International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn24S405

Importance of melatonin and its supplementation in the treatment of obesity, inflammatory processes, non-alcoholic hepatic steatosis, and hepatocellular carcinoma: a systematic review

Thaysa Andressa Brandão Vilela Teixeira[1*], Luciene Pereira de Oliveira[2], Maria Aparecida Orlando de Moraes Ferreira[3], Priscila Mendes Maia Rocha[4], Gabriela Ricardi[5], Katia Alves Ramos[6], Cristiane Reis e Lopes Telles[7], Antonio Carlos da Silva Junior[8], Ariadne Fonseca Carvalho Silva[9], Eduardo Vinicius França Moreira[10]

[1] CLIAGO Clinic, gynecology, Rio Branco, Acre, Brazil.
[2] Acre State Hospital Foundation, nephrology, Acre, Brazil.
[3] Women's Medicine Clinic. Gynecology. Unimed Volta Redonda Hospital, Rio de Janeiro, Brazil.
[4] Toledo Medical Clinic, Florianópolis, Santa Catarina, Brazil.
[5] USF MIMOSO 1 - Luis Eduardo Magalhães, Bahia, Brazil.
[6] University Center of Patos de Minas, nephrology, Minas Gerais, Brazil.
[7] Pouso Alegre Medical Center, Minas Gerais, Brazil.
[8] UFG - Federal University of Goiás, Goiás, Brazil.
[9] Ceri Clinic, Imperatriz, Maranhão, Brazil.
[10] IESS - Institute for Healthy Weight Loss of Sorriso. Av. João Batista Francio, Recanto dos Pássaros, Mato Grosso, Brazil.

*Corresponding author: Dr. Thaysa Andressa Brandão Vilela Teixeira.
CLIAGO Clinic, gynecology, Rio Branco, Acre, Brazil.
E-mail: thaysa19@icloud.com
DOI: https://doi.org/10.54448/ijn24S405
Received: 07-10-2024; Revised: 09-18-2024; Accepted: 09-28-2024; Published: 09-30-2024; IJN-id: e24S405

Editor: Dr. Idiberto José Zotarelli-Filho, MSc, Ph.D., Post-Doctoral.

Abstract

Introduction: There are more than 2.3 billion overweight and obese people in the world. One of the important neurohormones responsible for adipose tissue metabolism is melatonin (N-acetyl-5-methoxytryptamine) (MEL), which can modulate inflammatory processes by eliminating nitric oxide, reducing synthesis or inhibiting other pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-a), interleukin 6 (IL-6) and interleukin 8 (IL-8). **Objective:** It was to highlight the main considerations and clinical evidence of the importance of melatonin and its supplementation in the treatment of obesity, inflammatory processes, non-alcoholic fatty liver disease, and hepatocellular carcinoma. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from May to July 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 115 articles were found. A total of 28 articles were evaluated and 25 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 25 studies that did not meet the GRADE. Most studies presented homogeneity in their results, with X^2=85.7%>50%. It was concluded that obesity-related inflammation is related to a state of oxidative stress with high production of reactive oxygen species. Melatonin has been highlighted for its antioxidant and anti-inflammatory properties. 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). Studies involving drug and molecular therapies are proposed to control the progression of these diseases. It is necessary to perform a molecular analysis involving epigenetic, biochemical,

and inflammatory aspects related to melatonin supplementation, clarifying the effect of melatonin supplementation on obesity and liver diseases, including NAFLD and HCC. Thus, it is highlighted that the antioxidant and anti-inflammatory effect of melatonin is essential as a synergistic agent in weight loss and as prophylaxis and/or treatment of liver diseases.

Keywords: Obesity. Inflammatory processes. Melatonin. Non-alcoholic fatty liver disease. Hepatocellular carcinoma.

Introduction

In the scenario of chronic non-communicable diseases, there are more than 2.3 billion people who are overweight or obese in the world. Brazil has an estimated number of over 20.0 million people by 2025. Studies indicate that a reduction of approximately 10.0% in weight also favors the reduction of type 2 diabetes mellitus (DM2) **[1]**. In this scenario, one of the important neurohormones responsible for fatty tissue metabolism is melatonin (N-acetyl-5-methoxytryptamine) (MEL), produced by the pineal gland.

