

Advances in Salivary Diagnostics: Emerging Roles of Biosensors, Microfluidics and AI in Oral and Chronic Degenerative Non-Communicable Diseases Detection: A Systematic Review

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Abstract

Background: This review evaluates salivary biomarkers—including proteins, cytokines, microRNAs, DNA, RNA, metabolites, and extracellular vesicles—and their diagnostic potential in detecting diabetes, cardiovascular disease, inflammatory bowel disease, autoimmune and neurodegenerative disorders, periodontal disease, oral cancer, and dental caries. Thirty-two peer-reviewed studies (2015–2025) were synthesized to assess saliva’s role as a diagnostic fluid.

Methods: A structured search across major databases identified 822 studies. After screening 120 full texts, 34 studies met inclusion criteria (English language, peer-reviewed, diagnostic focus, and biomarker evaluation). Keywords included salivary diagnostics, oral disease biomarkers, systemic disease detection, salivaomics and point-of-care testing. Studies were categorized by disease type, biomarker class, analytical method (ELISA, RT-

PCR, microfluidics, biosensors, spectroscopy, AI-based tools), and design.

Results: Over 80% of included papers were reviews or meta-analyses emphasizing emerging technologies such as biosensors, microfluidics, and AI-enabled diagnostics. Oral cancer and potentially malignant disorders were most studied, with biomarkers like IL-8, IL-6, CD44, Cyfra21-1, and salivary micro RNAs demonstrating strong diagnostic accuracy. Periodontal studies identified cytokines, proteolytic enzymes, and microbial profiles as reliable indicators of inflammation. Salivary biomarkers such as glucose, cortisol, CRP, calprotectin, alpha-synuclein, and oxidative stress markers showed strong associations with systemic diseases, supporting saliva’s noninvasive diagnostic value.

Conclusion: Collective evidence supports saliva as a cost-effective, rapid, and patient-friendly diagnostic fluid for early disease detection and monitoring. Standardized

collection protocols, large-scale validation, and advanced technologies will be essential for its integration into precision medicine and clinical practice.

Keywords: Salivary diagnostics, salivaomics, microRNA, oral cancer, periodontal disease, systemic disease, biosensors, point-of-care testing, AI diagnostics.

Introduction

Saliva is a clear, slightly acidic bio fluid secreted by the major (parotid, submandibular, and sublingual) and minor salivary glands. It plays an essential role in maintaining oral health by aiding in lubrication, digestion, antimicrobial defense and tissue repair. Composed predominantly of water (around 99%), the remaining constituents include electrolytes (such as sodium, potassium, calcium, and phosphate), proteins (including enzymes, immunoglobulins, and mucins), hormones, DNA, RNA and microbiota. Its dynamic composition allows it to reflect both local and systemic physiological and pathological changes^{1&2}. Because of these properties, saliva has emerged as a promising non-invasive diagnostic fluid that can be easily collected, stored, and analyzed without the need for complex equipment or trained personnel^{3&4}.

The use of saliva as a diagnostic tool has gained significant attention over the last three decades due to its non-invasive, cost-effective, and patient-friendly nature^{1&3}. Unlike blood or tissue biopsies, saliva collection does not require specialized equipment or trained personnel, making it particularly suitable for routine health assessments and large-scale screenings. Saliva is a complex fluid composed of proteins, hormones, antibodies, enzymes, electrolytes, and nucleic acids that mirror both physiological and pathological states of the body².

Early developments in salivary diagnostics demonstrated its potential in detecting oral conditions such as oral

squamous cell carcinoma through biomarkers like HER2 and p53^{5&6} and inflammatory markers like interleukin-1 β (IL-1 β) in periodontal disease⁷. Saliva has also been explored for systemic disease detection; for instance, anti-HIV antibodies can be reliably detected using oral fluid based methods such as OraSure, and salivary ELISA tests offer rapid HIV screening.

In diabetes mellitus, significant correlations have been identified between salivary glucose and HbA1c levels, suggesting the feasibility of non-invasive glucose monitoring^{1&8}. Salivary C-reactive protein (CRP) has also been proposed as a predictive biomarker for acute myocardial infarction, with high specificity and sensitivity⁹. Furthermore, salivary markers have shown promise in detecting chronic kidney disease and neurological conditions through metabolites like urea and cortisol as well as autoimmune disorders such as Sjögren's syndrome¹⁰.

The introduction of the term "Salivaomics" in 2008 marked a turning point in salivary diagnostics, incorporating advanced molecular technologies such as genomics, transcriptomics, proteomics, metabolomics, and microbiomics to offer a holistic diagnostic approach^{11&12}. These developments have allowed for the identification of specific salivary RNA and protein signatures related to disease processes. Technological innovations—such as biosensors, PCR, and mass spectrometry—have further increased the sensitivity and accuracy of salivary diagnostics^{13&14}.

