SYSTEMATIC REVIEW

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Role of Nanoparticles as a Diagnostic and Therapeutic Tool in Oral Cancer: A Systematic Review

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Abstract

Background: Cancer has become a life-threatening disease having the second-highest mortality rate globally. In the year 2020, there were 19.3 million new cancer patients and approximately 10 million cancer-related deaths worldwide. WHO has reported that 14.6% (about 1 in every 6) of human deaths occur due to cancer annually.

Objectives: Cancer has become a life-threatening disease worldwide, with oral cavity and lip cancers becoming the 16th most common malignancy. Over 400,000 new cases are diagnosed annually. Early diagnosis is crucial. Today, nanoparticles play an important part in imaging, diagnosis, and delivering drugs, offering new hope in the fight against cancer. The purpose of this study is to achieve a comprehensive evaluation of the role of nanoparticles as a tool that can help in the diagnosis as well as treatment of oral cancer.

Materials and Methods: For this systematic review, three databases were used (PubMed Central, Google Scholar, and Cochrane). Articles containing combinations such as Nanoparticles [Oral Cancer], Nanoparticles [Drug Therapy], Oral Carcinoma [Nanotechnology], Oral Tumors [Nanomedicine], published in English and the last seven years were selected. 15 original articles were selected and studied thoroughly after using the inclusion and exclusion criteria.

Results: Nanoparticles show promising roles in the early identification and diagnosis of cancers related to the oral cavity and prove to be effective drug carriers targeting cancerous cells.

Conclusion: Nanoparticles offer an innovative approach to cancer treatment, enabling precise diagnosis and early detection of cancerous cells. They allow targeted drug delivery, minimize harm to the healthy cells of the body along with decreasing the harmful effects of conventional treatments. This advancement holds great promise for improving cancer therapy outcomes.

Keywords: *Nanoparticles, Oral cancer, Diagnostic tools, Oral Cancer therapy.*

Introduction

Cancer has become a life-threatening disease having the second-highest mortality rate globally.[1] In the year 2020, there were 19.3 million new cancer patients and approximately 10 million cancer-related deaths worldwide. [2, 3] WHO has reported that 14.6% (about 1 in every 6) of human deaths occur due to cancer annually. [4] The rise in cancer incidence can be attributed to several factors including population growth, an increase in life expectancy, and unhealthy lifestyles. Cancers of the lip and oral cavity (referred to as oral cancers here) collectively represent the 16th most common malignant neoplasm worldwide, with almost 355,000 new incident cases per year. [5] More than 400,000 estimated incident cases of oral cavity cancer are diagnosed annually worldwide, amongst which two-thirds of the cases are reported in Asian countries including Pakistan, India, Bangladesh, Sri Lanka, and Indonesia. [6] More than 90% of cancers related to the oral cavity are squamous cell carcinomas with two-thirds of cases reported in developing countries, half of which are South Asian cases. [7]

Poor prognosis of Oral cancer has been observed with a 40% of 5-year survival rate but if detected in its initial stages (Stage I and II), survival rates can reach up to 80%. [8] As a result of the asymptomatic nature of most oral cancers in their initial stages, most patients often delay seeking medical treatment until symptoms such as pain, bleeding or a mass appear in the oral cavity or neck. Up to 50% of these cases are then detected during the late stages (stages III and IV) of the cancer. [9] A delay of one month in the diagnosis of oral cancer can increase the risk of having advanced-stage cancer significantly. [10]

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Cancer treatment strategies depend upon multiple factors such as cancer stage, tumor location, patient age, and presence of existing diseases. First line treatment include chemotherapy, radiation therapy, and surgery as first-line treatments. [1, 4] The drawbacks of these treatment modalities include not having the ability to differentiate between cancerous and healthy body cells, damaging healthy tissues, and incomplete removal of a tumor leading to a reoccurrence of the disease.

