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Short Communication

Human Saliva: A Prognostic, Diagnostic and Therapeutic Tool-Kit

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Saliva is an extracellular fluid produced and secreted by salivary glands in the mouth. About 93% by volume is secreted by the major salivary glands and the remaining 7% by the minor glands. In humans, biochemically, approximately 99% of saliva is water and the other 1% is composed of organic and inorganic molecules [1]. Organic substances include exfoliated epithelial cells (from which DNA can be extracted), white blood cells, mucus,, enzymes (such as amylase and lipase), antimicrobial agents such as secretory IgA, and lysozymes [2]. Saliva consists of both full-length and partially degraded forms of mRNA, its association with macromolecules may protect salivary RNA from degradation [3]. Besides these, human saliva contains a huge number of microRNAs (miRNAs) are found to be associated with pathophysiology of the body. Saliva is supersaturated with certain electrolytes and ions. These help the pH of the saliva within a range from 6.2-7.4 and maintains a buffer state in the oral cavity. This prevents minerals from dissolving in the dental hard tissues. Initially, saliva is isotonic when formed in the acini. Gradually it becomes hypotonic when it travels through the duct network. The hypotonicity of unstimulated saliva allows the taste buds to perceive different tastes without being masked by normal plasma sodium levels. Saliva helps to secrete carbonic anhydrase (gustin), which is thought to play a role in the development of taste buds [4]. In a nut-shell, salivary content differs with respect to emotional, neurological, nutritional, metabolical status and above all immunological response of the person concerned.

Normally, saliva performs wetting, lubricating, forming bolus of chewing food and help in swallowing. It also helps in digestion, antimicrobial activity, facilitating remineralization of the tooth enamel, and maintaining normal taste sensation protects the oral mucosa from dehydration. Salivary enzymes (salivary amylase and lipase)- the most common form of enzymes found in saliva are essential for initiating the process of digestion of dietary starches and fats. These enzymes also play a role in breaking down food particles entrapped within dental crevices, thus protecting teeth from bacterial decay.

Saliva is usually formed in the oral cavity through an act called gleeking, which may be either voluntary or involuntary. The production of saliva is stimulated both by the sympathetic and the parasympathetic nervous system. The saliva stimulated by sympathetic innervations is thicker, and saliva stimulated parasympathetically is more thinner and fluid-like. Sympathetic stimulation of saliva is to facilitate respiration, whereas parasympathetic stimulation is to facilitate digestion. Normally, 1.5litre of saliva is secreted daily from the salivary glands in a healthy person. In humans, nearly 70-75% of total secretion is contributed by the submandibular glands, while 20-25% is secreted by the parotid glands and about 5-10% are secreted from the other salivary glands. Sometimes, due to hyposalivation sensation of having a dry mouth called as xerostomia is being observed. Consequently, pH falls, buffering capacity decreases and concentration of electrolytes increases. Immediate effect due the hyposalivation may leads to loss of taste, indigestion, hyperacidity, gingivitis, periodontitis, halitosis, dental caries, candidosis and sialodentitis. Notably, xerostomia is a common feature among diabetic (type 1 and type 2) patients and sunstroke victimised cases. On the contrary, when the salivary glands secretes excess amount of saliva, the condition is called hypersalivation. Un-

intentional overflow of accumulated extra saliva from the mouth of the victim is called drooling. Hypersalivation may be either temporary/short-term or permanent/long-term and very often precedes with nausea and emesis/vomiting.

Human saliva contains a number of antimicrobial agents that effectively removes both exogenous and endogenous microorganisms and their products from the mouth [5]. Lysozyme and lactoferrin are antimicrobial in mature. Salivary peroxidise has been proved to be anti-bacterial while histatin acts as both anti-bacterial and anti-fungal. A soluble form of antibacterial and antiviral protein named as gp340 binds to and aggregates a variety of bacteria. Originally gp340 referred to as salivary agglutinin and is thought to increase bacterial clearance from the mouth. However, when bound to the tooth surface, gp340 promotes bacterial adherence. The gp340 proteins are also found specific inhibitor of HIV-1 and influenza A infectivity. In contrast, in the female reproductive tract, most gp340 proteins are bound to the cell surface, where it can promote HIV-1 infection [6]. The anti-fungal activity of saliva against *Candida albicans* and *Cryptococcus neoformans* is well known. The histidine-rich peptides appear to be an effective antifungal agent as well, able to inhibit growth and kill *Candida albicans* at a very low concentration [7]. Saliva acts as a mirror of the body's health and could constitute the first line of defense against oxidative stress by controlling and/or modulating oxidative damages in the oral cavity [8].

