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Developing Aptasensors for Periodontitis associated Biomarkers Detection in Saliva: A Systematic review

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ABSTRACT

This study aimed to evaluate the effectiveness of Aptasensors in detecting salivary biomarkers linked to periodontitis.The literature search for this systematic review was conducted using the keywords "Aptasensors/Biosensors," "oral biomarkers," "oral diseases," "saliva," and "Aptamers" in the 'PubMed' and 'Google Scholar' databases for articles published between 2015 and 2025. The initial search yielded 249 publications relevant to the selected 10-year period of the study. After a thorough systematic review and application of the inclusion criteria, 13 studies were included.This reviewhas demonstrated that Aptasensors had achieved exceptional sensitivity for periodontitis associated biomarkers, analyzing ODAM at 1.63 nM, HBD-2 at 6.8 nM, and cortisol in the low nanomolar range. Aptamerspecific for Tannerella forsythiahad also showngreat specificity with minimal cross-reactivity. These innovative approaches had been successfully applied for periodontitis diagnosis, with aversatile multi-platform technique for ODAM (Lateral Flow, SPR, GO-FRET), a wearable smartwatch for cortisol analysis, and flow cytometry for periodontitis associated microbes' identification. The integration of Aptamers into Biosensors had enabled detection of periodontal disease and its associated stress conditions, in saliva and gingival crevicular fluid respectively, facilitating real-time analysisand early, chair-side diagnosis. Aptasensors are highly sensitive and specific, offering real-time analysis of underlying conditions by examining targeted biomarkers in saliva.

Introduction

Periodontitis a disease of oral cavity, is recognized as a chronic state of inflammation and considered as significant global issue, affceting 10% of individulas world wide approximately, with 1 billion of world polpulation as a severe form of periodontitis J. Frencken et al., 2017 & 1 others(1). The condiditon is bacteria induced, a host mediated inflammatory process leading to advaced and progreesive destruction of periodntium includong alveloar bone, periodontal ligament, cemetum and gingival tissue, eventually tooth loss if no therapy used Mohammad Hosseini Hooshiar et al., 2024 & 1 others(2).

Among different regions and polpulations the frequency of periodontitis and global burden varies significantly. The severe form of periodntitis has been stable for the recent two decdaes at approximately 11.2% globally, accoridng to some epidimiological data and notibaly in regions of Oceiania and South Latin America ranging from 4.5 to 20.4 persecent respectively J. Frencken et al., 2017(1). The disease is significantly demonstrating a clear age realted patterns, with increasse in prevalance in third and fourth decades of life, and a signicantly high peak is observed in age 40, and remains stable after 40. The predisposing rik factors are use of tobacco, poor oral hygiene, genetic predispoistion, stress, diabeties melllitus, and various other systemic conditions Mohammad Hosseini Hooshiar et al., 2024(1, 3).

Periodontitis a chronic inflammatory condition, creates a persistent source of inflammatory markers affceting distant orgnas and its severity and complications extends far beyond the oral cavity Ruchi Bhuyan et al., 2022(4). Two to three times higher risk of strokes and heart attacks has been reproted in individuals suffering from periodontitis due to the systemic inflammatory burden. Periodontal disease has been associated with diabetes mellitus in a bidirectional modal relationship, as poor glycemic controls worsens periodontitis whereas periodontitis adversely affcets the insulin resistance of patients. Furthermore other systemic conditions associated are respiratory diseases, adverse and poor pregnancy outcomes and Alzheimers diseases in individuals Ruchi Bhuyan et al., 2022(4, 5).

The impact on daily life is substantial, as periodontitis often progresses silently in its early stages without significant pain, leading to delayed diagnosis and treatment. Clinical fertaures include, swelling and rednes of gums, bleeding gums, halitosis, periodontal pocket formation, clinical attachment los and eventually tooth loss in advanced cases(6). The economic burden is significant and quality of life has been affceted due to the social and psyvhological influenec of teeth loss as periodontitis is timeconsuming and expensive to treatJohn J. Taylor et al., 2014(7).Traditional methods for diagnosisof periodontitis chieflydepends on clinical examination, periodontal probing, clinical attachment loss, bleeding on probing, depth of periodntal pocket, and radiographic assessment of alvelaor bone loss(8).

