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A novel approach in diagnosis and treatment of oral cancer

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Abstract
Oral squamous cell carcinoma (OSCC) is a group of highly malignant tumors that may arise from the surface epithelium or minor salivary glands. Approximately 85% to 95% of all oral cancer is squamous cell carcinoma (OSCC) which is a very aggressive cancer, representing one of the most common malignancies worldwide. Oral potentially malignant disorders (OPMDs) regroup a variegate set of different histological lesions, characterized by the potential capacity to transform in OSCC. The conventional treatment modalities of oral cancer include surgical excision, radiation therapy, chemotherapy, or a combination of these approaches. These traditional methods may not use effectively due to their poor bioavailability. Hence, reformulation of drugs or improved drug delivery may enhance bioavailability. Targeted therapy is a novel approach to deliver drugs to specific cells, organs, cell organelles to improve the collection of the delivered active components in the desired site of action and decrease the side effects and systematic toxicity that accompanied conventional therapy. Nanodentistry uses nanotechnological approaches with a particle size of 10-9 meters including nondiagnostic, nanoparticles, and nanodrugs for diagnosing, treatment, and prevention of oral and dental diseases to improve dental health. This review describes different nanoparticles accompanied by therapeutic agents for effective and useful diagnosis and treatment of oral cancer.

Keywords: Oral cancer, nanotechnology, targeted drug delivery, nanoparticles, chemoprevention

1. Introduction
Oral squamous cell carcinoma (OSCC) is a combination of highly malignant tumors that may emerge from the epithelium's surface, submucosal tissue, or small salivary glands. Almost 85%-95% of all oral cancer is OSCC [1]. Oral cancer is still the sixth cause of death in the world despite all advanced methods used for detection and treatment because of its relapses, resistance, and post-treatment failure [2]. Like any other disease, diagnosis of oral cancer is an important step starting with biopsy of the concerning area then investigation with computerized tomography (CT), Magnetic resonance imaging (MRI), positron emission tomography (PET) scan to determine if the tumor has metastases to distant parts depending on the grade or size of the tumor. Oral cancer involves the rapid growth of cells besides the ability of these cells to secrete enzymes, angiogenetic factors, growth factors, invasion factors, and many other elements that encourages the disease to disseminate [3]. The traditional treatment of oral cancer includes several approaches such as surgery, radiotherapy, and chemotherapy.
Nanotechnology is a field of research used for detecting and targeting a single cancerous cell, delivering and releasing drugs in a regulated manner, with enormous specificity and sensitivity so, it holds vast power for defeating many obstacles related to traditional methods: problems in detection, treatment, and diagnosis of cancer [4, 5]. Nanodentistry deals with materials whose size <100 nm in at least one dimension, therefore, have a much surface area/unit mass compared to greater particles. Many nanoparticles are used in the diagnosis and treatment of oral cancer such as carbon nanotubes, nanoshells, polymeric nanoparticles, dendrimers, quantum dots, and polynucleotide nanoparticles. This review summarizes the various nanoparticles utilized in the diagnosis and treatment of oral cancer.

2. Epidemiology
Oral cancer is a serious global health problem, with an estimated 377, 713 newly diagnosed cases and 177,757 expected deaths cases in 2020 for both sexes and all ages worldwide.

Also, the prevalence of the disease in the last five years was highest in Asia 60.9% followed by Europe 20.6%, North America 9.2%, Latin America and the Caribbean, and 3% in Africa [6]. Although this disease is typically for the elderly over the past three decades increasing, the number of patients at a younger age: 40-45 years old diagnosed with oral cancer [7, 8].

3. Pathophysiology of Oral Cancer

In recent studies, there were known facts that genetic and environmental components play a major role in oral cancer. Genetic events take place in its cellular division, proliferation, and differentiation and many studies have suggested that tumor deoxyribonucleic acid (DNA) in the plasma of cancer patients. Cellular pathways of the oral keratinocyte may be varied and involve the same fundamental elements, specific genetic alterations take place in cancerous and precancerous lesions of the oral cavity. Using comparative genomic hybridization recently reported deletions of certain chromosomes with gain in well-differentiated oral cancer, whereas in poorly differentiated tumors deletions and gain of other chromosomes were identified, therefore, proposed a relationship with tumor metastases [9].

