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DIETARY PHYTOCHEMICALS AND THEIR ROLE IN CHEMOPREVENTION OF CANCER

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ABSTRACT

Cancer is one of the most challenging health problems in the entire world today. It is a complex disease to treat. 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 anomalies 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 chemopreventive agents inhibit, retard or reverse multi-stages of carcinogenesis via their anticarcinogenic and antimutagenic properties and also suppress cancer proliferation through induction and stimulation of cell growth. Research has shown that they exert these abilities by counteracting certain signals that cause genotoxic damage and reduction-oxidation imbalance in cells. This discourse reviews the role of phytochemical chemopreventive agents, benefits and limitations associated with their use in cancer prevention.

Keywords: Cancer, Phytochemicals, WHO

INTRODUCTION

Cancer is a growing health problem around the World. It is one of the leading causes of morbidity and mortality worldwide. WHO reported more than 10 million cases of cancer per year worldwide. According to Hetts (Hetts 1998) this multistage carcinogenic disease is a net accumulation of atypical cells arising from excess proliferation, an insufficient apoptosis or a combination of the two. Cancer cells occur as a result of unique and complicated multiple genetic disorders that may arise from exposure to environmental and occupational carcinogenic agents or dietary habits and infectious agents (Sugimura 1992). Synthetic anticancer drugs evoke severe side effects and in many cases. The increased incidence of cancer in the world today justifies the application of phytochemical chemoprevention.

CHEMOPREVENTION WITH DIETARY PHYTOCHEMICALS: Chemoprevention has been in the limelight as a new anti-cancer strategy and various reviews focus on the subjects, principles, mechanisms and prospects of chemoprevention have been suggested (Bode and Dong 2000). Chemoprevention by photochemical lower the risk of cancer by radical scavenging, anti-oxidation mechanisms, anti-inflammatory and anti-proliferative mechanism (Kwak and Kenster 2010, Parys et al 2010, Surh 2003). These agents reported to interfere with tumor initiation, promotion and progression. Chemopreventive agents are broadly classified into two major categories- blocking agents and suppressing agents. Blocking agents inhibit the carcinogens from interaction with target molecules, metabolic activation or subsequently interaction with important cellular molecules- DNA, RNA and proteins. These agents suppress carcinogen activation and promote detoxification. While suppressing these agents prevent the tumor promotion and progression.
Plants have been used as a source of traditional medicines throughout history. Besides containing macronutrients like protein, fat, carbohydrate plants also have non-nutritive micronutrients-dietary fiber, vitamins and minerals. Plants also contain non-nutritive components like polyphenols, terpenes and

alkaloids that could serve considerable health advantages beyond the basic nutrition (Aggrawal and Shisodia, 2006). These non-nutritive components are called phytochemicals and have been reported to have substantial biological properties such as anti-carcinogenic and anti-mutagenic effects (Surh, 2003). Hundreds of phytochemicals have been identified as potential chemopreventive agent: allicin,anethol, capsaicin, catechins, cucumin, diallyl sulfide, dietary fiber, diosgenin, ellagic acid, eugenol, evodiamine, genistein, gingerol, indole-3-carbinol, isoflavones, lutein, lycopene, phytosterols, resveratrol, S-allyl cysteine, saponins, selenium, silymarin, ursolic acid, β-carotene to name a few. (Nichols and Katiyar, 2010).

PHYTOCHEMICALS USED AS CANCER CHEMOPREVENTIVE AND TREATMENT AGENTS

Apigenin from parsley: Apigenin is obtained from the vegetables like parsley, celery, chamomile (Hoensch 2011) and Egyptian plant *Moringa peregrine* (El-Afy TS2011). It demonstrates cytotoxic activities against breast cancer lines (MCF 7, colon cell line (HCT 116), and its cytotoxic activity is comparable to that of doxorubicin (TS 2011). This phytochemical is considered as a mediator for chemoprevention in the cancerous process and induces a process of autophagia (Ferriera2006). It induces apoptosis in human colon cancer prevention (LeonardiT2010), affects leptin/leptin receptor pathway, and induces cell apoptosisin lung adrenocarcinoma cell line (BrunoA2011).

