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Way to Cure Oral Squamous Cell Carcinoma with Theranostics and Nanoparticulate Approaches

Sankha Bhattacharya

Abstract

One of the most prevalent forms of oral cancer is oral squamous cell carcinoma (OSCC), a major cause of morbidity and mortality worldwide. Following a definite oral cancer diagnosis, OSCC is typically treated with a multidisciplinary approach including surgery, chemotherapy, and radiation. In contrast, conventional chemotherapy medicines may be ineffective and have a range of side effects. Many techniques have been proved and authorized for treatment and diagnostics of different types of oral cancer, while others are currently being investigated in clinical trials. This book chapter is aimed to explain the current preclinical status of nano-based techniques to successfully diagnose and treat OSCC. This book chapter would also emphasize recent theranostics approaches utilized to cure OSCC. Nanotechnology also improved cancer biomarker detection, making them faster and more sensitive. To overcome these constraints and improve *in situ* drug delivery, various nanoparticles have been employed as innovation drivers.

Keywords: squamous cell carcinoma (OSCC), matrix metalloproteases (MMPs), magnetic nanoparticles (MNPs), HSC-3 cells, vital protein endothelial growth factor (VEGF), C-reactive protein (CRP)

1. Introduction

According to the World Health Organization (WHO), cancer would take the lives of 10.3 million people globally by 2020, and patients with oral cancer would have a five-year survival rate of just 50% globally. Oral cancer is a challenging disease that affects about 600,000 individuals worldwide each year and is linked to a high rate of morbidity and mortality [1–4]. Mouth cancer is a group of tumors that may affect any area of the mouth, including the pharynx and salivary glands, as well as the surrounding tissues [5]. This term, on the other hand, is often interchanged with oral squamous cell carcinoma (OSCC), the most common malignant epithelial tumor of the oral cavity. OSCC is thought to be responsible for more than 90% of all oral neoplasms [6]. According to the current study results, year survival rates for OSCC range from 50 to 60%, depending on a number of factors such as the patient's lifestyle, the timing of diagnosis, and the location of the primary tumor [7, 8]. As a consequence, OSCC is linked with a poor prognosis in the medical community. Patients with OSCC who get conventional therapy have a significant recurrence rate of the illness, regardless of when treatment started (18–76%). The use of biopsy or histology testing to diagnose OSCC is time intensive, resulting in a

delay in treatment initiation, and as a result, a shorter overall survival time period is obtained [9]. Early-stage cancer detection is critical in determining the most suitable treatment for the patient, which has an impact on their total survival, as stated in the previous paragraph. According to recent research studies, the development of cancer is related to the molecular level of particular indicators in tumor tissue and bodily fluids. Molecular biomarkers, which are categorized as genomic, proteomic, and metabolomic profiles of body specimens, are used to identify the existence or absence of a certain malignancy, as well as its spread and recurrence, among other things. Science and technology focused on extremely small objects, and nanoscience and nanotechnology are providing innovative methods to cancer treatment and detection. Site-specific chemoprevention/therapy using nanoparticles for local drug delivery has recently gained popularity. It is a novel method for treating cancer that aims to overcome and minimize the limits of current cancer treatment and diagnostics. It can detect a single cancer cell *in vivo* and administer drugs straight to it. Nanotechnology has also improved the detection of cancer biomarkers [10–12]. Oral cancer is often treated with a multidisciplinary approach that involves surgery, chemotherapy, and radiation. However, conventional chemotherapy medicines may be ineffective and have side effects. Many nanoparticles have been employed as technological drivers of innovation to overcome these constraints. The present book chapter seeks to highlight developments in the use of new methods in the detection and treatment of oral cancer due to the significance of OSCC as a widespread public health issue. The purpose of this book chapter is to describe the current preclinical state of nano-based methods for oral cancer detection and therapy. This review also discussed (a) oral squamous cell carcinoma, (b) OSCC diagnosis using serum and saliva biomarkers, (c) nano-based OSCC biomarker detection, (d) OSCC therapy methods, and (e) nanotechnology techniques for OSCC treatment or diagnostic.

