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Saliva metabolomics: a non-invasive frontier for diagnosing and managing oral diseases

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Abstract

Salivary metabolomics represents a powerful noninvasive approach for diagnosing, monitoring, and managing oral diseases, providing valuable insights into the metabolic alterations associated with conditions such as oral cancer, oral precancerous lesions, periodontal diseases, and dental caries. Through the comprehensive analysis of salivary metabolites, this methodology facilitates the identification of disease-specific biomarkers reflective of underlying pathophysiological processes, including inflammation, microbial dysbiosis, and metabolic reprogramming. Despite its promising clinical potential, several significant challenges remain, notably the difficulty in establishing direct associations between specific salivary metabolites and distinct disease mechanisms, considerable inter-individual variability, and the inherent complexity of the oral microenvironment. Furthermore, issues related to data interpretation complexity, technological constraints, and the necessity for rigorous clinical validation continue to impede its broader clinical adoption. Nevertheless, ongoing advancements in analytical technologies and bioinformatics approaches hold considerable promise for addressing these limitations, positioning salivary metabolomics as a transformative tool for precision diagnosis and personalized treatment in oral health care.

Keywords Oral diseases, Saliva metabolites, Metabolomics, Early diagnosis, Disease monitoring

Introduction

Early and accurate diagnosis of oral diseases—particularly oral cancer, periodontal disease, and dental caries—is critical for improving patient prognosis and guiding timely therapeutic interventions. However, many oral diseases progress insidiously and often present with non-specific or subclinical symptoms in the early stages, making timely detection and monitoring particularly challenging in routine clinical practice [1, 2]. Conventional diagnostic approaches, such as tissue biopsy and radiographic imaging, are often invasive and may fail to capture dynamic pathological changes, limiting their utility for early detection and longitudinal assessment. Consequently, there is an urgent need for reliable, non-invasive biomarkers that can detect disease onset, monitor progression, and evaluate treatment responses with high sensitivity and specificity. Such biomarkers could not only facilitate earlier intervention but also improve therapeutic decision-making, enhance patient outcomes, and reduce healthcare costs through more efficient disease management.

Saliva metabolomics offers a compelling alternative to traditional diagnostic techniques, particularly in its ability to capture the metabolic alterations associated with oral diseases. As a noninvasive and readily accessible biofluid, saliva reflects both local oral pathology and systemic physiological changes [3–6]. Unlike blood or tissue samples, which may not fully represent oral-specific processes, saliva metabolomics offers a comprehensive view of the biochemical activities within the oral cavity,

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including interactions between the oral microbiome, immune system, and host metabolism. The analysis of salivary metabolites can uncover critical insights into disease pathways, such as the onset of inflammation, microbial dysbiosis, and shifts in metabolic networks—all of which are essential for understanding the progression of oral pathologies. Additionally, saliva collection is painless and suitable for repeated, longitudinal sampling, making it ideal for tracking disease dynamics and treatment responses without the need for invasive procedures [3, 7, 8].

In this review, we explore the potential of saliva metabolomics for diagnosing and monitoring oral diseases, focusing on its capacity to identify biomarkers for early detection, disease progression, and therapeutic assessment. The advantages of using saliva as a diagnostic medium are examined, along with key methodologies in metabolomic profiling and emerging metabolite-based biomarkers associated with oral pathological conditions such as oral cancer, periodontal diseases, and caries. Additionally, challenges hindering the clinical application of saliva metabolomics are discussed, including the complex composition of saliva, individual variability, and the need for comprehensive clinical validation.

The multifaceted advantages of saliva as a diagnostic tool for oral diseases

Saliva possesses distinct advantages as a diagnostic medium for oral diseases, surpassing traditional biofluids such as blood, tissue, and other body fluids in several key aspects [9]. Its unique interaction with the oral environment, coupled with its ease of collection and comprehensive biochemical representation, renders saliva a versatile and effective tool for understanding, diagnosing, and monitoring oral diseases [10]. Unlike blood, which reflects systemic changes diluted by various physiological processes, saliva directly interacts with the oral mucosa, teeth, and microorganisms, capturing localized metabolic and microbial changes with high specificity. This specificity facilitates the early detection of oral diseases at their point of origin, which may be missed by tissue biopsies limited to localized sampling sites [11]. Moreover, saliva's capacity to capture the continuous interaction between host and microbial activity offers a holistic view of oral disease progression [12]. Additionally, saliva collection is painless, simple, and non-invasive, avoiding the discomfort and risks associated with blood draws or tissue biopsies. This makes it particularly suitable for vulnerable populations such as children, elderly patients, or individuals with compromised immune systems [13]. The non-invasive nature also enables frequent sampling for longitudinal studies or monitoring the efficacy of interventions, which is challenging with tissue biopsies or other invasive methods [14]. Moreover, saliva not only reflects local oral changes but also serves as a window into systemic health. It contains a rich array of biomarkers, including metabolites, cytokines, hormones, and nucleic acids, that link oral diseases with systemic conditions such as diabetes, cardiovascular disease, and autoimmune disorders [15–17] (Fig. 1).

Notably, saliva is a reservoir of diverse biomolecules, from small metabolites to DNA and RNA, offering a multi-dimensional diagnostic platform [18]. Unlike blood, which may require specialized anticoagulants or stabilization protocols, saliva is easier to process and store. Tissue samples, while rich in site-specific information, are invasive to obtain and often lack the dynamic metabolic data present in saliva. Saliva's molecular diversity enables its application across a wide spectrum of oral diseases, from identifying early metabolic shifts in precancerous lesions to monitoring microbial dysbiosis in periodontitis [19]. Moreover, saliva's composition dynamically reflects real-time physiological and pathological changes, making it an ideal medium for monitoring disease progression or treatment response [20]. For example, in patients undergoing non-surgical periodontal therapy, salivary metabolomics can track residual inflammation and metabolic restoration, offering insights into therapy success and areas requiring further intervention [21]. The simplicity and cost-effectiveness of saliva collection make it highly scalable for population-level screening and research. Portable collection devices and advances in on-site analysis tools, such as point-of-care diagnostics, enhance its accessibility in low-resource settings [22]. Furthermore, advancements in technologies such as high-throughput metabolomics, proteomics, and next-generation sequencing have significantly enhanced the diagnostic potential of saliva. Sophisticated analytical platforms like nuclear magnetic resonance (NMR) spectroscopy and liquid chromatography-mass spectrometry (LC–MS) enable the detection of subtle metabolic changes with high sensitivity. This precision is particularly valuable for early-stage disease detection, providing insights into conditions such as oral cancer and precancerous lesions [23].

To facilitate the clinical implementation of salivary metabolomics, standardized protocols for sample collection, processing, and analysis have been established to ensure reproducibility and minimize technical variability [24, 25]. Typically, unstimulated saliva is collected in the morning following a fasting period using low-binding tubes, immediately cooled, centrifuged to remove cellular debris, and stored at − 80 °C. Stable-isotope internal standards and pooled quality control samples are incorporated to monitor instrument

