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The Potential of Salivary Lysozyme Level Examination as Caries Biomarker: A Scoping Review

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ABSTRACT (The content cannot exceed first page)

Salivary lysozyme is an antimicrobial enzyme naturally present in human saliva. It is widely recognized as a potential non-invasive biomarker for the early detection of dental caries, which remains a major global oral health concern. Lysozyme plays a significant role in oral immunity by degrading bacteria cell walls and maintaining microbial homeostasis. Therefore, this scoping review aimed to evaluate the potential of salivary lysozyme as a caries biomarker using PRISMA. The method was based on literature searches conducted in Scopus and PubMed databases between 2013 and 2023. The results showed that there were variations in lysozyme concentration according to caries status, where lower levels were often associated with a higher risk, but increased levels showed an active immune response to bacterial infection. Despite methodological differences among studies, there was association between salivary lysozyme concentration and caries severity, underscoring the diagnostic potential. Due to the non-invasive nature, ease of collection, and biochemical stability, salivary lysozyme examination could be applicable in both clinical and preventive settings. However, larger and standardized studies should be conducted in further studies to validate clinical reliability and diagnostic accuracy.

Keyword: Dental Caries, Muramidase, Saliva, and Biomarkers

ABSTRAK

Lisozim saliva, enzim antimikroba yang terdapat secara alami dalam saliva manusia, berpotensi menjadi biomarker non-invasif untuk deteksi dini karies gigi yang masih menjadi masalah kesehatan global. Scoping review ini menelaah potensi lisozim saliva sebagai penanda karies dengan metode PRISMA melalui pencarian literatur pada basis data Scopus dan PubMed (2013–2023). Lisozim berperan penting dalam imunitas rongga mulut melalui penghancuran dinding sel bakteri dan pengendalian keseimbangan mikroba. Hasil kajian menunjukkan variasi kadar lisozim sesuai dengan status karies; kadar yang rendah sering dikaitkan dengan risiko karies lebih tinggi, sedangkan kadar yang meningkat dapat mencerminkan respons imun aktif. Meskipun terdapat perbedaan metodologi antarstudi, temuan secara konsisten menunjukkan hubungan antara kadar lisozim saliva dan tingkat keparahan karies, menegaskan potensi diagnostiknya. Karena sifatnya yang non-invasif dan stabil, pemeriksaan lisozim saliva berpotensi diterapkan dalam praktik klinik maupun upaya pencegahan. Penelitian berskala lebih besar dengan metode terstandar masih diperlukan untuk memastikan validitas klinisnya.

Kata kunci: Karies Gigi, Muramidase, Saliva, Biomarker

1. Introduction

A major sign of poor oral and dental hygiene in the community is dental caries, which is a prominent health problem. Dental caries remains one of the most prevalent chronic diseases affecting children and adults worldwide. Due to the progressive demineralization of tooth structure caused by acidic waste of bacterial metabolism, this disease is strongly influenced by the interaction between dietary habits, oral hygiene, salivary function, and the host immune response. The progression is majorly affected by several factors, including host, dietary substrates, time, and the presence of microorganisms. Among various influencing factors, *Streptococcus mutans* is the main bacteria responsible for initiating tooth decay, while *Lactobacillus* contributes to its development. *Streptococcus* starts the process by eroding the enamel layer, and *Lactobacillus* further advances the decay into the deeper structures [1–3]. According to the Global Burden of Disease Study, the majority of the community is affected by dental caries globally, with a significant amount of incidence rate among preschool children in developed and developing countries. Despite preventive efforts, 60–90% of preschool children and approximately 100% of adults suffer from caries. In Indonesia, 72.3% of the population experiences caries, making oral and dental diseases the number one health issue, with a prevalence of 61%. Data from the Basic Health Research (RISKESDAS) in 2018 showed that the prevalence of caries in North Sumatra Province was 43.07%, where Medan City recorded 39.15% [4–6].

In dental caries prevention, saliva plays a major role by serving as a protective agent in oral cavity and acting as part of the body's innate defense system. Produced by the three major salivary glands, saliva is composed of approximately 99.5% water and 0.5% electrolytes and proteins. It contributes to various functions such as lubrication, aiding in mastication, improving taste perception, preventing oral infections, and protecting against tooth decay. As a complex fluid from the combined secretions of both major and minor salivary glands, the effectiveness of saliva is influenced by viscosity, pH balance, and microbial content. Additionally, there are ions that help regulate oral acidity and function as part of the buffering system, which includes phosphate, bicarbonate, and protein buffers [7,8].