Another treatment strategy is immunotherapy. Cancer immunotherapy is a type of cancer treatment modality that inhibits the growth and metastasis of cancer using the host's immune system. Many clinical research studies support that immunotherapy has shown promising effectiveness against different types of cancer. [1, 11] To tackle the challenges faced with current treatment strategies, a new and advanced scientific field has emerged known as "Nanomedicine". [12] This field uses nanoparticles for delivering drugs to the cancer cells thereby, increasing the efficacy of the drug and reducing adverse effects. Nanoparticles are also used for enhanced imaging leading to timely diagnosis, improved monitoring, and targeting of the cancer tissue. [13] Overall, nanoparticles provide promising methods to improve patient outcomes and transform the cancer industry. These solid supramolecular particles are in the range of 10 to 1000 micrometers in size. [14] Nanoparticles with their adaptable chemical and physical properties are becoming increasingly prevalent in targeted drug delivery systems with better bioactivity and effective therapy, decreasing their systematic toxicity for the treatment of oral cancer. These carriers, which mostly comprise of polymeric and inorganic NPs, can be used to load, stabilize, and transport chemotherapeutic medications in a range of loading content and release profiles. In addition to several other NPs, liposomes, dendrimers, magnetic nanoparticles, and quantum dots are used in the detection and management of oral cancer. [15]

This study aims to assess the usefulness of NPs in oral cancer, immunotherapy, and its potential to improve the prognosis of oral cancer patients.

Material and Methods

Information source:

Electronic databases like **PubMed Central, Google Scholar, and Cochrane** were used for this systematic review. A thorough search was conducted using Boolean operators: "(Nanoparticles) AND (Oral Cancer), (Oral Cancer) AND (Diagnostic Tools), (Oral Cancer) OR (Oral Tumors) (Nanoparticles) AND (Cancer Therapy)". The selection of study papers was narrowed down from the last seven years (2018 to 2024) to reduce cognitive burden. Following the application of inclusion and exclusion criteria, 47 original articles were meticulously examined.

Search method:

Four authors independently searched for articles using different keywords across three databases. A total of 47 articles were initially identified. After removing 5 duplicate articles, 42 articles remained. These were further scrutinized, and 27 articles were excluded due to limited access, incomplete data, and language other than English. This resulted in 15 original articles. Subsequently, specific criteria were applied to these articles.

Inclusion criteria:

1. Last seven years articles (2018 to 2024)
2. Open access articles
3. Articles having terms such as nanoparticles and oral cancer
4. Articles published in the English language
5. Full-length articles

Exclusion criteria:

1. Articles in a language other than English
2. Review articles
3. Incomplete data
4. Full text not available
5. Articles with no open access

Results

The 15 studies that were selected focus on the preparation, structure, mechanism, and use of nanoparticles in the diagnosis and oral cancer treatment. The selected studies for this review are shown in the evidence table 1.

Theranostic nanoparticles showed improved image-guided radiotherapy for oral cavity carcinoma by providing X-ray and MRI contrast, which enhanced tumor visualization, reduced tumor growth and metastasis, and increased oxidative stress and DNA harm in cancer cells, leading to tumor remission. They also supported future image-guided therapy by ensuring clear imaging during treatment. [25] Gold nanoparticles were promising for cancer diagnosis, particularly in oral cancer, as they distinguished between cancerous and normal cells, aiding in early detection and precise treatment planning, which could improve patient outcomes. [26]

Various studies discussed the use of nanoparticles in the treatment of oral cancers. For instance, Ru (II) modified TiO_2 nanoparticles showed both Type I and Type II photodynamic effects, resulting in lysosomal damage, HIF-1α gene silencing, and efficient OSCC cell removal along with downregulating factors suppressing the immune system, enhancing immune cytokines levels, and activating T cells (CD4+ and CD8+). It also inhibited tumor growth and enhanced cancer immunity in PDX and rat oral cancer models. [16] Similarly, the GQDs-FA-EVO nanocomposite system resulted in targeted therapy of OSCC, showing inhibition of OSCC cell growth, reduction in tumor volume, and good biocompatibility. [17]

A study by J. Zeng, Z. Tang et al. demonstrated that nanoparticle combinations such as AuNPs–BPNSs loaded with CDDP inhibited OSCC growth most effectively. [18] Also, CS-decorated PCL nanoparticles indicated 38.57% entrapment efficiency of 5-FU significantly inhibiting cancer cell proliferation in HNSCC proving to be an effective 5-FU drug carrier. [19] The vitality of malignant UPCI-SCC-154 cells was drastically decreased by nanoparticle RNA-

Table 1. Shows data tabulation according to the author, year, type of study, the aim of the study, nanoparticles used, and the outcomes of the study.