MEL is synthesized from serotonin by the initial conversion of tryptophan into serotonin, which produces N-acetylserotonin, whose molecule will then be converted into melatonin. This hormone acts as a regulator of the circadian rhythm and is also a potent antioxidant and anti-inflammatory. Melatonin secretion decreases with age and influences seasonal and circadian rhythms, the sleep-wake cycle, and reproduction, and presents a day/night secretion pattern sensitive to light, with an increase in the early evening and a decrease at the end of this period. 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 on lipid metabolism **[2,3]**.

In this regard, melatonin is considered an important chronobiotic that influences the circadian distribution of metabolic processes, synchronizing them with the cycle of feeding, resting, and fasting. In this case, it stands out in the regulation of energy flow and expenditure through the activation of brown adipose tissue. It is also worth noting that melatonin can cause the darkening of white adipose tissue, thus helping to regulate body weight. However, this process can be impaired during aging, as well as when shift work and night work (due to lighting). In this context, there is a reference to its association with insulin resistance, glucose intolerance, sleep disorders, and circadian metabolic disorganization, characterizing a state of chronological interruption and metabolic diseases that worsen general health. Thus, melatonin replacement may be an important factor in controlling these diseases, as well as in the inflammatory process **[4,5]**.

Furthermore, melatonin can modulate inflammatory processes by eliminating nitric oxide, a molecule involved in tissue damage 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-a), interleukin 6 (IL-6), and interleukin 8 (IL-8). 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 **[2-4]**.

In this sense, the present study carried out a systematic review to highlight the main considerations and clinical evidence of the importance of melatonin and its supplementation in the treatment of obesity, inflammatory processes, non-alcoholic fatty liver disease, and hepatocellular carcinoma.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. It was accessed on: 06/17/2024. The AMSTAR 2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. It was accessed on: 06/17/2024.

Search Strategy and Search Sources

The literature search process was carried out from May to July 2024 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following health science descriptors (DeCS/MeSH Terms) were used: "Obesity. Inflammatory processes. Melatonin. Non-alcoholic fatty liver disease. Hepatocellular carcinoma", and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

The 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 emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and

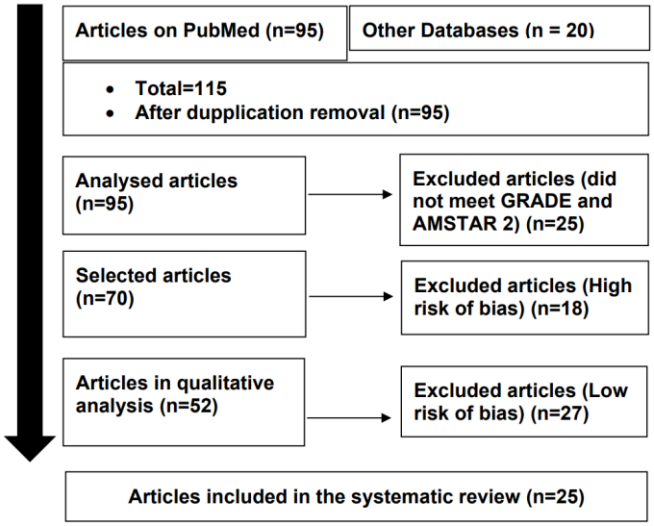
brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

As a corollary of the literature search system, a total of 115 articles were found that were submitted to eligibility analysis and, subsequently, 25 of the 28 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 presented homogeneity in their results, with X^2=85.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 25 studies that did not meet GRADE.

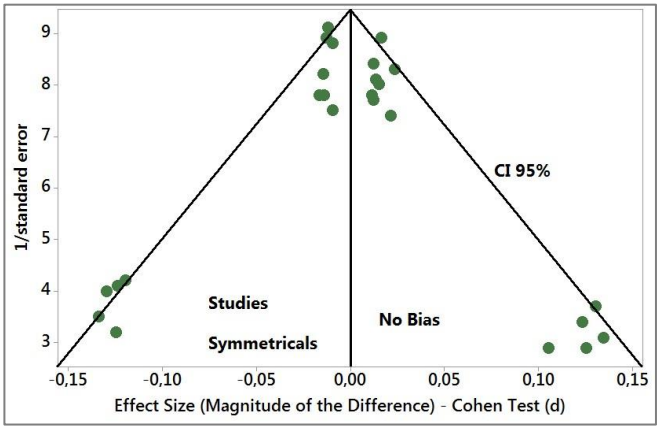
Figure 1. Flowchart of the articles selections.



