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**Review Article**

# The role of salivary biomarkers in dental caries: A systematic review

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## Abstract

Saliva plays a vital role in maintaining oral health and preserving tooth integrity. Its components help minimize tooth surface demineralization, protect against wear, and support enamel remineralization. There is a growing interest in utilizing salivary biomarkers for caries diagnosis and prediction. However, despite extensive research, a consensus among scholars has yet to be reached. This study aims to provide further evidence regarding the effectiveness of salivary biomarkers in diagnosing dental caries. A comprehensive electronic search was conducted across PubMed, Elsevier's Scopus, EMBASE, and Web of Science, and studies meeting the inclusion criteria were selected. The study selection process followed the PECOS framework, while the STROBE checklist was used to assess the risk of bias. A total of 18 studies were included in the analysis, all of which provided relevant data aligned with the study objectives. Findings revealed associations between salivary biomarkers and dental caries, with both positive and negative correlations. Due to significant heterogeneity among studies, a meta-analysis could not be conducted. Overall, salivary biomarkers play a crucial and complementary role in maintaining tooth integrity and may serve as reliable indicators for predicting or diagnosing dental caries.

**Keywords:** Dental Caries, Saliva, Salivary biomarkers, Oral Health and Diagnosis

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## 1. Introduction

Dental caries is a complex microbial disease and remains one of the most widespread health issues. Saliva, which bathes both hard and soft tissues in the oral cavity, comprises organic and inorganic elements that play a crucial role in host defense. Due to its rich composition, saliva serves as a potential biomarker for detecting dental caries. Clinicians can utilize salivary diagnostic kits to assess, prevent, and predict the progression of caries, enabling evidence-based treatment strategies. Biomarkers found in body fluids offer valuable information about physiological conditions, and a consistent, reproducible biomarker often termed a molecular signature can be instrumental in disease risk assessment, diagnosis, prognosis, and monitoring[1]. The average stimulated salivary flow rate is about 7 mL/min, while the unstimulated rate is approximately 3 mL/min[2]. Research on dental caries has produced varying outcomes, leading to the recommendation of systematic reviews in evidence-based dentistry to establish standardized associations between salivary components and caries development. Understanding saliva's physiological properties, antioxidant levels, protein and electrolyte variations, and their relationship with dental caries can enhance knowledge of the disease and improve preventive and therapeutic approaches.[2]

The physiology of saliva is influenced by both its flow rate and viscosity. The parasympathetic and sympathetic nervous systems regulate the neurohormonal signaling that controls salivary secretion. Saliva plays a crucial role in the oral microbiome and the formation of the oral biofilm, as well as in maintaining the overall oral environment. The interaction between saliva and the oral microbiota occurs through various mechanisms, including the clearance of

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microorganisms by binding to them, the oral pellicle acting as a site for microbial adhesion, enhancing microbial killing, and providing nutritional substrates for microbes[3].

**Table 1:** Quality assessment of the studies using STROBE criteria X-presence of criteria.

| Criteria | Inclusion Criteria | Exclusion 7Criteria | No Fluoride exposure during tooth development | Dental Caries diagnostic criteria | Radiographic exam | Experienced examiner calibrated examiner | Salivary collection description | Salivary analysis description |
|---|---|---|---|---|---|---|---|---|
| Hegde (2014)[10] | X | X | | X | | X | X | X |
| Gornowiz (2014)[13] | X | X | | X | | X | X | X |
| Gabryel Porowska (2014)[12] | X | X | | X | | X | X | X |
| Jurczak (2015)[14] | X | X | | X | | X | X | X |
| Teng-Yu (2015)[18] | | | | | X | X | X | X |
| Borghi (2016)[16] | X | X | | X | | X | X | X |
| Heba (2016)[25] | X | X | | X | | X | X | X |
| Castro (2016)[20] | X | X | | X | | X | X | X |
| Nireeksha (2017)[18] | X | X | | X | | X | X | X |
| Makawi (2017)[23] | X | X | | X | | X | X | X |
| Picco (2017)[15] | X | X | | X | | X | X | X |
| Muruge shappa (2018)[17] | X | X | | X | | X | X | X |
| Sejdini (2018)[19] | X | X | | X | | X | X | X |
| Monea (2018)[21] | X | X | | X | | X | X | X |
| Khasndelwa (2019)[19] | X | X | | X | | X | X | X |
| Angarita -Díaz (2021)[22] | X | X | | X | | X | X | X |
| Pateel (2022)[24] | X | X | | X | | X | X | X |
| Aparna K S (2023)[44] | X | X | X | X | | X | X | X |

| Risk of bias | Blinded study | Paired groups | Statistical analysis description |
|---|---|---|---|
| Low | | X | X |
| Low | | X | X |
| Low | | X | X |
| Low | | X | X |
| Low | X | X | X |
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| Low | | X | X |
| Low | | X | X |
| Low | | X | X |
| Low | | X | X |
| Low | | X | X |

The secretion of various ions within the salivary fluid helps maintain the viscoelastic properties of saliva, along with the presence of salivary proteins. This contributes to digestion, enhances antimicrobial defense, and supports functions such as taste and lubrication. Salivary proteins, such as proline-rich proteins, mucins, histatins, cystatins, and statherins, provide protective benefits to tooth surfaces by attracting calcium ions and promoting remineralization. The pellicle formed on the tooth surface slows down demineralization and reduces microbial adhesion, thus offering protection from fluctuations in pH. Additionally, the buffering capacity of saliva helps neutralize acids, further aiding in the protection of oral health.[3,4]

Saliva's physiology is influenced by its flow rate and viscosity, regulated through neurohormonal signaling by the parasympathetic and sympathetic nervous systems. Salivary fluid plays a crucial role in maintaining the oral microbiome, forming the salivary film, and preserving the overall oral environment. The interaction between oral microbiota and saliva occurs through various mechanisms, including microbial clearance via binding, the formation of oral pellicles that reduce microbial adherence, and protection of tooth surfaces from pH fluctuations. Additionally, saliva contributes to buffering capacity, facilitating acid neutralization.[5]

Several studies in systematic reviews highlight the significance of these salivary components in the initiation and progression of dental caries. Saliva also serves as a binding site for microbial adhesion while enhancing microbial clearance and providing essential nutrients for microbial metabolism. The secretion of various ions in salivary fluid maintains its viscoelastic properties, supporting digestion, antimicrobial defense, and sensory functions like taste and lubrication. Key salivary proteins such as proline-rich proteins, mucins, histatins, cystatins, and statherins help protect tooth surfaces, attract calcium ions, and promote remineralization[6]. Additionally, the acquired salivary pellicle plays a crucial role in slowing demineralization and safeguarding dental structures.

