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Next-Generation Saliva-Based Diagnostics: Integrating Biosensors, AI, and Sustainable Healthcare

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***Abstract*—The increased number of lifestyle-induced, metabolic, and chronic diseases has escalated the need for early, accurate, and patient-friendly diagnostic technologies. Traditional methods of invasive diagnostic processes through blood or tissue sampling are usually linked to pain, risk of infection, frequent visits to a hospital, and inability to realize continuous monitoring. Saliva has, in this context, become a very promising non-invasive diagnostic biofluid, given that it is a highly biochemically rich biofluid and well physiologically related to the systemic circulation. This is a systematic review of non-invasive salivary-based diagnostic systems with a special focus on biosensor systems, intelligent data processing architectures, and integrated system architectures of point-of-care and individual healthcare. The review is a critical assessment of salivary biomarkers, sensing strategies, nano-enabled transducers, signal conditioning strategies, machine learning and deep learning algorithms, and Internet-based health monitoring systems. The most important areas related to data governance, biological variability, clinical translation, and sensor reliability have been addressed. Lastly, the research direction of future work into the multi-disease, sustainable, and intelligent saliva-based diagnostic platforms is indicated. The review has shown that the combination of saliva-based diagnostics with sophisticated electronics and smart computing can change preventive and personalized healthcare.**

***Index Terms*—Salivary diagnostics, implantable biosensors, intelligent healthcare systems, sustainable electronics, machine learning.**

I. INTRODUCTION

Rapid urbanization, sedentary lifestyles, irregular eating habits, environmental exposure, and rising psychological stress are all factors that have contributed to the profound transformation of modern healthcare systems [3, 4]. Diabetes mellitus, cardiovascular disorders, chronic kidney disease, liver dysfunction, autoimmune diseases, along with various cancers are among the chronic and lifestyle-related diseases that have become more prevalent worldwide as a result of these factors [5, 7]. Significantly, a lot of these illnesses have been recognized at more youthful ages, putting unheard-of strain on the financial and medical infrastructure [9, 10]. Therefore, it is acknowledged that early diagnosis and ongoing monitoring are essential tactics for lowering the burden of disease, enhancing quality of life, and improving treatment outcomes.

Despite tremendous advancements in clinical medicine, invasive procedures such as blood sampling, biopsies, as well as imaging-based investigations continue to be the mainstay of conventional diagnostic practices [11]. Despite being clinically successful, these techniques are linked to patient discomfort, infection risk, reliance on trained staff, or limited suitability for routine monitoring. These restrictions are especially important when managing chronic illnesses, as routine evaluation of vital signs is crucial [12, 13, 14].

As a result, non-invasive diagnostics has become a major area of research interest. Saliva has drawn a lot of interest among the different biological fluids investigated for non-invasive testing because of its availability, safety, and diagnostic significance[17, 31]. Because saliva reflects each oral along with systemic physiological conditions, it is frequently referred to as a "mirror of the human body." Electrolytes, enzymes, hormones, immunoglobulins, cytokines, nucleic acids, metabolites, as well as microbial products are just a few of the many biomarkers found in it. Saliva is an effective substitute for diagnostic purposes because many of these components exhibit significant association with biomarkers that are typically measured in blood [32, 33].

The development of saliva-based diagnostic systems has been greatly accelerated by a combination of technological developments in biosensor technology, nano-engineered materials, microelectronics, along with intelligent computing. Fast, precise, and portable salivary analysis is now possible thanks to miniature sensors, low-power signal processing circuits, alongside data-driven algorithms [35]. The idea of intelligent and sustainable healthcare systems is closely aligned with these developments.

With an emphasis on biosensor technologies, intelligent processing of data, and sustainable system-level integration, this review seeks to present a methodical and thorough analysis of saliva-based non-invasive diagnostic systems. The paper identifies current successes, obstacles, and potential futures in this quickly developing field by synthesizing existing research [36, 37].

