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Different Clinical Uses and Advantages of Melatonin

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ABSTRACT

Introduction: Melatonin (N-acetyl-5-methoxytryptamine), an endogenous hormone produced by the pineal gland and released exclusively at night, is known to influence many biological processes in the body, including circadian rhythms, the immune system, and neuroendocrine and cardiovascular functions, due to its great therapeutic potential and safety for application. This molecule is being widely studied in order to establish safe and effective therapeutic protocols for the treatment of several disorders, such as sleep disorders, cardiovascular diseases, metabolic bone diseases, covid-19, schizophrenia, neurofetal protection, among others. In view of this, the present article aims to demonstrate the numerous possible applications and their respective benefits of melatonin use.

Keywords: Melatonin; Clinical uses; Advantages; Review.

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a molecule widely present in nature, present in unicellular organisms, plants, fungi and animals[1]. It was discovered in 1958 by Aaron Lerner, in which it is produced and secreted by pinealocytes, present in the pineal gland, from the amino acid tryptophan. Its higher plasmatic levels are found during the night period, with serum concentrations varying between 80 and 120 pg / ml, since the secretion is increased by darkness and suppressed by light, during the day the serum concentrations vary between 10-20 pg / ml[2]. Its secretion is made by the pineal gland during the nocturnal phase of the day[3]. Its metabolism occurs directly at the site of production or in the liver, and its effects occur through different pathways. It is important to point out that due to its rapid metabolism, some properties result from the action of its metabolites; the local concentration of melatonin and its metabolites define phenotypic regulations, acting in a receptor-dependent or receptor-independent manner[4]. Melatonin has long been recognized for its regulation of circadian and circannual functions, acting at different levels, regulating various biological functions (figure 1), with multiple sources and targets, being able to exert antioxidant, immunomodulatory, pro-apoptotic, antiproliferative, antiangiogenic effects, besides presenting other functions related to aging, obesity, insulin sensitivity, sexual maturation, antidepressant actions, antinociceptive, locomotor

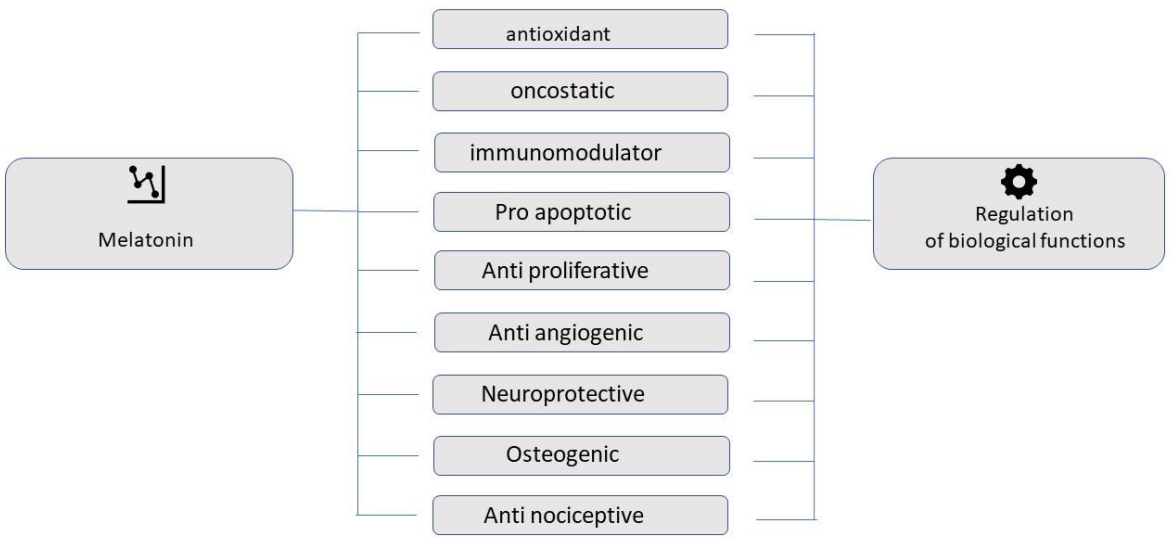

Figure 1. Schematic diagram demonstrating the biological functions related to melatonin. Source: personal collection.

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activity regulators, neuroprotectors, pain modulators, blood pressure reducers, control of hormone secretions (growth, adrenal and thyroid hormones) and as an antioxidant, onco- static and osteogenic agent[5,6].

Melatonin, can act by different molecular pathways, whose most characterized is by the activation of specific membrane receptors, being them high-affinity ML1 sites and low-affinity ML2 sites[7].

Melatonin levels decrease with age, so older adults are more likely to suffer from inadequate melatonin levels. Melatonin was first isolated in 1960 from 200,000 bovine pineal glands in a study that achieved a recovery of a few hundred micrograms, since then several studies, have been conducted about the use and benefits of melatonin. It is now known that exogenous melatonin supplementation is well tolerated and has no adverse effects in the short or long term[8].

In view of this, melatonin is widely studied in the literature, and its various applications have been documented, in search of establishing new therapies, in the health area. In the specific literature, one can find several studies that relate the use of melatonin for the treatment of bone lesions, cancer, COVID-19, autism, schizophrenia, sleep disorders, cardiovascular diseases and osteoporosis, due to its main actions, as shown in the figure below (figure 2).

This article, however, aims to address the different applications of exogenous melatonin and describe its positive effects for the treatment of different disorders and pathologies.

Melatonin and bone tissue:

Melatonin has the function of synchronizing the circadian cycle of all peripheral tissues, including bone tissue[9] by keeping metabolism in synchrony with the light-dark cycle. This will allow maximum bone growth to occur during the nocturnal phase of the day, when melatonin exhibits its highest plasma level. Reported that melatonin has shown great therapeutic potential in the bone microenvironment, with effects including regulation of bone metabolism, acceleration of osteoblastogenesis, inhibition of osteoclastogenesis and induction of apoptosis in mature osteoclasts, as well as suppression of osteolytic bone metastasis[10]. Several studies have suggested a beneficial effect of melatonin on bone metabolism, including anabolic effects and anti-absorptive effects, which result in osteogenesis. While the anti-absorptive effects are due to melatonin action on osteoclasts[11], promoting apoptosis in mature osteoclasts, consequently reducing their lifespan and suppressing bone resorption, the anabolic effects on bone remodeling promoted by melatonin are due to its action on osteoblasts[12].

In vitro studies have shown that melatonin promotes proliferation[13] and differentiation[14] of osteoblastic cells. The action of melatonin on osteoblastic cells is a determinant of whether mesenchymal stem cells are targeted for differentiation into osteogenic lineages[15]. In vivo studies have shown that topical application of melatonin is able to activate osteogenesis around titanium implants, thus allowing osseointegration[16].

