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A Systematic Review to Ascertain the Role of Inflammatory Biomarkers in the Diagnosis and Treatment Course of Dental Diseases

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ABSTRACT

Background: The use of biomarkers in dentistry can help dentists make more informed diagnosis and treatment decisions, and ultimately improve the oral health outcomes of their patients. This study aimed to identify markers in saliva and blood that are associated with periodontal and oral disease using randomized controlled trials (RCTs).
Methodology: Using the MeSH term "Biomarkers in dentistry" “Inflammatory biomarkers” and “oral diseases”. A literature review was conducted using PubMed, ScienceDirect, and Cochrane. Search engines changed the MeSH terms under PRISMA guidelines.
Results: In this systematic review seven studies were included which help in identifying, biomarkers that can aid the dentist in the diagnosis, monitoring, and evaluation of a variety of oral diseases and illnesses.
Conclusion: Thus, all the studies chosen for this systematic review prove that all the biomarkers can play a crucial role in assessing overall health and wellness. Their ability to identify early disease symptoms can result in prompt interventions and better outcomes.

Keywords: Biomarkers, salivary markers, inflammatory biomarkers, gingival crevicular fluid.

INTRODUCTION

Biomarkers have become an integral part of modern dentistry, offering groundbreaking insights into various aspects of oral health. These biological indicators, which can be measured accurately and reliably, play a crucial role in diagnosing, predicting, and monitoring oral diseases.[1] From periodontal disease to oral cancer, biomarkers help in understanding the underlying pathophysiological processes, enabling more precise and personalized treatment plans.

In the dynamic field of dentistry, the application of biomarkers encompasses several areas. Salivary biomarkers, for instance, are non-invasive tools that provide valuable information about systemic and local oral health conditions.[2] Advances in molecular biology and analytical techniques have facilitated the identification of specific biomarkers associated with dental diseases, which can be detected in saliva, gingival

crevicular fluid, and even blood. The importance of biomarkers in dentistry extends beyond diagnostics. They are pivotal in the development of new therapeutic approaches and in the evaluation of treatment outcomes.[3] By identifying disease at an early stage, biomarkers can lead to more effective and less invasive interventions, ultimately improving patient care and prognosis.

Saliva is an intriguing biological fluid that possesses every characteristic that makes it an ideal diagnostic tool. Collection of which is quick, easy, and non-intrusive[4]. Saliva is affected by systemic (e.g., disease) and/or environmental (e.g., stressors) changes, some of which are readily detectable through salivary analysis.

Salivary biomarkers can be used to diagnose and monitor conditions such as periodontal disease, and oral cancer, and Sjogren's syndrome is the second most prevalent autoimmune disorder,1, 2 affecting ~35 million individuals globally. A disease of the exocrine system, SS impairs the lacrimal and salivary glands leading to ocular and oral dryness, reduced saliva volume and flow rate (hyposalivation), and an altered proteomic (protein) composition.[5]

Inflammatory triggers may include environmental factors (e.g., virus), family history (i.e., autoimmune), and/or hormonal influences [6] 8-hydroxydeoxyguanosine (8-OHdG) is a significant marker that can be used to assess tissue damage in periodontitis and which is also one of the oxidative DNA damage indicators.[7]

Inflammatory Biomarkers:

Inflammatory biomarkers help in the early detection of oral diseases. These biomarkers have reportedly been found in biological specimens such as blood, urine, hair, feces, cerebrospinal fluid, sputum/saliva, and body tissues. For example, elevated levels of IL-1β and MMPs in saliva or GCF can indicate active periodontitis.[8] Tracking changes in biomarker levels can help assess the effectiveness of various oral disease treatments and interventions. A decrease in CRP or IL-6 levels post-treatment can indicate reduced inflammation. Biomarkers like CRP and fibrinogen can help evaluate the risk of developing systemic conditions associated with periodontal diseases, such as cardiovascular diseases.[9] Inflammatory biomarkers are essential in research to understand the underlying mechanisms of oral diseases and develop new therapeutic strategies.[10] Salivary marker protein-level detection has long been regarded as the gold standard in the diagnostics industry. [11]. Some of the inflammatory biomarkers in dentistry are as follows:

- **C-Reactive Protein (CRP)**: Elevated levels of CRP are associated with systemic inflammation and have been linked to periodontal disease. It is often used to evaluate the risk of cardiovascular disease, which has connections to periodontal health.
- **Interleukins (ILs)**: **IL-1β**: This cytokine is involved in the inflammatory response and is a significant marker in periodontal disease. It stimulates bone resorption and is often found in higher levels in patients with periodontitis. **IL-6**: This cytokine is a mediator of acute inflammation and is associated with both systemic and local inflammation in the oral cavity. **IL-8**: Known for attracting neutrophils to infection sites, elevated levels of IL-8 are found in inflamed periodontal tissues.
- **Tumor Necrosis Factor-α (TNF-α)**: TNF-α is a pro-inflammatory cytokine that plays a crucial role in inflammation and immune response. High levels are associated with periodontal disease and other inflammatory conditions in the mouth.[12]
- **Matrix Metalloproteinases (MMPs)**: **MMP-8 and MMP-9**: These enzymes break down extracellular matrix components and are associated with tissue destruction in periodontitis. Elevated levels are indicative of active periodontal inflammation.
- Myeloperoxidase (MPO): It has been noted that inflamed pulp tissue has an increased expression of MPO and active TIMP-2.

- **Prostaglandin E2 (PGE2)**: PGE2 is involved in the inflammatory process and bone resorption. It is often found in elevated levels in the gingival crevicular fluid (GCF) of patients with periodontitis.
- **Lipopolysaccharides (LPS)**: Found in the outer membrane of Gram-negative bacteria, LPS triggers a strong immune response and is associated with periodontal pathogens.[13]
- **Fibrinogen**: This protein is involved in blood clotting and inflammation. Elevated fibrinogen levels can be an indicator of systemic inflammation and are linked to periodontal disease.

Overall, the use of biomarkers in dentistry can help dentists make more informed diagnoses and treatment decisions, and ultimately improve the oral health outcomes of their patients.

Objective:

To use randomized controlled trials to find biomarkers in blood and saliva that are connected to oral diseases.

MATERIALS AND METHODS:

Search strategy:

The study used results from original publications and research papers that have been published on biomarkers in oral health in databases including PubMed, ScienceDirect, and Cochrane Central Register of Controlled Trials (CENTRAL). A literature search was performed using the MeSH term "Biomarkers" "Inflammatory biomarkers" and "oral diseases" to locate relevant material. Every search engine modifies the MeSH phrases according to PRISMA suggestions.

Eligibility criteria

Inclusion criteria:

1. Original article
2. Studies with randomized controlled trials
3. Studies published in English

Exclusion criteria:

1. Studies written in other languages were disqualified.
2. Articles without full text

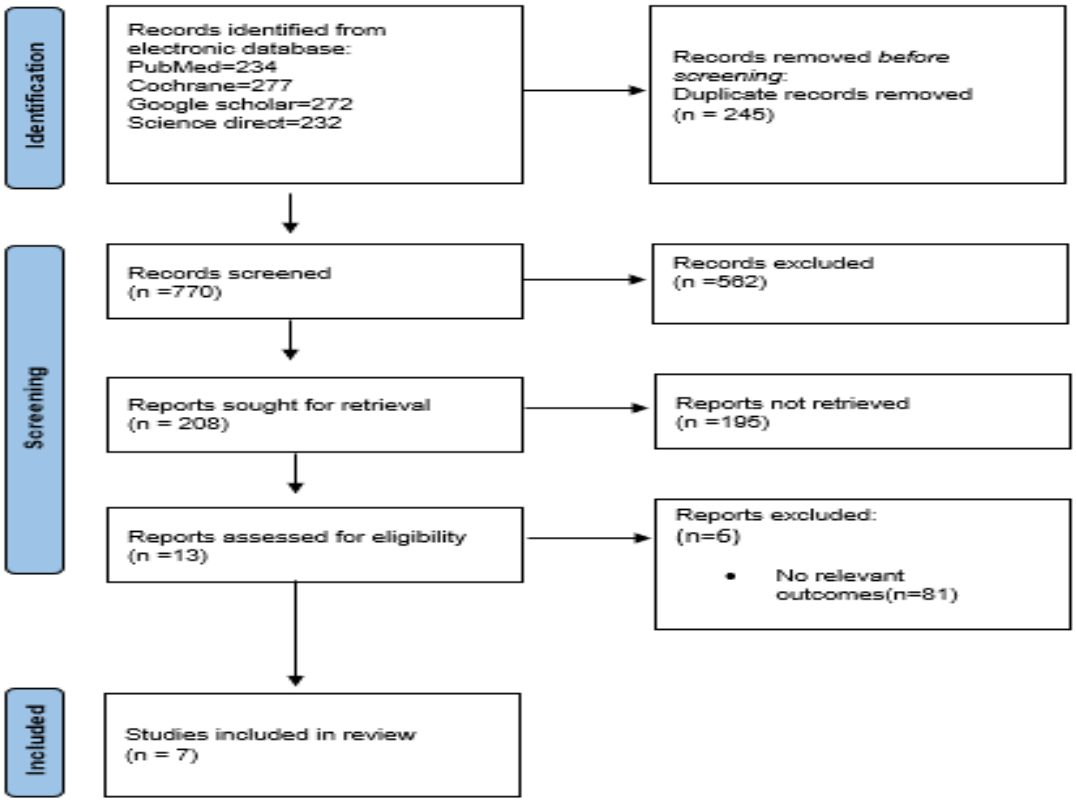

Figure 1: PRISMA flow diagram

The flowchart in Figure 1 illustrates the number of studies that were viewed, filtered, evaluated, and included in the systematic review as well as those that were excluded.

RESULTS

TABLE 1: THE CHARACTERISTICS OF THE STUDY THAT ARE INCLUDED IN THE SYSTEMATIC REVIEW

AUTHOR	YEAR	SAMPLE SIZE	GROUP CHARACTERISTIC	INTERVENTION
Maria L. Bryan S Michalowicz, et al[14]	2016	475	Participants with least moderate periodontitis (two or more tooth sites in at least two quadrants of the mouth with clinical attachment loss and probing depth ≥ 5mm19), a minimum of 16 natural teeth, no periodontal treatment in the last 6 months, and with type 2 diabetes (HbA1c at screening ≥7% and <9%) were enrolled. Glucose and insulin levels were determined from serum.	Treatment group participants received a minimum of 180 minutes of scaling and root planning (non-surgical mechanical cleaning of the tooth crown and root). Treatment group participants also received supportive periodontal care at the three-month visit. Participants in both groups were assessed by calibrated examiners at three and six months. The following periodontal clinical measurements were evaluated: probing depth (PD), clinical attachment level (CAL),bleeding on probing (BOP) from six sites on each tooth (apartfrom molars),gingival index and the presence or absence of plaque from six index teeth.
Gisele Quariguari et al[15]	2018	152	72 children with ECC and 80 caries-free children	Serum were collected and analysed for levels of proinflammatory cytokines (IL-6, TNF-α, and NGAL) in both ECC and treated individuals.
Simran Rastogi, Komal Rani, et al. [16]	2023	25	All 25 patients received instruction in proper oral hygiene, and models were made for the purpose of fabricating surgical guides and wax-ups.	Duration: 18 months Between 50 and 100 µg of the total protein was extracted from the PICF strip. For a single ELISA experiment, 30 µg of protein was totaled from each sample. The samples were analysed using commercially available ELISA kits (cathepsin-K, osteocalcin from CUSABIO, Wuhan, China; Human MMP-8 obtained from RayBio, GA, USA) in accordance with the manufacturer's instructions. Minimum detection values for ELISA kits were as follows: For osteocalcin 31.25 pg/mL; for MMP-8 6.9 pg/mL and cathepsin K 7.8 pg/mL. The biochemical data were expressed as concentrations (pg/mL).
Sexton WM, Lin Y,	2011	68	Complete medical and dental histories for sixty-eight patients were gathered from their	Duration: 16-28weeks Each subject had five millilitres of unstimulated whole expectorated

