inactive. Therefore, there is the activation

of the pineal gland along with the production of the MLT, which is released by the pinealocytes (REITER, 1991; JIMÉNEZ-HEFFERNAN et al., 2015).

In previous researches, it was hypothesized that MLT is synthesized in the cytosol of cells, but recent findings have shown that mitochondria are the original site of melatonin biosynthesis (LEUNG et al., 2020). The MLT biosynthetic pathway starts from the conversion of the amino acid tryptophan to 5-hydroxytryptophan through the action of tryptophan-5-hydroxylase (T-5-H) (ROCHA et al., 2011). Following this process, the enzyme 5-hydroxytryptophan decarboxylase (5-HTD) catalyzes the oxidation of 5-hydroxytryptophan to serotonin (PANDI-PERUMAL et al., 2008). Sequentially, serotonin is converted to N-acetylserotonin through the acetylation reaction performed by the enzyme N-acetyltransferase (NAT) and, finally, the enzyme acetylserotonin O-methyltransferase catalyzes the methylation reaction for the formation of MLT (REITER et al., 2009). This enzyme is the limiting factor in the production of this neuro-hormone (MACCHI; BRUCE, 2014) (Figure 1).



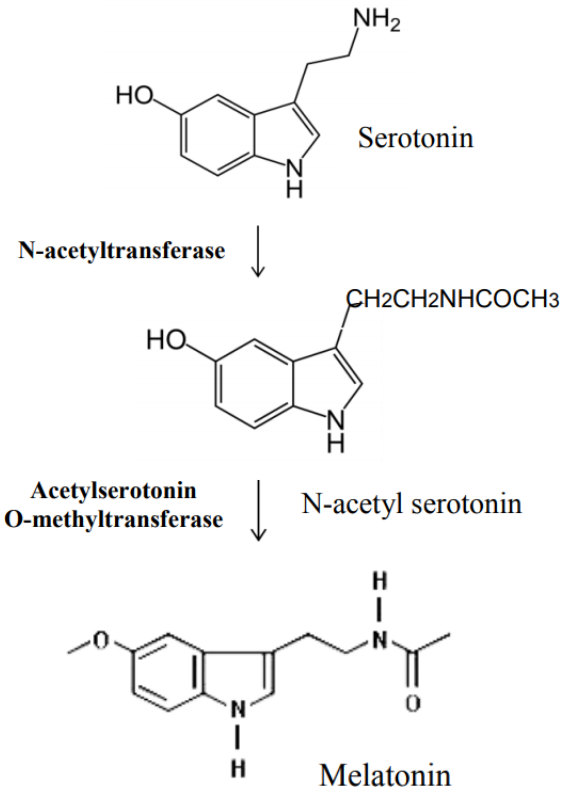


Figure 1 - Biosynthetic pathway of MLT. Source: Authors (2021).

After being produced and released, MLT acts on different systems in the body. In addition to its chronobiological function on the nervous system, studies have demonstrated other functional properties of MLT: antioxidant, by regulating pro-oxidants involved in the synthesis of nitric oxide and lipoxygenases, as well as to stimulate the activity of other antioxidant enzymes including superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase (LEE et al., 2016; GUNATA; PARLAKPINAR; ACET, 2020; WANG; GAO, 2021); anti-inflammatory, through the inhibition of prostaglandins and by regulating cyclooxygenase 2 (COX 2) (MAYO et al., 2015; SONG et al., 2014, ASGHARI et al., 2016; CHEN; ZHANG; LEE, 2020); and anti-apoptotic, by inhibiting unregulated mitosis and by suppressing linoleic acid reuptake (MOLPECERES et al., 2007; BLASK, SAUER; DAUCHY 2012; CARRASCAL et al., 2018).

Due to this wide range of functional properties, MLT is able to play an important role in the neuroprotection against the neurological disorders, particularly the neurodegenerative diseases, such as, Parkinson's and Alzheimer's Diseases, as

well as ischemia injuries, hypobaric hypoxia and Sleep Deprivation (SD) (ALONSO et al., 2015; HUANG et al., 2015; MONTEIRO et al., 2017; VINCENT, 2018). Since oxidative stress is linked to these different neurological disorders, it is essential to study the protective effects of MLT in the nervous system. In this aspect, this review aimed to highlight relevant information regarding the protective effects of MLT against neurological disorders and oxidative stress, thus reaffirming it as a promising potential antioxidant used in treatment of these harmful conditions.

2. Material and Methods

This study is characterized as an integrative literature review of an exploratory and investigative field, which allows the gathering of different information in order to formulate general conclusions about a given area of knowledge, through a synthesis of studies published in different databases (NETO et al., 2021). For that, the following steps were conducted:

I. Identifying the theme and selecting the research hypothesis for the elaboration of the integrative review;
II. Establishing the inclusion and exclusion criteria for studies or literature search;
III. Defining the information to be extracted from selected studies/categorization of studies;
IV. Evaluating the studies included in the integrative review;
V. Result interpretation;
VI. Presentation of the review/synthesis of knowledge.

The sources used in this research were: *Medical Literature Analysis and Retrieval System Online* (MEDLINE), *National Library of Medicine National Institutes of Health* (PUBMED), in addition to *Scientific Electronic Library Online* and *Science Direct*, it was used the advanced method search, the category title, abstract and keywords (NETO et al., 2021). In each database, the subject descriptors of the *Medical Subject Heading (MeSH) of PubMed* were delimited and crossed by using the terms “AND”/“OR”: “Protective Effects of Melatonin on Nervous System”, OR

“Antioxidant Action of Melatonin on Nervous System”, AND “Induction of Oxidative Stress on Nervous System” OR “Oxidative Stress Induced by Neuroinflamation”.

