



INFLUENCE OF VITAMINS AND ANTIOXIDANTS IN ORAL CARCINOGENESIS – A REVIEW

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ABSTRACT

Frequent forms of malignancy localized to the oral cavity are considered a major health problem, especially in developing countries. Research on the experimental oral carcinogenesis inhibition using topical beta-carotene has led to the observation that beta-carotene significantly inhibits the formation of DMBA (7,12-dimethylbenz anthracene) and hamster squamous cell carcinoma-induced oral pouch when used topically daily. In another study, 13-CIS-retinoic acid was used in the oral leukoplakia treatment where the efficacy of vitamin A in the oral leukoplakia treatment was highlighted. The efficacy of a mixture of ascorbic acid, glutathione, α -tocopherol, and β -carotene has shown that α -tocopherol and β -carotene can act synergistically to inhibit the growth of oral cancer. Analyzing the delay in oral cancer development using topical vitamin E demonstrated a significant delay in tumor formation compared to the animals from the control group. Extensive research has been conducted in experimental animals to indicate the anticancer activity of tocopherol, carotenoids, and retinoids on oral precancerous leukoplakia and oral cancer. The anticancer attributes of these micronutrients have been investigated in experiments on carcinogenesis inhibition, the prevention of oral cancer development, and oral carcinoma regression. Synergism has been shown in the anticancer activity of alpha-tocopherol and beta-carotene. Synergism has been shown between anticancer alkylating agents such as cyclophosphamide, melphalan, and beta-carotene. In conclusion, antioxidant micronutrients such as beta-carotene are oral carcinogenesis inhibitors; vitamin E and beta-carotene can induce oral leukoplakia clinical regression, a premalignant lesion of oral cancer.

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Introduction

Frequent forms of malignancy localized to the oral cavity are considered a major health problem, especially in developing countries [1-3]. They are favored by the frequency of protein-calorie malnutrition, associated with malabsorption, alcoholism, and various drug treatments. Epidemiological statistics show that personal and environmental habits, especially tobacco use associated with alcohol, are major risk factors in the progression and induction of oral cancer [4, 5]. Oxidative stress is a risk factor in the development of degenerative and chronic diseases such as neurodegenerative and cardiovascular diseases, aging, cancer, rheumatoid arthritis, cataracts, and autoimmune disorders. Through its mechanisms, the human body can counteract oxidative stress based on antioxidants provided naturally or exogenously through food and/or supplements. Antioxidants can scavenge free radicals, preventing and repairing wear and tear caused by reactive oxygen species (ROS), resulting in improved immune defenses and reduced cancer risk and degenerative diseases. Based on these facts, researchers have directed their interest toward finding phytochemicals with antioxidant effects, which can inhibit the propagation of oxidative stress-mediated by free radicals and protect the body against diseases [6, 7].

Living cells contain, in addition to their major components - proteins, nucleic acids, carbohydrates, and lipids - certain organic, active, and vital substances at very low concentrations (vitamins) with biological importance because some organisms cannot synthesize them and must obtain them from exogenous sources - food or supplements. The history of the effects of vitamins is one of the most important parts of medical biochemistry, with a profound impact on health and comfort, as well as the understanding of the catalytic processes that take place in the metabolism of the human body [8].

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The first vitamins were isolated between the 1930s and 1940s, and their molecular structure was established. Achievements of heroic proportions were needed for those times since to obtain milligram quantities of pure substance, hundreds of kilograms, even tons, of raw material were needed. Within a few years, thiamine (the anti-beriberi substance, vitamin B1), riboflavin (vitamin B2), and nicotinic acid (the anti-pellagra factor, vitamin B3) were identified. Later, it was proven that these vitamins are constituent elements of coenzymes. For example, the enzyme called pyruvate decarboxylase, which catalyzes the decarboxylation reaction of pyruvic acid, obtained from glycolysis, to acetaldehyde and carbon dioxide, a step in the alcoholic fermentation of sugar by yeasts, requires a thermostable cofactor, called cocarboxylase. Lohmann and Schuster managed to isolate cocarboxylase in 1936, and within a few months, they found that this cofactor contained a molecule of thiamine. Immediately after that, it was discovered that riboflavin and nicotinic acid are important components of other coenzymes involved in the enzymatic oxidation of monosaccharides [9].

