



Original Review Article**DOI: 10.26479/2018.0404.13****FOCUS ON MELATONIN LOCAL APPLICATION IN ORAL AFFLICTIONS: REVIEW****Shagun Khullar*, Sushama Talegaonkar, Harvinder Popli, Kushagra Khanna**

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ABSTRACT: Melatonin acts as a cell protector rather than hormone in oral cavity that provides medical and health benefits. Melatonin derived from the pineal gland. It possesses wide range of beneficial properties includes anti-inflammatory, anti-oxidant, anti-microbial and immunomodulatory properties following oral or topical administration, so it can be useful for both local and systemic disease treatments. Local drug delivery approach is more favorable than systemic approach because it provides a targeted and efficient drug delivery. This review mainly focuses on local therapeutic approaches of melatonin for most common oral conditions; including local inflammation, periodontal diseases, oral infection, and xerostomia, against DNA-Damaging agents, as promoter of bone formation, lichen planus, oral ulcers, mucositis and oral cancer. The aim of the present article is to highlights the therapeutic role of melatonin and its mechanism of action in the oral cavity diseases.

KEYWORDS: Melatonin, Oral cavity, Local application, Oral diseases.

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1. INTRODUCTION

The oral mucosa is the “skin” inside the mouth, and it covers most of the oral cavity beside the teeth. It has several functions like Protection, Sensation, Secretion, Thermal regulation, Permeation and absorption. It acts as a barrier. Moreover, it protects the deeper tissues such as fat, muscle, nerve and blood supplies from trauma, and also prevents the entry of bacteria and some toxic substances into the body. Oral mucosal diseases are the most prevalent diseases affecting humans. These diseases

can be treated by various topical therapeutic approaches [1]. Each therapy requires a distinct penetration and drug retention profiles in order to optimize treatment and minimize side effects [2].

Structure of oral mucosa

The oral mucosa consists of three layers i.e., epithelium, basement membrane and connective tissues. The outer layer is the epithelium, under which lies the supporting basement membrane. The basement membrane is, in turn supported by underlying connective tissues.

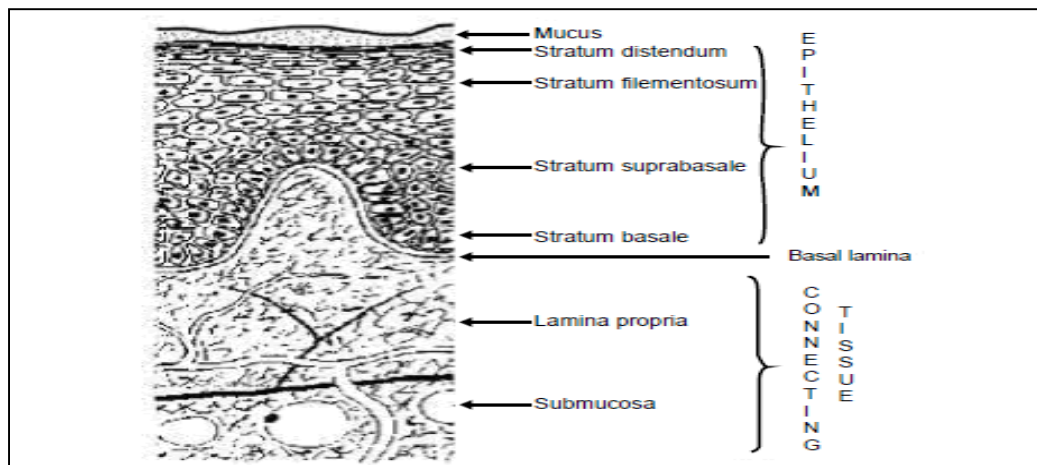


Figure 1: Structure of oral mucosa

The epithelium forms a protective layer for the tissues and is divided into two a) non-keratinized epithelium in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, cheeks, and vestibule lips b) keratinized epithelium which covers the hard palate and non-flexible areas of the oral cavity(mouth). The epithelial thickness varies depending on the site, within the oral mucosa. The basement membrane forms a layer between the epithelium and the connective tissues. It provides the required adherence between these layers. The underlying connective tissues provide most of the mechanical support of the oral mucosa. These tissues, also known as lamina propria, consist of collagen fibrils, blood vessels and smooth muscle [3].