## 2. Materials and Methods

The methodology for this study involved a systematic electronic search using PubMed, Scopus, Web of Science, and Google Scholar. The search strategy was designed to incorporate MESH terms such as “dental caries susceptibility,” “caries risk assessment,” “salivary biomarkers,” “saliva,” “proteins,” “electrolytes,” “biomarkers,” and “antioxidants,” with a restriction to human studies published between 2015 and 2023. For study selection, inclusion criteria required that the review article be published in English and follow the PECOS framework, which includes Population (P), Exposure (E), Comparator (C), Outcome (O), and Study Design (S). The target population consisted of healthy individuals, not on medication affecting salivary flow or composition. The exposure focused on salivary components as biomarkers for dental caries, while the comparator included individuals with or without a history of dental caries or those classified based on caries risk levels. The primary outcome was the presence of dental caries in permanent dentition. Eligible study designs included clinical trials, case-control studies, in vitro studies, cross-sectional studies, and cohort studies, provided they were published in peer-reviewed scientific journals. Exclusion criteria comprised case reports, review articles, book chapters, theses, and guidelines. Additionally, all selected studies were assessed using the STROBE criteria checklist to evaluate their suitability for inclusion in the systematic review.

### *2.1. Data collection*

Observational studies investigating the association between various salivary components and dental caries.

### *2.2. Risk of bias assessment*

The risk of bias for the selected articles was evaluated using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist,[7] which consists of twelve essential criteria. Studies that scored eight or higher were deemed to have a low risk of bias, those with scores ranging from four to seven were categorized as having a moderate risk of bias, and studies with scores of three or lower were considered to have a high risk of bias.

## 3. Results

### *3.1. Study search and selection*

A total of 1160 articles were retrieved as potentially relevant records from all the databases searched. Of the total sources, 729 sources were eliminated in the deduplication process. The 430 obtained sources were screened via their titles and abstracts, and 321 articles were excluded due to non-conformity with the study objective. The remaining 109 records were subjected to full-text screening based on the predefined eligibility criteria. Ninety-one studies that did not meet the eligibility standards were excluded from the study. Finally, 18 records were certified to meet the inclusion criteria fully and thus considered for inclusion in this study. Details of the search and selection results are presented in. **Figure 1**.

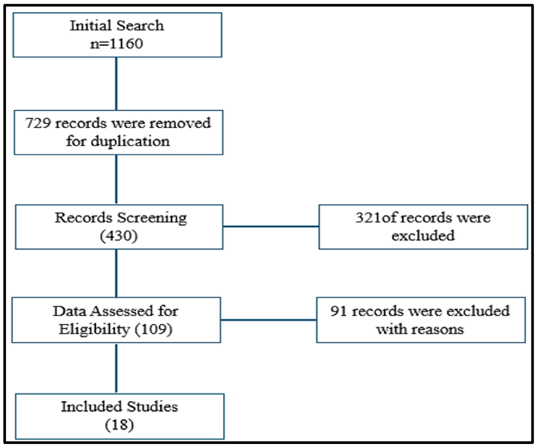


**Figure 1:** PRISMA flow diagram of search study selection process

Conflicting results were also observed in evaluating salivary total protein across three studies. Two studies found a positive correlation between high protein concentrations and the caries-active population.[10,17] while one study reported a negative correlation between high protein levels and caries-free participants.[20] Similarly, contradictory findings were seen in studies of carbonic anhydrase (CA VI), where one study found a positive correlation with high CA VI levels in the caries-active group[16]. In contrast, another found higher CA VI concentrations in caries-free participants.[23] Alpha-amylase results also varied; two studies[15,21] showed a positive association with higher enzyme concentrations in the caries-active group, whereas one study indicated relatively higher alpha-amylase concentrations in caries-free participants,[16] suggesting a protective role. It was proposed that as alpha-amylase levels decrease, the caries-active group is more likely to develop additional caries. For the zinc marker, two studies[10,19] presented conflicting results. However, a significant negative correlation was found for proteinase 3 (PR3),[18] statherin,[22,24] and LL-37,[8] where higher concentrations were observed in caries-free or low caries risk participants, indicating these molecules potentially reduce caries incidence in those groups.

In terms of saliva types, nine studies examined unstimulated saliva,[9,11,13,14,18,20,21,22] two studies focused on stimulated saliva,[24,25] three studies analyzed whole saliva,[8,15,16] and four studies assessed both whole unstimulated and stimulated saliva.[10,17,19,23] The majority of saliva samples were collected in the morning and afternoon (between 8:00 a.m. and 1:00 p.m.) in 12 studies, although six studies did not specify the time range for sample collection.[11,14,15,21,23,25] The most common dental caries index was the DMF (DMFS/DMFT), used in 15 studies. Three studies used different methods: one used visual detection[21], another used ICADS,[22] and the third used a combination of ICADS and DMFS.[16] For salivary biomarker assessment, six studies employed the ELISA test,[17,16,17,18,20,22] four used spectrophotometry,[10,15,16,17] two used radial immunodiffusions with the Diffu-Plate kit[11] [18,32] two used colorimetric tests.[9,23] Others used a range of other assays, such as high-sensitivity assays (USCNK),[12] AGAPPE,[8] and USCNK plus ELISA,[13] as well as ELISA combined with colorimetric kits.[24]

## 4. Correlation Between Salivary Biomarkers and Dental Caries

The included studies investigated various salivary biomarkers, including mucin, histatin, proline-rich proteins (PRP), lactoperoxidase, C-reactive proteins, cathelicidin (LL-37), immunoglobulin (IgA), albumin, statherin, total salivary protein, SOD, copper, zinc, proteinase 3 (PR3), alpha-amylase, and carbonic anhydrase (CA IV). Despite some established correlations between the concentration levels of these biomarkers and the pathogenicity of dental caries, contradictory results were noted for several markers. Immunoglobulin (IgA) was the most widely studied biomarker, with six studies examining it. [8,11,13,20,22,25] All but one study[13] found a negative correlation, where higher IgA concentrations were found in caries-free groups, highlighting its protective role in dental and oral health. Mucin, evaluated by two studies[8,12] [15,19], was positively associated with high cari8ies prevalence or high caries risk. Similar associations were found for histatin, 5[13,14] lactoperoxidase,[8,13] C-reactive protein,[8] SOD,[10] and copper,[10] which all showed positive correlations with dental caries.