The articles were then submitted to a filtering process consisting of the inclusion criteria: articles available electronically with full text online; in time horizon, classified as original articles; primary studies, published in English. It followed the methodology previously described in the study carried out by Neto et al., (2021). The temporal scope of publication included works published in the last decade (Figure 2).

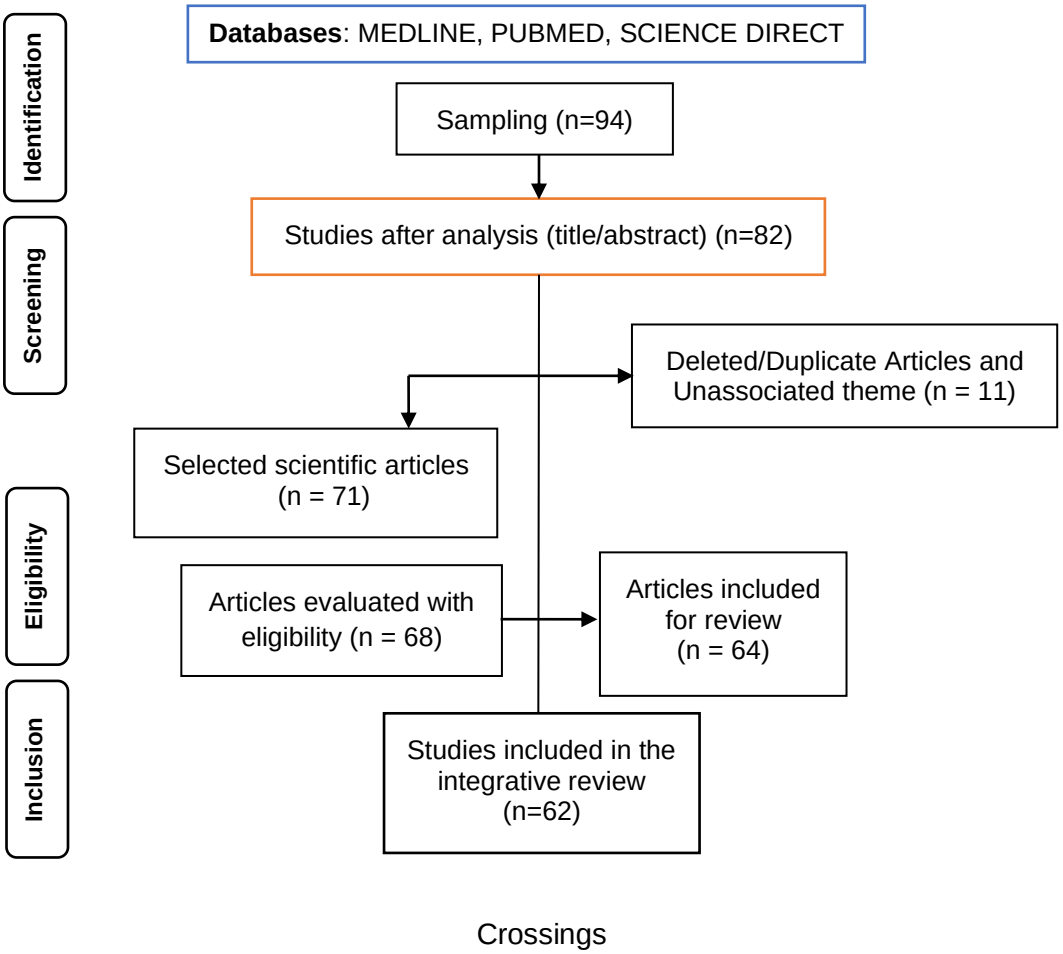


Figure 2 – Flowchart of the article search and selection process. Source: Scheme developed by the authors based on the methodology proposed by Neto et al., (2021).

3. Results and Discussion

The articles showed the protective effects of MLT in different regions of the nervous system of mammalian animals used as models in clinical and laboratory studies, specifying some of the mechanisms by which this neuro-hormone protects the nervous system against neuronal disorders and oxidative damage caused by a variety of internal and external factors, such as: sleep deprivation, hypoxia, ischemia, among others. Most of the analyzed studies pointed that the neuroprotective effects of MLT were directly or indirectly efficient on reducing the reactive species generated during the oxidative stress that cause damage to the nervous cells, as well as to the neurogenesis process. Part of these neuroprotective effects is attributed to the antioxidant and inflammatory properties of MLT, besides the formation of its secondary metabolites produced by the degradation of the neuro-hormone into N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and N-acetyl-5-methoxykynunamine (AMK), whose activities increase the action of enzymes antioxidants, as well as inhibiting the activity of pro-inflammatory mediators.

Indeed, pharmacological and toxicological studies of clinical interest have demonstrated such properties of MLT in several organs and body systems through the free radicals scavenging, including hydroxyl (OH^-), peroxyl (ROO^-), and superoxide (O^{2-}) radicals (ZHANG et al., 2017). Because of its ability to sequester both Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), MLT is able to reduce oxidative stress by eliminating excess hypochlorous acid, nitric oxide, peroxynitrite anion and hydrogen peroxide formed in this process. By definition, oxidative stress is a condition in which occurs an imbalance between the reactive generated species and the body's production of endogenous antioxidant substances, leading to changes in cells functions, and finally to the cells death (SILVA et al., 2004; DA SILVA; 2018).

