REVIEW ARTICLE

Natural Dietary Agents In Prevention of Oral Pre-cancer and Cancers

M. Srinivasa Raju, Sunira Chandra, Shveta Mahajan, Rajeev Gupta*

Introduction

Oral cancers are often preceeded by the development of premalignant lesions of the oral mucosa, also termed as intraepithelial neoplasia (1). The most effective way of approaching oral cancer prevention is to identify individuals who are at a high risk to develop such cancers and to treat them with agents that can suppress the development of additional premalignant lesions and inhibit the development of oral cancer in existing lesions (2).

Chemopreventive agents that can inhibit or reverse these changes by targeting specific molecular pathways have received increased attention as novel candidates for cancer prevention and therapy (3). Cancer chemo-preventive natural, synthetic, or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression (2). An ideal chemopreventive agent should be nontoxic, effective at lower doses, economical, potent and easily available (4). Human chemoprevention can intervene at many steps in carcinogenesis process (3).

Because of their safety, low toxicity, antioxidant properties, and general acceptance as dietary supplements, fruits, vegetables, and other dietary elements (phytochemicals and minerals) are being investigated for the prevention of cancer (5).The additive and synergistic effects of phytochemicals in fruits and vegetables are responsible for their potent antioxidant and anticancer activities (6). Chemopreventive phytochemicals can block initiation or reverse the promotion stage of multistep carcinogenesis and can also halt or retard the progression of precancerous cells into malignant ones (7). This review shall focus on various dietary chemopreventive agents which can reduce oral precancer and cancer risk including the various ayurvediuc agents.

Chemoprevention & Chemopreventive Agents

Chemoprevention began in the 1920's (5) and Cancer chemoprevention, was first defined in 1976 (8).Chemoprevention can be categorized as primary, secondary or tertiary. Primary prevention strategies seek to prevent de novo malignancies in an otherwise healthy population. Secondary prevention involves patients who have known premalignant lesions (ie, oral leukoplakia) and attempts to prevent the progression of the premalignant lesions into cancers. Tertiary prevention focuses on the prevention of Secondary Primary Tumors in patients cured of their initial cancer or individuals definitively treated for their premalignant lesions (3).

The chemical character of the chemopreventive will depend on the partial pressure of oxygen and the level of oxidative metabolites produced or derived in the cell (9). Chemopreventive agents can be placed into three broad categories. The first category is "blocking agents" that prevent carcinogenic agents from reaching or reacting with critical target site, thus act by exerting a barrier function. The second category of compounds is that which decreases the vulnerability of target tissue to carcinogenic stimuli. The third category is "suppressing agents" which prevents the evolution of neoplastic process in tissue that otherwise would become malignant (3).

There is a fourth group of compounds, which does not fit into any of the above categories. This includes a large number of compounds that have as a common feature, the capacity to inhibit component of the arachidonic acid cascade, blocking the prostaglandin synthesis and reducing the tumor development, resulting in normal differentiation (10). The various natural chemopreventive agents are discussed in detail as follows:

Antioxidants

Antioxidants are substances that are capable of counteracting the damaging, but normal, effects of the physiological process of oxidation. Antioxidants block the process of oxidation by neutralizing free radicals which are chemically active atoms that have a charge due to an excess or deficient number of electrons and scavenge the body to grab or donate electrons, thereby damaging proteins, and cells (11).

From the Department of Oral medicine and Radiology,Teerthanker Mahaveer Dental College, Moradabad - UP & *Department of Medical Oncology & Heamtology, Fortis Escorts Hospital , Amritsar- India

Correspondence to : Dr M. Srinivasa Raju, Prof & Head, Department of Oral Medicine and Radiology,Teerthanker Mahaveer Dental College, Moradabad

Type of Antioxidants

Vitamin C is an important free radical scavenger in plasma acts to regenerate active vitamin E in lipid membranes (10). It is believed that ascorbic acid combats cancer by promoting collagen synthesis and thus prevents tumors from invading other tissues (12). Vitamin C can protect against oxidative DNA damage and also inactivates nuclear factor-kB in endothelial cells during the inflammation process and hence can inhibit tumor promotion (13).

