Nutrition and Oral Cancer: A Review

Varsha Sangle [1], Smita Chaware [2], Ashwini Biradar [3], Gauri Ugale [4]
[1] Reader, [2] Lecturer, [3] Reader, [4] Professor
[1,2] Dept of Oral Pathology and Microbiology, MIDSR Dental College, Latur.
[3] Dept of Public Health Dentistry, MIDSR Dental College, Latur.
[4] Dept of Periodontics and Implantology, MIDSR Dental College, Latur.

Abstract:
Cancer is a leading cause of death worldwide. Cancer is a result of multiple genetic defects resulting from exposure to environmental, dietary and infectious agents. About 35% of known cancers are associated with tobacco use and about 55% with inappropriate nutritional habits. Cancer can be prevented by increasing defense mechanism, inducing cancer cells to apoptosis, decreasing angiogenesis of cancer cells. Nutritional factors play a major role in cancer prevention. Increase intake of vegetables and fruits can prevent cancer. The present paper describes the significant role of diet in cancer prevention along with an elaborate overview of various mechanisms by which several active nutrient molecules intercept carcinogenesis.

Keywords: anterior Cancer, Environmental, Genetic defects, Nutrition.

Corresponding Author: Dr. Varsha Sangle, Reader, Dept of Oral Pathology and Microbiology, MIDSR Dental College, Latur. Email id.: dr.varshadhas@gmail.com

INTRODUCTION:

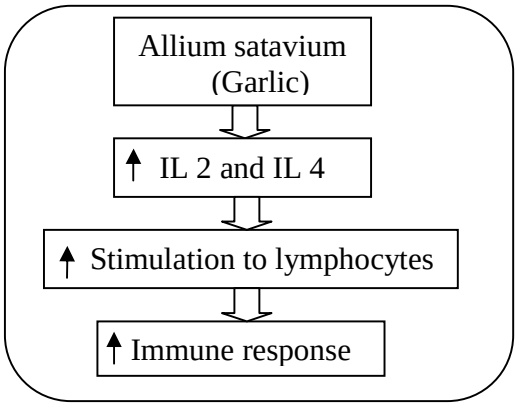
The benefits of a healthy, balanced diet on general health are well known. Since ancient times it is believed that certain foods are known to have components that enhance our immune system and thus effectively combat infections and other diseases.[1] The rising incidence of cancer is an alarming cause of concern in today's world. Cancer is the eventual outcome of the transformation of normal cells caused by DNA-reactive genotoxic carcinogens and the growth promotion of mutated cells by enhancing factors.[2] Many studies have consistently stated that abundant consumption of foods of plant origin, such as fruit, vegetables, whole grains, nuts, seeds, and tea, can decrease the risk of developing various cancers.[3] Some studies also suggest that vegetables provide an essential source of molecules with chemopreventive properties.[4]
Carcinogenesis is a multistep process that has check-point controls at each step. Thus the process of carcinogenesis can be intercepted at all these various levels by a variety of molecular events.[5] Different steps involved in carcinogenesis are initiation, promotion, progression, and growth. Initiation results from exposure to a carcinogen, which leads to the promotion of a normal cell to the cancer cell. These further advances to progression and growth of the cancer cells. These cancerous cells must accumulate several mutations in the genes involved in cell cycle arrest, resistance to apoptosis, and induction of angiogenesis to grow and invade the host tissues. The nutrients with their active components can act on genetic alterations occurring in cancer cells. They can also alter the regulation of apoptosis, cause cell cycle arrest, and control angiogenesis in tumor cells. Certain nutrients even restrict tumor growth potential.[1,6,7] The present paper describes the significant role of diet in cancer prevention and an elaborate overview of various mechanisms by which several active nutrient molecules intercept carcinogenesis.

