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Review Article

The protective role of carotenoids and polyphenols in patients with head and neck cancer

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Abstract

Head and neck cancer is a critical global health problem and approximately 650,000 patients per year are diagnosed with this type of cancer. In addition, head and neck cancer exhibits a high recurrence rate, readily causing second primary cancers in other locations, often yielding a poor prognosis. Current medical and surgical treatment options result in considerable impairment of speaking and swallowing functions, with side effects such as nausea, vomiting, bone marrow suppression, and renal damage, thereby impairing patients' quality of life. Thus, developing a prevention and therapeutic intervention strategy for head and neck cancer is vital. Phytochemicals have been shown to have a unique ability to protect cells from damage and modulation of cell repair. The chemopreventive activities of phytochemicals have also been demonstrated to be associated with their antioxidant properties and the induction and stimulation of intercellular communication via gap junctions, which play a role in the regulation of cancer cell cycle, differentiation, apoptosis, and stagnate cancer cell growth. Phytochemicals can also regulate cancer cell signaling pathways, reduce the invasion and metastasis of cancer cells, and protect normal cells during treatment, thus reducing the damage caused by chemotherapy and radiotherapy. The most studied of the chemopreventive effects of phytochemicals are the carotenoids and phenolics. In this review, we investigated the multiple mechanisms of carotenoids and polyphenols (PPs) for use in preventing head and neck cancer, reducing the side effects of chemotherapy and radiotherapy, improving patient survival rates, and reducing the occurrence rate of second primary cancers.

Keywords: chemotherapy; head and neck cancer; phytochemicals; radiotherapy; supplementary therapeutic agents

1. Introduction

Head and neck cancer is an umbrella term for cancer that occurs in the paranasal sinuses, nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, and salivary glands. More than 90% of these cancers are head and neck squamous cell carcinomas (HNSCCs).[1] People diagnosed with this type of cancer account for approximately 6% of the cancer population. Every year, approximately 650,000 people are diagnosed with head and neck cancer, and 320,000 people die of the disease.[2] Statistics released by the Health Promotion Administration (HPA) showed that the numbers of Taiwanese people diagnosed with oral or esophageal cancer are the highest among member countries of the Organization for Economic Cooperation and Development. In the Top Ten Deadly Cancers list published by the Ministry of Health and Welfare in 2012, oral cancer was ranked fifth. The recurrence rate is high in patients

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with head and neck cancer, and second primary cancer is likely to occur in locations such as the oral cavity, throat, and esophagus. Studies conducted by the HPA indicated that the risk of male patients with oral cancer developing a second primary cancer was 3.8 times that of other people. Additionally, the risk of patients with oral cancer (of both sexes) of developing second primary cancer was 2.4 times that of the risk of people with other types of cancer. The prognosis of patients with oral and second primary cancers is often poor. Thus, preventing and tracking the development of secondary primary cancer is vital.

The treatments performed on patients with head and neck cancer primarily involve surgical resection, radiotherapy, chemotherapy, or a combination of these methods. The medication used in chemotherapy is often cisplatin or fluorouracil (5-FU). However, resistance occurs frequently during treatment, and previously controlled cancer cells can redevelop. The toxicity of the medication may also result in side effects such as nausea, vomiting, bone marrow suppression, and renal damage, thereby impairing the quality of life of patients. Radiotherapy involves using rapid photons to collide with the basic atomic structure of organisms, causing the electrons traveling on peripheral tracks to leave the tracks. Consequently, oxidative stress occurs, generating large amounts of reactive oxygen species (ROS), damaging the DNA in cells. Thus, the cells lose their ability to divide and proliferate.[3] The side effects of radiotherapy primarily include oral mucositis, dermatitis, xerostomia, dysphagia, osteonecrosis, trismus, and neck muscle fibrosis. These conditions considerably jeopardize the quality of life of patients, thereby decreasing patient willingness to receive treatment. The primary causes of head and neck cancer are unhealthy habits such as betel nut chewing, smoking, and excessive drinking.[4,5] Insufficient vegetable and fruit intake is another contributor to oral cancer.[6] Riboli and Norat[7] analyzed numerous case–control studies and found that low vegetable and fruit intake contributed to an increased risk of oral, pharyngeal, and laryngeal cancer, as well as increasing the risk of recurrent primary cancers (e.g., lung and esophageal cancers) in early-stage head and neck cancer survivors.