Vitamins belong to two big groups: water-soluble and fat-soluble. Except for vitamin C, all water-soluble vitamins have well-defined coenzyme functions. In addition, several other water-soluble substances are necessary as growth factors for some organisms. However, their concentration is higher than that of vitamins; this group includes inositol, choline, and carnitine.

Fat-soluble vitamins K, E, D, and A are obtained by higher animals from exogenous sources; in the case of plants and microorganisms, it has not yet been established exactly what is the essential role of these vitamins even if they are components of coenzymes, they work in other ways, the reason for which are needed only in very small amounts [10].

The Influence of Vitamins on the Process of Oral Carcinogenesis

Vitamin A

Vitamin A, found in 3 forms - retinol, retinal, and retinoic acid, plays a vital role in vision processes, entering into the composition of rhodopsin, which is necessary for adaptation to darkness. Other important roles are those of preventing growth retardation and maintaining the integrity of epithelial cells; it also inhibits keratinization processes; it can also form reserves (in the form of retinol palmitate) in liver Kupfer cells, sufficient to satisfy the body's needs for 2 years. For intestinal absorption, vitamin A needs fat, pancreatic lipase, and bile salts [11, 12].

Retinol is transported into the cell by a specific protein (Cellular Retinol Binding Protein), which enters the nucleus and attaches to the chromatin protein receptors. There, retinol controls the expression of the genes accountable for the synthesis of the numerous proteins necessary for the formation of the cytoskeleton and cell matrix (keratin, collagen). This effect is well expressed in the epithelium and mesodermal tissues. Retinol stimulates killer T-lymphocytes, preventing cell malignancy, especially at the oral, laryngeal, stomach, intestinal, lung, and prostate levels. Retinol is toxic, and overdose can lead to numerous adverse effects [13].

Among the many biological functions of vitamin A, only its role in the visual apparatus of vertebrates is well known, namely in the sequence of molecular events, on the absorption of light energy provided by the pigment of retinal photoreceptor cells, leading to the formation of a specific photochemical compound. Vitamin A is essential for the retina and plays a vital role in the process of cell differentiation, especially of epithelial cells. It also plays a vital role in triggering a nerve impulse by the photo compound specialized in restoring the photosensitive form of rhodopsin. Furthermore, vitamin A's shortcoming affects all mammalian tissues, not just the retina. The discovery of the role of the retina in the visual cycle has by no means exhausted the question of the biological functions of vitamin A. It seems that, in general, vitamin A is involved in the transport of calcium ions through certain membranes, analogous to the mechanism in rod cells; such a role would explain the impact of vitamin A shortcomings and abuse on bone and connective tissue.

Research on the experimental oral carcinogenesis inhibition using topical beta-carotene has led to the observation that beta-carotene significantly inhibits the formation of DMBA (7,12-dimethylbenz anthracene) and hamster squamous cell carcinoma-induced oral pouch when used topically daily, substitute for the use of 0.25% DMBA in heavy mineral oils, 3 times/week, for 22 weeks, initially, in an experiment carried out on 40 young male hamsters divided into four equal experimental groups, group 1 with DMBA application to the left buccal pouch 3 times/week. Batch 2 with DMBA application is identical to batch 1 + beta-carotene 3 times/week, alternatively with the application of DMBA 0.25% in heavy mineral oils, 3 times/week for 22 weeks. The animals from group 3 were brushed only with beta-carotene, and the animals from group 4 were the control group, untreated. The results of this study led to another experiment with 80 animals, in which beta-carotene was used to inhibit oral carcinogenesis in an initiation-promotion process using 40% benzoyl peroxide as a promoter and 0.1% DMBA as an initiator. Thus, beta-carotene inhibited both the promotion and initiation of carcinogenesis [14, 15].