Most oral cancer patients are genetically more susceptible to progress malignancy because of some inherent deficiency of their capacity to maintain their genome in the presence of environmental stressors [10]. Oral cancer is including numerous genetic steps that change the normal functions of both tumor suppressor and oncogenes genes [11, 12]. All cellular signals act with each other in a very specific way so, when there is any diversification there will be an increase in oncogenic genes and a decrease in tumor suppressor genes, and abnormal cellular proliferation start.

4. Drug Delivery and Targeting

Conventional oral formulations may not be used effectively due to their poor bioavailability. Hence, reformulation of drug or drug delivery may increase oral bioavailability.

Targeted therapy is a novel treatment to deliver drugs to specific cells, organs, cell organelles to improve the collection of the delivered active ingredients in the site of action and decrease their collection in the healthy cells, tissues, and organs. In addition, targeted treatment help to decrease side effects and systematic toxicity that accompanied conventional therapy [13]. There are two divisions of drug targeting: passive and active targeting. Passive targeting naturally utilizes a passive distribution of a carrier and depends on specific conditions such as size, specific charge, and molecular mass in an entire tissue or organ. High molecular weight drugs due to slow venous are collected in the solid tumors and enhanced permeability and retention (EPR) effect lead to increase the permeability of the tumor vasculature accompanied by limited lymphatic drainage. This approach may utilize certain conditions in the disease cells or tissues such as low pH. In most cases, active targeting is achieved by adding to the surface of a carrier moiety: a ligand specific to a specific substance overexpressed on the targeted cell's surface. Fig. 1 illustrated several NPs used in the diagnosis and treatment of oral tumors.

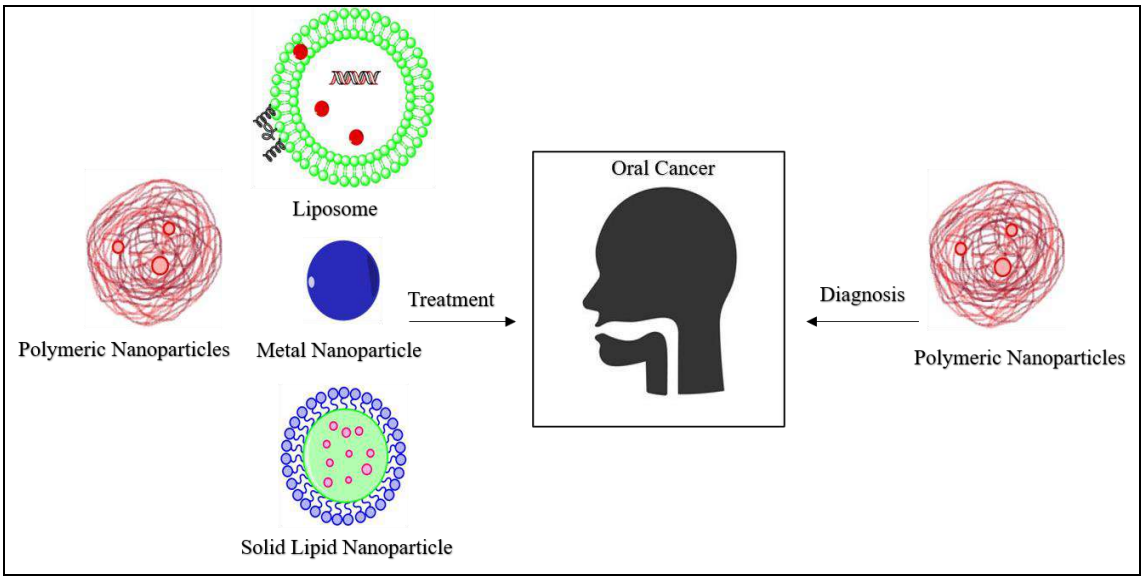

Fig 1: Several Nanoparticles are used to diagnose and treatment of oral tumors

5. Application of Nanoparticles in Oral Cancer Diagnosis

Oral cancer is a destructive tumor disease that attacks local tissue leading to metastasis and untreatable stage. The struggles in the diagnosis of the tumor at an early stage improve the high mortality rate. Although, the high-resolution imaging of oral epithelial tissues *in vivo* as the chemical analysis of saliva using enzyme-linked immunosorbent assay (ELISA), high-performance liquid chromatography (HPLC), microsatellite analysis, and novel optical systems full of promises as precious tools, they have many limitations to their diagnosis efficient utilization such as inability to detect the biomolecular changes *in vivo* related with carcinogenesis and requires long analysis time [14, 15].