Nutrients enhancing immune mechanism:

The immune system is the first line of defense in our body. Cancer occurs due to the formation of mutated cells; hence they are often encountered by the immune system (immune surveillance)[8] The nutrients such as β-carotene and α-tocopherol stimulate the immune cells like macrophages, mast cells, lymphocytes which in turn are responsible for the release of cytokines TNF- α and TNF- β. These chemical mediators identify cancer cells and destroy them by the apoptosis mechanism. β - carotene is present in broccoli, carrot, and a lesser amount in tomatoes, while α-tocopherol is present in cabbage and sweet potato.[6,8]

The extracts of *Allium sativum* (garlic) enhance the immune system significantly by stimulating the proliferation of lymphocytes by increasing IL-2 and IL-4 production.[9] Also, the garlic extract effects are seen with antioxidant activity or detoxification by binding to sulfur compounds in garlic. The mechanism of direct tumor cell inhibition has not yet been determined. Perhaps the most important action of garlic in the inhibition of cancer is by enhancing the immune response.[10,11]

Chart 1: Garlic causing an increased immune response.[9-11]



Nutrients modifying genetic alterations:

p53 is a tumor suppressor gene responsible for repairing damaged DNA at the G1 phase of the cell cycle. Mutation of this gene leads to the abnormal proliferation of cells with damaged DNA. The main cause of tumor progression is dysfunction of the *p53* gene resulting in uncontrolled check-points and failure in apoptosis of tumor cells.[6,7] Nutrients with phytochemicals like ellagic acid, β-carotenes, vitamin-E, and vitamin-C are responsible for the arrest of the dysfunctional *p53* gene. Ellagic acid is present in berries like raspberries, strawberries, and blackberries. Almonds are rich in vitamin E, and citrus fruits are a rich source of vitamin C.[1,6,7,8]

Nutrients regulating apoptosis:

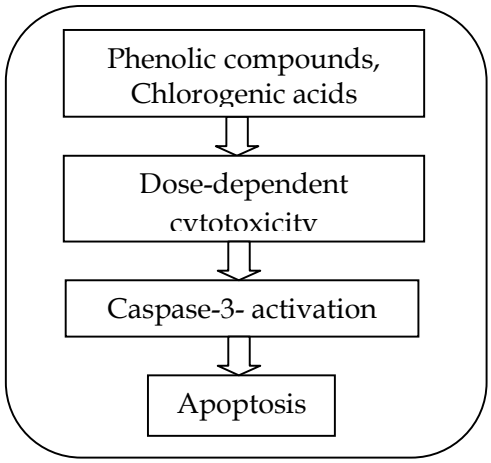
It is a known fact that dysregulated cell proliferation and apoptosis lead to cancer formation. The induction of apoptosis is one of the newest therapeutic concepts known to be effective against cancer cells. Many studies have been carried out that suggest apoptosis in cancer cells by using natural or synthetic agents.[7] At the molecular level, apoptosis takes place by two pathways. The intrinsic apoptotic pathway involves mitochondrial membrane permeabilization, the release of Cytochrome c into the cytosol, followed by activation of the caspase-3 mechanism, which acts as an executioner for cell death. Other pathway, i.e., the extrinsic pathway, is initiated by TNF-α and Fas ligand, which ultimately causes activation of the caspase-3 mechanism, which leads to cell death.[12]

Many studies suggest an absence of functional CKIs like p16, p21, p27, p57 found in oral squamous cell carcinoma. These CKIs are the regulators of apoptosis; studies show that overexpression of these CKIs such as p16, p21, p27, p57 results in induction of apoptosis. This mechanism is seen in the green tea users in which the active component epigallocatechin-3-gallate (EGCG) increases the expression of p21 and p27. This leads to cell cycle arrest and activation of the caspase-3 mechanism leading to apoptosis of tumor cells.[13,14]

