ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2023; 9(2): 131-137

www.oraljournal.com
Received: 15-02-2023
Accepted: 16-03-2023

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Melatonin and Periodontal Disease: A Review

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DOI: https://doi.org/10.22271/oral.2023.v9.i2b.1723

Abstract
Melatonin is an indoleamine derivative synthesised mainly in the pineal gland. Its association with periodontal disease and periodontal treatment with exogenous supplementation of Melatonin via oral route, topical application and as local drug delivery has been documented as evidences in the literature. This review article focuses on the melatonin functions in periodontium which includes its anti-inflammatory, antioxidant, antiresorptive and immunomodulatory properties.

Keywords: Melatonin, periodontal disease, periodontal treatment

Introduction
Melatonin is an endogenous hormone synthesised by the pineal gland. There are also extrapineal sites which secrete melatonin [1]. Melatonin is otherwise called nocturnal messenger [2]. In 1958, An American dermatologist, Aaron Lerner discovered and isolated melatonin (N-acetyl-5-methoxytryptamine) from bovine pineal gland extracts that lightened frog skin [3]. The structure of the primary active substance was identified as N-acetyl-5-methoxytryptamine and Lerner named it as "MT" (from Greek "melas"—black, and "tonin"—derived from serotonin) [3]. The extrapineal sites of melatonin synthesis includes the gastrointestinal tract, brain, liver, kidney, adrenal gland, heart, thymus, genital glands, placenta, uterus, platelets, eosinophilic leukocytes, natural killer cells and other immune system cells [3]. The main precursor for melatonin synthesis is Amino acid Tryptophan. Tryptophan is turned into serotonin by hydroxylation and decarboxylation reactions, which inturn gets converted to melatonin with the help of N-acetyltransferase (NAT) and hydroxyindole O-methyltransferase (HIOMT) enzymes [3]. A study demonstrated gingiva as an extra pineal site of melatonin biosynthesis and that MT_1 receptors were found to be present in the gingiva, confirming that melatonin could exert receptor mediated effects on the gingiva [4]. Authors concluded that the melatonin synthesized could protect the gingiva against oxidative stress and inflammation by its defense mechanism [4]. Habits like smoking are found to reduce the levels of expression of the enzymes involved in the melatonin synthesis and MT_1 receptor expression which could thereby reduce the cytoprotective benefits of melatonin [4]. All cells that contain mitochondria are found to synthesis melatonin in a non-circadian manner [5]. Plasma melatonin is 6-hydroxylated by hepatic cytochrome P_{450} monooxygenases and excreted in the form of 6-sulfatoxymelatonin [6]. The level of melatonin is less during the day and reaches till 50–100 pg/mL at night [7]. This physiological range of concentrations is found to be attained by oral supplementation of 0.1–0.3 mg melatonin [7].

Roles of melatonin
- Regulator of sleep/wake cycle [7].
- Immune protector [7].
- Antioxidant [3].
- Regulator of hormone synthesis [3].
- Cardio-protective [3].
- Regulates blood pressure [3].
- Antineoplastic [3].
- Slows down aging [3].

- Regulates hematopoiesis [3].
- Regulates pigmentation and protects skin from UV radiation [3].
- Regulates reproductive processes [3].

Circadian pattern: Circadian rhythm in humans is mainly regulated by melatonin [3]. When light reaches the retina, the retinal ganglion calls transmit the information through the retino-hypothalamic tract to the suprachiasmatic nucleus; from where, the signals then pass to the superior cervical ganglia. Through the sympathetic noradrenergic nerves, it reaches the pineal gland where it acts on the pinealocytes and suppresses the melatonin synthesis [3]. During sleep, the release of norepinephrine from the nerve endings activates melatonin synthesis. Hence, maximum levels of melatonin are seen at midnight and minimum at daytime [3].

Melatonin receptors: Melatonin actions are through both receptor mediated and receptor independent pathways. Melatonin acts through specific receptors which are G protein coupled receptors named as MT1 and MT2 [8]. Also MT3 has been identified as a specific receptor for melatonin [7]. The various actions of melatonin like immediate, prospective, chronobiotic, seasonal and trans generational effects are reviewed elsewhere [8].

Melatonin as a biomarker: Melatonin has both lipophilic and hydrophilic properties [9]. It diffuses easily through cell membranes and thus it is detected in other body fluids, e.g., saliva, urine, milk, sperm and amniotic fluid. Melatonin levels start to rise between 9 and 10 p.m., attains its peak level between 3 and 4 a.m., declines in the morning (between 7 and 9 a.m.) becoming low or undetectable during the day [9]. About 70% of plasma melatonin is plasma protein bound and the remaining 30% of melatonin is unbound and free. This unbound melatonin is secreted into saliva through passive diffusion. Thus, salivary melatonin concentration accounts for 24%–33% of plasma melatonin [9]. Melatonin has a very short half-life in blood and so frequent sampling allows accurate current measurement of the synthesis and circulation of the hormone at the time of collection [9]. 6-sulphatoxymelatonin is the main urine metabolite of melatonin and the level of which is a good marker of plasma melatonin level. But it is also influenced by the kidney function [9]. Salivary melatonin is three times lower than the plasma melatonin. Since correlation exists between levels in saliva and plasma and due to the advantages like ease of sampling and non-invasiveness, salivary sample is used to find the level of melatonin in many studies [9]. Available assays for measuring melatonin include RIA (radioimmunoassay), ELISA (Enzyme-Linked Immunosorbent Assay), HPLC (High Performance Liquid Chromatography) and FSCV (Fast Scan Cyclic Voltammetry) out of which the first two methods are commonly used. Factors that affect the levels include age, sex, genetic factors which are non-modifiable and light, season, posture and physical activity which are modifiable factors [9].

