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POTENTIAL OF PHYTOCHEMICALS IN CANCER PREVENTION

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Aim: To find the role of phytochemicals in prevention of cancer.

ABSTRACT:

Epidemiologic data support the association between high intake of vegetables and fruits and low risk of chronic diseases. There are several biologically plausible reasons why consumption of vegetables and fruits might slow or prevent the onset of chronic diseases. Vegetables and fruits are rich sources of a variety of nutrients, including Vitamins, trace minerals, and dietary fibre, and many other classes of biologically active compounds. These are also known as "Phytochemicals", can have complementary and overlapping mechanism of action, including modulation of detoxification enzymes, stimulation of immune system, reduction of platelet aggregation, modulation of cholesterol synthesis and hormone metabolism, reduction of blood pressure, and antioxidant, antibacterial, and antiviral effects. It is been proposed that the additive and synergistic effects of phytochemicals in fruit and vegetables are responsible for these potent anticancer activities and that the benefit of a diet rich in fruits and vegetables is attributed to the complex mixture of phytochemicals present in whole foods.

Cancer is one of the most challenging health problems in the entire world today. It is complex disease to treat. Even with advances in medical science disciplines such as surgery, radiotherapy and chemotherapy there is still no significant progress in its treatment. Conventional cancer therapies evoke severe side effects and in many cases, patients recover from cancer and die due to organ failure and immunosuppression. To redress these anamolies recourse to phytochemicals is advocated. The induction of apoptosis in a neoplastic cell line without affecting normal cells of the body is a key to the use of phytochemicals (chemopreventive agents) which perform a vital function in the battle against cancer. These active phytochemical chemopreventive agents found in fruits and vegetables modulate the molecular targets of cancer and induce cytoprotective enzymes that act in a co-ordinated fashion to detoxify and remove dangerous reactive substances formed by cancer causing agents. Research has shown that they exert these abilities by counteracting certain cell signals that cause genotoxic damage and reduction-oxidation imbalance in cells. This discourse reviews the role of phytochemical chemopreventive agents and benefits associated with their use in cancer prevention as it portends great promise for normal cell protection.

Keywords: Phytochemical, Antioxidant, Chemoprevention, Cancer, Anti-carcinogenic.

INTRODUCTION

To date, several hundred scientific studies have focused on the activity of non-nutritional compounds present in the diet, preventing the occurrence of degenerative diseases, such as cancer. Foods provide not only essential nutrients needed for life but also other for health promotion and diseases prevention. Phytochemicals are naturally occurring, non- nutritive biologically active chemical compounds in plants which act as a natural defence system for host plants and provide colour, aroma and flavour (1) eg, fruits, vegetables, grains, nuts, and seeds. There are an estimate of >5000 individual bioactive compounds which are also nowadays known as "phytochemicals". Present many have been identified but a large percentage still remain unknown and need to be identified before we can fully understand their health benefits in total. They often are categorised into various groups on the basis of their chemical structure (ie, polyphenols, organosulphur compounds, carotenoids, alkaloids, and nitrogen-containing compounds). The polyphenols can be divided further into flavonoids (Flavonols, Flavones, Catechins, Flavanones, Anthocyanidins, and Isoflavones), phenolic acids, stilbenes, coumarins, and tannins.

Cancer is one of leading cause of morbidity and mortality worldwide, despite enormous efforts of science researchers from various disciplines aimed at ameliorating the dismal outcome of cancer mortality. The rate of death from cancer has not declined significantly even with advances in surgery, radiotherapy and chemotherapy. Prevention of cancer remains evidently an essential part of the contest against cancer in the world (2, 3). Cancer cells occur as a result of unique multiple genetic disorders that may arise from exposure to environmental and occupational carcinogenic agents or dietary habits and infectious agents (4). The increased incidence of cancer in the world today justifies the application of phytochemical chemoprevention which use of common natural dietary compounds from plants to inhibit, block or reverse tumour multiplication at various stages such as initiation, promotion or progression of carcinogenesis. These phytochemicals lower the risk of cancer development in humans via for example, radical scavenging, anti-oxidation mechanisms, anti-inflammatory and anti- proliferative mechanisms (5, 6, 7). Phytochemicals are a potential alternative source of safer chemicals with anti-carcinogenic effects. Some sources of phytochemicals include broccoli, lettuce, cabbage, spinach, tomatoes, soybean, green tea, ginger, chilli pepper, turmeric, grapes, garlic, aloe and carrot (8, 9)