Curcumin from turmeric: Curcumin is the major components of popular Indian spice turmeric, *Curcuma longa*. Its anti-cancer effects have been studied for colon cancer, breast cancer (Bachmeier 2010), lung metastases and brain tumor (Senft2010). Curcumin modulate growth of tumor cells through regulation of multiple cell signaling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-x, cFLIP, XIAP, c-IAPI), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53,p21), death receptor pathway (DR4, DR5), mitochondrial pathways, and protein kinase pathway (JNK, Akt, and AMPK) (Ravindran 2009). Curcumin inhibits p65 and cell invasion by downregulation of COX-2 and MMP-2 expression (Su CC 2006); by suppression of gene expression of EGFR and modulation of Akt/mTOR signaling, and inhibition of cell growth (Chen2006, Johnson2009).

Crocetin from saffron: Saffron is a spice from the flower of the Saffron crocus and a food colorant present in the dry stigmas of the plant *Crocus sativus L.* Saffron is reported as a potential agent for a novel anti-cancer drug against hepatocellular carcinoma (Gutheil2011, Amin2011, Abdullaev2004). The ethanolic extracts are also reported for the studies on human lung cancer (Samarghandian 2011), pancreatin cancer cell line (Bakshi 2010), skin carcinoma (Das 2010), colorectal cancer cell (Aung 2007) and breast cancer (Chryssanthi 2011). Crocetin affects the growth of cancer cells by inhibiting nucleic acid synthesis, enhancing anti-oxidative system, inducing apoptosis and hindering growth factor signaling pathways (Gutheil2011). In another study conducted by Nam it has been shown that this is effective for the inhibition of LPS-induced nitric oxide release , for the reduction of the produced TNF-α, IL-1β, and intracellular reactive oxygen species, for the activation of NF-κB, and blockage of the effect of LPS on hippocampal cell death (Nam 2010).

Cyanidins from grapes: Cyanidin is an extract of pigment from red berries such as grapes, blackberry, cranberry, raspberry, or apples and plums, red cabbage and red onion. Its antioxidant and radical-scavenging effects reduce the risk of cancer. Cyanidin is reported to inhibit cell proliferation, and iNOS and COX-2 gene expression in colon cancer cells (Kim2008). C3G blocks ethanol-induced activation of the ErbB2/cSrc/FAK pathway in breast cancer cells and may prevent/reduce ethanol-induced breast cancer metastasis (Xu2011). Cyanidin markedly inhibited UVB-induced COX-2 expression and PGE2 secretion in the epidermal skin cell line by suppressing NF-κB and AP-1 which are regulated by MAPK. In this study, MKK-4, MEK1 and Raf-1 are targets of cyaniding for the suppression of UVB-induced COX-2 expression (Kim2010). Cyanidin-3-galactoside and cyanidin-3-glucoside are found to be BRCP substrates, and cyanidin, 3,5-diglucoside, and cyanidin -3- rutinoside are potential BRCP inhibitors but their effects were weak (Dreiseitel 2009).

Diindolylmethane (DIM)/ Indole-3-cabinol (I3C) from Brassica vegetables: Indole-3-cabinol (I3C) is found in Brassica vegetable, such as broccoli, cauliflower, collard greens. Diindolylmethane (DIM) is a digestion derivative of indole-3-carbinol via condensation formed in the acidic environment of the stomach. Both are studied for their anticarcinogenic effects. I3C has been studied for cancer prevention for tobacco smoke carcinogen-induced lung adenocarcinoma in A/J mice and it was found that the lung cancer preventive effects are mediated via

modulation of the receptor tyrosine kinase/P13KAkt signaling pathway, at least partially (Qian2011). I3C and DIM demonstrated tremendous anti-cancer effects against responsive cancers like breast, prostate and ovarian cancers (Acharya2010).