These results were complemented by another experiment in which 13-CIS-retinoic acid was used in the oral leukoplakia treatment where the efficacy of vitamin A in the oral leukoplakia treatment was highlighted. Forty-four (44) patients with this disease were included in the experiment, randomly divided into the experimental group of 24 patients and the placebo group of 20 patients. 13-CIS-retinoic acid was administered at a dose of 1 to 2 mg/kg body/day for three months, with a follow-up of the effect for six months. The results of the research led to the observation that 67% of the cases (16 patients) had major decreases in the lesion size, a result also observed in 10% (2 patients) of those who received placebo ($P = 0.0002$). Dysplasia was reversed in 10% (2 patients) of the placebo group ($P = 0.01$) and 54% (13 patients) of the drug group. Clinical drug response correlated with histological response occurred in 56% (9 of 16) of the evaluated patients. Recurrence also happened in 9 out of 16 patients, 2-3 months after the treatment ended. The toxic impacts of the drug were acceptable. However, some patients presented mild forms of cheilitis, dryness, and exfoliation of mucous membranes, conjunctivitis, and

hypertriglyceridemia, reactions considered adverse and which can be canceled either by decreasing the dose or temporarily stopping the drug [16, 17].

The preventive effect of vitamin E and beta-carotene on malignant lesions of the oral cavity was evaluated in several experiments, concluding that the most direct and definitive way to highlight the cancer prevention effect by a preventive agent is the reduction of the incidence of cancer in a clinical stage.

Vitamin C

Ascorbic acid is better known as vitamin C. It was discovered by Albert Szent-Györgyi, an American researcher of Hungarian origin, who was awarded the Nobel Prize (1937) for the isolation of ascorbic acid, which also underlines the importance of this substance for human health [18].

Vitamin C has multiple actions, with an important role in the oxidation-reduction processes of carbohydrate metabolism and the use of carbohydrates in blood coagulability and tissue regeneration; participates in the synthesis of corticosteroids, procollagen, and collagen; normalizes capillary permeability; decreases the need for pantothenic acid (vitamin B5), folic acid, E, A, vitamins B1, and B2 increases the body's resistance, probably due to its participation in the neutralization of reactive oxygen species that oxidize lipids and phospholipids and damage cells. These radicals can be neutralized under normal conditions by vitamin E and ascorbic acid. Vitamin E swallows a free radical (superoxide) oxidizing itself, but in the presence of ascorbic acid, it is immediately restored. Ascorbic acid favors the absorption of iron by converting its trivalent salts into bivalents, which are easily absorbed. Since ascorbic acid does not form reserves in the body, we need an adequate daily supply of vitamin C. Its insufficiency is felt by the fact that the body's resistance to diseases decreases, hemorrhagic diathesis and nasal, pulmonary, uterine hemorrhages and a certain degree of fatigue appear. Chronic deficiency leads to scurvy [19].

Linus Pauling has always supported the idea that taking vitamin C in high doses fights and prevents colds, acts to prolong the life of terminal cancer patients, and prevents other diseases that have important, sustained effects. Vitamin A, vitamin E, Selenium, and vitamin C are included in the group of antioxidants with an important effect in annihilating the action of free radicals, producing a renewal of the cells in the body permanently, thus maintaining a good state of health [20].

Previous experimental studies on the efficacy of a mixture of ascorbic acid, glutathione, α -tocopherol, and β -carotene have shown that α -tocopherol and β -carotene can act synergistically to inhibit oral cancer growth, but initial research on the synergistic anticancer activity of antioxidants have been extended to include decreased ascorbic acid and glutathione. The experimental group included 60 male hamsters (aged 4-5 weeks), which were divided into 6 equal groups. Groups 1-6 were treated with DMBA (7,12-dimethylbenz anthracene) (0.5% solution). Group two received a combination containing equal amounts of glutathione, vitamin E (dl- α -tocopherol), beta-carotene, and vitamin C (l-ascorbic acid) (12.5 μ g) administered orally via pipette. Groups 3, 4, and 5 were treated with vitamin C alone (50 μ g), glutathione (50 μ g), vitamin E alone (50 μ g), and β -carotene alone (50 μ g). Animals were exterminated at 12-14 weeks. Tumors were measured and counted, and tumor burden was determined for each experimental group. The antioxidant mixture significantly decreased tumor burden, while treatments of β -carotene, vitamin E, and glutathione depletion decreased tumor mass. Glutathione and β -Carotene had a greater chemopreventive effect than vitamin E, administered individually. Correlatively, treatment with vitamin C did not cause an antitumor effect but led to an increase in tumor burden up to week 14. In conclusion, the antioxidant mixture caused a reduction in tumors [15, 21, 22].

