Research Article

The crossroads of melatonin: Bibliometric analysis and mapping of global scientific research

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ABSTRACT

Melatonin is a molecule that has attracted a great deal of attention from the scientific community in the last 50 years. The aim of this study is to analyze the scientific production on related to melatonin using bibliometric tools. We performed a search in Web of Science, involving documents published between 1958 and 2019. We used bibliometric indicators to explore documents production, dispersion, distribution, time of duplication and annual growth, as Price's law of scientific literature growth, Lotka's law, the transient index and the Bradford model. We also calculated the participation index of the different countries and institutions. Finally, through bibliometric mapping, we explored the co-occurrence networks for the most frequently used terms in melatonin research. A total of 20,768 documents were retrieved. Scientific production was better adjusted to linear growth (r = 0.9535) than exponential (r = 0.9313). The duplication time of the documents obtained was 14.2 years. The transience index was 62%, which indicates that most of the scientific production is due to very few authors. The signature rate per document was 1.95. Thirty-four journals made up the Bradford core, highlighting *Journal of Pineal Research*. USA and University of Texas present the highest production. Map network visualization shows the generated term map detailing on clusters of closely related terms. The growth of the scientific literature on melatonin was linear, with a very high rate of transience, which indicates the presence of numerous authors who sporadically publish on this topic. No evidence of a saturation point was observed. In the last 10 years, there has been a relevant increase in documents on melatonin.

Key words: Melatonin, bibliometry, scientific production, collaborative networks.

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1. INTRODUCTION

Melatonin (*N*-acetyl-5-methoxytryptamine) is an indolamine synthesized and released mainly from the pineal gland of mammals, although it has also been found to be produced in non-mammalian vertebrates, in some invertebrates and in many plants (1). In addition, melatonin is also produced in various extra-pineal organs including ovary, thymus, retina, bone marrow, lymphocytes, gastrointestinal tract or skin (2), which indicates the outstanding physiological functions performed by this molecule.

Although, initially, the main role assigned to this methoxyndole was the control of the "biological clock" and the light-dark cycle, over the last 50 years the important role played by melatonin in the control of sleep (3), in the protection against different types of cancer (4-7), in gastrointestinal (8) and cardiovascular disorders (9, 10), neurodegenerative processes (11, 12), autoimmune pathologies (13) or infectious diseases (14) has been documented (1, 15).

A series of breakthrough findings, mainly the discovery and isolation of melatonin by the group led by Aaron B. Lerner in 1958 (16), enabled the development of a new research field around the main secretory product of the pineal gland (to deepen the historical development of the pineal gland, see López-Muñoz *et al*. (17-19). During the last five decades, scientific research on melatonin has undergone an impressive expansion that has translated into an extraordinary increase in the scientific literature that covers all of its different aspects. Therefore, the aim of this article is to analyze the published literature involving melatonin through bibliometric tools.

Bibliometric analysis is an useful tool to examine the research activity related with a specific domain or construct, or even related with a more general investigation field, both from the historical and sociological viewpoints. Bibliometrics includes the collection, processing and management of quantitative bibliographic data from scientific publications (20), and their statistical indicators allow measurement of the growth, size and distribution of scientific literature on the topic in question during a given time period (21). Our research group has studied, using a bibliometric approach, the evolution of scientific literature in different areas of neurosciences by several research groups, involving diverse psychiatric disorders and characteristics related, as well as specific therapeutic tools in the field of psychopharmacology (22-34), including the evolution of publications on the pineal gland during the period 1966-1994 (35), and 1900-2014 (36). In this sense, to detail its distribution, and interpret the changes that have affected its development, we focused our attention on the bibliometric analysis of the scientific production on melatonin since the discovery of this hormone in 1958 until 2019, to identify the groupings and trends of the research on this topic.

2. MATHERIAL AND METHODS

2.1. Data sources.

In the present bibliometric study, the databases that have been consulted are SCOPUS (Elsevier BV, Amsterdam, The Netherlands) and the main collection of Web of Science (WoS) (Institute for Scientific Information (ISI) and Clarivate Analytics, Philadelphia, USA), considered to be the most exhaustive within the biomedical field. While 19,469 documents were found in SCOPUS, in WoS the number of documents amounts to 20,768, which is why the latter database was used to carry out the present study. The WoS indexes journals with a high scientific quality and provides a unique citation report function.

2.2. Search strategy.

Using remote-download techniques, we selected documents that contained, in the *TI* (title) section, the descriptor “*melatonin**”, always confining the year of publication from the first document that appears in the database (1958) until the year 2019. Therefore, this study covers a 62-years period of scientific research on melatonin. To minimize the inclusion of off-topic items, we searched only in the “title”. Data were extracted from WoS database at one day (June 11, 2020) to avoid bias because of daily updating in the database.

This study took into account all original articles, brief reports, reviews, editorials, letters to the editor, and so on; it was also made sure that the duplicated documents were eliminated.

2.3. Data categorization.

After downloading the metadata and exact bibliographic details of all melatonin publications, the results were analyzed according to the criteria of chronological distribution, country of origin, affiliation, sources and authors of the documents, keywords and descriptors used. The methodology applied in this study was comparable to recent bibliometric studies of our group (32, 34, 37, 38).

2.4. Bibliometric indicators.

Among the bibliometric indicators of production, we applied Price’s Law (39). This law, undoubtedly the most widely used indicator for the analysis of productivity in a specific discipline or a particular country, takes into account an essential feature of scientific production, which is its exponential growth. In order to assess whether the growth of scientific production in this field follows Price’s Law of Exponential Growth, we carried out a linear adjustment of the data obtained, and another adjustment to an exponential curve.

Time of duplication and the annual growth rate is related to the growth of a subject of study. The first is an indicator that informs us of the time required for the scientific production of a given subject to double. The form of growth was studied from the equation of Egghe and Ravichandra Rao (40), this function is represented mathematically as: $C(t) = cg^t$, where $C(t)$ is the total number of documents produced at time t; c and g represent estimated constants of the observed data, taking into account that $c > 0$, $g > 1$, and $t \geq 0$; t is the number of chronological years studied in the research period (t = 0, 1, 2, ..., n). The model not only provides an average rate of growth, but also offers a rate of duplication. To estimate the duplication time (D) of the scientific literature, the following equation is used: $D = LN(2) / LN(g)$.

As an indicator of the publications’ repercussion we used the Impact Factor (IF). This indicator, developed by the Institute for Scientific Information (Philadelphia, PA, USA), is published annually in the *Journal Citation Reports* (JCR) section of the Science Citation Index (SCI). The IF of a journal is calculated on the basis of the number of times the journal is cited in the source journals of the SCI during the two previous years and the total number of articles published by that journal in those two years. The JCR lists scientific journals by specific areas, ascribing to each of them their corresponding IF and establishing a ranking of “prestige” (41) In this study, we used the IF data published in the JCR of 2018.

Another indicator included in the present analysis was the national Participation Index (PaI) in overall scientific production on this field. The PaI reflects the quotient between the number of documents generated by a given country and the total number of documents obtained in the repertoire.

Regarding investigators' productivity, Lotka's Law (42) intents to calculate the number of expected authors for a given number of papers. This law is expressed as: $An = Kn^{-b}$, $n = 1, 2, 3, ...$, where An represents the probability that an author produces n publications on a subject, while K and b are parameters to estimate depending on the data. According to this law, if the studied period is long enough, and the bibliographic search is as complete as possible "the number of authors that publish n papers is inversely proportional to n^2".

As a bibliometric indicator of the dispersion of the scientific information, Bradford's Law (43) has been applied. According to this law, in the scientific production of a given area, there is a core of selected journals that are more widely used by the investigators and several groups or zones (Bradford's zones) which include the same number of journals as the core. Thus, the number of journals in the different Bradford's zones would be: $1, n, n^2$,... This model allows one to determine which journals are more widely used by a scientific community working in a specific field.

