Journal of Young Pharmacists, 2026; 18(1):70-79.
https://www.jyoungpharm.org

Review Article

# Graphene-Based Electrochemical Biosensors for Oral Cancer Detection: Advances, Challenges, and Future Prospects-A Systematic Review

**Jeetendra Kumar Gupta[1], Priyanga Jaganath[2], Ramenani Hari Babu[3], Konatham Teja Kumar Reddy[4], Venkata Lakshamana Sagar Dantinapalli[5], Selvaraja Elumalai[6], Thota Chandrasekhar Yadav[7], Venkateswara Rao Rachumallu[8], Prabakaran Sankar[9], Jaya Shree Srinivasan[9], Lokeshvar Ravikumar[9,*]**

[1]Department of Pharmacology, Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, INDIA.
[2]Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai, Tamil Nadu, INDIA.
[3]Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, INDIA.
[4]Department of Pharmaceutical Analysis, Malla Reddy Institute of Pharmaceutical Sciences, Malla Reddy Vishwavidyapeeth (Deemed to be University), Secunderabad, Telangana, INDIA.
[5]Department of Chemistry, Raffles University, Neemrana, Alwar, Rajasthan, INDIA.
[6]Department of Chemistry, School of Basic and Applied Sciences, Raffles University, Neemrana, Rajasthan, INDIA.
[7]Koneru Lakshmaiah Education Foundation, Green Fields, Vaddeswaram, Andhra Pradesh, INDIA.
[8]Department of Pharmacology and Pharmacokinetics, Quest Life Sciences Pvt. Ltd., Research Foundation in Chennai, Chennai, Tamil Nadu, INDIA.
[9]Department of Pharmacology, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences (SIMATS), Thandalam, Saveetha Nagar, Thandalam, Chennai, Tamil Nadu, INDIA.

## ABSTRACT

Graphene-based electrochemical biosensors are emerging as powerful diagnostic platforms for early, non-invasive detection of oral cancer. This review critically evaluates recent advances in graphene-enabled salivary biosensing, emphasizing the role of graphene's unique physicochemical properties-such as large surface area, conductivity, and biocompatibility-in improving sensitivity and specificity. A comprehensive literature search was conducted using PubMed, Scopus, and ScienceDirect databases to identify peer-reviewed studies from 2010-2025 on graphene-based electrochemical biosensors for salivary biomarker detection. The findings indicate that graphene-integrated systems significantly enhance electrochemical detection techniques including voltammetry, impedance spectroscopy, and field-effect transistors. Major challenges remain in clinical translation, including reproducibility, scalability, and regulatory approval. Future perspectives involve integrating these biosensors with artificial intelligence, microfluidics, and telemedicine platforms to enable affordable, portable, and real-time oral cancer diagnostics. Overall, graphene-based biosensors represent a transformative step toward personalized, point-of-care cancer management.

**Keywords:** Electrochemical biosensors, Graphene nanomaterials, Non-invasive diagnostics, Oral cancer biomarkers, Salivary biosensing.

**Correspondence:**
**Mr. Lokeshvar Ravikumar**
Department of Pharmacology, Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences (SIMATS), Thandalam, Saveetha Nagar, Thandalam, Chennai-602105, Tamil Nadu, INDIA.
Email: lokeshvarr.scop@saveetha.com
ORCID: 0000-0001-6869-3446

**Received:** 03-11-2025;
**Revised:** 24-12-2025;
**Accepted:** 16-02-2026.

## INTRODUCTION

Early detection is crucial for improving survival and treatment outcomes in cancer, highlighting the need for rapid, sensitive, and non-invasive diagnostic tools. Biosensors have emerged as promising platforms due to their ability to detect cancer biomarkers with high specificity, providing real-time insights into disease presence, progression, and prognosis. Oral Squamous Cell Carcinoma (OSCC) remains a major global health issue, with over 350,000 new cases annually, especially in regions with prevalent tobacco, alcohol, and betel quid use. Conventional diagnostics, such as biopsies and imaging, are invasive, costly, and infrastructure-dependent, limiting early detection (Fadaka *et al*., 2019). Saliva has emerged as an attractive biofluid for diagnostics due to its non-invasive collection, affordability, and rich molecular content, including DNA, RNA, proteins, and metabolites. Graphene-based electrochemical biosensors have gained attention for salivary diagnostics, offering exceptional sensitivity and selectivity owing to graphene's two-dimensional structure,

**DOI:** 10.5530/jyp.20260170

**Publishing Partner :** Manuscript Technomedia. [www.mstechnomedia.com]

high conductivity, large surface area, and mechanical strength (Cheng *et al*., 2017). Electrochemical methods like amperometry, voltammetry, and impedance spectroscopy further enhance detection accuracy and speed. Despite laboratory successes, clinical translation faces challenges including biocompatibility, reproducibility, stability, and scalability. This review provides a critical synthesis of graphene-based salivary biosensors for oral cancer, examining design innovations, analytical performance, translational barriers, and future directions to bridge the gap between experimental research and clinical application (Akashanand *et al*., 2024). A systematic literature search was conducted using PubMed, Scopus, and ScienceDirect databases, and the study selection process is illustrated in Figure 1.

## Key Advantages of Saliva as a Diagnostic Fluid

Saliva has become a powerful medium for non-invasive diagnostics due to its accessibility, ease of collection, and reduced discomfort, cost, and infection risk compared to blood sampling. It is ideal for large-scale screenings and repeated sampling in longitudinal studies. Biochemically, saliva contains proteins, DNA, RNA, metabolites, and exosomes that reflect both local and systemic physiological states, with fewer interfering substances like clotting factors, facilitating sample handling (Yoshizawa *et al*., 2013). Its proximity to oral tissues allows early detection of neoplastic changes, making it highly relevant for oral cancer screening. Combined with multiplex biomarker detection and compatibility with point-of-care devices, saliva offers a highly effective matrix for future personalized healthcare applications (Bhattacharjya *et al*., 2025).

