ANTIOXIDANTS IN ORAL CANCER

Introduction

Oral cancer, also known as mouth cancer, tongue cancer, or oral cavity cancer, is a malignancy that affects the mucosal lining of the lips, mouth, or upper throat. It typically presents as a painless red or white patch in the oral cavity that progressively thickens, ulcerates, and enlarges. When located on the lips, the lesion may appear as a crusted, non-healing sore that gradually increases in size (Muthu K *et al.,*2018)

Common clinical symptoms include difficulty chewing or swallowing, persistent oral pain, numbness, speech difficulties, and swelling in the jaw or neck. Multiple risk factors are associated with oral cancer, including tobacco use (both smoked and smokeless), excessive alcohol consumption, infection with human papilloma virus (particularly HPV-16), chronic ultraviolet (UV) exposure (notably on the lips), poor oral hygiene, and diets deficient in fruits and vegetables (Irani S *et al.,*2020).

Diagnosis generally begins with a physical examination followed by a biopsy of any suspicious lesion. Imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scans are employed to determine the extent of disease spread (Edge S *et al*.,2010). Treatment strategies vary based on cancer stage and may involve surgical resection, radiation therapy, chemotherapy, targeted molecular therapies, or immunotherapy (Day *TA et al.,*2003).

Early detection is critical to improving survival rates, underscoring the importance of regular dental checkups and timely investigation of any abnormal oral symptoms. Preventive measures such as tobacco cessation, reduced alcohol consumption, good oral hygiene practices, UV protection for the lips, and HPV vaccination can significantly decrease the risk of oral cancer (Irani S *et al.,*2020).

Oral cancer remains one of the most prevalent malignancies globally, particularly in South and Southeast Asia, where tobacco and betel nut use is widespread (Borse V *et al.,*2020). In recent years, growing evidence has emphasized the role of oxidative stress in the pathogenesis of oral cancer. Oxidative stress results from an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defense

systems, leading to damage of DNA, proteins, and lipids. This mechanism contributes significantly to cancer initiation, progression, and therapeutic resistance, providing new opportunities for early diagnosis, prevention, and treatment (Katakwar P *et al.,*2016).

Oxidative Stress in Oral Cancer

Free radicals are highly reactive, unstable molecules implicated in the pathophysiology of various chronic diseases, including cancer. Oxidative stress refers to a state in which the production of these harmful molecules exceeds the body's ability to neutralize them using antioxidant defenses. This imbalance results in cellular damage, which can be assessed using biomarkers of oxidative stress(Kesarwala A H *et al.,*2017).

In the oral cavity, reactive oxygen species (ROS) a key subset of free radicals—can originate endogenously (through metabolic processes) or be introduced exogenously via exposure to cigarette smoke, alcohol, betel nut, air pollution, and other carcinogens (Katakwar P *et al.,*2016).

ROS are involved in normal physiological processes such as immune defense and cellular signaling. However, when ROS levels surpass the threshold of homeostatic control, they contribute to oxidative stress and cellular injury(Ionescu C *et al.,*2024).

The accumulation of ROS can cause significant damage to biomolecules such as DNA, proteins, and lipids. In the context of oral cancer, ROS promote mutagenesis, genomic instability, and epigenetic modifications. They also act synergistically with established risk factors such as smoking, alcohol consumption, and HPV infection—to amplify carcinogenic effects .Additionally, ROS play a role in other oral pathologies, including periodontitis and recurrent aphthous ulcers (Kesarwala A H *et al.,* 2016).

The recognition of oxidative stress as a driver of carcinogenesis has spurred interest in antioxidant-based interventions. As early as the 19th century, scientists observed the protective potential of antioxidants, later identifying vitamins A, C, and E as key compounds that mitigate oxidative damage(Katakwar P., 2016). These discoveries shifted the paradigm in disease prevention and laid the groundwork for modern antioxidant therapies.Currently, there is compelling evidence that oxidative stress plays a pivotal role in the initiation and progression of oral squamous cell carcinoma and

other head and neck cancers(Ionesu C *et al.,*2024). ROS not only cause direct cellular damage but also modulate key signaling pathways involved in cell proliferation, inflammation, and apoptosis. Therefore, targeting oxidative stress is an emerging strategy in oral cancer prevention and therapy (Kesarwala AH *et al.,*2016).

Interventions that lower ROS levels such as dietary supplementation with antioxidants, improved lifestyle choices, and pharmacological agents—may help reduce cancer risk and enhance treatment efficacy. Furthermore, biomarkers of oxidative stress are being actively explored for their potential utility in early cancer detection, prognosis, and the personalization of treatment approaches(Ionescu C *et al.,* 2024).

