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REVIEW

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The role of salivary proteins in early childhood caries: a scoping review

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Abstract

Early childhood caries (ECC) is one of the most prevalent chronic diseases in children and is influenced by microbial, host, and environmental factors. Saliva plays a significant role in oral defense and contains proteins involved in buffering capacity, immune responses, antimicrobial activity, and enamel remineralization. In recent years, salivary proteins have gained increasing attention as potential non-invasive biomarkers for ECC risk prediction and diagnosis. This scoping review explored the association between salivary proteins and ECC by synthesizing findings from studies published between January 2020 and August 2025. A systematic search of PubMed, EBSCOhost, ScienceDirect, and Google Scholar identified 612 records, of which 10 studies met the inclusion criteria, involving 646 children younger than six years. The review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines, included only English-language publications, and excluded grey literature. A wide range of salivary proteins was examined, including lysozyme, secretory Immunoglobulin A (IgA), histatin-5, cystatin S, α-amylase, matrix metalloproteinases (MMP-8 and MMP-20), statherin, defensins, cathepsin G, mucins, and lactoferrin. The findings indicated that elevated levels of lysozyme, histatin-5, MMP-8, β-defensins, α-defensin-3, cathepsin G, and β-defensin-2 were more consistently associated with caries-active (CA) children, whereas higher concentrations of secretory IgA, cystatin S, α-amylase, statherin, and Mucin-1 (MUC1) were more frequently observed in caries-free (CF) children. However, conflicting results were reported for lysozyme and statherin, likely reflecting methodological heterogeneity across studies. Overall, this review supports the potential role of salivary proteins as biomarkers for ECC, particularly when used in combination as part of a diagnostic panel. Further standardized and multicenter studies are needed to validate these findings and to support the development of saliva-based, child-friendly diagnostic tools for early ECC detection.

Keywords

Early childhood caries; Saliva; Salivary proteins; Biomarkers; Pediatric dentistry

1. Introduction

According to the American Academy of Pediatric Dentistry (AAPD), early childhood caries (ECC) is defined as the presence of one or more decayed, missing or filled surfaces in any primary tooth of children aged 72 months or younger [1]. It is one of the most common chronic conditions affecting children worldwide and continues to pose a significant burden on healthcare systems due to its high prevalence, rapid progression, and need for early intervention [2, 3]. ECC is a multifactorial disease driven by the interactions among microbial, host, and environmental factors. Dysbiosis within the oral microbiome, frequent sugar exposure, inadequate oral hygiene practices and host susceptibility collectively contribute to the initiation and progression of caries [4].

Saliva is a complex biological fluid that provides mechanical cleansing, buffers oral pH, supports enamel remineralization, and contains numerous antimicrobial and immune-related proteins [5]. Salivary proteins including, lactoferrin, immunoglobulins, mucins, cystatins, defensins and proline-rich proteins contribute to oral homeostasis and may reflect underlying biological processes associated with ECC [6]. Consequently, these proteins have emerged as promising non-invasive biomarkers with potential applications in caries risk assessment, early detection, and personalized prevention strategies.

Despite growing interest in this area, existing studies vary widely in terms of study populations, protein targets, analytical

methods, and diagnostic criteria for ECC. A comprehensive synthesis of recent evidence is therefore essential to clarify current understanding, identify research gaps, and guide the development of clinically significant biomarkers for ECC. Although many studies report links between individual salivary proteins and ECC, the evidence remains fragmented, due to wide variation in study design and analytical approaches. Most existing reviews have focused on specific biomarkers or narrative summaries, without systematically integrating findings by biological function, methodological differences, or consistency of evidence. With the rapid growth of salivary proteomics and increasing interest in non-invasive pediatric diagnostics, a scoping review is timely to map the current evidence, highlight methodological gaps, and identify which salivary proteins are most consistently associated with caries status.

This review not only summarizes existing studies but also provides an integrated framework for interpreting salivary protein biomarkers in ECC and guiding future research and diagnostic development. Specifically, it systematically maps the available literature on salivary proteins associated with early childhood caries, focusing on studies published between January 2020 and August 2025. This review also aims to identify salivary proteins investigated in relation to ECC, compare protein profiles between caries-active (CA) and caries-free (CF) children, and summarize analytical approaches and methodological variations across studies.