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). 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 among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=25 studies).



Source: Own Authorship.

Major Clinical Findings

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, as almost a third of the world's population has this type of dysfunction **[1]**. In Brazil, data from the latest Surveillance of Risk and Protective Factors for Chronic Diseases by Telephone Survey (VIGITEL, 2018) **[6]** showed that excess weight increased by 26.3% in 10 years, affecting 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 male adults and 19.6% of female adults (VIGITEL, 2018) **[6]**. Furthermore, obesity is considered one of the most serious public health problems in today's society, being a multifactorial condition that involves genetic, behavioral, and environmental factors. 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. It is worth noting the association of obesity with low-grade chronic inflammation, which contributes to the development of these systemic metabolic disorders **[3,7]**.

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 excess calories and inflammation of adipose tissue. Some of these mechanisms include dysregulation of fatty acid homeostasis, local hypoxia, mitochondrial dysfunction,

increased size and death of adipose cells, and mechanical stress **[8,9]**. It is known that inflammation is related to a state of oxidative stress with a high production of reactive oxygen species, compared to the levels of antioxidants, allowing their action and compromising the natural defense systems. In this context, melatonin has been highlighted for its antioxidant and anti-inflammatory properties. Considering that melatonin modulates several processes involved in obesity, there is a reference to the possibility of acquiring benefits from its use in various treatments. It is also noteworthy 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) **[10,11]**.

Non-alcoholic fatty liver disease (NAFLD) is characterized by the deposition of triglycerides (TG) in hepatocytes, exceeding 5-10% of the total weight of the organ, even without continuous intake of significant amounts of alcohol (>20 g/day). NAFLD is one of the main causes of chronic liver disease, with a worldwide prevalence of approximately 20 to 30%, becoming a target of growing public health concern **[12]**. In Brazil, this rate is still unknown; however, the Brazilian Society of Hepatology highlights high frequencies of steatosis (48%), nonalcoholic steatohepatitis (37%), and cirrhosis (5%). NAFLD is also considered a component of metabolic syndrome, due to the close association between these conditions. Approximately 90% of individuals with NAFLD have at least one characteristic of metabolic syndrome, in addition to the risk for cardiovascular disease (CVD), HCC, and type 2 diabetes mellitus in long-term follow-up **[1,6]**. In this context, melatonin stands out as an effective action against metabolic syndrome, reversing the harmful effect of dietary fructose in animal models, and modulating metabolic pathways such as lipogenesis, lipolysis, beta-oxidation, and gluconeogenesis. Furthermore, lipophilic melatonin passes freely through all biological membranes and accumulates mainly in mitochondria, where it influences mitochondrial structure and function via the peroxisome proliferatoractivated receptor gamma coactivator 1-alpha (PGC1) signal. Melatonin can be taken up in the liver, also by specific cellular and nuclear receptors in a dose-dependent manner **[13,14]**.

The oral administration of circulating melatonin in humans has a half-life ranging from 25 to 65 min. Melatonin is rapidly metabolized by enzymatic and non-enzymatic processes. Cytochrome P450 (CYP450) is the main enzyme for melatonin metabolism in animals and is mainly located in the liver. The main and secondary products of CYP450 are 6-hydroxy melatonin and N1-acetyl-N2-formyl-5methoxykynuramine (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 **[2]**. *In vivo*, studies have demonstrated the efficacy of melatonin to reduce the accumulation of intrahepatic lipid levels. A study by Stacchiotti et al. (2019) **[13]** indicates that the use of dietary melatonin may be promising for preventing and treating obesity in patients. Ou et al. (2019) **[14]** observed that chronic administration of melatonin reduces high-fat diet-induced dyslipidemia and hepatic lipid accumulation in an experimental model. However, studies are needed to elucidate the effect of melatonin as a treatment for NAFLD.

Investigation of epigenetic markers that predispose to NAFLD may contribute to 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 **[15]**. Simpler, less invasive, more accessible, and accurate screening tools are needed for the diagnosis, treatment, and prognosis of NAFLD. However, existing approaches are not sufficiently sensitive or specific to act as robust predictors of this disease alone. High-throughput 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 for the prevention of NAFLD **[15]**.