Tomato is rich in various carotenoids. Lycopene is one of them. Carotenoids induce apoptosis through caspase-3activation.[15] Resveratrol present in grapes induces apoptosis and inhibits the growth of various human tumor cells, including oral squamous cell carcinoma.[16] The allyl-sulfur compounds derived from garlic have significant anti-proliferative activity against human cancers.[17,18] Phenolic compounds present in ginger, chlorogenic acid, which is a phenolic compound present in coffee, can induce caspase-3-dependent apoptosis in cancer cells.[7] Curcumin is a major active polyphenolic component

of turmeric (*Curcuma longa*). It is established that curcumin induces apoptosis in tumor cells via a *p53*-dependent pathway.[19] Luteolin, a flavonoid present in apple, carrots, and broccoli, kills cancer cells by inducing apoptotic cell death in many cancers like epidermoid carcinoma and leukemia.[20] Luteolin causes activation of caspase -8, 10, 9, and 3 mechanisms which lead to apoptosis by extrinsic pathway.[21] It also activates the intrinsic apoptosis pathway by inducing DNA damage and *p53* activation.[22,23]

Chart 2: Nutrition's causing apoptosis in cancer cells.[7]



Nutrients controlling angiogenesis:

Angiogenesis is the process that stimulates the formation of new blood vessel networks. This process is essential for tumor growth by providing oxygen and nutrients to developing tumor cells. It is a proven fact that tumors cannot grow beyond 1mm3 unless they are vascularized.[24] The key receptors involved in tumor angiogenesis are vascular endothelial growth factor receptor-2 and platelet-derived growth factor receptor.

Nutrients like phytochemicals have strong anti-angiogenic activity against the tumor cells. Epigallocatechin-3-gallate (EGCG), an abundant polyphenol found in green tea, inhibits vascular endothelial receptor-2 and has an anti-angiogenic property.[25] Ellagic acid, a phenolic acid found in fruits like raspberries, strawberries, and grapes, and also delphinidin, an anthocyanidin in blueberries, block vascular endothelial growth factor receptor-2 activity as well as strongly inhibits platelet-derived growth factor receptor activity. This combined inhibitory effect leads to inhibition of angiogenesis of tumor cells.[26, 27]

Luteolin, a flavonoid, is known to be a potent angiogenesis inhibitor. Luteolin causes suppression of VEGF secretion, causing an anti-angiogenesis effect.[28] Tumor angiogenesis is dependent on the activity of MMP-9.[29] Luteolin may cause an anti-angiogenic effect via suppression of MMPs.[30]

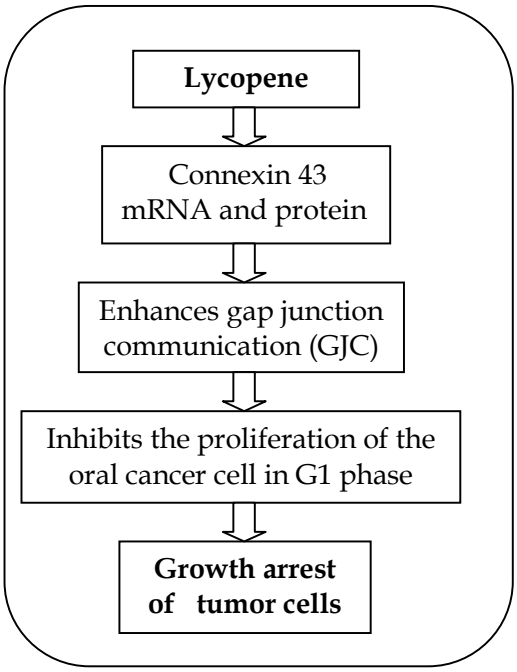
Nutrients causing cell cycle arrest:

Cell cycle arrest of cancer cells leads to the growth arrest of tumor cells. Studies suggest that EGCG present in green tea induces G0/G1- phase cell cycle arrest in human epidermoid carcinoma cells, inhibiting proliferation and inducing apoptosis in many cancer cells.[31-33]

