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Review on Antioxidants used in Cancer Prevention

Emeter, Nkoli .W

South East Zonal Biotechnology Centre, University of Nigeria, Nsukka, Enugu State, Nigeria.

NKOLYE@yahoo.com

Abstract
Chemoprevention is defined as the use of specific agents to suppress or reverse carcinogenesis and prevent the development of cancer. This is a review to ascertain the effectiveness of antioxidants in cancer prevention and treatment. Antioxidants are the substances which can scavenge free radicals and help to decrease the incidence of oxidative stress induced damage. Prevention of cancer is reviewed from the viewpoints of action mechanisms and clinical trials in order to introduce promising agents discovered by *in vitro* and/or *in vivo* studies to applications in humans using systematic method. Epidemiological studies of some published and cohort works on clinical trials from 2002 till date was used in evaluation of chemoprevention of cancer. A good number of the studies showed the effectiveness of fruits and vegetables in cancer treatment. Clinical trials of bladder cancer, prostate cancer, gastric cancer, hepatocellular (liver cells) carcinoma, breast cancer, head and neck cancer, colorectal cancer and lung cancer showed positive result on effectiveness of chemoprevention. Studies also revealed the advantages and toxic effects of these agents, example, in a chemoprevention trial of lung cancer, β-carotene was unexpectedly found to increase the risk of lung cancer among high-risk groups. It is evident that chemoprevention is effective in cancer treatment and prevention.
Keywords: antioxidants, cancer, prevention and treatment

1. Introduction

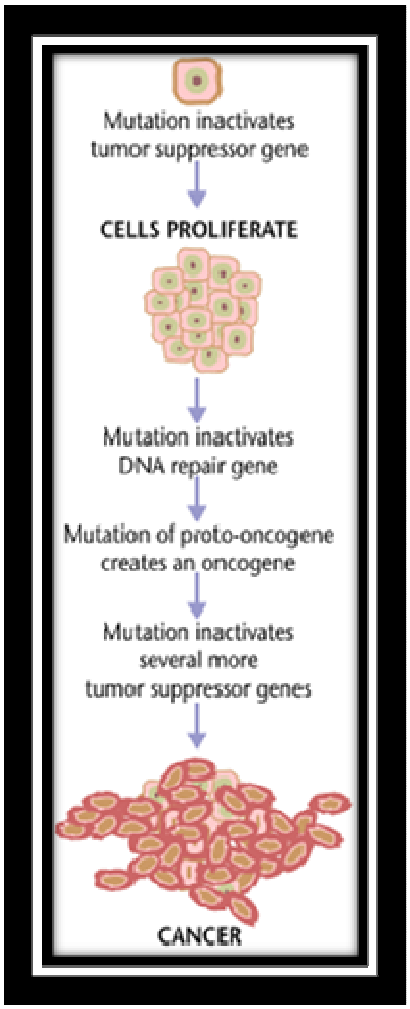
1.1 Cancer

Cancer is a disease in which abnormal cells divide without control and are able to invade other tissues (NCI, 2013).Cancer develops as a result of free radical induced oxidative stress causing a cellular redox imbalance found in various cancer cells which cannot be found in normal cells. It is related to oncogenic stimulation and modification of genetic material resulting from oxidative damage (Saikat and Raja, 2011). Cancer is caused by internal factors (such as inherited mutations, hormones, and immune conditions) and environmental/acquired factors such as tobacco, diet, radiation, and infectious organisms (Anand *et al*, 2008).
Free radicals are chemical entities with one or more unpaired electrons. These radicals cause DNA mutation, change in enzymatic activity, lipid peroxidation of cellular membrane and death. Examples of harmful free radicals are unpaired anions of oxygen, hydroperoxide and superoxide (Birangane *et al*., 2011).
DNA mutation also known as the change in genetic material or character of an individual is a vital step in carcinogenesis. Elevated levels of oxidative DNA lesions have been noticed in various tumours, involved in such damage, in the etiology of cancer.
Cancers are caused by a series of mutations. Each mutation alters the behaviour of the cell.
Three different levels of this disease prevention have been identified namely; primary prevention, secondary prevention and tertiary prevention.