Nanotechnology is introduced to improve sensitivity at the early stage of cancer. It can deliver highly toxic drugs directly to the tumor and detect a single cancerous cell *in vivo*. Advanced technologies can be used in diagnosing oral cancer such as cantilevers, nanoscale, nanotubes, nanopores, and quantum dots [16].

Nanoparticles (NP) can be used to improve sensitivity diagnosis and monitor the detection of cancer. These NP involve Solid Lipid Nanoparticles (SLN), Liposomes, and Inorganic NPs such as Gold nanoparticles (GNPs) [17].

Recently, GNPs have been considered as a diagnostic approach depending on their optical properties and their radiosensitivity depends on their size. These metallic NPs show a particular optical response to light that allows them to aloud scatter light when excited at the frequency of the surface plasmon resonance.

They can be easily conjugated to peptides or antibodies through bonding to a probe for particular cellular biomarkers or electrostatic charge interaction with high affinity and specificity for their encouraging physicochemical properties for use as optical probes in the early detection technique [18, 19].
Kah *et al*., 2007 [21] and Fălămaș *et al*., 2020 [21] showed that surface-enhanced Raman scattering of saliva samples based on GNPs provides an optical contrast for molecular-specific information to differentiate between cancerous and normal cells. Also, Kim *et al*., 2018 [22] assumed that using molecularly engineered inorganic GNPs obtained multiple, stimuli-responsive optical signal changes developed as a contrast agent in early-stage oral cancer.

6. Application of Nanoparticles in Oral Cancer Treatment

The common therapy approaches of oral cancer consist of surgical removal, radiation treatment, systemic chemotherapy, or a mixture of these treatments. Early-stage oral cancer patients are treated with surgery while advanced-stage and recurrent cancer cases surgery is used often together with radiation therapy, chemotherapy, or targeted therapy. Most stage I or stage II oral cavity and oropharyngeal cancer patients improve when treated with a single conceivable treatment (surgery or radiation), while locally advance operable cancer (stage III and stage IVA) is treated with combined modality. Palliative therapy saves for the inoperable locally advanced and metastatic tumors [23, 24]. Chemotherapy can be designed as palliative, not curative care. This treatment is either given alone or in combination with radiation (chemoradiation) according to the stage of the disease. Chemotherapy regimen for oral tumor involves Carboplatin, 5-fluorouracil (5-FU), Cisplatin, Paclitaxel (Taxol®), Docetaxel (Taxotere®), and Hydroxyurea. The combination of Cisplatin or Cetuximab and radiotherapy plus chemotherapy with or radiotherapy plus cetuximab, are the preferred treatments for locally advanced squamous cell carcinoma. The advanced treatment methods: immune therapy, gene therapy, and targeted therapy are better with lesser side effects. These new methods of treatment improve rates of survival and the quality of life of diseased patients [25-27].
Nanotechnology can be used to target a specific site action without side effects and improve the pharmaceutical formulation like decreased toxicity, modified pharmacokinetics, and increased stability. Some nanoscale delivery devices such as ceramic NPs, dendrimers, silica-coated micelles, and liposomes can be used to target cancer cells by attaching cell surface receptor ligands or monoclonal antibodies specifically to cancer cells leading to improve the selectivity of drugs and reducing their side effects. Cell permeability can be improved by surface modification of NPs and thus improve the therapeutic power of NPs as a drug transport vehicle. In addition, NPs have a size range between 5-200 nm thus are capable of stability during interaction with biological systems. However, increased tumor cell resistance and toxicity of the normal cells enhance obstacles in cancer treatment. In addition, nanotechnology can be used in the management of pain related to cancer. Also, it protects the patient from overdosing, spontaneous drug degradation of the oral administration [28]. Fig.2 illustrated different NPs involved in oral cancer treatment.