The rise of point-of-care (POC) platforms now enables rapid, low-cost, and user-friendly diagnostic testing, making them particularly beneficial in pediatric, geriatric, and special needs populations where blood collection may be difficult or distressing^{2&4}. Nevertheless, challenges persist, including inter-individual variability in saliva composition, lack of

standardized collection protocols, and potential contamination risks¹³.

Emerging solutions, such as machine learning algorithms and ultra-sensitive detection tools, aim to overcome these limitations and account for demographic, dietary, and lifestyle-related variables¹⁵. As the evidence base expands, saliva is increasingly being recognized as a transformative medium for real-time, non-invasive health monitoring, with tremendous potential for personalized medicine and early disease detection¹⁶.

Methods

Objective

To examine and consolidate the existing evidence on the diagnostic applications of saliva for detecting oral and systemic disorders, with emphasis on identifying salivary biomarkers and their clinical utility as noninvasive, early detection tools.

Research Strategy

This exploratory descriptive research employed a systematic literature review approach, using synthesis and evidence techniques to gather and analyze scientific data. The methodology was structured according to standardized scientific guidelines and included the following steps:

A comprehensive literature search of major databases (PubMed, Scopus, Web of Science, and Google Scholar) was conducted using keywords such as salivary diagnostics, oral disease biomarkers, systemic disease detection, salivaomics and point-of care testing. The search was restricted to studies published in English between 2015 and 2025, involving human participants, and available as fulltext articles from peer-reviewed journals.

Eligibility Criteria

Inclusion Criteria

1. Study Type: Original research articles including clinical trials (RCTs and non-RCTs), case-control studies, cohort studies, observational studies, systematic reviews, and meta-analyses.
2. Participants: Human subjects of any age, irrespective of gender, undergoing assessment for oral or systemic health using salivary diagnostics.
3. Interventions: Studies that explored the use of saliva as a diagnostic tool, particularly those evaluating salivary biomarkers (proteins, enzymes, DNA, RNA, or metabolites) associated with conditions such as dental caries, gingivitis, periodontitis, oral cancer, diabetes, cardiovascular diseases, infectious diseases (e.g., HIV, COVID-19), and neurological disorders.
4. Outcomes: Diagnostic accuracy, sensitivity, specificity, biomarker relevance, and correlation with clinical findings.
5. Language: Articles published in English only.
6. Time Frame: Studies published between 2015 and 2025.
7. Database Indexing: Only peer-reviewed articles indexed in PubMed, Scopus, Web of Science or Google Scholar were included

Exclusion Criteria

1. Focus of Study: Studies focusing solely on the therapeutic or preventive properties of saliva without diagnostic application, or those conducted on animal models without human data.
2. Publication Type: Non-peer-reviewed sources such as editorials, opinion pieces, conference abstracts, letters to the editor, and grey literature.
3. Duplicates: Duplicate publications reporting the same findings were excluded, with preference given to the most comprehensive or recent version.

4. Data Quality: Studies with incomplete results, ambiguous methodologies, or lacking clear outcome measures were excluded.

Methodology

Search Strategy A comprehensive literature search was conducted across four major databases: PubMed, Scopus, Web of Science and Google Scholar. The search strategy involved the use of combinations of relevant keywords and MeSH terms such as “saliva,” “diagnostic,” “salivary biomarkers,” “oral diseases,” “systemic diseases,” “non-invasive diagnostics,” “oral cancer,” “dental caries,” “diabetes,” “cardiovascular disease,” and “HIV.” Specific search strings were designed for each database, with the PubMed strategy focusing on salivary biomarkers and their diagnostic relevance for both oral and systemic disorders. Google Scholar was searched using terms like “salivary biomarkers,” “oral disease detection,” “systemic disorder screening,” “non-invasive diagnostics,” and “proteomics.”

Results

The inclusion criteria limited results to studies published in English, between 2015 and 2025, involving human participants, and available in fulltext from peer-reviewed journals indexed in major databases. A total of 823 articles were initially retrieved. After removal of duplicates, 246 unique articles remained—98 from PubMed, 72 from Scopus, 45 from Web of Science, and 33 from Google Scholar. Screening of titles and abstracts excluded 112 articles that lacked a diagnostic focus, used animal models, presented incomplete data, or failed to meet other inclusion criteria. 59 full-text articles were reviewed in detail, and based on eligibility criteria (English language, diagnostic focus, explicit biomarker evaluation, peer-reviewed source), 34 high-quality studies were included for qualitative synthesis.