Vitamin E the major anti-oxidant in all cellular membranes, protects polyunsaturated fatty acids against oxidation (10). It causes maintenance of membrane stability and immune function, inhibition of cancer cell growth and differentiation, free radical scavenging, inhibits DNA and RNA, protein synthesis in cancer cells. Riberio A S *et al* (14) evaluated the toxicity and efficacy of vitamin E in 43 patients with OL in use of 400 IU twice daily for 24 weeks and observed that 10 patients (23%) had complete clinical remission of lesion and 10 (23%) had a partial clinical response. Dosage of 800 IU/ day from 6 to 9 months was considered appropriate for chemoprevention of oral leukoplakia (14).

Retinoic Acid (Vitamin A) : The retinoids are a class comprising natural derivatives and synthetic analogues of vitamin A. Retinoids are able to reverse carcinogenesis through complex mechanisms including the modulation of epithelial differentiation and proliferation by regulating gene expression (14).

Novel Retinoids: These include CD437, Hetroarotinoids andFenretinide (4-HPR) or N-(4-hydroxyphenyl)Retionoid.Systemic use of 4-HPR with 200 mg/day for 3 months in35 patients demonstrated partial clinical resolution of OL of12 patients (14).

Vitamin K is a family of structurally similar fat-soluble 2-methyl-1,4-naphthoquinones, including phylloquinone (K1), menaquinones (K2), and menadione (K3).

One of the study found that the concentrations of 100-300 ng/ml of vit K1 arrested cell growth.Vitamin K2 has also been shown to work at the level of the cell cycle, acting on cyclins to inhibit the cell cycle and initiate differentiation. The cytotoxic action of the combination of vitamins C and K3 is characterized by a cell death that is morphologically distinct from apoptosis and necrosis, referred to as autoschizis (15).

Micronutrients, Trace Elements & Enzymes

Many metal compounds have emerged as potential anticancer agents. ***Calcium*** is apotential candidate for application to combat cancer and is involved in a number of signaling pathways, which link it to apoptosis (16).

Glutahione (GSH) is also likely associated with protection against oral cancer development because it is the major intracellular antioxidant, detoxifies many carcinogens through Phase II conjugation. Patients with oral cancer have been documented to have low blood GSH levels. The ***thiol N-acetyl cysteine*** is a precursor to intracellular cysteine and glutathione. It also acts as a cancer preventive agent due to its anti-oxidant activity, modulation of DNA repair, decreasing biological effective dose of carcinogens, inhibition of cell transformation and genotoxicity (17). ***Alpha Lipoic Acid*** (ALA), also known as thiotic acid, is an 8-carbon, cyclic disulfide thio-octanoic acid. ALA possesses metal chelating capacities which has been shown to reduce iron and copper mediated oxidative damage in vitro. It is also involved in the regulation of the nuclear factor-kappa B (NF-kB). NF-kB has been shown to regulate genes related to inflammation and cell cycle control, which have been implicated in the development of atherosclerosis, insulin resistance, and increasing chemosensitivity of mitotic lesions (18). ***Selenium*** (SE) is an essential cofactor for the major antioxidant enzyme glutathione peroxidase, which catalyses the oxidation of hydroperoxides. Selenium is also involved in cell signalling and immune response processes, which may contribute to its cancer chemopreventive potential (19).

Phytochemicals

Phytochemicals are defined as bioactive non nutrient plant compounds in fruits, vegetables, grains, and other plant foods. It is estimated that more than 5000 individual phytochemicals have been identified in fruits, vegetables and grains (3).

