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MINI-REVIEW **OPEN ACCESS**

Salivary Proteomics and Its Role in the Early Detection of Oral Cancer: A New Frontier in Noninvasive Diagnostics

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Abstract:
Oral cancer, especially Oral Squamous Cell Carcinoma (OSCC), is a major worldwide health issue, exhibiting a high mortality rate due to late detection. Conventional methods of diagnosis are invasive and painful for the patient. Saliva can be used as an attractive, non invasive, and economical source of biomarker information, and salivary proteomics the large scale analysis of proteins in human saliva can be a promising platform for identifying potential protein biomarkers. This paper discusses the evolution of saliva as a diagnostic tool, identifies saliva proteins as potential oral cancer biomarkers, explores new technologies used to perform salivary proteomics, and examines the barriers that hinder the acceptance of salivary proteomics as a diagnostic tool for patients. Considering ongoing progress, salivary diagnostics can be expected to be a game changer for early cancer diagnosis and mediate personalized treatment concepts.

Keywords: Salivary proteomics, Oral cancer, Salivary test, Oral squamous cell carcinoma, Protein biomarkers, Antimicrobial substances.

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1. INTRODUCTION

Saliva has traditionally been underappreciated as a diagnostic medium for disease. Nevertheless, its multifaceted constitution and non-invasiveness make it an attractive candidate for clinical application. Saliva, secreted by submandibular, sublingual and parotid glands, is made of water, electrolytes, many proteins, enzymes, immunoglobulins, hormones, and antimicrobial substances. These factors reflect the health of the mouth and the body [1, 2].

The advent of “salivaomics,” including genomics, transcriptomics, proteomics, metabolomics, and microbiomics, highlights the growing interest in saliva as a diagnostic fluid. Proteomics is especially noteworthy among all these omics, given that proteins play a critical role in the pathways leading to disease and biological processes [3-5].

2. BIOMARKERS IN SALIVA: SALIVARY BIOMARKERS OF ORAL CANCER

OC, particularly OSCC, occurs through a multi-step process that involves genetic and epigenetic alterations that drive cell transformation. Diagnosis is often delayed as the early lesions are usually asymptomatic or resemble benign lesions [6]. Such treatment delay leads to dismal prognoses and decreased survival. Saliva proteomics provides an unprecedented opportunity for the early diagnosis of these cancer-related molecular changes during the course of the disease. Several salivary proteins have been reported to be differentially up-regulated or modified in patients with oral cancer. These biomarkers represent different aspects of cancer, such as inflammation, angiogenesis, resistance to apoptosis, and metastasis [7-13]. These proteins can be used as diagnostic and prognostic biomarkers for identifying benign and malignant lesions, as well as disease recurrence. There are several key natural advantages of saliva diagnostics over tissue and blood sampling, as shown in Table 1:

Table 1. Key salivary protein biomarkers in oral cancer.

Biomarker	Functional Role	Diagnostic Relevance
IL-6, IL-8	Inflammatory and angiogenic cytokines	Indicate precancerous and cancerous changes
CD44	Cell adhesion and migration	Highly expressed in malignant oral tissues
Cyfra 21-1	Cytokeratin fragment	Elevated in OSCC, aids differentiation
CA 125	Tumor-associated antigen	Reflects tumor burden
p53 autoantibodies	Tumor suppressor mutation marker	Found in the saliva and serum of OSCC patients
MMP-8, MMP-9	Extracellular matrix degradation	Associated with invasion and metastasis
bFGF	Promoter of angiogenesis	Increased during active tumour progression

Table 1: Advantages of Saliva as a Diagnostic Medium.

Noninvasive: It does not use needles or surgery, so patients experience minimal pain and risk.

Cost Efficiency: Simpler collection, storage and blood processing reduce healthcare costs.

Safety: Less risk of infection, safer for the patient and medical professional.

Ease of Being Monitored Frequently: It allows for more than one time-point testing, making it suitable for long-term studies and disease diagnosis.

Patient Acceptance: Better compliance from patients to deliver a sample, as it is noninvasive.

Furthermore, as OSCC arises from the oral cavity, the saliva directly interacts with the diseased tissue. It is a significant fluid used to monitor disease-specific changes in this context.