| First Author, Year of Publication | Study Information and Findings |
| --- | --- |
| Hegde (2014)[10] | Country: India<br>Study Design: Experimental cohort study<br>Sample Size: 80 healthy participants<br>20 caries-free individuals (DMFT = 0)<br>60 caries-active individuals (DMFT > 10)<br>Participant Age: 25–50 years<br>Saliva Type: Stimulated and unstimulated saliva<br>Caries Index Score: DMFT (Decayed, Missing, and Filled Teeth)<br>Sample Collection Time: Noon<br>Data Analysis: Student's t-test<br>Method for Assessing Salivary Biomarkers/Proteins:<br>Atomic nitroblue tetrazolium chloride reduction method<br>Absorption spectrophotometry<br>Saliva Parameters/Proteins Assessed: Superoxide dismutase (SOD) activity<br>Total protein levels Copper and zinc concentrations<br>Biomarker Levels:<br>Total protein: Caries-free (0.19 ± 0.049) vs. Caries-active (0.35 ± 0.139)<br>Copper: Caries-free (0.237 ± 0.051) vs. Caries-active (0.511 ± 0.096)<br>Zinc: Caries-free (0.93 ± 0.50) vs. Caries-active (1.169 ± 0.21)<br>Key Findings:<br>Copper and zinc levels were significantly higher in caries-active participants.<br>Increased SOD activity was observed in the caries-active group.<br>Conclusion:<br>The concentration of total salivary protein, copper, and zinc increased with dental caries.<br>These biomarkers could serve as non-invasive indicators for diagnosing and monitoring caries progression. |
| Gornowicz (2014)[13] | Country: Poland<br>Study Design: Experimental cohort stud<br>Sample Size: 35 adolescents<br>Control group: 8 participants (DMF = 3)<br>Experimental group: 27 participants (DMF > 11<br>Participant Age: 18 years<br>Saliva Type: Unstimulated whole saliva<br>Caries Index Score: DMFT (Decayed, Missing, and Filled Teeth)<br>Sample Collection Time: Between 9:00 a.m. and 11:00 a.m.<br>Data Analysis: Mann–Whitney U nonparametric test<br>Method for Assessing Salivary Biomarkers/Proteins:<br>High-sensitivity assay kit (USCNK)<br>ELISA (Enzyme-Linked Immunosorbent Assay)-<br>Saliva Parameters/Proteins Assessed:<br>Secretory Immunoglobulin A (sIgA)<br>Histatin-5 Lactoperoxidase (LPO)<br>Biomarker Levels: sIgA (mg/dL): Control (8.10; range 2.1–22.2) vs. Experimental (13; range 7.2–23.8)<br>Histatin-5 (ng/mL): Control (16.89; range 14.11–29.95) vs. Experimental (66.84; range 14.11–649)<br>LPO (nmol/L): Control (2148; range 1305–3248) vs. Experimental (3047; range 1515–3313)<br><br>Key Findings: The experimental group (DMF > 11) exhibited significantly higher levels of sIgA, histatin-5, and lactoperoxidase compared to the control group.<br>The increase in salivary biomarkers suggests a strong association with dental caries presence.<br>Conclusion: Elevated levels of sIgA, histatin-5, and lactoperoxidase are strongly correlated with increased caries incidence.<br>These biomarkers have potential utility in diagnosing and predicting the onset and progression of dental caries. |
| Gabryel-Porowska (2014)[12] | Country: Poland<br>Study Design: Experimental cohort study<br>Sample Size: 35 patients<br>Control group: 8 participants (DMF = 3) |

| | |
|---|---|
| | Research group: 27 participants (DMF > 11)<br>Participant Age: 18 years<br>Saliva Type: Unstimulated whole saliva<br>Caries Index Score: DMFT (Decayed, Missing, and Filled Teeth)<br>Sample Collection Time: Between 9:00 a.m. and 11:00 a.m.<br>Data Analysis:<br>Mann–Whitney U nonparametric test<br>Shapiro–Wilk test / t-test<br>Method for Assessing Salivary Biomarkers/Proteins: High-sensitivity assay kits (USCNK)<br>Saliva Parameters/Proteins Assessed:<br>MUC5B<br>MUC7<br>MUC1<br>Biomarker Levels (ng/mL):<br>MUC5B: Control (0.05; range 0.05–0.78) vs. Research group (0.70; range 0.06–2.34)<br>MUC7: Control (0.17; range 0.06–0.32) vs. Research group (0.13; range 0.06–0.42)<br>MUC1: Control (0.17 ± 0.05) vs. Research group (0.24 ± 0.08)<br>Key Findings:<br>MUC1 and MUC5B protein levels were higher in the research group compared to the control group.<br>MUC7 levels showed a slight decrease, but the difference was not statistically significant.<br>Conclusion:<br>The study indicates a correlation between salivary mucins (MUC1 & MUC5B) and the prevalence of dental caries.<br>These salivary biomarkers could serve as effective indicators for the detection and diagnosis of dental caries. |
| Jurczak (2015)[14] | Country: Poland<br>Study Design: Experimental cohort study<br>Sample Size: 82 pediatric patients<br>Control group (ECC caries-free): 41 participants<br>Experimental group (patients with ECC): 41 participants<br>Participant Age: Not reported<br>Saliva Type: Unstimulated saliva<br>Caries Index Score: DMFT (Decayed, Missing, and Filled Teeth)<br>Sample Collection Time: Not reported<br>Data Analysis Methods:<br>t-test<br>One-way ANOVA<br>Method for Assessing Salivary Biomarkers/Proteins: ELISA<br>Saliva Parameters/Proteins Assessed:<br>Defensin-2<br>Histatin-5<br>Biomarker Levels (ng/mL):<br>Histatin-5:<br>Control group: 15.29 ± 1.16<br>Experimental group: 50.75 ± 2.11<br>Defensin-2:<br>Control group: 2.15 ± 0.07<br>Experimental group: 2.29 ± 0.05<br>Key Findings:<br>Significant increase in histatin-5 and defensin-2 levels was observed in the experimental group compared to the control group.<br>These elevated salivary biomarkers correlated with the progression of caries.<br>Conclusion:<br>The variation in salivary protein concentrations during dental caries progression suggests their potential as biomarkers for detecting and diagnosing early caries onset and disease progression. |
| Teng-Yu m (2015)[15] | Country: China<br>Study Design: Experimental study<br>Sample Size: 128 healthy children<br>No dental caries (NDC) (DMFT = 0): 46 participants<br>Low dental caries (LDC) (DMFT = 1–4): 49 participants |