## Graphene: A Multifunctional Platform for Advanced Biosensing

Graphene, a single layer of carbon atoms in a two-dimensional honeycomb lattice, has transformed nanomaterials due to its exceptional electrical, mechanical, and thermal properties (Mahalakshmi *et al*., 2025a). With a thickness of ~0.35 nm and interatomic bond length of 1.42 Å, its unique band structure enables efficient electron transport, high charge carrier mobility, and minimal energy loss, ideal for electronic and biosensing applications. Its biocompatibility, especially in forms like reduced Graphene Oxide (rGO), ensures minimal cytotoxicity, supports cell growth, and reduces inflammation, making it safe for oral cavity applications (Kaur *et al*., 2018). Slow physiological degradation further contributes to long-term stability. Graphene is produced via top-down methods (mechanical exfoliation, chemical reduction) and bottom-up methods (chemical vapor deposition, epitaxial growth), with CVD offering high-quality, scalable fabrication. Solution-based techniques like layer-by-layer deposition and Langmuir-Blodgett assembly allow fine-tuning for specific biosensor architectures (Nandhini and Karthikeyan, 2024). In biosensors, graphene's high surface area and superior electron transfer enable detection of ultra-low analyte concentrations. Functionalization with antibodies, aptamers, or enzymes enhances specificity and reduces interference, generating measurable electrical signals for rapid biomarker quantification (Goldoni *et al*., 2021). Graphene's mechanical flexibility supports wearable and portable diagnostics, particularly in biofluids like saliva. Compared to silicon, zinc, or gold, it offers greater chemical stability, reusability, and adaptability in complex biological environments. Scalable production and affordability position graphene as a foundation for next-generation salivary biosensors for early disease detection and point-of-care applications (Neumaier *et al*., 2019).

## Graphene Synthesis and Surface Modifications

The performance of graphene-based biosensors is closely linked to the synthesis method and subsequent surface modifications. Two common approaches for graphene synthesis include the Hummers' method for chemical oxidation of graphite to produce Graphene Oxide (GO) and Chemical Vapor Deposition (CVD) to create high-quality graphene films suitable for large-area sensor fabrication. Surface modification plays a crucial role in enhancing biorecognition and signal stability (Ullah *et al*., 2020). Functional groups such as carboxyl, hydroxyl, and epoxy moieties can be introduced during or after synthesis, allowing for covalent or non-covalent immobilization of biological probes like antibodies, aptamers, or enzymes. Such modifications not only improve selectivity and sensitivity but also reduce nonspecific interactions. Innovations in graphene hybrid nanocomposites such as integrating metal nanoparticles, metal oxides, or conductive polymers further amplify signal output and offer tailored biocompatibility, making them well-suited for complex biofluids like saliva (Magne *et al*., 2022).

## Salivary Biomarkers to Detect Oral Cancer

Saliva is emerging as a valuable diagnostic medium in oncology due to its rich molecular content, non-invasive collection, low interference, and suitability for repeated sampling. It contains DNA, mRNA, proteins, metabolites, and exosomes, reflecting tumor-associated molecular changes for early oral cancer detection (Kumar *et al*., 2021). Elevated cytokines (IL-6, IL-8, IL-1β), cancer antigens (Cyfra 21-1, CA 125), proteins (Mac-2 binding protein, profilin-1, CD59, catalase), and soluble CD44 show diagnostic potential as listed in Table 2. Dysregulated microRNAs and VEGF indicate early-stage disease, while MMP-9 and EGFR mark progression. Key DNA-based salivary biomarkers are summarized in Table 3. While important RNA biomarkers relevant to oral cancer are presented in Table 4. Challenges include low analyte levels, variability, biomolecule instability, and interference. Graphene-based biosensors overcome many of these issues via high surface area and enhanced sensitivity, enabling rapid, specific, and reliable salivary biomarker detection (Ullah *et al*., 2021).

## Electrochemical Graphene Biosensors for Salivary Biomarkers in Oral Cancer

The emergence of electrochemical biosensors has transformed disease diagnostics by enabling rapid, sensitive, and cost-effective detection of clinically relevant biomarkers. These sensors operate by converting specific biochemical interactions into quantifiable electrochemical signals, offering a robust platform for detecting disease markers, including those associated with oral cancer. In the context of saliva-based diagnostics, graphene plays a central role due to its exceptional conductive and surface properties, making it highly responsive to minute biological changes. Various electrochemical detection techniques have been adapted to work with graphene-based platforms for enhanced sensitivity and selectivity as summarized in Table 1, and representative fabrication and electrochemical measurement strategies for graphene-based immunosensors are illustrated in Figure 3.

### Cyclic Voltammetry (CV)

CV is one of the most widely employed techniques to evaluate redox behaviour of biomolecules. It applies a cyclic potential sweep to the sensor's electrode, recording current changes that reflect electrochemical activity. Graphene's high conductivity and large surface area enhance electron transfer, making it ideal for detecting low-abundance biomarkers such as Cyfra 21-1 and IL-8 in saliva. For instance, a CV biosensor based on $ZrO_2$-Reduced Graphene Oxide (RGO) demonstrated high performance in detecting Cyfra 21-1, with a wide dynamic range and low detection limits, supported by ELISA validation. Similarly, ZnO-rGO composites have been used for IL-8 detection, showing excellent response in clinical saliva samples (Karim, 2021).

### Differential Pulse Voltammetry (DPV)

DPV provides high-resolution data by applying pulsed voltage ramps and measuring resulting currents, enabling detection of biomarkers in complex media. Gold nanoparticles combined with RGO (AuNPs-rGO) have been used to develop immunosensors for IL-8, offering excellent stability, specificity, and reusability. Another design using cerium oxide-RGO composites has successfully detected Cyfra 21-1 with picogram-level sensitivity and negligible cross-reactivity.

### Electrochemical Impedance Spectroscopy (EIS)

EIS detects changes in electrical impedance caused by biomolecular interactions at the sensor interface. Label-free EIS sensors incorporating RGO have shown accurate quantification of Carcinoembryonic Antigen (CEA) and Cyfra 21-1 in saliva, effectively distinguishing healthy individuals from OSCC patients using portable prototypes. The impedance shifts due to antigen-antibody binding lead to quantifiable electrical signals, making EIS particularly valuable for point-of-care testing (Verma *et al.*, 2023).

### Field-Effect Transistor (FET) Sensors

Graphene-based FET sensors offer ultra-fast detection by measuring current changes in a semiconductor channel upon biomarker binding. Aptamer-functionalized graphene FETs have been developed to detect IL-6 in saliva, demonstrating detection within seven minutes and high sensitivity. These sensors are also being adapted for handheld devices connected to mobile platforms, integrating diagnostics with cloud-based data analysis (Verma *et al.*, 2017).

