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Pineal hormone-melatonin -therapeutic potential in oral medicine

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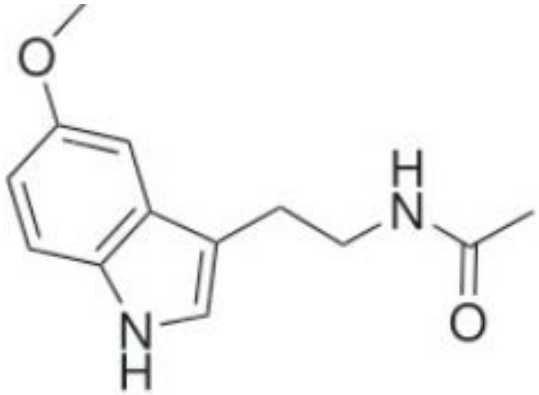
Abstract

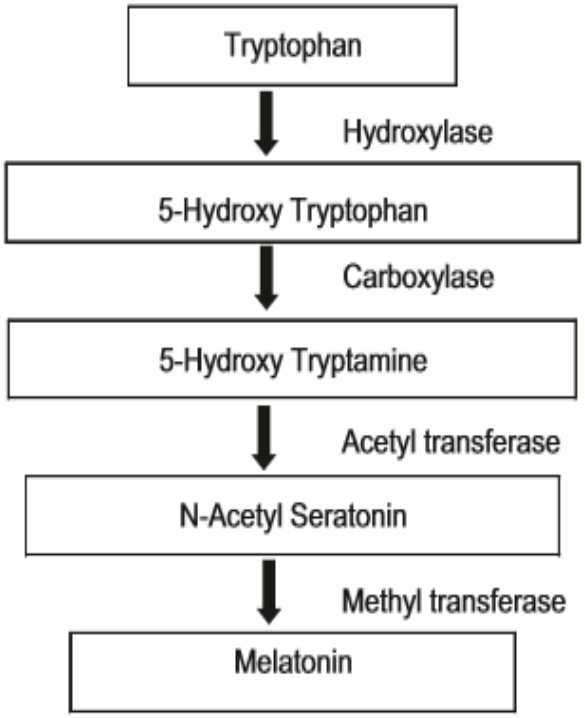
Melatonin (MLT) is a neuroendocrine hormone secreted mainly by the pineal gland. The most significant effects of melatonin are because of its potent antioxidant and antineoplastic properties. Thus, it is important for dental clinicians to be familiar with the possible therapeutic uses of melatonin for oral and perioral disorders. Additionally, melatonin does not have any toxicity but is a highly lipophilic substance and this property facilitates its penetration through cell membranes and compartments which suggests that MT could be used therapeutically. For instance, locally, in the oral cavity damage of mechanical, bacterial, viral and fungal origin, in postsurgical wounds caused by tooth extractions .Melatonin also, acting as a promoter of bone formation, suppressing inflammation of the gingiva and periodontum, to enhance osteointegration of dental implants and in auto-immunological disorders such as Sjogren syndrome, herpes lesions, aphthous ulceration, lichen planus and even to limit oral cancer.

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) was isolated and characterized in 1958 although one of its actions, that is, its ability to blanch the skin of amphibians, had already been shown in 1917[1]. It is a powerful hormone derived from an essential amino acid tryptophan[2]. The master circadian clock, located in the suprachiasmatic nuclei (SCN) in the hypothalamus, controls the secretion of melatonin from the pineal gland. It is also produced extra peritoneally including retina, ovary, placenta, kidneys, respiratory tract, gastrointestinal tract (GIT) and salivary glands. Melatonin is produced with a circadian rhythm characterized by elevated blood levels in the night, and hence it is known as the "chemical expression of darkness. highly effective free radical scavengers and stimulators of antioxidative enzymes. Arising out of its antioxidative actions, melatonin protects cells during severe inflammatory processes and reduces oxidative damage. Intense inflammatory processes contribute to the development of certain cancers, cellular damage caused by ionizing radiation, alterations in metabolism, and destruction of essential molecules and cells. The chemical structure of melatonin is:



Biosynthesis of melatonin



MLT is produced by pinealocytes through a sequence of enzymatic reactions. This process requires polysynaptic activation of β adrenergic receptors, which are indirectly regulated by neural stimulus from the suprachiasmatic nuclei (SCN). Information on light/dark environments is transmitted by the retina of the eye via retinohypothalamic tract to the SCN[2]. A neural signal is transferred to the upper thoracic cord and superior cervical ganglia, which conveys postganglionic sympathetic fibres (secretory fibres) to the pineal gland. MLT once formed is not stored in the pineal gland but is released into the blood or cerebrospinal fluid[2].

Sources of extra pineal melatonin

With the use of highly sensitive antibodies against melatonin and molecular biology techniques, melatonin was also identified in extra pineal tissues including the retina, Harderian gland, gut mucosa, cerebellum, airway epithelium, liver, kidney, adrenals, thymus, thyroid, pancreas, ovary, carotid body, placenta, endometrium, mast cells, natural killer cells, eosinophilic leukocytes, platelets, and endothelial cells .

Melatonin in saliva

Approximately 70% of MLT is usually bound to albumin in the blood. Thus, the salivary MLT is believed to be from the free MLT (unbound) component in the systemic circulation that passively enters the mucous/serous cells of the major salivary glands (parotid, sub maxillary, and sublingual glands)[2]. It is discharged from the acinar cells of the salivary glands due to the contraction of the myoepithelial cells. The proportion of plasma MLT entering the mouth via the salivary glands appears to be relatively stable and ranges from 24 to 33%. Because only the unbound MLT in plasma enters the saliva, salivary melatonin levels reflect the proportion of free circulating melatonin[2]. The salivary MLT level range from 1 to 5 pg/mL in the day and up to 50 pg/mL at night. Few studies have demonstrated that the salivary glands may synthesize MLT. Recently, a study by Shimozuma et al. found the expression of the enzymes that mediate the serotonin to MLT transformation by immunohistochemistry in the major salivary glands of the rat and in the human submandibular glands. Whether the minor salivary glands contribute to MLT concentration in the oral cavity is unknown[2].

Melatonin in gingival crevicular fluid

Many studies have demonstrated the presence of MLT in the gingival crevicular fluid (GCF) of humans[2]. A study by Srinath et al. compared the GCF MLT levels in

healthy, gingivitis and periodontitis patients. The measured levels GCF from individuals with a healthy mouth (absence of gingivitis) was 1.54 pg/mL compared to 2.17 pg/mL in salivary fluid. The salivary and GCF MLT levels were reduced to the lowest concentrations in patients with chronic periodontitis (salivary melatonin: 0.07 pg/mL; GCF melatonin: 0.06 pg/mL).Similar results were reported by Golpasand et al. and Cutando et al. All these studies concluded that severe inflammatory responses are associated with massive free radical generation and increased oxidative stress, which in turn leads to tissue damage and bone loss. Thus, the actions of MLT as an anti-inflammatory and antioxidative agent could be beneficial to abate the severity of inflammation and for improving the periodontal health[2].

Exogenous melatonin

MLT has been reported in foods including cherries (0.17–13.46 ng/g), bananas, grapes, tomato, cucumber, rice, cereals, herbs, olive oil, tea, wine and beer. Apart from natural sources, it is also available as a synthetic product in the form of sublingual tablets or oral sprays and topical gel[2]. At a therapeutic level of 0.5–5 mg, MLT is used for the management of sleep disorders and jet lag, and for the resynchronization of circadian rhythmsin situations such as blindness and shift work. Because of its sedative effect, it is also used as anxiolytic, analgesic, antihypertensive, anti-inflammatory, and antidepressant[2].