Things to be followed for sample collection includes samples should be collected between evening and morning hours due to circadian rhythm, subjects should take sufficient night rest. Subjects should be kept in low light intensity (red dim light) [9]. In addition to this, subjects are advised not to brush or drink 30min prior to sampling. Lipsticks should not be used. Unstimulated saliva and stimulated saliva are both used in studies. Most common method of saliva collection is using cotton swab [9].

Melatonin and Periodontal Disease

When exposed to periodontal pathogens, the immune cells start secreting proinflammatory cytokines and several mediators of inflammation that causes tissue damage [10]. Melatonin is found to exert its wide range of protective functions (antimicrobial, anti-inflammation, antioxidation, and bone protection) for the protection of periodontal tissues [10].

Melatonin as an antioxidant in periodontal disease: Dental plaque harbors lot of pathogens which induce the host cell to release proinflammatory cytokines like interleukins and TNF-α which in turn attracts PMNs to the site of insult. PMNs in turn produce proteolytic enzymes and oxygen by oxidative burst [11]. The human body has developed antioxidant systems to counteract the effects of ROS by detoxifying or modifying them to less reactive species [11]. Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of reactive oxygen species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products [12]. It was estimated that the number of oxidative hits to DNA per cell per day is about 10,000 in the human and thus the importance of antioxidant in maintenance of health becomes clear [13]. Evidences suggest that the increased level of reactive oxygen species plays one of the most critical roles in periodontitis [11, 14].

Keap1 (Kelch-like ECH Associated Protein 1) – Nrf2 (Nuclear Factor Erythroid 2 related factor 2) system is involved in monitoring oxidative stress. It is also found to be associated with aging. This system regulates the transcription of multiple antioxidant enzymes. Keap1-Nrf2 signaling is also regulated by Phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), protein kinase C, and Mitogen-Activated Protein Kinase (MAPK) [15]. The protective effects of melatonin are found to be derived through stimulating Nrf2/ARE signaling [16]. Melatonin directly scavenges free radicals through its receptor independent pathways and also it indirectly reduces oxidative stress by stimulating the antioxidant enzymes mediated through its receptors [17].

In a study, when type 2 diabetes patients with periodontal disease were given 250 mg melatonin per day (2 tablets) 1 hour before bedtime for 8 weeks after NSPT and were examined for the serum levels of interleukin-1β, malondialdehyde, total antioxidant capacity, superoxide dismutase, catalase, and glutathione peroxidase, the results showed that supplementation with melatonin significantly increased the serum level of antioxidants and that the levels of malondialdehyde and IL-1b were significantly reduced supporting the fact that the adjunctive effects of melatonin and NSPT may improve inflammatory and antioxidant parameters in type 2 diabetes mellitus patients with periodontal disease [18]. One another study in which periodontitis patients with obesity were prescribed 5mg melatonin once daily for one month from the day SRP is done, found that it improved the periodontal status as well as the total antioxidant capacity [19]. All these studies claims melatonin to be a potent antioxidant capable of eliminating the oxidative stress.

Melatonin levels in periodontal disease: Periodontal disease is an inflammatory condition affecting tooth supporting structures in which dysregulated immune response and oxidative stress mediate tissue destruction. Gingival, salivary and serum melatonin levels in periodontally healthy and chronic periodontitis patients were assessed in a study which

revealed that gingival melatonin levels were significantly lowered in chronic periodontitis patients with no significant difference in salivary and serum levels between healthy and periodontitis patients [20]. Authors also suggested that melatonin that is locally present in the gingiva could possibly be destroyed in the process of periodontal destruction due to the oxidative stress and could thereby be lowered in chronic periodontitis [20]. A study by Abdolsamadi H *et al.* reported a significant decrease in salivary melatonin level in both type 2 diabetes patients and in patients with periodontal disease. But in diabetic patients with periodontal disease, the levels of melatonin were found to be the lowest [21].

Melatonin as an immune modulator: Considering the immune enhancing property of melatonin, a study on the evaluation of the effect of tablet containing 3 mg melatonin daily at night for 4 weeks was prescribed and the effect on the hematological parameters was studied in patients with periodontitis. The study showed that melatonin had a positive effect on TLC and differential count of patients with periodontitis, paving a new way for the management of periodontitis which could hinder the disease progression. Melatonin activates several elements of the immune system that reduce tissue destruction during the inflammatory response, by free radical scavenging or by modulating the action of cytokines and adhesion molecules [22].