II. SYSTEMATIC REVIEW METHODOLOGY

To guarantee rigor, transparency, and repeatability in the selection of studies pertaining to saliva- Based non-invasive diagnostic systems, an organized approach to literature reviews was used. As shown in Fig. 1, the review procedure used a multi-stage screening framework that included database search, subject-specific filtering, abstract screening, and entire-text evaluation. First, a thorough search of pertinent scientific databases from 1985 to 2025 produced 324 records. In order to preserve current relevance, studies published prior to 2005 were eliminated, which led to the elimination of 98 records, 37 duplicate entries, as well 35 non-article records. Subject-based screening ended up with 154 publications, having filtered out all the publications that did not correspond with the study of saliva-based or non-invasive diagnostics. This was followed by an abstract-level screening to eliminate irrelevant and non-experimentally-validated studies to obtain 107 articles. Screening of full-text evaluated the depth methodological and challenges and proposed solutions of non-invasive saliva-based diagnostic systems and as a result, 21 articles were excluded. At last, 86 core studies were left, and eight high-quality systematic reviews concerning sustainable healthcare were incorporated, which comprised 94 articles that were then analyzed qualitatively and comparatively.

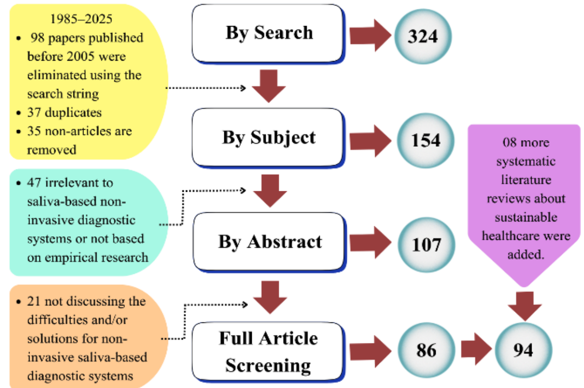

Fig. 1 Systematic literature search and screening process of saliva-based non-invasive diagnostic systems (1985-2025)

Three stages were used in review. To start with, the topical publications were selected on the basis of specific keywords regarding the salivary diagnostics, biosensors, point-of-care systems, machine learning and related health technologies [39, 41]. Second, the abstracts and full texts were filtered to be relevant to saliva based diagnostic systems. Lastly, the chosen studies were examined to derive the information about the biomarkers, sensing mechanisms, materials, signal processing methods, and system architectures [42, 43]. The data retrieved were grouped up to give a comparative and integrative view point. It focused on highlighting trends, shared problems, and solutions as opposed to an overview of individual studies. The methodology was used to ensure that the review is both in-depth and comprehensive, thus a good source of data to the researchers and system designers [44, 45].

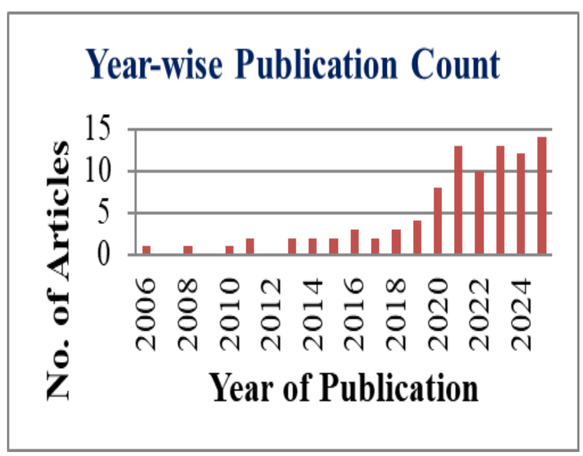

Fig. 2. The distribution of the research publications on saliva-based non-invasive diagnostic systems (2006-2025) by the year

Fig. 2 shows that studies on saliva-based non-invasive diagnostic systems have been on the rise. The period of early years (2006-2014) is characterized by slight activity, which is an initial phase of exploration of the field. It is seen that there is a moderate increase after 2015 and then a steep increase after 2019. The huge growth of 2020-2025 implies that the researchers are on a roll with the development of biosensors, artificial intelligence, and connected healthcare technologies, which points to the rising significance and maturity of the research field [46].

