COVID-19 and the Antiviral Effect of Saliva

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Human saliva is a complex fluid secreted by three major salivary glands, namely, parotid, submandibular, and sublingual as well as several minor glands located in the lips, tongue, palate, cheeks, and pharynx.[1] This brief letter focused on the antiviral function of saliva and its relationship with COVID-19.

The thin salivary pellicle layer protects the oral mucosa against various viruses and consists of proteins and peptides. The following components of saliva have antiviral function: cathelcidin (LL-37), lactoferrin, lysozyme, mucins, peroxidase, salivary agglutinin (gp340, DMBT1), sIgA, SLPI, and α and β defensins.[2] Histatin peptides, secreted by parotid and submandibular glands, have proven antimicrobial and antifungal features, and thus have gained wide currency in the therapeutic and biodental medicine fields. The three major histatin forms, Histatin-1, Histatin-3 and Histatin-5, contribute to the fight against external pathogenesis such as viruses and have shown to induce wound healing through epithelial migration stimulation. However, there is little data on the antiviral effect of histatins, which therefore necessitate further investigation.[3] Moreover, there are more than 20 types of mucins identified in the human body, which cover moist epithelial surfaces such as the gastrointestinal tract, respiratory tract, oral cavity, and eyes. Mucins are found to be effective against HIV-1 virus; if MUC5B and MUC7 are mixed with HIV-1 and then exposed to T cells, the T cells will not be infected.[4] Salivary gp340 has also illustrated antiviral efficacy against HIV-1 and acute respiratory infections such as influenza A.[2]

Oral saliva is being used for the evaluation of the systematic and oral health. In other words, since sampling oral saliva is noninvasive and therefore the risk of cross-infection is relatively low, human saliva as a biofluid can be used for the diagnosis and prognosis of oral infections, including respiratory diseases like COVID-19, Zika virus, HIV, herpes virus, and some others.[5-7]

The two major antibodies in human saliva are secretory IgA and IgG, both of which are known to play protective role against influenza viruses. IgA is found in the mucosal tissues and upper respiratory tract, offering first-line defense against respiratory infections, whereas IgG antibody is essential for the systemic immunity.[1,8] It is noteworthy that in laboratory condition, anti-HA S139/1 IgA has shown higher antiviral potential against influenza A virus infection than IgG.[8] On the other hand, microbial analysis illustrated high-affinity between angiotensin-converting enzyme 2 (ACE-2) and SARS-CoV-2. People with high-levels of ACE-2 may have more susceptibility to COVID-19, which can potentially target salivary glands.[7]

Human whole mouth fluid consists of salivary gland secretion, gingival crevicular fluids, secretory mucosa from the nasal cavity and pharynx, bacterial metabolism and desquamated epithelial cells. The salivary fluid is composed of organic and inorganic components which represent the physiology of the human body.[5] Saliva secretion, the flow rate of saliva, and its composition depend on several factors, including type and size of glands, nutritional status, gender, age, and emotional state. Maintaining good oral hygiene contributes to the normal functioning of the salivary glands against respiratory infections. It is noteworthy that saliva secretion in a healthy person ranges from 0.5 to 1 L per day, with an average of 0.6L.[1]

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred in December 2019 in Wuhan city, China. In February 2020, World Health Organization (WHO) named the virus, Coronavirus disease 2019 (COVID-19). There exist four genera of the virus: α-COV, β-COV, δ-COV, γ-COV, two of which infect humans and other mammals (α- & β-COVs), attacking their respiratory system. With regard to the morphological structure of COVID-19, it has three main proteins, including E protein, S protein, and M protein, which cause potential transmission of the virus from animals to humans as well as from humans to humans. COVID-19 can be transmitted through close contact with an infected person by way of sneezing, coughing, and inhalation of infected droplets or by mucous membranes of the mouth, nose and eyes. A safe and effective technology for diagnosing COVID-19 is the point-of-care method, using saliva as a form of liquid biopsy.[7,9] The COVID-19 outbreak can be indirectly compared with the Zika virus, a mosquito-borne flavivirus of

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zoonotic origin. Zika was transmitted through blood transfusions as well as human-to-human intimate contact, particularly saliva contact. Like COVID-19, ZIKA could be detected through various saliva tests.[6]

In light of the above-mentioned information in this letter, the antiviral effect of saliva, especially mucins, salivary agglutinin, IgA, IgG, and histatins, may play a role in neutralizing or annihilating COVID-19. However, it is suggested that more *in vivo* or *in vitro* studies examining saliva be done to obtain more precise and valid data on the antiviral function of saliva against COVID-19.

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Conflict of Interest

None declared.

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