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| | High dental caries (HDC) (DMFT = 5–15): 33 participants<br>Participant Age: 6 years<br>Saliva Type: Whole, unstimulated saliva<br>Caries Index Score: DMFT (Decayed, Missing, and Filled Teeth)<br>Sample Collection Time: Between 8:00 and 10:00 AM<br>Data Analysis Method: One-way ANOVA<br>Method for Assessing Salivary Biomarkers/Proteins: ELISA kit/test<br>Salivary Parameter/Protein Assessed: Salivary proteinase 3 (PR3)<br>Biomarker Levels (ng/mL):<br>NDC group: 17.82 ± 7.31<br>LDC group: 12.79 ± 6.19<br>HDC group: 11.07 ± 7.10<br>Key Findings:<br>PR3 levels significantly decreased as dental caries severity increased.<br>A negative correlation was observed between PR3 concentration and dental caries progression.<br>Conclusion:<br>The inverse relationship between PR3 levels and dental caries suggests that PR3 could serve as a potential biomarker for detecting and diagnosing caries prevalence. |
| Borghi (2016)[16] | Country: Brazil<br>Study Design: Longitudinal study<br>Sample Size: 100 children<br>Caries-free group: 55 participants<br>Caries-active group: 45 participants<br>Participant Age: 24 to 48 months<br>Saliva Type: Whole saliva<br>Caries Index Scores: DMFS (Decayed, Missing, and Filled Surfaces) and DMFT (Decayed, Missing, and Filled Teeth<br>Sample Collection Time: Between 8:00 and 10:00 AM<br>Data Analysis Methods: Shapiro–Wilk test, Mann–Whitney test, Spearman correlation<br>Method for Assessing Salivary Biomarkers/Proteins: ELISA kit and zymography<br>Salivary Biomarkers Assessed: Alpha-amylase and carbonic anhydrase VI (CAVI)<br>Biomarker Levels:<br>Alpha-amylase (U/mL):<br>Caries-free group: 99.2 ± 84<br>Caries-active group: 55.6 ± 52.8<br>CAVI Activity (U/mL):<br>Caries-free group: 0.250 ± 0.43<br>Caries-active group: 0.31 ± 0.65<br>Key Findings:<br>CAVI levels were significantly higher in the caries-active group.<br>Alpha-amylase levels were significantly higher in the caries-free group.<br>Children with lower alpha-amylase levels were more prone to developing early childhood caries (ECC).<br>Conclusion:<br>The negative correlation between alpha-amylase and dental caries suggests that this biomarker could serve as a predictive indicator for assessing the risk of caries progression. |
| Heba (2016)[25] | Country: Iraq<br>Study Design: Experimental cohort study<br>Sample Size: 60 healthy children<br>Caries-free group: 30 participants<br>Caries-active group: 30 participants<br>Participant Age: 7 to 10 years<br>Saliva Type: Stimulated saliva<br>Caries Index Scores: DMFT (Decayed, Missing, and Filled Teeth) and dmft (deciduous teeth index)<br>Sample Collection Time: Not reported<br>Data Analysis Methods: SPSS, ANOVA<br>Method for Assessing Salivary Biomarkers/Proteins: Radial immunodiffusion method using immunodiffusion plates (Diffu-Plate kit)<br>Salivary Biomarker Assessed: Immunoglobulin A (IgA) |

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| | Biomarker Levels (mg/dL):<br>Caries-free group: 127.29 ± 28.14 or 130.52 ± 29.17<br>Caries-active group: 112.22 ± 31.33 or 103.77 ± 24.20<br>Key Findings:<br>Salivary IgA levels were significantly higher in caries-free children compared to caries-active children.<br>This suggests that IgA may play a protective role against dental caries.<br>Conclusion:<br>The inverse correlation between IgA levels and dental caries prevalence suggests that IgA could serve as a prognostic biomarker for detecting and monitoring caries progression. |
| Castro (2016)[20] | - Country: Chile<br>- Study Design: Experimental cohort study<br>- Sample Size: 40 participants<br>Caries-free group: 20 individuals<br>Caries-active group: 20 individuals<br>Participant Age: 22–28 years<br>Saliva Type: Unstimulated saliva<br>Caries Index Scores: ICADS and DMFT<br>Sample Collection Time: Between 9:00 and 11:00 a.m.<br>Data Analysis: Student's t-test<br>Method for Assessing Salivary Biomarkers/Proteins: Bradford method using a spectrophotometer and Western blotting<br>Salivary Biomarkers Assessed: Total protein concentration and salivary IgA<br>Biomarker Levels:<br>Total protein concentration:<br>Caries-free group: 50.65 ± 7.5 g/mL<br>Caries-active group: 26.80 ± 2.5 g/mL<br>IgA levels:<br>Caries-free group: 11.27 ± 0.5 g<br>Caries-active group: 1.71 ± 0.2 g<br>Key Findings:<br>Total protein concentration was significantly higher in caries-free participants compared to those with active caries.<br>Salivary IgA levels were also notably higher in the caries-free group, suggesting a potential protective function.<br>Conclusion:<br>The observed association between salivary IgA levels and dental caries suggests that IgA could serve as a biomarker for assessing caries risk and monitoring disease progression. |
| Nireeksha (2017)[8] | Country: India<br>Study Design: Experimental cohort study<br>Sample Size: 80 participants<br>Caries-free group: 20 individuals<br>Caries-active group: 60 individuals<br>Participant Age: 25–40 years<br>Saliva Type: Whole saliva<br>Caries Index Scores: DMFT<br>Sample Collection Time: Between 10:00 and 11:00 a.m.<br>Data Analysis: ANOVA test followed by Tukey's post-hoc test<br>Method for Assessing Salivary Biomarkers/Proteins: AGAPPE<br>Salivary Biomarkers Assessed: Mucins, salivary proline, C-reactive protein, proteomics, and salivary immunoglobulin (IgA)<br>Biomarker Levels:<br>Total salivary protein concentration:<br>Caries-free group: 2.04 g/dL<br>Caries-active group:<br>Group I: 1.71 g/dL<br>Group II: 0.82 g/dL<br>Group III: 0.51 g/dL<br>Proline protein bands:<br>95% in the caries-free group |

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| | 65% in the caries-active group<br>Key Findings:<br>Higher levels of salivary total protein, IgA, and albumin-globulin were observed in the caries-free group.<br>In contrast, mucin and salivary C-reactive protein levels were significantly elevated in the caries-active group.<br>Conclusion:<br>The study identified both positive and negative correlations between various salivary biomarkers and dental caries, indicating their potential role in detecting the onset and progression of the disease. |
| Makawi (2017)[23] | Country: Egypt<br>Study Design: Experimental cohort study<br>Sample Size: 120 children<br>Caries-free/low caries risk: 60<br>Caries-active/high caries risk: 60<br>Participant Age: 3–5 years and 13–15 years<br>Saliva Type: Stimulated and non-stimulated saliva<br>Caries Index Scores: DMFT and dmft<br>Sample Collection Time: Not reported<br>Data Analysis: One-way ANOVA followed by Tukey's post-hoc test<br>Method for Assessing Salivary Biomarkers/Proteins: Ericsson method and Colorimetric ab65622 (Abcam)<br>Salivary Biomarkers Assessed: Carbonic anhydrase VI (CAVI) and phosphate buffer activity<br>Biomarker Levels:<br>CAVI levels:<br>Caries-free group: 6.75 ± 0.44<br>Caries-active group: 3.87 ± 1.47<br>Phosphate buffer activity:<br>Caries-free group: 5.94 ± 1.76<br>Caries-active group: 3.84 ± 0.42<br>Key Findings:<br>The caries-free/low-risk group exhibited significantly higher levels of CA VI and phosphate buffer activity compared to the caries-active/high-risk group.<br>A similar trend was observed in phosphate buffer concentrations, where the caries-free group showed superior levels compared to the caries-active group.<br>Conclusion:<br>The negative correlation between phosphate buffer activity, CAVI levels, and dental caries suggests that these biomarkers have the potential to predict and monitor the progression of dental caries. |
| Picco (2017)[15] | Country: Brazil<br>Study Design: Cross-sectional study<br>Sample Size: 74 children<br>Caries-free: 37<br>Caries-active: 37<br>Participant Age: 7–9 years<br>Saliva Type: Whole saliva<br>Caries Index Scores: DMFT<br>Sample Collection Time: Not reported<br>Data Analysis: Student's t-test and Mann–Whitney test<br>Method for Assessing Salivary Biomarkers/Proteins: ELISA and zymography<br>Salivary Biomarkers Assessed: Carbonic anhydrase VI (CAVI)<br>Biomarker Levels:<br>CAVI activity:<br>Caries-free group: 1383 ± 1076<br>Caries-active group: 3391 ± 2046<br>Key Findings:<br>Lower salivary CAVI levels were detected in the caries-free group.<br>In contrast, CAVI activity was significantly higher in the caries-active group, suggesting a relationship between elevated enzyme activity and dental caries.<br>Conclusion:<br>Salivary CAVI may serve as a potential biomarker for diagnosing and detecting dental caries. |