Epigallocatechin gallate (EGCG) from green tea: EGCG is the most abundant catechin compounds in green tea. Yang et al reviewed tea with cancer prevention on molecular level, molecular targets and human relevance of tea constituents (Yang 2007, 2006; Lambert 2003). It has been reported that EGCG binds and inhibits the anti-apoptotic protein Bcl-xl (Leone2003), a protein involved in both cancer cell and normal cell survival (Cherbonnel-Lasserre1997). EGCG suppressed AOM-induced colonic premalignant lesions in mice (Shimizu2008), interfered with EGFR signaling (Adachi2009), and inhibited hepatocyte growth factor-induced cell proliferation in human colon cancer cells (Larsen2010). EGCG inhibits mitogen-activated protein kinases (MAPK), cyclin dependent kinases, growth factor-related cell signaling, activation of activator protein I and NF-κB, topisomerase I and matrix metalloproteinases.

Fisetin from strawberries, apples: Fisetin is a flavone found in various plants such as Acacia greggii, Acacia berlandieri, Euroasian smoketree, parrot tree, strawberries, apple, persimmon, grape, onion, and cucumber (Gabor1966, Maher2011, Arai2000). Fisetin induces the expression of Nrf2 and the phase II gene product HO-1 in human retinal pigment epithelial (RPE) cells which could protect RPE cells from oxidative stress-induced death with a high degree of potency and low toxicity (Hanneken2006) and reduced hydrogen peroxide-induced cell death (Lee2011). Fisetin inhibited Wnt signaling through the modulation of beta-catenin expression, transcriptional activity and of the subsequent expression of Wnt target genes (Teiten 2011). Fisetin decreased cell viability with G-1 phase arrest and disrupted Wnt/β-catenin signaling (Syed 2011), exhibited an inhibitory effect on the abilities of adhesion, migration, and invasion, and significantly decreased the nuclear levels of nuclear factor kappa B (NF-κB) and aactivator protein-1 (AP-1) (Liao2009). Fisetin was also found to help to overcome the multidrug resistance caused by the high expression of the plasma membrane drug transporter P-glycoprotein (P-gp), which is associated with an elevated intracellular glutathione (GSH) content in various human tumors (Angelini2010).

Genistein from soyabean: Genistein ia an isoflavone originates from a number of plants such as lupine, fava beans, soybeans, kudzu, and psoralea, *Flemingia vestita*, and coffee. Genistein has been found to have antigiogenic effects and may block the uncontrolled cell growth associated with cancer, by inhibiting the enzymes that regulate cell division and cell survival. This phytochemical is considered as DNA topoisomerase II inhibitor (Markovits1989, Lopez-Lazaro2007). Estrogen metabolism produces genotoxic waste, which may cause disruption of cell cycle, apoptosis, DNA repair, and forms tumor. Genistein can compete with the estrogen by binding to its receptor and shows higher affinity towards estrogen receptor β and towards estrogen receptor α (Kuiper1998). Genistein was proved to increase the rate of growth of some estrogen receptor in breast cancer and rate of proliferation of estrogen-dependent breast cancer when not co-treated with an estrogen antagonist (Ju2006). In colon cancer, genistein is thought to contribute to reduced colonic inflammation in 2, 4, 6-trinitrobenzenesulfonic acid (TNBS)-induced colitis (Seibel2009).

Gingerol from gingers: Gingerol is the active component of fresh ginger with distinctive spiciness. Gingerol has been widely studied for its anticancerous effects for the tumors in colon (Jeong 2009), breast and ovarian (Lee 2008, Rhode 2007) and pancreas (Park 2006). Gingerol has demonstrated antioxidant, anti-inflammation , and antitumor promoting activities, decreases iNOS and TNF-alpha expression via suppression of IκBα phosphorylation and NF-κB nuclear translocation (Oyagbemi,2010).On human hepatocarcinoma cells, gingerol, along with 6-shogaol were found to exert anti-invasive activity against hepatoma cells through regulation of MMP-9 and TIMP-1, and 6shogaol further regulated urokinase-type plasminogen activity (Weng 2010).

