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Melatonin as a Biologic Modulator in Periodontal Surgical Treatment: A Mini-Review

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Abstract

Periodontitis is a chronic, multifactorial inflammatory condition characterized by the progressive breakdown of tooth-supporting tissues. It is a major public health issue due to its high prevalence and consequences, including tooth loss, impaired oral function and aesthetics, increased healthcare costs, and negative effects on general health. In periodontitis, tissue breakdown is primarily driven by an exaggerated immune-inflammatory response to microbial dysbiosis, making host modulation a key therapeutic goal. Melatonin, an endogenous hormone with antioxidant, anti-inflammatory, and bone-enhancing properties, has recently gained attention as an adjunctive aid in periodontal therapy. This mini-review focuses on several clinical studies and systematic reviews that have reported favorable outcomes in periodontal parameters when melatonin is applied alongside non-surgical periodontal therapy. Despite these encouraging findings, there is currently a lack of clinical trials evaluating its role in surgical regenerative therapy used to manage intrabony defects, where the need for adjunctive agents remains significant. This mini-review summarizes the current understanding of melatonin's mechanisms of action in periodontal tissues, highlights evidence from non-surgical applications, and underscores the gap in surgical research.

Keywords: Bone regeneration, Intrabony defect, Host modulation, Melatonin, Periodontitis, Xenograft.

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1. Introduction

Periodontitis is a chronic, bacteria-driven inflammatory condition that leads to the gradual breakdown of the supporting structures of the teeth. It is recognized as the leading cause of tooth loss and edentulism among adults globally [1]. It also serves as a persistent infectious burden and has been associated with systemic diseases such as cardiovascular and cerebrovascular disorders, diabetes, Alzheimer's disease, peripheral arterial disease, & respiratory conditions, adversely affecting overall well-being [2]. A common outcome of advanced disease is the development of intrabony defects, which threaten the long-term prognosis of affected teeth [3]. While non-surgical therapy helps in mitigating infection and inflammation, it is usually inadequate for managing such defects, making surgical treatment the preferred approach [4]. Barrier membranes were initially used to promote periodontal and alveolar bone regeneration by maintaining space [5], but their use is limited by drawbacks such as increased expense, exposure risk, and longer surgical duration. As an alternative, bone grafting alone has been proposed, especially for well-contained three-wall intrabony defects [5]. Various grafting materials have been introduced for periodontal regeneration, with xenografts showing particular effectiveness. Derived from bovine, porcine, or equine sources, xenografts act mainly through osteoconduction and provide advantages such as wide availability, slow resorption and absence of donor site morbidity [6].

Deproteinized bovine bone, in particular, retains a microporous structure that integrates well with host bone and has proven effective both with and without membranes [7]. Moreover, combining xenografts with other biomaterials may enhance their regenerative potential, though the most effective combinations remain unclear [8]. Melatonin (N-acetyl-5-methoxytryptamine) is mainly known for regulating circadian rhythms and is secreted by organs including pineal

gland, retina, bone marrow, and gastrointestinal tract. It exerts antioxidant, anti-inflammatory, & immunomodulatory effects by neutralizing free radicals and interacting with cellular proteins [9-10]. Evidence also indicates its significant role in bone repair, attributed to its influence on bone cell activity, antioxidant capacity, and ability to stimulate angiogenesis, figure 1 [11]. A 2025 systematic review reported promising results for melatonin in periodontal therapy, particularly when combined with non-surgical periodontal therapy (NSPT), where improved clinical outcomes were observed [12]. However, its local application with regenerative periodontal therapy has not yet been investigated. Given melatonin's antioxidant, host-modulating, and osteogenic properties, this mini-review aimed to explore the effectiveness of melatonin in surgical periodontal treatment.

2. Review of Literature

2.1. Biological Basis of Melatonin in Periodontal Regeneration

Melatonin acts through two G protein–coupled receptors, MT1 and MT2, which regulate various intracellular pathways and ion channels [13]. The gingiva is considered a site of local melatonin synthesis, and presence of MT1 receptors in human gingival tissue suggests a receptor-mediated role for melatonin in oral cavity [14]. There is an inverse relationship between salivary melatonin levels and periodontal disease severity, suggesting a protective role of melatonin in slowing disease progression [15]. Researchers have also proposed its use both as an adjunctive therapeutic agent and as a biomarker for monitoring periodontal status [16]. Additionally, bidirectional link between sleep disturbances and periodontitis has been reported, indicating that better sleep quality may enhance periodontal treatment outcomes [17]. Melatonin's antioxidant activity stems from its ability to directly neutralize reactive oxygen and nitrogen species, including hydroxyl radicals (OH•), superoxide (O_2^-), and nitric oxide (NO•). Through a unique "cascade reaction," melatonin not only scavenges free radicals but also generates metabolites such as cyclic 3-hydroxymelatonin, cyclic 3-hydroxymelatonin, N1-acetyl- N2-formyl-5-methoxykynuramine (AFMK), and and N1-acetyl-5-methoxykynuramine (AMK), which extend its antioxidative effects via successive redox reactions [18].

