Effects of Melatonin Suplementation in Human Pathologie: A Systematic Review

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ABSTRACT

Objectives: to analyse the main effects of melatonin dietary supplementation in different pathologies.

Method: systematic review related to the use of melatonin as a dietary supplement and its effects on PubMed, CINAHL, Scopus, ProQuest Health and Medical Complete, Scielo and Dialnet databases.

Results: the 613 obtained articles at baseline were finally reduced to 19 after the application of inclusion and exclusion criteria and the reverse search. Melatonin supplementation has shown its benefits in sleep disorders, aging, various chronic diseases and anthropometry.

Conclusions: the known benefits of melatonin are regulating the sleep-wake cycle and preventing oxidative stress of multiple health-disease processes. However, more research is needed to determine its applicability in numerous pathologies.

Keywords: Dietary supplements; Melatonin; Pathology; Systematic Review

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INTRODUCTION

Melatonin or N-acetyl-5-methoxytryptamine is a hormone mainly produced in the pineal gland during the dark phase of the circadian cycle. This is because melatonin biosynthesis varies along the 24-hour cycle and its response requires ambient light changes. Melatonin is also essential in a variety of neuroendocrine and neurophysiological circadian regulation processes. More specifically, its effects can be pineal origin effects, such as controlling daily sleep cycle, or extrapineal origin effects, such as anti-inflammatory or antioxidant effects, between others (1).

The extrapineal melatonin has multiple uses and so it is widely investigated at many levels. It uses as a treatment for pain or rheumatologic problems (2), neurodegenerative diseases (3) or gastrointestinal problems (4), are just some examples. Its presence is practically in all body fluids as well as in many organs for the correct regulation of cellular homeostasis (5). This implies the melatonin versatility as a potential treatment in a lot of pathological processes, especially those aggravated by aging (6).

Natural and exogenously, there are foods which have melatonin precursors such as tryptophan. Among these, the most common are dried fruits, legumes, fish, some cereals, milk and certain fruits, for example banana (7). Similarly, there are foods that have significant amounts of melatonin, such as barley, rice, tomato, extra virgin olive oil and some fruits like strawberry, cherries and grapes (8). All of this, in the Mediterranean diet context, which supports the benefits that its recommendation brings9.

Therefore, it is not surprising that a significant consumption of dietary melatonin supplements exists, in addition to those melatonin amounts that are naturally ingested. These supplements are sold without prescription (3) and, although it is not indicated to treat various conditions, including insomnia, some people use it as an alternative because the studies

results are encouraging (10). This study therefore aims to analyse the main effects of melatonin as a dietary supplement in different pathologies

METHODS

A systematic review about the use of melatonin as a dietary supplement and its effects was conducted.

Databases and search equation: PubMed, CINAHL, Scopus, ProQuest Health and Medical Complete, Scielo and Dialnet databases were consulted.

The terms of the search equation were obtained in MeSH thesaurus and the search equation was: "dietary supplements AND melatonin" and their corresponding translation in Spanish.

Inclusion and exclusion criteria: primary scientific articles published in English or Spanish in which the effect of melatonin as a dietary supplement was analysed, were included. There was no restriction by publication date and the studies with no human samples were excluded.

Selection process, critical appraisal and evidence level: the study selection was done in 4 steps. First the title and abstract were read, secondly the full texts were read. After that, a reverse search was made to find the largest number of documents and finally, a critical appraisal of the included studies was conducted to assess possible methodological bias.

For critical appraisal the Centre for Evidence-Based Medicine (EMBC) criteria from Oxford University was used (11).

All the process was done independently by two members of the team consulting a third person in case of disagreement.

RESULTS

After the search a total of 613 scientific manuscripts were obtained. After reading the title and abstract of 594 were excluded for not meeting the inclusion and exclusion criteria. The 19 remaining studies were reduced to a final sample of 13 after reading the full text and assessing

the methodological bias. After the reverse search the final sample was n=19. The search and selection process is detailed in Figure 1.

After reading and analysing the information of the included studies in Table 1, the following categories about melatonin use as dietary supplementation were obtained: Sleep disorders, Melatonin and aging, Melatonin and chronic diseases, and Use of melatonin in sports and weight control.

Sleep disorders

There are many documents that study the role of melatonin for sleep disorders. In 1993, Petrie et al (12) observed that melatonin use as a dietary supplement improved disorders associated with jet-lag. Likewise, in 1996 other authors, concerned about the melatonin effects on military work, obtained promising results towards jet-lag prevention in healthy patients suffering from similar disorders and cognitive degradation in deployments performed in short time periods (13).