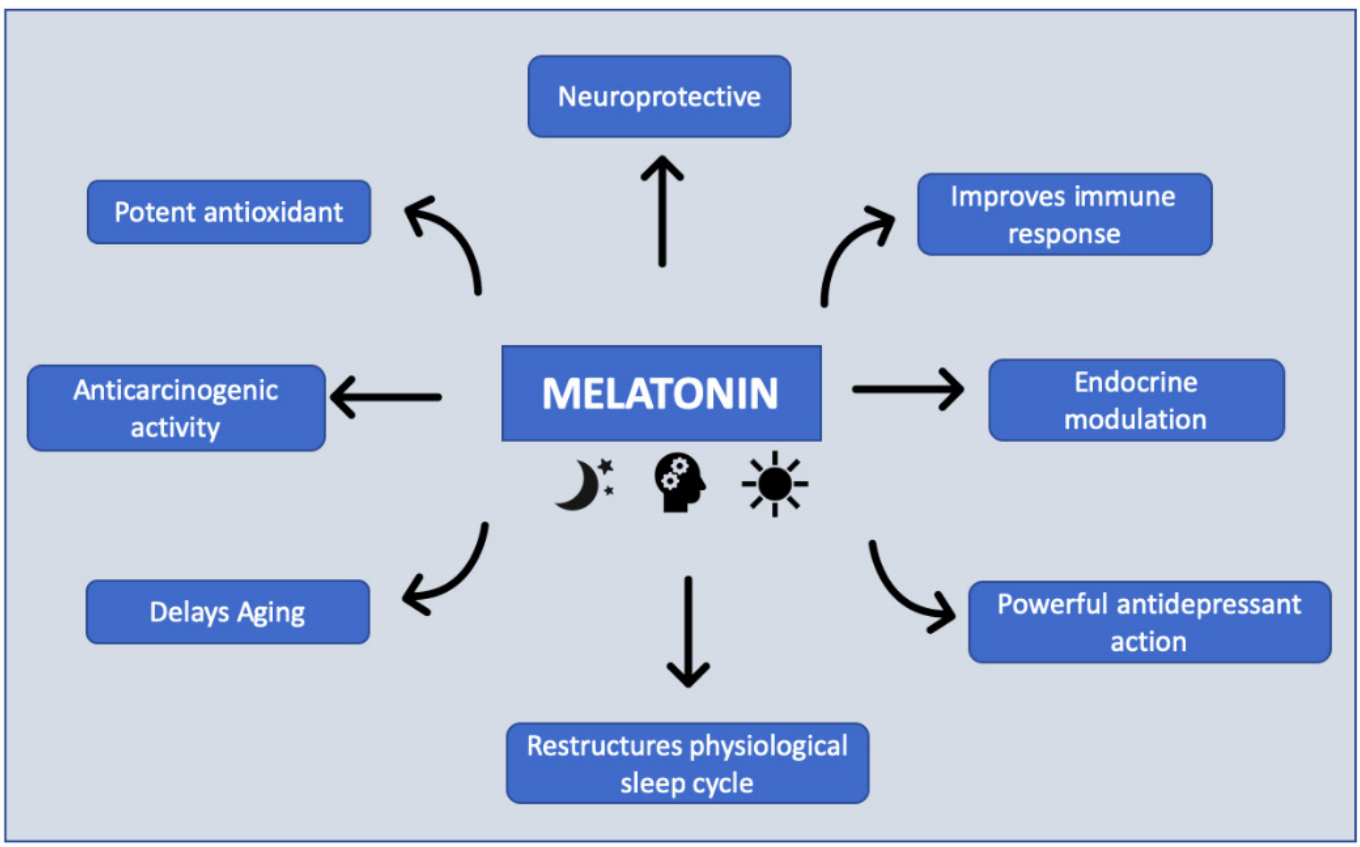

Figure 2. Actions of melatonin. Source: personal collection.

Thus, melatonin-induced osteoblastic cell formation occurs through increased expression of bone morphogenetic proteins (BMP-2 and BMP- 4), involved in osteoblast differentiation[14].

The homeostasis and maintenance of the bone microenvironment metabolism is kept in tune, with the help of melatonin, due to the beneficial effects, resulting from anabolic and antiresorptive actions. In humans, melatonin stimulates proliferation of bone cells and synthesis of Type I collagen in these cells and inhibits bone resorption by negatively regulating RANKL-mediated osteoclast formation and activation[17].

The mechanisms of action for these effects, may be by three routes: increasing osteogenic differentiation markers (Runx2, Opn, and Ocn) and increasing osteoblast activity; inhibiting the expression of osteoclast differentiation markers (Calcr, Ctsk, and Rank); and, scavenging free radicals[18].

Below is a figure demonstrating the bone neoformation induced by topical application of melatonin in critical defects of rat calvaria (figure 3), resulting from an ongoing research project by the research group of the department of Basic and Oral Biology, University of São Paulo of Ribeirão Preto. The figure, corroborates the idea that melatonin has osteogenic properties that favor bone repair, it can be observed the presence of a large area of newly formed bone, in addition to blood vessels and osteogenic cells.

Melatonin and osteoporosis:

Osteoporosis is a progressive bone disease, in which low bone mass and structural deterioration of bone tissue increase bone fragility and the subsequent risk of fracture. Like cardiovascular disease, osteoporosis is also responsible for a high rate of morbidity and mortality in the elderly population[19].

Bone loss and osteoporosis resulting from aging is related to the reduction of melatonin. Since its discovery, a plethora of research has been conducted, due to the potential use of this molecule, since melatonin is able to regulate bone density, as it promotes the acceleration of osteoblastogenesis, suppression of osteoclast differentiation and osteoclastogenesis and induction of apoptosis in osteoclasts, and suppression of osteolytic bone metastasis, interesting properties for osteoporosis treatment[20].

Wang X and colleagues[21], concluded that melatonin stimulates bone formation and reduces bone loss in ovarectomized rats, stemming from inhibiting osteoclast differentiation and promoting osteogenic differentiation.

In summary, current researches conclude that melatonin exhibits a great potential for osteoporosis treatment, considering that anti-osteoporotic drugs reduce the rate of bone loss and aid in fracture healing, but do not stimulate bone formation. Thus, melatonin emerges with great potential for the development of therapeutics that can effectively treat