However, it is important to take into account that reactive species can play some roles for the maintenance of the normal cell functions when at cytostatic levels (VIANA et al., 2020). Thereby, it contributes to the viability of basic cellular processes, such as, cell differentiation and proliferation (RAY; HUANG; TSUJI, 2012; BALDISSERA et al., 2019). On the other hand, at cytotoxic levels there is an increase production of ROS and RNS, and it triggers oxidative stress, which leads to cell damages (MITTLER, 2017). Important factors may contribute to the increase of

the production of reactive species, among them stand out herbicides, foods with high levels of fat and sugar, and different medications, as well as inflammatory neurogenesis impairments promoted by sleep deprivation (SD), lipopolysaccharide (LPS), hypoxia hypobaric (HH), ischemia reperfusion, and also neurodegenerative diseases (FENG et al., 2012; HARDELAND et al., 2012; SONG et al., 2014; ARIOZ et al., 2019; LEUNG et al., 2020; WANG; GAO, 2021).

3.1. MLT and Sleep Deprivation (SD)

It has been suggested that SD leads to oxidative stress as a result of changes in the membrane functions, protein damage, and it also reduce the intracellular antioxidant defenses in different areas of the brain (GUZMAN-MARIN et al., 2005). Hence, SD can suppress neurogenesis in different nervous system regions and it can also cause adverse effects on neurological behavioral outcomes (HAIRSTON et al., 2015). Laboratory evidence has shown that systemic or central administration of MLT effectively prevents neuronal damage in animals with SD by promoting the minimization of oxidative stress and by rescuing the neurogenesis deficits as well (CHANG; WU; LUAN, 2019; LEUNG et al., 2020).

In this context, Zhang et al., (2017) investigated the effect of exogenous MLT against the SD-induced oxidative stress in rats. The observational results showed that SD induced an anxiety-like behavior, whereas the treatment with MLT prevented these changes. Accurate analysis of malondialdehyde (MDA) levels and superoxide dismutase (SDO) enzymatic activity revealed a decrease in oxidative stress after the treatment with MLT, thereby giving indications of its antioxidant action in the nervous system of animals treated with this neuro-hormone (Table 1).

In another relevant study, Huang et al., (2014) investigated whether MLT supplementation prevents neuropathic symptoms and the increase of the microglial activation in the cuneal nucleus in a Model Rat Chronic Nerve Injury (MRCNI) during the SD period. Histological analyzes from the brain tissue revealed that MLT administration during SD significantly attenuated the microglial activation and the development of neuropathic pain, as well as the decrease of pro-inflammatory cytokines concentration responsible for leading to cascades of inflammatory

processes (Table 1). Additionally, Hinojosa-Godinez et al., (2019) analyzed the effects of MLT in cell proliferation in dentate gyrus of the hippocampal region of mice in long-term SD. MLT was able to restore the SD-induced reduction in the number of Neural Stem Cells (NSCs) by increasing the levels of methyl-CpG-binding protein 2 (MECP2) and by decreasing the levels of Sirtuin 1 (SIRT1) (Table 1).

Table 1 - Main findings regarding the protective effects of MLT in SD.

Oxidative stress induction	Nervous System Regions	MLT actions	Citations
Sleep Deprivation (SD)	Central Nervous System	Prevention against the progressive neuronal damage	Chang, Wu and Luan (2019)
		Decreased levels of pro-oxidant enzymes	Zhang et al., (2017)
	Brain and Cuneate Nucleus	Attenuation of microglia activation and decrease in neuropathic pain	Huang et al., (2014)
		Decreased levels of pro-inflammatory cytokine	Guzman-Marin et al., (2005)
	Dentate Gyrus of the Hippocampus	Restoring the reduced number of NSCs	Hinojosa-Godinez et al., (2019)
		Increased levels of methyl-CpG-binding protein 2	
		Decreased levels of Sirtuin 1 (SIRT1)	
		Protection against suppression of NSC	Sompol et al., (2011)

	proliferation	
	Prevention of reducing cell proliferation and cognitive deficits	Iggena et al., (2017)

3.2. MLT and Hypobaric Hypoxia (HH)

Hypobaric Hypoxia (HH) is a condition in which the partial pressure of oxygen in tissues/cells is reduced, consequently causing physiological and psychological dysfunctions, especially in the nervous system (MILLET; FAISS; PIALOUX, 2012; VORNICESCU et al., 2013). MLT has also been reported to protect the nervous system against HH. In this perspective, Huang et al. (2015) verified whether the MLT treatment might positively affect the expression of the nitric oxide system and protein nitration by providing neuroprotection against oxidative stress induced by HH in the hippocampal region of rats. The results obtained from the immunological and histochemical analyzes suggested that the administration of exogenous MLT prevented the symptoms produced by the hypobaric hypoxia by decreasing the microglial activation and the production of pro-inflammatory cytokines in the ischemic hippocampus (Table 2).

Similar results were observed in the study conducted by Wang et al. (2013), in which MLT attenuated neurobehavioral deficits (locomotor functions, and hyperactivity) by improving learning and memory performance. Besides, to reduce microglial activation, TNFα, interleukin-1β, and nitric oxide levels. MLT also increase the neuronal precursor cells after hypoxia; hence, it decreases cell death in the hippocampus of the rats (Table 2). Of note, when mouse cortical Neural Stem Cells (NSCs) were treated with MLT before being subjected to hypoxia incubation with N_2 and CO_2, the proliferation and neuronal differentiation of NSCs were restored by phosphorylation of certain molecules via the MT1 receptor (FU et al., 2011) (Table 2).

Table 2 - Main findings regarding the protective effects of MLT in HH.