Pathways for drug transport across the oral mucosa

The epithelial cell membrane is lipophilic while the intercellular space is relatively hydrophilic. Therefore the entire epithelium consists of hydrophilic and lipophilic regions, where the hydrophilic region is narrow around the lipophilic cell membrane. There are two pathways for the passive diffusion of the drug across the oral mucosa: paracellular and transcellular routes. For the hydrophilic compounds, paracellular route is preferred as they have low partition coefficient and cannot penetrate the lipophilic cell membrane. The major drawback encountered by hydrophilic molecules is the limited surface area of the intercellular space. Lipophilic compounds due to their high partition coefficients can penetrate the lipophilic cell membrane and hence transcellular pathway is preferred. Also, the surface area for this route is large and path length is short, they can easily go through the lipophilic cell membrane. However, in general drugs preferentially move through the route that offers least resistance and can transverse both routes of transport

simultaneously [4].

Advantages

1. Accessibility.
2. Targeted action of the drug.
3. Easily administered by unconscious and trauma patients.
4. Bypass the first pass metabolism.
5. Decrease drug dose.
6. Increase drug concentration
7. Rapid cell turnover time.
8. Low allergy potential.

Disadvantages

1. Drugs which possess bitter taste, obnoxious odour or irritate the mucosa cannot be administered by this route.
2. Drugs which are not stable at buccal pH cannot be administered by this route.
3. Relatively small surface area.
4. Limited maximum size of dosage form.
5. Rapid drug elimination.

SOME COMMON ORAL DISEASES:

1. Oral cancer
2. Periodontal/gingivitis disease
3. Infections
4. Mouth Ulcers
5. Cold sores
6. Lichen planus
7. Oral Candidiasis
8. Herpes simplex
9. Leukoplakia

TREATMENT

1. Chemotherapy
2. Radiotherapy
3. Antiseptic
4. Antibiotic
5. Anti-inflammatory
6. Topical analgesics and anesthetics
7. Topical corticosteroid
8. Antifungal

9. Antiviral

MELATONIN

Melatonin is a hormone synthesized from an essential amino acid tryptophan [5] and secreted by major cells of pineal gland called pinealocytes [6]. The secretion of melatonin is directed by an endogenous circadian clock. Maximum secretion of melatonin occurs at night, whereas minimum secretion occurs during the day. Hence it is also known as the chemical expression of darkness. Melatonin is highly lipophilic and this characteristic permits its penetration through the cell layers [7]. It is highly found in the bone marrow, in the digestive tract, and in subcellular organs, like mitochondria and cell nucleus [8]. Moreover it has strong antioxidant, anti-inflammatory, immunomodulator properties and acts as a novel cell protector in extra-pineal organs. Recent researches have shown that it is also originated in other organs including retina, ovary, placenta, kidneys, respiratory tract, gastrointestinal tract (GIT), and salivary glands [9, 10]. About 70% of melatonin is generally bound to albumin inside the blood. So, the salivary melatonin is believed to be from the free melatonin (unbound) part in the systemic circulation that passively enters the mucous cells of the major salivary glands (parotid, submaxillary and sublingual glands) [6]. The percentage of plasma melatonin getting into the mouth through salivary glands, ranges from 24 to 33%. Melatonin has been reported in foods including bananas, cherries, grapes, cucumber, tomato, cereals, rice, herbs, tea, olive oil, beer and wine. Additionally it is also available as a synthetic product in the form sublingual tablets, oral sprays or topical gel. Therapeutically, it is used for the management of sleep disorders and jet lag [8]. Advantages of melatonin as a therapeutic agent-

1. Non-toxic.
2. Rapid diffusion.
3. Penetrates all subcellular compartment
4. Devoid of pro-oxidant actions
5. Stimulates antioxidant enzymes
6. Directly applied on oral mucosa

