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Nanodiamonds in Oral Cancer Therapy: A Comprehensive Narrative Review

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Abstract

Background: *Oral cancer, predominantly oral squamous cell carcinoma (OSCC), remains a major global health concern characterized by late detection, aggressive progression, and limited therapeutic success. Despite advances in surgery, radiotherapy, and chemotherapy, treatment resistance and systemic toxicity continue to compromise clinical outcomes. Nanotechnology-based approaches offer new possibilities to improve drug delivery, selectivity, and treatment efficacy. This review summarizes current research on the application of nanodiamonds (NDs) in oral cancer therapy, focusing on their mechanisms of action, experimental findings, and translational potential.*

Methods: *A critical analysis of published studies was performed, highlighting investigations on ND-based drug and gene delivery systems in both in vitro and in vivo models of oral cancer. The reviewed evidence was categorized according to major mechanistic pathways, including apoptosis induction, drug resistance modulation, and theranostic applications.*

Results: *NDs possess a high surface area, favorable biocompatibility, and versatile surface chemistry, which enable efficient drug and gene conjugation. ND–drug complexes such as ND–doxorubicin have demonstrated enhanced cellular uptake, controlled release, and reduced cytotoxicity in preclinical settings compared with free drugs. ND-mediated gene delivery has also shown potential for suppressing oncogene expression and restoring drug sensitivity. Preliminary in vivo studies indicate good tumor-targeting ability and short-term safety. However, key challenges remain regarding large-scale synthesis, biological variability, long-term biodistribution, and regulatory classification.*

Conclusion: *Current preclinical evidence suggests that NDs are promising nanocarriers for oral cancer therapy. Nevertheless, their translation to clinical use requires further investigation into pharmacokinetics, immunological safety, and manufacturing reproducibility. Future work should aim to optimize ND formulations and design rigorous clinical trials to establish their therapeutic value in humans.*

Keywords: Nanodiamonds, Oncology, Drug delivery, Squamous carcinoma, Nano biotechnology.
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Introduction

Oral cancer is a significant global health concern, representing a major subset of head and neck malignancies[1]. The term "oral cancer" most commonly refers to oral squamous cell carcinoma (OSCC), which accounts for over 90% of all oral malignancies[2]. OSCC arises from the epithelial lining of the oral cavity, including the lips, tongue, buccal mucosa, floor of the mouth, hard palate, and gingiva[3]. Despite advancements in diagnostic tools and therapeutic approaches, oral cancer continues to have a relatively poor prognosis, largely due to late-stage diagnosis and treatment-resistant disease[4].

The global burden of oral cancer remains substantial, with approximately 390,000 new cases and 180,000 deaths reported worldwide in 2023, according to the GLOBOCAN 2023 estimates from the International Agency for Research on Cancer (IARC)[5]. The prevalence is particularly high in developing countries, especially in regions of South and Southeast Asia, including India, Bangladesh, Sri Lanka, and Pakistan. This geographical variation is attributed to region-specific risk factors, socioeconomic disparities, and limited access to early screening and healthcare infrastructure[6] (Figure 1).

Males are disproportionately affected by oral cancer compared to females, with a male-to-female ratio of approximately 2:1. This gender disparity is largely due to higher prevalence of risk behaviors such as tobacco and alcohol use among men[7]. Furthermore, the incidence increases with age, typically presenting in individuals over the age of 50; however, recent trends indicate a growing number of cases in younger populations due to emerging risk factors like human papillomavirus (HPV) infection[8].

Oral cancer is a multifactorial disease, with both environmental and genetic factors contributing to its pathogenesis. The most well-established etiological agents include[9] (Figure 2):

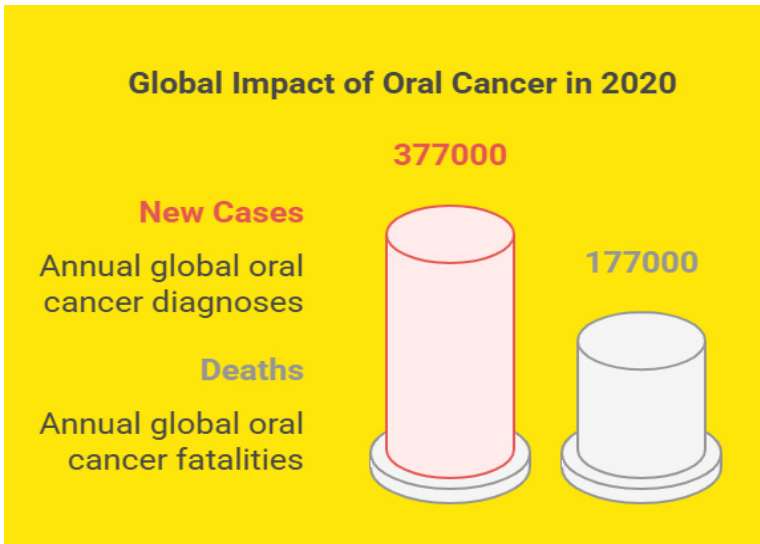

Figure 1. Global burden of oral squamous carcinoma

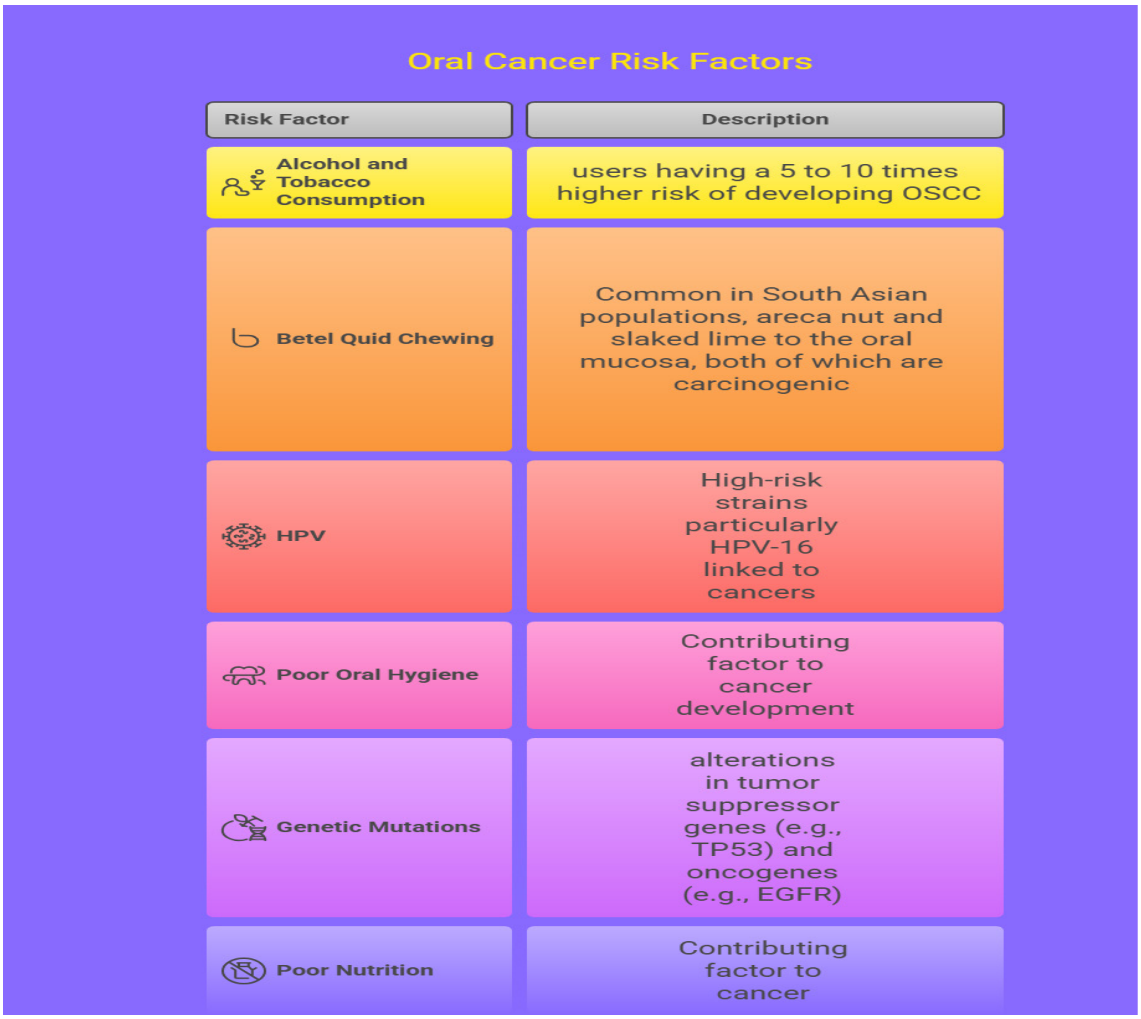

Figure 2. Risk factors of oral cancers

The most well-established etiological agents for OSCC include tobacco use, alcohol consumption, betel quid chewing, and HPV infection[10-15]. Tobacco remains the single most significant risk factor, increasing the likelihood of OSCC by up to tenfold among users compared with non-smokers. Alcohol acts synergistically with tobacco, further amplifying carcinogenic potential, while the traditional South Asian habit of betel quid chewing exposes the oral mucosa to carcinogenic compounds such as areca nut and slaked lime. In recent years, high-risk HPV strains—particularly HPV-16—have been increasingly associated with OSCC cases, especially in younger, non-smoking individuals. Additional factors such as poor oral hygiene, chronic mechanical irritation, and nutritional deficiencies may further contribute to malignant transformation (Figure 2).