Epidemiological studies have consistently shown that a high dietary intake of fruits and vegetables as well as whole grains in strongly associated with reduced risk of developing chronic diseases, such as cancer (10, 11). This suggests that change in dietary behaviour, such as increasing consumption of fruits, vegetables and whole grains, and related lifestyle is a practical strategy for significantly reducing the incidence of cancer.

PHYTOCHEMICALS AND CANCER:

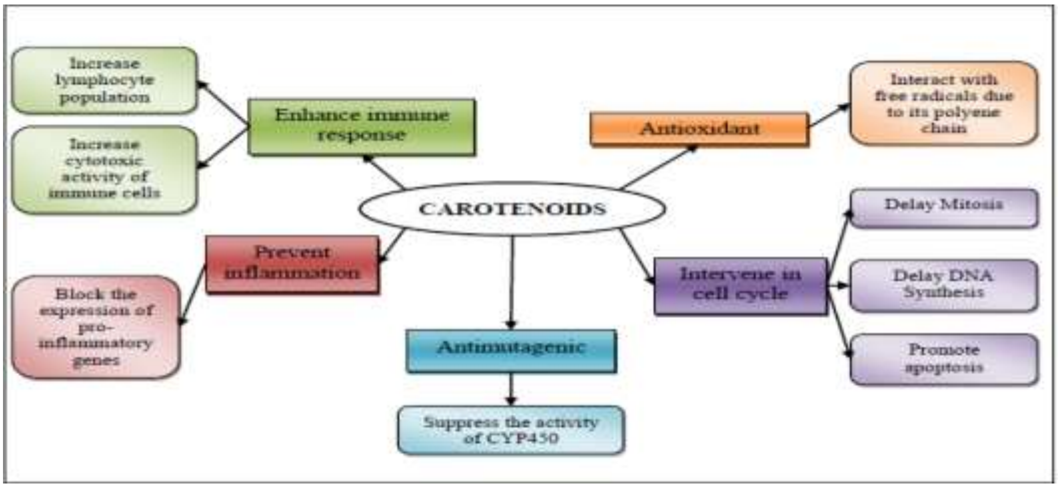
Cells in humans and other organisms are constantly ex- posed to a variety of oxidizing agents, some of which are necessary for life. These agents may be present in air, food, and water, or they may be produced by metabolic activity within cells. The key factor is to maintain a balance between oxidants and antioxidants to sustain optimal physiological conditions. Overproduction of reactive oxygen species can cause an imbalance, leading to oxidative stress, especially in chronic bacterial, viral, and parasitic infections. Oxidative stress can cause oxidative damage to large biomolecules such as lipids, proteins, and DNA, resulting in an increased risk for cancer (12, 13).To prevent or slow the oxidative stress induced by free radicals, sufficient amounts of antioxidants need to be consumed. Fruits, vegetables, and whole grains contain a wide variety of antioxidant compounds (phytochemicals), such as phenolics and carotenoids, and may help protect cellular systems from oxidative damage and also may lower the risk of chronic diseases (14, 15, 1)

Strong epidemiological evidence suggests that regular consumption of fruits and vegetables can reduce cancer risk. Block *et al* (16) reviewed 200 epidemiological studies that examined the relationship between intake of fruits and vegetables and cancer of the lung, colon, breast, cervix, esophagus, oral cavity, stomach, bladder, pancreas, and ovary. In 128 of 156 dietary studies, the consumption of fruits and vegetables was found to have a significant protective effect. The risk of cancer was 2-fold higher in persons with a low intake of fruits and vegetables than in those with a high intake. Significant protection was found in 24 of 25 studies for lung cancer. Fruits were significantly protective in cancer of the esophagus, oral cavity, and larynx. Fruits and vegetable intake was protective for cancer of the pancreas and stomach in 26 of 30 studies and for colorectal and bladder cancer in 23 of 38 studies.

