REVIEW ARTICLE

Additive and synergistic effect of phytochemicals in prevention of oral cancer

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ABSTRACT

Increasing the consumption of fruits, vegetables, and whole grains is a practical strategy to optimize good health and to reduce the risk of various chronic diseases and cancer. There are approximately 5,000 individual phytochemicals which have been identified. These interfere with multiple important cellular pathways and play an important role in maintaining balance between health and disease. This article aims to provide awareness of various additive and synergistic effects of these natural occurring chemical substances (phytochemicals) found in various fruits and vegetables. Their mechanism of action in preventing various chronic diseases and cancer is also been highlighted in this article. Grouping plant foods by color provides simplification, but it is also important as a method to help consumer's make-wise food choices and promote health. We believe phytochemicals can be best acquired through whole-food consumption and not through the pills or an extracts.

Key words
Cancer, chronic diseases, color, fruits, health, phytochemicals, vegetables

INTRODUCTION

The evolution of human dietary patterns has been driven by necessity, economics, and more recently, by the selection of foods carefully designed and promoted on the basis of taste, cost, and convenience, often without regard to their nutritional and health value.[1]

Food provides not only essential nutrients needed for life but also other bioactive compounds for health promotion and disease prevention. Previous epidemiologic studies have consistently shown that diet plays a crucial role in the prevention of chronic diseases.[2,3] Consumption of fruit and vegetables, as well as grains, has been strongly associated with reduced risk of cardiovascular disease, cancer (oral cancer), diabetes, Alzheimer disease, cataracts, and age-related functional decline.[2-4] This convincing evidence suggests that a change in dietary behavior such as increasing consumption of fruit, vegetables, and grains is a practical strategy for significantly reducing the incidence of chronic diseases and oral cancer.[5]

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The National Cancer Institute has identified about 35 plant foods that can prevent various oral diseases. Foods and herbs having these activities include garlic, soybeans, cabbage, ginger, licorice root, and the umbelliferous vegetables (including carrots, celery, coriander, parsley, and parsnips). Additional foods with anticancer activity include onions, flax, citrus, turmeric, cruciferous vegetables (broccoli, Brussels sprouts, cabbage, and cauliflower), tomatoes and sweet peppers, brown rice, whole wheat, oats, barley, various herbs (such as mints, rosemary, thyme, oregano, sage, and basil), cucumber, cantaloupe, and berries.[6,7]

Cells in humans and other organisms are constantly exposed to a variety of oxidizing agents, some of which are necessary for life. Overproduction of oxidants can cause an imbalance, leading to oxidative stress, especially in chronic bacterial, viral, and parasitic infections.[8] Oxidative stress can cause oxidative damage to large biomolecules such as proteins, DNA, and lipids, resulting in an increased risk for cancer and cardiovascular disease.[9,10] To prevent or slow down

the oxidative stress induced by free radicals, sufficient amounts of antioxidants need to be consumed. Fruits and vegetables contain a wide variety of phytochemicals such as phenolics and carotenoids that have wide variety of functions and can lower the risk of various chronic diseases.[5,6,11]

The "phyto" of the word phytochemicals is derived from the Greek word *phyto*, which means plant. Therefore, phytochemicals are the plant chemicals. These are the bioactive non-nutrient plant compounds found in fruit, vegetables, grains, and other plant foods. It is estimated that more than 5,000 phytochemicals have been identified and there are more than 150,000 edible plants on the earth, but a large percentage still remains unknown and need to be identified. Modern humans eat only 150 to 200 of these plants worldwide.[11,12] However, more and more convincing evidence suggests that the benefits of phytochemicals in fruit and vegetables may be even greater than is currently understood because oxidative stress induced by free radicals is involved in the etiology of a wide range of various chronic diseases.[5,11]

Therefore, it is important to identify these bioactive compounds responsible for prevention of chronic diseases and cancer. However, it is also important to know whether a purified phytochemical has the same health benefit as the phytochemical present in whole food or a mixture of foods?

