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Exploring the Impact of Vitamins and Antioxidants on Oral Carcinogenesis: A Critical Review

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Abstract

Oral carcinogenesis remains a pressing public health concern, especially in developing countries where its incidence is significantly high. The present study aimed to review the effect of vitamins and antioxidants on oral carcinogenesis. Research efforts targeting this disease have identified significant therapeutic effects associated with the use of certain micronutrients and antioxidants. For instance, experimental models demonstrated that the routine application of beta-carotene topically was effective in reducing the onset of oral pouch carcinoma induced by DMBA (7,12-dimethylbenz[a]anthracene) in hamsters. Additional findings highlighted the therapeutic value of 13-CIS-retinoic acid, a derivative of vitamin A, in the management of oral leukoplakia, underscoring its relevance in reversing pre-malignant lesions. A combination therapy involving ascorbic acid, glutathione, α-tocopherol, and β-carotene demonstrated that both α-tocopherol and β-carotene could act synergistically to suppress oral tumor progression. In addition, studies involving topical vitamin E showed a significant postponement in tumorigenesis when compared to control subjects. The collective experimental data affirm that retinoids, carotenoids, and tocopherols possess anti-neoplastic properties relevant to oral precancerous and cancerous lesions. The potential for synergistic enhancement of anticancer efficacy has also been observed when combining alpha-tocopherol and beta-carotene, as well as with known alkylating agents such as cyclophosphamide and melphalan. Collectively, these studies confirm that antioxidant micronutrients such as beta-carotene not only deter the development of oral carcinogenesis but also support the regression of oral leukoplakia, reinforcing their potential role in preventive and therapeutic strategies.

Keywords: Oral carcinogenesis, Vitamins, Micronutrients, Antioxidants, Ibuprofen

Introduction

Malignancies occurring in the oral region remain a significant public health challenge, particularly across developing nations, where their prevalence is closely linked to factors such as protein-calorie malnutrition, alcohol dependence, poor nutrient absorption, and the side effects of certain medications [1–3]. Lifestyle patterns and environmental exposures—most notably the combination of tobacco and alcohol consumption—have been strongly implicated in both the initiation and advancement of oral carcinogenesis [4, 5]. A major contributor to disease development is oxidative stress, which plays a role not only in cancer but also in various chronic and degenerative conditions including cardiovascular diseases, neurodegenerative disorders, rheumatoid arthritis, autoimmune diseases, aging, and cataracts. The body has internal defense systems to combat oxidative damage, largely dependent on antioxidants that may originate either from endogenous metabolic processes or be acquired externally via dietary intake or nutritional supplements. These antioxidants act by neutralizing reactive oxygen species (ROS), reducing cellular damage, enhancing immune resilience, and lowering the likelihood of developing cancer or other

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degenerative conditions. This understanding has steered scientific interest toward identifying phytochemicals with strong antioxidative functions that can curb free radical-induced oxidative stress, offering potential protective effects against numerous pathologies [6, 7].

Alongside macronutrients like lipids, proteins, nucleic acids, and carbohydrates, living organisms also rely on trace organic molecules known as vitamins, which are indispensable for maintaining physiological balance. Since many species, including humans, cannot synthesize certain vitamins, they must obtain them through external sources such as food or supplementation. The scientific exploration into the physiological functions of vitamins represents a foundational element of modern medical biochemistry, offering insights into metabolic regulation and contributing to improvements in overall well-being and health [8].

The foundational discoveries of vitamins took place during the 1930s and 1940s, a period marked by remarkable scientific efforts. At that time, researchers were compelled to process massive quantities of biological material—sometimes hundreds of kilograms or even tons—just to isolate mere milligrams of pure vitamin compounds. Among the earliest identified were thiamine (vitamin B1, associated with the prevention of beriberi), riboflavin (vitamin B2), and nicotinic acid (vitamin B3, effective against pellagra). It was later revealed that these vitamins serve as integral parts of coenzymes, enabling vital metabolic reactions. A prominent example is the enzyme pyruvate decarboxylase, which facilitates the decarboxylation of pyruvic acid into acetaldehyde and carbon dioxide—a pivotal stage in yeast-driven alcoholic fermentation. In 1936, Lohmann and Schuster successfully extracted the coenzyme cocarboxylase, which they shortly determined to contain a thiamine molecule. Soon thereafter, it was confirmed that riboflavin and nicotinic acid are also vital constituents of coenzymes involved in the oxidative metabolism of monosaccharides [9].

