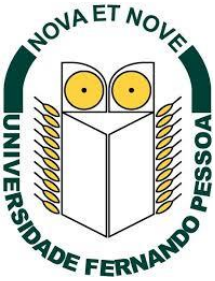
Simone Purpura

Effects of melatonin in the non- surgical treatment of periodontitis - Integrative Review of the Literature



Faculty of Health Sciences

University Fernando Pessoa

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Dissertation presented to the

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of the requirements for obtaining the

Master's degree in Dental Medicine

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ABSTRACT

Aim: To compare, in this integrative literature review, the results obtained in the use of melatonin in the oral cavity.

Methods: An electronic search was conducted, through online databases, such as PubMed, B-on and Cochrane, over the past 10 years. Conducted only in humans.

Thorough literature search of scientific articles was conducted by and electronic search in online databases, PubMed, B-On and Cochrane Library databases represented according to PRISMA diagram methodology for article selection with exclusion and inclusion criteria were applied to the search in order to obtain studies of greater scientific evidence in the available literature.

Results: From the scientific literature search, 2705 articles were found and potentially qualified. After the application of the inclusion and exclusion criteria, only four RCT, two Double-Blind, Placebo-Controlled Trial and 1 triple-blind placebo-controlled study were included and analyzed in this paper with a total of 7 articles.

Conclusions: The existing studies show excellent results and report that the application of melatonin in oral tissues is promising in the treatment of various diseases such as periodontitis and for the promotion of bone regeneration and osseointegration, however, scientific evidence is limited regarding the dosage and route of administration, so further scientific studies with a larger sample size and longer follow-up period are needed.

Keywords : melatonin; periodontal therapy; periodontitis.

RESUMO

Objectivo: Comparar, nesta revisão integrativa da literatura, os resultados obtidos na utilização da melatonina na cavidade oral.

Métodos: Foi realizada uma pesquisa electrónica, através de bases de dados em linha, tais como PubMed, B-on e Cochrane, ao longo dos últimos 10 anos. Conduzida apenas em humanos.

A pesquisa bibliográfica exaustiva de artigos científicos foi realizada e a pesquisa electrónica em bases de dados em linha, as bases de dados PubMed, B-On e Cochrane Library representadas de acordo com a metodologia do diagrama PRISMA para a selecção de artigos com critérios de exclusão e inclusão foram aplicadas à pesquisa a fim de obter estudos de maior evidência científica na literatura disponível.

Resultados: A partir da pesquisa da literatura científica, foram encontrados 2705 artigos e potencialmente qualificados. Após a aplicação dos critérios de inclusão e exclusão, apenas quatro RCT, dois Double-Blind, Placebo-Controled Trial e um estudo com placebo-controlado triple-blind foram incluídos e analisados neste artigo com um total de 7 artigos.

Conclusões: Os estudos existentes mostram excelentes resultados e referem que a aplicação de melatonina em tecidos orais é promissora no tratamento de várias doenças como a periodontite e para a promoção da regeneração óssea e osteointegração, no entanto, as provas científicas são limitadas no que diz respeito à dosagem e via de administração, pelo que são necessários mais estudos científicos com um tamanho de amostra maior e um período de seguimento mais longo.

Palavras-chave : melatonina; terapia periodontal; periodontite.

DEDICATION

"How far is it to the summit? ; You climb up and don't think about it."

(F.W. Nietzsche)

ACKNOWLEDGMENT

To my mother and father, pillars of my person, for always believing in me. Enduring and putting up with me.

To my brother ,partner in life and adventures.

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To alessia, my right arm in life and work, thank you for accompanying me on this path full of obstacles. For your support and help in the darkest moments, you gave me the strength to always give my best.

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Abbreviations

ABL.	Alveolar bone loss
AGEs	Advanced glycation end products
AIS scores	Athens insomnia scale
ALP	Alkaline phosphatase
AOPP	Advanced oxidation protein products
BOP	Bleeding on probing
CAL	Clinical attachment level
CAT	Catalase
CEJ	Enamel-cement junction
CG	Control Group
CI	Confidence interval
DM	Diabetes Mellitus
FANS	Non-steroidal anti-inflamatory
FMBS	Full mouth bleeding score
FMPS	Full mouth plaque score
GCF	Gingival crevicular fluid
GI	Gingival Index
GPx	Glutathione peroxidase
HbA1c	Hemoglobin glycade
HO	Oral hygiene

H_2O_2	Hydrogen peroxide
hs-CRP	Hs-C-reactive protein
IL-1b	Interleukin-1 beta
IL-6	Interleukin-6
MDA	malondialdehyde
MEL	Melatonin group
MMP-9.	Matrix metalloproteinase-9
NSPT	No surgical periodontal therapy
PD	Probing depth
PI	Plaque index
PPD	Periodontal Pocket Depth
RCT	Randomized control trial
ROS	Reactive oxygen species
SBI	Sulcus bleeding index
SG	Study group
SOD	Super- oxide dismutase
SRP	Scaling and Root Planing
TAC	Total antioxidative capacity
TG	Test Group
TNF-α	Tumor Necrosis Factor Alpha

I. INTRODUCTION

N-acetyl-5-methoxytryptamine, known as Melatonin is a hormone produced by the pineal gland, an endocrine gland located at the base of the brain, also called the epiphysis. Production occurs in cells, pinealocytes, until the age of 30, after which synthesis decreases. In fact, the production of melatonin decreases with increasing age (Najeeb *et al.*, 2016).

The production and release of this hormone depends on the conditions of exposure to light, with an increase in darkness during the night and a decrease in the hours of light during the day (Maria e Witt-Enderby., 2014). It is considered a pleiotropic molecule, as it plays several important roles for living organisms, including regulation of the circadian cycle, control of body temperature, it has great anti-inflammatory, antioxidant and free radical scavenging properties (Lodhi *et al.,* 2016). Being a highly lipophilic molecule, it spreads easily in tissues and thanks to its capacity to bind with serum albumin, through the bloodstream, it reaches the oral cavity, passively spreading in the saliva. Nevertheless, melatonin present in saliva is about one third of the one found in blood (Najeeb *et al.*, 2016).

