Innovations

Tiny Warriors - Nanoparticle-Based Therapies for Oral Cancer: A Comprehensive Review of Literature

[1]Dr. T. Dinesh Kumar (MDS),[2]Dr. R. Vijayakumar (Ph.D.),
[3]Dr. M. Rekha (MDS, DNB, MNAMS)
[3]Orcid ID: orcid.org/0000-0002-4306-5707

Corresponding Author: Dr. T. Dinesh Kumar

Structured Abstract:

Introduction: *Oral cancer poses a significant global health burden, necessitating innovative therapeutic approaches. Nanoparticle-based therapies offer promising avenues for enhancing treatment efficacy and minimizing adverse effects. This review examines recent advancements in nanoparticle-based treatments for oral cancer, emphasizing their transformative potential in improving patient outcomes.* ***Settings and Design:*** *A comprehensive review of current literature and clinical studies on nanoparticle-based therapies for oral cancer was conducted.* ***Methods and Material:*** *Relevant articles were identified from peer-reviewed journals using PubMed, Scopus, and Web of Science databases. The selection criteria focused on studies published within the last decade, highlighting clinical trials, preclinical studies, and innovative nanoparticle formulations.* ***Results:*** *The advancements in nanoparticle technology have demonstrated improved targeting of cancer cells, enhanced drug delivery, and reduced systemic toxicity. Clinical trials indicate promising outcomes in tumor regression, reduced recurrence rates, and improved patient survival.* ***Conclusions:*** *Nanoparticle-based therapies represent a transformative approach to treating oral cancer. Continued research and clinical trials are essential to integrate these therapies into standard clinical practice fully.*

Keywords: *Oral cancer, Nanoparticle-based therapy, Drug delivery, tumor targeting, Clinical trials, Nanomedicine, Therapeutic advances.*

Introduction

Oral cancer remains a prevalent and challenging malignancy worldwide, with high morbidity and mortality rates often attributed to late diagnosis and the aggressive nature of the disease. Traditional treatment modalities, including surgery, chemotherapy, and radiation therapy, are usually accompanied by substantial side effects and may not always achieve desired outcomes. The development of nanoparticle-based therapies has opened new avenues for

targeted drug delivery, potentially enhancing treatment efficacy while minimizing adverse effects.

Nanoparticles, defined as particles with at least one dimension less than 100 nanometers, can be engineered to carry therapeutic agents specifically to cancer cells. This targeted delivery approach improves the bioavailability and stability of drugs and reduces systemic toxicity by sparing healthy tissues. This review aims to provide a comprehensive overview of the various types of nanoparticles used in oral cancer therapy, their mechanisms of action, clinical applications, safety considerations, and prospects.

Methodology

Relevant articles were identified from PubMed, Scopus, and Web of Science databases, focusing on studies published in the last decade related to nanoparticle-based therapies for oral cancer. The inclusion criteria prioritized studies that discussed practical applications and innovative techniques. In contrast, exclusion criteria eliminated non-peer-reviewed articles, those lacking empirical evidence, or those unrelated to oral cancer treatment. Data extraction involved gathering key information such as methodology, significant findings, and limitations. A total of 84 references were included, each subjected to a quality assessment considering sample size, study design, and statistical analysis. The extracted data were synthesized to form a narrative aligned with the review's aims, emphasizing practical applications, innovative techniques, future directions, and potential policy implications, ensuring a comprehensive and rigorous review.

Generations of Nanotechnology

Nanotechnology, operating at 1-100 nm, allows for the exploitation of unique properties. It can be classified into six generations:

1. First Generation (N1): Passive Nanostructures - Molecular-level structures are controlled without dynamic properties, including aerosols, carbon nanotubes, nanoparticles, nanoclay platelets, and colloidal polymers.
2. Second Generation (N2): Active Nanostructures - These structures respond to external stimuli, such as pH or temperature, altering composition or behavior, including nanomedicines and bioactive agents.
3. Third Generation (N3): Integrated Nanosystems - These involve networking of nano-machines and molecules, such as 3D structures and nanobots.
4. Fourth Generation (N4): Heterogeneous Molecular Nanosystems - Achieving multi-functionality at the molecular level, applications include molecular devices and nanosystem biology for healthcare.

5. Fifth Generation (N5): Nano-Bio-Info-Cogno (NBIC) Platforms - These integrate nanotechnology with information technology, biotechnology, and cognitive science for healthcare.
6. Sixth Generation (N6): Nanosystem Convergence Networks - Involves interconnected nanosystem networks across domains, for health, production, infrastructure, and services.

Types of Nanoparticles and Their Applications

1. **Organic Nanoparticles (NPs)**

Lipid-Based Nanoparticles

Lipid-based nanoparticles (Thi, T et al, 2021), including liposomes(Torchilin, V, 2005)and solid lipid nanoparticles (SLNs), are biocompatible carriers enhancing drug solubility, stability, and bioavailability for oral cancer therapy. Liposomes encapsulate drugs like doxorubicin and cisplatin, improving delivery and reducing toxicity(Nekkanti et al, 2015). SLNs provide a stable matrix for controlled drug release.

Polymer-Based Nanoparticles

Polymer-based nanoparticlessuch as PLGA (Danhier, F et al, 2015), and chitosan(Sangnim, T et al, 2023), provide controlled drug release, targeting, and enhanced therapeutic efficacy. PLGA nanoparticles are biodegradable, releasing drugs at specific rates(Zielińska, A.et al, 2020), while chitosan's mucoadhesive properties improve drug retention at tumor sites. These nanoparticles enhance drug bioavailability and offer potential in oral cancer prevention, diagnosis, and treatment. However, challenges such as degradation, targeting inefficiencies, and potential toxicity remain (Alvi M et al, 2022). Despite their promise in advancing oral cancer therapy, further research is essential to fully address these challenges and realize their clinical potential (Zhang, G. M, et al, 2022).