CLASSIFICATION OF DIETARY PHYTOCHEMICALS

Phytochemicals found in the fruits and vegetables are many. Some of these important phytochemicals can be classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds [Table 1]. Most studied phytochemicals are the phenolics and carotenoids.[11]

Table 1: Classification of dietary phytochemicals

Phytochemicals
Carotenoids
Alpha–carotene
Beta–carotene
Beta–cryptoxanthan
Lutein
Zeaxanthia
Lycopene
Phenolics
Phenolic acid
Hydroxyl benzoic acids
Hydroxyl cinnamic acids
Flavonoids
Flavonols
Flavones
Flavanols
Flavanones
Anthocyanidins
Isoflavonoides
Stibencs
Courmarins
Tannins
Alkaloids
Nitrogen–containing compounds
Organosulfur compounds
Isothiocyanates
Indoles
Allylic sulfur compounds

Phenolics

Phenolics are compounds possessing one or more aromatic rings with one or more hydroxyl groups and generally are categorized as phenolic acids, flavonoids, stilbenes, coumarins, and tannins. Phenolics are the products of secondary metabolism in plants, providing essential functions in the reproduction and the growth of the plants; acting as defense mechanisms against pathogens, parasites, and predators, as well as contributing to the color of plants. In addition to their roles in plants, phenolic compounds in our diet may provide health benefits associated with reduced risk of chronic diseases.[11]

Phenolics content is found in apple, cranberry, red grape, strawberry, pineapple, banana, peach, lemon, orange, pear, and grapefruit.[13] Among vegetables, broccoli possesses the highest total phenolic content, followed by spinach, yellow onion, red pepper, carrot, cabbage, potato, lettuce, celery, and cucumber.[14] It is estimated that flavonoids account for approximately two-thirds of the phenolics in our diet and the remaining one-third are from phenolic acids.[11]

Flavonoids

Flavonoids are a group of phenolic compounds with antioxidant activity. More than 4,000 distinct flavonoids have been identified. Differences in the generic structure classify them as flavonols, flavones, flavanols (catechins), flavanones, anthocyanidins, and isoflavonoids. Flavonols (apigenin), flavanols (catechin, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate), flavanones (naringenin), anthocyanidins, and isoflavonoids (genistein) are common flavonoids in the diet.[11]

Flavonoids are most frequently found in nature as conjugates in glycosylated or esterified forms but can occur as aglycones, especially as a result of the effects of food processing. Many different glycosides can be found in nature; >80 different sugars have been discovered bound to flavonoids. Anthocyanidins give the red and blue colors in some fruits and vegetables. They are found in various fruits and vegetables and have been linked to reducing the risk of major chronic diseases.[15]

Flavonoids extend the activity of vitamin C, act as antioxidants, protect LDL cholesterol from oxidation to the unsafe cholesterol oxides, inhibit platelet aggregation, and have anti-inflammatory and antitumor action.[6,16] Quercetin is the major flavonol in the western diet. Rich source of quercetin are red and yellow onions, broccoli, red grapes, cherries, French beans, apple, etc. Quercetin possesses both anticarcinogenic activity and ability to inhibit LDL oxidation. Red wine and grape juice contains significant levels of phenolic flavonoids and red anthocyanin pigments. These compounds can act as antioxidants, protect against LDL oxidation, and inhibit platelet aggregation.[17,18]

Phenolic acids

Phenolic acids can be subdivided into two major groups, hydroxybenzoic acids and hydroxycinnamic acids. Hydroxybenzoic acid derivatives include p-hydroxybenzoic, protocatechuic, vanillic, syringic, and gallic acids. They are commonly present in the bound form and are typically a component of a complex structure such as lignins and hydrolyzable tannins. They can also be found in the form of sugar derivatives and organic acids in plant foods.[11]

Hydroxycinnamic acid derivatives include p-coumaric, caffeic, ferulic, and sinapic acids. They are mainly present in the bound form, linked to cell-wall structural components, such as cellulose, lignin, and proteins through ester bonds. Ferulic acids occur primarily in the seeds and leaves of plants, mainly covalently conjugated to mono and disaccharides, plant cell-wall polysaccharides, glycoproteins, polyamines, lignin, and insoluble carbohydrate biopolymers.[11]