Scoping review methodology was selected to address the objectives of this study. Although systematic reviews and meta-analyses are well suited for evaluating narrowly defined questions with homogeneous methodologies, the current literature on salivary protein biomarkers in early childhood caries is highly heterogeneous. Included studies vary widely in caries diagnostic criteria, saliva collection protocols, analytical platforms, and outcome reporting, precluding meaningful quantitative synthesis. In this context, a scoping review is more appropriate to map the breadth of available evidence, synthesize findings across diverse study designs, identify methodological gaps, and clarify areas where future systematic reviews or meta-analyses may become feasible.

2. Materials and methods

2.1 Study design

This scoping review was conducted using a structured methodological approach based on the Joanna Briggs Institute (JBI) framework and guided by the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [7, 8]. These guidelines ensured a transparent, systematic, and replicable approach to identifying and mapping existing literature related to salivary proteins and ECC, while addressing heterogeneity in study designs, methodologies, and outcome measures.

2.2 Research questions and study tools

This review aimed to explore the association between salivary proteins and ECC. The focused research question was:

"*What salivary proteins have been investigated in relation to ECC, and how do their concentrations differ between CA and CF children?*".

To address this question, a scoping review was conducted using the Population, Concept and Context (PCC) framework. The Population (P) of interest included children in early childhood, typically aged six years and below, without systemic diseases. The Concept (C) focused on salivary proteins, including but not limited to lactoferrin, immunoglobulins, mucins, and proline-rich proteins. The Context (C) involved the presence or absence of ECC, with studies examining differences or associations between CA and CF groups.

2.3 Eligibility criteria

Children aged 0–6 years were included, consistent with the accepted definition of early childhood caries and to capture the full developmental period during which ECC may occur. For consistency throughout this review, children with one or more CA lesions Decayed, Missing, Filled Teeth (DMFT/Decayed, Missing, Filled Surfaces (DMFS) $\geq$1 or equivalent diagnostic criteria) are referred to as CA, while children with no clinical evidence of caries (DMFT/DMFS = 0) are referred to as CF.

2.3.1 Inclusion criteria

1. Research Design: Observational, analytical, or laboratory-based study designs.

2. Population: Studies involving children aged 0–6 years providing detailed information on the clinical diagnosis of early childhood caries, using DMFT, DMFS, designated codes, visual inspection, intraoral examination, or International Caries Detection and Assessment System (ICDAS) criteria.

3. Concept: Studies assessing salivary proteins in relation to ECC.

4. Context: Studies conducted within the clinical context of ECC, involving comparisons between CA and CF children based on established diagnostic criteria.

5. Publication Date: Research published within the past five years (January 2020 to August 2025) in academic journals. A five-year timeframe was selected to ensure up-to-date evidence.

6. Language: Research articles published in English to ensure full understanding of the context.

7. Availability: Full-text articles must be accessible for evaluation.

2.3.2 Exclusion criteria

Studies were excluded if any of the following criteria applied:

1. Publication Date: Published before January 2020 or after August 2025.

2. Language: Not published in English to avoid translation bias or misunderstanding.

3. Accessibility: Full-text articles could not be accessed, preventing proper data extraction.

4. Article type: Review articles, editorials, letters, opinion pieces, and conference abstracts were excluded.

2.4 Information sources and search strategy

A comprehensive literature search was conducted using four major electronic databases: PubMed, EBSCOhost (Dentistry & Oral Sciences Source), ScienceDirect, and Google Scholar. These databases were selected to ensure broad coverage of relevant biomedical and dental research. The search strategy combined controlled vocabulary (such as Medical Subject Headings (MeSH) terms in PubMed) and free-text keywords, including "early childhood caries", "saliva", and "salivary proteins", linked using Boolean operators (AND, OR) to optimize sensitivity and specificity. The search was conducted in accordance with PRISMA-ScR guidelines, limited to English-language, peer-reviewed publications published between January 2020 and August 2025, and excluded grey literature to ensure data quality and comparability. Additional studies were identified by manually screening the reference lists of key articles and relevant reviews. The search strings and details are provided in Table 1.

