Saliva-Based Diagnostics: Applications, Limitations and Future Prospects in Systemic Disease Detection: A Review

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Abstract

The accessibility of collection, cost-effectiveness, and ability to mirror systemic physiological and pathophysiological conditions have rendered saliva an attractive non-invasive diagnostic medium. It contains many potential biomarkers, such as proteins, enzymes, hormones, metabolites, and nucleic acids, which can provide significant information about endocrine disorders, cardiovascular diseases, viral infections, autoimmune diseases, cancer, and genetic defects. This up-to-date review focuses on the types of existing salivary biomarkers, their clinical utilities, diagnostic impact, and recent technical advances reported in studies published between 2018 and 2025. Original articles and review papers were included to discover trends, challenges and possible future directions of saliva-based diagnostics. These findings suggest salivary diagnostics can attain sensitivity and specificity comparable with classical methods, enabling early detection, disease monitoring, and therapeutic recommendations. Despite problems of variability, collection methods and standardization, saliva-based diagnostics have vast potential for clinical utility. Additional investigation is expected to enhance their reliability and clinical application in systemic disease diagnosis.

Keywords: Clinical Biochemistry, Saliva, Biomarkers, Non-Invasive Diagnostics, Systemic Diseases.

1. Introduction

Saliva functions as a solvent for peptides, ions, and metabolites that are generated or excreted during the degradation of drugs and endogenous substances apart from previously mentioned roles. The molecular composition of saliva mirrors many conditions, and these biomarkers are used to diagnose disease (Zhang et al., 2016).

Alterations in salivary components are commonly associated with systemic conditions, neurological diseases, endocrine problems, viral infections and cancer as well as cardiovascular complications (Dave et al., 2020). These properties, make saliva a useful medium for monitoring disease and early diagnosis (Roca et al., 2024). Hormonal dysfunction, cancer, autoimmune diseases, viral infections and genetic disorders may be detected through the use of a saliva study it could track drug use and determine therapy doses (Schweigel et al., 2016).

Both endocrine disorders and diseases such as cancer, autoimmune conditions, viral disease, genetic disorders can be diagnosed from a saliva sample. It is also possible to monitor drug consumption and establish therapeutic dosages (ÖZBAY et al., 2008). One of important applications of salivary diagnostics in cardiology is the risk estimation for acute myocardial infarction in patients with insulin resistance. Thus, salivary alpha-amylase was found to be a diagnostic marker in patients with precordial pain of duration <4 hours for the diagnosis of acute myocardial infarction (AMI) (Shen et al., 2012). Furthermore, salivary proteome chips (e.g. myoglobin, myeloperoxidase and C-reactive protein) have been shown to be effective in diagnosing acute myocardial infarction (Floriano et al., 2009). Furthermore, in patients with cardiovascular disease, α-2-HS-glycoprotein proved to be decreased in saliva of the peptidome and therefore may serve as a candidate molecule for early diagnosis of cardiovascular diseases (Zheng et al., 2014). Although the general opinion was that saliva is a less sensitive sample compared to other biological fluids in molecular testing aimed at detecting respiratory viruses, the interest of using saliva has been re-proposed. Furthermore, it has been reported several times that saliva showed higher detection sensitivity for respiratory viruses compared with nasopharyngeal samples in studies using the reverse transcription polymerase chain reaction (Sheikhakbari et al., 2012). Likewise, identified saliva alongside nasopharyngeal specimens to present like detection rates with multiplex polymerase chain reaction. mBio Laboratories Aspen Corporate Park, South Africa Introduction With ongoing advances in scientific research, molecular testing on saliva is able to attain the diagnostic sensitivity and specificity equal or greater to those of nasopharyngeal swabs (Kim YoungGon et al., 2017). With the current COVID-19 pandemic, this finding is highly applicable. Regrettably, the nonuniformity of saliva sampling and handling can influence SARS-CoV-2 detection. There are different potential sources of saliva (oral cavity and post-oropharyngeal) that have specific properties. Another potential limitation on diagnostic applications of this technology is the high viscosity of saliva, which makes it difficult to collect and manipulate. More reliable practices are required. Thus, to improve the diagnosis and monitoring of salivary biomarkers for improving the quality of life, further investigation is needed regarding clinical research development, standardization and validation in saliva-based diagnostics. An additional research study also discovered a significant relationship between HbA1c and salivary glucose levels among diabetics. This indicated the possible use of saliva in monitoring blood glucose levels in diabetics (Cenzato et al., 2023). Apart from its diagnostic capability, saliva holds many advantageous features compared with the classical biological fluids (blood and CSF). Laboratory investigations of SCoV2 infection with saliva are highly acceptable, non-invasive and painless being collected in a stress-free environment without the need for qualified medical personnel, supported by good diagnostic performance making it suitable for utilization at larger scale deployment on mass screening basis, repeated collection of specimens or those populations who are not easily assessed like children, elderly patients, and critically ill cases