1.***Carotenoids:***-Carotenoids are fat-soluble compounds classifiable as xanthophylls, carotenes or lycopene. These are responsible for the colors of fruits and vegetables. Beta-Carotene:- Beta carotene a vitamin A precursor is the best quencher of singlet oxygen (11). Lycopene:- Lycopene is a carotenoid without provitamin A action. Lycopene may also exert an inhibition on abnormal fibroblasts in oral sub mucus fibrosis and also upregulates lymphocyte resistance to stress and suppresses the inflammatory response (20).

2. **Phenolics**:-Cranberry has the highest total phenolic content amongst fruits and broccoli possesses the highest total phenolic content amongst vegetables.

Phenolic acids:-Chlorogenic acid:- Cinnamic acid (found in coffee) yields chlorogenic acid (CGA). It was reported that CGA induced hydrogen peroxide, and showed differential effects in normal vs. oral cancer cells by inducing caspase-3-dependent apoptosis.

Flavonoids:- The classes of flavonoids includes chalcones, flavones, flavonols, flavonones, flavanols, anthocyanins and isoflavones. The cancer protective effects of flavonoids have been attributed to a wide variety of mechanisms, including free radical scavenging, modifying enzymesthat activate or detoxify carcinogens (21).

Genistein, a prominent isoflavone in soy products has also been shown to induce apoptosis in vivo.10 Bowman-Birk Inhibitor (BBI)is a soybean-derived serine protease inhibitor with both trypsin and chymotrypsin inhibitory activities. It is also a potential cancer chemopreventive agent with anticarcinogenic activities (21).

Flavanols: Silibinin is a polyphenolic flavonoid isolated from the milk thistle, Silybum marianum.Chen *et al* (22)suggested that silibinin can reduce the invasion and metastasis of tumor cells in squamous cell carcinoma cells of tongue.

Green tea polyphenols: - Epigallocatechin-3-Gallate (EGCG) the major component of tea has been reported to scavenge free radicals generated by Benzo(a)pyrene (BaP), Dimethyl benzanthracene (DMBA) and nitrosoamines. It acts as an antioxidant, blocks angiogenesis, inhibits the cell cycle, preventing cancerous cells from dividing and selectively causing cancerous cells to undergo apoptosis (3).

Anthocyanidins: Anthocyanins are the most abundant flavonoid constituents of fruits and vegetables. the anticancer effect of anthocyanins include:- antioxidant effects, anti-cell proliferation, induction of apoptosis, anti-inflammatory effects, anti-angiogenesis, anti-invasiveness, and induction of differentiation (23). Freeze-dried black raspberry ethanol extract :(RO-ET)/ FBR is obtained from black raspberries and suppresses cell proliferation without perturbing viability, inhibits both expression and translation of the complete angiogenic cytokine vascular endothelial growth factor (VEGF) (24).

Flavones: Apigenin is abundantly present in common fruits such as grapefruit, plant-derived beverages and vegetables such as parsley, onions, oranges, tea, chamomile, wheat sprouts thyme, peppermint,etc. Because of its potential antioxidant, anti-inflammatory, and anti-tumorproperties, antiviral, and purgative effects apigenin is a candidate cancer chemopreventive agent (25).

Ginger phenolics: Curcumin (diferuloyl methane): Curcumin is an important polyphenol derived from the rhizome Curcuma longa L. Curcumin has anti-inflammatory, antioxidant, anticarcinogenic, antiviral, and anti infectious activity. It has also been shown to be beneficial in all 3 stages of carcinogenesis (26)

Stilbenes:- The most well-known stilbene compound is resveratrol. Primarily found in peanuts, red wine, and grapes, resveratrol has been shown to be a potent anti-inflammatory, anti-cancer and chemoprotective agent. Resveratrol acts on the process of carcinogenesis by affecting the three phases: tumor initiation, promotion and progression phases and suppresses the final steps of carcinogenesis, i.e. angiogenesis and metastasis (27).