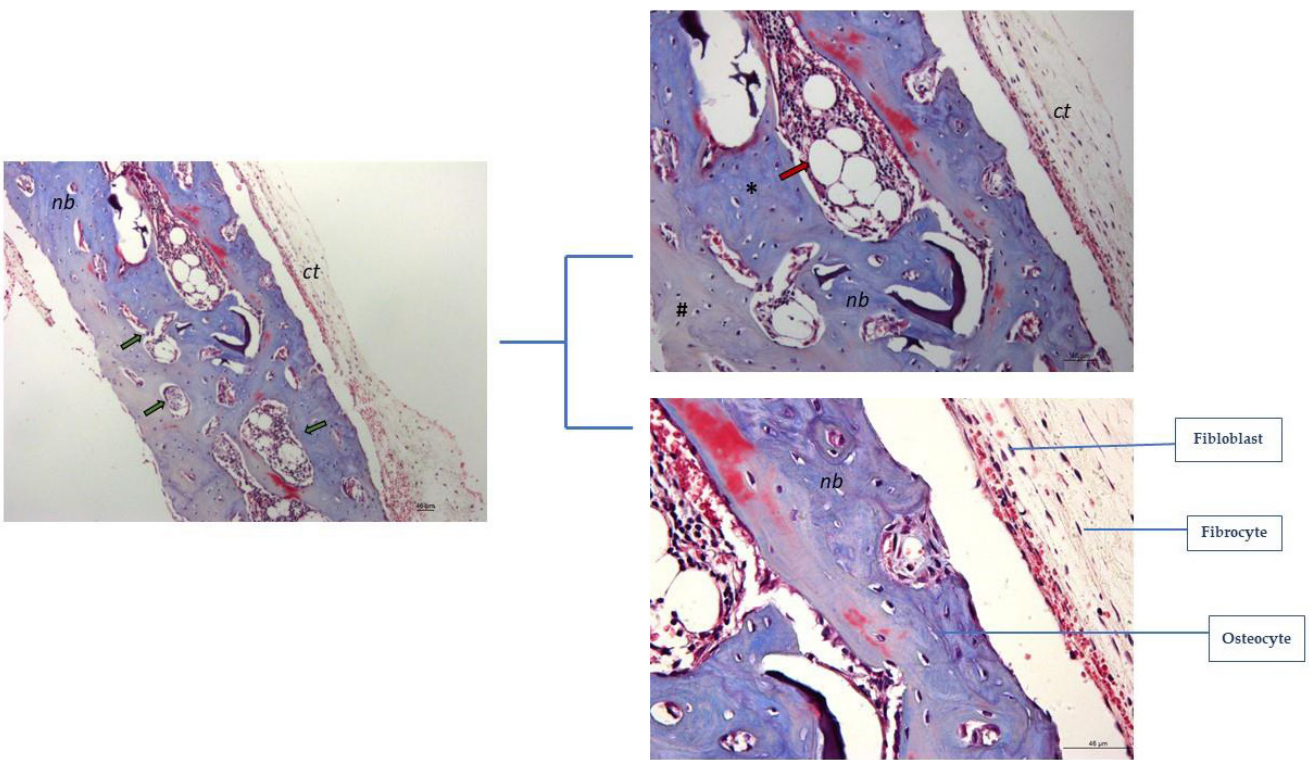

Figure 3. Image of experimental calvaria bone defect in rat, with topical application of melatonin. A: Neoformed bone at the extent of the defect (nb), with formation of bony tabulae (green arrows) and connective tissue adjacent to the defect area (ct). B: Formation of blood vessels (red arrow), neoformed bone (nb) with regions of more dense (*) and less dense (#) calcium deposition and connective tissue adjacent to the defect (ct). C: Presence of osteocytes in the bone matrix and fibroblasts and fibrocytes in the connective tissue. Staining: Masson's Trichrome. Magnification: 10x (A), 20x(B), 40x(C). Scale bars:
46 µm. Source: personal collection.Thus, we conclude that melatonin is directly related to the bone repair process, presenting great therapeutic potential in the bone microenvironment, being directly related to the treatment of bone diseases.

bone loss-related pathologies such as osteoporosis and osteolysis[22].

Melatonin and healthy ageing:

Aging is an extremely complex and multifactorial process, accompanied by circadian changes and closely associated with oxidative damage and mitochondrial dysfunction, which can lead to consequences such as metabolic disorders. In addition, aging has been associated with a significant reduction in sleep efficiency and continuity, which coincides with a significant reduction in the amplitude of the melatonin rhythm. Sleep cycle disturbances cause numerous pathophysiological changes that accelerate the aging process, in the central nervous system, sleep disruption impairs several functions, including the clearance of waste molecules. Melatonin deficiency may result in reduced antioxidant protection in the elderly, which may have significance not only for aging itself, but may also contribute to the incidence or severity of some age-related diseases[23].

In fact, aging may be a process resulting in part from relative melatonin deficiency, and melatonin may be effective in improving quality of life in the elderly[24, 25].

The decrease in plasma melatonin plays a particular role in the endocrine sequelae of aging. In addition, melatonin exerts a significant cytoprotective action by buffering free radicals and reversing inflammation through negative regulation of pro-inflammatory cytokines, suppression of low-grade inflammation, and prevention of insulin resistance.

There is a constant search for any therapeutic agent that improves the quality of life of the elderly. The administration of melatonin to elderly animals counteracts a significant number of senescence-related changes. In humans, melatonin is effective both as a chronobiotic and cytoprotective agent to maintain healthy aging. Circulating levels of melatonin are consistently reduced in the metabolic syndrome, ischemic and nonischemic cardiovascular diseases, and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Melatonin levels decrease considerably with aging, and its decline is associated with several age-related diseases. Several clinical trials have suggested the therapeutic potential of melatonin, due to its cytoprotective effects. However, more controlled studies are still needed, especially to establish the minimum necessary dose of melatonin[26,27].

The highest serum levels of melatonin occur at night, especially in winter, because of the longer nights. However, it is noted that this value decreases with aging, as shown in the figure below (figure 4)[28,29].

Melatonin and sleep disorders:

Due to the growing increase in sleep disorders, new treatment alternatives are being sought that aim to improve the quality of life of people who suffer from these pathologies. Currently, there are several drug treatments on the market for this purpose, however, these drugs have considerable side effects, so there is a growing demand for new therapeutic approaches that minimize these effects and do not have addictive potential[30].

As one ages, the ability to sleep decreases and, consequently, the incidence of sleep disorders gradually increases. It is known that melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced by the pineal gland its production is activated by the suprachiasmatic nucleus, inhibited by light and released exclusively at night, able to synchronize circadian rhythms and improve sleep quality, it is also already established in the literature that exogenous supplementation with melatonin has no adverse effects[31].

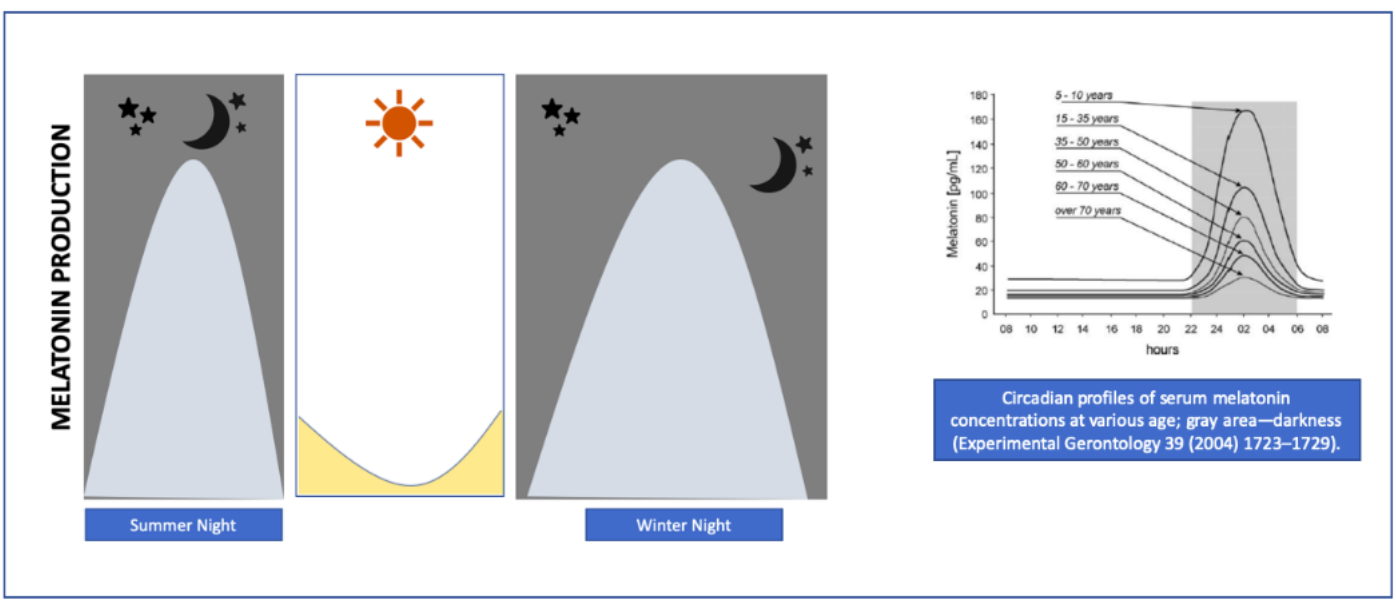

Figure 4. Melatonin production inversely proportional with age. Serum levels higher at night, especially in winter.