Looking ahead, research must leverage advanced technologies including genomics, transcriptomics, proteomics, epigenomics, and nanotechnology to elucidate the molecular mechanisms by which oxidative stress contributes to oral carcinogenesis. High-throughput methods such as whole-genome sequencing and RNA-seq can uncover specific gene alterations and regulatory pathways disrupted by ROS (Ionescu C *et al.,*2024) Additionally, enhancing endogenous antioxidant systems through pharmacological or gene therapy approaches holds promise for mitigating ROS-induced damage.By integrating modern technological platforms with molecular insights into oxidative stress, researchers can fill existing knowledge gaps and develop more effective strategies for the prevention, early detection, and management of oral cancer (Ionescu C *et al.,*2024).

Dietary Antioxidants in Oral Cancer Prevention

Normally, we take food is preventing oral cancer and researchers, scientists have been exploring natural ways to prevent it, specially using antioxidant nutrients like carotenoids, vitamin E and polyphenols.

Therapeutic Trials

Beta carotene (carrot), vitamin E (oils & nuts), and polyphenols are safe and used without side effects. these studies conducted in the lab using cells or animals show that these antioxidants can stop cancer cells' growth in the oral. These nutrients are at low levels in people who have a higher chance of getting oral cancer.This studies focus on treatment for oral precancer (Leukoplakia). Leukoplakia is a white patch in the mouth

that can become cancerous. Therapeutic trials with beta-carotene and vitamin E showed it can reduce patches. Different doses used to test showed the 50%- 70% results good responses without harmful effects (Harinder Garewal *et al.,* 1995)

Prospective Study of Vitamins C, E, and A and Carotenoids and Risk of Oral Premalignant Lesions in Men

Leukoplakia occurs at mouth (oral premalignant lesions (OPLs). It can change and later turn into oral cancer. The main reasons for these lesions are oxidative stress, smoking, and the use of tobacco, which damages DNA in the oral cavity. especially some nutrients like vitamin C, vitamin E, vitamin A, and carotenoids These antioxidants help to protect the body from this type of damage. This study focused on how people consuming vitamins or supplements could reduce the risk of developing OPLs.

Therapeutic Trials

This study showed that high intake of vitamin C (rich in fruits and vegetables) is linked to a lower risk of OPLs. mostly affects men. Men who ate high vitamin C-rich foods had almost 50% less risk than those who ate the least. Similarly, β-cryptoxanthin and α-carotene are natural antioxidants present in fruits. Men, especially smokers, who took high doses of vitamin E or β-carotene supplements had a higher chance of getting OPLs. Antioxidants from food may protect the oral cavity from cancer-related changes, so artificial supplements may not be safe, especially for smokers. This study found that eating fruits and vegetables naturally rich in antioxidants is good and safe for preventing oral cancer (Maserejian *et al.,* (2006).

Efficacy of oral lycopene in the treatment of oral leukoplakia

Oral leukoplakia is a common type of precancerous lesion in the mouth. patches appeared white in colour that can't be scraped off. These patches are linked to those who use tobacco, particularly smoking and chewing. This makes free radicals rich in harmful molecules that damage oral DNA and have a high chance of causing cancer. So, lycopene is a natural antioxidant found in tomatoes, watermelon, guava, and pink grapefruit that neutralizes these harmful radicals and is more effective than β-carotene in protecting cells from damage and helps to treat oral leukoplakia and prevent it from progressing into oral cancer.

Therapeutic trials

In this study,58 oral leukoplakia patients were divided into 3 groups.

GROUP	LYCOPENE (mg)	RESULTS
Group - A	8	80%
Group - B	4	66.25%
Group - C	placebo	12.5%

Microscopic tests confirmed better healing in the higher dose group. Lycopene was safe, no side effects and preventing oral leukoplakia (Maserejian *et al*.,2006)

Concentration effects of grape seed extracts in anti-oral cancer cells involving differential apoptosis, oxidative stress, and DNA damage

Oral cancer is cause serious healthissuese, specifically in Taiwan, where habits like betel quid chewing .Betel quid, arecoline it is a harmful chemical that causes DNA damage and oxidative stress, leading to cancer.GSE (Grape seed extract) acts as a natural antioxidant and is used as a therapeutic agent. It is a health supplement due to its powerful antioxidant properties and has been shown to have anticancer effects (Ching-Yu Yen *et al.,*2015)

In this study, researchers tested different concentrations of grape seed extract on oral cancer cells (Ca9-22) to understand its therapeutic effects

Low concentration (1–10 µg/ml)	**High concentration (50–400 µg/ml) showed**
• Mild antioxidant effect • No cell death observed. • It may help prevent oxidative stress.	• Strong anticancer effect • Apoptosis (cell death, ROS increase, Mitochondrial damage and DNA damage) • Inhibits cancer cell proliferation.

Vitamin E (α-Tocopherol) Exhibits Antitumour Activity on Oral Squamous Carcinoma Cells ORL-48

This study focused on how vitamin E (especially α-tocopherol) affects oral cancer cells (ORL-48). Scientists compared it with a common chemotherapy drug called Cisplatin. This drug was stronger at killing cancer cells, but it was toxic to normal skin cells. α-tocopherol was safer as it harmed cancer cells but didn't affect healthy cells much.α-tocopherol treated cells showed clear signs of apoptosis .Vitamin E had gentle anticancer agent that could still stop the growth of oral cancer cells.