Kaempferol from tea, broccoli, grapefruit: Kaempferol is a natural flavonol isolated from tea, broccoli, Witch-hazel, grapefruit, Brussel sprouts, apples etc. (Park 2006). Kaempferol has been studied for pancreatic cancer (Nothlings2007), and lung cancer (Cui 2008). It has been investigated for its antiangiogenic, anticancer, and radical scavenging effects (Gacche2011, Calderoon2011). Kaempferol showed moderate cytostatic activity of 24.8-64.7μM in cell lines of PC3, HeLa and K562 human cancer cells (Bigovic 2011). Luo et al found that kaempferol induces apotosis in ovarian cancer cells through the activation of p53 in the intrinsic pathway (Luo 2011). Niestroy et al studied that Kaempferol, BaP, and quercetin activated Nrf2pathway by induction of Nrf2, and its target genes NQO1, GSTP1, GSTA1 and GCLC. However, in spite of their own induction potential for Nrf2, both kaempferol and quercetin

counteract the effects of BaP on expression of AhR, AhRR, Nrf2, GSTP1 and NQO1 (Niestroy 2011).

Lycopene from tomato: Lycopene is a bright red pigment and phytochemical from tomatoes, red carrots, watermelons, and red papayas. It shows antioxidant activity and chemopreventive effects in many studies, mainly in prostate cancer. Its anti-cancer activity is attributed to activating cancer preventive enzymes such as phase II detoxification enzymes (Giovannucci1995). Lycopene finds role in the prevention of endometrial cancers and other tumors (Levy 1995), shows inhibitory effects on breast cancer cells (Nahum 2001), prostate cancer cells (Giovannucci1995) and colon cancer cells(Narisawa1996).

Phenethyl Isothiocyanate (PEITC) from cruciferous vegetable: PEITC from cruciferous vegetable such as watercress, broccoli, cabbage, etc. have been studied for induction of apoptosis in cell lines that are resistant to some currently used chemotherapeutic drugs. PEITC has strong potency against melanoma, chemopreventive against breast cancer cells (Hahm2011, Moon2011), non-small cell lung cancer (Yan2011), cervical cancer (Huong2011, Wang2011), oestrogenic sarcoma U-2 OS (Wu2011) prostate cancer (Xiao2010, Hwang2010, Powolny2010), and myeloma cell lines (Jakubikova2011).

Resveratrol from grapes: Resveratrol is a natural phenol and can be found in the red grapes skin, peanuts and in other fruits. In his study Jang et al reported that Resveratrol possess anti-initiation activity by inducing phase II drug metabolizing enzymes, anti promotion activity by mediating anti-inflammatory effects and inhibiting cyclooxygenase and hydroperoxidase functions, and anti-progression activity by inducing cell differentiation in human promyelocytic leukemia (Jang 1997). Resveratrol has anti-carcinogenesis effects in skin tumor (Kim2011, Nichols2010) and gastrointestinal tract tumor in rats (Li 2002). Resveratrol was found to inhibit metastasis via reducing hypoxia inducible factor-1α and MMP-9 expression in colon cancer cells (Wu2008).

Rosmarinic acid from rosemary: Rosmarinic acid (RA) is a natural antioxidant found in culinary spice and medicinal herbs such as lemon balm, peppermint, sage, thyme, oregano, and rosemary to treat numerous ailments, The extract of rosemary has vital roles in anti-inflammation, anti-tumor,and anti-proliferation in various studies. Rosmarinic acid inhibits the migration, adhesion, and invasion in Ls174-T human colon carcinoma cells (Xu2010). In human leukemia U938 cells, rosmarinic acid significantly sensitized TNF-α-induced apoptosis through the suppression of NF-κB and reactive oxygen species (ROS), and suppressed NF-κB activation through the inhibition of phosphorylation and degradation of IκBα (Moon2010). Rosmarinic acid has the potentiality to reduce 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 promoter activity and protein levels in colon cancer HT-29 cells (Scheckel2008).

