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REVIEW ARTICLE

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Systematic review of melatonin metabolism and circadian cycle regulation in the treatment of obesity and liver diseases

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Abstract

Introduction: In the context of obesity and liver disease, sleep disorders are associated with several metabolic disorders, including insulin resistance, obesity, hypertension, fatty liver disease, and cardiometabolic complications. In this regard, melatonin (N-[2-(5-methoxy-1H-indol-3-yl)ethyl] acetamide) stands out. It is a neurohormone secreted by the pineal gland and plays a fundamental role in maintaining the circadian rhythm. **Objective:** To present the main considerations regarding the importance of melatonin and circadian regulation, as well as the effect of melatonin supplementation on obesity and liver disease. **Methods:** The systematic review guidelines of the PRISMA Platform were followed. The search was conducted from May to June 2025 across the Scopus, Embase, PubMed, and ScienceDirect, Scielo, and Google Scholar databases. Study quality was based on the GRADE instrument, and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 182 articles were found. A total of 58 articles were evaluated, and 51 were included in this systematic review. Using the Cochrane risk of bias tool, the overall assessment resulted in 15 studies with a high risk of bias and 21 studies that did not meet the GRADE criteria. Most studies presented homogeneous results, with X^2=95.8%>50%. It was concluded that metabolic and liver diseases affect thousands of individuals worldwide, worsening quality of life and mainly compromising the productive period. Studies involving drug and molecular therapies are proposed to control the progression of these diseases. A molecular analysis involving epigenetic, biochemical, and inflammatory aspects related to melatonin supplementation is needed to clarify the effect of melatonin supplementation on obesity and liver diseases, including NAFLD and HCC. The elucidation of the antioxidant and antiinflammatory effect of melatonin and its use as a synergistic agent in weight

loss, as well as in liver diseases, in personalized treatment, were highlighted.

Keywords: Obesity. Liver diseases. Inflammatory processes. Melatonin.

Introduction

In the context of obesity and liver disease, sleep disorders are associated with several metabolic disorders, including insulin resistance, obesity, hypertension, fatty liver disease, and cardiometabolic complications. In this respect, melatonin (N-[2-(5-methoxy-1H-indol3-yl)ethyl]acetamide) stands out as a neurohormone secreted by the pineal gland, playing a fundamental role in maintaining the circadian rhythm. It is involved in the regulation of adipose tissue development (a dynamic endocrine organ that secretes hormones and cytokines), lipid accumulation, browning of white adipose tissue, and activation of brown adipose tissue **[1,2]**.

Melatonin is synthesized from serotonin by the initial conversion of tryptophan to serotonin, which produces N-acetylserotonin, whose molecule will then be converted into melatonin **[3]**. This hormone functions as a regulator of the circadian rhythm and is also a potent antioxidant and anti-inflammatory **[4]**. Melatonin secretion decreases with age, influencing seasonal and circadian rhythms, the sleep-wake cycle, and reproduction **[5]**. It exhibits a day/night secretion pattern, sensitive to light, with an increase in the early evening and a decrease at the end of this period **[6]**. In addition, it participates in several other biological functions, including the control of energy balance with a modulating effect on insulin secretion and action, as well as lipid metabolism **[7]**.

Also, melatonin is considered an important chronobiotic that influences the circadian distribution of metabolic processes, synchronizing them with the feeding, rest, and fasting cycle. In this case, it stands out in the regulation of energy flow and expenditure through the activation of brown adipose tissue **[8,9]**. It should also be noted that melatonin can cause the darkening of white adipose tissue, thus assisting in the regulation of body weight **[10]**.

This process, however, can be impaired during aging, as well as during shift work and night work (due to lighting). In this context, there is reference to its association with insulin resistance, glucose intolerance, sleep disorders and circadian metabolic disorganization, characterizing a state of chronological disruption and metabolic diseases with aggravation of general health **[11]**. Thus, melatonin replacement can be an important factor in controlling these diseases, as well as in the inflammatory process **[10,11]**.

In this sense, circadian rhythms (CRs) are endogenous rhythms that respond to external stimuli and regulate physiological functions. The suprachiasmatic nucleus (SCN) in the hypothalamus is the master clock of mammals that synchronizes all other tissue-specific peripheral clocks, mainly through gamma-aminobutyric acid (GABA) and vasoactive intestinal polypeptide (VIP). The SCN follows the Earth's 24-hour cycle by light entrainment through the retinohypothalamic tract. At the cellular level, the central clock genes CLOCK, BMAL1, PER1-PER3, CRY1, and CRY2 regulate CRs in a negative feedback loop. CR disorders can cause infertility, menstrual irregularities, as well as diabetes, obesity, fatty liver disease, and other metabolic syndromes. In addition, a disruption in the gut microbiome creates a pro-inflammatory environment. CR disorders increase the risk of mood disorders. People with neurodegenerative diseases demonstrate significant disturbances in their CRs and their sleep-wake cycles. Furthermore, CR disorders can also increase the risk of cancer by impacting DNA repair, apoptosis, immune surveillance, and cell cycle regulation **[12]**.