- Primary prevention is the prevention of the occurrence of diseases by (i) avoiding exposure to known cancer-causing agents, (ii) enhancement of host defence mechanisms, (iii) modifying life style and (iv) chemoprevention.

- Secondary prevention is the early diagnosis and intervention particularly at the preclinical stage with the objective of reversing, inhibiting or delaying the progress of the disease condition.
- Tertiary prevention deals with the reduction of the impact of the disease through prevention of complication and early deterioration.(Kakizoe, 2003)

Chemoprevention is defined as the use of specific agents to suppress or reverse carcinogenesis and prevent the development of cancer. Antioxidant is an example of chemopreventive agent (Kakizoe, 2003, CA cancer J, 2004).



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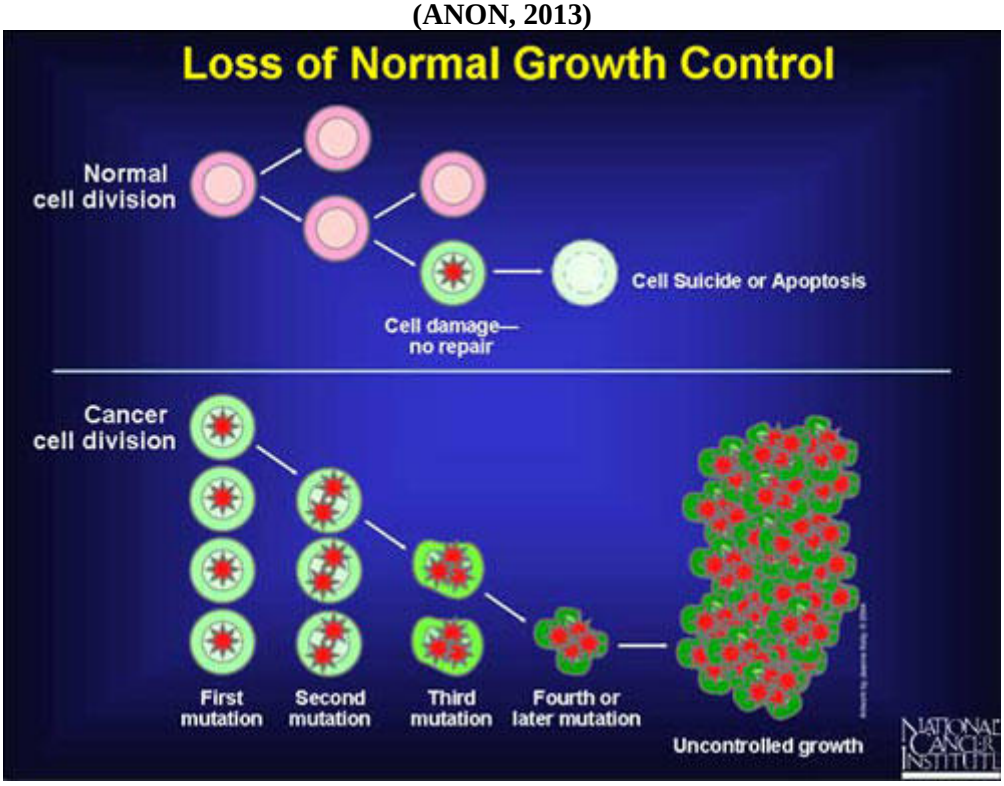

(NCI,2013)

Antioxidants are substances which can scavenge free radicals and help decrease the incidence of oxidative stress induced damage (Saikat and Raja, 2011). When antioxidants are present at low concentrations compared to those of oxidizable substrate (eg proteins, lipids, carbohydrates and nucleic acids) they significantly delay or prevent oxidation of that substrate (Birangane et al.,2011) or prevent oxidative damage caused by the presence of ROS (Jaouad and Torsten, 2010). These substances preserve normal cell cycle regulation, inhibit proliferation (rapid reproduction) and induce apoptosis. Apoptosis is a form of cell death necessary to make way for new cells and remove cells whose DNA has been damaged to the point at which cancerous change is liable to occur. They also inhibit tumour invasion and angiogenesis (the formation of new blood vessels as a result of tumor) and suppress inflammation (Saikat and Raja, 2011). Antioxidants are necessary in preventing the transfer of premalignant lesion to malignancy.

