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Review Paper

The Insight of Nanoplatforms in Oral Cancer Therapeutics: An Updated Comprehensive Review

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ABSTRACT:

Oral cancer is one of the most common causes of death worldwide. Its nature of local invasion after metastasis is a growing source of concern for the medical community as a whole. Despite several attempts to improve traditional diagnosis and treatment techniques, worldwide mortality has not decreased significantly. As a result, the focus of modern research is on creating novel treatment protocols and drug delivery systems to reduce morbidity and mortality. For current researchers, the use of nanotechnology for such breakthrough therapeutic procedures has become increasingly valuable. This review provides updated knowledge from the scientific literature on nanotechnology's application in the treatment of oral cancer. It can be useful for implementing innovative approaches for oral cancer therapy in the near future.

KEYWORDS: Oral cancer, Nanoparticles, Therapeutics

INTRODUCTION:

Cancer is a generic term for a large group of diseases that can affect any part of the body. It is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020.[1] Any cancer that affects the oral cavity is referred to as oral cancer. In 2018, 354,864 new cases of oral cancer were reported, and about 177,384 people died from it. Oral squamous cell carcinoma (OSCC), the sixth most common cancer worldwide with a 50% 5-year survival rate, accounts for more than 90% of oral malignancies.[2] Carcinogenesis is a multifactorial disease process that includes genetic and epigenetic alterations, potential environmental risk factors such as excessive alcohol intake, tobacco usage, infections such as human papillomavirus (HPV) and other factors (e.g., disruption of the circadian clock). Surgery, chemotherapy, and radiation therapy alone or in combination are the primary components of conventional therapy regimens for oral cancer. Although these modalities have made considerable strides in the treatment of oral cancer, they also have significant drawbacks and side effects.[3] Professor Norio Taniguchi first used the word "nanotechnology", but it wasn't until 1981, with the invention of the scanning tunnelling microscope, that contemporary nanotechnology really got underway.[4] One of the most popular sub-disciplines of nanotechnology is nanomedicine, which focuses on target-specific cancer therapy. It has the potential to significantly improve the bioavailability of the drug and cellular uptake at the site of the primary tumor, enabling hope for overcoming the drawbacks of traditional anticancer drugs and boosting therapeutic efficacy.[5] The aim of this article is to provide an insight into various nanotechnology-based therapeutic approaches, with a focus on oral cancer.

PHYSIOLOGY OF NANOPARTICLES:

Nanoparticles (NPs) can be used for biotagging or labelling since they are the same size as proteins or cells. Due to their distinct size (1-100 nm) and high surface-to-volume ratios, NPs have the potential to provide answers to the existing challenges in cancer therapy. They concentrate at the location of solid tumours due to the improved penetration and retention effect. [6]

MECHANISMS OF TARGETING:

One essential property of nano-carriers for drug administration is the ability to target cancer cells while shielding normal cells from damage. Passive and active

targeting are the two basic categories of targeting systems.[7,8] (Table.1)

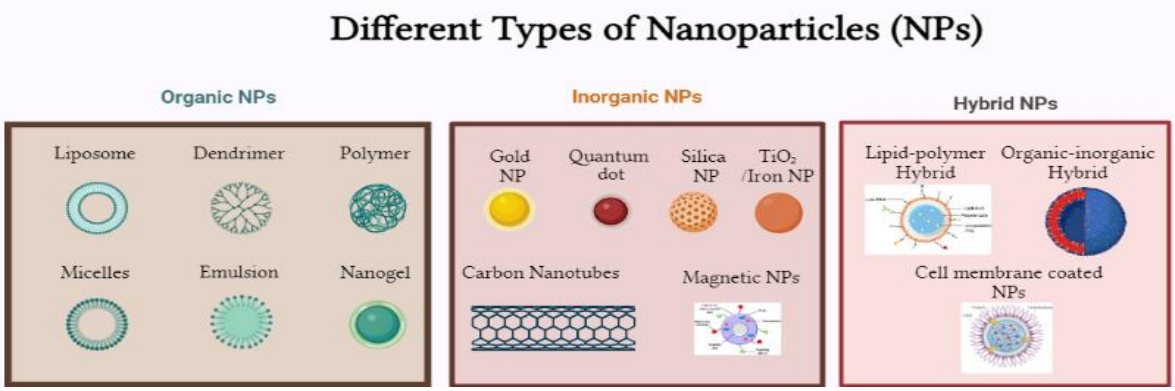
NANOPARTICLES	PASSIVE TARGETING	ACTIVE TARGETING
ACTION	Accumulate at the tumour site by Enhanced Permeation and Retention (EPR) effect.	Provide direct interactions between ligands and receptors on the surface of cancer cells.
ADVANTAGES	Prolonged systemic circulation Decreased side effects	Increase drug efficiency Crosses blood-brain barrier
LIMITATIONS	Multiple drug resistance. Certain tumors may not exhibit an EPR effect	Inhibited tumor penetration Non-specificity of ligands Receptor-mediated endocytosis
FORMULATIONS	Doxil, Abraxane, Genexol-PM	Herceptin R

