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REVIEW ON CHEMOPREVENTION OF CANCER BY DIETRY PHYTOCHEMICALS

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ABSTRACT

Cancer chemoprevention involves the use of different natural or biologic agents to reduce or reverse tumor growth**.** The evidences from several epidemiological studies propose that higher intakes of fruits and vegetables have been associated with lower risk of cancer. Dietary phenolic and polyphenolic substances, terpenoids, dietary fibers, fish oils, some micronutrients present in foods of both plant and animal origin, and a reduction of caloric intake appear to inhibit the process of cancer development. Many dietary factors possess antioxidant and anti-inflammatory properties and cause induction of phase II enzymes. Phytochemicals derived from such fruits and vegetables, referred to as chemopreventive agents include genistein, resveratrol, diallyl sulfide, S-allyl cysteine, allicin, lycopene, capsaicin, curcumin, 6-gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins and eugenol Because these agents have been shown to suppress cancer cell proliferation, inhibit growth factor signaling pathways, induce apoptosis, inhibit NF-κB, AP-1 and JAK-STAT activation pathways, inhibit angiogenesis, suppress the expression of anti-apoptotic proteins, inhibit cyclooxygenase-2, they may have untapped therapeutic value. Thus phytochemicals could play an important role in cancer chemoprevention.

KEYWORDS: Cancer, chemoprevention, mechanism of chemoprevention, molecular targets.

INTRODUCTION

Carcinogenesis is a multistep process characterized by a progression of distinct molecular changes that ultimately reprogram and transform a cell to undergo uncontrolled cellular

division.[1] With each interference, cells undergo changes fundamentally represented by tumor initiation, promotion and progression.[2,3] Tumor initiation is a rapid and irreversible process that starts with an exposure to a carcinogenic agent, followed by its distribution and transportation to tissues causing non-lethal mutations in cellular DNA. These "initiated cells" begin to accumulate additional irreversible genetic changes which persist with each new cycle of proliferation.[2] Functionally, initiated cells are more immune to inhibitory signals mediated by cell differentiation inducers and negative growth regulators.[4,5] Tumor promotion involves the selective clonal growth and proliferation of initiated cells allowing for additional mutations to accumulate. In contrast to initiation, tumor promotion is a relatively lengthy and reversible process in which actively proliferating preneoplastic cells begin to divide and propagate. Tumor progression, the final stage of neoplastic transformation, occurs after these mutations result in an invasive cellular phenotype with metastatic potential.[3,6] Advances in our understandings of tumor development show that each step is composed of highly variable and intricate systems. For instance, epigenetic changes of tumor suppressor genes through DNA methylation in pre-neoplastic tissues may result in accelerated carcinogenesis.[7,8] The dynamic regulation of proteins involved in cellular apoptosis by micro-RNAs may significantly impact both tumor promotion and progression [9]. Finally, more recent evidence has highlighted the critical role of the tumor microenvironment on the survival and mutation of preneoplastic cells.[5]