However these traditional diagnostic techniques have signifcant limitations, are inherently retrospective and reflects past tissue destruction rather than current disease activity or future progression risk and delays optimum patient care John J. Taylor et al., 2014(7). These techniques also lacks sensitivity to diagnose the disease at its early stages and doesn't offers real time monitoirng of disease progression and treatment. Additionally these approaches are subjective, depends on examiners skill and expertise and doesn't accurately predicts the patinets susceptibility of further progression of the condition Larissa Steigmann et al., 2020(9).

The significant limitations of these traditional diagnostic techniques have determined the advancement of innovative biosenosrs that are used to detect the specific disease associated biomarkers and have identified disease progression and before irreversilble damage Jayesh Korgaonkar et al., 2024(10).Biosensors combines biological recognition element (BRE) with transducers to generate a quantiofiable signals, proportaional to the concentration of targeted analyte in biological samples i.e blood, urine, sweat, gingival crevicular fluid, and saliva Mohammad Hosseini Hooshiar et al., 2024(11).

Apatmer based biosensor or Aptasensors are among the most promising diagnotic approach for periodntal disease. Aptamers are ssDNA or RNA oligonucleotides, exhibiting high affinity and greater specificity for diverse types of molecular targets and offers significant advantages over traditional antibody-based detection systems Muhammad Usman Ashraf et al., 2025(12).These synthetic molecules are reported to bind specifically to periodontal disease associated cytokines MMPs(matrix metalloproteinases), TNF- alpha,IL-6, IFN-gamma and bacterial proteins. Chief charcateristics of Aptamers are higher stability, no batch to batch variation, stored at room temeprtaure, invitro synthesis and environmental conditions that are repoerted to dentaure antibodies Muhammad Usman Ashraf et al., 2025(12, 13).

Recent advances in the field of Aptasensors have been shown a notable potential for detection of biomarkers associated with periodontitis.ODAM (odontogenic ameblast associated protein), a periodontitis biomarker has been detected by sandwich-type fluorescence aptasensors with excellent sensitivity and 100% specificity and distinguished between low-

risk and high-risk individuals Thi Thanh-Qui Nguyen et al., 2024(14). These diagnostic systems can be incorporated into point-of-care testing devices, enabling rapid diagnosis within 30 minutes and facilitating immediate treatment plan(15).

Prime oppurtunities has been created for personalized and non inasive periodntitis diagnosis with the integration of Apatsensors with innovative approaches such as microfluidics, nanotechnology, and artificial intelligence Muhammad Usman Ashraf et al., 2025.These revolutionshas been addressing the critical necessity for early intervention, real-time monitoring, and enhancedconsequneces in periodontal care and patient outcome. As the field of Aptasenosrs continue to evolve, it reprepent a transformatove and pivotal approaches revolutionizing the periodntal disease managemnet and significantly contributing to improved oral and systemic health consequneces globally(10, 16).

Methodology

This systematic review encompassed studies that evaluated salivary biomarkers in individuals affected by periodontitis. However, it is important to note that the protocol for this study was not registered prospectively in PROSPERO.

Eligibility Criteria

The criteria for inclusion and exclusion selected for the systematic review were as follows.

Inclusion Criteria

i. Articles on biosensors employing aptamer-based detection methods.
ii. Studies examining salivary biomarkers for periodontitis detection.
iii. Original, full-text articles that have been published.
iv. Articles published in English from 2015 to 2025.

Exclusion Criteria

i. Articles not available in English, as well as reports, theses, review articles, short communications, or duplicated studies.
ii. Articles that measured the specified salivary biomarkers of periodontitis in blood samples.

