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Role of Phytochemicals in Oral cancer Prevention – A Comprehensive Review

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Abstract

Oral cancer is caused by a variety of causes, including alcohol consumption, cigarette use, betel quid chewing, human papillomavirus infection, and nutritional inadequacies. It is critical to comprehend the molecular basis of oral cancer. Conventional oral squamous cell carcinoma therapy (e.g., surgery, radiation, and chemotherapy) as well as targeted molecular therapy still have a number of flaw. The use of phytochemical constituents to reduce the risk of developing cancer has gotten a lot of interest in recent years. These phytochemicals are ideal chemopreventive agents because they have little or no harm to healthy tissues. Phytochemicals, on the other hand, typically have low water solubility, bioavailability, and targeting, limiting their therapeutic application. To overcome these issues, a number of studies have looked into developing phytochemical delivery systems. The purpose of this article is to have an overview of oral cancer, such as the causes, diagnosis, and treatment options.

Key words:

Introduction

Oral cancer, which is a subtype of head and neck cancer, was one of the most frequent cancers worldwide. The OSCC is a malignant tumors neoplasm with squamous distinctiveness defined by the production of keratin or the occurrence of intercellular bridges [Sundaram et al., 2012]. It covers nearly 90% among all oral cancers and 38% of head and neck carcinomas [Hema et al., 2017]. Lips, frontal two-thirds of the oral tongue, floor of the mouth, buccal mucosa, upper and bottom gingivae, retromolar trigone, and hard palate have been some of the anatomy subgroups of the oral cavity [Montero et al., 2015]. The tongue, buccal mucosa, and lips are the three main subsites where the OSCC can be found [Pires et al., 2013]. According to the "Global Cancer Statistics 2018" published by the International Agency for Research on Cancer (IARC), there were 18.1 million new cancer diagnoses and 9.6 million cancer deaths worldwide in 2018. In men and women of all ages around the world, 354,864 new instances of lip and mouth cancer were reported, with 177,384 fatalities[Bray et al., 2018]. From 2018 to 2040, the count of lips and oral cancers would also rise from 354,864 to 545,396, and the number of fatalities will rise from 177,384 to 275,164, according to a data supplied by a technology which estimates upcoming cancer rates and death burden worldwide [Ferlay et al., 2020].

Phytochemicals

Scientists have been drawn to phytochemicals because of their ability to affect cell cycle control,

apoptosis evasion, angiogenesis, and metastasis. They've been shown to be effective as single treatments or in combination with other chemopreventive drugs. Vitamins, carotenoids, and dietary polyphenols, such as flavonoids, phylotaxeins, sulfur-rich compounds, and phenolic acid indoles, are all examples of phytochemicals [Surh et al., 2003] Phytochemicals are a novel alternative and forthcoming strategy that has less hazardous side effects. Such treatments might become topical or systemic, and while many others have been made a significant contribution to research of skin and breast carcinogenesis, just a few research on prevention of mouth carcinogenesis have been undertaken. As a result, initial detection and fast preventive actions should be used to increase the patient's quality of life. Despite the vast amount of literature on phytochemical molecular pathways, only a few would be tested in clinical studies.

Risk Factors for Oral Cancer

Tobacco Smoking

Tobacco smoking, specifically smokeless tobacco, is categorized as a type 1 cause of cancer in the oral mucosa by the IARC [Warnakulasuriya et al., 2018]. Smoking is responsible for 75% of all mouth cancer cases [Chaturvedi et al., 2019]. When compared to nonsmokers, smokers get a 2 to 5 times greater chance of acquiring mouth cancer [Viswanath et al., 2013]. OSCC produced by cigarette smoking has been linked to epigenetic varies in oral epithelial cells, immune suppression, and oxidative stress, according to a number of clinical and epidemiological studies. At There are at least 70 carcinogens and cancer-causing substances are found in tobacco smoke [CDC 2020]. Tobacco, hydrogen cyanide, formaldehyde, toxic substances (e.g., lead, arsenic), ammonia, radioactive materials (e.g., uranium), phenol, benzene, carbon monoxide, nitrosamines, and polyaromatic are examples of such carcinogens [Moracco et al., 2016]. Tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs) are two of them that have been linked to cancer [Xue et al., 2014]. The TSNAs, such as N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), are implicated in the metabolization of NNK and NNN, that cause damaging genetic variations in oncogenes and tumor suppressor genes by generating covalently linked DNA adducts [Hecht et al., 1998]. The carcinogen benzo[a]pyrene (BaP) is the prototype PAH that has been investigated the most. The major component of cigarette smoke is BaP. BaP can be metabolized by cytochrome P450 enzymes and activated in to another cancer causing reactive intermediate or metabolite. The substances generated could attach to DNA and create DNA adducts, which can obstruct replication of DNA [Conney et al., 1982]. Cytotoxic effect, teratogenic effects, genotoxicity, immunotoxicity, mutagenesis, and carcinogenesis have all been linked to metabolically activated BaP [Rengarajan et al., 2015].