ORAL CANCER THERAPEUTICS USING NANOTECHNOLOGY-BASED TREATMENT APPROACHES:

1. Nano drug-delivery systems
2. Nano photosensitizers in Photodynamic therapy
3. Nanotechnology-based cancer stem cell therapy
4. Gene therapy with Nanoparticles
5. Nanoparticles in cancer Immunotherapy
6. Biomimetic nanoparticles

NANO DRUG-DELIVERY SYSTEMS:

The physical and chemical characteristics of NPs can be altered and due to this property, it has gained popularity in targeted drug delivery systems. They can be organic, inorganic and hybrid NPs that can kill cancer cells by loading, stabilizing, and delivering chemotherapeutic drugs with various loading contents and release profiles.



ORGANIC NANOPARTICLES:

Organic NPs have been widely explored for decades and contain many types of materials like liposomes, polymer-based NPs, dendrimers, polymeric micelles and so on. Liposome, the first nano-scale drug approved for clinical application, consists of an outer lipid layer and a core entrapping either a hydrophobic or hydrophilic drug. Doxil (Doxorubicin HCl liposome injection), which was authorized in 1995 for the treatment of ovarian cancer and AIDS-related Kaposi's sarcoma, was the first nanosized liposomal medication to receive federal approval in the United States.[9] With decades of research, the development of liposomes has gone through several generations. They still represent a large proportion of clinical-stage nanotherapeutics due to their biodegradable, biocompatible, non-toxic, and non-immunogenic composition.[10] Polymer-based NPs are another type of NP with specific structural arrangements for drug delivery formed by different monomers. Polylactic-co-glycolic acid (PLGA), a common polymeric NP, encompasses the copolymerization of glycolic acid and lactic acid. PLGA is widely used as a carrier for drug delivery due to its better

biocompatibility and biodegradation, as well as the EPR effect.[11]

Gupta P et al used the nanoprecipitation approach to successfully encapsulate Docetaxel (DTX) in PLGA polymers at the nanoscale. The drug's release kinetics show that it releases the drug slowly. This in vitro research on the SCC-9 human tongue cancer cell line revealed that PLGA DTX NPs had higher antiproliferative efficacy than free DTX in a dose-dependent manner.[12] Dendrimers are a separate class of polymers that are also biocompatible, and they have a three-dimensional branch structure. The catalytic member of the telomerase complex, human telomerase reverse transcriptase (hTERT), is a promising therapeutic target for treating oral cancer. Liu X et al explored the properties and anticancer effects of short hairpin RNA (shRNA) against hTERT in oral cancer that is dendrimer-mediated by polyamidoamine (PAMAM). In vitro, dendrimer-mediated shRNA effectively suppressed the hTERT gene, inhibited cell growth and induced apoptosis. In a xenograft model, treatment with the shRNA dendriplex slowed the growth of the tumour. According to this study, RNA-mediated hTERT gene suppression in combination with dendrimer delivery may offer a promising method for treating oral cancer.[13] Additionally, polymeric micelles are another type of highly studied polymer NPs that exhibit polymer self-assembly into nano-aggregates due to their composition of amphiphilic copolymers. The hydrophilic portion promotes stability, which decreases the drug's uptake by the reticuloendothelial system and lengthens its duration in circulation, while the hydrophobic core allows the insoluble anticancer medications to be absorbed and administered effectively.[14]

INORGANIC NANOPARTICLES:

With a larger surface area to volume ratio, inorganic NPs have low toxicity, excellent tolerance of organic solvents, and good bioavailability, and they can be employed widely. Gold nanoparticles (AuNPs), carbon nanotubes (CNTs), quantum dots (QDs), magnetic nanoparticles (MNPs), and silica nanoparticles (SNPs) are some of the inorganic NPs that have been used extensively in diagnostic and therapeutic oncology, particularly in the treatment of oral cancer. Due to their inertness and lack of toxicity, AuNPs are viewed as a good choice for use in drug delivery systems. Surer SI et al synthesized the AuNP-conjugated cisplatin and cetuximab complexes (GNP–CTX–CDDP) as nanodrugs, and evaluated the efficiency of combination therapy with radiotherapy in the presence of the nano-drug complex for the radiotherapy-resistant oral cancer cell line, SCC-131 and found a greater reduction in their colony numbers.[15] Unique biological, physical, and chemical characteristics can be found in CNTs. They show the ease of cellular uptake, high drug loading and thermal ablation. SNPs of the type known as mesoporous silica nanoparticle carriers can encapsulate the most anticancer medication possible due to the enormous interior pore volume, which enables drug capture and release.[16] MNPs are frequently coated with organic components, including polymers and fatty acids, to increase their stability and biocompatibility, and they have great efficacy in chemotherapy and gene therapy for the treatment of cancer.[17] A tremendous promise for non-toxic chemotherapy exists with silver nanoparticles (AgNPs), which have unique qualities like surface plasmon resonance, electrical resistance, and high biocompatibility. Dziedzic et al. were among the first to demonstrate that OSCC cells, SCC-25 are less viable when Ag-NPs are administered alone.[18] Nano-crystals called QDs are made of a semiconductor core encased in a shell made of another semiconductor material. QDs nanocarriers boost drug efficacy and therapeutic index, promote drug molecule absorption, and lessen negative effects to enhance the physicochemical features of medications. Nanodiamonds (NDs) are tiny, have a high surface chemical interaction, are biocompatible and one of the most effective drug transporters. After a tumour has been removed, a localized area where cancer cells may still be present may be treated with a nano-diamond patch.[19]

HYBRID NANOPARTICLES:

Both organic and inorganic NPs have benefits and drawbacks. When these two are combined, a multifunctional carrier with superior biological properties is produced, which can boost treatment effectiveness and reduce drug resistance. Lipid-polymer hybrid NPs, which consist of an inner polymeric core and a lipid shell, have been demonstrated to be a promising drug delivery platform in the treatment of various cancers particularly oral cancer. Satapathy et al investigated the anti-angiogenic and anti-metastatic effects of a hybrid nanoparticle (QAuNP) made from quinacrine and gold on OSCC-CSCs. In a xenograft mouse model, QAuNP dramatically reduced cellular proliferation, induced apoptosis in vitro, blocked angiogenesis in vivo, and caused tumour regression. In the treatment of metastatic OSCC, QAuNP may serve as an effective therapeutic tool.[20] This form of hybrid NPs can encapsulate both hydrophilic and hydrophobic medicines to improve therapeutic efficacy because it combines the high biocompatibility of lipids with the structural integrity offered by polymer NPs. Meanwhile, this system can be efficiently internalised by cancer cells and avoid being quickly cleared by the reticuloendothelial system.

NANO PHOTOSENSITIZERS IN PHOTODYNAMIC THERAPY:

A new approach for treating a number of disorders is photodynamic therapy (PDT). It is based on the uptake of a photosensitizer (PS) molecule that, when excited by light of a specific wavelength, reacts with oxygen and produces oxidant species in target tissues, causing photooxidative stress (PhOxS), which results in photodamage of membranes and organelles, ultimately leading to cell death. To improve cellular targeting and uptake by the cell, certain PSs employed in PDT may need carrier systems, such as nanoparticles. Additionally, research has shown that adding specific nano-scale components to PS formulations may encourage an ambient triplet-excitation emission with a long lifetime. This can significantly increase photochemical efficiency, PS stability, tumour selectivity, and PDT success rate. Clinical experiments used Visudyne, the first photo nanomedicine formulation for PDT to receive approval in 2000. It is presently available in an aqueous liposomal formulation.[21]

NANOTECHNOLOGY-BASED CANCER STEM CELL THERAPY:

According to studies, stem cell markers play a significant role in boosting the effectiveness of chemotherapy and serving as a key component of targeted anticancer therapy. The effectiveness of targeted cell therapy drives the need for research into novel biomarkers in uncommon orofacial cancers, such as salivary gland and oral cancers, as well as the need to identify the most prevalent malignant stem cell markers that can serve as indicators for premalignant lesions, progression and the treatment of the malignant lesions. The various stem cell markers point to their potential roles as parts of a central regulatory system in embryological mechanisms that are particularly well-suited for self-renewal, retaining an undifferentiated state, and reorganizing adult cells.[22]