Other indicators that have been included are number of authors/paper index and author's productivity index (PI). PI allows the establishment of three levels of productivity: PI = 0 (transience index: authors with a single paper), $0 < PI < 1$ (those authors that published between 2 and 9 papers), and $PI \geq 1$ (very productive authors, with 10 or more papers).

2.5. Bibliometric mapping.

Bibliometric mapping is an important research topic in the field of bibliometrics (44). We have studied the keywords, and the co-occurrence networks for the most frequently used terms in the titles and abstracts of the publications related to melatonin over the time interval. Each term is demonstrated by a circle, where its diameter and the size of its label illustrate the frequency of the term, and its color reflects most frequently encountered topics in this field (45).

The analysis of keywords is included within the classification of relational and multidimensional indicators (46). By keyword analysis, we mean the study of the co-occurrences or joint appearances of two terms in a given text in order to identify the conceptual and thematic structure of a scientific domain.

We have also analyzed bibliographic coupling, a measure that uses citation analysis to establish a similarity relationship between documents. Bibliographic coupling occurs when two articles reference a third common article in their references. Bibliographic coupling was introduced by Kessler as a method of grouping technical and scientific documents and facilitating the provision of scientific information and the retrieval of documents (47).

Finally, we have applied the mapping to identify the collaborative networks of the institutions and authors, to determine which authors produce, how much and how they relate and collaborate.

2.6. Statistical analysis.

Statistical analysis tests were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0, to evaluate the growth pattern of research output, linear and exponential regression adjustments were compared for trend in the publication. The software VOSwiever (Centre for Science and Technology Studies, Leiden University, The Netherlands) was used to perform the bibliometric mapping (45).

3. RESULTS

In our repertoire have been included 20,768 documents about diverse aspects of the melatonin within the 62-years period (1958-2019). A notable increase in the number of publications on melatonin was observed (Figure 1). The mathematical adjustment to a lineal curve ($y = 16.297x - 32072$) as shown in Figure 1, confirms that this dataset does not follow Price's Law, with a correlation coefficient r = 0.9535, which indicates that only a 9.08% of variability remains unexplained by this adjustment. In contrast, the exponential adjustment of the values $y = 6E\text{-}78e^{0.0919x}$ contains a r = 0.9313, and thus, a percentage of unexplained variability of 13.27%. With these data, we can conclude that the repertoire analyzed is more in keeping with a linear fitting than an exponential one, therefore, it does not comply with the postulates of the Price's Law, and the growth in the area of melatonin is linear.

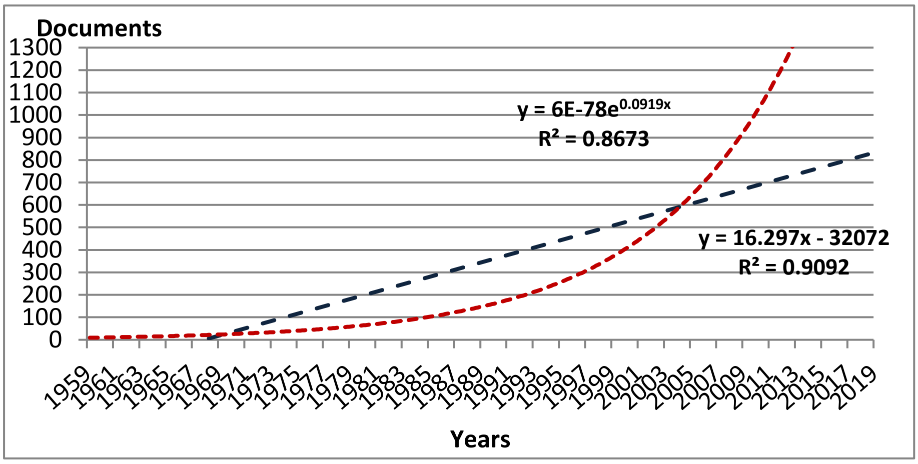

Fig. 1. Evolution in the number of international scientific publications on melatonin.

A linear adjustment of data and another adjustment to an exponential curve have been performed, to verify whether the analyzed production fits Price's Law.

As shown in Figure 1, the increase in the number of papers on melatonin is impressive, above all from the beginning of the eighties, overcoming as of 1991; the number of publications stabilizes in the late 1990s and grows from year 2010. Precisely, from the year 1985 there are 91.99% of the records, and from 1999 there are 70% of the documents. Figure 2 further illustrates this issue. There is an important accumulative increase in the scientific production in each decade over the preceding one, mainly in the 1990s (113.96%). We also see rates of increment in the last two decades ranging between 34.90% (2000s) and 51.15% (2010s).

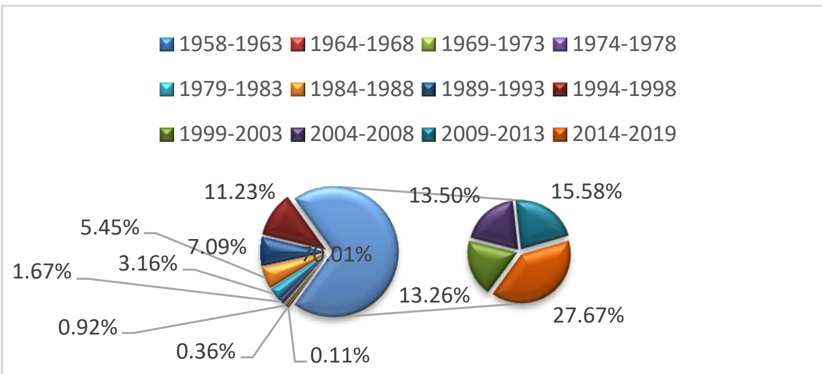

Fig. 2. Scientific production by five-year periods.

Table 1 shows the parameters and values obtained from the application of the exponential model by the non-linear regression method. The value of *c* and *g* are 53.785 and 1.050, respectively. With these values the Egghe and Ravichandra Rao equation can be established, and thus predict the growth of the published literature on melatonin: $C(t) = 53.785 \times 1.050^t$.

From this method, it is inferred that the literature on melatonin has grown at a rate of 5% per year with a production that doubles its size every 14.2 years. We have obtained that the model is explained at 94.6%.

Table 1. **Values of the parameters obtained with the exponential model.**

Parameter estimated

Parameter	Estimate	Sdt. Error	95% Confidence Interval	
			Lower bound	Upper Bound
c	53.785	5.948	41.887	65.683
g	1.050	.002	1.046	1.055

Correlations of parameter estimated

	c	*g*
c	1.000	-.983
g	-.983	1.000

ANOVA*

Source	Sum of Squares	df	Mean Squares
Regression	12441965.632	2	6220982.816
Residual	314742.368	60	5245.706
Uncorrected Total	12756708.000	62	
Corrected Tota	5800097.935	61	

Dependent variable: Docs

** R squared = 1 - (Residual Sum of Squares) / (Corrected Sum of Squares) = 0.946.*

Table 2 indicates the journals more widely used for the diffusion of scientific literature on melatonin, together with their respective impact factor (IF) according to the JCR of 2018, as well as other data of interest. A total of 2,408 journals have been included. The journal most used is the *Journal of Pineal Research*, with 2,208 papers (10.63%), followed, at a great distance, by *FASEB Journal* (276), *Neuroendocrinology Letters* (261) or *Neuroscience Letters* (247).

Table 3 shows the division by Bradford zones, the number of journals and articles, and the multiplication factor. The distribution of Bradford's zones for the entire set of journals is represented in Table 3. The first zone or core is composed of 34 journals (1.41% of all), accounting for 33.39% of all papers published.

Table 2: Main journals used for diffusion of research papers on melatonin.

	Journal	Nº Documents	PaI	IF	Quartile in Category
1	*Journal of Pineal Research*	2,208	10.63	15.221	Q1
2	*FASEB Journal*	276	1.33	5.391	Q1
3	*Neuroendocrinology Letters*	261	1.26	0.698	Q4
4	*Neuroscience Letters*	247	1.19	2.173	Q3
5	*Sleep*	241	1.16	4.571	Q1
6	*Brain Research*	220	1.06	2.929	Q2
7	*Life Sciences*	220	1.06	3.448	Q2
8	*Chronobiology International*	198	0.95	2.562	Q2
9	*General and Comparative Endocrinology*	198	0.95	2.445	Q3

IF = Impact Factor (JCR, 2018).