Studies has shown that melatonin released in saliva has numerous protective effects against various oral conditions such as: periodontal disease, oral cancer, herpes, local inflammatory processes (Metha and Kaur. *et al.*, 2014).

According to the world workshop, held in 2018, periodontitis is a disease, characterized by an inflammation associated with microbes, which causes the loss of the periodontal attachment composed of the periodontal ligament, cement, alveolar bone. The main cause of periodontitis was found in plaque bacteria, this pathology, if not diagnosed and treated in the early stages, can progress apically, giving rise to periodontal pockets. Periodontitis is detected as clinical attachment loss (CAL) with the aid of a standardized periodontal probe using the enamel-cement junction (CEJ) as a reference (Tonetti *et al.*, 2018).

The global prevalence of periodontal disease is expected to increase in the coming years due to the growth of the population composed mainly of the elderly (Tonetti *et al.*, 2017), and according to Najeeb and colleges the prevalence is between 40% and 90% (Najeeb

et al., 2016).

Different drugs have been evaluated as therapy for periodontal disease: non- steroidal anti-inflammatory drugs (FANS), tetracyclines and bisphosphonates. Systemic FANS or Topical FANS have had severe reactions when used for a long period of time (El-Sharkawy *et al.,* 2018).

Melatonin has the advantage over other drugs of being inexpensive and having a large margin of safety, a wide tissue impact and almost no side effects, suggesting its potential as a main or complementary treatment strategy for a wide range of diseases such as bone injury, osteoporosis, OA and periodontitis by exerting multiple effects.

The application of melatonin, which acts as a powerful antioxidant, can bring numerous advantages in periodontal disease, such as: restoration of the concentration of antioxidants, reduction of periodontal inflammation with the regulation of inflammatory cytokines, reduction of oxidative stress and significant reduction of bone resorption. and alveolar through the modulation of osteoclastic and osteoblastic activities (Arabacy *et al.,* 2015).

The anti-inflammatory property of melatonin allows, in fact, to eliminate ROS (exogenous and endogenous reactive oxygen species) and RNS (reactive nitrogen species) that are the cause of tissue damage in the periodontium, while playing an important role in the formation of osteoclasts (Najeeb *et al.,* 2016).

Melatonin also stimulates the synthesis of type I collagen fibers through the receptor located in pre-osteoblasts, which leads to the production, in these cells, of bone sialoprotein, ALP, osteopontin and osteocalcin, significantly reducing the time required, from 21 to 12 days, for their differentiation into mature osteoblasts (Cengiz *et al.,* 2012).

Thus, during this Integrative Review of the Literature, we intend to answer the following research question:

1- What are the benefits of melatonin in the non-surgical treatment of periodontitis?
2- What are the benefits in the use of melatonine for the oral cavity?
3- How far we can use it, and will it be its predictability in our patients?

I.I MATERIALS AND METHODS

The aim of this integrative review is to answer the previous clinical questions, Based on the aforementioned keywords referred, the problem of this study was developed through the PICO strategy in annex 6.1 and represented according to PRISMA diagram methodology for article selection included in this work in annex 6.2 (Huttin *et al.*, 2015; Moher *et al.*, 2009).

Based on the methodological objectives outlined the research was performed between 16 December 2021 and February 2022 was carried out through the research and analysis of scientific articles present in the MedLine (PubMed), On-Line Knowledge Library (B-On) and Cochrane Library databases using the keyword (((melatonin) AND (periodontal therapy)) AND (periodontitis)), and the Boolean connector "AND" to combined them.
The articles included were clinical trials and randomized control trials, in adult population females and males, full text article, in the last 10 years.
The exclusion criteria were animal studies, systematic review, no open access and languages other than English, Spanish, Portuguese and Italian.

This analysis was carried out independently by 2 reviewers, (S.P.) and (F.O.), and a 3rd review (F.C.) helped in case of disagreement into the selection of the articles to include. The results obtained were discussed by integrating the inclusion/exclusion criteria, by analyzing each article to be included in this review, by the title, abstract and by reading the full text of the article.

II. DEVELOPMENT

2.1 Results

After the search phase on the effect of melatonin in periodontal tissues, 7 articles demonstrating the efficacy of melatonin in subjects with periodontitis, with improvement in periodontal clinical parameters. The results presented below are described and summarized in table 6.3 in annex.

2.1.1 Ahmed *et al.*, 2021

This randomized control trial study has 3 months follow-up, had the objective of evaluating the effect of topical melatonin gel in addition to non-surgical periodontal therapy (NSPT) in patients with stage II periodontitis. Was conducted on a total of 24 patients ranging in age from 32 to 55 years, divided into 2 equal groups; a control group (CG) with NSPT and placebo gel administration and a test group (TG), with 5% melatonin gel application. Both groups were treated for 1 month, once a week.

At baseline and 3 months after NSPT, the following parameters were evaluated: plaque index (PI), Gingival Index (GI), Probing pocket depth (PPD) and clinical attachment level (CAL).

In the TG, the mean and standard deviation of total antioxidant capacity (TAC%) at baseline was 284.5± 33.2 (ÿmol/L), which increased to 584.4±64.1 (ÿmol/L) after treatment. The mean difference at baseline before and after treatment was 299.9 with a 95% confidence interval (CI) of (254.6-345.1), meaning it was statistically significant (P<0.001). Determination of antioxidant capacity was performed using a kit supplied by Immunodiagnostic, Germany, by reaction of the antioxidants in the sample with a defined amount of exogenously supplied (H2O2), and the antioxidants in the sample removed a certain amount of the supplied hydrogen peroxide.

Relative to the CG that at baseline recorded a mean ± standard deviation of TAC was 283.2±30.9 (ÿmol/L) that increased to 437.3 ± 60.4 (ÿmol/L) after the 3 months, with a mean difference of 154.1 with 95% CI (114.4 - 193.8) with P<0.001 statistically significant difference.

Although the 2 groups demonstrated a significant increase in TAC, the TG showed a statistically more significant percentage increase in TAC (109.21 ± 41.79%) than the CG with a percentage increase in TAC (56.25 ± 27.64%) with P < 0.001.