Kryscio RJ,et al..[17]			medical records and verified during the interview.	saliva collected; the samples were immediately placed on ice, aliquoted, and frozen at 80 degrees Celsius.Luminex human cytokine/chemokine multiplex kits were utilized by the University of Kentucky General Clinical Research Centre Core Laboratory. (Millipore, St. Charles, MO, USA) to measure the concentrations of salivary IL-1b, IL-8, MIP-1a, and TNF in duplicate. Human quantikine enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA) were used to measure the salivary levels of OPG and MMP-8 in duplicate for each subject using the manufacturer's instructions.
Meggan M H et al [18]	2013	53 Dialysis patients	53 were randomly assigned, with 26 participants assigned to immediate treatment and 27 assigned to a control arm for treatment after 6 months. 51 patients completed baseline appointments; 46 were available for 3-month follow-up, 45 were available for 6-month follow-up examinations, and 43 completed all visits.	For patients in the treatment group, intensive therapy included scaling and root planing, extraction of teeth that were beyond treatment, and administration of local-delivery antibiotics. For patients in the control group, this treatment was done after the trial was finished.
Gandhe et al [19]	2024	60	Before beginning root canal treatment (RCT), a blood sample was obtained from the antecubital fossa to evaluate the inflammatory markers, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). After 72 h, patients were recalled for follow-up appointments, and blood was taken from the antecubital fossa again to evaluate inflammatory markers.	In the control group, the determined Working Length(WL) was maintained, while in the experimental group, the WL was set till the apical foramen. Biomechanical preparation was done in both groups till F2 or F3 based on the initial apical file, followed by final irrigation and obturation based on the master apical file size.
Yousuf et al [20]	2024	27	Saliva samples were collected at three time intervals: before tooth extraction and 2 hours and 2 days after tooth extraction. The salivary biomarkers were investigated using a Luminex multiplex assay. These salivary biomarkers included tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), interleukin 1-beta (IL-1β), and interferon-gamma (IFN-γ).	Every patient gave a 5-ml sample of unstimulated whole saliva three times: prior to extraction, two hours after extraction, and two days after extraction. Patients were instructed not to eat or drink anything for one hour before to sample collection. The participants were instructed to spit into the collecting tube over the course of five minutes after gently rinsing their mouths with tap water for two minutes. Patients were told to let passive saliva run into the collection tube following extraction in order to avoid disrupting blood clots. Until

				analysis, all the samples were kept frozen at -80°C after being kept in an ice-cold box.

TABLE 2: THE FINDINGS FROM THE RESEARCH THAT WAS PROVIDED

AUTHOR	YEAR	OUTCOME	RESULT
Maria L. et al [14]	2016	Serum biomarker changes were not significantly impacted by either non-surgical periodontal therapy or the severity of periodontal disease in DPTT participants over the course of a six-month follow-up. Over the course of a six-month follow-up, neither non-surgical periodontal therapy nor the severity of periodontal disease in DPTT participants significantly affected serum biomarker changes. Correlations between changes in E-selectin, IL-6, and diabetes-related variables suggest that systemic inflammation in these diabetic patients may be primarily caused by diabetes mellitus.	There were no differences in any biomarkers at BL or 6 months ($p>0.05$) between the Treatment and Control Groups for any of the variables. Six months later, the Treatment Group's VCAM levels increased by an average (SD) of 17.9 (99.5) ng/mL ($p=0.006$), while E-Selectin decreased by 2.33 (16.08) ng/mL ($p=0.03$). There were no statistically significant correlations found between periodontal clinical parameters and diabetes-related variables or serum biomarkers. But in both Groups, there was a significant correlation between e-selectin levels and diabetes-related variables [fasting glucose and haemoglobin A1c (HbA1c)] at baseline (BL) and six months later. Over the course of the study, neither the body mass index (BMI) nor the HbA1c changed in either study group.
Gisele Quariguari et al [15]	2018	Higher serum levels of proinflammatory cytokines were associated to severity of caries in preschoolers, suggesting that chronic inflammation underlies ECC.	The high IL-6 (MR = 1.47, IC = 1.09-2.00, p = 0.012), TNF-α (MR = 1.33, CI = 1.00-1.78, p = 0.040) and NGAL (MR = 2.20, CI = 1.39-3.49, p = 0.001) were associated to ECC. After adjustment, the highest tertiles of IL-6 levels (MR = 1.54, IC = 1.13-2.10, p = 0.005), and NGAL (MR = 1.71, CI = 1.04-2.80, p = 0.032) remained associated to ECC; while TNF-α was no longer associated to ECC (MR = 1.31, CI = 0.98-1.75, p = 0.066).
Simran Rastogi et al [16]	2023	CatK and MMP-8 levels in this study decrease in both groups at 12 months, with the IL group exhibiting lower values than the DL group.	The trial involved all 25 patients, with a mean age of 28.7 ± 3.5 years, and 15 males (60%), and 10 females (40%). Throughout the 12-month follow-up period, no patients withdrew from the study. In the edentulous sites, a total of fifty implants measuring 3.75 mm or 4.2 mm in diameter and 10 mm or 11.5 mm in length were positioned. Data were collected at two weeks, three months, and twelve months after implant implantation.
Sexton WM, Lin Y et al [17]	2011	Salivary levels of MMP-8, MIP-1a, IL-1b, and OPG were found to reflect the severity of the disease and the response to treatment, indicating their potential use in monitoring the state of periodontal disease.	The Baseline, week 16, and week 28 evaluations were conducted on sixty-eight adults with chronic periodontitis, ages ranging from 25 to 69. 35 people were in the SRP group and 33 people were in the OHI. Male Caucasian Hispanic participants made up the majority of the participants. Although the mean number of teeth in both groups was similar, the OHI group had a 7-year age