Several clinical studies have provided robust evidence supporting the diagnostic potential of salivary proteomics in the detection of oral cancer. For instance, salivary Interleukin-8 [IL-8] and Interleukin-6 [IL-6] have been consistently reported to be elevated in patients with OSCC, with diagnostic sensitivities above 80% in some cohorts, highlighting their value as inflammatory biomarkers linked to malignant transformation. Similarly, CD44, a cell surface glycoprotein involved in tumour invasion and metastasis, has been detected at significantly higher concentrations in the saliva of OSCC patients compared to healthy controls, suggesting its role as a non-invasive diagnostic marker. More recently, Kaul-Ghanekar *et al*. (2025) [14] demonstrated that the salivary Epidermal Growth Factor (EGF) to Epidermal Growth Factor Receptor (EGFR) ratio could discriminate oral cancer patients from tobacco users without cancer, thereby underscoring the potential of proteomics-based salivary biomarkers in high-risk populations. Together, these findings validate that proteomic alterations in saliva closely mirror oncogenic changes in oral tissues and can be translated into clinically relevant diagnostic assays.

3. TECHNOLOGICAL ADVANCEMENT ASSOCIATED WITH THE SALIVARY PROTEOMICS

Proteomic studies depend on the mass determination and quantification of saliva proteins, often in minute amounts. Advances in analytical technologies have increased protein detection sensitivity, resolution, and quality. Mass Spectrometry (MS), Liquid Chromatography (LC), and electrophoresis are the standard tools used in salivary proteomics [15-17].

These methods are capable of profiling the salivary proteome with unprecedented accuracy and uncovering PTMs, including phosphorylation and glycosylation, which could have functional implications for proteins in disease (Table 2).

Table 2. Core technologies used in salivary proteomic analysis.

Technology	Function	Diagnostic Contribution
Mass Spectrometry	Protein identification and quantification	Detects biomarkers at low concentrations
LC-MS/MS	Protein sequencing and structural analysis	Comprehensive proteome profiling
2D Electrophoresis	Separation of proteins based on size and charge	Visual comparison of protein expression
Hexapeptide Libraries	Compress protein dynamic range	Enhances detection of rare proteins

4. CHALLENGES AND LIMITATIONS

However, salivary proteomics is associated with several technical and biological limitations:

4.1. Variation in Sample

The composition of saliva is affected by hydration, circadian rhythms, feeding, medications and oral hygiene.

4.2. PTMs: The Ornaments of Nature

Post-translational modifications make protein identification more complex and require sophisticated analytical instruments.

4.3. Lack of Standardized Saliva Procedures

The absence of standard protocols and methodological approaches used to collect, handle, and process saliva is a limitation to the study of saliva biomarkers due to issues regarding replication.

4.4. Cost and Infrastructure

Proteomic high-throughput technologies are costly and generally unavailable in low-resource settings.

These challenges can be overcome through joint efforts to develop guidelines and benchmarks, lower the cost of technology, and integrate proteomics into current clinical practices.

5. FUTURE PERSPECTIVES

This necessitates the need for salivary proteomics in personalized medicine in the future. The availability of POC devices for the fast testing of salivary biomarkers would dramatically change the way practitioners approach the screening and treatment of oral cancer [18-21]. Moreover, an integrated analysis of proteomic information with genomics, transcriptomics, and metabolomics (multi-omics) would increase the knowledge on the disease process [14, 22-24].

Validation of existing biomarker candidates and identification of robust signatures with high sensitivity and specificity require large-scale clinical trials [25, 26]. Artificial intelligence and machine learning–based algorithms may play a central role in deciphering complex proteomes to identify predictive patterns of disease.

Beyond preliminary biomarker discovery, clinical validation studies are beginning to establish salivary proteomics as a reliable tool for cancer detection and diagnosis. Large-scale proteomic profiling, combined with machine learning, has been shown to enhance the accuracy of distinguishing OSCC patients from controls by integrating multiple protein signatures rather than relying on single biomarkers. In a recent multi-centre study, a panel including MMP-9, Cyfra 21-1, and IL-8 achieved sensitivities and specificities above 85% for early oral cancer diagnosis, indicating that multiplex proteomic assays may soon complement or even replace invasive biopsy procedures. Furthermore, advances in point-of-care devices are facilitating the translation of these findings into chairside applications, where clinicians could rapidly screen at-risk individuals using small saliva samples. As highlighted by Kaul-Ghanekar *et al.* [14] and other emerging investigations, the integration of validated salivary biomarker panels with artificial intelligence-driven interpretation holds promise for achieving real-time, non-invasive, and highly accurate cancer diagnostics.