Author	Year	Type of Study	Aim of study	Type of nanoparticle	Conclusion
Zhou, Jia Ying Wang, et al [16]	2022	In vitro	The main purpose of this study was to present Ru (II)- modified TiO_2 NP system for OSCC treatment with hypoxia-adaptive photo -immunotherapy	Ru (II)-modified TiO_2	Ru (II)-modified TiO_2 promotes lysosomal damage, improves hypoxia, shows high PDT potency via O_2-dependent and independent pathways, induces pyroptosis, alleviates immunosuppressive environment, enhances antitumor immune responses, and high potency in models.
Ma, Yu Liu, Yan et al [17]	2022	In vitro	To explore a nanocomposite system made up of folic acid-modified graphene quantum dots ladened with evodiamine in the treatment of OSCC.	Folic acid-modified graphene quantum dots.	With 10% loading of EVO into GQDs-FA-EVO nanocomposite system, OSCC cells inhibition rate was 50%. 10% loading of EVO into GQDs-FA-EVO nanocomposite system in tumor-bearing nude mice resulted in a 19% decrease in tumor volume as compared to the EVO group after 18 days of treat-
J. Zeng, Z. Tang et al [18]	2021	In vitro	To investigate the function of Black phosphorus nanosheets-gold nanoparticles-cisplatin in the photothermal/ photodynamic treatment of OSCC.	Black phosphorus nanosheets, gold nanoparticles, and cisplatin.	BPNSs: These particles effectively reduced the spread and growth of OSCC, outdoing CDDP and AuNPs. Combination therapy: AuNPs-BPNSs combined with CDDP reduced OSCC metastasis and growth more efficiently owing to its better drug loading capacity, improved photothermal characteristics, combined photothermal and photodynamic therapy as well as synergistic effects of AuNPs, BPNSs, and CDDP
J.D Lima, L. Castellano et al [19]	2021	In vitro	The research objectives were to create a Chitosan/PCL NP system and assess the antineoplastic potential of 5-fluorouracil in head and neck cancer via activating autophagy.	Chitosan and polycaprolactone nanoparticles	The findings point to the potential use of CS-decorated PCL microparticles as a vehicle for 5-FU administration to improve head and neck squamous cell carcinoma treatment.

Author	Year	Type of Study	Aim of study	Type of nanoparticle	Conclusion
J. Lopes-Nunes, P. Simões [20]	2021	In vivo	The objective of the research was to synthesize RNA-coated liposomes and assess their capacity to target malignant cells with specific delivery of the ligands C8 and dexamethasone.	RNA-coated liposomes	These liposomes preserved non-cancerous cells while dramatically lowering the survival of cancerous cells, indicating the possibility of RNA-based medication delivery systems.
Q. Li, X. Liu et al [21]	2020	In vitro	To investigate the possibility of using chloroquine and cisplatin-loaded polylactide NP to stop the spread of oral squamous cell carcinoma via encouraging oxidative stress and cancer cell death.	PLA nanoparticles	CDDP/CQ-PLA NPs have promising properties for the therapeutic treatment of OSCC, including reduced autophagy, enhanced ROS, and apoptosis, excellent drug loading, and drug release qualities.
M.Tsai, Y. Sun et al [22]	2021	In vitro	To create iron-gold bimetallic NPs coupled with MMP-1 antibodies to precisely target and inhibit the proliferation of OSCC cells to induce hyperthermia-mediated cancer cell death	Iron-gold bimetallic nanoparticles (FeAu NPs)	FeAu NPs that have been treated with anti-MMP1 have better therapeutic benefits in stopping the growth of SCC, which suggests that they might be used as a platform for cancer cell death caused by heat shock.
L.Jin, Q .Wang et al [23]	2018	In vitro	The objective was to study the role of Fe_3O_4 NPs in delivering therapeutic siRNA into the cancerous cells of the oral cavity, targeting BCL2 and BIRC5, and to develop an effective treatment strategy for oral cancer.	PEI-modified magnetic Fe_3O_4 nanoparticles	The PEI-modified Fe_3O_4 NPs showed promising outcomes in delivering siRNA into cancerous cells of the oral cavity, resulting in high gene silencing efficiencies and improved inhibition of cell viability and migration.

