REVIEW

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Oral Squamous Cell Carcinoma: A New Era in Molecular Mechanisms and Emerging Targeted Therapies

Bhavana Harendra[1,2], Ashwini P[1], Kavana C P[3], Abhigna Nagaraj[3], Chandan Dharmashekar[1], Shuaib Pasha[3], Devanand D[2], Shivaprasad Kollur[4], Raghavendra G Amachawadi[5], Chandan Shivamallu[3]*

Abstract

Objective: Oral squamous cell carcinoma (OSCC), the most common oral cancer, presents a clinical challenge due to its complex tumor microenvironment (TME), dysregulated pathways, and poor prognosis. Current methods of diagnosing OSCC use liquid biopsy technologies (ctDNA/microRNAs/exosomes) instead of relying solely on traditional methods such as open surgical biopsy. Liquid biopsy technologies provide non-invasive ways to detect and monitor OSCC in early stages, compared with traditional open surgical biopsy methods. Treatment of OSCC currently relies on chemotherapeutics (cisplatin/5-FU), radiotherapy, and targeted agents (cetuximab). However, resistance is acquired due to TME remodelling (tumor microenvironment) and/or due to epithelial–mesenchymal transition (EMT) through processes such as ABC transporter efflux. This review elucidates key molecular mechanisms, including PD-L1-mediated immune evasion, PI3K/AKT/mTOR hyperactivation, EGFR overexpression, and NF-κB-driven inflammation, which promote proliferation, metastasis, and therapy resistance. One area of study involves the use of nanotechnology to convert phytocompounds (medicinal plants) into therapeutic agents by embedding phytocompounds into nanoparticles created using green synthesis techniques. EPR (Enhanced Permeability and Retention), ligand functionalization for OSCC targeting, improved bioavailability, and reduced toxicity are all advantages that the aforementioned systems provide, offering an opportunity to synergistically develop new therapies with chemotherapeutics for overcoming resistance. **Conclusion:** While numerous preclinical studies demonstrate that these newly developed therapies show increased efficacy compared with current therapy options, further work is needed in areas such as standardization, scaling, and clinical translation. As such, the importance of developing pathway-informed diagnostic tests and developing therapies that exploit pathway-specific activity with phytocompounds is emphasized. In addition, large-scale studies should be considered to evaluate the effectiveness of a pathway-informed approach in assessing and differentiating OSCC and personalized therapy strategies, to improve OSCC survival outcomes.

Keywords: Oral cancer- targeted therapy- nanoparticles- phytocompounds- combination therapy

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Introduction

An Overview of Cancer

Cancer is a chronic illness characterized by abnormal cell proliferation and duplication that is responsible for a significant number of deaths and afflictions throughout the world, cancer is one of the top three causes of death in the world, with approximately 18 million individuals diagnosed through the new diagnostic criteria of the American Cancer Society of 2023, and approximately 8 million people dying from cancer each year. In many developed countries there have been tremendous improvements regarding patient survival following this chronic illness; however, to continue to improve the prognosis of patients who endure this debilitating illness, additional advances must be made in research, technology and healthcare delivery [1].

Apart from its alarming prevalence, HNSCC is dangerous for several reasons: late diagnosis often occurs because the initial symptoms can be very vague, resulting in advanced-stage detection that complicates treatment; its aggressive nature allows for rapid metastasis to lymph nodes and distant sites, contributing to high mortality rates; the location of tumors can severely

*[1]Department of Microbiology, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India. [2]Department of Biochemistry, JSS Medical College, Academy of Higher Education and Research, Mysuru, Karnataka, India. [3]Department of Biotechnology and Bioinformatics, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India. [4]School of Physical Sciences, Amrita Vishwa Vidyapeetham, Mysuru, Karnataka, India. [5]Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, USA. *For Correspondence: chandans@jssuni.edu.in*

impact vital functions such as swallowing, speaking, and breathing, leading to extensive surgeries that affect patients' quality of life; psychosocial issues arise from visible disfigurement post-treatment, resulting in social isolation and increased psychological distress; resistance mechanisms in tumors often render standard therapies less effective; and the diverse etiology including tobacco use, alcohol consumption, and viral infections like human papillomavirus (HPV) complicates prevention strategies [2]. India, for instance, Is the highest for Lip and Oral cavity Cancer i.e. 143,759 cases per 100,000 population (2022), with 258,440 cases across Asia; this accounts for the largest number of anterior surface of the hard palate (A/S/H/S). with countries like India and Sri Lanka having particularly high male death tolls due to oral cancer. To combat the issues created by head and neck squamous cell carcinomas, we must utilize early detection techniques, create public health initiatives targeted toward reducing risk factors, and develop novel personalized therapy [3].

Major Causes of Oral Cancer

The development of Oral Squamous Cell Carcinoma (OSCC) is a complex process resulting from a combination of risk factors. Tobacco use, Alcohol abuse, Betel quid chewing, Human Papilloma Virus (HPV) infection, Nutritional Deficiencies, Immune Suppression, and Inherited Disorders such as Dyskeratosis Congenita and Fanconi Anemia, are all examples of risk factors for OSCC (Figure 1). Carcinogens associated with these processes, including Ethanol, Tobacco Specific Nitrosamines (TSNs), and other substances such as Polycyclic Aromatic Hydrocarbons (PAH) and long-term exposure to Heavy Metals, contribute to DNA injury and chronic inflammation. The presence of these risk factors, in addition to Epigenetic Modifications such as DNA methylation and Histone modifications, combined with Genetic Alterations, lead to the aberrant activation of Oncogenic Pathways (e.g. Epidermal Growth Factor Receptor (EGFR), Wingless/Wnt, Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT), Phosphatidylinositol 3-kinase/AKT/mTOR (PI3K/AKT/mTOR) and other pathways), and the inactivation of Tumor Suppressor Pathways; this process is the basis for the Initiation and Progression of OSCC [4, 5].

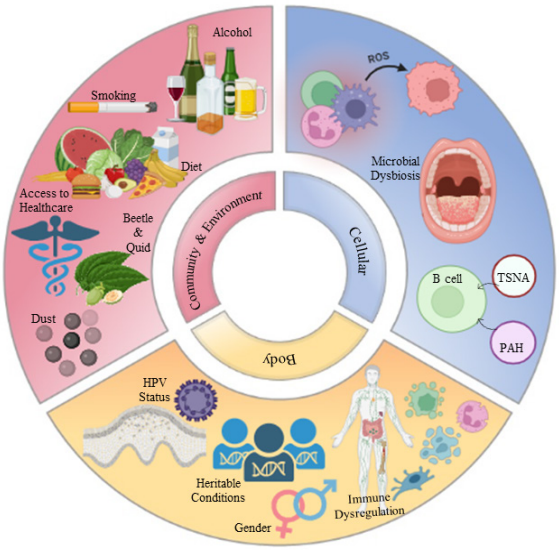

Figure 1. The Multifactorial Etiology of Disease, Encompassing Environmental and Community-Level Influences, Cellular Mechanisms, and Systemic Contributors

Tobacco consumption represents one of the most significant Risk Factors for OSCC. It involves the exposure of keratinocytes to various Carcinogenic Agents such as Benzopyrene and Tobacco Specific Nitrosamines (TSNs) e.g. N'-Nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Together, these agents are responsible for inducing DNA damage and mutations in the genetic material of Keratinocyte Stem Cells. Individuals who carry Genetic Polymorphisms in metabolic enzymes such as Cytochrome P450 (CYP) and Glutathione-S-Transferase (GST) are at an increased risk for Head and Neck Cancer (HNC). Finally, the concurrent use of Smokeless Tobacco and Marijuana increases an individual's likelihood of developing OSCC substantially [6].