Carcinogenesis is a multistep process, and oxidative damage is linked to the formation of tumors through several mechanism. Oxidative stress induced by free radicals causes DNA damage, which, when left unrepaired, can lead to base mutation, single- and double-strand breaks, DNA cross-linking, and chromosomal breakage and rearrangement (13, 17). This potentially cancer-inducing oxidative damage might be pre- vented or limited by dietary antioxidants found in fruits and vegetables. Studies to date have demonstrated that phytochemicals in common fruits and vegetables can have complementary and overlapping mechanisms of action (Table 1), including antioxidant activity and scavenging free radicals, tumor suppressor genes, induction of cell-cycle arrest and apoptosis and antibacterial and antiviral effects.

Table 1: **Proposed action of dietary phytochemicals in prevention of cancer.**

Phytochemicals	Action	Food source
Allyl sulphide	Antioxidant Anti-bacterial Blood purifier Anti-neoplastic	Onions, garlic, chives, leeks
Carotenoids	Anti-oxidant	Yellow-Orange vegetables and fruits, Green leafy vegetables, Red fruits
Curcumins	Anti-oxidant Anti-carcinogenic Wound healing Anti-inflammatory	Turmeric
Flavonoids	Anti-carcinogenic Anti-oxidant Anti-inflammatory Enhance vitamin C activity	Most fruits, vegetables, grains and nuts
Gingerol	Inhibit COX-2 Expression Relieves throat pain and cough	Ginger
Indoles and Isothiocynates	Immune modulator Anti-oxidant	Broccoli, Cabbage, Cauliflower, Brussels, Sprouts
Isoflavones	Anti-carcinogenic Decrease cholesterol level (LDL)	Soybeans, tofu
Lignans	Anti-carcinogenic	Soybeans, flaxseeds
Liminoids	Anti-oxidant Anti-inflammatory Anti-tumurogenic	Citrus
Phenolic acids	Anti-carcinogenic Anti-mutagenic COX-1 inhibitor	Berries, Grapes, Nuts, Whole Grains
Lycopene	Powerful anti-oxidant	Tomato
Isoprenoids	Suppress tumor growth	Grains, legumes
Saponins	Anti-tumerogenic	Beans, herbs
Terpenes	Anti-carcinogenic Anti-oxidant Anti-tumerogenic	Cherries, citrus, herbs
Caffeine	Anti-carcinogenic Anti-oxidant Anti-angiogenic	Tea



MECHANISM OF ACTION OF CERTAIN PHYTOCHEMICALS:

Carotenoids have been associated to cancer prevention, which may undergo by five mechanisms of action (18)