Supplementation with exogenous melatonin is able to alter sleep architecture, consequently improving its quality, as well as increasing sleep time and efficiency and decreasing sleep latency in patients suffering from sleep disorders, such as psychophysiological insomnia, and patients taking beta-blockers (suppression of endogenous secretion of nocturnal melatonin). In addition, melatonin is able to synchronize the sleep-wake cycle in blind individuals and in individuals suffering from jet lag and the onset of advanced sleep in individuals suffering from delayed sleep phase syndrome. These sleep restorative effects of exogenously administered melatonin represent a promising investigative route for early intervention to promote healthy physical and mental aging[32].

The figure below (figure 4), represents a schematic of the production of melatonin by the suprachiasmatic nucleus, which occurs during the night.

Sleep Breathing Abnormalities:

Sleep breathing abnormalities (SBDs) include obstructive sleep apnea (OSA), central sleep apnea disorders, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders.

The treatments for these disorders have significant disadvantages, requiring new therapies. In view of this need, it was observed that melatonin had a beneficial effect on the complications caused by these disorders, both in animal models and in human clinical trials. In addition, melatonin prevents the development of secondary cardiovascular diseases.

Cardinali DP and colleagues[33], reported that the use of melatonin analog drugs also increased total sleep time and sleep efficiency, as well as in reducing sleep latency, in patients with insomnia, but there is still a need for long-term studies of melatonin.

The table below, summarizes the effects of melatonin on some types of sleep disorders (table 1).

Melatonin and fetal neuroprotection:

It has been reported in the specific literature that melatonin is able to pass from the placenta to the fetus and display its effects, the use of melatonin during pregnancy and lactation period presents positive effects, and may decrease the risk of complication in risky pregnancies. The highest levels of melatonin in the gestational period are after 32 weeks[35], having as function to ensure the formation of the neural tube, protecting against damage and dysfunction caused by oxidative stress.

The human placenta produces melatonin through two en-zymes that metabolize serotonin into melatonin, serotonin N-acetyltransferase (AANAT) and N-acetylserotonin methyltransferase expressed in villous trophoblasts[36]. In the uterus of pregnant women, melatonin and oxytocin may act synergistically to promote and maintain strong uterine contractility[37].

Liu S and colleagues[38], reported in a rat study that in gestational diabetes, there is a decrease in melatonin levels, increasing glucose transport to the embryos, consequently increasing the oxidative status of the cells, decreasing free radical scavenging, increasing oxidative metabolism or both, which may lead to various diabetic embryopathies. Furthermore, they concluded that melatonin, may help protect the neural tube of the embryo, in diabetic pregnancy in addition to its high safety of use, with no adverse effects.

Table 1. Summarizes the effects of melatonin on some types of sleep disorders (33 e 34)

Sleep disorders	Effetcts of Melatoninn
Insomnia	1. Improves the quality of sleep 2. Increase total sleep time 3. Improves sleep efficiency 4. Decreases sleep onset latency
SBDs (Sleep-related breathing disorders)	1.Lowers blood pressure 2. Increases blood flow in poorly perfused tissues 3. Antihypertensive effects 4. Management of cardiovascular diseases
Central hypersomnia disorders	1. Decreases plasma levels of TNF-alpha and IL-1-beta 2. Increases BDNF, S100B and IL-10 3. Prevents neuronal dopamine loss or negative regulation of the dopaminetransporter 4. Antiapoptotic effects
CRSWDs (Circadian rhythm sleep-wake disorder (circadian rhythm sleep disorder)	1. Reduces nocturnal activity 2. Reduces activity and position changes during naps 3. Modulates the circadian rhythm of the sleep-wake cycle 4. Improves Sleep Efficiency
Parasomnias	1. Decreases muscle tone during REM sleep 2. Reduces injuries 3. Less adverse effect

Evidence was found in in vitro studies that revealed that melatonin, when given during pregnancy, may help protect the developing fetal brain from injury due to its antitioxidant, anti-inflammatory, and anti-apoptotic potential[39].

Pre-eclampsia is a condition caused by placental dysfunction, which can put the fetus at risk due to increased oxidative stress, thus due to the protective potential of melatonin, its use may be beneficial.

Fetal brain protection against free radicals, induced by increased oxidative stress, occurs due to the antioxidant, anti inflammatory and anti apoptotic effects of melatonin, in addition to the ability to indirectly increase gene expression[40].

Laste G *et al.*[41] published a review on the importance of melatonin during risky pregnancies and suggested further studies related to this subject

Furthermore, in the literature, studies are found showing decreased maternal blood levels in preeclamptic pregnancies compared to normotensive pregnancies, so melatonin can be used as a potential treatment for preeclampsia[42].

However, further studies are still needed to establish this therapy, which evaluate infants over a long period of time, defining the long-term effects of melatonin[43].

Melatonin and Cardiovascular Diseases:

Cardiovascular diseases are the main cause of mortality and morbidity, and the prognosis is not always so favorable, even with the evolution of treatments. Epidemiological studies indicate that melatonin is reduced in patients with some kind of cardiovascular disease, indicating an inverse relationship, supporting the idea that melatonin has a fundamental role of protective effect related to cardiovascular pathologies (hypertension, cardiovascular diseases, heart failure, arrhythmias, myocardial infarction, diabetes, obesity, etc). Melatonin presents a cardioprotective effect, due to the fact that it is an antioxidant and anti inflammatory agent, being able to produce beneficial effects in lesions caused by ischemia/reperfusion (IR) injury in several organs, including heart, liver, kidney, intestine, testis, brain and lung[44,45,46].

Melatonin supplementation protects the heart in several experimental models, animal studies demonstrate the ability to regulate blood pressure with the presence of melatonin[47], as well as human studies have also shown favorable results for treating patients with hypertension and normotensive patients, with decreased blood pressure, decreased tachycardia, and increased antioxidant defense[48].

Studies have reported that melatonin prevents atherosclerotic progression through various signaling pathways by producing anti-inflammatory and anti-proliferative effects, which result in the reduction of atherosclerotic plaque lesions[49].

There are reports that melatonin has significant effects on ischemia-reperfusion injury, chronic intermittent myocardial hypoxia injury, pulmonary hypertension, hypertension, heart valve disease, vascular disease, and lipid metabolism, and is an excellent therapeutic option because it is an inexpensive and well-tolerated drug[50].

Jiki and colleagues[51], reported the beneficial cardioprotective effects of endogenous and supplemental melatonin for cardiovascular diseases, as well as its safety of consumption.