**Table 1: Comparative Overview of Nanomaterials Used in Biosensors.**

| Nanomaterial | Advantages | Limitations | Diagnostic Use | References |
|---|---|---|---|---|
| Graphene | High surface area, conductivity, flexible, biocompatible | Aggregation; complex synthesis | Salivary biomarker detection in oral cancer | (Mahalakshmi *et al.*, 2025c) |
| Gold NPs | Optical features, easy functionalization, biocompatible | Aggregation; costly | Colorimetric/electrochemical biosensors | (Kumalasari *et al.*, 2024) |
| Carbon Nanotubes | Conductive, stable | Limited functionalization; potential toxicity | Electrochemical cancer sensing | (Karagianni *et al.*, 2026) |
| Silicon | Tunable optical/ electronic properties | Brittle; less biocompatible | Optical biosensors | (Mahalakshmi *et al.*, 2025c) |
| Quantum Dots | Bright, tunable emission | Toxicity; complex synthesis | Fluorescent biosensors | (Tandale *et al.*, 2021) |
| Metal Oxides | Catalytic, cost-effective | Lower conductivity | Electrochemical diagnostics | (P. Kumar *et al.*, 2024) |

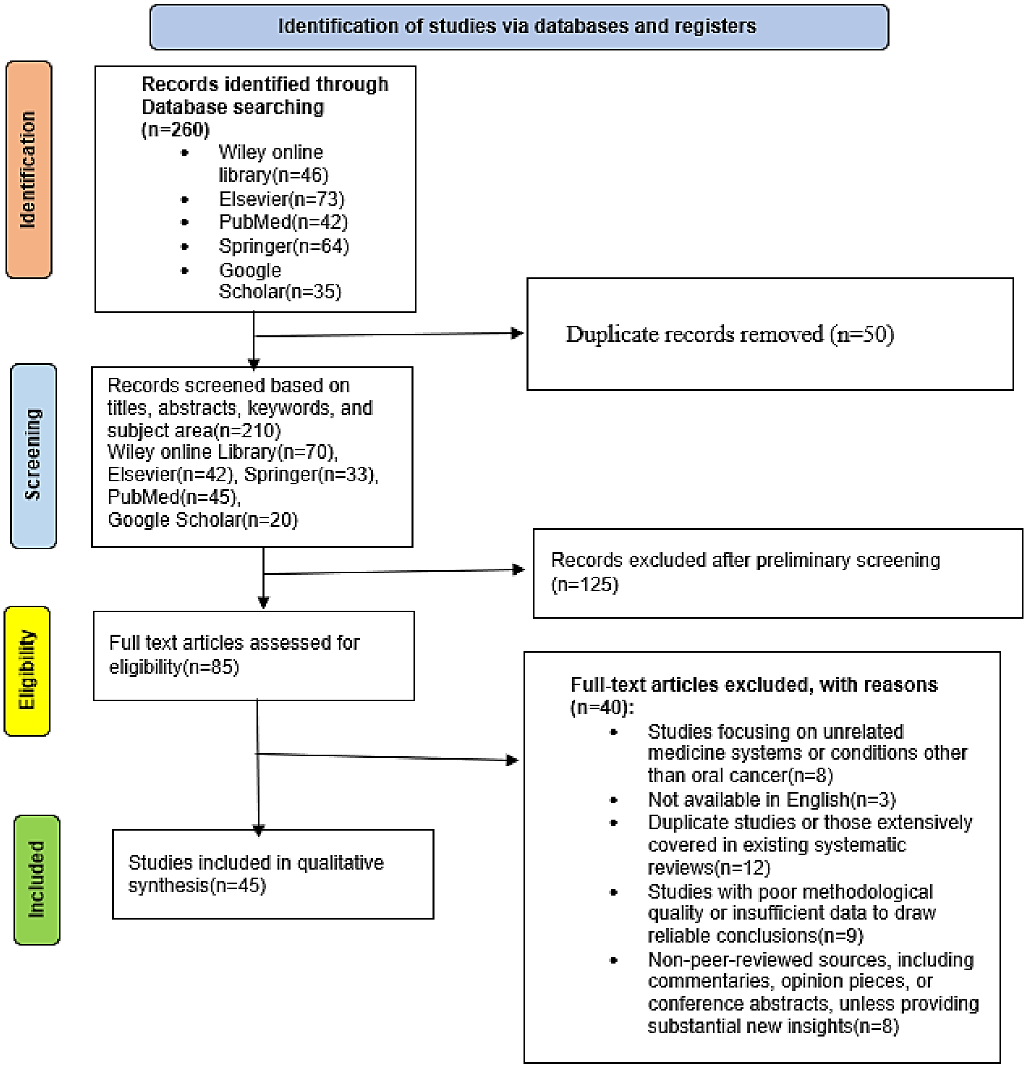

**Figure 1:** Study selection process.

## Amperometric Sensors

Amperometry involves measuring current at a constant potential, offering real-time monitoring of electroactive species. A self-reporting biosensor composed of graphene oxide, gadolinium hexacyanoferrate, and gold nanoparticles achieved sensitive detection of Cyfra 21-1 without needing external redox mediators, providing a direct and simplified detection system suitable for clinical use.

## Chronoamperometry (CA)

CA sensors step the voltage at fixed intervals and track current over time to monitor redox reactions. A graphene oxide-aptamer sensor was designed to detect TNF-α, showing high sensitivity in the picogram range. The molecular beacon-based electrochemical detection strategy for TNF-α is depicted in Figure 4. This system enables longitudinal monitoring of inflammatory markers in oral cancer patients (Devaraji and Ravikumar, 2024).

## Photoelectrochemical (PEC) Biosensors

PEC combines optical and electrochemical principles for enhanced sensitivity. A novel PEC sensor using graphene oxide, silver nanoclusters, and hemin detected the oral cancer-associated gene ORAOV1 at femtomolar levels, demonstrating ultra-sensitive diagnostics. Graphene-powered electrochemical techniques enable rapid, specific detection of salivary biomarkers and can be adapted for wearable or portable formats, supporting early oral cancer diagnosis and treatment monitoring, especially in decentralized or resource-limited settings (Ahmad *et al.*, 2023). Challenges of Graphene-Based Electrochemical Biosensors for Salivary Biomarker Analysis in Oral Cancer.Graphene-based electrochemical biosensors hold promise for non-invasive oral cancer detection, but clinical use remains challenging. Patient heterogeneity, low-abundance salivary biomarkers, and saliva's complex composition can compromise accuracy. Functionalizing graphene for selective binding is difficult, and unstable modifications may cause signal drift and poor reproducibility. Additional hurdles include salivary variability, scalable production, batch consistency, long-term stability, affordability, and point-of-care compatibility. Clinical deployment requires multidisciplinary expertise, standardized validation, robust trials, and regulatory guidance. Future research should focus on optimizing surface functionalization, enhancing sensor stability in physiological conditions, and fostering cross-disciplinary collaboration. Standardized testing across diverse populations is critical to ensure reliability and enable real-world application of graphene-based biosensors in oral cancer diagnostics (Pirzada and Altintas, 2019).