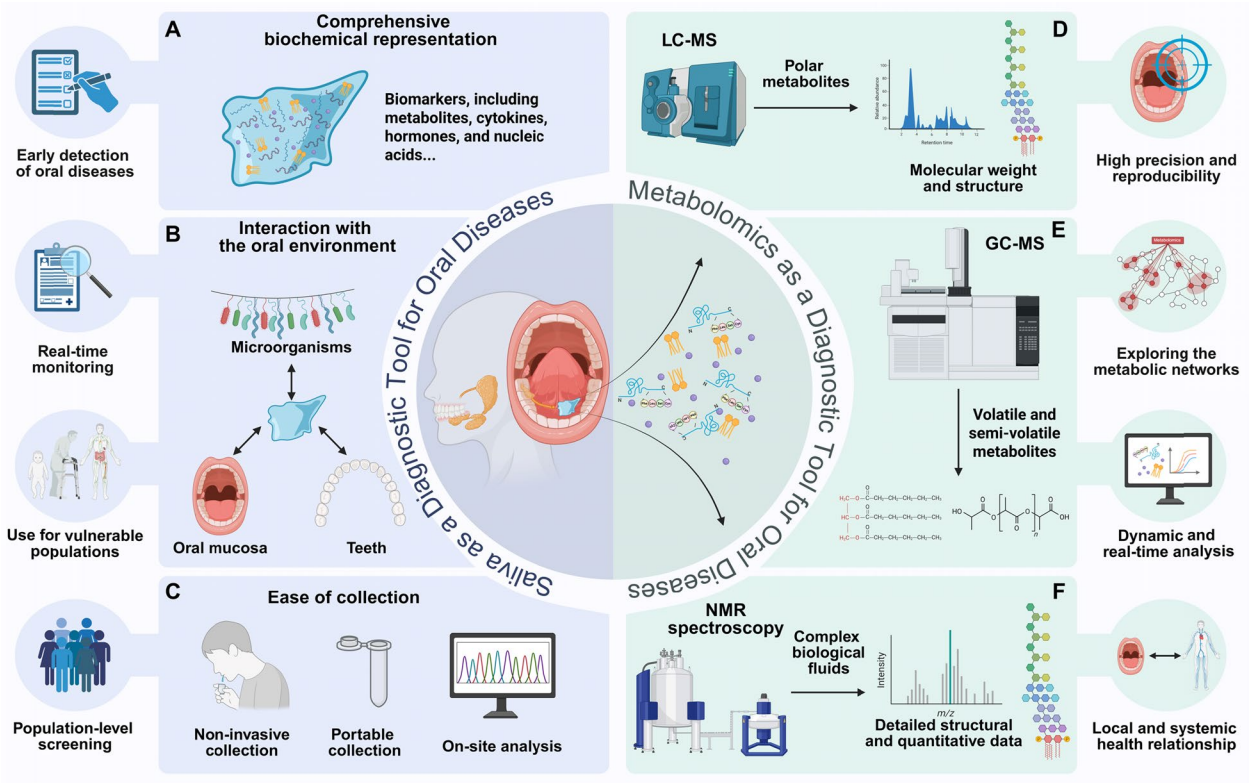

Fig. 1 The multifaceted advantages of saliva and metabolomics as a diagnostic tool for oral diseases. **A–C** Saliva contains a wide range of biomarkers and interacts continuously with the oral microenvironment, providing a readily accessible, non-invasive medium for early disease detection, real-time monitoring, and large-scale screening. **D–F** Metabolomics, as a diagnostic approach, employs advanced techniques such as LC–MS, GC–MS, and NMR spectroscopy. Each method targets specific categories of metabolites, delivering high precision and reproducibility. These approaches enable the visualization of complex metabolic networks and facilitate dynamic monitoring of disease progression. Notably, it not only captures localized oral changes but also reflects systemic health

performance and correct for batch effects, with data normalization strategies such as probabilistic quotient normalization or total ion current normalization applied in accordance with the Metabolomics Standards Initiative (MSI). Salivary metabolite profiling can be performed using both untargeted and targeted approaches. Untargeted platforms, such as hydrophilic interaction liquid chromatography coupled with high-resolution mass spectrometry and gas chromatography–mass spectrometry (GC–MS), enable broad-spectrum detection of metabolic features without prior selection [26]. Targeted methods, including liquid chromatography–tandem mass spectrometry in multiple reaction monitoring mode and proton NMR spectroscopy, offer high precision and quantification of predefined metabolites, making them well suited for clinical validation and multicenter studies [27]. These standardized methodologies provide a robust analytical foundation for the reliable identification of salivary biomarkers across diverse oral disease contexts.

Overview of metabolomics

Metabolomics is the systematic study of all metabolites present in a biological sample, such as amino acids, lipids, sugars, and organic acids. It aims to provide a comprehensive analysis of the dynamic changes in metabolites, offering insights into biological processes, disease mechanisms, and drug responses. By capturing the full spectrum of metabolites within a biological system, metabolomics provides critical insights into the biochemical pathways that underpin health and disease, thereby supporting early disease detection, guiding therapeutic interventions, and advancing personalized medicine [28–30].

The core principle of metabolomics lies in the qualitative and quantitative analysis of metabolites using advanced analytical techniques. These techniques, such as LC–MS, GC–MS, and NMR spectroscopy, are employed to measure changes in metabolite levels across various biological conditions [31, 32]. LC–MS combines liquid chromatography, which separates metabolites based on their physical and chemical properties, with

mass spectrometry, which provides information about the molecular weight and structure of the metabolites. This method is particularly effective for analyzing polar metabolites and those that are difficult to isolate [33–35]. GC–MS, on the other hand, is best suited for analyzing volatile and semi-volatile metabolites, such as fatty acids and organic acids, providing high resolution and sensitivity [36, 37]. NMR spectroscopy is a non-destructive method that can provide detailed structural and quantitative data about metabolites. Unlike mass spectrometry, NMR spectroscopy does not require prior sample separation, making it well-suited for the analysis of complex biological fluids. It is particularly advantageous for detecting high-abundance metabolites and for elucidating metabolic networks in living systems [38, 39].

Metabolomics can be categorized into targeted and untargeted approaches, each serving distinct purposes in metabolic analysis. Targeted metabolomics involves the analysis of a predefined set of metabolites, focusing on known biomarkers or specific metabolic pathways. This approach is characterized by its high precision and reproducibility, as it targets a limited number of metabolites, often using internal standards for accurate quantification. Targeted metabolomics is ideal for absolute quantification, providing precise concentration measurements of specific metabolites. It is particularly useful for hypothesis testing, disease monitoring, and tracking metabolic alterations associated with specific conditions or therapeutic interventions. Furthermore, this approach is well-suited for validating previously identified biomarkers and ensuring the consistency and reliability of findings across different samples and conditions [40–42]. In contrast, untargeted metabolomics entails the comprehensive and unbiased profiling of all detectable metabolites within a biological sample, without reliance on predefined selection criteria. This approach offers a holistic view of the metabolic landscape, making it particularly valuable for investigating the complexity of metabolic networks and uncovering previously unrecognized metabolic alterations associated with disease. Although it is less focused on absolute quantification, untargeted metabolomics provides exceptional discovery potential, yielding insights into novel disease mechanisms and facilitating the identification of new therapeutic targets [43–45]. One of the key characteristics of metabolomics is its high sensitivity and resolution. Techniques such as LC–MS and NMR can detect metabolites at very low concentrations, allowing for the identification of early-stage biochemical changes that may not be detectable by other methods [46]. Moreover, metabolomics provides a dynamic and real-time analysis of metabolic changes, making it ideal for monitoring disease progression, therapeutic responses, and environmental influences on metabolic processes. This dynamic nature distinguishes metabolomics from static analyses like genomics or proteomics, which provide valuable but more fixed snapshots of biological systems [47, 48]. Metabolomics also plays a critical role in understanding the relationship between local and systemic health. By analyzing metabolites in body fluids, it is possible to detect subtle shifts that reflect systemic changes or the impact of oral health on overall well-being. Importantly, high-throughput metabolomics enables large-scale studies that analyze multiple samples simultaneously, making it possible to discover biomarkers for early diagnosis, prognosis, and treatment monitoring. These studies can be used to explore disease mechanisms, identify therapeutic targets, and track changes in metabolic networks. Additionally, advances in bioinformatics and statistical modeling enable the extraction of meaningful insights from complex datasets, facilitating the identification of novel biomarkers and metabolic pathways that might otherwise remain undetected [49].

The reliability of salivary metabolomic biomarkers is influenced by both biological and technical variability. Biologically, individual factors such as age and sex affect baseline metabolic profiles due to differences in hormonal regulation, immune function, and salivary gland physiology. Circadian rhythms also contribute to diurnal variations in salivary composition, with measurable changes in amino acids, cortisol, and other metabolites observed throughout the day [50]. Dietary habits and recent food intake can result in short-term fluctuations in salivary metabolite levels, particularly affecting concentrations of glucose, lipids, and short-chain fatty acids [51]. In addition, systemic health conditions such as diabetes, cardiovascular diseases, and autoimmune disorders may alter salivary metabolite composition by modulating systemic inflammatory and metabolic responses [52]. Salivary flow rate, influenced by hydration status, medication use, and autonomic regulation, affects the dilution and concentration of metabolites. Furthermore, the oral microbiome can produce microbial-derived metabolites that vary between individuals and confound host-derived biomarker signals [53]. On the technical side, variability may arise from differences in sample collection timing, handling, storage conditions, and instrument performance. These biological and technical factors must be carefully controlled and accounted for to ensure the reproducibility and translational relevance of salivary metabolomic biomarkers [54]. Importantly, robust validation across large, well-characterized cohorts is essential to confirm the reproducibility, diagnostic accuracy, and clinical applicability of candidate salivary biomarkers.

Salivary metabolomics for oral disease diagnosis and management

Oral diseases, ranging from precancerous lesions to chronic inflammation, often involve subtle metabolic and microbial shifts that are critical for early detection and intervention [55]. Salivary metabolomics, by analyzing the biochemical and microbial profiles in saliva, offers a non-invasive and highly sensitive approach to identifying biomarkers, monitoring disease progression, and assessing treatment efficacy [56, 57]. This method provides a dynamic tool for improving the understanding and management of oral health conditions, complementing traditional diagnostic techniques and offering new opportunities for clinical application (Table 1).