2. Squamous cell carcinoma of the oral cavity

Oral cancers are a group of cancers that develop in different parts of the mouth, each with its own set of risk factors, incidence, and treatment options [13]. Understanding the mechanisms of cancer initiation and progression may aid us in selecting the most appropriate therapeutic strategy at the appropriate time. Despite advances in therapeutic methods, the morbidity and mortality ratios for squamous cell carcinoma of the oral cavity have remained unchanged for the past 30 years. After a carcinogenic insult to the oral cavity, it occurs in several steps, resulting in various molecular changes that disrupt cellular growth, proliferation, and differentiation. The latter is marked by cellular transformation and carcinogenesis. Oral carcinogenesis follows the same pattern as other cancers, starting with a precursor lesion and progressing to localized and metastatic disease [14]. The histological grade of dysplasia indicates how far the disease has progressed from normal to hyperplasia. The most common cellular events discovered in these examinations are changes in nuclear size and shape, enlarged cells and nuclei, enhanced mitotic picture, and increased nucleus/cytoplasm ratio. Elevated cellular density, dyskeratosis, hyperplasia of basal cells, bulbous drop-form of rete pegs, and secondary nodules on rete tips are pathological features of tissues in the later stages of squamous cell carcinoma.

3. Biomarkers in oral squamous cell carcinoma (OSCC)

Early detection of OSCC improves life quality while lowering the cost and side effects of medical treatments. Because OSCC has such a high recurrence

rate, early detection is crucial in determining the disease's prognosis [15]. OSCC remains a significant challenge due to the disease's nature, despite recent advances in this area. As a result, as discussed in this book chapter, monitoring the level of biologic markers with high specificity and sensitivity is a promising diagnostic tool for both primary and recurrent oral cancer detections. According to the National Institutes of Health, biomarkers are indices of normal or pathological conditions that can be reliably and precisely measured [16]. Mutated DNA, mRNA, metabolomes, secreted proteins, and small molecules are examples of biomarkers [17, 18]. A cancer biomarker is a molecule that is secreted by a tumor or produced in response to the onset or progression of cancer. In addition, the ideal biomarker should be a noninvasive method with high-positive and high-negative predictive values that reflect the stage of cancer. As a result, the marker can be used to predict treatment efficacy, diagnosis, and prognosis in cancer patients.

3.1 OSCC salivary biomarkers

Saliva collection is easy and painless, making it a promising biomarker discovery tool. The changes in the saliva genome and protein profile after the onset of cancer or as the disease progresses in oral cancer have been studied in several studies [19, 20]. When collecting, processing, and storing saliva, however, some acquaintances should be considered. Cross-validation is required before extrapolating biomarkers into clinical applications. Different data collection, processing, and analysis techniques could explain the wide range of results seen in studies looking for salivary oral cancer biomarkers. As a result, more research is needed to standardize the aforementioned techniques as well as reference levels in order to obtain valid biomarkers.

3.2 Salivary RNA-base biomarkers

In the mouth, salivary RNAases were supposed to break down RNA. These alluring biomarkers, on the other hand, are obstinate, being carried in apoptotic bodies or actively liberated from cellular vesicles such as exosomes. Oral cancer patients have been found to have low levels of miRNA 200a and miRNA 125a, but significantly higher levels of miRNA 31. Upregulated miRNA 184 and downregulated miRNA 145 have also been linked to malignant oral cancer.

3.3 Salivary protein-based biomarkers

Cancer biomarkers could include oxidative stress markers. Carbonylation causes irreversible protein damage, which leads to cell toxicity. In OSCC patients, the infiltration of reactive radicals into the oral epithelial cells results in a significant increase in salivary carbonyls. Matrix metalloproteases (MMPs) are enzymes that degrade a wide range of proteins. During OSCC, which is highly invasive and metastatic, different types of MMPs have been shown to be significantly altered. MMP-2 and MMP-9 expression in oral cancer patients has been linked to a poor prognosis in the wild. The immune system produces proteins called interleukins (IL). In cellular signaling cascades, naturally occurring proteins play a variety of roles, some of which are critical in cancer. Interleukin-6 (IL-6) and interleukin-8 (IL-8) are two different types of interleukin-6. The prevalence of OSCC has been reported to be on the rise. The cytokeratin fragment 21-1 is a squamous tumor marker (Cyfra 21-1).