2.5 Selection of evidence sources (study selection process)

The screening process was conducted independently by two researchers, who reviewed all retrieved records based on the following criteria: (i) studies that involved children in early childhood (typically under six years old) who were free from systemic diseases, and (ii) studies that examined salivary proteins in the context of ECC, either through clinical or *in vitro* analysis. Eligibility assessment was guided by the predefined inclusion and exclusion criteria. Discrepancies during study selection were resolved through discussion, and, when necessary, a third reviewer was consulted to reach consensus. The rationale for each inclusion and exclusion criterion is outlined in Table 2.

2.6 Data charting process and data items

Extraction and synthesis of information from the included articles were summarized and presented in tables (**Supplementary Table 1**, Ref. [9–18]; **Supplementary Table 2**, Ref. [9–18]), organized under descriptive, methodological, and thematic categories corresponding to the objectives and research questions of this scoping review. To ensure systematic reporting and consistency throughout the review process, a charting table was developed during the protocol stage to record relevant information, including author, year, country, study population, salivary proteins investigated, methods of analysis, and main findings.

The data extraction process was conducted using a structured charting form, which was piloted independently by two researchers on a sample of three articles. Following this pilot, the form was refined to ensure alignment with the review objectives and the PCC (Population, Concept, Context) framework. The finalized charting table was then applied consistently across all included studies and updated iteratively throughout the review process as new insights emerged.

A critical evaluation of the evidence regarding the association between salivary proteins and ECC was performed. The charted data were mapped to address the following core review questions:

1. What types of salivary proteins are associated with ECC?
2. What are the differences in salivary protein profiles between CA and CF children?
3. What laboratory or clinical methods are commonly used to identify salivary proteins in studies related to ECC?
4. What is the magnitude of the association between salivary

TABLE 1. Search strategy.

Database	Rationale	Search string	Filters
PubMed	A highly reliable source for peer-reviewed, evidence-based studies relevant to dentistry, oral health, and biomedical research.	"Early childhood caries" AND "saliva" AND "salivary proteins"	Year: 2020–2025; Full text; English; Human species; Age: birth–18 years
EBSCOhost (Dentistry & Oral Sciences Source)	Provides a wide range of peer-reviewed journals in dentistry, oral biology, and related clinical sciences, making it highly relevant for examining the relationship between ECC and salivary proteins.	"Early childhood caries" AND "saliva" AND "salivary proteins"	Year: 2020–2025; Full text; Academic journals; Peer reviewed
ScienceDirect	Allows access to numerous high-impact journals, many of which publish interdisciplinary research combining basic science, clinical application, and public health perspectives.	"Early childhood caries" AND "saliva" AND "salivary proteins"	Year: 2020–2025; Research articles; Open access and open archive; Subject areas: Medicine and Dentistry, Biochemistry, Genetics and Molecular Biology, and Immunology and Microbiology
Google Scholar	Provides an easy way to search for full text or metadata of scholarly literature across a wide range of publishing formats and disciplines.	"Early childhood caries" AND "saliva" AND "salivary proteins"	Year: 2020–2025

ECC: Early childhood caries.

TABLE 2. Rationale for each inclusion and exclusion criteria.

Criterion	Rationale for inclusion and exclusion
Population: Children (typically ≤6 years old).	ECC is defined as caries affecting children under 6 who are free from systemic disease; focusing on this group ensures relevance to the research question.
Concept: Studies investigating salivary proteins in relation to ECC.	Salivary proteins are the core focus of this review because this may serve as biomarkers.
Context: Studies comparing CA and CF groups.	This comparison is necessary to determine potential associations between salivary proteins and caries status.
Study design: Clinical studies, observational studies, and *in vitro* studies involving saliva analysis.	Both *in vivo* and *in vitro* studies provide valuable insight into the chemical and functional roles of salivary proteins.
Date of publication: From 01 January 2020 to 31 August 2025.	Focuses the review on recent evidence and current understanding of salivary proteins in ECC.

