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# MELATONIN AND THE BENEFITS OF ITS SUPPLEMENTATION DURING PERI-MENOPAUSE AND MENOPAUSE

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**Abstract:** Melatonin is a hormone produced by the pineal gland, and its main role is to regulate the circadian cycle. However, the function of melatonin goes further, playing a significant role in relation to psychomotor changes, sleep disorders and a positive influence on well-being. Due to the reduction in serum levels not only of gonadal hormones but also of melatonin during the peri-menopause and menopause periods, women experience depression, anxiety, insomnia, obesity and consequently a lower quality of life. Although there is still lack of proof of the safety regarding doses and the chronic use of melatonin, the exogenous administration of this hormone is suggested as an alternative treatment for these psychosomatic and metabolic disorders related to menopause. This review aims to present and update information about the benefits and possible deleterious effects of melatonin as an adjuvant therapy in the peri-menopause and menopause.

**Keywords:** Melatonin, alternative treatment, menopause, peri-menopause, psychosomatic disorders, metabolic disorders, safety.

## BACKGROUND

The climacteric comprises the period in which a woman goes from the reproductive period to the non-reproductive period, and she experiences endocrine and biological changes (GURSOY; KISELI; CAGLAR, 2015; MIRANDA; FERREIRA; CORRENTE, 2014). The period within the last confirmed menstruation 12 months after the amenorrhea corresponds to menopause and to the consequent gradual reduction of female sex hormones, which results from loss of ovarian follicular activity (MARLATT; BEYL; REDMAN, 2018).

Variations in the age and the status that women enter menopause are reported as early, late, artificial and natural menopause. Early menopause occurs before women are aged 45, late menopause is after they are aged 53 and artificial menopause involves oopherectomy or ovariohysterectomy – surgical procedures that consist of the excision of female gonads (ANTUNES; MARCELINO; AGUIAR, 2003).

As a result of the reduction in the level of the hormone in this period, physiological and behavioral changes occur (MARLATT; BEYL; REDMAN, 2018). The most common alterations are "hot flashes", night sweats, sexual dysfunctions, increased accumulation of abdominal adipose tissue, obesity, osteoporosis, cardiovascular diseases and neuropsychiatric alterations, which are commonly reported as mood swings, irritability, depression and insomnia (BONANNI. et al., 2019; JEHAN et al., 2015; MARLATT; BEYL; REDMAN, 2018; NIE et al., 2017; TOFFOL et al., 2014, 2021). These clinical signs negatively interfere with the quality of life of women (FREITAS; BARBOSA, 2015, 2015; NIE et al., 2017; TOFFOL et al., 2021).

The period of peri-menopause and menopause corresponds not only to a drop in the level of gonadal hormones but also to serum melatonin levels (TOFFOL et al., 2014). The lower plasma concentration of melatonin is mainly associated with psycho-motor signs of menopausal women, correlated with the hypothalamic-pituitary-ovarian axis (TOFFOL et al., 2014; GREENDALE et al., 2020; JEHAN et al., 2015, 2017).

The use of hormone therapies with steroids aimed at attenuating these symptoms is an option; however, the use of hormones such as estrogen according to Toffol et al. (2013) can accentuate psychological symptoms such as anxiety and depression when comparing with cases of women who do not use hormone therapy. In addition, they may cause unwanted effects such as thromboembolism

(SRIPRASERT et al., 2020), Alzheimer's disease (SAVOLAINEN-PELTONEN et al., 2019), cardiovascular disease, breast cancer (BERAL et al 2011; Collaborative Group on Hormonal Factors in Breast Cancer, 2019), ovarian and endometrial thromboembolic stroke, gallbladder disease, dementia and urinary incontinence.

