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Review Article

Dietary Antioxidants: True Fighters against Oxidative Stress Induced Cancer

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ABSTRACT

Abnormal activation or silencing of mitogen activated protein kinase (MAPK) pathways, protein kinase C (PKC) and phosphatidyl inositol -3- kinase (PI3k) result in uncontrollable cell growth which leads to translation of normal cells to cancer cells. Many phytochemical chemo preventive agents are capable of controlling these enzymes and preventing abnormal cell growth and proliferation. Diets rich in fruits and vegetables are gaining increased importance due to their significant role in reducing the risk of degenerative diseases such as cancer, cardiovascular diseases and other chronic diseases. This review summarize current information on different groups of dietary antioxidants and their possible role in chemo-prevention of most important human cancers.

Key words: *Free radicals, Dietary antioxidants, Chemo preventive agents.*

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INTRODUCTION

Oxidative stress is a physiological state where high levels of reactive oxygen species (ROS) and free radicals are generated. Several signaling pathways associated with carcinogenesis can additionally control ROS generation and regulate ROS downstream mechanisms, which could have potential implications in anticancer research. Various cellular targets affected by oxidative stress include DNA, phospholipids, proteins and carbohydrates on the cell membrane. Oxidized and injured DNA has the potential to induce genetic mutation. The body makes some of the antioxidants it uses to neutralize free radicals. These antioxidants are called endogenous antioxidants. However, the body relies on external (exogenous) sources, primarily the diet, to obtain the rest of the antioxidants it needs. These exogenous antioxidants are commonly called dietary antioxidants. Fruits, vegetables, and grains are rich sources of dietary antioxidants. Some dietary antioxidants are also available as dietary supplements.[1]

The present study aims to discuss various mechanisms through which dietary antioxidants controls generation of cancer and tumor progression. The main objective of this review is to provide detailed information on various classes of antioxidant phytochemicals present in fruits and vegetables and their role in chemoprevention.

Oxidative stress induced Carcinogenesis:

Oxidative stress is defined as a discrepancy between production of free radicals and reactive metabolites, so-called oxidants or reactive oxygen species (ROS), and their eradication by defending mechanisms, referred to as antioxidants. This disparity leads to damage of important biomolecules and cells, with potential impact on the whole organism. During endogenous metabolic reactions, aerobic cells produce ROS such as superoxide anion (O^{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\cdot}$), and organic peroxides as normal products of the biological reduction of molecular oxygen. Proteins and lipids are also significant targets for oxidative attack, and modification of these molecules can increase the risk of mutagenesis.[2,3,4]

Relationship between Oxidative stress and Carcinogenesis:

Active oxygen may be involved in carcinogenesis through two possible mechanisms: (1) the induction of gene mutations that result from cell injury and (2) the effects on signal transduction and transcription factors.[5,6] Cellular targets affected by oxidative stress include DNA, phospholipids, proteins, and carbohydrates on the cell membrane. Oxidized and injured DNA has the potential to induce genetic mutation.[7,8]

Reactive oxygen species are considered to be a pro-neoplastic factor as they stimulate proliferation, invasiveness, angiogenesis and metastasis, and inhibit apoptosis.[9,10,11] They are able to stimulate development of a neoplasm in the promotion stage through influencing genes related to apoptosis and proliferation. As a result of 'an attack' of free radicals, the concentration of Ca2 + ions increases within the intracellular area, which results in activation of proto-oncogenes such as c-fos, c-jun, c-myc or activated protein kinase C (PKC). That, in turn, intensifies proliferation and speeds up the carcinogenesis.[12,13,14] High concentrations of ROS and their derivatives influence activation of transcription factors including NF-kB, which results in induction of cytokine gene expression and of growth factors. That leads to intensified proliferation of cells and occurrence of neoplastic lesions in otherwise healthy tissue. [13,15,16]. Reactive oxygen species also influence activity of proteins involved in the cell cycle, such as p53 protein[15]. If there is no oxidative stress or after a period of mild stress, p53 activity is related to the antioxidant response of the cell through activation of transcription of MnSOD and GPx1 coding genes. High levels of production of reactive oxygen species may also cause increased activity of p53 protein.[17]

Mechanisms of phytochemicals in chemoprevention:

In abnormal activation or silencing of mitogen activated protein kinase (MAPK) pathways, protein kinase C (PKC) and phosphatidyl inositol -3- kinase (P13k) result in uncontrollable cell growth which leads to translation of normal cells to cancer cells. Many phytochemical chemo preventive agents are capable of controlling these enzymes and preventing abnormal cell growth and proliferation.[18,19]

Free radicals, inflammatory cytokines, and cancer causing agents activate and release nuclear factor-kappa B (NF-kB). Then the released NF-kB is transferred to the nucleus. In the nucleus NF-kB binds and expresses genes that prevents normal cell death and causes abnormal cell multiplications, invasion, inflammation and metastasis in the cells.[20,21]

Activator protein 1 (AP 1) is a heterogeneous set of dimeric protein consisting of transcription factors c-JUN and c-FOS are caused by tumor necrosis factor (TNF), interleukin 1 (IL-1) and environmental stress. Its stimulation is associated with control of cell development, inflammation and cell damage. Research has shown that it controls genes involved in apoptosis, cell adjustment, integration and multiplication, and causes cancer and tumor progression. The primary site of many

phytochemical chemopreventive agents such as curcumin, gingerol, capsaicin, epigallocatechin gallate, genistein and resveratrol is NF-kB and AP1.[1,21]

DIETARY ANTIOXIDANTS

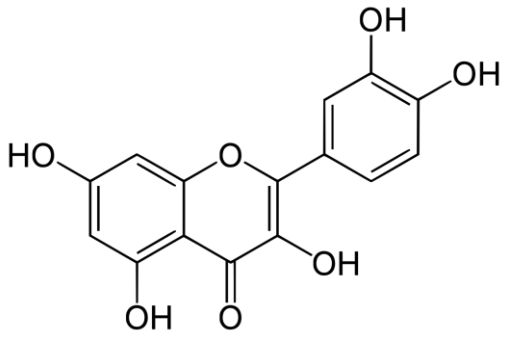
Diet rich in fruits and vegetables are gaining increased importance due to their significant role in reducing the risk of degenerative diseases such as cancer.

The Major Classes of antioxidant phytochemicals are given below:

1. Polyphenols
2. Terpenoids
3. Caroteniods
4. Organosulfur compounds
5. Isothiocyanates
6. Indole Compounds
7. Phytosterols

Some selected phytochemical chemo preventive agents from the above classes are described below:

Quercetin: It (3, 3', 4', 5, 7 – pentahydroxy flavone) belongs to an extensive class of polyphenolic flavonoid compounds almost ubiquitous in plants and plant food sources. Frequently quercetin occurs as glycosides e.g., rutin in which the hydrogen of the R-4 hydroxyl group is replaced by a disaccharide. Presently, the oral use of quercetin appears safe and possibly useful in cancer patients.[22]



Major molecular mechanisms of action:

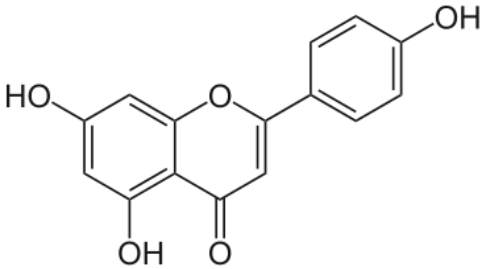
Down regulation of mutant p53 protein: Quercetin was found to down regulate expression of mutant p53 protein to nearly undetectable levels in human breast cancer cell lines. The inhibition of expression of p53 was found to arrest the cells in the G2-M phase of the cell cycle. Mutations of p53 are among the most common genetic abnormalities in human cancers.

G1 Phase Arrest: Quercetin has been found to arrest human leukemic T-cells in the late G1 phase of the cell cycle.

Tyrosine kinase inhibition: Tyrosine kinases are group of proteins located in or near the cell membrane involved in the transduction of growth factor signals to the nucleus. In patients with advanced cancers, intravenous administration of quercetin (dosages 60-1700 mg) led to inhibition of lymphocyte tyrosine kinase. Quercetin was the first tyrosine kinase inhibiting compound tested in a human phase I trial.