(Malamud, 1992; Yoshizawa et al., 2013) . Additionally, saliva lowers the threat of infection transmission to healthcare workers and decreases biohazard considerations applicable to blood sampling (Pfaffe et al., 2011).

Table 1: The salivary biomarkers in various systemic diseases. (Pfaffe et al., 2011)

S. number	Diseases	Biomarkers	Source of biomarkers
(1)	Autoimmune diseases (1) Sjogren's syndrome (2) Multiple sclerosis (3) Sarcoidosis	Lactoferrin, beta 2 microglobulin, lysozyme C, cystatin C, salivary amylase, and carbonic anhydrase IgA production Alpha-amylase and kallikrein	Saliva
(2)	Bone turnover markers	Body mass index, D-PYR, OC concentration, calcaneus T scores, hepatocyte growth factor, interleukin-1 beta, salivary osteonectin, and ALP activity	Serum and saliva
(3)	Cardiovascular markers	Cardiac troponins, C-reactive protein, myoglobin, myeloperoxidase, ICAM-1, CD 40, and salivary lysozyme	Serum and saliva
(4)	Dental caries and periodontal diseases	*Streptococcus mutans* and lactobacilli count, aspartate aminotransferase, alkaline phosphatase, uric acid, albumin, pIgR, Arp 3, CA VI, IL-1Ra, PLS-2, LEI, and IGJ	Saliva
(5)	Diseases of the adrenal cortex	Salivary cortisol	
(6)	Drug level monitoring	Nicotine, cannabinoids, cocaine, phencyclidine, opioids, barbiturates, diazepines, amphetamines, ethanol, cotinine, methamphetamine, endogenous γ-hydroxybutyric acid, and 3,4-methylenedioxymethamphetamine	Serum and saliva
(7)	Forensic evidence	Blood group antigens and DNA testing	Saliva
(8)	Genetic disorders (1) Cystic fibrosis (2) Ectodermal dysplasia	Cathepsin-D, sodium, potassium, chloride, calcium, magnesium, and lactate dehydrogenase Inorganic constituents, total protein	Saliva
(9)	Infections (1) Viral infections (2) Bacterial infections (3) Fungal infections	Measles virus-specific IgM HIV—HIV-1, HIV-2—antibodies, salivary proteins *Mycobacterium tuberculosis*, MUC 5B, and MUC 7 Candidiasis immunoglobulins, Hsp 70, and calprotectin, histatins, mucins, basic proline rich proteins, and peroxidases	Serum and saliva
(10)	Malignancy	lnc RNA, miRNA, CCNI, EGFR, FGF19, FRS2 and GREB1, AGPAT1, B2M, BASP2, IER3, and IL1B, p53, CA15-3, C-erb2, CA 125, FGF 2, PSA, cortisol, lactate dehydrogenase, silver nitrate and nitrite, and salivary adenosine deaminase	Serum and saliva
(11)	Occupational and environmental medicine	Salivary cortisol, IgA, lysozyme, chromogranin, alpha-amylase, lead, and cadmium	Serum and saliva
(12)	Psychological research	Salivary amylase, cortisol, substance P, lysozyme, secretory IgG, and testosterone	Saliva
(13)	Renal diseases	Cortisol, nitrite, uric acid, sodium chloride, pH, alpha-amylase, and lactoferrin. Salivary phosphate, serum creatinine, and glomerular filtration rate	Serum and saliva

Recent developments in proteomics, metabolomics, transcriptomics as well as the microfluidic processing technologies have made this diagnostic approach more sensitive and reliable. These are the technologies that have made it possible to detect salivary biomarkers that are disease specific and strongly related to pathological changes taking place within systemic circulation (Panta & Wong, 2019). As a consequence, saliva is now considered as a mirror of systemic health displaying physiological and pathological states at the moment they occur (Giannobile et al., 2009).