4. Serum biomarkers

During tumor development, the release of synthesized markers into the circulation results in an increase in markers in cancer patients' serum, which can be used to predict the development of the cancer itself. The secreted origins of tumor-specific or tumor-associated serum biomarkers are known. Taking regular measurements of these biomarkers could provide valuable insight into how patients respond to anticancer treatments in the long run. Both the progression of the disease and its treatment are discussed in detail. Adiponectin is a protein hormone that can be found in the bloodstream and performs a number of different functions. It aids in the digestion of glucose and fatty acids in the bloodstream. Guo et al. discovered that the levels of adiponectin were higher. The incidence of tongue squamous cell carcinoma (TSCC) has dropped significantly. Hypoadiponectinemia has also been associated with lymphoma in some studies. The prognosis for TSCC metastasis is abysmal. Another protein, hemoglobin (Hb), being associated with an increased risk of oral cancer in the opposite direction. Reduced hemoglobin levels and anemia have been linked to increased tumor oxygenation and lymph node metastasis, and Hb corrections have been shown to improve prognosis in cancer patients.

Low hemoglobin levels indicate advanced OSCC, especially in larger tumors requiring more radical treatment. Pro-inflammatory cytokines are a group of small proteins that play a role in inflammation. Oral cancer is the most common link. In a prospective study, Schiegnitz et al. looked at the role of IL-6, 8, soluble IL-2 receptor (SIL-2R), MHC class I polypeptide-related sequence B (MICB), and tumor necrosis factor alpha (TNF- α) in OSCC. According to their findings, all of these biomarkers showed an upward trend in serum samples from oral cancer patients. Promising OSCC prognostic indicators have been identified as IL-6 and SIL-2R. Chang et al. also discovered a link between oral cancer clinical manifestations and blood levels of 12 cytokines. However, the results of a different study refuted these assertions. Individual or panels of serum cytokines are not appropriate oral cancer biomarker candidates due to these discrepancies and heterogeneous literature searches. However, it has been suggested that some inflammatory and immune system-related proteins are self-contained. Oral cancer metastasis indicator C-reactive protein (CRP), for example, is an IgG analog that stimulates the release of pro-inflammatory cytokines. CRP is an inflammatory marker that has been linked to a variety of diseases and cancers. Previous research has looked into the relationship between OSCC size, stage, and subsequent survival and CRP serum levels. Elevated serum CRP has been proposed as a predictor of poor prognosis and a low survival rate in oral cancer patients. The soluble protein Decoy receptor 3 (Dcr3) prevents programmed cell death. It is a member of the TNF receptor family. Several cancers have been found to have a high rate of cell death and amplification. According to estimates, when lymph node metastasis occurs at the same time as OSCC, the prognosis is worsened. In this context, serum MMPs have also been investigated. Liu et al. investigated the link between MMP-9 and pathological manifestations in oral cancer patients in a survey. A higher level of this factor was discovered to be linked to a shorter life expectancy. On the other hand, some of these serum proteins have been suggested as potential biomarkers for OSCC diagnosis but not prognosis prediction. For example, MMP-3 levels have not been linked to OSCC clinicopathological features. As potential biomarkers, different levels of growth factors in the serum of oral cancer patients have been proposed. Vascular. In various tumor propagation processes, the vital protein endothelial growth factor (VEGF) is thought to induce angiogenesis. Nodal metastasis and advanced OSCC have been linked to higher levels of this factor. Furthermore, in a 6-month cumulative survival study, the results of a 12-month study OSCC serum insulin-like growth factor (IGF) and survival were found to be strongly linked.