1.2 Mechanism of Action of Protective Roles of Antioxidants against Free Radicals
(1)Use of suicidal and chain breaking antioxidants to scavenge and destroy reactive oxygen species (ROS).
(2) use of catalytic systems to neutralise or divert reactive oxygen species (ROS)
(3) binding or inactivation of metal ions to prevent generation of ROS by Haber-Weiss reaction
(4) absorbing energy, electron & quenching of ROS (Saikat and Raja, 2011).

Oxygen radicals such as singlet oxygen, peroxy radicals, superoxide anion and hydroxyl radicals are associated with carcinogenesis acting in initiation, promotion and progression phases. Oxygen radicals exert a mutagenic effect by oxidizing DNA bases, and radicals also cause DNA strand breaks and chromosome deletions/rearrangements (Kakizoe, 2003).
Food consumption is a major source of exogenous antioxidants. Antioxidants are abundant in vegetables and fruits and are also found in grain cereals, teas, legumes, nuts and other food products (Saikat and Raja, 2011). Decrease in intake of nutritional and antioxidant food increases the chance of oxidative stress which may lead to cell damage, therefore intake of such natural antioxidants give protective effect against free radical induced diseases (Saikat and Raja 2011, Boyer and Liu 2004).
National Research Council recommended consumption of five or more servings of fruits and vegetables a day.

Laboratory and epidemiologic studies along with secondary endpoints carried out in treatment trials showed a strong scientific rationale for the hypothesis that a pharmacologic approach--chemoprevention--can reduce cancer risk. Numerous chemopreventive agents, including naturally occurring vitamins, minerals, phytochemicals, and synthetic compounds, have proved to be safe and effective in preclinical and clinical studies (Greenwald, 2005). Block et al., (2009) in their dietary study, found that consumption of fruit and vegetables had a significant protective effect on cancer and other diseases.

Jaouad and Torsten (2010) referred to exogenous antioxidants as double-edged swords in cellular redox state.

Timothy et al attributed the low rates of cancer in Africa to high consumption of dietary fibre. According to them, fibre increases stool bulk and speeds the transit of food through the colon thereby diluting the gut contents and reducing the absorption of carcinogens by the colonic mucosa. They also pointed out that many dietary factors may not act in isolation but act through interaction with other dietary, lifestyle and / or genetic factor that alter cell growth and affect cancer risk.

Block et al., (2009) in their review study stated that persons with low fruit and vegetable intake (at least the lower one-fourth of the population) experience about twice the risk of cancer compared with those with high intake. Fruits were significantly protective in cancers of oesophagus, oral cavity and larynx. They confirmed a strong evidence of a protective effect of fruit and vegetable consumption in cancers of pancreas, stomach, colorectal, and bladder. Cancers of ovary, cervix and endometrium had a significant protective effect also. In meta-analysis breast cancer had a strong protective effect. Cartmel et al., (2011) also pointed out that low fruit and vegetable intake has been associated with increased risk of primary head and neck cancers., also pharynx and larynx cancers. They stated that increase of intake following diagnosis reduce the risk of second primary cancer which occur in the lung and oesophagus.

Epidemiologic studies have consistently linked abundant consumption of foods of plant origin, such as fruits, vegetables, whole grains, legumes, nuts, seeds and tea, with decreased risk of developing various types of cancers (Kakizoe, 2003). Beliveau and Gingras, (2007) in their cancer study reported that as many as 80% of the study showed a substantial decrease in risk with higher intake of at least one vegetable or fruit category examined. This is particularly true for cancers of the upper gastrointestinal tract which indicated that as many as

75% of colorectal cancers, the second leading cause of death in Canada, could be prevented by increasing the amount of plant-based food in the diet. These observations suggest that food of vegetable origin is an essential source of molecules with chemopreventive properties (Beliveau and Gingras, 2007). A case control study in Hawaii showed that apple and onions intake was associated with a reduced risk of lung cancer in both male and female (Boyer and Liu, 2004). Health beneficial effects of apple and onion against lung cancer was attributed basically on individual components such as quercetin, owing to its potent chemopreventive activity against carcinogens invitro and invivo animal studies (Jaouad and Torsten, 2010).

