

## Melatonin in Periodontal Diseases-A Review

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**Melatonin is a substance that is secreted by multiple organs in Humans. In addition to playing a role in the regulation of the circadian cycle, it is also known to have antioxidant, anti-inflammatory, and antioncotic effects on human tissues. Oral cavity is an easy target for many conditions such as periodontitis, mucositis, cancers, and cytotoxicity from various drugs or biomaterials. Research on melatonin as a therapeutic agent has suggested that it is effective in treating the aforementioned pathologic conditions effectively. Furthermore, melatonin tends to favour bone regeneration by behaving as an osteoconductive scaffold. The aim of this review is to summarize the uses and potential of melatonin in management of periodontal diseases.**

**Keywords:** Melatonin, inflammation, anti oxidant, oral cavity, periodontitis, bone formation.

Periodontitis is a chronic inflammatory disease affecting the supporting tissues of the tooth which are collectively called, the periodontium.<sup>1</sup> The main etiology for periodontal disease is the microbes in the dental plaque. These microorganisms are capable of synthesizing enzymes that could damage the host tissue and in response to these microbes the host tries to wade off the infection by activating the innate and adaptive immune systems. Activation of the innate and adaptive immune system tries to counteract the microbial attack, but at the same time causes major destruction of the host tissue by producing high amounts of inflammatory cytokines, proosteoclastogenic factors, and matrix metalloproteinases.<sup>2</sup> One of the important factor in worsening the damage to the existing periodontium is the generation of free radicals and reactive oxygen species, which could originate from the bacteria and also from neutrophils which are the first line of defence.<sup>3,4</sup> Furthermore, there is an

imbalance between the oxidant and antioxidant systems.

Melatonin (N-acetyl-5-methoxy tryptamine) is a substance which is secreted by multiple organs such as the pineal gland, retina, bone marrow, the gastro-intestinal tract, whose main role is to regulate the circadian rhythm (day and night cycles).<sup>5</sup> It plays an anti-inflammatory, anti-oncotic, and immunomodulatory role by acting as a scavenger of free-radicals by interacting with cell membrane and intracellular proteins.<sup>6</sup>

### Melatonin For The Treatment Of Periodontal Disease

When it comes to the oral cavity, the antioxidant nature of melatonin makes it a favourite substance. Melatonin enters the oral cavity by diffusing into the saliva from the blood stream. Since a majority of melatonin remains bound to serum albumin, its level in the saliva is one third the level in blood.<sup>7</sup> It exerts its effects by interacting with melatonin receptor 1 (MT1) and

melatonin receptor 2 (MT2) receptors on cells.<sup>8,9</sup> Its antiinflammatory properties have been studied and reported on human gingival fibroblasts.<sup>10</sup>

Furthermore, intraperitoneal administration of melatonin has proved to successfully reduce the severity of periodontitis in diabetic rats.<sup>11</sup> Similarly, topical application of melatonin in diabetic patients resulted in down regulation of proinflammatory factors thereby diminishing the progression of bone loss due to periodontitis.<sup>12-14</sup> Similar Studies in diabetic animal models have shown a diminished oxidative stress index and reduced alveolar bone loss with the use of melatonin.

Cyclooxygenase (COX)-2 is a key enzyme that catalyzes the two sequential steps responsible for biosynthesis of prostaglandins (PGs) from arachidonic acid which plays a critical role in the inflammatory response, the overexpression of which has been associated with several types of pathology, including periodontal disease. Studies have shown that melatonin was capable of exerting a suppressive effect on Cox-2.<sup>15</sup> In addition to the above mentioned, melatonin down regulates proinflammatory factors such as C reactive protein (CRP), interleukin 6 and TNF alpha<sup>12</sup>, receptor activators of nuclear factor kappa-B ligand/osteoprotegrin ratios thereby causing a decrease in periodontal inflammation.

Studies have shown that salivary acid phosphatase, alkaline phosphatase, osteopontin and osteocalcin levels had significantly improved following topical administration of melatonin.<sup>13</sup>

This makes melatonin a potential therapeutic agent against periodontal diseases. They could be used as an adjunct to scaling, root planning and surgical debridement to improve the outcomes of periodontal therapy.