## Clinical Validation and Regulatory Considerations

Despite promising laboratory performance, translating graphene-based biosensors into clinical diagnostics requires rigorous validation. This includes clinical trials, reproducibility studies, and comparison with gold-standard diagnostic tools. Standardization of sample collection, biomarker thresholds, and analytical protocols is essential for ensuring consistency across patient populations. The overall structure and working principle of graphene-based electrochemical biosensors for salivary biomarker detection are illustrated in Figure 2. Regulatory hurdles remain a significant barrier. For clinical approval, biosensors must meet stringent criteria set by organizations such as the U.S. FDA, CE, or ISO standards, covering aspects like

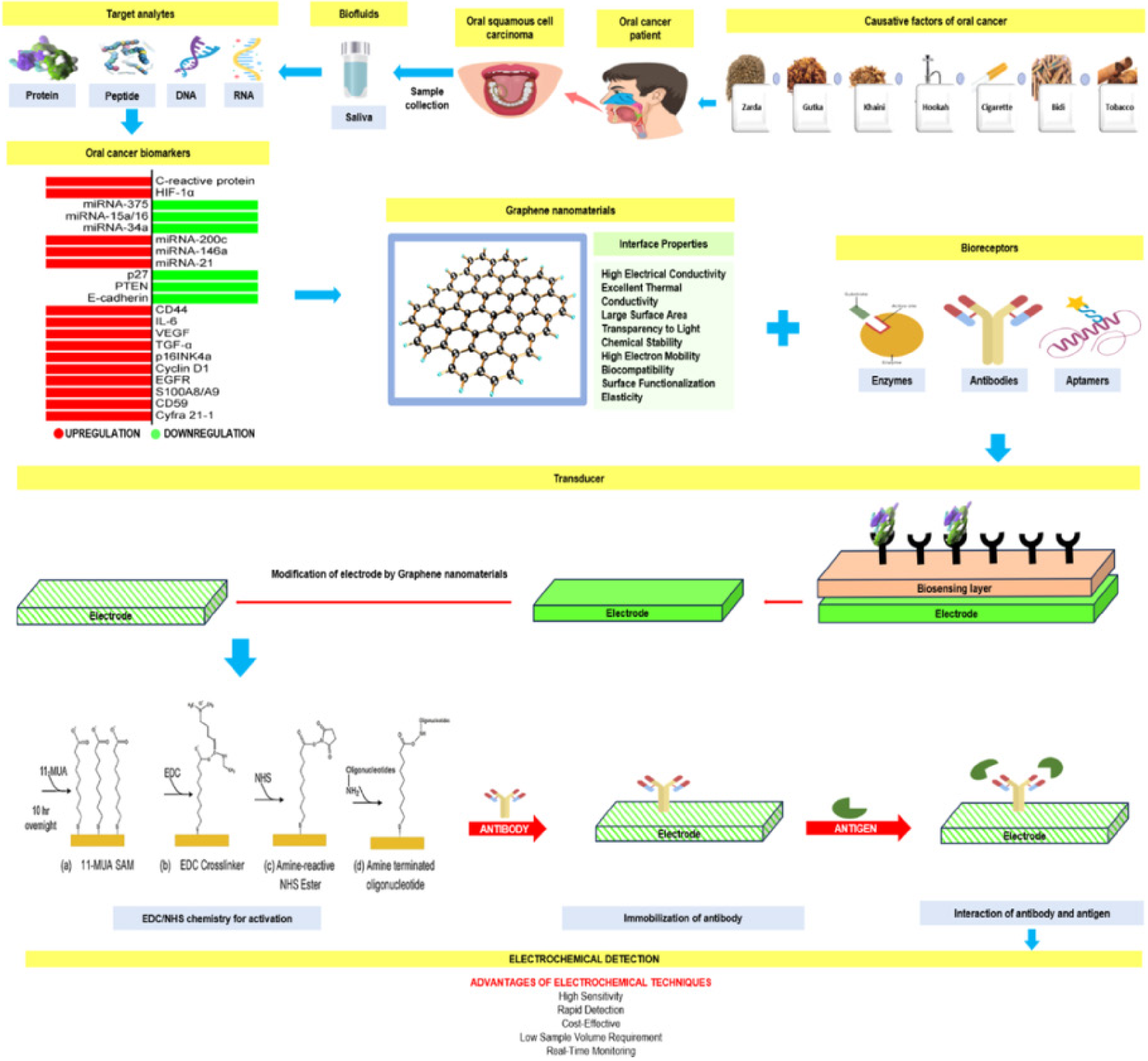

**Figure 2:** Illustrates the structure and function of graphene-based electrochemical biosensors designed for detecting salivary biomarkers associated with oral cancer (Mahalakshmi *et al.*, 2025b).

**Table 2: Protein Biomarkers in Oral Cancer.**

| Sl. No. | Biomarker | Key Properties and Applications | References |
|---|---|---|---|
| 1 | Catalase | Used in OSCC diagnosis | (Ravikumar and Velmurugan, 2024) |
| 2 | CD44 | High diagnostic/prognostic accuracy | |
| 3 | CD59 | Overexpressed in saliva; T-cell activation | |
| 4 | Cyfra-21-1, TPA, CA125 | Salivary markers; indicate early chemo response | (Ilhan *et al*., 2020) |
| 5 | Defensin-1 | Elevated; improves early detection | |
| 6 | IL-1α | Regulates inflammation and angiogenesis | |
| 7 | IL-1β | Increased in oral cancer; modulates immune/inflammatory response | |
| 8 | IL-6 | Proangiogenic/inflammatory; aids early diagnosis and prognosis | |
| 9 | IL-8 | Elevated in oral cancer; also relevant in periimplantitis | (Hao *et al*., 2019) |
| 10 | Involucrin | Differential expression in OSCC vs healthy tissue | |
| 11 | M2BP | Overexpressed; involved in cell adhesion/matrix interaction | |
| 12 | MMP-11 | Invasive/metastatic; poor prognosis marker | |
| 13 | MMP-2 | Promotes metastasis and vascular growth | |
| 14 | MMP-8 | Elevated in saliva; useful in periodontal assessment | |
| 15 | MMP-9 | Supports angiogenesis; dysplasia-to-cancer transition | (Mahalakshmi *et al*., 2025d) |
| 16 | MRP14 | Regulates leukocyte movement and inflammation | |
| 17 | Profilin | Varied levels between OSCC and healthy controls | |
| 18 | S100A12 | Differential expression in oral cancer | |
| 19 | Salivary Alpha Amylase | Potential diagnostic marker; breaks down starch | |
| 20 | TGF-β | Unchanged levels; limited diagnostic value | |
| 21 | TNF-α | Stimulates proliferation, inhibits apoptosis, induces inflammation | (Mesrati *et al*., 2021) |

safety, accuracy, and reliability. Addressing these requirements will involve collaborative efforts across academia, industry, and regulatory bodies to accelerate the bench-to-bedside transition (Song *et al*., 2025).