Melatonin can modulate inflammatory processes by eliminating nitric oxide, a molecule involved in tissue injury as a secondary inflammatory mediator. There are reports that melatonin can reduce the synthesis or inhibit other pro-inflammatory mediators, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 8 (IL-8) **[13]**. In this sense, metabolic and liver diseases become targets of studies with melatonin, aiming to clarify its association with molecular mechanisms and possible use in clinical practice.

Thus, the present study aimed to present the main considerations of the importance of melatonin and the regulated circadian cycle, as well as the effect of melatonin supplementation in obesity and liver diseases.

Methods

Study Design

This study followed a concise systematic review model, following the PRISMA systematic review guidelines. Available on: Transparent reporting of systematic review and meta-analysis: //www.prisma-statement.org/). Accessed on: June, 12,2025.

Research Strategy and Sources

The literature search process was conducted from May to June 2025 and developed based on Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various periods to the present. The following descriptors were used (DeCS/MeSH Terms): *"Obesity. Liver diseases.*

Inflammatory processes. Melatonin", and using the Boolean operator "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

As a corollary to the literature search system, a total of 182 articles were found, which were submitted to eligibility analysis, and then 51 of the 58 final studies were selected to compose the results of this systematic review. The listed studies presented medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=95.8%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 15 studies with a high risk of bias and 21 studies that did not meet the GRADE criteria.

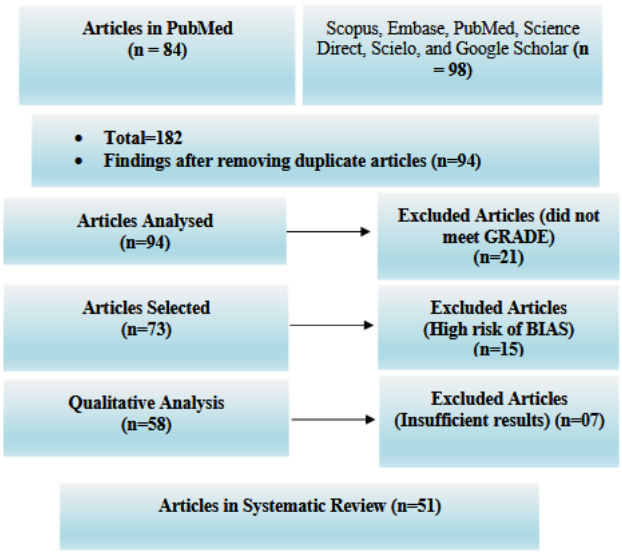

Figure 1. Flowchart showing the article selection process. Source: Own authorship

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test

(d). The precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are presented at the top.

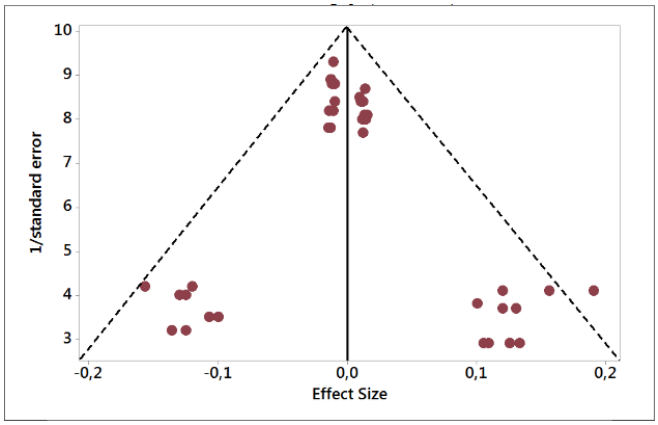

Figure 2. The symmetrical funnel plot does not suggest a risk of bias between the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=51 studies). Source: Own authorship.