Organo-sulfur compounds called isothiocyanates found in papaya restore the cell cycle to eliminate cancer. Isothiocyanates can inhibit both the formation and development of cancer cells through multiple pathways and mechanisms.[34] Flavonoids have been found to inhibit the proliferation of many cancer cells by arresting cell cycle progression either at the G1/S or G2/M check-points.[35,36] The G1 cell cycle arrest induced by luteolin is associated with the inhibition of CDK2 activity. This arrest is achieved by up-regulation of the CDK inhibitors p27/kip1 and p21/waf1, or direct inhibition of CDK2 activity.[37, 38]

The nutrient lycopene acts as an antioxidant, which traps the ROS and reduces oxidative damage to lipids, proteins, and DNA by lowering oxidative stress. Studies show that lycopene inhibits the proliferation of tumor cells and enhances their gap junction communication (GJC).[39] The gap junctions are water-filled pores allowing an exchange of low molecular weight compounds. Lycopene enhances GJC by increasing levels of connexin-43 mRNA and protein, a major gap junction protein. There is decreased expression of connexins-43 in human tumors compared to normal tissue. Hence increased GJC may reverse the malignant process in carcinogenesis.[7,39] Lycopene is present in abundance in tomatoes, apricots, papaya, and yellow pigmented fruits.[40]

Chart 3: Lycopene causing an anticarcinogenic effect.[7,39]



Allyl sulfur compounds present in garlic and onion can slow or prevent the growth of tumor cells. These compounds make cells vulnerable to the stress-created by-products of cell division. As cancer cells divide rapidly, they create more stress compared to normal cells. Hence cancer cells are damaged by the presence of allyl sulfur compounds.[41] Lau *et al.* stated that *Allium sativum* extracts have anti-tumor activity in sarcomas, squamous cell carcinomas, and mammary carcinomas.[42]

Table no 1- Showing different food with their active components causing anticarcinogenic effect.

Food	Active components	Anticarcinogenic activity	References
Apple , cabbage, carrrot	Luteolin (Flavonoids)	Apoptosis in tumor cells and restricts angiogenesis to tumor cells	20
Broccoli	β - carotene	A potent immune response against cancer cells	6,7,8
Blackberries	An anthocyanidin	Growth arrest of cancer cells by antiangiogenic effects	6,7,8
Grapes	Rasveratrol	pro-apoptotic activity against tumour cells	6,7,16
Green Tea	Epigallocatechin-3-gallate (EGCG)	Apoptosis in tumour cells and growth arrest of tumor cells.	13,14
Ginger	Phenolic compounds	Apoptosis in tumour cells	7
Onion, Garlic	Allyl sulphur compounds	Apoptosis in tumour cells and antiproliferate activity against human cancers and toxic to cancer cells.	10,11, 19,41
Papaya	Isothiocyanide	Restore the cell cycle to eliminate cancer	34
Raspberries	Ellagic acid, (a phenolic acid)	Growth arrest of cancer cells by inhibition of angiogenesis of tumour cells	26,27
Strawberries	Delphinidin,	Growth arrest of cancer cells by blocking angiogenic factors	26,27
Sweet potatoes	β - carotene	A potent immune response against cancer cells	6,7,8
Tomatoes	Lycopene	Inhibites the tumour growth and can reverse the carcinogenesis process	15
Turmeric	Curcumin	Induces apoptosis in tumor cells	19

SUMMARY:
Many studies indicate that abundant consumption of food of plant origin reduces the risk of cancer. The chemopreventive effect is related to the high content of nutrients like phytochemicals, lycopene, phenolic compounds, β-carotene, flavonoids, etc. These foods have a potent anticancer property. Thus, the present paper is a compilation of various nutrients and their effect in preventing cancer progression.