## Next-Generation Graphene Biosensors for Oral Cancer Diagnosis

Graphene-based electrochemical biosensors offer personalized, non-invasive oral cancer diagnostics. Integration with AI/ML enables real-time analysis, biomarker pattern recognition, and personalized treatment guidance. Future multiplexed platforms can detect multiple salivary biomarkers, providing precise diagnosis, staging, and prognosis. Affordable, portable, and wearable devices-supported by microfluidics, lab-on-chip systems, and telemedicine-allow rapid, continuous monitoring of nucleic acids, proteins, and metabolic or ionic markers, revealing tumor and systemic health insights. Clinical adoption requires validation, regulatory approval, standardization, and ethical compliance. The convergence of graphene nanotechnology, biosensor design, and digital health promises accurate, accessible, and proactive oral cancer diagnostics for individualized patient care (Daweshar *et al*., 2024).

## Integration with mHealth and Wearable Technologies

The future of graphene-based biosensing extends beyond standalone diagnostics to integrated mobile health (mHealth) platforms. By coupling biosensors with smartphones, cloud computing, and wireless communication modules, real-time monitoring of salivary biomarkers becomes possible. These systems can automatically transmit diagnostic data to clinicians or centralized databases, supporting rapid decision-making and personalized care. Furthermore, advances in wearable biosensors, such as graphene-coated mouthguards, dental patches, or intraoral strips, could enable continuous, real-time analysis of salivary components. These innovations can transform oral cancer management from periodic check-ups to dynamic, patient-driven health monitoring Mishra *et al*., 2024).

## CONCLUSION AND FUTURISTIC OUTLOOK

Graphene-based electrochemical biosensors are revolutionizing oral cancer diagnostics by offering sensitive, selective, and non-invasive salivary detection. Their high surface area, conductivity, and mechanical strength allow ultra-low biomarker detection, supporting early-stage diagnosis and improved

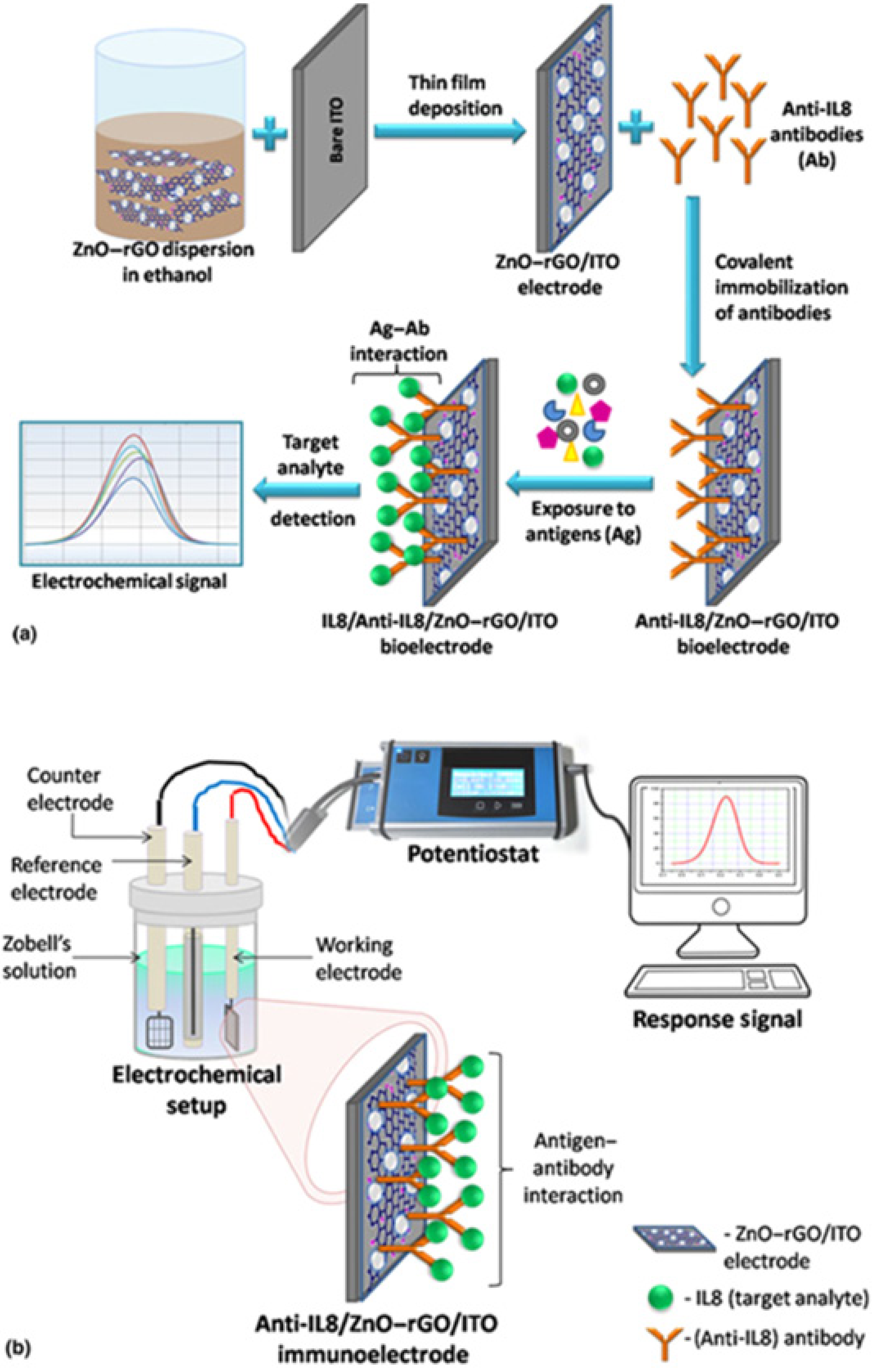

**Figure 3:** Presents a schematic overview showing (a) the fabrication steps of the Anti-IL8/ZnO-rGO/ITO immunosensor and (b) the electrochemical setup employed to perform electro-analytical measurements with the fabricated sensor (Mahalakshmi *et al.*, 2025e).