Sulforaphane from cruciferous vegetables: Sulforaphane is an organosulfur compound obtained from cruciferous vegetables like broccoli, Brussels sprouts and cabbages. Sulforaphane has exhibited induction of phase II drug metabolism enzymes of xenobiotic transformation, such as quinine reductase and glutathione S-transferase, and enhances the transcription of tumor suppression proteins. It protected skin against UV radiation damage (Talalay2007) and inhibited histone deacetylase (HDAC) activity (Dashwood2007). Sulforaphane induced cytotoxicity and lysosome-and mitochondria-dependent cell death in colon cancer with deleted p53. It also increased Bax in the presence of JNK-mediated Bcl-2 inhibition followed by mitochondrial release of cytochrome c and activation of apoptosis (Rudolf2009). In human colon HT-29 cancer cells, sulforaphane increased AP-1-luciferase activity dose-dependently and then decreased at higher doses, and induced JNK activity (Jeong2005). In human prostate cancer PC-3 cells sulforaphane suppressed NF-κB and NF-κB-regulated gene expression through IκB-alpha, and IKK pathway (Xu2005). Sulforaphane demonstrated synergistic effects when combined with EGCG in HT-29 AP-1 human colon carcinoma cells (Khor 2006), or with dibenzoylmethane in $Apc^{Min/+}$ mice for reducing intestinal adenomas (Xu2005), or with phenethyl isothiocyanate in down-regulating inflammation markers TNF, IL-1, NO, PGE2 and inducing phase II/antioxidant enzymes like HO-1, NQO1 in RAW 264.7 cells. There are many laboratories very active in the research on sulforaphane and it is a promising compound for its druggability.

Triterpenoids from wax-like coatings of fruits and medicinal herbs: Triterpenoids are biosynthesized in plants by cyclization of squalene, a triterpene hydrocarbon and precursor of all steroids (Philips 2006). This group of phytochemicals is sub-classified into cucurbitanes, dammaranes, ergostanes, friedelanes, lanostanes, limonoids, lupanes, oleananes, tirucullanes, ursanes (Bishayee2011) and so on. Triterpenoids had been used in various in vitro

and in vivo studies for the chemoprevention and therapy of breast cancer and pancreatic cancer (Chidambara2011) using triterpenoids. This group of phytochemicals exert their chemopreventive and anti-cancer activities via enhancing apoptosis, NO, stimulating DR4, DR5, caspase-3/7, caspase 8, Bax, JNK, MAPK, p38, decreasing phosphor-STAT3, PARP cleavage, suppressing COX-2, IL-1β, NF-κB, IKKα/β, cyclin D1,cyclin a, cyclin B1, ERα protein and mRNA, HER2 phosphorylation caveolin -1, Akt, JAK1, STAT 3, Bc12, c-Jun, c-Fos, JNK, mTOR, blocking cell cycle at G1, G-S, G2-M, etc .

Vitamin D from mushroom: Light exposed mushroom could also be excellent source of Vitamin D. Vitamin D has been involved in breast cancer (Buyru2003), colon cancer (Gorham2007), ovarian cancer (Garland2006), and pancreatic cancer (Skinner2006). The mechanism of action is still not clear but may be vitamin D receptor (VDR) appears playing an important role.Vitamin D2 (ergocalciferol) and D3 (cholecalciferol) are the two physiologically relevant vitamin Ds. Vitamin Ds anti-cancer effect may be mediated via vitamin D receptors (VDR) in cancer cells (Buyru2003). Increased risk of breast cancer has been linked with the polymorphisms of VDR gene (Chen2005). Kovalenko et al showed that low diet vitamin D or VDR deletion provided a prostrate environment that is permissive to early pro-carcinogenic events that enhance prostate cancer risk (Kovalenko2011). Stefanska et al reported that vitamin D3 possess high efficacy in the reduction of PTEN promoter methylation by a complex regulation of the DNA methylation machinery (Stefanska2011). But vitamin D supplementation failed to demonstrate a benefit in prostate cancer patients in clinical practice (Buttigliero2011). Therefore, vitamin D's skin cancer and prostate cancer prevention are still inconclusive (Clipp2011, Barnett2011).