A high-fiber, low-fat diet may increase the effectiveness of standard cancer treatment agents; proposed mechanisms for these impacts include the production of butyric acid increased levels and potential mutagens binding in the gastrointestinal tract using high fiber and decreased levels of growth-promoting factors such as certain fatty acids, low-fat estrogen, and prostaglandins. We therefore suggest a working hypothesis that antioxidant multivitamin supplementation, combined with lifestyle and dietary modifications, may improve the standard efficacy and experimental cancer treatments [23, 24].

Vitamin D

Vitamin D occurs in several forms, but the most important are ergocalciferol (D2) and cholecalciferol (D3). In the body, calciferols are transformed into cholecalciferol, which undergoes hydroxylation. The first hydroxylation takes place in the liver (25-hydroxycholecalciferol), and the second in the kidneys under the influence of parathyroid hormone (1,25-dihydroxycholecalciferol or calcitriol). Calcitriol stimulates the synthesis of a calcium transporter protein that facilitates the calcium absorption and phosphate from the small intestine and their reabsorption in the renal tubules, leading to an increase in the concentration of calcium in the blood and bone mineralization. Vitamin D intervenes in the metabolism of calcium, phosphorus, and minerals necessary to support and maintain bone and dental health, optimizing their absorption. Together with vitamins C and A, it acts preventively in the case of colds [25].

Following a study carried out by injecting cholecalciferol in radioactive form, the formation of a radioactive derivative of it, 2,5-hydroxycholecalciferol, with greater biological activity than cholecalciferol, was identified in the blood and tissues. This form of vitamin D resulting from the conversion of cholecalciferol in the liver is the most common in animals.

In another series of experiments, radioactive 2,5-hydroxycholecalciferol was injected into animals, and it was found that it was metabolized to 1,2,5-dihydroxycholecalciferol. This compound is much more biologically active; its administration produces fast stimulation of calcium ion absorption using the intestine. E. Kodicek's experiments showed that the kidney is the site of the formation of 1,2,5-dihydroxycholecalciferol, which seems to be the biologically active form of vitamin D and can directly act on the main targets, the bones, and small intestine [26, 27].

Vitamin E

Tocopherols are analogs of vitamin E. The most active of them is alpha-tocopherol, which participates in the heme biosynthesis, cell proliferation, tissue respiration, heme proteins, porphyrin, and other significant processes of tissue metabolism, prevents hemolysis of red blood cells, increases vascular permeability and capillary fragility. It has antioxidant action and protects polyunsaturated fatty acids against oxidation by inactivating free radicals. In this process, tocopherol oxidizes itself, but its antioxidant activity is restored by ascorbic acid. Free radicals are suspected to be the cause of cardiovascular disease, rheumatoid arthritis, emphysema, and cancer based on the fact that they interact with polyunsaturated fatty acids in cell membranes, nucleotides in DNA, and hydrogen sulfide bonds in proteins. It increases the utilization of vitamin A, inhibits the production of prostaglandins, and stimulates an essential cofactor of steroid metabolism. Vitamin E leads to increased antibody synthesis and stimulates cell-mediated immunity and macrophage activity. The insufficiency of vitamin E does not manifest itself through concrete symptoms; it is included in the composition of many multivitamins, minerals, or microelements. Tocopherols, based on their antioxidant activity, prevent the autooxidation of polyunsaturated fatty acids when they are exposed to molecular oxygen. This autooxidation leads to the polymerization of unsaturated fatty acids, a process similar to that which takes place in the "drying" of linseed oil, with the formation of a hard, insoluble polymer [28-30].