Oral precancerous lesions (OLP)

Oral precancerous lesions subtly reshape the local oral environment, making saliva metabolites effective for early detection and monitoring [58]. These lesions alter epithelial integrity and induce localized inflammation, leading to the release of metabolic byproducts such as oxidative stress markers and inflammatory mediators into saliva [59] (Fig. 2A). The increased epithelial activity and metabolic remodeling in precancerous tissues result in the accumulation of disease-specific metabolites in saliva, capturing early pathological changes prior to systemic manifestation. For instance, salivary metabolomic profiling in patients with asymptomatic OLP reveals elevated levels of acetate, methylamine, and pyruvate, along with decreased tyrosine concentrations compared to healthy controls. Multivariate analysis identifies methylamine and tyrosine as potential biomarkers for distinguishing OLP. These findings suggest that salivary metabolites, particularly tyrosine, could serve as non-invasive biomarkers for early detection and monitoring of OLP progression [60]. Similarly, ultra-performance liquid chromatography coupled with high-resolution mass spectrometry identified 19 salivary metabolites differentiating OLP patients from healthy controls, including amino acid and lipid metabolites. A biomarker panel of three metabolites achieved diagnostic utility, revealing metabolic disruptions associated with OLP progression and highlighting potential pathways for early detection and understanding of its pathology [61]. Multi-omics analysis reveals significant shifts in the oral microbiome and metabolome of OLP patients compared to healthy controls. Increased abundance of specific bacterial genera such as *Pseudomonas* and distinct saliva metabolites correlates with OLP's clinical features, suggesting microbial and metabolic components in its pathogenesis and potential for diagnostic biomarkers [62] (Fig. 2B). Additionally, salivary metabolomic profiling identifies key metabolites, including guanine, carnitine, and N-acetylputrescine, as potential biomarkers to differentiate oral leukoplakia from healthy controls, achieving high diagnostic accuracy. Additionally, 7-methylguanine distinguishes dysplastic from non-dysplastic OLP with moderate discrimination ability [63].

Oral cancer

Oral cancer is characterized by profound metabolic reprogramming, distinguishing it from precancerous lesions and highlighting the value of saliva as a diagnostic medium in advanced disease [64]. Malignant tumors undergo extensive metabolic reprogramming, such as enhanced glycolysis, altered amino acid pathways, and lipid peroxidation, which result in a distinct biochemical profile detectable in saliva [65, 66, 67]. Furthermore, the invasive behavior of oral cancer disrupts vasculature and surrounding tissues, facilitating the release of tumor-specific metabolites and inflammatory mediators into the oral cavity. These cancer-driven alterations establish a unique saliva metabolic signature that closely mirrors disease progression and therapeutic response, providing a minimally invasive yet highly effective approach for monitoring malignancy [68]. Beyond serving as a diagnostic tool, saliva metabolites may actively contribute to oral cancer pathogenesis, saliva from oral squamous cell carcinoma (OSCC) patients, enriched in kynurenic acid (KYNA) and colonized by *Streptococcus mutans*, fosters OSCC progression in rat models. KYNA alters the tumor microenvironment, boosting immunosuppressive neutrophils and inducing $CD8^+$ T cell exhaustion, undermining PD-L1 and IL-1β blockade therapies. These findings suggest targeting oral microbiota and metabolites could enhance OSCC treatments and prevention [69] (Fig. 2C, D). Additionally, saliva metabolomics reveals metabolic alterations in OSCC induced by dibenzo[def,p]pyrene (DB[a,l]P) in a mouse model. Untargeted LC–MS/MS profiling identifies significant enrichment of phosphatidic acid, a known mammalian target of rapamycin complex (mTORC) activator, and disruptions in lipid metabolism pathways [70]. Importantly, saliva metabolomics has shown great promise in the detection, prognosis prediction and treatment monitoring in oral cancer [71, 72]. For instance, saliva metabolomics in Japanese patients with OSCC identified 25 discriminatory metabolites, including choline, branched-chain amino acids, urea, and 3-hydroxybutyric acid. These findings highlight metabolic disruptions in OSCC and suggest potential biomarkers for non-invasive diagnosis [73]. Similarly, salivary metabolomic analysis identifies *N*-acetyl-D-glucosamine, L-pipecolic acid, and L-carnitine as key biomarkers for tongue squamous cell carcinoma, with a combination of these metabolites achieving an area under the curve

Table 1 Application of saliva metabolomics in the early detection and monitoring of oral diseases

Disease	Saliva Metabolites	Methods	Clinical application	Refs.
OLP	Acetate, methylamine, pyruvate, tyrosine	UPLC-HRMS	Early detectors of OLP	[60]
WSLs	Proline, glycine	16S rRNA-seq UPLC-MS/MS	Biomarkers of WSLs	[115]
OSCC	Kynurenic acid	UPLC-MS/MS	OSCC preventions and therapeutics	[69]
OSCC	Phosphatidic acid	LC–MS/MS	Early detection and cancer interception	[70]
OSCC	Choline, urea, 3-hydroxybutyric acid	CE-MS	Non-invasive diagnosis	[73]
TSCC	*N*-acetyl-D-glucosamine, L-pipecolic acid, L-carnitine	LC–MS	Disease monitoring and prognosis	[74]
OSCC	Malic acid, maltose, protocatechuic acid, catechol	GC–MS	Assistance in the identification of oral cancer salivary biomarkers	[75]
OSCC	Glycine, proline	NMR, LC–MS/MS, LC-Q-TOF	Early diagnosis	[76]
OSCC	1-Methylhistidinesphinganine-1-phosphate, ubiquinone	Q-TOF, LC–MS	Preventing malignant transformation of OLK	[78]
HNC	N1-acetylspermine	LC–MS/MS	Early diagnosis	[81]
HNSCC	Fucose, proline, 1,2-propanediol	NMR spectroscopy	Point-of-care platforms for HNSCC	[82]
OSCC	Indole-3-acetate, ethanolamine	Logistic regression	Non-invasive screening of OSCC and OLP	[84]
OSCC	Decanedioic acid, l-proline, pentanoic acid	GC–MS	Early diagnosis and prediction	[85]
Periodontitis	Tryptophan, phenylalanine	CPSI-MS	Preclinical screening of SP	[88]
Periodontitis	Ethanol, taurine, isovalerate, butyrate, glucose	1H-NMR spectroscopy	Periodontal screening, detection, and monitoring	[89]
AgP	Pyruvate, lactate, proline, phenylalanine, tyrosine	NMR spectroscopy	Distinguishing chronic and aggressive periodontitis	[90]
Periodontitis	Phenylacetate	UHPLC-MS/MS	Early intervention in the initial stage of periodontitis	[91]
Periodontitis	2-Pyrrolidineacetic acid, butyrylputrescine	UPLC-MS/MS	For self-screening of periodontitis	[92]
Generalized periodontitis	Lactate, pyruvate, tyrosine	NMR spectroscopy	Using to monitor treatment stages	[21]
Periodontitis	Tryptophan, glutathione	16s rRNA-seq	Potential tool in the diagnosis and prognosis evaluation of periodontitis	[94]
Active carious	Taurine, mannose	NMR spectroscopy	Advancing personalized approaches to dental caries prevention	[99]
Caries	Histamine, l-histidine, succinate	LC–MS/MS	Biomarkers for monitoring the treatment effects of dental caries	[100]
SECC	2-benzylmalate, epinephrine, 3-Indoleacrylic acid	16S rRNA seq	Future strategies for personalized caries	[101]
BMS	Paraxanthine, theophylline	UPLC-Q-TOF–MS	Potential therapeutic approaches for BMS	[104]
Primary BMS	L-dopa, l-tyrosine, tyramine	LC/MS	Early diagnosis	[105]
Idiopathic xerostomia	Caffeine	UPLC-QTOF- MS	Developing diagnostic markers and therapeutic strategies	[107]
pSS	Pyrimidine nucleotides, nucleosides	LC–MS	Biomarkers for diagnosis and treatment	[126]
M-TMD	Phenylacetate, dimethylamine, maltose, acetoin, isovalerate	^{1}H-NMR	Diagnosing and monitoring treatment for musculoskeletal disorders	[109]
Apical root resorption	Butyrate, fumarate, α-linolenic acid	^{1}H NMR	Early diagnosis and monitoring	[114]
WSLs	Proline, glycine	16S rRNA-seq UPLC-MS/MS	Biomarkers for the diagnosis and treatment of WSLs	[115]
Oral candidiasis	Tyrosine, choline, phosphoenolpyruvate	CE-TOF–MS	Verification of Candida presence	[110]
Halitosis	5-aminovaleric acid, *N*-acetylornithine	16S rRNA-seq	Identification of halitosis	[111]
RAU	Estrone sulfate, dehydroepiandrosterone sulfate	LC–MS/MS	Potential diagnostic utility	[112]
RIOM	Histidine, tyrosine	CE-TOF–MS	Predicting the severity of OM	[113]

