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Detection of Dental Caries Using Salivary Biomarkers – A Systematic Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Systematic Review

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ABSTRACT

Background: Saliva is a mixture of organic and inorganic components that comes in constant contact with the hard and soft tissues of the oral cavity. One of the most frequent disorders is dental caries, which is a multifactorial microbial disease of the tooth. Of which saliva plays a significant role in the process of dental caries.
Aim: To systematically identify and evaluate the ability of salivary biomarkers in detection of dental caries.
Methods: A comprehensive search was done using electronic data bases such as PubMed Central, Cochrane Database of Systematic Reviews, Google Scholar and direct web search. The title scan was used to find relevant articles, which were then read and appraised for inclusion. This review analyses all research that investigated the use of salivary protein biomarkers to detect dental caries.
Results: Electronic database search identified 16 articles. After evaluating the title, abstract, and full text of these articles, only 4 were selected for the present systematic review. A final of 4 studies were included based on the inclusion criteria to meet the research question. All the studies analyzed the salivary biomarkers in dental caries detection.
Conclusion: Salivary biomarkers are a significant indicator in detection of dental caries and can be used in determining the further treatment planning.

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Keywords: Saliva; biomarkers; dental caries; organic components.

1. INTRODUCTION

Biomarker refers to measurable and quantifiable biological parameters than can serve as indicators for health and physiology-related assessments, such as pathogenic processes, environmental exposure, disease diagnosis and prognosis or pharmacologic responses to a therapeutic intervention [1]. Physiological, anatomical, and biochemical biomarkers are all available. Potential molecular and biochemical indicators found in biological fluids can be employed for detection, prognosis, and monitoring [2].

Saliva is a biological fluid that is slowly gaining traction as a powerful diagnostic tool to detect abnormalities. Also it is an easily accessible fluid that can be obtained using a noninvasive method [3]. Recent researches have discovered a slew of actions mediated by both the inorganic and organic components of saliva that should be taken into account when evaluating the effects of saliva on dental caries. Dental caries affects a substantial section of the world's population due to its high prevalence and complex nature. Because teeth are constantly bathed in saliva, the components and characteristics of this oral fluid are crucial in the development and progression of dental caries. Some of these researches have changed the way we think about dental caries, shifting it from a bacterially driven multifactorial illness to one that may be impacted by hereditary salivary variables. Salivary components that are genetically controlled may influence both the colonization and removal of microbes from the oral cavity [4]. Saliva is the primary habitat for oral microbes, and saliva microorganisms influence plaque structure and the development of caries lesions is not only driven by microorganisms but also the dietary habits which includes the frequency of carbohydrate intake, pH & stickiness of food debris and host factors such as salivary flow rates, immune responses, genetic predispositions & hygiene measures [5]. Salivary protein is considered as one important factor for monitoring health and illness. Saliva proteins have been shown to influence dental health and homeostasis, maintain a stable ecology, and limit the growth of cariogenic bacteria [6]. Despite the fact that several studies have demonstrated that previous caries experience is the best predictor of future caries, salivary biomarkers are widely promoted, which provides simple chair side kits for the purpose. Salivary diagnostics has developed into a sophisticated discipline that is a part of the larger subject of molecular diagnostics, which is now widely recognized as a key factor in a wide range of biomedical fundamental and clinical areas. The discovery of adequate salivary biomarkers could allow for the early diagnosis of caries lesion formation as well as the early identification of high-risk patients.

The aim of this current study is to systematically evaluate the ability of the salivary protein biomarkers to detect the occurrence of dental caries which could help in the early diagnosis of dental caries especially in children.

2. MATERIALS AND METHODS

2.1 Search Strategy for Identification of Studies

The search technique followed the standards for systematic reviews published by the Cochrane guidelines. For the years 2020-2021, papers were pulled from PubMed Central, Cochrane Database of Systematic Reviews, and Google Scholar. We also used the internet to find publications that were related to our interests. This study comprised studies that evaluated the ability to identify dental caries using salivary protein biomarkers. Article names and abstracts were scrutinized. The selected articles' text was extracted and evaluated further.

2.2 Search Methodology

The search methodology applied was using the following keywords:

“Salivary Protein Biomarkers” AND “Dental Caries” Filters: published in the last 1 year.

