METABOLOMIC PROFILING OF SALIVA IN PEDIATRIC DENTAL CARIES: A SCOPING REVIEW

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ABSTRACT

Introduction : Dental caries is one of the most common chronic oral diseases in children. Its development involves complex interactions among diet, oral microbiota, host factors, and saliva. Salivary metabolomics, the analysis of small molecules in saliva, has emerged as a promising approach to identify biomarkers associated with caries. This scoping review aims to map the existing evidence on salivary metabolomics in pediatric caries, focusing on analytical methods, major findings, and clinical implications.

Methods : Following PRISMA-ScR guidelines, PubMed, Scopus, and ScienceDirect were searched for English-language articles published between 2015 and 2025. Eligible studies included participants ≤18 years old, applied validated metabolomic platforms, and investigated salivary metabolites in relation to dental caries. Studies not using saliva, involving adults, systemic diseases, or non-metabolomic approaches were excluded.

Results and Discussion : Eight studies fulfilled the inclusion criteria. NMR and LC-MS were the most common platforms. Frequently reported metabolites elevated in caries-active children included acetate, lactate, formate, and certain amino acids such as tyrosine and glycine. These metabolic shifts reflect bacterial activity and amino acid breakdown. However, methodological differences limited comparability across studies, and evidence from longitudinal or predictive modeling studies remains scarce.

Conclusion : Salivary metabolomics offers promise for identifying non-invasive biomarkers of pediatric caries. While preliminary data are encouraging, consistent methodologies and larger studies are needed to validate metabolomic markers for early diagnosis and caries risk assessment.

Keyword :
Metabolomic, saliva, child, dental caries

INTRODUCTION

Dental caries in children, particularly Early Childhood Caries (ECC), continues to pose a major public health challenge, affecting more than 530 million children worldwide according to the World Health Organization (WHO)[1]. Caries is a dynamic, multifactorial disease primarily driven by microbial biofilm activity and dietary sugars, leading to progressive demineralization of dental hard tissues. Among the many biological fluids involved in oral health, saliva plays a central role in maintaining oral homeostasis.[2] Beyond its physical functions, saliva contains a complex mixture of electrolytes, proteins, and small molecules that directly reflect host–microbe interactions in the oral cavity.[3]

Most studies on the microbial diversity of dental caries have been conducted at the genetic level. While genomics offers insights into gene-related processes, many key cellular functions—such as metabolite production, energy transfer, and intercellular signaling—are regulated at the metabolic level. Metabolomics therefore holds strong potential for clinical diagnosis, and saliva has emerged as an attractive sample because of its simplicity and value for early disease detection.[4]

Metabolomics refers to the comprehensive analysis of small-molecule metabolites in biological fluids, including saliva.[5] The salivary metabolome reflects the real-time molecular phenotype of oral health and can capture biochemical alterations that precede clinical symptoms. Advances in analytical technologies have further strengthened this approach, allowing a deeper understanding of the mechanisms underlying the initiation and progression of dental caries.[3]

Despite these opportunities, research on salivary metabolomics in pediatric dental caries remains fragmented. Differences in study design, age groups, sampling methods, and analytical platforms limit comparability and slow translation into clinical practice. To date, no review has systematically mapped this emerging field in children with caries.

This scoping review therefore aims to synthesize current evidence on salivary metabolomic profiling in pediatric dental caries, with particular emphasis on analytical methods, key metabolic alterations, and their potential clinical relevance. By identifying consistent biomarkers and highlighting methodological gaps, this review provides a foundation for future research and the development of non-invasive diagnostic strategies for early caries detection in children.

METHODS

Protocol

This scoping review adhered to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and was structured using the PCC framework (Population, Concept, Context).