Melatonin receptors

Melatonin has specific membrane and nuclear receptors that have been cloned and three subtypes have been identified[3]. They were initially named Mel-1a, and Mel-1b, Mel-1c. The Mel-1a receptor gene has been mapped to human chromosome 4q35.1. Its primary expression is in the pars tuberalis of the pituitary gland and aging lower the levels of salivary melatonin with no variability in terms of gender. Recent evidence has suprachiasmatic nucleus[4]. Mel-1b has been mapped to chromosome 11q21-22, and its main expression is in the retina and brain. Mel-1c is not found in mammals. Mel-1a, Mel-1b are now renamed as MT1 and MT2 by International Union of Basic and Clinical Pharmacology (IUPHAR). These two are members of a group of membrane receptors known as G-protein-coupled receptors that share a large part of amino acid sequences[3]. The recently discovered MT3 receptor is a cytosolic enzyme, Quinone reductase. Using gene knockout technology results to date suggests that the phase-shifting receptor is MT2, while MT1 is associated with acute suppression of suprachiasmatic nucleus electrical activity in addition to its important actions within the pars tuberalis; MT1 potentiates adrenergic vasoconstriction and MT2 modulates dopamine release in the retina[3].

Circadian rhythm

The rhythmic production of melatonin is a consequence of neural impulses from the biologic clock, that is, from SCN and hypothalamus[5]. It is known as the “chemical expression of darkness” as most of its synthesis occurs during night. In healthy individuals, peak serum melatonin levels are seen between 12.00 a.m.–2.00 a.m. and 2.00–4.00 a.m., with minimum secretion occurring during the day 12.00 p.m.–2.00 p.m[5]. Following its secretion unbound melatonin diffuses passively into the saliva and oral mucosa to enter the oral cavity. So, salivary melatonin represents the percentage of free melatonin. The presence of melatonin in saliva is confirmed by several techniques such as automated solid phase extraction, high-performance liquid chromatography, and fluorescence detection.[5]Salivary melatonin levels (2–4 pg/mL) form 24–33% of the plasma melatonin levels. Factors such as smoking, exposure to light, alcohol consumption, and observed its presence in the gingival crevicular fluid (GCF). GCF melatonin levels are 60% lower than serum

levels and 30% lower than salivary levels. Measurement of salivary melatonin is a reliable technique to monitor the circadian rhythms of melatonin[5].

Physiologic melatonin levels

Normal plasma MLT levels range between 14 and 60 pg/mL[2]. MLT has its highest levels in plasma during night time and early mornings (60–200 pg/mL) peaking between 12 AM and 4 AM and is lowest during the day (between 12 PM and 2 PM).Mean endogenous MLT production rates have been calculated to be approximately 30 µg per day. The salivary MLT widely varies between 1.5 and 3.5 pg/mL because it depends on various factors that control the functioning of salivary glands. The presence of melatonin in the GCF of humans was reported by Srinath et al.; the mean GCF MLT level varies between 0.5 and 2 pg/mL[2].

Physiologic functions of melatonin[2]

Function	Probable Mechanism
Odontogenesis	Increased alkaline phosphatase (ALP) activity. Expression of dentine sialoprotein (DSP) Differentiation of dental papilla cells by the activity of mitochondrial complex I and complex IV
Osseous remodeling	Promotes osteoblast differentiation and bone formation Stimulates synthesis of type 1 collagen fibers Inhibits bone resorption by interfering with the activity of osteoclasts Increase genic expression of bone sialoprotein and other protein markers Down regulates RANKL-mediated osteoclast formation and activation
Osteointegration	Promotes osteoblast differentiation and bone formation Acts as a local growth factor
Immunological	Activates CD + 4 lymphocytes by increasing the production of IL-2 and IFN-γ Modulates immune functions by activating CD + 4 cells and monocytes
Antibacterial	Reduces the lipid levels in microorganisms Reduces the intracellular substrates in organisms
Antiviral	Induces production of IL-1β which is useful in viral infections
Antifungal	Enhances phagocytic function and reduces oxidative stress originating during candidiasis
Anti-inflammatory	Inhibits inflammatory enzyme Cyclooxygenase by binding to the active sites of COX-1 and COX-2
Antioxidant	Direct effects: Neutralizes reactive oxygen species such as OH, ROO, H2O2, and O Stabilizes the lipid bilayers of mitochondrial membranes and improves electron transport chain Indirect effects: Regulates nitric oxide production Increases gene expression and activities of glutathione promoting removal of H2O2 and super oxide dismutase
Antineoplastic	Scavenges reactive oxygen species Inhibits the growth of oral squamous cell carcinoma cells Due to antioxidant action, inhibits the malignant transformation of potentially malignant disorders

Melatonin in oral health and disease

The role of melatonin in the oral cavity (both in physiological and pathological processes) is basically related to its antioxidant and anti-inflammatory effects, as well as acting as a mediator in bone formation and resorption[2].