Saliva is rich in proteins such as lysozyme, lactoferrin, and salivary peroxidase, which play important roles in soft tissue healing and protection against oral infections. These proteins contribute to caries prevention by acting directly or indirectly through different mechanisms that target dental plaque and oral bacteria, thereby influencing the vulnerability of tooth to decay. The composition of salivary proteins is influenced by factors such as time, food intake, psychological condition, smoking, diseases (periodontal disease and diabetes), age, and gender [9–11].

Generally, salivary proteins have protective, antimicrobial, and lubricating properties, which play a major role in the digestive system. These proteins are essential in modulating the colonization of microorganisms on tooth and soft tissues to enhance enamel remineralization and slow down demineralization. Furthermore, microbial adhesion to enamel and bacteria growth are prevented, showing the potential to maintain a stable ecosystem in oral cavity [9].

Discovered by Alexander Fleming in 1922, lysozyme is an antimicrobial enzyme present in several bodily fluids, including human saliva. The primary role is to break down bacteria cell walls by facilitating the hydrolysis of peptidoglycan. This action weakens the cell walls, leading to lysis, thereby making lysozyme an essential part of salivary defense system against microbial invasion [12]. Lysozyme is secreted by major and minor salivary glands in oral cavity, as well as from crevicular fluid and leukocytes. It is considered a key component of the nonspecific immune defense, contributing to microbial homeostasis and inhibiting early colonization of cariogenic bacteria. Beyond the enzymatic function, lysozyme also promotes bacteria aggregation and adhesion, which facilitates autolysin activation and antimicrobial effectiveness under several environmental conditions, including low salivary flow or high bacteria load [13].

Lysozyme is an antibacterial enzyme found in relatively high levels in bodily fluids like serum, plasma, amniotic fluid, saliva, and tears, while present in lower amounts in urine, bile, and cerebrospinal fluid. This enzyme resides in the granules of phagocytic cells and is recognized as a powerful agent against Gram-positive bacteria. In oral cavity, salivary lysozyme possesses muramidase activity, enabling cleavage to the $\beta(1\rightarrow4)$ linkage between N-acetylmuramic acid and N-acetylglucosamine in bacteria peptidoglycan layer, thereby degrading bacterial cell walls, particularly under hypo-osmotic conditions. Due to the strong cationic nature, lysozyme contributes to bacteria aggregation and adhesion, stimulating autolysins that further break down bacteria walls structure [14,15].

Based on the functional properties, salivary lysozyme has been proposed as a potential biomarker for caries. Several studies report higher levels of salivary lysozyme in caries-free individuals, suggesting the role as a protective factor. However, other show high activity in children with active caries, indicating a host immune response to bacteria challenge rather than a preventive role. These inconsistent results show the need for further investigation into the role of lysozyme in pathogenesis of caries [16].