Despite the need for more randomized clinical trials for clinical practice, melatonin is known to decrease complications associated with infarction, myocardial injury, hypertrophy, and may have a synergistic effect with surgical or non-surgical treatment of these patients.

Melatonin and schizophrenia:

Schizophrenia is a chronic disorder that affects the ability to think, feel and behave clearly, its etiology and pathophysiology remain a challenge, as they are not fully known and present a combination of genetic, environmental and brain chemical alterations factors, therefore the existing treatments have limitations and tend to be needed throughout life, with a combination of drugs and therapies.

Some evidence has suggested that schizophrenic patients have reduced melatonin levels, a fact that considerably affects the quality of life of these patients[52].

People with schizophrenia may have sleep disturbances as symptoms, and because of melatonin's ability to improve sleep quality, it can be used as a therapeutic to decrease these symptoms[53].

Although it has been shown that there is a relationship between melatonin and this disease, the findings of the studies are still inconclusive. Today, there are easy and inexpensive methods to measure melatonin, making it easier to conduct new research, since research on therapeutic applications is very scarce compared to the new research conducted on the role of melatonin as a marker for schizophrenia[54].

Melatonin and autism:

Autism is a health condition characterized by deficits in social communication (socialization and verbal and non-verbal communication) and behavior (restricted interest or hyper-focus and repetitive movements). Autistic children tend to have sleep disorders and consequently have reduced sleep quality, a fact that can further aggravate the symptoms of the autistic disorder.

The action of melatonin in different pathologies has been frequently studied, and it has been reported that in autistic patients, there seems to be a lower production of this hormone, instigating several studies with different formulations of the use of melatonin with immediate or prolonged release.

It has been reported that melatonin not only helps to minimize the problem, but also to reduce behavioral disturbances. Positive effects on sleep quality and latency, and improvement of behavioral impairments in autistic patients have been reported, however, more studies need to be conducted[55].

It is worth noting that the dosage, depends on the age and weight of the child and the effects of topical use of melatonin depend on several factors, such as age, time of administration, dose and association with other substances. In addition, the use of melatonin does not present any side effects.

Rossignol DA *et al.* (2011), reported that melatonin administration in autistic children improves behavior, sleep quality and decreases side effects in these children[55]. In conclusion, melatonin is a safe, effective, well-tolerated, and potent therapeutic agent to aid in sleep disorders in children and adolescents with autism. Further exploration of the factors that influence the pharmacokinetics of melatonin may improve its use and the establishment of new therapeutics[56,57].

Melatonin and COVID-19

The COVID-19 pandemic has infected and killed millions of people worldwide. These large numbers necessitated the rapid development of clinical trials to evaluate therapies capable of reducing the alarmingly high mortality rate; as a result, a large number of drugs have been studied in patients with COVID-19.

Melatonin is known to have numerous beneficial effects for humans, considering viral infections, melatonin exhibits anti inflammatory, antioxidant and immunosuppressive properties[58]. It is possible to observe the decrease of melatonin in viral infections, a fact that reflects its importance, Simko F and collaborators identified that melatonin suppression, increases the susceptibility to SARS-CoV-2 infection[59].

The efficacy of melatonin as adjunctive therapy has been demonstrated in a variety of diseases, however, there are few studies evaluating the use of melatonin in patients with COVID-19[60].

Studies in animals, point to the efficacy and safety of melatonin for treating patients with COVID-19 by reducing viremia and viral load. In addition, melatonin brings other beneficial effects to COVID-19 patients, such as reducing vascular permeability, reducing anxiety, and improving sleep quality[61].

In the paper Zhang R *et al*[61] demonstrated that oral melatonin, when added to standard treatment, was more effective than standard treatment alone in hospitalized patients with severe COVID-19. Better rates of thrombosis, sepsis, and mortality support the adjuvant efficacy of melatonin in attenuating this infectious disease. Given melatonin's superior performance as an inexpensive, highly safe and readily available drug, it is highly recommended that this be addressed in future studies.

Although the safety of melatonin, even at high doses, is already well established in the literature, monitoring of administration in patients with COVID-19 and further experimental and clinical studies are needed.

Melatonin and beverages (wine and beer):

The various beneficial effects of melatonin on the human body are already well established in the literature, including benefits in sleep quality and in the treatment of several pathologies, such as cardiovascular diseases, bone diseases, neurodegenerative diseases, Parkinson's, Alzheimer's, sleep disorders, among others.

Part of these effects is due to the antioxidant capacity of melatonin, which is able to act on reactive molecules.

In view of so many benefits, different ways of exogenous melatonin administration are being sought, one of them is through the consumption of wine and beer. Wine and beer are beverages that have melatonin and its intake can reach considerable plasma levels to exert the desired effects, thus, through diet, moderate consumption of these beverages is a good source of melatonin absorption[62].

Melatonin and cancer treatment:

The conventional treatment against cancer, still has several disadvantages, such as decreased quality of life of patients and undesirable tissue responses, and even with treatment the prognosis often remains unfavorable. Thus, new approaches are desirable to improve the treatment and quality of life of cancer patients.

Currently, it is known that melatonin can also act in the treatment against cancer, since it has anti-cancer mechanisms. There are studies in literature that report these significant effects, especially in hormone-dependent neoplasms[63]. The antitumor activity of melatonin is due to apoptosis regulation, angiogenesis inhibition, antioxidant activity, antimetastatic and circadian disruption prevention

The main advantage of the use of melatonin in cancer treatment and prevention is due to the ability to potentiate the therapeutic effects when associated with other conventional therapies, besides reducing the side effects of drugs, such as drug resistance and improving the quality of life of these patients. Sanchez-Barcelo EJ *et al.* (2012) reported the benefits of melatonin as an adjuvant in drug treatment and the lack of contraindications for continuous use, besides that melatonin is able to diffuse into various tissues and cells of the body, protecting against different damages, mainly due to radiation. A considerable number of clinical studies have suggested decreased side effects of chemotherapy and radiation therapy, and increased efficiency when melatonin is administered, due to its antioxidant role and ability to penetrate all types of cells in the body, protecting different organs against

radiation[64,65,66].

Studies have suggested that the anticancer effect of melatonin is not tissue-specific and its therapeutic and preventive properties have been reported as different types of cancer.

Farhood B *et al.* (2019), mentioned that melatonin, can modulate responses to radiation through various pathways, different from other conventional antioxidants, ensuring radioprotective and radiosensitive effects, decreasing undesirable reactions to different organs. In addition to all this, some studies have revealed that it has a synergistic effect with radiation on tumor cells[67].

Ahabrach H *et al.* (2021), concluded that circadian rhythm and blood melatonin concentration are altered in breast cancer patients, affecting quality of life, furthermore, he reported that due to the antioxidant role, new therapies can be developed[66].

New studies about the pharmacokinetics and bioavailability of exogenous melatonin need to be performed, as these are factors that are not yet fully understood and affected by factors that depend from person to person[68].

In summary, the safety, lack of contraindication and high efficiency of melatonin justifies its use in cancer prevention and treatment.

Melatonin and skin:

The skin plays an important role in protecting against damage from ultraviolet (UV) radiation, because besides being a target for the protective actions of melatonin, it is also a site of synthesis and metabolism[69].

Topical application of melatonin and its metabolites along with endogenous production has great potential for defense against ultraviolet radiation due to its antioxidant effects[70]. The radioprotective effect is given by melatonin and its metabolites[71].