In the TG, the mean ± standard derivation of MMP-9 was 77.71 ± 2.86 (pg/μL) decreased to 31.20 ± 2.3 (pg/ μL) 3 months after treatment with P<0.001.

In the CG, MMP-9 was 77.53 ± 3.4 (pg/μL) and then decreased to 47.1 ± 1.8 (pg/μL) 3 months after treatment with P<0.001 indicating statistically significant difference.

Although the two groups demonstrated statistically significant decrease in MMP-9 the TG showed a more significant reduction than the CG (−59.57 ± 14.42%), with a reduction of - 39.25 ± 16.46% with P < 0.001.

2.1.2 Koneÿcná *et al.*, 2021

In a 2 week RCT the effect of exogenous melatonin on induced periodontitis on animals (rats) and in patients with periodontitis was analyzed. Only the part of the study related to humans is discussed according to the inclusion criteria.

Twenty patients of the same age same sex with periodontitis were evaluated.

Patients were divided into two groups: placebo n=10 and Melatonin n=10.

In the MEL patient group, a 20-mL melatonin solution (5 mg/ml) was administered and used to rinse the oral cavity before sleep and after brushing teeth for 14 days and the results were analyzed 2 weeks after the treatment, Patients in the placebo group initially had these values:

BOP (65.69 ± 11.99), SBI (3.06 ± 0.52), PI (1.53 ± 0.94) with P<0.01

Two weeks after treatment, the Placebo group had: BoP (60.73 ± 11.50), the SBI group (2.821±0.41) and the PI group (1.38±0.91). No statistically significant differences were detected. In the MEL (melatonin) group, patients initially had these values: BoP (60.15±20.99), SBI (2.581±0.87), PI (1.69±1.34).

After 2 weeks after treatment, the MEL group had: BoP (52.64±21.53), SBI (2.37±0.88), PI (1.45±1.34). Melatonin was significantly higher in patients supplied with melatonin compared to placebo-supplied patients ($p < 0.05$; $t = 2.3$). Markers of oxidative stress, AGEs, AOPP, as well as TAC did not differ between placebo group and melatonin group (p = n.s) Neither radiography nor TAC revealed any significant effects of melatonin on ABL.

2.1.3 Anton *et al.*, 2021

In this RCT, the effect "of scaling and root planning" in addition to systemic melatonin treatment of periodontal parameters and glycemic control in patients with type 2 diabetes and chronic periodontitis is evaluated. The study was carried out on 54 patients with diabetes and periodontitis divided into two groups: SG (n = 27, subjects with SRP + melatonin) and CG (n = 27, subjects with SRP + placebo). Parameters were assessed 8 weeks after treatment. Patients were instructed to follow nutritional recommendations and continue their normal physical activity during the study. All patients in the study group and those in the control group received non-surgical periodontal treatment (ultrasonic scaling) and manual root planning in one session.

Patients in the study group received two melatonin tablets 250 mg (3 mg of melatonin) and subjects in the control group received two placebo tablets 250 mg, and taste for 8 weeks, 1 hour before bedtime. The tablets were taken by direct ingestion with an adequate amount of water. Values before starting treatment. (Periodontal parameters)

Control group: PD (4.53 ± 1.01) CAL (3.02 ± 0.93), plaque index (100), BOP (100)

Study group: PD (4.65 ± 1.04), CAL (3.05 ± 0.56), plaque index (100), BOP (100)

P0 with p values in the: PD (p0.15), CAL (p0.1), plaque index (p 0.9), BOP (p 0.9)

Values after treatment, control group: PD(4.40 ± 1.02) with, CAL(2.98 ± 0.96) with, plaque index(48), BOP(40) and the study group: PD(2.27 ± 0.7), CAL(1.24 ± 0.45), plaque index(24), BOP(20) P1 with p values in the: PD ($p<0.001$), CAL ($p<0.001$), plaque index(p 0.07), BOP(p 0.09) p0 = p Value between groups at baseline; p1= p Value between groups at 8 weeks severity of periodontitis before treatment control group : superficial-(168), moderate-(257), acute-(72),HbA1c(7.6137±0.62) study group: superficial-(174), moderate-(252), acute-(76),HbA1c(7.6243±0.71) after treatment control group: superficial-(191),moderate-(232),acute-(74),HbA1c(7.5823±0.57) study group: superficial-(257), moderate-(202),acute-(53),HbA1c(6.2781±0.31) p0 values: superficial (p0.24), moderate (p.081), acute (p0.64),HbA1c(0.738) p1 values: superficial($p<0.001$), moderate($p<0.05$), acute ($p<0.05$), HbA1c($p<0.001$) melatonin therapy decreased the mean values of PD and CAL in the study group after treatment completion ($p<0.001$);

singular SRP therapy also resulted in decreases in the control group but without reaching the level of statistical significance. Both the bacterial plaque index and the BOP decreases

were more significant for subjects receiving melatonin therapy.

Regarding the periodontitis severity, there were no significant differences between the study groups at baseline. Significant changes were observed for all severity categories (superficial, moderate, and severe) in the study group after 8 weeks, while in the control group we observed a slight decrease in the number of teeth with moderate and severe periodontitis ($p > 0.05$) and a significant increase in the number of teeth with superficial periodontitis ($p < 0.05$)

2.1.4 Javid *et al.*, 2020

A Double-Blind, Placebo-Controlled Trial had the duration of 8 weeks with the intention of investigate the antioxidant and anti-inflammatory properties of melatonin in patients with DM or type 2 with periodontal disease with NSPT.

Fifty patients with diabetes 2 with periodontal disease were analyzed divided into 2 groups: intervention group, received 250 mg p/day (2 tables) of sodium starch glycolate, magnesium stearate, and 3 mg net melatonin and control group, who received 250 mg p/day placebo tablets with the ingredients containing cellulose, silicon dioxide, magnesium stearate, starch and a few taste of peppermint oil matching with the melatonin tablets for shape, color, size administered always one hour before bedtime for the duration of 8 weeks.

Supplementation with melatonin in addition to NSPT significantly increased serum levels of TAC, SOD, CAT and GPx in the intervention group ($P = 0.02$, 0.008, 0.004 and 0.004, respectively). The mean changes of SOD, CAT and GPx were significantly ($P = 0.02$, 0.04 and 0.04, respectively) greater in the intervention group than in the control group. The results did not change in terms of significance ($P < 0.05$) after adjusting for confounding factors.