Table 3. Distribution of the journals subset in Bradford´s zones.

	Nº of journals	% of journals	Nº of articles	% of articles	Bradford factor
Core	34	1.41	6,935	33.39	
Zone 1º	263	10.92	7,139	34.38	7.73
Zone 2º	2,111	87.67	6,694	32.23	8.02
Total	2,408	100.00	20,768	100.00	7.87

Another widely accepted bibliometric indicator is the formulated in Lotka's Law on the productivity of investigators. In summary, this law would be observed when less than one tenth of the authors are responsible of one third of the papers. The productivity index (PI; logarithm of the *n* values for each author) led to the establishment of three accepted levels of productivity (Table 4). There are 1,369 authors (3.38% of the total) that have a PI ≥ 1 and that can be considered as large producers, i.e., they have published 10 or more papers in this field. In clear contrast, the index of transience (occasional authors) is very high, well 25,108 authors (62% of the total) have produced only one paper (PI = 0). The co-authorship index for the 20,768 records is 1.95 authors per document.

Table 4: Classification of authors based on productivity.

	NP ≥ 1 (10 or more articles)	0 < NP < 1 (2-9 articles)	NP=0 (1 article)	Total
Number of authors	1,369	14,020	25,108	40,497
% Authors	3.38	34.62	62.00	100.00

In Table 5, the 9 most active authors in this dataset are listed, and Table 6 shows the top 10 most cited articles during the 62-year period analyzed. These 10 articles accumulate 2.02% of all citations. The citation index represents the number of times that an article has been referenced in other documents and is one of the most used tools to analyze the research productivity. The total number of citations in the melatonin research area is 553,071, representing an average citation rate per document of 26.63. The bibliographic coupling of the documents is shown in Figure 3.

Table 5: Most productive authors.

	Author	Documents	PI	h-index*	Organizations
1	Reiter RJ	1,098	5.22	146	University of Texas Health San Antonio
2	Tan DX	262	1.26	83	University of Texas at San Antonio
3	Arendt J	199	0.96	72	University of Surrey
4	Cardinali DP	198	0.95	59	Pontifical Catholic University of Argentina
5	Pevet P	187	0.90	63	Universite de Strasbourg
6	Delagrange P	155	0.75	48	Institut de Recherches Internationales Servier
7	Brown GM	140	0.67	53	University of Toronto
8	Acuña-Castroviejo D	136	0.66	60	University of Granada
9	Pang SF	129	0.62	41	CK Life Sci Int Inc

* *Web of Science, December 2020.*

Table 6: Top 10 most cited articles.

	Article	Author	Source	Year	Citation
1	Pineal melatonin - cell biology of its synthesis and of its physiological interactions	Reiter	*Endocrine Reviews*	1991	1,793
2	Light suppresses melatonin secretion in humans	Lewy *et al.*	*Science*	1980	1,310
3	Regulation of antioxidant enzymes: a significant role for melatonin	Rodriguez *et al.*	*Journal of Pineal Research*	2004	1,293
4	Melatonin, hydroxyl radical-mediated oxidative damage, and aging - a hypothesis	Poeggeler *et al.*	*Journal of Pineal Research*	1993	1,172
5	Isolation of melatonin, the pineal gland factor that lightens melanocytes	Lerner *et al.*	*Journal of the American Chemical Society*	1958	1,089
6	One molecule, many derivatives: A never-ending interaction of melatonin with reactive oxygen and nitrogen species?	Tan *et al.*	*Journal of Pineal Research*	2007	1,030
7	Action spectrum for melatonin regulation in humans: Evidence for a novel circadian photoreceptor	Brainard *et al.*	*Journal of Neuroscience*	2001	924
8	Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses	Reppert *et al.*	*Neuron*	1994	898
9	Actions of melatonin in the reduction of oxidative stress - A review	Reiter *et al.*	*Journal of Biomedical Science*	2000	878
10	The melatonin rhythm - both a clock and a calendar	Reiter	*Experientia*	1993	785

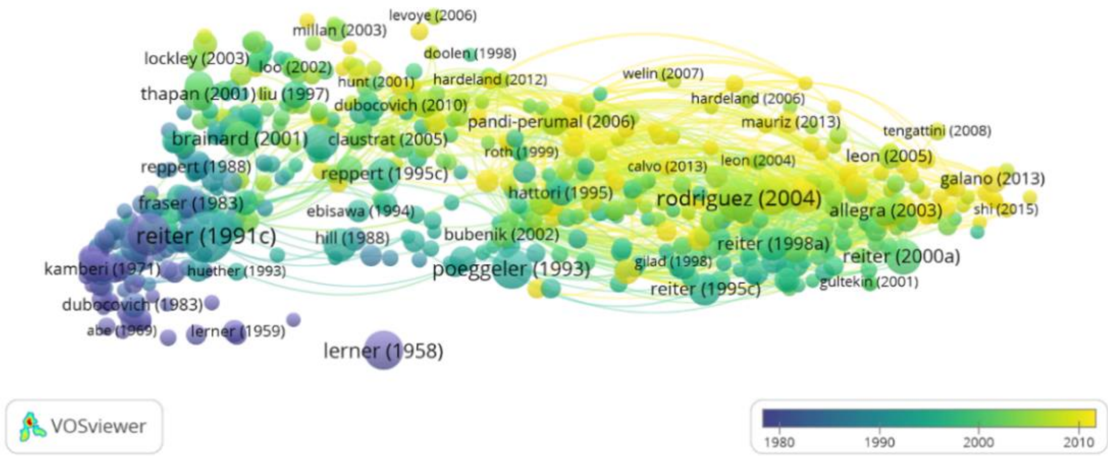

Fig. 3: Bibliographic coupling of documents.

After a manual data cleansing, due to the lack of standardization in the names of the authors who sign the documents, it is confirmed that the most productive author is Russel J. Reiter, at University of Texas Health San Antonio, who has the 5.22% of the total documents published on melatonin. The Figure 4 shows their collaboration network, highlighting among the most important clusters authors such as Dun-Xian Tan, at University of Texas San Antonio, Daniel P. Cardinali, at Pontifical Catholic University of Argentina, Shiu-Fun Pang, at CK Life Sciences International, or Juan Ramón Calvo, at University of Seville.

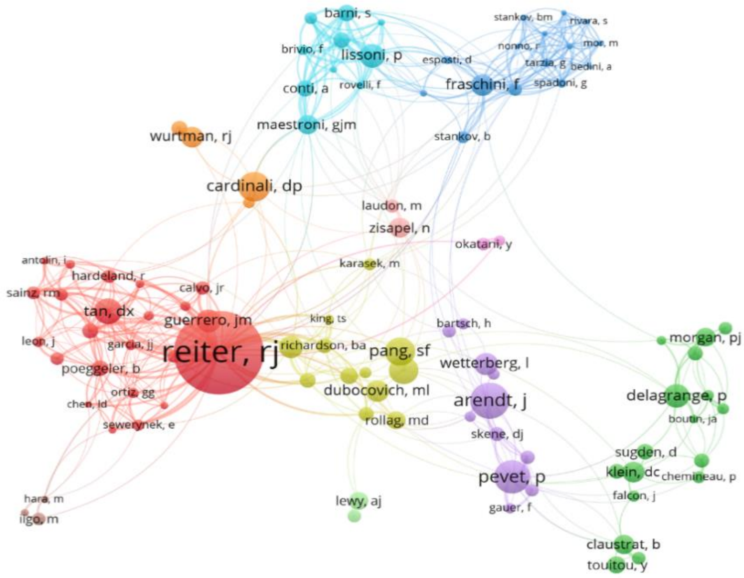

Fig. 4. Collaborative network of the most productive author in melatonin research.