GENE THERAPY WITH NANOPARTICLES:

Exogenous nucleic acids, such as genes, gene segments, oligonucleotides, miRNAs or siRNAs are inserted into cells to alter a target gene's expression, produce mRNA or synthesize an exogenous protein. Therapeutic nucleic acids (TNAs) administered ex-vivo or in-vivo have been shown to transfer genes into tumour cells. The ex-vivo method involves the collection of patient-derived tumour cells, their normal 2D monolayer propagation, genetic manipulation and subsequent reintroduction into the host. Depending on the precise localisation, TNAs may be delivered via oral, ocular, transdermal, or nasal delivery methods to the tumor cells in-vivo, systemically via intravenous administration, or in a pre-systemic manner. Delivering TNAs to cancer cells has made it possible to treat cancer by suppressing oncogenes or re-activating tumor suppressor genes. The simplicity with which these nanostructures can be functionalized with various biocompatible chemicals, such as PEG, and targeting moieties (such as antibodies), encourages the active targeting of these moieties to the particular cancer cells with little toxicity.[23]

NANOPARTICLES IN CANCER IMMUNOTHERAPY:

Cancer treatment has entered a new era because of the introduction of immunotherapy. The anti-tumor immune response is mostly used in cancer immunotherapy. Nano vaccines, synthetic antigen-presenting cells (APCs), and targeting the immunosuppressed tumour microenvironment (TME) are all components of NP-associated immunotherapy. Tumor-associated antigens (TAAs) and adjuvants are delivered via nano vaccines to APCs such as dendritic cells (DCs). Additionally, NPs can operate as adjuvants by themselves to boost APC antigen presentation and encourage DC maturation, which will activate cytotoxic T cell's anti-tumor function. TAAs can be delivered into DCs cytoplasm by NPs such as liposomes, gold NPs, PLGA NPs, micelles, and dendrimers, which improves the immune response against tumour cells. Inorganic NPs, like mesoporous silica, and polymers, like acetylated dextran (AcDEX) have been demonstrated to serve as an adjuvant in immunotherapy, stimulating the immune response.[24]

BIOMIMETIC NANOPARTICLES FOR ORAL CANCER THERAPY:

Currently, to improve the bioavailability and targeting ability of therapeutic medications, biomimetic carriers are in use. These include vitamin-coated NPs, exosomes secreted by various cells, synthetic peptides and virus-like particles.[3]

ADVANTAGES OF NANOPARTICLES IN CANCER THERAPY:

- The application of nanotechnology in cancer therapy increases the concentration of drugs within cells while minimising damage to healthy tissue.
- The NPs can be programmed to control drug release based on temperature or PH sensitivity.
- To get around the adverse effects of conventional treatment, surface-modified NPs extend the drug's half-life and circumvent this process.
- It is known that NPs can pass the blood–brain barrier and can be delivered in cases of brain tumours via a variety of methods, including EPR effect, focused

ultrasound, peptide-modified endocytosis, and transcytosis.

- While acting as a carrier, NPs improve the stability of drugs by inhibiting the enclosed cargo's degradation.

CHALLENGES IN THE CLINICAL APPLICATION OF NANOPARTICLES:

- NPs encounter certain challenges that fall under the categories of biological, technical, and research design-related problems.
- Limitations in the route of administration, tempered biodistribution, the passage of NPs over biological barriers, and their breakdown and toxicity are biological obstacles.
- Even if NPs are made of biosafety materials, several studies have demonstrated that free radicals produced by NPs frequently harm healthy cells.
- Scale-up synthesis, equal optimisation, and performance projections are NPs' technological hurdles.
- There are many study design issues that have a substantial impact on clinical studies, including study size, intent, and timing of NP treatments along the course of treatment.[25]

CONCLUSION:

For the treatment of oral cancer, recent developments in nanotechnology are promising and few are in day-to-day practice. These carriers can be loaded with anticancer cargoes based on their targeted drug delivery systems with tailored architectures and diverse physicochemical features. Currently, in-vitro or in-vivo studies are still the main focus of most research. Further research is required to translate the concepts of nanotechnology towards usable applications in a multidisciplinary setting for the treatment of oral cancer. In the near future, the emergence of personalized medicine will result in improved therapeutic outcomes, lower costs and high survival rates that will benefit both oncologists and patients.

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