Vitamin E from plant oil: Vitamin E represents a family of compounds comprising both tocopherols and tocotrienols and is a fat-soluble antioxidant that exists in foods like wheat germ oil, sunflower oil, and safflower oils. Both these tocopherols and tocotrienols have anti-tumor activitydue to their antioxidant properties. Both show antiproliferative, proapoptic and COX-2 inhibiting effects in in vitro studies (Wada2011). In vitro and in vivo studies showed the activity of tocotrienols (hypomethylated forms) in cytoprotection, cancer prevention and even in chemotherapy (Viola2011). Nesaretnam and Meganathan reported that tocotrienols have their roles in inflammation and cancer by cellular signaling pathways of NF-κB, STAT3, and COX-2 (Nesaretnam2011). Unlike tocopherols, tocotrienols possess an unsaturated isoprenoid side chain that confers superior anti-cancer properties. In pancreatic cancer cell lines, tocotrienols selectively inhibit the HMG-CoA reductase pathway through posttranslational degradation and suppress the activity of transcription factor NF-κB. Sylvester et al discussed the approach to combine tocotrienols with agents that have complementary anticancer mechanisms of action to achieve synergistic anticancer response (Sylvester2011).

MECHANISMS INVOLVED IN CANCER CHEMOPREVENTION

Chemopreventive agents as inhibitors of the NF-κB activation pathway: The multistep process of carcinogenesis consists of three phases: tumor initiation, promotion and progression phases. 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. These dietary agents have been classified as chemopreventive agents since their ability to delay the onset of the carcinogenic process has been studied extensively. Because these chemopreventive agents are derived from natural sources, they are considered pharmacologically safe.

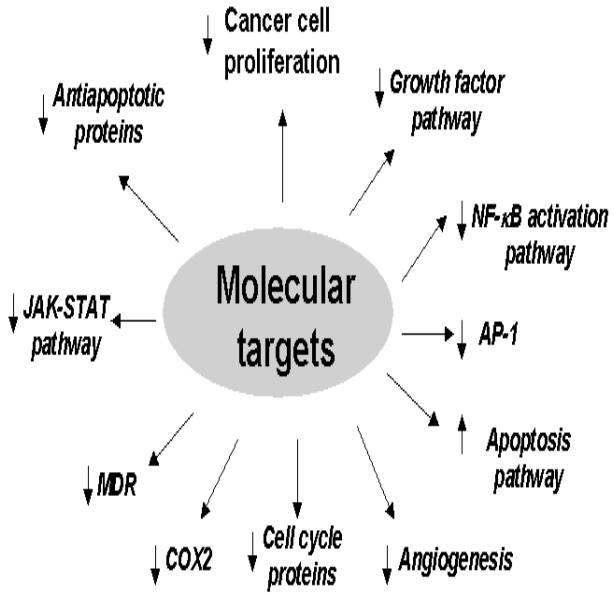

Fig1 Molecular targets of chemopreventive agents in cancer

Chemopreventive agents as inhibitors of the NF-kB activation pathway : NF-κB is a family of

closely related protein dimers that bind to a common sequence motif in the DNA called the κB site (Garg2002). Research over the past decade has revealed that NF-κB is an inducible transcription factor for genes involved in cell survival, cell adhesion, inflammation, differentiation and growth. In most resting cells, NF-κB is sequestered in the cytoplasm by binding to the inhibitory IκB proteins which blocks the nuclear localization sequences of NF-κB. NF-κB is activated by a variety of stimuli such as carcinogens, inflammatory agents, tumor promoters including cigarette smoke, phorbol esters, okadaic acid, H_2O_2 and TNF. These stimuli promote dissociation of IκB-α through phosphorylation, ubiquitinylation and its ultimate degradation in the proteasomes. This process unmasks the nuclear localization sequence of NF-κB, facilitating its nuclear entry, binding to κB regulatory elements and activation of transcription of target genes.