Beyond direct scavenging, melatonin stimulates antioxidant enzymes and is found in much higher concentrations within mitochondrial matrix than in blood plasma, emphasizing its role in regulating redox balance and preserving mitochondrial integrity [19-20]. Melatonin's anti-inflammatory potential is largely attributed to its ability to suppress nuclear factor kappa B NF-κB activity, leading to reduced production of pro-inflammatory cytokines such as Interleukin-1beta (IL-1β) and Tumor necrosis factor-alpha (TNF-α). It is also recognized as an anti-TNF-α agent & has been shown to modulate immune function by enhancing macrophage antigen presentation and stimulating natural killer cell activity [21-22]. Melatonin has been shown to downregulate Matrixmetalloproteinase-9 (MMP-9) at both protein & gene expression levels [23]. In addition, melatonin inhibits pro-inflammatory enzyme cyclooxygenase-2 (COX-2) and can interact with active sites of COX-1 and COX-2, suggesting its role as a natural endogenous regulator of inflammatory processes [24]. Melatonin supports bone regeneration by promoting osteoblast proliferation and enhancing type I collagen synthesis in both human bone cells and osteoblastic cell lines [25].

Melatonin helps regulate bone and periodontal homeostasis by restoring receptor activator of nuclear factor kappa B ligand/osteoprotegerin (RANKL/OPG) balance through suppression of Toll-like receptor 4/myeloid differentiation primary response 88 (TLR4/MyD88)-driven proinflammatory cytokine production. It also reduces (IL-1β)–induced expression of C-X-C motif chemokine ligand 10 (CXCL-10), matrix metalloproteinase-1 (MMP-1) in periodontal ligament cells, highlighting its anti-inflammatory and protective role [26-27]. Melatonin enhances the expression of osteogenic markers in mesenchymal stem cells (MSCs) and supports bone matrix mineralization. It promotes the osteogenic differentiation of MSCs in bone marrow via wingless-type (Wnt)/β-catenin pathway while inhibiting their adipogenic differentiation through peroxisome proliferator-activated receptor gamma (PPARγ) pathway. Activation of MT2 suppresses osteoclast formation by inactivating the NF-κB pathway. In co-culture conditions, exogenous melatonin stimulates MSC osteogenesis and inhibits osteoclastogenesis of peripheral blood monocytes (PBMCs) via MT2-mediated mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 (MEK1/2) and Mitogen-Activated Protein Kinase Kinase 5 (MEK5) pathways. Additionally, melatonin reduces (RANKL) expression and further inhibits osteoclast activity through receptor-independent mitogen-activated protein kinase (MAPK) and nuclear factor of activated T-cells cytoplasmic 1 (NFATc1) pathways [28-33].

Pharmacological doses of melatonin have been shown to enhance osteoblast activity by stimulating their proliferation and increasing alkaline phosphatase (ALP) expression in a dose-dependent manner. In vitro studies demonstrate that melatonin upregulates type I collagen, bone sialoprotein, osteopontin, and osteocalcin, thereby supporting extracellular matrix mineralization. Animal models further confirm these findings, as melatonin administration has been associated with increased femoral bone formation. Studies in rabbits and rats have shown that melatonin accelerates neovascularization, increases vessel density, and supports cortical bone formation during early healing stages. Since vascularization precedes osteogenesis by providing minerals and facilitating migration of osteogenic cells, these findings emphasize melatonin's dual function in enhancing both angiogenesis and bone regeneration [34-39]. Furthermore, evidence suggests that melatonin can regulate bone resorption indirectly by influencing calcitonin activity. It has been shown to upregulate calcitonin expression in osteocytes, which in turn suppresses osteoclast formation and activity. This mechanism highlights its role as a modulator of bone metabolism beyond its direct antioxidant and osteogenic effects [40]. Collectively, these multifaceted biological actions of melatonin, including antioxidant defense, modulation of inflammatory mediators, promotion of angiogenesis, and stimulation of osteogenesis, contribute to periodontal regeneration, (Figure 2).