Estrogen receptor binding capacity: Quercetin has been shown to induce type II estrogen receptor(ER II) expression in estrogen receptor human breast cancer cells. The induction of ER II allows for greater growth inhibition of ER cells with quercetin treatment. In cultured human melanoma cells, quercetin was found to bind ER II sites with an affinity similar to tamoxifen and diethylstilbestrol.[23]

Apigenin: It is a naturally occurring plant flavone (4', 5, 7,-trihydroxyflavone) abundantly present in common fruits and vegetables. The common sources are parsley, celery, rosemary, oregano, thyme, basil, coriander, chamomile, cloves, peppermint, red wine and licorice.

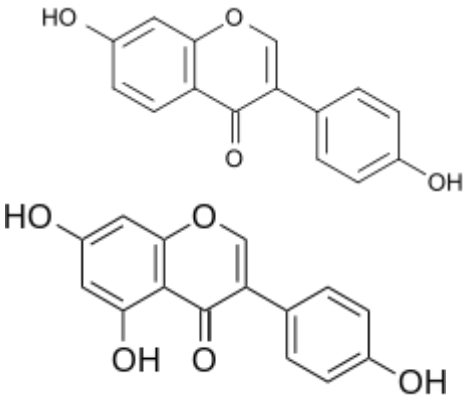


Apigenin has been shown to possess remarkable anti-inflammatory, antioxidant and anti-carcinogenic properties. Laboratory studies have demonstrated that apigenin promotes metal chelation, scavenges free radicals, and stimulates phase II detoxification enzymes in cell culture and in *in vivo* tumor models. Exposure to apigenin prior to a carcinogenic insult has been shown to afford a protective effect in murine skin and colon cancer models. Apigenin is a strong inhibitor of ornithine decarboxylase, an enzyme that plays a major role in tumor promotion. In addition, apigenin has been shown to increase the intracellular concentration of glutathione, enhancing the endogenous defense against oxidative stress.

The anti-carcinogenic effects of apigenin have been demonstrated in a skin carcinogenesis model. Topical application of apigenin inhibited dimethyl benzanthracene-induced skin tumors. In addition, apigenin administration diminished the incidence of UV light-induced cancers and increased tumor free survival in similar experiments.[24]

Genistein: Isoflavones such as genistein & daidzein are isolated from Soya beans. These are the fully ripe seeds of the plant *Glycene soya* and *Glycine*

max belonging to the family *Leguminosae*. *Glycine max* inhibit growth & spread of various cancers such as cancers of the breast, uterus, cervix, ovary, lung, stomach, colon, pancreas, liver, kidney, urinary bladder, prostate, testis, oral cavity, larynx, and thyroid. *Glycine max* is also effective in nasopharyngeal carcinoma, skin cancer, malignant lymphoma, rhabdomyosarcoma, neuroblastoma, malignant brain tumors and leukemia.



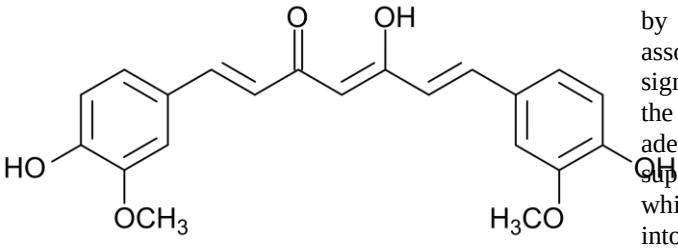
Diadzein

Genistein

Genistein targets many cellular proteins like extracellular signal-regulated kinase 1/2 (ERK1/2), nuclear transcription factor kappaB (NF-kB), mitogen-activated protein kinase (MAPK) and phosphoinositide 3 kinase (PI3K) that can attribute to its anticancer therapeutic effect.[25,26]

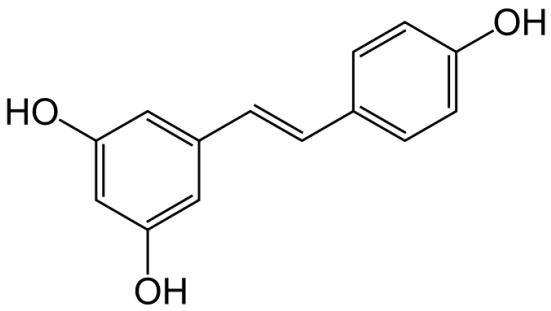
Curcumin: It (Di-feruloyl-methane) and curcuminoids isolated from Turmeric. It consists of dried as well as fresh rhizomes of *Curcuma longa* belonging to the family *Zingiberaceae*.