Therefore, alternative solutions without deleterious health effects are sought to alleviate the clinical signs that result from menopause (GOLLSCHEWSKI et al., 2008). And melatonin appears as a protagonist in the choice of adjuvant therapy for the treatment of these disorders. Studies show results of improvement in psychosomatic symptoms in peri-menopausal and menopausal women, due to the ability of melatonin to re-synchronize circadian rhythms and consequently cause beneficial effects related to improvement of sleep quality and mood (BONANNI et al., 2019; CHOJNACKI et al., 2016; HESS et al., 2012; MAGANHIN et al., 2008). In addition to the positive effect on sleep, melatonin is closely linked to the female reproductive functioning (JEHAN et al., 2015; KOTLARCZYK et al., 2012; REITER et al., 2009; TALPUR et al., 2018).

Because of the lower level of melatonin according to age and stage of reproductive life, and the influence of this hormone during peri-menopause and menopause, this review aims to present and update the relationship between melatonin and the reproductive function, as well as its effects as a treatment for physical and emotional disorders related to this period. The possible deleterious effects in the indiscriminate use of this hormone are also approached in this review.

## METHODS

In order to perform this non-systematized literature review, the keywords "Melatonin", "Cytotoxicity", "Menopause", "Behavior", "Anxiety" and their equivalents in English were searched on the following databases: Scientific Electronic Library Online (SciELO), US National Library of Medicine, National Institutes of Health (PubMed), the academic literature platform of the publisher Elsevier (ScienceDirect) and *Revista Brasileira de Análises Clínicas* (RBAC). The criteria for inclusion and exclusion of articles, aiming at the development of the present work took into account the content of the title and the abstract of each article searched.

Therefore, articles included in the research were those that report the function of melatonin in the human body and its connection to behavior regarding fear, anxiety and stress; articles that report the changes that menopause causes to the female body and the consequences of reduced estrogen and also of melatonin production; and experimental articles with the use of melatonin as a treatment. In addition to them, articles that obtained information on cytotoxicity regarding the use of melatonin in different dosages and possible deleterious effects were also included.

Experimental and review articles were used, written either in English and / or Portuguese language, found in the aforementioned databases, and whose publications are not prior to 15 years in relation to the year of this study.

Articles that did not contain in their title or abstract any information that referred to the object of this work, neither any comments from other articles or letters to the editor were excluded. After checking and reading these studies and using the inclusion and exclusion criteria, a total of 1,082 pieces of work were found; however, 77 pieces of work were accepted for fitting the aim of this study.

## MAIN TEXT

## MELATONIN: SYNTHESIS AND PHYSIOLOGY

Discovered by American dermatologist Aaron Lerner and colleagues in 1958, melatonin was initially extracted from bovine pineal glands. The aim was to develop a skin lightening product (LERNER et al., 1958). Subsequently, melatonin was identified in other living beings such as plants, fungi, bacteria, invertebrate and vertebrate animals, including humans (ZHAO et al., 2019).

Melatonin is an indolamine produced mainly in the pineal gland by pinealocytes and in other tissues such as the retina, the ciliary body of the iris, lacrimal glands, ovaries, lymphocytes and the large intestine, but in these areas its production is used only for local action, while the pineal gland produces melatonin for distribution throughout the body (MAGANHIN et al., 2008; PARK et al., 2018; TAMURA et al., 2020; ZHAO et al., 2019).

This hormone is synthesized by sympathetic noradrenergic stimulation via postganglionic innervation originating in the superior cervical ganglion. Its greatest production occurs at night, from essential amino acid tryptophan, which is hydrolyzed by enzyme tryptophan hydroxylase (TPH) into 5-hydroxytryptophan (5-HTP), and it undergoes the action of the 5-HTP decarboxylase enzyme, resulting in 5-hydroxytryptamine (serotonin or 5-HT). This, in turn, is converted into N-acetylserotonin (NAS), and by means of enzyme arylalkylamine-N-acetyltransferase (AANAT) enzyme acetylserotonin-oxymethyltransferase (ASMT) gives rise to 5-meloxy-N-acetyltryptamine – melatonin (DUBOCOVICH; MARKOWSKA, 2005; HE et al., 2016; ROBERTS; FITZPATRICK, 2013).

Unlike the hormones that are dependent on the hypothalamic-pituitary axis, the production of melatonin does not depend on feedback mechanisms. Thus, the level of melatonin in the plasma does not regulate its own production and is in line with the synthetic activity of the pineal gland, as there is no storage of melatonin by the gland (REITER; TAN; GALANO, 2014).