The systematic search was limited to these two terms to guarantee that no relevant articles were disregarded. Adding another term would have narrowed the search, but it would have also raised the chances of missing important titles. Titles were examined independently by two researchers after duplicates were removed, using established inclusion and exclusion criteria. The remaining papers were reviewed in their entirety, and a decision was made based on the relevancy of the abstracts and complete texts.

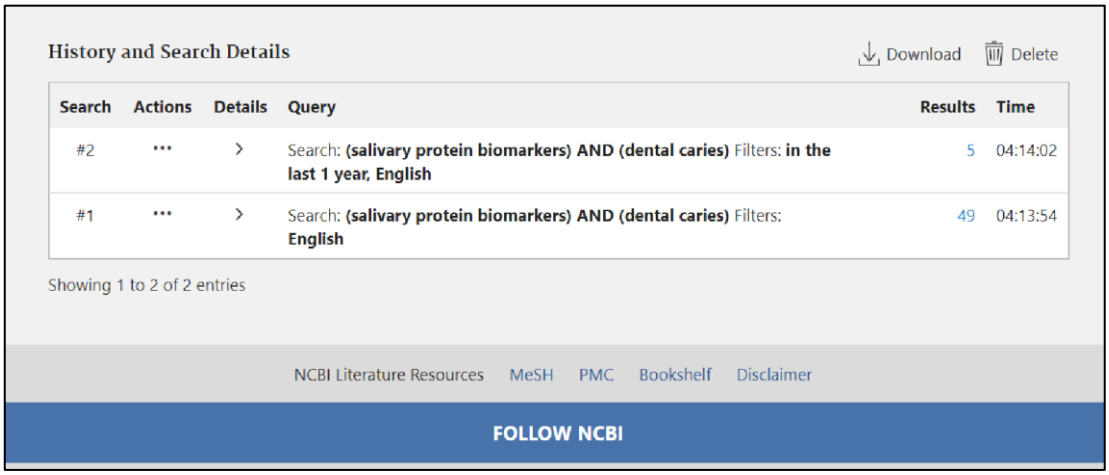

Fig. 1. Image showing the PubMed search strategy

Fig. 2. Image showing the google scholar search strategy

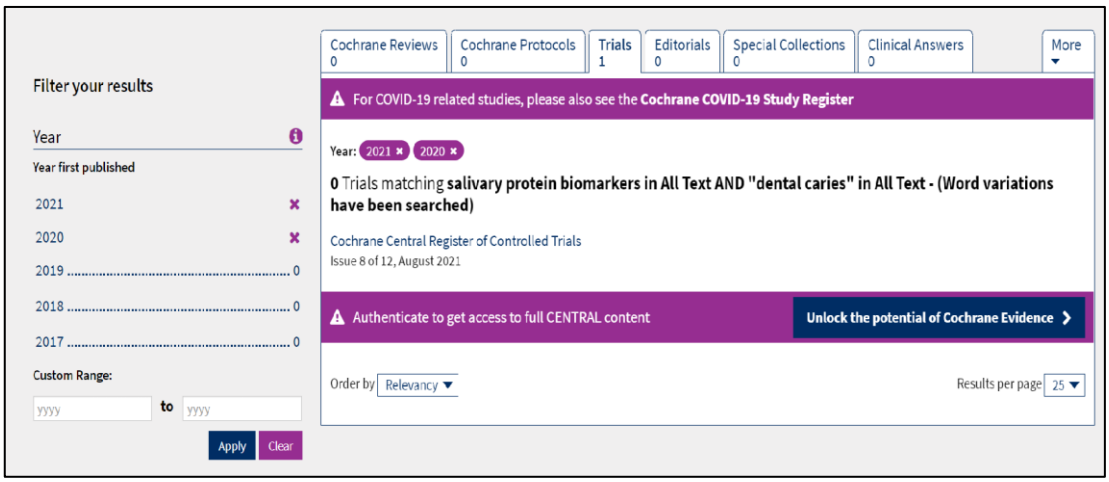

Fig. 3. Image showing the Cochrane library search strategy

2.3 Selection of Studies

Inclusion criteria:

- Original research articles were included.
- Original research articles performed with salivary protein biomarkers/ proteomic studies were included.
- Articles published in English language were included in the review.
- Articles published in the last 1 year (2020-2021) were included.

Exclusion criteria:

- Case reports and review articles were excluded.
- Studies published in other languages were excluded.
- Studies that used other variables of saliva other than protein biomarkers were excluded.