Curcuma longa suppress cancer at every step, i.e. initiation, growth and metastasis. Curcumin inhibits growth & spread of various cancers including that of breast, lung, esophagus, liver, colon, prostate, head & neck and skin.



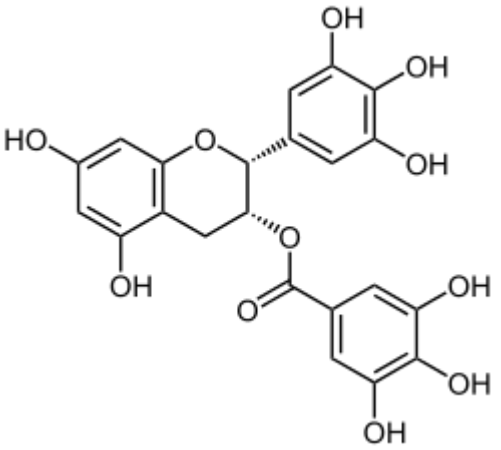
It inhibits angiogenesis, a crucial step in the growth and metastasis of cancer. Curcumin act synergistically to inhibit growth & spread of estrogen-positive breast cancer. Curcumin works even in multidrug-resistant breast cancers. It reduces NF-kB activity, regulated by PAK1, leading to decreases in cell proliferation by reducing the mRNA and protein expression of cyclin D1 and suppresses cell cycle progression from the G1 to S phases. Therefore, curcumin inhibits the proliferation and invasion of various cancer cells.[27] Curcumin suppresses adhesion of cancer cells, thus preventing metastasis. Curcumin is particularly effective in radiotherapy-resistant prostate cancer. Curcumin is effective even in advanced stages of cancer. Curcumin also protects from stomach cancer and colon cancer. Curcuma longa also possesses antimutagenic, antioxidant, immunostimulant, anti-inflammatory, hepatoprotective and radioprotective properties.[27,28]

Resveratrol: It (3, 5, 4'-trihydroxy-trans-stilbene), a polyphenol derived from red grapes, berries, and peanuts is an excellent scavenger of hydroxyl, superoxide and other radicals. It also protects against lipid peroxidation in cell membranes and DNA damage caused by reactive oxygen species generation Resveratrol was further demonstrated to be an anti- tumor and chemo preventive agent; and found to affect cellular proliferation through its action on tumor initiation, promotion, and progression.[29]



Resveratrol inhibits cell cycle progression of nitrosamine-stimulated KATO-III and RF-1 cells by inducing cell cycle arrest in the G0/G1 phase through inhibiting kinase C-mediated mechanisms and induces apoptotic cell death in various adenocarcinoma cell lines[30,31] Another mechanism by which resveratrol regulates cell proliferation is associated with the MEK1/2-ERK1/2-c-Jun signaling cascade, a critical signaling pathway in the proliferation and growth of human adenocarcinoma cells. Resveratrol was found to suppress the phosphorylation of MEK1/2-ERK1/2, which subsequently inhibits translocation of c-Jun into the nuclear compartment, leading to inhibition of cell proliferation.[32]

Epigallocatechin Gallate (EGCG): It is an anti-oxidant polyphenol flavonoid isolated from green tea (prepared leaves and leaf buds of *Thea sinensis* belonging to the family *Theaceae)*. Epigallocatechin gallate (EGCG), also known as epigallocatechin-3-gallate, is the ester of epigallocatechin and gallic acid, and is a type of catechin.[33]

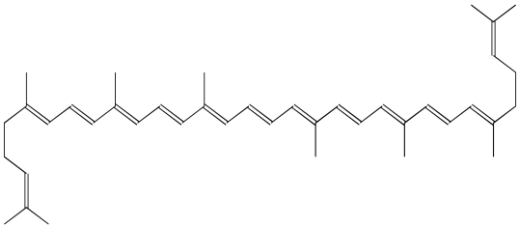


EGCG is a potent antioxidant that may have therapeutic applications in the treatment of many disorders (e.g. cancer). It is found mainly in white tea, green tea and, in smaller quantities, black tea; during black tea production, the catechins are mostly converted to theaflavins and thearubigins, and theabrownins. It is also found in various vegetables, nuts, as well as carob powder at 109 mg per 100g. In a high temperature environment, an epimerization change is more likely to occur; however as exposure to boiling water for 30 minutes leads to only a 12.4% reduction in the total amount of EGCG, the amount lost in a brief exposure is insignificant. There is evidence from rodent and *in vitro* studies that EGCG may be useful in preventing or treating various gastrointestinal, prostate and other cancers. However the dose needed for effectiveness is high, (far higher than is obtainable through drinking tea) and so companies and academic groups have focused on developing novel analogs or combinations to improve the potential for EGCG to be useful in treating or preventing cancer.