5. OSCC treatment strategies based on nanomaterials

Low levels of cancer biomarkers in tumor tissue or body fluids, a narrow margin between non-cancerous and cancerous samples, and the sensitivity of measurement assays are all major roadblocks to precise cancer biomarker detection. As a result, the ideal biomarker is one that can detect even the tiniest tumor cells using specific biomarkers before cancer progresses and clinical symptoms emerge. Previously, a variety of methods for measuring multiple biomarkers were developed, with immunoassays like ELISA becoming the most popular technique for protein detection due to low detection limits. However, this area has some limitations, including a long detection time, high costs, and a small sample size. Some novel approaches are currently being used. Polynucleotide barcodes, multiplexed bead platforms, and microarrays, for example, have superior limits of detection but are costly and require technical expertise. They are widely available in clinics and are efficient and cost-effective methods for detecting cancer biomarkers, despite scientists' attempts to put in place some quick and sensitive measures. Nanotechnology, for example, is gaining popularity among scientists in this field. In a study by Sungyub et al., gold nanoparticles were used to conjugate with DNA probes in oral cancer salivary samples. S100 calcium-binding protein P (S100P) mRNA was found to have a detection limit of 3 nM as a potential OSCC biomarker. The use of nanotechnology in the *in vitro* treatment of oral cancer is demonstrated in Figure 1.