2.4 Data Extraction

Once the articles to be reviewed were finalized, data were collected from each article, tabulated and was verified and interpreted.

3. RESULTS

3.1 Study Selection

PubMed electronic database yielded 5 studies, Google Scholar yielded 9, Cochrane yielded 0 and a Web search yielded 2 papers. There were 15 studies left after the duplicates were removed. 11 articles were deleted after title and abstract scanning because they did not match the criteria for inclusion and exclusion. These full text articles' bibliographies were examined for studies not found in electronic databases. From the cross-reference, no relevant studies were discovered. 4 studies fulfilled the targeted research's inclusion and exclusion criteria. Fig. 4 shows the PRISMA flowchart that represents the study selection procedure.

3.2 Study Characteristics

The study characteristics of the included articles are summarized in Table 1. The studies included in this review have shown to have positive results regarding the dental caries prediction from salivary protein biomarkers.

2 studies have performed analysis using population above 18 years of age (young adults and middle aged) and 2 studies performed analysis using population below 18 years of age (pre-schoolers and school age). No gender variation was seen in any of the included researches.

2 studies used unstimulated whole saliva whereas one study preferred the use of stimulated saliva. 1 study has not mentioned their sample type used for the analysis.

All the studies have performed salivary protein marker analysis and have analyzed variable parameters according to their rationale. One study has found 44 salivary protein biomarkers (19 cytokines, 7 chemokines, 4 growth factors, 2 metalloproteinases,1 metallopeptidase inhibitor, 1 protease, and 10 orally associated bacteria), of which they have identified 4 salivary protein biomarkers (salivary protein biomarkers) exhibited strong correlation with the dental caries predilection. Another study evaluated only IL-6 biomarker to predict the dental caries and have found a strong correlation between the IL-6 levels and the extent and severity of the carious lesions. Other 2 studies did not analyze the correlation between dental caries occurrence with salivary biomarkers in particular. They have performed molecular database analysis and proteomic analysis with the respective samples and they have also acquired a positive correlation.

4. DISCUSSION

Biomarker assays may make this method easier and allow dentists to track patients' progress toward healthy dental microenvironments more precisely. Salivary proteins were the biological biomarker used in the literature search to predict dental caries. But dental caries is a complex disease of the teeth, finding a single biochemical sign to predict the severity of the illness is difficult [7]. All these studies have performed biomarker analysis with freshly collected saliva sample but the difference lies with the type of saliva sample, which is the unstimulated and stimulated saliva. The unstimulated whole saliva is collected using different simple methods and it is preferred more than the stimulated saliva, as it best duplicates baseline saliva production and composition from both the major and minor glands in the resting state [8]. The stimulated whole saliva is largely gathered during mastication or gustatory stimulation, provides a much larger sample

volume, albeit the stimulation dramatically affects the contributions from the various glands, and yet it's highly reliable in comparison to the unstimulated state [8,9]. However this methodological difference in saliva sample collection greatly limits the amount of sample. Previous literature evidence states that saliva sample collecting procedures in researches help in arriving at a positive findings. Furthermore, they establish a foundation for the use of stimulated whole saliva in stress response measurement, an appealing conclusion given the importance of this response in both disease and exercise applications, where low flow rates associated with unstimulated whole saliva may compromise dependability [8].