Melatonin and odontogenesis

MLT concentrations change in a specific manner during the lifespan of humans. MLT is a lipophilic hormone and crosses the placenta easily; therefore, prenatally, the foetus obtains melatonin from mother[6]. A study by Kivela et al. found that MLT could be detected in infant blood during the first 2 weeks of life but there was no daily rhythm[5]. The night-time rise in MLT concentrations is noted in the 6th to 8th week of life, and its circadian rhythm seems to be established at approximately 3 months of age[6]. After this period, the MLT concentration continues to increase[2]. The level of nocturnal MLT secretion reaches the highest in the ages between 4 and 7 years, and by the time of puberty, MLT concentrations slowly begin to decline. Interestingly, during this period, odontogenic apparatus undergoes crucial changes such as histogenesis, development, eruption, replacement and maturity[2].

A study by Ohtsuka et al. has demonstrated that complete lesion of the SCN led to a failure of the dentine incremental line appearance, and thus they presumed that this was associated with changes in hormones under tight circadian control. Because MLT is secreted in the SCN of the brain, it may be involved in the development of circadian dental formation. Liu et al. conducted a study to investigate the effects of MLT on the proliferation and differentiation of rat dental papilla cells (rDPCs) in vitro and dentine formation in vivo. The study results demonstrated that MLT suppresses the proliferation and promotes the differentiation of rDPCs[6].

Immunohistochemical analysis revealed that melatonin 1a receptor (Me 1a R) was expressed in secretory ameloblasts, the cells of stratum inter medium and stellate reticulum, external dental epithelial cells, odontoblasts, and dental sac cells[2].

Melatonin and periodontal health[7]

Melatonin in Periodontal tissue is destroyed in the course of periodontitis by disproportionate immunologic responses to a triggering agent such as bacteria in plaque. Free radicals are released from the phagocytic cells, such as neutrophils and macrophages, and migrate to the inflamed area, significantly damaging the periodontal tissue. Lipid peroxidation is a major factor in the induction and progression of chronic periodontitis. Increased reactive oxygen species (ROS) captured by MLT and its metabolites in the inflamed area would be beneficial in reducing the degree of tissue damage. It may also influence fibroblast activity and bone regeneration by promoting osteoblast differentiation and bone formation.

Almughrabi et al. compared salivary and GCF MLT levels in four groups of patients, i.e. healthy periodontum, simple gingivitis, chronic periodontitis, and aggressive periodontitis. The MLT levels were inversely related to the severity of periodontal destruction. Cutando et al. demonstrated the use of melatonin in suppressing the periodontal disease in diabetic patients because they are more predisposed to periodontitis. Before the use of MLT, patients had significantly elevated salivary levels of alkaline and acid phosphatase as well as higher values of osteopontin (bone sialoprotein) and osteocalcin compared to nondiabetic controls. Following the topical application of MLT (1% orabase cream formula) to the gingiva once daily for 20 days, there were significant reductions in each of these parameters. Moreover, the gingival index and pocket depth were also reduced because of melatonin use[7]. Collectively, many studies have revealed that MLT reduces the severity of the inflammatory response of periodontitis. The implication is that it may be of use as an agent to preserve the periodontal health, particularly in aged individuals when endogenous MLT levels diminish and in other situations such as smoking and diabetes.