Fruits and vegetables have high potential for preventing incidence of cancer due to their broad range of health promoting phytochemicals. World cancer Research Fund/ American Institute for Cancer Research provided convincing evidence for the inverse association between fruit and vegetable consumption and cancer risk based on their cohort, case control and epidemiological studies (Schreiner et al., 2006).
Guenoveva and Rajendra (2011) stated that vegetables of cruciferous family have effect on carcinogenesis during initiation and promotion phases of cancer development.

Ugbogu et al., (2013) in their study stated that chemopreventive agents retard, inhibit or reverse multi-stages of carcinogenesis and gave examples of these agents as curcumin, gingerol and resveratrol.

2.1 Benefits of Antioxidants
Antioxidants preserve normal cell cycle regulation, inhibits proliferation (rapid reproduction) and induces apoptosis (a form of cell death necessary to make way for new cells and to remove cells whose DNA has been damaged to the point at which cancerous change is likely to occur). They inhibit tumour invasion and angiogenesis (formation of new blood vessels as a result of a tumour). Antioxidants help suppress inflammation.
Vitamin C, E and β- carotene which are antioxidants have protective role against cancer. Antioxidant diet or consumption of antioxidant like vitamins E, C, and selenium play potential role in enhancing the efficacy of cancer treatment, they also protect against side effects to normal tissues that are associated with treatment (Saikat and Raja, 2011).

2.2 Risks of Antioxidants
Natural antioxidants, if taken in greater quantity than required concentrations can cause significant, sometimes even deadly physiological effects. The estimated intake for vitamin C, vitamin E and carotenoids range between high micromolar and low millimolar levels in human plasma and organs, while polyphenol concentrations is found in the high nanomolar to low micromolar range. An interactive and often synergistic action between endogenous and exogenous antioxidants helps to maintain a balance between oxidation and antioxidation.
It has been stipulated that consumption of vitamin C more than 3000 mg/day for several days can lead to illnesses such as kidney stones, and an increased need for oxygen.
Intake of vitamin C with any acid can lead to excess uric acid excretion and erosion of dental enamel. Vitamin E supplements may amplify the risk of bleeding in some individuals.
Vitamin A overdoses (1600-3200 mg/kg) for extended period can lead to symptoms such as fatigue, breast soreness, gastrointestinal stress, renal problems, vascular inflammation, and thyroid problems.
Coenzyme Q10 also causes severe haemorrhage if taken in very large quantity, and can act like pro-oxidant in high concentrations.
The dietary antioxidants like β-carotene, vitamin C, vitamin E produce complicated and conflicting results in cardiac health as reported by different researchers.
Synthetic antioxidants at very large doses may produce toxic effects. Even though at normal level synthetic antioxidants seem to pose no side effect, long term use may led to chronic health problems. Public awareness and proper investigation regarding this is necessary to minimize the toxic effect of antioxidants (Saikat and Raja, 2011).

3.0 Antioxidant Vitamins
3.1 Vitamin C (Ascorbic Acid)
- Vitamin C is the major water-soluble antioxidant and acts as a free radical scavenger. Vitamin C inhibits malignant transformation in vitro, decreases chromosome damage in lymphocytes caused by exposures to bleomycin and inhibits in vivo nitrosation in the stomach, resulting in decreased levels of serum nitrosamines. (Kakizoe, 2003). Vitamin C blocks the formation of nitrosamines and faecal mutagens, enhances the immune response, and accelerates detoxification of liver enzymes. Chemotherapy (like bleomycin) and radiation therapy (x-ray and γ-ray) in cancer can generate free radicals which are reactive atom or molecule and cause threatening of the integrity and survival of surrounding normal cells (Saikat and Raja, 2011).