The treatment of oral cancer typically involves a multimodal approach, including surgery, radiation therapy, and chemotherapy. While early-stage tumors can often be treated successfully with surgical resection alone, advanced stages frequently require combined therapies[10]. However, treatment remains associated with significant challenges (Figure 3):

- Late diagnosis: More than 50% of cases are diagnosed at stage III or IV, when the tumor has already invaded deeper tissues or metastasized to regional lymph nodes. This dramatically reduces survival rates[11].
- High recurrence rates: Even after complete surgical removal, the risk of local recurrence or second primary tumors is considerable[12].
- Treatment-related morbidity: Surgical interventions, especially extensive resections, can lead to disfigurement, speech difficulties, and impaired mastication or swallowing, profoundly affecting patients' quality of life[13].
- Chemoresistance: Oral cancers often exhibit intrinsic or acquired resistance to conventional chemotherapeutic agents like cisplatin and 5-fluorouracil, limiting treatment efficacy[14].

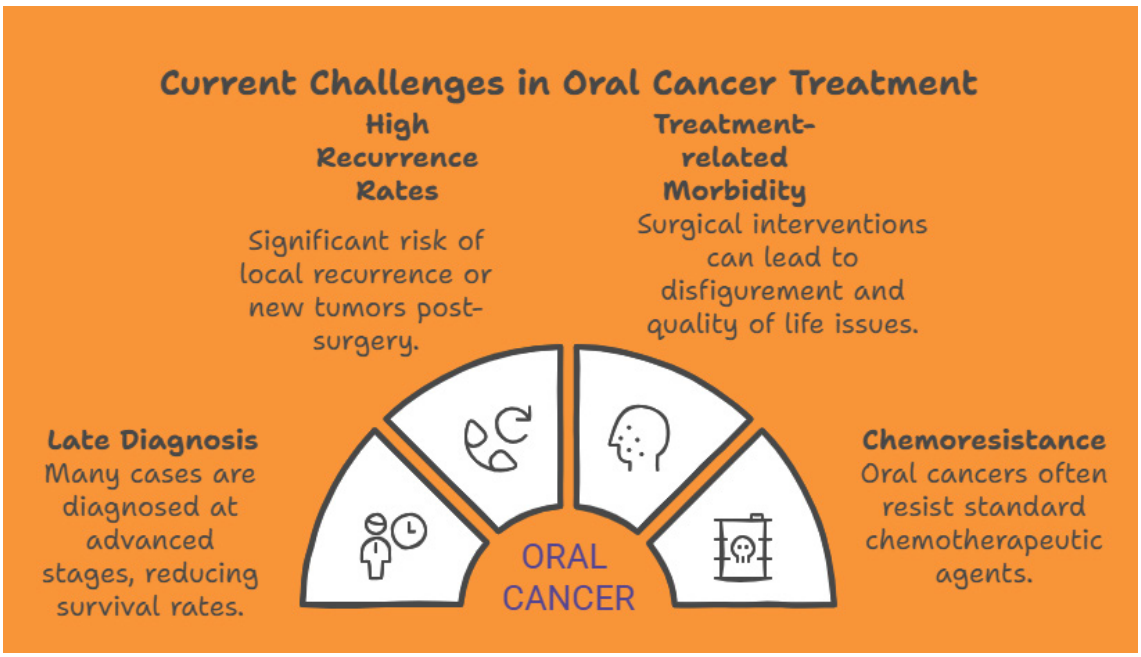

Figure 3. Current challenges in treatment of oral cancer

These limitations underscore the urgent need for more effective and targeted treatment modalities.

Early detection of oral cancer is pivotal for improving patient outcomes[15]. When diagnosed at an early stage (I or II), the 5-year survival rate can exceed 80%, compared to less than 30% for late-stage diagnoses[16]. Early-stage tumors are also more amenable to conservative treatments with minimal morbidity. Unfortunately, due to the asymptomatic nature of early lesions and the lack of widespread screening programs, early diagnosis remains a major hurdle[17].

Moreover, even with systemic therapies, the effectiveness of treatment is often compromised by issues related to non-specific drug distribution, systemic toxicity, and drug resistance. Traditional chemotherapeutics circulate throughout the body, affecting both healthy and cancerous tissues, which results in severe side effects and reduced patient compliance[18].

To overcome these limitations, significant attention has been directed toward the development of targeted drug delivery systems. Nanotechnology, in particular, offers promising solutions by enabling site-specific drug delivery[19], controlled

release, special surface characterization[20] and reduced systemic toxicity[21]. Among various nanomaterials, nanodiamonds (NDs) have emerged as a particularly attractive platform due to their high biocopatibility, tunable surface chemistry, and ability to carry chemotherapeutic agents efficiently. The integration of such novel drug delivery systems[22] into clinical practice may revolutionize the current paradigm of oral cancer treatment, improve therapeutic efficacy while minimizing adverse effects.

Materials and Methods

Search strategy: Four independent reviewers conducted a comprehensive literature search in PubMed, Scopus, Web of Science, and the Cochrane Library databases, covering publications from January 1, 2005, to February 15, 2025. The search strategy employed the following terms and Boolean operators:

("nanodiamonds" OR "nanodiamond-based systems") AND ("oral cancer" OR "oral squamous cell carcinoma" OR "OSCC" OR "head and neck cancer") AND ("drug delivery" OR "gene delivery" OR "theranostics").

In addition, the reference lists of all included studies and relevant reviews were screened manually to identify further eligible articles.

Inclusion criteria: Studies were considered eligible if they met the following criteria:

1. Investigated ND-based systems for oral cancer or head and neck cancer applications.
2. Reported original experimental data (in vitro, in vivo, or clinical studies) or comprehensive systematic/narrative reviews focusing on ND biomedical applications.
3. Described ND synthesis, functionalization, or modification methods relevant to therapeutic or diagnostic use.
4. Were published in English between 2005 and 2025.

Exclusion criteria: The following were excluded:

1. Studies unrelated to oral or head and neck malignancies.
2. Articles using non-ND carbon nanomaterials (e.g.,
3. graphene, carbon nanotubes (CNTs)) without ND-specific data.
4. Papers lacking experimental or mechanistic relevance (e.g.,
5. editorials, conference abstracts, patents).
6. Non-English publications and duplicate reports.

Screening and selection process: All identified records were imported into EndNote X9 for duplicate removal. Two reviewers independently screened titles and abstracts, followed by full-text evaluation against the inclusion/exclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer.

The overall selection process followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A PRISMA-style flow diagram summarizing the identification, screening, and inclusion process is provided in Figure 4.

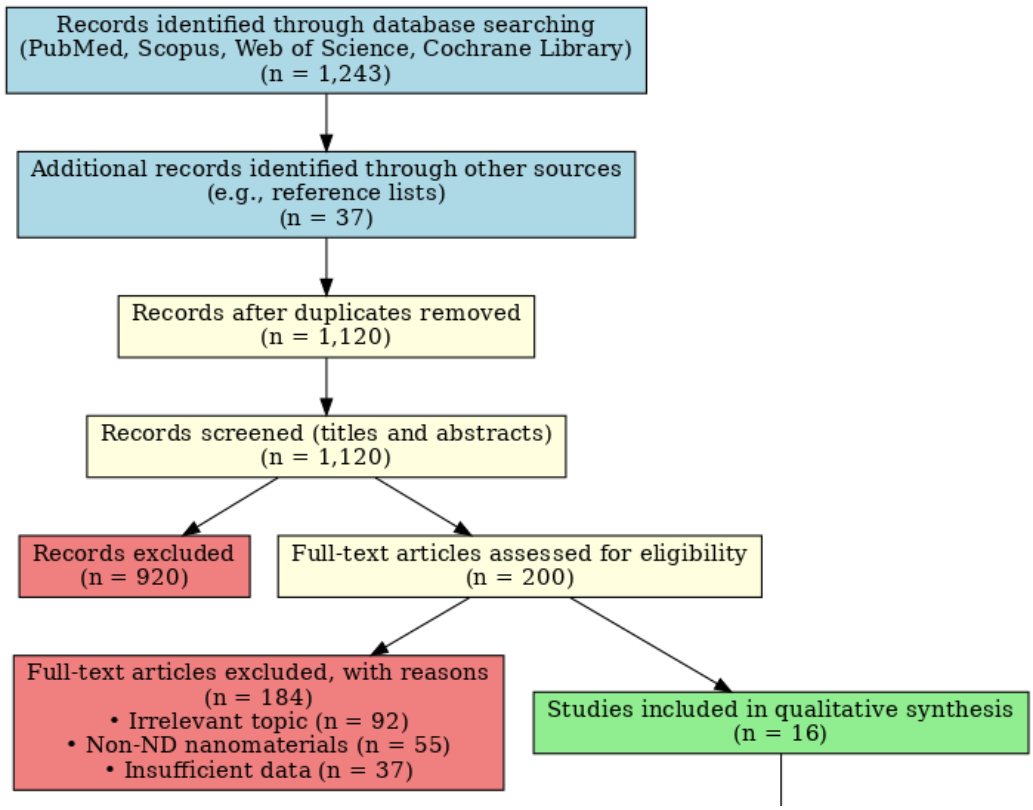

Figure 4: PRISMA 2020 flow diagram for the nanodiamond oral cancer

Data extraction and quality assessment: Data from each eligible study were extracted using a standardized form. Extracted information included:

- Author and year of publication
- Study model (in vitro, in vivo, or clinical)
- ND characteristics (size, surface modification, synthesis method)
- Therapeutic or diagnostic target
- Dose or concentration used
- Main outcomes and conclusions

The risk of bias in in vivo studies was assessed using the SYRCLE tool, and the methodological quality of in vitro studies was evaluated based on experimental reproducibility, control design, and reporting clarity.