One of the metabolites from Ethanol is Acetaldehyde, a and carcinogenic compound; it elicits numerous effects on the body, the most pertinent to carcinogenesis are the generation of reactive oxygen species (ROS) and the induction of oxidative stress. Genetic alterations within the enzymes responsible for converting ethanol to acetaldehyde (ADH) and removing acetaldehyde from the body (ALDH), increase the likelihood of developing cancer (Figure 2). The combination of smoking and heavy drinking greatly increases the risk of developing oral squamous cell carcinoma (OSCC) by increasing the permeability of the oral mucosa. Betel quid, popular throughout Southeast Asia and the Indian subcontinent, is made from several components, two of which, Areca nut and tobacco, lead to oxidative DNA damage, as well as ROS and are associated with oral cancer and precancerous lesions such as leukoplakia and oral submucous fibrosis [7].

HPV infection

Human Papillomavirus (HPV) infections specifically those caused by the high-risk strains of HPV such as 16 impact the regulation of normal cell division. HPV E7 and E6 oncogenes overproduce the E7 and E6 oncogenes, by inhibiting the cellular tumor suppressor proteins p53 and pRb. This leads to uncontrolled cell proliferation and a rising incidence of HPV-related oropharyngeal cancers, especially in younger populations without significant tobacco or alcohol use [8].

Nutritional deficiencies

Nutritional deficiencies in antioxidant vitamins A, C, E, selenium, and β-carotene increase the risk of oral squamous cell carcinoma (OSCC) by impairing the body's ability to counteract oxidative stress and DNA damage. The deficiency of any of the following antioxidant vitamins increases the likelihood of developing oral cancer as a result of oxidative stress and damage to DNA. Both β-carotene and vitamin E (α-tocopherol) demonstrate

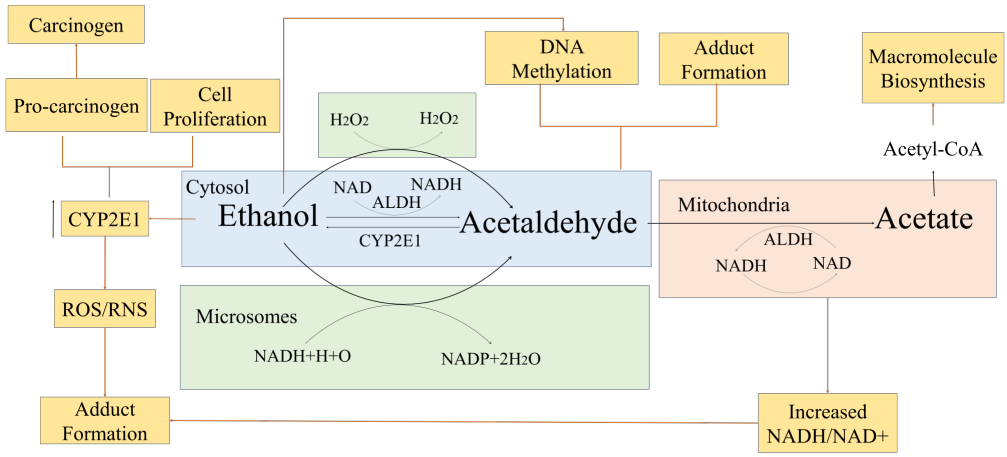

Figure 2. Metabolism of Ethanol Includes the Metabolic Pathways for Acetaldehyde Produced by Alcohol Dehydrogenase (ADH) and Cytochrome P4502E1 (CYP2E1) Located in the Cytoplasm and then the Conversion of Acetaldehyde to acetate by aldehyde dehydrogenase (ALDH) within mitochondria. This process results in the formation of reactive nitrogen and oxygen species (RNS/ROS) and DNA methylation and the formation of a variety of adducts, which promote carcinogenesis. Acetaldehyde acts as a pro-carcinogen by inducing cellular division and producing further adducts. The acetate formed during the conversion of acetaldehyde to acetyl-CoA contributes to the synthesis of macromolecules and modifies the ratio of NADH/NAD+.

the potential to enhance the immune system and also inhibit mutagenesis via multiple mechanisms as well as link evidence supporting the potential for β-carotene to reduce the risk of oral cancer; however, confirmation is needed from large-scale clinical trials to establish definitive connections [9]. Vitamin C may also be useful as a chemopreventive nutrient via the modulation of carcinogen metabolism and the immune system, and has been associated through epidemiological evidence with low levels of fruit and vegetable intake and the increased risk of oral cancer [10].

The prolonged exposure to heavy metals, includes industrial chemicals such as asbestos and formaldehyde, and fungal infections (especially those caused by Candida spp.) are environmental factors that contribute to the development of OSCC through chronic inflammation and the production of carcinogenic agents like nitrosamines. The presence of a Candida infection is associated with premalignant lesions that can lead to cancer when they are exposed to other risk factors, including the use of tobacco and the deficiency of iron [11].

Lifestyle-related activities are also known to increase the chance of developing oral cancers, including using alcohol-based mouthwash and drinking maté (a hot beverage made from the leaves of an evergreen shrub hybrid from Argentina). Both of these practices can expose the mouth to cancer-causing agents, and both may cause thermal damage. While there is not enough evidence available to support the safety of using mouthwash, the use of maté may lead to higher rates of oral and pharyngeal cancers in specific populations. All these lifestyle, nutritional, and environmental influences collectively demonstrate the need for comprehensive and integrated prevention efforts as they point to the complexity and multi-dimensional nature of OSCC risk [12].

Immune Evasion Strategies

The immune system is a crucial part of the concentration on identifying and removing cancer cells; but OSCC has devised different ways to evade immune detection. One of the primary reasons for this is the extremely high mutational load due to DNA damage from smoking and drink-induced consumption of alcoholic beverages, resulting in mutation of crucial immune-recognition components, including HLA and APM.Moreover, OSCC cells express immune checkpoint molecules, including programmed death ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), thus creating an immunosuppressive environment that prevents effective anti-tumor immune responses [13].

Tumor Microenvironment Influencers

The tumor microenvironment plays a significant role in the progression of OSCC. It includes all the stromal cells, such as cancer-associated fibroblasts, tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells. The active CAFs express factors such as α-smooth muscle actin and fibroblast activation protein, thus promoting metastasis. TAMs, particularly the M2 subtype, along with MDSC, supress T cell activity as a whole, thus creating an immunosuppressive microenvironment conducive to OSCC growth [14].