The recommended Dietary Allowance (RDA) of 60mg/day is acceptable for vit. C (Birangane et al., 2011).

3.2 Vitamin E (α-Tocopherol)

Vitamin E is a lipid-soluble vitamin among which α-tocopherol is the most potent and abundant. It acts as an antioxidant to protect unsaturated lipids in cell membranes and as a free radical scavenger. Vitamin E has a capacity to inhibit N-nitrosation. N-Nitroso compounds have relevance to various cancers. N-Nitrosamines occur in nitrite in cured meat and due to these effects, vitamin E is one of the possible agents for chemoprevention of bladder cancer (Kakizoe, 2003). Vitamin E protects against immunocompetency which is the ability of the body to develop immunity (by increasing humoral antibody production, resistance to bacterial infections, cell-mediated immunity, natural killer cell activity (white blood cells), blocking of nitrosamine formation, and prevention of cancer formation (Saikat and Raja, 2011). Low plasma levels of vitamin E have been related to increased risk of prostate cancer (CA cancer J, 2004).

3.3 Beta Carotene

This is found in dark green orange fruits or vegetables such as spinach, carrots, sweet potato and fruits like apricot, papaya and vegetable. The deeper the colour of vegetable or fruit, the greater is the carotene content. Beta carotene is a vitamin c precursor hence can fulfil nutritional requirement for vitamin A. Beta carotene has immune regulatory properties which retard development of cancer cells. It increases the number of circulating lymphoctyes, enhances the proliferation and induction of cytotoxic T cells and helper T cells are equally increased. Beta carotene increases tumour necrosis factor and enables natural killer cells to be more effective (Birangane et al., 2011). Photoprotective role of β-carotene is to protect against ultraviolet (UV) light-induced cancer (Saikat and Raja, 2011).

3.4 Lycopene

Lycopene a carotenoid present in tomatoes is a powerful quencher of singlet oxygen. Epidemiological study strongly suggested that lycopene consumption in tomato products contribute to reduction of risk of prostate cancer (Farombi, 2004). Lycopene is found in the following fruits, watermelon, apricots, guava, grapefruit and tomatoes. The mechanisms for the anticancer effect of lycopene involves scavenging of Reactive Oxygen Species (ROS), up-regulation of detoxification systems, interference with cell proliferation, induction of gap-junctional communication, inhibition of cell-cycle progression, and modulation of signal transduction pathways. Other carotenoids reported to have anticancer activity include beta-carotene, alpha-carotene and lutein (Pharm. Res. 2008).

3.5. Resveratrol

Resveratrol is a polyphenol found in the skin of grapes and peanuts. In vitro experiments have shown that prostate cancer can be prevented using resveratrol. Resveratrol was also found to decrease expression of prostate-specific antigen (PSA), an androgen-responsive gene (ARG) that is often used as marker for prostate cancer cell growth. They also suggested that resveratrol's protective effects against prostate cancer could be due to modulation of steroid hormone-mediated pathways. (Thomas et al., 2008).

Resveratrol exhibits anticancer properties as suggested by its ability to suppress proliferation of a wide range of tumour cells, including lymphoid and myeloid cancers, multiple myeloma, cancers of the breast, prostrate, stomach, colon, pancreas and thyroid, melanoma, head and neck squamous cell carcinoma, ovarian carcinoma and cervical carcinoma (Farombi, 2004).

4. FRUITS WITH ANTIOXIDANT PROPERTIES

Asparagus- has a cleansing effect on the lymphatic system and kidney. It contains protein compounds called histones which act as cell-growth normalizers on cancer-cell division.

• **Avocados**- are perhaps the best overall source of essential fatty acids, glutathione and are a great source of protein. Avocados are easily digested, making them an ideal food for people recovering from surgery or for the very sick.

• **Bitter melon**. The fruit and leaves of bitter melon are a source of a guanylate cyclase inhibitor which has been shown to inhibit prostate cancer.