Melatonin in osseous remodelling [8]

Tooth extraction is commonly associated with extensive polymorphonuclear leukocyte infiltration to the site with massive reactive oxygen species (ROS)/reactive nitrogen species generation leading to elevated oxidative stress, including DNA damage. A study by Cutando et al. showed that topically applied MLT into the evacuated sockets following tooth removal from beagle dogs significantly reduced all parameters of oxidative stress in tissues. By limiting the tissue damage, MLT would limit the negative consequences of tooth removal and encourage more rapid healing of the wound.

Melatonin in osteointegration of dental implants

A variety of substances are used to enhance peri-implant bone response, namely, growth factors, bone morphogenetic proteins, and recently, hormones such as growth hormones and MLT. There is some evidence that topical application of MLT may act as a biomimetic agent in the placement of endosseous dental implants. Many

studies have demonstrated the relationship between MLT and bone metabolism around implants and have shown that it acts as a local growth factor, with paracrine effects on cells[9].

A study was done by Cutando et al. to assess the effect of MLT on osteointegration of dental implants. They added 1.2 mg lyophilized MLT powder after extraction of tooth from the mandible of beagle dogs and before implant placement. When the implant sites were examined 2 weeks later, the amount of bone in contact with the implant surface was significantly greater in the MLT-treated sockets than that in the controls. A similar study by Munoz et al. demonstrated the synergistic effect on osseointegration of dental implants when both MLT and growth hormones were applied directly into the extraction sockets of dogs[10].

Role in Reducing Toxicity due to Dental Materials [11]

Several cytotoxic and genotoxic effects of dental methacrylate monomers promote oxidative processes. Melatonin's antioxidative action may protect against these effects by reducing oxidative DNA damage induced by methacrylates. Melatonin when used as a component of dental materials exhibited biocompatibility without altering the properties of these dental materials. Alternatively, the regular use of melatonin oral rinse may reduce the side effects of methacrylate monomers.

Protective Action of Melatonin against DNA-Damaging Agents

Melatonin has a long history of studies documenting its ability to prevent DNA damage induced by toxic chemicals and ionizing radiation[12,13]. Also, results of many studies performed in vitro suggest protective effects of melatonin in normal cells against several agents present in the environment, including lead,[14,15] arsenic and fluoride, both singly and in combination. In the study, melatonin also inhibited sister chromatid exchanges and stimulated cell proliferation. Reactive oxygen species are implicated in induction of programmed cell death, that is, apoptosis. On the other hand, melatonin displays strong antioxidative properties and it is a potent anti-apoptotic agent. Therefore, melatonin's action as a scavenger of reactive oxygen species and its involvement in the repair of the damage mediated by these species may be considered[16].

Melatonin and salivary secretion[17]

Based on new evidence, MLT may have a potential in the treatment of xerostomia. Its ability to regulate the secretory activity of the salivary glands may be exerted through a direct action on MLT receptors on the secretory units and partially depending on nitric oxide (NO) generation at the level of neuronal NO synthase. It has been also shown to evoke protein/ amylase secretion from the parotid gland of the anesthetized rat.

Melatonin in oral infections

MLT may have immunotherapeutic potential in viral and bacterial infections.

Melatonin in oral mucositis[18]

The antioxidant properties of MLT may be beneficial for the treatment of local inflammatory lesions and for accelerating the healing process. It has been shown to inhibit the inflammatory enzyme cyclooxygenase-2 (COX-2) by binding to the active sites of COX-1 and COX-2 indicating that it may act as a natural inhibitor of the function of these enzymes and thereby act as an endogenous inhibitor of inflammation. MLT may also protect against ionizing radiation. The ulcerated and inflammatory lesions characteristic of radiation mucositis are a result of massive oxidative damage and the release of toxic cytokines. In light of these data, it would seem important to test MLT more extensively alone or in combination with other agents as a protector against radiotherapy and chemotherapy-mediated mucositis.

