

Melatonin as a Marker of Aging Process

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Abstract: Skin aging is a change in the structure of the skin which is a consequence of increasing age. Exposure to ultraviolet (UV) light, which can induce the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) thereby damaging cells, can trigger aging. The appearance of signs of skin aging can interfere with appearance so many people start using skin care products. Human skin cells are known to synthesize and possess several types of melatonin receptors. This study aims to determine melatonin as a marker of the aging process. This research method is a systematic literature review (SLR) on journal papers published from 2014-2021. The results show that aging is associated with increased free radicals and decreased tissue antioxidant capacity and that exogenous melatonin plays a protective role in aging through its action on free radicals. The production of endogenous intracutaneous melatonin, together with topically applied exogenous melatonin and its metabolites, represent the two most powerful defense systems against external damage to the skin. Melatonin is in an optimal position to scavenge radicals and reduce levels of oxidative damage. Given the "free radical aging theory", including all its iterations, high levels of melatonin in mitochondria are expected to protect against age-related decline in organisms. Also, there are many age-related diseases, as a contributing factor, to free radical damage. In women with aging skin, Melatonin-based creams significantly increase skin tonicity and skin hydration with a significant reduction in skin roughness, supporting the antiaging effect of the skin.

Keywords: Melatonin, Aging Process, Free Radicals

1. Introduction

Aging is a change in the structure of the organism that occurs gradually over time, which is not caused by disease or accident and can lead to an increased risk of death. (Gosling, 2003) Aging can occur in various parts of the human body, including the skin. The appearance of skin aging is characterized by the presence of wrinkles on some parts of the skin. (Rexbye et al., 2006) Several factors, such as exposure to ultraviolet (UV) light, are thought to contribute to and even accelerate the onset of skin aging. (Yaar et al., 2002) ; (Christensen et al., 2004) ; (Rexbye et al., 2006) UV-induced skin aging is characterized by pigmentation, more visible and deep wrinkles, and telangiectasias (Yaar et al., 2002) .

These signs of skin aging can interfere with appearance; so many people are starting to pay more attention to the condition of their skin. Helfrich et al. said that people today tend to be obsessed with looking young (youth-obsessed), as evidenced by the high public demand for cosmetic products and anti-aging products. (Helfrich et al., 2008) In 2004, sales of these products in the United States reached 12.4 billion dollars. This figure is expected to increase to 16.5 billion dollars in 2010 and will continue to increase (Helfrich et al., 2008) .

One of the skin care products that are now starting to be sold in the market is the substance melatonin in the form of creams and sprays that are used at night before going to bed. Melatonin is a hormone produced by the pineal body in the dark. (Gosling, 2003) Actually, the main function of melatonin is to regulate a person's sleep pattern because it is related to the regulation of circadian rhythms, so melatonin is more widely used to treat insomnia and jetlag. (Rogers et al., 2003) ; (Srinivasan et al., 2010) However, it turns out that human skin cells also have several types of melatonin receptors, so melatonin can also act on skin cells. (Slominski et al., 2008) In addition, the reduced amount of melatonin produced by the body due to pinealectomy or

removal of the pineal body is known to accelerate the aging process, so it is suspected that melatonin also has an antiaging function. (Arendt, 2001) However, the function of melatonin as an antiaging skin due to UV rays is not well understood. Exposure to ultraviolet (UV) light, which can induce the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that damage cells, can accelerate the onset of aging. The appearance of signs of skin aging can interfere with appearance so many people start using skin care products. Human skin cells are known to synthesize and possess several types of melatonin receptors. This study aims to determine melatonin as a marker of the aging process.

2. Research Methods

The method in this study has several process flows, namely:

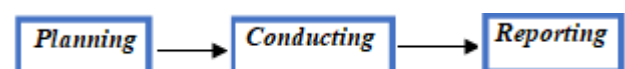


Figure 1: Research Stages

Figure 1. is the research stage consisting of the planning stage which is the initial stage of conducting SLR, then entering the conducting stage, namely the implementation stage of the SLR, and the last stage is Reporting which is the stage of writing the SLR into a report.

Research Question

At this stage, questions are determined according to the research topic. The following is a research question in this study:

- 1) RQ1: What is the method used to collect data about Melatonin as an anti-aging effect?
- 2) RQ2: What are the factors that influence aging?
- 3) RQ3: What is the effect of melatonin as a marker of the aging process?

Search Process

Search process is a stage search to find sources that match the research question. The source search process is carried out at the site address. <https://scholar.google.co.id/>.

Inclusion and Exclusion Criteria

At this stage, the criteria are determined from the data found, whether the data is suitable to be used as a data source for research or not. The following are the criteria for a data to be said to be worthy of being a research data source, namely:

- 1) The data obtained has a time span from 2014 to 2021.
- 2) Data obtained from sources <https://scholar.google.co.id/>.
- 3) The data used are only journal papers related to melatonin as a marker of the aging process.

Quality Assessment

At this stage the data that has been found will be evaluated based on the following questions:

- 1) QA1: Is the journal paper published in the period 2014-2021?
- 2) QA2: Does the journal paper discuss? Related to melatonin as a marker of the aging process?
- 3) QA3: Does the journal paper write down the signs of aging?