Exogenously administered melatonin, like endogenous melatonin, is metabolized via the liver through the activity performed by hepatic cytochrome P450, predominantly the CYP1A2 isoform, followed by conjugation with sulfuric acid (90%) or glucuronic acid (10%) and finally being excreted in the urine. Only 5% of the unmetabolized serum melatonin is excreted in the urine. Oral administration has first-pass metabolism and an absolute bioavailability of approximately 15%. Melatonin metabolites are excreted via the kidneys. In healthy people, melatonin elimination has a half-life of 30 – 45 minutes; this time range can be tripled in patients with liver and kidney disorders (MARRA et al., 2019).

Being rather lipophilic, melatonin bathes different tissues up to the point it reaches their membrane receptors – MT1 (also known as MTNR1A or Mel1A) and MT2 (also known as MTNR1B or Mel1B). Both membrane receptors are coupled to the $G_i$ protein; the MT1 receptor being composed of 350 amino acids with affinity for the $G_q$ or $G_{11}$ proteins. Such a condition allows this receptor to activate phospholipase C, increase the production of diacylglycerol and inositol triphosphate (IP3), and consequently increase intracellular calcium concentration and protein kinase C activity, in addition to being responsible for inducing sleep (LI et al., 2019).

MT2, composed of 363 amino acids, is responsible for the regulation of circadian rhythms, and also physiological and

neuroendocrine functions (CLAUSTRAT; BRUN; CHAZOT, 2005; DUBOCOVICH; MARKOWSKA, 2005; REITER et al., 2009; WANG et al., 2021; ZHANG; ZHANG, 2014).

There is a third receptor – MT3 (MTNR1C or Mel1c), which belongs to the quinone reductase family. It is found in the cytosol of some cells, it is not coupled to a G protein and it has a molecular structure similar to an enzyme, the quinone reductase. To date little is known about its functioning (LI et al., 2021; REITER; TAN; GALANO, 2014).

The influence of melatonin extends its role as a circadian pacemaker to the control of the reproductive function and even to bone balance (GREENDALE et al., 2020). One of its most important roles is to transmit information about the photoperiod, which is closely linked to physiology because it establishes functions that vary according to season, namely: reproduction, body coat, appetite, body weight and sleep. The photoperiod is often critical for the timing of pubertal development, which includes changing gonadotropic hormone excretion levels and influencing steroid feedback in gonadotropic regulatory systems in the hypothalamus (PARK et al., 2018; ZAWILSKA; SKENE; ARENDT, 2009).

Daily variation and sensitivity to light, which suppresses melatonin activity, are characteristics found in several species regardless of whether the species is diurnal, nocturnal or with a pattern of twilight activities. Melatonin levels are high during the dark phase of any natural or enforced light-dark cycle (ZHAO et al., 2019). The onset of endogenous melatonin release is at night, after 9:00 pm, reaching its peak release between 2:00 am and 4:00 am. It is normally inhibited between 7:00 am and 9:00 am, coinciding with the peak of endogenous cortisol secretion, and performing circadian rhythmic production synchronized to the environment lighting phase referred to day and night; this can be inhibited by artificial light (MARRA et al., 2019).

## MELATONIN AND THE REPRODUCTIVE FUNCTION

Regarding reproductive physiology, melatonin has a direct relationship with the ovarian function (TALPUR et al., 2018; WANG et al., 2021). In oocyte mitochondria it promotes maturation and reduces stress by reactive oxygen species in oocytes, besides promoting luteinization of granulosa cells, embryo fixation and maintenance of pregnancy (PARK et al., 2018; SOLIMAN et al., 2015; TAMURA et al., 2020; WANG et al., 2021).

This occurs as a result of the presence of MT1 and MT2 receptors in the ovarian follicles that influence the modulation of steroidogenesis, especially in progesterone production and in the expression of luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) receptors (HARDELAND, 2012; MAGANHIN et al., 2008; ROCHA et al., 2011; TALPUR et al., 2018; WANG et al., 2021).