- **Population:** Participants under 18 years old.
- **Concept:** Salivary metabolomic profiling

- **Context:** Association with dental caries status or severity

Search Strategy

A comprehensive search was conducted in PubMed, Scopus, and Sciencedirect for studies published between 2015 and 2025. Search terms included combinations of MeSH terms and free-text keywords related to: “Saliva”, “Metabolomic”, “Early childhood caries”, “dental caries” and “children”. Full search strategies are summarized in Table 1 of the original manuscript.

Tabel 1. Search Strategy.

Database	MeSH/Keywords	Results
Pubmed	(((((saliva[MeSH Terms]) AND (metabolomics[MeSH Terms])) OR (salivary metabolomics)) AND (early childhood caries)) OR (dental caries[MeSH Terms])) AND (child[MeSH Terms])	2,883
Scopus	(TITLE-ABS-KEY (saliva) AND TITLE-ABS-KEY (metabolomics) OR TITLE-ABS-KEY (metabolomic profiling) AND TITLE-ABS-KEY (early childhood caries) OR TITLE-ABS-KEY (dental caries) AND TITLE-ABS-KEY (child))	14
Sciencedirect	"saliva" AND "metabolomics" AND "dental caries" AND (children OR pediatric)	89

Study Selection Process

Two reviewers (RI, AS) independently screened the titles and abstracts. Eligible studies were further reviewed in full text. Disagreements were resolved by discussion and consensus. Studies were included if they:

- Participants: Children ≤18 years old
- Outcome: Salivary metabolomic data analyzed in relation to dental caries (presence, severity, or activity)
- Methods: Metabolomics platforms (LC-MS, GC-MS, NMR, CE-MS, etc.)
- Language: English
- Publication years: 2015–2025

Exclusion criteria included:

- Studies on adults
- Participants with systemic diseases or syndromic conditions
- Participants using antibiotics or other systemic medications within the last 3 months

- Studies not analysing saliva
- Non-metabolomic approaches (e.g., only microbiome or protein analysis)
- Reviews, editorials, commentaries, conference abstracts without full text
- Animal studies

Data Extraction and Synthesis

A standardized data extraction form was used to collect information on study design, aims, participants, caries status, platform, key metabolits and conclusion. A narrative synthesis was performed to map the findings and highlight methodological differences, observed key metabolite outcomes, and research gaps (Table 2).