2.2. Clinical Evidence of Melatonin's adjunctive role in Non-surgical Periodontal Treatment

Increasing evidence supports the complementary use of melatonin in non-surgical periodontal therapy as summarized in the Table 1.

Several clinical studies have demonstrated that both systemic and local applications of melatonin can enhance the outcomes of non-surgical periodontal therapy. Improvements were consistently reported in probing depth (PD) reduction, clinical attachment level (CAL) gain, and decreases in inflammatory biomarkers, alongside an upregulation of antioxidant defenses. Topical gels, oral supplements, and dietary formulations all showed beneficial effects, supporting melatonin's role as an effective adjunct to conventional periodontal treatment. These findings collectively underscore the potential of melatonin to improve periodontal treatment outcomes through its anti-inflammatory, antioxidant, and tissue-regenerative effects.

2.3. Current Gaps in Surgical Periodontal treatment

Although various scaffolding materials have been developed for periodontal regeneration, many show limitations that can lead to suboptimal outcomes. This highlights the need to explore biologically active agents that can stimulate and modulate the complex processes of periodontal wound healing and bone regeneration. When alone or combined with bone substitutes that serve as space-maintaining scaffolds, such agents may enhance the regenerative potential of periodontal tissues. Over the past two decades, studies have investigated the use of these biological agents in treating intrabony defects, often in different concentrations and with various graft materials; however, definitive evidence regarding the most effective combinations is still lacking [50-53]. Based on the aforementioned benefits of melatonin in bone regeneration and periodontal healing, it appears to be a promising adjunct for surgical therapy of intraosseous defects. However, evidence in this area is still scarce. Most available data come from experimental models, with only a few studies assessing its effect on periodontal regeneration as shown in table 2. Another important gap is the absence of standardized protocols regarding the delivery method and dosage of melatonin administration during surgery. Future research should aim to evaluate melatonin both as a stand-alone regenerative agent and in combination with commonly used graft materials. Such studies are necessary to determine whether melatonin alone can provide sufficient regenerative benefits, or whether its synergistic use with xenografts and other biomaterials offers superior outcomes.