Dendrimers:

Dendrimers, highly branched structures with a large surface area, can carry multiple drugs and target specific tissues, making them ideal for delivering chemotherapeutic agents and genetic material in oral cancer(Xiong, Z et al,2018;Jiang, L, et al 2018).

Micelles:

With their core-shell structure, micelles enhance solubility and prolong drug circulation, effectively targeting cancer cells with drugs like salinomycin and methotrexate(Keskin, D et al, 2017; Zhu, Met al, 2017).

Hydrogels:

Hydrogels, hydrophilic polymer networks, adhere to mucosal surfaces and release drugs in response to stimuli, offering localized cancer treatment with reduced side effects by delivering drugs like paclitaxel or DOX directly to tumor sites(Giri et al, 2012).

2. **Inorganic Nanoparticles (NPs)**

Metal-Based Nanoparticles

Inorganic Nanoparticles (NPs) are pivotal in oral cancer therapy, harnessing unique optical, electronic, and chemical properties of metal-based nanoparticles, including gold(Zhang, Q et al, 2022), and silver nanoparticles, utilized for their therapeutic potentials(Wang, Y et al, 2024). Metal nanoparticles (MNPs) enhance the therapeutic index of drugs through targeted delivery and multidrug resistance prevention, finding applications in vivo(Xu, J. et al, 2022) and in vitro diagnostics, biocompatible materials development, and nutraceutical production(Sengani, M et al,2017;Alalaiwe, A. 2019). Eco-friendly green synthesis of MNPs(Noruzi, M et al,2011) is an emerging trend in bionanotechnology.Heidari A, et al. (2024) highlighted that metal NPs, such as gold, silver, and iron oxide, possess intrinsic anticancer properties useful in targeting tumors.

Gold Nanoparticles (AuNPs): Gold Nanoparticles (AuNPs) leverage surface plasmon resonance for imaging, photothermal therapy (PTT), and drug delivery(Fadel, M., & El-Kholy, A. I. 2024). Vines JB et al. (2019) showcased their application in targeted photothermal therapy for oral cancer, emphasizing their precision and minimal systemic side effects.

Silver Nanoparticles (AgNPs): Silver Nanoparticles (AgNPs) induce apoptosis in cancer cells due to their ability to generate reactive oxygen species (Dziedzic, A et al, 2016;Yakop, F et al, 2018).

Iron Oxide Nanoparticles (FeNPs): These are used for magnetic targeting and hyperthermia therapy due to their superparamagnetic properties, enhancing the delivery of chemotherapeutic agents and serving as MRI contrast agents(Yang, X et al, 2011).

Calcium Phosphate Nanoparticles (CaPNPs): Calcium Phosphate Nanoparticles (CaPNPs), composed of biodegradable calcium phosphate, facilitate targeted drug delivery while minimizing systemic toxicity, degrading into non-toxic byproducts(Pourbaghi-Masouleh, M., & Hosseini, V. (2013).

Silica Nanoparticles (SiNPs): Silica Nanoparticles (SiNPs), especially mesoporous silica nanoparticles (MSNPs), feature high surface area and

adjustable pore sizes for targeted drug delivery and controlled release, improving cancer treatment efficacy(Kesse, S et al, 2019).

Carbon-Based Nanoparticles: Carbon-based nanoparticles, like carbon nanotubes (CNTs) and graphene, offer unique electronic properties and high surface area, suitable for drug delivery and photothermal therapy(Hosseini, S et al ,2023). Sajjadi M et al. (2021) discussed their applications in targeted cancer therapy. Sargazi S et al. (2022) and Priyam J (2023)explored carbon-based nanomaterials for personalized cancer medicine and theranostics.

Carbon Nanotubes (CNTs): Carbon Nanotubes (CNTs), consisting of rolled graphene sheets, are used for their high mechanical strength and conductivity in delivering anticancer drugs and facilitating photothermal therapy(Tian, Z. et al, 2011).

Quantum Dots (QDs): Quantum Dots (QDs), semiconductor nanoparticles, are utilized for their luminescent properties in imaging and targeted drug delivery(Peer, D. et al, 2007).

Nanodiamonds (NDs): Nanodiamonds (NDs) are noted for their chemical stability and interaction with biological molecules, enhancing drug delivery and reducing drug resistance(Wei, S et al, 2019).

3. **Hybrid Nano Particles:**
   Hybrid Nano Particles, combining properties of both organic and inorganic nanoparticles, represent a significant advancement in drug delivery systems. Lipid-polymer hybrid nanoparticles, merging the biocompatibility of lipids with polymers' structural integrity, have been developed for treating various cancers(Zhao, X et al,2015;Li, Y et al, 2019;Wang, Q et al, 2017l;Zhang, R. et al, 2017), demonstrating enhanced drug encapsulation and efficient internalization by cancer cells. These systems offer a promising approach to improving treatment effectiveness and overcoming drug resistance, showcasing the dynamic potential of nanotechnology in enhancing oral cancer therapy.

Mechanisms of Action of Nanoparticles in Oral Cancer Therapy

Nanoparticles (NPs) offer a range of mechanisms that can be harnessed for oral cancer therapy (Taneja, N et al, 2021). These mechanisms include:

1. **Targeted Drug Delivery:**

Yao Y et al (2020) stated that Nanoparticle-based drug delivery systems offer several specific advantages:

Improved Stability and Biocompatibility: Nanoparticles can enhance the stability of drugs by protecting them from degradation in the biological environment. Their biocompatibility ensures minimal toxicity and adverse reactions, making them suitable for therapeutic applications.