Regarding the geographical distribution of the research production in this area (Table 7), USA is the clear leader (PaI = 24.77), followed by China (PaI = 8.26), Spain (PaI = 7.44), France (PaI = 5.63) and Turkey (PaI = 5.42). The 10 most productive countries add up to a production of over 70% of the total. The most productive institutions in this field are shown in Table 8. Note that almost 10% of scientific production was generated at the University of Texas. It should be noted that research in this area occurs mainly in the field of the University. Proof of this is that, among the 20 most productive institutions, 16 are universities.

Table 7. Geographical distribution of research production.

	Country	Documents	PaI
1	USA	5,144	24.77
2	China	1,716	8.26
3	Spain	1,545	7.44
4	France	1,169	5.63
5	Turkey	1,125	5.42
6	Italy	1,066	5.13
7	England	972	4.68
8	Germany	919	4.43
9	Japan	896	4.31
10	Canada	776	3.74
11	India	667	3.21
12	Poland	651	3.13
13	Brazil	557	2.68
14	Australia	516	2.48
15	South Korea	511	2.46
16	Iran	415	2.00
17	Argentina	374	1.80
18	Switzerland	327	1.57
19	Israel	309	1.49
20	Netherlands	282	1.36

PaI = Participation Index.

Table 8. Most productive institutions.

	Institution	Documents	PaI
1	University of Texas System	2,354	8.96
2	Centre National de la Recherche Scientifique CNRS	471	1.79
3	Institut de Recherches internationales SERVIER	412	1.57
4	Universidade de Sao Paulo	302	1.15
5	University of California System	291	1.11
6	National Institutes of Health NIH USA	254	0.97
7	University of Surrey	252	0.96
8	Harvard University	234	0.89
9	Institut National de la Santé et de la Recherche Medicale INSERM	229	0.87
10	University of London	216	0.82
11	Universidad de Granada	206	0.78
12	Universidad Complutense de Madrid	198	0.75
13	Universite de Strasbourg	192	0.73
14	Universites de Strasbourg Etablissements Associes	191	0.73
15	Universidad de Buenos Aires	190	0.72
16	Northwestern University	169	0.64
17	Universidad de Sevilla	161	0.61
18	Medical University Lodz	159	0.61
19	University of Aberdeen	157	0.60
20	University of Hong Kong	156	0.59
21	Università degli Studi di Milano	156	0.59
22	Institut National de Recherche pour l’Agriculture, l’Alimentation et l’Environnement INRAE	154	0.59

23	University of Toronto	154	0.59
24	Tehran University of Medical Sciences	149	0.57
25	Mahidol University	141	0.54
26	Tel Aviv University	139	0.53
27	Université de Paris	138	0.53
28	McMaster University	137	0.52
29	University of Gottingen	135	0.51

PaI = Participation Index.

Collaboration between different institutions is a key factor in the development of scientific production in any area of knowledge. The Figure 5 shows the collaboration relationships of the most productive institutions. The leader, the University of Texas System, highlighting the collaboration network with the Northwestern University and universities of Sao Paulo, Granada and Seville.

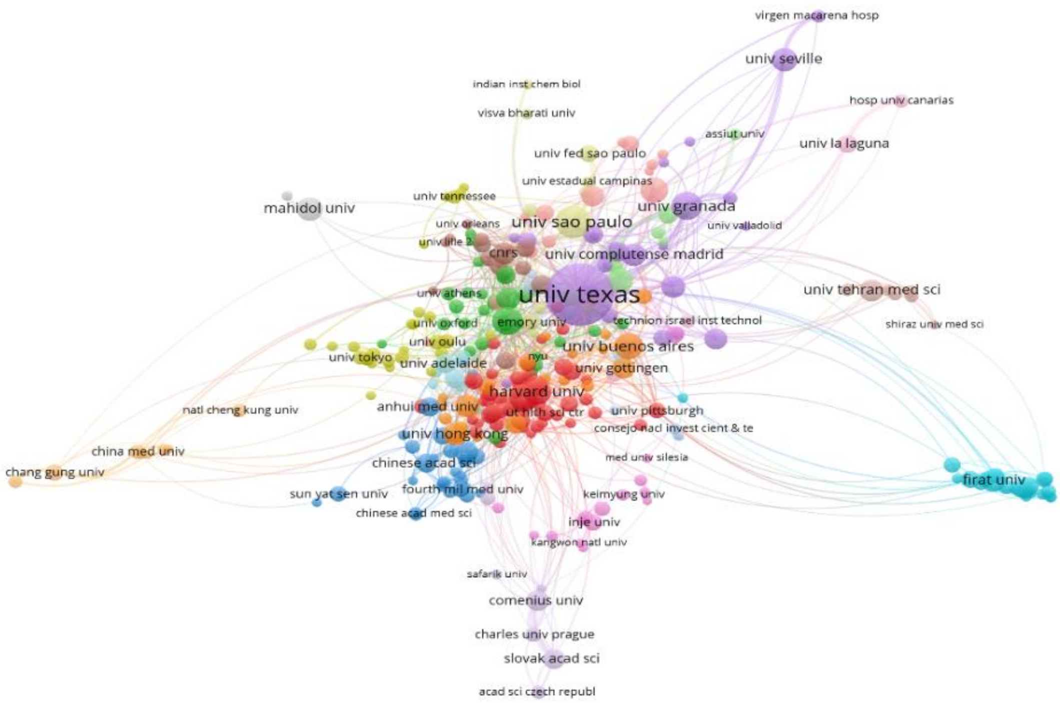

Fig. 5. Map of collaboration between institutions.

The Figure 6 shows the main funding Agencies that support melatonin research. The United States Department of Health Human Services and the National Institutes of Health (NHI) are the Agencies that have been mentioned in a greater number of documents of the analyzed repertoire. Apart from the US Agencies, the funds of the Spanish Administration, National Natural Science Foundation (China) and the Foundation for Research Aid of the State of Sao Paulo(Brazil) stand out.

The most common language of the publications is English (98.13%), followed by Spanish (0.48%), French (0.44%), and Russian (0.37%). Meanwhile, in the analysis of the type of document, original articles accounted for 67.15% of the repertoire, meeting abstracts the 16.47%, reviews the 5.50%, proceeding papers the 4.76%, and letters the 1.96%.

Analysis of subject areas shows that 30.19% of the documents fits in "Neurosciences" area (6,269 documents), 22.91% in “Endocrinology” (4,757 documents), 18.65% in “Physiology” (3,874 documents) and 11.62% in “Biochemistry” (2,413 documents) (Table 9).

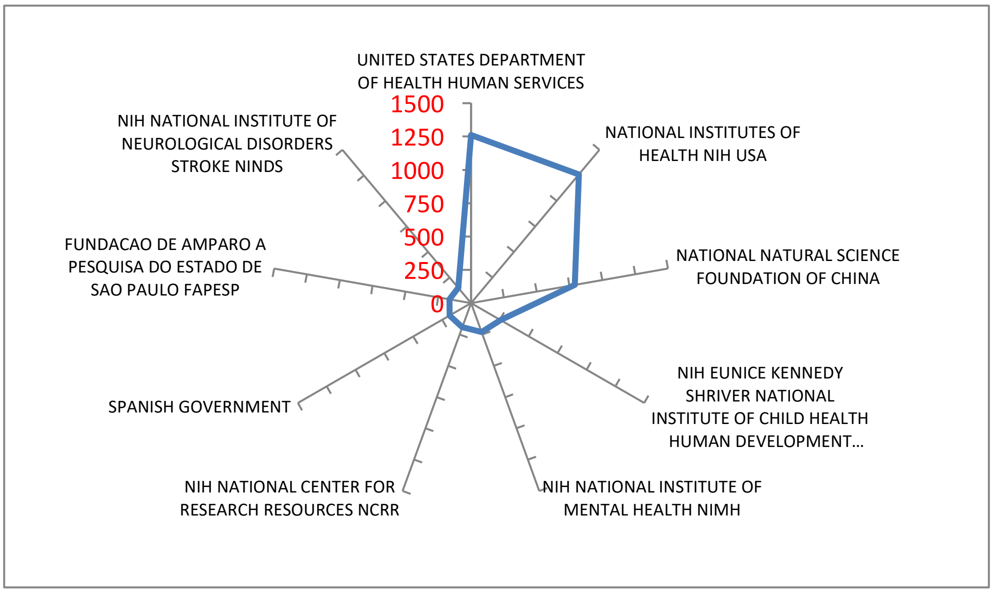

Fig. 6: Main funding Agencies.