Its possible benefit as a nutritional chemopreventive agent for cancer, atherosclerosis, and neurodegenerative diseases is generating increased scientific interest. EGCG has demonstrated chemopreventive and chemotherapeutic actions in cellular and animal models of cancer.

- EGCG selectively induces apoptosis in human carcinoma cell lines.
- It inhibits MAP kinase mediated signaling pathways.[34,35]
- EGCG blocks the activation of EGF receptors and HER-2 receptors which are over-expressed or constitutively active in many human malignancies.
- It interferes with angiogenesis by suppressing VEGF activity.
- EGCG inhibits telomerase and DNA methyltransferase, two enzymes involved in cancer gene expression and cellular immortality.[36,37]

Lycopene: A member of the carotenoid family of phytochemicals is a lipid soluble antioxidant that is synthesized by many plants and microorganisms but not by animals and human. Tomatoes and tomato-based foods account for more than85% of all the dietary sources of lycopene.

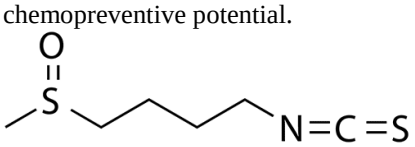


It is a highly unsaturated open straight chain hydrocarbon consisting of 11 conjugated and 2 unconjugated double bonds. It is responsible for the red color of many fruits and vegetables such as the tomatoes. Because of the presence of double bonds in the structure of lycopene, it can exist in both the *cis* and *trans* isomeric forms. In nature, lycopene is present primarily in *trans* isomeric form .It is a highly stable molecule.

The antioxidant property of lycopene has been the main focus of research to study its biological role. However, it has also been shown to exert its effect via other mechanisms that include gene function regulation, gap-junction communication, hormone and immune modulation, carcinogen metabolism and metabolic pathways involving phase II drug-metabolizing enzymes of all the cancers.

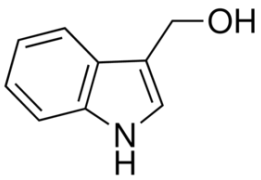
The role of lycopene in the prevention of prostate cancer has been studied the most. Different studies showed that lycopene intake as well as serum lycopene levels were inversely related to several cancers including prostate, breast, cervical, ovarian, liver and other organ sites. Several other studies since then demonstrated that with increased intake of lycopene and serum levels of lycopene the risk of cancers were reduced significantly. Other than prostate cancer there is now growing evidence in support of the protective role of lycopene in cancers of other sites including breast, lung, gastro intestinal, cervical, ovarian and pancreatic cancers. Tissue culture studies using human cancer cell lines have shown that their growth is inhibited significantly in the presence of lycopene in the growth media.[38]

Sulforaphane: It is a molecule within the isothiocyanate group of organosulfur compounds. It contains the typical NCS group has huge cancer chemopreventive potential.



Sulforaphane occurs in plants bound to a sugar molecule: sulforaphane glucosinolate. Sulforaphane glucosinolate is found in cruciferous vegetables such as broccoli, cauliflower, cabbage and kale. The richest source of sulforaphane are broccoli sprouts.
There is a positive correlation between the general consumption of cruciferous vegetables and the decreased incidence of some cancers including non-Hodgkin's lymphoma, liver, prostate, cervical, ovarian, lung, and gastrointestinal tract. Oral administration of sulforaphane inhibited or retarded experimental multistage carcinogenesis models including cancers of the breast, colon, stomach, and lung. Previously, these anticancer effects were attributed to modulation of carcinogen metabolism by the inhibition of metabolic activation of phase I enzymes and the induction of phase II detoxification enzymes and glutathione (GSH) levels. It modulates cell death, cell cycle, angiogenesis, susceptibility to carcinogens, invasion and metastasis and possesses antioxidant activities. It functions as an inhibitor of phase I enzymes and also as an inducer of phase II detoxification enzymes through different ways. NF-E2- related factor-2(Nrf-2), as well as mitogen-activated protein kinase (MAPK), is regulated by SFN. [39,40]

