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Salivary Metabolites In Various Oral Diseases: A Review

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Abstract
Background:
Saliva has emerged as a valuable diagnostic fluid due to its non-invasive collection, ease of handling, and rich biochemical composition. It reflects both local and systemic health conditions, offering a promising alternative to blood-based diagnostics in clinical settings.
Objective:
This review aims to summarize and compare the metabolomic alterations observed in saliva across various oral diseases, highlighting their diagnostic relevance and potential clinical applications.
Methods:
A comprehensive literature review was conducted using PubMed, Scopus, and Web of Science databases to identify relevant studies published between 2000 and 2025. Articles were selected based on their focus on salivary metabolomics in the context of oral diseases, including oral squamous cell carcinoma, periodontitis, dental caries, and systemic disorders with oral manifestations.
Results:
Distinct salivary metabolite patterns were identified in multiple oral diseases. Elevated levels of polyamines, choline derivatives, and short-chain fatty acids were observed in conditions such as oral cancer and periodontitis. Conversely, amino acids and glucose were frequently downregulated. These metabolic changes showed meaningful associations with disease presence, severity, and progression, supporting their role as potential diagnostic and prognostic biomarkers.
Conclusion:
Salivary metabolomics holds significant promise as a non-invasive, real-time diagnostic tool for a wide range of oral conditions. While current evidence is encouraging, further validation through standardized, multicentric studies is necessary before routine clinical implementation can be achieved.

Keywords: *Saliva, Metabolomics, Oral cancer, Periodontitis, Dental caries, Biomarkers*

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I. Introduction

Saliva has emerged as a powerful, non-invasive diagnostic medium offering significant potential in the early detection and monitoring of both oral and systemic diseases. It is a complex biological fluid secreted by

major (parotid, submandibular, sublingual) and numerous minor salivary glands, enriched by gingival crevicular fluid, oral epithelial cells, microorganisms, and food debris. Unlike blood or tissue biopsies, saliva collection is painless, cost-effective, and repeatable making it particularly suitable for population-wide screening and longitudinal studies.[1]

The term "salivaomics" encompasses the multiple 'omics' components found in saliva, including the genome, transcriptome, proteome, microbiome, and metabolome. Among these, metabolomics the comprehensive study of small molecule metabolites offers a real-time snapshot of host–microbiome interactions, pathophysiological alterations, and disease-associated biochemical shifts. [1] Salivary metabolomics specifically examines these molecules within the context of oral health, offering valuable insights into inflammatory, neoplastic, and infectious oral conditions. [2]

Recent advances in analytical platforms, including mass spectrometry (MS), nuclear magnetic resonance (NMR), and gas chromatography (GC), have enhanced the sensitivity and specificity of salivary metabolite detection. This progress has catalyzed biomarker discovery for conditions such as oral squamous cell carcinoma (OSCC), periodontal disease, dental caries, and potentially malignant disorders. Despite inter-individual variability and the dynamic nature of the oral environment, salivary metabolomics holds strong promise for integration into clinical workflows. [2]

This review aims to synthesize and evaluate current evidence on salivary metabolites associated with various oral diseases. It highlights methodological advances, key findings, and potential biomarkers while also addressing challenges and future directions. Special emphasis is placed on microbial-derived metabolites, metabolic pathway alterations, and their diagnostic value in oral oncology, periodontology, and cariology.

II. Salivary Metabolomics: Principles And Methods

Saliva is a rich reservoir of diverse low-molecular-weight metabolites, many offering diagnostic clues in both local and systemic diseases. [1] These salivary metabolites include amino acids, organic acids, lipids, polyamines, nucleotides, and carbohydrates. Amino acids like glutamate, valine, and leucine reflect protein degradation and immune responses, while organic acids such as lactate, acetate, and butyrate arise from microbial fermentation and are associated with conditions like dental caries and periodontitis. [2] Lipids and polyamines like cadaverine and putrescine are increasingly studied for their roles in inflammation, microbial dysbiosis, and tumorigenesis. Many of these metabolites are either directly produced by oral microbes or are secreted by host tissues in response to disease progression, especially in disorders like oral squamous cell carcinoma (OSCC), potentially malignant disorders, and inflammatory conditions. [3]