Melatonin as an antibacterial agent: Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Fusobacterium nucleatum are the major periodontopathic organisms with many virulence factors like proteinases, cytolethal distending toxin, collagenases, hemolysin, hydrogen sulfide, epithelia toxin, and ammonia which damages the host [23]. The permeability barrier in these bacteria protects them from certain antibiotics but melatonin since it is lipophilic in nature, it crosses the cell membrane easily. Also, melatonin has affinity to metal ions and so it binds to the metal ions making itself unavailable for bacterial utilization and survival. *P. gingivalis* and *A. actinomycetemcomitans*, by activation of NOS and calcium-dependent peptidyl-arginine deiminases induce hypercitrullination [23]. Melatonin at its physiologic concentrations, not only exhibits NO and peroxynitrite scavenging activity but also is known to inhibit NOS activity [23]. The bacteriostatic mechanisms of melatonin in-vitro as proposed by He F *et al.* is as follows**:** melatonin acts by reducing the availability of metal ion in the cytoplasm; by interfering with the cell wall formation, thus curbing the cell proliferation; by regulating the expressions of cell division associated genes or by suppressing the content and activity of metabolism-related enzymes to inhibit bacterial growth and proliferation; Melatonin resists Gram-negative bacteria by inhibiting bacterial citrate synthase thus reducing the synthesis of citric acid; when combined with colistin, it acts by enhancing the permeability of bacterial outer membrane and oxidative damage and the effect of efflux pumps is inhibited, leading to bacterial damage [24]. He F *et al.*, also proposed the bacteriostatic mechanisms of melatonin in animals as follows: i) melatonin decreases polymicrobial sepsis through its receptors MT1 and MT2; ii) melatonin inhibits NLRP3 inflammasome to alleviate acute lung injury; iii) decreases pro-inflammatory cytokines and increases anti-inflammatory cytokines through p38MAPK signaling pathway; iv) blocks LPS-induced activation of NF-kB inhibiting the release of proinflammatory factors**;** v) blocks activation of STAT1; vi) activates Nrf2, evidenced by reduced pro-inflammatory mediators (e.g., IL-1b, IL-6, NO and GM-CSF) and increased anti-inflammatory cytokine (e.g., IL-10); vii) Targets TLR to alleviate H. pylori-induced gastritis by promoting TLR4 and inhibiting TLR2 to regulate TGF-β1 and Foxp3 expression; viii) antioxidant function e.g., melatonin signaling via MT2 promotes NCF-1 recruitment from lipid rafts to non-lipid rafts to block the ROS-mediated JNK pathway, preventing autophagic intestinal cell death; ix) MT2 signaling inhibits the ROS-mediated phosphorylation of PKCd and ERK to reduce region-specific hypermethylation in the Muc2 promoter, combating V. vulnificus infection [24].
Melatonin was found to inhibit the three prime periodontal pathogens *in vitro* [P. Gingivalis, F. Nucleatum, and A. actinomycetemcomitans]. The authors concluded that "The presence of peripheral melatonin receptors on periodontal tissues especially on periodontal fibroblasts projects a bigger picture of its potential to be considered as an *in vivo* antibiotic and anti-inflammatory drug to maintain periodontal health and equilibrium" [23]. The first melatonin receptor agonist approved for human use is Ramelteon, a melatonin derivative [25]. A study with melatonin receptor agonist on P.g induced inflammation found that the melanin receptor agonist was able to inhibit biofilm formation, reduce established biofilm, decrease the viability of P.G in biofilms, decrease the proteinase activity of gingipains, inhibit the mRNA expression of virulence factors and also decrease the proinflammatory cytokine release induced by P.g LPS [25]. The authors suggested that melatonin receptor agonists might be useful as the novel "Perioceutics" agents in the treatment of periodontal disease [25]. As reviewed by Murakami *et al.*, P. gingivalis which is not only involved in periodontal diseases but also plays an important role in causing atherosclerosis is prevented by melatonin. The mechanism behind prevention was found to be through its inhibitory effect on the cox2 expression and NFkB stimulation induced by PG fimbriae [26].

Melatonin supplementation and periodontal treatment

Oral melatonin supplementation: Though oral antibiotics and SRP are primary treatment modality followed in periodontal treatment protocol, antibiotic resistant species are common. Thus oral melatonin could serve as an adjunct to those primary treatments offered in periodontal disease since oral supplementation of melatonin was also found to be beneficial in periodontal treatment in many studies. Melatonin 3mg tablet once daily for 20 days in patients with periodontal disease along with non-surgical periodontal treatment (NSPT) had significantly improved the periodontal status by decreasing probing depth, plaque index, attachment loss and gingival index [27]. A study was done to find if vitamin C (60mg for females and 75mg for males for 4 weeks) along with melatonin (2mg/day for 4 weeks) given after SRP to chronic periodontitis patients was found to be beneficial. The study's results demonstrated that the combination therapy with melatonin and vitamin C enhances the effect of non-surgical periodontal therapy as measured by the probing depth and CAL. The author suggested the synergistic effect of vitamin C and melatonin to be the reason for such a result as vitamin C recycles melatonin [28]. The same was found when type 2 diabetic patients with periodontal disease were treated with NSPT and two melatonin tablets (250 mg) containing 3 mg of melatonin daily for 8 weeks 1h before bedtime. The results showed improvement in clinical parameters though lowered plaque level was seen in both scaling and root planning (SRP) alone and SRP with melatonin groups.