Enhanced Permeability and Retention (EPR) Effect: Nanoparticles can exploit the EPR effect, characterized by the tendency of nanoparticles to accumulate more in tumor tissues due to their leaky vasculature and poor lymphatic drainage. This enhances the concentration of therapeutic agents at the tumor site, improving treatment efficacy. This effect, combined with the physicochemical characteristics of nanocarriers, determines the efficiency of drug delivery in cancer therapy.

Precise Targeting: Nanoparticles can be engineered with specific ligands or antibodies that recognize and bind to receptors overexpressed on target cells, such as cancer cells. This allows for targeted delivery of drugs, reducing off-target effects and increasing therapeutic precision.

2. **Photo thermal Therapy:**
   Certain nanoparticles, such as gold NPs, can absorb light and convert it into heat. When these NPs are targeted to tumor cells and exposed to a specific wavelength of light, they generate localized hyperthermia, which can destroy cancer cells. This method shows promise in treating oral squamous carcinoma. The nanoparticles designed for photothermal therapy can absorb specific wavelengths of light and convert them into heat, effectively destroying tumor cells with minimal invasiveness.

3. **Photodynamic Therapy:**
   Photosensitizing agents can be delivered by using nanoparticles to cancer cells. Upon activation by light, these agents produce reactive oxygen species (ROS), causing oxidative damage and cell death in targeted cancer cells.

4. **Gene Therapy:**
   NPs can be utilized to deliver genetic material, such as small interfering RNA (siRNA) or plasmid DNA, to silence oncogenes or express tumor suppressor genes in cancer cells. This approach can modify the genetic landscape of cancer cells, leading to apoptosis or tumor growth inhibition.

5. **Chemotherapy Enhancement:**
   Nanoparticles can enhance the efficacy of chemotherapeutic drugs by improving their solubility, stability, and bioavailability. Encapsulation of drugs within NPs can also protect them from degradation and enable controlled release, providing a sustained therapeutic effect.

6. **Immune Modulation:**
   NPs can modulate the immune system to recognize and attack cancer cells. They can be designed to deliver immune-modulating agents or act as adjuvants, boosting the body's immune response against the tumor.

7. **Magnetic Hyperthermia:**
   When exposed to an alternating magnetic field, iron oxide nanoparticles can generate heat. This magnetic hyperthermia can selectively destroy cancer cells, either alone or in combination with other therapies.

8. **Bioimaging and Diagnostics:**
   NPs can also be employed as contrast agents in imaging techniques such as MRI, CT, or PET scans, allowing for precise tumor imaging and monitoring of treatment response.

Nanotechnology in Oral Cancer Detection

Nanotechnology has revolutionized the early detection of oral cancer through non-invasive techniques that improve diagnostic accuracy. Nano-based imaging modalities, such as Magnetic Resonance Imaging (MRI), Optical Coherence Tomography (OCT), and Surface Plasmon Resonance (SPR) scattering, offer significant advancements.

Magnetic Resonance Imaging (MRI)

For instance, nanoparticles like superparamagnetic iron oxide (SPIO) enhance MRI contrast (Villaraza, A. et al, 2010; Aryal, S et al, 2014), while folate-conjugated chitosan and magnetic PLGA nanoparticles improve imaging in oral cancer models (Shanavas, A et al, 2017;Chandran, P et al, 2017).

Optical Coherence Tomography (OCT):

Enhanced by gold nanoparticles (AuNPs), OCT provides high-resolution imaging for better tumor margin identification(Green, B, et al, 2016; Kim, C. S et al, 2009).

Photoacoustic Imaging:

Using gold nanoparticles, photoacoustic imaging detects lymph node micrometastases with high accuracy (Xu, C, et al, 2018; Jiang, Y, S et al, 2017;Bao, C, et al, 2016).

Surface Plasmon Resonance Scattering and Surface-Enhanced Raman Spectroscopy (SERS):

Surface Plasmon Resonance Scattering and Surface-Enhanced Raman Spectroscopy (SERS), particularly with gold nanoparticles, effectively distinguish malignant lesions (Hou, C., et al, 2017; Harmsen, S., et al, 2017; Galloway, T. A., et

al, 2017; Wang, Y. W., et al, 2017).SERS with gold nanorods also detect cancer biomarkers in saliva with high sensitivity (Chakraborty, D, et al, 2018).

Quantum Dots Imaging:

Quantum dots, offering unique luminescent properties, excel in molecular and cell imaging for oral cancer (Liu, L, et al, 2013; Zhao, J. J, et al, 2011; Zhu, C. N, et al, 2017).

Nano-Based Ultrasensitive Biomarker Detection

Additionally, nanotechnology enables ultra-sensitive detection of cancer biomarkers through magnetic beads (Janissen, R, et al, 2017; Li, X, et al, 2018.) and multiplexed approaches (Munge, B. S. et al, 2016), enhancing diagnostic precision and reducing false positives and negatives

Applications of Nano particles in Oral Cancer (Senevirathna, K et al, 2020)

1. Mechanisms contributing to cancer drug resistance include the overexpression of drug efflux pumps, defects in apoptotic pathways, and hypoxic conditions. Nanoparticles targeting these mechanisms can potentially enhance the reversal of multidrug resistance.
2. The use of nanoparticles in immunotherapy holds promise for enhancing treatment efficacy.
3. Nanoparticle-based drug delivery systems offer several advantages in cancer treatment, such as improved pharmacokinetics, precise targeting of tumor cells, reduced side effects, and mitigation of drug resistance (Dadwal et al., 2018; Palazzolo et al., 2018).
4. In cancer therapy, nano-carriers target tumor cells through the carrier effect of nanoparticles and the positioning effect of targeting agents after absorption.
5. Nanoparticles provide a platform to encapsulate drugs and facilitate their delivery into the bloodstream (Kipp, 2004; Zhang et al., 2008).
6. Due to nanoparticles' size and surface properties and enhanced permeability and retention effects, nano-carriers can extend the half-life of drugs and promote their accumulation in tumor tissues (Bertrand et al., 2014; Kalyane et al., 2019).
7. Targeting systems safeguard normal cells from the cytotoxic effects of drugs, thereby reducing the adverse effects of cancer therapies.
8. The drugs encapsulated within nano-carriers include traditional chemotherapy agents and nucleic acids, indicating their potential roles in cytotoxic and gene therapy (Chen et al., 2015).
9. Beyond chemotherapy and gene therapy, numerous studies have explored the application of nanoparticle-based drugs in immunotherapy and cancer ablation treatments (Riley and Day, 2017). Nanoparticle-based drug

delivery systems are believed to enhance immunotherapy and counteract the tumor's immunosuppressive microenvironment.