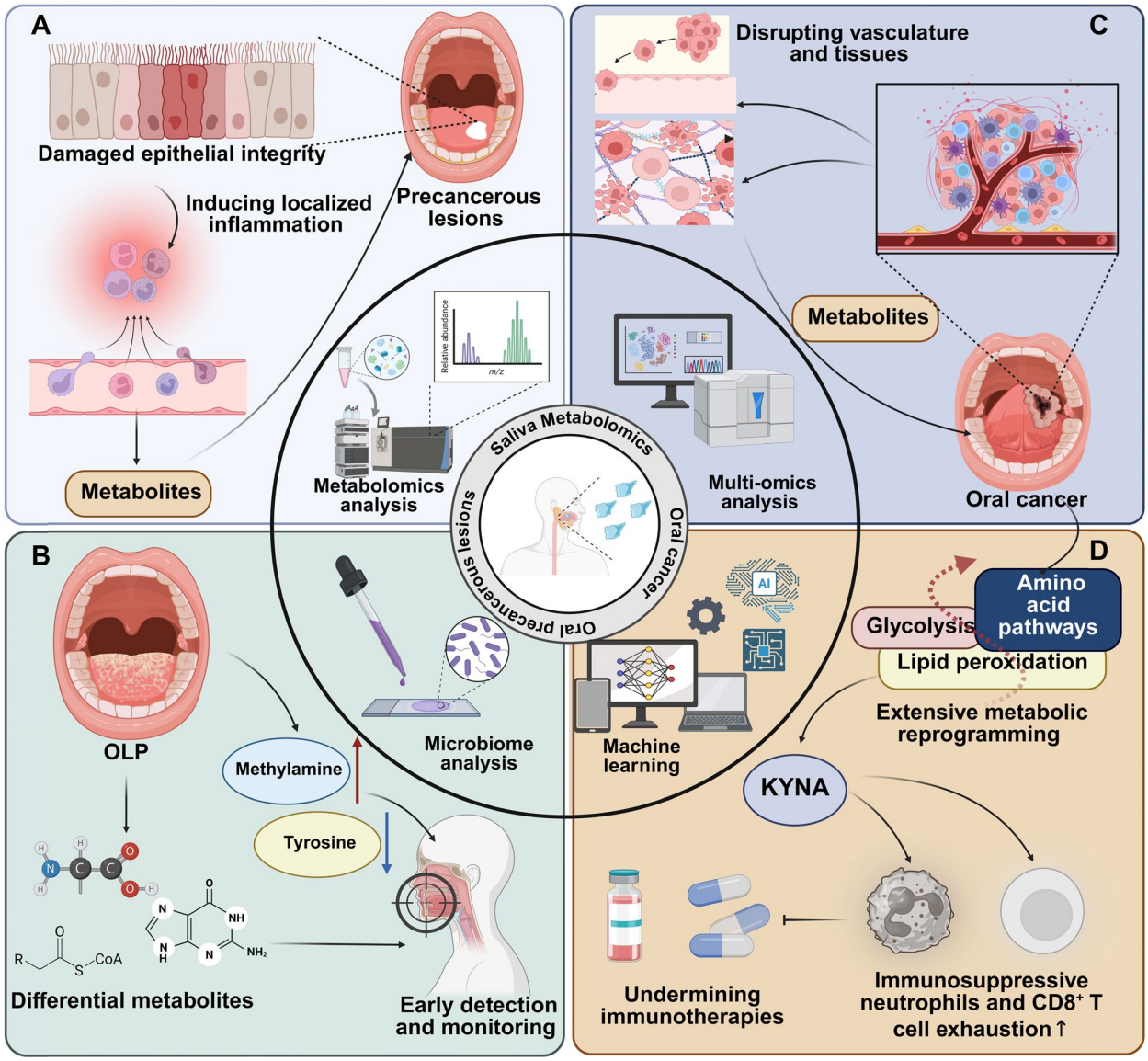

Fig. 2 Salivary metabolomics in the diagnosis and management of oral precancerous lesion and oral cancer. **A** In oral precancerous lesions, epithelial damage disrupts barrier integrity, leading to the release of metabolic byproducts into saliva. **B** Microbiome and metabolomic analyses identify differential metabolites, enabling early detection and monitoring. **C** In oral cancer, disrupted tissue and vasculature facilitate the release of tumor-specific metabolites and inflammatory mediators into the oral cavity, resulting in a distinct biochemical profile detectable in saliva. **D** Saliva from OSCC patients, enriched with KYNA, promotes immunosuppressive neutrophil activity and induces $CD8^+$ T cell exhaustion, compromising the efficacy of PD-L1 and IL-1β blockade therapies

(AUC) of 0.901 [74]. Additionally, metabolic profiling of OSCC identified key pathways, including the malate-aspartate shuttle, beta-alanine metabolism, and the Warburg effect. Salivary metabolites such as malic acid, maltose, protocatechuic acid, and catechol demonstrated high diagnostic potential [75]. Moreover, saliva metabolomics reveals distinct metabolite profiles in oral cavity squamous cell carcinoma (OCC), identifying glycine and proline as significantly altered in OCC compared to controls. Four metabolites, including glycine and proline, correlate with early-stage OCC. No significant metabolite differences were found in oral potentially malignant conditions (OPC) vs. controls or OCC with vs. without nodal metastasis. These findings highlight the potential of salivary metabolites as biomarkers for OCC detection and early-stage diagnosis [76]. An integrated LC/MS approach identified 14 salivary metabolites for the early diagnosis of OSCC. Five biomarkers—propionylcholine,

N-acetyl-L-phenylalanine, sphinganine, phytosphingosine, and *S*-carboxymethyl-L-cysteine-yielded high diagnostic accuracy (AUC =0.997), sensitivity (100%), and specificity (96.7%) in distinguishing early-stage OSCC from controls [77]. Likewise, salivary metabolomics revealed significant upregulation of metabolites such as 1-methylhistidine and sphinganine-1-phosphate in oral leukoplakia and OSCC, with downregulation of l-homocysteic acid and ubiquinone. These findings highlight the potential of salivary metabolites as biomarkers for early detection, malignant transformation prevention, and improved prognosis in oral cancer [78]. Conductive polymer spray ionization mass spectrometry (CPSI-MS) combined with machine learning distinguishes OSCC and premalignant lesions from healthy conditions with 86.7% accuracy. Dysregulated metabolites identified in saliva were validated at the tissue level using desorption electrospray ionization MS imaging, confirming altered metabolic pathways. Integrated metabolomic profiling of saliva and tumor tissues identified 17 overlapping metabolites differentiating oral cancer from controls, with two biomarkers achieving high diagnostic accuracy. This approach refines biomarker discovery by eliminating coincidental differences, advancing non-invasive screening for oral cancer [79]. Interestingly, salivary metabolite profiles correlated significantly with SUVmax in 18 F-fluorodeoxyglucose positron emission tomography/computed tomography (18 F-FDG PET/CT) among oral cancer patients, with 11 metabolites linked to delayed-phase maximum standardized uptake value (SUVmax). A logistic regression model utilizing two metabolites distinguished oral cancer patients from controls with an AUC of 0.738. These findings suggest salivary metabolites as potential non-invasive screening markers for identifying oral cancer patients with elevated SUVmax [80]. Notably, polyamine metabolites, including N1-acetylspermine (ASP), N8-acetylspermidine, and N1, N12-diacetylspermine, were quantitatively assessed using targeted metabolomics in the saliva and urine of head and neck cancer (HNC) patients. Elevated levels of ASP were detected in both saliva and urine from HNC patients compared to healthy controls. These results suggest that polyamine metabolites could serve as potential non-invasive biomarkers for the early diagnosis of HNC [81]. NMR spectroscopy identified significant salivary metabolic changes in head and neck squamous cell carcinoma, including elevated fucose and 1,2-propanediol and decreased proline levels. A biomarker combination of fucose, glycine, methanol, and proline achieved 92.1% classification accuracy, highlighting fucose as a potential diagnostic marker [82]. Alterations in saliva metabolite profiles are strongly associated with OSCC prognosis. Comprehensive salivary metabolomic analysis identified 3-methylhistidine as a significant prognostic factor for overall survival in OSCC. Elevated levels of 3-methylhistidine were associated with poorer outcomes, highlighting its potential as a non-invasive biomarker for predicting OSCC prognosis and guiding clinical management [83]. Importantly, profiling salivary metabolites effectively differentiates oral cancer from oral precancerous legions. For instance, salivary metabolomics identified indole-3-acetate and ethanolamine phosphate as key markers distinguishing OSCC from OLP, achieving high diagnostic accuracy [84]. Similarly, metabolic profiling using GC–MS identified 15 salivary metabolites, including decanedioic acid, l-proline, and pentanoic acid, that differ significantly among OSCC, OLK, and healthy controls. These metabolites demonstrate potential as tumor-specific biomarkers for early diagnosis and prediction of OSCC and OLK [85].