Wheat bran is a good source of ferulic acids, which are esterified to hemicellulose of the cell walls. Free, soluble-conjugated, and bound ferulic acids in grains are present in the ratio of 0.1:1:100.[19] Food processing, such as thermal processing, pasteurization, fermentation, and freezing, contributes to the release of these bound phenolic acids.[20] Caffeic, ferulic, p-coumaric, protocatechuic, and vanillic acids are present in almost all plants. Chlorogenic acids and curcumin are also major derivatives of hydroxycinnamic acids present in plants. Chlorogenic acids are the ester of caffeic acids and are the substrate for enzymatic oxidation leading to browning, particularly in apples and potatoes. Curcumin is made of two ferulic acids linked by a methylene in a diketone structure and is the major yellow pigment of mustard.[11]

Carotenoids

Carotenoids are nature's most widespread pigments and have also received substantial attention because of both their provitamin and antioxidant properties. More than 600 different carotenoids have been identified in nature. Lycopene and β-carotene are examples of acyclized and cyclized carotenoids, respectively. Carotenoid compounds most commonly occur in nature in the all-trans form. β-carotene, α-carotene, and β-cryptoxanthin are able to function as provitamin A. Zeaxanthin and lutein are the major carotenoids in the macular region (yellow spot) of the retina in humans.[11]

Carotenoid pigments play important functions in photosynthesis and photoprotection in plant tissues. The photoprotection role of carotenoids originates from their ability to quench and to inactivate reactive oxygen species such as singlet oxygen formed from exposure of light and air. This photoprotection role is also associated with its antioxidant activity in human health. Carotenoids can react with free radicals and become radicals themselves. Astaxanthin, zeaxanthin, and lutein are excellent lipid-soluble antioxidants that scavenge free radicals, especially in a lipid-soluble environment. Carotenoids at sufficient concentrations can prevent lipid oxidation and related oxidative stress. It also stimulates immune function. Person with high levels of serum carotenoids have reduced risk of heart disease and cancer.[6,11,21]

Orange, vegetables, and fruits, including carrots, sweet potatoes, winter squash, pumpkin, papaya, mango, and cantaloupe, are rich sources of the carotenoid β-carotene. Tomatoes, watermelons, pink grapefruits, apricots, and pink guavas are the most common sources of lycopene.[6,11]

SIGNIFICANCE OF COLOR

Pigments provide color to food and enhance enjoyment of eating experience. Presently, there are almost 2,000 known plant pigments in our food.[6] Phytochemicals present in the fruits and vegetables are colorful and indicate their unique physiological roles [Table 2].[1,22] All the colored phytochemicals that absorb light in the visible spectrum have antioxidant properties. Colorful fruits and vegetables can be recommended for increased diversity of intake for the consumer. For example, red food contains lycopene, the pigment in tomato, which is

Table 2: Color code for phytochemicals present in various fruits and vegetables

Color	Phytochemicals	Fruits and vegetables
Red	Lycopene	Tomatoes and tomato products such as juice, soups, and pasta sauces
Red-Purple	Anthocyanins and polyphenols	Grapes, blackberries, red wine, raspberries, blueberries
Orange	Alpha and beta-carotene	Carrots, mangos, pumpkin
Orange-Yellow	Beta-cryptoxanthin and flavonoids	Cantaloupe, peaches, tangerines, papaya, oranges
Yellow-Green	Lutein and zeaxanthin	Spinach, avocado, honeydew melon
Green	Glucosinolates and indoles	Broccoli, bok choi, kale
White-Green	Allyl sulfides	Leeks, garlic, onion, chives

a powerful antioxidant and helps in reduction of various chronic diseases and cancer.[22,23]

A method for selecting fruits and vegetables based on color keyed to the content of phytochemical is a way of translating the science of phytochemical nutrition into dietary guidelines for the public. It can also help consumers change dietary patterns to include more fruits and vegetables by including one serving from each of the seven color groups. Although, the color method is superior to the current system of simply encouraging increased fruit and vegetable intakes, it dose not account for actual phytochemical delivery to the consumers. Today there is no labeling law that enables fruit and vegetable manufactures to the list the phytochemicals in there products. Further, fruits and vegetables are developed and preserved to transport them over long distances and extend their shelf life rather than for their flavor or nutritional content.[22]

PHYTOCHEMICALS AND CANCER

Risk reduction encompasses the following two strategies: (1) prevention, i.e., the reduction in exposure to carcinogens (such as smoking or radiation) and (2) protection, i.e., the deliberate intervention to enhance mostly endogenous mechanisms that reduce the risk arising from exposure to carcinogens.[24]