• **Broccoli**, **cauliflower**, **Brussels sprouts**, **apples**, **grapefruit**, **carrots**, **green onions**, **apricots and cherries** - contain D-glucarate a natural compound produced in small amounts by humans and some plants. It encourages the detoxification of environmental carcinogens and estrogenic tumor promoters (Connor, 2009).

Cruciferous vegetables also known as cabbage family vegetables which include cabbage, broccoli, cauliflower and kale contain anti-cancer phytochemicals known as glucosinolates.

• **Broccoli and onions** - contain quercetin a flavone which has a cancer inhibiting effect by preventing a defect in the tumor suppressor gene.

• **Carrots**, sweet potatoes, collard greens, cantaloupe, squash, apricots, fresh pumpkin, kale, spinach, mangos, papaya- contain beta-carotene which is considered one of the most promising anti-cancer agents. A study

showed that the more beta-carotene men got in their diet the less lung cancer they developed. It also prevent a second tumor in patients who have been cured of an initial cancer but now stand at an increased risk of developing new cancers in the upper part of the

• **Celery** - contains abundant amounts of phthalides and polyacetanes. These are two phytochemicals that have been shown to inhibit cancer. They are able to detoxify many carcinogens and are of particular help in reversing some of the damage done by cigarette smoking.

• **Chili peppers** - contain capsaicin which may neutralize the carcinogenic effect of nitrosamines, which are powerful carcinogens that can form in the stomach. Capsaicin may also block carcinogens in cigarette smoke from locking onto DNA -possibly preventing genetic damage that can lead to lung and other cancers.

• **Dark green leafy** vegetables, legumes, nuts, contain vitamin E. German nutritionists suggest that vitamin E when taken together with food may reduce human exposure to cancer-causing nitrosamines. Vitamin E was effective in preventing their formation especially when used in conjunction with vitamin C.

• **Garlic**, **onions**, **leeks, and shallots (album vegetables).** According to the National Cancer Institute garlic is one of the best foods for protection against cancer. It contains the anti-cancer mineral selenium which stimulates white blood cell production and induces apoptosis (cancer cell death). Alliums contain compounds that stimulate the production of enzymes that neutralize the free radicals linked with cancer. They also contain saponins which prevent cancer cells from multiplying and allyl sulfides that increase the production of glutathione S-transferase and other enzymes that enhance carcinogen excretion.

• **Garlic, onions, Brazil nuts and greens** - contain selenium which causes cancer cells to die before they spread, repairs damaged DNA, protects against free radicals and aids the body's natural detoxification process.

• **Red peppers, fresh orange juice, broccoli, apple juice, green peppers, grapefruit juice, cranberry juice, papaya and fresh strawberries** contain vitamin C which fights free radicals. Vitamin C appears to offer some protection against all cancers

Apple contain phytochemical –quercetin, catechin, phloridzin and chlrogenic acid which are antioxidants. They have antioxidant activity; inhibit cancer cell proliferation, decrease lipid oxidation and lower cholesterol.

• **Raw spinach and parsley** - are good sources of glutathione and chlorophyll. Parsley is also rich in polyactylenes which block the formation of tumor-promoting prostaglandins.

• **Tomatoes, watermelons, red peppers, and carrots** contain lycopene which may explain a recent Italian study that found that people who ate raw tomatoes at least 7 times a week halved their risk of several cancers compared to those who ate tomatoes no more than once a week.

• **Tomatoes, green peppers, strawberries and carrots** - contain p-coumaric and chlorogenic acids which hook onto nitric oxides in the foods we eat and spirit them out of the body before they canform cancer causing nitrosamines.

• **Turmeric and cumin** - contain curcumin an anti-mutagenic agent that supports the liver in detoxification of carcinogens and helps to block environmental carcinogens. Curcumin is useful in virtually all types of cancer, because of its fundamental mechanism of actions against cancer progression. In particular, preliminary studies suggest that curcumin is likely to inhibit prostate, breast, skin, colon, stomach and liver cancers and is suitable for use in conjunction with chemotherapy. The recommended dosage for curcumin is 200-400 mg one to three times a day. To enhance absorption it is taken along with proteolytic enzymes. This combination is best taken on an empty stomach 15-20 minutes before meals or between meals. (Murray et al , 2002).