REFERENCE

1. Hiroyuki Tsuda, Yutaka Ohshima, Hiroshi Nomoto et al. Cancer prevention by natural compounds. Drug Metab.Pharmacokin.19(4):245-263(2004)
2. Weisburger JH. Antimutagens, anticarcinogens and effective worldwide cancer prevention. J Environ Pathol Toxicol Oncol. 1999; 18: 85 – 93
3. Nasim Taghavi, Ismail Yazdi. Type of food and risk of oral cancer. Archives of Iranian Medicine, vol. 10, No.2, April2007.
4. Lee W. Wattenberg. Chemoprevention of cancer. Cancer Research 45, 1-8, January 1985.
5. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70
6. Richard Beliveau, Denis Gingras. Role of nutrition in preventing cancer. *Canadian Family Physician,November 2007, vol.53,no.11,* 1905-1911.
7. Stephen Hsu, Baldev Singh, George Schuster. Induction of apoptosis in oral cancer cells: agents and mechanisms for potential therapy and prevention. Oral Oncology (2003)01-13.
8. Manveen K Jawanda. Antitumor activity of antioxidants – an overview. International journal of dental clinics volume 1, issue 1, oct-dec 2009.
9. S.Ejaz,L.C.Woong,A.Ejaz.Extracts of garlic (ALLIUM SATIVUM) in cancer chemoprevention; Experimental Oncology 25, 93-97,2003(june)
10. Suby Oommen, Ruby John Anto, Gopal Srinivas etal.Allicin (from garlic) induces caspase-mediated apoptosis in cancer cells; European Journal of Pharmacology 485 (2004) 97– 103
11. Abdullah TH, Kandil O, Elkadi S, Carter J. Garlic revisited: therapeutic for the major diseases of our times? J Nat Med Assoc 1998;80:439-4
12. Vijay Kumar, Abul K.Abbas,Nelson Fausto etal. Robbins Basic pathology. 8th edition, pages 19-22.
13. Stephen HSU, Jill Lewis, Baldev Singh.Green tea polyphenol targets the mitochondria in tumor cells inducing caspase3-dependent apoptosis.Anticancer Research 23:1553-1540(2003).
14. Masahito Shimizu, Yohei Shirakami, Hisataka Moriwaki.Targeting Receptor Tyrosine Kinases for Chemoprevention by Green Tea Catechin, EGCG; Int. J. Mol. Sci. 2008, 9, 1034-1049
15. Paola Palozza, Simona Serini, Fiorella Di Nicuolo. Modulation of apoptotic signalling by carotenoids in cancer cells; Arch Biochem Biophys. 2004 Oct 1;430(1):104-9
16. Elattar T, Virji A. The effect of red wine and its components on growth and proliferation of human oral squamous carcinoma cells. Anticancer Res 1999; 19:5407
17. Pinto J, Rivlin R. Antiproliferative effects of allium derivatives from garlic. J Nutr 2001;131:1058S
18. Knowles L, Milner J. Possible mechanism by which allyl sulfides suppress neoplastic cell proliferation. J Nutr 2001;131:1061S
19. Annapurna A, Suhasin G, Raju B Akondi et al. Anti-cancer activity of Curcuma longa linn.(Turmeric); Journal of Pharmacy Research 2011,4(4),1274-1276
20. Cheng A-C, Huang T-C, Lai C-S, Pan M-H. Induction of apoptosis by luteolin through cleavage of Bcl-2 family in human leukemia HL-60 cells. *Eur. J. Pharmacol.* 2005;509:1–10
21. Horinaka M, Yoshida T, Shiraishi T, Nakata S, Wakada M, Nakanishi R, Nishino H, Matsui H, Sakai T. Luteolin induces apoptosis via death receptor 5 upregulation in human malignant tumor cells. *Oncogene.* 2005;24:7180–7189.
22. Plaumann B, Fritsche M, Rimpler H, Brandner G, Hess RD. Flavonoids activate wild-type p53. Oncogene. 1996;13:1605–1614.
23. Shi R, Huang Q, Zhu X, Ong YB, Zhao B, Lu J, Ong CN, Shen HM. Luteolin sensitizes the anticancer effect of cisplatin via c-Jun NH2-terminal kinase-mediated p53 phosphorylation and stabilization. Mol. Cancer Ther. 2007;6:1338–1347