First proposed in 1976 in the USA by National Cancer Institute scholar Michael Sporn,[8] cancer chemoprevention involves using natural or synthetic substances to prevent, block, suppress, or reverse cancer in the initiation, promotion, and progression stages. Chemoprevention consists of Level 1 and Level 2 prevention—that is, treating pathological changes that occur prior to cancer, and preventing post-surgery recurrence and the occurrence of second primary cancer, respectively. This strategy is vital in current cancer prevention and treatment. The substances used to achieve chemoprevention must be safe and the effective doses should be limited to minimal levels to prevent significant toxicity. Additionally, vegetables and fruits have the potential ability to prevent and inhibit cancer[9,10] primarily because these foods contain large amounts of natural chemicals, called phytonutrients or phytochemicals. As determinants of the color, aroma, and taste of plants, phytochemicals are vital for plants to grow healthily. Phytochemicals are defined as bioactive nonnutrient plant compounds in fruits, vegetables, grains, and other plant foods, and can be classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds.[11] Regarding the mechanism of the effects that phytochemicals have on the human body, Liu[12] argued that phytochemicals can reduce the risks of cardiovascular diseases and cancer possibly because of their antioxidant activity. Lampe[13] indicated that phytochemicals regulate detoxifying enzymes and the immune system, possibly by altering the metabolism of cholesterols and steroid hormones. Phytochemicals can be used to develop novel chemoprevention and chemotherapy methods and function as assistive alternatives for conventional treatments. Although there are no recommended dietary allowances for phytochemicals, higher doses increase the risk of toxicity. Therefore, it is not recommended to take megadoses of purified phytochemicals as dietary supplements before strong supporting scientific evidence confirms its safety.[11] In this review, we primarily focus on exploring the protective effects and mechanisms of carotenoids and polyphenols (PPs) on patients with head and neck cancer.

2. The prevention and treatment effects of phytonutrients on patients with head and neck cancer

2.1. Carotenoids

Carotenoids are fat-soluble pigments; >700 types of carotenoids have been extracted and identified. However, only 24 of these carotenoids have been found in human blood and tissues, and two of them exist in the retina and lens of the human eye. The most extensively researched carotenoids include β-carotene, lycopene, lutein, and zeaxanthin. The carotenoid concentration in blood is an effective indicator of dietary intake. Carughi and Hooper[14] found that healthy people who have been on a 2-week low-carotenoid diet (<0.4 mg/d) exhibited blood carotenoid levels that were <60% of the initial levels observed at the beginning of the experiment. After the participants consumed carotenoid-rich vegetables and fruits for 1 week, the carotenoids in the blood increased to the original value. The human body can absorb large amounts of carotenoids from natural foods (e.g., vegetables and fruits). Specifically, β-carotene, α-carotene, and β-cryptoxanthin in the human body have vitamin A activity, which means that these carotenoids can be converted to retinol. Additionally, carotenoids are superior antioxidants, capable of capturing singlet oxygen and participating in restoring gap junction intercellular communication (GJIC). GJIC abnormalities are significantly related to cancer cell generation.[15] Studies have shown that the levels of β-carotene, lycopene, and vitamin E observed in the blood plasma of patients with HNSCC[16,17] and oral leukoplakia[18] were lower than those of healthy people. Sakhi et al[19] indicated that the levels of lutein, zeaxanthin, α-carotene, β-carotene, lycopene, and total carotenoids observed in the blood of patients with HNSCC were lower than those of healthy people. Because patients with HNSCC consume smaller amounts of vegetables