Combined non-surgical periodontal treatment and melatonin provided additional improvements to severe periodontal condition and the glycemic control of patients as measured by HbA_1c. Melatonin might be beneficial in improving the periodontal status of patients with diabetes as it is protective against both the diseases wherein both the diseases have oxidative stress to play an important role in their pathogenesis [29]. *An increased level of ferritin, an acute phase protein is* seen in inflammatory diseases [30]. Though not that significantly different from that of the controls, melatonin at a dose of 3mg given once daily for 30 days showed a decrease in ferritin level than in SRP group [30]. A study on pinealectomized rats with periodontal disease demonstrated reduced plasma concentrations of TNF-α and the absence of alveolar bone resorption after melatonin supplementation (5 mg/kg) [31]. Melatonin has anti-inflammatory effects such as inhibiting the rolling and neutrophil adhesion (Markus *et al.*, 2007; Lotufo *et al.*, 2001) which decreases the pro-inflammatory cytokine and chemokine levels [31]. It inhibits binding of NFκB to DNA, thus preventing the translocation of NFκB to the nucleus (Choi *et al.*, 2011; Chuang *et al.*, 1996; Negi *et al.*, 2011; Szczepanik, 2007) [31]. The authors suggested that such actions of melatonin on TNF-α might have ceased the inflammatory process and alveolar bone resorption in the treated animals [31]. Thus systemic melatonin administration as an adjunct to non-surgical periodontal therapy can be a viable option in treating periodontitis. Also further research in this aspect is needed to validate the same.

As Local Drug Delivery: The intrapocket application of 5% melatonin gel in stage II periodontitis patient using a plastic disposable syringe with plastic flexible tip resulted in significant reduction of probing depth and MMP-9 levels, while significantly increasing the attachment level as well as total antioxidant capacity without any adverse effects. This inhibition of the MMP-9 activity by melatonin was suggested to be due to the suppression of TNF-α release by melatonin [32]. Locally delivered melatonin gel as an adjunct to non-surgical periodontal therapy (NSPT) and root conditioning with EDTA, in treatment of intrabony defect in chronic periodontitis patients, clinically showed improvements in periodontal disease parameters and biochemically showed a significant reduction in osteocalcin in the GCF samples 12 weeks after treatment thus claiming the use of melatonin gel as a local drug delivery agent and a viable option to be considered as an adjunct to non-surgical periodontal treatment [33].

Melatonin levels after non-surgical periodontal treatment: In a study, after NSPT, the salivary melatonin levels were found to be significantly increased and seemed to correlate with the decrease in periodontal inflammation [34]. Nonsurgical periodontal treatment was found to increase the salivary melatonin levels up to 50% levels of the hormone in patients with severe periodontitis and moderate periodontitis. The melatonin levels in patients with gingivitis increased approximately 15% to levels very close to those in healthy subjects [35]. NSPT increased salivary melatonin levels only in gingivitis patients but not in chronic periodontitis and aggressive periodontitis patients. The authors claimed that the gingivitis can be resolved by NSPT but periodontal diseases might need additional surgical treatment for complete periodontal healing and so the salivary melatonin levels didn't show any significant increase in patients with periodontal diseases [36]. A study confirmed the role of melatonin as a biomarker for periodontal disease by sensitivity and specificity analysis using ROC curve and they found the area under the curve (0.87) showed an excellent performance. The same study also compared the melatonin levels in saliva before and after SRP in chronic periodontitis patients and demonstrated an improvement in the levels of salivary melatonin [37]. Since there are contradictions in the findings of these studies, further research is needed to confirm if the levels of melatonin increase after NSPT and the mechanism behind it.

Melatonin and Effect on bone: Melatonin influences bone metabolism not only through its actions on osteoblasts and osteoclasts directly by increasing type 1 collagen synthesis, increased expression of bone sialoprotein, osteocalcin, downregulation of RANKL and upregulation of OPG, but also through some indirect effects like free radical scavenging, immunomodulatory actions and modulating P/Ca2+ balance by increasing estrogen/calcitonin and decreasing parathormone/glucocorticoids [38]. As reviewed by Zhao Y *et al.*, Mesenchymal stem cells express MT2R type of melatonin receptor and melatonin is found to mediate osteoblastic differentiation of these cells [39]. One of the reasons would be melatonin receptors are G protein coupled receptors (GPCR) and that GPCRs are known to play a role in bone homeostasis. Melatonin through Wnt/β-catenin pathways and ERK1/2 pathways favours osteogenic differentiation of MSCs [39]. Melatonin is found to enhance the function of bone morphogenic protein - 4 and in presence of which melatonin increases osterix which promotes osteoblast differentiation [39]. Mel is involved in the upregulation of various osteogenic molecules, including BMP-2, BMP-4, osteocalcin, Runx2, and sp2 [39]. Melatonin also prevents osteoblast apoptosis by attenuating Endoplasmic Reticulum (ER) stress in diabetic patients [39]. In addition to the effects discussed, Melatonin also increases the level of VEGF that contributes to angiopoiesis at the site of bone injury and promotes healing by preventing ischemic injuries. In surgeries following bone injuries, the application of melatonin helps to improve the sleep quality of patients and relieve pain. The combined application of melatonin and bone graft materials is found to be beneficial in healing [40]. The positive effects of melatonin on osteoporosis was found to be reduction in the levels of the NLRP3 inflammasome in subjects suffering from estrogen deficiency; attenuation of the autophagy of osteoblasts in patients with diabetes, which is considered to be beneficial in reducing bone loss and regulation of calcium metabolism and prevents osteoporosis [40].