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| Murugeshappa (2018)[17] | Country: India, Malaysia, and China<br>Study Design: Experimental cohort study<br>Sample Size: 70 participants<br>Caries-free: 35<br>Caries-active: 35<br>Participant Age: 7–12 years<br>Saliva Type: Stimulated and unstimulated saliva<br>Caries Index Scores: DMFT<br>Sample Collection Time: Between 10 a.m. and 1 p.m.<br>Data Analysis: Mann–Whitney test and independent t-test<br>Method for Assessing Salivary Biomarkers/Proteins: ELISA and Cayman protein determination kits<br>Salivary Biomarkers Assessed: Salivary immunoglobulins and salivary total proteins<br>Biomarker Levels:<br>Salivary IgA:<br>Caries-active group: 0.079086 mcg/mL<br>Caries-free group: 0.114286 mcg/mL<br>Salivary Total Proteins:<br>Caries-active group: 2.71<br>Caries-free group: 1.8<br>Key Findings:<br>A positive association was observed between caries and salivary total protein levels.<br>A negative correlation was found between caries and salivary IgA levels.<br>Conclusion:<br>The relationship between dental caries and salivary biomarkers suggests their potential role in detecting and diagnosing caries progression. |
| Sejdini (2018)[19] | Country: Kosovo<br>Study Design: Cross-sectional study<br>Sample Size: 106 schoolchildren<br>Caries-free: 25<br>Caries-active: 81<br>Participant Age: 12–13 years<br>Saliva Type: Stimulated and unstimulated whole saliva<br>Caries Index Scores: DMFT<br>Sample Collection Time: Morning (8 a.m. to 10 a.m.)<br>Data Analysis: Statistics for Windows/Release 7.0<br>Method for Assessing Salivary Biomarkers/Proteins: Spectrometer analysis<br>Salivary Parameter Assessed: Zinc salts (Zn)<br>Biomarker Levels:<br>Caries-Free Group: 6.72 mmol/L<br>Caries-Active Group: 0.07 mmol/L<br>Key Findings:<br>Zinc concentrations were significantly higher in the caries-free group compared to the caries-active group.<br>The results indicate a potential protective role of zinc in reducing caries incidence.<br>Conclusion:<br>The strong correlation between zinc levels and reduced caries prevalence suggests that zinc may serve as a valuable biomarker for detecting and assessing the risk and progression of dental caries. |
| Monea (2018)[21] | Country: Romania<br>Study Design: Experimental cohort study<br>Sample Size: 142 children<br>Participant Age: 9–12 years<br>Saliva Type: Unstimulated saliva<br>Caries Index Scores: Visual detection of dentinal caries<br>Sample Collection Time: Not reported<br>Data Analysis: GraphPad Prism 7.03 and the Mann-Whitney test<br>Method for Assessing Salivary Biomarkers/Proteins: Spectrophotometer<br>Salivary Parameter Assessed: Salivary alpha-amylase |

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| | Biomarker Levels:<br>Caries-Free Group: 150.53 ± 2.45 U/mL or 147.28 ± 2.1 U/mL<br>Caries-Active Group: 156.83 ± 1.59 U/mL or 158.18 ± 2.41 U/mL<br>Key Findings:<br>The salivary enzyme alpha-amylase was found to be higher in caries-active children compared to caries-free children.<br>Conclusion:<br>The correlation between salivary alpha-amylase levels and dental caries risk suggests that saliva can serve as a non-invasive diagnostic fluid for detecting and monitoring caries susceptibility.<br><br>Top of Form<br><br>Bottom of Form |
| Khandelwa (2019)[9] | Country: Romania<br>Study Design: Experimental cohort study<br>Sample Size: 142 children<br>Participant Age: 9–12 years<br>Saliva Type: Unstimulated saliva<br>Caries Index Scores: Visual detection of dentinal caries<br>Sample Collection Time: Not reported<br>Data Analysis: GraphPad Prism 7.03 and the Mann-Whitney test<br>Method for Assessing Salivary Biomarkers/Proteins: Spectrophotometer<br>Salivary Parameter Assessed: Salivary alpha-amylase<br>Biomarker Levels:<br>Caries-Free Group: 150.53 ± 2.45 U/mL or 147.28 ± 2.1 U/mL<br>Caries-Active Group: 156.83 ± 1.59 U/mL or 158.18 ± 2.41 U/mL<br>Key Findings:<br>The salivary enzyme alpha-amylase was found to be higher in caries-active children compared to caries-free children.<br>Conclusion:<br>The correlation between salivary alpha-amylase levels and dental caries risk suggests that saliva can serve as a non-invasive diagnostic fluid for detecting and monitoring caries susceptibility.Bottom of Form |
| Angarita-Díaz (2021)[22] | Country: Colombia<br>Study Design: Pilot study<br>Sample Size: 24 children (12 caries-free, 12 caries-active)<br>Participant Age: 6 to 12 years<br>Saliva Type: Unstimulated saliva<br>Caries Index Scores: ICDAS<br>Sample Collection Time: Between 8 a.m. and 11 a.m.<br>Data Analysis: Mann–Whitney U test and Kruskal–Wallis test<br>Method for Assessing Salivary Biomarkers/Proteins: ELISA<br>Salivary Parameters Assessed: IgA, fibronectin, cathelicidin LL-37, and statherin<br>Biomarker Levels:<br>IgA Concentration: Higher in caries-free children (48,250) compared to caries-active children (37,776)<br>LL-37 Levels: 56.1 in caries-free vs. 46.3 in caries-active group<br>Statherin Levels: 93,199.1 in caries-free vs. 94,734.6 in caries-active group<br>Key Findings:<br>Statherin levels were higher in caries-free children compared to caries-active children.<br>Slightly elevated IgA and lower fibronectin concentrations were observed in the caries-free group.<br>Conclusion:<br>The biomarkers showed a significant correlation with dental caries, indicating their potential use in detecting and diagnosing caries progression. |
| Pateel (2022)[24] | Country: Malaysia<br>Study Design: Cross-sectional study<br>Sample Size: 188 healthy adults (29 caries-free, 159 caries-active)<br>Participant Age: 18 to 50 years<br>Saliva Type: Stimulated whole saliva |