Vitamins are generally grouped into two major categories: fat-soluble and water-soluble. Except for vitamin C, water-soluble vitamins predominantly function as coenzymes in numerous biological systems. Additionally, certain water-soluble organic compounds like choline, inositol, and carnitine, while required in somewhat greater concentrations than traditional vitamins, also act as essential growth factors for specific organisms. On the other hand, fat-soluble vitamins—including vitamin K, vitamin E, vitamin D, and vitamin A—must be derived externally by higher animals, as their endogenous synthesis is either absent or insufficient. Although their biochemical roles in plants and microbes remain partially undefined, these vitamins are not usually part of coenzymatic systems and appear to operate through alternative pathways, requiring only trace amounts for effective physiological impact [10].

The present study aimed to review the effect of vitamins and antioxidants on oral carcinogenesis.

Results and Discussion

The role of vitamins in oral carcinogenesis

Vitamin A

Vitamin A exists in three biologically active forms—retinol, retinal, and retinoic acid—each contributing uniquely to physiological functions, especially in visual mechanisms. It is a crucial component of rhodopsin, the light-sensitive pigment in the retina responsible for night vision. In addition to its ocular importance, vitamin A plays essential roles in promoting growth, sustaining epithelial cell health, and hindering abnormal keratinization. Within the liver, particularly in Kupffer cells, it is stored as retinol palmitate, providing long-term reserves that may suffice for up to two years. Its intestinal absorption, however, depends on the presence of dietary fats, pancreatic lipase, and bile salts [11, 12].

Once absorbed, retinol is delivered to target cells via cellular retinol-binding protein (CRBP), facilitating its entry into the nucleus where it interacts with chromatin-associated receptors. This interaction modulates the expression of genes responsible for synthesizing key structural proteins, such as collagen and keratin, which are integral to maintaining epithelial and mesodermal tissue architecture. Importantly, retinol enhances the activity of cytotoxic T-lymphocytes, offering protection against malignant cellular transformation, particularly in tissues of the oral cavity, larynx, stomach, intestines, lungs, and prostate. Despite these benefits, excessive intake of retinol is associated with toxicity and can produce a range of adverse outcomes [13].

While its contribution to the visual system is widely recognized—especially in mediating the conversion of light into neural signals through rhodopsin—the influence of vitamin A extends far beyond vision. It governs epithelial cell differentiation and is involved in

the generation of photo-induced nerve impulses. Deficiency affects not only the retina but also multiple tissues throughout the body. Additionally, vitamin A has been proposed to regulate calcium ion transport across cellular membranes, a mechanism thought to mirror its action in retinal rod cells. This regulatory function may account for the alterations seen in connective tissue and bone structure in cases of both deficiency and overdose of this micronutrient.

Experimental efforts to assess the chemopreventive potential of beta-carotene against oral carcinogenesis have yielded significant insights. One study involved 40 juvenile male hamsters, systematically divided into four groups to evaluate the suppressive effects of topically applied beta-carotene on oral cancer induction using DMBA (7,12-dimethylbenz[a]anthracene). In this model, group 1 received only DMBA applications (0.25% in heavy mineral oils) to the left buccal pouch thrice weekly over 22 weeks. Group 2 was treated with alternating applications of DMBA and beta-carotene, following the same frequency. Group 3 received only beta-carotene, while group 4 remained untreated as the control. Notably, animals in group 2 exhibited a marked inhibition in the development of squamous cell carcinoma within the oral pouch, indicating a significant protective effect of beta-carotene [14, 15].

Building upon these findings, researchers extended the study to a larger cohort of 80 animals, investigating the dual-stage inhibition of carcinogenesis—initiation and promotion—by beta-carotene. In this model, 0.1% DMBA served as the carcinogenic initiator, while 40% benzoyl peroxide was employed as the promoter. Results revealed that beta-carotene significantly hindered both the early transformation events and the subsequent promotion phase, demonstrating its potential to curb the full course of oral cancer progression [14, 15].