Melatonin is found to exert the effects like antibiosis, regulating of the balance of RANKL and OPG, and lowering the pro-inflammatory factors and ROS formation in periodontal tissues [40]. Melatonin decreases the number of osteoclasts; increases the number of osteoblasts and also increases the number of cement oblasts [40]. The restoration of lipid metabolism by melatonin was found to be beneficial to periodontal healing because of the link established between obesity and periodontitis [40]. In addition, sleep quality is improved [40]. On the whole, melatonin application can efficiently improve CAL and reduce PD, which promotes the healing of periodontal tissues [40]. Studies suggested that melatonin supplementation in periodontal disease significantly inhibits alveolar bone resorption in rats, claiming that melatonin has protective functions in diseases of the oral cavity [32]. Topical melatonin was found to increase salivary

levels of alkaline phosphatase, acid phosphatase, osteocalcin and osteopontin indicating a beneficial effect on decreasing periodontitis and in slowing osteoclastogenesis, improving the quality of alveolar bone and preventing the progression of periodontal disease [41].

Melatonin in dental implants: 1.2 mg of melatonin when applied to osteotomy sites of dental implant showed a positive effect on proximal bone level and cortical plate thickness around dental implants. The authors claimed the formative action of melatonin on bone cells as the reason for its effect on dental implant sites [42]. A study, where melatonin solution prepared by crushing the 3 mg melatonin tablet (Meloset®) and mixing it with saline in a ratio 3mg/ml was used to irrigate the implant sites, showed a significant improvement in the implant stability measured at 3 months; also it showed significant reduction in the crestal bone loss suggesting that melatonin as an irrigant is beneficial in dental implant treatment [43]. A study by Ravi Kiran *et al.* used 3mg melatonin alongside bone graft and periocol membrane around implants and showed that topical application of melatonin in immediately placed dental implants showed a reduction in crestal bone loss and mean bone volume loss was reduced in melatonin groups thus improving osseointegration and increasing the survival rate [44]. All these studies suggest that melatonin can be used as a biomimetic agent which can improve osseointegration of dental implants.

Melatonin and stem cell: Periodontal ligament stem cells (PDLSCs) form the principal cellular fraction of the periodontal ligament space in states of health, disease, repair, and regeneration [45]. *An in vitro* study on the metabolic changes in these stem cells infected with *Porphyromonas gingivalis* lipopolysaccharide was conducted and the results found were increase in the level of Krebs cycle enzymes, succinate, and hypoxia-inducible factor 1 alpha (HIF-alpha) [45]. With the results of the invitro study, Balaji *et al.* hypothesized that a potential role could be played by melatonin and proposed that exogenous supplementation of melatonin could help in targeting metabolic dysregulation in periodontitis by increasing alpha-ketoglutarate generation, thereby decreasing the succinate production in PDLSC followed by exosomal extrusion of the alpha-ketoglutarate into the periodontal microenvironment; by inhibiting stabilization of HIF-alpha in the PDLSC; by mediating the conversion of proinflammatory M1 macrophage to anti-inflammatory M2 macrophage phenotype through the utilization of the alphaketo glutarate exosomes produced by PDLSC [45]. All these actions of melatonin have been proposed to help in the resolution of periodontal disease and foster the healing mechanisms in the diseased periodontium [45]. Melatonin administration could also potentially reduce the levels of ROS and NF kappa B in the PDLSC through its antioxidant and anti-inflammatory mechanisms [45]. Thus, the authors concluded that "Though it is not known if melatonin receptors are present on PDLSC, the hypothesis still holds good based on the fact that melatonin exerts both receptor-independent and receptor dependent effects" [45]. A study wherein, human PDLSCs were isolated and cultured, were investigated for the cellular senescence as measured by the senescence-associated β-galactosidase (SA-β-gal) activity and expression of senescence-related proteins and the autophagy as measured by examining the autophagic vesicles, autophagic flux and associated proteins after melatonin supplementation showed that the hormone was able to enhance the cell rejuvenation by restoring the autophagic processes most likely via the PI3K/AKT/mTOR signaling pathway in an MT-dependent manner. The authors claimed it to be the first report to identify the potential of melatonin as autophagy restoring agent through the above mentioned signaling pathway [46]. When melatonin was added to the cultured DPSCs from healthy human teeth at varying concentrations and DPSCs were examined for their proliferative ability, it showed melatonin was able to stimulate osteogenic differentiation of DPSCs rather than adipogenic and chondrogenic differentiation claiming it to be an osteopromoter [47].