Alcohol

Alcohol intake has long been thought to be a major risk factor for mouth tumor. Drinking of alcohol subtle changes such as (1) modifying the structure of the oral cavity and thereby rising permeability; (2) dissolving the lipid component of the epithelial tissue and therefore lowering its width and affecting muscle wastage; and (3) DNA synthesis and repair are disrupted by the mutagenic and carcinogenic effects of the metabolite acetaldehyde, which interfere with DNA synthesis and repair enzymes. Oral cancer risk is increased as a result of these alterations. [Ogden et al., 2018].

Betel Quid

The International Agency for Research on Cancer (IARC) determined that betel quid and areca nut are also psychostimulants and psychoactive substances, and that also class I carcinogens in humans. Areca nut contains betel quid alkaloids and polyphenols, that could also induce oral and pharyngeal melanoma [Chen et al., 2017]. The active element in the areca nut is betel quid alkaloids, and the greatest source of toxicity is arecoline in alkaloids, followed by arecaidine. In mammalian cells, arecoline and arecaidine can cause DNA strand breakage, chromosomal abnormalities, sister chromatid exchange, and micronucleus production [Sundqvist et al., 1989]. Furthermore, through nitrosation reactions in the oral and gastrointestinal tracts of humans, arecoline can generate areca nut–specific nitrosamine compounds (areca-specific N-nitrosamines), causing aberrant cell proliferation and malignancy [Ernst et al. 1987]. Areca nut polyphenols have both carcinogenic and anti-carcinogenic properties. Polyphenols' positive benefits, according to some publications, include antioxidant capacity to reduce oxidative stress damage [Stagos et al., 2019], and also biomedical impacts via chromatin remodeling as well as other epigenetic changes [Russo et al., 2017]. Polyphenols, on the other hand, have been demonstrated in a number of studies to be a main functional cause of cancer because they generate reactive oxygen species (ROS) and 8-OH-dG when coupled with lime to form oral environment alkalines (pH 9.5), which degrade DNA [Nair et al., 2004]. Although lime is not carcinogenic in and of itself, the contact among polyphenols and lime is the most important factor in ROS production. Moreover, ROS can target salivary proteins and oral cavity, causing alterations in the structural system of the oral mucosa and assisting harmful drug permeation [Mhaske et al., 2009].

Human Papillomavirus

More than 200 distinct human papillomavirus (HPV) subtypes were secluded from human people, the much more frequent of which is the increased subtype HPV-16, which would be designated as a causative agent of oral and pharyngeal tonsil malignancies by the International Agency for Research on Cancer (IARC).Oral cancer can also be caused by the less prevalent variant HPV-18. HPV promotes mutagenesis impacts through into the two primary virus-encoded oncoproteins E6 and E7, according to evidence. Such proteins affect the cell cycle, cell death, and genetic stability signaling pathways by raising the genetic change of tumor suppressor genes p53 and RB1, as well as the deterioration of their products, that could lead to tumors in human oral epithelial cells[Hallikeri et al., 2019].

Nutritional Deficiencies

Nutritional and mineral insufficiencies (e.g., carotenoids, antioxidant vitamins, phenols, terpenoids, steroids, indoles, and fibers) are caused by a lack of vegetables and fruits in the diet, that raises the chances of carcinoma. Phytochemicals are protective bioactive molecules found in these meals. Oral illnesses are thought to be exacerbated by a deficiency in phytochemicals [Grimm et al., 2015].