Table 9: Distribution of the documents according to the main research areas.

Research areas	Documents	PI
Neurociences and Neurology	6,269	30.19
Endocrinology and Metabolism	4,757	22.91
Physiology	3,874	18.65
Biochemistry and Molecular Biology	2,413	11.62
Pharmacology and Pharmacy	2,262	10.89
Cell Biology	1,208	5.82
Life Sciences Biomedicine and Other Topics	1,113	5.36
Research Experimental Medicine	1,071	5.16
Chemistry	869	4.18
Psychiatry	771	3.71
Reproductive Biology	727	3.50
General Internal Medicine	632	3.04
Oncology	599	2.88
Agriculture	587	2.83
Zoology	530	2.55
Science Technology and Other Topics	529	2.55
Toxicology	422	2.03
Veterinary Sciences	407	1.96
Biophysics	350	1.69

Finally, the maps presented in Figure 7 show the frequency of appearance of the keywords provided by the documents themselves and those derived from the title and abstract of the same, respectively. Figure 7A shows the bibliometric map with the selected keywords, being the size of the keyword tags proportional to the frequency of occurrences of the terms and their weight. The central conglomerate of the map indicates a high interrelation of the keywords that comprise it, while the clusters located at the edges of the maps indicate a lower interrelation of said keywords. The larger the circle, the higher the frequency of occurrence of the specific term and the smaller the distance between two terms/circles, the higher the co-occurrence of the terms. Colors indicate clusters of closely related terms. Cluster analysis based on term co-occurrence identified four major clusters (red, green, blue and yellow), being the main term (*melatonin*) situated in the red cluster, highly connected with terms from the others clusters. As we can see in this Figure 7A, in the keywords provided by the authors, the terms *melatonin*, *pineal gland* and *antioxidant* stand out in the central clusters. Conversely, in the keywords of the title and abstract of the documents (Figure 7B), the term *cell* appears as the central cluster.

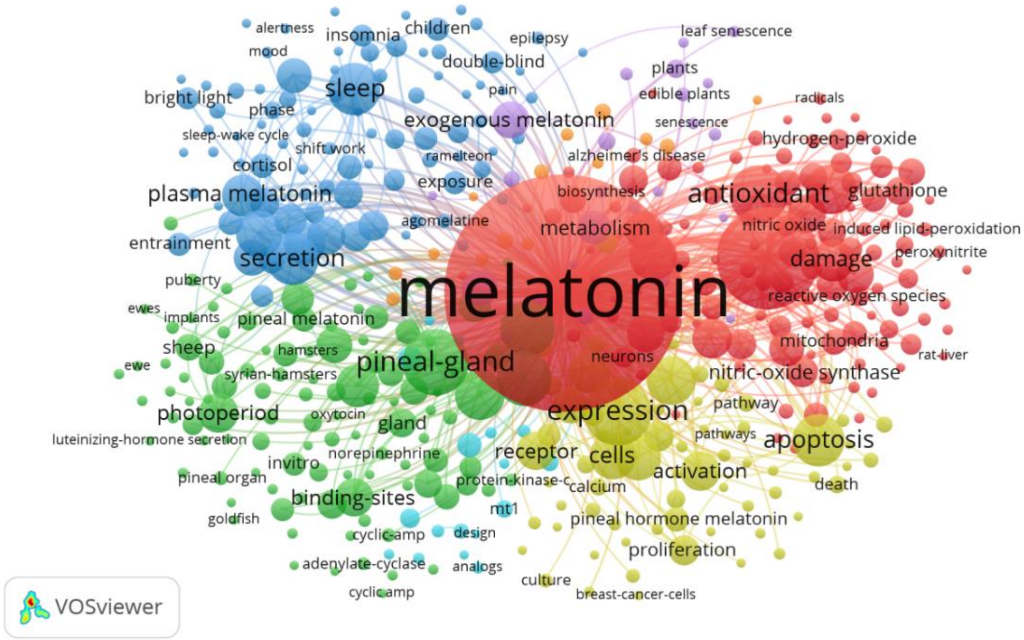

Fig. 7A. VOSviewer co-occurrence autor keywords map.

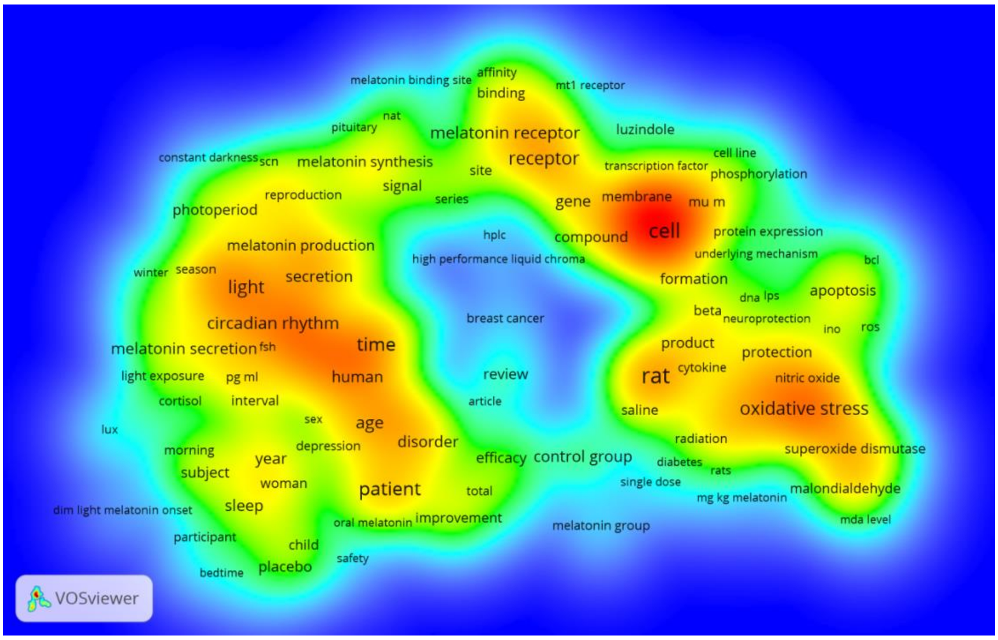

Fig. 7B. VOSviewer co-occurrence term map of title and abstract words.

DISCUSSION

Bibliometric studies constitute useful tools for assessing the social and scientific importance of a given discipline over a specific time period. The term "bibliometrics" was introduced by Pritchard in 1969, to define the application of mathematical and statistical methods to the process of dissemination of written communication in the area of scientific disciplines, using quantitative analysis of the different aspects of this type of communication (48). These analyses give an overview of the growth, size and distribution of the scientific literature related to a particular discipline, and the study of the evolution of not only the biomedical specialty, field of specialization or issue in question, but also the scientific production of an institution, country, author or research group (49). The design of the present analysis permitted a global assessment on the growth of scientific publications on melatonin since 1958.

In Figure 1, after the mathematical adjustment, the number of publications on melatonin shows an exponential growth after 1966; this curve does not evidence the saturation phenomenon described by Price (39) in his theory on the expansion of the scientific literature. This phenomenon assumes a faster growth rate for science that for any other human activity, and that its size would double every 10-15 years. In our case, and considering the starting point in 1958, scientific production doubles every 14.2 years, with an annual growth of 5%.