Parallel to animal research, a clinical trial explored the use of 13-CIS-retinoic acid, a vitamin A derivative, in managing oral leukoplakia. The study enrolled 44 participants diagnosed with the condition, who were randomly distributed into two groups: 24 received the active compound at a dosage of 1–2 mg/kg/day for three months, while 20 were assigned to the placebo group. Outcomes were monitored for an additional six months. Significant lesion regression was recorded in 67% (16 individuals) of those treated, contrasting sharply with only 10% (2 individuals) in the placebo arm ($P = 0.0002$). Additionally, dysplasia reversal was achieved in 54% (13 patients) of the treatment group compared to 10% (2 patients) in the placebo group ($P=0.01$). Histopathological improvements coincided with visible clinical responses in 56% (9 out of 16) of the evaluated patients. However, recurrence was reported in more than half of the responders (9 out of 16) within 2–3 months post-treatment. While the therapy's adverse effects—such as cheilitis, dry mucosa, conjunctivitis, exfoliation, and hypertriglyceridemia—were present, they were generally manageable through either dose adjustments or temporary discontinuation of the drug [16, 17].

Further investigations into the anticancer properties of vitamin E and beta-carotene also support their role in the prevention of malignant transformations within the oral cavity. Ultimately, the clearest demonstration of a preventive compound's efficacy lies in its ability to reduce the incidence of clinically manifested cancers, an outcome observed in these comprehensive studies.

Vitamin C

Commonly referred to as ascorbic acid, vitamin C was first isolated by Albert Szent-Győrgyi, a Hungarian-born American scientist, who received the Nobel Prize in 1937 for his groundbreaking work in isolating this compound, underscoring its importance in human health [18].

Vitamin C is involved in a variety of physiological processes, particularly in redox reactions associated with carbohydrate metabolism, blood clotting, and the healing of tissues. It is essential in the production of corticosteroids, procollagen, and collagen, and plays a key role in regulating capillary permeability. Moreover, it reduces the body's need for vitamins such as B5 (pantothenic acid), folic acid, and vitamins A, E, B1, and B2, and helps strengthen immune responses by neutralizing harmful reactive oxygen species. These species, which damage cell membranes and lipids, are typically counteracted by vitamin E and ascorbic acid. Vitamin E captures these radicals and oxidizes itself in the process, but it is quickly regenerated in the presence of vitamin C. Additionally, ascorbic acid enhances iron absorption by reducing its trivalent form to a bivalent one, making it more bioavailable. Since ascorbic acid cannot be stored in the body, a daily intake is crucial. A lack of vitamin C manifests through a weakened immune system, hemorrhagic disorders, and fatigue, and can ultimately lead to scurvy [19].

Linus Pauling, a prominent figure in the study of vitamin C, was a strong proponent of its high-dose use, claiming it could prevent the common cold, extend the lives of

those with terminal cancer, and help prevent other chronic diseases. Together with vitamins A and E, and selenium, vitamin C is considered a key antioxidant that combats free radicals, thereby supporting cell renewal and promoting general well-being [20].

In animal studies exploring the anticancer effects of antioxidants, a combination of ascorbic acid, glutathione, α-tocopherol, and β-carotene was found to suppress the growth of oral cancer. These studies examined how α-tocopherol and β-carotene might work together to inhibit cancer progression. In one experiment involving 60 male hamsters (aged 4-5 weeks), six different treatment groups were established, with all receiving DMBA (7,12-dimethylbenz anthracene) at a concentration of 0.5%. Group 2 was treated with a mixture containing equal amounts of glutathione, vitamin E (dl-α-tocopherol), β-carotene, and vitamin C (l-ascorbic acid), delivered orally. Other groups received the compounds individually. After a period of 12 to 14 weeks, the results showed that the antioxidant blend significantly reduced tumor burden, while individual treatments with β-carotene, vitamin E, and glutathione also led to a decrease in tumor size, with glutathione and β-carotene being more effective than vitamin E alone. Interestingly, treatment with vitamin C alone did not reduce tumor size and instead increased tumor burden by the 14th week. In conclusion, the combined antioxidant therapy resulted in a significant reduction in tumors [15, 21, 22].

Furthermore, adopting a high-fiber, low-fat diet may enhance the effectiveness of standard cancer treatments. This effect may stem from increased butyric acid production, the ability of fiber to bind to mutagens in the gastrointestinal tract, and the reduction of growth-promoting factors such as certain fatty acids and prostaglandins. Based on these findings, it is hypothesized that combining antioxidant multivitamin supplementation with dietary and lifestyle modifications could potentially enhance the efficacy of both conventional and experimental cancer therapies [23, 24].