Other Factors

Several studies have shown that immune conditions (e.g., congenital immune response defects

and organ transplant receivers who would be given immunosuppressants), environmental pollutants (e.g., arsenic, chromium, and nickel), work - related exposures (e.g., ultraviolet radiation), microbes (e.g., bacteria), and genetic diseases all increase the risk of cancer. (e.g., Fanconi anemia, dyskeratosis congenita, and Bloom syndrome) [Srinivasprasad et al.. 2015].

OSCC Diagnosis

TNM Staging System (Tumor, Node, Metastasis)

The tumor, node, and metastasis (TNM) staging analysis is founded on determining the size of the main tumor (T), the extent of regional lymph node involvement (N), and the involvement of distant metastases (M) (M) [Brierley et al., 2016]. The degree of incursion of the main tumor and the extramedullary expansion of lymph node metastases have indeed been added to the T and N pathophysiological categories, including both, in the eighth edition of the AJCC TNM staging manual. However, histological evaluation of local lymph nodes indicated metastatic development in roughly 20–40% of individuals with OSCC who had no clinical or imaging indication of metastasis to lymph nodes [Massano et al., 2006]. As a result, TNM staging is typically inadequate for identifying the factors that influence OSCC lifespan. Additional features of the tumor, like the high variation and kind of invasion, could help with definitive diagnosis, therapy selection, and confident evaluation of management outcomes.

Imaging Evaluation

Medical imaging, like computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), is critical for identifying as well as deciding the focus of such primary lesion, local lymph node spread, and metastatic disease in early. OSCC because it usually involves superficial lesions [Chi et al., 2015]. CT can help with regions of composite mineral deposits, lesion density and pattern, as well as the amount of surrounding bone and neurovascular involvement, among other things. MRI is also useful in diagnosing head and neck pathophysiology since it has a good contrast resolution than CT for determining the amount of local soft-tissue intrusion, medial bone involvement, and perineural incursion. PET scans could also offer physiochemical information on cellular metabolism by injecting biological radioactive substances with varied biological material properties into the patient's vein. PET imaging may detect abnormalities before CT or MRI images because these events frequently occur before tissue structural changes [Singh et al., 2017]. The PET method's inability to properly discern location, on the other hand, is a major flaw. This problem is solved by combining anatomically better imaging techniques (e.g., CT and MRI) with PET (i.e., PET–CT and PET–MRI).

Biopsy

Despite noninvasive imaging methods could be utilized to define head and neck malignancies, tissue sample remains the gold standard for soft-tissue tumor diagnosis. The method of exfoliative cytology is painless and non-invasive. The hinders or exfoliated cells could be gathered for microscopic analysis, and the cytomorphometric alterations can be used to determine whether the cells are dysplastic or malignant. The most prevalent procedures are incisional and excisional biopsies. Excisional biopsy involves removing tumor and some surrounding healthy tissue, whereas incisional biopsy takes a

very small piece of a questionable tissue sample from the lesion or mass for diagnostic test. Fine needle aspiration biopsy is a procedure that involves drawing a little quantities of liquid and also very small tissue blocks from the a tumor with a slim, hollow needle linked to a syringe and then examining the presence of cancer cells below a microscope. Liquid biopsy is a noninvasive diagnostic method that evaluates samples of blood, saliva, or other bodily fluids (e.g., urine, seminal plasma, pleural effusion, cerebrospinal fluid, sputum, and feces) [Peng et al., 2017].

Biomarkers

Biomarkers are “biomolecules found in blood, other bodily fluids, or tissues that signal normal or aberrant processes, conditions, or diseases, and could be used to track the body's reaction to disease or condition therapies”. Researchers have examined into using changes in DNA and protein in saliva, serum, and tissue samples as biomarkers to help in OSCC identify and prognosi . The deletion of particular chromosomal regions in identified or suspected tumor suppressor genes has been shown in various studies to become an initial analyst of the advancement of oral precancerous lesions. Oral epithelial dysplasia can be caused by abnormal DNA methylation, which is a prevalent feature in malignant tumors and leads to tumorigenesis, aggressiveness, invasiveness, and malignant transformation.[Shaw., 2006]. MicroRNAs (miRNAs) are noncoding RNAs that play a role in posttranscriptional gene regulation. They can behave as oncogenes or tumor suppressor genes, regulating the expression of target genes implicated in cancer biology. As a result, dysregulation of certain miRNAs can lead to cancer development and progression, making them promising candidates for biomarkers in oral malignancies. Furthermore, quantitative proteomics technology has been used to investigate possible biomarkers for local and systemic diseases, which could aid in the identification of specific proteins implicated in disease progression and the rapid diagnosis of disorders[Amiri-Dashatan et al., 2018].