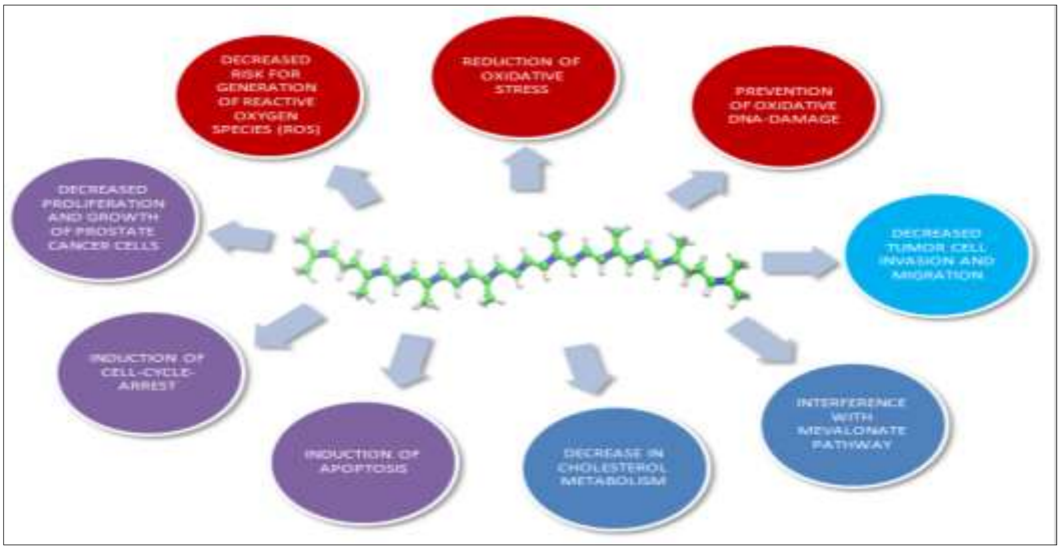
(1) Membrane Antioxidant

(2) Involvement in the Control of Cell Differentiation and Proliferation

(3) Anti-mutagenic Effect

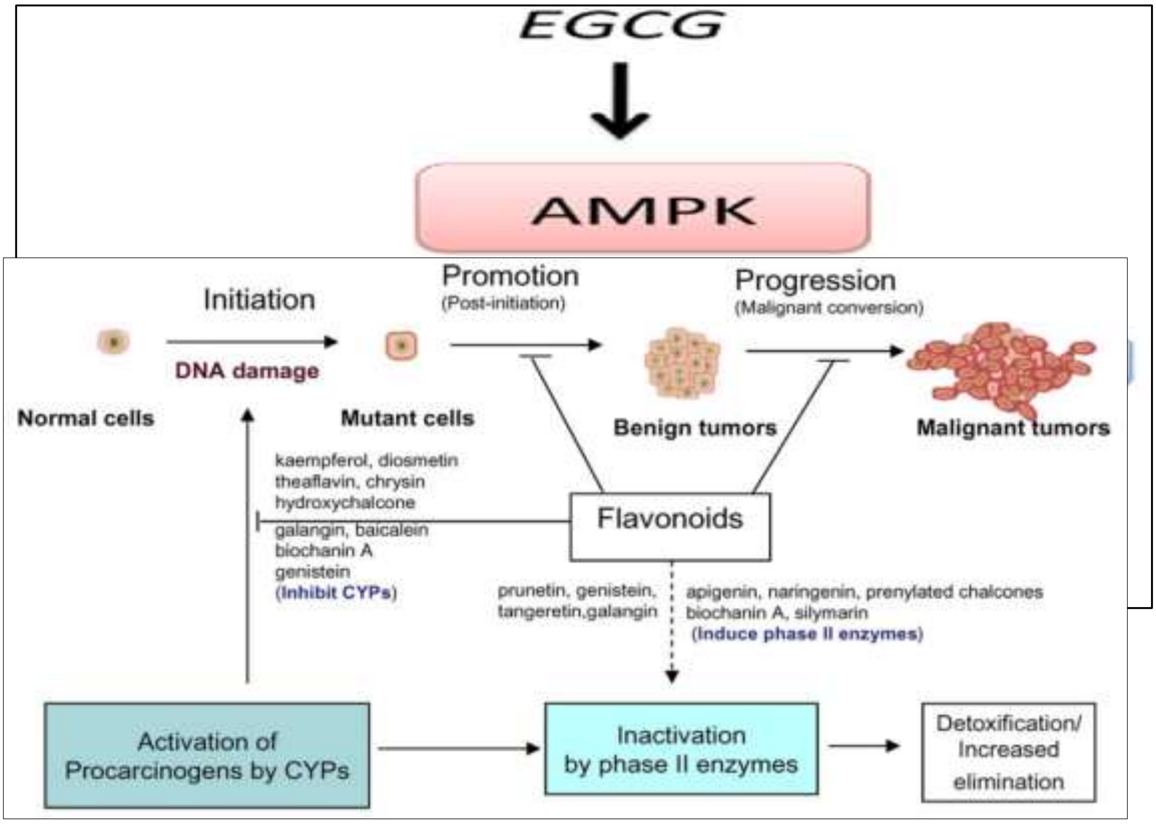
(4) As Anti-Inflammatory Agents And

(5) Their Ability to Produce an Immune Response in Cancer



The cancer-preventive effect of lycopene mediated by its ability: (19)

- To Induce apoptosis
- To reduce the amount of oxidative DNA damage in cell culture