Vitamin D

Vitamin D is available in several forms, primarily as ergocalciferol (D2) and cholecalciferol (D3). Once in the body, these forms are converted into cholecalciferol, which then undergoes two stages of hydroxylation. The initial hydroxylation occurs in the liver, forming 25-hydroxycholecalciferol. The second hydroxylation, which takes place in the kidneys and is regulated by parathyroid hormone, produces the active form, 1,25-dihydroxycholecalciferol (calcitriol). Calcitriol plays a key role in promoting the production of calcium transport proteins that enhance the absorption of calcium and phosphate in the small intestine, as well as their reabsorption in the kidneys. This helps elevate blood calcium levels and supports bone mineralization. Vitamin D, along with vitamins C and A, also acts as a preventive measure against common colds by supporting the body's ability to absorb and process essential minerals such as calcium and phosphorus [25].

Research involving cholecalciferol in its radioactive form identified the creation of 2,5-hydroxycholecalciferol in the blood and tissues, a metabolite with greater biological activity than the original cholecalciferol. This form of vitamin D, which is generated in the liver, is the most prevalent in animals.

In further studies, the radioactive form of 2,5-hydroxycholecalciferol was administered to animals, where it was converted into the even more biologically active 1,2,5-dihydroxycholecalciferol. This compound quickly promotes calcium absorption in the intestines. Research by E. Kodicek demonstrated that the kidneys are responsible for producing the 1,2,5-dihydroxycholecalciferol, the active vitamin D form, which directly influences both the small intestine and bones [26, 27].

Vitamin E

Tocopherols are compounds related to vitamin E, with alpha-tocopherol being the most biologically active form. This compound is integral in processes like heme production, cellular growth, tissue respiration, and the synthesis of heme proteins and porphyrins. Additionally, alpha-tocopherol prevents red blood cell breakdown, boosts capillary permeability, and increases the fragility of capillaries. Its primary role, however, lies in its function as an antioxidant, where it guards polyunsaturated fatty acids from oxidative damage by neutralizing free radicals. During this neutralization, tocopherol itself undergoes oxidation, but it can be regenerated by ascorbic acid. Free radicals are believed to play a central role in the development of conditions such as cardiovascular diseases, rheumatoid arthritis, emphysema, and certain cancers due to their interaction with fatty acids in cell membranes, DNA nucleotides, and protein structures. Tocopherol also facilitates the utilization of vitamin A, suppresses prostaglandin

synthesis, and acts as a cofactor in steroid metabolism. Furthermore, vitamin E enhances immune responses by stimulating antibody production, boosting cell-mediated immunity, and increasing macrophage activity. While vitamin E deficiency does not manifest through specific symptoms, it is commonly found in multivitamin preparations and micronutrient supplements. Its antioxidant capability is crucial for preventing the oxidation of polyunsaturated fats when exposed to oxygen, which can otherwise lead to the formation of insoluble polymers in a process akin to the hardening of linseed oil [28-30].

In terms of cardiovascular health, vitamin E is known for reducing the risk of ischemic heart disease by lowering blood pressure. It also helps prevent blood clot formation and aids in clot dissolution. Additionally, it contributes to the body's ability to resist fatigue and accelerates the healing process of burns. However, high doses of vitamin E may lead to an increase in blood pressure, particularly in individuals with pre-existing hypertension. For people with conditions like hypertension, diabetes, or thyroid disorders, caution is advised when using vitamin E, with gradual dosage increases recommended (the typical daily dosage for adults is between 8-10 IU, with roughly 70% of the vitamin excreted through feces) [31].

Research involving oral cancer regression has shown promising results with the use of vitamin E and beta-carotene in animal models. These models, particularly hamsters with oral cancer, have become a standard in studying oral mucosal carcinogenesis and are considered highly effective for researching cancer formation. These malignant tumors, which are epidermoid carcinomas, develop slowly following exposure to carcinogenic polyaromatic hydrocarbons and are preceded by precancerous lesions, such as leukoplakia, that resemble human cases [32-34].

Experiments that focused on delaying the onset of oral cancer using topical vitamin E in hamsters showed a significant postponement of tumor development in the experimental group compared to the control group [35]. Furthermore, in a similar study investigating tumor progression and angiogenesis in golden hamsters, vitamin E was found to inhibit both carcinogenesis and the expression of tumor growth factor alpha (TGF-α), thereby limiting tumor growth [36].