These studies comprised comprehensive reviews, systematic reviews, and a network meta-analysis, with a focus on salivary biomarkers for oral diseases (dental caries, periodontal disease, oral cancer, OPMDs), systemic disorders (diabetes, cardiovascular disease, inflammatory bowel disease, autoimmune disorders, Parkinson’s disease), and emerging applications such as extracellular vesicles, microRNAs, biosensor-based PoC devices, and AI assisted diagnostic platforms. Overall, the evidence demonstrated that saliva is a rich and versatile diagnostic fluid containing proteomic, genomic, transcriptomic, metabolomic, and microbiomic biomarkers, with growing clinical applicability in precision medicine and early disease detection.

Discussion

Saliva, a readily accessible biofluid, has evolved from being a mere oral secretion to a powerful diagnostic tool. Its transformation—from early conceptual studies to precise biomarker identification and the development of point-of-care technologies—firmly establishes its role as a non-invasive medium capable of mirroring both oral and systemic physiological and pathological changes^{1&51}. Unlike blood sampling, saliva collection is painless, non-invasive, and can be performed by non-trained personnel, thereby improving patient compliance and comfort across pediatric, geriatric, and disabled populations. It also reduces the risk of blood-borne pathogen exposure to healthcare workers and supports repeated sampling and population-based screenings due to its cost-effectiveness³.

Saliva possesses several intrinsic advantages that make it suitable for diagnostics. Its ease of collection without specialized equipment enables frequent sampling in non-clinical settings, a sharp contrast to invasive venipuncture that demands trained professionals and sterile conditions¹³.

Saliva based tests are significantly more economical, reducing laboratory costs and making them ideal for large-scale health surveillance programs⁵². Despite its simplicity, saliva contains a complex array of analytes—including enzymes, proteins, DNA, RNA, hormones, and metabolites—that accurately reflect both oral and systemic health status there by expanding its diagnostic utility across medical fields⁵¹.

In the realm of oral disease diagnostics, saliva has shown particular efficacy in detecting inflammatory conditions and early-stage malignancies. In oral squamous cell carcinoma (OSCC), a highly aggressive cancer, biomarkers such as HER2/neu and p53 have been detected in saliva, showing strong correlations with biopsy-confirmed malignancy^{53&6}. Elevated HER2/neu levels in unstimulated saliva and the detection of mutated p53 genes and autoantibodies offer a promising non-invasive alternative to tissue biopsy. Additionally, microRNAs (miRNAs) like upregulated miR-184 and down regulated miR-21 and miR-145, along with elevated matrix metalloproteinases (MMPs), further serve as OSCC indicators⁵⁴. Proteomic profiles differentiate healthy and diseased states⁵⁵.while salivary microbiome dysbiosis, notably with carcinogenic oral bacteria, adds another dimension to OSCC diagnostics⁵⁶. Salivary diagnostics have also revolutionized the assessment of periodontal and peri-implant diseases. Elevated levels of cytokines such as IL-1 β , IL-6, and TNF- α in saliva have been strongly associated with clinical signs of periodontitis and gingivitis^{7&14}. Biomarkers like MMP-8 and MMP-9, critical in connective tissue degradation, are found in higher concentrations in affected individuals⁵⁷. Their predictive value improves when combined with microbial profiling, with bacteria such as Porphyromonas gingivalis, Tannerella forsythia and Prevotella intermedia showing

diagnostic sensitivities above 89%⁵⁸. Immunoglobulins (IgA, IgG, IgM) and oxidative stress markers further enhance periodontal disease diagnostics⁵⁷.

In dental caries, saliva provides diagnostic insights by reflecting microbial presence, buffering capacity, and immune response. Low salivary IgA, decreased flow rate, and altered viscosity are associated with higher caries risk⁵⁸.

The presence of Streptococcus mutans, Lactobacillus spp, and reduced levels of protective salivary proteins such as statherin and histatin are significant markers⁵⁹. In potentially malignant disorders like oral leukoplakia, salivary miRNAs and inflammatory cytokines aid in assessing malignant transformation risk and mucosal tissue damage⁶⁰.

Saliva's diagnostic reach extends beyond the oral cavity. In diabetes mellitus, salivary glucose has shown a strong correlation with blood glucose, supporting its use in non-invasive glucose monitoring⁶¹. Elevated salivary levels of chromogranin A, secretory IgA, potassium, and total proteins in diabetics affirm saliva's relevance⁶². Portable biosensor systems for salivary glucose are now emerging as viable tools for routine monitoring, especially for vulnerable groups⁶³.