Melatonin and Herpes Viral Infection[19,20,21]

The beneficial effects of melatonin in herpes infections of the oral cavity have been compared with Acyclovir. In this case, melatonin proved beneficial in reducing the severity of herpes at least as effectively as the prescription drug. This is consistent with the actions of melatonin on other viral infections where it has also been found to reduce the severity of those infections. The benefits of melatonin in these situations seem to stem from the immunomodulatory actions of melatonin in the stimulation of IL-1B, which has antiviral effects. The suppressive actions of melatonin on herpes may also relate to its stimulation of NK, CD4 cells, and so forth. At this point, the precise mechanism whereby melatonin may reduce the severity of herpes infections remains unknown. To promote the regression of the symptoms of herpes virus infection, a formulation containing 2.5mg melatonin and 100mg SB-73 (a mixture of magnesium, phosphate, fatty acids, and protein extracted from Aspergillus oryzae) with no reported side effects has been developed. This formulation is based on published information indicating that melatonin has known immunomodulatory properties. As it is considered a supplement, with natural ingredients, it may be fine utility in the treatment of herpes infections by individuals who cannot afford prescription drugs. Other studies have documented the antiviral actions of melatonin. Currently known effects of SB-73 on immune system components include stimulation of production of T lymphocytes and cytokines, particularly interleukin-2 (IL2) and interferon-gamma (INF-gamma)leading to increased activity of natural killer (NK) cells. SB-73 given either before or after viral infection increased the number of bone marrow granulocyte-macrophage progenitor cells (CFU-GMs) . As it is known that IFN-gamma has immune regulatory, antiviral activities, it may be hypothesized that the action of SB-73 involves immunotherapeutic one.

Melatonin and Candidiasis[22,23]

As an immuno modulator, melatonin reportedly exhibits protective effects in severe sepsis/shock induced by bacterial lipopolysaccharide in animal models. Melatonin reduced IL6 levels and shortened time to improvement in animals with Candida sepsis. Levels of TNF-alpha and adhesion molecules in melatonin-treated septic rats were reduced compared with those in untreated septic rats. Considering these findings, melatonin may have therapeutic benefits in Candida sepsis and classic antimycotic treatment because of this immune-regulatory effects. Thus, melatonin may also be useful as a topical and/or systemic treatment of oral candidiasis. Terron et al. Evaluated the effect of melatonin on the ingestion and destruction of Candida albicans (live particles) by the ring dove (Streptopelia risoria) at different durations of incubation with physiological as well as with a pharmacological concentration of melatonin. Also, some study results support the proposal that melatonin enhances phagocytic function and at the same time reduces oxidative stress originating during candidiasis.

Melatonin as Antineoplastic Agent[24]

There are several mechanisms by which melatonin, at greater than physiological concentrations, can exert its oncostatic actions:

- Antioxidant effect
- The regulation of estrogen receptor expression and transactivation
- Modulation of the enzymes involved in the local synthesis of estrogen
- Modulation of the cell cycle, differentiation, and apoptosis
- Inhibition of telomerase activity
- Antiangiogenesis
- Prevention of circadian disruption
- Activation of the immune system and epigenetic factors

Melatonin as an anti-oxidant

Free radicals are molecules or portion of molecules that possess an unpaired electron in their valence orbital. This electron-deficient state makes these agents highly reactive, and, as a consequence, they damage adjacent molecules by abstracting an electron from or donating an electron to them. Because of their high reactivity, free radicals and related reactants damage small biomolecules (i.e., vitamins, amino acids, carbohydrates, and lipids) as well as macromolecules (i.e., proteins, lipids, nucleic acids); the latter can lead to destruction of supra molecular elements (i.e., cell membranes, mitochondria, and lipoproteins). In particular, their attack on fats causes lipid peroxidation, which, in turn, brings about the formation of additional lipid radicals and toxic metabolites; hence, the initiation of lipid peroxidation sets in motion a chain of events that can lead to extensive cellular damage.

Free radicals often cause damage to the nitrogen bases of DNA as well as to proteins. Ultimately, the damage may contribute to diseases, such as cancer, neuro degeneration, and autoimmune conditions.[25]

When the balance between free radicals (oxidants) and antioxidant defense systems is disrupted, a condition of oxidative stress occurs. Reversal of this oxidative state is important to protect the body from its ill effects. Various anti-oxidants like vitamin A, C and E have been tried but they all fail to provide adequate protection against ROS in majority of clinical trials, thus, the current focus is to find out a natural antioxidant e.g., derived from plants, endogenous oxidative enzymes[26,27].