ECC: Early childhood caries; CA: caries-active; CF: caries-free.

proteins and caries status, and what are the implications for their use as predictive biomarkers?

The extracted data were analyzed based on the type of protein, saliva collection and processing methods, analytical approach (*e.g.*, Western blot, ELISA, proteomics), and population characteristics. Most studies quantified targeted proteins using enzyme-linked immunosorbent assays (ELISA), reflecting a hypothesis-driven approach. In contrast, a smaller number of studies employed proteomic techniques, such as liquid chromatography–mass spectrometry (LC–MS/MS), enabling broader protein profiling. Variations were also observed in sample preparation procedures, including centrifugation conditions, protein normalization strategies, and the use of commercial versus in-house assay kits. Attention was given to studies comparing CA and CF children, either clinically or via *in vitro* experiments. Differences in study design, diagnostic criteria for ECC, and sample handling methods were extracted and summarized to facilitate comparison across studies and highlight sources of analytical heterogeneity.

3. Results

3.1 Study selection

The database search identified 612 records. After removing duplicates and ineligible records, 119 articles remained for title and abstract screening. Following this screening, 119 full-text articles were assessed for eligibility. Of these, 20 articles could not be retrieved, and 89 were excluded for not meeting the inclusion criteria. Ultimately, 10 studies fulfilled the eligibility criteria and were included in this scoping review. Fig. 1 presents the PRISMA-ScR flow diagram illustrating the study selection process and the reasons for exclusion.

3.2 Primary characteristics of included studies

Supplementary Table 1 summarizes the primary characteristics of the 10 included studies [9–18]. All studies were conducted in Asia and collectively recruited 646 participants, comprising 313 CA children (48.5%) and 333 CF children (51.5%), with ages ranging from 9 months to 6 years. Most studies utilized unstimulated saliva samples, with only one study employing stimulated saliva [11]. Saliva collection times varied widely (08:00 AM to 12:00 PM), and reported sample volumes ranged from approximately 1 mL to 5 mL.

Caries assessment methods varied across studies. While the Decayed, Missing and Filled (DMF) index (DMFT/DMFS) was most frequently applied, four studies employed alternative approaches, including visual inspection, intraoral examination, designated codes, and caries detector liquid [10, 11, 13, 16]. Criteria for defining caries status also differed. Three studies classified DMFT ≥1 as indicative of CA children [9, 12, 17], while two studies defined CA children as DMFT/DMFS >4 [14, 16]. Conversely, five studies identified children with DMFT/DMFS = 0 as CF [9, 12, 14, 16, 17]. One study further differentiated low-risk children with DMFT scores between 1 and 4 [18]. This variation in caries assessment and classification criteria, including distinctions between CF and low-risk children, represents a key methodological source of heterogeneity across the included studies and should be considered when interpreting the findings.

3.3 Association between salivary proteins and caries

A range of salivary proteins was investigated across the included studies, namely: (1) lysozyme, (2) IgA, (3) histatin-5, (4) submandibular gland androgen regulatory protein 3B (SMR-3B), (5) Mucin-7, (6) cystatin S, (7) α-amylase, (8) MMP-8, (9) MMP-20, (10) statherin, (11) β-defensin, (12) α-defensin-3, (13) cathepsin G, (14) β-defensin-2, (15) MUC1, (16) MUC2, and (17) lactoferrin (**Supplementary Table 2**). Significant increases in salivary levels were reported in CA children for lysozyme [9], histatin-5 [10], MMP-8 [14], β-defensin [15], α-defensin-3 and cathepsin G [16], and β-defensin-2 [17]. Conversely, elevated levels in CF children were observed for IgA [10, 18], cystatin S [12], α-amylase [13], statherin [15], and MUC1 [18]. No statistically significant associations were noted for MMP-20 [14], statherin [17], lactoferrin, or lysozyme [18]. Notably, conflicting findings emerged for lysozyme and statherin: lysozyme levels were