Chemopreventive agents as inhibitors of the AP-1 activation pathway: Activated protein-1 (AP-1) is another transcription factor that regulates the expression of several genes that are involved in cell differentiation and proliferation. Functional activation of the AP-1 transcription complex is implicated in tumor promotion as well as malignant transformation. This complex consists of both homo or hetero dimers of the members of the JUN and FOS family of proteins (Eferl2003). This AP-1 mediated transcription of several target genes can also be activated by a complex network of signaling pathways that involves external signals such as growth factors, mitogen activated protein kinases (MAPK), extracellular-signal regulated protein kinases (ERK) and JUN-terminal kinases (JNK). Some of the target genes that are activated by AP-1 transcription complex mirror those activated by NF-κB and include Cyclin D1, bcl-2 , bcl-X_L, VEGF, MMP and urokinase plasminogen activator (uPA). Expression of genes such as MMP and uPA especially promotes angiogenesis and invasive growth of cancer cells. Most importantly, AP-1 can also promote the transition of tumor cells from an epithelial to mesenchymal morphology which is one of the early steps in tumor metastasis. These oncogenic properties of AP-1 are primarily dictated by the dimer composition of the AP-1 family proteins and their post-transcriptional and translational modifications.

Chemopreventive agents as inhibitors of cell proliferation and initiators of apoptosis: Several reports were published which showed that activation of NF-kB promotes cell survival and proliferation and down regulation of NF-kB sensitizes the cells to apoptosis Expression of several genes including bcl-2, bcl-X_L, cIAP, survivin, cyclin D1, TRAF1, TRAF2 have been reported to be up-regulated by NF-kB (Garg2002). The proteins coded by these genes function primarily by blocking the apoptosis pathway. Several studies have demonstrated that NF-kB activation promotes cell survival and proliferation mechanisms and that suppression of NF-kB leads to an abrogation of these mechanisms. Similarly, c-JUN is primarily a positive regulator of cell proliferation since c-JUN deficient fibroblasts have a marked proliferation defect *in vitro* and *in vivo*.

Chemopreventive agents as inhibitors of growth factor activation pathway: The potent cell proliferation signals generated by various growth factor receptors such as the epidermal growth factor (EGF)-receptor, insulin-like growth factor (IGF)-1 receptor and VEGF-receptor networks constitute the basis for receptor driven tumorigenicity in the progression of several cancers (Hahn2002). Several chemopreventive phytochemicals including curcumin, genistein, resveratrol and catechins have been recently shown to be powerful inhibitors of several growth factor receptors, including EGFR. Some of these phytochemicals, such as curcumin also possess the capacity to inhibit the ligand stimulated activation of the EGF-Receptor indicating that they have the potential to break the autocrine loops that are established in several advanced cancers (Korutla1995).

These chemopreventive chemicals function by inhibiting other tyrosine kinases such as c-src which are involved in the coupling of activation of the G-protein coupled receptor to the transactivation of EGF-Receptor which occurs extensively in established cancers. Curcumin was earlier shown to not only inhibit the tyrosine kinase activity of this receptor but also deplete the protein itself, by interfering with the function of the ATP dependent GRP94 chaperone protein which is involved in the maintenance of the properly folded state of the receptor (Hong1999).

Chemopreventive agents as inhibitors of the JAK-STAT pathway: Even though cancer arises by several genetic or epigenetic mechanisms contributing to a number of abnormal oncogenic signaling pathways, all seem to converge on a very limited number of nuclear transcription factors that function as final effectors, starting specific gene expression patterns for a particular cancer. They are the canonical STAT (signal transducers and activators of transcription) family of proteins (Yu2004). They can be activated by phosphorylation through JAK kinases or cytokine receptors, G-protein

coupled receptors or growth factor receptors such as EGFR or by platelet derived growth factor receptor that have intrinsic tyrosine kinase activity, or by intracellular non-receptor tyrosine kinase recruitment. Of the seven STAT proteins known so far, constitutive activation of STAT3 and STAT5 have been implicated in human cancers such as multiple myeloma, lymphomas, leukemias and several solid tumors which makes them logical targets for cancer therapy. These STAT proteins contribute to cell survival and growth by preventing apoptosis through increased expression of anti-apoptotic proteins such as bcl-2 and bcl-X_L.