In infectious diseases, saliva serves as a rapid, accurate medium for disease detection. Anti-HIV antibodies have been reliably detected through salivary ELISA tests. During the COVID-19 pandemic, saliva-based RT-PCR tests demonstrated accuracy comparable to nasopharyngeal swabs, facilitating mass testing⁶⁴. Saliva is also being used for hepatitis virus detection, respiratory pathogen screening, and tuberculosis diagnostics⁶⁵. In cardiovascular disease diagnostics, salivary CRP levels have demonstrated a strong correlation with serum CRP and cardiovascular risk (Malathi N et al.,2014)⁶⁶. Other markers such as myeloperoxidase, MMP-8, and MMP-9

are being studied for their association with acute myocardial infarction⁶⁷. Though cardiac troponins and CK-MB are present in saliva in smaller quantities, research is ongoing to enhance detection sensitivity for heart related conditions. Autoimmune diseases like Sjögren's syndrome have shown characteristic changes in saliva composition, including reduced flow, elevated cytokines (IL-18, IL-2, IL-17), and novel miRNAs such as miR-5100, which are being validated as disease-specific markers⁶⁸. Similarly, in renal disorders, elevated levels of salivary urea and creatinine have correlated with serum levels, suggesting diagnostic potential⁶⁹. Salivary cortisol has also proven effective in diagnosing adrenal function abnormalities and chronic stress⁷⁰. Furthermore, preliminary studies indicate that biomarkers like tau protein, α -synuclein, and amyloid-beta are detectable in saliva, opening pathways for early diagnosis of neurodegenerative diseases like Alzheimer's and Parkinson's⁷¹.

Technological advancements have propelled salivary diagnostics into a new era. The concept of "Salivaomics"—which integrates genomics, transcriptomics, proteomics, metabolomics, and microbiomics—has made comprehensive disease profiling possible using saliva (Wong, 2012; Cuevas-Córdoba & Santiago-García, 2014)^{72&73}. Genomic analysis allows for identification of human and microbial DNA; transcriptomics focuses on RNA signatures like mRNA and miRNA⁷⁴. Proteomics maps salivary proteins; metabolomics captures small molecule profiles⁷⁵ and microbiomics helps detect pathogenic oral flora⁷⁶. Biosensors and point-of-care (POC) devices have transformed saliva testing from laboratory procedures into real-time, user-friendly tools. Examples include mouthguard biosensors for uric acid and sodium, smartphone-based kits, and microfluidic chips⁷⁷. These

devices are particularly valuable in community dentistry, rural healthcare, and special needs populations due to their affordability and ease of use.

Artificial intelligence and machine learning are now being integrated with salivaomics to manage complex datasets and improve diagnostic accuracy⁷⁸. Algorithms help identify patterns among multiple biomarkers, reduce false positives, and tailor diagnostic outcomes to individual biological variability. Techniques such as random forests and neural networks are being employed to predict disease status based on salivary biomarker inputs⁷⁹. Despite these advances, several challenges persist. Variability in saliva composition due to age, diet, and hydration, lack of universal collection protocols, and contamination risks remain barriers⁸⁰. Standardization of sampling, storage, and biomarker quantification protocols is crucial to achieve clinical integration⁸¹. Furthermore, most studies remain observational or in pilot stages; thus, large-scale, multicenter clinical trials are needed to validate findings and ensure reproducibility across populations and settings⁸².

Conclusion

This review affirms the transformative potential of saliva as a reliable, non-invasive, and cost-effective diagnostic fluid for early detection of both oral and systemic diseases. Drawing evidence from 32 peer-reviewed studies, it is evident that salivary biomarkers such as IL-1 β , MMP-8, HER2/neu, glucose, CRP, and various microRNAs exhibit high sensitivity and specificity across conditions including periodontal disease, oral squamous cell carcinoma, diabetes, cardiovascular diseases, autoimmune disorders, and neurodegenerative conditions. Saliva's unique properties—easy collection, patient acceptability, and safety—make it ideal for use in pediatric, geriatric, and large-scale community health settings.

The integration of advanced technologies such as salivaomics, microfluidic biosensors, and point-of care platforms, along with artificial intelligence-driven analytics, has significantly enhanced the accuracy, speed, and accessibility of salivary diagnostics. Despite these advantages, clinical implementation is still hindered by variability in salivary composition, lack of standardized protocols, and limited multicenter validation. Addressing these challenges through large-scale trials, protocol harmonization, and cross-disciplinary collaboration is essential for translation into routine practice. In conclusion, with continuous innovation and robust clinical validation, saliva stands poised to revolutionize early disease detection, personalized healthcare, and public health monitoring on a global scale.