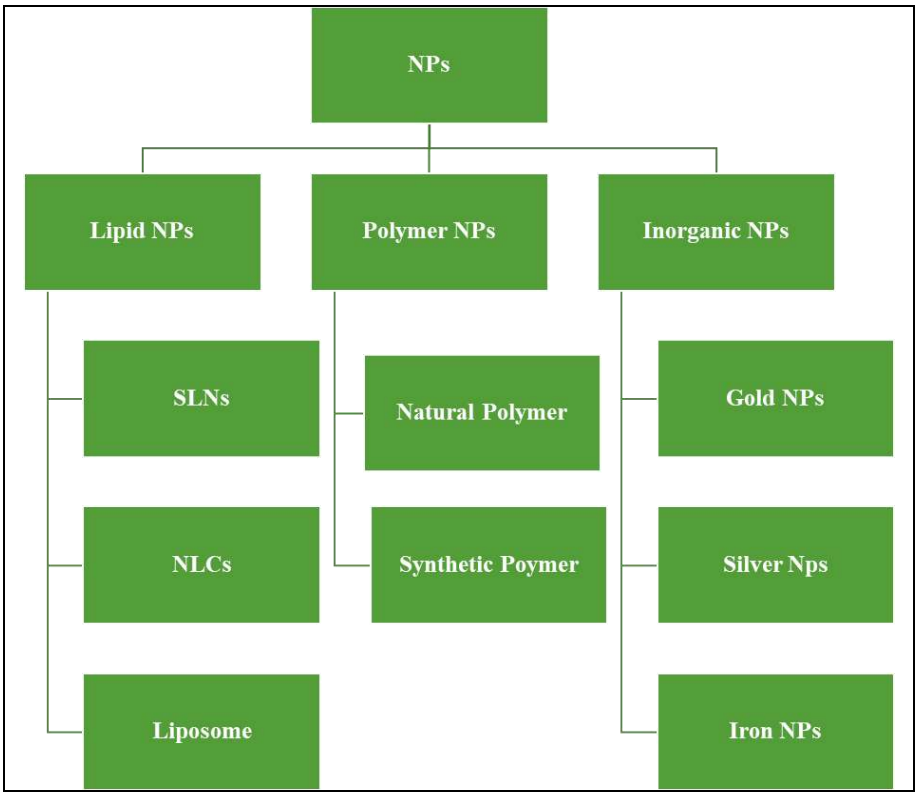

Fig 2: Types of NPs used in the treatment of oral cancer

Natural Polymers NPs: Chitosan, Albumin, Gelatin, Eudragit. Synthetic Polymers: PLA, PLGA, PEG

6.1 Application of Nanoparticles in Treatment of Oral Cancer

6.1.1 Application of Lipid Nanoparticles in Oral Cancer

6.1.1.1 Application of Solid Lipid Nanoparticles (SLNs) in Oral Cancer

Solid Lipid Nanoparticles (SLNs) are a new generation of lipid emulsion with submicron-sized particles (50-1000 nm) where the liquid lipid has been replaced by a solid lipid. Like lipids of foods, SLN suffers the same metabolic pathways, they also have

been considered as drug absorption enhancers by the oral route [29]. There are several advantages of SLN: control and target of drug release, increased enhanced drug content, high drug stability, feasible for carrying both hydrophilic and lipophilic and drug, easy to scale up and sterilize, and excellent biocompatibility. Li *et al*., 2020 [30] demonstrated that andrographolide- solid lipid nanoparticles (ADG-SLNs) are more effective than free ADG in promoting cell cycle arrest and apoptosis in human immortalized oral epithelial cancer.

6.1.1.2 Application of Nanostructured Lipid Carriers (NLCs) in Oral Cancer

Nanostructured Lipid Carriers (NLCs) offer advantages over SLN as improved drug release modeling and higher capacity for lipophilic compounds. The differences between NLCs and SLN depend on a combination of liquid and solid lipids, that together stayed solid at body and room temperature. NLCs Chaudhari *et al*., 2021 [31] encapsulated herbal constituents like quercetin and piperine that are derived from eatable sources into lipid matrix-mediated NLCs to improve the bio-accessible of the drugs and prove their high anticancer activity *in vitro* against oral cancer cells.