Later, Nunes et al (14) observed how the sleep in patients with chronic obstructive pulmonary disease (COPD) was improved. This improvement in sleep quality and in their disease was also observed by Pereira (15) in patients with gastroesophageal reflux disease (GERD). Even though, this improvement did not occur in patients with other problems, as kidney failure, because melatonin chronic use caused a reduction of melatonin beneficial effect on sleep (16).

Other studies informed that melatonin improves quality of life by having a restful sleep, and also acting as an antioxidant (17). Its application in elderly patients combined with conventional hypnotics (18) or magnesium and zinc supplements have been also studied 25.

Melatonin and aging

Melatonin, due to its multiple properties and applications, has also been analysed in studies focused on elderly population. The most significant effects were improvement in sleep

quality, cognitive function and behavioural disorders, the prevention of metabolic and cardiovascular complications, and even improving quality of life in patients with Alzheimer's disease (18-23).

Melatonin and chronic diseases

Pereira (15) studied the beneficial effects of melatonin, combined with other compounds, in patients with GERD. It was also mentioned how Nunes et al (14) did the same in patients suffering from COPD. Like these, other authors inform that melatonin is beneficial for patients suffering from other chronic diseases like diabetes (22, 24) or hypertension (23). While some studies reported that melatonin effects can be lower16 or even adverse at cardiovascular levels (25).

Use of melatonin in anthropometry

Regarding exercise performance, some studies informed of little melatonin effectiveness for it (26-27) excepting an alertness increase. Although, Ochoa et al (28), said that high-intensity-exercise oxidative stress could be reduced.

Concerning weight control, it seems that melatonin alone does not significantly influence body mass index reduction (29), however in combination with other supplements as fish oil it helps preventing complications in patients with gastrointestinal cancer (30).

DISCUSSION

Melatonin use is spreading. At the beginning, its research was focused on sleep disorders, due to melatonin important functions on its regulation (1). Today, it is demonstrated that lack of sleep can lead to high oxidative stress, which can implicate aging and health problems (31). These disorders can occur at any age and can develop diverse health problems both in adults (32) and children (33).

Since melatonin benefits are gradually getting know, it is logical to see how its consumption is increasing. As an antioxidant it is well known (1, 34), so its applicability is diverse, either for elderly population (6) or menopausal women (35), among others.

Taking into account melatonin´s antioxidant capacity and its improvement in sleep quality, its use was spreading in many patients, being old adults' groups the main target. In fact, there are studies that show how sleep improving in older people can improve other ailments such as fatigue and chronic pain (36). It is also well known that sleep is a problem in

elderly population, who often abused sleep-inducing drugs, which, although it is infrequently, can cause cognitive and behavioural changes (37). Therefore, and considering the already proven relationship between insufficient sleep and the onset of depression, dementia or neurodegenerative diseases such as Alzheimer's or Parkinson's, it is logical the research that is being done about multiple melatonin applications (38, 39).

Melatonin research has proliferated in many other specialties. Psychiatric problems like esquizofrenia (40), digestive (41), skin (33), metabolic (42) or respiratory problems (34), and particularly those that course with chronic inflammation (43) like rheumatologic (44) or autoimmune problems (45), or those related to cancer suffering (46), are some of them. All of these problems are due to circadian rhythms alterations and, because oxidative stress is inherent to the inflammatory process, melatonin has a great therapeutic potential for them (43).

In line with the above, another problem which has widespread interest today is obesity and its complications (47). Obesity can be developed at any age although if it appears from childhood its prognosis is worst (48). Therefore, it is important to emphasize properly, with a multidisciplinary approach, the healthy lifestyles (49). Obesity is also associated with oxidative stress, promoting insulin resistance development and metabolic syndrome, thus melatonin could play an important role as a therapeutic agent in these cases (50).

Derived or parallel to overweight problems, melatonin role in sports world is also being studied, although their results as an ergogenic aid are unclear (51). Numerous studies have investigated its use for improving athletic performance, but the results have been only

positive for improving sleep in people who perform exercise (35) and to prevent exercise oxidative stress (52).