Periodontal diseases

Periodontal diseases lead to significant metabolic changes in the oral environment, driven by microbial imbalance, inflammation, and tissue destruction. These alterations are mirrored in saliva, which directly reflects the condition of the periodontal tissues. Inflammatory markers, proteases, and lipid peroxidation products released during disease progression can be detected in saliva, making it a valuable medium for monitoring periodontal disease. Saliva metabolomics offers the potential to identify biomarkers linked to microbial shifts and host immune responses, facilitating early detection, real-time monitoring, and evaluation of treatment efficacy in periodontal diseases. For instance, salivary metabolite profiling using ^{1}H-NMR spectroscopy reveals distinct metabolic signatures associated with early gingival inflammation, as indicated by the full-mouth bleeding score. Specific metabolites linked to enzymatic activities of oral bacteria may serve as indicators of preclinical gingivitis, distinguishing individuals with early inflammatory changes. This approach suggests the potential for salivary biomarkers to detect gingivitis at an early, subclinical stage [86] (Fig. 3A). Likewise, salivary metabolomics identified cadaverine, 5-oxoproline, and histidine as key biomarkers reflecting periodontal inflammation severity, with high diagnostic accuracy. Post-debridement samples improved detection of subgingival metabolites, providing a refined model for monitoring periodontitis activity [87] (Fig. 3B).

In addition, profiling saliva metabolites using conductive polymer spray ionization mass spectrometry provides a rapid, non-invasive method for detecting severe periodontitis. Dysregulated metabolites, particularly amino acids, were identified in patients with severe periodontitis, with notable changes observed after plaque removal. These findings underscore amino acid metabolism as a key player in periodontitis progression [88]

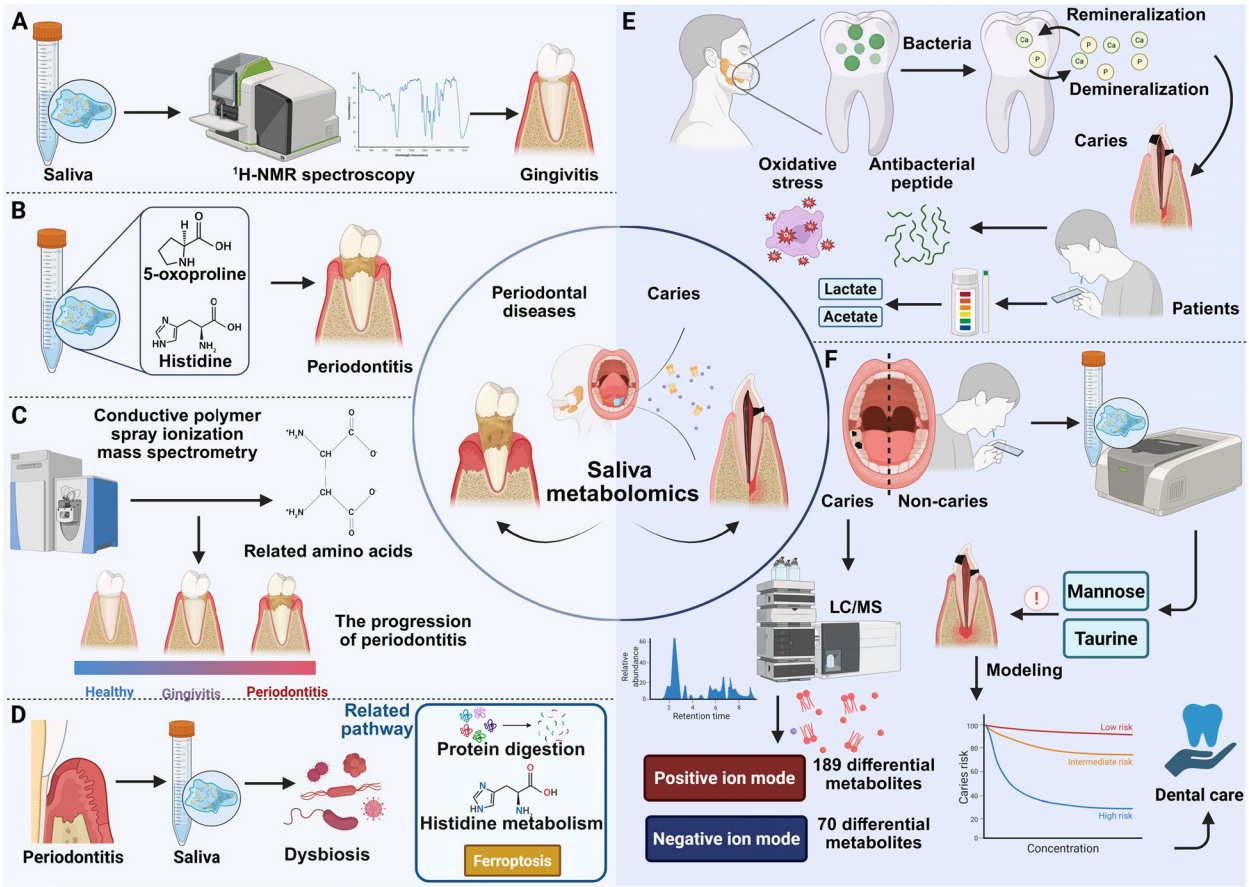

Fig. 3 Saliva metabolomics in the diagnosis and monitoring of periodontal and caries diseases. **A** ^{1}H-NMR spectroscopy is used to analyze saliva samples for the identification of biomarkers associated with gingivitis. **B** Salivary metabolites, such as 5-oxoproline and histidine can serve as key biomarkers reflecting the severity of periodontal inflammation. **C** Analysis of saliva metabolites using conductive polymer spray ionization mass spectrometry, emphasizing the critical role of amino acid metabolism in the progression of periodontitis. **D** In periodontitis patients, significant changes in the microbial composition of saliva have been observed, particularly in pathways related to protein digestion, histidine metabolism, and ferroptosis, compared to healthy controls. **E** The metabolic activity of cariogenic bacteria generates acid-producing byproducts like lactate and acetate, which can be easily detected in saliva. **F** The presentation of differences in saliva metabolites in positive and negative ion modes, with key metabolites such as taurine and mannose, shows great potential as reliable biomarkers for caries

(Fig. 3C). Moreover, untargeted salivary metabolomics identified ethanol, taurine, isovalerate, butyrate, and glucose as robust biomarkers distinguishing periodontitis from healthy controls. A metabolite panel demonstrated high diagnostic accuracy across cohorts, offering potential for periodontal screening and therapy monitoring [89]. Similarly, salivary metabolomics distinguished chronic and aggressive periodontitis (AgP) patients from healthy individuals with 81% accuracy, identifying altered levels of pyruvate, lactate, proline, phenylalanine, and tyrosine. However, metabolic profiles of chronic and AgP overlapped, highlighting shared pathways in disease mechanisms [90]. Notably, salivary metabolomics revealed age-dependent associations with periodontal variables, with phenylacetate consistently linked to periodontal tissue destruction and bacterial activity across all age groups. These findings highlight phenylacetate as a promising biomarker for periodontitis and provide insights into host-microbe metabolic interactions in oral health [91]. Interestingly, salivary metabolite profiling identified 84 metabolites linked to periodontal health, with 2-pyrrolidineacetic acid and butyrylputrescine emerging as consistent markers of oral dysbiosis. Nine baseline metabolites were associated with future tooth loss, reflecting processes such as tissue destruction and cell proliferation [92]. Saliva metabolomics reveals distinct metabolic signatures linked to periodontitis and systemic diseases, particularly in type 2 diabetes. Metabolites such as threonate, cadaverine, and lactate correlate with periodontal inflammation, while disruptions in liver

lipid metabolism are associated with increased cardiometabolic risk. These findings underscore the potential of saliva as a non-invasive diagnostic tool for assessing both oral and systemic health [93]. Therapeutic interventions can significantly alter the salivary metabolomic profile in periodontal disease, but full alignment with a healthy state is not observed. Non-surgical periodontal therapy (NST) significantly altered the salivary metabolomic profile in generalized periodontitis patients, with partial least squares (PLS) achieving 100% accuracy in distinguishing pre- and post-treatment profiles. Despite improved clinical parameters, post-NST profiles remained distinct from healthy individuals, highlighting persistent metabolic differences associated with periodontal disease. Similarly, NST improved clinical parameters in generalized chronic periodontitis but did not fully restore the salivary metabolomic profile to that of healthy controls. NMR spectroscopy revealed distinct metabolic changes post-treatment, with differences in metabolites such as lactate, pyruvate, and tyrosine persisting between treated and healthy individuals, underscoring a retained metabolic signature of disease [21]. Integrating oral microbiome and salivary metabolite profiling enhances the understanding of periodontal disease pathogenesis. For instance, salivary microbiome and metabolome analysis in periodontitis patients reveals significant changes in microbial composition and 103 differential metabolites compared to healthy controls. Dysbiosis is associated with upregulated pathways in protein digestion, histidine metabolism, and ferroptosis, while tryptophan and glutathione metabolism are altered in patients. Correlation analysis links clinical parameters with pathogen abundance and disease-related metabolites, suggesting that salivary profiling could serve as a valuable tool for diagnosing, monitoring, and understanding periodontitis pathogenesis [94] (Fig. 3D). Similarly, saliva metabolomics and microbiome profiling reveal distinct microbial and metabolic signatures in generalized periodontitis. Elevated levels of *Treponema*, *Peptococcus*, and other genera, alongside metabolites such as urea, beta-alanine, and thymine, were associated with aggressive and chronic periodontitis. Key pathways, including pyrimidine and arginine metabolism, were significantly altered between disease subtypes [95].