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Flowchart of the Literature Search and Study Selection

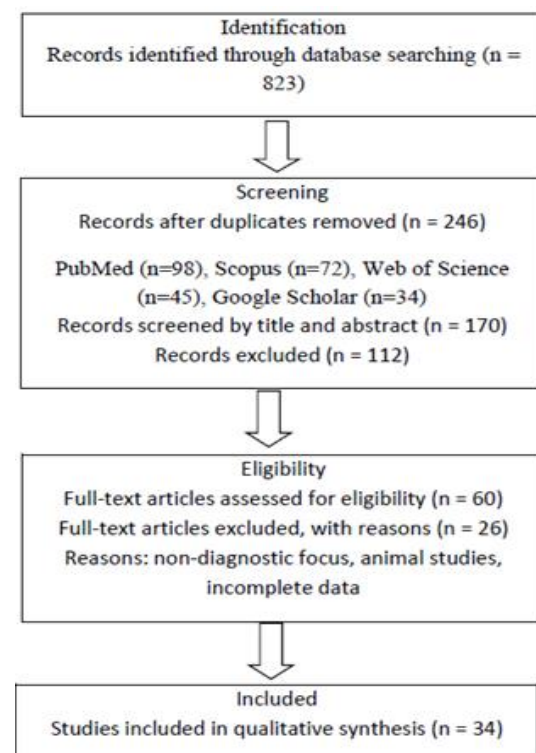


Table 1

S. NO	AUTHORS	YEAR	STUDY TYPE	FOCUS AREA	RESULTS	REFERENCE
1	Kiani M, Yanko N, Pankevych AI	2015	Comprehensive Review	Applications of saliva in disease diagnostics	Saliva contains proteomic, genomic, and microbiological biomarkers useful for diagnosing oral, systemic, infectious, autoimmune, hereditary diseases, and cancers. Highlighted diagnostic tools (ELISA, RT-PCR, OFNASET) enabling sensitive, non-invasive, and real-time diagnostics.	(17)
2	Champatray S, Nayak SR, Das SR, Jena I, Nayak G, Goel RB	2015	Review Article	Saliva as an emerging, non-invasive diagnostic tool	Saliva shown to be a "mirror of body health," containing multiple biomarkers (proteins, mRNA, antibodies, metabolites) useful for diagnosing oral diseases (dental caries, gingivitis, periodontitis, oral cancer) and systemic conditions (autoimmune, cardiovascular, renal, endocrine, infectious diseases). Highlights advanced technologies like proteomics, transcriptomics, PCR, and point-of-care devices.	(18)
3	Khaitan T, Kabiraj A, Tomar Bhattacharya PT, Ginpally U, Jha H	2015	Review	Diagnostic efficacy of saliva in oral and systemic health	Saliva contains enzymes, hormones, antibodies, antimicrobial components, and growth factors—functionally similar to serum. With sensitive detection technologies, low analyte levels are no longer a barrier. Individual gland secretions help identify gland-specific pathologies; whole saliva supports evaluation of systemic disorders.	(19)
4	Prasad S, Tyagi AK, Aggarwal BB	2016	Review	Detection of inflammatory biomarkers in saliva and urine	Saliva and urine were highlighted as valuable, non-invasive biofluids for detecting inflammatory biomarkers. The review emphasized their potential in diagnosis, prevention, and treatment monitoring of chronic diseases including cancer, diabetes, and cardiovascular disorders.	(20)

5	Nagi R, Reddy-Kantharaj YB, Rakesh N, Janardhan-Reddy S, Sahu S	2016	Systematic Review	Efficacy of light-based detection systems for early detection of oral cancer and potentially malignant disorders	Light-based adjunctive diagnostic systems (VELscope, ViziLite, autofluorescence) enhanced visualization of mucosal changes and helped identify suspicious lesions, but sensitivity and specificity varied widely. They are best used as adjuncts to conventional examination and biopsy rather than standalone diagnostic tools.	(21)
6	Khurshid Z, Haq JA, Khan RS, Zafar MS, Altaf M, Najeeb S	2016	Review Article	Human saliva and its role in oral & systemic health	Saliva was described as a complex biofluid containing proteins, enzymes, electrolytes, growth factors, hormones, DNA, and RNA, playing crucial roles in maintaining oral homeostasis, digestion, antimicrobial defense, and wound healing. It also holds significant diagnostic potential for oral and systemic diseases due to the presence of disease-specific biomarkers.	(22)
7	Kaczor-Urbancowicz KE, Martin Carreras-Presas C, Aro K, Tu M, Garcia-Godoy F, Wong DT	2017	Review Article	Saliva diagnostics – current views and future directions	Saliva was highlighted as a non-invasive diagnostic medium containing proteomic, genomic, transcriptomic, metabolomic, and microbiomic biomarkers. Advances in salivomics, nanotechnology, biosensors, and point-of-care devices have improved detection of oral and systemic diseases, positioning salivary diagnostics as a promising frontier for personalized and preventive medicine.	(23)
8	Khan RS, Khurshid Z, Yahya Ibrahim Asiri F	2017	Review Article	Advancing point-of-care testing using human saliva as liquid biopsy	The review emphasized saliva as a liquid biopsy for point-of-care testing. It described its potential in detecting oral and systemic diseases through molecular biomarkers and highlighted recent advances in biosensors, microfluidics, and lab-on-a-chip technologies that make PoC testing rapid, non-invasive, and cost-effective.	(24)