Author	Year	Type of Study	Aim of study	Type of nanoparticle	Conclusion
A. Mustafa, M. Indiran et al [24]	2024	In vitro	To synthesize and characterize a chitosan-based nanogel containing thiocolchicoside and lauric acid, and to evaluate its antitumor characteristics against cancerous cells of the oral cavity, its ability to induce oxidative stress, and increase ROS levels.	chitosan-based nanogel, thiocolchicoside and lauric acid	These NPs showed promising anticancer properties against oral cavity cancerous cells by causing oxidative stress and increasing ROS levels.
G. Sharma, M. Razeghi et al [25]	2023	In vivo	To evaluate the use of theranostic nanoparticles in pre-procedure radiotherapy planning as well as enhancing the efficacy of radiotherapy for tumors of the head and neck.	Theranostic Nanoparticle	These particles help in planning pre-procedure radiotherapy along with improved radiotherapy efficacy of head and neck tumors.
J.Kah, K.Kho et al [26]	2022	invitro	This study was done to explore the function of antibody-conjugated gold nanoparticles in early cancer detection through reflectance-based optical imaging and surface-enhanced Raman spectroscopy (SERS).	Gold nanoparticle	The results showed that these particles can distinguish between healthy and cancerous cells using optical contrast and antibody conjugation for biomarker mapping under confocal reflectance microscopy. Additionally, SERS spectra of saliva from AuNPs films could distinguish between normal individuals, and oral carcinoma patients, signifying the ability of a simple SERS-based saliva assay in early diagnosis of oral malignancy.
Essawy, Marwa M.et al [27]	2021	In vivo	The study's objective was to explore the use of AuNP-Based nanoparticles in delivering anti-cancer drugs during cancer therapy.	Gold nanoparticles	Both PH-sensitive and PH-resistant doxorubicin nanoconjugates exhibited effective cellular and nuclear uptake in oral cell carcinoma cells. The PH-sensitive linker may play an important function in improving the therapeutic effect of DOX facilitating its release within the acidic tumor microenvironment.

Author	Year	Type of Study	Aim of study	Type of nanoparticle	Conclusion
K. Lai, F. Cheu et al [28]	2019	In vitro, In vivo	To develop Gefitinib and curcumin -loaded nanoparticles and investigate their anti-tumor properties in oral cancer.	Gefitinib and curcumin-loaded nanoparticles	These nanoparticles effectively induce apoptosis in cancerous cells in vitro through caspase and mitochondria-dependent pathways. In vivo, these nanoparticles significantly reduce tumor size without adverse effects on mice.
J. Wang, S. Gao. et al [29]	2018	In vitro	To investigate the role of ZnO nanoparticles on CAL 27 human tongue cancerous cells (CAL 27)	ZnO NPs	Zinc oxide nanoparticles reduced the viability of CAL 27 tongue cancer cells in a dose-dependent manner. These particles enhanced reactive oxygen species levels, lowered mitochondrial membrane potential, and triggered mitophagy in CAL 27 cells over time.
D.Jing, N. Jiam, F. Wang [30]	2022	In vivo	To investigate the use of DCM-[PTX] as a radiosensitizer in combination with radiotherapy and SBRT for treatment of oral cancerous cells	DCM-[PTX] NPs	Disulphide crosslinked micelles encapsulating paclitaxel and DiD (DCM/-[PTX-DiD]) showed synergistic anti-tumor effects when combined with radiotherapy, especially SBRT

functionalized liposomes loaded with either C8 or dexamethasone, but the viability of non-malignant NHDF cells was not affected. Furthermore, these liposomes demonstrated efficient cellular internalization, with increased uptake by the cancerous cell line. [20] A nanogel containing thiocolchicoside (CTL nanogel) showed strong anticancer effects by inducing oxidative stress in cancer cells and interacting with specific targets to inhibit their growth. It could be a non-toxic chemotherapy option, treating cancer without harming healthy cells. [24]

Nanoparticles made of iron and gold tagged with MMP-1 in squamous cell carcinoma (SCC), demonstrated their potential for cancer cell death and shrinking tumors in mice when exposed to a magnetic field. These nanoparticles possessed super magnetic properties that enabled them to effectively target and kill cancer cells with hyperthermia. Furthermore, researchers successfully delivered siRNAs into oral cancer cells silencing the cancer-related genes BCL2 and BIRC5, significantly inhibiting cancer cell growth and migration. [23] Further research revealed that CDDP/CQ -PLA NPs had outstanding drug-loading and release characteristics, which decreased autophagy, raised ROS levels, and accelerated apoptosis in Cal-27 cells (21) and that PH-resistant DOX nanoparticles were superior in inducing apoptosis and shrinking tumors compared to pH-sensitive ones. [27] Encapsulating gefitinib and curcumin in PLGA polymer led to significant tumor weight reduction. [28] whereas, ZnO nanoparticles decreased CAL 27 cell viability, improved intracellular ROS levels, lowered mitochondrial membrane potential, and activated mitophagy, showing potential for cancer treatment. [29] Furthermore, combination of nanoparticle formulation disulphide cross-linked micelle (DCM) encapsulated paclitaxel (PTX) or DCM-[PTX/DiD] with stereotactic body radiotherapy SBRT showed better efficacy in oral tumor cancer growth inhibitions compared to the combination with conventional radiotherapy. [30]