*In vitro* studies have shown that melatonin increases progesterone production in human corpus luteum cells (TAKETANI et al., 2011). *In vivo* studies have shown an increase in progesterone production as well as an improvement in the productive efficiency in sows and mice (PARK et al., 2018). Melatonin receptors were evidenced in their follicular cells, correlating the production of ovarian melatonin in these species as well as in humans (ROCHA et al., 2011).

The MT2 receptor performs roles that include control, storage and distribution of lipids in the ovaries; cholesterol in its turn is the precursor of progesterone. Cytosolic cholesterol from oocytes is transported to the mitochondria and to the endoplasmic

reticulum to finally synthesize progesterone (WANG et al., 2021).

In humans, melatonin production is greater during childhood, acting as inhibitor to GnRH secretion, since melatonin has receptors on GnRH-releasing cells. However, when the human being reaches 10 years of age there is a reduction in the release of melatonin, sending signals to the hypothalamus to inform that the moment of onset of puberty has come (HE et al., 2016).

The regulation of reproduction in non-human mammals occurs at the time of greatest melatonin release, thus being characterized by seasonal reproduction since melatonin depends on the amount of light that the animals are exposed to, with different concentrations of the production of this hormone according to each season of the year (LI et al., 2018). In short-day animals, such as rodents and sheep, melatonin production stimulates GnRH secretion; whereas in long-day animals, such as horses, melatonin production inhibits GnRH secretion. Considering these parameters, it is possible to understand that the difference in length of the day can create signals capable of activating or not sexual activity in a species-specific manner (ROCHA et al., 2011).

## PERI-MENOPAUSE AND MENOPAUSE – MELATONIN EFFECTS

In a physiological female reproductive cycle, there is production of GnRH by the hypothalamus, which exerts control over the ovarian and menstrual cycle. Its release stimulates the secretion of follicle-stimulating hormone (FSH), with consequent follicular growth in the ovary and LH, which helps with the development of follicles by promoting ovulation and formation of the corpus luteum. Both hormones stimulate the release of estrogen, found in greater concentration after the development of the corpus luteum,

following ovulation, and then the release of more estrogen in addition to progesterone. Estrogen acts in the maintenance and development of female reproductive structures, and through negative feedback. When there are adequate concentrations, it can inhibit the release of GnRH, FSH and LH (TORTORA; DERRICKSON, 2012).

The female body goes through a few stages until it reaches the period called post-menopause. The first stage is pre-menopause, a period in which the remaining follicles in the ovary no longer respond adequately to the hormonal stimuli of FSH and LH, leading to lower production of estrogen and progesterone. As a result, the anovulatory cycle develops, that is, an egg is not released. During the menstrual cycle, the time between cycles gets longer. This period can last several years. Then comes the second stage – peri-menopause. This is a period of irregular cycles until a year after the last menstrual period. The third stage is menopause, the period of the last menstruation, when the activity of the ovaries ends. As a result, there is not enough estrogen production to induce the proliferation of the endometrium and consequent menstruation. The last phase, which is called post-menopause, lasts until the end of a woman's life (AVIS et al., 2015).

In addition to the dramatic drop in the level of reproductive hormones during menopause, there is also a gradual reduction in melatonin levels (EL KHOUDARY et al., 2019; GREENDALE et al., 2020; TOFFOL et al., 2021). According to Greendale et al. (2020) there is a 30% reduction in melatonin secretion in menopausal women with a mean age of 52 years, when compared to peri-menopausal women with a mean age of 46 years and to cyclical women.

Vasomotor symptoms, cardiovascular diseases, musculoskeletal disorders, osteoarthritis and osteoporosis are among

the most frequent complaints in the peri-menopause and post-menopause stages (AVIS et al., 2015; BONANNI et al., 2019; JOFFE; MASSLER; SHARKEY, 2010; TOFFOL et al., 2014; ZOLFAGHARI et al., 2020).