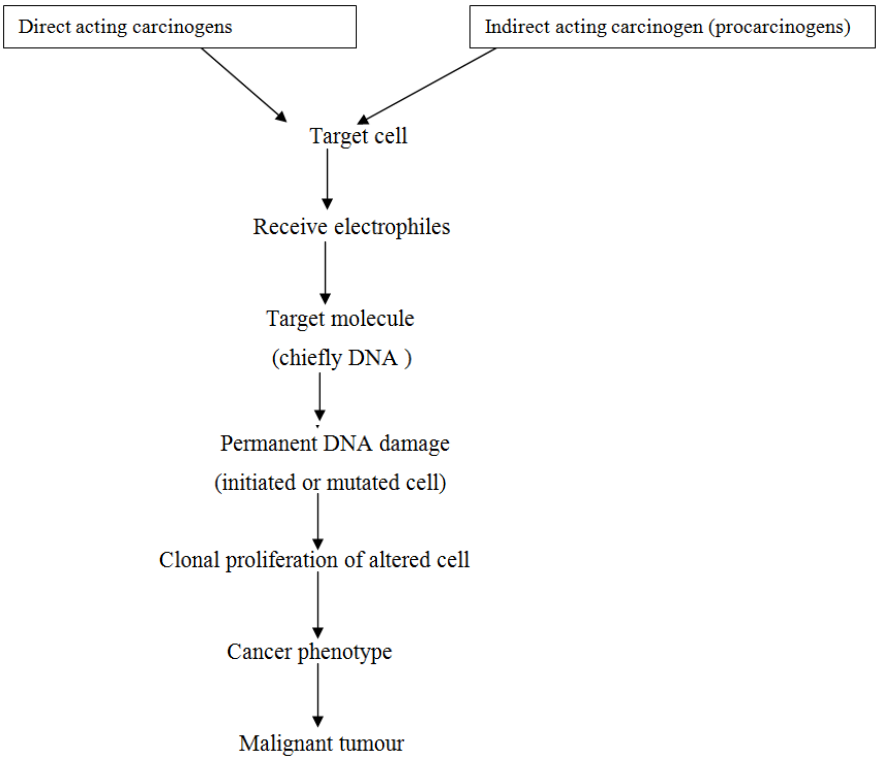

Fig. 1: Process of carcinogenesis.

CHEMOPREVENTION

Chemoprevention is the use of natural, synthetic, or biologic, chemical agents to reverse, suppress, or prevent carcinogenic progression.[11] Incidence of cancer can be controlled and reduced to a certain extent by chemoprevention. Chemoprevention can be divided into three main areas: 1) primary prevention in high risk healthy individuals; 2) cancer prevention in individuals that already had developed pre malignant lesions 3) prevention of secondary forms of cancers in patients already treated for a primary cancer[12] Chemopreventive molecules target each of these steps including anti-initiation strategies (e.g. DNA repair, detoxification, free-radical scavenging and carcinogen metabolism) and antipromotional/ antiprogression strategies (e.g. free-radical scavenging, proliferation suppression, differentiation induction, immunity enhancement, inflammation reduction, increase in apoptosis, altered gene expression and decrease in angiogenesis)[13,14] No toxicity is expected from a chemopreventive agent because of its long history of human consumption as herbal medicines, botanical dietary supplements or edible plants[13,15,16] Bioactive components of dietary phytochemicals with chemopreventive properties include curcumin, genistein, resveratrol, diallyl sulphide, S-allyl cysteine, allicin, lycopene, capsaicin, diosgenin, (6)-gingerol, ellagic acid, ursolic acid, silymarin, anethol, catechins, eugenol, isoeugenol, isothiocyanates, indol-3-carbinol, isoflvones, phytoestrols, folic acids, b-carotene and flavonoids[17] These dietary agents are believed to suppress the transformative, hyperproliferative and inflammatory processes that initiate carcinogenesis. These inhibitory influences may ultimately suppress the final steps of carcinogenesis, namely angiogenesis and metastasis.[18]

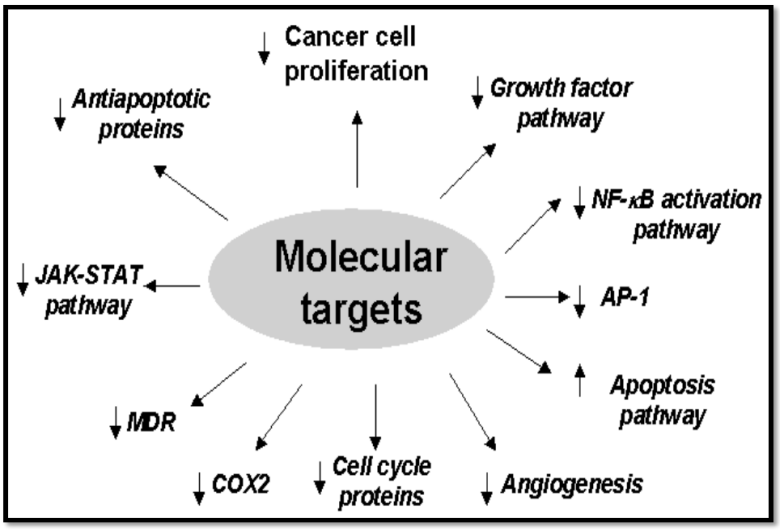

Fig. 2: Molecular targets of chemopreventive agents in cancer.[18]

MECHANISMS OF ACTION OF CHEMOTHERAPEUTIC AGENTS

1. Disruption in cell signal transduction pathways

Cancer is strongly associated with defects in signal-transduction proteins which results in uncontrolled or inappropriate cell growth. Herbal drugs block signal transduction in cancer by various routes as following.