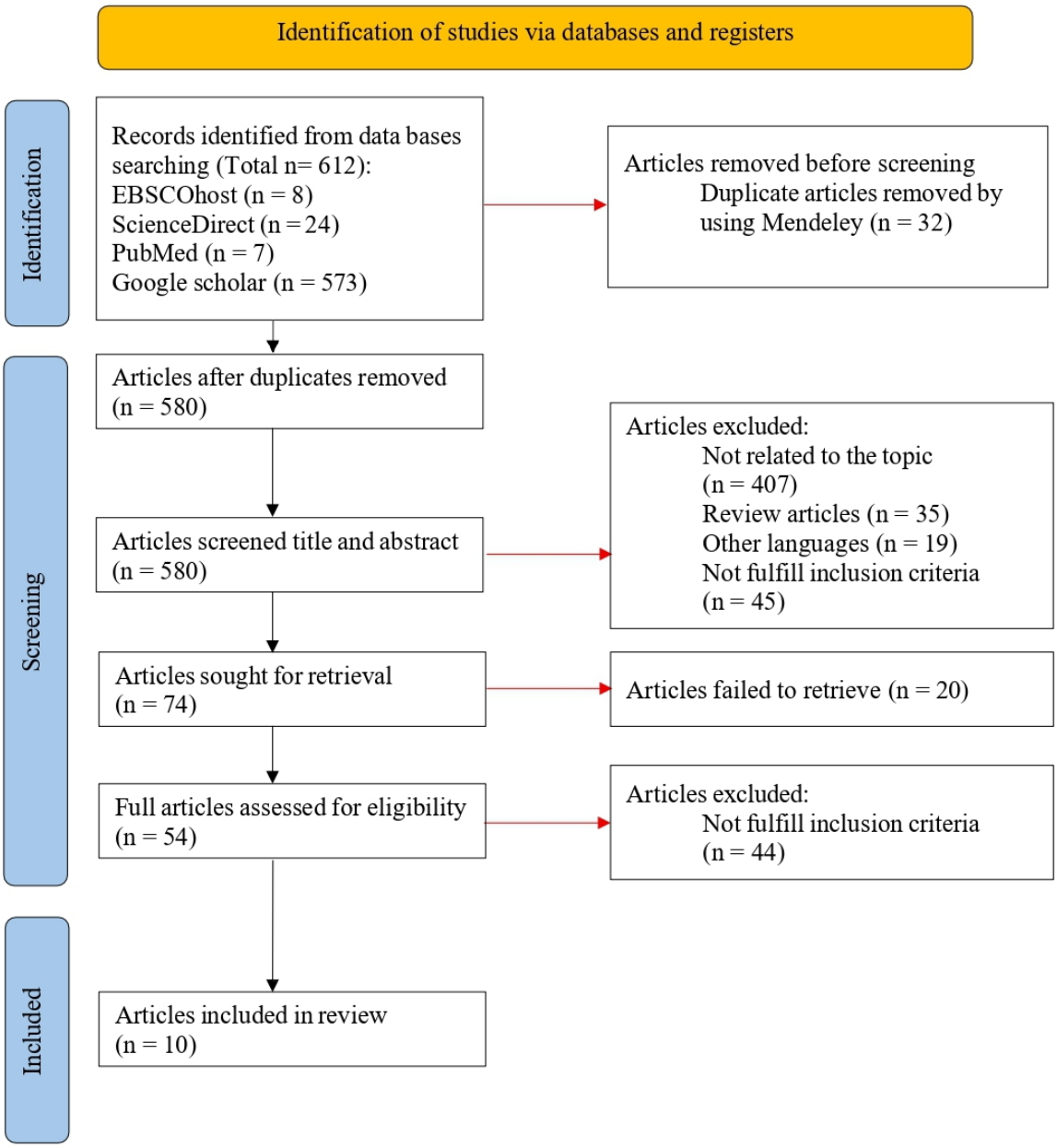

FIGURE 1. Flowchart of literature search and selection criteria adapted from the PRISMA.

significantly elevated in CA children in one study [9] but showed no significant difference in another [18]. Similarly, both studies on statherin reported decreased levels in CA children, though statistical significance was observed in one study [14] and not in the other [17].