Conclusion

Thus this review has shown light on its antioxidant, anti-bacterial, immunomodulatory, anticytokine, antiresorptive, osteopromotive, other stimulatory roles on the periodontium. This article to some extent has mentioned the signaling, bacteriostatic pathways involved in the mechanism of action of melatonin proposed by many authors. Also, the evidences suggest that melatonin supplementation when included in the periodontal treatment protocol could be beneficial in periodontal healing. But still many researches are needed to find the mechanism by which melatonin participates in the pathogenesis of periodontal disease; also to confirm its effect as an adjunct to periodontal treatment by oral supplementation / as a local drug delivery agent/as an irrigant during surgery/ as a graft material/ as toothpaste/ as mouth rinse/ gummies. The dose of melatonin at which oral supplementation is more effective should be confirmed by comparative studies. With the evidences available, Melatonin could be used as a potential biomarker in periodontal disease and as a host modulatory agent in periodontal treatment.

References

1. Meenakshi SS, Malaiappan S. Role of melatonin in periodontal disease - A systematic review. Indian J Dent Res. 2020;31(4):593-600. DOI: 10.4103/ijdr.IJDR_227_18. PMID: 33107463.
2. Gómez-Moreno G, Cutando-Soriano A, Arana C, Galindo P, Bolaños J, Acuña-Castroviejo D, *et al.* Melatonin expression in periodontal disease. J Periodontal Res. 2007;42(6):536-40. PMID: 17956466. DOI: 10.1111/j.1600-0765.2007.00978.x.
3. Kvetnoy I, Ivanov D, Mironova E, Evsyukova I, Nasyrov R, Kvetnaia T, *et al.* Melatonin as the Cornerstone of Neuroimmunoendocrinology. Int. J. Mol. Sci. 2022;23:1835. https:// doi.org/10.3390/ijms23031835
4. Madapusi BT, Rao SR. Preliminary Evaluation of Human Gingiva as an Extrapineal Site of Melatonin Biosynthesis in States of Periodontal Health and Disease. J Clin of Diagn Res. 2018;12(1):ZF01-ZF07. https://www.doi.org/10.7860/JCDR/2018/32451/11078
5. Reiter RJ, Sharma R, Rosales-Corral S, Manucha W, Chuffa LGA, Zuccari DAPC. Melatonin and Pathological Cell Interactions: Mitochondrial Glucose Processing in Cancer Cells. Int J Mol Sci. 2021;22(22):12494. doi: 10.3390/ijms222212494. PMID: 34830375; PMCID: PMC8621753.
6. Hardeland R. Melatonin metabolism in the central nervous system. Curr Neuropharmacol. 2010;8(3):168-81. DOI: 10.2174/157015910792246244. PMID: 21358968; PMCID: PMC3001211.
7. Ferlazzo N, Andolina G, Cannata A, Costanzo MG, Rizzo V, Currò M, *et al.* Is Melatonin the Cornucopia of