In addition, HCC is the most frequent type observed in 85-90% of primary liver tumors, with approximately 782,000 new cases diagnosed per year. Globally, it is the second leading cause of cancerrelated death, with approximately 746,000 deaths/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 an increasing proportion of patients with NAFLD who are at high risk of HCC in the absence of cirrhosis **[16]**.

The high mortality associated with this type of cancer is mainly attributed to the difficulty in diagnosing patients at an early stage. The diagnosis of HCC is obtained through imaging tests, such as computed tomography, magnetic resonance imaging, and ultrasound, and also with the aid of biochemical markers, such as alpha-fetoprotein. In cases where radiological tests are inconclusive, histology remains the gold standard **[17]**.

The gradual accumulation of mutations in oncogenes and chromosomal alterations are involved in human carcinogenesis **[18]**. HCC results from a

complex and heterogeneous malignancy process characterized by 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 several signaling pathways, including Hedgehog (Hh), angiogenesis, and Wnt/β-catenin **[19]**.

It is known that obesity is related to a risk factor for several types of cancer, especially HCC. 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 **[2,20-22]**. Maintaining circadian rhythms may be a critical point for cancer development, and dysregulation of circadian clock genes has been implicated in the loss of cell cycle control and tumor formation. Thus, pharmacological targeting of circadian regulators may be an essential strategy in the fight against cancer. In this case, melatonin stands out, responsible for a variety of physiological functions **[23]**, including anti-apoptotic and pro-apoptotic activities. It is the only chronobiotic hormone known for regulating the growth of neoplastic cells. Supplemental melatonin has been reported in clinical trials to decrease chemotherapy-related side effects and improve patient survival, combating several types of malignant tumors. Melatonin induces apoptosis, promotes cell cycle arrest, and suppresses angiogenesis and metastasis, without causing toxicity to normal cells **[24]**.

Melatonin possibly disrupts the stability of the transcriptional complex between some angiogenic transcription factors. 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 hepatocarcinoma cell line). Melatonin inhibits the nuclear translocation of HIF-1α but does not affect HIF-1α mRNA, indicating that its effects occur at a post-transcriptional level **[25-28]**.

Conclusion

It was concluded that obesity-related inflammation is related to a state of oxidative stress with high production of reactive oxygen species. Melatonin has been highlighted for its antioxidant and anti-inflammatory properties. 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. Studies involving drug and molecular therapies are proposed to control the progression of these diseases. It is necessary to perform a molecular analysis involving epigenetic, biochemical, and inflammatory aspects related to melatonin supplementation, clarifying the effect of melatonin supplementation on obesity and liver diseases, including NAFLD and HCC. Thus, it is highlighted that the antioxidant and anti-inflammatory effect of melatonin is fundamental as a synergistic agent in weight loss and as a prophylaxis and/or treatment of liver diseases.

CRediT

Author contributions: **Conceptualization -** Thaysa Andressa Brandão Vilela Teixeira, Luciene Pereira de Oliveira, Maria Aparecida Orlando de Moraes Ferreira, Priscila Mendes Maia Rocha, Gabriela Ricardi, Katia Alves Ramos, Cristiane Reis e Lopes Telles, Antonio Carlos da Silva Junior, Ariadne Fonseca Carvalho Silva, Eduardo Vinicius França Moreira; **Data curation -** Thaysa Andressa Brandão Vilela Teixeira, Luciene Pereira de Oliveira , Maria Aparecida Orlando de Moraes Ferreira, Priscila Mendes Maia Rocha; **Formal Analysis -** Thaysa Andressa Brandão Vilela Teixeira, Luciene Pereira de Oliveira, Gabriela Ricardi, Katia Alves Ramos, Cristiane Reis e Lopes Telles, Antonio Carlos da Silva Junior, Ariadne Fonseca Carvalho Silva, Eduardo Vinicius França Moreira; **Investigation -** Thaysa Andressa Brandão Vilela Teixeira, Maria Aparecida Orlando de Moraes Ferreira, Priscila Mendes Maia Rocha; **Methodology -** Thaysa Andressa Brandão Vilela Teixeira, Gabriela Ricardi, Katia Alves Ramos, Cristiane Reis e Lopes Telles, Antonio Carlos da Silva Junior, Ariadne Fonseca Carvalho Silva, Eduardo Vinicius França Moreira, Moniquy Quintela Orlando de Moraes, Amarildo Aparecido Ferreira Júnior; **Project administration -** Thaysa Andressa Brandão Vilela Teixeira; **Supervision -** Thaysa Andressa Brandão Vilela Teixeira; **Writing - original draft -** Thaysa Andressa Brandão Vilela Teixeira, Luciene Pereira de Oliveira, Maria Aparecida Orlando de Moraes Ferreira, Priscila Mendes Maia Rocha, Gabriela Ricardi, Katia Alves Ramos, Cristiane Reis e Lopes Telles, Antonio Carlos da Silva Junior, Ariadne Fonseca Carvalho Silva, Eduardo Vinicius França Moreira; **Writing-review & editing-** Thaysa Andressa Brandão Vilela Teixeira, Luciene Pereira de Oliveira, Maria Aparecida Orlando de Moraes Ferreira, Priscila Mendes Maia Rocha, Gabriela Ricardi, Katia Alves Ramos, Cristiane Reis e Lopes Telles, Antonio Carlos da Silva Junior, Ariadne Fonseca Carvalho Silva, Eduardo Vinicius França Moreira, Sarah Bernardon de Oliveira, Hugo Menezes Lopes.