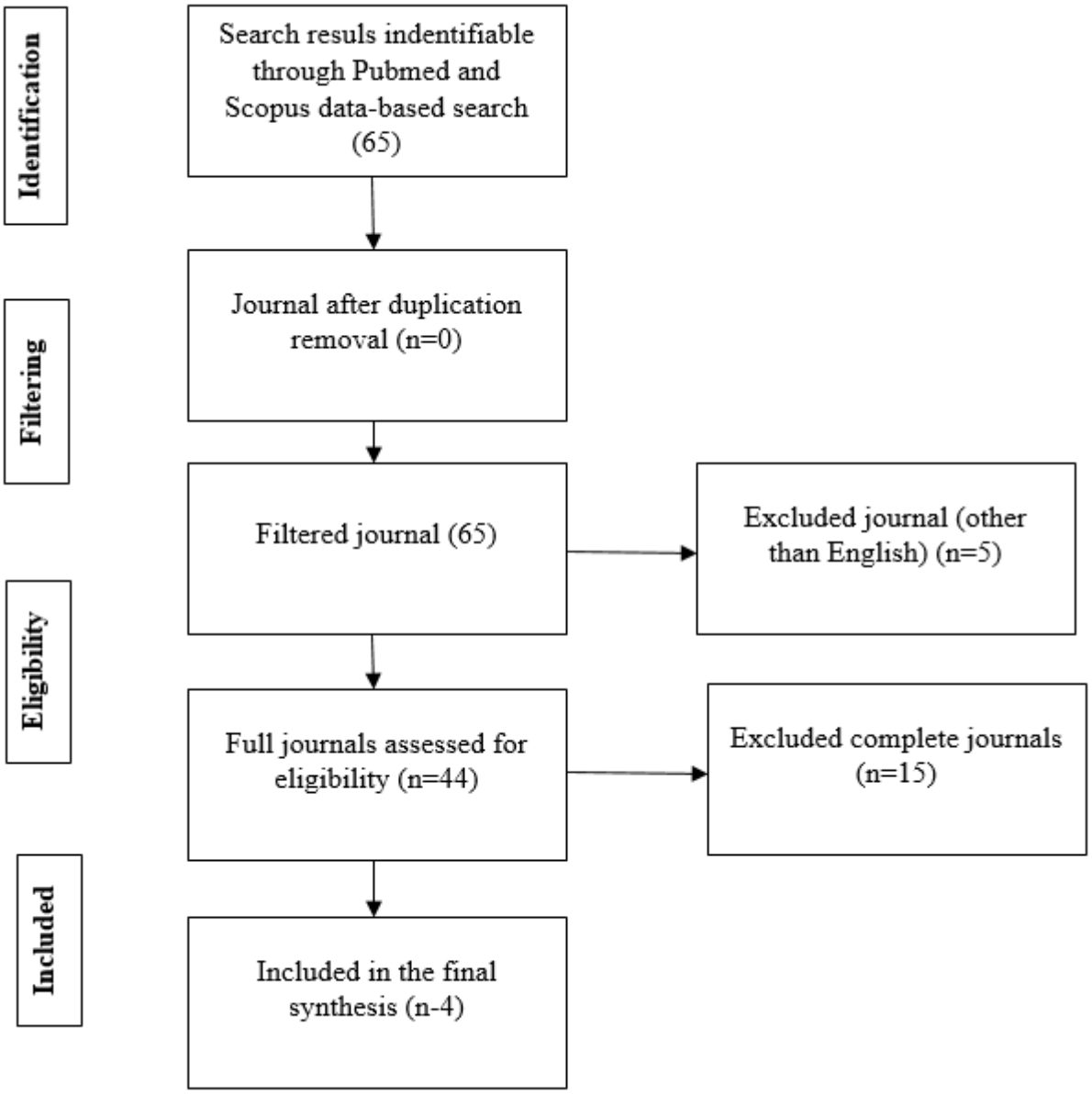
Biomarkers create opportunities for early disease detection, monitoring, and risk assessment. Regarding caries, identifying reliable salivary biomarkers can revolutionize diagnostic strategies by providing non-invasive, cost-effective, and rapid assessment tools. Due to the accessibility in saliva and biological relevance, lysozyme is a strong candidate, particularly in pediatric populations where early detection and prevention are crucial [17]. However, the variability in lysozyme measurements, different analytical methods, population characteristics, and sampling contribute to the challenge of establishing a definitive role for salivary lysozyme as caries biomarker. This shows the need for understanding how lysozyme levels correlate with caries risk and progression to move forward with clinical applications [18,19].

Based on the increasing interest in salivary diagnostics and the need for evidence-based preventive strategies in oral health, a comprehensive review of existing studies on salivary lysozyme and association with dental caries is essential. This scoping review will allow for mapping the breadth and depth of available evidence to identify key concepts, gaps, and future study directions in the field. Although several studies have investigated salivary lysozyme levels in individuals with and without caries, the results obtained are inconsistent. Some reports showed higher lysozyme concentrations in caries-free individuals, suggesting a protective role against bacteria colonization. Meanwhile, others found elevated levels in active caries, showing an immune response to bacterial infection. This inconsistency suggests uncertainty about the primary function of lysozyme as a protective biomarker or reactive indicator of disease activity. Moreover, methodological variations, such as variations in saliva collection procedures, analytical methods, and study populations, further complicate interpretation and comparison.

The discrepancies show a significant knowledge gap, underscoring the need for a comprehensive scoping review to map existing results, identify methodological variations, and clarify the diagnostic potential of salivary lysozyme as a biomarker for caries. Therefore, this scoping review aims to explore the existing studies regarding the potential of salivary lysozyme level examination as a biomarker for caries. The main objective is to summarize and synthesize existing results, evaluate methodological variations, and assess whether salivary lysozyme has a predictive or diagnostic value in caries detection. The results are expected to serve as a foundation for future studies and the development of clinical protocols for caries risk assessment using salivary biomarkers.