			difference (p= 0.003). There was no discernible difference in the subjects' smoking habits, race, or gender between the groups. Clinical parameters that indicated the presence of generalized chronic periodontitis were similar between the two groups in terms of %CALX2 mm, %PD sites X4 mm, %PD sites X5 mm, and %BOP (p>0.05).
Meggan M H et al[18]	2013	Outcome included clinical periodontal parameters (probing depth, clinical attachment level, bleeding on probing, gingival index, and plaque index), as well as serum albumin and interleukin 6 levels at three and six months post intervention.	Three periodontal metrics were found to have improved statistically significantly in the treatment group after three months as compared to the control group: mean probing depth (P = 0.008), extent of probing depth ≥4 mm (P = 0.02), and extent of gingival index ≥1 (P = 0.01). After six months, nevertheless, all group differences disappeared, with the exception of probing depth ≥4 mm (P = 0.04). After adjusting for body mass index, diabetes, and plaque index, there was no discernible difference between the groups at any point in time for either the serum albumin or the high-sensitivity interleukin 6 level.
Gandhe et al[19]	2024	Reduction in inflammatory markers was more effective in RCT with apical enlargement than non treated tooth.	*P* values of the CRP and ESR of the control group were 0.02 and 0.03, respectively, which indicates it is significant whereas the *P* values of the ESR and CRP of the experimental group were 0.0002 and 0.0008 which indicates it is highly significant. Results indicate that the experimental group is more effective compared to the control group in reducing inflammatory markers.
Yousuf et al[20]	2024	Salivary proinflammatory biomarker levels in type II diabetes patients are often similar to or lower than those in healthy control participants. Following tooth extraction, proinflammatory cytokines behave differently in people with type II diabetes than in healthy persons. When individuals with type II diabetes undergo dental extractions, salivary proinflammatory indicators typically exhibit a delayed early response.	IL-1β levels were considerably lower in type II diabetes patients at baseline (P = 0.016). Furthermore, two hours following extraction, IL-1β and TNF-α levels in type II DM patients were considerably lower than in healthy control subjects (P = 0.046 and P = 0.020, respectively). Furthermore, the DM group exhibited significantly higher levels of IL-6 (P = 0.010) than the control group two days following tooth extraction.

Table 2 shows the outcome data and provides a condensed overview of the important findings of biomarkers commonly used in dentistry. The following factors were studied: Author's name, year of study, outcome, and results of the four included studies

Table 3: BIAS EVALUATION AS INCLUDED IN THE RESEARCH

Author Name, Year	**Random Sequence generation**	**Allocation concealment**	**Blinding of outcome**	**Incomplete outcome data**	**Blinding Of participant and personnel**	**Selective reporting**	**Judgemental bias**

Maria L et al [14]	+	+	?	+	?	+	+
Gisele Quariguari et al[15]	+	_	?	_	?	+	+
Simran Rastogi et al [16]	+	+	+	_	+	?	?
Sexton WM, Lin Y ,et al..[17]	_	+	?	+	+	?	?
Meggan M H et al [18]	+	?	?	?	?	?	?
Gandhe et al [19]	+	?	+	?	+	-	?
Yousuf et al [20]	?	?	?	+	?	?	?

Table 3 presents a biased analysis of the included studies, all of which produced positive results. The symbols + denotes low bias risk, - high bias risk, and ? denotes unclear bias risk.

DISCUSSION

Biomarkers in dentistry have gained increasing attention in recent years. In dentistry, the use of biomarkers has the potential to revolutionize the way oral health is assessed, diagnosed, and treated. This systemic review discusses the results among the seven included studies. Several oral diseases can be detected with biomarkers. Periodontal disease, oral cancer, and dental caries are some common examples. Saliva biomarkers, such as specific enzymes or proteins, can detect the presence or progression of these diseases. Dentists can detect potential problems early on and treat them appropriately by analysing these biomarkers. It's incredible how biomarkers can aid in the early detection and treatment of oral diseases.