Melatonin is considered an effective cancer protective agent and this property is mainly due to its free radical scavenging activity and its indirect antioxidant actions.

Aging is associated with increased incidence of neoplastic diseases because of the accumulated molecular damage inflicted by lifetime ROS exposure. Because melatonin production also wanes with age, its deficiency has been suggested as one of the probable causes for increased incidence of cancer cases among the elderly. It is well-known that glutathione exists at high concentration intracellularly and protects cells from free radicals and oxidative stress. Melatonin regulates the production of reduced glutathione by stimulating its rate limiting enzyme γ- glutamylcysteine synthase. This action in turn is essential for reducing the generation of hydrogen peroxide (H_2O_2) and hydroxyl (-OH) radicals within the cell. This interaction may explain the oncostatic effect of melatonin on cancer cells transformed by oxidative stress[28].

Melatonin's effect on angiogenesis in cancer[27]

Angiogenesis is an essential step in the development of primary tumours.

Endothelin-1

Endothelin-1 synthesis in blood vessels is considered as one of the main stimulants of angiogenesis in primary tumours. Endothelin-1 directly stimulates endothelial as well as perivascular cells by releasing proangiogenic substances such as vascular endothelial growth factor. These effects are arrested by melatonin which suppresses

the formation of endothelin-1 by inhibiting endothelin-converting enzyme-1.

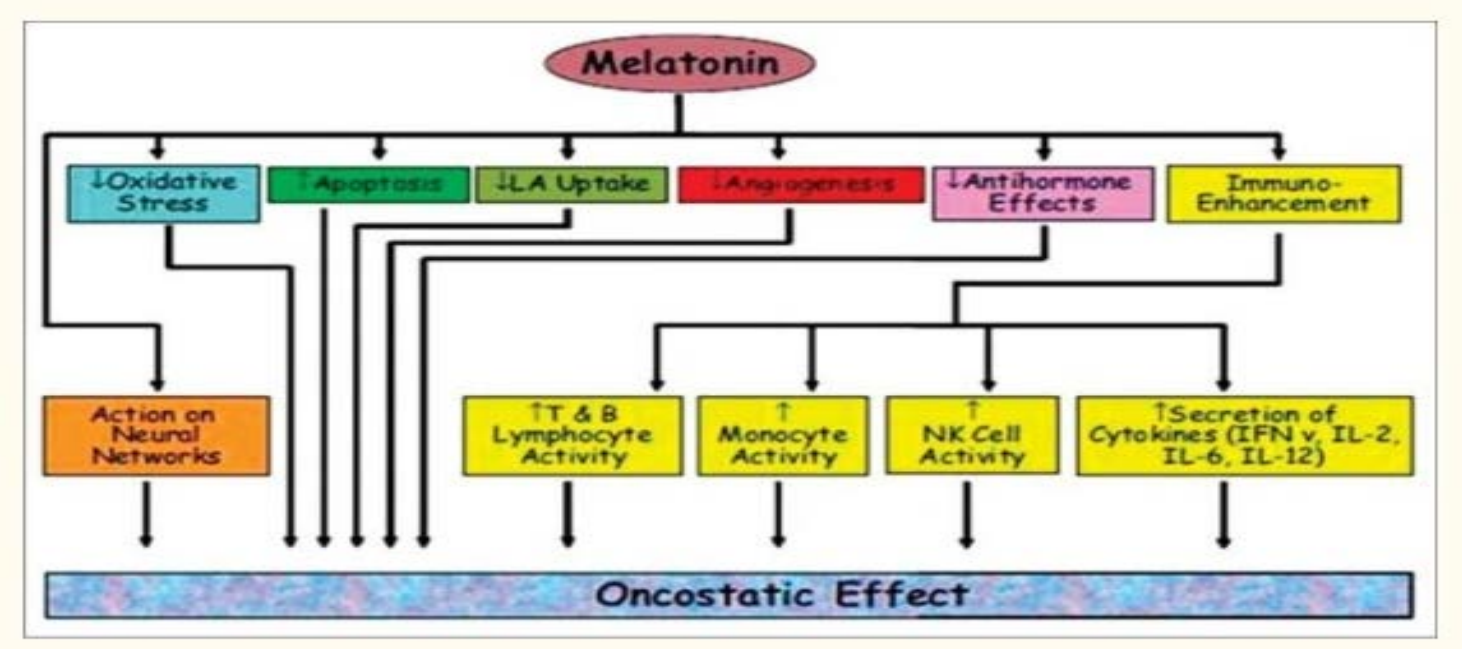
Melatonin and apoptosis in cancer cells[29]