and fruits, which contain rich carotenoids, carotenoid levels in the blood plasma of these patients are relatively low; consequently, the risk of developing oral, pharyngeal, and laryngeal cancer increases.[6] Previous studies have also shown that relatively high plasma levels of glutathione[20] and carotenoid[21] were observed after radiotherapy in HNSCC patients that can increase the survival rates of these patients. Sakhi et al[21] observed that compared with healthy people, patients first diagnosed with HNSCC exhibited significantly higher oxidative stress prior to receiving radiotherapy. The total hydroperoxide (derivatives of reactive oxygen metabolites, d-ROMs) level in blood, an indicator of oxidative stress, is relatively high. Subsequently, the side effects resulting from radiotherapy affect eating; consequently, vegetable and fruit intake decreases, which lessens antioxidant intake. Additionally, the free radicals resulting from the radiation necessitate increased antioxidant usage. Therefore, the antioxidant levels in patients' blood decreases. Because of the location of tumors and the side effects of radiotherapy, the average β-carotene dietary intake of HNSCC patients is 50% less than that of healthy people.[19]

Meyer et al[22] studied 540 HNSCC patients and found that when patients' average dietary intake of β-carotene was low during radiotherapy, the risks of severe side effects and local recurrence increased. The dietary intake of β-carotene and high-dose β-carotene supplements are both effective in reducing the frequency and severity of radiotherapy-induced side effects. In other words, β-carotene can protect normal tissues from radiation injury. However, β-carotene supplements increased cancer recurrence rates, possibly because the antioxidant capacity of β-carotene supplements also protects tumor cells from radiation injury, thereby jeopardizing the effect of radiotherapy. By contrast, the β-carotene derived from dietary intake poses no such problem. Sakhi et al[19] observed that HNSCC patients after receiving radiation therapy exhibited three to four times lower carotenoid levels than a healthy control group. A longitudinal study of the survival rates of the HNSCC patients indicated that the postradiation carotenoid (i.e., lutein, α-carotene, and β-carotene) levels in blood were positively correlated with progression-free survival (PFS).

Regarding recommended carotenoid intake, Le Marchand et al[23] examined HNSCC patients and patients with lung squamous cell carcinoma and found that increasing their daily vegetable and fruit intake from four to eight servings and maintaining this regimen for 3 months resulted in significantly increased carotenoid levels in the blood and improved survival rates. In summary, blood carotenoid level can be used as a reference indicator of vegetable and fruit intake. Increasing vegetable and fruit intake can prevent the development of HNSCC and reduce the frequency and severity of radiotherapy-induced side effects and local recurrence rates for HNSCC patients while increasing PFS.

2.2. PPs

PPs constitute the largest group of phytochemicals. More than 8000 PPs have been identified, which can be divided into the following structural categories: phenolic acids, flavonoids, lignans, and stilbenes. Specifically, phenolic acids and flavonoids account for 30% and 60% of the known PPs, respectively. Fig. 1 shows the categories, chemical structures, and representative compounds of PPs.

Additionally, PPs have antioxidant capacity. The phenolic groups can accept an electron to form relatively stable phenoxyl radicals, thereby ending chain oxidation and thus protecting cells from oxidative damage. Consequently, the risks of degenerative diseases associated with oxidative stress can be reduced. Studies have shown that within hours of consuming vegetables, fruits, and drinks (e.g., tea or red wine) rich in PPs, the body exhibits significantly increased antioxidant capacity.[24,25] Duthie et al[26] argued that PPs can alter gene expression, increase apoptosis, upregulate gap junction communication, activate P-glycoproteins, and regulate the activity of enzymes related to carcinogen activity and