Oxidative stress induction	Nervous System Regions	MLT actions	Citations

Hypobaric hypoxia (HH)	Hippocampus	Reduction of ischemia in the hippocampus region	Huang et al. (2015)
		Decreased in microglial activation and production of pro-inflammatory cytokines	
		Improvement in short and long term neurobehavioral deficits	Wang et al. (2013)
		Attenuation of the hippocampal impairments after hypoxia	
		Increased proliferation and neuronal differentiation of NSCs during hypoxia	Fu et al., (2011)

3.3. MLT and Ischemia Reperfusion Injury (IRI)

Ischemia-Reperfusion injury (IRI) is defined as the exacerbation of cellular dysfunction and death, following restoration of blood flow to a previous ischemic tissues, which paradoxically causes further damage by threatening the function and viability of the organs (COWLED; FITRIDGE, 2011). According to the same authors, ROS has a destructive role in mediating tissue damage during IRI. Once the ischemic tissue is reperfused, an influx of molecular oxygen catalyzes xanthine oxidase to degrade hypoxanthine to uric acid, so that liberating the highly reactive superoxide anion (O_2^-), which is subsequently converted to hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH^\bullet$) (COWLED; FITRIDGE, 2011).

As previously mentioned, MLT is able to reduce oxidative stress by eliminating ROS excess, and as consequence it can be used to mitigate the damages in IRI. To illustrate this, Chern et al., (2012) performed an assay in which they induced the mice to a Moderated Cerebral Ischemic/ Reperfusional injury (MCI/R), and it was found that the MLT treatment could reduce the post-stroke free

radical production by increasing the number of the neuroblasts and proliferative cells in the peri-infarcted cortex area (Table 3). Similar to this, male rats were taken to a Moderated Cerebral Artery Occlusion (MCAO), which conduced to focal cerebral IRI.

Moreover, MLT (intraperitoneally injected) was able to reduce the chances of having an infarct and damages to the white matter in the subventricular zone of the brain. After the focal cerebral ischemia being held, the molecular analysis showed a down regulation of inflammatory factors, including TLR4, NF-κB, and IL-1β (ZHAO et al., 2019). MLT also protected the nerve fibers from ischemic degeneration and it decreased the edema, as well as the damage in the myelin sheaths and axons caused by the IRI in the rat sciatic nerve (SAYAN et al., 2014) (Table 3).

Table 3 - Main findings regarding the protective effects of MLT in IRI.

Oxidative stress induction	Nervous System Regions	MLT actions	Citations
IRI	Cortex	Attenuation of blood-brain barrier lesions and reduced free radical production	Chern et al., (2012)
	Subventricular zone and white matter area	Attenuation of white matter damage by regulating the TLR4/NF-κB pathway	Zhao et al., (2019)
	Sciatic Nerve	Increase Super Oxide Dismutase levels (SOD)	Sayan et al., (2014)

3.4. MLT and Lipopolysaccharide (LPS)

Experimental studies conducted in laboratories have demonstrated the neuroprotective effect of MLT against neuroinflammation induced by LPS, a condition that can also trigger oxidative stress in the nervous system. Due to its ability to inhibit

some important inflammatory pathways, such as, cyclooxygenase 2 (COX 2), MLT is able to regulate either the increased production of prostaglandins or pro-inflammatory enzymes in damaged tissues (Table 4) (MAYO et al., 2015; CARRASCAL et al., 2018; WANG; GAO, 2021).

For instance, Song et al. (2014) determined the effect of MLT on Neural Stem Cells (NSCs) against lipopolysaccharide (LPS)-induced neuroinflammation in the nervous system of rats. The authors suggested that MLT inhibited the production of nitric oxide (NO) and protected the NSCs against oxidative stress caused by neuroinflammation by reducing the levels of pro-inflammatory cytokines, which trigger specific phosphorylation cascades that, ultimately, lead to the inflammatory process (Table 4). In comparison, Arioz et al., (2019) assessed the effects of MLT on behavioral changes and inflammatory cytokine expression in the hippocampus of mice in LPS-induced depressive-like behavior (DLB). The results showed that MLT prevented NLRP3 inflammasome activation induced by the LPS in murine microglia *in vitro*, which was evidenced by the inhibition of NLRP3 expression, caspase-1 cleavage, as well as the interleukin-1β (IL-1β) secretion (Table 4).

Table 4 – Protective effects of MLT in LPS-induced neuroinflammation and in DLB.

Oxidative stress induction	Nervous System Regions	MLT actions	Citations
Lipopoly-saccharide (LPS)	Dentate Gyrus and Hilar Zone of Hippocampus	Reduced IL-18-induced inhibition of proliferation, neurosphere formation, and neuronal differentiation	Li et al., (2017)
		Ameliorates Neural Stem Cells (NSCs) progression and neuronal differentiation	Wang et al., (2017) Ghareghani et al., (2017)
		Decreased levels of inflammatory cytokine expression in hippocampus	Song et al., (2014) Wang, Gao (2021)
		Increased oligodendrocyte	Alluri et al., (2016)

	differentiation in cultured NSCs	Ghareghani et al., (2017)
	Prevents NLRP3 inflammasome activation induced by the LPS	Arioz et al., (2019)

3.5. MLT and Neurogenesis Impairments

Neurogenesis impairments can be caused by depression, pinealectomy, aging, environmental factors and neurodegenerative diseases (YOO et al., 2012; HOEHN et al., 2016; CHEN; ZHANG; LEE, 2020; LEUNG et al., 2020). It has been stated that MLT provides a decline in the neurogenesis deficits through the formation and maturation of dendrites in neurons and in preexisting interneurons from specific regions of the nervous system (FIGUEIRO-SILVA et al., 2018). For instance, it was shown that MLT promotes a differentiation of new nervous cells in the hilar zone of the hippocampal region of mice and rats (ALONSO et al., 2015). In dentate gyrus of the hippocampal region, MLT could increase the number of neuronal precursor cells, as well as to modulate both dendrite maturation and complexity of new-born neurons in mice (RAMÍREZ-RODRÍGUEZ et al., 2020) (Table 5).