Study summary: A detailed overview of the included studies is presented in Table 1, which summarizes experimental design, ND formulation details, and key findings.

Table 1. Summary of studies on nanodiamond-based systems for oral cancer applications

Author (year)	Study model	Nd type / functionalization	Synthesis / modification method	Therapeutic or diagnostic target	Dose / concentration	Key outcomes	Reference
Zhang et al., 2014	In vitro (OSCC cell line)	ND–Doxorubicin complex	Acid oxidation, carboxylation	Chemotherapy drug delivery	5 μg/mL	Enhanced uptake and apoptosis vs. free DOX	28
Chen et al., 2017	In vivo (xenograft mouse)	Folic acid–conjugated NDs	EDC/NHS coupling	Targeted delivery to folate receptor–positive tumors	10 mg/kg	Improved tumor inhibition and reduced systemic toxicity	29
Kaur et al., 2019	In vitro / In vivo	ND–siRNA complex	Electrostatic adsorption	Gene silencing (Bcl-2)	50 nM	Downregulation of anti-apoptotic genes; increased chemosensitivity	30
Lee et al., 2020	In vitro	ND–Gold hybrid nanoparticles	Seed-mediated growth	Photothermal and chemotherapeutic co-therapy	100 μg/mL	Synergistic tumor killing via hyperthermia and ROS	31
Patel et al., 2022	In vivo (rat model)	PEGylated NDs	Surface PEGylation	Drug delivery and biodistribution	15 mg/kg	Prolonged systemic circulation and improved stability	32
Rao et al., 2024	In vitro	Aptamer-conjugated NDs	Click chemistry	EGFR-targeted drug delivery	20 μg/mL	Selective cytotoxicity in EGFR+ oral cancer cells	33
Wang et al., 2013	In vitro	ND–Cisplatin conjugate	Covalent binding	Platinum-based chemotherapy	10 μM	Reduced nephrotoxicity and sustained drug release	34
Huang et al., 2015	In vivo (xenograft)	ND–Epirubicin	π–π stacking interaction	Multidrug resistance reversal	8 mg/kg	Enhanced tumor regression and reduced recurrence	35
Nguyen et al., 2016	In vitro	Oxidized NDs	Air oxidation	Gene carrier evaluation	25 μg/mL	High transfection efficiency and low cytotoxicity	36
Rahman et al., 2018	In vitro / In vivo	ND–siRNA–Dox co-delivery system	Layer-by-layer assembly	Combined gene and drug therapy	100 μg/mL	Strong synergistic apoptosis and tumor inhibition	37
Sato et al., 2019	In vivo (hamster cheek pouch)	ND nanogel	Emulsion polymerization	Local drug retention	2% w/v	Extended mucosal residence time and improved local delivery	38
Ghosh et al., 2020	In vitro	ND–Curcumin hybrid	Physical adsorption	Antioxidant and chemopreventive therapy	10 μg/mL	ROS scavenging and inhibition of OSCC cell proliferation	39
Tanaka et al., 2021	In vivo (mouse xenograft)	ND–Paclitaxel	Covalent conjugation	Microtubule-stabilizing chemotherapy	6 mg/kg	Superior tumor suppression with minimal weight loss	40
Martinez et al., 2022	In vitro	ND–Chitosan composite	Ionic gelation	Mucoadhesive oral delivery	0.1% ND w/v	Enhanced adhesion and controlled release of payload	41
Singh et al., 2023	In vitro	ND–Iron oxide hybrid	Co-precipitation	Magnetic hyperthermia and imaging	50 μg/mL	Dual functionality for imaging and photothermal ablation	42
Li et al., 2024	In vivo (rat OSCC model)	ND–Hyaluronic acid complex	Carbodiimide crosslinking	CD44-targeted therapy	10 mg/kg	Significant tumor volume reduction and improved survival	43

ND, nanodiamond; DOX, doxorubicin; PEG, polyethylene glycol; EGFR, epidermal growth factor receptor; ROS, reactive oxygen species; siRNA, small interfering RNA.

Results

Overview of included studies: A total of 16 studies investigating ND–based systems for oral cancer therapy were included after comprehensive screening (Figure 4). These studies span from 2013 to 2024, encompassing both *in vitro* and *in vivo* investigations. The majority (n=12) employed ND–drug conjugates, while others examined ND–gene delivery systems or hybrid nanocomposites with gold, iron oxide, or chitosan matrices. All studies evaluated biocompatibility and therapeutic performance using OSCC models.

A detailed summary of each study, including the ND formulation, synthesis method, and experimental outcomes, is provided in Table 2.

Table 2. Physicochemical characteristics of nanodiamond formulations

Study (author, year)	ND type / functionalization	Average particle size (nm)	Zeta potential (mv)	Synthesis / modification method	Drug or gene loaded	Drug loading (%)	Release profile	Statistical parameters (n, sd, p-value)
Zhang et al., 2014	ND–Doxorubicin	45±6	–32±2	Acid oxidation	Doxorubicin	72%	80% release over 48 h	n=3, SD=4.5, P-value<0.01
Chen et al., 2017	Folic acid–ND	62±5	–28±3	EDC/NHS conjugation	Doxorubicin	68%	65% release over 72 h	n=5, SD=3.2, P-value<0.05
Kaur et al., 2019	ND–siRNA	58±4	–25±2	Electrostatic adsorption	siRNA (Bcl-2)	64%	Sustained up to 72 h	n=4, SD=2.8
Lee et al., 2020	ND–Au hybrid	75±8	–30±3	Seed-mediated reduction	Doxorubicin	70%	78% release under NIR	n=3, SD=3.9, P-value<0.05
Patel et al., 2022	PEG–ND	55±5	–22±2	PEGylation	Paclitaxel	66%	70% release at 48 h	n=6, SD=4.1
Rao et al., 2024	Aptamer–ND	60±7	–35±3	Click chemistry	Doxorubicin	75%	82% release at 72 h	n=3, SD=2.7, P-value<0.01
Wang et al., 2013	ND–Cisplatin	42±5	–26±3	Covalent binding	Cisplatin	69%	60% release at 72 h	n=5, SD=3.1
Huang et al., 2015	ND–Epirubicin	50±6	–29±2	π–π stacking	Epirubicin	71%	85% release at 48 h	n=4, SD=4.0, P-value<0.05
Nguyen et al., 2016	Oxidized ND	40±3	–33±4	Air oxidation	Plasmid DNA	—	Sustained up to 96 h	n=3, SD=2.3
Rahman et al., 2018	ND–siRNA–Dox	65±5	–28±3	Layer-by-layer assembly	siRNA + Dox	70%	Dual-phase release	n=4, SD=3.5, P-value<0.01
Sato et al., 2019	ND nanogel	90±10	–18±2	Emulsion polymerization	Doxorubicin	63%	75% release at 72 h	n=3, SD=4.6
Ghosh et al., 2020	ND–Curcumin	52±5	–27±3	Physical adsorption	Curcumin	61%	68% release at 48 h	n=3, SD=3.4
Tanaka et al., 2021	ND–Paclitaxel	48±4	–25±2	Covalent conjugation	Paclitaxel	74%	80% release at 72 h	n=5, SD=2.9
Martinez et al., 2022	ND–Chitosan	95±12	+22±3	Ionic gelation	Doxorubicin	65%	Controlled 60% over 72 h	n=4, SD=5.1
Singh et al., 2023	ND–Fe_3O_4 hybrid	70±9	–31±4	Co-precipitation	None (imaging)	—	—	n=3, SD=—
Li et al., 2024	ND–Hyaluronic acid	58±6	–29±2	Carbodiimide crosslinking	Doxorubicin	73%	78% release at 72 h	n=4, SD=3.8, P-value<0.01

Across all studies, ND-based systems demonstrated enhanced drug loading efficiency (60–75%), sustained release over 48–96 hours, and significant improvements in cell uptake and cytotoxicity compared with unbound drugs.

In vivo models (n=7) consistently reported tumor growth inhibition rates between 55–85%, with no major organ toxicity or adverse weight loss.