After intervention, serum levels of MDA and IL-1b were significantly reduced in the intervention group ($P < 0.001$ and $P = 0.008$, respectively).

The intervention group showed lower mean changes in MDA than the control group, and these changes were statistically significant ($P = 0.008$). Furthermore, after adjusting for confounding factors, the results did not change in terms of significance.

2.1.5 Tinto *et al.*, 2019

The aim of this preliminary randomized, triple-blind placebo-controlled study, was to evaluate oral melatonin supplementation as a food integrator and not as a drug because they would use 1 mg per day after NSPT and HO instruction during 1 months .The follow-up of the patients was 6 months.

They analyzed 23 patients divided in 2 groups: CG composed of 10 patients who were treated with 1mg oral placebo capsules for 30 days and TG composed of the remaining 10, treated with 1mg oral melatonin capsules for 30 days. Diagnosis of untreated severe stage III (interdental CAL ≥5 mm, ≤4 teeth lost, maximum PD ≥ 6 mm) periodontitis, according to the definition of 2017 of World Workshop on the classification of periodontal and peri-implant diseases and conditions.

Both treatments were effective in reducing PD, but no statistical difference was found when comparing post-treatment PD (probing all sites), P = .62. When considering the primary outcome, melatonin administration resulted in a greater mean change in PD in the 6 months evaluation, when compared to CG: for 4-5 mm sites 1.86 (0.81) vs 1.04 (0.69), P = .00001 and for >5 mm sites 3.33 (1.43) vs 2.11 (0.96), P = .00012. No differences were found for FMBS% and FMPS%.

2.1.6 Bazyar *et al.*, 2018

This is an 8-week study (double-blind, placebo-controlled trial) aimed to examine the effect of melatonin supplementation in addition to non-surgical periodontal treatment in patients with type 2 diabetes and chronic periodontitis.

The study was a carried out on 50 patients with type 2 diabetes and chronic periodontitis divided into 2 groups.

An intervention group who received 6 mg of melatonin (2 capsules) once daily. A control group who was given 6 mg placebo (2capsules) 1 a day.

Melatonin levels were significantly higher in the intervention group than in the control group. IL-6 and hs-CRP levels were significantly ($p = 0.008$ and $p = 0.017$, respectively) reduced in the intervention group. The mean changes of IL-6 were significantly lower in the intervention group compared with the control group ($p = 0.04$). In the intervention group, PD and CAL decreased significantly ($p < 0.001$). There were significant

differences in the mean changes of PD and CAL between the intervention and control groups after intervention ($p < 0.001$).

2.1.7 El-Sharkawy *et al.*, 2018

This is an RCT with 74 patients randomized into 2 groups with 6 months, aiming to evaluate the additive effect of melatonin supplementation in insomniac subjects with generalized chronic periodontitis after SRP.

In the MEL group, 38 patients participated who underwent root smoothing with a 2-month regimen of 10 mg oral melatonin capsules 1 time daily before bedtime. While 36 patients who underwent root smoothing with the addition of oral placebo capsules participated in the CG.

The MEL showed significantly greater measures of CAL gain and PD reduction than the CG at 3 and 6 months of therapy evaluations, $P < 0.01$. Similarly, salivary TNF-α levels and AIS scores were significantly lower in the MEL than in the CG. BoP% improved significantly in both groups with no difference. However, salivary TNF-α levels showed no correlation with other clinical variables in both the MEL and CG. Patients in the melatonin and placebo groups showed average drug compliance of 90.4% and 87.5%, respectively. No major adverse reactions were observed during the first 2months of the trial in both melatonin and placebo groups. Headache, dizziness, nausea, constipation, diarrheal, and abdominal cramp were recorded in a range from zero to a maximum of two cases of both melatonin and placebo capsules over the 2 month regimen

III. DISCUSSION

All of the articles described in the result section are randomized controlled trials (one from Tinto *et al.,* was a preliminary triple-blind studie and the ones from Bazyar *et al.*, and Javid *et al.,* that were Double-Blind, Placebo-Controlled Trial).

A variety of parameters were analized in the different sitidies local parameters such as PD and BOP and others of systemic assessment such as IL-6, TNF, hs-CRP, MMP-9, IL-1beta, MDA, oxidation level assessed.

Melatonin administration was either topically (mouthwash or gel) or systemically by capsule administration. All the studies support the use of melatonine to helping non surgycal periodontal treatment, except the one from Konecná's *et al*., These study instruted patients to use 20 mL of melatonin 5 mg/mL solution to rinse the oral cavity before sleep and after brushing teeth for 14 days. The patients, where observed one year after the two week melatonin treatment, showed no improvement; in fact, the scoring parameters and oxidative stress markers did not change. The probable causes of study failure may depend on various factors such as: the presence of refractory periodontitis that was not evaluated, the type of administration (oral rinse), the duration of treatment, and the concentration of melatonin administered. Mouthwash administration is a topical treatment, consequently its effect depends on the amount and speed of absorption of melatonin from the oral mucosa and the time that patients spend rinse their mouths. Melatonin as a mouthwash will probably never be able to produce positive periodontal results because a simple rinse that on average lasts 30 seconds or less and will not give the mucosa the time to absorb the full amount of melatonin (Nardi *et al.*,2009).

The only study topical application of melatonine was Ahmed *et al*., 2021 using gel with 5 % concentration intrapocket to increase the bioadhesion properties of the material and thus prolong its biological effects. . The results were positive in terms of improvement of periodontal parameters. The systemic use of melatonine was used in El-Sharkawy *et al* ., 2018, Bazyar *et al*., 2018, Tinto *et al*., 2019, Javid *et al*., 2020, Anton *et al*., 2021 giving melatonin capsules of 10mg, 6mg, 1mg, 3mg, respectively. According to the study by Balaji *et al.*, 2021 Systemic administration of melatonin was more effective than typical administration (mouthwash or gel). This can be explained by the fact that GCF (periodontal defense fluid) is an exudate composed of plasma and as such has the task of transporting molecules into the bloodstream, and also we must emphasize that gingival tissues are highly vascularized. The results obtained, in periodontal parameters, were better in the studies that supported the use of melatonin capsules as helping treatment for periodontitis.