6.1.1.3 Application of Liposomes in Oral Cancer

Liposomes are small vesicles of one or more phospholipids colloidal spheres that encapsulate both hydrophilic and hydrophobic drugs. They have many benefits such as biocompatibility, biodegradability, biocapacity to entrap hydrophilic and lipophilic drugs therefore and low toxicity, resulting in targeting of chemotherapeutic drugs to cancer cells without destroying the neighboring normal cells. Liposome formulations in gene therapy have a great potential against oral cancer such as synthetic liposomal-DNA (lipoplexes) [32]. Cheung *et al*., 2020 [33] incorporated Zinc phthalocyanine was in extruded liposomes POPG: POPC (palmitoyl-oleoyl phosphatidylglycerol and palmitoyl-oleoyl phosphatidylglycerol) leading to moderate cytotoxicity in FaDu cells and extensive cytotoxicity in CAL 27 cells of human pharyngeal cancer cells and OSCC cells upon light activation.

6.1.2 Application of Polymeric Nanoparticles in Oral Cancer

Polymeric nanoparticles are extensively used as pharmaceutical carriers to develop the drug's stability and regulate its targeted delivery. They can be either nanospheres or nanocapsules and can be used in various methods of drug administration as oral, parenteral, pulmonary, dermal, ocular, and rectal.

They can be produced from diverse polymers: natural or synthetic polymers like polysaccharides, polylactide-polyglycolide, polylactic acid (PLA), polyethylene glycol (PEG), and chitosan [34, 35]. Polymeric NPs have several advantages such as improved stability, protection of the drug from environmental conditions, controlled release, less expensive, and excellent tolerability. However, they may be toxic to the patients, have slow degradation speed, and have poor strength. Therefore, it is important to reduce toxicity and improve their compatibility for use in the biomedical field. They could help in the post-surgery treatment of oral cancer by improving the retention time of drug delivery. Chemotherapy is related to the high rate of excretion of antineoplastic agents to normal and cancer cells. Then, polymers with mucoadhesive futures may improve the penetrability and effectiveness of chemotherapeutic drugs. Mazzarino and co-workers, 2015 [36] loaded curcumin with chitosan-coated NP and showed a decrease in the SCC-9 human oral cancer cells viability. In addition, Satapathy and co-workers, 2015 [37] formulated a nanoformulation by encapsulating quinacrine (anti-cancer drug) and the nano form of metallic silver with PLGA (poly (lactic-co-glycolic acid)): a biocompatible and biodegradable polymer. This formulation showed inhibition in the DNA repair mechanism and angiogenesis of the oral squamous cancerous cells *in vitro*.

6.1.3 Application of In Organic Nanoparticles to Treatment of Oral Cancer

6.1.3.1 Application of Gold Nanoparticles (GNPs) in Oral Cancer

Gold Nanoparticles (GNPs) have been used in the detection and treatment of various tumors including oral neoplasm because of their easy synthesis, high surface area, stability, and low toxicity. These features employed its use as the collection of the therapeutic agents at the tumor site and as a nanocarrier of many drugs. The core of GNPs can be manufactured in a vast range between 1-150 nm diameters that enable easy-adjust dispersion. In addition, the negative charge of GNPs enables them for simple modification. Overall, GNPs can be easily designed by different biomolecules, drugs, genes, and targeting ligands, [38]. Satapathy *et al*., 2018 [39] designed a hybrid-nanoparticle with quinacrine and metallic gold NPs (QGNP) formulation that inhibited cellular proliferation leading to apoptosis *in vitro*, disorganized angiogenesis *in vivo*, and relapse of the tumor in xenograft mice model strengthen its use as a powerful therapeutic agent against metastasis oral cancer. Moreover, Liu *et al*., 2020 [40] designed a nanoplatform of PDPN antibody, Polyethylene glycol-stabilized and doxorubicin (DOX)-conjugated gold NPs (GNPs). GNPs that improved capacity of drug loading, the efficiency of cellular uptake, and low toxicity against oral cancerous cells. Also, Rathinaraj *et al*., 2020 [41] improved a nanoconjugate of folate-gold-bilirubin (FGB) which showed a stronger inhibitor of tumor growth. Furthermore, Essawy *et al*. 2021 [42] showed an improved survival rate and tumor shrinkage in animals treated with DOX-GNPs compared with other animals.