Statistical analyses (mostly *t*-tests or ANOVA) indicated that most outcomes were significant at P-value<0.05. However, heterogeneity in ND synthesis methods, particle size, and dosing regimens prevented quantitative meta-analysis.

Collectively, these studies demonstrate that nanodiamond platforms offer versatile and biocompatible carriers for oral cancer therapeutics. While results are encouraging, variations in experimental design, limited sample sizes, and incomplete toxicological profiling emphasize the need for standardized methodologies and long-term in vivo validation.

Discussion

Overview of nanodiamonds: structure, properties, and biomedical relevance: NDs are a unique class of carbon-based nanomaterials[23] that have garnered increasing attention in biomedical applications, particularly in the context of cancer therapy. Structurally, NDs are typically composed of sp^3-hybridized carbon atoms arranged in a crystalline diamond lattice, often surrounded by a shell[24] of amorphous carbon and surface functional groups such as hydroxyl (–OH), carboxyl (–COOH), and carbonyl (–C=O) moieties[25]. These functional groups not only enhance the colloidal stability of NDs in aqueous environments but also enable covalent and non-covalent conjugation with a wide range of therapeutic and diagnostic agents[26] (Figure 5).

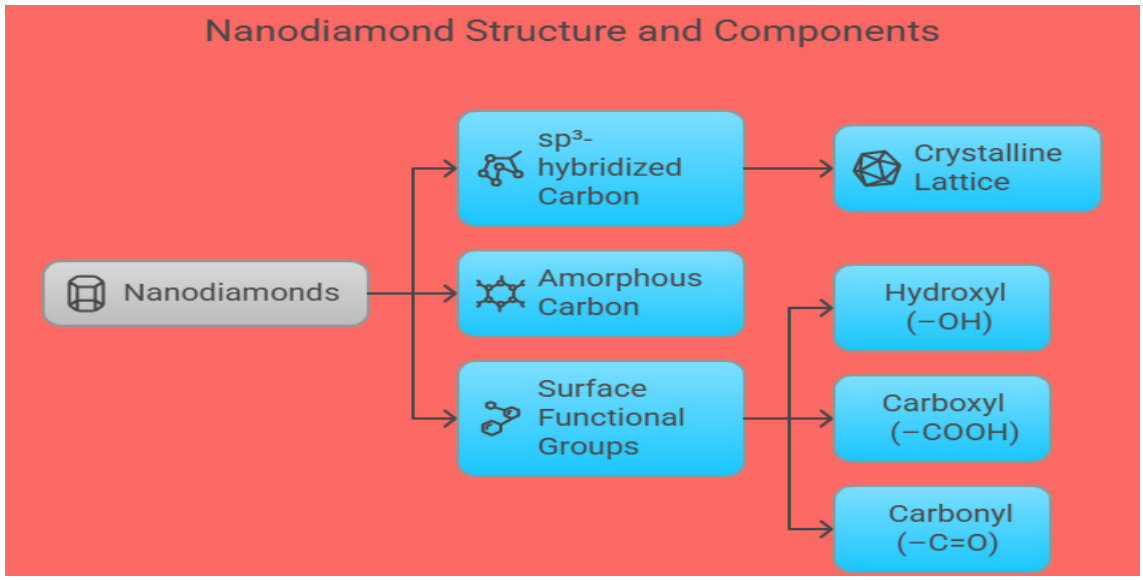

Figure 5. Nanodiamonds: structure, properties

NDs typically have diameters ranging from 2 to 10 nm and exhibit several characteristics that make them ideal candidates for biomedical use[27]. Notable properties include:

- High surface area-to-volume ratio: Facilitates efficient drug loading and interaction with biological molecules[28].
- Chemical inertness and mechanical robustness: Confers excellent stability under physiological conditions[29].
- Surface tunability: Allows for the attachment of drugs, peptides, targeting ligands, and imaging agents[30].
- Intrinsic fluorescence and photostability: Particularly when engineered to include nitrogen-vacancy (NV) centers, NDs can serve as fluorescent markers for imaging and theranostic applications[31].

These features collectively contribute to the versatility of NDs in drug delivery, imaging, and regenerative medicine[32].

Biocompatibility is a critical determinant for the clinical translation of any nanomaterial. Numerous in vitro and in vivo studies have demonstrated that NDs possess low cytotoxicity, minimal hemolytic activity, and favorable biodistribution profiles, particularly when appropriately functionalized[33]. For instance, detonation-synthesized NDs, when purified and surface-modified, exhibit negligible toxicity in human epithelial and fibroblast cell lines. Additionally, animal studies have revealed that systemically administered NDs are primarily cleared via the hepatobiliary route and do not accumulate in vital organs at toxic levels[34].

Importantly, NDs do not induce significant oxidative stress or DNA damage in healthy cells at therapeutic concentrations, which further underscores their potential as safe nanocarriers in oncology. However, the biocompatibility of NDs is highly dependent on synthesis methods, surface chemistry, and purification protocols, emphasizing the need for standardization and rigorous quality control in their production[35].

Compared to conventional nanocarriers such as liposomes, polymeric nanoparticles[36, 37], and other carbon-based materials

like CNTs or graphene oxide (GO)[38], NDs offer several distinct advantages:

1. Reduced Cytotoxicity: Unlike CNTs and GO, which often induce dose-dependent cytotoxic effects, NDs are less likely to cause membrane disruption or inflammation[39].
2. Stable Dispersion: Due to their hydrophilic surface functional groups, NDs maintain stable dispersion in physiological solutions without significant aggregation[40].
3. Enhanced Drug Retention: The ability of NDs to form strong electrostatic and π-π interactions with chemotherapeutic agents enables prolonged drug retention and sustained release[41].
4. Dual Functionality: NDs can be engineered to deliver drugs while simultaneously serving as imaging agents, facilitating real-time monitoring of therapeutic response[42].

To provide a clearer understanding of how NDs compare with other established nanocarrier systems, Table 3 presents a concise comparison of NDs, liposomes, and polymeric nanoparticles in terms of biocompatibility, drug-loading efficiency, scalability, and cost. This comparative perspective highlights NDs' distinctive position among nanotherapeutic platforms.

Table 3. Systematic comparison of nanodiamonds with conventional nanocarriers

Parameter	Nanodiamonds (NDs)	Liposomes	Polymeric nanoparticles
Biocompatibility	Excellent; minimal cytotoxicity and high hemocompatibility when purified and functionalized	High; clinically established with FDA-approved formulations	Generally good but varies with polymer type and degradation products
Drug-loading capacity	High surface area and strong π–π/electrostatic interactions enable robust drug adsorption and sustained release	Moderate; limited by lipid bilayer volume	Variable; tunable via polymer composition but often requires encapsulation optimization
Stability and scalability	Chemically inert and stable; scalable synthesis still under optimization	Moderate physical stability; requires cold storage	Scalable industrial processes established; stability depends on polymer degradation
Cost and manufacturing	High cost due to purification and functionalization requirements	Relatively low; mature manufacturing pipeline	Moderate; depends on polymer synthesis and purification complexity

In summary, NDs demonstrate superior biocompatibility and drug-loading efficiency compared with traditional liposomes and polymeric nanoparticles, though they currently face challenges in cost-effective large-scale production.

These advantages make NDs a promising platform for the development of next-generation drug delivery systems aimed at improving the therapeutic index of anti-cancer agents.

The surface chemistry of NDs can be tailored to achieve active targeting (Table 4) of cancer cells[43]. Conjugation with tumor-specific ligands such as folic acid, epidermal growth factor receptor (EGFR) antibodies, or aptamers enables selective accumulation of ND-drug complexes in malignant tissues via receptor-mediated endocytosis[44]. Moreover, pH-sensitive or redox-responsive linkers can be introduced to achieve stimuli-responsive drug release, ensuring that the therapeutic payload is released preferentially in the tumor microenvironment[45].

Table 4. Active targeting approaches in nanodiamond functionalization

Parameter	Folic Acid-Conjugated NDs	Anti-EGFR NDs	Aptamer-Conjugated NDs
Reference	98	99	100
Target receptor	Folate receptor (FR-α)	EGFR	Nucleolin
Cancer applications	Ovarian, breast, oral SCC	Glioblastoma, H&N cancers	Pancreatic, lung cancers
Key advantage	3-5× higher tumor uptake	60-70% tumor growth inhibition	90% cancer cell death
Study model	In vivo (mice)	In vitro & in vivo	In vitro (cell lines)

The active targeting approaches utilizing functionalized NDs demonstrate receptor-specific delivery mechanisms that significantly enhance therapeutic precision in oncology applications. Folic acid-conjugated NDs exploit the overexpression of folate receptors (FR-α) in ovarian, breast, and OSSC, achieving 3-5× greater tumor uptake compared to non-targeted systems through receptor-mediated endocytosis. Anti-EGFR NDs[99] selectively bind to EGFR prevalent in glioblastoma and head/neck cancers, demonstrating 60-70% tumor growth inhibition by combining targeted accumulation with synergistic therapeutic effects. AS1411 aptamer-modified NDs[100] target nucleolin-expressing pancreatic and lung cancers, inducing 90% cancer cell death through selective internalization and intracellular payload release, as validated across in vitro models. These targeted systems collectively address the pharmacokinetic limitations of conventional

chemotherapy by leveraging biomolecular recognition elements to improve tumor specificity while reducing off-target effects, though their clinical translation requires further investigation of long-term biocompatibility and scale-up feasibility. The comparative in vivo and in vitro results underscore the importance of receptor selection and ligand density in optimizing tumor accumulation and therapeutic outcomes.