Most studies, on the effect of melatonin on periodontitis, have obtained statistically significant results. For example, the studies conducted by Ahmed *et al* ., 2021 ,El-Sharkawy *et al* ., 2018,Tinto *et al* ., 2019, Anton *et al* ., 2021, Chitsazi *et al* ., 2017, Bazyar *et al* ., 2018 considered clinical parameters such as PD and CAL obtaining same

results with different melatonin concentration levels and follow up (for results see table pag 23).

The results obtained in the PD and CAL parameters are reliable parameters since they were obtained from a quantitative assessment. For example, in the study by El-Sharkawy *et al* ., 2018, periodontal measurements in 10 patients were performed twice in the 2 days before the conclusion of the RCT. Calibration was approved when PD and CAL measurements, in the two times, had a deviation of 1 mm in more than 90% of all measurements.

Also in the study by Anton *et al* ., 2021 the PD and CAL were assessed by a periodontal specialist. The assessment was performed by test-retest exercises in 10 subjects before the start of the study. For probing depth (PD), intra-examiner predictability was 85%, and for clinical attachment loss (CAL) was 82%. An additional calibration exercise was performed during the study, with a predictability of 83% for PD and 81% for CAL.

PD levels decreased in a statistically significant manner and also a gain in CAL was obtained. Tinto *et al* ., 2019 observed that the results were significant for the melatonin group for the 4-5 mm sites (with P = .00001 and in the >5 mm sites: with P = .00012). These results show us that melatonin, as mentioned earlier, has a powerful antioxidantand immunomodulatory function that make it a key molecule for periodontal protection. In fact, results, indicate that melatonine is able to protect cells from oxidative stress is able to neutralize up to ten molecules of reactive oxygen species (ROS), in contrast to classical antioxidantsthat can neutralize only one molecule of ROS. (Balaji *et al., 2022*). Of course, each study also analyzed other clinical parameters Ahmed *et al* ., 2021 considered as the level of MMP-9, (belonging to the collagenase family) which is found to be significantly involved in connective tissue destruction and after melatonin treatment, compared with the control site, there was a statistically significant reduction in MMP-9 of -39.25±16.46% with P<0.001. This study was also supported by Rudra *et al* ., 2013, which highlights the effect of melatonin on MMP-9 in association with other diseases, and demonstrates significant inhibition of MMP-9 activity in both a dose- and time-dependent manner. Other studies, conducted by Montero *et al* ., 2017, Calvo-Guirado JL *et al*., 2010, Gómez-Moreno *et al*., 2015, Arabaci *et al*., 2015, Cutando *et al*., 2007 in addition to reporting an improvement in bone formation found increased osteoblast differentiation. In particular, Cutando *et al.,* 2007 showed that at 2 weeks of melatonin

placement (1.2 mg lyophylized powdered melatonin) in implants, all parameters of osseointegration significantly increased: percentage of bone contact, total peri-implant bone, bone intervite, and percentage of new bone formation. During bone resorption, osteoclasts generate high levels of superoxide anions that contribute to the bone degradative process. Melatonin, which is an important free radical scavenger and a strong antioxidant, eliminates free radicals generated by osteoclasts during the process of bone resorption by protecting cells from oxidative attacks (Gerardo Gómez-Moreno *et al.*, 2015, Allegra M *et al.*, 2003, Jie Liu *et al.*, 2013).

El-Sharkawy *et al* ., 2018 conducted a study on the benefits of melatonin in patients with chronic periodontitis and sleep disorders.Another parameter analyzed, in addition to those exposed above, was TNF-ÿ level and AIS scores. At 3 and 6 month intervals, a statistically significant reduction in these two parameters was observed in the melatonin group ($P < 0.01$) in agreement with the study by Cutando A *et al*., 2015 (reduction in serum TNF-α and other pro-inflammatory cytokines following topical application of melatonin), whereas, in contrast, Bazyar's *et al*., 2018 study, did not obtain statistically significant results of TNF-ÿ reduction and thus did not show improvement, probably due to different samples and duration of administration, but did obtain a reduction in inflammatory markers IL-6 and hs-CRP ($P = 0.008$ and $P = 0.017$, respectively) in the intervention group. IL-6 parameters were analyzed by blood analysis, a method with high reliability . IL-6 at baseline parameters of the control and intervention group were 2.16 ± 0.91 and 2 ± 0.92 respectively in contrast to the results obtained after 8 weeks in the intervention group which see a statistically significant decrease 1.42 ± 0.73 compared to the control group 2.08 ± 0.87 which had no statistically significant change. TNF-ÿ Bazyar values coincide with the study conducted by Köse O. *et al*., 2016 ,Kara *et al*., 2012.

Anton *et al*., 2021 evaluated, in their studies, other parameters such as BOP and HbA1c. Plaque index and BOP, after systemic administration of melatonin (received two melatonin tablets 250 mg that containing 3 mg melatonin) , decreased showing significantly lower values. There was also a significant reduction in HbA1c during the studies due to both root polishing treatment, but, especially the reduction was shown in the melatonin-treated group compared to the control group. The results on effectiveness in glycemic control are also exposed in the study by Ostadmohammadi *et al*., 2019.

A couple of studies used pacientes with DM and periodontal desiase like Anton *et al.*, 2021, Javid *et al.,* 2020, Bazyar *et al .,* 2018 and Ostadmohammadi *et al .,* 2019. The latter in addition to calculating HbA1c also detected the value of serum insulin levels, the results on effectiveness in glycemic control are also exposed in the study. Thus, Anton and colleges 2021 confirmed the veracity of previous studies showing that melatonin not only acts on paradontal parameters but also has a relevant effect on glycemic control preventing major complications in both diseases. These different results probably can be attributed to the difference in the analyzed sample, follow up, and the different dosage of melatonin administered. Javid *et al.,* 2020 analyzes the effect of melatonin in addition to NSPT in patients with diabetes mellitus or type 2 and periodontal disease.The intervention group consisted of 25 patients who received 2 tablets daily of 250 mg for 8 weeks. The results obtained showed that melatonin intake significantly changed various clinical parameters. Serum levels of IL-1beta and MDA in the intervention group, compared with the baseline group, decreased statistically significantly (with IL-1beta with $P = 0.008$ and MDA with $P < 0.001$, respectively), while serum levels of SOD, GPx, CAT and TAC increased in the intervention group compared with baseline (for results see table results,pag 23). There is a close relationship between diabetes and periodontitis. Diabetes increases oxidative stress that affects insulin secretion and action , accelerates the progression of periodontitis and consequently there is an increase in ROS and MDA.