Acknowledgment
Not applicable.

Ethical Approval
Not applicable.

Informed Consent
Not applicable.

Funding
Not applicable.

Data Sharing Statement
No additional data are available.

Conflict of Interest
The authors declare no conflict of interest.

Similarity Check
It was applied by Ithenticate[@].

Peer Review Process
It was performed.

References
1. WHO - World Health Organization. Available at: https://www.sbcbm.org.br/endescola-e-obesidade/ Accessed on: June 27, 2024.
2. Challet E, Pévet P. Melatonin in energy control: Circadian time-giver and homeostatic monitor. J Pineal Res. 2024 May;76(4):e12961. doi: 10.1111/jpi.12961.
3. Ku H, Kim Y, Kim AL, Lee G, Choi Y, Kim B. Protective Effects of Melatonin in High-Fat Diet-Induced Hepatic Steatosis via Decreased Intestinal Lipid Absorption and Hepatic Cholesterol Synthesis. Endocrinol Metab (Seoul). 2023 Oct;38(5):557-567. doi: 10.3803/EnM.2023.1672.
4. Amaral FGD, Cipolla-Neto J. A brief review about melatonin, a pineal hormone. Arch Endocrinol Metab. 2018 Aug;62(4):472-479. doi: 10.20945/2359-3997000000066. PMID: 30304113.
5. Hardeland R. Aging, Melatonin, and the Pro- and Anti-Inflammatory Networks. Int J Mol Sci. 2019 Mar 11;20(5):1223. doi: 10.3390/ijms20051223.
6. VIGITEL BRASIL. Ministério da Saúde. Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico (VIGITEL). Disponível em: <http://portalarquivos.saude.gov.br/images/pdf/2017/abril/17/Vigitel_17-4-17-final.pdf>. Acessado em 10 de outubro de 2022.
7. Chen C, Lou T. Hypoxia inducible factors in hepatocellular carcinoma. Oncotarget, 2017, 8(28), 46691.
8. Cheng J, Yang HL, Gu CJ, Liu YK, Shao J, Zhu R, He YY, Zhu XY, Li MQ. Melatonin restricts the viability and angiogenesis of vascular endothelial cells by suppressing HIF-1α/ROS/VEGF. Int J Mol Med. 2019 Feb;43(2):945-955. doi: 10.3892/ijmm.2018.4021.
9. Cipolla-Neto J, Amaral FG, Afeche SC, Tan DX, Reiter RJ. Melatonin, energy metabolism, and obesity: a review. J Pineal Res. 2014;56(4):371-381.
10. Fall T, Mendelson M, Speliotes EK. Recent advances in human genetics and epigenetics of adiposity: pathway to precision medicine? Gastroenterology. 2017, 152(7):1695-1706.
11. Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology. 2019 Jan;156(2):477-491.e1. doi: 10.1053/j.gastro.2018.08.065. Epub 2018 Oct 24.
12. Lin S, Hoffmann K, Gao C, Petrulionis M, Herr I, Schemmer P. Melatonin promotes sorafenibinduced apoptosis through synergistic activation of JNK/c-jun pathway in human hepatocellular carcinoma. Journal of Pineal Research, 2017, 62(3), e12398.
13. Stacchiotti A, Grossi I, García-Gómez R, et al. Melatonin Effects on Non-Alcoholic Fatty Liver Disease Are Related to MicroRNA-34a-5p/Sirt1 Axis and Autophagy. Cells. 2019; 8(9):1053. doi:10.3390/cells8091053.
14. Ou TH, Tung YT, Yang TH, Chien YW. Melatonin Improves Fatty Liver Syndrome by Inhibiting the Lipogenesis Pathway in Hamsters with High-Fat Diet-Induced Hyperlipidemia. Nutrients 2019, 11, 748.
15. Mortezaee, et al. Retinoic acid as the stimulating factor for differentiation of Wharton's Jelly-Mesenchymal stem cells into hepatocyte-like cells. Avicenna Journal of Medical Biotechnology, 2015, 7(3), 106.
16. Mortezaee, K., Khanlarkhani, N. Melatonin application in targeting oxidative-induced liver injuries: A review. Journal of Cellular Physiology,

