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REVIEW ARTICLE

Therapeutic potential of melatonin in oral medicine and periodontology

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Abstract Melatonin (*N*-acetyl-5-methoxy tryptamine) is a substance secreted by multiple organs in vertebrates. In addition to playing a part in the circadian cycle of the body, melatonin is known to have antioxidant, antiinflammatory, and antioncotic effects on human tissues. Oral cavity is affected by a number of conditions such as periodontitis, mucositis, cancers, and cytotoxicity from various drugs or biomaterials. Research has suggested that melatonin is effective in treating the aforementioned pathologies. Furthermore, melatonin has been observed to enhance osseointegration and bone regeneration. The aim of this review is to critically analyze and summarize the research focusing on the potential of melatonin in the field of oral medicine. Topical administration of melatonin has a positive effect on periodontal health and osseointegration. Furthermore, melatonin is particularly effective in improving the periodontal parameters of diabetic patients with periodontitis. Melatonin exerts a regenerative effect on periodontal bone and may be incorporated into of periodontal scaffolds. The cytotoxic effect of various drugs and dental materials may be countered by the antioxidant properties of melatonin. Topical administration of melatonin promotes the healing of tooth extraction sockets and may also impede the progression of oral cancer. Although, there are a number of current and potential applications of melatonin, further long term clinical and animal

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studies are needed to assess its efficacy. Moreover, the role of melatonin supplements in the management of periodontitis should also be assessed.

Introduction

Melatonin (*N*-acetyl-5-methoxy tryptamine) is a substance secreted by multiple organs including the pineal gland, retina, bone marrow, the gastro-intestinal track, and the immune system. Its main function is the regulation of the circadian rhythm (day—night cycles) [1]. It plays an anti-inflammatory, antioncotic, and immunomodulatory role by scavenging free-radicals and via interactions with cell membrane and intracellular proteins [2]. The chemical structure of melatonin is shown in Figure 1.

Melatonin is capable of entering the oral cavity by diffusing into the saliva from blood. As the majority of the melatonin remains bound to serum albumin, the amount of melatonin in saliva is approximately one third of that present in the blood [3]. Melatonin mainly exerts antioxidant effects by interacting with melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) receptors on cells [4,5]. Perhaps, a potent antiinflammatory property of melatonin is linked to its ability to act as a scavenger of exogenous and endogenous reactive oxygen species (ROS) and reactive nitrogen species (RNS) [6]. In addition, both ROS and RNS have been associated with DNA mutations leading to carcinogenesis [7]. The existence of MT1 receptors on healthy and cancerous oral mucosal cells is suggestive that melatonin may act as an antiinflammatory or antioncotic agent in the oral cavity [8]; for example, its antiinflammatory effects have been reported on human gingival fibroblasts [9]. Furthermore, intraperitoneal melatonin has been reported to reduce periodontitis in diabetic rats [10]. Similarly, topical application of melatonin in diabetic patients has diminished the progression of periodontal bone loss as evident by the down-regulation of proinflammatory factors [11—13]. Hence, it has been suggested that melatonin may be used in the management of periodontitis and antioncotic agents for oral cancer cells [8,14,15]. The aim of this review is to critically analyze and summarize the research focusing on the potential of melatonin in the fields of oral medicine and periodontology.

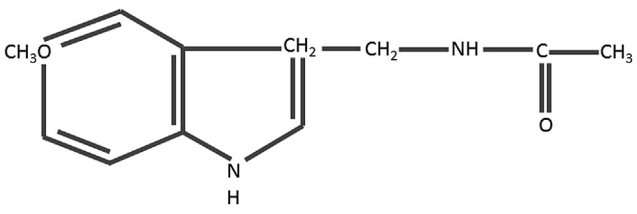

Figure 1. Chemical structure of melatonin (*N*-acetyl-5-methoxy tryptamine).

Melatonin for the treatment of periodontitis

Periodontitis results in progressive destruction of tooth supporting tissues (cementum, periodontal ligament, and alveolar bone) and subsequently loss of teeth. In spite of various surgical and nonsurgical therapeutic options, the global prevalence of periodontitis is still remarkably high (40—90%) [16]. In addition to *in vitro* studies [9], animal studies and clinical trials have documented the therapeutic effects of melatonin on periodontitis (Table 1).

Local and systemic administration of melatonin in rats with lipopolysaccharide-induced periodontitis reduced the level of enzymes (such as serum aspartate aminotransferase, alanine transaminase, and blood urea nitrogen) significantly compared with rats in the control group [17,18]. Similarly, locally administered melatonin significantly reduced bone resorption compared with rats receiving no treatment. These studies suggested that topical administration of melatonin can be used as an adjunct to conventional treatment protocols such as scaling, root planing, and surgical debridement to improve the outcomes of periodontal therapy.

As diabetes mellitus has a two-way relationship with periodontal diseases [19], melatonin has been used for therpeutic applications for cases of diabetes-induced perdiontitis. It has been reported that administration of melatonin reduced osteoclast activity and alveolar bone loss in the diabetic rats with periodontitis melatonin [20]. In addition, diminished oxidative stress index and reduced alveolar bone loss have been observed in similar diabetic animal models [10]. The effects of melatonin on diabetic patients appear twofold: (1) the inherent antiinflammatory and antioxidant properties of melatonin reduce the magnitude of inflammation in the periodontal tissues [2]; and (2) melatonin scavenges the ROS produced due to diabetes and, therefore, reduces the inflammatory effects of diabetes on the periodontium [21].

Melatonin not only down-regulates the expression of proinflammatory factors such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha [11], but it also down-regulates receptor activators of nuclear factor kappa-B ligand/osteoprotegerin ratios to reduce periodontal inflammation [11—13]. In addition to up-regulation of salivary acid phosphatase, alkaline phosphatase, osteopontin, and osteocalcin, it results in significant improvements in gingival index and pocket depth. These facts are indicative of enhanced osteoblast differentiation and bone formation following topical administration of melatonin [12]. However, further well-designed studies with longer follow-up periods are needed to ascertain the long-term efficacy of melatonin in treating periodontitis in the clinical settings.