Consensus has been building over more than a quarter of a century that diets rich in fruits and vegetables are associated with lower risks of developing various types of malignancies. These consensuses are supported by a growing number of sophisticated epidemiologic studies. Major reviews of this field include two reports from the National Academy of Sciences of the United States, i.e., In 1982,[25] the National Academy of Sciences of the United States included guidelines in their report on diet and cancer, emphasizing the importance of fruits and vegetables. The value of adding citrus fruits, carotene-rich fruits and vegetables, and cruciferous vegetables to the diet for reducing the risk of cancer was specifically highlighted. In 1989,[26] a report from the National Academy of Sciences on diet and health recommended consuming five or more servings of fruits and vegetables daily for reducing the risk of both cancer and heart disease. The Five-a-Day program was developed as a tool to increase public awareness of the health benefits of fruits and vegetable consumption and to promote adequate intakes of known vitamins. Plant-based foods, such as fruits, vegetables, and whole grains, which contain significant amounts of bioactive phytochemicals, may provide desirable health benefits beyond basic nutrition to reduce the risk of chronic diseases.

Of more than 200 case-control and cohort studies, nearly 80% have reported significant inverse relations between consumption of plant foods and the risk of developing most types of cancer. Studies also suggested that for some cancer of the aerodigestive tract, a dietary intake of 400-600 g of fruits and vegetables per day is associated with a 50% reduction in risk.[27]

Multiple mechanisms are undoubtedly involved in the protective effects of diets rich in fruits and vegetables.[28-30] These depend not only on qualitative and quantitative changes in major nutrient and non-nutrient dietary components, such as the reduction in meat and fat intake and corresponding increase in fiber consumption, but also changes in the intake of essential nutrients. Far less well understood are the effects of chronic consumption of substantial quantities of non-nutrient plant components, including a myriad of unique phytochemicals that plants accumulate, sometimes to substantial levels, for their own needs.[31] It is therefore very difficult to identify the relative contributions of various components of a plant-based diet to overall cancer risk reduction.[32,33]

Carcinogenesis is a multistep process, and oxidative damage is linked to formation of tumors through several mechanisms. Oxidative stresses induced by free radicals cause DNA damage, which, when left unrepaired, can lead to base mutation, single- and double-strand breaks, DNA cross-linking, chromosomal breakage, and rearrangement.[8,10] This damage may be limited by dietary antioxidants in fruits and vegetables through modulation of detoxification enzymes, scavenging of oxidative agents, stimulation of the immune system, hormone metabolism, and regulation of gene expression in cell proliferation and apoptosis.[34]

Studies to date have demonstrated that phytochemicals commonly found in fruits and vegetables can have complementary and overlapping mechanisms of actions [Table 3], including antioxidant activity and scavenging free radicals; regulation of gene expression in cell proliferation, cell differentiation, oncogenes, and tumor suppressor genes; induction of cell-cycle arrest and apoptosis; modulation of enzyme activities in detoxification, oxidation, and reduction; stimulation of the immune system; regulation of hormone metabolism; and antibacterial and antiviral effects.[13,14,34,35]

Evidence suggested that dietary antioxidants can reduce cancer risk. Strong epidemiological evidence suggests that regular consumption of fruits and vegetables can reduce cancer risk. Block *et al.*[36] reviewed 200 epidemiological studies that examined the relationship between intake of fruits and vegetables and cancer of the lung, colon, breast, cervix, esophagus, oral cavity, stomach, bladder, pancreas, and ovary. In 128 of 156 dietary studies, the consumption of fruits and vegetables was found to have a significant protective effect. The risk of cancer was 2-fold higher in persons with a low intake of fruits and vegetables than in those with a high intake. Significant protection was found in 24 of 25 studies for

lung cancer. Fruits were significantly protective in cancer of the esophagus, oral cavity, and larynx. Fruits and vegetable intake was protective for cancer of the pancreas and stomach in 26 of 30 studies and for colorectal and bladder cancer in 23 of 38 studies. A prospective study involving 9,959 men and women in Finland showed an inverse association between the intake of flavonoids and incidence of cancer at all sites combined.[37] After a 24-year follow-up, the risk of lung cancer was reduced by 50% in the highest quartile of flavonol intake. The effect of onions was particularly strong against squamous-cell carcinoma. Consumption of quercetin from onions and apples was found to be inversely associated with lung cancer risk.[38]

SUMMARY AND CONCLUSIONS

Prevention is a more effective strategy than treatment. The additive and synergistic effects of phytochemicals in fruits and vegetables have been proposed to be responsible for their wide variety of functions [Table 4].