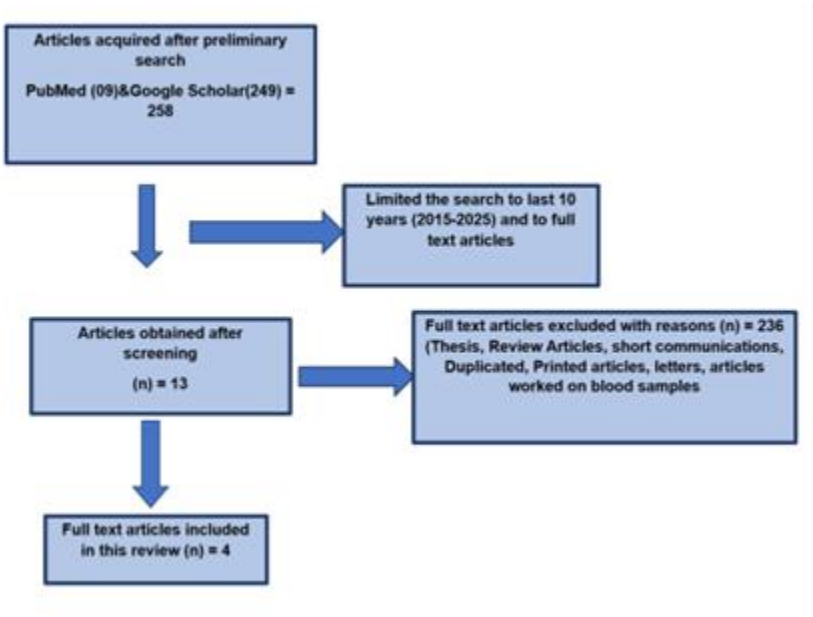
Search Strategy

The search strategy was based on three core concepts: (a) salivary biomarkers for periodontitis, (b) biosensor-based detection methods, and (c) the use of aptamers in these biosensors. A combination of Medical Subject Headings (Mesh) and keywords was used, including “Aptasensors,” “Biosensors,” “Periodontitis,” “Salivary Biomarkers,” “Diagnosis,” and “Aptamers,” to retrieve relevant literature for this systematic review.

Study Selection

A comprehensive and systematic literature search was conducted to analyze all relevant original research articles, exploring the search engines Google Scholar and PubMed. Inclusion strategy as was applied carefully and actively to selected keywords following the articles published in the range of year 2015 to 2025. In order to maintain thematic relevance, focus was clearly maintained on excluding the articles. Endnote X9 was used to import all the identified and selected studies, for efficient management of references and for removal of duplicated articles.

Screening process was divided into two phases: first, two reviewers independently examined the titles and abstracts of the articles to evaluate the eligibility based on predefined and established inclusion and exclusion criteria. The second phase had potentially involved full text articles relevant to the study, verified their status as original research articles and confirmed their relevance to the given inclusion criteria. Inconsistencies between reviewers were determined through discussion and consultation with a third reviewer. The process of screening is summarized in the PRISMA flowchart as Figure 1.



Data Collection

Data was extracted from the original research articles and systematically compiled into a structured Table 1, cited the predefined parameters of interest. This tabulated presentation facilitated comparative analysis and synthesis of the conclusions across the selected studies.

Data synthesis

Based on the extracted data, a systematic synthesis was conducted, which revealed that type of biosensors adapted, their limit of detection (LOD), nanoparticles integrated, different probes utilized, specificity, and sensitivity and various diagnostic biomarkers associated with periodontitis in saliva, were evaluated across the selected studies.

Results

S.No	Author	Oral Disease	biomarker	Aptasensor Used	LOD	Current	Sensitivity	Specificity	Label/MNPs/ Probe	Conclusion/ Remarks	Year
1	Bang Hyun Lee	Periodontal disease	ODAM (OD-64, OD-35 Aptamers)	Lateral Flow, SPR, GO-FRET	1.63nM in saliva	Lateral flow	Detects ODAM in saliva and GCF	Validated	FAM(GO-FRET), AuNPs, Cy5 CLSM Imaging	Detects the disease at early stages and is a chair side technique	2019
3	Hirotaka Minagawa et al.,	Inflammatory periodontitis	HBD-2	Magnetic beads for pull down assay	6.8nM	N/A, Affinity based	High affinity	Specific to hBD-2, no cross reactivity	hBD-2, DNA Aptamer	A clone HBD2 $^{A\text{-}apt1}$ obtained that binds to the salivary stress marker	2020
4	Bo wang et al.,	Stress related disorders (Periodontitis & Bruxism)	Cortisol	Aptamer-FET array (Smartwatch with multichannel SMU)	Low nM range (Saliva and sweat)	Field effect gating, no faradic current	Detects physiological cortisol fluctuations	Validated against TSST (Trier social stress Test)	IN_2O_3 semiconductor, label free Aptamer	Gives real stress mentoring by measuring salivary cortisol and it's a first wearable cortisol tracker	2022
2	Danuta Mizgalska et al.,	Periodontitis	Tannerella forsythia	Flow cytometry	250nM	Not applicable/ Florescence	sensitive	Minimal cross reactivity, tested against Gingivalis and E.coli	TF1/TF2 (ssDNA), FAM labelled Aptamers	Provides new diagnostic assays and advance tools to study the composition of periodontitis associated dysbiosis bacteriome	2023