2. Nuclear factor (NF-kB) pathways with activator protein (Ap-1)

Nuclear factor (NF-kB) with activator protein-1 (AP-1) are transcription factors regulates many gene expression involved in oncogenesis, apoptosis, etc. by extracellular signals. It is mainly a protein complex that regulates transcription of DNA, cytokine production and cell survival. Incorrect regulation of NF-kB associated with cancer, inflammatory and autoimmune diseases.[19] Medicinal herbs inhibit the growth of cancer cells by this mechanism, like botanical extract of mountain ginseng inhibits the growth of lung cancer cells through regulating NF-kB signaling pathway.[19]

3. Protein tyrosine kinase (PTK) pathways

It is a type of enzyme that can transfer a phosphate group to a protein in the cell. Hence, it is called PTK. It functions as an active and not active in many cellular reactions. It causes growth in signal transduction to cells.[20]

4. Modification in cycle of cell

The natural and constant balance of cycle of cell ensures standard cell escalation. The change in cell cycle concludes the tumor. Elongation of the cell cycle caused by the existence in the control points in G1 and G2 phases. Neoplastic cells are not capable of preventing cell division at the control points (G1/S and G2/M), and proliferation of cells becomes deregulated.[20]

5. Mitogen-activated protein kinases (MAPK) signal pathways

MAPK signaling pathway induces signals for the division of cells. Hence, carcinogenesis caused by deregulation of MAPK signal pathways.[19] Such technique is applied to induce apoptosis.[21]

6. Cyclooxygenase (Cox-2) pathways

Cyclooxygenase is known as a Cox-2 inhibitor which catalyzed the prostaglandin synthesis. Inhibition of COx-2 affects the growth of tumor cells through inhibiting cell proliferation[22]

7. Intervention with microscopically small tubules

Microscopically small tubules are known as microtubules present in the cytoplasm of cells. Microtubules play a vital role in preventing alignment of the daughter chromosomes and consequently stop of mitosis at anaphase, which finally followed by apoptosis.[23] It was reported that herbaceous plant phytochemicals such as vinca alkaloids (vincristine and vinblastine) and taxanes are important microtubulin-binding factors.

8. Topoisomerase inhibitor

Herbal drugs are having a crucial role in cancer treatment with balancing capacity of topoisomerases. Camptothecins inhibit topoisomerase-I, and epipodophyllotoxins inhibit topoisomerase II.[23]

CHEMOPREVENTIVE AGENT

1. Vitamin A

Vitamin A is obtained from the diet. It is present mainly in the form of retinyl esters. These esters are subsequently de-esterified to retinol. Irreversible oxidation of retinol takes place to form retinoic acid.[24] Retinoic acid is a form of vitamin A that has the ability to bind with nuclear receptor sites in the cells. It is essential for the normal growth and differentiation of epithelial cells.[25] Two separate divisions of nuclear receptors are present that regulate the effects of vitamin A on cellular differentiation. They in turn modify the effects of agents such as prostaglandins, vitamin D, and steroid and thyroid hormones. The chemopreventive action of vitamin A and its derivatives is based on restoring the expression of retinoic acid receptor beta mRNA. It in turn promotes normal tissue growth and differentiation.[26]

2. Vitamin E

Several human intervention trials have examined the ability of vitamin E to prevent carcinogenesis. The chemopreventive mechanisms of vitamin E include stimulation of wild-type p53 tumor suppressor gene, activation of heat shock proteins, down-regulation of mutant p53 and antiangiogenic effect brought about by blockage of transforming growth factor-alpha.[27]

3. Vitamin C

Vitamin C being a potent water-soluble antioxidant has generated interest in the field of chemoprevention as a potential cancer-preventive agent. Vitamin C is required for the recycling of glutathione, which is an endogenous antioxidant. It has been theorized to protect

against the ability of cancer cells to invade tissue, in part by strengthening the cellular matrix.[28]

