Nanoparticle‑based immunosensors for enhanced DNA analysis in oral cancer: A systematic review

Neha Gupta¹, Ankur Bhargava², Sonal Saigal¹, Vini Mehta³

1 Department of Oral Pathology, Microbiology and Forensic Odontology, Dental College, Rajendra Institute of Medical Sciences (RIMS), Ranchi, 2 Department of Oral Pathology and Microbiology, Hazaribag College of Dental Sciences and Hospital, Hazaribag, Jharkhand, 3 Department of Dental Research Cell, Dr. D. Y. Patil Dental College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pimpri, Pune, Maharashtra, India

To investigate the diagnostic and therapeutic potential of nanoparticle (NP)-based immunosensors in the field of oral cancer. PubMed, Embase, Scopus, Web of Science, and Google Scholar databases were explored for NP applications in oral cancer. Data extraction in terms and quality assessment of all the articles were done. Out of 147, 17 articles were included in this review. A majority of the studies showed improved sensitivity and specificity for saliva analysis using an enzyme-linked immunosorbent assay based on gold NPs, improving early identification. Additionally, novel therapeutic approaches, utilising NP‑based immunosensors, demonstrated targeted drug delivery, coupled chemo‑photothermal therapy, and gene silencing. Imaging methods have made it possible to distinguish between malignant and healthy states, such as surface-enhanced Raman scattering and optical coherence tomography. The reviews' findings highlight the transformational potential of NP‑based immunosensors in addressing the difficulties associated with diagnosing and treating oral cancer. However, for an accurate interpretation and application of NP‑based solutions in clinical practise, it is essential to be thoroughly aware of the intricacies involved, and the synthesised data in this review support the continued investigation and improvement of NP-based therapies in the ongoing effort to improve the management of oral cancer. **Abstract**

Keywords: DNA analysis, immunosensors, nanoparticles, oral cancer, systematic review

Address for correspondence: Dr. Vini Mehta, Department of Dental Research Cell, Dr. D. Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pimpri, Pune - 411018, India. E‑mail: vini.mehta@statsense.in

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INTRODUCTION

Oral cancer has a disconcerting 5‑year survival rate of about 50%, making it the sixth most common malignancy worldwide.^[1] A number of incapacitating symptoms, including dysphagia, altered facial look, chronic pain, and psychological distress, are brought on by cancer's aggressive nature, which is characterised by rapid dispersion, invasive

tendencies, and a propensity for metastasis.[2] Its aetiology is based on genetic variations that affect cell cycles, which are exacerbated by excessive alcohol and tobacco use.[3,4] Diagnostic difficulties frequently lead to postponed treatments, which are worsened by difficult therapeutic modalities such surgery, radiotherapy, and chemotherapy, each of which has constricting adverse effects.^[4] Optimising

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diagnostic precision and reducing therapeutic side effects become crucial to meet these demands.

Recent developments in biomaterials with unique (bio) physicochemical properties have shown the ability to modify cellular behaviour and even to aid in the prevention of disease, biological restitution, and tissue regeneration.[5‑7] Notably, the development of nanomaterials and their widespread integration into biomedical therapies and diagnostics have drawn a lot of interest.^[8,9] NPs offer a promising way to overcome limitations associated with standard diagnostic and therapeutic approaches by taking advantage of the distinct pathophysiological traits of tumours, which are characterised by hypoxia, angiogenesis, an acidic extracellular pH, and a lack of lymphatic drainage.^[10] NPs selectively concentrate within tumour interstitial spaces, granting an extended retention duration, by taking advantage of the abnormal permeability of tumour blood vessels, as highlighted by the enhanced permeability and retention (EPR) effect.[8,9] Emerging active targeting techniques are being investigated in order to get around ambiguities in the tumour microenvironment, even if the EPR effect has been used for NP‑mediated detection and treatment. Antiepidermal growth factor receptor medicines are an example of how ligand or antibody coupling facilitates NPs' engagement with tumour‑specific receptors and results in increased targeted efficiency and less systemic toxicity.[10]

In addition to imaging agents, NPs play critical roles in the distribution of medications such chemoradiotherapeutic agents and photosensitizers for photodynamic therapy.[11] Additionally, certain NPs possess regulated optical, magnetic, and electrical properties that can be used to generate therapeutic heat and light for the diagnosis and treatment of oral cancer.^[12] The use of biosensors^[9-11] and innovative nanotechnology-based techniques that incorporate gene therapy^[13] also offer prospects for the early detection and treatment of cancer. By using ultrasmall dimensions, reactivity, and changeable functionalization, a wide variety of NPs, including organic and inorganic NPs, have discovered extensive application.[12] Keeping these advancements in mind, this systematic review aimed to thoroughly investigate and synthesise the body of recent scientific literature relating to the use of NP‑based immunosensors for advancing DNA analysis in the context of oral cancer. The main goal was to carefully assess the current research landscape in order to determine the degree to which NP‑based immunosensors improve DNA analysis procedures, particularly pertinent to the detection and characterisation of oral cancer.