Therapeutic trials

This study was conducted in vitro. Strong anticancer effect of α-tocopherol in cell models and its low toxicity to normal cells, the researchers suggested future trials, like using α-tocopherol in animal models or combining it with cisplatin to improve cancer treatment while reducing side effects (Zulkapli *et al.,* 2016).

Antioxidants: Types and Mechanisms of Action

Antioxidants are a class of chemical substances naturally found in our food which can prevent or reduce the oxidative stress of the physiological system. The body is constantly producing free radicals due to regular use of oxygen. These free radicals are responsible for the cell damage in the body and contribute to various kinds of health problems, such as heart disease, diabetes, macular degeneration, and cancer (Ayoka TO *et al*., 2022).

Types of antioxidant

Antioxidants, according to their chemical properties, can be generally divided into two main types: enzymatic and non-enzymatic**.** This classification is determined by the way each type acts at the molecular level to fight oxidative stress (Ayoka TO *et al*., 2022).

Enzymatic antioxidants

Enzymatic antioxidants are protein-based molecules naturally made by the body that help eliminate free radicals through specific biochemical reactions. Important examples include superoxide dismutase (SOD)**,** catalase**,** and glutathione peroxidase. These

enzymes function together to transform dangerous reactive oxygen species into safe substances such as water and oxygen (Moussa, Z *et al*., 2020).

Non-Enzymatic antioxidants

Non-enzymatic antioxidants are low-molecular-weight compounds that directly neutralize free radicals. They can be synthesized within the body or acquired through food. Examples include vitamin C**,** vitamin E**,** glutathione**,** carotenoids (such as beta-carotene and lycopene), and polyphenols found in plant-based sources. These antioxidants help safeguard cells from oxidative harm and enhance the activity of the body's natural defence enzymes (Moussa, Z *et al*., 2020).

Mechanism of action

Antioxidants work through several mechanisms to protect cells and tissues from damage caused by **oxidative stress**, which results from an imbalance between free radicals and the body's ability to counteract them.

Antioxidants neutralize free radicals by stabilizing these reactive molecules and preventing them from causing cellular damage. Free radicals are unstable because they have unpaired electrons, which makes them highly reactive with cellular components like lipids, proteins, and DNA (Almohktar A *et al*., 2019). Antioxidants act by donating an electron or hydrogen atom to the free radical, thereby neutralizing its reactivity without becoming unstable themselves (Ashutosh Kumar Shukla *et al*., 2019). For example, vitamin C donates electrons in aqueous environments, while vitamin E protects cell membranes by halting lipid peroxidation (Maret G *et al*., 2011). In addition to these non-enzymatic antioxidants, the body also relies on enzymatic systems such as superoxide dismutase, catalase, and glutathione peroxidase, which convert reactive oxygen species into harmless substances like water and oxygen. By interrupting oxidative chain reactions and reducing the overall load of reactive species, antioxidants protect cells from oxidative stress and help maintain biological balance (Moussa, Z *et al*., 2020).

Antioxidants reduce oxidative stress by neutralizing excess free radicals and preventing them from damaging cellular components. Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the body's ability to detoxify them, leading to damage of lipids, proteins, and DNA. Antioxidants counteract this imbalance through several mechanisms: they scavenge free radicals by donating electrons, chelate metal

ions that catalyse ROS formation, and support the activity of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Nimse, S. B *et al*., 2015). These actions collectively reduce the accumulation of ROS, interrupt chain reactions of oxidative damage, and restore redox balance within cells. By lowering oxidative stress, antioxidants help protect against inflammation, aging, and the development of chronic diseases like cancer, cardiovascular disorders, and neurodegenerative conditions.

Challenges and Future Directions: Bioavailability and Efficacy of Antioxidants & Personalized Nutrition in Cancer Prevention

A significant challenge in antioxidant research is the poor bioavailability and variable efficacy of many antioxidant compounds. Although numerous antioxidants show strong activity in laboratory settings, their effectiveness in the human body is often limited because they are poorly absorbed, rapidly metabolized, or degraded before reaching target tissues. This reduces their ability to neutralize harmful free radicals and provide therapeutic benefits, especially in complex diseases like cancer. Moreover, the diverse metabolic pathways and interactions within the human body create variability in how antioxidants perform, making it difficult to standardize doses or predict outcomes reliably (Birgit *et al.*, 2008).

Looking forward, personalized nutrition offers a promising strategy to improve cancer prevention through antioxidants. By tailoring antioxidant intake based on an individual's genetic profile, lifestyle, and environmental exposures, it is possible to optimize the protective effects of these compounds. Advances in genomics, metabolomics, and data analytics enable the identification of people who may benefit most from specific antioxidants or dietary patterns. Furthermore, innovations in delivery methods, such as nanoencapsulation, could enhance antioxidant stability and absorption. Together, these approaches aim to overcome current limitations, making antioxidant-based interventions more effective and personalized in reducing cancer risk (Zucca, P *et al*., 2020).

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