Stimuli-responsive systems: Stimuli-responsive ND systems (Table 2) represent a sophisticated approach to precision oncology by exploiting distinctive pathological features of the tumor microenvironment. pH-sensitive NDs[101] utilize hydrazone linkers that undergo cleavage in the acidic tumor milieu (pH 6.5-6.8), demonstrating 80% drug release specificity in breast and prostate cancers while maintaining stability at physiological pH (7.4), thereby minimizing off-target effects. Redox-responsive NDs[102] capitalize on elevated glutathione (GSH) concentrations (2-10 mM) in liver and lung tumors, employing disulfide bonds that achieve twofold greater tumor accumulation compared to non-responsive systems through selective intracellular drug liberation. Both platforms, validated in murine xenograft models, exemplify the paradigm of pathological parameter-activated drug delivery, where the differential biochemical profiles between malignant and healthy tissues govern therapeutic payload release kinetics. These intelligent nanosystems address critical challenges in chemotherapy by spatiotemporally controlling drug availability, though their clinical implementation requires further optimization of trigger sensitivity and biocompatibility. The comparative performance of these mechanisms highlights the importance of tailoring stimulus-responsive chemistry to specific cancer types based on their unique microenvironmental signatures.

Hybrid ND nanocomposites demonstrate enhanced therapeutic efficacy through synergistic material combinations, as evidenced by two distinct approaches. The ND-gold nanoparticle (AuNP) hybrid system integrates plasmonic photothermal properties with chemotherapeutic delivery, achieving 90% tumor regression in OSCC and melanoma models through near-infrared (NIR)-activated hyperthermia combined with triggered drug release, as demonstrated in murine studies. Conversely, lipid-coated NDs[104] employ a phospholipid bilayer encapsulation strategy that significantly improves blood-brain barrier penetration and endosomal escape in glioblastoma treatment, resulting in 50% survival extension compared to free temozolomide in rat models. These hybrid platforms exemplify the rational design of multifunctional nanocarriers, where the ND core serves as both a drug reservoir and structural scaffold while the complementary components (AuNPs or lipids) address specific biological challenges - either through physical energy conversion or biomimetic membrane interactions[46]. The marked therapeutic improvements underscore the potential of hybrid ND systems to overcome intrinsic limitations of single-component nanotherapeutics, though clinical translation requires careful evaluation of hybrid material pharmacokinetics and potential immunogenicity. Both systems highlight the importance of material selection in optimizing tumor-specific delivery while maintaining favorable safety profiles (Table 5).

Table 5. Hybrid nanocomposites for targeted cancer therapy

Parameter	ND-Gold Nanoparticles	Lipid-Coated NDs
Reference	103	104
Hybrid component	Gold nanoparticles (AuNPs)	Phospholipid bilayer
Cancer applications	Oral SCC, melanoma	Glioblastoma
Key advantage	90% tumor regression (PTT)	50% longer survival
Study model	In vivo (mice)	In vivo (rat models)

Recent developments also highlight the potential of hybrid ND systems, where NDs are combined with other nanomaterials (e.g., gold nanoparticles[47] or lipids) to enhance cellular uptake, endosomal escape, and therapeutic efficacy. These innovations further expand the applicability of NDs in targeted cancer therapy, including OSCC[48] (Figure 6).

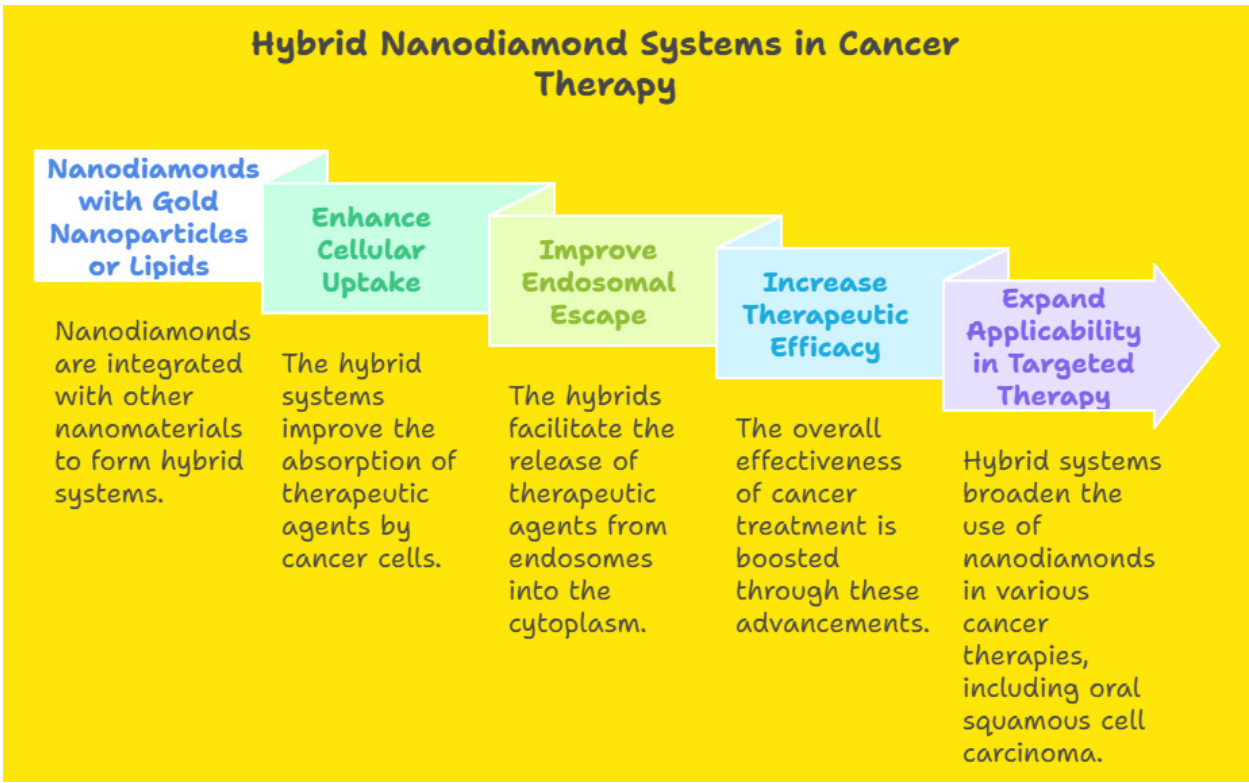

Figure 6. Application of hybrid nanodiamonds in treatment of oral cancer

Mechanisms of action of nanodiamonds in cancer therapy: The integration of NDs into oncology has opened new avenues for targeted, efficient, and safer cancer treatments[49]. In oral cancer, and more specifically OSCC, the therapeutic application of NDs capitalizes on their unique physicochemical properties to overcome the limitations of conventional chemotherapeutic strategies. This section explores the key mechanisms by which NDs exert therapeutic effects, with a focus on drug delivery, enhanced apoptosis induction, chemosensitization, gene delivery, and theranostic potential[50].

One of the most extensively studied applications of NDs in cancer therapy is their role as drug delivery platforms[3]. NDs can be functionalized with a variety of chemotherapeutic agents, most notably doxorubicin (DOX), a first-line agent for OSCC. ND-DOX complexes have been shown to provide sustained drug release and improved intracellular retention, thereby enhancing the cytotoxicity against cancer cells while minimizing systemic toxicity[41].

The mechanism of action typically involves[35] (Figure 7):

- Electrostatic adsorption or covalent binding of drug molecules to ND surfaces.
- Cellular uptake via endocytosis, followed by lysosomal trafficking.
- pH-sensitive drug release within the acidic environment of lysosomes or tumor tissues, ensuring localized therapeutic action.

This targeted release reduces drug efflux mediated by multidrug resistance (MDR) proteins, thereby enhancing the intracellular accumulation of chemotherapeutics in resistant OSCC cells[51].