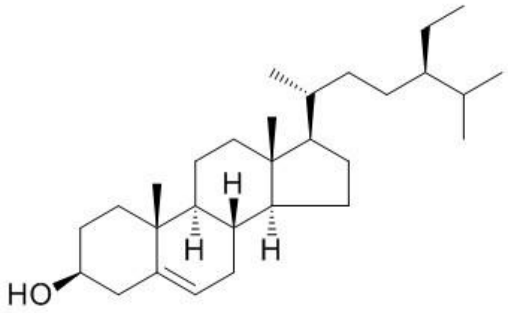
Indole-3-carbinol: Cruciferous vegetables contain indole-3-glucosinolate, which during metabolism yields indole-3-carbinol (I3C) and dimeric product 3, 3′-diindolylmethane (DIM).



It is an indole derivative which has shown to inhibit cell proliferation and induce apoptosis in prostate cancer cells. The mechanisms through which indole -3- carbinol exerts its anticarcinogenic effects include modulations in cell cycle regulatory proteins and inhibition of cell survival pathways (PI3K/Akt) and NF-kB transcription factor (Further, it has been shown that indoles are strong androgen antagonists and that they inhibit PSA production in human prostate cancer cells. These findings suggest that dietary indoles are useful in the chemoprevention of prostate cancer.

Indole-3-carbinol blocks estrogen receptor sites on the membranes of breast and other cells, thereby reducing the risk of cervical and breast cancer. Indole-3-carbinol increases the ratio of 2-hydroxyestrone to 16 alpha-hydroxyestrone and inhibits the 4-hydroxylation of estradiol. This is a favorable action of indole-3-carbinol because 16 alpha-hydroxyestrone and 4-hydroxyestrone have carcinogenic action. The estrogen metabolite 2-hydroxyestrone has protective against several types of cancer. Studies with animals have demonstrated that indole-3-carbinol reduced the carcinogenic effects of aflatoxins.[41]

β-sitosterol (SIT): It is one of several phytosterols (plant sterols) with chemical structures similar to that of cholesterol.



Sitosterols are white, waxy powders with a characteristic odor. They are hydrophobicand soluble in alcohols. It is found in pecans, avocados, *Cucurbita pepo* (pumpkin seeds), cashew fruit, rice bran, wheat germ, corn oils, soybeans and dandelion coffee.

β-Sitosterol is recognized as a valuable component of diet that possesses anticancer effects due to its interaction with various cellular targets and pathways. β-Sitosterol may inhibit P-glycoprotein, a membrane transporter encoded by the MDR1 gene in human cells mediating drug efflux. P-glycoprotein plays a key role in the phenomenon of multidrug resistance (MDR) due to the cellular efflux of anticancer therapeutics from human cancer cells. MDR is in many cases responsible of an unsuccessful chemotherapy as a result of MDR in cancer.[42]

β-sitosterol, β-sitosterol glucoside or a mixture of these two compounds modulate the growth of estrogen-responsive breast cancer cells. Additionally, expression of the antiapoptotic marker bcl-2 in tumors was downregulated.[43]

CONCLUSION

Diets rich in fruits and vegetables are gaining increased importance due to their significant role in reducing the risk of chronic diseases such as cancer. Researches have shown that dietary antioxidants like quercetin, apigenin, genistein, curcumin, resveratrol, epigallocatechin gallate, lycopene, sulforaphanes, indole-3-carbinols and β-sitosterol controls generation of cancer and tumor progression through their interaction with various cellular targets and pathways. The primary site of these chemopreventive agents is NF-kB, MAPK and

AP1. The link between cancer and diet is just as mysterious as the disease itself. Much research has pointed toward certain foods and nutrients that may help to prevent certain types of cancer. No single phytochemical or food can protect from cancer or any other disease. But taking a varied diet with lots of fruits, vegetables, beans and whole grains does seem to offer the most protection, based on existing evidence. In fact, estimates suggest that less than 30% of a person's lifetime risk of getting cancer results from uncontrollable factors. The rest we have the power to change, including the diet.