Therefore, it can be hypothesized that the reduction of oxidative stress through the application of melatonin would be effective in the treatment of diabetes and periodontal disease (Mizutani *et al.,* 2021)

Same results were obtained by other authors (Adem Kara *et al.,* 2012, and Köse O. *et al.,* 2016, Vahidreza Ostadmohammadi *et al.,* 2019) for IL-1beta and MDA levels.

Specifically, in the study conducted by Vahidreza Ostadmohammadi *et al.,* 2019, melatonin was administered to patients for 12 weeks and there were not only improvements in clinical paramenti such as MDA (beta= -0.21 mmol/L, 95% CI -0.36 to -0.06, P = .005) , TAC(beta= 253.87 mmol/L, 95% CI 189.18-318.56, P < .001), but also for the parameter HbA1c (beta=-0.58%, 95% CI -1.16 to -0.002, P =.04) and serum insulin levels (beta= -1.89 mIU/mL, 95% CI -3.34 to -0.45, P = .01).

Through these results we can conclude that melatonin protects against oxidative stress which, as mentioned earlier, is the main cause of cellular and periodontal tissue damage, improves mitochondrial function, and stimulates the expression and activation of antioxidant enzymes including CAT, SOD, and GPx as stated before by Prado NJ *et al*., 2018 and Koneycná *et al*., 2021.

Gómez-Moreno *et al*., 2015 conducted a systematic review on the function of topical melatonin application on implants, stating that melatonin is directly involved with bone remodeling and new bone formation, mediated by osteoclastic and osteoblastic activity. Results that were supported by Arabacı *et al*., 2015 who have obtained excellent results on alveolar bone resorption in rats with periodontitis.

IV. CONCLUSION

Melatonin is a simple molecule but with great potential. As showed in this integrative review, melatonin treatment has been supported by many authors as an adjunctive treatment to classical nonsurgical treatment. The excellent results are due to Melatonine antioxidant and anti-inflammatory principles that play a key role in periodontal homeostasis by preventing and preempting periodontal destruction. The authors analyzed in this study used dosages ranging from 1 to 10 mg of melatonin and obtained statistically significant results in paradontal parameters.

Therefore, it is suggested that melatonin can exert its antioxidant and anti-inflammatory properties at low dosages. The osteogenic effect of melatonin has also been affirmed and studied but further investigations with larger sample sizes, longer follow-ups and adequately reporting the doses needed for successful treatment will be needed. Hopefully further studies will dwell more on the potential of this molecule, demonstrating with significant results, its effect in the oral cavity from prevention and treatment of periodontitis to bone regeneration and osseointegration of implants to cancer treatment and prevention.

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VI. ANEX

Table 1

Strategy Population, Intervention, Comparison, Outcome (PICO) for question formulation

Population	Patients over 18 years old, both sex with periodontal disease.
Intervencion	Melatonine.
Comparison	Periodontal treatment with application of melantonin or without.
Outcomes	Melatonin showed better results in: CAL gain , PD reduction, bone gain and periodontal inflammation.

Figure 1: Diagram Preferred Reporting Items for Systematic Reviews and Meta analysis (PRISMA)