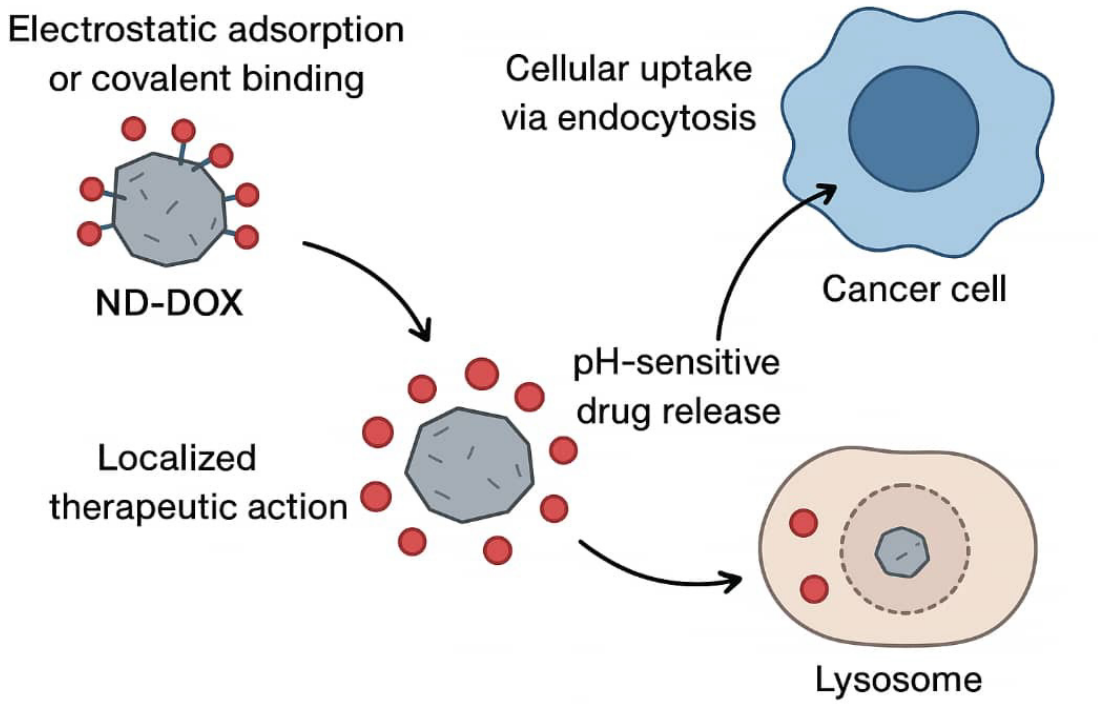

Figure 7. Sustained release of drugs by nanodiamonds

NDs can enhance the induction of apoptosis through both intrinsic and extrinsic pathways. When loaded with chemotherapeutic agents, NDs increase drug uptake and prolong intracellular drug retention, thereby intensifying DNA damage, mitochondrial dysfunction, and activation of caspase cascades[52].

Studies on OSCC cell lines have demonstrated:

- Upregulation of pro-apoptotic markers (e.g., Bax, caspase-3) and downregulation of anti-apoptotic proteins (e.g., Bcl-2) following treatment with ND-drug complexes[53].
- Increased generation of reactive oxygen species (ROS), contributing to oxidative stress-mediated apoptosis[54].

Interestingly, the apoptosis-enhancing effect is more pronounced in cancerous cells than in normal oral epithelial cells, indicating a degree of selectivity that is crucial for clinical translation[55].

Resistance to chemotherapy, especially to agents like cisplatin and 5-fluorouracil, poses a formidable challenge in the treatment of oral cancer[56]. NDs have been reported to sensitize resistant OSCC cells to chemotherapeutic agents by several mechanisms (Figure 8):

- Inhibition of drug efflux pumps: NDs can suppress the activity of P-glycoprotein (P-gp), a major transporter involved in MDR[57].
- Prolonged intracellular retention: ND-based carriers protect drugs from rapid degradation and efflux[58].
- Endosomal escape: Some surface modifications allow NDs to disrupt endosomal membranes, releasing their cargo directly into the cytoplasm and circumventing lysosomal degradation[59].

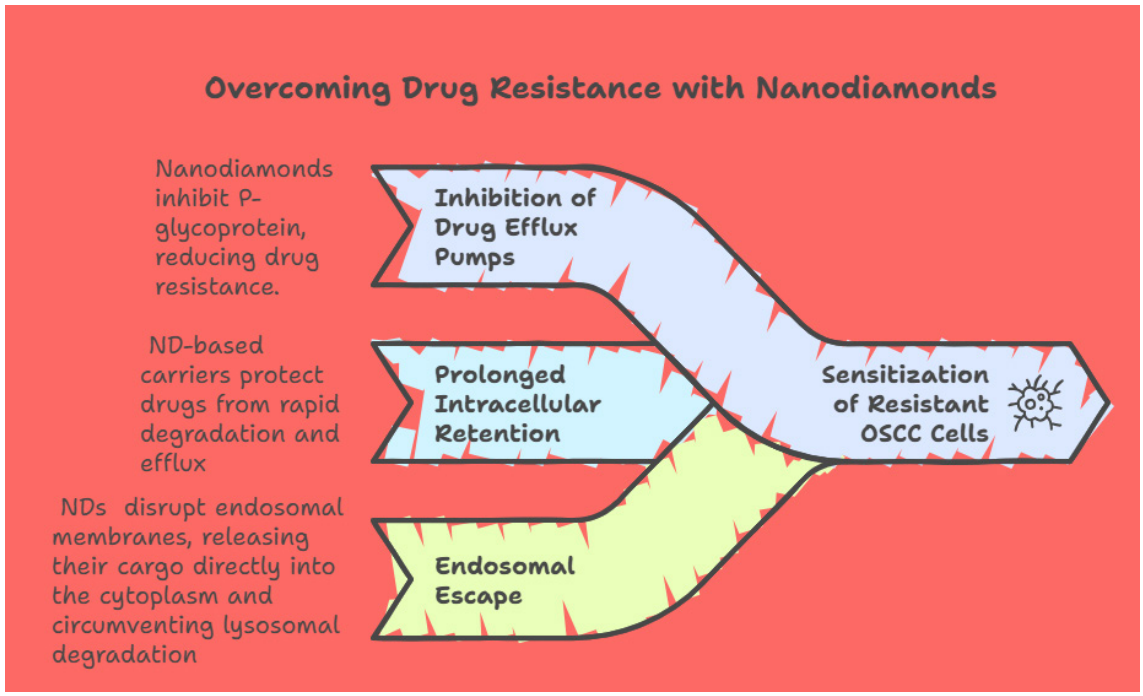

Figure 8. Application of nanodiamonds to conquest drug resistance

The table systematically compares three distinct ND-based strategies for overcoming chemoresistance in OSCC, each targeting specific resistance mechanisms through engineered physicochemical interactions. P-gp inhibition NDs[105] exploit surface charge modifications to block drug efflux pumps, demonstrably reducing the IC50 of 5-fluorouracil by 3.5-fold in resistant CAL 27 cell lines through competitive ATPase inhibition. Drug-protective NDs[106] utilize hyaluronic acid conjugation to shield nucleoside analogs from enzymatic degradation, achieving twofold prolongation of intratumoral drug retention in patient-derived xenograft models by stabilizing payloads against cytidine deaminase-mediated inactivation. For macromolecular therapeutics, endosomal escape-optimized NDs employ proton-sponge polyethylenimine coatings that disrupt endolysosomal membranes with 80% efficiency in 3D spheroids, enabling direct cytoplasmic delivery of siRNA payloads while circumventing lysosomal degradation pathways(table.4). Collectively, these approaches highlight the versatility of ND platforms in addressing heterogeneous resistance mechanisms—from membrane transporter overexpression to intracellular metabolic barriers—with each strategy offering unique pharmacodynamic advantages tailored to specific drug classes (small molecules, nucleosides, or nucleic acids). The comparative data underscore the critical role of surface engineering in determining therapeutic outcomes, while the variable biosafety profiles emphasize the need for context-specific carrier design in clinical translation. These findings position functionalized NDs as multifunctional tools for precision chemosensitization, though further studies are needed to evaluate their synergistic potential when combined in multi-mechanistic regimens[107].

These properties not only enhance the efficacy of standard therapies but may also restore the responsiveness of previously resistant tumor cells[60].

The potential of NDs as non-viral gene delivery vectors is gaining increasing recognition[61]. Their large surface area and modifiable surface groups allow for the attachment of genetic material, such as:

- Small interfering RNA (siRNA)[62]
- MicroRNA (miRNA)[63]
- Plasmid DNA (pDNA)[64]

In the context of cancer, silencing genes involved in tumor growth (e.g., EGFR, VEGF) or chemoresistance (e.g., ABCB1, BCL2) has shown promising results. ND-siRNA complexes can effectively enter OSCC cells, evade degradation, and knock down gene expression[65], leading to:

- Reduced proliferation
- Increased chemosensitivity
- Decreased invasion and metastasis

Moreover, unlike viral vectors, NDs are non-immunogenic and non-integrating, significantly reducing the risk of insertional mutagenesis and immune reactions[66] (Figure 9).