4. Discussion

The primary contribution of this scoping review lies in the integrative synthesis of salivary protein biomarkers in ECC, rather than the identification of novel proteins. By grouping biomarkers according to biological function, assessing the consistency of evidence across studies, and explicitly highlighting methodological heterogeneity and knowledge gaps, this review provides a higher-level interpretation of the existing literature. This approach moves beyond simply reiterating individual protein associations, offering a structured perspective on which biomarkers appear most promising, which findings remain preliminary, and where future efforts should be focused.

This scoping review synthesized recent evidence on salivary proteins associated with ECC and highlighted that saliva contains a complex repertoire of host-derived biomolecules reflecting both protective functions and pathological processes in the oral cavity. Across the 10 included studies, two overarching patterns were consistently observed: (i) CA children exhibited elevated levels of proteins linked to innate immune activation and tissue degradation, and (ii) CF children displayed higher concentrations of proteins involved in enamel protection, immune exclusion, and pellicle formation. These patterns underscore the multifactorial nature of ECC, in which biological susceptibility interacts with microbial dysbiosis and environmental factors.

The salivary proteins identified in this review were organized according to shared biological functions. Broadly, biomarkers could be grouped into three categories: (i) inflam-

matory and innate immune proteins (*e.g.*, MMP-8, defensins, cathepsin G, lysozyme, histatin-5), (ii) enamel-protective and pellicle-associated proteins (*e.g.*, cystatin S, statherin, MUC1), and (iii) immune-regulatory and enzymatic proteins (*e.g.*, secretory IgA and α-amylase). This functional classification emphasizes distinct biological patterns associated with CA and CF states.

4.1 Upregulated host-defense proteins in CA children

A key finding was the consistent elevation of innate immune proteins including lysozyme, histatin-5, MMP-8, β-defensin, α-defensin-3, cathepsin G, and β-defensin-2 in CA children. These proteins, typically released during microbial challenges or inflammation, suggest that ECC is associated with a heightened inflammatory response.

The increased Lysozyme level, as reported by Maulitasari *et al.* [9], likely represents a compensatory response to elevated *Streptococcus mutans* burden. This aligns with prior studies showing lysozyme disrupts bacterial cell walls and rises during oral inflammation. However, Zhang *et al.* [18] report contradictory findings, indicating that lysozyme alone cannot reliably distinguish ECC status, as its expression may be influenced by gingival health or microbial load rather than caries alone.

Similarly, histatin-5, an antimicrobial peptide with antifungal and antiplaque properties, was markedly elevated in CA children. This supports the hypothesis that its upregulation is an attempt to control cariogenic biofilms. The observed co-variation between histatin-5 and low sIgA further suggests a compensatory mechanism, where deficiencies in mucosal immunity trigger greater reliance on innate peptides [10].

Matrix metalloproteinase-8 (MMP-8) emerged as a particularly promising marker, strongly associated with severe ECC, this is biologically plausible, as MMP-8 mediates collagen breakdown in demineralized dentin, directly contributing to lesion progression. In contrast, MMP-20, primarily active during tooth development, did not differ between CA and CF children, indicating limited relevance to active caries [14]. Defensins (β-defensin, β-defensin-2, α-defensin-3) and cathepsin G were also elevated, reflecting epithelial defence and neutrophil activation typical of ECC's inflammatory environment. Notably, cathepsin G remained significant after adjusting for confounders, suggesting its potential as a robust marker of caries severity [15–17].

Collectively, these findings indicate that ECC is characterized not only by microbial dysbiosis but also by upregulated mucosal immune and inflammatory responses, likely representing compensatory mechanisms against cariogenic biofilms.

4.2 Protective salivary proteins in caries-free children

CF children consistently showed higher levels of proteins involved in maintaining enamel integrity, microbial clearance and immune regulation. These include secretory IgA (sIgA), cystatin S, α-amylase, statherin and MUC1 [12, 13, 18]. These biomarkers are recognized as key components of the salivary innate immune defense due to their roles in microbial aggregation, inhibition of adhesion and modulation of host-microbe interactions [19].