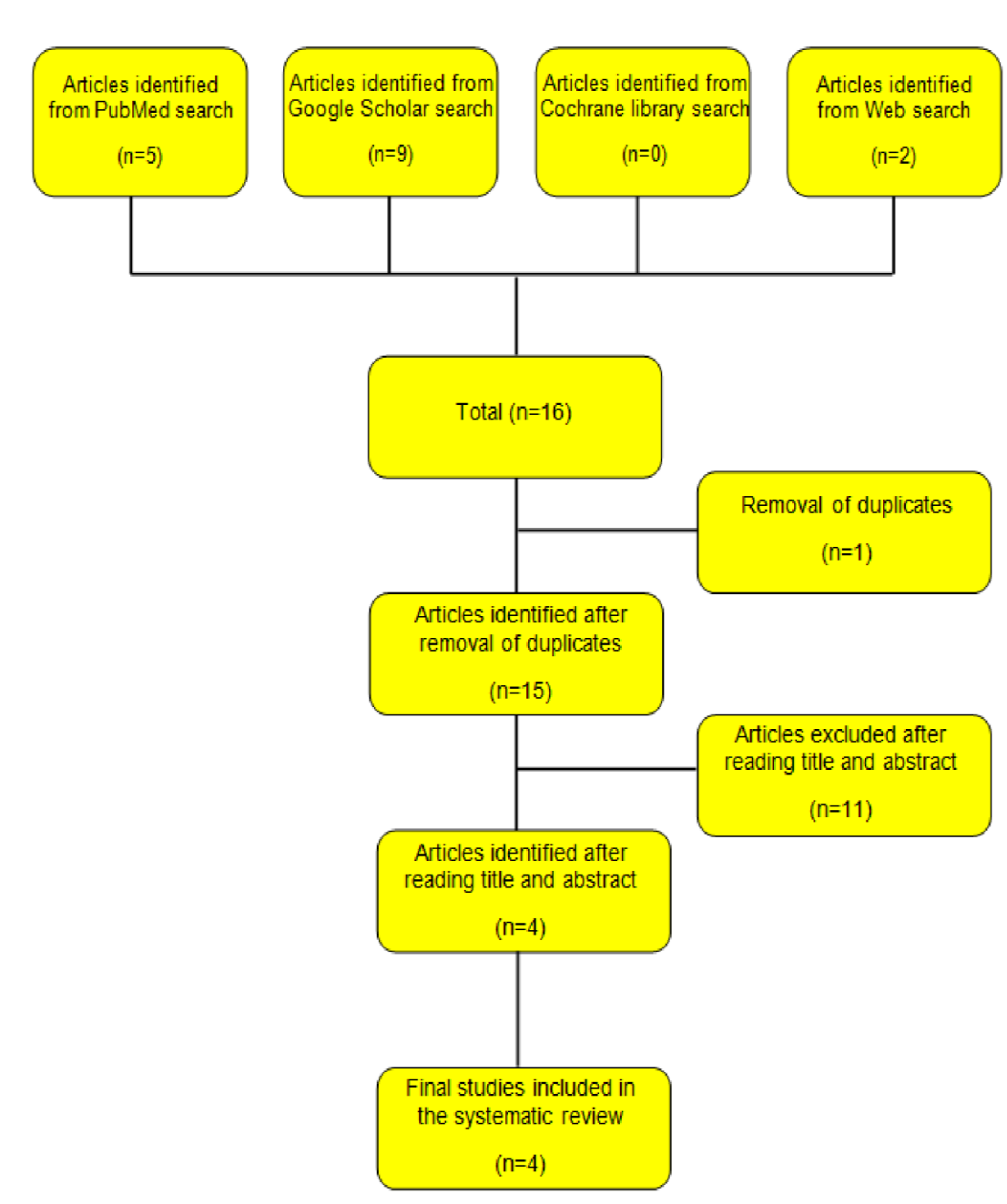

Fig. 4. Image showing the PRISMA flowchart

Table 1. Summary of the case study characteristics included in the review.

S.No	Author	Year	Country	Sample size	Age group	Type of saliva	Parameters analyzed	Results	Conclusion	Limitations
1)	Paqué, P.N., et al. (5)	2021	Zurich, Switzerland	120	>18 years	Whole unstimulated saliva	19 cytokines, 7 chemokines, 4 growth factors, 2 metalloproteinases,1 metallopeptidase inhibitor, 1 protease, and 10 orally associated bacteria	four salivary biomarkers were found to exhibit strong correlation - interleukins IL-4 and IL-13, the interleukin receptor IL-2-RA, and the chemokine eotaxin/CCL11	The current research identified four biomarkers (IL-4, IL-13, IL-2-RA, and eotaxin/CCL11) that enabled the correct diagnosis of dental caries.	This study focused on the screening of putative biomarkers that can predict dental caries, a complete explanation of the underlying pathways and relevant mechanisms was not possible.
2)	Govula K, et al. (12)	2021	Tamilnadu, India	20	18–39 years	Not mentioned	IL-6	The levels of IL-6 reduced significantly after the complete removal of caries and restoring those teeth with restorative materials showing that there exists a strong correlation between the two.	A strong correlation is present between the IL6 level and the extent and severity of the carious lesions. Post-treatment, there is a significant reduction of the IL-6 values, which can be attributed to the	Less sample size and shorter duration of follow-up (45 days)