MATERIALS AND METHODS

We preregistered a protocol for the study before initiating it [PROSPERO Registration: CRD42023 492140]. The latest edition of the Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement^[14] was adopted to guide the study's methodology.

Focussed question

What is the diagnostic and therapeutic potential of nanoparticle (NP)-based immunosensors in the field of oral cancer?

Search strategy and selection criteria

Studies which investigated the use of NP‑based immunosensors to find, measure, or analyse DNA biomarkers directly connected to oral cancer. Studies published in peer‑reviewed journals or grey literatures were eligible for this systematic review and meta‑analysis. We excluded editorials, conference proceedings, and systematic reviews.

From conception until November 30, 2023, electronic searches of the following resources were performed in PubMed/MEDLINE, Embase, Scopus, Web of Science, and Google Scholar. The search algorithm used a variety of appropriate MeSH terminologies to gather any potential qualifying results linked to NP‑based immunosensors to improve DNA analysis procedures, particularly pertinent to the detection and characterisation of oral cancer. [Table 1]

Rayyan online systematic review software was used to delete duplicate references both electronically and manually. Furthermore, reference lists of all relevant papers exploring the oral health status of prisoners were searched to find possibly suitable articles.

Two independent reviewers examined titles and abstracts and identified papers that would fit within the inclusion parameters. After obtaining the full texts, two independent reviewers applied the eligibility criteria and, by consensus, came up with the final selection of articles to be considered. Researchers contacted study authors to request full papers if they were not publicly available. Three investigators assessed each article's eligibility, and any discrepancies were resolved out through a discussion.

Data extraction

Two reviewers independently extracted the data on a structured extraction form to obtain the following information: (1) Name of the author and year of publication; (2) NP applications; (3) detection methods; (4)

sensitivity and specificity; (5) imaging techniques; and (6) therapeutic approaches. The degree of concordance was measured using Cohen's Kappa coefficient, a commonly used statistical indicator of inter-rater agreement. The determined Cohen's Kappa score was 0.85, indicating that the reviewers' data extraction methods were in good agreement with one another.

Table 1: Search strings utilised across the different databases

Bias assessment

Selected studies were assessed by two independent reviewers for methodological quality using the modified version of the CONSORT tool[15] for *in vitro* studies and given an overall estimation of risk of bias (i.e. low risk, unclear, or high risk) according to mutually decided criteria. Studies scoring >70% were categorized as low risk, scores between 40% and 70% were labelled as unclear risk of bias, and scores less than 40% were designated as high risk of bias.

RESULTS

The search identified 147 articles, from which 76 duplicates were removed. Seventy-one articles were eligible for inclusion and title and abstract were screened by two reviewers; 35 underwent full-text screening and $17^{[16-32]}$ fully satisfied the inclusion criteria. All included studies underwent critical appraisal; the inter‑reviewer appraisal score was 8.25, indicating a high level of agreement between reviewers [Figure 1].

Quality assessment

The overall quality ratings of the studies were low risk of bias ($n = 8$), unclear risk of bias ($n = 4$), and high risk of bias (5). The main flaws in the included research were an inadequate or no information on sample size, sampling technique, and a reliable standard used for monitoring the condition [Figure 2].

A thorough summary of studies concentrating on the application of NP‑based immunosensors in the field of oral cancer diagnostics and treatment is presented collectively in Table 2. The table summarises a wide range of research, each showing particular uses of NPs, detection strategies, assessments of their sensitivity and specificity, imaging modalities, and therapeutic approaches. The studies in the table show major improvements and prospective gains of NP‑based strategies in tackling the difficulties of managing oral cancer. The selected investigations[16‑32] cover a wide range of methodologies, including label‑free immunosensors, microfluidic biosensors, Raman spectroscopy, and immunosensors. These methods seek to increase the sensitivity and accuracy of oral cancer detection, perhaps providing instruments for an early diagnosis and better patient outcomes. The table also highlights novel therapeutic approaches based on NP‑based platforms. These interventions include thermal ablation, targeted drug delivery, gene silencing, combination chemo‑photothermal therapy, and targeted drug delivery. Such therapeutic approaches make use of the special qualities of NPs to boost treatment effectiveness while reducing negative side effects on healthy tissues.