6.1.3.2 Application of Silver Nanoparticles (AgNPs) in Oral Cancer

Silver nanoparticles (AgNPs) are used to treat different types of tumors because of the antitumor characteristics that enable them to stimulate the death of the cancerous cells in the same traditional way chemotherapy does. The function of the anti-neoplastic of AgNPs may be related to the releasing of metallic silver (Ag0) and silver cation (Ag+) that can both improve the damage of mitochondrial and DNA, destruction of a phospholipid bilayer membrane, oxidative stress, and genotoxicity leading to necrosis or apoptosis or cell death. Also, the AgNPs have antiviral, photosensitizer and/or radiosensitizer, and anticancer agents [43-45]. Barua *et al*. 2017 [46] prepared AgNPs formulations that were strong biocompatible and have the power to improve the chemotherapy with non-toxic and antibacterial attributes drugs for mouth cancer. Yakop *et al*., 2018 [47] formulated a silver nanoparticle Clinacanthus nutans (AgNps-CN) which showed a great inhibition against OSCC (HSC-4 cell lines).

6.1.3.3 Application of Iron Nanoparticles (FeNPs) in Oral Cancer

Iron nanoparticles (FeNPs) are designed as biocompatible nanoparticles which contribute to super paramagnetic drug delivery system and by the external functional magnetic field

can be employed to target tumor site. Jahanbani *et al*., 2020 [48] formulated superparamagnetic iron oxide nanoparticles (SPIONs) that showed a decrease in the potential of succinate dehydrogenase in complex II of the mitochondria which were attained from neoplasm oral tongue squamous.

7. Application Chemopreventive Agents in Oral Cancer

Cancer chemoprevention was introduced to be favored as a powerful approach for decreasing the prevalence of cancer in the last decades. It is also known as a pharmacological strategy to control or counter cancer disease. The chemopreventive factor should be easy to administer and use, cost-effective and has low toxicity with few or no side effects, and can be either antiproliferative agents as retinoids or anti-mutagens as green tea extract [49]. Fig.3 illustrated the chemopreventive agents used in the prevention of oral cancer.