Caries

Caries is uniquely suited for saliva metabolite-based biomarker discovery due to the direct interaction between saliva and tooth surfaces, where early demineralization occurs [96]. The metabolic activity of cariogenic bacteria, such as *Streptococcus mutans*, produces acidogenic byproducts like lactate and acetate, which are readily detectable in saliva [97]. Furthermore, the dynamic equilibrium between demineralization and remineralization processes in the enamel is reflected in changes to salivary calcium and phosphate levels [98] (Fig. 3E). Saliva also captures host responses, including shifts in oxidative stress markers and antimicrobial peptides, which modulate the cariogenic environment. These localized biochemical changes provide a sensitive and non-invasive means of detecting caries at its earliest stages, monitoring disease progression, and evaluating therapeutic interventions. For instance, salivary metabolomics identified distinct profiles in children with active carious lesions compared to healthy controls, highlighting differences in saccharides and amino acids, including elevated taurine and mannose in caries cases. Predictive modeling using these metabolites achieved moderate accuracy, suggesting their potential as biomarkers for caries risk assessment. These findings underscore the value of salivary metabolomics in advancing personalized approaches to dental caries prevention and management [99]. Notably, saliva metabolomics reveals distinct metabolic profiles between caries-active and caries-free children, with 189 differential metabolites identified in the positive ion mode and 70 in the negative ion mode. Key metabolites, including histamine, L-histidine, and succinate, were enriched in the caries-active group and linked to altered metabolic pathways [100] (Fig. 3F). Additionally, altered salivary metabolomes and microbiomes are linked to severe early childhood caries (SECC). Key metabolites, including 2-benzylmalate, epinephrine, and 3-Indoleacrylic acid, correlate with caries status, revealing disrupted pathways such as amino acid, purine, and pyrimidine metabolism. Specific oral bacteria, including *Veillonella* and *Porphyromonas*, are associated with differential metabolites. These findings suggest that salivary metabolites and microbial profiles may serve as biomarkers for SECC, offering insights into its pathophysiology and potential avenues for personalized prevention and treatment strategies [101].

Burning mouth syndrome

Burning mouth syndrome (BMS) is a chronic pain disorder marked by persistent burning sensations in the oral cavity, typically in the absence of observable clinical lesions, thereby underscoring the need for reliable non-invasive diagnostic approaches [102]. Saliva directly interacts with affected oral tissues and reflects localized neurogenic inflammation, oxidative stress, and altered epithelial metabolism, all of which are implicated in BMS pathophysiology. Metabolomic changes in saliva provide unique insights into the underlying mechanisms of pain and sensory dysfunction. For instance, in patients with BMS, particularly those exhibiting psychiatric symptoms such as depression or anxiety, analyses of oral microbiota and salivary

metabolites reveal no significant microbial differences from healthy controls, but a reduction in microbial diversity and an increase in pro-inflammatory species. Metabolomic profiling highlights alterations in amino acid and lipid metabolism linked to immunological responses, suggesting these factors may influence the pathogenesis and management of BMS [103]. Additionally, salivary metabolomics in BMS revealed 394 differentially expressed metabolites, with significant downregulation of the caffeine metabolism pathway and reduced levels of caffeine and its metabolites, paraxanthine and theophylline. Pathway enrichment analysis identified 30 key metabolites linked to 25 metabolic pathways [104]. Moreover, a comparative analysis of the salivary metabolome in primary BMS revealed shifts in tyrosine metabolism, including L-dopa, L-tyrosine, and tyramine, identified using LC/MS. These changes may indicate an adaptive response to chronic pain or impaired dopaminergic transmission. However, no significant differences in cytokines, neuroinflammatory markers, or steroid hormones were detected, emphasizing the role of metabolomic alterations over inflammatory pathways in BMS pathophysiology [105].

Xerostomia

Xerostomia, or dry mouth, results from altered salivary gland function, leading to significant shifts in the composition of saliva [106]. The altered saliva metabolite profile provides direct insights into glandular dysfunction and its downstream effects on oral health. Additionally, saliva reflects local immune responses and compensatory metabolic adaptations, offering a comprehensive profile of xerostomia's pathophysiology. Salivary metabolomic profiling identifies 195 differentially expressed metabolites in idiopathic xerostomia, with alterations notably concentrated in the caffeine metabolism pathway. This pathway's disruption underscores a potential neuropathic influence in the disease's pathology. These insights offer a foundation for developing diagnostic markers and therapeutic strategies for xerostomia [107]. Additionally, metabolomic profiling of saliva revealed distinct metabolic signatures in dry mouth conditions associated with head and neck cancer (HNC) and primary Sjögren's syndrome (pSS). Both groups exhibited elevated salivary pyrimidine nucleotides and nucleosides, implicating purinergic signaling, alongside dysregulated amino acid metabolism. Notably, DL-3-aminoisobutyric acid levels were significantly higher in HNC patients, with a similar trend in pSS. These findings enhance understanding of dry mouth pathophysiology and suggest potential biomarkers for diagnosis and treatment [108].

Temporomandibular disorders

Saliva captures metabolites and inflammatory mediators associated with muscle metabolism and dysfunction, reflecting biochemical changes linked to TMD of muscular origin (M-TMD). For instance, salivary metabolomic profiling of patients with TMDs of muscular origin reveals eight key metabolites, including L-isoleucine, methylmalonic acid, and lactic acid, distinguishing them from healthy controls. NMR-based metabolomics, coupled with multivariate analysis, provides valuable insights into the metabolic alterations associated with TMDs, highlighting its potential for understanding the pathogenesis and identifying biomarkers for this condition. Similarly, salivary metabolomics in women with TMD of muscular origin reveals distinct metabolic profiles characterized by changes in phenylacetate, dimethylamine, maltose, acetoin, and isovalerate. Post-treatment profiles show reduced distinctions from controls, indicating a shift toward normalization. These metabolites emerge as potential biomarkers for TMD, highlighting the utility of salivary analysis in diagnosing and monitoring treatment outcomes for musculoskeletal disorders [109].

Other oral diseases

Saliva metabolomics provides a comprehensive approach to understanding the biochemical changes underlying diverse oral diseases, revealing disease-specific metabolic signatures. For instance, salivary metabolomics reveals distinct metabolic alterations associated with oral candidiasis. Analysis identified 51 metabolites, with significant changes in both unstimulated and stimulated saliva of Candida-positive individuals. Elevated levels of tyrosine, choline, and phosphoenolpyruvate, among others, were observed in unstimulated saliva, while metabolites like ornithine and butyrate were decreased in stimulated saliva [110]. Additionally, halitosis was associated with distinct salivary microbiota and metabolite profiles. Elevated levels of *Prevotella*, *Alloprevotella*, and *Megasphaera*, alongside increased 5-aminovaleric acid and *N*-acetylornithine, characterized the halitosis group. Correlations suggest *Alloprevotella* and *Prevotella* contribute to cadaverine and putrescine pathways, shedding light on halitosis mechanisms [111]. Notably, saliva from recurrent aphthous ulcer (RAU) patients showed significant metabolic alterations, including decreased estrone sulfate and dehydroepiandrosterone sulfate, implicating imbalances in tryptophan metabolism and steroid hormone biosynthesis. These findings suggest metabolic disruptions linked to psychogenic, endocrine, and immunological factors in RAU, with potential diagnostic utility for identified metabolites [112]. Radiotherapy-induced oral mucositis (RIOM) in HNC patients was linked to distinct

salivary metabolites. Pretreatment levels of histidine and tyrosine significantly differentiated high-grade from low-grade mucositis, while gamma-aminobutyric acid and 2-aminobutyric acid were elevated in severe cases. These findings suggest salivary metabolomic profiling as a tool for predicting mucositis severity and guiding timely interventions [113].