- Inhibits proliferation of various cancer cell lines with down regulation of cyclin D1 and consequent cell cycle arrest at the G0/G1 phase and G2/M phase of the cell cycle.
- To inhibit signalling of insulin-like growth factor-I (IGF-I)

Flavonoids are thought to affect their anticancer properties by a variety of mechanisms (20) One route is by

- Inhibiting cytochrome P450 (CYPs) from activating pro-carcinogens.
- Inducing phase II enzymes induction of phase II metabolizing enzymes such as glutathione-S-transferase, quinone reductase, and UDP-glucuronyl transferase, facilitating carcinogen elimination from the body.
- Flavonoids have been demonstrated to inhibit proliferation in many kinds of cultured human cancer cell lines, whereas less or no toxic to human normal cells.
- Perturbations in cell cycle progression may account for the anti-carcinogenic effects of flavonoids.
- Flavonoids have been shown to induce apoptosis in some cancer cell lines.

Epigallocatechin gallate (EGCG) widely plays a role in prevention of breast and colon cancer by (21)

- Stimulates AMPK, leading to suppression of breast cancer cell growth by inhibition of mTor (MTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription)and activation of p21.

- Inhibition of COX-2 by EGCG-induced AMPK activation leads to apoptosis in colon cancer cells

MECHANISM OF CANCER PREVENTION BY PHYTOCHEMICALS: The potential mechanisms of phytochemical chemo-preventive agents are categorised into two basic groups namely; blocking agents and suppressing agent.