Inhibition of oral cancer by micronutrient, antioxidant, and anti-inflammatory therapy

Research into the anticancer properties of tocopherols, carotenoids, and retinoids has been conducted in laboratory animals, specifically targeting oral precancerous conditions like leukoplakia and oral cancer. The results consistently demonstrate the cancer-fighting potential of these micronutrients, with significant findings related to their role in blocking carcinogenesis, preventing the onset of oral cancer, and promoting the regression of oral tumors. Among the notable findings, a synergistic effect has been observed between alpha-tocopherol and beta-carotene, enhancing their collective anticancer potential. Similar synergistic interactions have been observed between alkylating agents used in chemotherapy, such as cyclophosphamide and melphalan, and beta-carotene.

Micronutrients

Research shows that beta-carotene is effective in both preventing and slowing down the progression of carcinogenesis by targeting critical phases like promotion and initiation. A range of studies, including those conducted on animal models and oral cancer cell lines from both human and animal sources, have shown that beta-carotene plays a vital role in inhibiting the growth and spread of oral cancers. The mechanisms behind the anticancer effects of these micronutrients are diverse, including their ability to activate immune system components that can destroy cancer cells, as well as their role in enhancing the expression of heat shock proteins and suppressing genes like p53 that regulate cancer cell growth [37].

Further investigation into the link between serum micronutrient levels and the risk of oral and pharyngeal cancers was conducted using a case-control study involving 25,802 adults in Washington County, MD. Blood samples taken in 1974 and stored at -70 °C were analyzed in 1990 to assess the relationship between nutrient levels and cancer risk. The study revealed that individuals diagnosed with pharyngeal and oral cancer between 1975 and 1990 had significantly lower levels of carotenoids, particularly beta-carotene, compared to healthy controls. Notably, individuals with higher serum levels of carotenoids exhibited about one-third of the cancer risk compared to those with lower levels. Additionally, higher levels of α-tocopherol in the blood were associated with a reduced risk of developing oral cancer, although extremely high concentrations of both α-tocopherol and selenium were linked to increased risks.

These findings align with previous epidemiological studies and reinforce the potential role of α-tocopherol and carotenoids in preventing oral and pharyngeal cancers [38].

Antioxidants

The anticancer effects of micronutrients and antioxidants have been extensively researched through cell culture experiments and animal studies, revealing their role in reversing and preventing the progression of precancerous lesions. While the precise biological mechanisms responsible for cancer regression and inhibition are still being explored, antioxidants appear to function through a wide variety of pathways common to many studied agents. These micronutrients utilize several shared mechanisms of anticancer activity, which include: the inhibition of tumors via immune cytokines, the activation of cancer-suppressing genes such as the "wild-type" p53, and the suppression of tumor angiogenesis by inhibiting factors like TGF alpha that stimulate blood vessel growth in tumors [39].

Antioxidants exhibit distinct anticancer properties that set them apart from other agents, such as retinoids. Retinoids, for instance, primarily induce cell differentiation, which leads to the programmed cell death (apoptosis) of neoplastic cells. Furthermore, when different antioxidant nutrients are combined, their anticancer effects appear to be enhanced, likely due to the synergistic optimization of their activity at varying oxygen reduction potentials. A key feature of these antioxidant micronutrients is their ability to selectively target cancer cells, leaving normal cells unaffected, thus ensuring minimal collateral damage while exerting their anticancer effects [40].

Ibuprofen administration

A study investigating the effects of ibuprofen on oral tumor formation involved 80 male and female hamsters of the species Mesocricetus auratus, divided into four groups. In this experiment, it was found that ibuprofen inhibited tumor development. The hamsters in group 1 had their left oral mucosa treated with a 0.1% DMBA (7,12-dimethylbenz anthracene) solution dissolved in heavy mineral oil. Group 2 animals received the same DMBA treatment for 24 weeks, but additionally, they were given ten mg of ibuprofen orally twice a week. Group 3 animals were administered only the anti-inflammatory agent, while group 4 was left untreated as a control. After 24 weeks, the animals were euthanized in groups of four (two males and two females from each group), and the size of any tumors was measured. The findings showed that ibuprofen notably reduced tumor formation, with fewer and smaller tumors observed in group 2 compared to group 1. Tumors in group 2, at 28-29 weeks, were smaller in size than those in group 1, which did not receive ibuprofen [41].