2. Methods and Materials

The review protocol was developed based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a structured and transparent process. The inclusion criteria were defined as studies published between 2013 and 2023, written in English, and comprised clinical trials or cross-sectional designs that assessed salivary lysozyme levels in relation to dental caries. However, studies that did not meet the criteria were excluded, such as non-English articles, inaccessible full texts, or those outside the specified date range or types. The primary data source used for literature retrieval was the “PubMed” and “Scopus” databases. Subsequently, a systematic search was conducted using the keywords “Lysozyme,” “Dental Caries,” and “Saliva.” The search process included initial screening of titles, abstracts, and keywords, followed by a more detailed assessment based on full-text eligibility. Study selection was guided by relevance to the question and adherence to the inclusion criteria. Data analysis included extracting essential information, comprising objectives, design, sample size, methods of saliva collection and lysozyme measurement, as well as statistical analysis. Although a formal quality assessment tool was not applied, the included studies were compared in terms of methodology, sample characteristics, and outcome consistency. Methodological limitations or variations were discussed to evaluate the reliability of results.


Identification
Search resuls indentifiable through Pubmed and Scopus data-based search (65)
Filtering
Journal after duplication removal (n=0)
Filtered journal (65)
Excluded journal (other than English) (n=5)
Eligibility
Full journals assessed for eligibility (n=44)
Excluded complete journals (n=15)
Included
Included in the final synthesis (n-4)

3. Results

Table 1. Search Results for Studies on the Potential of Examination of Salivary Lysozyme Levels as Caries Biomarker

No	Title/Study	Year	Location	Objective	Study design	Number of respondents	Intervention/ Exposure	Measurement method	Analysis method	Results
1	Analysis of Salivary IgA, Amylase, Lactoferrin, and Lysozyme Before and After Comprehensive Dental Treatment in Children: A Prospective Study	2017	Department of Pediatric Dentistry and Prevention	Evaluate the IgA levels, amylase, lactoferrin, and lysozyme in saliva before and after comprehensive dental treatment in children with early childhood caries.	Cross sectional	30	Tooth caries	A total of 30 children between the ages of 36 and 60 months, each with a deft score of 5 or higher, were included in this study. Before receiving dental treatment, whole saliva stimulated with paraffin was collected in a sterile measuring cup over a 5-minute period. The collected saliva samples were then quantitatively assessed for concentrations of IgA, amylase, lactoferrin, and lysozyme using the enzyme-linked immunosorbent assay (ELISA) method.	Students' T-test	Among children with ECC, complete oral rehabilitation combined with improved home oral hygiene led to a significant decline in salivary concentrations of IgA, amylase, lactoferrin, and lysozyme after 3 months. Specifically, salivary lysozyme levels showed a marked decrease, reducing from 3.76 and 10.62 μg/ml to 3.44 and 10.27 μg/ml, with the change being statistically significant ($P < 0.001$).
2	Relationship of Salivary Lactoferrin and Lysozyme Concentrations with Early Childhood Caries	2015	Department of Pediatric Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran	To determine the relationship between salivary lysozyme and lactoferrin concentrations with	Cross sectional	42	Teeth caries	Unstimulated saliva was obtained from the buccal and labial anterior vestibule using a needleless disposable syringe. A total of 15 children diagnosed with ECC received comprehensive dental treatment, and a second saliva sample was	chi-square, Student's t-test, and Wilcoxon signed-rank test	The average lysozyme concentration was significantly greater in the CF group than in ECC, with the difference reaching statistical significance ($P = 0.04$).