Low melatonin secretion may lead to unbalanced bone remodeling, bone mass reduction and marrow adipogenesis, thus favoring bone problems, including fractures. Studies show that melatonin positively influence several osteoblast differentiation markers, negatively regulate several adipocyte differentiation marker terminals, directly inhibit adipogenic differentiation and significantly increase osteogenic differentiation, thus improving bone density. It has been cited as an anti-osteoporosis type of medication (AMSTRUP et al., 2015; ZHANG et al., 2010)

Psychic symptoms such as mood swings, insomnia, anxiety, depression, cognitive decline and consequently lower productivity at work are also reported at this stage (AVIS et al., 2015; HESS et al., 2012; MARLATT; BEYL; REDMAN, 2018; PALACIOS et al., 2010; GUARNIERI, 2019).

These clinical signs are related to hormonal decline in this stage. The quality of sleep, mood and metabolism are related to progesterone, which exerts anxiolytic and sedative properties, stimulates benzodiazepine receptors and favors deeper sleep. Estrogen, in its turn, decreases sleep latency and the number of awakenings (GERVAIS; MONG; LACREUSE, 2017).

The piece of research performed by El Khoudary et al. (2019) evaluated women for 10 years during peri-menopause and menopause. Their study showed that insomnia occurred in 46-48% of menopausal women versus 38% in peri-menopausal ones. In another study performed by Bonanni et al. (2019) 80% of women reported "hot flashes", a common symptom of menopause.

As for melatonin, studies with transgenic mice suggest involvement in insomnia, depression and usual neurological performance, showing psychological changes such as depression in humans when there is no presence of MT1 receptors (COMAI et al., 2015). In humans, low levels of melatonin are also associated with the severity of depression (SUNDBERG et al., 2016). The lower concentration of MT1 and MT2 also induced depression and anxiety-like behaviors in mice (LIU et al., 2017). Studies with exogenous administration of melatonin in peri-menopausal and menopausal women show positive results regarding improvement in sleep quality, depression and psychosomatic symptoms (BONANNI et al., 2019; CHOJNACKI et al., 2015a, 2016, 2018; LI et al., 2019).

Gastric disturbances may also occur due to low estrogen levels, which exert a protective effect by inhibiting the secretion of hydrochloric acid and pepsin, and by stimulating the secretion of mucus and bicarbonates (TUO et al., 2011). Melatonin administration in women with menopausal gastric disorders was beneficial in relieving symptoms (CHOJNACKI et al., 2020). Eating disorders and weight gain in peri-menopausal and menopausal women are also reported. Melatonin has shown a glycemic regulating effect, decreasing insulin resistance, and also contributing to adipose tissue loss and lean mass gain (AMSTRUP et al., 2016; CAGNACCI et al., 2001).

Considering the pieces of research that have already been performed, there are indications of beneficial effects of exogenous use of melatonin in women in the phase in which the transition from peri-menopause to menopause occurs, associated with the clinical signs of this phase, as shown in Table 1.

| Reference | Aim | Analyzed patient | Administered dose | Study evidence |
|---|---|---|---|---|
| D'Anna et al. (2017) | To evaluate effects on serum insulin and serum thyroid profile of a dietary supplement (myo-inositol) administered alone or in combination with melatonin in women during the menopausal transition. | 40 women aged 45-55 y-o with amenorrhea for at least 6 months | A myo-inositol 2 g BID group and another group: myo-inositol 2 mg plus melatonin 3mg administered orally before sleeping | The combination of myo-inositol plus melatonin positively affected the metabolism of glucose |
| Chojnacki et al. (2018) | To evaluate the effect of melatonin supplementation on the release of female hormones and on the alteration of climacteric symptoms | 60 women at post-menopause aged 51-64 y-o | 3 mg in the morning and 5 mg via orally at sleep time for 12 months | Melatonin supplementation exerts a positive effect on psychosomatic symptoms in postmenopausal women |
| Chojnacki et al. (2020) | To assess the role of melatonin in the pathogenesis of chronic dyspepsia in menopausal women and examine the effect of Helicobacter pylori infection | 152 women aged 49 – 64 y-o at menopause | 1 mg in the morning and 3 mg via orally at sleep time | Melatonin supplementation is useful in the treatment of dyspepsia associated with H. pylori, particularly in menopausal women with low hormone levels |
| Amstrup et al. (2015) | To investigate whether melatonin treatment could improve bone mass and integrity in menopausal women | 81 women with osteopenia at menopause | 1 mg, 3 mg, via orally at sleep time | Treatment with melatonin increased bone mineral densitometry in the femoral neck of one female and increased volumetric bone density in her spine |
| Amstrup et al. (2016) | To determine the effects of melatonin in the body composition | 81 women at menopause | 1 mg, 3 mg, via orally at sleep time | Reduced fat mass and increased lean mass |
| Chojnacki et al. (2015) | To evaluate the effectiveness of fluoxetine and its association with melatonin in the treatment of mood and sleep disorders | 64 women at menopause with excess wight, aged 54-65 y-o | Fluoxetine 20 mg in the morning and melatonin 5 mg at sleep time | Combined administration of fluoxetine and melatonin was beneficial to treat mood, sleep and appetite disorders |
| Cagnacci et al. (2001) | To investigate whether melatonin influences glucose tolerance and insulin sensitivity in menopausal women | 22 women at menopause | 1 mg via orally | Melatonin reduced glucose tolerance and insulin sensitivity |