4. Green Tea

One of the most widely consumed beverages across the world is tea. Green tea, black tea, or oolong is the various forms of tea available. Black tea comprises around 80% of tea products. Epicatechin (EC), epigallocatechin (EGC), EC-3-gallate, and EGC-3-gallate (EGCG) are the four main polyphenols present in green tea. EGCG, is the most active phenolic compound in green tea. Experimental studies conducted in chemically induced rodent carcinogenesis models and in different cancer cells in culture have demonstrated EGCG to have potential antitumor activity and chemopreventive action.[29,30]

5. Curcumin

Curcumin inhibits cell growth in many types of cancers, including some uncommon types, i.e. cholangiocarcinoma, medulloblastoma, and uterine leiomyosarcoma (refs). Curcumin has been shown to be beneficial in all 3 stages of carcinogenesis. In fact, a number of studies showed beneficial effects of curcumin in neoplastic and pre-neoplastic diseases, among the others, multiple myeloma, pancreatic and colon cancers [52, alter refs]. Beneficial effects of curcumin are related to the inhibition of NF-κB and, consequently, induce *anti-inflammatory, antioxidant, and antitumor effects* (refs). Curcumin was shown to be a strong inhibitor of NF-κB activity and its inhibitory effect on NF-κB related pathways often leads to cellular apoptotic response. Nuclear factor kappa B (NF-κB) is a strong mediator of inflammation and, in a majority of systems, supports the pro-proliferative features of cancer cells. The application of various anticancer drugs, cytostatics, triggers signals which lead to an increase in cellular NF-κB activity.[31]

6. Lycopene

Lycopene is the most promising carotenoid with effects related to cancer prevention and therapy. Moreover lycopene plays an important role in regulating hormone action, cell cycle, apoptosis, gap-junction communication and epigenetics, suggesting that their antioxidant activity may not be solely responsible for their anticancer effect[32] . lycopene reveals to be a promising agent in cancer therapy, especially for prostate cancer. A recent study reported that lycopene administration increased the antitumor activity of docetaxel in castration-resistant prostate tumor models.[33]

7. Quercetine

Food-derived flavonoid quercetin, widely distributed in onions, apples, and tea, is able to inhibit growth of various cancer cells indicating that this compound can be considered as a good candidate for anticancer therapy. Quercetin is abundant in vegetables and fruits.[35] usually in glycosylated, for example in form of rutin.[35] However, a study analyzed the inhibition of quercetin vs rutin on azoxymethane-induced colorectal carcinogenesis in rats, supporting that quercetin probably represents the active form inhibiting cancer respect to rutin.[35] In fact quercetin is one of the most promising phytochemicals that could be use for cancer chemoprevention. Efficacy against several cancer types was demonstrated in both *in vitro* and *in vivo* assays and different epidemiological studies demonstrated its effect against lung cancer.[36] Quercetin has an antioxidant effect as well as modulating different intracellular signalling cascades. In fact quercetin possesses free radicals scavenging *antioxidant activity* and several anticancer effects including *anti-mutagenic, and anti-proliferative activities*, regulating several cell-signaling pathways, cell cycle, and apoptosis.

8. Genistein

Genistein is a soy isoflavone identified as dietary components having an important role in reducing the incidence of breast and prostate cancers, giving a rationale for the lower incidence of these forms of cancer in Asian countries such as Japan and China that consume a traditional diet high in soy products, compared to United States and European countries (reviewed in[37]). Moreover, it has been shown that genistein inhibits the activation of NF-κB and AKT signaling pathways, both of which are known to maintain a homeostatic balance between cell survival and apoptosis. More in details, genistein treatment abrogated NF- κB DNA binding in cell lines and in UV-light-stimulated skin of SENCAR (sensitivity to carcinogenesis) mice.[38,39] Inactivation of NF-κB by genistein was also associated with down regulation of AKT in several cell lines[40,41], suggesting that inhibition of the interaction between AKT and NF-κB might be interpreted as a novel mechanism responsible for pro-apoptotic activity of genistein.