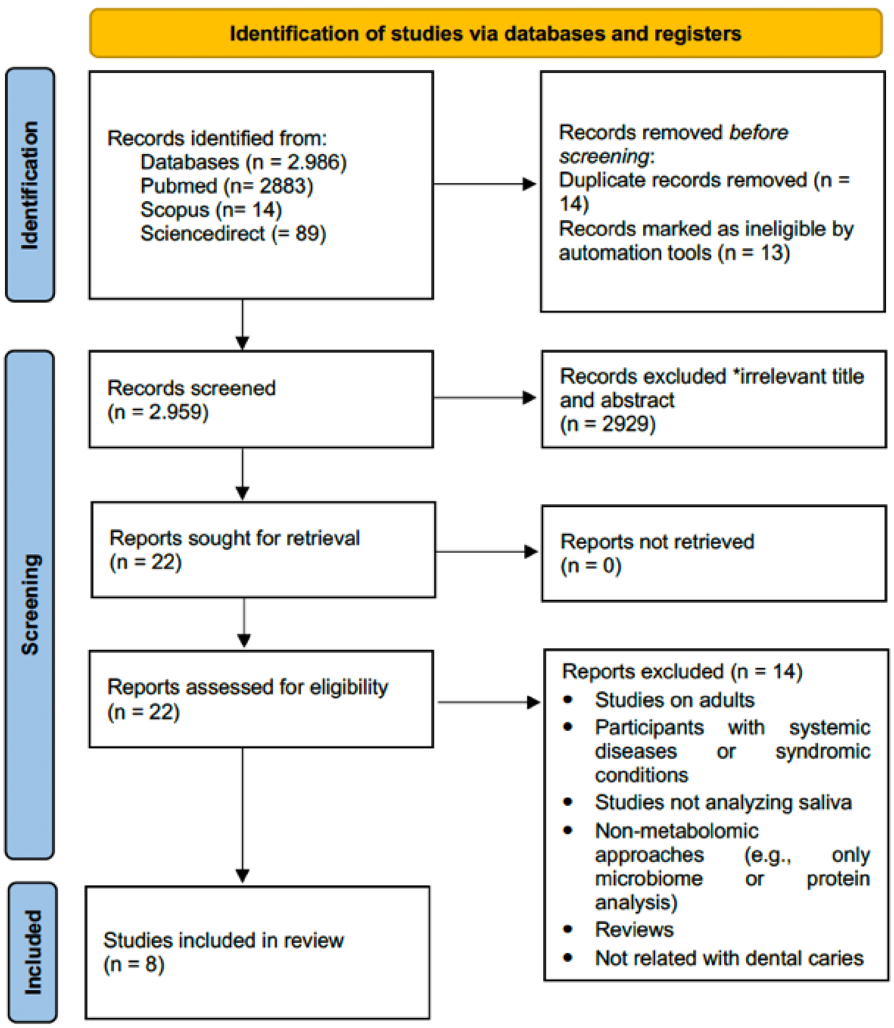

Figure 1. PRISMA flow diagram showing the selection of articles included in the review.

RESULTS

A total of eight studies met the inclusion criteria and were analyzed in this scoping review. All studies enrolled pediatric participants (age ≤18 years), analyzed unstimulated or stimulated saliva in relation to caries status, and conducted metabolomics profiling using platforms including nuclear magnetic resonance (NMR), liquid chromatography–mass spectrometry (LC-MS), and/or gas chromatography–mass spectrometry (GC-MS).

Participants' ages ranged from 3 to 18 years, with sample sizes ranging from 20 to 68 children per study. Most studies compared children with active caries (ECC or severe ECC(SECC)) to caries-free controls; a few studies additionally explored caries severity, specific microbial associations, or the metabolomic profile of supragingival pellicle as well as saliva.[6-12]

Metabolomic Approaches

Three studies utilized NMR, while five used LC-MS, with one study additionally employing GC-MS. Collectively, the included studies covered a broad range of metabolite classes, including amino acids, organic acids, short-chain fatty acids (SCFAs), carbohydrates, and in some cases, lipids and nucleotides.

NMR, LC-MS, and GC-MS differ in analytical sensitivity, metabolite coverage, and quantification characteristics, the metabolites reported as altered may partly reflect platform-specific detectability. NMR is highly reproducible and inherently quantitative for relatively abundant metabolites but is less sensitive for low-abundance species. LC-MS generally offers higher sensitivity and wider coverage but is more affected by ionization efficiency, matrix effects, and batch variation. GC-MS provides robust separation for volatile or derivatized small polar compounds (e.g., organic acids) but requires derivatization and is less suited to large or thermolabile metabolites.

Multivariate and univariate statistics including principal component analysis (PCA), orthogonal partial least squares discriminant analysis (OPLS-DA), random forest, ROC curve analyses, and pathway enrichment analyses were employed.

Altered Salivary Metabolites

Several metabolite classes were consistently reported as altered in children with caries compared to caries-free peers (Table 3) :

- Organic Acids:
  - Lactate and Formate: Universally elevated in ECC/SECC, reflecting increased bacterial glycolysis and acidogenic activity.[9,10,12]
  - Succinate, Acetate, and Propionate: Also increased, with succinate emerging repeatedly as a caries-associated metabolite.[7,9,13]
- Amino Acids:

  - Glycine and Proline: Consistently lower in children with caries; proline decrease possibly reflects greater proteolytic activity and/or collagen matrix breakdown.[7,10,11]
- Carbohydrates and SCFAs:
  - Sugars (mannose, fructose, ribose, allose, maltopentose, sucrose) were increased in high-caries children, alongside SCFAs produced by bacterial fermentation.[10,11]

Multimetabolite Biomarker Panels

Several studies attempted to derive biomarker panels for diagnostic purposes, such as Kim et al. (2023) developed a panel of four metabolites—formate, lactate, glycine, and proline—which distinguished ECC from healthy children with high accuracy (AUC = 0.92) and Havsed et al. (2024) and Pan et al. (2025) similarly found that multi-metabolite models (3–5 salivary markers) improved discriminatory power over single metabolite approaches.