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| | Caries Index Scores: DMFT<br>Sample Collection Time: Between 10:00 a.m. and 1:00 p.m.<br>Data Analysis: SPSS (Spearman's rho and Pearson's correlation coefficient)<br>Method for Assessing Salivary Biomarkers/Proteins: ELISA Kit and colorimetric assay kit<br>Salivary Parameters Assessed: Statherin, Proline-Rich Proteins (PRP), and Calcium<br>Biomarker Levels:<br>PRP Statistical Correlation: r = 0.025, P = 0.733<br>Calcium Correlation: r = 0.015, P = 0.841<br>Statherin Levels: Showed an inverse relationship, with a declining trend as caries levels increased<br>Key Findings:<br>No statistically significant correlation was found between PRP, calcium, and dental caries progression.<br>Statherin levels decreased as caries severity increased.<br>Conclusion:<br>The inverse correlation between statherin and PRP levels suggests their potential roles in caries progression. These biomarkers may serve as indicators for diagnosing or predicting dental caries incidence. |
| Aparna K S (2023)[44] | Country: Not specified<br>Study Design: Cross-sectional comparative study<br>Sample Size: 60 participants<br>Control Group: 30 participants (DMFT = 3)<br>Experimental Group: 30 participants (DMFT > 11)<br>Participant Age: 18–40 years Saliva Analysis<br>Saliva Type: Unstimulated whole saliva Caries Index Score: DMFT (Decayed, Missing, and Filled Teeth) Sample Collection Time: Between 9:00 a.m. and 11:00 a.m.<br>Data Analysis: Mann–Whitney U nonparametric test Methodology for Salivary Biomarker Assessment<br>Techniques Used: High-sensitivity assay kit (USCNK)<br>ELISA (Enzyme-Linked Immunosorbent Assay)<br>Salivary Biomarkers Assessed:<br>Secretory Immunoglobulin A (sIgA) – Control: 8.10 mg/dL (range 2.1–22.2), Experimental: 13 mg/dL (range 7.2–23.8)<br>Histatin-5 – Control: 16.89 ng/mL (range 14.11–29.95), Experimental: 66.84 ng/mL (range 14.11–649) Lactoperoxidase (LPO) – Control: 2148 nmol/L (range 1305–3248), Experimental: 3047 nmol/L (range 1515–3313)<br>Key Findings The experimental group (DMFT > 11) exhibited significantly higher levels of sIgA, histatin-5, and lactoperoxidase compared to the control group.<br>The increase in these salivary biomarkers suggests a strong association with dental caries presence.<br>Conclusion<br>Elevated levels of sIgA, histatin-5, and lactoperoxidase are strongly correlated with increased caries incidence.<br>These biomarkers hold potential diagnostic and predictive value for assessing the onset and progression of dental caries. |

## 5. Discussion

### *5.1. Summary of key findings*

This study aimed to highlight the essential role of salivary biomarkers in detecting and diagnosing dental caries across different age groups. The research sought to establish a potential link between various proteins present in saliva and the prevalence of caries. Articles included in the study met the standard STROBE quality assessment criteria. All selected studies demonstrated a correlation between salivary biochemical markers and the development and severity of dental caries.

The study identified several key biochemical markers in saliva, including antimicrobial peptides (AMPs) such as cathelicidin peptide LL-37, beta-defensins, statherin, and histatins. Additionally, major salivary glycoproteins like proline-rich proteins (PRPs), mucins, and immunoglobulins, along with minor glycoproteins, were found to play a role in oral cavity defense. However, findings regarding the association of these biomarkers with caries varied. While some studies reported a statistically significant correlation between salivary biomarkers and caries presence, others noted that the concentration of specific biomarkers increased with higher caries experinece.

It is important to consider that factors such as sample size, age, and saliva type influenced the comparability of results across different studies, as these variables varied significantly. Despite these inconsistencies, the observed relationship between salivary biochemical markers and dental caries supports the reliability of salivary biomarkers as potential tools for caries prediction and diagnosis.

## 6. Enzymatic Biomarkers and Dental Caries

Several salivary enzymatic biomarkers, including alpha-amylase, proteinase-3, and carbonic anhydrase VI (CA VI), have been linked to caries occurrence. Studies by Malawi et al.[23] and Picco et al.[15] reported that CA VI levels were higher in caries-free individuals than in those with active caries, emphasizing its protective role in buffering and neutralizing acids. Conversely, salivary alpha-amylase has been found in higher concentrations in caries-active individuals, as observed in some studies, while others have reported the opposite.[21] This enzyme contributes to dietary starch hydrolysis, leading to acid production in dental plaque, thereby accelerating demineralization and caries progression. The inconsistency in findings suggests that the relationship between alpha-amylase and caries susceptibility is complex and warrants further investigation.

## 7. Antimicrobial Peptides and Salivary Proteins

Antimicrobial peptides (AMPs) such as LL-37, beta-defensins, statherin, and histatins play a significant role in inhibiting bacterial growth within the oral cavity. LL-37 has been reported in higher concentrations among caries-free individuals[22], whereas histatin (HTN-5) levels were elevated in caries-active subjects. These findings suggest that salivary AMPs can serve as useful biomarkers for assessing caries risk.[13]

Salivary glycoproteins, including mucins (MUC1), immunoglobulins, and proline-rich proteins (PRPs), also exhibit correlations with dental caries. Increased MUC1 levels have been associated with a higher caries experience (DMFT > 11), potentially due to their role in bacterial adhesion and inflammatory response. Elevated cytokine levels, such as interleukin-1B and interleukin-6, further influence MUC1 expression in the oral cavity.[28]

## 8. Protective Role of Statherin and Proline-Rich Proteins

Statherin, known for its strong affinity for hydroxyapatite, plays a protective role by binding calcium and maintaining saliva's saturation state, thereby preventing spontaneous precipitation of phosphate and calcium. Studies indicate that statherin levels are higher in caries-free individuals, underscoring its role in enamel remineralization[22]. Similarly, PRPs contribute to caries prevention by binding to *Streptococcus mutans*, minimizing acid production, and supporting enamel integrity. However, conflicting findings suggest that specific PRP subtypes may have varying effects on dental plaque formation and caries susceptibility.[31]

## 9. Immunoglobulins and Their Role in Caries Prevention

Immunoglobulins, particularly IgA, are crucial for humoral immunity and bacterial neutralization in the oral cavity. Several studies, including those by Kuriakose et al.[32] and Ranadheer [33] report higher IgA concentrations in caries-free individuals, reinforcing its protective role against *Streptococcus mutans*. However, some studies suggest the opposite, highlighting the complexity of immunoglobulin responses in caries development.[34-36]

## 10. Salivary Proteins and Caries Progression

Salivary total protein levels have shown a significant association with dental caries experience, although contradictory findings exist. C-reactive protein (CRP), known for its role in immune response and inflammation, has been found in higher concentrations in caries-active individuals. Similarly, salivary albumin appears to play a protective role, with lower levels correlating with increased caries incidence. Studies by Mungia et al.[38] and Yoshihara et al. confirm the association between albumin and caries prevention, further emphasizing the role of salivary proteins in oral health.[37]

## 11. Antioxidant Activity and Caries Susceptibility

Superoxide dismutase (SOD), an antioxidant enzyme that neutralizes free radicals, has been found in higher concentrations among caries-active individuals. Its increased activity may reflect a response to oxidative stress associated with caries progression.