In light of these characteristics, saliva-based diagnostics are a promising resource for personalized medicine as well as early disease and general health state monitoring. Nevertheless, the application of salivary biomarkers in daily practice is still limited since they must be supported by standardized measures such as sampling protocols, analytical techniques and large-scale clinical testing for verification accuracy, reproducibility and impact (Javaid et al., 2016).

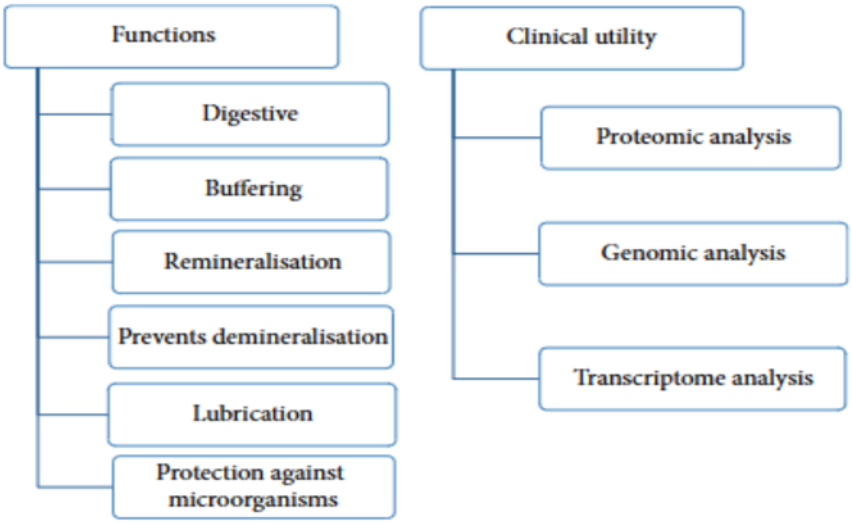

Figure 1: Functions and clinical utility of saliva. (Lee et al., 2009)

A comprehensive review of the potential and limitations of salivary biomarkers for monitoring and diagnosis of systemic disease is presented. This includes studying how they can be utilized for drug metabolism and therapeutic dosage surveillance, diagnosis of endocrine diseases, cardiovascular conditions, viral infections, autoimmune disorders, and cancer, as well as genetic defects. The review article focuses on the effectiveness of salivary-based diagnostics compared to traditional methods and discusses pros (e.g., early detection, non-invasive nature) and cons (e.g., sensitivity of biomarkers, collection and processing variation). This review also aims to discuss the future of improving salivary diagnostics in clinical utility and reliability, including: (i) adjusting collection procedures under ideal conditions to ensure disease predictive strength; (ii) advancing analytical methodologies (with higher than previously reported sensitivity/specificity values) to diagnose a disease with greater accuracy; and (iii) validating biomarkers for monitoring/treating/preventing diseases.

2. Materials and Methods

This review was carried out using an extensive literature search of the application of saliva as a diagnostic medium for systemic diseases. Scientific publications that were pertinent to this review were identified by a systematic search of electronic databases (PubMed, Scopus, Web of Science, and Google Scholar). We used a combination of keywords that included “salivary biomarkers,” “saliva diagnostics,” “systemic diseases”, "cardiovascular diseases", "endocrine disorders", and "viral infections". For the review to only include the most recent and clinically applicable information, articles from 2018 to 2025 and prior literature were included. Both research articles and review papers were selected to cover the full state of knowledge. Articles reporting on animal model only, conference abstracts without full-text access, non-English publications, and studies with insufficient methodological information were excluded.

The details were collected from the selected studies such as profile of various types of salivary biomarkers (proteins, enzymes, nucleic acids and metabolites), clinical and diagnostic applications, sensitivity and specificity, Advantages and Disadvantages, recent technological advances like molecular assays & biosensor-based platforms etc. After data extraction,

qualitative synthesis was conducted to explore the trends, gaps, and future directions in salivary diagnostics-specifically for systemic diseases

3. Discussion

3.1. Overview of Saliva-Based Diagnostics

Because saliva contains a wide range of signs, including proteins, nucleic acids, and metabolites, it has become a viable non-invasive diagnostic fluid for systemic disorders.