CONCLUSION

Salivary proteomics is emerging as an innovative technique for detecting and monitoring oral cancer. The noninvasive profiling of proteins specific to the disease process enables new opportunities for regular screenings, monitoring responses to treatment, and screening for recurrences. Although technical and practical hurdles remain, the continued development of proteomic and bioinformatics technologies is gradually and surely clearing the path for saliva-based diagnostics to be accepted into routine clinical practice.

With further research, salivary diagnostics could enhance overall survival rates among OSCC patients and set new benchmarks for the early detection of many systemic diseases.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: V.B.: Study conception and design, R.F.: Data collection; C.B.: Analysis and interpretation of results; D.F., L.C., G.G.: Draft manuscript; C.B.: D.F.: All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

OSCC = Oral Squamous Cell Carcinoma
MS = Mass Spectrometry
LC = Liquid Chromatography
EGF = Epidermal Growth Factor
EGFR = Epidermal Growth Factor Receptor
IL-8 = Interleukin-8
IL-6 = Interleukin-6

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Wang C, Yu W, Wu X, Wang S, Chen L, Liu G. Proteomic insights into molecular alterations associated with Kawasaki disease in children. Ital J Pediatr 2025; 51(1): 56. http://dx.doi.org/10.1186/s13052-025-01853-8 PMID: 39984993

[2] Tsebesebe NT, Mpofu K, Sivarasu S, Mthunzi-Kufa P. Arduino-based devices in healthcare and environmental monitoring. Discov Internet Things 2025; 5: 46. http://dx.doi.org/10.1007/s43926-025-00139-z

[3] Ali Ahmed MA, Shetty S, Rahman B, Gopalakrishnan ARK, Ismail AA, Acharya AB. Evaluation of salivary Ki-67 in health and periodontitis. BMC Oral Health 2025; 25(1): 366. http://dx.doi.org/10.1186/s12903-025-05719-7 PMID: 40065293

[4] Chen Q, Wu Z, Ma Y. Transcriptomics-based exploration of ubiquitination-related biomarkers and potential molecular mechanisms in laryngeal squamous cell carcinoma. BMC Med Genomics 2025; 18(1): 84. http://dx.doi.org/10.1186/s12920-025-02148-x PMID: 40355841

[5] Nayar S, Turner JD, Asam S, *et al.* Molecular and spatial analysis of tertiary lymphoid structures in Sjogren's syndrome. Nat Commun 2025; 16(1): 5. http://dx.doi.org/10.1038/s41467-024-54686-0 PMID: 39747819

[6] Ayhan H, Sevin S, Karaaslan S, Ayaz F. Immunomodulatory effects of medicinal leech saliva extract on *in vitro* activated macrophages. Immunol Res 2025; 73(1): 9. http://dx.doi.org/10.1007/s12026-024-09575-5 PMID: 39671012

[7] Northrop-Albrecht EJ, Kim Y, Taylor WR, Majumder S, Kisiel JB, Lucien F. The proteomic landscape of stool-derived extracellular vesicles in patients with pre-cancerous lesions and colorectal cancer. Commun Biol 2025; 8(1): 228. http://dx.doi.org/10.1038/s42003-025-07652-5 PMID: 39948151

[8] Samodova D, Stankevic E, Søndergaard MS, *et al.* Salivary proteomics and metaproteomics identifies distinct molecular and taxonomic signatures of type-2 diabetes. Microbiome 2025; 13(1): 5. http://dx.doi.org/10.1186/s40168-024-01997-5 PMID: 39794871

[9] Ezzat D, Azab A, Kamel IS, *et al.* Phytomedicine and green

nanotechnology: enhancing glass ionomer cements for sustainable dental restorations: a comprehensive review. Beni-Suef Univ J Basic Appl Sci 14, 48 (2025).
http://dx.doi.org/10.1186/s43088-025-00633-x

[10] Tang J, Liu J, Zhou Z, *et al.* Oral submucous fibrosis: Pathogenesis and therapeutic approaches. Int J Oral Sci 2025; 17(1): 8.
http://dx.doi.org/10.1038/s41368-024-00344-6 PMID: 39890798

[11] Michiels S, Wölflick S, Simões J, Schlee W. Exploring app-based physiotherapy for somatic tinnitus: Results from a pilot study. J Clin Med 2024; 13(23): 7203.
http://dx.doi.org/10.3390/jcm13237203 PMID: 39685670

[12] Hernández-Teixidó C, Barrot de la Puente J, Miravet Jiménez S, *et al.* Incidence of diabetic retinopathy in individuals with type 2 diabetes: A study using real-world data. J Clin Med 2024; 13(23): 7083.
http://dx.doi.org/10.3390/jcm13237083 PMID: 39685542