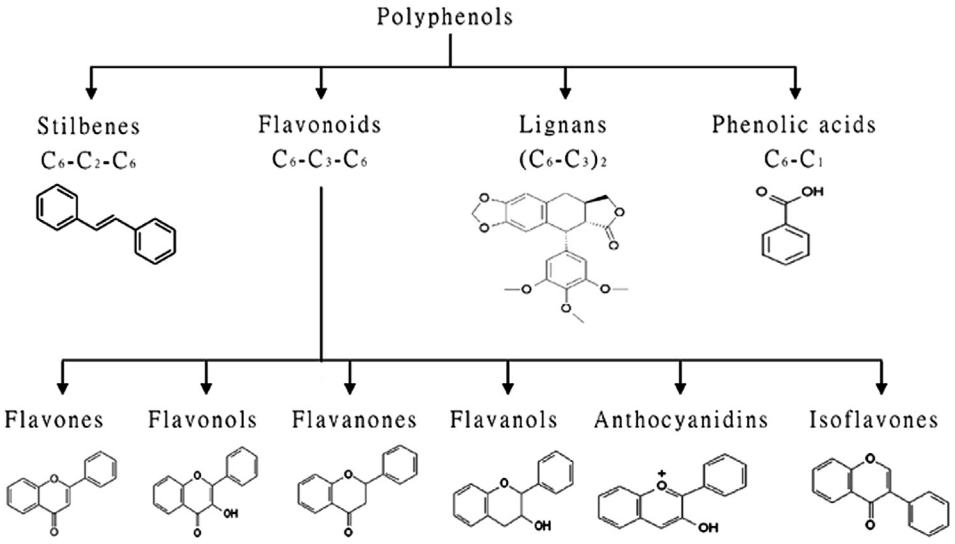

Fig. 1. The categories, chemical structures, and representative compounds of polyphenols (PPs).

detoxification. Lambert et al[27] indicated that PPs can disrupt the initiation, promotion, and progression of tumor cells, exhibiting anticancer properties. Additionally, PPs can prevent oral cancer, possibly because PPs come in contact with tissues directly before being absorbed and metabolized,[28] and the biologically active ingredients inhibit the proliferation of oral cancer cells in the surface of epithelial cells.[29]

The PP content of food is affected by factors such as the variety, ripeness, and storage of food. Therefore, no comprehensive reference table for food ingredients is available. Ovaskainen et al[30] assessed the diet records of Finnish adults and identified an average daily PP intake of approximately 863 mg, of which 75% was phenolic acids, 14% was proanthocyanidins, and 10% was anthocyanins and other flavonoids. However, little is known regarding the absorption, bioavailability, biodistribution, and metabolism of PPs. Free aglycones allow intestinal absorption, whereas the majority of PPs exist in food in the form of esters, glycosides, and polymers. These PPs can only be absorbed after hydrolysis by intestinal enzymes or colonic microflora. Microorganisms in the oral cavity and intestines can decompose PPs to aglycones or occasionally to form aromatic acids. The metabolic detoxification process causes the absorbed PPs to bind and form methylation, glucuronidation, and sulfation derivatives.[31] Consequently, aglycones cannot be detected or only a low level of aglycones can be detected in the blood after PPs are absorbed. PPs can be observed in numerous tissues, primarily in the mucous membrane of the digestive tract. The highest PP level is observed in the oral mucosa.[32] The most easily absorbed PPs are isoflavones and gallic acid, followed by flavanones, catechins, and quercetin glycosides, and the least easily absorbed are proanthocyanidins, anthocyanins, and galloylated catechins. However, all PPs are primarily discharged through urine and bile.[29,31,33–35] Several studies have indicated that PPs have anti-HNSCC activity, including but not limited to catechins and proanthocyanidins.