Furthermore, Morley-Fletcher et al., (2011) observed through the survival of the proliferative cells and the increase of the neurogenesis in dentate gyrus that MLT could reduce depression and anxiety-like behavior in female rats taken to prenatal restraint stress. Similarly, Hoehn et al., (2016) observed an improvement in neurogenesis process in the hippocampus of mice after the treatment with MLT, whose actions could, similarly, decrease the depression and anxiety-like behavior. It was also reported by Stefanovic et al., (2016) a decrease in depression-like symptoms after MLT intraperitoneally being injected in wistar rats. The analysis of the underlying molecular mechanisms showed a decrease in vesicular monoamine transporter 2 (VMAT2) expressions and an increase in Monoamine Oxidase A (MAO-A) expression (Table 5).

Besides depression, the roles of MLT on neurogenesis were further confirmed by the loss-of-function pinealectomy experiments, in which the pineal

gland (the primary production site of MLT) is surgically removed from the animals (LEUNG et al., 2020). In this case, the low production or the absence of MLT can negatively affect the expression of some receptors for this neuro-hormone in neurons from the cortical layer of the hippocampus CA3 region (OZACMAK; BARUT; OZACMAK, 2009, FENG et al., 2012). Indeed, after the rats being pinealectomized, the levels of MLT decreased and the neurogenesis in the hippocampus declined (RENNIE; DE BUTTE; PAPPAS, 2019). Since MLT is involved in the chronobiological functions of mammalian animals, this fact consequently results in dysregulation of the hippocampus physiology in the light/dark cycle (PANDI-PERUMAL et al. 2008; MUSSHOFF et al., 2012) (Table 5).

The neurogenesis activity of MLT is also an important factor for the survival, proliferation and differentiation of the nervous cells in neurodegenerative diseases. In this context, several studies have suggested that MLT, as well as its metabolites, can be used to treat symptoms related to these diseases (WU; SWAAB, 2015; CHEN et al. 2016; LEE et al., 2016; REHMAN et al., 2019; GUNATA; PARLAKPINAR; ACET, 2020). At the molecular level, it has been shown that the excess of reactive species generated during the process of oxidative stress leads to neuronal death in the substantia nigra and the dentate gyrus of the hippocampal region, characteristic disorders of Parkinson's Disease (PD) and Alzheimer's Disease (AD), respectively (MANOHARAN et al., 2016; MONTEIRO et al., 2017).

Since the condition of oxidative stress is an important contributing factor for the development of these diseases, MLT can be used as a promising substance in alleviating symptoms resulted from the loss of nervous structure and function in these regions of the nervous system by acting directly and indirectly as a suppressor of free radicals (ROSSOR et al., 2010; CHEN.; GUO; KONG, 2012; ALONSO et al., 2015; UYANIKGIL, et al. 2017; CHEN; ZHANG; LEE, 2020) (Table 5).

Table 5 – Protective effects of MLT in Neurogenesis Impairments.

Oxidative stress induction	Nervous System Regions	MLT actions	Citations
		Repairment from the loss of dendrites in the hippocampal neurons	Dominguez-Alonso, Ramirez-Rodriguez and

			Benitez-King (2012)
		Indirect formation and maturation of new dendrites	Figueiro-Silva et al., (2018)
Depression and Anxiety-Like Behavior	Hilar Zone and Dentate Gyrus of the Hippocampal Region	Modulation of the cell survival of new neurons	Ramirez-Rodriguez et al., (2020)
		Modulation of the mitochondrial DNA copy number and oxidative phosphorylation proteins	Sarlak et al., (2013) Alonso et al., (2015)
		Survival of the proliferative cells and increased neurogenesis	Morley-Fletcher et al., (2011) Hoehn et al., (2016)
Pinealectomy	Cortical Layer of the CA3 Region of the Hippocampus	Improvement in light/dark cycle dysregulation	Musshoff et al., (2012)
		Increased of gene expression in order to produce MLT receptors	Feng et al., (2012)
Neurodegenerative diseases	Substantia Nigra, Dentate Gyrus and Hilar Zone of Hippocampus	Free radical suppression	Alonso et al., (2015) Chen, Zhang and Lee (2020)
		Attenuation of symptoms related to neurodegenerative diseases	Rossor et al., (2010) Alonso et al., (2015)
		Indirect induction of new neuron formation	Rehman et al., (2019)
		Reduced loss of nerve structure and function	Asghari et al., (2016)

Improved dopaminergic neuronal differentiation of human amniotic fluid mesenchymal stem cells	Wu and Swaab (2015) Gunata, Parlakpinar and Acet (2020)

4. Conclusions

From the theoretical basis analyzed in this study, it is possible to sum up that melatonin (MLT) has important protective effects on different regions of the nervous system because of its potential antioxidant and anti-inflammatory actions already proven in laboratorial and clinical researches conducted in last decades. As reaffirmed in this work, MLT is capable of scavenging free radicals (both reactive oxygen and nitrogen species at cytotoxic levels), which contributes to ameliorate the oxidative stress condition generated in the NS disorders.

In this case, exposure to herbicides, excessive consumption of processed foods and inflammatory pathologies, as well as the use of different medications, such as immunodepressive drugs, are the most relevant causes involved in the imbalance of generated reactive species and in the body's endogenous antioxidant defense system impairments, which might lead to NS disorders development.