Cancer patients may experience micronutrient deficiencies due to several factors, including poor dietary habits and side effects from treatments. Many patients also exhibit chronic inflammation, which can influence the levels of trace elements and vitamins in the bloodstream. Before tumor-induced malnutrition sets in, factors like anorexia, food aversions, and the side effects of medications such as cytokines significantly contribute to micronutrient shortages in these individuals.

Tumor patients often show low levels of vitamins and trace elements in their blood long before any clinically significant changes in nutritional status occur or the cancer is diagnosed. At the same time, the levels of immunomodulatory and antioxidant micronutrients such as L-glutathione, L-cysteine, L-carnitine, vitamin C, gamma-tocopherol, and vitamin A may be compromised. These nutrients are not easily stored in the body, as the body cannot synthesize them internally, and their presence must rely on food and supplements. For instance, vitamin B1 is stored for only 4 to 10 days in tissues, vitamin K for 2 to 6 weeks, and vitamin C, D, and the vitamin B complex for 2 to 4 months. Vitamin E has a storage capacity of 6 to 12 months.

The nutritional status of cancer patients has a profound impact on the success of treatments and healing. Thus, it is crucial to assess the patient's nutritional state early, immediately after confirming the cancer diagnosis, and incorporate nutritional support into the treatment plan from the outset [42].

Malnutrition is a leading cause of death among cancer patients. By the time cancer is diagnosed, nearly 50% of patients have already experienced significant weight loss, with over 20% losing more than 10% of their body weight within six months, qualifying them as malnourished. A study conducted in German hospitals found that 38% of cancer patients were malnourished [43].

Conclusion

Micronutrients with antioxidant properties, such as beta-carotene, play a role in inhibiting oral carcinogenesis, and both vitamin E and beta-carotene have demonstrated the ability to reverse oral leukoplakia, a precancerous condition associated with oral cancer. When considering antioxidant therapy for oral precancerous conditions, it is essential to assess the disease context and its metabolic effects while aligning with available scientific evidence. The progression of oral precancerous lesions can be significantly enhanced through antioxidant therapy, which works synergistically with chemotherapeutic agents. The combination of vitamin C, beta-carotene, and chemotherapy drugs has proven beneficial, increasing the overall efficacy of cancer treatment.

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References

1. Peres MA, Macpherson LMD, Weyant RJ, Daly B, Venturelli R, Mathur MR, et al. Oral diseases: A global public health challenge. Lancet. 2019;394(10194):249-60. doi:10.1016/S0140-6736(19)31146-8
2. Gao F, Feng Y, Hu X, Zhang X, Li T, Wang Y, et al. Neutrophils regulate tumor angiogenesis in oral squamous cell carcinoma and the role of Chemerin. Int Immunopharmacol. 2023;121:110540. doi:10.1016/j.intimp.2023.110540
3. Gupta J, Aggarwal A, Tewari RK, Agrawal N, Jain V. Co-existence of oral cancer and some in dental patients: A retrospective institutional study. Ann Dent Spec. 2020;8(4):87.
4. Wu YH, Wu YC, Chu FY, Cheng SJ, Sun A, Chen HM. Significantly higher frequencies of hematinic deficiencies and hyperhomocysteinemia in oral precancer patients. J Formos Med Assoc. 2019;118(9):1299-307. doi:10.1016/j.jfma.2019.05.016
5. Negrut RL, Cote A, Maghiar AM. Exploring the potential of oral microbiome biomarkers for colorectal cancer diagnosis and prognosis: A systematic review. Microorganisms. 2023;11(6):1586. doi:10.3390/microorganisms11061586
6. Kim JA. Peroxisome Metabolism in Cancer. Cells. 2020;9(7):1692. doi:10.3390/cells9071692
7. Ștefan PA, Coțe A, Csutak C, Lupean RA, Lebovici A, Mihu CM, et al. Texture analysis in uterine cervix carcinoma: Primary tumour and lymph node assessment. Diagnostics (Basel). 2023;13(3):442. doi:10.3390/diagnostics13030442
8. Ford TC, Downey LA, Simpson T, McPhee G, Oliver C, Stough C. The effect of a high-dose vitamin B multivitamin supplement on the relationship between brain metabolism and blood biomarkers of oxidative stress: a randomized control trial. Nutrients. 2018;10(12):1860. doi:10.3390/nu10121860
9. Palmieri F, Monné M, Fiermonte G, Palmieri L. Mitochondrial transport and metabolism of the vitamin B-derived cofactors thiamine pyrophosphate, coenzyme A, FAD and NAD+, and related diseases: A review. IUBMB Life. 2022;74(7):592-617. doi:10.1002/iub.2612
10. Alfaifi AM, Tashkandi MA, Yousef JM. Roles for taraxacum officinale and vitamins (C, K) on bone formation and resorption heparin-induced in rats. Arch Pharm Pract. 2023;14(2):83.
11. Bethesda L. Clinical and research information on drug-induced liver injury [Internet]. National Institute of Diabetes and digestive and kidney diseases. 2012.
12. Vicaş RM, Bodog FD, Fugaru FO, Grosu F, Badea O, Lazăr L, et al. Histopathological and immunohistochemical aspects of bone tissue in aseptic necrosis of the femoral head. Roman J Morphol Embryol. 2020;61(4):1249.
13. de Carvalho Melo-Cavalcante AA, da Rocha Sousa L, Alencar MVOB, de Oliveira Santos JV, da Mata AMO, Paz MFCJ, et al. Retinol palmitate and ascorbic acid: Role in oncological prevention and therapy. Biomed Pharmacother. 2019;109:1394-405. doi:10.1016/j.biopha.2018.10.115
14. Plante I. Dimethylbenz(a)anthracene-induced mammary tumorigenesis in mice. Methods Cell Biol. 2021;163:21-44. doi:10.1016/bs.mcb.2020.09.003
15. Pantiș C, Cheregi CD, Căiță GA, Szilagyi G. An overview of the distribution and adequacy of human resources working in hospitals. J Organ Behav Res. 2023;8(1):348-55. doi:10.51847/UbjZ8OfNUA