10. In 2010, a targeted nanoparticle-based system delivered small interfering RNA (siRNA) to patients with solid tumors (Davis et al., 2010). Another clinical study reported superior tumor treatment efficacy with an actively targeted polymeric nanoparticle containing the chemotherapeutic docetaxel (DTXL) compared to a solvent-based DTXL formulation (Hrkach et al., 2012).
11. Hybrid nanoparticles combine the properties of different nanoparticles, thereby enhancing the functionality and stability of each drug delivery system (Mottaghitalab et al., 2019).
12. Nanoparticles offer certain advantages in combating anti-tumor multidrug resistance (MDR) by providing platforms for combination drug therapy and inhibiting some mechanisms of drug resistance, such as efflux transporters on cell membranes (Li et al., 2016).

Randomized Controlled Trials:

Nanoparticles are emerging as advanced tools for targeting the tumor microenvironment in oral cancers, enhancing the effectiveness of therapies like chemotherapy, photodynamic therapy, and immunotherapy by delivering therapeutic agents directly to tumors and modulating the tumor microenvironment (Zhang, H et al, 2024)

Samiraninezhad et al. (2023) developed a chitosan-based doxepin nanogel for treating chemotherapy-induced oral mucositis, showing significant reductions in mucositis severity over 14 days compared to controls, indicating potential as an effective alternative treatment. Ramezani et al. (2023) demonstrated that curcumin mouthwash and nanocapsules significantly reduced radiation-induced oral mucositis severity and pain in a randomized trial involving 37 patients, suggesting curcumin's safety and efficacy in this context.

Clinical Trials:

Hoffmann et al. (2021) evaluated NBTXR3, a radio enhancer nanoparticle, in elderly or frail patients with locally advanced head and neck squamous cell carcinoma, finding it well-tolerated with preliminary signs of antitumor activity. Adkins et al. (2021) investigated the CACTUX regimen in head and neck squamous cell carcinoma, noting a higher objective response rate and favorable overall survival compared to the historical EXTREME regimen. Tan et al. (2017) explored surface-enhanced Raman spectroscopy (SERS) for early oral squamous cell carcinoma detection, achieving 80.7% sensitivity and 84.1% specificity. Kanai et al. (2012) evaluated THERACURMIN, a nanoparticle curcumin formulation, finding increased plasma curcumin levels and enhanced bioavailability. Damascelli et al. (2007) reported a 75% overall response rate

using nanoparticle albumin-bound paclitaxel in advanced head and neck squamous cell carcinoma. Yang et al. (2003) showed enhanced targeted delivery and therapeutic efficacy of Cucurbitacin BE nanoparticles in cervical lymph nodes in oral cancer.

Safety and Regulatory Considerations:
Nanoparticle toxicity and biocompatibility are critical concerns, with factors like size, shape, and surface charge influencing toxicity. Surface modifications can enhance biocompatibility (Sahu et al., 2016). Regulatory approval involves stringent requirements from bodies like the FDA, necessitating comprehensive safety and efficacy data.

Future Directions and Challenges:
Research should enhance nanoparticle targeting, overcome biological barriers, and tailor nanoparticles for personalized medicine. Long-term safety studies and advanced monitoring technologies are essential for tracking nanoparticles in the body.

Conclusion:
Nanoparticle-based therapies offer promising advancements in oral cancer treatment through targeted drug delivery and personalized medicine approaches. However, several challenges remain, including the need for comprehensive safety evaluations, regulatory approvals, and the development of more efficient and specific targeting strategies. Continued interdisciplinary research, collaboration between academia, industry, and regulatory bodies, and integrationof advanced technologies will be essential in advancing nanoparticle-based therapies from the laboratory to clinical practice.

Author Address:
[1]**Author Designation**: Research scholar
Author Affiliation: Research scholar, Department of Dentistry, Bharath University of Higher Education and Research and Professor and Head of the Department, Department of Oral and Maxillofacial Pathology, JKKN Dental College and Hospital, India

[2]**Author Designation**: Head of the Department,
Author Affiliation: Head of the Department, Department of Physiology, Sree Lakshmi Narayana Institute of Medical Sciences and Hospital, Osudu, Agaram village, Villianur commune, Kudupakkam post, Puducherry, India

[3]**Author Designation**: Research scholar
Author Affiliation: Research scholar, Department of Dentistry, Bharath University of Higher Education and Research and Professor and Head of the Department, Department of Oral and Maxillofacial Surgery, JKKN Dental College and Hospital, India