9	Lakshmi KR, Nelakurthi H, Kumar AS, Rudraraju A	2017	Review Article	Oral fluid-based biosensors for rapid and non-invasive diagnosis	The article discussed the role of saliva as a diagnostic fluid and focused on the development of biosensors for rapid, sensitive, and non-invasive disease detection. It highlighted applications in detecting infectious, systemic, and oral diseases, and emphasized biosensors as promising tools for future chairside diagnostics.	(25)
10	Viswanath B, Choi CS, Lee K, Kim S	2017	Review Article	Diagnostic tools for diabetes mellitus using saliva	The review highlighted saliva as a promising biofluid for non-invasive diabetes monitoring. It discussed salivary biomarkers such as glucose, amylase, and cortisol, along with recent advances in biosensors and lab-on-a-chip technologies, which offer rapid, accurate, and painless diagnostic alternatives to blood-based methods.	(26)

11	Maheswari TU, Venugopal A, Sureshbabu NM, Ramani P	2018	Systematic Review	Salivary microRNA as biomarkers in oral potentially malignant disorders	The review evaluated salivary microRNAs as diagnostic biomarkers for OPMDs. Evidence showed altered expression of specific microRNAs in saliva of affected patients, suggesting their potential for early detection, disease monitoring, and risk prediction of malignant transformation.	(27)
12	Helmerhorst EJ, Dawes C, Oppenheim FG	2018	Review Article	Complexity of oral physiology and its influence on salivary diagnostics	The review emphasized how variability in oral physiology—including flow rate, circadian rhythms, glandular contributions, and protein composition—affects the interpretation of salivary biomarkers. It highlighted the need to account for these physiological factors to improve the reliability and accuracy of saliva-based diagnostics.	(28)

13	Mihaylova Z, Maria G, Bogdan C, Daniela M, Pavel S, Nikolay I, Alexandru IA, Paula P	2018	Review Article	Salivary diagnosis in oral and systemic diseases	The article highlighted saliva as a valuable diagnostic fluid containing proteins, enzymes, hormones, antibodies, and nucleic acids useful in detecting oral diseases (periodontitis, oral cancer, caries) and systemic conditions (cardiovascular, endocrine, infectious, autoimmune). It emphasized saliva's advantages as a simple, non-invasive, and cost-effective diagnostic tool.	(29)
14	Roi A, Rusu LC, Roi CI, Luca RE, Boia S, Munteanu RI	2019	Review Article	Diagnosis of systemic and oral diseases using salivary biomolecule	The review discussed salivary proteins, nucleic acids, metabolites, and microbiota as potential biomarkers for both oral diseases (caries, periodontitis, oral cancer) and systemic conditions (diabetes, cardiovascular, autoimmune, and infectious diseases). It emphasized saliva as a non-invasive medium with high diagnostic value and highlighted emerging technologies like lab-on-a-chip and biosensors for clinical application.	(30)

15	Ilea A, Andrei V, Feurdean CN, Băbțan AM, Petrescu NB, Câmpian RS, Boșca AB, Cîm B, Tertîș M, Săndulescu R, Cristea C	2019	Systematic Review	Saliva as a biofluid for multilevel health assessment	The review highlighted saliva as a "magic biofluid" containing a wide spectrum of biomarkers—proteins, nucleic acids, metabolites, and microbiota—reflecting both oral and systemic health. It emphasized its role in diagnostics, monitoring disease progression, and point-of-care applications using biosensors and lab-on-a-chip technologies.	(31)
16	Bougea A, Keros C, Stefanis L	2019	Systematic Review	Salivary alpha-synuclein as a biomarker for Parkinson's disease	The review evaluated studies on salivary alpha-synuclein and its isoforms in Parkinson's disease patients. Findings showed that decreased total alpha-synuclein and altered oligomeric/total ratios could differentiate patients from healthy controls, suggesting saliva as a promising non-invasive biomarker, though larger standardized studies are needed.	(32)