S.No	Author	Year	Country	Sample size	Age group	Type of saliva	Parameters analyzed	Results	Conclusion	Limitations
									complete removal of dental caries.	
3)	SFF Guedeset al. (13)	2020	Ceara, Brazil	126	2–6 years	Stimulated saliva	Data analyses were conducted with Progenesis QI.	122 were differentially expressed in comparisons among children with different caries status. 8 proteins (HAUS4, CAH1, IL36A, IL36G, AIMP1, KLHL8, KLH13, and SAA1) were considered caries-related proteins.	The identification of exclusive proteins for caries-free or carious-related conditions may help in understanding the mechanisms of caries and predicting risk as well as advancing in caries control or anti-caries approaches.	investigations on the mechanisms of salivary proteins for caries susceptibility or caries resistance, as well as their conversion from the laboratory stages to the clinical practice, are needed.
4)	Chen, et al (6)	2020	Chongqing, China	20	6-8 years	unstimulated saliva	Proteomic analysis of saliva samples was performed using the iTRAQcoupled LCMS/MS method to detect protein biomarkers of	The results of the salivary proteome identified 9135 unique peptides and 1662 proteins group from 20 salivary samples. Two hundred fifty-eight proteins were differentially expressed	As a critical host factor of caries, the salivary proteins are different in caries-free and caries-active groups.	No particular salivary protein biomarker and its correlation with dental caries have been studied. The specific information about the

S.No	Author	Year	Country	Sample size	Age group	Type of saliva	Parameters analyzed	Results	Conclusion	Limitations
							caries risk in children	between the caries-free and caries-active groups.		proteins in the saliva need to be Investigated.

All the studies have used different parameters as well as different methodologies to evaluate the presence of salivary protein biomarkers. All the studies have also managed to produce positive correlation between the salivary protein biomarkers and dental caries. One study included in this review has found 4 reliable salivary markers out of existing potential 44 biomarkers and was discovered to have great promise as classifiers for distinguishing between healthy individuals and caries patients [5]. They were Interleukins IL-4 and IL-13, the interleukin receptor IL-2-RA and the chemokines eotaxin/CCL11 [5]. Another included study has found a positive correlation between IL-6 exhibitions with caries prediction [10]. Previous literature evidences have proved that caries affected teeth exhibit significantly increased GCF levels of IL-4 and IL-6 when compared to healthy teeth, even in shallow lesions [11]. This increase in expression of interleukins could be because of the correlation of carious lesions with the periodontal pathology. When considering the close connectivity between dental and periodontal tissues, a comparable pathological pattern provides a backdrop for pathological activity across diseases, in the course of increased local inflammation, which may occur even in the early stages of enamel caries. Depending on the extent of the caries lesion, the dental pulp defends itself against caries by releasing different type of cytokines [12]. Inflammatory cytokines have been linked to pulpal inflammation and immunosenescence, both of which have been linked to dental caries. Inflammation and immunological induction are closely associated phenomena, such as the successful resolution of the inflammatory process, which leads to the change from innate to adaptive immunity [10].

2 studies have performed proteomic analysis to evaluate the correlation between salivary markers and dental caries. One study found that protein SH3L2 were exclusively present in enamel caries and 8 proteins (HAUS4, CAH1, IL36A, IL36G, AIMP1, KLHL8, KLH13, and SAA1) were considered caries-related proteins when compared to caries-free children; they were up-regulated proteins in the caries groups [13]. Another study performed salivary proteome and identified 9135 unique peptides & 1662 proteins group from 20 salivary samples. 258 proteins were differentially expressed between the cariesfree and caries-active groups [6]. Given the unique protein profile associated with caries prevalence and severity, more research into the mechanisms underlying salivary proteins for caries susceptibility or resistance, as well as their translation from the laboratory to clinical practice, is required. These proteomic evidences are in concordance with the few previous researches. Few salivary peptides have been found to be associated with early childhood caries (ECC) [14,15].

These discoveries of various salivary protein biomarkers in relation to dental caries can be considered as a keyhole but further more investigations are necessary to finally conclude their reliability on prediction of carious lesions. All these studies have set the groundwork for the development of simple and cost-effective saliva-based diagnostic tools for determining the presence or absence of dental caries on an individual basis.

5. CONCLUSION

The salivary protein biomarkers show a positive correlation in predicting the carious lesions regardless of the age and gender. Yet large scale investigations are necessary to substantiate the positive findings which may help in understanding the mechanisms of caries and predicting risk as well as advancing in caries control or anti-caries approaches.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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