Table 1. Study with administered melatonin doses and evidence of the effects produced on women at peri-menopause /menopause.

In addition, the use of exogenous melatonin assists in the control of conditioned fear, as an alternative for the treatment of post-traumatic stress (HUANG; YANG; LI, 2017). In an animal model, a study simulating Alzheimer's disease showed positive results regarding lower levels of anxiety and depression associated with its administration (NIE et al., 2017). In another study performed in sheep, the use of melatonin was associated with less social isolation and with calming effects in stressful situations (GUESDON et al., 2013).

Due to the beneficial characteristics and positive effects on the improvement of symptoms resulting from menopause, women seek the exogenous use of melatonin in search of a better quality of life as an alternative to hormonal treatments (GURSOY; KISELI; CAGLAR, 2015).

## EXOGENOUS MELATONIN

Melatonin can be administered exogenously – orally, in capsules, tablets and liquids, or as transdermal patches. The main indications of melatonin for menopausal women are sleep disorders, depression and anxiety (BONANNI et al., 2019; CHOJNACKI et al., 2015a; TOFFOL et al., 2014).

The fact that this hormone is endogenously produced and occurs naturally in some foods allows it to be sold as a dietary supplement in the United States under the Food Supplement Health and Education Act of 1994, without pre-marketing approval by the Federal Drug Administration (FDA). Also in other countries it is available over-the-counter for the treatment of insomnia and depression (POSADZKI et al., 2018). In the European Union, the 2 mg/day dose is allowed by the European Medicines Agency (EMA).

In 2021, the National Health Surveillance Agency (Anvisa) in Brazil, approved the use of melatonin for the formulation of food supplements, restricting its use to people aged 19 years and over; and in a maximum dose of 0.21 mg. However, doses above the indicated are widely prescribed and used in studies as shown in Table 1.

As melatonin receptors are found in virtually all tissues, their administration possibly affects the vast majority, if not all, of the body's cells, resulting in different physiological and pathophysiological actions of melatonin (REITER; TAN; GALANO, 2014). The use of supra-physiological doses, often without medical prescription, leads to concern and to the need for studies on their use regarding their toxicity and apoptotic capacity (KOCYIGIT et al., 2018; SEABRA et al., 2000).

## MELATONIN X TOXICITY

The process of apoptosis occurs through factors that activate pro-apoptotic molecules such as DNA damage, scarcity of growth factors and nutrients, heat shock and intracellular accumulation of reactive oxygen species (HENGARTNER, 2000). Morphological changes observed in cells undergoing apoptosis result from the activation of specific enzymes called caspases. Such enzymes modulate the apoptotic process and act as primary markers in apoptosis assays even before morphological signs are evident (JULIEN; WELLS, 2017).