3.***Organosulfur Compounds & Allium Vegetables***

3H-1,2-Dithiole-3-thiones (dithiolethiones) are a class of organosulfur compounds. Dithiolethiones are a well-known class of cancer chemopreventive agents, whose key mechanism of action involves activation of Nrf2 signaling and induction of Phase 2 enzymes. Oltipraz is by far the most extensively studied cancer chemopreventive agent among dithiolethiones. In vitro, garlic oil and extracts of individual organosulfur compounds strongly inhibit the bacterial growth of H. pylori (28).

Cruciferous Vegetables

The plant family Cruciferae (also called the mustard family or Brassicaceae) includes vegetables like broccoli, cauliflower, cabbage, Brussels sprouts and contain indoles and sulforophane, which has anticancer properties. Crucifers also contain a group of secondary metabolites called glucosinolates (GS) that are enzymatically hydrolyzed to produce nitriles, isothiocyanates, and thiocyanates that help protect against cancer by detoxification, protection against oxidative stress, tumor growth inhibition and apoptosis (29).

Spirulina (Blue -Green Microalgae)

It refers to the dried biomass of Arthrospira platensis, an oxygenic photosynthetic bacterium found worldwide in fresh and marine waters. Karkos *et al* (30) reported that 45% of their study cohort showed complete regression of leukoplakia after taking Spirulina supplements for 1 year.

Conclusion

Chemoprevention of oral precancers and cancers is the need of the hour today with the growing list of all types of carcinogen exposures. Studies on the blood levels of micronutrients in high risk populations have found deficiencies of multiple micronutrients. Therefore, it is not possible to point to one single nutrient as being responsible for the protective effect; rather, it is more likely that all nutrients play a role. The mechanism of action of these vitamins suggests a synergistic role. Total vegetable intake, green vegetable intake, cruciferous vegetable intake, yellow vegetable intake, total fruit intake, and citrus fruit intake have shown strong and consistent results.The associations for fruit intake have been

somewhat stronger than that for vegetable intake. This may be due to the fact that fruits are not cooked, so no loss of nutrients occurs. This discussion is limited to published English language articles; therefore, unpublished data and non-English language articles are excluded. This could lead to a biased view if the excluded studies had results systematically different from those reviewed. Also, different agents of chemoprevention cannot be evaluated completely due to their lack of complete research.