The relationship between salivary biomarkers and dental caries is complex, with various enzymes, peptides, and proteins playing distinct roles in either promoting or preventing caries development. While certain biomarkers, such as CA VI, statherin, and IgA, exhibit protective effects, others, like alpha-amylase and mucins, contribute to caries progression. The inconsistencies in findings suggest that multiple factors, including genetic predisposition, environmental influences, and host immune responses, must be considered when assessing caries risk through salivary biomarkers. Further research is needed to establish definitive correlations and enhance the predictive accuracy of these biomarkers in dental caries diagnosis and prevention.[38,39]

### *11.1. Significance of the study*

Traditional methods for detecting dental caries include visual-tactile examinations, radiographs, caries detection dyes, and fiber-optic transillumination (FOTI).[40] However, technological advancements have introduced alternative diagnostic tools such as fluorescence, electrical conductance, and lasers, which provide more accurate data.[41] Dentists typically combine multiple diagnostic methods to identify and manage dental caries. Nevertheless, there is still debate about which diagnostic technique is most accurate, particularly when it comes to detecting incipient lesions.[42]

In recent years, there has been growing interest in non-invasive, personalized approaches to dentistry. Molecular assays using salivary biomarkers offer a promising tool for detecting caries at earlier stages and assessing an individual's caries risk[43]. This approach enables a more conservative and personalized strategy for diagnosing and managing caries in patients. The current study identified various molecular signatures that could be utilized for diagnosing, predicting, assessing risk, and monitoring dental caries.

## 12. Strengths and Limitations

A significant strength of this study is its large sample size of 1455 individuals, which enhances its statistical power. Additionally, the study adhered to the PRISMA statement and used predefined eligibility criteria based on the PECOS framework. This ensured that only high-quality studies were included, thereby improving the reliability of the results.

However, the study has several limitations. Most of the included studies were cohort or cross-sectional, with only one longitudinal and one pilot study. This design introduces potential participant selection bias, which could negatively affect the quality of the findings. Future research would benefit from including higher-quality studies with longer follow-up periods to provide more conclusive data on salivary biomarkers for caries detection and prognosis.

Another limitation is the variability in sample sizes across the studies. Some studies had relatively small sample sizes, which could impact the statistical power when comparing outcomes between caries-active and caries-free groups. Such studies may not provide sufficient evidence to support the use of salivary biomarkers as reliable diagnostic tools for dental caries.

Moreover, the studies showed high heterogeneity in terms of participant age and geographic location, which could influence the results. Additionally, variations in the types of saliva analyzed whole, unstimulated, stimulated, or a combination contributed to the variability in data and may affect the overall conclusions of the study.

## 13. Conclusions

This systematic review included 18 studies to produce the study results. Despite conflicting findings on the association between salivary makers and dental caries, each included study provided evidence of a relationship between components of saliva and caries. Given such a consensus, this study concludes that the salivary biomarker component concentration levels could be significant in detecting and diagnosing dental caries for both children and adults.

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None.

## 15. Conflict of Interest

None.

## Reference


1. Hemadi AS., Huang R., Zhou Y., Zou J. Salivary proteins and microbiota as biomarkers for early childhood caries risk assessment. *Int J Oral Sci.* 2017;9:e1
2. Cunha-Cruz J, Scott J, Rothen M, Mancl L, Lawhorn T, Brossel K. Salivary characteristics and dental caries: Evidence from general dental practices. *J Am Dent Assoc.* 2013;144(5):e31-40.
3. Proctor GB. The physiology of salivary secretion. *Periodontal 2000.* 2016;70(1):11-25.
4. Scannapieco FA. Saliva-bacterium interactions in oral microbial ecology. *Crit Rev Oral Biol Med.* 1994;5(3-4):203-48.
5. Guy H. The secretion, components, and properties of saliva. *Carpenter Annu Rev Food Sci Technol.* 2013;4:267-76.
6. Van Nieuw Amerongen A, Bolscher JG, Veerman EC. Salivary proteins: Protective and diagnostic value in cariology? *Caries Res.* 2004;38(3):247-53.
7. Cuschieri S. The Strobe Guidelines. *Saudi J Anaesth.* 2019;13(1):S31–4.
8. Nireeksha N., Hegde, M, Kumari N.S., Ullal H., Kedilaya V. Salivary Proteins as Biomarkers in Dental Caries: In Vivo Study. *Dent Oral Craniofac Res*. 2017;3(2):4238–44.
9. Khandelwal, A.; Palanivelu, A. Correlation between Dental Caries and Salivary Albumin in Adult Population in Chennai: An in Vivo Study. *Braz Dent Sci.* 2019;22(2):228–33.
10. Hegde M.N., Hegde N.D., Ashok, A., Shetty S. Biochemical Indicators of Dental Caries in Saliva: An in Vivo Study. *Caries Res.* 2014;48(2):170–3.
11. Doifode D. Damle S.G. Comparison of Salivary IgA Levels in Caries Free and Caries Active Children. *Int J Clin Dent Sci.* 2011;210–4.
12. Gabryel-Porowska H., Gornowicz A., Bielawska A., Wójcicka A., Maciorkowska E., Grabowska S.Z. Mucin Levels in Saliva of Adolescents with Dental Caries. *Med Sci Monit.* 2014;20,72–7.
13. Gornowicz A., Tokajuk G., Bielawska A., Maciorkowska E., Jabło´nski R., Wójcicka A. The Assessment of SIgA, Histatin-5, and Lactoperoxidase Levels in Saliva of Adolescents with Dental Caries. *Med Sci Monit.*2014;20(4)1095–100.
14. Jurczak A., Ko scielniak D., Papie˙ M., Vyhouskaya P., Krzy sciak W. A Study on-Defensin-2 and Histatin-5 as a Diagnostic Marker of Early Childhood Caries Progression. *Biol Res.* 2015;48: 61.
15. Picco D.d.C.R., Lopes L.M., Rocha Marques M., Line S.R.P., Parisotto,T.M. Nobre Dos Santos, M. Children with a Higher Activity of Carbonic Anhydrase VI in Saliva Are More Likely to Develop Dental Caries. *Caries Res.* 2017;51(4): 394–401.
16. Borghi G.N, Rodrigues L.P, Lopes L.M., Parisotto T.M. Steiner-Oliveira C. Nobre-dos-Santos, M. Relationship among Amylase and Carbonic Anhydrase VI in Saliva, Visible Biofilm, and Early Childhood Caries: A Longitudinal Study. *Int J Paediatr Dent.* 2017;27(3):174–82.
17. Murugeshappa D.G., Math S.Y., Kalra D., Ch,P.R., Pateel D.G.S. Biochemical & Immunological Assessment of Dental Caries. *Ann Med Health Sci Res.* 2018;8(3):336–9.
18. Yang T.Y., Zhou W.J., Du Y., Wu S.T., Yuan WW., Yu Y. Role of Saliva Proteinase 3 in Dental Caries. *Int J Oral Sci.* 2015;7(3):7174–8.
19. Sejdini M., Begzati A., Salihu S., Krasniqi S., Berisha N., Aliu N. The Role and Impact of Salivary Zn Levels on Dental Caries. *Int J Dent. 2018*; 8137915.
20. Castro R.J., Herrera R., Giacaman R.A. Salivary Protein Characteristics from Saliva of Carious Lesionfree and High Caries Adults. *Acta Odontol Latinoam.* 2016;29(2):178–85.