SYNTHESIS AND SECRETION

Melatonin is formed by a series of enzymatic reactions. First step involves conversion of tryptophan into serotonin via hydroxylation and decarboxylation. In second step serotonin converted into N-acetyl-serotonin by the action of enzyme N-acetyltransferase and the last step involves methylation of N-acetyl-serotonin to form melatonin by the enzyme hydroxyindole-O-methyltransferase [11]. Melatonin released during the dark, this process requires activation of polysynaptic beta adrenergic receptors that are indirectly regulated by neural stimuli from suprachiasmatic nucleus (SCN). Information on light/dark environments detected by the retina and transmitted via retinohypothalamic tract to the SCN. A neural signal is transferred to the upper thoracic cord and superior cervical ganglia after which it conveyed from the post ganglionic sympathetic fibers to the pineal gland to

produce melatonin [12]. As soon as melatonin formed, immediately released into the blood or cerebrospinal fluid (CSF) [10].

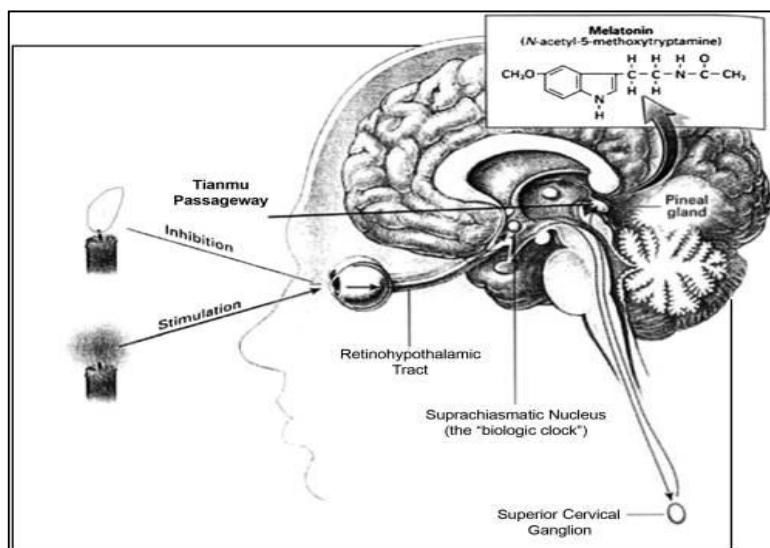


Figure 2: Process of melatonin secretion

MECHANISM OF ACTION

The mechanism of melatonin entails the membrane receptors (MT1, MT2), nuclear receptors of the retinoid related orphan nuclear hormone of (RZR/ROR) family and cytosolic binding sites [13]. Additionally it has receptor -independent activity. The MT1 receptor has been situated to human chromosome 4q35.1. Its primary expression is in the anterior pituitary gland (pars tuberalis) and suprachiasmatic nucleus. MT2 receptor has been situated to chromosome 11q21-22, and its main expression is in the retina and brain. MT3 receptor is not found in mammals. Both MT1 and MT2 receptors are G-protein coupled membrane receptors. MT1 receptor is paired to different G-proteins that mediate adenylyl cyclase inhibition and phospholipase C_{β} activation. The MT2 receptor is also paired to inhibition of adenylyl cyclase and additionally, it inhibits the soluble guanylyl cyclase pathway. The Function of MT1 receptor includes reproduction, metabolous, and vasoconstriction whereas MT2 receptor is involved in the release of dopamine in the retina, the control of circadian rhythms, and vasodilation. Receptors belong to the RZR/ROR subfamily involves i) $ROR\alpha$ receptor, present in all mammalian tissues, and found in lymphocytes, neutophils, and monocytes, ii) $ROR\beta$ subtype which is present in the retina, brain, pineal gland and spleen. Melatonin interacts directly with cytosolic proteins, including calmodulin and calreticulin, which are involved in the cytoskeleton regulation and control of nuclear receptors [14].

APPLICATION IN ORAL CAVITY

In this review, we consider the therapeutic role of melatonin in the following oral afflictions-

- 1) Inflammation; 2) periodontal diseases; 3) Oral infection; 4) Xerostomia;
- 5) Against DNA-Damaging Agents; 6) As a Promoter of Bone Formation; 7) Oral ulcer
- 8) Lichen planus; 9) Oral cancer; 10) Oral mucositis.