The representative studies on saliva-based non-invasive diagnostic systems are systematically summarized in Table 1 and it provides understanding of how sensing technologies, analytical methods and areas of application have evolved. The chosen sources indicate a strong shift in the traditional electrochemical and biochemical sensing platforms toward smart, wearable, and AI-based biosensing platforms. Taken altogether, these researches prove that saliva is a valid diagnostic tool and highlight its appropriateness to use it as continuous health monitoring, early disease diagnosis, and personalized care in the context of sustainable and non-invasive clinical testing [47, 48, 49]

Table I. Overview of Major research on SALIVA-Based Non-Invasive Diagnosis System

Ref No.	Year	Authors	Primary Focus	Technology Used	Key Contribution
[1]	2025	Patel et al.	Wearable diagnostics	Flexible biosensors	Clinical translation of wearable biosensors
[2]	2025	Wang et al.	Saliva-based diagnostics	Electrochemical biosensors	Precision healthcare sensing
[6]	2025	Kumar et al.	Sustainable healthcare	Low-power electronics	Energy-efficient diagnostic platforms
[15]	2024	Mohan et al.	Saliva biosensing	Electrochemical & nano-biosensors	Enhanced sensitivity and selectivity
[18]	2024	Gupta et al.	Metabolic disorder diagnosis	Electrochemical saliva sensors	Accurate non-invasive metabolic monitoring
[24]	2024	Sharma et al.	AI-assisted diagnostics	Machine learning models	Improved disease classification accuracy
[27]	2023	Chen et al.	Intelligent biosensors	Deep learning-enabled sensors	Automated biosignal interpretation
[28]	2023	Majumder et al.	Remote health monitoring	Wearable sensors	Continuous and remote monitoring systems
[38]	2023	Singh et al.	Saliva biosensors	Electrochemical sensing	Recent trends and challenges
[40]	2022	Javaid et al.	Wearable healthcare	IoT-enabled biosensors	Comprehensive review of wearable biosensors

III. SALIVA AS A DIAGNOSTIC BIOFLUID

The saliva has presented a very promising biofluid in non-invasive diagnosis of diseases and health monitoring due to its great biochemical content and great physiological connectivity with the body in general. Saliva has obvious benefits over the traditional diagnostic fluids of blood and urine, including ease of collection, safety to the patient, and the ability to use it in continuous or repeated monitoring [50]. The recent years of the last twenty years have seen an increasing interest in salivary diagnostics due to the development of biosensor technology, analytical chemistry, and biomedical data processing [51]. Human saliva is mainly water and the rest of the percentage is made up of a wide variety of clinically relevant polysaccharides, electrolytes, metabolites, enzymes, hormones, immunoglobulins, cytokines, nucleic acids and microbial products [52, 53].

Salivary concentrations of systemic biomarkers can be determined by passive diffusion, ultrafiltration and active transport, leading to significant associations between salivary and blood biomarkers [54, 55]. Hormonal indicators, including cortisol, testosterone and estrogen are widely studied since salivary measurements are biologically active fractions of hormones. In the same manner, the metabolic biomarkers such as glucose, urea and creatinine show diagnostic significance of diabetes and renal disorders. The saliva also has immunological drugs and nucleic acids which aid in immune profiling, detection of infectious diseases and molecular diagnostics [56, 57]. Moreover, salivary biomarkers that were linked with oral and systemic cancers demonstrate its prospects of early, non-invasive oncological screening. The fact that saliva can be designed to work with portable and wearable platforms also makes it a pillar of the next-generation point-of-care and digital health technology, which can provide real-time, personalized health monitoring [59, 60].

VI. SALIVA-BASED BIOSENSOR TECHNOLOGIES

The saliva-based diagnostic systems performance is essentially based on the biosensor technologies employed in the detection and quantification of biomarkers. Biosensors transform biological recognition events into measurable signals and have to be sensitive and selective because many salivary analytes are present at low concentration [61, 62].