Salivary Metabolic Pathways Enriched in Caries

- Amino acid metabolism: Histidine metabolism (histamine, L-histidine) and degradation of branched-chain amino acids were consistently activated in caries.[7,13]
- Carbohydrate and TCA cycle metabolism: Enhanced sugar fermentation and increased intermediates of the TCA cycle (citrate, isocitrate, aconitate, malate) indicated intensified bacterial metabolism in caries-active children.[9]
- Suppressed pathways: Glyoxylate/dicarboxylate, purine, and pyrimidine pathways appeared inhibited in caries-affected children.[13]

Host Factors, Diet, and Microbiome Associations

Salivary metabolite shifts were correlated with frequency of sugary food/drink intake and oral hygiene behaviors (Havsed et al. 2024; Pan et al. 2025). Multi-omics studies (Su et al. 2023, Li et al. 2023, Pan et al. 2025) linked signature metabolites (e.g., histamine, SCFAs, sugars) with specific microbial taxa, including Streptococcus mutans, Scardovia wiggsiae, Veillonella, and Candida albicans.

Salivary Microbiome-Metabolome Integration & Biomarker Potentials

Several studies found that integrating salivary microbiome profiles with metabolomics improved caries risk stratification. For example, Li et al. (2023) identified a biomarker panel of 2-benzylmalate, epinephrine, 2-formaminobenzoylacetate, and 3-indoleacrylic acid (AUC=0.73 for SECC). Pan et al. (2025) suggested histidine and glutathione metabolism strongly associated with caries-related microbial species and ECC status

Table 2. Literature Presentation Data

Author, Year	Study design	Aim	Participants	Caries Status	Platform	Key Metabolites	Conclusion
Seonghye Kim, et al.[7] 2023	Cross-sectional	to identify a salivary metabolite biomarker panel for the diagnosis of ECC.	54 children. (3-5 years old)	ECC vs. caries-free.	NMR	↑ Formate, lactate, GPC ↓ Glycine, proline, alanine, isoleucine, lysine, tyrosine.	A biomarker panel of formate, lactate, proline, and glycine showed good diagnostic potential for ECC. These findings support the use of salivary metabolites as promising non-invasive biomarkers for early caries detection in children.
Kristian Havsed, et.[8] al. 2024	Cross-sectional	to identify caries-associated metabolites and proteins in saliva samples from adolescents that had a	40 children. (Adolescents 14–18 years old)	Children with active caries vs. caries-free.	NMR	Citrate, ethanolamine, 2-hydroxyvalerate, ↑lactate: succinate ratio; panel of 3–5 metabolites (afternoon saliva) enables group discrimination	No single marker was sufficient, but a panel of 3–5 salivary metabolites (especially in afternoon samples) could distinguish caries status in adolescents; future prediction models should account for multiple factors.

		caries experience and those that were caries-free					
Shaochen Su, et al.[9] 2023	Cross-sectional	to investigate the variations in dental caries related microbiome abnormality and metabolomics shift in children.	28 children. (3–6 years old)	Children with high caries vs. no-caries.	Untargeted LC-MS	↑ Salivary sugars (fructose, sorbose, ribose, allose, mannose, sucrose) ↑ TCA cycle intermediates (citrate, isocitrate, aconitate, malate) ↑ Amino acids (arginine, lysine, tryptophan, proline) ↓ Fatty acids (palmitic, stearic, oleic, arachidonic acids) ↑ Glycerophosphocholine, phosphorylcholine, glycerophosphoethanolamin	Alterations in both oral microbiota and saliva metabolites are linked to childhood dental caries, and some changes (especially increased sugars and specific bacteria) may serve as biomarkers for early detection or risk assessment.
Yueheng Li, et al.[6] 2023	Cross-sectional	To compare the differences	20 children.	Children with caries-	Untargeted LC-MS/MS	↑ Histamine, L-histidine, succinate, arachidonic acid in caries-active	The enriched differential metabolites