References

1. *Thi, T. T. H., Suys, E. J. A., Lee, J. S., Nguyen, D. H., Park, K. D., & Truong, N. P. (2021). Lipid-based nanoparticles in the clinic and clinical trials: From cancer nanomedicine to COVID-19 vaccines. Vaccines, 9(4), 359.*
2. *Torchilin, V. (2005). Recent advances with liposomes as pharmaceutical carriers. Nature Reviews Drug Discovery, 4(2), 145–160.*
3. *Nekkanti, Vijaykumar & Kalepu, Sandeep. (2015). Recent Advances in Liposomal Drug Delivery: A Review. Pharmaceutical Nanotechnology. 3. 35-55.*
4. *Danhier, F., Ansorena, E., Silva, J. M., Coco, R., Le Breton, A., & Préat, V. (2012). PLGA-based nanoparticles: an overview of biomedical applications. Journal of controlled release: official journal of the Controlled Release Society, 161(2), 505–522.*
5. *Sangnim, T., Dheer, D., Jangra, N., Huanbutta, K., Puri, V., & Sharma, A. (2023). Chitosan in Oral Drug Delivery Formulations: A Review. Pharmaceutics, 15(9), 2361.*
6. *Zielińska, A., Carreiró, F., Oliveira, A. M., Neves, A., Pires, B., Venkatesh, D. N., Durazzo, A., Lucarini, M., Eder, P., Silva, A. M., Santini, A., & Souto, E. B. (2020). Polymeric nanoparticles: Production, characterization, toxicology and ecotoxicology. Molecules, 25(16), 3731.*
7. *Alvi, M., Yaqoob, A., Rehman, K., & et al. (2022). PLGA-based nanoparticles for the treatment of cancer: Current strategies and perspectives. AAPS Open, 8(12).*
8. *Zhang, G. M., Nie, S. C., Xu, Z. Y., Fan, Y. R., Jiao, M. N., Miao, H. J., Liang, S. X., & Yan, Y. B. (2022). Advanced polymeric nano agents for oral cancer theranostics: A mini review. Frontiers in Chemistry, 10.*
9. *Xiong, Z., Shen, M., & Shi, X. (2018). Dendrimer-based strategies for cancer therapy: Recent advances and future perspectives. Science China Materials, 61(11), 1387–1403.*
10. *Jiang, L., Zhou, S., Zhang, X., & others. (2018). Dendrimer-based nanoparticles in cancer chemotherapy and gene therapy. *Science China Materials, 61*(11), 1404–1419.*
    Keskin, D., & Tezcaner, A. (2017). Micelles as delivery system for cancer treatment. Current Pharmaceutical Design, 23(35).
11. *Zhu, M., Chen, S., Hua, L., et al. (2017). Self-targeted salinomycin-loaded DSPE-PEG-methotrexate nanomicelles for targeting both head and neck*

squamous cell carcinoma cancer cells and cancer stem cells. Nanomedicine (London, England), 12(4), 295–315.

12. *Giri, Tapan & Thakur, Amrita & Alexander, Amit & Ajaz, Ajazuddin & Badwaik, Hemant & Tripathi, Dulal. (2012). Modified chitosan hydrogels as drug delivery and tissue engineering systems: Present status and applications. Acta Pharmaceutica Sinica B. 2. 439–449.*
13. *Zhang, Q., Hou, D., Wen, X., Xin, M., Li, Z., Wu, L., & Pathak, J. L. (2022). Gold nanomaterials for oral cancer diagnosis and therapy: Advances, challenges, and prospects. Materials Today Bio, 15, 100333.*
14. *Wang, Y., Chang, L., Gao, H., Yu, C., Gao, Y., & Peng, Q. (2024). Nanomaterials-based advanced systems for photothermal/photodynamic therapy of oral cancer. European Journal of Medicinal Chemistry, 272, 116508.*
15. *Xu, J. J., Zhang, W. C., Guo, Y. W., Chen, X. Y., & Zhang, Y. N. (2022). Metal nanoparticles as a promising technology in targeted cancer treatment. Drug Delivery, 29(1), 664-678.*
16. *Sengani, M., Grumezescu, A. M., & Rajeswari, V. D. (2017). Recent trends and methodologies in gold nanoparticle synthesis – A prospective review on drug delivery aspect. OpenNano, 2, 37–46.*
17. *Alalaiwe, A. (2019). The clinical pharmacokinetics impact of medical nanometals on drug delivery systems. Nanomedicine: Nanotechnology, Biology and Medicine, 17, 47–61.*
18. *Noruzi, M., Zare, D., Khoshnevisan, K., & Davoodi, D. (2011). Rapid green synthesis of gold nanoparticles using Rosa hybrida petal extract at room temperature. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 79, 1461–1465.*
19. *Hheidari, A., Mohammadi, J., Ghodousi, M., Mahmoodi, M., Ebrahimi, S., Pishbin, E., & Rahdar, A. (2024). Metal-based nanoparticles in cancer treatment: Lessons learned and challenges. Frontiers in Bioengineering and Biotechnology, 12, 1436297.*
20. *Fadel, M., & El-Kholy, A. I. (2024). Gold nanoparticles in photodynamic and photothermal therapy. In P. Kesharwani (Ed.), Gold Nanoparticles for Drug Delivery (pp. 365-391). Academic Press.*
21. *Vines, J. B., Yoon, J. H., Ryu, N. E., Lim, D. J., & Park, H. (2019). Gold nanoparticles for photothermal cancer therapy. Frontiers in Chemistry, 7, 167.*
22. *Dziedzic, A., Kubina, R., Buldak, R., Skonieczna, M., & Cholewa, K. (2016). Silver nanoparticles exhibit a dose-dependent anti-proliferative effect against human squamous carcinoma cells attenuated in the presence of berberine. Molecules, 21(3), 365.*
23. *Yakop, F., Ghafar, S. A. A., Yong, Y. K., Yazan, L. S., Hanafiah, R. M., & Lim, V. (2018). Silver nanoparticles Clinacanthus Nutans leaves extract induced*

apoptosis towards oral squamous cell carcinoma cell lines. Artificial Cells, Nanomedicine, and Biotechnology, 46(Suppl 2), 131–139.