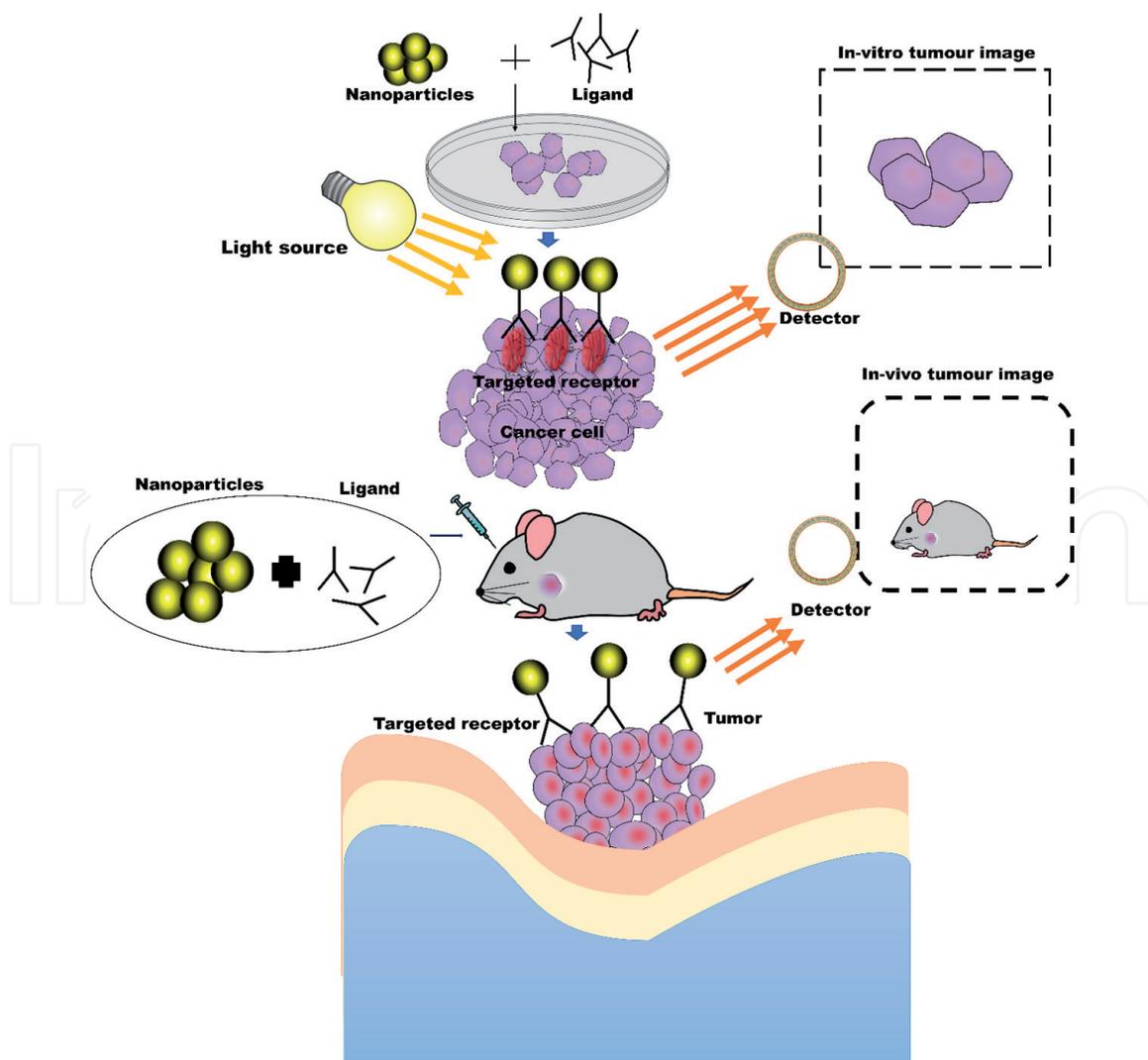


Figure 1. In vitro and in vivo imaging of oral cancer using nanotechnology has been demonstrated.

6. OSCC treatment strategies based on nanomaterials

Traditional therapeutic approaches to treating OSCC are associated with a number of side effects that can be both temporary and permanent. Oral carcinogenesis has been shown to respond well to novel treatment approaches. This group could include therapeutic molecules such as siRNAs and various active targeting ligands. Several natural products have also shown promise in the treatment of oral cancer by interfering with various cell signaling pathways such as free radical scavenging, inhibiting the formation of DNA adducts, and regulating the properties of apoptosis-related genes. However, these compounds' low bioavailability and solubility have limited their clinical application. As a result, it is critical to improve preventative and therapeutic strategies. For the development of drug delivery systems, the time of drug contact with oral tumor cells is an important consideration. As a result, a sustained and targeted mucoadhesive drug delivery system into the oral cavity has been developed. The residence time of nanoparticles can improve drug mucus interaction and result in better results. The studies also revealed that local delivery of nanoparticles can be used for site-specific chemoprevention and therapy. Nonspecific drug uptake is reduced by cells to improve drug targeting into the oral cancer site. The reticuloendothelial system (RES) and improved plasma half-life, which result in lower drug dosage, are two other advantages. The aspects of cancer therapy are based on nanoparticles. According to scientific reports, various types of nanoparticles have been tested for cancer therapy. Some of the most recent nanoparticles that have been tested for the treatment of drug-resistant cancer cells include magnetic nanoparticles (MNPs), liposomes, polymeric nanoparticles, gold (Au) nanoparticles, and nano-diamonds. Various nanotechnology approaches can be used to selectively target cancer biomarkers and cancer cells. The use of specific crosslinkers against cancer cells, such as antibodies or aptamers, can also facilitate the development of early detection methods. **Figure 2** summarizes the potential therapeutic approaches.