				early childhood caries (ECC).				collected using the same procedure three months post-treatment. The levels of lysozyme and lactoferrin were then measured and documented using the ELISA method.		
3	Salivary Lysozyme in Relation to Dental Caries among Thai Preschoolers	2015	Khon Kaen University, Khon Kaen, Thailand	To analyze the levels and activity of salivary lysozyme in preschool children in Thailand with different dental caries statuses.	Cross sectional	64	Teeth caries	Saliva was collected from preschool children, with 32 individuals in each group. Salivary lysozyme was measured using the Western blotting method.	Students' T-test	Preschool children with severe caries showed high salivary lysozyme levels and activity compared to those without disease. Lysozyme concentration in saliva of S-ECC group was 24.4 μg/ml, while CF had a concentration of 16.3 μg/ml, with a statistically significant difference (P = 0.02).
4	Activity and Distribution Pattern of Enzymes in the In-Situ Pellicle of Children	2019	Germany	To investigate the activity and distribution pattern of key enzymes within the in-situ pellicle of	Cross sectional	54	Caries-free children with no decayed, missing, or filled teeth (dmft = 0), children with dental restorations but without active lesions (dmft ≥ 2),	Lysozyme activity was determined through a fluorescence-based assay using Micrococcus lysodicticus as the substrate with excitation at 485 nm and emission at 535 nm.	The Kruskal–Wallis test was used to compare differences among the three study groups, followed by the Mann–Whitney U-test for	Transmission Electron Microscopy (TEM) showed that lysozyme was the most abundant enzyme detected and appeared in cluster-like formations both in and on pellicle surface. The mean number of gold-labelled lysozyme particles per 1 μm section of pellicle was 4.83 ± 2.64

				children with different caries experiences. Specifically, it evaluated whether enzymes such as amylase, lysozyme, peroxidase, and glucosyltransferase (GTF isoforms B, C, and D) differed in their activity or localisation depending on caries activity or restoration status.			and caries-active children with at least two carious lesions requiring treatment (dmft ≥ 2).		pairwise comparisons. The Bonferroni–Holm correction with a significance threshold of $p < 0.002$ was applied to minimize type I errors.	in caries-free children, 15.16 ± 3.18 in children with restorations, and 1.50 ± 1.17 in caries-active children. On pellicle surface, the corresponding values were 3.50 ± 2.67, 4.60 ± 2.09, and 0.83 ± 1.26, respectively. Although these data were presented descriptively without inferential statistical testing, the trend indicated that lysozyme density was highest in the restoration group and lowest in caries-active group. This suggested that lysozyme played a protective role, enhanced after caries treatment.

The synthesis of the four included studies showed a complex, bidirectional relationship between salivary lysozyme levels and caries activity. This suggested that lysozyme could function as a risk biomarker, indicating reduced defense capacity, and as a response biomarker showing immune activation to microbial challenge. Rather than interpreting lysozyme concentration as a static measure, these results showed the dynamic physiological role in maintaining oral microbial homeostasis.

Across studies, lysozyme levels in caries-free children were higher than those with caries-active conditions, indicating a protective baseline function of the enzyme in oral defense. For example, Moslemi et al. (2015) showed significantly greater lysozyme concentrations in caries-free children (mean 9573.81 ng/mL) compared to caries-active (mean 2180 ng/mL, $p = 0.04$) [14]. The results correlated with the ability of lysozyme to hydrolyze the peptidoglycan wall of *Streptococcus mutans* and *Lactobacillus*, the major cariogenic bacteria, thereby limiting adhesion and proliferation. The observation that higher basal lysozyme levels coincide with caries resistance showed the significant role as a risk biomarker, where protective capacity decreased after compromising host defense.

Lertsirivorakul et al. (2015) reported significantly elevated lysozyme concentrations and enzymatic activity among Thai preschool children with severe early childhood caries (S-ECC) [15]. Lysozyme concentration in this group reached 24.4 μg/mL against 16.3 μg/mL in caries-free group ($p = 0.02$). These data suggested that lysozyme production would increase as part of a compensatory immune response to intense bacteria challenge, functioning as a response biomarker. This elevation showed the activation of the host innate immune system, where salivary glands and leukocytes upregulated antimicrobial proteins to mitigate infection. From an immunological standpoint, the results showed that lysozyme levels predicted disease risk, alongside inflammatory activity and bacteria load during active lesions.

Sharma et al. (2017) further observed a significant reduction in lysozyme levels after comprehensive dental rehabilitation and reinforcement of oral hygiene . The observation showed that the mean concentration decreased from 10.62 μg/mL to 10.27 μg/mL ($p < 0.001$). This decrease supported the idea that secretion was stimulated by antigenic exposure. After reducing bacteria burden through treatment, the immune drive subsided, and lysozyme levels normalized. Similarly, Moslemi et al. and Lertsirivorakul et al. suggested that lysozyme responded dynamically to the host–microbe equilibrium rather than serving as a fixed indicator of disease.