21. Monea M., Stoica A.L., Analysis of Salivary Level of Alpha-Amylase as a Risk Factor for Dental Caries. *Acta Med. Transilv*. 2018;23(1):93–5.
22. Angarita-Díaz M.P., Simon-Soro A., Forero D., Balcázar F., Sarmiento L. Evaluation of Possible Biomarkers for Caries Risk in Children 6 to 12 Years of Age. *J Oral Microbiol.* 2021;13(1):1956219.
23. Makawi Y., El-Masry E., El-Din H.M. Salivary Carbonic Anhydrase, PH and Phosphate Buffer Concentrations as Potential Biomarkers of Caries Risk in Children. *J Unexplor Med.* 2017;2(1):9–15.
24. Pateel D.G.S., Gunjal S., Dutta S. Association of Salivary Statherin, Calcium, and Proline-Rich Proteins: A Potential Predictive Marker of Dental Caries. Contemp. C*lin Dent*. 2022;13(1):84–9.
25. Yassin H.N. Comparison of Immunoglobulin IgA Level in the Stimulated Saliva of Caries-Free and Caries-Active Children Aged 7–10 Years. *J Baghdad Coll Dent.* 2016;28(3):155–8.
26. Levine N. Outfitting Your Practice for Safety and Efficiency. *Dent Prod Rep.* 2020;54(2):41–4.
27. Hegde M. Correlation between Dental Caries and Salivary Albumin in Adult Indian Population—An in Vivo Study. *Br J Med Med Res*. 2014;4:4238–44.
28. McAuley J.L., Linden S.K., Png C.W., King R.M., Pennington H.L., Gendler S. JMUC1 Cell Surface Mucin Is a Critical Element of the Mucosal Barrier to Infection. *J Clin Investig.* 2007;117(8):2313–24.
29. Wang K., Wang Y., Wang X., Ren Q., Han S., Ding L. Comparative Salivary Proteomics Analysis of Children with and without Dental Caries Using the ITRAQ/MRM Approach. *J Transl Med.* 2018;16(1):11.
30. Vitorino R., Lobo M.J.C., Duarte J.R., Ferrer-Correia A.J., Domingues P.M., Amado F.M.L. The Role of Salivary Peptides in Dental Caries. *Biomed Chromatogr.* 2005;19(30):214–22.
31. Mandel I.D., Zorn M., Ruiz R., Thompson R.H., Ellison S.A. The Proteins and Protein-Bound Carbohydrates of Parotid Saliva in Caries-Immune and Caries-Active Adults. *Arch Oral Biol*. 1965;10 471–5.
32. Sundaresan C., Mathai V., Khosla E., Gaffoor F.M.A., Kuriakose S. A Comparative Study of Salivary Buffering Capacity, Flow Rate, Resting PH, and Salivary Immunoglobulin A in Children with Rampant Caries and Caries-Resistant Children. *J Indian Soc Pedod Prev Dent.* 2013;31(2):69-73.
33. Ranadheer E., Nayak U.A., Reddy N.V., Rao V.A.P. The Relationship between Salivary IgA Levels and Dental Caries in Children. *J Indian Soc Pedod Prev Dent.* 2011;29,106–12.
34. Bagherian A., Jafarzadeh A., Rezaeian M., Ahmadi S., Rezaity M.T. Comparison of the Salivary Immunoglobulin Concentration Levels between Children with Early Childhood Caries and Caries-Free Children. *Iran J Immunol.* 2008; 5(4):217–21.
35. Colombo N.H., Pereira J.A., Da Silva M.E.R., Ribas L.F.F., Parisotto T.M. Relationship between the IgA Antibody Response against Streptococcus Mutans GbpB and Severity of Dental Caries in Childhood. *Arch. Oral Biol.* 2016;67, 22–7.
36. AlAmoudi N., Al Shukairy H., Hanno A., A Comparative Study of the Secretory IgA Immunoglobulins (s.IgA) in Mothers and Children with SECC versus a Caries Free Group Children and Their Mothers. *J Clin Pediatr Dent.* 2007; 32(1):53–6.
37. Gawri S., Shukla P., Chandrakar A. A Survey of Micro Flora Present in Dental Caries and It's Relation to Enviornmental Factors Recent. *Res Sci Technol.* 2012;16(3)9–12.
38. Mungia R., Cano S.M., Johnson D.A., Dang H., Brown J.P. Interaction of Age and Specific Saliva Component Output on Caries. *Aging Clin Exp Res.* 2008;20(6):503–8.
39. Yoshihara A., Hanada N., Miyazaki H. Association between Serum Albumin and Root Caries in Community-Dwelling Older Adults. *J Dent Res.* 2003;82(3):218-22.
40. Sadasiva K., Kumar K.S., Rayar S., Shamini S., Unnikrishnan M., Kandaswamy D. Evaluation of the Efficacy of Visual, Tactile Method, Caries Detector Dye, and Laser Fluorescence in Removal of Dental Caries and Confirmation by Culture and Polymerase Chain Reaction: An in Vivo Study. *J Pharm Bioallied Sci.* 2019;11(2):S146–50.
41. Ghodasra R., Brizuela M. Dental Caries Diagnostic Testing; StatPearls Publishing: Treasure Island, FL, USA, 2022.
42. Foros P., Oikonomou E., Koletsi D., Rahiotis C. Detection Methods for Early Caries Diagnosis: A Systematic Review and Meta-Analysis. *Caries Res.* 2021;55(4):247–59.
43. Paqué P.N., Herz C., Wiedemeier D.B., Mitsakakis K., Attin T., Bao K. Salivary Biomarkers for Dental Caries Detection and Personalized Monitoring. *J Pers Med.* 2021;11(3):L235.
44. Aparna KS., Manjunath P., Puranik Uma SR. Association between dental caries experience and salivary profile among autoimmune thyroid disease subjects - a cross sectional comparative study. *F1000 Res.* 2023;12:833.


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