Oral oncogenesis is a type of cancer that starts in the mouth and spreads to the rest of the body. Nanocarriers are also being developed that are functionalized with various targeting agents (ligands, tumor-associated proteins). Antigens, antibodies, and aptamers have shown promise in improving the cancer cell delivery of a specific target. In a variety of main cancer immunotherapy or target drug/gene delivery pathways, this strategy can use a single agent or a combination of agents. It can be viewed as a primary strategy involving specific interactions between the nanocarrier and receptors on the target cancer cell, which could promote nanocarrier internalization endocytosis through receptors. A basic understanding of cell biology, tumor biology, and immunology is required for the rational design of NPs for cancer therapeutics, and advances in nanotechnology will be heavily reliant on advances in cancer biology. Magnetic nanoparticles (MNPs) are one of the most researched nano-delivery systems in cancer treatment. The MNPs showed high efficiency and ideal drug loading when coated with oleic acid and embedded with anticancer agents such as doxorubicin and paclitaxel, according to the reports. Various researchers have investigated them for therapeutic approaches such as hyperthermic therapy, that is, magneto hyperthermia (MHT). The toxicity of this method was reduced while the specific lysis of tumor cells was increased. Candido et al. investigated the effects of polyphosphate-coated MNPs on human OSCC (UM-SCC14A). Their findings showed that cancer treatment with magneto hyperthermia can be effective related to cell death in the target cancer tissue. According to the authors, there were two main findings from MNP-based magneto hyperthermia treatment: a high level of apoptosis and fibrosis, as well as an inhibition effect on cell proliferation. As a carrier for anticancer drug delivery, polymeric nanoparticles