Chemopreventive agents as inhibitors of multi-drug resistance: The use of chemotherapy to treat cancer invariably results in the development of broad resistance to a wide variety of drugs with different chemical structures and mechanism of action. The multidrug resistance (MDR) related P-Glycoprotein is inherently expressed at high levels in cancers derived from epithelial tissues such as kidney, prostrate and colon. In the multidrug resistant human cervical carcinoma cells (KB-V1), curcumin was shown to down regulate the expression of P-glycoprotein at the protein as well as at the RNA levels (Anuchapreeda2002). Treatment of these cells increased their sensitivity to vinblastine, which was consistent with the increased accumulation of the rhodamine (Rh123) dye. Recent reports suggest that agents such as curcumin may interfere with the drug resistance processes mediated by Topoisomerase-II (TOPO-II) poisons, either by inhibiting the associated heat shock proteins or by inhibiting the intracellular proteasomal function (Aggarwal2003).

Chemopreventive agents as inhibitors of COX-2: Many studies revealed the importance of regulation of cyclo-oxygenase-2 (COX-2) expression in the prevention and in the treatment of several malignancies. Over expression of this enzyme is a consequence of deregulation of transcriptional and post- transcriptional control. Several growth factors, cytokines, oncogenes, tumor promoters stimulate COX-2 transcription. Depending upon the stimulus and the cell type, different transcription factors including AP-1, NF-IL-6, NF-κB can stimulate COX-2 transcription (Subbaramaiah2003). Curcumin was one of the first chemopreventive phytochemicals shown to have significant COX-2 inhibiting activity through the suppression of NF-κB. Thus, non-toxic compounds such as curcumin is useful in the treatment of several cancers targeting angiogenesis since COX-2 expression stimulates angiogenesis (Iniguez2003). COX-2 inhibitors are useful in the treatment of advanced breast cancers through inhibition not only of HER-2/neu activity but also of aromatase activity (Subbaramaiah 2003).

Chemopreventive agents as inhibitors of angiogenesis: Angiogenesis is the formation of new blood vessels from existing ones. It is the basis of several physiological processes such as embryonic development, placenta formation and wound healing. Several inhibitors of angiogenesis are in clinical trials. These include curcumin, resveratrol and catechins (Arbiser1998, Brakenhielm2001, Lamy2002, Chen2004). Curcumin can interfere with the activity of MMP-2 and 9, reducing the degradation of ECM which forms the basis of angiogenic switch (Chen2004). By inhibiting several growth factor receptors such as EGF-R and VEGF-R, it can also significantly have effect upon the mechanisms of angiogenic switch and vessel cooption that are necessary for the sprouting growth of new blood vessels in the tumor (Dorai2001). Most notably, curcumin and to a lesser extent genistein can also interfere with the expression of VEGF by processes other than hypoxia, such as transforming growth factor (TGF)-β release, COX-2 overexpression, hydrogen peroxide release from bone cells, constitutive and aberrant EGF-R in established cancers.

CONCLUSION

Natural dietary phytochemicals have been widely used in in vitro, in vivo, and preclinical cancer prevention and treatment studies. Some of these clinical trials have shown various degrees of success. Because of their pharmacological safety, most chemopreventive agents can be used in combination with chemotherapeutic agents to enhance the effect at lower doses and thus minimize chemotherapy-induced toxicity. As cancer chemoprevention and treatment using natural phytochemicals have been such an attractive approach, further efforts are fully justifiable to thoroughly understand their potencies, pharmacokinetic performances, pharmacodynamic responses, metabolisms, toxicities, drug-drug interactions, polymorphisms, and then formulations, stabilities and degradations, and dosage regimemens. Natural dietary phytochemicals have been and will continue to be a promising and active research area in the near future.

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