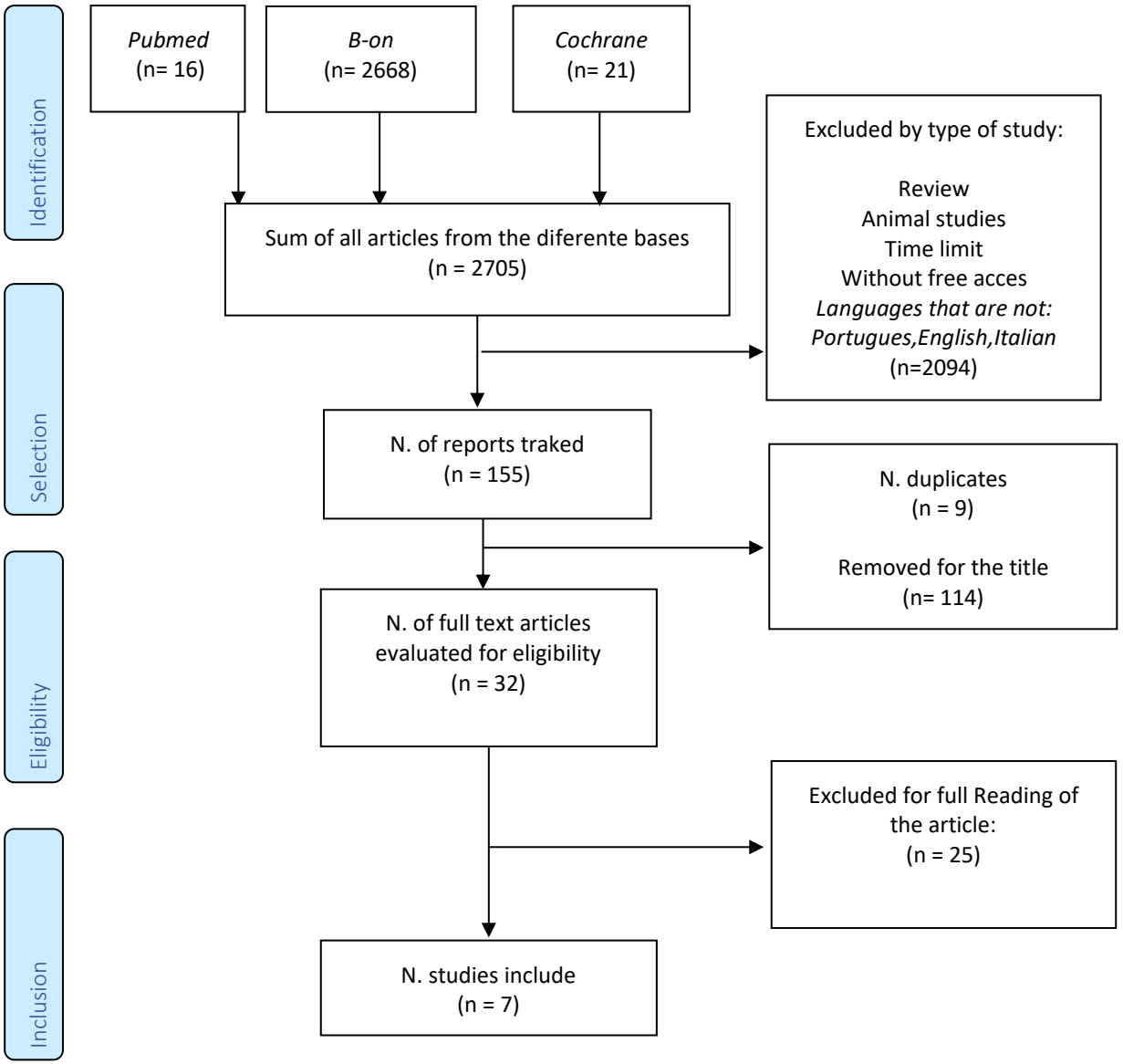

Table 2 : Results table

Author	Type study / follow up	Sample characterization	Clinical features	Treatment	Adverse effects	Results
Ahmed *et al.*, 2021	-RCT -12 weeks	- 24 Patients -Divided into **CG** (n=12) and **SG** (n=12) -Age: 32 to 55 years old	-Patients with stage II periodontitis was diagnosed as having interdental CAL is detectable at ≥2 nonadjacent teeth, or buccal or oral CAL ≥3 mm with pocketing >3 mm is detectable at ≥2 teeth and CAL 3-4mm and maximum probing depth ≤5mm	**-CG:** non-surgical therapy and placebo gel administration **-SG:** with 5% melatonin gel application and non-surgical therapy . 4 weeks for once a week	No adverse effects were found	**Baseline VS treatment** **-TAC: CG**(283.2 ± 30.9 VS 437.3 ± 60.4), **SG**(284.5 ± 33.2 VS 584.4±64.1) **-MMP-9: CG**(77.53 ± 3.4 VS 47.1 ± 1.8),**SG**(77.71 ± 2.86 VS 31.20 ± 2.3)

Author	Type study / follow up	Sample characterization	Clinical features	Treatment	Adverse effects	Results
Koneÿcná *et al.*, 2021	-RCT -2 weeks	- 20 Pacientes -2 group: **CG** (n=10) , SG (n=10- **-CG :** 47±6 years old **-SG :** 44 ± 7 years old -Gender-matched	-Patients' refractory periodontitis with of at least 20 teeth, 40% sites with a probing depth (PD) 4mm and clinical attachment level (CAL) 2mm, more than 40% of sites with bleeding on probing (BOP), and at least two sites with radiographically alveolar bone loss (ABL) of 2 mm verified by radiography	**-SG:** 20-mL melatonin solution (5 mg/ml) Once/day for 2 weeks **-CG** : rinse the oral cavity with solution without melatonin Once/day for 2 weeks	No adverse effects were found	**Before treatment** **-BOP: CG** (65.69 ± 11.99), **SG**(60.15±20.99), **-SBI: CG**(3.06± 0.52), **SG**(2.581±0.87), **-PI:CG** (1.53 ± 0.94),**SG**(1.69±1.34). **Two weeks after treatment:** **-BOP: CG**(60.73 ± 11.50), **SG**(52.64±21.53) **-SBI:**CG(2.821±0.41),SG(2.37±0.88), **-PI:**CG(2.581±0.87), SG (1.45±1.34)

Author	Type study / follow up	Sample characterization	Clinical features	Treatment	Adverse effects	Results
Anton *et al.*, 2021	- RCT - 8 weeks	-54 patients divided two groups: **-SG :**(n = 27) **-CG:**(n = 27) **-SG:** 53.24 ± 3.4 years old with 44% female and 56% male **-CG:** 52.21 ± 3.1 years old with 40% female and 60% male	-Patients with type 2 diabetes and chronic periodontitis -Subjects with fastening blood glucose levels higher than 126 mg/dL and glycated haemoglobin higher than 6.5% were defined as diabetic	-1 capsule/ day for 8 weeks **-SG:** two melatonin tablets (250 mg) with 3 mg melatonin **-CG:** two placebo tablets (250 mg) -Both have done before scaling and root planning	No adverse effects were found	**After treatment :** **-PD: SG**(2,27 ± 0,7), **CG** (4,40 ± 1,02) **- CAL: SG**(3,05 ± 0,56), **CG**(2,98 ± 0,96) **-SRP therapy: CG** decrease without reaching of statistical significance **-PI and BOP**: **SG** decrease more significant for subjects receiving melatonin **-Periodontitis severity: SG** significant changes were observed for all severity categories (superficial, moderate, and severe) **CG** a slight decrease in the number of teeth with moderate and severe periodontitis ($p > 0.05$) and a significant increase in the number of teeth with superficial periodontitis ($p < 0.05$).