17	Pay JB, Shaw AM	2019	Review Article	Salivary C-reactive protein as a biomarker of systemic inflammation	The review examined salivary C-reactive protein (CRP) as a potential non-invasive biomarker for systemic inflammation. Evidence indicated a correlation between salivary and serum CRP levels, suggesting its utility for monitoring inflammatory conditions, though standardization of collection and assay methods is necessary for clinical application.	(33)
18	Eftekhari A, Hasanzadeh M, Sharifi S, Dizaj SM, Khalilov R, Ahmadian E	2019	Review Article	Salivary protein bioassays for non-invasive cancer diagnosis	The review focused on saliva-based protein bioassays as alternatives to conventional diagnostic methods for cancer. It highlighted salivary proteins as reliable biomarkers with high diagnostic value, discussed advances in biosensing technologies, and emphasized their potential for early, non-invasive, and cost-effective cancer detection.	(34)

19	Kart Ö, Yarat A	2019	Review Article	Saliva as a diagnostic tool in oral diseases	The review highlighted saliva as a valuable diagnostic medium for oral diseases such as dental caries, periodontitis, and oral cancer. It emphasized the presence of biomarkers including proteins, enzymes, DNA, RNA, and metabolites, and concluded that saliva provides a simple, non-invasive, and reliable tool for early disease detection.	(35)
20	Nijakowski K, Surdacka A	2020	Systematic Review	Salivary biomarkers for diagnosis of inflammatory bowel diseases	The review assessed salivary biomarkers for Crohn's disease and ulcerative colitis. Findings showed elevated inflammatory mediators (such as cytokines, calprotectin, and oxidative stress markers) in saliva of IBD patients, supporting its use as a non-invasive diagnostic tool, though larger standardized studies are required.	(36)

21	Setti G, Pezzi ME, Viani MV, Pertinhez TA, Cassi D, Magnoni C, Bellini P, Musolino A, Vescovi P, Meleti M	2020	Systematic Review	Salivary microRNAs for diagnosis of cancer and systemic diseases	The review analyzed studies on salivary microRNAs as diagnostic biomarkers. Altered expression profiles of specific microRNAs were consistently linked with various cancers (oral, gastric, pancreatic) and systemic conditions, highlighting their potential as highly sensitive and specific non-invasive diagnostic tools.	(37)
22	Derruau S, Robinet J, Untereiner V, Piot O, Sockalingum GD, Lorimier S	2020	Systematic Review	Vibrational spectroscopy of saliva for disease diagnostics	The review evaluated vibrational spectroscopy techniques (Raman and infrared) applied to saliva for diagnostic purposes. Results showed high potential in detecting cancers, diabetes, and infectious diseases through biochemical fingerprinting, supporting saliva spectroscopy as a rapid, non-invasive diagnostic approach, though standardization is needed.	(38)

23	Buzalaf MA, Ortiz AD, Carvalho TS, Fideles SO, Araujo TT, Moraes SM, Buzalaf NR, Reis FN	2020	Review Article	Saliva as a diagnostic tool for dental caries, periodontal disease, and cancer	The review summarized salivary biomarkers for caries, periodontal disease, and oral cancer. While several promising markers (proteins, enzymes, metabolites, DNA, RNA) have been identified, the authors concluded that more robust, validated biomarkers are still needed for reliable clinical application.	(39)
24	Boroumand M, Olinas A, Cabras T, Manconi B, Fanni D, Faa G, Desiderio C, Messina I, Castagnola M	2021	Review Article	Saliva as a bodily fluid with diagnostic applications	The review outlined both established and emerging diagnostic uses of saliva, covering proteomics, peptidomics, metabolomics, and microbiome analysis. It highlighted applications in oral diseases, cancer, systemic conditions, and drug monitoring, emphasizing saliva's versatility as a non-invasive and easily accessible diagnostic fluid.	(40)

25	Yangyang Cui, Mengying Yang	2022	Review Article	Diagnostic applications of saliva in human organ diseases	Saliva is a vital body fluid that reflects both normal physiology and disease states. Rich in biomarkers, it offers a non-invasive, convenient, and reliable tool for health monitoring and disease diagnosis. Increasingly used for detecting systemic conditions and predicting disease progression, saliva's molecular composition and diagnostic value have been widely studied. This review highlights its role in diagnosing disorders of 14 organs, factors influencing salivary diagnostics, and advances such as AI and microfluidic technologies, underscoring its long-term significance in prevention, diagnosis, and treatment.	(41)
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28	Oudah S, Ali IN, Hanan Z	2024	Review Article	Salivary biochemical analysis for diagnosis of systemic and oral diseases	The review focused on salivary biochemical constituents—enzymes, proteins, metabolites, hormones, and nucleic acids—and their diagnostic potential. It highlighted applications in detecting oral diseases (caries, periodontitis, oral cancer) and systemic disorders (diabetes, cardiovascular, autoimmune), emphasizing saliva as a cost-effective, rapid, and non-invasive diagnostic medium.	(44)
29	Khijmatgar S, Yong J, Rübtsamen N, Lorusso F, Rai P, Cenozo N, Gaffuri F, Del Fabbro M, Tartaglia GM	2024	Systematic Review & Network Meta-analysis	Salivary biomarkers for early detection of OSCC and HNSCC	The review and network meta-analysis evaluated salivary biomarkers for diagnosing OSCC and HNSCC. Results showed that markers such as IL-8, IL-6, CD44, Cyfra21-1, and certain microRNAs demonstrated high diagnostic accuracy. The study concluded that salivary biomarkers hold strong potential for early, non-invasive detection of head and neck cancers, though standardization and validation are still required.	(45)