The success of salivary metabolomics largely depends on the quality and consistency of sample collection. Whole-mouth saliva (WMS) is the most commonly analyzed form and can be collected in either an unstimulated or stimulated state. Unstimulated saliva is collected under resting conditions, typically after an hour of fasting, with subjects refraining from oral movements. Stimulated saliva, obtained through gustatory agents or chewing, increases flow but alters its biochemical composition. Saliva may also be obtained directly from major glands (parotid, submandibular, sublingual), though such methods are less convenient. Several pre-analytical variables such as time of collection, hydration, oral hygiene, and recent food intake can significantly influence the metabolite profile. Proper handling includes rapid chilling, centrifugation to remove debris, addition of protease inhibitors, and long-term storage at −80°C to preserve integrity. [3]

Analytical platforms for salivary metabolomics are centered around two principal technologies: nuclear magnetic resonance (NMR) and mass spectrometry (MS). NMR spectroscopy is robust, reproducible, and non-destructive, capable of identifying a broad spectrum of hydrophilic metabolites without the need for extensive sample preparation. However, it lacks the sensitivity of MS. Mass spectrometry, particularly when coupled with separation techniques like liquid chromatography (LC-MS), gas chromatography (GC-MS), or capillary electrophoresis (CE-MS), offers high sensitivity and specificity. LC-MS is ideal for a wide range of non-volatile compounds, whereas GC-MS is better suited for analyzing volatile and thermally stable compounds such as short-chain fatty acids. CE-MS excels in detecting ionic and small polar molecules. These techniques have enabled the identification of disease-specific metabolite patterns, especially in OSCC, periodontitis, and caries. [2-4]

Despite the technological advances, several challenges remain in salivary metabolomics. Inter-individual variability due to genetics, age, gender, microbiota composition, and lifestyle factors can complicate interpretation. Intra-individual factors like circadian rhythms, stress, and hydration also affect metabolite concentrations. [3] Furthermore, the lack of universal protocols for saliva collection, processing, and analysis leads to inconsistencies across studies. The oral cavity's dynamic environment housing host cells, immune components, and microbial biofilms further complicates the task of tracing metabolite origins. Analytical issues such as ion suppression in MS or spectral overlap in NMR can affect quantification accuracy. Consequently, interpretation of results requires careful consideration, and broader clinical application will require standardized methodologies, rigorous validation, and integration with multi-omics approaches for greater diagnostic precision. [4]

III. Salivary Metabolites In Specific Oral Diseases

Oral Squamous Cell Carcinoma (OSCC)

Oral squamous cell carcinoma (OSCC) is a prevalent and often lethal malignancy, characterized by late-stage diagnosis and high recurrence rates. Salivary metabolomics has identified distinct metabolic alterations associated with OSCC, offering promise for early, non-invasive detection. Among the most consistently upregulated salivary metabolites in OSCC are polyamines (e.g., putrescine, cadaverine) and choline derivatives, which are linked to cellular proliferation and membrane turnover. Conversely, amino acids such as valine, leucine, and glutamate are often downregulated, possibly reflecting altered protein metabolism and tumor-induced catabolism. [5]

Several studies have assessed the diagnostic performance of these biomarkers using receiver operating characteristic (ROC) curve analysis, with area under the curve (AUC) values frequently exceeding 0.90, indicating high sensitivity and specificity. For instance, combinations of metabolites such as choline, valine, and polyamines have yielded AUCs in the range of 0.85–0.94, outperforming some traditional blood-based biomarkers. Furthermore, unlike serum or plasma, saliva directly interfaces with the oral tumor microenvironment, potentially offering greater local specificity. Nevertheless, while metabolomic salivary profiles show promise, their clinical translation requires larger multicentric validation and comparison with tissue and blood-based diagnostic platforms. [4]

Periodontal Disease

Periodontal diseases, primarily periodontitis, are chronic inflammatory conditions that damage the supporting structures of the teeth. The inflammatory environment and microbial dysbiosis in periodontitis significantly alter the salivary metabolome. Notably, short-chain fatty acids such as butyrate, acetate, and propionate are elevated in affected individuals, reflecting the activity of anaerobic periodontal pathogens. Similarly, polyamines and certain amino acids including alanine, glycine, and glutamate are found in higher concentrations, likely due to tissue breakdown and bacterial metabolism. [5]

Studies have demonstrated correlations between the levels of these metabolites and clinical parameters such as clinical attachment loss and probing pocket depth, suggesting that salivary metabolomics may serve as an adjunctive tool in grading disease severity and monitoring treatment response. These biomarkers may aid early detection and patient stratification, potentially reducing the burden of advanced periodontitis. [5]

Dental Caries

Dental caries remains one of the most common oral diseases worldwide and is strongly influenced by microbial metabolism. Saliva from caries-active individuals exhibits an acidogenic profile, with increased levels of lactic acid, acetic acid, and propionic acid metabolites produced by cariogenic bacteria such as *Streptococcus mutans* and *Lactobacilli* during carbohydrate fermentation. [5]