**Table 3:** DNA biomarkers.

| Sl. No. | Biomarker | Key Properties and Applications | References |
|---|---|---|---|
| 1 | 8-OHdG | Reduced levels in saliva | (S. Kumar *et al.*, 2019) |
| 2 | Chromosomal regions 3p, 9q, 13q, 17p | Linked to early oral cancer | |
| 3 | Cyclin D1 (CCND1) | Amplification/overexpression; poor prognosis | |
| 4 | p27 (CDKN1B), TP63, TP73 | Allelic loss on 9p | |
| 5 | DAPK1 | Apoptosis regulator; often hypermethylated | |
| 6 | DCC | Netrin receptor; present in saliva of patients | |
| 7 | EDN1 | Tumor-promoting G-protein receptor | (Wu *et al.*, 2018) |
| 8 | Ki67 | Elevated in saliva; proliferation/metastasis marker | |
| 9 | KIF1A | Involved in apoptosis and DNA repair | |
| 10 | LDH | Overexpressed in saliva; key in anaerobic glycolysis | |
| 11 | LINE-1 | Hypomethylated in oral cancer | |
| 12 | MINT31 | Regulates calcium channels | |
| 13 | RASSF1α | Tumor suppressor; inhibits growth via RAS | (Guo *et al.*, 2023) |
| 14 | RARβ, FHIT, p15, TIMP3, APC | Frequently methylated | |
| 15 | TIMP1 | Detected in saliva; prognosis marker | |
| 16 | TIMP3 | Immune response and T-cell recognition | |
| 17 | TP53 | DNA repair and apoptosis; LOH linked to cancer | |
| 18 | p16INK4A | Sonic hedgehog signaling pathway | |
| 19 | p16INK4A, MGMT, DAPK1, GSTP1 | Frequently methylated in saliva | |
| 20 | VEGF, BCL-2, Claudin 4, YAP1, MET | Predicts radio-resistance in OSCC | (Shpitzer *et al.*, 2009) |

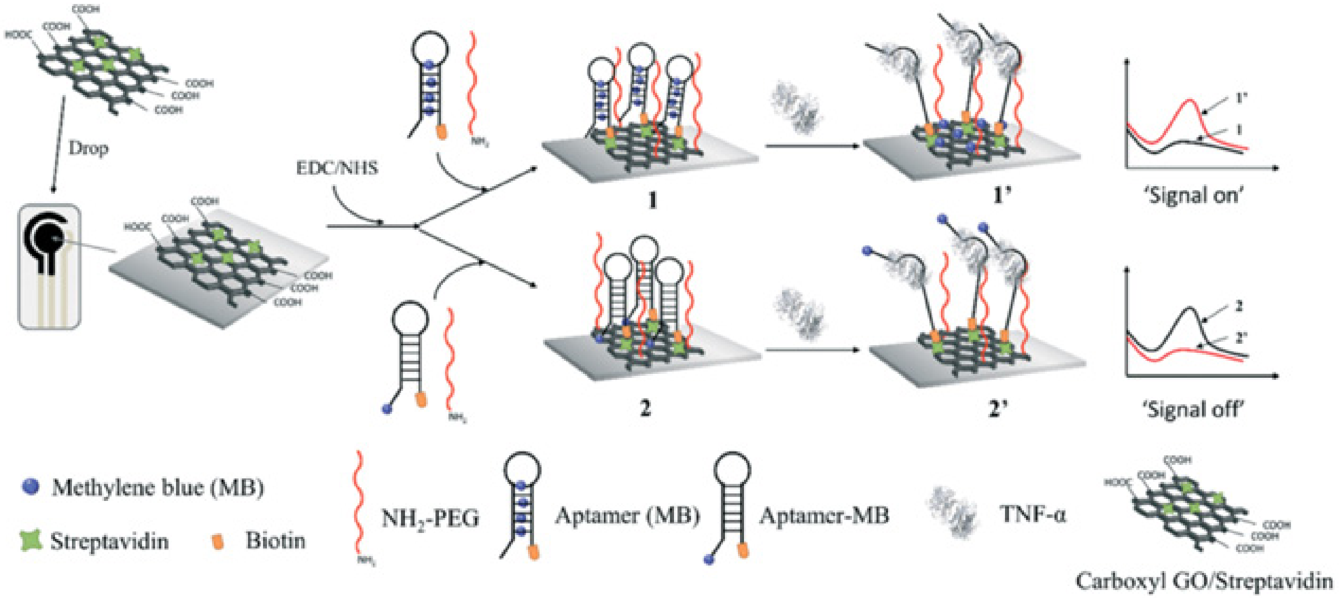

**Figure 4:** Shows an electrochemical molecular beacon-based biosensor designed for detecting TNF-α in saliva, highlighting its potential use in early diagnosis of oral cancer (Mahalakshmi *et al.*, 2025e).

**Table 4: RNA Biomarkers in Oral Cancer.**

| Sl. No. | RNA Biomarker | Key Properties and Applications | References |
|---|---|---|---|
| 1 | circRNA-5 | Saliva/serum; promotes tumor growth/metastasis | (Fan *et al.*, 2020) |
| 2 | DYRK1A | Differentiates oral cancer from normal tissue | |
| 3 | H3F3A | Nucleosome maintenance; marker of proliferation | |
| 4 | IL-1β | Saliva; regulates inflammation, apoptosis, proliferation; diagnostic marker | |
| 5 | IL-8 | Saliva; angiogenesis, immune modulation, cell cycle control | (Lee *et al.*, 2011) |
| 6 | lncRNA | Linked to metastasis and progression | |
| 7 | miRNA-125a | Saliva; suppresses cell growth | |
| 8 | miRNA-133 | Inhibits tumor progression via Bcl2/RhoA | |
| 9 | miRNA-145 | Promotes apoptosis; regulates KRAS, c-Myc, DFF45 | (Jung *et al.*, 2021) |
| 10 | miRNA-184 | Enhances growth; suppresses apoptosis via c-Myc | |
| 11 | miRNA-200a | Tumor suppressor; early metastasis indicator | |
| 12 | miRNA-21 | Saliva; promotes growth/invasion via Wnt/β-catenin targeting DKK2 | |
| 13 | miRNA-31 | Promotes proliferation/metastasis; monitors recurrence | |
| 14 | S100P | Differential in OSCC; regulates cell cycle/differentiation | (Kaur *et al.*, 2022) |

prognosis. These sensors enable real-time, low-cost, point-of-care testing, increasing accessibility and accuracy. Current challenges include stable surface functionalization, reproducible fabrication, scalable production, and limited single-analyte detection. The future lies in multiplexed platforms capable of simultaneously detecting multiple salivary biomarkers, integrated with microfluidics, lab-on-chip systems, and AI-driven analytics. Coupled with telemedicine, they can facilitate remote monitoring, personalized disease management, and broader healthcare access. Ongoing research to overcome technical and regulatory barriers will be key to clinical translation. Graphene-based biosensors have the potential to redefine oral cancer detection, enabling earlier diagnosis, precise monitoring, and improved patient outcomes, forming the backbone of next-generation diagnostic tools (Khan *et al.*, 2023).

## ACKNOWLEDGEMENT

None.