Table 1:Comparison of Aptasensors technology for salivary periodontitis associated biomarkers (2015-2025) showing advances in sensitivity and detection approaches

Study Selection

The search across electronic databases yielded a total of 258 research papers. The articles obtained after screening of titles, abstracts and methodologies adapted and following the exclusion criteria 13 articles were included. An additional screening for detecting periodontitis related salivary biomarkers was performed and only 4 articles met the criteria. This analysis highlighted the methodological variations and comparative presentation metrics of the assessed parameters in the Table 1.

Study Characteristics

All 258 research articles primarily identified were from the year 2015- 2025. Only 4 studies were selected after screening from 2019, 2020, 2022 and 2023. These researches demonstrating the increase in inclination of researchers towards the exploration of Aptasensors for the detection periodontitis biomarkers in salivary samples. These included research articles were in vivo studies i.e., the analysis was performed on the saliva of patients from periodontitis, although the targeted biomarkers were varying. The difference among the selected articles is in the type of biosensors and its methodology applied, however the Aptamers against specific biomarkers were integrated as BRE into the transduction systems of the Aptasensors. The difference among these Aptasensors is in their methodologies, Vertical flow chip, calorimetric approaches and electrochemical methods, and Aptameric GFET. The strategies applied involved the metal nanoparticles, label and probes used and aptamer against the analytes.

The presented table summarizes the key findings from our systematic review, which identified and analyzed four distinct Aptasensor technologies developed for the diagnosis and monitoring of periodontitis. The results demonstrate a significant advancement in moving beyond traditional diagnostic methods towards highly sensitive, specific, and point-of-care capable tools.It has been demonstrated in Table? that four distinct biosensing systems has been developed and reported for diagnosis of oral diseases chiefly periodontitis, utilizing Aptamer for detection purpose as a core element, however the systems and their specifications differ significantly. from each other. The systems given in the table, along with characteristics to compare their performance and the different parameters summarizing the characteristic four diagnostic systems for periodontitis. The first mentioned system for ODAM a host derived protein biomarker for periodontitis has been detected by Bang Hyun Lee et al. via biosensor in saliva and GCF (Gingivoclavicular Fluid) of active individuals. The use of these multiple approaches such as simple lateral flow strips and GO-FRET (Graphene Oxide-Forster Resonance Energy Transfer) assay are presenting a potential for chair side diagnosis and real time analysis of oral diseases.The GO-FRET system has reported a highly sensitive, able to detect ODAM with a low level of 1.63nM in saliva of periodontitis patients. HBD-2 (Human Beta-Defensin 2), an inflammatory biomarker also known as salivary stress marker was analyzed by Hirotaka Minagawa et al., for periodontitis. A specific aptamer against Human Beta-Defensin 2 was selected and it showed great specificity and no cross reactivity with similar antigens, suggesting it a as highly reliable tool for enumerating host inflammatory response in periodontitis

The system utilized a simple, affinity-based method by magnetic beads to pull down and isolate the biomarker HBD-2 and achieved a detection limit of 6.8 nM. A system developed by Bo Wang et al. (2022), detected the levels of cortisol in patients with periodontitis and bruxism with Field-Effect Transistor (Aptamer-FET), a label free system measuring change in electrical current upon detection.Finally, T*annerella forsythia* bacterium, a chief microbe in the pathogenesis of periodontitis is targeted by Danuta Mizgaiska et al. (2023), utilizing flow cytometry. The system has been integrating FAM (fluorescently labelled) Aptamers for detection of pathogenic bacteria with a detection limit of 250nM.