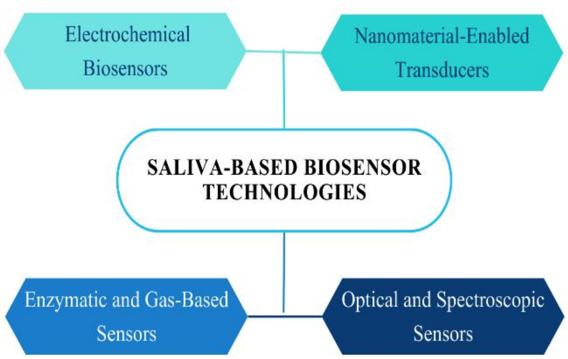

Fig. 3. Categorization of non-invasive diagnostic saliva-based biosensor technologies

Saliva-based diagnostic devices utilize a wide range of biosensing methodologies which can be broadly broken down into electrochemical biosensors, nanomaterial-enabled transducers, enzymatic and gas-based sensors as well as optical and spectroscopic sensors as shown in Fig. 3.

A. Electrochemical Biosensors

The most commonly used electrochemical biosensors possess sensitivity, immediate reaction, and the ability to be connected to portable electronics, thus considering the fact that salivary diagnostics is largely performed using electrochemical biosensors [63]. Amperometric sensors detect current produced as a result of redox reaction and are extensively applied in glucose and urea detection. Voltammetric methods give electrochemical abundant information and allow detection of multi-analytes.

B. Nanomaterial-Enabled Transducers

Nanomaterials like gold nanoparticles, carbon nanotubes, graphene and two-dimensional materials have made huge improvements on performance of biosensors [65]. Their high surface area and desirable electrical characteristics augment biomolecule immobilization and signal transduction, which facilitates ultra-low detection limits which are applicable in salivary diagnostics [66].

C. Enzymatic and Gas-Based Sensors

Enzyme sensors make use of biochemical reactions to produce measurable signals. A interesting example is urea detection with urease where ammonia was generated in the process of enzymatic hydrolysis which was detected with gas sensitive transducers [67]. These sensors are appealing to the simplicity and low cost, and the stability and selectivity are still problematic issues.

D. Optical and Spectroscopic Sensors

Fluorescence and spectroscopic techniques of optical sensing have high label-free detection and specificity. Such methods come in handy especially when it comes to protein, nucleic acid and cancer biomarkers detection, but system complexity may act as a barrier to portability [69, 70].

V. INTELLIGENT COMPUTING AND CONNECTED SYSTEM INTEGRATION

Salivary biosensors produce raw signals that are normally weak and prone to noise, drift and biological variability. These signals are also critical to transform into clinical use information using smart computing techniques [72, 73].

Signal conditioning and feature extraction improves the level of data and dimensionality. Machine learning and neural networks, and ensemble machine learning have been found to be very successful in disease state classification based on salivary biomarker pattern [75, 76]. Deep learning systems enable features to be learned automatically and are applicable particularly in continuous monitoring application.

Real time transmission of data, remote monitoring, and longitudinal health analysis are possible through interrelated architecture of the system [77]. Wireless communications, analytics on clouds, and mobile health interfaces correlate with the support of the personalized and preventative healthcare delivery [78]. To be able to run sustainably, adaptive data transmission and energy efficient calculation is required.

The practical saliva-based diagnostic systems are placed in priorities of portability, low consumption of power, and easy-to-use designs. Wearable and handheld devices can have biosensors, signal conditioning circuits, microcontrollers and wireless modules on miniature platforms [79, 80]. Issues in sustainable design include low power electronics, reusable sensors and reduced biomedical waste.

VI. CHALLENGES AND FUTURE RESEARCH DIRECTIONS

Although there has been a significant advancement in saliva-based non-invasive diagnostic systems in recent years, they still face multiple impediments that prevent them from being applied clinically and commercialized at very large scale [81]. The biological variability of saliva is one of the most important issues. The composition of saliva is also affected by several physiological and external conditions, such as the circadian rhythm, hydration, diet, medication, oral health, and metabolism (individual differences) [83, 84]. This variability can bring about uncertainty in the quantification of biomarkers and can have an impact on the diagnostic accuracy unless accounted to. The absence of standardized procedures on the way saliva should be collected, stored and preprocessed also complicates on reproducibility as well as cross-platform comparison [85].