9. Resveratrol

Resveratrol is a phytoalexin found in many fruits and plants including red wine, grapes, berries and peanuts.[42] The roots of the p*olygonum cuspidatum*, or Japanese knot weed, contains the highest naturally occurring levels of resveratrol and has been used in traditional Japanese and Chinese medicinal treatments for dermatitis, bacterial infections and

inflammation. Plants produce resveratrol in response usually to mechanical injuries, ultraviolet radiation and as a defense for viral and fungal infections[42,43] Early studies identified that resveratrol has anticancer effects against several different tumor type and affects multiple stages of tumor initiation and proliferation. Specifically, resveratrol can induce cancer cell apoptosis by interfering with multiple signaling pathways activated in transformed cells.[44]

10. Capsicum Annum

C. annuum is widely used as vegetables and food colorants which are a good source of carotenoid pigments[45,46]. The red carotenoids in paprika (*C. annuum* L.) are mainly capsanthin, capsorubin, and capsanthin 3,6-epoxide in which capsanthin and capsorubin have been reported to show antioxidative activities.[47,48]

11. Glucosinolate Derived Organo Sulphur Compound

Cruciferous vegetables, including broccoli, cabbage, and cauliflower, among others, are the major sources of organosulfur compounds. Cruciferous vegetables contain over 120 glucosinolates that give rise after hydrolysis to different aglycone metabolic products, such as the group of isothiocyanates, which are principally responsible for the antitumor activities of cruciferous plants. The hydrolysis of glucosinolates requires the activity of myrosinase enzymes, which are present in the cruciferous plant itselfand in the human gut.[49]

12. Allium Sativum

Garlic and its organo sulfur constituents exert anticancer effects by enhancing carcinogen detoxification and immunity, ROS scavenging, suppressing proliferation, angiogenesis and inflammation, inducing apoptosis and DNA repair, and inhibiting angiogenesis.[50] These effects are mediated through the inhibition of hepatic CYP-mediated activation of NFkB, induction of drug-metabolizing enzymes, downregulation of cyclins, CDK, Bcl-2 and Bcl-xL, transcriptional activation of CDK inhibitors, Bax, Bad and p53, and inhibition of HDAC activity.[50,51,52]

13. Neem Limenoids

Neem (*Azadirachta indica* A. Juss), a rich source of limonoids exhibits antioxidant, anti inflammatory and anticancer cinogenic effects.[53] Several laboratoy studies demonstrated that the neem limonoids nimbolide and azadirachtin inhibit the growth of malignant cells *in vitro* and *in vivo* by targeting XME, cell proliferation, apoptosis, invasion, and angiogenesis.[54,55]

14. Ellagic Acid

Ellagic acid, a dimer of gallic acid (hydroxybenzoic acid derivative),[56] is the main polyphenol in pomegranate. It is responsible for more than 50% of the antioxidant activity of pomegranate juice. It has mainly been studied in relation to prostate cancer, showing antiproliferative activity,[57] but it was also found to induce cell cycle arrest, antiproliferative effect, and apoptosis on cells from several cancer types at concentrations that are within or below those found in plasma after oral intake[58] These effects were principally related to the inhibition of NF-κB[56] and IGF-II,[59] the induction of p53/p21 expression, and the modulation of pro- and anti-apoptotic proteins.

15. Luteoline

This is one of the most effective antitumor flavones, and is found in many medicinal herbs and vegetables such as parsley, celery, pepper, and dandelion. Plants rich in luteolin were used in traditional Chinese medicine to treat hypertension, inflammatory disease, and cancer. Diets rich in flavones correlate with a lower risk of breast cancer, and luteolin intake has been reported to significantly decrease the incidence of ovarian cancer. The concentration of luteolin in standard daily nutrition is relatively low (<1 mg/day), but it is available at low cost in higher amounts from plants that are not traditionally consumed, such as *Reseda luteola*. Luteolin is usually glycosylated in plants, and it is released from dietary components during absorption. It inhibits the proliferation of various tumor cell types, including nasopharyngeal and oral squamous cancers. At the molecular level, it inhibits several tumor-related signaling pathways such as Akt and NF-κB pathways.[60]

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