And each paper will be given a value based on the questions above.

- 1) Yes: for journal papers that match the questions on the quality assessment.
- 2) Not: for journal papers that do not match the questions on the quality assessment.

Data Collection

At this stage, the data needed in the research is collected for further analysis. The following are the steps for data collection:

- 1) Visit site <https://scholar.google.co.id/>.
- 2) Enter the keyword "Melatonin as a marker of aging".
- 3) In "Custom range", enter 2014 in the first box and 2021 in the second box. This indicates that the selected journal paper range is from 2014-2021.

Data Analysis

The data that has been collected in the previous stage will be analyzed at this stage. The results that have been analyzed will answer all research questions that have been previously determined.

Documentation

The data that has been collected in the previous stage will be analyzed at this stage. The results that have been analyzed will answer all research questions that have been previously determined.

3. Results and Discussion**3.1 Results**

Search Process Results and Inclusion and Exclusion Criteria

The results of the search process and inclusion and exclusion criteria are only 11 journal papers that have met the criteria, namely journal papers published in the 2014-2021 period and have discussions related to "melatonin" and "markers of the aging process". The information obtained is then grouped into several types of journals. The following are the types of journals that have been successfully obtained:

Table 1: Grouping by Journal Type

No	Journal Type	Year	amount
1	Journal of Clinical and Experimental Investigations	2014	1
2	Climacteric	2015	1
3	Molecular medicine reports	2017	1
4	Neurochemical research	2018	1
5	Cosmetics-MDPI	2018	1
6	Clinical, cosmetic and investigational dermatology	2018	1
7	Molecules-MDPI	2018	1
8	Advances in Gerontology-Spinger	2019	1
9	Food and Chemical Toxicology	2019	1
10	International journal of molecular sciences,	2019	2

Quality Assessment Results

The following are the results of the quality assessment which are written in table form:

Table 2: Quality Assessment Results

No	Author	Year	QA1	QA2	QA3	Results
1	Hakan Yüziak, Kazime Gonca Akbulut, Sara Yüziak	2014	Yes	Yes	Yes	accepted
2	AY GURSOY, M. KISELI, GS CAGLAR	2015	Yes	Yes	Not	accepted
3	Xin-Hong Guo, Yan-Hua Li, Yu-Sheng Zhao, Yong-Zhi Zhai and Li-Cheng Zhang	2017	Yes	Yes	Yes	accepted
4	Anorut Jenwitheesuk · Seongjoon Park · Prapimpun Wongchitrat · Jiraporn Tocharus · Sujira Mukda · Isao Shimokawa · Piyarat Govitrapong	2018	Yes	Yes	Yes	accepted
5	Massimo Milani and Mario Puviani	2018	Yes	Yes	Yes	accepted
6	Massimo Milani, Adele Sparavigna	2018	Yes	Yes	Yes	accepted
7	Russel J. Reiter, Dun Xian Tan, Sergio Rosales-Corral, Annia Galano, Xin Jia Zhou and Bing Xu	2018	Yes	Yes	Yes	accepted
8	Rudiger Hardeland	2019	Yes	Yes	Yes	accepted
9	Je-Won Ko, Na-Rae Shin, Tae-Yang Jung, In-Sik Shin, Changjong Moon, Sung-Ho Kim, In-Chul Lee, Sung-Hwan Kim, Won-Kee Yun, Hyoung-Chin Kim, Jong-Choon Kim	2019	Yes	Yes	Yes	accepted
10	LB Kim, AN Putyatina, GS Russkikh, and OB Tsypysheva	2019	Yes	Yes	Yes	accepted
11	Iryna Rusanova Laura Martinez-Ruiz, Javier Florido, Cesar Rodriguez-Santana, Ana Guerra-Librero, Dario Acuna-Castroviejo and Germaine Escames	2019	Yes	Yes	Yes	accepted

Data Analysis

At this stage the data is analyzed and the results will answer

the Research Question (RQ) that has been determined previously and will discuss the factors that affect customer satisfaction that often appear from 2014-2019.

Results from RQ2: The method used for data collection

Based on Research Question 2 or RQ2 regarding Results from RQ2: The method used to collect data about Melatonin as an anti-aging effect, the results obtained are paper categories based on research methods. From the results shown in table 3, it shows that the most widely used method is experimental, then qualitative descriptive, then prospective studies and reviews.

Table 3: Categories of Research Methods

No	Research methods	Research Papers	amount
1	Experimental	[1], [3], [4], [5], [7], [8], [9], [10]	8
2	Descriptive Qualitative	[2]	2
3	3 months prospective study, split-face, assessor-blinded, random	[6]	1
4	Review	[11]	1

Results from RQ2: Factors Causing Aging

Based on Research Question 1 or RQ2 about the factors that cause aging, a paper category is produced based on the factors that cause aging. From the results shown in table 4, it shows that the first factor that causes aging is free radical boards from UV rays; the second factor is age, then the lack of antioxidants and the effects of hormones.