Hypoxia and Its Ramifications

Hypoxia is a hallmark of OSCC and is mediated by hypoxia-inducible factors. It is associated with increased aggressiveness of the tumor, metastasis, and resistance to therapy. The HIF-mediated response activates genes involved in metabolism, angiogenesis, and immune modulation. Moreover, the changes caused by hypoxia are influenced by the mutation status of the tumor suppressor protein p53, further affecting the behavior of the disease [15].

Oral Microbiome Implications

The oral microbiome, composed of many diverse

microbial species located within the oral cavity, can affect the progression of oral squamous cell carcinoma (OSCC). Some specific types of bacteria that have been linked to the development of OSCC include *Porphyromonas gingivalis, Fusobacterium nucleatum,* and *Prevotella intermedia.* Risk factors such as smoking, drinking, and being infected with human papillomavirus (HPV) can change the make-up of oral microbial ecosystems, creating a complicated relationship between the oral microbiome and OSCC [16].

There is an intricate balance between the tumor microenvironment and OSCC. Dysregulation of this environment creates an opportunity for the initiation and continuation of OSCC. It is a very complex interaction between immune response, alterations to the stroma, lack of oxygen (hypoxia), and imbalances in the oral microbiome that creates many possibilities for future treatment strategies targeting OSCC.

Genetic Predispositions and Immune Deficiency

OSCC is also increased in individuals with heritable disorders like dyskeratosis congenita and Fanconi anemia, primarily caused by the inability to repair DNA. This leads to genomic instability. Immune deficiency due to diseases and/or immunosuppression, from therapies or medications, disrupts the body's ability to detect and respond correctly to cancer, thus creating an increased chance of oral cancer developing. Likewise, OSCC results from disruptions in various cellular processes, including those controlling protein synthesis, autophagy, the cell cycle, metabolism, angiogenesis, invasion, migration, and apoptosis, which all occur via the abnormal activation of signalling networks (comprised of proteins) such as: EGFR, PI3K/AKT/mTOR, JAK/STAT, MET, Wnt/Beta-catenin, and RAS/RAF/MAPK (Figure 3). Amongst these, one of the pathways that is most critical to OSCC is the PI3K/AKT/mTOR axis, which is activated often by both genetic alterations and by the activation of EGFR signalling. The PI3K/AKT/mTOR pathway regulates cellular proliferation, cellular survival, cellular angiogenesis, cellular therapy resistance, along with suppression of cellular apoptosis and cellular autophagy. Some of the oncogenic factors that have been reported to stimulate the activity of this pathway include ZNF703, PDGF-D, CCL18, and MUC1. Dual inhibiting of PI3K and mTOR has been shown to be more efficacious in terms of therapeutic effect on G1 cell cycle arrest, downregulation of cyclin D1/CDK4 and suppression of protein synthesis, and in sensitizing OSCC cells to radiotherapy; these combined effects results in a substantial decrease in tumor size when examined in animal models. Additionally, the activation of this pathway and the crosstalk with other pathways; such as EGFR, MAPK, JAK/STAT, MET, and Wnt/Beta-catenin; results in the amplification of the oncogenic effects of the PI3K/AKT/mTOR pathway. Moreover, tumour microenvironments, driven primarily by cancer-associated fibroblasts and immune cells, induce the immunosuppressive characteristics of the tumour and induce an increase in metastatic potential.

Overall, the centrality of PI3K/AKT/mTOR signaling within OSCC's interconnected oncogenic network underscores the rationale for multi-targeted therapeutic strategies to overcome resistance and improve patient outcomes [17].

Diagnosis of Oral Cancer: Key Approaches and Techniques

The diagnostic landscape for oral squamous cell carcinoma (OSCC) is rapidly evolving, integrating state-of-the-art technologies that enhance early detection and monitoring (Figure 4). One of the most promising

Table 1. The TableSummarizes the Diagnostic Methods for Oral Potentially Malignant Lesions (OPMLs) and Oral Squamous Cell Carcinoma (OSCC)

Diagnostic Method	Pros	Cons
Liquid Biopsy	Minimally invasive	Still in early development
	Rapid results	Requires extensive validation through multi-center trials
	Potential for early detection of molecular changes	
Autofluorescence	Non-invasive	Limited sensitivity for high-risk lesions
	- Quick visualization of lesions	- May miss subtle dysplastic changes
	- Can help differentiate between normal and abnormal tissues	
Chemiluminescence	- Fast and easy to perform	- Lower specificity; may produce false positives
	- Can enhance visualization of lesions	- Limited effectiveness in identifying malignant lesions
Conventional Visual Examination	- Reliable and widely accepted method	- Subjective interpretation can lead to variability
	- Provides immediate results and clinical context	- May overlook small or subtle lesions
Optical Coherence Tomography (OCT)	- High-resolution imaging allows for detailed assessment of tissue structure	- Limited by hyperkeratosis, which can obscure images
	- Non-invasive with real-time results	- Impeded by bleeding due to light absorption and scattering
Oral Brush Cytology (OBC)	Simple and quick sample collection	Controversial effectiveness; results can be inconsistent
	Can provide cellular information for diagnosis	Lack of standardized diagnostic criteria
Nano-Based Diagnostics	Potential for targeted drug delivery and enhanced sensitivity	Still at the experimental stage
	Innovative approach that may improve diagnostic accuracy	Requires extensive clinical trial data for validation

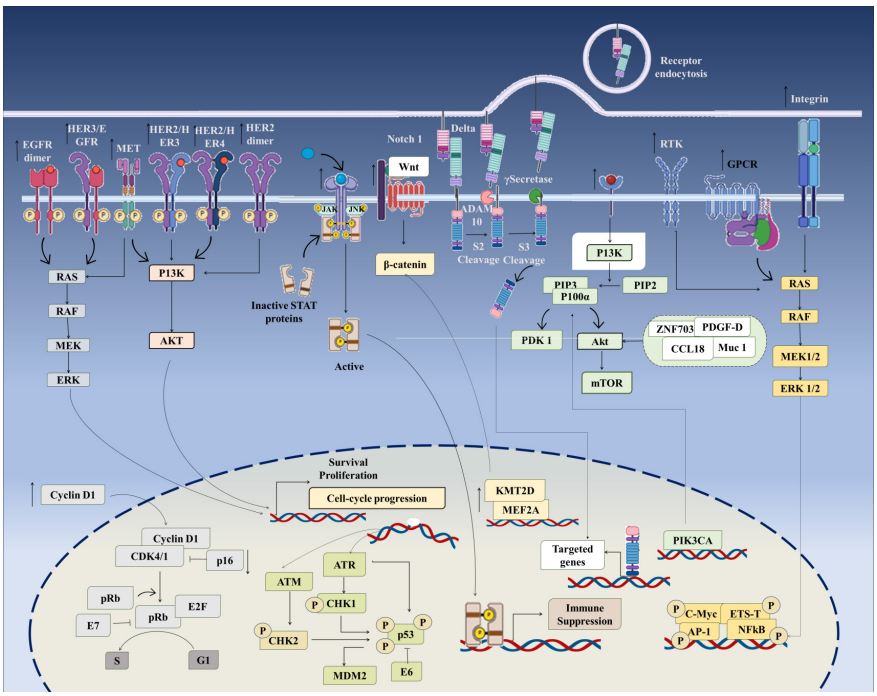

Figure 3. The Intricate Signaling Pathways Involving Cell Proliferation and Survival, Depicting the Role of Various Receptors and Intracellular Molecules and Their Functions in Cell Cycle Regulation and Response to DNA Damage