Vitamin E reduces ischemic heart risk by having a hypotensive effect. It prevents the formation of blood clots and helps to dilute them, increases the body's resistance by providing increased amounts of oxygen, alleviates fatigue, and accelerates the healing of burns. The administration of preparations with vitamin E can induce an increase in blood pressure in people with high blood pressure. In people with hypertension or diabetes and those suffering from thyroid hyperfunction, vitamin E should be administered with caution, increasing the dose gradually (the daily dose required for an adult is 8-10 IU per day, the amount that is eliminated through feces in the proportion of 70 %) [31].

Oral cancer regression and emerging concepts of inhibition using experimental administration of vitamin E and beta-carotene in hamsters with oral cancer are excellent models for oral mucosal carcinogenesis and are now widely considered as one of the best global experimental models for carcinogenesis. Malignant tumors are epidermoid carcinomas that develop slowly in response to the carcinogenic use of polyaromatic hydrocarbons and are preceded by dysplastic and keratotic lesions comparable to human precancerous leukoplakia [32-34].

Analyzing the delay in the development of oral cancer using topical vitamin E in an experimental model with young hamsters. The experimental group demonstrated a significant delay in tumor formation compared to the animals from the control group [35].

In a similar experimental inhibition of tumor carcinogenesis and angiogenesis experiment conducted on 40 male golden hamsters, vitamin E was found to inhibit both carcinogenesis and tumor angiogenesis and tumor growth factor alpha (TGF- α) expression [36].

Oral Cancer Inhibition by Micronutrient, Antioxidant, and Anti-Inflammatory Therapy

To show the anticancer activity of tocopherol, carotenoids, and retinoids on oral precancerous leukoplakia and oral cancer, an extensive study has been done in laboratory animals. The anticancer attributes of these micronutrients have been investigated in experiments on carcinogenesis inhibition, the prevention of oral cancer development, and oral carcinoma regression. Synergism has been shown in the anticancer activity of alpha-tocopherol and beta-carotene. Synergism has been shown between anticancer alkylating agents and beta-carotene, such as cyclophosphamide and melphalan.

Micronutrients

Beta-carotene has been found to inhibit both the main steps of carcinogenesis - promotion and initiation. Animal research of oral cancer inhibition, regression, and prevention were demonstrated using tissue culture studies by normal epithelial cells, animal-derived, and human-derived oral cancer cell lines. Anticancer activity mechanisms of oral micronutrients have been investigated. These include stimulating elements of the immune system to annihilate cancer cells and increasing the heat shock protein expression and suppressor genes such as the protein p53 [37].

To study the relationship between serum micronutrients and oral subsequent risk and pharyngeal cancer, case-control research was done on a 25,802 adult cohort in Washington County, MD, whose blood samples were prepared in 1974 and stored at -70 °C for further study. Nutrient serum levels in 28 individuals with oropharyngeal cancer between 1975 and 1990 were compared with levels in matched controls. Serum levels of all carotenoids, especially β -carotene, were lower in people with developed pharyngeal and oral cancer. The risks of this malignancy are reduced substantially by increasing the serum levels of each of the carotenoid. People with high levels of total carotenoids had about a third of the risk of developing cancer compared to people with low levels of carotenoids. High serum α -tocopherol levels were also related to the reduced risk of oral cancer in later years, but the risks increased significantly with increased serum α -tocopherol and selenium concentrations. The results of the current study are consistent with several previous epidemiological studies of dietary factors for pharyngeal and oral cancer and provide further records for the potential role of α -tocopherol and carotenoids in these malignancies chemoprevention [38].

Antioxidants

The anticancer properties of micronutrients and antioxidants have been well studied in cell culture studies and experimental animal models. Studies also show regression and inhibition of precancerous lesions.

The biological mechanisms for cancer regression and inhibition are just now gradually understood, and antioxidant nutrients seem to act by a large number of pathways common to most agents studied. These different micronutrients act using a complex group of "common pathways" of anticancer activity according to the three important mechanisms: tumor inhibition using immune cytokines; cancer suppressor genes stimulation, such as "wild-type" p53; tumor angiogenesis inhibition using angiogenesis-stimulating factors inhibition, such as TGF alpha [39].