Main Clinical Findings – Melatonin, Obesity, and Liver Diseases

Obesity is a chronic disease resulting from an imbalance between caloric intake and energy expenditure, triggering excessive accumulation of body fat. It is noted that the global incidence of obesity has increased since 1980, with almost a third of the world's population presenting this type of dysfunction **[14]**. In Brazil, data from the latest Surveillance of Risk and Protective Factors for Chronic Diseases by Telephone Survey (VIGITEL, 2018) **[15]** showed that overweight increased by 26.3% in 10 years, reaching 57.7% of men and 50.5% of women. Regarding the condition of obesity, an estimated prevalence of 18.9% was calculated in the entire Brazilian population, being present in 18.1% of adult males and in 19.6% of adult females (VIGITEL, 2018) **[15]**. For the classification/diagnosis of obesity in adults, the most commonly used parameter is the body mass index (BMI), proposed by Quetelet (1869) **[16]**. It is obtained by the ratio of body mass in kilograms to height in meters squared (kg/m^2).

It is considered one of the most serious public health problems in current society **[17]**, being a multifactorial condition involving genetic, behavioral, and environmental factors **[18-20]**. It is associated with an increased risk of chronic diseases, including type II diabetes mellitus, dyslipidemia, systemic arterial hypertension, cardiovascular diseases, and some types of cancer **[21-24]**. The association of obesity with chronic low-grade inflammation is highlighted, which contributes to the development of the aforementioned systemic metabolic disorders **[25]**. Obesity causes several intrinsic and extrinsic signals capable of triggering an inflammatory response in adipose tissue. These mechanisms are usually considered the link between chronic caloric excess and adipose tissue inflammation. Some of these mechanisms include dysregulation of fatty acid homeostasis, local hypoxia, mitochondrial dysfunction, increased size and death of adipose cells, as well as mechanical stress **[26]**.

Inflammation is known to be related to a state of oxidative stress with a large production of reactive oxygen species, compared to antioxidant levels, allowing their action and compromising natural defense systems. In this context, melatonin has received attention for its antioxidant and anti-inflammatory properties. Considering that melatonin modulates several processes involved in obesity, there is a reference to the possibility of obtaining benefits from its use in various treatments **[27]**. It should also be noted that the high prevalence of obesity in the world population also confers an increased risk for the development of non-alcoholic fatty liver disease (NAFLD), as well as other liver diseases, including hepatocellular carcinoma (HCC).

NAFLD is characterized by the deposition of triglycerides (TG) in hepatocytes, exceeding 5-10% of the total organ weight **[28]**, even without continuous intake of significant amounts of alcohol (>20 g/day) **[29]**. NAFLD is one of the main causes of chronic liver disease, with a worldwide prevalence of approximately 20 to 30%, becoming a growing public health concern **[30]**. In Brazil, this rate is still unknown; however, the Brazilian Society of Hepatology highlights high frequencies of steatosis (48%), non-alcoholic steatohepatitis (37%), and cirrhosis (5%) **[31]**. NAFLD is also considered a component of metabolic syndrome, due to the close association between these conditions. Approximately 90% of individuals with NAFLD present at least one characteristic of metabolic syndrome, in addition to a risk for cardiovascular disease (CVD), HCC, and type 2 diabetes mellitus in long-term follow-up **[29]**.

In this context, melatonin stands out for its effective action against metabolic syndrome, reversing the harmful effects of dietary fructose in animal models, modulating metabolic pathways such as lipogenesis, lipolysis, beta-oxidation, and gluconeogenesis. In addition, lipophilic melatonin freely passes through all biological membranes and accumulates mainly in mitochondria, where it influences mitochondrial structure and function via the peroxisome proliferator-activated receptor gamma (PGC1) coactivator signal. Melatonin can also be taken up in the liver by specific cellular and nuclear receptors in a dose-dependent manner **[32]**.

Oral administration of circulating melatonin in humans has a half-life ranging from 25 to 65 min **[33]**. Melatonin is rapidly metabolized by enzymatic and non-enzymatic processes. Cytochrome P450 (CYP450) is the main enzyme for melatonin metabolism in animals and is located mainly in the liver. The main and secondary products of CYP450 are 6-hydroxymelatonin and N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), respectively. The non-enzymatic process of melatonin metabolism is mediated by its interaction with reactive oxygen species (ROS) and nitric oxide synthase (NOS) during oxidative stress **[34]**.

In vivo studies have demonstrated the effectiveness of melatonin in reducing the accumulation of intrahepatic lipid levels. Stacchiotti et al. (2019) **[35]** reported that melatonin attenuated NAFLD in leptin-deficient mice and in hypercholesterolemic Apo E knockout mice by increasing Syntuin-1 (SIRT1) protein in hepatocytes. This also indicated that the use of melatonin in the diet may be promising for preventing and treating obesity in patients. Or et al. (2019) **[36]** observed that chronic administration of melatonin reduces high-fat dietinduced dyslipidemia and hepatic lipid accumulation in an experimental model. However, studies are needed to elucidate the effect of melatonin as a treatment for NAFLD.