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REFERENCES

1. Pandey K.B and Rizyi S.I. Plant polyphenols as dietary antioxidant in human health and disease. Oxid Med Cell Longev. 2009; 2(5): 270-8.
2. Shobha R.I and Andallu B. Oxidative Stress and Cancer: Role of Anti- Carcinogenic Herbs and Spices. American J Phytomed. 2013; 1(3):351-69.
3. Birben E, Sahiner U.M. et al, Oxidative Stress and Antioxidant Defense. World Allergy Organ J. 2012; 9-16.
4. Levi A, Maria C.F. and Alvaro G. Reactive nitrogen species in cellular signalling. Exp biol med. 2015; 240(6):711-17.
5. Khansari N, Shakiba Y and Mahmoudi M. Chronic Inflammation and Oxidative Stress as a Major Cause of Age- Related Diseases and Cancer. Recent Pat Inflamm Allergy Drug Discov. 2009; 3:73-80.
6. Manju K, Jat R.K and Anju G. A Reveiw on medicinal plants used as a source of anticancer agents. Int. J. Drug Res. Tech.2012; 2(2):177-81.
7. Klaunig J.E and Kamendulis L.M. The role of Oxidative stress in Carcinogenesis. Annu Rev Pharmacol Toxicol.2004; 44:239-67.
8. Noda N and Wakasugi H. Cancer and Oxidative stress. J Japan Med Associ. 2000; 24(11):1571-4.
9. Halliwell B. Oxidative stress and cancer: have we moved forward? Biochem J. 2007; 401:1–11.
10. Malins DC, Polissar NL, Gunselman SJ. Progression of human breast cancers to the metastatic state is linked to hydroxyl radical-induced DNA damage. Proc Natl Acad Sci USA. 1996; 93:2557–63.
11. Liu Y, Borchert GL, Donald SP. MnSOD inhibits proline oxidase-induced apoptosis in colorectal cancer cells. Carcinogenesis. 2005; 26:1335–42.
12. Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007; 39:44–84.
13. Klaunig JE, Kamendulis LM. The role of oxidative stress in carcinogenesis. Annu Rev Pharmacol Toxicol. 2004; 44:239–67.
14. Hwang TS, Choi HK, Han HS. Differential expression of managanese superoxide dismutase, copper/zinc superoxide dismutase, and catalase in gastric adenocarcinoma and normal gastric mucosa. Eur J Surg Oncol. 2007; 33:474–9.
15. Mates JM, Segura JA, Alonso FJ, Marquez J. Intracellular redox status and oxidative stress: implications for cell proliferation, apoptosis, and carcinogenesis. Arch Toxicol. 2008; 82:273–99.
16. Pikarsky E, Porat RM, Stein I, et al. NF-κβ functions as a tumour promoter in inflammation-associated cancer. Nature. 2004; 431:461–6.
17. Bensaad K, Vousden KH. Savior and slayer: the two faces of p53. Nat Med. 2005; 11:1278–9.
18. Powell SM, Zilz N, Beazer-Barclay Y, Bryan TM, Hamilton SR, Thibodeau SN, Vogelstein B, Kinzler KW. APC mutations occur early during colorectal tumorigenesis. Nature. 1992; 359:235–37.
19. Jaiswal AS, Marlow BP, Gupta N, Narayan S. Beta-catenin-mediated transactivation and cell-cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells. Oncogene. 2002; 21:8414–27.
20. Yu LL, Wu JG, Dai N, Yu HG, Si JM. Curcumin reverses chemoresistance of human gastric cancer cells by downregulating the NF-κB transcription factor. Oncol Rep. 2011; 26:1197–1203.
21. Cai XZ, Wang J, Li XD, Wang GL, Liu FN, Cheng MS, Li F. Curcumin suppresses proliferation and invasion in human gastric cancer cells by downregulation of PAK1 activity and cyclin D1 expression. Cancer Biol Ther. 2009; 8:1360–68.
22. Sudjaroen Y. Plant-Derived Phenolic Antioxidants and Cancer Prevention. Thai Cancer J. 2009; 29: 126-33.
23. Lamson D.W, Brignall M.S. Antioxidants and cancer III: Quercetin. Altern Med Rev. 2000:196-208.
24. Patel D, Shukla S, Gupta S, Apigenin and cancer chemoprevention: Progress, potencial and promise. Int J Oncol. 2007:233-45.

25. Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, et al. Genistein and cancer: current status, challenges, and future directions. Adv Nutr. 2015; 6:408–19.
26. Dai W, Wang F, He L, Lin C, Wu S, Chen P, et al. Genistein inhibits hepatocellular carcinoma cell migration by reversing the epithelial-mesenchymal transition: partial mediation by the transcription factor NFAT1. Mol Carcinog. 2013; 54:301–11.
27. Wilken R, Veena M.S, Marilene B.W, et al. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Mol Cancer. 2011; 10: 12.
28. Hecker K.D, Bonanome A, Coval S.M, et al. Bioactive compounds in foods: Their role in the prevention of cardiovascular disease and cancer. Am J Med. 2002:71-88.
29. Stocco B, Toledo K, Salvador M, et al. dose –dependent effect of Resveratrol on bladder cancer cells: chemoprevention and oxidative stress. Maturitas.2012: 2-8.
30. Atten MJ, Attar BM, Milson T, Holian O. Resveratrol-induced inactivation of human gastric adenocarcinoma cells through a protein kinase C-mediated mechanism. Biochem Pharmacol. 2001; 62:1423–32.
31. Atten MJ, Godoy-Romero E, Attar BM, Milson T, Zopel M, Holian O. Resveratrol regulates cellular PKC alpha and delta to inhibit growth and induce apoptosis in gastric cancer cells. Invest New Drugs. 2005; 23:111–19.
32. Aquilano K, Baldelli S, Rotilio G, Ciriolo MR. trans-Resveratrol inhibits H2O2-induced adenocarcinoma gastric cells proliferation via inactivation of MEK1/2-ERK1/2-c-Jun signalling axis. Biochem Pharmacol. 2009; 77:337–47.
33. Ahmad N, Mukhtar H. Green tea polyphenols and cancer: Biologic mechanism and practical implications. Nutr Rev.1999:78-83.
34. Fiedor J, Burda K. Potential role of carotenoids as antioxidants in human health and disease. Nutrients. 2014:466-88.
35. Chung JY, Huang C, Meng X, Dong Z, Yang CS. Inhibition of activator protein 1 activity and cell growth by purified green tea and black tea polyphenols in H-ras-transformed cells: structure-activity relationship and mechanisms involved. Cancer Res. 1999; 59:4610–17.
36. Chung JY, Park JO, Phyu H, Dong Z, Yang CS. Mechanisms of inhibition of the Ras-MAP kinase signaling pathway in Ras 12 cells by tea polyphenols (-)-epigallocatechin-3-gallate and theaflavin-3,3'-digallate. FASEB J. 2001; 15:2022–24. 37. Dong Z, Ma W, Huang C, Yang CS. Inhibition of tumor promoter-induced activator protein 1 activation and cell transformation by tea polyphenols, (-)-epigallocatechin gallate, and theaflavins. Cancer Res. 1997; 57:4414–19.
37. Rao A.V, Rao L.G. Carotenoids and human health. Pharmacol Res. 2007:207-16
38. Mohammad Fahad U. Sulforaphane (SFN): An Isothiocyanate in a Cancer Chemoprevention Paradigm Medicines, Medicines. 2015; 2(3): 141–56.
39. Yanaka A, Fahey JW, Fukumoto A, Nakayama M, Inoue S, Zhang S, Tauchi M, Suzuki H, Hyodo I, Yamamoto M. Dietary sulforaphane-rich broccoli sprouts reduce colonization and attenuate gastritis in Helicobacter pylori-infected mice and humans. Cancer Prev Res. 2009; 2:353–60.
40. Jing-Ru Weng, Chen-Hsun Tsai, Samuel K. Kulp and Ching-Shih Chen. Indole-3-carbinol as a chemopreventive and anti-cancer agent. Cancer Lett. 2008; 262(2):153.
41. Ovesna Z, Vachalkova A, Horvathova K. Taraxasterol and betasitosterol: new naturally compounds with chemoprotective /chemopreventive effects. Neoplasma. 2004; 51: 407-14.
42. Grattan BJ. Plant Sterols as Anticancer Nutrients: Evidence for Their Role in Breast Cancer. Nutrients. 2013; 5: 359-87.