24. Francesca Tosetti, Nicoletta Ferrari, Silvio De Flora et al.'Angioprevention: angiogenesis is a common and key target for cancer chemopreventive agents. The FASEB Journal.2002;16:2-14.
25. Sylvie Lamy, Denis Gingras, Richard Beliveau. Green tea catechins inhibit vascular endothelial growth factor receptor phosphorylation.Cancer Res January 15,2002.62;381.
26. Lyne Labrecque, Sylvie Lamy, Amelie Chapus. Combined inhibition of PDGF and VEGF receptors by ellagic acid, a dietary-derived phenolic compound. Carcinogenesis (2005) 26(4): 821-826.
27. Sylvie Lamy, Melanie Blanchette, Jonathan Michaud-Levesque et al. Delphinidin, a dietary anthocyanidin, inhibits vascular endothelial growth factor receptor-2 phosphorylation. Carcinogenesis(may 2006) 27(5):989-996.
28. Bagli E, Stefaniotou M, Morbidelli L, Ziche M, Psillas K, Murphy C, Fotsis T. Luteolin inhibits vascular endothelial growth factor-induced angiogenesis; inhibition of endothelial cell survival and proliferation by targeting phosphatidylinositol 3′-kinase activity. *Cancer Res*. 2004;64:7936–7946
29. Deryugina EI, Quigley JP. Matrix metalloproteinases and tumor metastasis. *Cancer Metastasis Rev*. 2006;25:9–34
30. Chithan Kanadaswami, Lung-Ta Lee, Ping-Ping H Lee et al. The Antitumor Activities of Flavonoids; in vivo 19: 895-910 (2005)
31. Ahmad N, Feyes DK, Nieminen AL, Agarwal R, Mukhtar H. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. J Natl Cancer Inst 1997;89:1881-6.
32. Lepley DM, Li B, Birt DF, Pelling JC. The chemopreventive flavonoid api-genin induces G2/M arrest in keratinocytes. Carcinogenesis 1996; 17: 2367-75.
33. Ahmad N, Cheng P, Mukhtar H. Cell cycle dysregulation by green tea polyphenol epigallocatechin-3-gallate. Biochem Biophys Res Commun 2000;275:328-34.)
34. Bianchini F, Vainio H.Isothiocyanates in cancer prevention. Drug Metab Rev. 2004 Oct;36(3-4):655-67
35. Günter Seelinger 1, Irmgard Merfort 2, Ute Wölfle Anti-carcinogenic Effects of the Flavonoid Luteolin; Molecules 2008, 13, 2628-2651
36. Lindenmeyer F, Li H, Menashi S, Soria C, Lu H. Apigenin acts on the tumor cell invasion process and regulates protease production. Nutr. Cancer. 2001;39:139–147.)
37. Casagrande F, Darbon JM. Effects of structurally related flavonoids on cell cycle progression of human melanoma cells: regulation of cyclin-dependent kinases CDK2 and CDK1. Biochem. Pharmacol. 2001;61:1205–1215
38. Diane F. Birt, Suzanne Hendrich, Weiqun Wang.Dietary agents in cancer prevention: flavonoids and isoflavonoids. Pharmacology & Therapeutics 90 (2001) 157– 177
39. Adetayo O. Omoni, Rotimi E. Aluko. The anti-carcinogenic and anti-atherogenic effects of lycopene: a review. Trends in food science and Technology; volume16, issue8, August2005, pages 344-350.
40. Levy J, Bosin E, Feldman B et al. Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene.Nutr Cancer.1995;24(3):257-66.
41. Weisberger AS, Pensky J. Tumor inhibition by a sulfhydryl-blocking agent related to an active principle of garlic(Allium sativum). Cancer Res.1958;18:1301-8
42. Lau BHS, Tadi PP, Tosk JM. Allium sativum(garlic) and cancer prevention. Nutr Res 1990;937-48.