The information highlighted in this review promotes relevance by synthesizing the promising potential use of MLT in the treatment of human neurological disturbances, including neurodegenerative diseases. It is expected that further clinical and laboratory studies, especially conducted in human beings, can fully enable the use of this neuro-hormone by clarifying in detail the mechanisms by which it acts to protect the human nervous system.

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REFERENCES

ALONSO, A. D. et al. Melatonin stimulates dendrite formation and complexity in the Hilar Zone of the rat Hippocampus: Participation of the Ca^{2}+/Calmodulin complex. **International Journal of Molecular Sciences**, 16: 1907-1927, 2015.

ARIOZ, B. I. et al. Melatonin attenuates LPS-Induced Acute Depressive-Like Behaviors and microglial NLRP3 inflammasome activation through the SIRT1/Nrf2 pathway. **Frontiers in Immunology**, v. 10, e1511, 2019.

ASGHARI, M. H. et al. A review of the protective role of melatonin during phosphine-induced cardiotoxicity: focus on mitochondrial dysfunction, oxidative stress and apoptosis. **Journal of Pharmacy and Pharmacology**, v. 6, p. 01-08, 2016.

ASGHARI, A. et al. Effects of melatonin and metformin co-administration on testicular ischemia/reperfusion injury in rats. **Journal of Pediatric Urology**, v. 12, p. 410-417, 2016.

BALDISSERA, M. D. et al. A caffeine-supplemented diet modulates oxidative stress markers and prevents oxidative damage in the livers of Nile tilapia (*Oreochromis niloticus*) exposed to hypoxia. **Fish Physiology and Biochemistry**, v. 45, p. 1041-1049, 2019.

BALI, I. et al. The effects of melatonin on liver functions in arsenic-induced liver damage. **Ulus Cerrahi Derg**, v. 32, p. 233-237, 2016.

BLASK, D. E.; SAUER, L. A.; DAUCHY, R. T. Melatonin as a chronobiotic / anticancer agente: cellular, biochemical and molecular mechanisms of action and their implications for circadian-based cancer therapy. **Current Topics in Medinal Chemistry**, v. 2, p. 113-132, 2012.

CARRASCAL, L. et al. Role of Melatonin in the inflammatory process and its therapeutic potential. **Current Pharmaceutical Design**, v. 24, n. 14, p. 1563-1588, 2018.

CHEN, D.; ZHANG, T.; LEE, T. H. Cellular mechanisms of Melatonin: insight from Neurodegenerative Diseases. **Biomolecules**, v. 10, n. 8, e1158, 2020.

CHEN, X.; GUO, C.; KONG, J. Oxidative stress in neurodegenerative diseases. **Neural Regeneration Research**, v. 7, n. 5, p. 376–385, 2012.

CHEN, Y. et al. Melatonin induces anti-inflammatory effects to play a protective role via endoplasmic reticulum stress in acute pancreatitis. **Cellular Physiology and Biochemistry**, v. 40, p. 1094-1104, 2016.

CHERN, C. M. et al. Melatonin ameliorates neural function by promoting endogenous neurogenesis through the MT2 melatonin receptor in ischemic-stroke mice. **Free Radical Biology and Medicine**, v. 52, p. 1634–1647, 2012.

CLAUSTRAT, B.. BRUN, J.; CHAZOT, G. The basic physiology and pathophysiology of Melatonin. **Sleep Medicine Reviews,** v. 9, p. 11-24, 2015.

COOMANS, C. P.; RAMKISOENSING, A.; MEIJER, J. H. The suprachiasmatic nuclei as a seasonal clock. **Frontiers in Neuroendocrinology**, v. 37, p. 29-42, 2015.

COWLED, P.; FITRIDGE, R. Pathophysiology of Reperfusion Injury. *In*: FITRIDGE, R.; THOMPSON, M. Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists [Internet]. Adelaide (AU): University of Adelaide Press; 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534267. Accessed on August 18, 2021.

DA SILVA, C. S. et al. Caffeine-supplemented diet modulates oxidative stress markers and improves locomotor behavior in the lobster cockroach *Nauphoeta cinerea*. **Chemical and Biological Interactions**, v. 12, p. 01-08, 2018.

DZIEGIEL, P., OKOLOW-PODHORSHA, M. & ZABEL, M. Melatonin: Adjuvant therapy of malignant tumors. **Medical Science Monitor**, v. 14, p. 64-70, 2018.

FENG, Z. Ligustilide alleviates brain damage and improves cognitive function in rats of chronic cerebral hypoperfusion. **Journal of Ethnopharmacology**, v. 144, p. 313-321, 2012.

FIGUEIRO-SILVA, J. et al. The Melatonin analog IQM316 may induce adult hippocampal neurogenesis and preserve recognition memories in Mice. **Cell Transplant**, v. 27, p. 423–437, 2018.

FU, J. et al. Melatonin promotes proliferation and differentiation of neural stem cells subjected to hypoxia *in vitro*. **Journal of Pineal Research**, v. 51, p. 104–112, 2011.

GHAREGHANI, M. et al. Melatonin increases oligodendrocyte differentiation in cultured neural stem cells. **Cellular and Molecular Neurobiology**, v. 37, p. 1319–1324, 2017.

GUNATA, M.; PARLAKPINAR, H.; ACET, H. A. Melatonin: A review of its potential functions and effects on neurological diseases. **Revue Neurologique**, v. 176, n. 3, p. 148-165, 2020.