		in salivary metabolites between cariesactive and caries-free children in the mixed dentition, and explore their correlation with caries status.	(8–9 years old)	active vs. caries-free.			including histamine, Lhistidine and succinate were correlated with the presence of dental caries, but their role in the caries process needs to be further investigated
Oscar Musalem-Domingue z, et al.[10] 2023	Case control	To identify the metabolomi c differences in the saliva of healthy children versus children with active carious lesions and	68 children. (6–12 years old)	Childre n with active caries vs no active caries.	NMR	↑taurine and mannose in children with caries, ↓glycine and glucose in children free caries.	Difference in the salivary metabolomic profiles, specifically in the groups of saccharides and amino acids, suggesting an association of these with the level of caries risk.

		to estimate the predictive capacity of a model based on the salivary metabolomic profile.					
Annika Schulz, et al.[11] 2020	Cross-sectional	to characterise the metabolomic profile of in-situ pellicle in children with different caries activity for the first time in comparison to saliva.	57 children. (4–6 years old)	Children with caries-active, inactive, or caries-free.	Targeted LC-MS/GC-MS	Targeted panel (amino acids, organic acids, carbohydrates, fatty acids; e.g., acetate/propionate/lactate; glycine/proline); no significant differences between caries vs caries-free in saliva and pellicle.	Salivary and pellicle metabolomic profiles showed no significant differences by caries status; targeted metabolites are not suitable as caries biomarkers in young children.

Ting Pan, et al.[13] 2025	Cross-sectional	to compare the prevalence of specific microbial species and salivary metabolomics profile in children with and without ECC, and to explore the correlation between salivary metabolites and targeted microbes.	54 children. (<6 years old)	Children with ECC vs. caries-free	Untargeted LC-MS	↑ Histamine, glutathione, cysteine sulfinic acid, arachidonic acid in ECC ↓ Citric acid, aconitic acid, purine and pyrimidine metabolites in ECC	Metabolomic pathways may reflect host-microbe interaction in ECC status. Key metabolites may be further identified to predict caries risks in children.
Kai Li, et al.[12] 2023	Case control	to analyse alterations in the salivary microbiome and metabolome	60 children. (4-6 years old)	Children with SECC and without caries.	Untargeted LC-MS	↑ Cytidine, 3-indoleacrylic acid, epinephrine, guanosine, stachydrine, 2-benzylmalate in SECC ↓ L-erythrulose 4-phosphate,	Distinct shifts in the salivary metabolome and microbiome were found in SECC children; four metabolites (2-benzylmalate,

		of children with SECC (Severe Early Childhoold Caries)				galactosylglycerol, uridine 5'-diphosphate, Val-Pro-Val, PC(16:0/16:0) in SECC	epinephrine, 2-formaminobenzoylacetate, 3-indoleacrylic acid) may serve as potential biomarkers for caries status.

Table 3. Main Salivary Metabolites Altered in Pediatric Dental Caries

Metabolite/Group	**Direction in Caries**
Lactate, formate	↑
Succinate, acetate, etc.	↑
Glycine, proline	↓
Mannose, sugars (various)	↑
Histamine, L-histidine	↑
Taurine	↑
Amino acids (total)	↓
SCFAs	↑
TCA cycle intermediates	↑
Purine, pyrimidine	↓
Fatty acids (various)	varies