Author	Type study / follow up	Sample characterization	Clinical features	Treatment	Adverse effects	Results
Javid *et al.*, 2020	-Double-Blind, Placebo-Controlled Trial - 8 weeks	-50 patients divided into - 2 groups: **SG** and **CG** -Male and female aged 30–60 years	-Patients with diabetes 2 with mild to moderate periodontal disease (PD 4 mm and CAL = 1–4 mm) with body mass index of 18.5–30 kg/m2	**-SG:**250 mg per day (2 tablets) of sodium starch glycolate, magnesium stearate, and 3 mg melatonin **-CG:** received 250 mg per day placebo tablets with cellulose, silicon dioxide, magnesium stearate, starch and a few taste of peppermint oil 1 once/ day for 8 weeks	No adverse effects were found	**Baseline Vs after treatment** **-SOD: CG** (14.27 ± 2.52 VS 14.49 ± 2.58 with P 0.1),**SG**(13.91 ± 2.75 VS 15.53 ± 4.37 with P 0.008) **-CAT: CG**(23.14 ± 3.52 VS 22.72 ± 5.58 with P 0.77), **SG**(24.23 ± 4.54 VS 27.47 ± 4.12 with P 0.004) **-GPX: CG**(231.18 ± 67.28 VS 233.18 ± 62.66 with P 0.71),**SG**(243.04 ± 68.37 VS 262.04 ± 62.45 with P 0.004) **- TAC: CG**(0.318 ± 0.06 VS 0.327 ± 0.08 with P 0.48),**SG**(0.289 ± 0.04 VS 0.313 ± 0.05 with P 0.02) **-MDA: CG**(17.49 ± 1.38 VS 17.17 ± 1.39 with P 0.1), **SG**(17.2 ± 1.82 VS 16.13 ± 1.76 with P <0.001) **-IL-1b: CG**(2.47 ± 0.48 VS 2.33 ± 0.54 with P 0.12),**SG**(2.41 ± 0.55 VS 2.06 ± 0.48 with P 0.008.

Author	Type study / follow up	Sample characterization	Clinical features	Treatment	Adverse effects	Results
Tinto *et al.*, 2019	-Triple-blind placebo-controlled study - 6 months	-20 patientes -Divided into 2 groups: **SG** and **CG** -Healthy adult patients aged between 30 and 70 years old	-Diagnosis of untreated severe stage III periodontits (interdental CAL ≥5 mm, ≤4 teeth lost, maximum PD ≥ 6 mm)	-Both groups received non-surgical periodontal therapy and oral hygiene instruction. **-CG:** were treated with 1mg oral placebo capsules for 30 days **-SG:** were treated with 1mg oral melatonin capsules for 30 days.	Main side effects were: -Sleepiness (20%) -Headache (10%); - -Symptoms resolved spontaneously after few days and did not compromise patient's compliance.	**Baseline Vs after treatment** **-PD: CG**(3.40±0.81VS 2.67±0.85 with P 0.2),**SG**(3.72±0.90 VS 2.45±0.91 with P 0.2) **-PD 4-5mm: CG**(1.04 (0.69)),**SG**(1.86 (0.81)) **-PD ≥6 mm: CG**(2.11 (0.96)),**SG**(3.33 (1.43)) **- FMBS % and FMPS%:** No differences were found for

Author	Type study / follow up	Sample characterization	Clinical features	Treatment	Adverse effects	Results
Bazyar *et al.*, 2018	-Double-blind, placebo-controlled trial - 8 weeks	-50 patients divided into 2 groups: **-SG: (**n=22) **-CG:** (n=22) -Males and females, age between 30 and 60 years old .	-Patients with type 2 diabetes and chronic periodontitis with mild and moderate periodontitis (PD ≥ 4 mm and CAL = 1–4 mm). -Body mass index of 18.5–30 kg/m2, confirmed DM2 (no more than 5 years since diagnosis).	**-SG :** 6 mg of melatonin (2 capsules) once daily. **-CG**: who was given 6 mg placebo (2capsules) 1 a day.	No adverse effects were found	**Baseline VS after treatment** **-PD: CG**(4.54 ± 1.01 VS 4.36 ± 1.04 with P 0.1), **SG**(4.45 ± 0.96 VS 2.59 ± 1.04 with P<0.001) **-CAL: CG**(3±0.75 VS 2.77 ± 0.68 with P 0.021), **SG**(3.04 ± 0.78 VS 1.59 ± 0.59 with P < 0.001) **-IL-6: CG**(2.16 ± 0.91 VS 2.08 ± 0.87 with P 0.58), **SG**(2±0.92 VS 1.42 ± 0.73 with P 0.008) **- TNF-α: CG**(8.65 ± 3.87 VS 8.5 ± 3.95 with P 0.81), **SG**(9.05 ± 3.56 VS 8.24 ± 3.45 with P 0.1) **-MELATONIN: CG**(4.32 ± 1.93 VS 4.07 ± 1.91 with P 0.43), **SG**(4.52 ± 1.78 VS 5.03 ± 1.68 with P 0.005)

Author	Type study / follow up	Sample characterization	Clinical features	Treatment	Adverse effects	Results
El-Sharkawy *et al.*, 2018	- RCT - 6 month	-74 patientes -divided into 2 groups: **-SG:** (n=38) **-CG:** (n=36) **- SG:** 45.6 ± 7.1 years old with 21 male and 17 female **- CG:** 46.7 ± 8.3 years old with 20 male and 16 femele	-Patients with insomniac individuals with generalized chronic periodontitis and have at least 20 teeth, with diagnosed moderate to severe periodontitis chronic (radiographic evidence of bone loss and presence of PD ≥ 5 mm and at least three sites in each quadrant with attachment loss ≥4 mm).	**-SG:** root smoothing with a 2-month regimen of 10 mg oral melatonin capsules 1 time daily before bedtime **-CG:** root smoothing with the addition of oral placebo capsules participated	-Milde adverse reactions observed, ranged from zero to a maximum of two cases of both melatonin and placebo. -Headache - Dizziness - Nausea - Constipation - Diarrheal - Abdominal cramp	**Baseline VS after treatment** **-PD: CG**(4.4 ± 0.7 VS 3.0±0.8), **SG**(4.3 ± 0.8 vs 2.3 ± 0.9) **-PI: CG**(2.44 ± 0.67 vs 0.95 ± 0.17),**SG**(2.35 ± 0.45 VS 0.81 ± 0.23) **-GI: CG**(2.21 ± 0.24 VS 0.69 ± 0.15),**SG**(2.14 ± 0.36 VS 0.68 ± 0.17) **-BOP%:CG**(59 ± 19 VS 18 ± 2.8),**SG**(63 ± 21 VS 12 ± 2.1) **-CAL:CG**(4.7 ± 1.0 VS 3.4 ± 1.2),**SG**(4.8 ± 0.9 VS 2.6 ± 1.0)