CONCLUSION

Melatonin is a hormone with a wide variety of applications. Its known benefits are regulating the sleep-wake cycle and prevent oxidative stress of multiple health and disease processes. The potential of this hormone now, as a supplement, and in the future as a therapeutic agent, is still to be determined, because more studies are needed to corroborate the known properties and those to be discovered.

AUTHORS' NOTE

E Mármol Peis, GA Cañadas-De la Fuente, JL Gómez-Urquiza and R Fernández-Castillo conceived paper, oversaw data collection, wrote manuscript and approved final version. F Ocaña Peinado, R Guisado Barrilao and IM Guisado Requena participated in study design and interpretation of data, critically revised manuscript and approved final version. The authors declare that they have no conflicts of interest.

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Table 1: Summary of included studies (n=19)

Authors (Year)	City, Country	Design	Sample	Results	Evidence level	Grade of recommendation
Adamczyk-Sowa et al. (2014) [17]	Zabrze, Poland.	Randomized clinical trial	122 (102 + 20)	Melatonin acts as an antioxidant and improves quality of life by regulating sleep-wake cycle.	1b	A
Atkinson et al. (2001) [26]	Liverpool, United Kingdom.	Randomized clinical trial	10-12	Melatonin intake before sleep has not demonstrate to improve athletes performance.	1b	A
Cazzola et al. (2012) [20]	Pavia, Italy.	Randomized clinical trial	25 (11 + 14)	Melatonin use in Alzheimer´s patients improve erythrocyte by: increasing saturation level, membrane fluidity and membrane acetylcholinesterase activity.	1b	A
Comperatore et al. (1996) [13]	Alexandria, EEUU.	Randomized clinical trial	29	Melatonin use prevent sleep disorders and cognitive degradation in military deployments.	1b	A
Garzón et al. (2009) [18]	Seville, Spain.	Randomized clinical trial	53 (18 + 35)	Melatonin administration significantly improves sleep and behaviour disorders in elderly people and it acts as a coadjutant in hypnotic drug therapy.	1b	A
Kedziora-	Bydgoszcz,	Randomized	17	Melatonin supplementation can be an additional	1b	A

Kornatowska et al. (2008) [22]	Poland.	clinical trial		support treatment for hypotension therapy in patients with essential hypertension.		
Kedziora-Kornatowska et al. (2009) [23]	Bydgoszcz, Poland.	Randomized clinical trial	30 (15 + 15)	Melatonin, due to its antioxidant function, can help preventing complications in old age noninsulin dependent diabetes patients.	1b	A
Lusardi et al. (2000) [25]	Pavia, Italy.	Randomized clinical trial	47	Melatonin could aggravate the disease in hypertensive patients	1b	A
McCarty et al. (2010) [24]	Washington, EEUU.	Multicentre cross-sectional	467	Melatonin supplementation improved quality of life in young patients (8-18 years) with diabetes.	2c	B
Mero et al. (2006) [27]	Helsinki, Finland.	Randomized clinical trial	10	Melatonin intake during the day has no effects in resistance physical activity. It only increases alert state. It does not increases growth hormone or it even decrease its secretion.	1b	A
Nachtigal et al. (2005) [29]	Washington, EEUU.	Cross-sectional	15655	Melatonin has no effect decreasing body mass index.	2c	B
Nunes et al. (2008) [14]	Fortaleza, Brazil.	Randomized clinical trial	30	Melatonin can improve sleep in chronic obstructive pulmonary disease patients.	1b	A

Ochoa et al. (2011) [28]	Granada, Spain.	Randomized clinical trial	20 (10 + 10)	Melatonin was effective for reducing oxidative stress after high intensity physical activity.	1b	A
Pereira (2006) [15]	Campinas, Brazil.	Randomized clinical trial	251 (176 + 175)	A supplement with melatonin, vitamins and amino acids contributed to revert gastroesophageal reflux clinic symptoms and also improved patients' sleep.	1b	A
Persson et al. (2005) [30]	Uppsala, Sweden.	Randomized clinical trial	24	Melatonin, combined with fish oil, contributed to improved weight stabilization in patients with cachexia and advanced gastrointestinal cancer.	1b	A
Petrie et al. (1993) [12]	Auckland, New Zealand.	Randomized clinical trial	52	Melatonin may have beneficial effects for jet-lag recovery and associated sleep disorders.	1b	A
Rondanelli et al. (2011) [19]	Pavia, Italy.	Randomized clinical trial	43 (22 + 21)	Night melatonin, zinc and magnesium administration may improve sleep quality and quality of life in nursing homes patients with primary insomnia.	1b	A
Rondanelli et al. (2012) [21]	Pavia, Italy.	Randomized clinical trial	25 (20 + 5)	Old adults with mild cognitive impairment who received an oil emulsion of phospholipid-DHA, which contains melatonin and tryptophan, showed significant improvements in some cognitive function measurements ("Mini-Mental State Examination" and "Mini Nutritional Assessment").	1b	A