Orthodontic therapy-related complications

Saliva metabolomics provides critical insights into the biochemical and microbial changes induced by orthodontic treatments, uncovering associations with therapy-related complications. For instance, orthodontically induced external apical root resorption (OIEARR) is associated with altered salivary metabolites, including butyrate, fumarate, and α-linolenic acid, reflecting inflammation, oxidative stress, and energy metabolism dysregulation in periodontal tissues. Salivary metabolomics using ^{1}H NMR demonstrated effective discrimination between patients with and without OIEARR, highlighting its potential for early diagnosis and monitoring [114]. Interestingly, adolescents undergoing clear aligner therapy are at increased risk for developing white spot lesions (WSLs), potentially due to alterations in the oral microbiome and metabolome. Analysis revealed higher abundances of specific taxa, including *Lachnoanaerobaculum*, *Rothia*, and *Subdoligranulum*, in those with WSLs. Metabolomic changes, particularly in amino acids like proline and glycine, were associated with disrupted metabolic pathways. These findings highlight the role of oral microbiota dysbiosis in WSL development, offering potential biomarkers for early detection and management of WSLs linked to clear aligner use [115] (Fig. 4).

Collectively, these findings underscore the clinical relevance of salivary metabolomics across a wide range of oral diseases. Salivary metabolomics has demonstrated substantial promise across the clinical spectrum of oral diseases, with applications in early diagnosis, prognostic stratification, and longitudinal disease monitoring. From precancerous lesions and OSCC to periodontitis, caries, and therapy-associated complications, salivary metabolite profiles have consistently distinguished disease states from health, reflected disease severity, and dynamically responded to therapeutic interventions [60, 69, 87, 98]. Importantly, longitudinal studies have shown that these profiles evolve in parallel with clinical progression or remission, indicating their potential as non-invasive biomarkers to track the natural course of disease and evaluate treatment outcomes in real time. However, its clinical translation requires careful consideration of biological variability—including age, circadian rhythm, diet, and oral microbiota—as well as technical factors related to sample handling and analytical reproducibility. Integrating salivary metabolomics with clinical, microbiological, and imaging data through multi-modal approaches may further enhance diagnostic precision and biological interpretability [50, 51, 53]. With continued validation in large, prospective cohorts and the establishment of standardized workflows, salivary metabolomics holds considerable potential to support personalized, longitudinal management of oral diseases.

Challenges and perspectives

Despite its considerable promise as a non-invasive diagnostic tool, the clinical application of saliva metabolomics faces several distinct challenges. These stem from the inherent complexity of saliva as a biological fluid and the dynamic, multifactorial nature of the metabolic processes it represents [116].

Firstly, one significant challenge in applying saliva metabolomics is the difficulty in establishing clear, direct links between specific metabolomic changes in saliva and the underlying mechanisms for oral diseases. Unlike blood, which is a more stable biofluid and reflects systemic changes more directly, saliva is influenced by both local oral conditions and systemic factors. The dynamic interplay between the oral microbiome, host immune responses, and environmental factors complicates the interpretation of metabolic changes. In diseases such as oral cancer or periodontal disease, salivary metabolite profiles may overlap with systemic diseases like diabetes or cardiovascular disorders, complicating efforts to distinguish disease-specific biomarkers. This complexity underscores the need for a deeper understanding of how salivary metabolic alterations specifically reflect disease mechanisms [117].

Secondly, saliva composition is highly individualized, influenced by a range of factors such as age, sex, diet, oral hygiene, genetics, and medication use. For instance, systemic antibiotic use in the past three months was strongly linked to elevated levels of taurine, glycine, and ornithine. These findings highlight the influence of external factors such as antibiotics on salivary metabolites [118] (Fig. 5C). Similarly, salivary metabolite profiles for oral cancer detection are influenced by collection timing post-meal. Metabolomic analysis identified 51 discriminatory metabolites at 12 h post-dinner, compared to fewer at 1.5 and 3.5 h after breakfast. The 12-h fasting period yielded the highest diagnostic accuracy, emphasizing its importance for standardized saliva collection in biomarker discovery. This inherent variability makes it challenging to establish consistent diagnostic biomarkers across different individuals [119]. Additionally, the oral microbiome and salivary gland function vary widely between individuals, and these factors can significantly

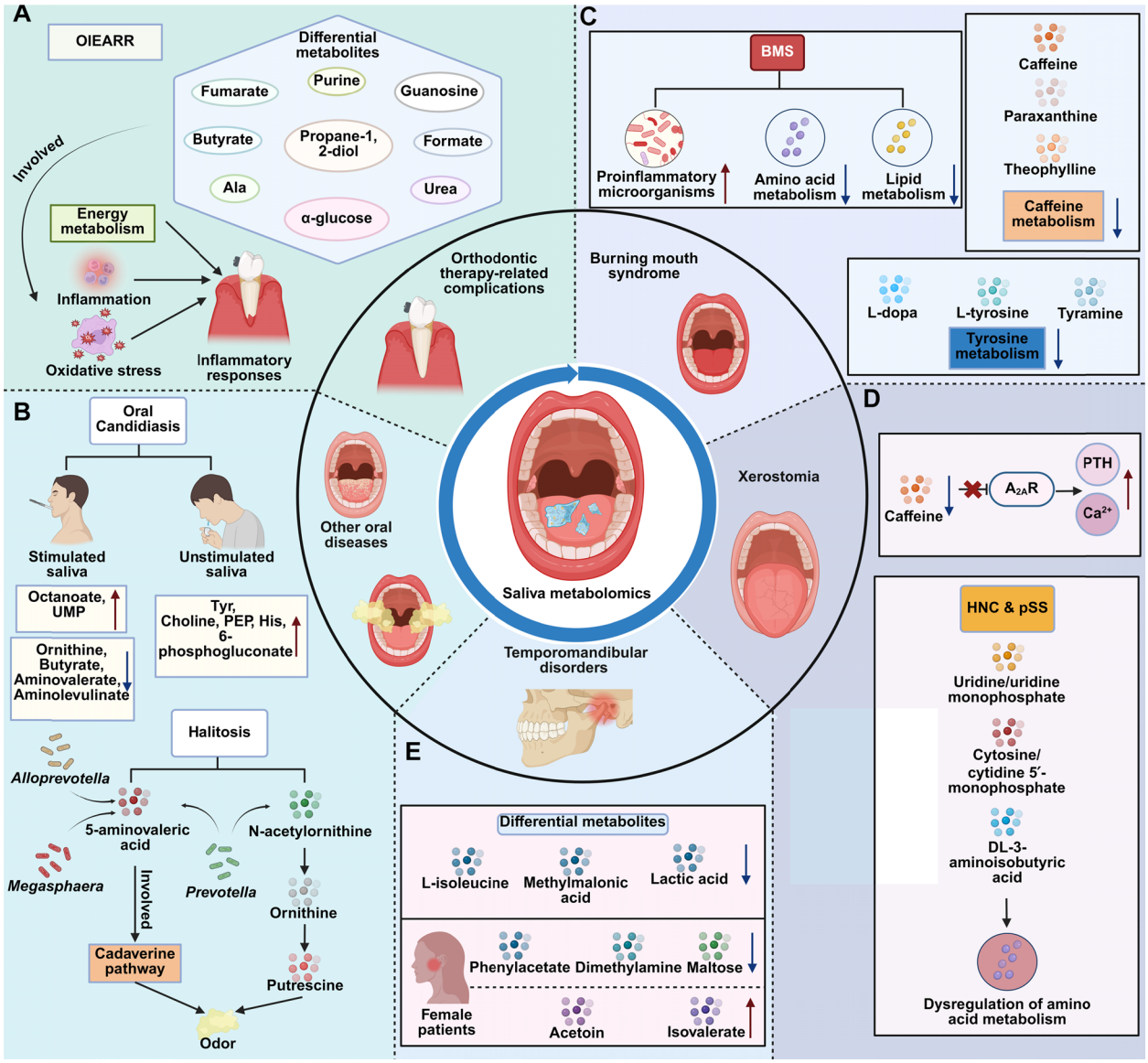

Fig. 4 Saliva metabolomics in the diagnosis and monitoring of various oral diseases. **A** OIEARR shows changes in salivary metabolites such as butyrate, fumarate, and α-linolenic acid, reflecting inflammation, oxidative stress, and dysregulation of energy metabolism in periodontal tissues. **B** Oral candidiasis presents distinct metabolite profiles in both unstimulated and stimulated saliva. In halitosis, elevated levels of 5-aminovaleric acid and *N*-acetylornithine, along with microbial contributions, are observed. **C** In BMS, disruptions in amino acid and lipid metabolism are linked to immune responses. Caffeine metabolism is downregulated, and alterations in tyrosine metabolism may contribute to mouth dryness in xerostomia. **D** In xerostomia, elevated pyrimidine nucleotides and DL-3-aminoisobutyric acid, along with disrupted amino acid metabolism, are observed. **E** TMDs are associated with metabolites including L-isoleucine, methylmalonic acid, and lactic acid, whereas inn women with TMDs, distinct metabolic profiles are observed, characterized by alterations in phenylacetate, dimethylamine, maltose, acetoin, and isovalerate

alter the metabolic profile of saliva. To address this variability, improving the precision of metabolomics techniques through better analytical methods, such as high-resolution mass spectrometry and more robust data normalization procedures, could help reduce confounding effects (Fig. 5A). Furthermore, expanding clinical cohorts to include diverse populations and accounting for these external factors in study design could increase the reliability of findings. Longitudinal studies that track individual baseline profiles, accounting for diet, medication, and health status, may also help to differentiate disease-specific biomarkers from those influenced by external variables. These strategies will enhance the clinical applicability of salivary metabolomics by providing