Maria L et al.[13] reported that this study examined the effects of treating gum issues in persons with type 2 diabetes on specific blood markers, systemic inflammatory biomarkers and they looked for any associations between diabetes and tooth health. 475 patients with diabetes and gingival disease were studied. While some patients received care right away, others had to wait. They discovered no significant variations in the two groups' blood after six months. However, one blood parameter in the treated group slightly increased while another somewhat decreased. They discovered that one of the substances in the blood was connected to diabetes, indicating that diabetes may be contributing to more disorders than just gum disease. In the end, correcting gingival disease with the help of these biomarkers were proven.

Gisele Quariguari et [14] suggests that high serum levels of IL-6, TNF-α and NGAL were associated to high number of carious teeth, suggesting that chronic inflammation underlies caries in early childhood.

Simran et al[15] reported that MMP-8 and Cathepsin-K (CatK), two substances in the fluid around dental implants, were the subjects of this investigation. Their goal was to identify any inflammation or bone-building. They examined two groups of 25 individuals each, who were both in their late twenties. Over a 12-month period, they examined the fluid surrounding the implants and discovered that both groups had comparable amounts of MMP-8 and CatK. Bone biomarkers. Despite the fact that the group who had their implants put in right away had slightly lower levels, the variations weren't substantial enough to matter. Therefore, it doesn't seem to matter much

when you get dental implants immediately or later how your body responds.

This study by Sexton WM [16] et al investigated the potential for saliva to provide information regarding gingival disease (periodontitis) and the effectiveness of treatment. They looked at 68 adults, some of whom received guidance on how to take care of their gums (OHI group), and others who also received guidance and underwent a more thorough cleaning procedure known as scale and root planning (SRP). They took samples of saliva at various intervals and tested them for IL-1, IL-8, MIP-1, MMP-8, OPG, and TNF- salivary biomarkers. They measured gingival health as well. By week 16, both groups had improved, but the SRP group had done so more quickly. They discovered that in patients who reacted favorably to treatment, levels of OPG, MMP-8, and MIP-1 decreased more. The strongest indicator of how well a treatment was working was MMP-8. So, these substances in saliva can help us see how serious gum disease is and if treatment is working.

Meggan et al [17] investigated that there was reduced level of inflammatory biomarker Il-6 after the intensive treatment, consisting of scaling and root planing, extraction of hopeless teeth, and placement of local-delivery antibiotics which suggests the biomarkers role in the periodontal disease and treatment.

Gandhe et al [18] investigated that Periapical lesions and periodontal disease are prevalent chronic infection diseases that cause persistent inflammatory reactions. CRP and ESR levels evaluated before the RCT were high. After Root canal treatment the collected serum CRP and ESR levels were decreased in systematically healthy individuals suggesting that inflammatory markers were more effectively reduced in RCT.

Yousuf et al [19] explores the salivary biomarkers level after tooth extraction in Diabetic patients and the study reported that in patient with type II Diabetes Mellitus, Salivary proinflammatory biomarker levels of TNF-α, IL-1β, IL-6, and IFN-γ concentrations are generally lower than in healthy individuals.

A systematic review by Dan-Krister et al[20] indicated that in irreversible pulpitis, the various expressions of inflammatory biomarkers were found in both pulp and gingival crevicular fluid when compared to healthy individuals. This presence expresses that pulpal biomarkers may play as accurate and biological based diagnostic tool in endoontics.

Systematic analysis of Sultan et al[21] highlighted the diagnostic and prognostic potential of various salivary markers, including CD9, CD81, suPAR, galectin-1, MMP-9, S100A8, LDH, AST, and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α). These biomarkers offer valuable insights into periodontal disease, from early detection to severity assessment and treatment planning. Their non-invasive nature and ease of sample collection make them attractive tools for clinicians and researchers alike. Thus, these studies help us to know the wellness of biomarkers commonly used in dentistry.

CONCLUSION

Thus, all the studies chosen for this systematic review prove that all the biomarkers can play a crucial role in assessing overall health and wellness. Their ability to identify early disease symptoms can result in prompt interventions and better outcomes. People can actively maintain their well-being by keeping an eye on their biomarkers. Dental professionals can use biomarkers to help with the diagnosis, follow-up, and assessment of a range of oral health conditions. Additionally accurate and real-time assessments of oral diseases for the general public, either at home or at the dental office, are much needed.

Declaration by Authors

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