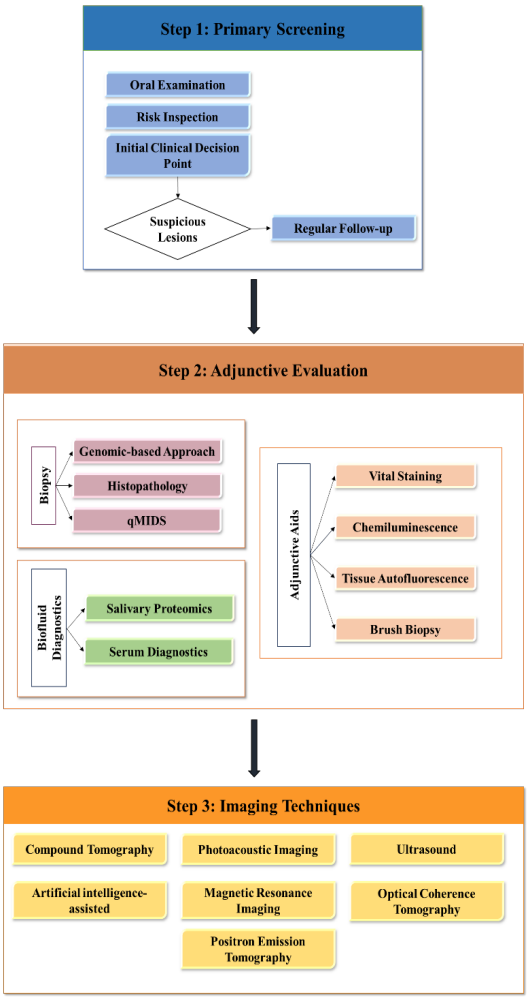

Figure 4. Stepwise Diagnostic Pathway for Oral Squamous Cell Carcinoma (OSCC), Progressing from Primary Clinical Screening and Risk Assessment to Adjunctive Molecular, Biofluid, and Chairside Evaluations.

advancements is liquid biopsy, which utilizes blood and saliva samples to identify key biomarkers such as circulating tumor cells (CTCs), cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes. These biomarkers provide valuable insights into tumor progression and metastasis; for instance, the presence of ctDNA can indicate specific mutations or methylation changes associated with advanced tumor stages. Studies have demonstrated that elevated levels of cfDNA and ctDNA correlate with more advanced disease, offering a non-invasive method to monitor cancer progression [18].

In clinical settings, liquid biopsy has shown practical applications, such as the use of salivary biomarkers for OSCC diagnosis. Research indicates that specific microRNAs (miRNAs) in saliva can serve as reliable indicators of OSCC, with studies reporting high sensitivity and specificity in detecting cancerous changes. For example, a panel of miRNAs, including miR-21 and miR-93, has been identified as potential biomarkers for early detection, demonstrating significant differences in expression levels between OSCC patients and healthy controls [19].

New innovations in light-based detection technology have created new opportunities for the identification of oral cancer through the use of devices utilizing light. Two such devices are ViziLite® (which utilizes chemiluminescence to illuminate pathological alterations within the cavity) and VELscope® (which uses tissue's natural fluorescence emitters as one method to discover possible malignant lesions). These devices both have the potential to provide substantial amounts of false-positive outcomes, due to their lower specificity than conventional histology methods. A means of utilizing optical coherence tomography (OCT) in order to achieve real-time *in vivo* high-quality imaging for oral cancer diagnosis is theoretically possible; however,

Table 2. An Overview of Treatments for Head and Neck Cancer, Including Their Mechanisms such as DNA Damage, EGFR Inhibition, and Immune System Enhancement, as well as Their Clinical Trial Applications such as Combination Therapies and Novel Immunotherapies

Therapy Type	Drug/Treatment	Mechanism of Action
Chemotherapy	Cisplatin	A platinum-based chemotherapeutic drug is utilized to induce damage in DNA due to the formation of covalent bonds between this drug and DNA as well as its producing inter- and intrastrand crosslinking between nucleotides at the N7 location on guanine. As a result of this, disruption occurs during the replication and transcription of DNA. This disruption eventually results in programmed cell death, known as apoptosis, of cancer cells, leading to the destruction of cancer cells.
	5-Fluorouracil (5-FU)	5-Fluorouracil (5-FU) is converted metabolically into fluorodeoxyuridine monophosphate (FdUMP) by its metabolites, which irreversibly inhibit the activity of thymidylate synthase. When escalating the levels of dTMP by inhibition of thymidylate synthase, DNA can no longer be synthesized due to the depletion of the nucleotide. 5-FU and FdUMP metabolites can also be incorporated into ribonucleic acid (RNA) as fluorouridine triphosphate (FUTP) and further disrupt proper processes of RNA, thus resulting in (^damage to cells^) due to the inability of the cells to ^compared to cells which do not have this drug incorporated^ in RNA.
	Docetaxel	Docetaxel binds to the β-tubulin component of microtubules, thus stabilizing the microtubules and preventing their depolymerization/chemical breakdown. By doing this, docetaxel disrupts the formation of mitotic spindles and results in the development of a mitotic catastrophe and apoptotic destruction of fast-dividing cancerous cells.
Targeted Therapy	Cetuximab	Cetuximab is a specific targeting monoclonal antibody to the extracellular component of the epidermal growth factor receptor (EGFR). Binding of cetuximab will prevent the interaction between the EGFR and its ligands and thus, prevent the subsequent activation of the receptor. Consequently, the signaling cascade that ultimately results in cell proliferation, new blood vessel development (angiogenesis), enhanced cell viability and communication with nearby tissues will be primarily impaired, thus resulting in a suppression of the growth of tumors by cetuximab.
	Erlotinib	Erlotinib is a selective tyrosine kinase inhibitor that acts by reversibly binding to the ATP-binding site of the epidermal growth factor receptor. This prevents autophosphorylation of EGFR and subsequent signaling pathways, including RAS/RAF/MEK/ERK and PI3K/AKT, thus inhibiting tumor cell proliferation and survival.
	NVP-BEZ235	NVP-BEZ235 (Dactolisib) is a dual PI3K/mTOR inhibitor that blocks ATP binding, suppressing oncogenic signaling and inducing G1 cell-cycle arrest and apoptosis. It also inhibits DNA-PKcs and ATM, impairing DNA double-strand break repair and thereby sensitizing cancer cells to radiation and chemotherapy.
	Flavopereirine	Flavopereirine, an alkaloid, exerts its anticancer effects by inducing oxidative stress and mitochondrial dysfunction, leading to apoptosis in cancer cells. It also inhibits key signaling pathways involved in cell proliferation and survival, such as PI3K/AKT and MAPK.
	FLI-06	FLI-06 is a small molecule that blocks the Notch signaling pathway at the level of the endoplasmic reticulum and has been demonstrated to disrupt ER-Golgi trafficking. The disruption of the flow of vesicles from the ER to the Golgi resulted in the blockage of protein secretion and cell signaling, both important for tumor cell survival and proliferation.
	OMP-18R5	OMP-18R5 (tarextumab) is a monoclonal antibody that binds to multiple Notch receptors, including Notch 1, 2, 3, and 4, and blocks ligand-receptor interactions, thereby inhibiting downstream pathways that are involved in the maintenance of cancer stem cells, tumor growth, and metastasis.
Immunotherapy	Pembrolizumab (Keytruda®)	Pembrolizumab is a humanized monoclonal antibody that works by blocking the programmed cell death protein 1 (PD-1) receptor on T cells, preventing interaction with PD-L1 and PD-L2 ligands. It restores T-cell activity and amplifies the ability of the immune system to identify and destroy tumor cells.
	Nivolumab (Opdivo®)	Nivolumab is a fully human monoclonal antibody that inhibits the programmed cell death protein 1 (PD-1) receptor, blocking its interaction with PD-L1 and PD-L2. This reactivates T-cell-mediated immune responses, enhancing the immune system's ability to recognize and eliminate cancer cells.
Radiotherapy Sensitizer	Cetuximab	As a radiotherapy sensitizer, cetuximab enhances the effects of ionizing radiation by binding to the epidermal growth factor receptor (EGFR) and inhibiting its downstream signaling pathways involved in DNA repair, cell proliferation, and survival. This increases tumor radiosensitivity by impairing repair of radiation-induced DNA damage and promoting apoptosis in cancer cells.
Combination Therapies	Cisplatin + Radiotherapy	The combination of cisplatin and radiotherapy enhances cancer cell death synergistically by complementary mechanisms. Cisplatin induces DNA crosslinks and inhibits DNA repair, while radiotherapy causes DNA double-strand breaks; together, they amplify genomic instability, impair cell repair mechanisms, and trigger apoptosis in rapidly dividing tumor cells.
	Pembrolizumab + Chemo	Combination therapies using pembrolizumab, along with chemotherapy, have synergistic anticancer effects through complementary actions. When chemotherapy is given, it triggers cell death through immunogenic means (causing immunogenic cell death) and releases tumor-related anti-tumor antigens. Pembrolizumab works by blocking the PD-1/PD-L1 interaction, leading to a reversal of the inhibition of T cells, allowing them to recognize and destroy cancer cells resulting in complementary actions against tumors through synergistic effects.
Emerging Therapies	Novel Immunotherapies	CAR T-cell treatments, the use of checkpoint inhibitors and the use of cancer-specific vaccines to target specific items involved in the interaction between the cancer and the immune system.