Investigating epigenetic markers that predispose to NAFLD could contribute new biomarkers for early diagnosis of the disease and allow preventive or therapeutic strategies to be developed for individuals at high risk of isolated NAFLD or associated with HCC **[37,38]**. Simpler, less invasive, more accessible, and accurate screening tools are needed for the diagnosis, treatment, and prognosis of NAFLD. However, existing approaches are not sensitive or specific enough to act as robust predictors of this disease in isolation. Highthroughput methods, such as Genome Wide Association Studies (GWAS), epigenome, and proteome, would facilitate the identification of specific markers to distinguish different phenotypes of hepatic steatosis. There is great interest in identifying genetic biomarkers as a means of preventing NAFLD.

Furthermore, HCC is the most frequently observed, accounting for 85-90% of primary liver tumors, with approximately 782,000 new cases diagnosed annually. Globally, it is the second leading cause of cancer death, with approximately 746,000 deaths per year. In general, most risk factors lead to the formation and progression of cirrhosis, with an incidence of 80-90%, whose association with HCC is well established. However, there is a growing proportion of patients with NAFLD who have a high risk of HCC in the absence of cirrhosis **[30]**.

The high mortality rate associated with this type of cancer is mainly attributed to the difficulty in diagnosing patients in the early stages. HCC diagnosis is obtained through imaging tests, such as computed tomography, magnetic resonance imaging, and ultrasound **[39]**, and also with the aid of biochemical markers, such as alpha-fetoprotein. In cases where radiological examinations are inconclusive, histology remains the gold standard **[40]**.

The gradual accumulation of mutations in oncogenes and chromosomal alterations is involved in human carcinogenesis **[41]**. HCC results from a complex and heterogeneous malignant transformation process characterized by the progressive differentiation of phenotypically abnormal nodular lesions in the liver. Continuous and chronic inflammation causes damage to liver cells and regeneration of the affected tissue. These events, considered underlying causes of HCC, promote the accumulation of genetic and epigenetic alterations and dysregulation of various signaling pathways, including Hedgehog (Hh), angiogenesis, and Wnt/β-catenin **[42]**.

It is known that obesity is a risk factor for several types of cancer, especially HCC **[43]**. Obesity, metabolic syndrome, and NAFLD are responsible for 30 to 40% of the increase in HCC in developed countries, and the risk of mortality from HCC in men with a BMI of 35-40 kg/m2 is 4.5 times higher than in patients with normal body weight **[43,44]**. Maintaining circadian rhythms can be a critical point for cancer development, and dysregulation of circadian clock genes has been implicated in loss of cell cycle control and tumor formation. Thus, pharmacological targeting of circadian regulators may be an essential strategy in the fight against cancer **[45]**.

In this case, melatonin stands out as responsible for a variety of physiological functions **[46-49]**, including anti-apoptotic and pro-apoptotic activities. It is the only known chronobiotic hormone for regulating the growth of neoplastic cells. It has been reported in clinical trials that supplemental melatonin decreases chemotherapy-related side effects and improves patient survival by combating various types of malignant tumors **[50,51]**. Melatonin induces apoptosis, promotes cell cycle arrest, and suppresses angiogenesis and metastasis without causing toxicity to normal cells **[31]**.

Melatonin possibly disrupts the stability of the transcriptional complex between some angiogenic transcription factors. The application of melatonin (1 mM) for 24 hours reduced the levels of HIF-1α (hypoxia-inducible factor 1-alpha), STAT3 (signal transducer and activator of transcription 3), and VEGF (vascular endothelial growth factor) proteins in HepG2 cells (human hepatocellular carcinoma cell line) **[13]**. Melatonin inhibits nuclear translocation of HIF-1α, but has no effect on HIF-1α mRNA, indicating that its effects occur at a post-transcriptional level **[20]**.

CONCLUSION

It was concluded that metabolic and liver diseases affect thousands of individuals worldwide, worsening quality of life and primarily compromising productive life. Studies involving drug and molecular therapies are proposed to control the progression of these diseases. A molecular analysis involving epigenetic, biochemical, and inflammatory aspects related to melatonin supplementation is necessary to clarify the effect of melatonin supplementation on obesity and liver diseases, including NAFLD and HCC. The elucidation of the antioxidant and anti-inflammatory effects of melatonin was highlighted, and its use as a synergistic agent in weight loss, as well as in liver diseases, in personalized treatment, was justified.

CRediT

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