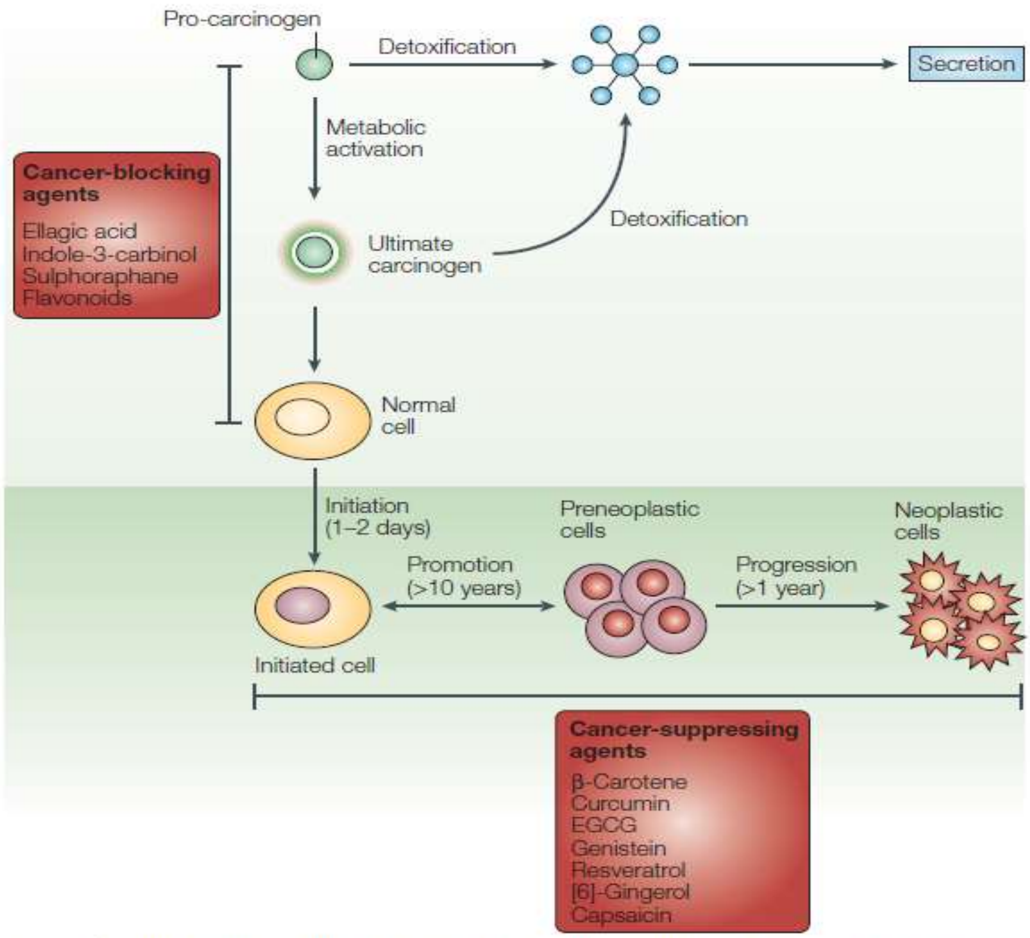


Figure 1 | **Dietary phytochemicals that block or suppress multistage carcinogenesis.** Carcinogenesis is initiated with the transformation of the normal cell into a cancer cell (initiated cell). These cells undergo tumour promotion into preneoplastic cells, which progress to neoplastic cells. Phytochemicals can interfere with different steps of this process. Some chemopreventive phytochemicals inhibit metabolic activation of the procarcinogens to their ultimate electrophilic species, or their subsequent interaction with DNA. These agents therefore block tumour initiation (blocking agents). Alternatively, dietary blocking agents can stimulate the detoxification of carcinogens, leading to their secretion from the body. Other phytochemicals suppress the later steps (promotion and progression) of multistage carcinogenesis (suppressing agents). Some phytochemicals can act as both blocking and suppressing agents. Adapted from REF. 128.

Figure 1: Classification of chemopreventive agents on the basis of their mechanism of action on cancer multistage

Figure 1 above shows chemo-preventive agents that can inhibit the metabolic activation of pro-carcinogens, preventing them from transforming to carcinogens. On the other hand initiated cells are also suppressed by some of these agents inhibiting initiated cells from translating to neoplastic cells (22).

Blocking agents: These are substances like indole-3-carbinol, sulforaphane and flavonoids which avert cancer causing agents from accomplishing their effects on the normal cells, inhibit their metabolic stimulation, and also enhance their detoxification (23).

Suppressing agents: They function by interfering with the promotion and progression of carcinogenesis through their effect on cell proliferation, integration and programmed cell death which inhibits translation of initiated cells to form cancerous cells (7, 24). These agents such as Beta-Carotene, Curcumin, Gingerol and Resveratrol suppress carcinogenesis through blocking phase 1 enzymes, initiation of phase 2 enzymes, preventing reactive oxygen species from damaging DNA, suppressing type 2 cell multiplications generated by carcinogenesis and inhibiting normal cells from transforming to cancer cells (25). The inherent potential of these phytochemicals in the chemoprevention of cancer cannot be overemphasized especially considering their robust safety records when compared with conventional anti-cancer therapies.

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

Dietary modification by increasing the consumption of a wide variety of fruits, vegetables, and whole grains daily is a practical strategy for consumers to optimize their health and to reduce the risk of chronic diseases such as Cancer. Phytochemical extracts from fruits and vegetables have strong antioxidant and anti-proliferative activities, and the major part of total antioxidant activity is from the combination of phytochemicals. The benefit of a diet rich in fruits and vegetables is attributed to the complex mixture of phytochemicals present in these and other whole foods. This partially explains why no single antioxidant can replace the combination of natural phytochemicals in fruits and vegetables in achieving the observed health benefits. This balanced natural combination of phytochemicals present in fruits and vegetables cannot simply be mimicked by pills or tablets. Therefore, the evidence suggests that antioxidants are best acquired through whole food consumption, not from expensive dietary supplements.

Chemoprevention by edible phytochemicals is now considered to be an inexpensive, readily applicable, acceptable and accessible approach to cancer control and management. With healthcare costs being a key issue today, it would be cost-effective to promote the awareness and consumption of phytochemicals as a cancer-preventive strategy for the general public.

Phytochemicals in cancer chemoprevention are considered as the cheapest option in cancer treatment. Despite little understanding of the mechanisms of some phytochemical chemopreventive agents, phytochemicals are believed to play significant roles in controlling, inhibiting, and blocking signals which can cause translation of normal cells to cancer cells. Thus from this point of view, there is a greater need for nutraceuticals (in phytochemicals) which will serve as functional supplement for cancer prevention.

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