*Note: ↑ = increased in caries/ECC; ↓ = decreased

DISCUSSION

Salivary metabolomics enables the high-throughput analysis of low-molecular-weight metabolites such as amino acids, organic acids, sugars, and nucleotides.[5,14] Because saliva directly reflects both microbial activity and host responses in the oral cavity, it provides a unique opportunity to identify biomarkers of dental caries through non-invasive sampling.[15-17] Unlike traditional markers such as pH, buffering capacity, or microbial counts—which are often influenced by transient factors[18,19]—metabolomic profiling offers a more stable and comprehensive view of the biochemical changes associated with caries development.[7,10,13]

Across the included studies, children with caries consistently showed alterations in their salivary metabolomic profiles. Organic acids such as lactate, formate, acetate, and succinate were repeatedly elevated, reflecting enhanced bacterial fermentation, particularly from cariogenic species including Streptococcus mutans, Scardovia wiggsiae, and Veillonella. In contrast, protective amino acids such as glycine and proline were reduced, possibly indicating increased proteolysis and pellicle degradation.[6-9,11,13] These consistent findings support the role of microbial metabolism in shaping the salivary biochemical environment of caries-active children. Notably, an earlier study by Fidalgo et al. (2013) reported similar trends, with higher levels of lactate, acetate, butyrate, and fatty acids, and lower levels of phenylalanine, propionate, and saccharides in children with caries. Their work achieved nearly 90% classification accuracy using NMR-based salivary metabolomics, reinforcing the diagnostic potential of metabolite profiling in pediatric caries.

Not all findings were consistent. Schulz et al. reported no significant differences in salivary or pellicle metabolomic profiles across caries groups. This discrepancy may be related to methodological differences, including targeted versus untargeted metabolomics, heterogeneity in saliva collection methods, and confounding factors such as diet and oral hygiene. These variations underscore the importance of standardized protocols in sampling, storage, and analysis to ensure reproducibility across studies.

Recent multi-omics approaches have further emphasized the interplay between salivary metabolites and the oral microbiome. Studies integrating microbiome and metabolome data demonstrated strong correlations between metabolites such as histamine, glutathione, and short-chain fatty acids with microbial taxa including S. mutans, Candida albicans, and Ligilactobacillus salivarius.[6,9,13] Such integrative strategies may offer more robust biomarkers and improve understanding of host–microbe interactions underlying caries progression.

Overall, this review provides a clearer understanding of how metabolomic shifts in saliva reflect the complex host–microbe interactions underlying caries development in children. By demonstrating the value of multi-metabolite panels and microbiome–metabolome integration, it highlights the potential of salivary metabolomics as a non-invasive and clinically relevant approach for early caries risk assessment.

Limitation and Future Direction

This scoping review has several limitations. The included studies were heterogeneous in analytical platforms, saliva collection methods, and reporting, which complicated comparison. Most involved small sample sizes, broad age ranges, and cross-sectional designs, limiting generalizability and causal inference. Although some biomarker panels showed high diagnostic accuracy, these findings remain preliminary and require validation in larger cohorts.

The review was also limited by its methodology, as only English-language articles published between 2015 and 2025 were included. Many potentially relevant studies were excluded for not using saliva, lacking a direct link to caries, or focusing on adults or syndromic populations.

As salivary metabolomics in pediatric dentistry is still an emerging field, it is expected that studies to date are small, heterogeneous, and exploratory in nature. By synthesizing the available evidence and highlighting these gaps, this review provides an essential foundation for guiding future research. Future studies should standardize saliva collection and metabolomic analysis, employ larger longitudinal designs, and integrate multi-omics approaches to advance salivary metabolomics toward clinical application in pediatric caries.

CONCLUSION

This scoping review shows that salivary metabolomics can distinguish children with and without caries through characteristic metabolic shifts, notably increased organic acids and decreased protective amino acids. Multi-metabolite panels and microbiome–metabolome integration offer greater diagnostic potential than single biomarkers. However, methodological heterogeneity and the lack of longitudinal validation remain major barriers. Standardized protocols and larger pediatric cohorts are needed before salivary metabolomics can be translated into reliable tools for early caries risk assessment in children.

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