Caspases are responsible for cleaving substrates that contain aspartic acid residues, such as the poly (ADP-ribose) polymerase enzyme, cell cycle regulatory proteins, structural proteins such as laminin and actin, among others. In humans, more than 14 types of caspases are already known; caspases 1, 4 and 5, for instance, are fundamental in the inflammatory process, while caspases 2, 3 and 10 are predominantly involved in apoptosis (JULIEN; WELLS, 2017).

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Depending on the stage at which they participate in the apoptosis process, caspases can be called initiators (caspases 8 and 10) or executors (caspases 3 and 7). In cell culture, melatonin inhibits the proliferation of human breast cancer cells (MCF-7), inducing a cell cycle arrest, dependent on an increase in the expression of the p21WAF1 protein, which is mediated by the p53 pathway, thus causing unbalance to the process between mitosis and apoptosis (CHOI et al., 2002).

Although studies have shown the antioxidant capacity of melatonin, recent *in vitro* studies have demonstrated the possibility of pro-oxidant effects, which may be cytotoxic in healthy cells (KOCYIGIT et al., 2018), due to the ability of melatonin to produce reactive oxygen species (KOCYIGIT et al., 2018; RADOGNA et al., 2009; SÁNCHEZ-SÁNCHEZ et al., 2011; WANG et al., 2012, 2021; ZHOU et al., 2014). This increases caspase activity, as well as apoptotic and antiproliferative function, especially in cancer cells (SÁNCHEZ-SÁNCHEZ et al., 2011; WANG et al., 2012; ZHOU et al., 2014).

There are few reports on the dose-dependent proliferative or antiproliferative effects of melatonin and its relationship with the ability to produce reactive oxygen species in both cancer cells and normal cells (KOCYIGIT et al., 2018).

In any case, the prolonged use of medications can cause liver damage, thus limiting the normal functions of this organ (BERTOLAMI, 2005). Hepatotoxic effects can lead to the development of liver failure, which can be classified as either acute or chronic. Drugs with pro-oxidant effect and cytotoxic properties may result in cellular apoptosis; the tissue that suffers chronic injury is replaced by a fibrous tissue (HALL; GUYTON, 2011; KOCYIGIT et al., 2018).

When this phenomenon occurs, the lysis of hepatocytes releases enzymes into the bloodstream and increases the serum concentration of gamma-glutamyl transferese (GGT), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) (BERTOLAMI, 2005).

Other changes that patients in these conditions can present are jaundice, and hyperbilirubinemia; in more severe cases, steatosis and fibrosis; and in even more severe levels hepatocarcinoma can occur (HALL; GUYTON, 2011).

Hepatotoxic reactions or liver damage caused by drugs are the second leading cause of acute liver failure (BERTOLAMI, 2005). Due to this evidence of indiscriminate use of melatonin at doses above the recommended ones and evidence of cell damage, further research is suggested in relation to doses of melatonin at safe levels. This is especially the case in menopausal women who have metabolic changes due to age and who seek alternative means to control peri-menopause and menopause symptoms (PU et al., 2017).

## CONCLUSIONS

Changes in hormone levels resulting from the peri-menopause and menopause periods are associated with a lower quality of life due to physiological and psychological disorders triggered at this stage. Melatonin has been used to alleviate symptoms that produce physical discomfort and emotional conditions in menopausal patients. Despite studies with the use of melatonin in cases of psychological or biological changes, it is important that more studies be carried out to evaluate the performance of the supplement in women in peri-menopause and menopause so that there is greater reliability for the prescription of this hormone.

## List of Abbreviations

AANAT: enzyme arylalkylamine-N-acetyltransferase

ALP: Alkaline phosphatase

ALT: Alanine aminotransferase

Anvisa: National Health Surveillance Agency

ASMT: Enzyme acetylserotonin-oxymethyltransferase

EMA: European Medicines Agency

FDA: Federal Drug Administration

GGT: Gamma-glutamyl transferese

FSH: Follicle-Stimulating Hormone

GnRH: Gonadotropin-releasing hormone

LH: Luteinizing hormone

NAS: N-acetylserotonin

TPH: Enzyme tryptophan hydroxylase

5-HTP: 5-hydroxytryptophan

5-HT: 5-hydroxytryptamine

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