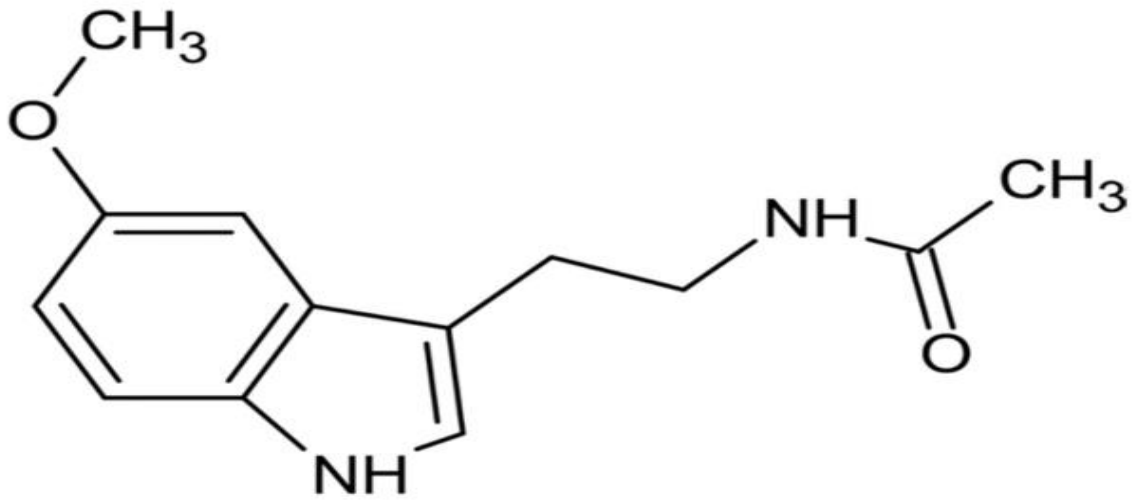

Figure 1: Chemical structure of Melatonin

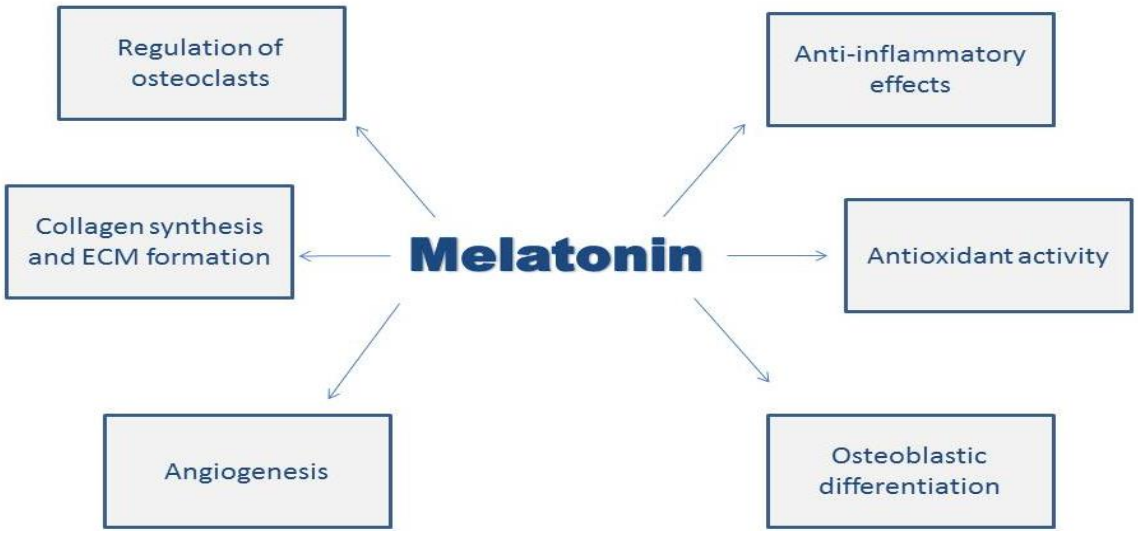

Figure 2: Schematic representation of the multifaceted actions of melatonin in periodontal regeneration

Table 1: Evidence of Melatonin as an Adjunct in Non-Surgical Periodontal Therapy

Study	Intervention	Follow up	Outcome
Cutando et al., 2014 [41]	Topical 1% melatonin orabase cream daily for 30 days	1 months	-↓ Gingival index, PD
Chitsazi et al., 2017 [42]	Oral 2 mg melatonin/day + NSPT for 30 days	3–6 months	-↑ CAL , ↓ PD
Bazyar et al., 2019 [43]	NSPT + melatonin tablets orally, two tablets/day containing each for 8 weeks)	2 months	-↓ PD, Bleeding on Probing (BOP), Plaque index (PI) -↑ CAL -Improved biochemical parameters
El-Sharkawy et al., 2019 [44]	Oral 10 mg melatonin/day + NSPT	2 months	↑ CAL, ↓ PD, ↓ Salivary TNF-α
Tinto et al.,2020 [45]	NSPT + melatonin capsules (orally, 1 mg/day for 30 days)	6 months	↓ PD, PI, BOP
Ahmed et al., 2021 [46]	Oral 10 mg melatonin/day + NSPT	3 months	↓ Gingival crevicular fluid MMP-9
Gonde et al., 2022 [47]	Topical 1% melatonin gel + NSPT	6 months	Improved clinical and radiographic outcomes
Tang & Wang, 2024 [48]	Topical 1% melatonin gel + NSPT	6 months	↑ Bone fill, ↑ Clinical parameters, ↓ Inflammation
Pratap et al., 2025 [49]	Topical 1% melatonin gel + subgingival instrumentation	3-6 months	↑ Clinical outcomes, ↑ Antioxidant activity

Table 2: Evidence of Melatonin in Surgical Periodontal Management

Studies	**Model**	**Intervention**	**Defect type**	**Duration**	**Outcomes**
Hazzaa et al., 2023 [54]	Rat autogenous bone graft model	Topical 1% melatonin gel	1-wall osseous defect	4–6 weeks	↑ Bone fill, ↓ Endothelial nitric oxide synthase (eNOS) expression
Golpasandhagh et al., 2023 [55]	Rat osseous defect model	Topical 5% and 1% melatonin gel	Osseous defects	4 weeks	Dose-dependent ↑ ossification, 5% most effective
El-Amrawy et al., 2023 [56]	Rat periodontitis model	Melatonin administration	Induced experimental periodontitis	4 weeks	↑ Alveolar bone and gingival tissue repair

3. Conclusion

Melatonin holds considerable promise as an adjuvant in periodontal regeneration, attributable to its antioxidant, anti-inflammatory, and bone-stimulating characteristics. This mini-review provides up-to-date insights into the biological actions of melatonin and its adjunctive role in periodontal therapy, with emphasis on both experimental and clinical studies. Current evidence highlights its beneficial role, particularly in non-surgical periodontal treatment. These findings shed light on melatonin's potential as a biologically active agent in enhancing periodontal regeneration and encourage future investigations to establish its clinical utility in surgical regenerative procedures of intrabony defects.

Declaration of Conflicting Interest

The authors declare that there is no conflict of interest.

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