Secretory IgA (sIgA) plays a critical role in immune exclusion by preventing bacterial adhesion, as widely described in mucosal immunity literature [20]. Most studies reported higher sIgA in CF children, although earlier literature indicates that sIgA may occasionally increase in response to bacterial load [21]. Age was positively associated with sIgA, emphasizing the need for age-standardized comparisons in future research [22].

Salivary α-amylase (sAA) was also higher in CF children, consistent with its role in agglutinating bacteria and clearing carbohydrates from the oral cavity [13]. While some older studies suggested sAA increases with caries activity, differences in population age and caries detection criteria may explain these inconsistencies [23].

MUC1, a low-molecular-weight mucin involved in lubrication and microbial adhesion inhibitions, was more abundant in CF children, whereas MUC2 tended to be higher in CA children [18]. This aligns with mucin biology literature, which demonstrates distinct functional roles of mucin subtypes in oral defense [24], suggesting that different mucins may differentially influence caries susceptibility and warrant further proteomic investigation.

Considering the evidence collectively, only a subset of salivary proteins showed consistent associations with caries status. MMP-8 emerged as the most reliable biomarker, consistently elevated in CA children across multiple studies, reflecting its role in active tissue degradation and inflammation. In contrast, cystatin S, α-amylase, and sIgA were more frequently associated with CF status, suggesting protective functions. Other proteins, including lysozyme, histatin-5, and statherin, showed variable or conflicting results and should be regarded as preliminary candidates requiring further validation.

4.3 Methodological heterogeneity and sources of variability

Although methodological heterogeneity was observed across the included studies, several key sources of variability warrant systematic consideration, as they likely contribute to inconsistencies in reported associations between salivary proteins and early childhood caries.

4.3.1 Caries diagnostic criteria

Substantial variability was evident in the diagnostic criteria used to define early childhood caries (ECC) and caries-free (CF) status. Studies employed differing approaches, including visual inspection, DMFT/DMFS indices, ICDAS scoring, and caries-detecting dyes. These non-uniform definitions complicate direct comparisons, as biomarkers associated with early enamel lesions may differ from those linked to cavitated or advanced disease.

4.3.2 Saliva collection and storage protocols

Saliva collection protocols varied considerably across studies with respect to stimulation status (stimulated *vs.* unstimulated), fasting duration prior to collection, collection devices, and timing. Age represents an additional source of hetero-

geneity; the included studies encompassed children aged 0–6 years, a period characterized by substantial developmental changes in salivary gland function, immune maturation, tooth eruption patterns, and oral microbial ecology, all of which may influence salivary protein composition. While some studies reported mean age or narrow age bands, few provided age-stratified analyses, limiting assessment of age-specific biomarker patterns. As a result, it was not possible to systematically assess age-specific biomarker patterns within this review. This broad developmental spectrum should therefore be considered when interpreting differences in salivary protein associations across studies.

Storage conditions also differed, including variations in centrifugation, storage temperature, and freeze–thaw cycles. These pre-analytical factors can affect protein stability and concentration, potentially influencing biomarker detectability and reproducibility.

4.3.3 Laboratory assays and analytical platforms

Marked heterogeneity was observed in laboratory methods. Studies employed ELISA, multiplex bead-based assays, mass spectrometry, and Western blotting. Variations in assay sensitivity, specificity, detection limits, and target specificity may partially explain discrepancies in reported protein levels.

4.3.4 Sample handling and assay variability

Few studies reported detailed sample handling procedures or provided inter- and intra-assay variability. Limited reporting of kit manufacturers, batch consistency, calibration standards, and quality control measures restrict evaluation of analytical reliability and may contribute to variability in biomarker quantification. The lack of standardized reporting further limits reproducibility across studies.

4.3.5 Limited number of studies

Only ten studies met the inclusion criteria, reflecting both the limited number of recent investigations on salivary proteins in ECC and the application of strict eligibility criteria, including focus on pediatric populations ($\leq$6 years), full-text peer-reviewed publications, and clearly defined caries assessment methods. While consistent patterns were observed for certain proteins, the small evidence base limits generalizability and precludes definitive conclusions. The results should therefore be interpreted as indicative rather than conclusive, highlighting areas for future research.