Hertel et al. (2019) provided a structural perspective by visualizing lysozyme distribution in the in-situ pellicle of children with varying caries experiences. Transmission electron microscopy showed that lysozyme formed cluster-like aggregates on and in pellicle, where the highest density was observed in children with restorations (15.16 ± 3.18 particles/μm²) and the lowest in caries-active (1.50 ± 1.17 particles/μm²). This spatial pattern suggested that lysozyme participated in the reconstitution of local immune defense after treatment, while the depletion in active lesions indicated functional exhaustion or degradation by bacteria enzymes. Therefore, the localization and distribution density compared to overall quantity showed the functional state of oral immunity.

The studies showed that the direction of lysozyme alteration depended on the disease stage. In the early or preventive stage, a higher lysozyme concentration indicated robust mucosal defense (risk biomarker). During active infection, the host upregulated lysozyme secretion in response to bacteria invasion (response biomarker). After treatment or microbial clearance, levels decline or redistribute, marking restored immune balance. This U-shaped biological pattern showed that the enzyme was not a unidirectional indicator of disease but a dynamic immune sentinel responding to changes in microbial challenge and host condition.

Methodological variability, including stimulated versus unstimulated saliva, ELISA versus Western blot quantification, and differences in caries severity criteria, partly explained the discrepancies among studies. However, the consistent results across all studies were that lysozyme levels correlated with microbial burden and immune activation, regardless of analytical method. Moreover, future investigations should standardize sample collection and incorporate longitudinal monitoring to clarify whether shifts in lysozyme precede clinical caries onset or simply accompany active disease.

4. Discussion

Lysozyme is a protein secreted by both major and minor salivary glands, playing a crucial role in preserving oral ecosystem balance. It affects dental biofilm formation by preventing the attachment of *Streptococcus mutans* and regulating the aggregation of free-floating bacteria into biofilms. The association

between salivary lysozyme levels and caries shows a complex interplay including the enzyme interaction with oral microorganisms, the host immune response, and environmental factors that contribute to caries progression [10].

As an enzyme found in saliva, lysozyme plays an important role in salivary defense. It can damage bacterial cell walls, including pathogenic bacteria in oral cavity, composed of peptidoglycan. Specifically, lysozyme cleaves glycosidic bonds in peptidoglycan, causing the breakdown of bacteria cell wall. This leads to lysis, where cell membrane ruptures and bacteria die, indicating direct inhibition of caries-causing bacteria by damaging the fundamental structure of cell walls. The potential can reduce the number of pathogenic bacteria in the mouth and support body natural defense against infection and disease, including caries [14].

Dental caries includes complex interactions between bacteria, salivary components, and the immune system response. As part of the immune system, lysozyme plays a role in responding to and combating bacterial invasion [15]. An increase in salivary lysozyme levels shows various conditions in oral cavity and the immune system. When the level rises, there is an enhancement in saliva ability to fight pathogenic bacteria and maintain the balance of oral microbiota. This increase occurs because of inflammation or infection in oral cavity. Therefore, high lysozyme levels indicate that the immune system is actively combating microorganisms causing caries or other oral health issues [15].

A reduction in microbial load is associated with a corresponding decrease in lysozyme levels. Previous studies have shown that lysozyme concentrations are significantly higher before treatment compared to levels measured after three months. Caries stimulates a nonspecific immune response, potentially increasing the production. By decreasing the antigenic burden, dental treatment contributes to a reduction in lysozyme levels. Although the decrease in salivary protein levels after treatment is statistically significant, the results show that comprehensive dental care combined with high oral hygiene practices in children influences the immune activity in oral cavity. By reducing oral microbial presence, extensive dental intervention gradually decreases the initial immune response. Changes in salivary protein composition can also play a key role in modulating protective function against caries [14,15].

Inconsistent results among previous studies are attributed to different variables in experimental conditions. This influences salivary lysozyme, such as differences in saliva collection methods, oral environment due to varying dentition, or aging. Other factors include criteria for determining caries status and different measuring methods. Therefore, standardization of methods for measurement under various oral environmental conditions is essential to validate the role of salivary lysozyme in the development of early childhood caries [14].