Several studies have shown melatonin's antiapoptotic effect in immune cells, mainly through direct and indirect mechanisms.In contrast, *in vitro* melatonin has been shown to promote apoptosis in breast and colon cancer cells. Melatonin induced apoptosis on MCF-human breast cancer cells by increasing the expression of p21 and p53 proteins that are related to cell cycle control. Melatonin's proapoptotic effect on tumor cells may have a wide range of therapeutic applications.

Melatonin as immunoenhancer

Immunosurveillance is one of the major mechanisms by which cancerous cells are detected and destroyed and natural killer (NK) cells play an important role in Immunosurveillance against neoplastic growth. The decline in immune function with aging has been shown to increase the risk for cancerous growth[30].

Melatonin's oncostatic effects can be attributed to its stimulatory potential on lymphocytes, monocytes/macrophages, and NK cells. Melatonin enhances the production of IL-1, IL-6, tumor necrosis factor (TNF), and IL-12 from the monocytes and enhances the production of IL-2, IFN-Y and IL-6 from cultured human peripheral blood mononuclear cells. In addition to stimulating the production of several cytokines that regulate immune function, melatonin enhances immune function by directly stimulating polymorphonuclear cells, macrophages, NK cells, and lymphocytes. Because NK cells are effective against a variety of tumours, especially leukaemias and lymphomas, the regulation of NK cell activity and the enhancement of the cytolytic function of NK cells by melatonin have considerable significance for possible therapeutic applications[31,32].



Advantages

- It is endogenously produced.
- It is nontoxic.
- Diffuses rapidly into all cells and body fluids.
- Penetrates all subcellular compartments.
- Generally devoid of pro-oxidant actions.
- Stimulates a number of antioxidant enzymes.
- It could be applied directly on oral mucosa

Conclusion

While the inflammatory and oxidative mechanisms of the oral diseases are being unraveled, the use of novel antioxidant and anti-inflammatory substances is warranted. Melatonin may have clinical applications in reducing oral diseases, limiting tissue damage that is a result of free radicals, stimulating the immune response, reducing the progressive loss of alveolar bone, promoting the regression of symptoms of herpes viral infection, impeding local inflammatory lesions, and possible treatment of xerostomia and oral cancer also with the biocompatibility of melatonin with the tissues of the oral cavity and the need of defense against cytotoxic an dgenotoxicaction of methacrylate-based dental materials. Melatonin has the following positive aspects

It is endogenously produced, it is nontoxic, it diffuses rapidly into all cells and body fluids, it penetrates all subcellular compartments, it is generally devoid of pro-oxidant actions, and it stimulates a number of antioxidant enzymes. Melatonin released into the oral cavity via the saliva may have yetto-be identified benefits for oral health. Melatonin from the blood into the saliva may play an important role in suppressing oral diseases. It may have beneficial effects in periodontal disease, herpes, and oral cancer, amongst others. Individuals, as the result of pathologies that are characterized by a malfunction of the salivary glands, may have an elevated capacity to develop diseases of oral cavity. The administration of melatonin, in local or systemic form, might be indicated in these patients, with the goal of protecting their mouth against inflammatory and infectious processes of a diverse nature. The functional aspects of melatonin in the oral cavity need additional in vestigating and may prove to be a fertile area for research.

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