24. *Yang, X., Hong, H., Grailer, J. J., Rowland, I. J., Javadi, A., Hurley, S. A., Xiao, Y., Yang, Y., Zhang, Y., Nickles, R. J., Kai, W., Steeber, D. A., & Gong, S. (2011). cRGD-functionalized, DOX-conjugated, and 64Cu-labeled superparamagnetic iron oxide nanoparticles for targeted anticancer drug delivery and PET/MR imaging. Biomaterials, 32(17), 4151–4160.*
25. *Pourbaghi-Masouleh, M., & Hosseini, V. (2013). Amorphous calcium phosphate nanoparticles could function as a novel cancer therapeutic agent by employing a suitable targeted drug delivery platform. Nanoscale Research Letters, 8(1), 449.*
26. *Kesse, S., Boakye-Yiadom, K., Ochete, B., Opoku-Damoah, Y., Akhtar, F., Filli, M., Farooq, M. A., Maviah Mily, B. J., Murtaza, G., & Wang, B. (2019). Mesoporous silica nanomaterials: Versatile nanocarriers for cancer theranostics and drug and gene delivery. Pharmaceutics, 11(2), 77.*
27. *Hosseini, S. M., Mohammadnejad, J., Najafi-Taher, R., Zadeh, Z. B., Tanhaei, M., & Ramakrishna, S. (2023). Multifunctional carbon-based nanoparticles: Theranostic applications in cancer therapy and diagnosis. ACS Applied Bio Materials, 6(4), 1323-1338.*
28. *Sajjadi, M., Nasrollahzadeh, M., Jaleh, B., Soufi, G. J., & Iravani, S. (2021). Carbon-based nanomaterials for targeted cancer nanotherapy: Recent trends and future prospects. Journal of Drug Targeting, 29(7), 716-741.*
29. *Sargazi, S., Er, S., Mobashar, A., Gelen, S. S., Rahdar, A., Ebrahimi, N., Hosseinikhah, S. M., Bilal, M., & Kyzas, G. Z. (2022). Aptamer-conjugated carbon-based nanomaterials for cancer and bacteria theranostics: A review. Chemico-Biological Interactions, 361, 109964.*
30. *Priyam, J., & Saxena, U. (2023). Therapeutic applications of carbon nanomaterials in renal cancer. Biotechnology Letters, 45(11-12), 1395-1416.*
31. *Tian, Z., Yin, M., Ma, H., Zhu, L., Shen, H., & Jia, N. (2011). Supramolecular assembly and antitumor activity of multiwalled carbon nanotube–camptothecin complexes. Journal of Nanoscience and Nanotechnology, 11(2), 953–958.*
32. *Peer, D., Karp, J. M., Hong, S., Farokhzad, O. C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. Nature Nanotechnology, 2(12), 751–760.*
33. *Wei, S., Li, L., Du, X., & Li, Y. (2019). OFF–ON nanodiamond drug platform for targeted cancer imaging and therapy. Journal of Materials Chemistry B, 7(21), 3390–3402.*
34. *Zhao, X., Li, F., Li, Y., Wang, H., Ren, H., Chen, J., et al. (2015). Co-delivery of HIF1α siRNA and gemcitabine via biocompatible lipid-polymer hybrid nanoparticles for effective treatment of pancreatic cancer. Biomaterials, 46, 13–25.*

35. *Li, Y., Xiao, Y., Lin, H. P., Reichel, D., Bae, Y., Lee, E. Y., et al. (2019). In vivo β-catenin attenuation by the integrin α5-targeting nano-delivery strategy suppresses triple negative breast cancer stemness and metastasis. Biomaterials, 188, 160–172.*
36. *Wang, Q., Alshaker, H., Böhler, T., Srivats, S., Chao, Y., Cooper, C., et al. (2017). Core shell lipid-polymer hybrid nanoparticles with combined docetaxel and molecular targeted therapy for the treatment of metastatic prostate cancer. Scientific Reports, 7, 5901.*
37. *Zhang, R. X., Ahmed, T., Li, L. Y., Li, J., Abbasi, A. Z., & Wu, X. Y. (2017). Design of nanocarriers for nanoscale drug delivery to enhance cancer treatment using hybrid polymer and lipid building blocks. Nanoscale, 9, 1334–1355.*
38. *Taneja, N., Alam, A., Patnaik, R. S., Taneja, T., Gupta, S., & K, S. M. (2021). Understanding nanotechnology in the treatment of oral cancer: A comprehensive review. Critical Reviews in Therapeutic Drug Carrier Systems, 38(6), 1-48.*
39. *Yao, Y., Zhou, Y., Liu, L., Xu, Y., Chen, Q., Wang, Y., Wu, S., Deng, Y., Zhang, J., & Shao, A. (2020). Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. Frontiers in Molecular Biosciences, 7, 193.*

    Villaraza, A. J., Bumb, A., & Brechbiel, M. W. (2010). Macromolecules, dendrimers, and nanomaterials in magnetic resonance imaging: The interplay between size, function, and pharmacokinetics. Chemical Reviews, 110, 2921–2959.
40. *Aryal, S., Key, J., Stigliano, C., Landis, M. D., Lee, D. Y., & Decuzzi, P. (2014). Positron emitting magnetic nanoconstructs for PET/MR imaging. Small, 10(12), 2688–2696.*
41. *Shanavas, A., Sasidharan, S., Bahadur, D., & Srivastava, R. (2017). Magnetic core-shell hybrid nanoparticles for receptor targeted anti-cancer therapy and magnetic resonance imaging. Journal of Colloid and Interface Science, 486, 112–120.*
42. *Chandran, P., Sasidharan, A., Ashokan, A., Menon, D., Nair, S., & Koyakutty, M. (2011). Highly biocompatible TiO2+ nano-contrast agent with enhanced longitudinal relaxivity for targeted cancer imaging. Nanoscale, 3(11), 4150–4161.*
43. *Green, B., Tsiroyannis, C., & Brennan, P. A. (2016). Optical diagnostic systems for assessing head and neck lesions. Oral Diseases, 22(3), 180–184.*
44. *Kim, C. S., Wilder-Smith, P., Ahn, Y. C., Liaw, L. H. L., Chen, Z., & Kwon, Y. J. (2009). Enhanced detection of early-stage oral cancer in vivo by optical coherence tomography using multimodal delivery of gold nanoparticles. Journal of Biomedical Optics, 14(3), 034008.*