16. Palma VM, Koerich Laureano N, Frank LA, Rados PV, Visioli F. Chemoprevention in oral leukoplakia: Challenges and current landscape. Front Oral Health. 2023;4:1191347. doi:10.3389/froh.2023.1191347
17. Davidescu L, Chanez P, Ursol G, Korzh O, Deshmukh V, Kuryk L, et al. Late breaking abstract – masitinib in severe asthma: Results from a randomized, phase 3 trial. Eur Respir J. 2020;56(64):4612.
18. Grzybowski A, Pietrzak K. Albert Szent-Györgyi (1893-1986): The scientist who discovered vitamin C. Clin Dermatol. 2013;31(3):327-31. doi:10.1016/j.clindermatol.2012.08.001
19. Lykkesfeldt J, Tveden-Nyborg P. The pharmacokinetics of Vitamin C. Nutrients. 2019;11(10):2412. doi:10.3390/nu11102412
20. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. Nutrients. 2020;12(1):236. doi:10.3390/nu12010236
21. Shklar G, Schwartz J, Trickler D, Cheverie SR. The effectiveness of a mixture of beta-carotene, alpha-tocopherol, glutathione, and ascorbic acid for cancer prevention. Nutr Cancer. 1993;20(2):145-51. doi:10.1080/01635589309514281
22. Ranganadhareddy A, Varghese RP. Bioplastic production from microalgae and applications: A review. J Biochem Technol. 2022;13(4):30-4. doi:10.51847/iwUfTfnvEL
23. Bodnar P, Bedeniuk A, Bodnar T, Bodnar L. The function of systemic inflammatory response indicators in the development of thrombotic problems in malignancy. J Biochem Technol. 2023;14(2):6-11. doi:10.51847/g8EP2icVsi
24. Prasad KN, Kumar A, Kochupillai V, Cole WC. High doses of multiple antioxidant vitamins: Essential ingredients in improving the efficacy of standard cancer therapy. J Am Coll Nutr. 1999;18(1):13-25. doi:10.1080/07315724.1999.10718822
25. Benedik E. Sources of vitamin D for humans. Int J Vitam Nutr Res. 2022;92(2):118-25. doi:10.1024/0300-9831/a000733
26. Hurst EA, Homer NZ, Mellanby RJ. Vitamin D metabolism and profiling in veterinary species. Metabolites. 2020;10(9):371. doi:10.3390/metabo10090371
27. Ahmad S, Alwothaina MH, Albagami MA, Alrajhi SAS, Alammar AM, Ansari SH. Oral complications of radiotherapy for head and neck cancer; knowledge of dentists in Riyadh, Saudi Arabia. Clin Cancer Investig J. 2023;12(3):6-12. doi:10.51847/ZT1ZsHFR0L
28. Huyen NT, Nghi PH, Phuong ĐTL, Trang TTT, Huyen LT. Public debt and prosperity nexus in Asian countries: nonlinearity and threshold analysis. J Organ Behav Res. 2023;8(1):74-91. doi:10.51847/tw5g65dco8
29. Tudoran C, Tudoran M, Abu-Awwad A, Cut TG, Voiță-Mekereș F. Spontaneous hematomas and deep vein thrombosis during the recovery from a SARS-CoV-2 infection: Case report and literature review. Medicina. 2022;58(2):230.
30. Tudoran C, Tudoran M, Giurgi-Oncu C, Abu-Awwad A, Abu-Awwad SA, Voiţă-Mekereş F. Associations between oral glucose-lowering agents and increased risk for life-threatening arrhythmias in patients with type 2 diabetes mellitus—A literature review. Medicina. 2023;59(10):1760.
31. Noerman S, Kokla M, Koistinen VM, Lehtonen M, Tuomainen TP, Brunius C, et al. Associations of the serum metabolite profile with a healthy Nordic diet and risk of coronary artery disease. Clin Nutr. 2021;40(5):3250-62. doi:10.1016/j.clnu.2020.10.051
32. Xin J, Jiang X, Ben S, Yuan Q, Su L, Zhang Z, et al. Association between circulating vitamin E and ten common cancers: Evidence from large-scale Mendelian randomization analysis and a longitudinal cohort study. BMC Med. 2022;20(1):168. doi:10.1186/s12916-022-02366-5
33. Lascu CF, Buhaș CL, Mekeres GM, Bulzan M, Boț RB, Căiță GA, et al. Advantages and limitations in the evaluation of the neurological and functional deficit in patients with spinal cord injuries. Clin Pract. 2022;13(1):14-21.
34. Nguyen DN. Csr theory and practice in Vietnam hospitality and tourism sector: A literature review. J Organ Behav Res. 2023;8(1):197-213. doi:10.51847/6xeoexvF6T
35. Toh JWT, Wilson RB. Pathways of gastric carcinogenesis, helicobacter pylori virulence and interactions with antioxidant systems, vitamin C and phytochemicals. Int J Mol Sci. 2020;21(17):6451. doi:10.3390/ijms21176451