The micronutrients act with different anticancer properties, in some respects, from other action mechanisms, for example, retinoids. They mainly act by stimulating cell differentiation, resulting in the neoplastic cells' apoptosis.

A combination of different antioxidant nutrients has been shown to enhance anticancer activity by synergizing their action, possibly due to their anticancer activity optimization at various oxygen reduction potentials. It acts selectively for cancer cells, not affecting normal cells; this is the main characteristic of antioxidant micronutrients [40].

Ibuprofen Administration

In the study on the inhibition of the development of tumors of the oral mucosa by the administration of ibuprofen in 80 male and female hamsters of the species *Mesocricetus auratus* that were divided into four equal groups, it was found that ibuprofen prevented tumor formation. The membranes of the left oral mucosa of animals in group 1 were brushed with a 0.1% solution of DMBA (7,12-dimethylbenz anthracene) in heavy mineral oil. The left oral mucosa was similarly stained with DMBA for 24 weeks, but the animals also received 10 mg of ibuprofen systemically administered orally twice weekly. Animals in group 3 received only the anti-inflammatory, and those in group 4 represented the untreated control group. After 24 weeks, the animals were killed in groups of 16 (two females and two males from four experimental groups). Tumor sizes were recorded. Ibuprofen prevents tumor formation at 25-27 weeks. Tumors at 28-29 weeks in group 2 were less and smaller than those in group 1 (without ibuprofen) [41].

Results and Discussion

In cancer patients, micronutrient deficiencies can occur for various reasons, including unbalanced dietary intake and adverse treatment effects. In addition, several patients show signs of a response of chronic inflammation that may affect circulating concentrations of trace elements and certain vitamins. The existing malnutrition, even before the malnutrition caused by the tumor itself, the lack of appetite related to anorexia, the aversion to multiple foods, also because of the medicinal substances such as cytokines, are among the important causes of micronutrient deficiency in patients.

Compared to healthy individuals, tumor patients may already have measurable concentrations of vitamins and trace elements in serum and blood before the diagnosis of cancer and long before clinically relevant changes in nutritional status occur. At the same time, the supply and reserves of immuno-modulatory and antioxidant micronutrients (L-glutathione, L-cysteine, L-carnitine, vitamin C, gamma-tocopherol, and vitamin A), nutrients that are not easily stored by the body, due to the body does not make stores for micronutrients and cannot synthesize them endogenously but can play an important role only through food and supplements (for example, vitamin B1 with a 4-10 days tissue storage capacity (SC)); vitamin K with - SC 2-6 weeks); vitamin C, D, and vitamin B complex, with a storage capacity in tissues - SC of 2-4 months); vitamin E with a tissue storage capacity - SC of 6-12 months)).

Treatment success and healing processes in neoplastic diseases are strongly affected by nutritional status. For this reason, the patient's nutritional status should be identified early, immediately after the cancer's definite diagnosis, and nutritional care should be included in the therapeutic planning from the beginning [42].

Malnutrition is the most common cause of death in cancer patients. By the time the tumor is identified, approximately 50% of all patients have already lost weight, and more than 20% of patients lose more than 10% of their initial weight within 6 months, thus meeting the criteria for malnutrition. In a malnutrition study in German hospitals, 38% of examined tumor patients were malnourished [43].

Conclusion

Antioxidant micronutrients such as Beta-carotene are oral carcinogenesis inhibitors; vitamin E and beta-carotene can cause clinical regression of oral leukoplakia, a premalignant lesion of oral cancer. The administration of antioxidants in oral precancerous pathologies must necessarily take into account all the context of the disease and its metabolic implications and agree with all the scientific data related to that disease. The evolution of oral precancerous lesions is significantly improved by the administration of antioxidant therapy due to the synergistic effect between antioxidants and chemotherapeutic drugs. The synergistic effect between vitamin C, beta-carotene, and chemotherapy drugs has had good results, increasing the effectiveness of cancer therapy.

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