the 21st Century? Antioxidants (Basel). 2020;9(11):1088. DOI: 10.3390/antiox9111088. PMID: 33167396; PMCID: PMC7694322.
8. Amaral FGD, Cipolla-Neto J. A brief review about melatonin, a pineal hormone Arch Endocrinol Metab. 2018;62/4. DOI: 10.20945/2359-3997000000066
9. Rzepka-Migut B, Paprocka J. Melatonin-Measurement Methods and the Factors Modifying the Results. A Systematic Review of the Literature. Int J Environ Res Public Health. 2020;17(6):1916. PMID: 32183489; PMCID: PMC7142625. DOI: 10.3390/ijerph17061916.
10. Wang C, Wang L, Wang X, Cao Z. Beneficial Effects of Melatonin on Periodontitis Management: Far More Than Oral Cavity. Int J Mol Sci. 2022;23(23):14541. DOI: 10.3390/ijms232314541. PMID: 36498871; PMCID: PMC9739298.
11. Dahiya P, Kamal R, Gupta R, Bhardwaj R, Chaudhary K, Kaur S. Reactive oxygen species in periodontitis. J Indian Soc Periodontol. 2013;17(4):411-6. DOI: 10.4103/0972-124X.118306. PMID: 24174716; PMCID: PMC3800399.
12. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, *et al.* Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev, 2017, 8416763. DOI: 10.1155/2017/8416763. Epub 2017 Jul 27. PMID: 28819546; PMCID: PMC5551541.
13. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci USA. 1993;90(17):7915-22. DOI: 10.1073/pnas.90.17.7915. PMID: 8367443; PMCID: PMC47258.
14. Liu C, Mo L, Niu Y, Li X, Zhou X, Xu X. The Role of Reactive Oxygen Species and Autophagy in Periodontitis and Their Potential Linkage. Front. Physiol. 2017;8:439. doi: 10.3389/fphys.2017.00439
15. Yu C, Xiao JH. The Keap1-Nrf2 System: A Mediator between Oxidative Stress and Aging. Oxidative Medicine and Cellular Longevity. 2021;2021:6635460. DOI: 10.1155/2021/6635460. PMID: 34012501; PMCID: PMC8106771.
16. Wang H, Wang H, Huang H, Qu Z, Ma D, Dang X, *et al.* Melatonin Attenuates Spinal Cord Injury in Mice by Activating the Nrf2/ARE Signaling Pathway to Inhibit the NLRP3 Inflammasome. Cells. 2022;11:2809. https://doi.org/10.3390/cells11182809
17. Reiter RJ, Manchester LC, Tan DX. Neurotoxins: free radical mechanisms and melatonin protection. Current Neuropharmacology. 2010;8(3):194-210. PMID: 21358970; PMCID: PMC3001213. DOI: 10.2174/157015910792246236.
18. Zare Javid A, Hosseini SA, Gholinezhad H, Moradi L, Haghighi-Zadeh MH, Bazyar H. Antioxidant and Anti-Inflammatory Properties of Melatonin in Patients with Type 2 Diabetes Mellitus with Periodontal Disease Under Non-Surgical Periodontal Therapy: A Double-Blind, Placebo-Controlled Trial. Diabetes Metab Syndr Obes. 2020;13:753-761. DOI: 10.2147/DMSO.S242208. PMID: 32256092; PMCID: PMC7090208.
19. Hussam Sami Ismail, Maha SH Mahmood. Potential Antioxidant Effect of Systemic Melatonin Therapy on Obese Periodontitis Patient, J Res Med Dent Sci. 2021;9(4):129-136.
20. Balaji TM, Vasanthi HR, Rao SR. Gingival, plasma and salivary levels of melatonin in periodontally healthy individuals and chronic periodontitis patients: a pilot study. J Clin Diagn Res. 2015;9(3):ZC23-5. DOI: 10.7860/JCDR/2015/11311.5652. Epub 2015 Mar 1. PMID: 25954699; PMCID: PMC4413149.
21. Abdolsamadi H, Goodarzi MT, Ahmadi Motemayel F, *et al.* reduction of melatonin level in patients with type ii diabetes and periodontal Diseases. Journal of Dental Research, Dental Clinics, Dental Prospects. 2014;8(3):160-165. PMID: 25346835; PMCID: PMC4206758. DOI: 10.5681/joddd.2014.029.
22. Marawar A, Marawar P, H ND, Kunkulol R, Narwane S. Evaluation of Effect of Melatonin on Hematological Parameters in Patients of Periodontitis. Int. J. Clin. Biomed. Res. 2019;5:46–49.
23. Ganganna A, Rudariah CB, Rao R, Prakash VM. Antibacterial activity of melatonin against prime periodontal pathogens: An *in vitro* study. J Int Oral Health. 2021;13:164-8.
24. He F, Wu X, Zhang Q, Li Y, Ye Y, Li P, *et al.* Bacteriostatic Potential of Melatonin: Therapeutic Standing and Mechanistic Insights. Front. Immunol. 2021;12:683879. DOI: 10.3389/fimmu.2021.683879
25. Zhou W, Zhang X, Zhu C-L, He Z-Y, Liang J-P, Song Z-C. Melatonin Receptor Agonist as the ªPerioceuticsº Agents for Periodontal Disease through Modulation of *Porphyromonas gingivalis* Virulence and Inflammatory Response. PLoS ONE. 2016;11(11):e0166442.
26. Murakami Y, Machino M, Fujisawa S. Porphyromonas gingivalis Fimbria-Induced Expression of Inflammatory Cytokines and Cyclooxygenase-2 in Mouse Macrophages and Its Inhibition by the Bioactive Compounds Fibronectin and Melatonin. ISRN Dent. 2012;2012:350859. DOI: 10.5402/2012/350859. Epub 2012 Apr 1. PMID: 22545218; PMCID: PMC3321536.
27. Thomas M, Setty S, Kaveeshwar V, Narayan Puranik S. Efficacy of Melatonin Supplementation as an Adjunct to Periodontal Therapy. International Journal of Drug Research and Dental Science. 2023;5(1):1-7. https://doi.org/10.36437/ijdrd.2023.5.1.A.
28. Chitsazi M, Faramarzie M, Sadighi M, Shirmohammadi A, Hashemzadeh A. Effects of adjective use of melatonin and vitamin C in the treatment of chronic periodontitis: A randomized clinical trial. J Dent Res Dent Clin Dent Prospects. 2017;11(4):236-240. EPUB 2017 Dec 13. PMID: 29354250; PMCID: PMC5768956. DOI: 10.15171/joddd.2017.041.
29. Anton D-M, Martu M-A, Maris M, Maftei G-A, Sufaru I-G, Tatarciuc D, *et al.* Study on the Effects of Melatonin on Glycemic Control and Periodontal Parameters in Patients with Type II Diabetes Mellitus and Periodontal Disease. Medicina. 2021;57:140. https://doi.org/10.3390/medicina57020140
30. Faramarzi M, Sadighi M, Chitsazi M, Esmailzadeh M, Foladvand G. The effect of adjunctive use of melatonin as a supplement on serum ferritin level in periodontal patients: A randomized, controlled trial. Dent Res J (Isfahan). 2021;18:39. PMID: 34322215; PMCID: PMC8314985.
31. Fernando Marani, Rodrigo Martins dos Santos, Maria Sara de Lima Coutinho Material, Thaís Verônica Saori Tsosura, Fernando Yamamoto Chiba, Renato Felipe Pereira, *et al.* Supplementation with Melatonin Prevents Alveolar Bone Resorption in Rats with Periodontal Disease and Pinealectomy Journal of the International Academy of Periodontology. 2021;23(3):211–223.
32. Ahmed E, Shaker OG, Yussif N, Ghalwash DM. Effect of locally delivered melatonin as an adjunct to