It is worth noting that some metabolites exhibit an even greater impact than melatonin alone, all of these metabolites can potentially affect mitochondrial functions in skin cells and consequently the skin phenotype[72].

In addition to antioxidant and oncotastic effects, melatonin may play a role in regulating skin and barrier functions[69].

In mammals, the skin is able to synthesize and metabolize melatonin, and its cutaneous effects are a consequence of its local concentration and of its metabolites. Protection against UV damage also occurs through the effect of melatonin and its metabolites.

However, that of topically applied melatonin and its derivatives needs further evaluation and more assessments in future clinical trials.

Future prospects:

Due to the enormous potential presented by melatonin and its safety profile already established in literature, there are numerous therapeutic applications for melatonin. Emerging researches aim to establish different therapies with exogenous melatonin alone or in association that allow greater safety, better effectiveness and fewer adverse effects for drug manufacturing, for treatment of pathologies of various classes, besides the protective effect and improvement in biological functions related to this endogenous hormone

The table below (Table 2), summarizes all the applications of melatonin and its respective effects, cited in this article.

Table 2. Summarizes all the applications of melatonin and its respective effects, cited in this article.

Applictions of Meltonin	Effect of melatonin	References
Bone Metabolism	• Increase in markers of osteogenic differentiation • Increased osteoblast activity • Inhibition of the expression of osteoclast differentiation markers • Inhibition of free radicals	Nakade *et al.*, 1999[13] Roth *et al.*, 1999[17] Park *et al.*, 2011[14]
Osteoporosis	• Stimulates bone formation • Reduces bone loss • Inhibition of osteoclast differentiation • Promotion of osteogenic differentiation.	Coyle D. *et al.*, 2019[19] MacDonald IJ *et al.*, 2021[20]
Sleep disorders	• Improves sleep quality and efficiency • Reduce nocturnal activity • Reduces muscle tone during REM sleep • Reduces blood pressure • Decreases sleep onset latency	Xie Z *et al.*, 2017[30] Zisapel N., 2018[31]
Cardiovascular disease	• Antioxidant agent • Anti-inflammatory agent • Anti-proliferative agent	Reiter RJ. *et al.*, 2014[37]
Autism	• Therapeutic benefits of melatonin have been observed for sleep disorders in autism, notably on sleep latency and sleep quality.	Palagini L. *et al.*, 2021[71] Rossignol DA, *et al.*, 2011[53]

COVID-19	• Indirect antiviral actions • Anti inflammatory, anti oxidant, immune strengthening	Ameri A. *et al*., 2021[56]
Schizophrenia	• Potential for a possible therapeutic and/or adjuvant agent in the management of schizophrenia.	Morena-Fumero AL. *et al*., 2013[52]
Cancer	• Adjuvant action with chemotherapy to enhance therapeutic effects.	Kubatka P. *et al*., 2018[61] Farhood B. *et al*, 2019[64]
Drinks	• Melatonin concentrations in wine and beer make them two excellent vehicles for incorporating melatonin into the diet naturally.	Marhuenda J. *et al*., 2021[60]
Pregnancy at risk	• Decreases the risk of injury to the fetus • Treatment for pre-eclampsia • Protection against oxidative stress	Laste G. *et al*., 2021[41] Lanoix D *et al*., 2012[42]
Skin	• Protection against ultraviolet radiation • Tissue homeostasis • Antioxidant defense	Slominski, A. T *et al*., 2017[69] Fischer TW *et al*., 2006[67]

Conclusion

In view of all the above, it is evident the great therapeutic potential associated with melatonin and the great importance of studies on these various applications, to discover safe and effective parameters in the establishment of new therapies.

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References

1. Pandi-Perumal SR, BaHammam AS, Ojike NI, Akinseye OA, Kendzerska T, Buttoo K, Dhandapany PS, Brown GM, Cardinali DP. Melatonin and Human Cardiovascular Disease. J Cardiovasc Pharmacol Ther. 2017 Mar;22(2):122-132.
2. Touitou Y, Bogdan A, Auzéby A, Selmaoui B. Mélatonine et vieillissement [Melatonin and aging]. Therapie. 1998 Sep-Oct;53(5):473-8. French. PMID: 9921040.
3. Zawilska JB, Skene DJ, Arendt J. Physiology and pharmacology of melatonin in relation to biological rhythms. Pharmacol Rep. 2009; 61:383–410
4. Slominski, A. T., Semak, I., Fischer, T. W., Kim, T. K., Kleszczyński, K., Hardeland, R., & Reiter, R. J. (2017). Metabolism of melatonin in the skin: Why is it important?. Experimental dermatology, 26(7), 563–568.
5. Lima FB, Machado UF, Bartol I, Seraphim PM, Sumida DH, Moraes SM, Hell NS, Okamoto MM, Saad MJ, Carvalho CR, Cipolla-Neto
J. Pinealectomy causes glucose intolerance and decreases adipose cell responsiveness to insulin in rats. Am J Physiol. 1998;275(6):934-41.
6. Bonmati-Carrion MA, Tomas-Loba A. Melatonin and Cancer: A Polyhedral Network Where the Source Matters. Antioxidants (Basel). 2021 Feb 1;10(2):210.)
7. Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, Fougerou C. Melatonin: Pharmacology, Functions and Therapeutic Benefits. Curr Neuropharmacol. 2017 Apr;15(3):434- 443
8. Lerner AB, Case JD, Takahashi Y. Isolation of melatonin and 5-methoxyindole-3-acetic acid from bovine pineal glands. J Biol Chem. 1960 Jul;235:1992-7.
9. Hardeland R, Madrid JA, Tan DX, Reiter RJ. Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. J Pineal Res. 2012; 52:139–166.
10. Liu PI, Chang AC, Lai JL, Lin TH, Tsai CH, Chen PC, Jiang YJ, Lin LW, Huang WC, Yang SF, Tang CH. Melatonin interrupts osteoclast functioning and suppresses tumor-secreted RANKL expression: implications for bone metastases. Oncogene. 2021 Feb;40(8):1503-1515.
11. Koyama H, Nakade O, Takada Y, Kaku T, Lau KH. Melatonin at pharmacologic doses increases bone mass by suppressing resorption through down-regulation of the RANKL-mediated osteoclast formation and activation. J Bone Miner Res. 2002; 17(7):1219-29.
12. Liu PI, Chang AC, Lai JL, Lin TH, Tsai CH, Chen PC, Jiang YJ, Lin LW, Huang WC, Yang SF, Tang CH. Melatonin interrupts osteoclast functioning and suppresses tumor-secreted RANKL expression: implications for bone metastases. Oncogene. 2021 Feb;40(8):1503-1515.
13. Nakade O, Koyama H, Ariji H, Yajima A, Kaku T. Melatonin stimulates proliferation and type I collagen synthesis in human bone cells in vitro. J Pineal Res. 1999; 27:106-10.
14. Park KH, Kang JW, Lee EM, Kim JS, Rhee YH, Kim M, Jeong SJ, Park YG, Kim SH. Melatonin promotes osteoblastic differentiation through the BMP/ERK/Wnt signaling pathways. J Pineal Res. 2011; 51:187-94.
15. Zhang L, Su P, Xu C, Chen C, Liang A, Du K, Peng Y, Huang D. Melatonin inhibits adipogenesis and enhances osteogenesis of human mesenchymal stem cells bysuppressing PPAR-gamma expression and enhancing Runx2 expression. J Pineal Res. 2010; 49:364-72.
16. Cutando A, Gómez-Moreno G, Arana C, Muñoz F, Lopez-Peña M, Stephenson J. Melatonin stimulates osteointegration of dental implants. J Pineal Res. 2008;45:174– 9.
17. Roth JA, Kim BG, Lin WL, Cho MI (1999) Melatonin promotes osteoblast differentiation and bone formation. J Biol Chem. 1999; 274:22041-47.
18. Wang X, Liang T, Zhu Y, Qiu J, Qiu X, Lian C, Gao B, Peng Y, Liang A, Zhou H, Yang X, Liao Z, Li Y, Xu C, Su P, Huang D. Melatonin prevents bone destruction in mice with retinoic acid- induced osteoporosis. Mol Med. 2019 Aug 28;25(1):43.
19. Coyle D. Cost-Effectiveness of Pharmacological Treatments for Osteoporosis Consistent with the Revised Economic Evaluation Guidelines for Canada. MDM Policy Pract. 2019;4:2381468318818843.
20. MacDonald IJ, Tsai HC, Chang AC, Huang CC, Yang SF, Tang CH.