Therapeutic Alternatives

Phytoconstituents and their diverse action mechanisms

Although fruits and vegetables are very simple to consume, the relevance of phytochemicals and their dietary benefits must be conveyed to the general audience. Phytochemicals are a diverse set of non-nutritive compounds that are thought to help prevent cancer. There are more than 5000 phytochemicals in the globe, yet only 150 to 200 plants are ingested by humans, according to estimates[Liu et al., 2004].

They are divided into two categories: vitamins and dietary polyphenols. Furthermore, they are useful in enhancing the efficiency of cytotoxic medications while decreasing the damaging effects on normal cells. As a result, these phytochemicals can be used in conjunction with chemopreventive drugs to provide superior clinical results in the prevention of oral cancer. Chemoprevention, or the use of particular natural and synthetic chemicals to prevent the occurrence of oral carcinogenesis, is a valuable and promising method. Michael B.Sporn created the term "chemoprevention" in 1976 [Theisen et al., 20001]. Obstructing agents, suppressing agents, and agents that lower venerability to oncogenesis are the three basic groups they fall into. These medicines, however, work through a variety of pathways,

including antioxidant characteristics, anti-lipid peroxidative activity, anti-proliferative activity, free radical scavenging capabilities, and anticancer initiative properties, among others: Medicinal plants high in bioactive phytochemicals and antioxidants have gained popularity as potential chemopreventive medicines in recent years. Spirulina, curcumin, beta-carotene, dietary flavonoids, chalcone, green tea, garlic, black raspberries, piperine, and dietary turmeric, among other dietary components and bioactive elements, have showed chemopreventive potential in oral carcinogenesis [Manoharan et al., 2009]. These findings lay the groundwork for clinical trials of novel phytoconstituents for cancer stem cell protection. They could also help in the discovery of new cancer prevention strategies and the improvement of patients' long-term survival. We've compiled a list of some of the most well-known agents, along with an updated evaluation of the literature.

Anticancer Bioactivity of Phytochemicals

The pathogenesis of cancer is caused by the excess generation of oxidants (reactive oxygen and nitrogen species) in the human body. Phytochemicals found in fruits, vegetables, and grains have been shown to protect against cancer formation. Phytochemicals' preventive properties may be linked to their antioxidant activity. According to studies, lifestyle adjustments might protect over than two-thirds of human malignancies, and dietary patterns are responsible for about 35% of cancer mortality [Zhang et al.2015]. Multistage carcinogenic processes are hypothesized to be linked to free radicals. Peroxyl radicals and lipid peroxidation can both produce DNA alterations that are required for the carcinogenic process to begin. By preventing DNA damage, antioxidant phytoconstituents could control the onset of cancer causing processes. Green tea polyphenols, milk thistle silymarin, and grape seed proanthocyanidins, for example, may protect the skin from the harmful imfacts of UV radiation (e.g., skin cancer risk) by lowering Ultra violet inflammation, oxidative stress, DNA damage, and immunological reactions. Phytoconstituents may also suppress cell proliferation and cause cancer cells to die. The induction of quinone reductase was greater in quercetin, genistein, and resveratrol. Quinone reductase overexpression is regarded to be a helpful biomarker for anticarcinogenesis. Furthermore, genistein inhibited breast cancer growth by demethylating and reactivating methylation-silencing tumor suppressor genes. [Xie et al., 2014]. Human breast cancer cells may be harmed by lycopene and -carotene, which limit cell proliferation, stop the cell cycle, and enhance apoptosis. To summarize, oxidative stress plays a role in all stages of carcinogenesis (initiation, promotion, and progression) either directly through DNA damage or indirectly through cell signal transduction regulation. As a result, chemoprevention relies heavily on reducing oxidative stress. Because of their antioxidant qualities, dietary phytochemicals have a lot of potential. Metastasis is a significant side effect of cancer treatment. In various in vitro and in vivo models, flavonoids have been demonstrated to have anti-cancer actions via modulating key signaling pathways involved in important steps of metastatic progression. [Chikara et al., 2018]. Epigenetic changes may occur before genetic mutations in the early stages of carcinogenesis, making epigenetics an attractive target for early cancer therapies employing epigenetic biologically active chemicals. Curcumin, quercetin, apigenin, ()-epigallocatechin-3-gallate (EGCG), genistein, resveratrol, sulforaphane, and diallyl disulfide are just a few of the phytochemicals that have been shown to have considerable chemopreventive impacts by targeting multiple anticancer pathways and also epigenetic mechanisms. [Guo et al., 2015]. CSCs are an unusual subpopulation of cancer cells with