DISCUSSION

Based on the synthesized findings, this study's importance is crucial for improving our understanding of the prospective uses and game‑changing effects of NP‑based technologies in the field of oral cancer detection and therapy. The wide range of studies summarised in this review demonstrate how multifaceted NPs are in tackling the complex problems related to oral cancer, consequently generating breakthroughs with significant therapeutic significance. The collection of research on NP applications for oral cancer diagnosis provides a thorough overview of state-of-the-art diagnostic techniques.

Chakraborty *et al.*[16] demonstrated the enhanced sensitivity and specificity of gold NP-based enzyme-linked

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Figure 1: PRISMA 2020 flow diagram for this review

immunosorbent assay (ELISA) for saliva analysis. Fălămaș et al.^[20] employed surface-enhanced Raman scattering (SERS) with gold NPs to differentiate healthy and cancerous conditions based on Raman signals in saliva. Wang *et al.*[31] showcased the potential of microfluidic DNA biosensors employing magnetic beads‑based hybridization and electrophoretic driving mode for fluorescent detection, which exhibited high sensitivity, robust resistibility, and short analysis time, holding promise for clinical diagnosis.

Therapeutic interventions were also explored. Jin *et al.*[21] employed polyethyleneimine (PEI)‑modified Fe3O4 NPs for siRNA‑based therapy, achieving high gene silencing efficiencies and inhibiting cell viability and migration. Legge *et al.*[25] demonstrated targeted thermal ablation of tumours using magnetic iron oxide NPs conjugated with antibodies, leading to increased killing of targeted cells. Liu Z *et al.*[28] developed a PDPN Ab‑AuNP‑DOX nanoplatform for combined chemo‑photothermal therapy, showcasing enhanced antitumor efficacy through *in vitro* and *in vivo* studies.

Furthermore, studies delved into innovative detection methods. Ding *et al.*[19] designed label‑free immunosensors using VANTAs on interdigitated electrodes for detecting CIP2A, offering wide linear sensing ranges and a low detection limit for early‑stage cancer screening. Xu *et al.*[32] introduced DNA‑templated quantum dots (QDs)

for detecting IL‑8 protein, demonstrating exceptional sensitivity and specificity in electrochemical biosensing. While some studies focused on specific imaging techniques, such as plasmonic Au nanoclusters for optical coherence tomography in early-stage cancer detection,^[23] others explored multifunctional approaches. Kah *et al.*[22] utilized gold NPs for coupled surface plasmon resonance and self-assembled SERS-active films, aiming to differentiate normal and cancerous cells and achieve early diagnosis.

The use of biosensor-based detection methodologies offers a variety of benefits over conventional methodologies, including affordability, user-friendliness, miniaturisation capabilities, and the removal of the need for specialised data analytical procedures. Despite this, biosensors created by fabrication procedures have some drawbacks, including limited sensitivity, innate instability, and other issues.[33] Given these limitations, combining advances in biosensing modalities with those in nanotechnology appears as a tactical way to get around them, significantly enhancing approaches relevant to the detection and diagnosis of oral squamous cell carcinoma (OSCC). The development and production of nanobiosensors using a variety of nanomaterials, including gold nanoparticles (AuNPs), QDs, dendrimers, metal oxides, and carbon-based nanocomposites, have been made possible by this innovative environment.^[34]

Biosensors' performance has been significantly improved by the intrinsic properties of the aforementioned

Figure 2: Bias evaluation in the selected papers

nanomaterials, which enable them to detect substances faster, at higher thresholds, and with more reproducibility.[35,36] These nanobiosensors are now effectively equipped to carry out autonomous analyses with increased promptness and simplified operability thanks to this trajectory of breakthroughs. These nanobiosensors also result in a reduced need for sample volume while providing exceptional precision (achieving an error rate of less than 1%), notable specificity, and cost-effectiveness. As a result, the support for nano‑enabled biosensing techniques for the early detection of oral cancer gains a convincing justification, suggesting an improvement in patient care and therapeutic outcomes.[37] Notably, the emergence of nanotechnology‑driven miniaturised devices represents a pivotal point in preclinical and clinical investigative

realms, spanning fields like targeted drug administration, personalised medicine, and the newly emerging field of "nanodiagnostics."

The development of NP‑based immunosensor technologies is given the essential drive by the evolution of nanotechnology.[38,39] A nanobiosensor's effectiveness is dependent on a number of parameters, including specificity, sensitivity, linearity, shelf life, detection threshold, reaction kinetics, and repeatability.[40] As a result, customised optimisation techniques are required. NP‑based frameworks clearly outperform their bulk equivalents, according to comparative evaluations, thanks to their generous relative surface areas and the quantum confinement phenomena. Additionally, NPs' increased surface-to-volume ratio leads to higher chemical reactivity

Table 2: Characteristics of the included articles representing the diagnostic potential of NPs pertaining to oral cancer detection and treatment

Contd...