45. *Xu, C., Chen, F., Valdovinos, H. F., Jiang, D., Goel, S., Yu, B., et al. (2018). Bacteria-like mesoporous silica-coated gold nanorods for positron emission tomography and photoacoustic imaging-guided chemo-photothermal combined therapy. Biomaterials, 165, 56–65.*
46. *Jiang, Y., & Pu, K. (2017). Advanced photoacoustic imaging applications of near-infrared absorbing organic nanoparticles. Small, 13(1700710).*
47. *Bao, C., Conde, J., Pan, F., Li, C., Zhang, C., Tian, F., et al. (2016). Gold nanoprisms as a hybrid in vivo cancer theranostic platform for in situ photoacoustic imaging, angiography, and localized hyperthermia. Nano Research, 9(1043–1056).*
48. *Hou, C., Galvan, D. D., Meng, G., & Yu, Q. (2017). Long-range surface plasmon resonance and surface-enhanced Raman scattering on X-shaped gold plasmonic nanohole arrays. Physical Chemistry Chemical Physics, 19, 24126–24134.*
49. *Harmsen, S., Wall, M. A., Huang, R. M., & Kircher, M. F. (2017). Cancer imaging using surface-enhanced resonance Raman scattering nanoparticles. Nature Protocols, 12, 1400–1414.*
50. *Galloway, T. A., Cabo-Fernandez, L., Aldous, I. M., & Hardwick, L. J. (2017). Shell isolated nanoparticles for enhanced Raman spectroscopy studies in lithium-oxygen cells. Faraday Discussions, 205, 469–490.*
51. *Wang, Y. W., Reder, N. P., Kang, S., Glaser, A. K., Yang, Q., Wall, M. A., et al. (2017). Raman-encoded molecular imaging with topically applied SERS nanoparticles for intraoperative guidance of lumpectomy. Cancer Research, 77(4506–4516).*
52. *Chakraborty, D., Viveka, T. S., Arvind, K., et al. (2018). A facile gold nanoparticle–based ELISA system for detection of osteopontin in saliva: Towards oral cancer diagnostics. Clinica Chimica Acta, 477, 166-172.*
53. *Liu, L., Miao, Q., & Liang, G. (2013). Quantum dots as multifunctional materials for tumor imaging and therapy. Materials (Basel), 6, 483–499.*
54. *Zhao, J. J., Chen, J., Wang, Z. P., Pan, J., & Huang, Y. H. (2011). Double labeling and comparison of fluorescence intensity and photostability between quantum dots and FITC in oral tumors. Molecular Medicine Reports, 4, 425–429.*
55. *Zhu, C. N., Chen, G., Tian, Z. Q., Wang, W., Zhong, W. Q., Li, Z., et al. (2017). Near-infrared fluorescent Ag2Se-cetuximab nanoprobes for targeted imaging and therapy of cancer. Small, 13(1602309).*
56. *Janissen, R., Sahoo, P. K., Santos, C. A., da Silva, A. M., von Zuben, A. A. G., Souto, D. E. P., et al. (2017). InP nanowire biosensor with tailored biofunctionalization: Ultrasensitive and highly selective disease biomarker detection. Nano Letters, 17, 5938–5949.*
57. *Li, X., Wei, L., Pan, L., Yi, Z., Wang, X., Ye, Z., et al. (2018). Homogeneous immunosorbent assay based on single-particle enumeration using*

upconversion nanoparticles for the sensitive detection of cancer biomarkers. Analytical Chemistry, 90, 4807–4814.

58. *Munge, B. S., Stracensky, T., Gamez, K., DiBiase, D., & Rusling, J. F. (2016). Multiplex immunosensor arrays for electrochemical detection of cancer biomarker proteins. Electroanalysis, 28(12), 2644–2658.*
59. *Senevirathna, K., Jayawickrama, S. M., Jayasinghe, Y. A., Prabani, K. I. P., Akshala, K., Pradeep, R. G. G. R., Damayanthi, H. D. W. T., Hettiarachchi, K., Dorji, T., Lucero-Prisno, D. E., Rajapakse, R. M. G., Kanmodi, K. K., & Jayasinghe, R. D. (2023). Nanoplatforms: The future of oral cancer treatment. Health Science Reports, 6(8), e1471.*
60. *Dadwal, A., Baldi, A., & Kumar Narang, R. (2018). Nanoparticles as carriers for drug delivery in cancer. Artificial Cells, Nanomedicine, and Biotechnology, 46(sup2), 295-305.*
61. *Palazzolo, S., Bayda, S., Hadla, M., Caligiuri, I., Corona, G., Toffoli, G., & Rizzolio, F. (2018). The clinical translation of organic nanomaterials for cancer therapy: A focus on polymeric nanoparticles, micelles, liposomes, and exosomes. Current Medicinal Chemistry, 25(34), 4224-4268.*
62. *Kipp, J. E. (2004). The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. International Journal of Pharmaceutics, 284(1-2), 109-122.*
63. *Zhang, L., Gu, F. X., Chan, J. M., Wang, A. Z., Langer, R. S., & Farokhzad, O. C. (2008). Nanoparticles in medicine: Therapeutic applications and developments. Clinical Pharmacology & Therapeutics, 83(5), 761-769.*
64. *Bertrand, N., Wu, J., Xu, X., Kamaly, N., & Farokhzad, O. C. (2014). Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology. Advanced Drug Delivery Reviews, 66, 2-25.*
65. *Kalyane, D., Raval, N., Maheshwari, R., Tambe, V., Kalia, K., & Tekade, R. K. (2019). Employment of enhanced permeability and retention effect (EPR): Nanoparticle-based precision tools for targeting of therapeutic and diagnostic agents in cancer. Materials Science and Engineering: C, 98, 1252-1276.*
66. *Chen, W. H., Lecaros, R. L. G., Tseng, Y. C., Huang, L., & Hsu, Y. C. (2015). Nanoparticle delivery of HIF1α siRNA combined with photodynamic therapy as a potential treatment strategy for head-and-neck cancer. Cancer Letters, 359(1), 65-74.*
67. *Riley, R. S., & Day, E. S. (2017). Gold nanoparticle-mediated photothermal therapy: Applications and opportunities for multimodal cancer treatment. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 9(4), e1449.*
68. *Davis, M. E., Zuckerman, J. E., Choi, C. H. J., Seligson, D., Tolcher, A., Alabi, C. A., Yen, Y., Heidel, J. D., & Ribas, A. (2010). Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. Nature, 464(7291), 1067-1070.*