aberrant self-renewal, proliferation, or apoptosis regulation, which leads to cancer growth, invasiveness, metastasis formation, and resistance to chemotherapy. EGCG, resveratrol, genistein curcumin, sulforaphane, and diallyl trisulfide have all been shown in studies to target CSCs and display their anticancer properties. Phytochemicals also have low or no toxicity to healthy tissue, making them potential chemopreventive agents.

Phytochemicals' Oral Cancer Prevention Molecular Mechanisms

Alternative cancer treatments are needed due to the continual rise in cancer deaths, the failure of current chemotherapies, and their toxicities [Ranjan et al., 2009]. Phytoconstituents could suppress or antagonize factors that are downregulated in tumor cells, and they would be used to augment the effects of conventional therapy or as a stand-alone treatment. Because phytochemicals have long been part of the human diet, the risk of serious side effects could be reduced in health care settings than with synthetic compounds that are being recently established. Phytoconstituents could have chemoprotective qualities by preventing key events in tumor genesis and progression, reversing the premalignant stage. Phytoconstituents could potentially help to avoid tumor growth by blocking or delaying tumour growth and encouraging cell growth. In addition, phytoconstituents could increase innate immune surveillance and transformed cell eradication [Kotecha et al., 2006].

Improvements in Phytochemical Bioavailability and Delivery Systems

Natural chemicals' medicinal benefits are frequently restricted by their poor water solubility, poor bioavailability, and poor targeting. Numerous studies have concentrated on the development of phytoconstituents delivery methods in attempt to tackle these challenges (e.g., liposomes, nanoparticles, nanoemulsions, films, adjuvants, micelles, and phospholipid complexes) [Mirzaei et al., 2017]. Flavonoids, resveratrol, celastrol, curcumin, berberine, and camptothecin would be able to escape drug metabolism, overcome physiological barriers, and deliver larger concentrations at cancer sites using these delivery systems. For example, resveratrol seems to have a long circulation half-life, while the flavonoids quercetin and EGCG often have low micromolar concentrations in the blood, which can be enough for cytoprotective but not anticancer effects. Various resveratrol delivery technologies have been implemented (e.g., the resveratrol encapsulation in lipid nanocarriers or liposomes, emulsions, micelles, insertion into polymeric nanoparticles, solid dispersions, and nanocrystals). These mechanisms can speed up the absorption of high amounts of resveratrol, resulting in increased plasma concentrations. [Chimento et al., 2019]. Moreover, polyphenol nanoencapsulation (EGCG, quercetin, curcumin, and resveratrol) may improve circulation, localisation, efficacy, and minimize the risk of multidrug resistance.

Nano Chemoprevention

By merging nanotechnology and chemoprevention, researchers were able to achieve a new step in cancer prevention, dubbed nano chemoprevention. Toto, it is a new branch of chemoprevention research that has exploded in popularity since it is a cost-effective, acceptable, and relevant approach to cancer control and management. Nano particulate systems' tunability and surface function encapsulates one or more entities of chemopreventative drugs with low solubility, low bioavailability, and harsh

solvents [Siddiqui et al., 2010]. Biocompatible and biodegradable nano carriers such as polymers like Poly lactic acid (PLA), Poly (DL-lactide -co-glycolide acid) (PLGA), starch, and chitosan, which have all been employed for drug delivery, can be used to make water soluble medicines.

Conclusion

Finally, because we consume a large number of bioactive phytochemicals in the form of fruit and vegetable ingredients, their health-promoting properties and unique biological activities should have been recognized and highlighteds. New phytochemicals that contribute in the prevention of mouth cancer should be combined with significant upcoming technologies like nano chemoprevention. As a result, whole food consumption should be prioritized over mono plant chemical use. Furthermore, phytochemicals' additive and synergistic actions can be coupled with chemotherapy and radiotherapy to reduce dosages and toxicity. The evaluation and broader work in phytochemicals must be done in the context of oral cancer.

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