Human saliva has long been used for the monitoring of drugs and alcohol abuses. Moreover, utilization of saliva in HIV-testing is very common for AIDS diagnosis. Recently, the whole saliva has been utilised as a diagnostic tool-kit, Due to its easy accessibility, saliva became the epicenter of diagnosis of various diseases. Presence of various molecular markers, such as mRNAs and miRNAs in many systemic diseases including cancer have been reported. Although RNAs were believed to quickly degrade in the saliva due to the effect of salivary ribonucleases, several studies have confirmed that RNAs in saliva can exist as stable molecules [9]. Both mRNAs and miRNAs are well protected and preserved abundantly inside the exosomes originated from the endoplasmic reticulum [10].

Park., *et al*. have found significantly reduced levels of miR-125a and miR-200a in the saliva of oral cancer patients as compared to healthy controls [11]. In another study, Liu., *et al*. have explored the clinical application of miR-31 as a biomarker in oral cancer. Liu., *et al*. have demonstrated that salivary miR-31 was significantly elevated in all the stages of oral cancer irrespective of the tumor size [12]. It was shown in their study that levels of miR-31 were higher in saliva as compared to blood, miR-125a plays an important role in cell proliferation and can effect the genes involved in MAPK metabolism. Korpal., *et al*. reported that *miR-200a* is involved in tumor suppression and early metastasis [13]. In a study Prasad., *et al*. concluded that miRNA- 21 is over expressed in oral submucus fibrosis (OSMF) and chewing habit patients. But the expression levels were not significantly associated with the severity of the disease process [14]. In another study, Natarajasundaram., *et al.* have reported that among the different lesions, leukoplakia had significant upregulation of miRNA-21 and miRNA-31. Out of these two, miRNA-21 can be used as a diagnostic marker with specificity of 66% and sensitivity of 69% [15]. Wiegand., *et al*. opined that Salivary miR-20b, -21 and -26b, and significant changes in miR-16 and -134 were directly associated with psychological stress of the individual. Significant correlations with alpha-amylase suggest their integration in sympathetic stress regulation processes [16]. Al-Rawi., *et al*. *in silico* analysed and identified four miRNAs (miRNA 155,146 a/b and 203) as immune modulators. All these four miRNAs were found to be over expressed in patients with periodontitis and/or diabetes and miRNA-155 was the most reliable predictors of periodontitis among non-diabetics [17]. Fadhil., *et al*. reported that salivary miR-let- 7a-5p and miR-3928 were significantly down regulated in saliva of head and neck squamous cell carcinoma (HNSCC) patients relative to age and sex-matched healthy controls. However, miR-let 7a-5p and miR-3928 were correlated with lymph node metastasis and tumour size respectively [18]. In a case-control study, Wu., *et al*. reported that expression of salivary miR-3679-3p, miR-574-5p, miR-205-5p, and miR-6131 in saliva were up regulated and miR-30b-3p, miR-575, and miR-650, were down-regulated in case of nasopharyngeal carcinoma (NPC) patients when compared with the healthy controls [19].

It is a matter of great concern that most of the people are unaware of the real science of saliva. They simply and forcibly eject away the saliva from their mouth here and there as spit, Such type of spitting is very common among the addicted groups of chewers, smokers and alcoholics. In many parts of the world, it is considered rude and a social taboo, and has even been outlawed in many countries. Due to spitting, spreading of microbial contagious diseases including tuberculosis, SARS-CoV-2 etc cannot be ignored [20].

Spitting in public places pose a serious health hazard to the public and therefore, it must be banned.

In fact, saliva acts as the mirror of the human body and reflects the health status of the individual. Analysis of saliva may be useful for the diagnosis of various diseases including hereditary and metabolic disorders, autoimmune and infectious diseases, premalignant and malignant cancer and even psychological stress disorders. Expression pattern of salivary miRNA in various systemic diseases has given a new dimension to the current research as it has been demonstrated to be tremendous potential in clinical applications. Sampling of saliva is easy, economic and non-invasive. Presence of a number of potential biomarkers for oral and systemic diseases, human saliva may be considered as a promising tool-kit for prognosis, diagnosis, and therapy of multifarious diseases.

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