69. *Hrkach, J., Von Hoff, D., Mukkaram Ali, M., Andrianova, E., Auer, J., Campbell, T., De Witt, D., Figa, M., Figueiredo, M., Horhota, A., Low, S., McDonnell, K., Peeke, E., Retnarajan, B., Sabnis, A., Schnipper, E., Song, J. J., Song, Y. H., Summa, J., Tompsett, D., ... Zale, S. (2012). Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. Science Translational Medicine, 4(128), 128ra39.*
70. *Mottaghitalab, F., Farokhi, M., Fatahi, Y., Atyabi, F., & Dinarvand, R. (2019). New insights into designing hybrid nanoparticles for lung cancer: Diagnosis and treatment. Journal of Controlled Release, 295, 250-267.*
71. *Li, P., Zhou, G., Zhu, X., Li, G., Yan, P., Shen, L., Xu, Q., & Hamblin, M. R. (2012). Photodynamic therapy with hyperbranched poly(ether-ester) chlorin(e6) nanoparticles on human tongue carcinoma CAL-27 cells. Photodiagnosis and Photodynamic Therapy, 9(1), 76-82.*
72. *Zhang, H., Zhou, F., Yang, Q., & Huang, M. (2024). Targeting the oral tumor microenvironment by nanoparticles: A review of progresses. Journal of Drug Delivery Science and Technology, 91, 105248.*
73. *Samiraninezhad, N., Rezaee, M., Gholami, A., Amanati, A., & Mardani, M. (2023). A novel chitosan-based doxepin nano-formulation for chemotherapy-induced oral mucositis: A randomized, double-blinded, placebo-controlled clinical trial. Inflammopharmacology, 31(5), 2411-2420.*
74. *Ramezani, V., Ghadirian, S., Shabani, M., Boroumand, M. A., Daneshvar, R., & Saghafi, F. (2023). Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: A preliminary randomized controlled clinical trial. BMC Cancer, 23(1), 354.*
75. *Hoffmann, C., Calugaru, V., Borcoman, E., Moreno, V., Calvo, E., Liem, X., Salas, S., Doger, B., Jouffroy, T., Mirabel, X., Rodriguez, J., Chilles, A., Bernois, K., Dimitriu, M., Fakhry, N., Hee Kam, S. W., & Le Tourneau, C. (2021). Phase I dose-escalation study of NBTXR3 activated by intensity-modulated radiation therapy in elderly patients with locally advanced squamous cell carcinoma of the oral cavity or oropharynx. European Journal of Cancer, 146, 135-144.*
76. *Adkins, D., Ley, J., Atiq, O., Powell, S., Spanos, W. C., Gitau, M., Rigden, C., Palka, K., Liu, J., & Oppelt, P. (2021). Nanoparticle albumin-bound paclitaxel with cetuximab and carboplatin as first-line therapy for recurrent or metastatic head and neck cancer: A single-arm, multicenter, phase 2 trial. Oral Oncology, 115, 105173.*
77. *Tan, Y., Yan, B., Xue, L., Li, Y., Luo, X., & Ji, P. (2017). Surface-enhanced Raman spectroscopy of blood serum based on gold nanoparticles for the diagnosis of oral squamous cell carcinoma. Lipids in Health and Disease, 16(1), 73.*

78. *Kanai, M., Imaizumi, A., Otsuka, Y., Sasaki, H., Hashiguchi, M., Tsujiko, K., Matsumoto, S., Ishiguro, H., & Chiba, T. (2012). Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. Cancer Chemotherapy and Pharmacology, 69(1), 65-70.*
79. *Damascelli, B., Patelli, G., Tichá, V., Di Tolla, G., Frigerio, L. F., Garbagnati, F., Lanocita, R., Marchianò, A., Spreafico, C., Mattavelli, F., Bruno, A., & Zunino, F. (2007). Feasibility and efficacy of percutaneous transcatheter intraarterial chemotherapy with paclitaxel in albumin nanoparticles for advanced squamous-cell carcinoma of the oral cavity, oropharynx, and hypopharynx. Journal of Vascular and Interventional Radiology, 18(11), 1395-1403.*
80. *Yang, K., Wen, Y., & Wang, C. (2003). Clinical application of anticancer nanoparticles targeting metastasis foci of cervical lymph nodes in patients with oral carcinoma. Hua Xi Kou Qiang Yi Xue Za Zhi, 21(6), 447-450. [PMID: 14732978]*
81. *Sahu, D., Kannan, G. M., Tailang, M., & Vijayaraghavan, R. (2016). In vitro cytotoxicity of nanoparticles: A comparison between particle size and cell type. Journal of Nanoscience, 2016, 4023852.*