at present, costs associated with acquiring and operating OCT equipment prohibit the broad-based application of this technology [20].

In years to come, continuing technological advancements should provide additional opportunities to successfully diagnose oral cancer, including the applications of nanotechnology and artificial intelligence (AI). Use of nanotechnology will assist in expediting the development of nanoparticles (that can be utilized within light-based detection technologies) and improve their characteristics from an optical standpoint. AI, particularly through deep learning algorithms, such as convolutional neural networks (CNNs), will dramatically improve our ability to diagnose oral cancers through the ability of AI systems to more accurately analyse very large and complex sets of imaging data from different perspectives.

Table 3. Phytocompounds that are Therapeutically Relevant and Currently waiting for FDA Approval for Cancer Therapy

Phytocompound	Source	Mechanism
Curcumin	Turmeric (Curcuma longa)	Inhibits NF-κB, AP-1, STAT3 pathways; induces apoptosis, inhibits angiogenesis and metastasis.
Resveratrol	Grapes, berries, peanuts	Inhibits p53, NF-κB, Bcl-2 family proteins; induces apoptosis, inhibits cell proliferation.
Epigallocatechin-3-gallate (EGCG)	Green tea (Camellia sinensis)	Inhibits EGFR, NF-κB, VEGF pathways; induces apoptosis, inhibits angiogenesis and cell proliferation.
Genistein	Soybeans (Glycine max)	Modulates Akt, NF-κB, MAPK pathways; induces apoptosis, inhibits cell proliferation.
Berberine	Berberis species	Induces apoptosis, inhibits cell cycle progression, modulates AMPK, NF-κB, MAPK pathways.
Quercetin	Apples, onions, berries	Induces apoptosis, inhibits cell proliferation, modulates PI3K/Akt, MAPK, NF-κB pathways.
Apigenin	Parsley, celery, chamomile	Induces cell cycle arrest, promotes apoptosis, inhibits angiogenesis through modulation of p53, NF-κB, MAPK pathways.
Ginsenosides	Ginseng (Panax ginseng)	Induces apoptosis, inhibits cell proliferation, modulates PI3K/Akt, MAPK, NF-κB pathways.
Lycopene	Tomatoes, watermelon, pink grapefruit	Inhibits IGF-1, Wnt/β-catenin, NF-κB pathways; induces apoptosis, inhibits cell proliferation.
Sulforaphane	Broccoli, Brussels sprouts, cabbage	Inhibits Nrf2, NF-κB, MAPK pathways; induces apoptosis, inhibits cancer cell growth by modulating epigenetic mechanisms.
Honokiol	Magnolia bark	Induces apoptosis, inhibits angiogenesis, modulates NF-κB, STAT3, PI3K/Akt pathways.
Gingerol	Ginger (Zingiber officinale)	Inhibits NF-κB, COX-2, MAPK pathways; induces apoptosis, inhibits metastasis.
Withaferin A	Ashwagandha (Withania somnifera)	Induces apoptosis, inhibits cell proliferation, modulates NF-κB, STAT3, PI3K/Akt pathways.
Baicalein	Scutellaria baicalensis (Chinese skullcap)	Inhibits NF-κB, MAPK, PI3K/Akt pathways; induces apoptosis, inhibits cancer cell growth.
Thymoquinone	Black cumin (Nigella sativa)	Induces apoptosis, inhibits cell proliferation, modulates NF-κB, PI3K/Akt, MAPK pathways.
Ellagic Acid	Pomegranates, strawberries, raspberries	Inhibits NF-κB, PI3K/Akt, MAPK pathways; induces apoptosis, inhibits cell proliferation.
Capsaicin	Chili peppers	Induces apoptosis, inhibits cell proliferation, modulates NF-κB, STAT3, PI3K/Akt pathways.

Recent studies have demonstrated the validity of AI systems' performance in terms of their diagnostic accuracy level for images derived from histopathological tissue samples from the oral cavity, exceeding 90%. As a result, there is strong potential for AI to augment the decision-making process of pathologists, enabling them to make better-informed decisions regarding their diagnoses [21].