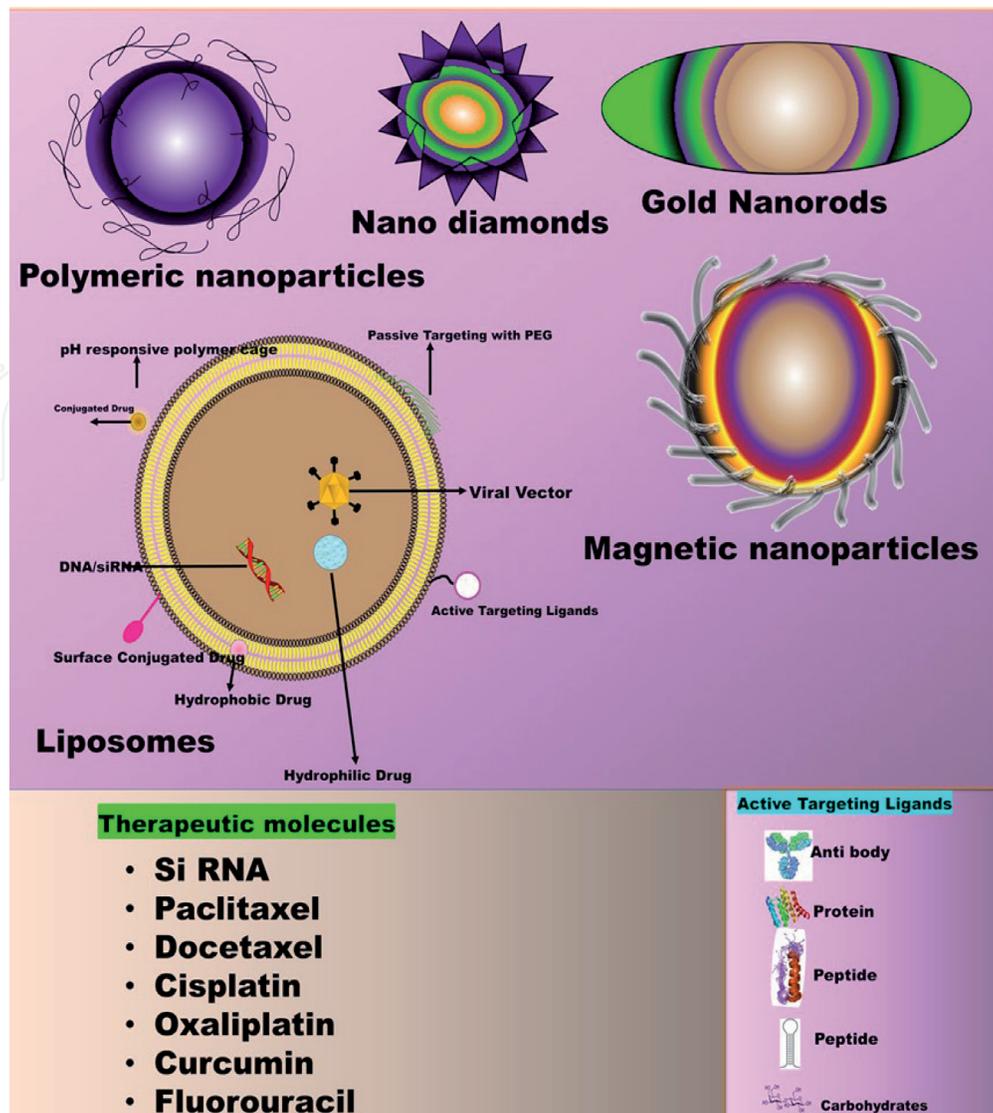


Figure 2. There have been advancements in the treatment of oral cancer. A wide range of drugs and/or therapeutic molecules are used to treat oral cancer. Nanocarriers show promise in the development of effective oral oncology therapy, in addition to active targeting ligands.

have been shown to be impactful. It is one of the most widely used nanoparticles *in vitro* and *in vivo*. However, before they can be used in clinical trials, they must overcome a number of challenges. In addition to low molecular weight drugs, polymeric nanoparticles have demonstrated the ability to transport macromolecules such as proteins and genes. Hydrophilic polymers, such as polyethylene glycol (PEG), aid in the stabilization of nanoparticles, which improves drug targeting into cancer sites by reducing nonspecific drug uptake by cells, according to the studies. These nanoparticles are less toxic, have a higher level of stability, and have a higher loading capacity, according to reports. Because of the properties of drugs that are not soluble in water, the use of biodegradable polymers has increased dramatically in recent years, such as increased plasma half-life and reticuloendothelial system inhibition of fast clearance (RES). Biodegradable linkages can be used as a backbone to assist in the formation of high-surface-area nanoparticles. In the case of apoptosis induction in SCC-9 human OSCCs, PCL nanoparticles with curcumin were coated with chitosan, which showed promising outcomes of this research. When Sulfikarali et al. used the nanoprecipitation method to create naringenin-loaded polymeric (Eudragit E) nanoparticles and tested their anticancer activity in hamster carcinogenesis, they discovered that they had a significant anticancer effect. The prepared nanoparticles (with an average size of 90 nm) had an encapsulation

efficiency of 88%, indicating that they were effective at encapsulating their surroundings. They discovered that a polymeric drug-loaded nanoparticle improved the anticancer efficacy of naringenin and had better antilipid peroxidative, antiproliferative, and antioxidant properties than the free drug. When developing controlled-release mucoadhesive drug delivery systems, the time at which the drug comes into contact with oral tumor cells is an important factor to take into account. The development of a long-acting, targeted mucoadhesive drug delivery system for the oral cavity may be advantageous as a result. To create a mucoadhesive patch of methotrexate (MTX)-loaded liposomes for targeted delivery in OSCC, Jin et al. used the thin film hydration method, which they developed in-house. The liposomes that were prepared had a mean particle size of 105 nm and a loading efficiency of 54%, respectively. Using an MTT assay, HSC-3 cells were utilised to examine the cytotoxicity of the liposomes that had been generated. The mucoadhesive buccal patches had appropriate bioadhesive qualities as well as the potential to offer sustained MTX release, according to the scientists. According to their findings, oral mucoadhesive patches for oral cancer can be utilised as a primary strategy to bypass the constraints of targeted delivery in oral cancer chemotherapy, lowering the required dose while reducing drug toxicity. According to the researchers' findings, the nanoparticles they prepared had a pro-oxidant effect in HSC-3 cells due to the high levels of ROS present in their experiments. Due to the ease with which they can be prepared, their high biocompatibility, and their ideal functionalization properties, gold (Au) nanoparticles are gaining attention in the field of cancer therapy. It is possible that their ability to conjugate with other biomolecules without altering their biological properties will prove to be a very useful option for the treatment of oral cancer, having the ability to conjugate a wide range of mucoadhesive substances. The combination of biopolymers and the outstanding properties of Au nanoparticles, such as their non-cytotoxicity, has resulted in their widespread application, which is used in a variety of biomedical applications and drug delivery systems to treat a variety of oral cancer cells of different types. Furthermore, these nanoparticles are one of the most well-known cancer nanoparticles due to their surface plasmon resonance, which is a property of surface plasmon resonance. The importance of early detection cannot be overstated. In order to improve the early detection of diseases such as cancer, as previously stated, many studies are being conducted and expanded. For bio-imaging and diagnostic applications, nano-diamonds have attracted considerable attention due to their low toxicity, ideal surface properties, and stable fluorescence that does not fade when exposed to ultraviolet light. These nanoparticles can also be used to immobilize proteins, making them excellent candidates for local drug delivery into oral diseases such as oral cancer.