2017, 233(5), 4015-4032.

17. Mortezaee K, Pasbakhsh P, Kashani IR, Sabbaghziarani F, Omidi A, Zendedel A. Dehpour AR. Melatonin pretreatment enhances the homing of bone marrow-derived mesenchymal stem cells following transplantation in a rat model of liver fibrosis. Iranian Biomedical Journal, 2016, 20(4), 207.
18. Navarro-Alarcon M., Ruiz-Ojeda F. J., Blanca-Herrera R. M., Serrano M. M., Acuna-Castroviejo D., Fernandez-Vazquez G., et al. (2014). Melatonin and metabolic regulation: a review. Food Funct. 5, 2806–2832. 10.1039/C4FO00317A.
19. Paolini, B., Maltese, P.E., Del Ciondolo, I., et al. Prevalence of mutations in LEP, LEPR, and MC4R genes in individuals with severe obesity. Genet Mol Res 15(3), 2016. doi: 10.4238/gmr.15038718.
20. Pena, S.D.J., Pietro, G.D., Fuchshuber-Moraes, M., et al. The genomic ancestry of individuals from different geographical regions of brazil is more uniform than expected. PLoS One 6(2):e17063, 2011. doi: 10.1371/journal.pone.0017063.
21. Prado NJ, Ferder L, Manucha W, Diez ER. Anti-inflammatory effects of melatonin in obesity and hypertension. Current Hypertension Reports. 2018;20(5):p. 45. doi: 10.1007/s11906-018-0842-6.
22. Reiter RJ, Dun-Xian T, Lorena FB. "Melatonin: a multitasking molecule." Progress in brain research. 2010, 181: 127-151.
23. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008, 371:569 e 578.
24. Saitta C, Pollicino P, Raimondo G. Obesity and liver câncer. Ann Hepatol. 2019, 18(6):810-815. doi: 10.1016/j.aohep.2019.07.004.
25. Salehi B, Sharopov F, Fokou PVT, Kobylinska A, Jonge L, Tadio K, Sharifi-Rad J, Posmyk MM, Martorell M, Martins N, Iriti M. Melatonin in Medicinal and Food Plants: Occurrence, Bioavailability, and Health Potential for Humans. Cells. 2019 Jul 5;8(7):681. doi: 10.3390/cells8070681.
26. Sánchez-López AL, Ortiz GG, Pacheco-Moises FP, Mireles-Ramírez MA, Bitzer-Quintero OK, Delgado-Lara DLC, Ramírez-Jirano LJ, Velázquez-Brizuela IE. Efficacy of Melatonin on Serum Pro-inflammatory Cytokines and Oxidative Stress Markers in Relapsing Remitting Multiple Sclerosis. Arch. Med. Res. 2018;49:391–398. doi: 10.1016/j.arcmed.2018.12.004.
27. Satyanarayanan SK, Chien YC, Chang JPC, Huang S-Y, Guu TW, Su H, Su KP. Melatonergic agonist regulates circadian clock genes and peripheral infammatory and neuroplasticity markers in patients with depression and anxiety. Brain Behav Immun. 2019.
28. Schwalbe N, Wahl B. Artificial intelligence and the future of global health. Lancet. 2020 May 16;395(10236):1579-1586. doi: 10.1016/S0140-6736(20)30226-9.