Discussion

This systematic review highlights important developments and cutting-edge strategies in the application of photodynamic therapy and nanocomposites for the prevention and treatment of OSCC, However, limitations include the limited light response range of TiO_2

and ongoing exploration of clinical translation. [16] FA-decorated GQDs help in the delivery of anticancer drug EVO to OSCC cells but do not address potential long-term effects, interactions with other medications, stability over time, challenges during experimental procedures, and resistance development. [17] BPNSs and AuNPs show superior inhibitory effects on OSCC compared to traditional drugs however, the risk of developmental perturbation with BPNSs remains even at lower concentrations. [18]

Chitosin/PCL nanoparticle is a novel carrier for 5-FU suggesting potential therapeutic utility. [19] While the RNA-ligand delivery system shows promising results in selectively targeting malignant cells, it does not address limitations associated with the stability of RNA-coated liposomes or its potential long-term effects on cellular function. [20] Theranostic nanoparticles enhance radiation therapy for head and neck tumors. These nanoparticles improve treatment precision by providing better imaging and help control tumor growth by enhancing the response to radiation. Overall, they show promising results in reducing metastasis and improving outcomes for patients. [25] Gold nanoparticles show early oral cancer detection, enhanced imaging, and chemical analysis. This allows for personalized treatment plans, catching cancer sooner for better outcomes and reducing the need for invasive procedures, making diagnosis simpler and more accurate. [26]

The chitosan-based nanogel, containing thiocolchicoside and lauric acid, shows strong anticancer effects against oral cancer cells, offering a promising option for non-toxic chemotherapy and targeted therapy. It works by inducing oxidative stress and affecting genes that promote cancer cell death. While this nanogel shows potential for cancer treatment, more research and clinical studies are necessary to ensure its effectiveness and safety in humans. Further studies will confirm its potential and guide its optimal use in oral cancer treatment. [24] MMP-1 antibody-conjugated FeAu nanoparticles show good results in treating squamous cell carcinoma (SCC) by inducing cancer cell death through hyperthermia and enhancing efficacy with the MMP-1 antibody, suggesting potential for targeted treatments. CDDP/CQ-PLA NPs offer a potential treatment for oral squamous cell carcinoma (OSCC) by triggering oxidative stress and promoting apoptosis, though more research is needed to understand their mechanisms.

Additionally, nanotechnology-based gene therapy shows potential for revolutionizing cancer treatment by downregulating gene expression and improving patient outcomes. [22] DOX-N-N-AuNPs can be used for treating difficult OSCC tumors, especially when combined with laser ablation, outperforming traditional methods. For TSCC, combining Gefitinib and curcumin effectively reduces cell viability, improving on individual treatments. [28] ZnO nanoparticles, with their antibacterial and UV shielding properties, activate the PINK1/Parkin pathway to damage cancer cell mitochondria and promote cell death, showing potential in cancer therapy. [29] Low-dose disulphide cross-linked micelle DCM-PTX NP acts as an efficient radiosensitizer in oral cancer preclinical models. This combination enhances nanoparticle retention at the tumor site and has a synergistic antitumor effect when used in combination with radiotherapy especially SBRT. [30]

Limitations

1. This study is built on the data available and the qualities of studies from which the data is sourced.
2. Only a limited number of databases were consulted for this study.
3. This systematic review does not address the potential long-term effects of various nanoparticles, their stability over time, resistance developed, and interaction with other drugs.

Conclusion

Nanoparticles represent an innovative approach for the fight against oral cancer. They are highly effective in the diagnosis and early identification of cancerous cells, improving the probability of effective treatment. By enabling targeted drug delivery, nanoparticles ensure that cancer therapies specifically attack malignant cells without harming healthy, non-malignant cells. This precision decreases the harmful effects typically related to traditional cancer treatments, making the overall treatment process more tolerable for patients. As research continues to advance, the use of nanoparticles could revolutionize oral cancer treatment, offering a safer, more efficient, and highly targeted approach to managing and potentially curing this life-threatening disease.

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2. **Saira Afridi:** Literature review and original draft writing
3. **Abid Khan:** Creating figures, charts, or other visual representations of data.
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