Another minimally invasive option that is becoming

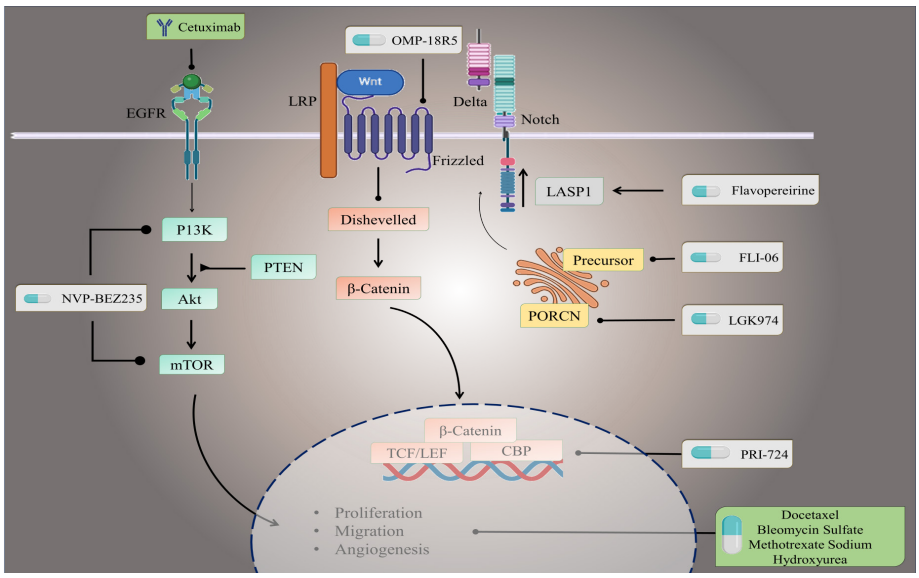

Figure 5. Overview of FDA Approved Head and Neck Cancer Drugs (Cetuximab, Docetaxel, Bleomycin sulphate, Hydroxyurea) and targeted inhibitors (NVP-BEZ235, OMP-18R5, Flavopereirine, FLI-06, LGK974, and PRI-724), and illustrating pathway crosstalk.

Table 4. This Table Compares Traditional and Nanoparticle-Based Formulations of Various Anticancer Drugs

Drug	Traditional Formulation	Nanoparticle-Based Formulation	Advantages of Nanoparticle-Based Formulation
Doxorubicin (DOX)	Commonly used for treating various cancers, including oral cancer. Clinical efficacy hindered by dose-dependent cardiotoxicity and systemic side effects.	Liposomal-encapsulated doxorubicin (DOXIL®)	Enhances pharmacokinetics, reduces cardiotoxicity, improves tumor targeting, controlled release, extended circulation time, and reduced off-target effects.
Paclitaxel	Potent anticancer drug used for solid tumors, including oral cancer. Limited by poor solubility and systemic toxicity.	Abraxane® (paclitaxel bound to albumin nanoparticles)	Improves solubility, enhances tumor accumulation, reduces hypersensitivity reactions, offers improved drug stability, controlled release, and enhanced tumor penetration.
Cisplatin	Widely used for various cancers, including oral cancer. Clinical use limited by nephrotoxicity and ototoxicity.	Polymeric nanoparticles (e.g., poly(ethylene glycol)-poly(glutamic acid) micelles)	Enhances drug delivery efficiency, reduces systemic toxicity, offers targeted delivery, controlled release, and reduced off-target effects.
Docetaxel	Potent anticancer drug for solid tumors. Limited by poor oral bioavailability and systemic toxicity.	Chitosan-based core-shell nano-capsules containing docetaxel, incorporating silver nanoclusters and folic acid-grafted chitosan.	Enhances tumor targeting, improves drug stability, controlled release, increased bioavailability, and reduced systemic toxicity.
Methotrexate	Antimetabolite agent used in anticancer chemotherapy. Limited by systemic toxicity and off-target effects.	Nanoparticles loaded with methotrexate	Improves drug stability, prolongs circulation time, targets specific cancer cells, offers targeted delivery, controlled release, and reduces systemic toxicity.

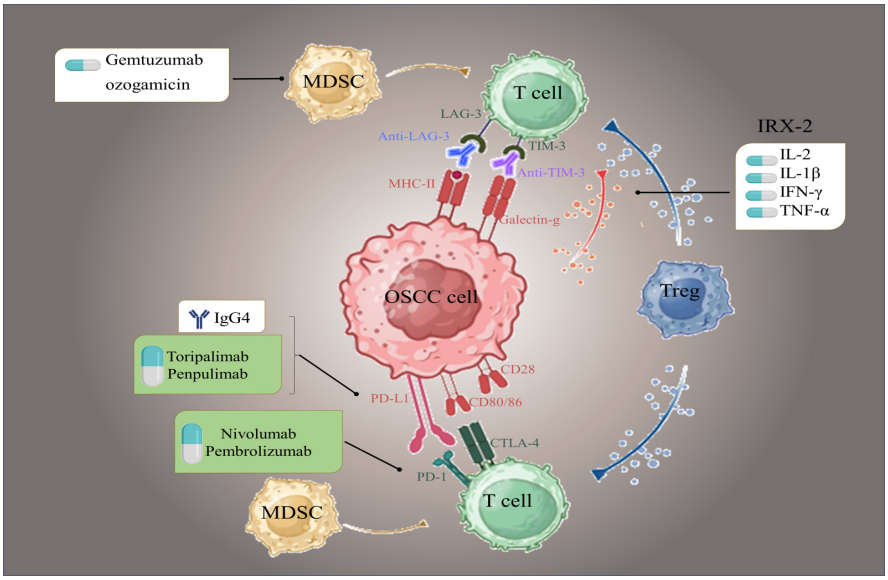

Figure 6. The Interactions between OSCC (Oral Squamous Cell Carcinoma) Cells and Immune Cells, Including T Cells, Regulatory T Cells (Treg), and Myeloid-Derived Suppressor Cells (MDSC). Key therapeutic targets are highlighted, such as the blocking of LAG-3, TIM-3, PD-1 pathways by anti-LAG-3, anti-TIM-3, pembrolizumab, and nivolumab (FDA approved), PD-L1 pathways by Toripalimab and Penpulimab (FDA approved) as well as the impact of the IRX-2 cytokine cocktail on immune modulation.

more common for detecting dysplastic lesions in the oral cavity, is oral brush cytology (OBC). OBC has shown to have both high sensitivity and specificity; however to use OBC widely in clinical practice, it will require the establishment of standardized diagnostic criteria. Microfluidic systems are also being studied as an effective way of screening for oral cancer because they enable quick and efficient analyses of molecular and cellular biomarkers associated with oral squamous cell carcinomas (OSCC).

When you compare traditional methods of diagnosing oral cancer such as biopsies and visual inspections and the new technology of OBC and microfluidic systems, it is clear that non-invasive techniques, such as OBC and microfluidic analysis, provide immediate results on the processes that cause oral cancer and do not require extensive surgical intervention. More research must be done in this area so that we can improve patient outcomes through earlier detection of oral cancer and individualized treatment [22].

Overcoming Limitations of Current Diagnostic

To address these challenges, there are ongoing active research studies of some promising technologies. For instance, in liquid biopsy, there is interest in the identification of salivary biomarkers that may improve diagnostics. Salivary microRNAs or miRNAs, like miR-21

and miR-200a, have been shown to be reliable indicators of OSCC; sensitivities of over 80% and specificities around 75% have been reported in some studies. These findings suggest that saliva could be an important constituent in future diagnostic protocols because of its ease of collection and the amount of information it can yield [19].