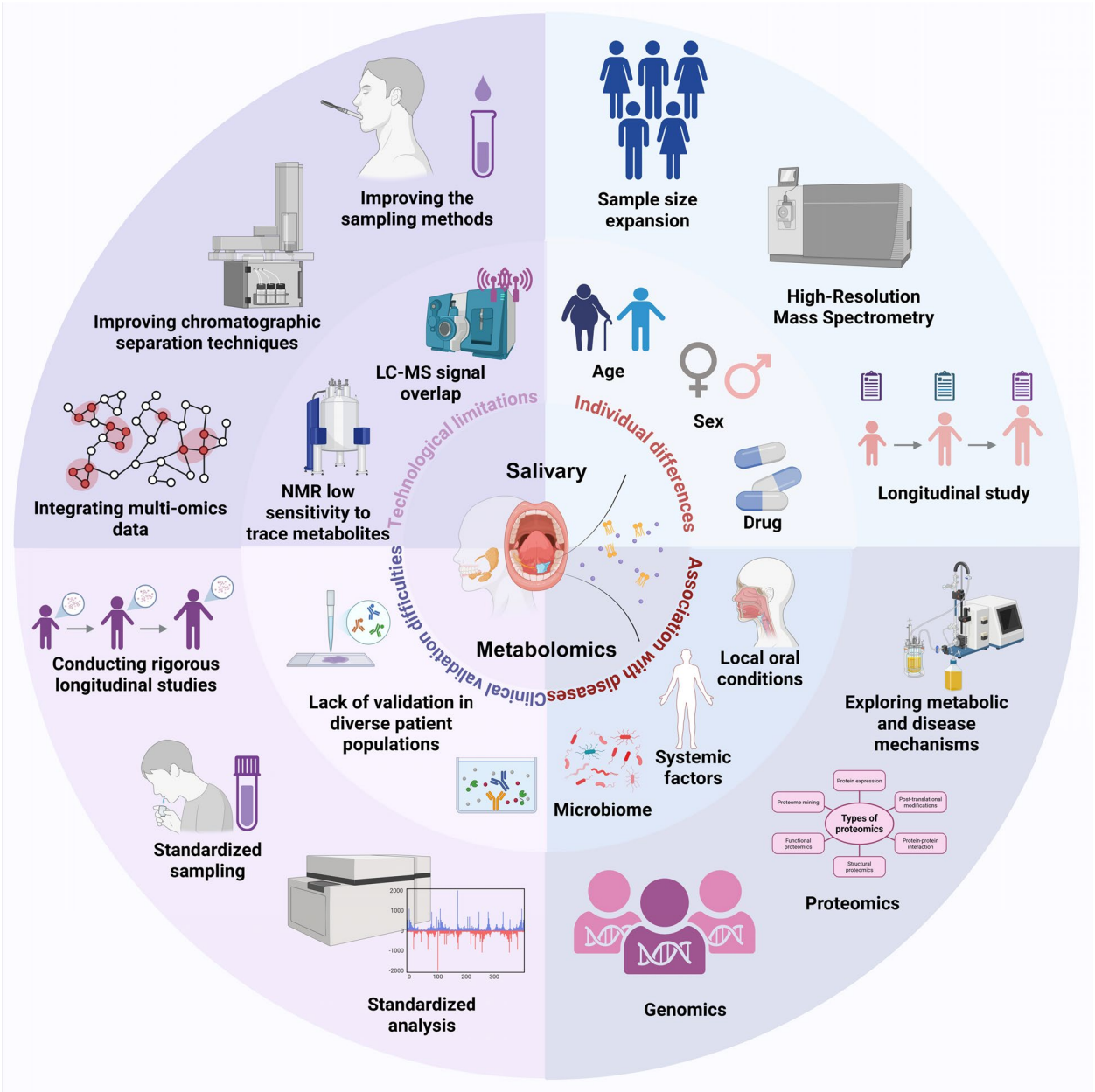

Fig. 5 Challenges and prospects in salivary metabolomics. In the technological aspect, it shows challenges like LC–MS signal overlap, low NMR sensitivity, and the complexity of salivary composition, while suggesting solutions such as improved chromatographic techniques, integration of multi-omics data, and enhanced sampling methods. In terms of clinical application, it points out the need for validation in diverse populations and the issue of inconsistent analysis methods, with strategies including standardized sampling, standardized data analysis, and rigorous longitudinal studies to boost reliability. Individual differences also play a role, as age, sex, medication, microbiome, and systemic conditions can affect salivary composition. Expanding sample sizes, longitudinal studies, and accounting for individual differences can improve the specificity of biomarkers. Finally, the complex interplay of local oral conditions, systemic factors, and disease mechanisms is depicted, indicating that a multi-disciplinary approach combining metabolomics, proteomics, and genomics is essential for exploring and validating disease-specific biomarkers

more standardized and reliable biomarkers across different patient groups [120] (Fig. 5D).

Thirdly, despite significant advances in analytical techniques such as LC–MS, GC–MS, and NMR spectroscopy, there remain technical limitations that hinder the precision and comprehensiveness of salivary metabolomic analyses. For instance, while LC–MS provides high sensitivity for detecting metabolites, the complexity of saliva,

which contains a wide range of metabolites, proteins, and microbial products, can lead to challenges in resolving overlapping signals and distinguishing low-abundance metabolites [121]. Furthermore, NMR, although capable of providing structural information, lacks the sensitivity and resolution of mass spectrometry for detecting metabolites at low concentrations. These limitations can lead to incomplete or inaccurate metabolic profiling, which impedes the identification of robust biomarkers for clinical use. To address these challenges, strategies such as improved sample preparation, enhanced chromatographic techniques, and the use of hyperpolarization in NMR can enhance sensitivity and resolution [122, 123]. Additionally, integrating multi-omics data and employing advanced bioinformatics tools can refine data analysis, reduce variability, and improve the reliability of findings, ultimately increasing the clinical applicability of salivary metabolomics [124].

Lastly, the clinical validation of salivary biomarkers represents a significant challenge. While preliminary studies highlight the potential of saliva metabolomics in identifying disease-specific biomarkers, much of the research remains in the discovery phase. To achieve clinical applicability, these biomarkers must undergo rigorous validation across heterogeneous patient populations [125]. This requires well-designed longitudinal studies to establish the reliability and reproducibility of biomarkers in early disease detection, monitoring disease progression, and evaluating therapeutic responses. In the absence of robust validation, the integration of saliva metabolomics into clinical practice remains limited (Fig. 5B).

Conclusion

In summary, salivary metabolomics represents a promising non-invasive approach for the diagnosis and monitoring of a broad spectrum of oral diseases. Its capacity to reflect both localized and systemic metabolic alterations offers distinct advantages for early detection, disease progression tracking, and assessment of therapeutic efficacy. However, several challenges remain, including incomplete understanding of the mechanistic links between salivary metabolites and disease processes, substantial inter-individual variability, and the complex dynamics of the oral microenvironment. Furthermore, technical limitations, data interpretation complexities, and the lack of large-scale clinical validation hinder its routine clinical implementation. Despite these obstacles, continued advancements in analytical technologies, standardization protocols, and multi-omics integration are expected to enhance the diagnostic accuracy and clinical relevance of salivary metabolomics. Ultimately, this approach holds the potential to transform the landscape of oral disease management through more personalized, precise, and mechanism-informed strategies.

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Author contributions
LC, and SH conceived of the presented idea. LC, XZ, SH, XC, YL, ZZ, and PL wrote the manuscript. XC, YL, ZZ, and PL created the graphs. All authors contributed to and approved the final manuscript.

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Availability of data and materials
The data generated are included within the manuscript.

Declarations

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