The results show lysozyme as a dynamic biomarker, where high levels show an acute immune response to active caries (a reactive “alarm” signal of infection). Meanwhile, low baseline levels indicate weakened innate defense, potentially predisposing to lesion development. This can be explained by lysozyme role as an innate immune effector, secreted through salivary acinar cells and neutrophils in gingival crevices. The production can also be stimulated by inflammatory cytokines and bacteria antigens. During active caries, dental plaque bacteria such as *Streptococcus mutans* invade the enamel pellicle and trigger localized inflammation. The host counters by recruiting immune cells and boosting salivary gland output of antimicrobial proteins. In advanced or chronic caries, the protective system becomes overwhelmed or exhausted, as prolonged high bacteria load might consume available lysozyme or certain bacteria may produce enzymes and inhibitors that cause degradation. An ultrastructural study by Hertel et al. (2019) supported this interpretation, where a visualized distribution was observed in the in-situ pellicle [20]. Furthermore, caries-active children were observed to have the sparsest lysozyme clusters on pellicle, while children with past caries (restorations without active lesions) showed the densest deposition.

Previous studies hypothesized that in active disease, pellicle was depleted or enzymatically broken down by bacteria. After therapeutic intervention, lysozyme re-integrated into pellicle as local immunity was reconstituted. This suggests that the direction of lysozyme level change depends on disease stage. The enzyme can serve as a “response” biomarker (rising during acute microbial challenge) and as a “risk” biomarker (low levels signaling insufficient defense in caries-prone individuals). This dynamic behavior underscores the enzyme role as an active participant in mucosal immunity rather than a static trait. Based on the results, a high level indicates ongoing infection, while a low level (in the absence of acute infection) shows vulnerability to future caries. The dual nature of immune system, which includes an initial robust lysozyme-mediated attack

on biofilm and potential lagging or waning with chronic strain, correlates with known paradigms of host–pathogen interactions in oral cavity.

This current systematic review evaluated the relationship between salivary lysozyme levels and ECC. Some studies, such as Lertsirivorakul et al. (2015), reported significantly increased levels and activity in children with S-ECC, suggesting a compensatory immune response to higher bacterial challenge [15]. Meanwhile, Moslemi et al. (2015) found higher concentrations in caries-free children, indicating a potential protective role of lysozyme against caries development [14]. Sharma et al. (2017) observed a significant reduction in salivary lysozyme levels after comprehensive dental treatment, indicating that the concentrations would be influenced by bacteria load and oral hygiene status. These variations show the complex role of salivary lysozyme, which acts both as biomarker of oral immune response and a reflective marker of caries activity. The potential inclusion of lysozyme in modulating plaque biofilm and bacteria adherence further supports the relevance in caries susceptibility and prevention.

Translating the results into practice, salivary lysozyme shows promising potential as a non-invasive biomarker for caries risk assessment, but harnessing it will require innovative clinical tools. One envisioned application is the development of a rapid chairside test (analogous to a pregnancy test or glucose strip) that measures lysozyme levels in saliva to identify children at high risk for dental caries. This test can take the form of a lateral-flow immunoassay, where a small drop of unstimulated saliva is applied to a paper strip pre-coated with anti-lysozyme antibodies. In minutes, strip shows a colored line indicating whether lysozyme is above a certain threshold. This lateral-flow assay is inexpensive, quick, and usable in community settings or school screenings without the need for laboratory infrastructure. A more technologically advanced method is a biosensor-based system, such as an electrochemical sensor or a microfluidic "lab-on-a-chip" device, that detects and quantifies lysozyme in saliva in real-time. Biosensors use antibody-coated electrodes or nanomaterial-based sensors that produce a measurable electrical or optical signal proportional to lysozyme concentration. These methods offer immediate results (~5–10 minutes), are painless and child-friendly (only requiring spitting into a collection tube or saliva wick), and can be repeated periodically to monitor changes. Therefore, salivary diagnostics is a growing field, with successful examples like saliva glucose sensors for diabetics and cortisol tests for stress. Lysozyme-based caries risk test will build on similar principles of accessibility and speed.

The clinical advantages of salivary lysozyme test are numerous, including early identification of at-risk children before cavitations. For instance, when children lysozyme levels are found to be unusually low for their age, clinicians can prescribe intensive preventive measures such as fluoride varnish, dietary counseling, and frequent recalls, even without cavities. A high level in children with incipient lesions confirms active bacteria challenge and the need for prompt therapeutic intervention. This test is non-invasive and easily repeatable, which is suitable for young patients and epidemiological surveys. In school dental programs, salivary lysozyme test is used to screen large populations efficiently, as saliva collection is far simpler and more acceptable compared to blood tests. The screening can also complement existing caries risk assessment tools by adding a biological dimension. Currently, dentists estimate risk using factors like past caries experience, dietary habits, fluoride exposure, and occasionally microbiological tests (counting *Streptococcus mutans* colonies).