GUZMAN-MARIN, R. et al. Sleep deprivation suppresses neurogenesis in the adult hippocampus of rats. **European Journal of Neuroscience**, v. 22, p. 2111–2116, 2005.

HADUCH, A. et al. Melatonin supports CYP2D-mediated serotonin synthesis in the brain. **Drug Metabolism and Disposition***,* v. 44, p. 445-452, 2016.

HAIRSTON, I.S. et al. Sleep restriction suppresses neurogenesis induced by hippocampus-dependent learning. **Journal of Neurophysiology**, v. 94, p. 4224–4233, 2015.

HARDELAND, R. et al. Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. **Journal of Pineal Research**, v. 52, p. 139-166, 2012.

HINOJOSA-GODINEZ, A. et al. Melatonin modifies SOX2+ cell proliferation in dentate gyrus and modulates SIRT1 and MECP2 in long-term sleep deprivation. **Neural Regeneration Research**, v. 14, p. 1787–1795, 2019.

HOEHN, R. et al. Melatonin acts as an antidepressant by inhibition of the acid sphingomyelinase/ceramide system. **Neurosignals**, v. 24, p. 48–58, 2016.

HUANG, C. C. et al. Effects of melatonin on the nitric oxide system and protein nitration in the hypobaric hypoxic rat hippocampus. **BioMed Central Neuroscience**, v. 16, n. 61, p. 02-11, 2015.

HUANG, C. H. et al. Sleep deprivation aggravates median nerve injury-induced neuropathic pain and enhances microglial activation by suppressing melatonin secretion. **Sleep**, v. 37, n. 9, p. 1513-1523, 2014.

IGGENA, D.; WINTER, Y.; STEINER, B. Melatonin restores hippocampal neural precursor cell proliferation and prevents cognitive deficits induced by jet lag simulation in adult mice. **Journal of Pineal Research**, v. 62, e12397, 2017.

JIMÉNEZ-HEFFERNAN, J. A. et al. Cytologic features of the normal pineal gland of adults. **Diagnostic Cytopathology**, v. 43, n. 8, p. 642-645, 2015.

KIM, A. H.; LEE, K. H.; LEE, B. H. Neuroprotective effect of melatonin against kainic acid-induced oxidative injury in hippocampal slice culture of rats. **International Journal of Molecular Sciences***,* v. 15, p. 5940-5951, 2014.

KUMAR, A. et al. 2011. Effect of nitric oxide in protective effect of melatonin against chronic constriction sciatic nerve injury induced neuropathic pain in rats. **Indian Journal of Experimental Biology**, 49: 664-671.

LEE, C. H. et al. Effects of melatonin on cognitive impairment and hippocampal neuronal damage in a rat model of chronic cerebral reperfusion. **Experimental and Therapeutic Medicine***,* v. 11, p. 2240-2246, 2016.

LERNER A. B. et al. Isolation of melatonin, the pineal gland factor that lightens melanocytes. **Journal of the American Chemical Society**, 80: e2587, 1958.

LEUNG, J. H. W. et al. Protective effects of Melatonin on neurogenesis impairment in neurological disorders and its relevant molecular mechanisms. International Journal of Molecular Sciences, v. 21, n. 16, e5645, 2020.

LI, X. et al. Effect of melatonin on neuronal differentiation requires CBP/p300-mediated acetylation of histone H3 lysine 14. **Neuroscience**, v. 364, p. 45–59, 2017.

MACCHI, M. M.; BRUCE, J. N. Human pineal physiology and functional significance of melatonin. **Frontiers in Neuroendocrinology**, v. 25, n. ¾, p. 177-195, 2014.

MANOHARAN, S. et al. The role of reactive oxygen species in the pathogenesis of Alzheimer's disease, Parkinson's disease, and Huntington's disease: A Mini Review. **Oxidative Medicine and Cellular Longevity**, v. 2016, p. 01-15, 2016.

MAYO, J. C. et al. Anti-inflammatory actions of melatonin and its metabolites, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMAK) and N^1-acetyl -5-methoxykynuramine (AMK), in macrophages. **Journal of Neuroimmunology**, v. 165, n. 1/2, p. 139-149, 2015.

MILLET, G. P.; PIALOUX , R. F. V. Point: Counterpoint: Hypobaric hypoxia induces/does not induce different responses from normobaric hypoxia. **Journal of Applied Physiology**, v. 112, p. 1783–1787, 2012.

MITTLER, R. ROS are good? **Trends in Plant Science**, v. 22, p. 11-19, 2017.

MOLPECERES, V. et al. Melatonin is able to reduce the apoptotic liver changes induced by aging via inhibition of the intrinsic pathway of apoptosis. **Journals of Gerontology Series A: Biological Sciences and Medical Sciences**, v. 62, n. 7, p. 687-695, 2007.

MONTEIRO, M. C. et al. Neuroprotection in neurodegenerative disease: From basic science to Clinical applications. **Oxidative Medicine and Cellular Longevity**, v. 2017, e2949102, 2017.

MORLEY-FLETCHER, S. et al. Chronic agomelatine treatment corrects behavioral, cellular, and biochemical abnormalities induced by prenatal stress in rats. **Psychopharmacology**, v. 217, p. 301–313, 2011.

MUSSHOFF, U. et al. Melatonin receptors in rat hippocampus: molecular and functional investigations. **Hippocampus**, v. 12, p. 165-173, 2012.

NETO, J. C. et al. Review of the medicinal use of *Rhaphiodon echinus* Schauer (Lamiaceae): biological and pharmacological activities. **Research, Society and Development**, v. 10, n. 3, p. 01-12, 2021.