## ABBREVIATIONS

**OSCC:** Oral Squamous Cell Carcinoma; **DNA/RNA:** Deoxyribonucleic acid and Ribonucleic acid; mHealth: Mobile Health; **AI/ML:** Artificial Intelligence and Machine Learning; **GO:** Graphene Oxide; **CVD:** Chemical Vapor Deposition; **AuNPs:** Gold Nanoparticles; **CV:** Cyclic Voltammetry; **DPV:** Differential Pulse Voltammetry; **EIS:** Electrochemical Impedance Spectroscopy; **FET:** Field-Effect Transistor sensors; **CA:** Chronoamperometry; **PEC:** Photoelectrochemical.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## REFERENCES

Ahmad, M., Hasan, M., Tarannum, N., Hasan, M., & Ahmed, S. (2023). Recent advances in optical and photoelectrochemical nanobiosensor technology for cancer biomarker detection. In Biosensors and Bioelectronics. X, 14, Article 100375. https://doi.org/10.1016/j.biosx.2023.100375

Akashanand, Q. S., Zahiruddin, Q. S., Jena, D., Ballal, S., Kumar, S., Bhat, M., Sharma, S., Kumar, M. R., Rustagi, S., Gaidhane, A. M., Jain, L., Sah, S., & Shabil, M. (2024). Burden of oral cancer and associated risk factors at national and state levels: A systematic analysis from the global burden of disease in India, 1990–2021. Oral Oncology, 159, Article 107063. https://doi.org/10.1016/J.ORALONCOLOGY.2024.107063

Bhattacharjya, T., Nalepa, M.-A., Dědek, I., Jakubec, P., Panáček, D., & Otyepka, M. (2025). Recent advances in graphene-based electrochemical biosensors for major non-communicable diseases. Current Opinion in Electrochemistry, 53, Article 101737. https://doi.org/10.1016/J.COELEC.2025.101737

Cheng, F., Hong, H., Yang, S., & Wei, Y. (2017). Individualized network-based drug repositioning infrastructure for precision oncology in the Panomics era. Briefings in Bioinformatics, 18(4), 682–697. https://doi.org/10.1093/bib/bbw051

Daweshar, E., Pankaj, Mewada, R., & Kumar, S. (2024). A comprehensive review on quantification of various biomarkers for the detection of oral carcinoma via electrochemical biosensors. Microchemical Journal, 207, Article 111741. https://doi.org/10.1016/J.MICROC.2024.111741

Devaraji, M., & Ravikumar, L. (2024). The role of liquid biopsy in early detection and monitoring of oral cancer. Oral Oncology Reports, 11, Article 100618. https://doi.org/10.1016/J.OOR.2024.100618

Fadaka, A. O., Pretorius, A., & Klein, A. (2019). Biomarkers for stratification in colorectal cancer: MicroRNAs. In Cancer Control, 26(1), Article 1073274819862784. https://doi.org/10.1177/1073274819862784

Fan, H.-Y., Jiang, J., Tang, Y.-J., Liang, X.-H., & Tang, Y.-L. (2020). CircRNAs: A new chapter in oral squamous cell carcinoma biology. In OncoTargets and Therapy, 13, 9071–9083. https://doi.org/10.2147/OTT.S263655

Goldoni, R., Farronato, M., Connelly, S. T., Tartaglia, G. M., & Yeo, W.-H. (2021). Recent advances in graphene-based nanobiosensors for salivary biomarker detection. In Biosensors and Bioelectronics, 171, Article 112723. https://doi.org/10.1016/j.bios.2020.112723

Guo, Y., Xu, T., Chai, Y., & Chen, F. (2023). TGF-β signaling in progression of oral cancer. In International Journal of Molecular Sciences, 24(12), Article 10263. https://doi.org/10.3390/ijms241210263

Hao, Z., Pan, Y., Shao, W., Lin, Q., & Zhao, X. (2019). Graphene-based fully integrated portable nanosensing system for on-line detection of cytokine biomarkers in saliva. Biosensors and Bioelectronics, 134, 16–23. https://doi.org/10.1016/j.bios.2019.03.053

Hassn Mesrati, M. H., Syafruddin, S. E., Mohtar, M. A., & Syahir, A. (2021). CD44: A multifunctional mediator of cancer progression. In Biomolecules, 11(12), Article 1850. https://doi.org/10.3390/biom11121850

Ilhan, B., Lin, K., Guneri, P., & Wilder-Smith, P. (2020). Improving oral cancer outcomes with imaging and artificial intelligence. Journal of Dental Research, 99(3), 241–248. https://doi.org/10.1177/0022034520902128

Jung, J. E., Lee, J. Y., Park, H. R., Kang, J. W., Kim, Y. H., & Lee, J. H. (2021). MicroRNA-133 targets phosphodiesterase 1C in Drosophila and human oral cancer cells to regulate epithelial-mesenchymal transition. Journal of Cancer, 12(17), 5296–5309. https://doi.org/10.7150/jca.56138

Karagianni, A., Tsierkezos, N. G., Ntziouni, A., Terrones, M., & Kordatos, K. V. (2026). Carbon nanotubes as electrochemical sensors for neurotransmitters: Synthesis, doping, and applications. Carbon, 246, Article 120832. https://doi.org/10.1016/J.CARBON.2025.120832

Karim, M. E. (2021). Biosensors: Ethical, regulatory, and legal issues. In G. Thouand (Ed.),Handbook of cell biosensors (pp. 679–705). Springer International Publishing. https://doi.org/10.1007/978-3-030-23217-7_23

Kaur, J., Jacobs, R., Huang, Y., Salvo, N., & Politis, C. (2018). Salivary biomarkers for oral cancer and pre-cancer screening: A review. In Clinical Oral Investigations, 22(2), 633–640. https://doi.org/10.1007/s00784-018-2337-x

Kaur, J., Preethi, M., Srivastava, R., & Borse, V. (2022). Role of IL-6 and IL-8 biomarkers for optical and electrochemical based point-of-care detection of oral cancer. Biosensors and Bioelectronics. X, 11, Article 100212. https://doi.org/10.1016/j.biosx.2022.100212

Khan, A., DeVoe, E., & Andreescu, S. (2023). Carbon-based electrochemical biosensors as diagnostic platforms for connected decentralized healthcare. Sensors and Diagnostics, 2(3), 529–558. https://doi.org/10.1039/D2SD00226D

Kumalasari, M. R., Alfanaar, R., & Andreani, A. S. (2024). Gold nanoparticles (AuNPs): A versatile material for biosensor application. Talanta Open, 9, Article 100327. https://doi.org/10.1016/J.TALO.2024.100327

Kumar, N., Salehiyan, R., Chauke, V., Joseph Botlhoko, O., Setshedi, K., Scriba, M., Masukume, M., & Sinha Ray, S. (2021). Top-down synthesis of graphene: A comprehensive review. In FlatChem, 27, Article 100224. https://doi.org/10.1016/j.flatc.2021.100224

Kumar, P., Rajan, R., Upadhyaya, K., Behl, G., Xiang, X.-X., Huo, P., & Liu, B. (2024). Metal oxide nanomaterials based electrochemical and optical biosensors for biomedical applications: Recent advances and future prospectives. Environmental Research, 247, Article 118002. https://doi.org/10.1016/J.ENVRES.2023.118002

