The expression of melatonin and its receptors in the oral cavity could protect against severe acute respiratory syndrome coronavirus 2 entry

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Abstract
The recent times have envisaged a mammoth global threat in the form of the novel coronavirus infection caused by the severe acute respiratory syndrome coronavirus (SARS Cov 2) virus. This deadly virus has been found to possess a spike glycoprotein in its structural assembly that it uses to penetrate the host tissues. The oral cavity has been found to be a vulnerable portal of entry of the SARS Cov 2 virus due to the expression of the Angiotensin-converting enzyme 2 enzyme. Moreover, oral diseases such as periodontitis and oral cancer make the oral tissues more vulnerable to SARS Cov2 entry due to the overexpression of molecules such as Cathepsin L and Extracellular matrix metalloproteinase inducer (EMMPRIN) which are used by the virus for binding and entry. Melatonin an endogenous indoleamine has been found to be protective against the SARS Cov 2 entry due to its modulatory effects on Cathepsin L and EMMPRIN. This paper highlights the mechanisms involved and suggests the adjunctive use of melatonin as a supplement in the form of gels, mouth washes, and lozenges to prevent SARS Cov 2 viral entry into the oral cavity.

Keywords:
Melatonin, Oral cavity, Severe acute respiratory syndrome coronavirus 2

Introduction
The whole world is now battling the novel coronavirus disease which is taking away scores of human lives. This deadly disease was first reported in Wuhan in China in December 2019 following which it has spread to almost all the countries of the world.[1] This disease with influenza-like symptoms causes respiratory distress and lung damage in some affected individuals leading to severe morbidity and mortality. The main route of human-to-human transmission has been suggested to occur by droplet which has necessitated social distancing. Despite numerous measures by various health authorities, this disease scourge has not yet left mankind and is still afflicting the human race giving them sleepless nights. Even the introduction of vaccines against, this disease has not eradicated the disease from this world.

It is in this dire situation that researchers are pondering as to how this virus enters the human system. The oral cavity is one of the strong portals of entry of the severe acute respiratory syndrome coronavirus (SARS Cov 2) virus into the human body. It is well known that the oral stomatognathic system including the oral cavity, teeth, and their supporting apparatus and paraoral structures is an important organ system. It is also known that the oral cavity has a strong defense system to prevent entry of foreign invaders such as bacteria, viruses, fungi, and parasites. This innate defense system is comprised of the saliva and gingival crevicular fluid[2] which contain abundant defense molecules and immunoglobulins. In addition to this, the oral tissues express a plethora of defensins which are proteins that belong to the class of antimicrobial peptides.[3] It has been speculated that melatonin, an endogenous indoleamine could also be a part of the defense system of the oral cavity and a
hypothesis has been elucidated to explain how melatonin could contribute to defense against SARS Cov 2 entry into the mouth and consequently the human system. This paper sheds light on the abovementioned hypothesis.

**SARS Cov 2 Entry into the Human System Through the Oral Cavity: Role of Cathepsin L and Extracellular Matrix Metalloproteinase Inducer (EMMPRIN)**

Once the SARS Cov 2 virus enters the human system, it has an affinity to bind to Angiotensin-converting enzyme 2 (ACE2)[4] and EMMPRIN, also referred to as BASIGIN/CD147, is another significant target for the entry of SARS Cov 2 virus into the mouth. This molecule has interestingly been documented to be a receptor for the spike glycoprotein (SP) of the SARS Cov 2 virus and facilitates viral entry and dissemination in the host. A research study has demonstrated that Meplazumab, an anti-CD147 antibody, was found to prevent the viral entry into the human host system.[10]

Hence, data from this segment reveal that two important proteins, namely, Cathepsin L and EMMPRIN are involved in SARS Cov2 entry. It is also noteworthy that both Cathepsin L and EMMPRIN are overexpressed in oral diseases such as periodontitis[12,13] and oral cancer.[14,15] This makes patients with these conditions more vulnerable to the SARS Cov 2 infection as there is an increased chance of viral entry into the host. With the background information with regard to Cathepsin L and EMMPRIN being targets in the oral tissues for viral entry, the further sections will detail how melatonin could protect the oral tissues in states of health and disease from SARS Cov 2 infection by modulating Cathepsin and EMMPRIN.

**The Role Melatonin and its Receptors in the Oral Cavity in Combating SARS Cov 2 Virus Entry**

Melatonin, a ubiquitous molecule chemically denoted as N-Acetyl-5 methoxytryptamine, has been found to play a very important role in human physiology.[16] This multifaceted amine was initially believed to be produced only by the pinealocytes of the pineal gland to regulate the biological clock and circadian process in the human body. However, research has shown that melatonin has potent antioxidant,[17] anti-inflammatory,[18] immunomodulatory,[19] and oncostatic properties.[20] Melatonin production has been documented in many extrapineal sites including the oral cavity where salivary glands[21] and gingiva[22] have been shown to synthesize and secrete melatonin.

Melatonin has been found to inhibit and dysregulate Cathepsin L production when administered exogenously to experimental animals.[23] In an *in vitro* study gingival fibroblast line interleukin 6 as an injurious stimulus has found to increase Cathepsin L production through the Caveolin -1 mediated JNK- AP-1 signaling pathway.[24] This point needs mention here as Melatonin has been found to be an inhibitor of JNK signaling in diverse cellular models.[25] This mechanism of melatonin mediated cathepsin inhibition through the JNK signaling pathway could operate in the oral tissues also. Since melatonin has been documented to be synthesized and secreted in the oral tissues, it could play a protective role against coronavirus entry serving as a cathepsin inhibitor. With regard to EMMPRIN, melatonin through its antioxidant activities has been found to inhibit the CD147 signaling pathway which the SARS Cov 2 virus uses to enter the host.[26] It, hence, appears that the presence of melatonin and its biosynthesis in the oral tissues is a protective barrier to prevent SARS Cov 2 entry into the mouth.

Interestingly, melatonin levels in oral tissues have also been found depleted in states of periodontal disease[27] and oral cancer.[28] Hence, the loss of this protective molecule coupled with increased cathepsin and EMMPRIN levels as previously explained could render these patients vulnerable to the novel coronavirus infection.

**Clinical Implications**

It is at this juncture, we hypothesize that melatonin supplementation could potentially reduce the risk of oral mucosa mediated SARS Cov 2 infection. Melatonin in gel formulation has been tried as a pharmacomodulatory agent in periodontal disease management. Similar formulations such as mouthwashes, gels, oralbase, and local drug delivery systems containing melatonin could be used, especially in patients with periodontal disease and oral cancer and could also be prescribed as a supplement in healthy subject. Since melatonin is a lipophilic molecule with good bioavailability and high tissue penetrability, it could easily diffuse into the oral tissues. Since there are no major adverse effects that have been reported with melatonin.
topical use, this drug could definitely be exploited as an adjuvant to reduce the risk of oral mucosa mediated coronavirus infection.

References