There were four main scientific events that made possible the impressive advance in this research field: *i*) the isolation of melatonin in 1958 by Lerner and coworkers; *ii*) the finding that this endocrine organ is directly controlled by external environmental factors (50-53); *iii*) the onset of clinical trials with melatonin in different diseases since the beginning of the 1980s and the characterization of melatonin receptors and the definition of their pharmacological profiles (54); and finally *iv*) the development of new therapeutic tools of melatonergic action during the first decade of XXI century, as ramelteon and agomelatine (55). The appearance of the first two breakthroughs in a short period of time (1958-1965) initiated the basis of the current scientific knowledge of the melatonin, which changed the old concept of the pineal gland as a vestigial organ without physiological importance, to one that considered it to be a "neuroendocrine transducer" (56).

Mid 1950s, Lerner began his studies to identify the factor responsible for blanching the skin in amphibians, which concluded in 1958 with the isolation, from 250,000 bovine pineal glands, of an indolamine extract that he named "melatonin". This discovery marks the main milestone in this area of knowledge because finally, a chemical substance, synthesized and released from the pineal gland, is endowed with an endocrine function (18). During the following years, several authors (50, 52, 57-60) showed that melatonin synthesis in mammals is under control of environmental light through the sympathetic innervation originating in the superior cervical ganglia (61). In 1965, two papers were published where the neuroendocrine nature of the pineal gland was definitively confirmed. Hoffman and Reiter (53) observed that the gonadal changes in rodents exposed to dark conditions totally disappeared after pinealectomy. Wurtman and Axelrod (56) introduced the term "neuroendocrine transducer" to refer to the pineal gland. With this concept, these authors tried to explain the principle of the pineal physiology, i.e.; the transformation of external luminic information that reach the gland from the retina and through a nervous pathway to an endocrine response consisting in the synthesis and release of the hormone melatonin.

By this time, a new discipline stimulated by the publication in 1958 of the book entitled *Die physiologische Uhr* (*The Physiologic Clock*) by Erwin Bünning was also developing (62). This discipline called "chronobiology" rapidly consolidated during the sixties, became firmly linked with pineal physiology. The development of chronobiology has been a powerful support to the scientific expansion of the study of the melatonin.

As it has been mentioned previously, there seems to be three well-defined periods in the growth of the scientific production on melatonin: a first period until around 1980, a second period until 2010, where the increase in the number of publications is more pronounced, and the last decade, in which the growth of publications is much more exponential. The first years of the decade of the eighties provided the main facts that led to the maturity of melatonin research. In 1977, under the leadership of Professor Johannes Ariëns Kappers and Dr. Paul Pévet, the *European Pineal Study Group* (EPSG) was founded (today known as *European Pineal Society*, EPS), and its first meeting was held in Amsterdam in 1978. The scientific results of this conference are published in the issue number 52 of the prestigious series *Progress in Brain Research* (1979). Two years later, the most complete and comprehensive book on the pineal gland was published under the authorship of Professor Lutz Vollrath: *The Pineal Gland* (63). In this work, all the scientific knowledge on this organ in all the animal species studied up to that time was reviewed. Probably, the final step in this development process was the launching in 1984 of a specific journal devoted to this field: *Journal of Pineal Research*, initially edited by Professors Russel J. Reiter, Wilbur B. Quay and Michal Karasek. This journal constitutes the nucleus or first Bradford's zone in the analysis that we carried out on the dispersion of the scientific literature on melatonin research, with 10.63% of the total production analyzed. Furthermore, the journal's founder, Professor Reiter, is, by a huge difference, the most productive author in our repertoire, with 1,098 documents and more than 5% of the total production. Similarly, he is the author of the most cited article of the history on melatonin: "Pineal melatonin. Cell biology of its synthesis and of its physiological interactions", published in *Endocrine Reviews* in 1991 (see Tables 5 and 6). Figure 3 shows the bibliographic coupling network of this paper.

During these 30 years of growth in the second period, research on melatonin followed the natural evolution of biomedical research, where basic approaches to diverse disciplines are progressively substituted by more clinically oriented applications. Endocrinology initially, and psychiatry and pharmacology later, have taken over morphological and physiological disciplines that dominated pineal research during the sixties and the seventies. Similarly, the application of techniques of cellular and molecular biology, including immunohistochemistry, tissue culture, *in situ* hybridization, or microinjection techniques (64), played an important role in the expansion of the scientific literature on melatonin and pineal physiology until the late twentieth century (mainly the interrelation between the central nervous system and the gland).

Finally, during the last decade, the exponential growth of scientific production on melatonin is associated with a greater orientation towards the study of the systemic effects of the melatonin and their derivatives, and their clinical implications. Thus, new research areas in this field seem to be the relationship of the melatonin to reproductive function disorders, psychiatric disorders including depression, manic-depressive disease, schizophrenia, sleep disorders and alterations of the biological rhythms ("jet lag"), or even cancer and degenerative diseases of aging, are increasingly recognized (15). The general growing tendency of melatonin in recent years, together with the absence of a "saturation point" in the growth of the scientific production on this matter, leads to encouraging horizons for this indolamine.

In fact, throughout these 62 years, the research areas in which the most documents on melatonin have been published correspond to basic disciplines, such as the neurosciences, physiology, biochemistry, pharmacology or cell biology, and to a much lesser extent, clinical disciplines, such as endocrinology, psychiatry, internal medicine or oncology (see Table 9). The rise of clinical research with melatonin and its therapeutic analogues during the last decade is possibly behind the exponential growth of the literature observed in these years and its possible future growth. The VOSviewer co-occurrence keywords and terms maps (Figure 7) also shows us which have been the most relevant topics in the history of research on melatonin:

sleep, antioxidant, oxidative stress, expression, apoptosis, receptors, photoperiod, binding-sites, light, or circadian rhythm.

Another interesting quantitative aspect of this bibliometric analysis is the quality of the scientific production. We approached this problem with the evaluation of the repercussion index of the publications included in the dataset. The Impact Factor (IF) is a repercussion index that, in spite of its limitations and biases, such the underestimation of original papers when compared with reviews, higher scores for English-language edited journals, or the tendency to ignore certain areas of knowledge that only concern to a small number of investigators (41), is the most frequently used tool by the scientific community to evaluate the quality of research papers. It is notable the high number of journals with an IF > 2.5 included in the list of the most used 9 journals (*Journal of Pineal Research*, *FASEB Journal*, *Sleep*, *Brain Research*, *Life Sciences*, and *Chronobiology International*) (Table 2). Likewise, the importance of the authors who research on this topic is demonstrated, since among the first nine, we find seven with an h-index above 30 and five above 40.

Melatonin research is a multidisciplinary field where very different areas of knowledge, both basic (neurosciences, pharmacology, biochemistry, physiology, toxicology, etc.), and clinically-oriented, (endocrinology, neurology, neurosurgery, psychiatry, radiology, pharmacology, internal medicine, oncology, etc.) converge (see Table 9). As a result, the most widely used journals for publication by melatonin investigators are those with multidisciplinary content (*Journal of Pineal Research, FASEB Journal, Brain Research, Life Sciences, Neuroscience Letters*), together with those related to endocrinology (*Neuroendocrinology Letter, Endocrinology, Neuroendocrinology Letters, General and Comparative Endocrinology, Journal of Clinical Endocrinology and Metabolism*) (see Table 2).

Although the average index of signatures / paper of the documents is 1.95, team-working research and author collaborations are reflected in our repertoire. This low figure is explained by the temporal amplitude of our repertoire, since the index signatures / document was much lower in the articles published before the nineties. Since then, it is clear that a tendency exists towards the increment in the number of authors on scientific papers, and that this effect is mainly due to a higher degree of collaboration between different investigators. This increase in scientific collaboration is not only the result of interdepartmental support, which is essential given the high complexity and diversity of the current technology and methodology, but a notable increase in the collaboration of melatonin research groups located in different countries is apparent, as shown in the collaboration network maps in Figures 4 and 5. But, we must also bear in mind that the index of transience is very high. This indicates that 25,108 authors (62% of the total) are occasional authors, who have contributed to the scientific production on melatonin only tangentially.