36. Yang CS, Luo P, Zeng Z, Wang H, Malafa M, Suh N. Vitamin E, and cancer prevention: Studies with different forms of tocopherols and tocotrienols. Mol Carcinog. 2020;59(4):365-89. doi:10.1002/mc.23160
37. Terao J. Revisiting carotenoids as dietary antioxidants for human health and disease prevention. Food Funct. 2023;14(17):7799-824. doi:10.1039/d3fo02330c
38. Zheng W, Blot WJ, Diamond EL, Norkus EP, Spate V, Morris JS, et al. Serum micronutrients and the subsequent risk of oral and pharyngeal cancer. Cancer Res. 1993;53(4):795-8.
39. Zahra KF, Lefter R, Ali A, Abdellah EC, Trus C, Ciobica A, et al. The involvement of the oxidative stress status in cancer pathology: A double view on the role of the antioxidants. Oxid Med Cell Longev. 2021;2021:9965916. doi:10.1155/2021/9965916
40. Suwannasom N, Kao I, Pruß A, Georgieva R, Bäumler H. Riboflavin: The health benefits of a forgotten natural Vitamin. Int J Mol Sci. 2020;21(3):950. doi:10.3390/ijms21030950
41. Cornwall H, Odukoya O, Shklar G. Oral mucosal tumor inhibition by ibuprofen. J Oral Maxillofac Surg. 1983;41(12):795-800. doi:10.1016/s0278-2391(83)80046-9
42. Yang J, Wei H, Zhou Y, Szeto CH, Li C, Lin Y, et al. High-Fat diet promotes colorectal tumorigenesis through modulating gut microbiota and metabolites. Gastroenterology. 2022;162(1):135-49. doi:10.1053/j.gastro.2021.08.041
43. Arends J, Muscaritoli M, Anker S, Audisio R, Barazzoni R, Bosnjak S, et al. Overcoming barriers to timely recognition and treatment of cancer cachexia: Sharing progress in cancer care task force position paper and call to action. Crit Rev Oncol Hematol. 2023;185:103965. doi:10.1016/j.critrevonc.2023.103965