Melatonin Inhibits Osteoclastogenesis and Osteolytic Bone Metastasis: Implications for Osteoporosis. Int J Mol Sci. 2021 Aug 30;22(17):9435.
21. Wang X, Liang T, Zhu Y, Qiu J, Qiu X, Lian C, Gao B, Peng Y, Liang A, Zhou H, Yang X, Liao Z, Li Y, Xu C, Su P, Huang D. Melatonin prevents bone destruction in mice with retinoic acid- induced osteoporosis. Mol Med. 2019 Aug 28;25(1):43.
22. MacDonald IJ, Tsai HC, Chang AC, Huang CC, Yang SF, Tang CH. Melatonin Inhibits Osteoclastogenesis and Osteolytic Bone Metastasis: Implications for Osteoporosis. Int J Mol Sci. 2021 Aug 30;22(17):9435
23. Karasek M. Melatonin, human aging, and age-related diseases. Exp Gerontol. 2004 Nov-Dec;39(11-12):1723-9.
24. Cardinali DP, Furio AM, Reyes MP. Clinical perspectives for the use of melatonin as a chronobiotic and cytoprotective agent. Ann N Y Acad Sci. 2005 Dec;1057:327-36.
25. Haimov I, Laudon M, Zisapel N, Souroujon M, Nof D, Shlitner A, Herer P, Tzischinsky O, Lavie P. Sleep disorders and melatonin rhythms in elderly people. BMJ. 1994 Jul 16;309(6948):167.
26. Cardinali DP. Melatonin and healthy aging. Vitam Horm. 2021;115:67-88.
27. Öztürk G, Akbulut KG, Güney Ş. Melatonin, aging, and COVID-19: Could melatonin be beneficial for COVID-19 treatment in the elderly? Turk J Med Sci. 2020 Oct 22;50(6):1504-1512.
28. Danilenko KV, Kobelev E, Zhanaeva SY, Aftanas LI. Winter-summer difference in post-awakening salivary α-amylase and sleepiness depending on sleep and melatonin. Physiol Behav. 2021 Oct 15;240:113549.
29. Olcese J, Jockers R. Editorial: Melatonin in Health and Disease. Front Endocrinol (Lausanne). 2020 Nov 26;11:613549.
30. Xie Z, Chen F, Li WA, Geng X, Li C, Meng X, Feng Y, Liu W, Yu F. A review of sleep disorders and melatonin. Neurol Res. 2017 Jun;39(6):559-565.
31. Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br J Pharmacol. 2018 Aug;175(16):3190-3199.
32. Stanford SC. Recent developments in research of melatonin and its potential therapeutic applications. Br J Pharmacol. 2018 Aug;175(16):3187-3189.
33. Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. Melatonin and its analogs in insomnia and depression. J Pineal Res. 2012 May;52(4):365-75.
34. Xie Z, Chen F, Li WA, Geng X, Li C, Meng X, Feng Y, Liu W, Yu F. A review of sleep disorders and melatonin. Neurol Res. 2017 Jun;39(6):559-565.
35. Nakamura Y, Tamura H, Kashida S, Takayama H, Yamagata Y, Karube A, Sugino N, Kato H. Changes of serum melatonin level and its relationship to feto-placental unit during pregnancy. J Pineal Res. 2001 Jan;30(1):29-33.
36. Lanoix D, Beghdadi H, Lafond J, Vaillancourt C. Human placental trophoblasts synthesize melatonin and express its receptors. J Pineal Res. 2008 Aug;45(1):50-60.
37. Reiter RJ, Tan DX, Korkmaz A, Rosales-Corral SA. Melatonin and stable circadian rhythms optimize maternal, placental and fetal physiology. Hum Reprod Update. 2014 Mar-Apr;20(2):293-307.
38. Liu S, Guo Y, Yuan Q, Pan Y, Wang L, Liu Q, Wang F, Wang J, Hao A. Melatonin prevents neural tube defects in the offspring of diabetic pregnancy. J Pineal Res. 2015 Nov;59(4):508-17.
39. Wilkinson D, Shepherd E, Wallace EM. Melatonin for women in pregnancy for neuroprotection of the fetus. Cochrane Database Syst Rev. 2016 Mar 29;3(3):CD010527.
40. Sagrillo-Fagundes L, Assunção Salustiano EM, Ruano R, Markus RP, Vaillancourt C. Melatonin modulates autophagy and inflammation protecting human placental trophoblast from hypoxia/reoxygenation. J Pineal Res. 2018 Nov;65(4):e12520).
41. Laste G, Silva AAD, Gheno BR, Rychcik PM. Relationship between melatonin and high-risk pregnancy: A review of investigations published between the years 2010 and 2020. Chronobiol Int. 2021 Feb;38(2):168-181
42. Lanoix D, Beghdadi H, Lafond J, Vaillancourt C. Human placental trophoblasts synthesize melatonin and express its receptors. J Pineal Res. 2008 Aug;45(1):50-60.
43. Ghotbizadeh Vahdani F, Hantoushzadeh S, Nazari F. Melatonin as fetal neuroprotection: Links and risks. Biomed J. 2020 Dec;43(6):496-497.
44. Dominguez-Rodriguez A, Abreu-Gonzalez P, Sanchez-Sanchez JJ, Kaski JC, Reiter RJ. Melatonin and circadian biology in human cardiovascular disease. J Pineal Res. 2010 Aug;49(1):14-22.
45. Dominguez-Rodriguez A, Abreu-Gonzalez P, Reiter RJ. The potential usefulness of serum melatonin level to predict heart failure in patients with hypertensive cardiomyopathy. Int J Cardiol. 2014 Jun 15;174(2):415-7.
46. Dominguez-Rodriguez A, Abreu-Gonzalez P, Piccolo R, Galasso G, Reiter RJ. Melatonin is associated with reverse remodeling after cardiac resynchronization therapy in patients with heart failure and ventricular dyssynchrony. Int J Cardiol. 2016 Oct 15;221:359-63.
47. Simko F, Pechanova O, Repova Bednarova K, Krajcirovicova K, Celec P, Kamodyova N, Zorad S, Kucharska J, Gvozdjakova A, Adamcova M, Paulis L. Hypertension and cardiovascular remodelling in rats exposed to continuous light: protection by ACE- inhibition and melatonin. Mediators Inflamm. 2014;2014:703175.)
48. Green EA, Black BK, Biaggioni I, Paranjape SY, Bagai K, Shibao C, Okoye MC, Dupont WD, Robertson D, Raj SR. Melatonin reduces tachycardia in postural tachycardia syndrome: a randomized, crossover trial. Cardiovasc Ther. 2014 Jun;32(3):105- 12.
49. Pourhanifeh MH, Dehdashtian E, Hosseinzadeh A, Sezavar SH, Mehrzadi S. Clinical Application of Melatonin in the Treatment of Cardiovascular Diseases: Current Evidence and New Insights into the Cardioprotective and Cardiotherapeutic Properties. Cardiovasc Drugs Ther. 2022 Feb;36(1):131-155.
50. Sun H, Gusdon AM, Qu S. Effects of melatonin on cardiovascular diseases: progress in the past year. Curr Opin Lipidol. 2016 Aug;27(4):408-13.
51. Jiki Z, Lecour S, Nduhirabandi F. Cardiovascular Benefits of Dietary Melatonin: A Myth or a Reality? Front Physiol. 2018.
52. Shamir E, Laudon M, Barak Y, Anis Y, Rotenberg V, Elizur A, Zisapel N. Melatonin improves sleep quality of patients with chronic schizophrenia. J Clin Psychiatry. 2000 May;61(5):373-7
53. Uguz AC, Demirci K, Espino J. The Importance of Melatonin and Mitochondria Interaction in Mood Disorders and Schizophrenia: A Current Assessment. Curr Med Chem. 2016;23(20):2146-58.
54. Morera-Fumero AL, Abreu-Gonzalez P. Papel da melatonina na esquizofrenia. Int J Mol Sei . 2013;14(5):9037-9050. Publicado em 25 de abril de 2013.
55. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol. 2011 Sep;53(9):783-792
56. Lalanne S, Fougerou-Leurent C, Anderson GM, Schroder CM, Nir T, Chokron S, Delorme R, Claustrat B, Bellissant E, Kermarrec S, Franco P, Denis L, Tordjman S. Melatonina: da farmacocinética ao uso clínico no autismo Desordem do Espectro. Int J Mol Sci. 2 de fevereiro de 2021;22(3):1490.
57. Yenen AS, Çak HT. Melatonin and Circadian Rhythm in Autism Spectrum Disorders. Turk Psikiyatri Derg. 2020 Fall;31(3):201-211. English, Turkish.
58. Anderson G, Reiter RJ. Melatonin: Roles in influenza, Covid-19, and other viral infections. Rev Med Virol. 2020 May;30(3):e2109.
59. Simko F, Reiter RJ. Is melatonin deficiency a unifying pathomechanism of high risk patients with COVID-19? Life Sci. 2020 Sep 1;256:117902
60. Ameri A, Asadi MF, Kamali M, Vatankhah M, Ziaei A, Safa O, Mahmudi M, Fathalipour M. Evaluation of the effect of melatonin in patients with COVID-19-induced pneumonia admitted to the Intensive Care Unit: A structured summary of a study protocol for a randomized controlled trial. Trials. 2021 Mar 8;22(1):194.
61. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, Liu C, Reiter RJ. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 2020 Jun 1;250:117583.
62. Marhuenda J, Villaño D, Arcusa R, Zafrilla P. Melatonin in Wine and Beer: Beneficial Effects. Molecules. 2021 Jan 11;26(2):343.
63. Kubatka P, Zubor P, Busselberg D, Kwon TK, Adamek M, Petrovic D, Opatrilova R, Gazdikova K, Caprnda M, Rodrigo L, Danko J, Kruzliak P. Melatonin and breast cancer: Evidences from preclinical and human studies. Crit Rev Oncol Hematol. 2018 Feb;122:133-143
64. Li Y, Li S, Zhou Y, Meng X, Zhang JJ, Xu DP, Li HB. Melatonin for