Table 4: Factors that Cause Aging

No	Causative factor	Research Papers	amount
1	Free Radicals	[1], [3], [5], [6], [7], [8], [11]	7
2	Antioxidant	[1], [10]	2
3	Age	[3], [5], [7], [8], [10], [11]	6
4	Hormone	[4], [6]	2

Results from RQ3: Effects of melatonin as a marker of the aging process

Based on Research Question 3 or RQ3 about the effect of melatonin as a marker of the aging process, the results obtained are paper categories based on the effect of melatonin. From the results shown in table 5.

Table 5: Effects of Melatonin

No	Melatonin Effect	Research Papers	Amount
1	Increases organ defense against free radicals	[1], [3], [7], [11]	4
2	Exerts anti-inflammatory, antioxidant and other beneficial actions in aging	[2], [8], [9], [10]	4
3	Improves skin tonicity and skin hydration with a significant reduction in skin roughness, supports the skin's antiaging effect. This molecule is applied topically.	[5], [6], [11]	3

Summary of Data Analysis Results

From the results of each Research Question or RQ, information about research methods, factors that cause aging and the effect of melatonin as a marker of the aging process has been obtained which has been widely studied by researchers from 2014 to 2021.

Table 6: Most RQ Frequency Categories

RQ	Aspect	Most Frequency Category
1	Research methods	Experimental
2	aging factor	Free radicals
3	Melatonin Effect	Increases organ defense against free radicals, and exerts anti-inflammatory, antioxidant and other beneficial actions in aging

3.2 Discussion

Based on the literature surveyed in this review, it can be assumed that aging may be associated with increased free radicals and reduced tissue antioxidant capacity and exogenous melatonin may play a protective role in aging by means of its action on free radicals. (Yüzük et al., 2014) mention melatonin is an infusion hormone secreted from the pineal gland in the dark, which plays a role in regulating many biological functions such as sleep, reproduction, circadian rhythm and immunity. In addition to its many biological effects, it has strong radical sweeping features. It is stated that melatonin levels decrease with aging. It has been stated that the application of exogenous melatonin can prevent the increase in radical yellowing with aging against this physiological decrease in melatonin levels.

These results are in line with the opinion (Gursoy et al., 2015) Aging women got a benefit from the beneficial effects of melatonin on general health, not as a primary drug but when used as a dietary supplement in addition to routine medications. The effect of melatonin is most likely a consequence of free radical scavenging activity at the mitochondrial level (Guo et al., 2017) . Melatonin metabolites are also free radical scavengers. (Galano et al., 2013) reported the sustained protection afforded by melatonin metabolites via a free radical scavenging cascade. Melatonin efficiently protects against oxidative stress through enhanced immunity, anti-inflammatory and homeostatic activity in mitochondria, and inhibits cancer development (Galano et al., 2011) .

Randomized and controlled split-face trial (Milani & Puviani, 2018) showed that topical Mel cream (day and night product) improved the clinical signs of facial skin aging. However, in this trial the main outcomes were mainly evaluated clinically. So far, no trials have been conducted to assess the effect on skin aging parameters of topical Mel through an objective, operator-independent instrumental evaluation. In our experiment, we evaluated the anti-aging effect of melatonin cream through a computerized, operator-independent skin analysis system. The results of this trial show that topical melatonin can significantly reduce coarse and fine wrinkles.

The protective effect of Melatonin against ultraviolet (UV) skin damage is mediated through direct and indirect radical scavenging action and antioxidant enzyme stimulatory action. (Milani & Puviani, 2018) ; (Milani & Sparavigna, 2018) ; (Rusanova et al., 2019) . Women with aging skin with untreated control side, this topical Mel formulation improves skin hydration and skin tonicity with clinical improvement in the aspect of wrinkles. melatonin has much greater antioxidant activity than metformin at cardiac level. Experimental treatments that include melatonin and

metformin may be timely and may yield useful data for the design of clinical studies with an interest in modifying the aging process. (Yüzüak et al., 2014) ; (Guo et al., 2017) ; (Jenwitheesuk et al., 2018) ; (Milani & Puviani, 2018) ; (Reiter et al., 2018) ; (Hardeland, 2019) ; (Ko et al., 2019) and (Kim et al., 2019) . Melatonin should not be considered an ordinary antioxidant; published data, which is extensive, suggests otherwise. The fact that it is consumed in the diet and produced exogenously, probably in every mitochondrial/chloroplast-containing cell of any living organism, makes melatonin unique. In addition, the fact that melatonin is so closely associated with mitochondria should be of significant concern in any study where end points include delaying disease onset, improving quality of life, or extend the longevity (Reiter et al., 2018) .

4. Conclusion

Based on the results of the research that has been done, it can be concluded that based on the results of the Systematic Literature Review or SLR, the method most studied by researchers is experimental. The most common factor that causes aging is the result of free radicals. Therefore, the effect of melatonin as an aging process according to research is that it increases the organ's defense against free radicals, and exerts anti-inflammatory, antioxidant, and other beneficial actions in aging.

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