3.2. Applications / Strengths of Saliva-Based Biomarkers

The value of saliva in monitoring early and systemic diseases has been explored. Salivary determinations of glucose have been studied as an alternative to blood glucose testing, especially in diabetics. It was reported that the levels of salivary glucose are significantly correlated with blood glucose, suggesting saliva has potential in diabetes control. cardiovascular diseases (CVDs) increase in the same direction during recent decades of time Salivary C-reactive protein (CRP) The connection between salivary biomarkers and CVDs is reliably manifested from altered levels of CRP among subjects with CVDs (Olsen et al., 2016).

Saliva is an attractive fluid in diabetes detection since the level of glucose concentration in saliva and blood are highly related to each other. Studies have demonstrated that other biomarkers, such as cortisol and amylase, along with salivary glucose may provide information on glycaemic management and complications of diabetes (de Lima et al., 2023). These measurements are vital for diabetes management as it monitors the level of glucose in blood and feedback on the patient's stress and metabolic conditions. Salivary glucose and glycemia/HbA1c levels are positively correlated, and this correlation grows along with the increase of glycemia/HbA1c concentrations (Mascarenhas et al., 2014).

Several contagious diseases are detected and monitored, largely from saliva. These studies offered proof-of-concept evidence that saliva-based testing could provide a dependable, more acceptable alternative to nasopharyngeal swab sampling during the COVID-19 pandemic. Tests for SARS-CoV-2 using spit have comparable sensitivity and specificity to those using other methods, research finds. The non-invasive nature of saliva's collection method has rendered it an attractive alternative for mass screening, enhancing patients' cooperation especially in populations for whom conventional methods can present challenges (Babady et al., 2021). Other pathogens such as HIV, hepatitis viruses, and respiratory disease-associated bacteria have also been Isolated from saliva. Salivary IFN-γ is valuable for the diagnosis of TB and was associated with oral conditions among HIV-positive individuals (To et al., 2020).

In OPMDs, few salivary miRNAs including down-regulated miR-21 and 145 and up-regulated miRNA 184 can act as potential predictive biomarkers for malignant transformation (Sathisha & Sowmya, 2024). To be able to evaluate these diagnostic and prognostic potentials of MMTV proves as described by studies, more exploration in other populations is suggested. In addition, salivary pro-inflammatory cytokines, including TNF-alpha, IL-1β, IL-2, and IL-6 are associated with the extent of oral mucosal tissue injury in cancer patients and can serve as early biomarkers for GVHD (Cristaldi et al., 2019).

3.3. Limitations / Challenges in Salivary Diagnostics

Some of the benefits saliva provides for oral health include it being a natural lubricant, an agent that forms a protective pellicle on enamel and one that speedily helps heal soft tissue injuries. It also helps in food mastication and swallowing (Ilea et al., 2019). Saliva collection is easier, less expensive and major work is not needed when compared to serum collection. Saliva requires less manipulation during diagnostic testing and can be sampled at home. Saliva does have several drawbacks however; such as lower biomarker concentrations (10–1500 times less than plasma), and changes in flow rate when eating, stressed or exercising. Saliva can be collected using one of these two methods: unstimulated flow (similar to passive drool) and stimulated flow (e.g., chewing gum, swabs, lozenges). Each method presents limitations that could compromise the integrity of the biomarkers, such as changes in pH or contamination (Srisuttee et al., 2020).

Amylase test tablets, two-dimensional electrophoresis and mass spectrum are several typical methods to detect saliva which have largest drawback of low specificity and true positives or negatives (Ren et al., 2022). Of these, both LC-MS requires high laboratory work and large sample size that often yield low reproducibility (Khanum et al., 2017). Raman spectroscopy (RS), enzyme-linked immunosorbent assay (ELISA), surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS), quantitative mass spectrometry, saliva kits, omics, and single-cell sequencing technology are the more advanced techniques in saliva detection nowadays (Kendrick et al., 2019).

Saliva kits have since become useful tools for diagnosing several diseases, even AIDS. A new saliva-based AIDS test kit in China has recorded more than 99% accuracy, making it convenient for rapid, accurate, and painless testing importance for surveillance. They are infection control tools that allow for visual interpretation of information in general life. These kits are defined as in vitro immunodiagnostic reagents that can assist in the qualitative identification of HIV1/2 antibodies in oral secretions. Saliva-based diagnostic test result cannot be used as a singular basis for the affirmative diagnosis; it must be carried alongside other diagnostic tools. The Aliva kits are a game-changing innovation in disease diagnosis. Given their accessibility and lack of invasion, Aliva kits provide more opportunities for use in diagnosing and screening a significant number of medical diseases; since they are used for testing and self-testing in low resource settings, Aliva kits can go a long way in improving to medical treatment (Aro et al., 2017).