Discussion

The ability to detect periodontitis associated biomarkers and pathogens, in the early stages and monitoring of therapy has been enhanced with the development of innovative approaches such as Aptasensors. Our systematic review has characterized and evaluated the significant featuresof Aptasensor technologies for the diagnosis and analysis of periodontitis. The field of diagnosis has been shifted from conventional clinical examination to a stateof robust innovative approaches such as molecular diagnostics via Aptasensors as summarized in Table 1. Significant aspects and the implications of periodontal therapy have been highlighted in the review, moreover, the theme emerged from the current data is the strategic variation in the periodontal diagnostics targets. The efficiency of wearable technologies could be enhanced by integration of Aptasensors to give real time analysis, disease monitoring and shifting dental diagnostics from reactive to proactive care(17, 18).

It has also been suggested that the reviewed Aptasensors do not rely on a single biomarker of periodontitis however, instead achieved a multi-faceted approach. The comparative analysis of these Aptasensors has revealed a distinct role in the

diagnosis of periodontitis associated biomarkers and pathogens. The multi-platform approach targeting ODAM has been emerged as the most versatile and useful for clinical deployment, combining its great sensitivity and dual format innovative approach, such as lateral flow strip a chair side technique with a laboratory-based GO-FRET assay(19). The integrated approach by Bang Hyun Lee et al., utilized for analysis of ODAM in periodontitis patients has improved immediate screening of diseases and also gives precise quantification in real time. Additionally, Hirotaka Minagawa et al, introduced wearable cortisol tracker and shifted the paradigm for monitoring periodontitis disease via, measuring stress related cortisol in real time and provide an incomparable data in spite of its emphasis on an indirectly associated biomarker(20). For etiological studies of periodontitis, the pathogen-specific flow cytometry Aptasensorhad become a significant research tool for dissecting microbial dysbiosis, though its lower sensitivity and dependance on lab apparatushave limited its clinical point-of-care use. Moreover, the Aptasensor for HBD-2 has utilized highly specific magnetic bead assay, and provided a valuable validation of host inflammatory response in periodontitis(21).

Hence, based on the specifications provided summarized in Table 1, the Aptasensor developed by Bang Hyun Lee et al. has been considered the most impactful system for future clinical integration. Its higher position is anchored on its unique versatility, as it is the only platform engineered for the full translational pathwayfrom sophisticated laboratory endorsementutilizing highly sensitive GO-FRET and SPR to a simple, low-cost, and rapid lateral flow strip for chair-side diagnosis of periodontitis. The flexibility of these designed Aptasensor has made itinstantly valuable for both researchers and clinicians use. Furthermore, it has demonstrated the best analytical performance of the systems discussed, with a proven and high sensitivity of 1.63 nM, that is critically significant for detecting the disease in its earlystages. Ultimately, its extraordinary design as a "chair-side approach" has directly resolve the persistent clinical challenge of delayed diagnosis and enables immediate decision making for management of disease.

In summary, wearable Aptasensor, byBo Wang is considered a revolutionary concept for the near future, focusing on a single, indirectly associated biomarker of periodontitis such as cortisol and makes ita significant tool for monitoring disease risk rather than a primary diagnostic tool for periodontitis(22). For a direct, sensitive, and clinically adequate diagnostic tool available in the short term, the multi-platform approach targeting ODAM, considered as the most robust and practical system.

Conclusion and Future Perspectives

Hence, we concluded from the current systematic review that the future of periodontal diagnostics has been revolutionized by Aptasensors inventions, with multi-platform systems like the ODAM detecting Aptasensors, leading the near-term clinical impact by enabling sensitive, early detection of periodontitis at the point-of-care. These Aptasensors hasprovide a comprehensive diagnostic overview by simultaneously monitoring chief host biomarkers and specific pathogens. This evolution will ultimately modify oral disease diagnosis and dental medicine towards proactive, personalized care and will momentouslyadvance patient outcomes.

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