The analysis of liquid biopsy samples has been further enriched with the introduction of Next-Generation Sequencing technologies. Differentially expressed miRNAs linked to malignant progression in oral lesions have been found by NGS-based studies. For example, the study by Sun et al. identified the following miRs: miR-222-3p, miR-150-5p, and miR-423-5p as OSCC progression predictive biomarkers. In the future, as these approaches get more refined and their efficacy validated by clinical trials, there may be a hope to improve significantly the patient's outcomes in the management of OSCC [23] (Table 1).

Clinical Implications and Therapeutic Opportunities

Oral cancer refers to malignancies affecting the oral cavity, including the lips, tongue, gums, and roof and floor of the mouth. The most common form is squamous cell carcinoma (SCC), although other types such as melanoma, sarcomas, lymphomas, and salivary gland cancers can also arise. Treatment approaches depend on the cancer's location, type, and stage. These include chemotherapy, radiotherapy, immunotherapy, and surgery. Radiotherapy primarily works by generating reactive oxygen species (ROS), causing DNA damage in cancer cells. Chemotherapy drugs like cisplatin and 5-Fluorouracil (5-FU) induce DNA damage, inhibit DNA repair mechanisms, and activate tumor suppressor genes. For some patients, a combination of chemotherapy and radiotherapy is used for enhanced therapeutic effect. A few of the chemotherapeutic drugs are mentioned in Table 2 [24].

Surgery and Radiotherapy

Currently surgery is the most common treatment option for oral squamous cell carcinoma. Different techniques used include conventional surgical, endoscopic and robotic surgery to remove the entire tumor to prevent local recurrence and provide long-term survival rates. After surgery if the tumor cannot be completely removed, or the tumor has other adverse pathological features like large size, positive clinical margins, or evidence of invasion into surrounding soft tissue, postoperative treatment with radiation is frequently warranted.

Adjuvant chemotherapy

Chemotherapy though not curative on its own, is increasingly combined with radiotherapy either preoperatively or postoperatively, especially in advanced cases, to enhance treatment efficacy [25]. Reconstruction, particularly with free flap techniques, plays a crucial role in restoring oral function and aesthetics, significantly improving postoperative quality of life and minimizing complications [26].

The Microbiome as a therapeutic target

Research on the microbiome and its interaction with the tumor has created a new field of therapy for cancer treatments. These therapies are directed at treating imbalances in the various microorganisms colonizing the human body. The complexity of the interactions between the microbiome and the host is now being recognized as capable of influencing the progression of various diseases including cancer. Specifically, the use of fecal microbiota transplantation (FMT) has been seen as very beneficial, increasing the response to immune checkpoint inhibitors when performed in conjunction with the checkpoint inhibitors themselves. Data from clinical trials show that patients receiving FMT have better responses to treatments than patients receiving no FMT. Therefore, it appears that a healthy gut/intestinal microbiome may positively affect the efficacy of cancer treatments, including immunotherapy, because patient response has been correlated with the composition of the gut microbiome [27].

Certain micro-organisms in the oral cavity, such as Porphyomonas gingivalis and Fusobacterium nucleatum, are often implicated in the pathogenesis of OSCC and have been specifically identified and documented as primary causative agents of OSCC. Such types of pathogens elicit a chronic inflammatory and oxidative environment, thus a tumor-promoting state, conducive for cancer development in the tissue; it has even been shown recently that Fusobacterium nucleatum levels tend to be relatively higher in a cancerous group than in controls [16].

The increased focus on the microbiome provides an exciting opportunity to potentially use the microbiome as a means for therapeutic intervention in cancer treatment. Understanding how the oral microbiome influences the development of OSCC will enable health professionals to begin utilizing innovative ways to prevent, detect, and treat cancers. In addition, integrating research on the microbiome into clinical practice may result in the development of a personalized treatment plan tailored to each individual based on the unique characteristics of their microbiome, both for OSCC and potentially other types of cancer.

Pathway inhibitors

Targeted therapy using pathway inhibitors tries to interrupt the activity of molecular pathways responsible for the development and progression of oral squamous cell carcinoma (OSCC). This is done by blocking proteins or signals that cause cancer cell proliferation and survival, which could reduce the size of the tumor and improve the prognosis of patients. An example is those that target epidermal growth factor receptor, as it has produced excellent results in the clinical stages in OSCC in shrinking tumors and improving rates of response upon adding them with standard treatments of chemotherapy and radiotherapy (Figure 5) [25, 26].

Immunotherapy for OSCC include

Among the strategies to exploit the immune response against cancer, the use of immune checkpoint inhibitors (ICIs) has gained the most attention with pembrolizumab and nivolumab having demonstrated efficacy through blocking the PD-1 pathway resulting in enhanced T-Cell mediated tumor immunity. Ongoing research continues to

explore other immune checkpoints, including lag-3 and Tim-3, with the aim of reactivating exhausted T-cells in the tumor environment and improving the efficacy of ICIs (Figure 6). Additionally, therapies targeting cytokines such as IRX-2 have been designed to enhance both adaptive and innate immune responses by reversing immunosuppression, enhancing the totality of the anti-tumor immune response, and modifying the activity of myeloid-derived suppressive cells (MDSCs) and regulatory T-cells (Tregs) to help facilitate immune-mediated tumor control [28].

Clinical Evidence and Case Studies

These approaches to cancer therapy have been validated through clinical studies. For example, published case reports of patients with OSCC localized to the floor of their mouth experiencing significant tumor shrinkage following the administration of neoadjuvant pembrolizumab treatment. By only one cycle of this immunotherapy, T-cell infiltration and PD-L1 expression increased in the tumor. Thus, the rate of necrosis became very high a level of 75% of the tumor mass had turned necrotic, leaving behind only 25% vital tumor cells. Up to June 2020, this patient remained recurrence-free. Thus, the use of neoadjuvant immunotherapy has great promise for advanced OSCC.

Furthermore, there are ongoing clinical trials to assess different combinations of immunotherapies and their impacts on patient outcomes. For example, studies to evaluate the combination of PD-1 inhibitors with LAG-3 or TIM-3 blockers are being carried out to see if dual checkpoint blockade is superior to monotherapy. Ongoing research and clinical trials continue to optimize these approaches to improve the outcomes of OSCC patients [29].