3.4. Future Prospects / Technological Advancements

With further technical enhancements and combining with multimers platforms, saliva-based diagnostics are expected to be a key player for the future non-invasive disease detection. In recent estimates, point-of-care systems, including lab-on-a-chip/microfluidic technology, will enable fast decentralized testing at patient side instrument by-passing a centralised laboratory (Jiang et al., 2019). The potential of using biosensors with nanotechnology improvements could significantly enhance the LOD (limit of detection) for salivary biomarkers which is expected to detect autoimmune diseases, viral infections and cancer at an early stage (Marazuela & Moreno-Bondi, 2002). With multi-omics analyses (PMID:29981193), including proteomics, metabolomics, transcriptomics and genomics, as well as an AI algorithm, saliva testing can evolve to predictive and preventive medicine. This enables early prediction and customised health care (Visweswara Rao & Hua Gan, 2015). Moreover, to ensure robustness and reproducibility of findings, future research will focus on developing standardized

procedures for saliva collection, on optimizing analytical methods, and validating in larger/more heterogeneous population(s) (Chouhan et al., 2023). Wearable and smartphone-linked saliva analysers are just a few of the burgeoning new technologies that could revolutionize patient-centred care and allow individuals to monitor their health better in remote or resource-challenged environments (Hayes et al., 2018).

4. Conclusion

Saliva-based diagnostics is emerging as a promising field in non-invasive, precision medicine based on the convergence of next-generation biosensing techniques along with multi-omics and AI to analytics. Full exploitation of saliva as a regular diagnostic and monitoring medium will need continuous technical improvement and rigorous clinical validation. Saliva-based diagnostics has become an innovative field of modern clinical biochemistry, providing a convenient and patient-friendly methodology as compared to the conventional form of invasive diagnostic tool. 1,2 Indeed, high-throughput techniques combined with large-scale analytical studies on the salivary content have demonstrated that saliva can accurately report oral and systemic process dynamics in health and disease. This makes it a valuable tool for early diagnosis, risk stratification, prognosis and serial monitoring of an extensive range of systemic diseases including cancers, autoimmune diseases, endocrine abnormalities, cardiovascular pathologies and infectious diseases. The ease, non-invasiveness, safety, low cost of saliva collection and its potential for mass testing during outbreak also contribute to its clinical utility and broaden the application in hospital- and population-based services. However, despite these substantial benefits, some drawbacks still exist that limit the complete clinical application of salivary diagnostics. Variation in saliva composition arising from hydration status, circadian rhythm, stress, use of medication or oral health issues is a challenge to maintaining biomarker reliability. Furthermore, the naturally low concentration of certain analytes in saliva, when compared to serum, requires highly sensitive analytical systems. With significant inter-study variance found for saliva collection, refining processing procedure, and storage conditions should be optimized in addition to harmonizing and broadening its clinical evaluation across populations before saliva can expect to be used as a routine diagnostic specimen. Future of Saliva-Based Diagnostics With continued technological improvements, it is anticipated that in the near future saliva-based diagnostics will provide greater precision with improved sensitivity and clinical utility. Novel technologies, such as biosensors based on nanomaterials, lab-on-a-chip microfluidic devices, point-of-care test systems based on smartphone applications, and wearable sensors for oral fluid analysis are promising candidates for rapid and decentralized diagnostics. In addition, the fusion of multi-omics with artificial intelligence and machine learning algorithms is predicted to transform predictive and personalized medicine by exploiting saliva as a complex biological fluid. These advances will not only enhance early diagnosis but personalization of treatment options, home monitoring the disease, and prophylactic health.

In conclusion, despite some challenges relating to the science and methodology, a range of saliva-based diagnostics are clearly well on their way to establishing themselves as indispensable partners alongside blood/urine in systemic disease diagnosing sooner rather than later. Ongoing technological development, stringent clinical validation, and standardization of protocols will be essential to fully unleash the diagnostic potential of saliva. Saliva will continue to evolve from a secondary diagnostic fluid to an active component in healthcare—meaning better disease detection, patient comfort, and accessibility for more personalized treatment plans to come.

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