The institutions that generate the largest body of research on melatonin are, without a doubt, the universities. Among the top 20 institutions are 16 universities, and the rest are public research centers (Centre National de la Recherche Scientifique, in France) or private (Servier Laboratories), or health institutions, such as the National Institutes of Health NIH USA or the Institut National de la Santé et de la Recherche Medicale in France. Among the Universities, the University of Texas System stands out by far, although 3 other North American universities are among the 20 most productive institutions, followed by 3 Spanish universities and another 3 British (Table 8). Between all of them there are dense networks of collaboration (see Figure 5). In the specific case of the most prolific author's Institution, these collaborations are very patent with other North American universities (Northwestern University, University of Pittsburgh, Spanish universities (University of Seville, University of Granada, Complutense University of Madrid, University of La Laguna), Brazilian (University of Sao Paulo) and Asian (University of Tehran Medical Sciences, Tel Aviv University, University of Hong Kong, China Agricultural University).

The fact that the USA is responsible for 24.77% of all the documents in the repertoire can be correlated with the data provided in Figure 6, where the documents that express the funding of the research by different North American Agencies are shown, highlighting the United States Department of Health Human Services and the National Institutes of Health (NHI). In this regard, it should be made clear that a country's scientific production in a given field tends to reflect a science research and development policy. In general, there is confirmation of the notion that the higher the funds invested, the greater the research production (24, 26).

Bibliometry has become a fundamental tool for evaluating the results of scientific activity (65). However, previous bibliometric studies have addressed limitations characteristic of this sociometric approach (66). Regarding this particular chapter, there are some main limitations. First, we might have excluded some papers on melatonin if the authors did not put our study inclusion descriptors in the titles or as key words. Second, it is clear that the papers that have been included in this work constitute a partial sample of the global production in this discipline, and that the scientific literature on melatonin is considerably larger, but the boundaries that the bibliographic databases introduce determine the subsequent analysis. Third, the use of the SCI impact factor to determine the merit or quality of scientific contributions is debatable. The citation count applied in calculating the impact factor may not directly reflect the importance or quality of one study; on the contrary, it may only represent the topic of a given study being "more fashionable", or even "not yet mature" and/or "in need of more studies" (67, 68). However, the well-known reputation of the journals included in the databases used and its wide coverage make for a representative sample of the international research on melatonin. Despite the inherent limitations of bibliometric studies, we feel that, given the applied design, we have offered a comprehensive overview of the evolution of the international scientific production and research impact assessment on melatonin.

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AUTHORSHIP

FLM and FJPM conceived the idea and they have made substantial contributions to conception, design, supervision and writing-original draft. AR, JE and CA critically revised the manuscript. FJPM performed the bibliometric analysis. FLM and AR wrote the final draft. All co-authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Karasek M (1999) Melatonin in humans—where we are 40 years after its discovery. *Neuroendocrinol. Lett.* **20**: 179-188.
2. Venegas C, García JA, Escames G, *et al.* (2012). Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. *J. Pineal Res.* **52**: 217-27.
3. Zisapel N (2018) New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. *Br. J. Pharmacol*. **175**: 3190-3199.
4. Ma Z, Yang Y, Fan C, *et al*. (2016) Melatonin as a potential anticarcinogen for non-small-cell lung cancer. *Oncotarget* **7**: 46768-46784.

5. Reiter RJ, Rosales-Corral SA, Tan DX, *et al*. (2017) Melatonin, a Full Service Anti-Cancer Agent: Inhibition of Initiation, Progression and Metastasis. *Int. J. Mol. Sci.* **18**: 843. doi: 10.3390/ijms18040843.
6. Kubatka P, Zubor P, Busselberg D, *et al*. (2018) Melatonin and breast cancer: Evidences from preclinical and human studies. *Crit. Rev. Oncol. Hematol*. **122**: 133-143.
7. Gil-Martín E, Egea J, Reiter RJ, Romero A (2019) The emergence of melatonin in oncology: Focus on colorectal cancer. *Med. Res. Rev*. **39**: 2239-2285.
8. Esteban-Zubero E, López-Pingarrón L, Alatorre-Jiménez MA, *et al*. (2017) Melatonin's role as a co-adjuvant treatment in colonic diseases: A review. *Life Sci.* **170**: 72-81.
9. Tengattini S, Reiter RJ, Tan DX, *et al*. (2008) Cardiovascular diseases: protective effects of melatonin. *J. Pineal Res*. **44**: 16-25.
10. Sun H, Gusdon AM, Qu S (2016) Effects of melatonin on cardiovascular diseases: progress in the past year. *Curr. Opin. Lipidol*. **27**: 408-413.
11. Ramos E, Egea J, de Los Ríos C, *et al*. (2017) Melatonin as a versatile molecule to design novel multitarget hybrids against neurodegeneration. *Future Med. Chem*. **9**: 765-780.
12. Cardinali DP (2019) Melatonin: Clinical Perspectives in Neurodegeneration. *Front. Endocrinol. (Lausanne)* **10**: 480. doi: 10.3389/fendo.2019.00480.
13. Zhao CN, Wang P, Mao YM, *et al*. (2019) Potential role of melatonin in autoimmune diseases. *Cytokine Growth Factor Rev*. **48**: 1-10. doi: 10.1016/j.cytogfr.2019.07.002
14. Elmahallawy EK, Luque JO, Aloweidi AS, *et al*. (2015) Potential Relevance of Melatonin Against Some Infectious Agents: A Review and Assessment of Recent Research. *Curr. Med. Chem*. **22**: 3848-3861.
15. Sánchez-Barceló EJ, Mediavilla MD, Tan DX, Reiter RJ (2010) Clinical uses of melatonin: evaluation of human trials. *Curr. Med. Chem.* **17**: 2070-2095.
16. Lerner AB, Case JD, Takahashi Y, *et al*. (1958) Isolation of melatonin, the pineal gland factor that lightens melanocytes. *J. Am. Chem. Soc.* **80**: 2587.
17. López-Muñoz F, Marín F, Álamo C (2010) El devenir histórico de la glándula pineal. I: de válvula espiritual a sede del alma. *Rev. Neurol.* **50**: 50-57.
18. López-Muñoz F, Marín F, Álamo C (2010) El devenir histórico de la glándula pineal. II: de sede del alma a órgano neuroendocrino. *Rev. Neurol* **50**: 117-125.
19. López-Muñoz F, Marín F, Álamo C (2016) History of pineal gland as neuroendocrine organ and discovery of melatonin. *Melatonin, Neuroprotective Agents and Antidepressant Therapy,* eds López-Muñoz F, Srinivasan V, De Berardis D, Álamo C, Kato TA (Springer International, New Delhi), pp 1-23.
20. Moed HF, Burger WJM, Frankfort JG, Van Raan AFJ (1985) A comparative study of bibliometric past performance analysis and peer judgement. *Scientometrics* **8** (3-4): 149-159.
21. López Piñero JM (1972) *El análisis estadístico y sociométrico de la literatura científica* (Centro de Documentación e informática Médica de la Facultad de Medicina de Valencia, Valencia).
22. López-Muñoz F, Marín F, Boya J (1996). Evaluación bibliométrica de la producción científica española en neurociencia. Análisis de las publicaciones de difusión internacional durante el periodo 1984-1993. *Rev. Neurol.* **24**: 417-426.
23. López-Muñoz F, Álamo C, Rubio G, *et al*. (2003) Bibliometric analysis of biomedical publications on SSRIs during the period 1980-2000. *Depres. Anxiety* **18**: 95-103.
24. López-Muñoz F, Vieta E, Rubio G, *et a*l. (2006) Bipolar disorder as an emerging pathology in the scientific literature: a bibliometric approach. *J. Affect. Dis.* **92**: 161-170.
25. López-Muñoz F, Álamo C, Guerra JA, Rubio G (2006) Twenty-four years of scientific publications on selective serotonin reuptake inhibitors (SSRI): a bibliometric approach.