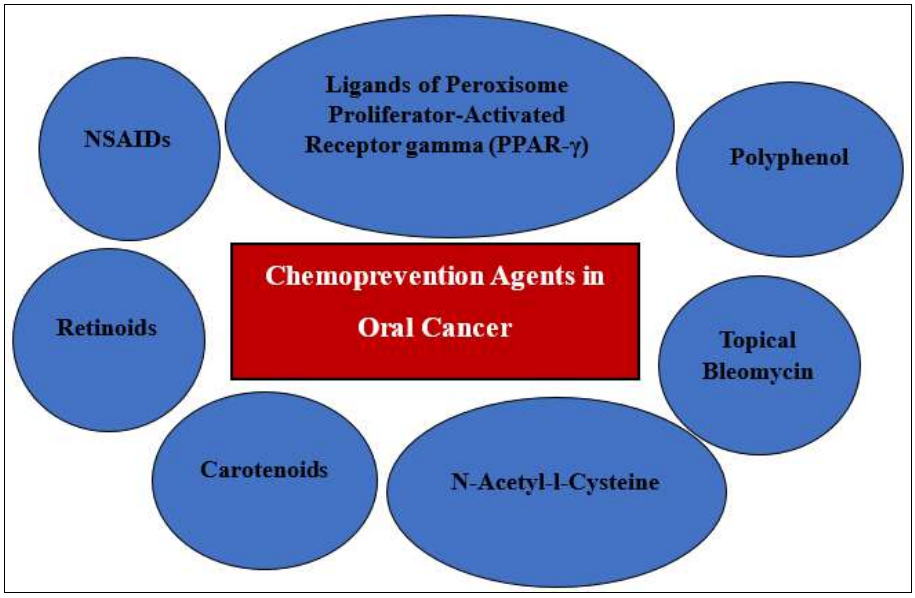

Fig 3: Types of chemopreventive agents used in the prevention of oral cancer

7.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are prostaglandin synthesis inhibition and have anti-inflammatory effects. These drugs can be used to reduce the severe pain associated with cancer patients and improve their life. In addition, they have a role in angiogenesis inhibition in inflamed lesions that can be considered as one of the histological determinations of different diseases such as rheumatoid arthritis, obesity, and cancer [50-52]. Metanalysis in 2017 by Shi *et al*. showed that a significant decrease in the severity of head and neck cancers involving oral cancer among individuals taking NSAIDs and mostly seen with the use of aspirin, ibuprofen, and COX-2 inhibitor than other NSAIDs [53]. However, another clinical trial in 2004 did not identify a relationship between using topical and systemic NSAIDs with oral premalignant lesions treatment [54]. In addition, the selective COX-2 inhibitors can also be related to the elevated risk of cardiovascular diseases as well a high dose of aspirin is related to a high risk of lung cancer [55, 56]. Thus, choosing suitable NSAIDs is necessary to get benefit from their therapeutic effects overcoming the harmful effect.

7.2 Carotenoids

Carotenoids are various groups of organic pigments occurred in different plants. They have activity of vitamin A that can be transformed to retinol, then producing an antiproliferative effect. Carotenoids have antioxidant effects, reduce the destruction of DNA from reactive oxygen species, and have chemopreventive effects in many types of cancers like head and neck cancers. Leonici *et al*. in 2015 [57] showed a decrease in the head and neck cancers rate with dietary carotenoid intake (especially, dietary beta-carotene intake resulting in a decrease of 46% in the severity of oral cavity cancer). However, the increased danger has been demonstrated from the dispensation of beta-carotene in severe lung cancer patients. These results may be referred to as the strong doses of supplements dispensed. Further studies are needed to understand why the intake of dietary carotenoids can have a protective effect, whereas beta-carotene supplementation looks to produce deterioration against oral cancer [56].

7.3 Retinoids

Retinoids including vitamin A (retinol) and its analogs such as isotretinoin that exhibit their effects on the modulation of gene expression, apoptosis, and cell proliferation. Koch *et al*., 1978 [58] first clinically identified the activity of vitamin A analogs on the reduction of oral leukoplakia followed by Hong *et al*., 1986 [59] who demonstrated the activity of oral isotretinoin in the treatment of oral premalignant lesions. The study also demonstrated the reoccurrence of oral premalignant lesions with therapy discontinuation. Another study by Hong *et al*. in 1990 [60] demonstrated that high doses of isotretinoin daily can help in preventing second primary tumors, but it does not prevent recurrences of the disease. As long-term use of the systemic administration of isotretinoin is associated with toxic effects, the low dose did not show efficacy in decreasing the second primary tumors rates. Also, high doses of vitamin A supplementation can improve the mortality risk [61].

7.4 Topical Bleomycin

Bleomycin is a cytotoxic antibiotic that has an antineoplastic effect through several mechanisms by interfering with thymidine inclusion over synthesis of DNA and encouraging breaks of DNA strands to engage in the treatment of both hematologic and solid malignancies. Bleomycin can be administrated through intravenous, intramuscular, or subcutaneous injection. A metanalysis of Chau *et al*. in 2017 [62] demonstrated that topical

bleomycin is effective in oral premalignant lesions therapy. The local formulation of bleomycin has the advantage to administer a high dose with low toxicity. Although this study describes that the average duration of the treatment within 2 weeks, the topical bleomycin with 1% concentration caused severe side effects such as erosion, erythema, and discomfort at the site of application. Therefore, more researches are recommended to determine the suitable dose of topical bleomycin to use as a chemotherapeutic agent with minimum side effects.

7.5 Polyphenol

Polyphenols are a large accumulation of phytochemicals occurred in plants, mainly in seeds, leaves, and fruits. They have been demonstrated as protective agents against reactive oxygen species because of their potential antimutagenic activity *in vitro* and clinical studies. Tea and tea extracts are polyphenols dietary of plant-derived and were employed in many clinical types of research to examine their activity to decrease oral cancer development.