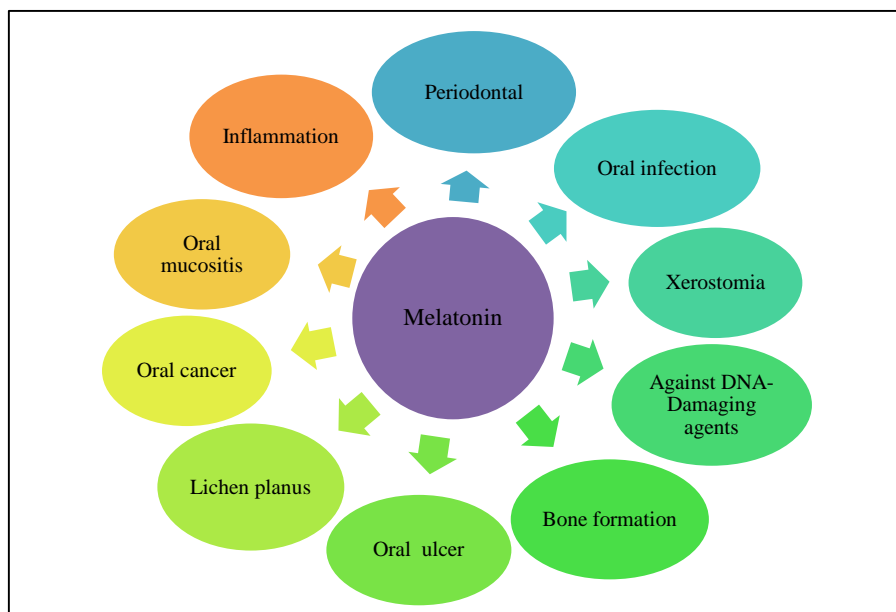


Figure 3: Therapeutic role of melatonin in oral afflictions

Action of Melatonin against Inflammation

Melatonin has antioxidant properties, which can be useful for the treatment of the local inflammatory conditions and for speed up healing process [10]. Melatonin exerts its anti-inflammatory actions by inhibits the prostaglandins synthesis, production of adhesion molecules and NF- κ B binding to DNA. Melatonin also reduces the leukocyte-endothelial adhesion and leukocyte transendothelial cell migration. It has been shown that melatonin reduces the polymorphonuclear leukocytes to the inflammatory sites [15, 16]. Moreover, melatonin inhibits inflammatory enzyme COX-2 by binding to the active sites of COX-1 and COX-2 and thereby indicating it as an inhibitor of the activity of these enzyme and inflammation [7].

Melatonin in Periodontal Disease

Periodontal disorder is a very common inflammatory condition. Damage to periodontal tissues results from a direct impact of the toxic products released by the bacteria and from the action of the immune system stimulated by means of the bacterial infection [17, 8]. Lipid peroxidation is a primary cause in the initiation and development of chronic periodontitis [18]. Melatonin exerts a protective role against periodontal inflammatory process by its antioxidant and anti-inflammatory action [7]. It inhibits the nitric oxide [NO] and interleukin -6 (IL-6) production induced by bacterial lipopolysaccharide (LPS). Massive reactive oxygen species (ROS) confined by melatonin in the inflamed area might be beneficial in lowering the tissue harm [19]. Moreover, melatonin influence fibroblast activity and bone regeneration [20].

Melatonin in Xerostomia

Based on the evidence, melatonin may have a potential in the treatment of xerostomia [21]. It has the ability to regulate the secretory activity of the salivary glands may be exerted through a direct action on melatonin receptors at the secretory units and partly depending on nitric oxide (NO)

production at the level of neuronal NO synthase. Additionally it has been observed that from the parotid gland of the anesthetized rat, protein and amylase evoke [22] [9].