References

1. Goodin S, Shiff SJ. NSAIDs for the chemoprevention of oral cancer: Promise or Pessimism?*Clin Cancer Res* 2004;10(5):1561-64.
2. Messadi DV, Wilder-Smith P, Wolinsky L. Improving oral cancer survival: the role of dental providers. *J Calif Dent Assoc* 2009;37(11):789-98.
3. Shukla Y, Pal SK. Dietary cancer chemoprevention: An overview. *Int J Hum Genet* 2004; 4(4): 265-76.
4. Kim JW, Amin AR, Shin DM. Chemoprevention of head and neck cancer with green tea polyphenols. *Cancer Prev Res (Phila)* 2010;3(8):900-09.
5. Amin AR, Kucuk O, Khuri FR, Shin DM. Perspectives for cancer prevention with natural compounds. *J Clin Oncol* 2009;27(16):2712-25.
6. Liu RH. Potential synergy of phytochemicals in cancer prevention: mechanism of action. *J Nutr* 2004;134 (12 Suppl):3479-85.
7. Surh YJ. Cancer chemoprevention with dietary phytochemicals. *Nat Rev Cancer* 2003;3(10):768-80.
8. Greenwald P. From carcinogenesis to clinical interventions for cancer prevention. *Toxicology* 2001;166:37-45.
9. Schwartz JL. Biomarkers and molecular epidemiology and chemoprevention of oral carcinogenesis. *Crit Rev Oral Biol Med* 2000;11(1):92-122.
10. Tamimi RM, Lagiou P, Adami HO, Trichopoulos D. Prospects for chemoprevention of cancer. *J Intern Med* 2002;251(4):286-300.
11. Shetti A, Keluskar V, Aggrawal A. Antioxidants: Enhancing oral and general health. *JIAOMR* 2009;21(1):1-6.
12. Naidu KA. Vitamin C in human health and disease is still a mystery? An overview. *Nutr J* 2003;2:7.
13. Lee KW, Lee HJ, Surh YJ, Lee CY. Vitamin C and cancer chemoprevention: reappraisal. *Am J Clin Nutr* 2003;78(6):1074-8.
14. Ribeiro AS, Salles PR, da Silva TA, Mesquita RA. A review of the nonsurgical treatment of oral leukoplakia. *Int J Dent* 2010;13:12-15
15. Lamson DW, Plaza SM. The anticancer effects of vitamin K. *Altern Med Rev* 2003;8(3):303-18.
16. Hsu S, Singh B, Schuster G. Induction of apoptosis in oral cancer cells: agents and mechanisms for potential therapy and prevention. *Oral Oncol* 2004;40(5):461-73.
17. Richie JP Jr, Kleinman W, Marina P, *et al*. Blood iron, glutathione, and micronutrient levels and the risk of oral cancer. *Nutr Cancer* 2008;60(4):474-82.
18. Poh ZX, Goh KP. A Current Update on the Use of Alpha Lipoic Acid in the Management of Type 2 Diabetes Mellitus. *Endo Metabol & Immune Dis - Drug Targets* 2009,9(4): 392-98.
19. Donaldson MS. Nutrition and cancer: a review of the evidence for an anti-cancer diet. *Nutr J* 2004;13: 3-19.
20. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis.*OOOE* 2007;103(2):207-13.
21. Moon YJ, Wang X, Morris ME. Dietary flavonoids:Effects on xenobiotic and carcinogen metabolism. *Toxicology in Vitro* 2006;20:187-210.
22. Chen PN, Hsieh YS, Chiang CL, *et al*. Silibinin Inhibits Invasion of Oral Cancer Cells by Suppressing the MAPK Pathway.*J Dent Res* 2006; 85(3):220-25.
23. Wang LS, Stoner GD. Anthocyanins and their role in cancer prevention.*Cancer Lett* 2008;269(2): 281-90.
24. Rodrigo KA, Rawal Y, Renner RJ, *et al*. Suppression of the Tumorigenic Phenotype in Human Oral Squamous Cell Carcinoma Cells by an Ethanol Extract Derived From Freeze-Dried Black Raspberries. *Nutr Cancer* 2006 ; 54(1): 58-68.
25. Shukla S, Gupta S. Apigenin: A Promising Molecule for Cancer Prevention.*Pharm Res* 2010;27(6): 962-78.
26. Balasubramanian S, Eckert R. Keratinocyte proliferation, differentiation, and apoptosis - differential mechanisms of regulation by Curcumin, EGCG and apigenin.*Toxicol Appl Pharmacol* 2007; 224(3): 214-19.
27. Delmas D, Lançon A, Colin D, *et al*. Resveratrol as a Chemopreventive Agent: A Promising Molecule for Fighting Cancer. *Current Drug Targets* 2006; 7:1-18.
28. Zhang Y, Munday R. Dithiolethiones for Cancer Chemoprevention: Where Do We Stand? *Mol Cancer Ther* 2008;7(11): 3470-79.
29. Keck AS, Finley JW. Cruciferous Vegetables:Cancer Protective Mechanisms of Glucosinolate Hydrolysis Products and Selenium. *Integrative Cancer Therapies* 2004;3(1):5-12.
30. Karkos PD, Leong SC, Karkos CD, *et al*. Assimakopoulos, Spirulina in Clinical Practice: Evidence-Based Human Applications.*Eviden Based Complem Alternative Med* 2008;2011:1-4.