These acid by-products contribute to enamel demineralization and cavity formation. The salivary metabolome is particularly sensitive to dietary habits and fluoride exposure. For instance, studies have shown that dietary sucrose intake and low salivary buffering capacity correlate with elevated organic acid concentrations. Additionally, fluoride exposure modulates bacterial metabolism and can shift the salivary metabolite profile towards a less cariogenic state. Thus, metabolomic monitoring could provide a valuable tool for evaluating caries risk and the efficacy of preventive strategies. [5]

Potentially Malignant Disorders (PMDs)

Potentially malignant disorders (PMDs) such as oral leukoplakia, oral submucous fibrosis (OSMF), and oral lichen planus exhibit unique salivary metabolite signatures that reflect early pathophysiological changes. Altered levels of metabolites associated with oxidative stress, including glutathione, uric acid, and lipid peroxidation by-products, have been reported in individuals with PMDs. [6]

These biomarkers may offer valuable early diagnostic potential, as oxidative damage is a known contributor to carcinogenic transformation. Moreover, preliminary evidence suggests that specific metabolite profiles could help predict progression risk, distinguishing high-risk lesions from benign conditions. Salivary metabolomics thus holds potential not only for detection but also for risk stratification and surveillance of PMDs, potentially improving outcomes through earlier therapeutic intervention. [6]

Systemic Diseases with Oral Manifestations

Saliva also reflects systemic metabolic disturbances, making it a useful fluid for detecting oral manifestations of systemic diseases. In diabetes mellitus, studies have consistently found altered salivary levels of glucose, ketone bodies (e.g., β-hydroxybutyrate), and branched-chain amino acids, which are associated with hyperglycemia, insulin resistance, and oral dryness. These changes can contribute to the increased prevalence of periodontal disease and candidiasis among diabetic patients. [6]

In Sjögren's syndrome, a condition marked by autoimmune destruction of salivary glands, reduced concentrations of salivary flow-related metabolites such as urea, phosphate, and electrolytes are commonly observed, often accompanying decreased salivary volume. Beyond these, altered metabolite patterns have also been reported in patients with cardiovascular diseases, gastrointestinal disorders, and autoimmune conditions, supporting the role of saliva as a window to systemic health. [6]

Table 1 :Comparative Table of Key Salivary Metabolites

Disease	Elevated Metabolites	Decreased Metabolites	Diagnostic Accuracy	Reference
OSCC	Choline, Acetate, Polyamines	Glutamate, Histidine, Valine	AUC 0.92	Kashyap et al. (2024)
Periodontitis	Butyrate, Propionate, Alanine	Glucose	Moderate (AUC 0.70–0.80)	Mikkonen et al. (2015)
Dental Caries	Lactic acid, Acetic acid, Propionic acid	Buffering ions (e.g., phosphate)	Emerging data	Pereira et al. (2020)
PMDs	Oxidative stress markers (e.g., Uric acid, MDA)	Antioxidants (e.g., Glutathione)	Potential early markers (needs validation)	Hyvärinen et al. (2023)
Diabetes	Glucose, Ketone bodies, BCAAs	Citrate, Some amino acids	High for combined metabolic profiles	Zhao et al. (2025)
Sjögren's Syndrome	—	Urea, Phosphate, Electrolytes	Good for distinguishing SS from xerostomia	JCM Review (2020)

IV. Future Prospects And Clinical Applications

The future of salivary metabolomics lies in its seamless integration with other high-throughput omics technologies such as proteomics, transcriptomics, and microbiomics, paving the way for a more comprehensive understanding of oral pathophysiology. This multi-omics approach can unravel complex interactions between host responses and microbial activity, identify co-expressed molecular signatures, and enhance the specificity of diagnostic biomarkers. For instance, combining metabolomic and transcriptomic data could help distinguish between benign inflammatory lesions and early-stage malignancies by mapping altered gene–metabolite networks. [6]

An exciting advancement on the horizon is the development of point-of-care salivary diagnostic devices, enabling chairside disease detection without the need for laboratory infrastructure. Portable biosensors, microfluidic chips, and lab-on-a-chip systems are being explored to detect specific salivary metabolites or panels in real-time. These innovations hold great potential in community settings, rural outreach, and early screening programs, particularly for conditions like OSCC and periodontitis, where early diagnosis significantly impacts prognosis. [7]