#### **Melatonin As An Antioxidant & Free Radical Scavenger**

Melatonin is a potent antioxidant and scavenger of free radicals.<sup>16,17</sup> An important characteristic that distinguishes melatonin from other free radical scavengers is that even the metabolites of melatonin have the capability to act as scavengers. This is termed as "Cascade reaction".<sup>16</sup> Kara *et al* in their study suggested that melatonin could stimulate various antioxidant enzymes.<sup>18</sup>

Melatonin acts principally by electron

donation.<sup>19</sup> Melatonin has the capability of donating one or more electrons to free radicals thereby detoxifying them, during this process there is also formation of certain metabolites such as- c3OHM, AFMK, and AMK, also have similar scavenging capabilities.<sup>20</sup> After donating an electron to OH•, melatonin becomes a free radical itself, the indolyl radical cation with very low reactivity, thereby being non toxic to cells.<sup>21</sup>

#### **Melatonin As A Promoter Of Bone Formation**

Melatonin is known to stimulate the proliferation of osteoblasts and promote bone formation.<sup>22</sup> It acts as osteoconductive scaffold.<sup>23,24</sup> Clafshenkel *et al* in 2012 developed a novel calcium aluminate-melatonin material and used it as a scaffold in calvarial defects in animal models and found a significant amount of bone regeneration.<sup>25</sup> A study by Kose *et al* showed that myeloperoxidase activity, number of osteoclasts, density of neutrophils and also RANKL/Osteoprotegrin ratio were increased in periodontitis which could be the cause for increased alveolar bone loss.<sup>11</sup> Roth *et al* studied the effects of melatonin administration on myeloperoxidase activity and alveolar bone destruction and found that there was a reduction in gingival tissue myeloperoxidase levels and further stimulated the proliferation of osteoblasts to promote bone formation.<sup>22</sup>

Cudanto *et al.* evaluated the effectiveness of topical melatonin (1% orabase cream formulation). He tested it by applying it onto the surface of attached gingiva for 20 days in diabetic individuals with periodontitis and healthy individuals with periodontitis and observed a significant decrease in clinical parameters such as gingival index and probing depth, biochemical parameters such as alkaline and acid phosphatase enzyme levels, and RANKL levels, OPG levels.<sup>13</sup>

#### **Melatonin As An Anti Inflammatory Agent**

Inflammation is a normal and an essential response to any insult.<sup>19</sup> As discussed earlier, melatonin interacts directly with COX-2 and also blocks the transcriptional factors that triggers the production of pro inflammatory cytokines. Mohmood *et al* first showed the anti-inflammatory effects of melatonin in a dose-dependent manner in rats.<sup>26</sup>

#### **Melatonin As An Anti Microbial Agent**

Melatonin possesses antimicrobial

properties against numerous bacteria and virus.<sup>27,28</sup> A recent study by Wei Zhou *et al* was the first of its kind to evaluate the effects of melatonin and a melatonin receptor agonist Ramelteon against *Porphyromonas gingivalis*.<sup>29</sup> They concluded that both melatonin and its receptor agonist were capable of inhibiting biofilm formation, decreased the viability of *Porphyromonas gingivalis*, showed an anti-inflammatory response by acting on the lipopolysaccharide. They also found a reduction in proinflammatory IL 6 and IL 8, inhibition of mRNA expression of gingipains while having no cytotoxicity towards Human gingival fibroblasts.

#### Melatonin As A Marker In Periodontal Disease

Cutando<sup>7</sup>, Almughrabhi<sup>30</sup> and Gómez-Moreno<sup>31</sup> in their studies stated that the levels of salivary and serum melatonin differed with varying degrees of periodontitis. They found an inverse correlation between the levels of salivary melatonin and periodontal destruction. The higher the destruction, the lower were the levels of melatonin. Bertl *et al* found that salivary melatonin levels improved significantly after non surgical periodontal therapy in patients with periodontitis.<sup>32</sup>

#### CONCLUSION

Melatonin administration shows promise in the management of periodontal diseases. It plays essential roles in modulating various immune responses and most of the studies have been favourable to usage of melatonin for therapy. However, more clinical trials and animal studies where melatonin is locally delivered to the target site are required to ascertain whether melatonin has potential as a therapeutic agent.

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