2.2.1. Green tea polyphenols

Green tea polyphenols (GTPs) can be divided into four main categories: epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG). The effects of EGCG on the inhibition of cancer cell generation have been extensively researched and have received significant attention. Epidermal growth factor receptors (EGFRs) are a type of glycoprotein receptor and perform various functions by activating the protein tyrosine kinase in cells. Excessive EGFR expression is often observed in patients with head and neck cancer. These receptors allow cancer cells to grow, transfer, and develop resistance rapidly. EGCG can inhibit the signaling pathways of EGFRs, thereby inhibiting cancer development and progression. Amin et al[36] found that the synergy between EGCG and EGFR blockers can inhibit HNSCC growth. Amin et al[36] also indicated that the synergy between Erlotinib and EGCG inhibits HNSCC growth by inhibiting the activity of nuclear factor-κβ (NF-κβ). In an *in vitro* study, the effects of EGCG on the multiple-step carcinogenesis of oral cancer were examined. The results showed that EGCG can inhibit the growth of human oral leukoplakia cell lines, MSK Leuk1, MSK Leuk1s, and 1483 HNSCC cell lines, as well as the phosphorylation of retinoblastoma protein. Consequently, cell cycle arrest occurs in the Growth 1 (G1) phase, and progression is inhibited.[37] The catechins in tea inhibit the activity of oral squamous cell carcinoma (OSCC), thereby inhibiting the production of matrix metalloproteinases (MMPs). Thus, the invasion and migration of cancer cells can be controlled[38] and cancer cell apoptosis and growth arrest are induced.[39] Yamamoto et al[40] observed that drinking green tea causes the EGCG concentration in saliva to reach 50 μM (i.e., the normal physiological concentration), which ensures the protection of normal salivary gland cells and the alleviation of damage caused by chemotherapy medication such as γ-irradiation and cisplatinum (II) diammine dichloride (CDDP). However, EGCG also protects oral cancer cells, thereby hindering the effects of chemoradiotherapy. When EGCG concentration is high (e.g., 200 μM), the cytotoxicity of CDDP to OSCC cell lines (OSC-2 and OSC-4) can be increased. Shin et al[41] demonstrated that EC protected the human keratinocyte line (HaCaT) *in vitro* from radiation by inhibiting ROS generation, maintaining the mitochondrial integrity, and blocking mitogen-activated protein kinase (MAPK) activation. Moreover, EC is an effective means of reducing oral mucositis and facilitates wound healing after radiation exposure in the oral cavity of rats. Pisters et al[42] used green tea extracts to treat late-stage cancer patients. The results of a Phase I clinical test showed that the dose of the green tea extract (i.e., 1000 mg/m^2) was within the safe range. Seeram et al[43] conducted a pilot study with smokers and found that doses of 2000–2500 mg/day of green tea extract can reduce the DNA damage caused by smoking and increase apoptosis. Nevertheless, long-term studies that use higher doses must be conducted to verify the benefits of applying GTPs to prevent and treat head and neck cancer.

2.2.2. Proanthocyanidins

Proanthocyanidins are polyphenolic compounds that can be found in fruits such as grapes, cranberries, and blueberries. Also called condensed tannins, proanthocyanidins are formed by monomeric flavan-3-ols. Based on the degree of polymerization, they can be divided into monomeric, oligomeric, and polymeric proanthocyanidins. Grapes are rich in proanthocyanidins, approximately 60–70% of which are stored in the grape seeds. Grape seed proanthocyanidins (GSPs) form dimers, trimers, tetramers, and oligomers.[44] Ye et al[45] argued that GSPs exert cytotoxicity on tumor cells but cause no side effects on normal cells. The results of animal studies have shown that GSPs can prevent tumor generation and have no apparent toxicity on animals.[46] A HNSCC study conducted by Prasad and Katiyar[47] indicated that GSPs significantly decreased the viability of human HNSCC cells while inducing apoptosis. In the same study, the scholars observed that GSPs were not toxic to normal human bronchial epithelial cells and that GSPs can inhibit the expression of cyclins (cyclin D1 and cyclin D2) and cyclin-dependent kinases (Cdks) in HNSCC cells. Thus, the cell cycle progression in these uncontrolled

cells was interrupted. Additionally, GSPs inhibit the activity of Cdk–cyclin complexes by increasing the expression of Cdk inhibitory (Cdki) proteins (Cip1/p21, Kip1/p27) and the binding of Cdki and Cdks. Consequently, cell cycle arrest occurs in the G1 phase[48,49]; thus, cells are "offered" the options of restoration or apoptosis. The same study also indicated that GSPs cause, in a dose-dependent manner, HNSCC cells to release cytochrome c from mitochondria. Subsequently, the cytochrome c enters the cytoplasm, activating or cleaving caspase-3 and poly (ADP-ribose) polymerase in the cytoplasm. Thus, apoptosis is induced. King et al[50] found that GSP extract can significantly inhibit, in a dose-dependent manner, the cell line proliferation of human OSCC and reduce the proliferation-promoting effects that human papillomavirus 6 has on OSCC cells. In conclusion, proanthocyanidins are phytonutrients that have great potential for treating HNSCC.