[13] Moreno-Juste A, Poblador-Plou B, Laguna-Berna C, *et al.* Multimorbidity in patients with chronic liver disease: A population-based study in the epichron cohort, spain. J Clin Med 2024; 13(23): 7198.
http://dx.doi.org/10.3390/jcm13237198 PMID: 39685662

[14] Kaul-Ghanekar R, Kharat RS, Raina P, Chaudhary A, Walekar-Ghaisas S. Salivary EGF: EGFR ratio as potential early diagnostic biomarker for oral cancer detection in tobacco chewers: A preliminary cross-sectional study. BMC Oral Health 2025; 25(1): 663.
http://dx.doi.org/10.1186/s12903-025-05982-8 PMID: 40301868

[15] Ding T, Liu C, Li Z. The mycobiome in human cancer: Analytical challenges, molecular mechanisms, and therapeutic implications. Mol Cancer 2025; 24(1): 18.
http://dx.doi.org/10.1186/s12943-025-02227-8 PMID: 39815314

[16] Yi X, Liu E, Wang Y. Post-genome-wide association study dissects genetic vulnerability and risk gene expression of Sjögren’s disease for cardiovascular disease. J Transl Med 2025; 23(1): 531.
http://dx.doi.org/10.1186/s12967-025-06568-2 PMID: 40350475

[17] Chacko N, Ankri R. Non-invasive early-stage cancer detection: Current methods and future perspectives. Clin Exp Med 2024; 25(1): 17.
http://dx.doi.org/10.1007/s10238-024-01513-x PMID: 39708168

[18] Chen X, Song F, Xiao P, *et al.* Spermine accumulation *via* spermine synthase promotes tumor cell proliferation in head and neck squamous cell carcinoma. BMC Cancer 2025; 25(1): 402.
http://dx.doi.org/10.1186/s12885-025-13820-x PMID: 40045286

[19] Aalam SMM, Varela AR, Khaderi A, *et al.* Establishment of salivary tissue-organoid biorepository: Characterizing salivary gland stem/progenitor cells and novel differentiation marker PSMA/FOLH1. NPJ Regen Med 2025; 10(1): 23.
http://dx.doi.org/10.1038/s41536-025-00410-5 PMID: 40399315

[20] Joon V, Dhankar V, Chauhan T, *et al.* Advanced spectroscopic techniques for body fluid identification: complementing conventional methods. Egypt J Forensic Sci 15, 7 (2025).
http://dx.doi.org/10.1186/s41935-025-00425-5

[21] Di Febo R, Saeed Z, Serafini F, *et al.* Diagnostic and prognostic roles of endothelial- and platelet-derived extracellular vesicles in cardiovascular diseases. J Transl Med 2025; 23(1): 553.
http://dx.doi.org/10.1186/s12967-025-06522-2 PMID: 40380176

[22] Wu L, Liu C, Hu W. Comprehensive investigation of matrix metalloproteinases in skin cutaneous melanoma: Diagnostic, prognostic, and therapeutic insights. Sci Rep 2025; 15(1): 2152.
http://dx.doi.org/10.1038/s41598-025-85887-2 PMID: 39820824

[23] Yousif G, Murugesan S, Djekidel MN, *et al.* Distinctive blood and salivary proteomics signatures in Qatari individuals at high risk for cardiovascular disease. Sci Rep 2025; 15(1): 4056.
http://dx.doi.org/10.1038/s41598-025-87596-2 PMID: 39901062

[24] Khabazian A, Koopaie M, Khabazian T, Manifar S, Kolahdooz S, Tafakhori A. Evaluation of salivary nitric oxide levels and anxiety in multiple sclerosis patients, with and without Xerostomia: Correlation with clinical variables. BMC Oral Health 2025; 25(1): 507.
http://dx.doi.org/10.1186/s12903-025-05878-7 PMID: 40200257

[25] Forszt D, Gerreth K, Karpienko K, *et al.* Salivary chemokines and growth factors in patients with ischemic stroke. Sci Rep 2025; 15(1): 12676.
http://dx.doi.org/10.1038/s41598-025-97974-5 PMID: 40221607

[26] Tong Y, Bai S, Ou L, *et al.* Gene expression profiling and pathway analysis in head and neck squamous cell carcinoma: Focus on disulfidptosis. Discov Oncol 2025; 16(1): 556.
http://dx.doi.org/10.1007/s12672-025-02344-2 PMID: 40246729