Recurrences and Metastasis

The prognosis of Oral Squamous Cell Carcinoma (OSCC) is closely linked to the risks of recurrence and metastasis, which necessitate ongoing monitoring. While conventional FDA-approved therapies have advanced, their efficacy in advanced OSCC is often limited by significant side effects. As a result, dietary phytochemicals such as flavonoids, carotenoids, and glucosinolates found in plant foods are gaining recognition for their chemopreventive and therapeutic roles, acting through immune enhancement, anti-inflammatory effects, and DNA protection [30]. Some of the most well-known examples include Curcumin found in *Curcuma Longa* (turmeric) and Resveratrol derived from *Vitis Vinifera* (grape), which exhibit anticancer effects by altering specific signalling pathways in the cellular environment. Global use of herbal medicine and Phytopharmaceuticals has resulted in the creation of various therapeutic agents used for the treatment of cancers, such as Vincaleukoblastine and Vincristine derived from *Catharanthus Roseus* (Madagascar Periwinkle), Paclitaxel from *Taxus Brevifolia* (Pacific Yew), L-Dopa derived from *Mucuna Pruriens* (Velvet Bean), and Reserpine from *Rauvolfia Serpentina* (Indian Snakeroot) (Table 3). Complementary and alternative medicine (CAM), particularly phytotherapy, is often used alongside standard treatments to enhance detoxification, reduce side effects, and strengthen immune responses. The greatest limitation of treating cancer with several phytochemicals stems from their poor solubility and bioavailability. As a result of advances in Nanotechnology, including polymer and lipid-based nanoparticles, the ability for plant compounds to be delivered and effectively packaged for administration has improved dramatically. They allow better targeting and compliance by patients. These advancements highlight the expanding role of particular medicinal plants and the development of innovative drug delivery systems under the umbrella of integrative management of OSCC [31].

Targeted Chemotherapy with Nanoparticles: A Novel Approach

Standard chemotherapy treatments for head and neck cancers are limited due to their non-specificity, which causes unhealthy tissue exposure that leads to severe side effects such as nausea and vomiting, hair loss, and decreased immunity. The use of nanoparticle-based technologies to specifically target tumours represents a new approach to treatment that can increase treatment effectivity, reduce the amount of treatment needed, and decrease systemic toxicity. Metal-based nanoparticles, particularly, are showing great promise because of their unique physicochemical properties and biocompatibility. For example, zinc oxide nanoparticles induce apoptosis in vitro by pH-dependent ion dissociation and reactive oxygen species generation, and will be investigated for use in photodynamic therapy and in gene therapy for cancer treatment. Copper oxide nanoparticles have increased catalytic activity and improved stability due to their green synthesis, which makes them safer for patients. Titanium dioxide nanoparticles are inexpensive, stable and can be used effectively for controlled drug and gene delivery under acidic conditions, such as those found in tumours, and are commonly used in photodynamic therapy. Finally, selenium nanoparticles have been shown to protect DNA from oxidative stress, making them good candidates to deliver siRNA and for cancer therapy. Nanoparticles of palladium (Pd) and platinum (Pt) are known for their high porosity and photocatalytic activity, respectively. Although PtNPs are already extensively used for drug delivery, there remains much room for improvement in the area of cytotoxicity.

In addition, conjugated with cetuximab, gold nanoparticles (AuNPs) can act as both a photothermal therapeutic and also improve the effectiveness of photothermal therapies through their ability to act as a heat source when irradiated with a laser. On the other hand, AgNPs induce apoptotic cell death in oral squamous cell carcinoma (OSCC) through their ability to generate reactive oxidative species. IONPs conjugated with doxorubicin have demonstrated improved drug delivery to the tumor site and a significant reduction in tumor growth. Platinum-based nanoparticles that deliver cisplatin have improved the ability of oncologists to provide targeted therapy while minimizing the adverse effects of the drug, due to the platinum nanoparticles' ability to better deliver the drug to the tumor.

Furthermore, clinical studies have established the safety and clinical efficacy of TiO_2 nanoparticles when used to treat oral cancers, which together have fundamentally changed the way that modern oncologists treat patients with oral cancer. The foundation of these advances demonstrates that metal-based nanoparticles can fundamentally enhance the ability of oncologists to deliver oral cancer therapies and their clinical effectiveness. (Table 4) [32, 33].

Plant-based nanomaterials

Conjugates between nanoparticles and phytocompounds utilize the unique properties of nanoparticles to deliver, stabilize and provide better efficacy of cancer-related phytochemicals. The goal of this approach is to enhance the bioavailability of cancer-related phytochemicals and direct their delivery to target cancer cells while minimizing side effects.

For example, AuNPs conjugated with various phytochemicals have improved the bioavailability and anticancer activity of cancer-related phytochemicals. Resveratrol-conjugated AuNPs have been shown to inhibit the growth of tumors in breast, pancreatic and prostate cancer. AuNPs conjugated with withanolide-A have been shown to inhibit the proliferation of breast cancer cells more effectively than other phytochemicals. Phytochemical-coated AuNPs from *Mangifera indica, Emblica officinalis, Curcuma longa*, and *Glycyrrhiza glabra* (Nano Swarna Bhasma) demonstrate selective cytotoxicity in breast cancer. Silibinin-conjugated AuNPs (Sb-AuNPs) increase anticancer activity in lung cancer cells [34].

Green-synthesized zinc oxide nanoparticles from Cinnamomum verum bark extract have shown to halt cell growth and induce apoptosis in oral cancer cells. Gingerol, particularly when included in Pro-Liposomes, had the highest level of anti-cancer activity against OC. Drug delivery systems using Nanoparticles have already achieved significant advances in improving the efficacy of cancer therapies through better drug delivery and targeting of tumour cells and reducing toxic side effects. It demonstrates the great potential for the use of Nanotechnology in the treatment of cancer. Combination therapies using Nanotechnology with Bioactive compounds within Phytocompounds demonstrate great potential in supporting and improving the bioavailability of Drugs, targeting tumour cells and modulation of the oncogenic pathways important to Oral Squamous Cell Carcinoma (OSCC). However, despite these advancements, future studies are required to improve the strategies used for the development of Nanotherapeutics and to establish the safety, efficacy and clinical applicability of these strategies [35].

Conclusion and Future Directions

Oral Squamous Cell Carcinoma (OSCC) is the most aggressive and least successful cancer due to its diagnosis at advanced stages, the complex etiology and the poor efficacy of established treatment modalities (i.e. surgery, radiation and chemotherapy).Recent advances in nanomedicine and phytochemical-conjugated nanoparticles, incorporating agents like curcumin, resveratrol, and epigallocatechin gallate (EGCG), offer significant therapeutic potential by enhancing drug solubility, stability, and bioavailability, enabling targeted delivery to tumor cells, and modulating oncogenic pathways to induce apoptosis and suppress metastasis with minimal harm to healthy tissues. Nanoparticle technologies including liposomal and micellar based drug carriers have enhanced the susceptibility of drugs to effective, continuous release while localizing active ingredients. The utilization of artificial intelligence (AI) and Molecular Modelling would further improve the ability for early diagnosis, drug development and tailoring individual treatments for tumour types specific to the genetics of the patient. Biocompatibility issues, as well as difficulties associated with producing these types of carriers on a large scale, and the fact that regulatory authorities have yet to approve these products for use; these obstacles may hinder the transition from preclinical to clinical settings. Future advances in the management of patients suffering from OSCC may require the involvement of AI assisted diagnostics as well as long-term follow-up on the role of HPV vaccination, clinical validation studies on utilising nanoparticles as drug carriers, and the rationale combination of traditional therapies with novel alternatives such as phytochemicals, or immunotherapy to develop more efficacious yet safer and patient specific chemotherapy agents designed to improve survival and the patient's overall quality of life.

Author Contribution Statement

Conceptualization, writing, original draft preparation- BH. and CS.; validation - AP., CS., DD and SPK.; review and editing, KCP, CD,SP and ANU.; visualization, RA. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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