4.3.6 Salivary composition and sample quality considerations

An additional source of variability relates to factors influencing salivary composition and sample quality, which were inconsistently reported across studies. Few studies accounted for salivary flow rate or normalized protein levels to total protein concentration, despite directly impacting measured biomarker levels. Circadian variation was rarely controlled, with saliva collected at different times of day or without standardized timing, potentially affecting protein expression profiles. Moreover, limited information was provided regarding sample contamination, including the presence of blood, food debris, or gingival inflammation, which may confound salivary protein measurements.

The inconsistent consideration and reporting of these pre-analytical factors further limit comparability across studies and complicates interpretation of biomarker associations. Collectively, these methodological differences underscore the need for cautious interpretation of individual findings and highlight the importance of standardized protocols for caries diagnosis, saliva collection and processing, and laboratory analysis in future research.

4.4 Toward a multimarker diagnostic approach

Based on this review, no single salivary protein is sufficient to serve as biomarker for ECC. This aligns with broader biomarker research, where multimarker panels generally outperform single-protein indicators due to the multifactorial nature of disease pathways [25, 26]. Combining multiple salivary proteins—including inflammatory markers (MMP-8 and defensins), protective proteins (statherin, cystatin S and sIgA), and enzymatic regulators (α-amylase)—is likely to improve diagnostic accuracy.

In addition, high-throughput proteomics procedure combined with machine learning offers a promising method for developing a saliva-based diagnostic panel suitable for chairside screening in children. Proteomics has demonstrated strong potential for identifying complex biomarker signatures [27, 28], and machine learning has shown excellent accuracy in classifying caries risk from multidimensional salivary data. However, further validation in large and diverse paediatric populations is needed before these models can be used in routine practice [29].

The development of saliva-based diagnostic kit would align with the goals of minimally invasive dentistry which enable early detection, personalized prevention and timely intervention. Moreover, the kit would particularly be valuable for young children who often struggle with conventional diagnostic procedures.

4.5 Knowledge gaps and future directions

Despite growing interest in salivary proteins as potential biomarkers for ECC, significant gaps remain. Most studies included in this review were cross-sectional, limiting insight into the temporal relationship between salivary protein expression and caries initiation or progression. Longitudinal validation across independent pediatric populations is scarce, and the influence of age-related immune maturation, oral microbiome dynamics, and behavioral factors on salivary protein profiles remains insufficiently characterized.

In addition, several practical and methodological challenges must be addressed before salivary protein panels can be translated into clinical tools. Evidence on assay feasibility, cost-effectiveness, and standardization across laboratories is limited, and common confounding factors—such as diet, oral hygiene, fluoride exposure, and concurrent oral inflammation—are often inadequately controlled. The lack of longitudinal and real-world testing further restricts understanding of how salivary protein profiles perform in routine clinical settings.

Addressing these gaps will be essential to determine whether salivary protein panels can serve as reliable, non-invasive adjuncts for ECC risk assessment.

5. Conclusions

This scoping review highlights the potential of salivary proteins as biomarkers for early childhood caries. Elevated levels of proteins involved in host defense and inflammation (*e.g.*, lysozyme, histatin-5, MMP-8, β-defensins, cathepsin G) were associated with caries activity, whereas protective proteins (*e.g.*, secretory IgA, cystatin S, α-amylase, statherin, MUC1) were more prevalent in caries-free children (CF) children. While several salivary proteins show promise as biomarkers, substantial methodological heterogeneity and important gaps in knowledge limit definitive conclusions regarding their diagnostic or predictive utility.

Future research should prioritize standardized caries definitions, harmonized saliva collection and analytical protocols, and longitudinal study designs to allow robust validation of candidate biomarkers. Such efforts will be essential for developing reliable, non-invasive salivary diagnostics for early childhood caries.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

NSMZ—Conceptualization, collection of data, data analysis, resources, writing original draft preparation, editing. NIBS—funding acquisition, conceptualization, visualization, revision, approval, supervision. SAAG, RMH, NMI—visualization, revision, approval, supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/2072871695448719360/attachment/Supplementary%20material.docx.

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