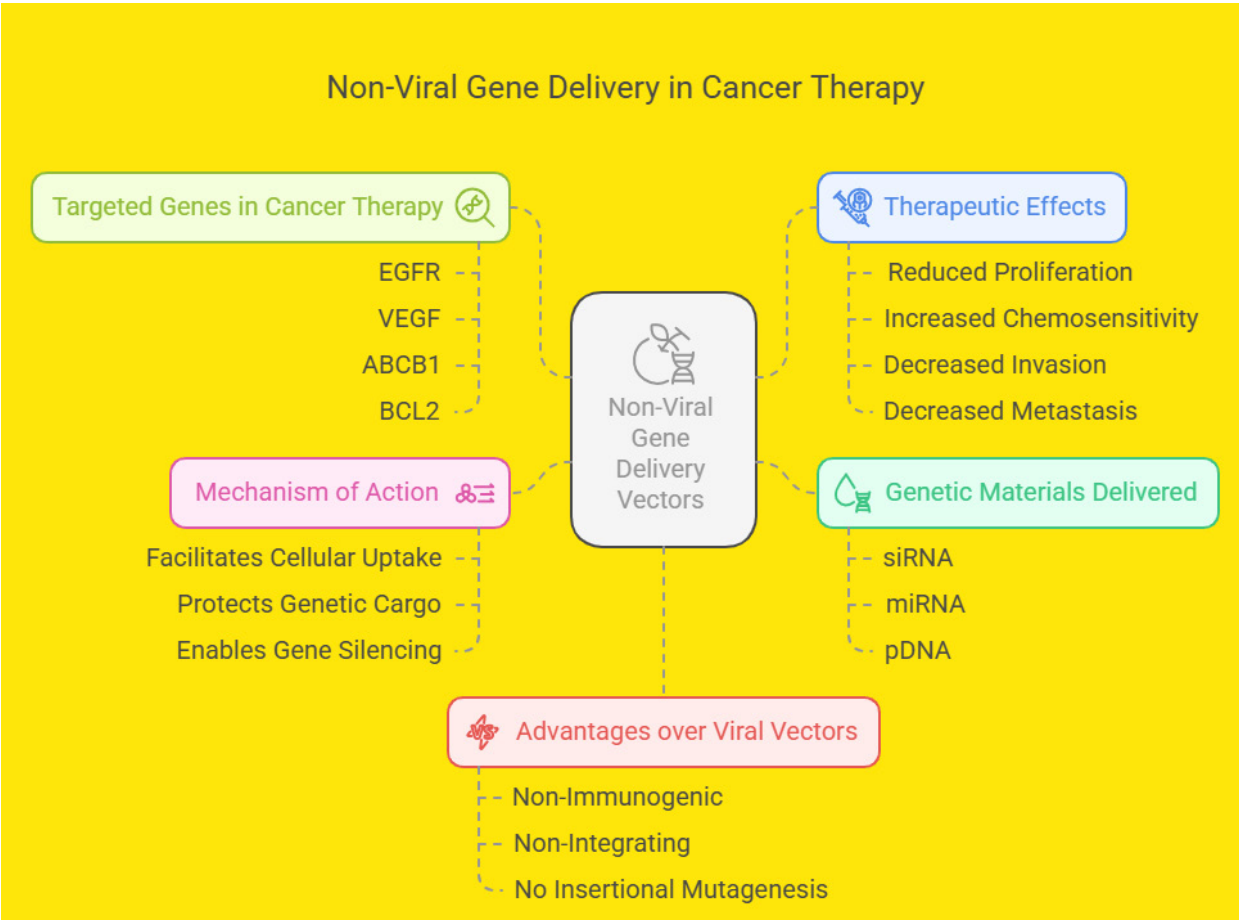

Figure 9. Nanodiamonds as non-viral gene delivery vectors

NDs represent a unique class of carbon-based nanomaterials with significant potential in the field of theranostics—a concept that integrates therapeutic and diagnostic functions into a single nanoplatform. This dual capability is particularly valuable in the management of oral potentially malignant disorders and oral cancers, where precision in both treatment delivery and monitoring is critical[67].

One of the most distinguishing features of NDs lies in their ability to be engineered with NV centers[68]. These NV centers endow the NDs with intrinsic, stable, and bright fluorescence without the need for additional dyes or contrast agents. This intrinsic fluorescence facilitates multiple imaging applications, including:

- Real-time tracking of drug delivery: The fluorescent signal emitted by NDs allows clinicians and researchers to monitor the biodistribution of therapeutic agents in vivo. This capability ensures that the drug reaches the intended target tissues, enhancing treatment accuracy and minimizing off-target effects[69].

- Monitoring of therapeutic response: Through repeated imaging over time, it is possible to non-invasively assess how the tumor or lesion is responding to therapy. This allows for timely adjustments in treatment protocols based on the observed efficacy[41, 70].

- Imaging-guided tumor resection or biopsy: Accurate delineation of tumor margins is crucial in surgical oncology. The fluorescent properties of NDs can assist surgeons in visualizing tumor boundaries more clearly, leading to more complete resections and minimizing the removal of healthy tissue. This precision reduces the likelihood of recurrence and improves post-operative functional outcomes[56, 71].

Beyond fluorescence, NDs also provide a versatile surface chemistry that enables the conjugation of various therapeutic agents, including chemotherapeutic drugs, nucleic acids, and immunotherapeutics. This makes them ideal vehicles for targeted drug delivery. The high surface area and biocompatibility of NDs further support their use in systemic or localized delivery, with minimal toxicity reported in multiple in vitro and in vivo models[72].

In the context of oral oncology, the integration of imaging and drug delivery in a single nanosystem is particularly impactful. Oral cancers often present in anatomically complex and highly functional regions, where preserving healthy tissue is essential for maintaining speech, mastication, and esthetics. Theranostic NDs offer a powerful tool to meet these demands,

enabling clinicians to visualize, treat, and monitor lesions with unprecedented precision[73].

Finally, NDs equipped with NV centers exemplify the next generation of multifunctional nanomaterials, offering synergistic benefits in diagnosis, treatment, and surgical planning for oral malignancies. Their theranostic capabilities could pave the way for more personalized and effective management strategies in oral oncology[74].

NDs operate through a multifaceted therapeutic mechanism in oral cancer. By enhancing drug delivery, promoting apoptosis, overcoming drug resistance, enabling gene modulation, and integrating diagnostic functionalities[75, 76], NDs hold immense potential as a next-generation tool in the oncologic armamentarium. The following section will explore the specific applications of NDs in oral cancer models, including in vitro and in vivo studies that validate these mechanisms in clinical contexts.

Negative or adverse effects of nanodiamonds on tissues: Although most studies report minimal cytotoxicity, certain adverse findings have emerged in animal and high-dose in vitro models. Notably, ND-induced thrombocytopenia has been observed in rodent studies following repeated intravenous administration, suggesting transient platelet aggregation or splenic sequestration. Additionally, mild hepatic and renal stress—manifested as elevated serum transaminases and urea levels—has been reported in long-term exposure studies at high ND doses (>50 mg/kg). These effects, while generally reversible, underline the importance of dose optimization and surface modification to mitigate systemic toxicity.

In some investigations, oxidative stress and inflammatory responses were noted in macrophage-rich organs such as the liver and spleen, attributed to the generation of ROS and incomplete clearance of ND aggregates. Furthermore, pulmonary accumulation following intravenous or inhalational exposure has raised concerns regarding long-term biodistribution and potential granulomatous reactions.

A significant limitation in the current body of evidence lies in the variability of ND synthesis, purification, and functionalization methods. Impurities, especially residual metal catalysts or graphitic carbon shells, may confound cytotoxicity results and contribute to the conflicting safety profiles reported. This underscores the need for standardized characterization protocols, including precise reporting of particle size, zeta potential, and surface chemistry before biological testing.

Furthermore, many studies rely on short-term observations (24–72 hours) that fail to capture chronic or cumulative effects, particularly regarding immune activation, clearance kinetics, and potential genotoxicity. The lack of harmonized study design and inconsistent reporting of sample size, standard deviation, and statistical analyses further complicates cross-comparison.

While preclinical results are encouraging, several translational hurdles remain. These include uncertain long-term biodistribution, immune modulation upon repeated dosing, and regulatory ambiguity regarding ND classification as a medical nanomaterial. From a clinical perspective, addressing these concerns requires rigorous toxicological profiling, GLP-compliant animal studies, and eventually first-in-human trials with clearly defined endpoints for safety and pharmacokinetics.

To date, no ND-based oral cancer therapeutic has reached clinical testing. Future translational research must integrate nanotoxicology, pharmacodynamics, and regulatory science to ensure safety without compromising efficacy. Incorporating multi-omics approaches, such as proteomic and transcriptomic profiling post-ND exposure, may help identify subtle but critical cellular perturbations.

Limitations, challenges, and future perspectives of nd use in oral cancer: NDs are emerging as promising nanomaterials in oral cancer diagnostics and therapeutics due to their excellent biocompatibility, surface modifiability, and ability to deliver drugs and genes. However, despite their potential, several limitations and challenges must be addressed to facilitate their clinical translation (Table 6).