Nonsurgical Therapy on GCF Antioxidant Capacity and MMP-9 in Stage II Periodontitis Patients: A Randomized Controlled Clinical Trial. Int J Dent. 2021;2021:8840167. DOI: 10.1155/2021/8840167. PMID: 33628250; PMCID: PMC7884121.
33. Dina AbdAllah E. Evaluation of the Effect of Local Melatonin Gel Application in the Treatment of Intrabony Defects in Chronic Periodontitis Patients: Mansoura Journal of Dentistry, 2019;6(2):15-18. DOI: 10.21608/mjd.2019.199180
34. Dr. Bipin Kumar Yadav, Dr. Chaitanya Vandan, Dr. Neelabha Krishnan, Dr. Hani Yousuf Naik, Dr. Kumari Upasana, Dr. Nitin Bhagat. Impact of non-surgical periodontal therapy on the levels of melatonin in the saliva of subjects having periodontal diseases. Eur. Chem. Bull. 2023;12(Special Issue 1):2368-2376.
35. Hagh LG, Yousefimanesh H, Mohammadi F, Ahangarpour A. Evaluation of nonsurgical treatment effects on salivary melatonin level in Periodontal Disease: A Radioimmunoassay Study. World J Dent 2013;4(4):217-223
36. Kubra Kundak, Aysen Yarat, Basak Dogan, Leyla Kuru. Effect of Non-surgical Periodontal Therapy on Salivary Melatonin Levels Clin Exp Health Sci. 2022;12:1032-1039.
37. Purrahmani A, Soghli N, Qujeq D, Kiakojori A, Gholinia H. Changes in Salivary Melatonin Levels by Scaling and Root Planing in Patients with Chronic Periodontitis. J Kermanshah Univ Med Sci. 2021;25(2):e113275. DOI: 10.5812/jkums.113275.
38. Galindo Moreno P, Avila Ortiz G, Wang HL, Padial Molina M, Ortega Oller I, O'Valle F. The role of melatonin in periodontal and periimplant bone homeostasis and regeneration. J Oral Science Rehabilitation. 2016;2(2):8–15.
39. Zhao Y, Shao G, Liu X, Li Z. Assessment of the Therapeutic Potential of Melatonin for the Treatment of Osteoporosis Through a Narrative Review of Its Signaling and Preclinical and Clinical Studies. Front. Pharmacol. 2022;13:866625. DOI: 10.3389/fphar.2022.866625
40. Lu X, Yu S, Chen G, Zheng W, Peng J, Huang X, *et al.* Insight into the roles of melatonin in bone tissue and bone-related diseases (Review). Int J Mol Med. 2021;47(5):82. DOI: 10.3892/ijmm.2021.4915. Epub 2021 Mar 24. PMID: 33760138; PMCID: PMC7979260.
41. Cutando A, López-Valverde A, Gómez-de-Diego R, Arias-Santiago S, de Vicente-Jiménez J. Effect of gingival application of melatonin on alkaline and acid phosphatase, osteopontin and osteocalcin in patients with diabetes and periodontal disease. Med Oral Patol Oral Cir Bucal. 2013;18(4):e657-63. PMID: 23524437; PMCID: PMC3731095. DOI: 10.4317/medoral.18832.
42. Zaid Yasser M, Ali Abdulkareem A, Saif Saliem S. Effect of Topical Melatonin Application on the Peri-Implant Proximal Bone Level and Cortical Plate Thickness (Pilot Clinical Trial). Journal of Research in Medical and Dental Science. 2020;8(7):394-399
43. Ravella H, Rao M, Manthena S, Koneru S, Preethi P, Anumolu V. The Effect of melatonin on implant stability and marginal bone level around the implant. J Dent Indones. 2022;29(2):105-112
44. Ravi Kiran S, Bammidi N, Kumar AK, Kumar PS, Karnam Y. Evaluation of the effect of topical melatonin application on immediately placed dental implants Using Cone Beam Computed Tomography (CBCT). Cureus. 2022;14(5):e25233. DOI: 10.7759/cureus.25233. PMID: 35755538; PMCID: PMC9217677.
45. Balaji TM, Varadarajan S, Bandyopadhyay D, *et al.* Melatonin could Alleviate the Dysregulation of Metabolic Reprogramming in Periodontitis-Implications in Host Modulatory Therapy. World J Dent. 2021;12(2):166–170
46. Tan YZ, Xu XY, Dai JM. *et al.* Melatonin induces the rejuvenation of long-term ex vivo expanded periodontal ligament stem cells by modulating the autophagic process. Stem Cell Res Ther. 2021;12:254. https://doi.org/10.1186/s13287-021-02322-9
47. Patil S, Alamoudi A, Zidane B, Alzahrani KJ, Alzahrani FM, Banjer HJ, *et al.* Dose-Dependent effects of melatonin on the viability, proliferation, and differentiation of dental pulp stem cells (DPSCs). J. Pers. Med. 2022;12:1620. https://doi.org/10.3390/jpm12101620

How to Cite This Article
Mahalakshmi A. Melatonin and Periodontal Disease: A Review. International Journal of Applied Dental Sciences. 2023;9(2):131-137.