A salivary biomarker offers a direct measurement of host response or susceptibility, filling a gap between clinical exam and laboratory culture. Since lysozyme shows the host–microbe interaction, it might integrate various risk factors such as poor oral hygiene and high bacteria load into one readout. Additionally, tracking can help evaluate the effectiveness of interventions. After restoring carious tooth and improving oral hygiene, a previously high lysozyme level might decrease towards normal due to the reduction in the immune stimulus, as observed by Sharma et al. This condition indicates that the treatment and prevention plan is succeeding in lowering cariogenic challenge. When lysozyme remains elevated or a low level fails to increase after intervention, it requires re-evaluation of the risk factors or uncovering persistent issues such as unidentified plaque accumulation or hyposalivation.

This review has several limitations that should be taken into consideration. First, the studies included had relatively small sample sizes and were conducted in geographically and demographically distinct populations, thereby limiting the generalizability of the results. Second, methodological heterogeneity was observed among the studies, particularly in saliva collection protocols (stimulated vs. unstimulated), assay methods (ELISA, lysoplate, Western blot), and caries diagnostic criteria. These differences could account for the variability and inconsistency in lysozyme measurements across studies. Third, most studies focused only

on lysozyme as a single biomarker, without evaluating other interacting salivary proteins such as lactoferrin, immunoglobulin A, or amylase, which could have additive, synergistic, or compensatory effects. Fourth, the cross-sectional design of several studies limited the ability to infer causality or understand longitudinal changes in lysozyme levels in response to caries progression or treatment.

Despite these limitations, the results provide meaningful implications for both studies and clinical practice. Salivary lysozyme appears to be associated with caries activity, as a defensive antimicrobial response to increased bacterial load or protective factor in caries-free individuals. This dual role underscores the potential as a non-invasive biomarker for assessing caries risk in children. Clinically, understanding the dynamics of salivary lysozyme contributes to the development of personalized preventive strategies, such as saliva-based diagnostics or targeted antimicrobial therapies. Regarding future investigations, larger-scale, longitudinal studies are recommended to evaluate lysozyme alongside other salivary enzymes and immune markers, using standardized methods. The results will be crucial to clarify the diagnostic and prognostic value of early childhood caries and enhance the biological understanding of salivary defense mechanisms.

5. Conclusion

In conclusion, this scoping review shows that salivary lysozyme has potential as biomarker for caries activity in children. However, studies show inconsistent patterns, as some relate low lysozyme levels with caries status, indicating a possible protective role. Others report high levels in severe cases, showing an upregulated immune response. Pellicle-based studies show no significant association, suggesting that lysozyme localization may matter more than total concentration. Due to the inconsistency, salivary lysozyme can be considered a dependent and potentially responsive biomarker of caries activity.

The existing information on salivary lysozyme as biomarker for dental caries remains limited by several methodological and conceptual constraints. This is because most studies use a small sample size, with cross-sectional or short-term designs, causing difficulty in assessing lysozyme dynamics and caries progression. Furthermore, there is considerable heterogeneity in saliva collection, analytical methods, and participant characteristics. Another limitation is analyzing lysozyme alone and neglecting synergy with other salivary defenses. Since caries occurs from complex microbial and host interactions, single-marker studies give incomplete results. Therefore, future studies should use standardized, longitudinal designs with multi-biomarker panels and modern tools like proteomics and machine learning to better relate salivary defenses with caries development.

As a recommendation, further studies should prioritize larger, longitudinal, and standardized investigations that integrate salivary lysozyme assessment with other complementary biomarkers (lactoferrin, peroxidase, secretory IgA, or total antioxidant capacity). Combining molecular, microbiological, and clinical parameters would provide a more comprehensive understanding of the dynamic interactions between host immunity, saliva composition, and caries pathogenesis. Furthermore, the validation of lysozyme as salivary biomarker for early caries detection requires a multidimensional and translational study framework.

6. Acknowledgement

None.

7. Conflict of Interest

The authors declare no conflicts of interest to disclose concerning this review.

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