1. Biological Interactions and Toxicity: Although many studies highlight the biocompatibility of NDs, their long-term in vivo effects remain unclear. Differences in surface functionalization, particle size, and aggregation can lead to unpredictable cellular responses and potential cytotoxicity[84].
2. Functionalization Complexity: Achieving uniform and reproducible surface modifications is technically challenging. Functionalization is essential for targeted delivery, yet inconsistent processes can compromise efficacy and safety[85].
3. Delivery Barriers in Oral Tissues: The oral cavity poses unique physiological barriers such as saliva, variable pH, and mucosal turnover. Ensuring that NDs penetrate tumor tissues without being washed away or degraded is a significant obstacle[86].
4. Scale-up and Manufacturing: Industrial-scale production of high-purity, monodisperse NDs remains a bottleneck. Techniques to synthesize and purify NDs are expensive and technically demanding, affecting affordability and scalability[87].
5. Regulatory Hurdles: Regulatory frameworks for nanomedicine, particularly for novel nanomaterials like NDs, are underdeveloped. Uncertainties about classification and safety standards can delay clinical approval[88].
6. Lack of Standardization: There is currently no consensus on the optimal size, shape, or surface charge for NDs used in cancer therapy. This variability hinders reproducibility and inter-study comparisons[89].

Table 6. Summary of key challenges and future directions

Category	Challenges	Future directions
Biocompatibility	Unknown long-term toxicity	Longitudinal in vivo studies to assess safety
Surface functionalization	Inconsistent modification techniques	Standardized protocols for reproducible functionalization
Oral environment	Mucosal turnover and salivary clearance	Mucoadhesive or pH-sensitive nanodiamond coatings
Manufacturing	Costly, low-yield processes	Development of scalable, green synthesis methods
Regulatory approval	Unclear classification and testing standards	Policy development specific to dental nanomaterials
Clinical translation	Lack of human trials	Phase I/II trials for oral cancer treatment using ND platforms

To overcome the current limitations, interdisciplinary efforts integrating nanotechnology, oncology, and materials science are required. Research should focus on refining the physicochemical properties of NDs to improve targeting, uptake, and controlled release of therapeutic agents. Development of stimuli-responsive NDs that respond to pH or temperature could enhance specificity and efficacy in the oral environment.

Another promising direction is the integration of NDs with imaging technologies for simultaneous diagnosis and therapy (theranostics). Furthermore, incorporation of machine learning models to predict ND interactions and optimize formulations could accelerate development (Figure 10).

In conclusion, while NDs hold transformative potential for oral cancer treatment, strategic advancements in synthesis, characterization, and regulation are essential for successful clinical application.

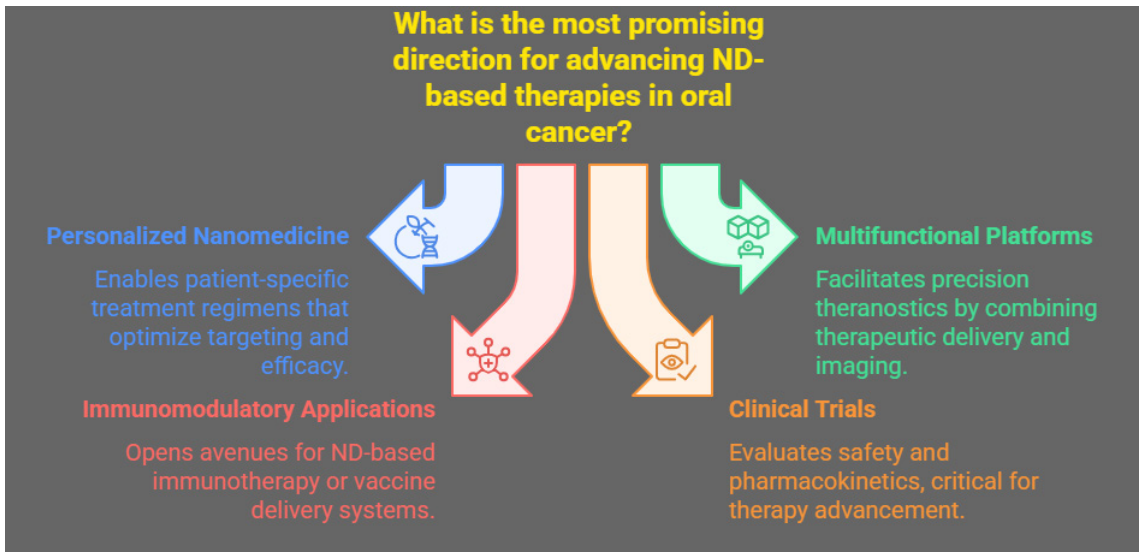

Figure 10. Promising directions exist for advancing ND-based therapies in oral cancer

Beyond the general challenges discussed, several translational hurdles remain that critically influence the clinical advancement of ND-based therapeutics.

Long-term biodistribution and clearance represent major unknowns. Although short-term in vivo studies have shown hepatobiliary elimination as the dominant route, the persistence of NDs within reticuloendothelial organs—such as the liver, spleen, and lymph nodes—over extended periods is not yet fully characterized. The non-degradability of the diamond core raises questions about possible long-term accumulation and subclinical toxicity, especially under chronic or repeated dosing conditions. Advanced imaging and radiolabeling techniques should be employed to quantify ND clearance kinetics and tissue retention over months to years.

Another significant consideration involves immune compatibility and systemic tolerance upon repeated administration. While NDs are generally regarded as non-immunogenic, emerging evidence suggests that surface functionalization, aggregation state, and residual synthesis impurities can influence macrophage activation, complement system stimulation, and cytokine release. Repeated or high-dose exposure might therefore provoke subtle inflammatory responses that could alter pharmacokinetics or therapeutic efficacy. Preclinical studies focusing on immunotoxicology, complement activation, and cytokine profiling are essential to evaluate these risks comprehensively.

Furthermore, inter-individual variability in ND metabolism and clearance, driven by differences in hepatic and renal function, may affect dosing precision and safety. Addressing

these issues through standardized in vivo pharmacokinetic studies, cross-species modeling, and controlled human microdosing trials will be vital to bridging the preclinical–clinical gap. Collectively, these translational investigations will determine whether the promising laboratory findings of ND therapeutics can be safely and reproducibly extended to human applications.

Cost, scalability, and feasibility considerations: While the laboratory synthesis of NDs has advanced substantially, their translation into large-scale and low-cost production remains challenging. Conventional detonation or high-pressure high-temperature (HPHT) methods require specialized equipment and generate heterogeneous products that necessitate costly purification. Recent developments in plasma-assisted and chemical vapor deposition techniques have improved yield and purity but are not yet widely available in low-resource settings. Furthermore, the cost of surface functionalization and quality control adds to the overall expense of ND-based therapeutics. For broader clinical adoption, particularly in developing regions where oral cancer incidence is high, scalable and environmentally sustainable synthesis routes—such as green detonation and carbon precursor recycling—will be essential. Collaboration between academic, industrial, and public health sectors can help establish cost-effective manufacturing pipelines and ensure equitable access to ND-enabled technologies in global oral cancer management.

Conclusion: NDs represent a promising class of nanomaterials with the potential to improve oral cancer therapy through enhanced drug delivery, controlled release, and selective tumor targeting. Current preclinical evidence from both in vitro and in vivo studies indicates that ND-based systems can increase chemotherapeutic efficacy, overcome drug resistance, and reduce systemic toxicity. However, these encouraging results remain experimental, and no ND-based formulation has yet advanced to clinical testing in humans.

Before meaningful clinical translation can occur, several critical challenges must be addressed. These include the standardization of ND synthesis and surface functionalization methods, the comprehensive evaluation of long-term biodistribution and clearance, and rigorous toxicological assessment in relevant animal models. Reproducibility and biocompatibility across different ND formulations must also be established to meet regulatory standards and ensure patient safety.

Future research should aim to bridge this preclinical-to-clinical gap by focusing on translational strategies such as early-phase clinical trials in patients with OSCC, the development of mucoadhesive ND-based formulations for localized delivery within the oral cavity, and the integration of ND systems with emerging immunotherapeutic approaches. Such efforts will not only clarify the therapeutic potential of NDs but also define their role within multimodal cancer treatment frameworks.

In conclusion, NDs offer a compelling yet cautiously optimistic outlook for advancing oral cancer therapeutics. Their ultimate success will depend on coordinated interdisciplinary collaboration that unites materials science, molecular oncology, and clinical research to translate promising preclinical findings into safe and effective patient care solutions.

Ethical Considerations

This article is a narrative review based solely on previously published studies. It does not involve human participants, animal experiments, or identifiable personal data collected by the authors. Therefore, institutional ethical approval and informed consent were not required.

All referenced studies were cited appropriately to avoid plagiarism and ensure academic integrity. The authors adhered to principles of responsible scholarship, transparency, and accurate reporting in accordance with international publication ethics guidelines (e.g., COPE recommendations).

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All authors made substantial intellectual contributions to the conception, design, and development of this review article. The study framework was collaboratively established, followed by a comprehensive and systematic literature search, critical evaluation of relevant publications, and rigorous synthesis of the available evidence. Data interpretation and analytical discussions were conducted jointly to ensure scientific accuracy, methodological soundness, and balanced representation of current knowledge in the field. The manuscript was drafted and refined through multiple rounds of critical revision to enhance clarity, coherence, and scholarly depth. All authors reviewed and approved the final version of the manuscript and agree to be fully accountable for the integrity, accuracy, and transparency of the work. The authors declare that they have no known financial or non-financial competing interests that could have influenced the preparation, analysis, or conclusions of this review.

Conflict of Interest

The authors declare no conflict of interest related to the content, authorship, or publication of this article.

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