7. Conclusion

Oral cancer is a type of cancer that primarily affects oral epithelial cells, but it can also spread to other parts of the body and be fatal. The most common type of cancer is OSCC, which accounts for more than 90% of all oral cancers. OSCC remains a serious public health concern despite extensive research because of its poor prognosis. Novel chemoprevention technologies are becoming increasingly important as traditional therapeutic methodologies are frequently insufficient. Nanotechnology has proven to be extremely beneficial in this case. Nanoparticle-based diagnostic methods for OSCC detection and diagnosis are capable of providing real-time, appropriate, and cost-effective diagnoses. They can show molecular-targeted imaging, nano-scale biomarker analysis, and post-treatment OSCC prediction. Bioconjugate nanoparticles have a wide range of applications for

amplified transduction of biomolecular recognition events, as demonstrated by the studies described above. Because of their optical and electrochemical applications, such nanoparticle labels serve as the foundation for ultrasensitive protein and nucleic acid assays. This book chapter summarized the most recent advances in nanoparticles for oral cancer diagnosis and treatment. Nanoparticles have been studied for their unique physicochemical properties, such as their ultrasmall size, high reactivity, and ability to be functionalized. It has been demonstrated that accurate and timely oral cancer diagnosis tools, as well as highly effective oral cancer treatment strategies, exist. Nanoparticles can be used to visualize oral cancer, deliver therapeutic agents to tumors selectively, and destroy tumors by using a variety of therapeutic techniques. Hybrid systems, in particular, will garner more attention because they provide nanoparticles with a flexible platform for achieving bio-multifunctionality. The use of nanomedicine in the modern diagnosis and treatment of oral cancer is very exciting. Despite the fact that nanoparticles have a wide range of potential applications in the treatment and prevention of diseases, the nanomedicine field is currently limited in its use of nanoparticle technologies in the prevention and treatment of oral cancer. The studies in this collection focused on therapeutic activities, which were mostly conducted *in vitro* or in preclinical oral cancer models. Because of the complex pathophysiology of oral cancer, such as abnormal hemodynamics, the pharmacokinetics and biodistribution of therapeutic agents can vary, leading to misleading results. Because of the high sensitivity of the new nanoparticle-based sensing protocols, they can detect disease markers, biothreat agents, and infectious agents that are not detectable by traditional methods. Methods of the past early disease detection or terrorist attack warnings could be provided by such highly sensitive biodetection schemes. Although the use of nanoparticle tags for protein detection is still in its early stages, the lessons learned in ultrasensitive DNA detection should be useful. Nonspecific adsorption issues, which frequently limit bioaffinity assay detectability, must be carefully considered for the successful implementation of the new signal-amplification strategies. Proper washing and surface blocking steps should be used to avoid amplifying the cation of background signals (associated with non-specific adsorption of the nanoparticle). Although there were *ex vivo* studies of tissue and saliva samples, as well as *in vivo* training in animal models, more experiments must be applied before these strategies can be implemented. In the near future, nanobiosensors are expected to play a larger role in electroanalytical science. For clinical applications, protocols for the synthesis and functionalization of nanoparticles must be developed. Early disease detection, genetic mutations, and bio-targets appear to have the greatest implications. Nanomaterial-based biosensors offer quick, simple, and sensitive cancer detection systems that could be useful in anticancer biosensor research.

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Competing interests

The author declares that the author has no competing interests.

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