7.5.1 Green Tea Extract

The extract of Green tea contains polyphenol epigallocatechin 3-gallate (EGCG) in great amounts that regulate apoptosis, arrests cells in the G0/G1 phase, and blocks angiogenesis over inhibition the secretion of vascular endothelial growth factor receptor (VEGFR) in tumor cells and phosphorylation of VEGFR. Tsao *et al*. in 2009 [63] showed that partial or complete relapse among oral premalignant lesions patients received green tea extract in phase II randomized, placebo-controlled. However, this study demonstrated that high doses of the green tea extract give a great response than the low doses of it and this may refer to downregulation of stromal VEGF expression in patients taking higher doses of the extract and a potential effect of green tea extract resulting in angiogenesis inhibition [63].

7.5.2 Curcumin

Curcumin has been determined as an effective agent in the chemoprevention of breast, colon, prostate, and oral cancers. Many studies *in vitro* have determined its ability to inhibit the cyclooxygenase-2 (COX-2) and nuclear factor-kappa B (NF-κB) gene expression in oral premalignant cancer. Chronic exposure to mutagens developed the reactive oxygen species and inflammation resulting in irregular activation of NF-κB and development of OSCC [64, 65]. Rai *et al*. in 2010 [66] demonstrated the antioxidant activity of curcumin by oral leukoplakia, increasing salivary as well as serum concentrations of vitamin C and E in lichen planus and submucous fibrosis patients. The biotransformation of curcumin in the gut and enterohepatic cycling of metabolites result in the poor bioavailability of curcumin and make it more difficult to use as a chemoprevention agent. Many studies are recommended to determine the potential use of curcumin as a chemoprevention agent in oral cancer.

7.6 N-Acetyl-l-Cysteine

In general, N-acetyl-L- cysteine (NAC) is used to overcome acetaminophen toxicity by depletion of glutathione reserves leading to improving the antioxidant system of the body. NAC also has been investigated to have anti-inflammatory against influenza, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease (COPD). In addition, NAC has potent antineoplastic activity and has inhibited the phosphorylation of epidermal growth factor (EGF)- induced EGF receptor (EGFR) as the overexpression of EGFR has been expressed in more than 80% of head and neck cancer cells and is related with high rates of relapse and low rates of survival [67]. Zandwijk *et al* in 2002 [68] determined the activity of NAC and Vitamin A that may encourage the diagnosis of patients that were previously treated for head and neck carcinoma by repressing second primary tumors. Temam *et al*. study in 2012 [69] demonstrated that NAC in a human tongue squamous carcinoma (a type of tumor, expresses higher EGFR levels than other cancer cells) improved apoptosis and cell cycle arrest *in vitro*.

7.7 Ligands of Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ)

Proliferator-Activated Receptor gamma (PPAR-γ) heterodimerizes with retinoic acid receptors upon activation via ligand binding and controls the genes expression included in metabolic pathways for glucose metabolism and lipid biosynthesis. Synthetic ligands of PPAR-γ (like the thiazolidinedione medications) have been advanced for the treatment of type II diabetes mellitus because they develop the sensitivity of insulin. Activation of PPAR-γ may have proapoptotic action and an antiproliferative. The studies *in vitro* have determined a relative reduction in expression of COX-2 with increment expression of PPAR-γ thus proposing having anti-inflammatory activity. Therefore, ligands of PPAR-γ may have a role in the chemoprevention of different types of carcinomas, such as OSCC [70]. Govindarajan and Siegel in 2017 [71] administrated thiazolidinedione to diabetic patients with advanced head and neck tumors and showed a decrease in the incidence of the tumor compared to others who depend on di*et al*one to control their diabetes. However, this result is limited because the sample involved in this study involves diabetic male patients only.

8. Conclusions

Oral cancer treatment required invasive treatment following physical examination and post-treatment monitoring. Chemotherapeutic agents remain an effective option for the effective therapy approach of cancer; however, most chemotherapeutic agents are restricted with some limitations as poor oral bioavailability related to their physicochemical properties. Nanotechnology appears to revolutionize clinical dental practice. Optimal application of the benefits and possibilities performed by nanotechnology encourages its use in the diagnosis and treatment of oral cancer. However, like any other novel technology, nanotechnology carries a powerful potential for biocompatibility, misuse, ethics, abuse, and funding issues if not properly controlled.

9. Conflict of Interest

Not available

10. Financial Support

Not available

11. References

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