and stability. In addition, the increased surface area of these scaffolds makes it possible to accommodate a large number of ligands, enhancing binding affinities and selectivity.[41] The quantum confinement effect, in which the mobility of electrons is restricted within particular energy bands due to size‑induced confinement, emerges as a result of the transition to the nanoscale world.[42] This event invariably leads to an increase in band gaps and a corresponding decrease in wavelengths—crucial dynamics influencing the characteristics of the materials. Together with their inherent qualities, the morphological properties and dimensions of NPs, including nanospheres, nanotubes, and nanowires, have a significant impact on how they behave.^[16-18,22-24,28,43] It is significant that the decrease in nano material (NM) particle size has shown a concomitant improvement in their biosensing proclivity.^[44-46] The use of multiplexing techniques that unify the detection of various biomarkers emerges as a requirement given the clinical complexity involved in the early detection of potentially malignant diseases or OSCC via single biomarkers. It is feasible to achieve this multiplexed manner of detection by immobilising various biorecognition moieties—tailored specifically for chosen targets—on the surface of NPs.^[46,47] Clinical platforms for minimally or noninvasive OSCC detection have provided effective confirmation of this method.[45,48]

It is interesting to note that the addition of 3D‑nanocarbon tubes increased sensitivity by more than 20 times, outperforming conventional sandwich ELISA designs.[49] Upconversion nanoparticles (UCNPs), which exhibit photon upconversion phenomena upon activation by near‑infrared light and thereafter emit within the visible electromagnetic spectrum,^[50,51] are notable iterations of nanomaterials used within biosensing paradigms. According to the information gathered, it may be possible to use energy shifts in the red and blue wavelength domains in combination with biocompatible UCNP composites that are powered by fluorescence resonance energy transferbased (FRET) to identify OSCC biomarkers. These UCNP

composites have the ability to find OSCC tissues and cancer model tissues that express matrix metalloproteinase 2 (MMP2). Clearly, the created nanocomposite produces blue fluorescence in the absence of MMP2, while radiation exposure causes FRET-induced red fluorescence, [48-51] highlighting their importance within the clinical range of OSCC diagnosis.

Despite the insights the study's findings have made, it is crucial to recognise and outline the review's limitations, which must be taken into account for a thorough grasp of the consequences. First off, it is difficult to make direct comparisons and generalisations because of the variety of NP‑based technologies and approaches described in this review. The reliability and portability of the results to clinical settings may be impacted by variations in NP properties, production methods, and experimental conditions. Additionally, the variety of papers included show a natural variability in sample sizes, study plans, and outcome metrics. The development of uniform procedures or globally applicable standards for the application of NP‑based methods in the detection and treatment of oral cancer may be hampered by this intrinsic variation. The development of a comprehensive framework for evaluating the success of various therapies throughout the field may be hampered by the lack of standardised criteria for evaluating sensitivity, specificity, and therapeutic efficacy. Furthermore, most of the research listed in this study are preclinical in nature and were mostly carried either *in vitro* or using animal models. Even while this review set the foundation for NP‑based techniques' potential, the move to human clinical trials is still a significant issue. Clinical translation needs meticulous validation, delivery mechanism optimisation, and meticulous safety profile assessment, all of which call for lengthy durations and significant financial investments. Last but not least, the studies' temporal scope raises the prospect that they could be impacted by developments in NP technology, characterisation strategies, and analytical approaches. Newer methods and technology could develop as the study

of NPs and oral cancer progresses, thereby changing the diagnostic and treatment landscape and making certain discoveries obsolete or less useful.

CONCLUSION

As per the synthesized findings, NP-based immunosensors present a viable route for enabling more precise and effective detection of oral cancer biomarkers and improving early-stage diagnosis. Combining NPs with well-known detection techniques, such as ELISA, Raman spectroscopy, and electrochemical biosensing, showed considerable gains in sensitivity, specificity, and precision—important qualities for accurate disease diagnosis. Additionally, novel ways for effective gene delivery, photothermal therapy, and targeted medication administration are made possible by the utilisation of the particular physicochemical properties of nanomaterials, offering fresh therapeutic prospects with significant clinical promise. The comprehensive review of studies also highlights the dynamic environment of NP applications in the field of oral cancer, presenting them as key instruments in the development of personalised medicine. To confirm the translational efficacy and safety of NP‑based interventions, the review also highlights the significance of addressing methodological variations, assay standardisation, and the need for extensive long-term clinical investigations. The review as a whole supports the critical function of NP‑based immunosensors in enhancing the accuracy of DNA analysis for oral cancer, transcending traditional paradigms of diagnostic and treatment approaches. The combination of these results highlights the revolutionary potential of NP platforms, spurring developments in early detection, individualised treatment plans, and therapeutic precision.

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Conflicts of interest

There are no conflicts of interest.

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