Russcher et al. (2013) [16]	Netherlands	Randomized clinical trial	42	Melatonin chronic use decrease its beneficial effects on haemodialysis patients´ sleep.	1b	A

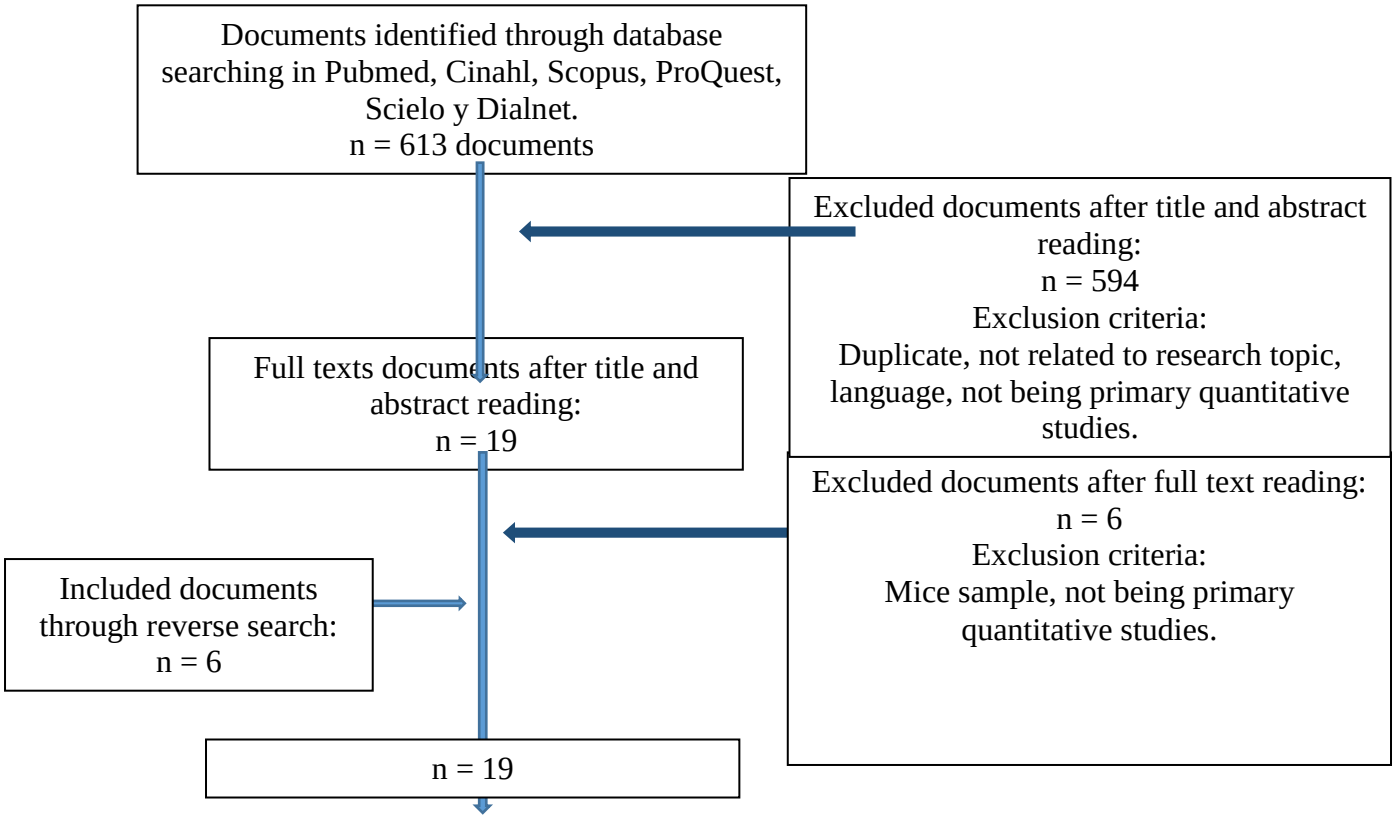

Figure: Flow diagram selection