Table II. The identified challenges and research directions identified in the literature

Ref. No.	Challenge Category	Observed Issue	Impact on System	Suggested Research Direction
[16], [63], [87], [94]	Biological variability	Inconsistent saliva composition	Reduced diagnostic accuracy	Standardized sampling protocols
[19], [58], [64], [71]	Sensor sensitivity	Low biomarker concentration	False negatives	Nanomaterial-enhanced transducers
[20], [21], [22], [68]	Data analytics	Black-box AI models	Limited clinical trust	Explainable AI techniques
[23], [25], [26], [74]	System integration	Limited real-time monitoring	Delayed diagnosis	IoT-based continuous monitoring
[29], [30], [32], [35],[82]	Sustainability	High power consumption	Reduced device lifetime	Low-power and sustainable electronics

Table II is a compilation of key technical, clinical and translational challenges in the literature that are cross mapped to research directions. The mentioned studies indicate that the problems with biological variability, sensor stability, data reliability, and large-scale clinical validation persist. Concurrently, the table highlights new opportunities, such as multi-analyte sensing, explainable artificial intelligence, standard validation procedures, and combination with smart healthcare infrastructures that jointly outline the critical directions in which saliva-based diagnostic systems are to be developed to be used in practice [86, 88].

Technologically speaking, biosensor reliability and durability is still a major concern. Saliva contains proteins, enzymes and microbial components that can be a source of sensor fouls, surface corrosion and signal drift caused by long usage [89]. The wearable and continuous monitoring systems in particular find it difficult to achieve long-term stability of components of biorecognition specifically the enzymes and antibodies. Furthermore, sensor selectivity may be influenced by sensitiveness towards non-target analytes and environmental change such as temperature and humidity as well as needs more advanced calibration and compensation methods [90, 91].

Clinical translation is another major challenge. Many saliva-based diagnostics systems have been reported as at the proof-of-concept or lab validation stages. The research should be carried out in extensive clinical trials on the different population to establish a firm association of the salivary biomarkers and the illnesses

[92]. In addition, the regulatory approval involves strict verification of safety, accuracy and repeatability, which presupposes the organization of the work of the researchers, clinicians and regulatory bodies [93].

The aim of future research is on creating sensing platforms, which can be used to enhance diagnostic confidence by using multi-biomarkers. It is possible to increase the levels of transparency and trust in data-driven diagnostic decisions through the adoption of explainable artificial intelligence. It will be necessary to create standardized salivaomics databases and harmonized protocols to be used in the benchmarking and validation. The new generation of wearable, scalable and environmental responsible salivary diagnostic systems are likely to be determined by advances in flexible electronics, low-power system development, and sustainable materials [94].

VII. CONCLUSION

The use of non-invasive diagnostic Saliva-based systems is a game changer in the current healthcare facilities as it offers end-user friendly, affordable, and user-friendly alternative to the traditional invasive diagnostic systems. This is because of the complex biochemical makeup of saliva, which is coupled with its physiological relationship to the systemic circulation which allows detection of a vast diversity of disease-relevant biomarkers. The current advances in biosensor technologies such as electrochemical, optical, enzymatic and nanomaterial based methods have tremendously improved the sensitivity, selectivity and reliability of salivary diagnostics.

The saliva-based diagnostic ability is further enhanced by incorporation of smart computing method. The machine learning and deep learning models will help in effective interpretation of multidimensional and complex salivary data in order to classify diseases and to sub-classify risks. The related system architectures allow real-time monitoring, remote care, and personalized feedback, which is in line with the goals of preventive and sustainable healthcare.

Despite the issues associated with biological variability, sensor robustness, standardization and clinical validation, there is constant interdisciplinary research to overcome these problems. The intersection of the biosensing technologies, smart data analysis, and wearable electronics is speeding up the shift towards saliva-based diagnostics as a concept that takes the experimental research to the real-world healthcare option.

To sum up, non-invasive diagnostic technologies related to saliva have a huge potential in early detection of diseases, chronic disease management and personal healthcare. These systems have the potential to become an inseparable part of intelligent and sustainable healthcare systems in the future as standardization initiatives continue, and technological innovation is progressively enhanced to provide new functionalities.

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