Focus on Serotonin Uptake Inhibitor Research, ed Shirley AC (Nova Science Publishers, Inc., New York), pp 191-219.
26. López-Muñoz F, Álamo C, Quintero-Gutiérrez FJ, García-García P (2008a) A bibliometric study of international scientific productivity in attention-deficit hyperactivity disorder covering the period 1980-2005. *Eur. Child Adolesc. Psychiatry* **17**: 381-391.
27. López-Muñoz F, García-García P, Sáiz-Ruiz J, *et al*. (2008) A bibliometric study of the use of the classification and diagnostic systems in psychiatry over the last 25 years. *Psychopathology* **41**: 214-225.
28. López-Muñoz F, Shen WW, Shinfuku N, *et al*. (2014) A bibliometric study on second-generation antipsychotic drugs in the Asia-Pacific Region. *J. Exp. Clin. Med.* **6**: 111-117.
29. López-Muñoz F, Povedano FJ, García-García P, *et al*. (2015) Evolution of international scientific production on Attention-Deficit Hyperactivity Disorder: A bibliometric analysis of the last 34 years. *Attention Deficit Hyperactivity Disorder (ADHD): Epidemiology, Treatment and Prevention,* eds López-Muñoz F, Álamo C (Nova Science Publishers, Inc., New York), pp 1-22.
30. López-Muñoz F, Sanz-Fuentenebro FJ, Rubio G, *et al*. (2015) Quo vadis clozapine?. A bibliometric study of 45 years of research in international context. *Int. J. Mol. Sci.* **16**: 23012-23034.
31. López-Muñoz F, Srinivasan V, Gutiérrez-Soriano A, *et al*. (2016) A bibliometric analysis of scientific research on atypical antipsychotic drugs in India during 1998-2013. *Mol. Med. Chem.* **2**: e1113. doi: 10.14800/mmc.1113.
32. López-Muñoz F, Tracy DK, Povedano-Montero FJ, *et al*. (2019) Trends in scientific literature on atypical antipsychotic drugs in United Kingdom: A bibliometric study. *Ther. Adv. Psychopharmacol.* **9**: 1-12. doi: 10.1177/2045125318820207.
33. García-García P, López-Muñoz F, Rubio G, *et al.* (2008) Phytotherapy and psychiatry: Bibliometric study of the scientific literature from the last 20 years. *Phytomedicine Int. J. Phytother*. *Phytopharmacol.* **15**: 566-576.
34. Povedano-Montero FJ, Weinreb RN, Raga-Martínez I, *et al*. (2020) Detection of neurological and ophthalmological pathologies with Optical Coherence Tomography using retinal thickness measurements: A bibliometric study. *Appl. Sci.* **10**: 5477. doi:10.3390/app10165477.
35. López-Muñoz F, Boya J, Marín F, Calvo JL (1996) Scientific research on the pineal gland and melatonin: a bibliometric study for the period 1966-1994. *J. Pineal Res*. **20**: 115-124.
36. López-Muñoz F, Povedano FJ, Álamo C (2016) Bibliometric study of scientific research on melatonin during the last 25 years. *Melatonin, Neuroprotective Agents and Antidepressant Therapy*, eds López-Muñoz F, Srinivasan V, De Berardis D, Álamo C, Kato TA (Springer International, New Delhi), pp 25-42.
37. Redondo M, León L, Povedano FJ, *et al*. (2017). A bibliometric study of the scientific publications on patient-reported outcomes in rheumatology. *Sem. Arthr. Rheum*. **46**: 828-833.
38. Okoroiwu HU, López-Muñoz F, Povedano-Montero FJ (2018) Bibliometric analysis of global Lassa fever research (1970-2017): A 47 - Year study. *BMC Infect. Dis.* **18**: 639.
39. Price DJS (1963) *Little Science, Big Science* (Columbia University Press, New York).
40. Egghe L, Ravichandra Rao IK (1992) Classification of growth models based on growth rates and its applications. *Scientometrics* **25**: 5-46.
41. Garfield E (1979) *Citation indexing. Its theory and application in science, technology and humanities* (Wiley, New York).
42. Lotka AJ (1926) The frequency distribution of scientific productivity. *J. Wash. Acad. Sci.* **16**: 317-323.
43. Bradford SC (1948) *Documentation* (Crosby Lockwood and Son Ltd., London).

44. Börner K, Chen C, Boyack KW (2003) Visualizing knowledge domains. *Annu. Rev. Inf. Sci. Technol.* **37**: 179-255.
45. van Van Eck NJ, Waltman L (2010) Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* **84**: 523-538.
46. Leydesdorff L, Welbers K (2010) The semantic mapping of words and co-words in contexts. *J. Informetr.* **5**: 469-475.
47. Kessler MM (1963) Bibliographic coupling between scientific papers. *Am. Doc.* **14**: 10-25.
48. Pritchard A (1969) Statistical bibliography or Bibliometrics. *J. Document.* **25**: 348-369.
49. Bordons M, Zulueta MA (1999) Evaluación de la actividad científica a través de indicadores bibliométricos. *Rev. Esp. Cardiol.* **52**: 790-800.
50. Fiske VM, Bryant GK, Putnam J (1960) Effect of light in the weight of the pineal in the rat. *Endocrinology* **66**: 489-491.
51. Quay WB (1961) Reduction of mammalian pineal weight and lipid during continuous light. *Gen. Comp. Endocrinol.* **1**: 211-217.
52. Wurtman RJ, Roth W, Altschule MD, Wurtman JJ (1961) Interactions of the pineal and exposure to continuous light on organ weights of female rats. *Acta Endocrinol. (Kbh.)* **36**: 617-624.
53. Hoffman RA, Reiter RJ (1965) Pineal gland: Influence on gonads of male hamsters. *Science* **148**: 1609-1611.
54. Dubocovich ML (1988) Pharmacology and function of melatonin receptors. *FASEB J.* **2**: 2765-2733.
55. Álamo C, López-Muñoz F, García-García P (2014) Agomelatine: A neuroprotective agent with clinical utility beyond depression and anxiety. *Melatonin: Therapeutic Value and Neuroprotection*, eds Srinivasan V, Gobbi G, Shillcutt SD, Suzen S (CRC Press Taylor & Francis Group, Boca Raton) pp 309-324.
56. Wurtman RJ, Axelrod J (1965) The pineal gland. *Sci. Am.* **213**: 50-60.
57. Wurtman RJ, Axelrod J, Philips LS (1963) Melatonin synthesis in the pineal gland: control by light. *Science* **142**: 1071-1073.
58. Wurtman RJ, Axelrod J, Fischer JE (1964) Melatonin synthesis in the pineal gland: effect of light mediated by the sympathetic nervous system. *Science* **143**: 1328-1330.
59. Axelrod J, Weissbach H (1960) Enzymatic O-methylation of N-acetylserotonin to melatonin. *Science* **131**: 1312.
60. Quay WB (1963) Circadian rhythm in rat pineal serotonin and its modifications by estrous cycle and photoperiod. *Gen. Comp. Endocrinol.* **3**: 473-479.
61. Kappers JA (1960) The development, topographical relations and innervation of the epiphysis cerebri in the albino rat. *Z. Zellforsch. Mikrosk. Anat.* **52**: 163-215.
62. Bünning E (1958) *Die physiologischen Uhr* (Springer Verlag, Berlin).
63. Vollrath L (1981) The Pineal Organ. In: *Handbuch der Mikroskopischen Anatomie des Menschen*, vol. VI/7 (Springer Verlag, Berlin).
64. Welsh MG (1994) Current methodologies for the study of pineal morphophysiology. *J. Pineal Res.* **16**: 113-120.
65. White HD, McCain KW (1989) Bibliometric. *Ann. Rev. Inf. Sci. Technol.* **24**: 119-186.
66. Johnson MH, Cohen J, Grudzinskas G (2012) The uses and abuses of bibliometrics. *Rep. BioMed. Online* **24**: 485-486.
67. Ha TC, Tan SB, Soo KC (2006) The journal impact: too much of an impact. *Ann. Acad. Med. Singapore* **35**: 911-916.
68. Coleman R (1999) Impact factors: use and abuse in biomedical research. *Anat. Rec.* **257**: 54-57.

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