OZACMAK, V. H,; BARUT, F.; OZACMAK, H. S. Melatonin provides neuroprotection by reducing oxidative stress and HSP70 expression during chronic cerebral hypoperfusion in ovariectomized rats*.* **Journal of Pineal Research**, v. 47, p. 156-163, 2009.

PANDI-PERUMAL S. R. et al. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. **Progress Neurobiology***,* v. 5, n. 3, p. 335-353, 2008.

PHONCHAI, R. et al. Potential effects and molecular mechanisms of melatonin on the dopaminergic neuronal differentiation of human amniotic fluid mesenchymal stem cells. **Neurochemistry International**, v. 124, p. 82-93, 2019.

RAMÍREZ-RODRÍGUEZ, G.B. et al. Melatonin modulates dendrite maturation and complexity in the dorsal- and ventraldentate gyrus concomitantly with its antidepressant-like effect in male Balb/C mice. **International Journal of Molecular Sciences**, v. 21, e1724, 2020.

RAY, P. D.; HUANG, B. W.; TSUJI, Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signalling. **Cell Signaling**, v. 24, p. 981-990, 2012.

REHMAN, S. U. et al. Neurological enhancement effects of Melatonin against Brain Injury-Induced Oxidative Stress, Neuroinflammation, and Neurodegeneration via AMPK/CREB signaling. **Cells**, v. 8, n. 7, e760, 2019.

REITER, R. J. et al. Melatonin and reproduction revised. **Biology of Reproduction**, v. 81, n. 3, p. 445-456, 2009.

REITER, R. J. Pineal melatonin: cell biology of its synthesis and of its physiological interactions. **Endocrionology Reviews**, 12: 151-180, 1991.

RENNIE, K.; DE BUTTE, M.; PAPPAS, B.A. Melatonin promotes neurogenesis in dentate gyrus in the pinealectomized rat. **Journal of Pineal Research**, v. 47, p. 313–317, 2019.

ROCHA, R. M. P. et al. Melatonin and animal reproduction: implications for ovarian physiology. **Acta Veterinária Brasilica**, v. 5, n. 2, p. 147-157, 2011.

ROSSOR, M. N. et al. The diagnosis of young-onset dementia. **The Lancet Neurology***,* v. 9, 8, p. 793-806, 2010.

SARLAK, G. et al. Effects of melatonin on nervous system aging: neurogenesis and neurodegeneration. **Journal of Pharmacological Sciences**, v. 123, n. 1, p. 09-24, 2013.

SAYAN, H. et al. Beneficial effects of melatonin on reperfusion injury in rat sciatic nerve. **Journal of Pineal Research**, v. 37, p. 143–148, 2014.

SOMPOL, P. et al. N-acetylserotonin promotes hippocampal neuroprogenitor cell proliferation in sleep-deprived mice. **Proceedings of National Academy of Sciences**, v. 108, p. 8844–8849, 2011.

SILVA, R. H. et al. Role of hippocampal oxidative stress in memory deficits induced by sleep deprivation in mice. **Neuropharmacology**, v. 46, p. 895-903, 2004.

SONG, J. et al. The protective effect of melatonin on neural stem cell against LPS-induced inflammation. **BioMed Research International**, 2015: 01-13, 2014.

STEFANOVIC, B. et al. Melatonin mediated antidepressant-like effect in the hippocampus of chronic stress-induced depression rats: Regulating vesicular monoamine transporter 2 and monoamine oxidase A levels. **European Neuropsychopharmacology**, v. 26, p. 1629–1637, 2016.

UYANIKGIL, Y. et al. Useful effects of melatonin in peripheral nerve injury and development of the nervous system. **Journal of Brachial Plexus and Peripheral Nerve Injury**, v. 12, p. 01-06, 2017.

VIANA, J. W. M. et al. Protective effect of Vitamin C against behavioral, histological changes and mortality rate induced by Paraquat in *Drosophila melanogaster*. **Austin Food Science**, v. 5, n. 1, e1036, 2020.

VINCENT, B. Protective roles of melatonin against the amyloid-dependent development of Alzheimer's disease: A critical review. **Pharmacological Research**, v. 134, p. 223–237, 2018.

VORNICESCU, C. et al. Neuroprotective effect of melatonin in experimentally induced hypobaric hypoxia. **Romanian Journal of Morphology and Embryology***,* v. 54, n. 4, p. 1097–1106, 2013.

WANG, W. GAO, J. Effects of melatonin on protecting against lung injury (Review). **Experimental and Therapeutic Medicine**, v. 21, n. 3, e228, 2021.

WANG, Z. et al. Melatonin improves short and long-term neurobehavioral deficits and attenuates hippocampal impairments after hypoxia in neonatal mice. **Pharmacological Research**, v. 76, p. 84–97, 2013.

WU, Y. H.; SWAAB, D. F. The human pineal gland and melatonin in aging and Alzheimer's disease**. Journal of Pineal Research***,* v. 38, p. 145-152 2015.

YOO, D.Y. et al. Melatonin improves D-galactose-induced aging effects on behavior, neurogenesis, and lipid peroxidation in the mouse dentate gyrus via increasing pCREB expression. **Journal of Pineal Research**, v. 52, p. 21–28, 2012.

ZHANG, L. et al. Melatonin prevents sleep deprivation-associated anxiety-like behavior in rats: role of oxidative stress and balance between GABAergic and glutamatergic transmission. **American Journal of Translational Research**, v. 9, n. 5, p. 2231-2242, 2017.

ZHAO, Y. et al. Melatonin attenuates white matter damage after focal brain ischemia in rats by regulating the TLR4/NF-κB pathway. **Brain Research Bulletin**, v. 150, p. 168–178, 2019.