26	Basilicata M, Pieri M, Marrone G, Nicolai E, Di Lauro M, Paolino V, Tomassetti F, Vivarini I, Bollero P, Bernardini S, Noce A	2023	Review Article	Saliva as biomarker for oral and chronic degenerative non-communicable diseases	The review explored saliva's diagnostic potential for oral diseases and chronic degenerative NCDs, particularly chronic kidney disease, highlighting salivary proteomic and microbiome alterations and proposing microbiota modulation via pre-/pro-/syntotics as both diagnostic and therapeutic strategies.	(42)
27	Karunasagar MK, Beela A, Shamala S, Karthick M, Jeyakumar S	2023	Review Article	Salivary biomarkers for systemic and oral diseases	The review emphasized saliva as a promising diagnostic fluid containing biomarkers such as proteins, enzymes, DNA, RNA, and metabolites. It highlighted saliva's role in detecting oral conditions like caries, periodontal disease, and oral cancer, as well as systemic diseases including diabetes and cardiovascular disorders, supporting its use as a simple, rapid, and non-invasive diagnostic tool.	(43)

30	Okuyama K, Yanamoto S	2024	Narrative Review	Role of saliva in oral and systemic health, oral cancer, and beyond	The review discussed saliva's multifaceted role in maintaining oral and systemic health, its diagnostic potential in oral cancer, and emerging applications in broader systemic diseases. It emphasized saliva as a non-invasive medium with biomarker utility and highlighted advances in salivomics, AI-based analysis, and personalized medicine.	(46)
31	Cui L, Zheng J, Lu Y, Lin P, Lin Y, Zheng Y, Xu R, Mai Z, Guo B, Zhao X	2024	Review Article	Salivary extracellular vesicles in oral and systemic diseases	The review highlighted salivary extracellular vesicles (EVs) as emerging tools for diagnostics, disease monitoring, and therapeutics. It discussed EV cargo such as proteins, nucleic acids, and metabolites as biomarkers for oral cancer, systemic diseases, and neurological disorders, and emphasized advances in nanotechnology-based EV detection platforms.	(47)

32	Albagieh H, Alshehri AZ, Alduraywish AS, Aldaws A, AlBalawi SS, Shaqqaf HF, Alnubayi RA, Shaqqaf Sr HF	2025	Review Article	Evaluation of salivary diagnostics for dental and systemic disease detection	The review assessed current applications of salivary diagnostics, highlighting benefits such as non-invasiveness, rapidity, and cost-effectiveness. It discussed biomarkers for oral diseases, cancer, cardiovascular and metabolic disorders, while also noting challenges like variability in saliva composition, standardization of collection, and assay techniques. Future directions emphasized biosensors, salivaomics, and AI-based platforms for clinical translation.	(48)
33	Foroughi M, Torabinejad M, Angelov N, Ojcius DM, Parang K, Ravnan M, Lam J	2025	Review Article	Pathogenesis , biomarkers, and diagnostic innovations in periodontal disease	The review explored the interplay between periodontal and systemic health, focusing on inflammation-driven mechanisms and salivary biomarkers such as cytokines, enzymes, and microbial markers. It highlighted saliva as a promising medium for early detection and monitoring of periodontal disease, and emphasized novel diagnostic innovations including biosensors and point-of-care devices.	(49)

34	Kausar R, Batool A, Bukhari AA, Shaikh AR, Aleem A, Minhas M, Hussain M	2025	Review Article	Salivary diagnostics and personalized medicine in oral pathology	The review highlighted the role of saliva as a non-invasive diagnostic fluid for oral diseases, linking salivary biomarkers with personalized medicine approaches. It emphasized applications in early detection, disease monitoring, and individualized treatment planning, underscoring saliva's potential in precision oral healthcare.	(50)
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