Moreover, salivary metabolomics offers a promising avenue for personalized oral healthcare. Individual metabolic profiles can guide customized preventive or therapeutic strategies, identify high-risk patients, and tailor interventions based on biological responses rather than one-size-fits-all models. [1] Such precision medicine approaches could revolutionize the management of chronic oral diseases like periodontal disorders or recurrent ulcers, where host susceptibility varies greatly among individuals. [4]

Another key application is in treatment monitoring and recurrence prediction, especially in oral oncology and PMDs. Serial monitoring of salivary metabolite trends can provide dynamic feedback on therapeutic efficacy, detect biochemical relapses earlier than clinical manifestations, and reduce reliance on invasive surveillance tools. Metabolomic shifts may also help in assessing healing trajectories following periodontal therapy or surgical interventions, enhancing the scope of non-invasive follow-up care. [6]

V. Limitations Of Current Studies

Despite the promising potential of salivary metabolomics, several limitations hinder its widespread clinical application. One of the most significant issues is the small sample size in many studies, which limits statistical power and generalizability. Most available data are derived from single-center trials with heterogeneous populations, where variables such as age, gender, diet, oral hygiene, systemic health, and microbiome composition are not uniformly controlled. This variability introduces bias and reduces the reliability of disease-specific metabolic signatures. [7,8]

Another challenge is the lack of standardization in sample collection, processing, and analytical protocols. Differences in salivary stimulation methods, collection timing, use of preservatives, centrifugation speeds, storage conditions, and analytical platforms (e.g., NMR vs. LC-MS) lead to inconsistent findings across studies. This lack of methodological uniformity complicates cross-study comparisons and meta-analyses, slowing the translation of findings into clinical guidelines. [8]

Furthermore, there is a pressing need for longitudinal and multicentric studies to validate salivary metabolite biomarkers over time and across diverse populations. Most current studies are cross-sectional, offering

only snapshots of disease states without capturing dynamic changes during disease progression, remission, or treatment response. Multicentric research can also help standardize protocols, minimize geographic or ethnic bias, and support regulatory approval of salivary diagnostics for clinical use. [9]

VI. Discussion

Salivary metabolomics has emerged as a valuable approach for exploring disease-specific biochemical changes in oral health and systemic conditions with oral manifestations. [1] Across diseases like OSCC, periodontitis, dental caries, and PMDs, distinct metabolite signatures have been consistently reported ranging from elevated polyamines and short-chain fatty acids to reduced amino acids and antioxidants. [10]

These findings underscore the utility of saliva as a diagnostic fluid, especially due to its ease of collection and proximity to oral lesions. Importantly, many salivary metabolites reflect both host and microbial activity, making them sensitive indicators of pathophysiological changes. [10] However, variability in study design, sample handling, and analytical platforms limits comparability and reproducibility of results across studies. [3]

Furthermore, while some salivary biomarkers have shown strong diagnostic potential (e.g., ROC AUC > 0.90 in OSCC studies), few have undergone clinical validation or regulatory approval. The integration of metabolomics with proteomic and transcriptomic data could improve specificity and move salivary diagnostics closer to routine practice. [11]

This review highlights the need for standardized methodologies and larger, well-controlled studies that account for confounding factors like diet, microbiome composition, and systemic health. Ultimately, the success of salivary metabolomics will depend on its translation from exploratory research to practical, point-of-care applications that support personalized oral healthcare.[12]

In conclusion, salivary metabolomics bridges the gap between molecular insights and clinical applicability, heralding a future of precision diagnostics in oral healthcare.meta

VII. Conclusion

Salivary metabolomics represents a powerful, non-invasive diagnostic tool with immense potential for the early detection, monitoring, and personalized management of various oral diseases. By capturing dynamic biochemical alterations linked to conditions such as oral cancer, periodontal disease, dental caries, and potentially malignant disorders, salivary metabolite profiling offers a real-time window into both local and systemic pathophysiological processes. [12] Its ease of collection, patient comfort, and compatibility with high-throughput analytical platforms make saliva an ideal alternative to blood or tissue-based diagnostics. [13]

Despite these advantages, the field still requires robust clinical validation. Larger, multicentric, and longitudinal studies are necessary to confirm the reliability and reproducibility of identified biomarkers across diverse populations. [13] Additionally, the standardization of protocols from sample collection to data analysis is crucial to enable meaningful comparisons and support regulatory acceptance. [14]

Looking ahead, with continued advancements in technology, integration of salivary metabolomics into routine dental and medical practice is a realistic and promising goal. This integration will pave the way for precision oral healthcare, enabling clinicians to detect disease earlier, tailor interventions to individual metabolic profiles, and monitor treatment responses non-invasively, ultimately improving patient outcomes and reducing healthcare burdens. [15]

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