Melatonin in Oral Infections

Melatonin possesses antioxidant and immunomodulatory effects against a variety of bacterial and viral infections. The beneficial effect of melatonin in herpes infections is seems to be due to the immunomodulatory actions of melatonin in the stimulation of IL-1 β [23]. Antiviral actions of melatonin is also relate to the stimulation of NK, CD4 cells. Melatonin may have therapeutic effects in Candida sepsis because of its immune regulatory effects and results in decreased TNF- α and adhesion molecules [24].

Melatonin in Oral Ulcers

Melatonin is a powerful free-radical scavenger and wide spectrum antioxidant. Protect the mucosa against various irritants. Moreover, it protects the oral cavity and GI tract from diseases like stomatitis, esophagitis, gastritis and peptic ulcer [6]. Due to this reason melatonin may be taken into consideration as a novel protector performing via the COX/Prostaglandin and NOS/NO system [25].

Melatonin in Oral Lichen Planus

Oral lichen planus (OLP) is a chronic inflammatory condition causing oral mucosal damage and ulcerations. It appears as erythema and white lines on oral mucosa. It has been taken into consideration that malignant disorder associated with an increased chance for oral cancer [26]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are considered as the contributory factor in inflammation mediated carcinogenesis. The Protective effects of melatonin in oral mucosa are due to the anti-oxidative and anti-inflammatory properties, and rescue the injured oral epithelial cells from apoptosis process. Melatonin also plays an immunomodulatory function through the enhancement of phagocytosis and reduction of inflammatory response [10].

Melatonin in oral cancer

Melatonin exerts oncostatic action through various biological mechanisms including antioxidant, antiproliferative, antiapoptotic effect, immunostimulatory, anti-inflammatory and antiangiogenic [27]. Melatonin plays a therapeutic role against oral cancer due to its free radical scavenging properties [28]. Melatonin also increases the antitumor action of interleukin-2 [7, 18]. Melatonin plays a vital role in treating the oral cancer by exogenous restoration of melatonin receptor 1A (MTNR1A), inhibited the growth of oral squamous carcinoma cells. Moreover, melatonin inhibits the cancer cell proliferation.

Melatonin in Oral Mucositis

Melatonin shows antioxidant action which may be useful for the treatment of local inflammatory lesions as it suppresses the inflammatory enzyme COX-2 [29]. Melatonin may also protect against ionizing radiation [30]. The ulcerated and inflammatory lesions are the characteristics of radiation mucositis, results from massive oxidative damage and the release of toxic cytokines. So it is highly

consider either alone or in combination with other agents as a protector towards radiotherapy and chemotherapy-mediated mucositis [31].

Melatonin action against DNA-Damaging Agents

Melatonin prevents DNA damage caused by toxic substances and ionizing radiation. Melatonin may have protective effects against various agents present in the environment, like lead, arsenic and fluoride [32]. Reactive oxygen species are involved in the process of apoptosis (programmed cell death). Melatonin helps in regulating the apoptotic process by its free radical scavenging properties. Therefore melatonin shows a powerful antioxidant properties and it is a potent antiapoptotic agent [7].

Melatonin promotes Bone Formation

Melatonin promotes bone formation as it stimulates the synthesis of type 1 collagen fibers in human. In chronic inflammatory conditions, free radicals are produced by activated phagocytes, including monocytes, macrophages, and neutrophils which may results in osteoclasts or matrix degradation. Melatonin protect organisms from bone resorption by its antioxidant and free-radical scavenging properties [8].

2. CONCLUSION

Recent studies have brought to light that melatonin has a role in oral diseases and conditions. It could be concluded that melatonin holds a promising future in local therapeutic applications specific for oral diseases such as mouth ulcer, mucositis, infections, and precancerous lesions. The antioxidant and immunomodulatory effects of melatonin encourages us to look at the possible use of this molecule and suggesting that this molecule must be considered as a effective alternative with no side effects. Development of novel drug delivery systems such as nanoparticles and solid lipid nanoparticles loaded with melatonin seems to be very promising in enhancing its efficacy and likely to be one of the thrust areas of research in future. Further experimental studies are needed to provide better evidence of melatonin function in preventing and controlling the diseases of the oral cavity.

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