Thousands of phytochemicals are present in whole foods. These compounds differ in molecular size, polarity, and solubility, which may affect the bioavailability and distribution of each phytochemical in different macromolecules, subcellular organelles, cells, organs, and tissues. Increasing the consumption of fruit and vegetables, whole grains, and soy is a practical strategy to optimize good health and to reduce the risk of various chronic diseases and cancer. The benefit of a diet rich in fruits and vegetables is attributed to the complex mixture of phytochemicals present in these and other whole foods. This partially explains why no single antioxidant can replace the combination of natural phytochemicals in fruits and vegetables in achieving the observed

Table 3: Proposed mechanisms of dietary phytochemicals in prevention of cancer

Proposed mechanisms of action
Antioxidant activity (Scavenge free radicals and reduce oxidative stress)
Inhibition of cell proliferation
Induction of cell differentiation
Inhibition of oncogene expression
Induction of tumor suppress gene expression
Induction of cell-cycle arrest
Induction of apoptosis
Inhibition of signal transduction pathways
Enzyme induction and enhancing detoxification
Phase II enzyme
Glutathione peroxidase
Catalase
Superoxide dismutase
Enzyme inhibition
Phase I enzyme (Block activation of carcinogens)
Cyclooxygenase-2
Inducible nitric oxide synthase
Xanthine oxide
Enhancement of immune functions and surveillance
Anti-angiogenesis
Inhibition of cell adhesion and invasion
Inhibition of intonation and nitration
Prevention of DNA binding
Regulation of steroid hormone metabolism
Regulation of estrogen metabolism
Antibacterial and antiviral effects

Table 4: Commonly present phytochemicals in fruits and vegetables and their actions

Phytochemicals	Actions	Food source
Allyl sulfide	Anti-oxidant Anti-bacterial Blood purifier Anti-neoplastic	Onions, garlic, chives, leeks
Carotenoids	Anti-oxidant Immune modulator	Yellow-orange vegetables and fruits, green, leafy vegetables, red fruits
Curcumins	Anti-oxidant Anti-carcinogenic Anti-bacterial Wound healing Anti-inflammatory	Turmeric
Flavonoids	Anti-carcinogenic Anti-oxidant Anti-inflammatory Enhance vitamin C activity	Most fruit, vegetables, grains and nuts
Gingerols	Inhibit COX-2 expression Relives throat pain and cough	Ginger
Indoles and isothiocyanates	Immune modulator Anti-oxidant	Broccoli, cabbage, cauliflower, brussels, sprouts
Isoflavones	Anti-carcinogenic Decrease cholesterol levels (LDL)	Soybeans, tofu
Lignans	Anti-carcinogenic	Soybeans, flax seed
Liminoids	Anti-oxidant Anti-inflammatory Anti-tumurogenic	Citrus
Phenolic acids	Anti-carcinogenic Anti-mutagenic COX-1 inhibitor	Berries, grapes, nuts, whole grains
Lycopene	Powerful anti-oxidant	Tomato
Isoprenoids	Suppress tumor growth	Grains, legumes
Saponins	Anti-tumurogenic	Beans, herbs
Terpenes	Anti-carcinogenic Anti-oxidant Anti-tumurogenic	Cherries, citrus, herbs
Caffeine	Anti-carcinogenic Anti-oxidant Anti-angiogenic	Tea

health benefits. This balanced natural combination of phytochemicals present in fruits and vegetables cannot simply be mimicked by pills or tablets.

The exact amount of fruits and vegetables needed each day to minimize cancer risks is not known. However, the evidence of the benefits of fruits and vegetables suggest that it is not premature to advice increased intake of a variety of colorful fruits and vegetables. Grouping plant foods by color provides simplification, but it is also important as a method to help consumers make wise food choices and promote health. We believe that the various phytochemicals are best acquired through whole-food consumption and not through the pills or an extracts. Further research on the health benefits of phytochemicals in whole foods is warranted.

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