the prevention and treatment of cancer. Oncotarget. 2017 Jun 13;8(24):39896-39921
65. Sanchez-Barcelo EJ, Mediavilla MD, Alonso-Gonzalez C, Reiter RJ. Melatonin uses in oncology: breast cancer prevention and reduction of the side effects of chemotherapy and radiation. Expert Opin Investig Drugs. 2012 Jun;21(6):819-31
66. Reiter RJ, Rosales-Corral SA, Tan DX, Acuna-Castroviejo D, Qin L, Yang SF, Xu K. Melatonin, a Full Service Anti-Cancer Agent: Inhibition of Initiation, Progression and Metastasis. Int J Mol Sci. 2017 Apr 17;18(4):843.
67. Farhood B, Goradel NH, Mortezaee K, Khanlarkhani N, Salehi E, Nashtaei MS, Mirtavoos-Mahyari H, Motevaseli E, Shabeeb D, Musa AE, Najafi M. Melatonin as an adjuvant in radiotherapy for radioprotection and radiosensitization. Clin Transl Oncol. 2019 Mar;21(3):268-279.
68. Ahabrach H, El Mlili N, Errami M, Cauli O. Circadian Rhythm and Concentration of Melatonin in Breast Cancer Patients. Endocr Metab Immune Disord Drug Targets. 2021;21(10):1869-1881.
69. Talib WH, Alsayed AR, Abuawad A, Daoud S, Mahmod AI. Melatonin in Cancer Treatment: Current Knowledge and Future Opportunities. Molecules. 2021 Apr 25;26(9):2506.
70. Fischer TW, Sweatman TW, Semak I, Sayre RM, Wortsman J, Slominski A. Constitutive and UV-induced metabolism of melatonin in keratinocytes and cell-free systems. FASEB J. 2006 Jul;20(9):1564-6
71. Slominski AT, Kleszczyński K, Semak I, Janjetovic Z, Zmijewski MA, Kim TK, Slominski RM, Reiter RJ, Fischer TW. Local melatoninergic system as the protector of skin integrity. Int J Mol Sci. 2014 Sep 30;15(10):17705-32.
72. Slominski, A. T., Zmijewski, M. A., Semak, I., Kim, T. K., Janjetovic, Z., Slominski, R. M., & Zmijewski, J. W. (2017). Melatonin, mitochondria, and the skin. Cellular and molecular life sciences : CMLS, 74(21), 3913-3925.
73. Slominski AT, Zmijewski MA, Semak I, Kim TK, Janjetovic Z, Slominski RM, Zmijewski JW. Melatonin, mitochondria, and the skin. Cell Mol Life Sci. 2017 Nov;74(21):3913-3925.
74. Palagini L, Manni R, Aguglia E, Amore M, Brugnoli R, Bioulac S, Bourgin P, Micoulaud Franchi JA, Girardi P, Grassi L, Lopez R, Mencacci C, Plazzi G, Maruani J, Minervino A, Philip P, Royant Parola S, Poirot I, Nobili L, Biggio G, Schroder CM, Geoffroy PA. International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders. Front Psychiatry. 2021 Jun 10;12:688890.

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