Kumar, S., Panwar, S., Kumar, S., Augustine, S., & Malhotra, B. D. (2019). Biofunctionalized nanostructured yttria modified non-invasive impedometric biosensor for efficient detection of oral cancer. Nanomaterials, 9(9), Article 1190. https://doi.org/10.3390/nano9091190

Lee, Y.-H., Zhou, H., Reiss, J. K., Yan, X., Zhang, L., Chia, D., & Wong, D. T. W. (2011). Direct saliva transcriptome analysis. Clinical Chemistry, 57(9), 1295–1302. https://doi.org/10.1373/clinchem.2010.159210

Magne, T. M., de Oliveira Vieira, T., Alencar, L. M. R., & Junior, F. F. M. Gemini-Piperni, S., Carneiro, S. V., Fechine. Law, and Medicine U. D., Freire, R. M., Golokhvast, K., Metrangolo, P., Fechine, P. B. A., and Santos-Oliveira, R. (2022). Graphene and its derivatives: understanding the main chemical and medicinal chemistry roles for biomedical applications. In Journal of Nanostructure in Chemistry (Vol. 12, Issue 5). https://doi.org/10.1007/s40097-021-00444-3.

Mahalakshmi, D., Nandhini, J., Meenaloshini, G., Karthikeyan, E., Karthik, K. K., Sujaritha, J., Vandhana, & Ragavendran, C. (2025a). Graphene nanomaterial-based electrochemical biosensors for salivary biomarker detection: A translational approach to oral cancer diagnostics. Nano TransMed, 4, Article 100073. https://doi.org/10.1016/J.NTM.2025.100073

Min, H., Zhu, S., Safi, L., Alkourdi, M., Nguyen, B. H., Upadhyay, A., & Tran, S. D. (2023). Salivary diagnostics in pediatrics and the status of saliva-based biosensors. In Biosensors, 13(2), Article 206. https://doi.org/10.3390/bios13020206

Mishra, A., Singh, P. K., Chauhan, N., Roy, S., Tiwari, A., Gupta, S., Tiwari, A., Patra, S., Das, T. R., Mishra, P., Nejad, A. S., Shukla, Y. K., Jain, U., & Tiwari, A. (2024). Emergence of integrated biosensing-enabled digital healthcare devices. In Sensors and Diagnostics. Royal Society of Chemistry, 3(5), 718–744. https://doi.org/10.1039/d4sd00017j

Nandhini, J., & Karthikeyan, E. (2024). Crosstalk between cancer-associated fibroblasts (CAF) and tumour cells in head and neck cancer—Unraveling the complex pathway and CAF-targeted therapy. Oral Oncology Reports, 12, Article 100690. https://doi.org/10.1016/J.OOR.2024.100690

Neumaier, D., Pindl, S., & Lemme, M. C. (2019). Integrating graphene into semiconductor fabrication lines. In Nature Materials, 18(6), 525–529. https://doi.org/10.1038/s41563-019-0359-7

Pirzada, M., & Altintas, Z. (2019). Nanomaterials for healthcare biosensing applications. In Sensors, 19(23), Article 5311. https://doi.org/10.3390/s19235311

Ravikumar, L., & Velmurugan, R. (2024). Innovations in early detection of oral cancer: Advancing diagnostic technologies and reducing global disparities. Oral Oncology Reports, 11, Article 100620. https://doi.org/10.1016/J.OOR.2024.100620

Shpitzer, T., Hamzany, Y., Bahar, G., Feinmesser, R., Savulescu, D., Borovoi, I., Gavish, M., & Nagler, R. M. (2009). Salivary analysis of oral cancer biomarkers. British Journal of Cancer, 101(7), 1194–1198. https://doi.org/10.1038/sj.bjc.6605290

Song, J., Luo, Y., Hao, Z., Qu, M., Huang, C., Wang, Z., Yang, J., Liang, Q., Jia, Y., Song, Q., Zhang, Q., & Luo, S. (2025). Graphene-based wearable biosensors for point-of-care diagnostics: From surface functionalization to biomarker detection. Materials Today. Bio, 32, Article 101667. https://doi.org/10.1016/J.MTBIO.2025.101667

Tandale, P., Choudhary, N., Singh, J., Sharma, A., Shukla, A., Sriram, P., Soni, U., Singla, N., Barnwal, R. P., Singh, G., Kaur, I. P., & Suttee, A. (2021). Fluorescent quantum dots: An insight on synthesis and potential biological application as drug carrier in cancer. Biochemistry and Biophysics Reports, 26, Article 100962. https://doi.org/10.1016/J.BBREP.2021.100962

Ullah, S., Shi, Q., Zhou, J., Yang, X., Ta, H. Q., Hasan, M., Ahmad, N. M., Fu, L., Bachmatiuk, A., & Rümmeli, M. H. (2020). Advances and trends in chemically doped graphene. In Advanced Materials Interfaces, 7(24). https://doi.org/10.1002/admi.202000999

Ullah, S., Yang, X., Ta, H. Q., Hasan, M., Bachmatiuk, A., Tokarska, K., Trzebicka, B., Fu, L., & Rummeli, M. H. (2021). Graphene transfer methods: A review. In Nano Research, 14(11), 3756–3772. https://doi.org/10.1007/s12274-021-3345-8

Verma, D., Yadav, S. K., Kalkal, A., Pradhan, R., & Packirisamy, G. (2023). An ultrasensitive electrochemical immunosensor comprising green synthesized α-Fe2O3NPs_rGO nanocomposite for determination of oral cancer. IEEE Sensors Letters, 7(12), 1–4. https://doi.org/10.1109/LSENS.2023.3330915

Wu, Y.-C., Ning, L., Tu, Y.-K., Huang, C.-P., Huang, N.-T., Chen, Y.-F., & Chang, P.-C. (2018). Salivary biomarker combination prediction model for the diagnosis of periodontitis in a Taiwanese population. Journal of the Formosan Medical Association, 117(9), 841–848. https://doi.org/10.1016/j.jfma.2017.10.004

Yoshizawa, J. M., Schafer, C. A., Schafer, J. J., Farrell, J. J., Paster, B. J., & Wong, D. T. W. (2013). Salivary biomarkers: Toward future clinical and diagnostic utilities. In Clinical Microbiology Reviews, 26(4), 781–791. https://doi.org/10.1128/CMR.00021-13

**Cite this article:** Gupta JK, Jaganath P, Babu RH, Reddy KTK, Dantinapalli VLS, Elumalai S, *et al*. Graphene-Based Electrochemical Biosensors for Oral Cancer Detection: Advances, Challenges, and Future Prospects-A Systematic Review. J Young Pharm. 2026;18(1):70-9.