• **Citrus fruit peels** - contain a remarkable anti-cancer substance called D-limonene. Plant fiber of citrus fruit has been shown to inhibit metastasis in prostate cancer by competing with tumor cell surface galectins, which are essential for successful establishment of secondary cell colonies.

• **Cranberry**- contains the anti-cancer constituent, proanthocyanidin which has an anti-oxidant capability more than that of vitamin E.

• **Fruit** - contains caffeic acid which enhances production of enzymes that make carcinogens more water-soluble. Fruit also contains ferulic acid which binds to nitrates in the stomach preventing production of carcinogenic nitrosamines.

• **Grapefruit** - contains the flavonoid naringenin which slows the growth of human breast cancer cells

• **Grapes, many berries and some nuts** contain a phytoalexin component called resveratrol which has shown cancer chemopreventive activity. Resveratrol has been found to act as an antioxidant, antimutagen and anti-inflammatory. It has also been shown to inhibit the development of breast cancer and induce antiprogression activity in human myelocytic leukemia.

• **Grapes, strawberries, raspberries and nuts** contain ellagic acid which blocks the body's production of enzymes used by cancer cells. In one study an extract of Concord grapes was shown to be as effective as the cancer drug methotrexate in slowing tumor growth. Ellagic acid is particularly effective in the inhibition of lung cancer caused by tobacco.

• **Red grapes (especially the seeds), blueberries, blackberries, cherries and grapes**- contain oligomeric proanthocyanidins known as OPC's, which help to protect DNA from free radicals due to radiation and chemicals and slow down the mutation of cancer cells.
• **Tangerines** - contain tangertin which inhibits cell-endothelial adhesion, a very important step in the metastatic process of cancer
• **Fiber** from fruits, vegetables, beans and whole grains. Since 1980 till date, studies have shown that, fiber protects against colon cancer. Fruits and vegetables contain soluble fiber. The combination of these two forms of fiber promotes bowel regularity and protects against colon cancer.
Spinach and peanuts - contain CoQ10 which protects against cancer by strengthening the immune system and zapping free radicals.
Yogurt. Researchers have found that the dialyzate fraction of yogurt possesses anti-tumor activity. Lactobacilli and bifidobacteria found in yogurt produce compounds within the colon that increase beta glucaronization and nitroreductase, which help the body to excrete carcinogens and hormones more efficiently. Yogurt also contains higher levels of free-form amino acids than milk, mainly due to the proteolytic action of the lactobacillus (Connor, 2009).
Dietary intake of fruit 250g and vegetable 375g per day is acceptable by International Health Bodies eg World Cancer Research Fund/American Institute for Cancer Research and Health Education Authority (UK) (Schreiner and Huyskens 2006).

5. SUGGESTIONS

There is need for continued research to help identify the therapeutically important constituents and dietary components that have antioxidant action. It is necessary to quantify these components and assess their potential for in vivo antioxidant activity and their interactions with target tissue. It is imperative to reveal the relationship between intake of antioxidants and their dose-dependent functional effects. The specific role of antioxidants with variation of species or genetic differences needs to be identified.

6. DEBATE

In as much as antioxidant molecules have been found to have anti-carcinogenic properties, there are still doubts on their efficiency .We still have debates as to whether consuming antioxidants (in food or supplement form) actually benefits health in all conditions and the requirement of antioxidants. There is also limited scientific data to support the use of antioxidant supplements to prevent disease based on clinical trials in humans.

7. CONCLUSION

The increasing incidence of cancer led to this review on antioxidants. Further research is needed to help understand the safety aspects of dietary antioxidants and it is advisable that antioxidant supplements should not be used as a replacement for a healthy diet. Encouraging a varied diet (healthy food with antioxidant activity) still remains the best advice in gaining the benefits of antioxidants and other bioactive components available from food for healthy living and reduction of cancer. We should stay alive and healthy with our natural fruits and vegetables.

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