2.2.3. Other PPs

Red grape skin is rich in resveratrol, and the resveratrol content of red wine is approximately 2.0–40.0 μM.[51] Resveratrol is an inducer of multiple cell death pathways including apoptosis, autophagy, and mitotic catastrophe.[52] ElAttar and Virji[53] argued that the resveratrol in red wine can effectively inhibit the growth and proliferation of oral squamous carcinoma cells (SCC-25). Tang et al[54] demonstrated that resveratrol inhibits esophageal squamous cell carcinoma (ESCC) EC109 and EC9706 cell growth by inducing cell cycle arrest at the sub-G1 phase, resulting in subsequent apoptosis. Resveratrol-induced apoptosis is enhanced by the inhibition of autophagy. Quercetin can be found in glycosylated form in fruits, nuts, vegetables, and red wine. Initial digestion can be performed in the oral cavity through β-glycosidases, and the cleavaged glycosides hydrolyze to the aglycones. Dietary flavonoid glucosides may thus be hydrolyzed in the oral cavity by both bacteria and shedded epithelial cells to deliver biologically active aglycones at the surface of epithelial cells. The aglycones quercetin and genistein both potently inhibited the proliferation of oral cancer cells.[29] Curcumin, a xanthophyl that exists in turmeric, has antioxidant and immunomodulatory capacities and can inhibit angiogenesis and induce apoptosis.[55] Khafif et al[56] found that curcumin can effectively inhibit the occurrence of precancerous lesions in normal oral epithelial cells of humans and cell line growth of squamous cell carcinoma. Recent evidence has revealed that curcumin is a potent autophagy inducer in human cancer cell lines *in vitro*, such as oesophageal squamous and adenocarcinoma cell lines OE21, OE33, and KYSE450 cells[57] and oral squamous cell carcinoma cells YD10B.[58] Both apoptosis and autophagy are often simultaneously observed after curcumin treatment.[58,59] Eukaryotic elongation factor-2 kinase (EEF2K) is a controller of endoplasmic reticulum (ER) stress-induced autophagy and apoptosis in cancer cells. The integrated regulation of autophagy and apoptosis by EEF2K controls cellular fate and modulates the efficacy of curcumin.[59] In a clinical trial conducted by Cheng et al,[60] the scholars prescribed an oral supplement of curcumin to cases with a high risk of squamous cell carcinoma. The dose was up to 8 g/day, with no toxicity observed. The results of cell experiments regarding head and neck cancer indicated that curcumin can inhibit cancer cell proliferation by adjusting caspase-3-dependent signaling and the signaling pathways of cells such as NF-κβ.[61,62] Clark et al[63] found that curcumin inhibited the activity of MMP-9 in nicotine-activated cells and the nicotine-induced migration of HNSCC. Curcumin inhibits the adverse effects of nicotine by blocking nicotine-induced activation of the AKT/mammalian target of rapamycin (MTOR) pathway in HNSCC, which impedes cell migration.

In conclusion, in addition to discontinuing unhealthy habits such as betel nut chewing, smoking, and drinking, the prevention and treatment of head and neck cancer can be achieved by increasing dietary intake of vegetables and fruits, which are rich in phytochemicals. Thus, internal antioxidant capacity is enhanced and normal cells are protected. Additionally, phytochemicals can be used to control the progression of tumor cell cycles, preventing canceration. When applied for preventing and treating head and neck cancer, phytochemicals can decrease the side effects of chemoradiotherapy and increase the survival rates of patients in addition to decreasing the recurrence rate of second primary cancer. Thus, phytochemicals have great potential for relevant treatments. The benefit of a diet rich in a wide variety of fruits and vegetables daily is attributed to the complex mixture of phytochemicals. It is best to use several anticancer and antioxidant agents for synergistic prevention along all the possible pathways. The clinical application of cancer chemoprevention is at an initial stage, and the mechanism of phytochemicals in assisting cancer prevention and treatment warrants further research.

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