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# New strategies in cancer chemoprevention by phytochemicals

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## 1. ABSTRACT

Fruits, vegetables, spices, herbs and/or beverages are typical foods containing various phytochemicals that have been used for prevention and treatment of a variety of human ailments since time immemorial. Nowadays, a large number of individuals are motivating towards the use of phytochemicals inorder to prevent or treat chronic diseases. Recent research efforts have been greatly emphasized on the recognition of naturally occurring plant derived substances that are capable of inhibiting, retarding or reversing the development of cancer. Several epidemiological annotations and a number of laboratory studies have indicated cancer chemopreventive and anti-carcinogenic potential of plant derived agents that have been traditionally used for treatment of varied human disorders in different parts of the globe. Molecular mechanisms which are involved for eliciting the effects of phytochemicals in cancerous cells are noticed in a range of experimental systems. This has opened up new avenue for researchers working in the field of chemoprevention and merits further scrutiny to establish the role of phytochemicals in prevention of fatal human diseases like cancer.

## 2. INTRODUCTION

Many food products have been recognized as contributors of good health above and beyond of their nutritional values. Dieticians have laid emphasis on the importance of fruits and vegetables consumption in the daily diet for better health and well being, and now these are being scientifically proven for their contribution. Epidemiological studies have also proved that high dietary intake of fruits and vegetables as well as whole grains are strongly associated with reduced risk of developing chronic diseases (1-3). The National Academy of Sciences of the United States emphasized the importance of fruits and vegetables in the diet and recommended the consumption of 5 or more servings of fruits and vegetables daily to reduce the risk of both cancer and heart disease (4,5). The value of adding citrus fruits, carotene rich fruits and vegetables and cruciferous vegetables to the diet for reducing the risk of cancer was specifically highlighted by the group.

Plant-based foods contain significant amounts of bioactive phytochemicals, reported to provide desirable health benefits beyond basic nutrition to reduce the risk of

chronic diseases. The word phytochemicals is derived from the Greek word phyto, which means plant. In definition "phytochemicals are chemicals present in plant and defined as bioactive non-nutrient plant compounds in fruits, vegetables, grains, and other plant foods". According to an estimate >5000 individual phytochemicals have been identified but a large percentage still remain unknown and needs to be identified (6). These can be classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds. In area of cancer chemoprevention phytochemicals have been proven safe and effective in various preclinical and clinical studies and suggest that regular consumption of fruits and vegetables might reduce cancer risk. Block *et al* 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 (7). A prospective study involving 9959 men and women in Finland showed an inverse association between the intake of flavonoids and incidence of cancer at all sites combined (8). After a 24-y follow-up, the risk of lung cancer was reduced by 50% in the highest quartile of flavonol intake. Consumption of quercetin from onions and apples was found to be inversely associated with lung cancer risk (9). Boyle *et al* showed that increased plasma levels of quercetin after a meal of onions was accompanied by increased resistance to strand breakage by lymphocyte DNA and decreased levels of some oxidative metabolites in the urine (10).

Researches have revealed that preventing cancer is easier than treating it. Chemotherapy is designed for curing cancer after its appearance; however, chemoprevention involves the abrogation or delay in the onset of cancer. A number of studies have provided evidence that a wide range of food derived phytochemicals or their synthetic derivatives represent a cornucopia of potential new compounds for prevention and treatment of cancer. These phytochemicals may help and protect cellular systems from oxidative damage, induce cell-cycle arrest and apoptosis; modulate enzyme activities in involved in detoxification, stimulate immune system; regulate hormone metabolism and also may lower the risk of cancer (11-13). Dietary phytochemicals include genistein, resveratrol, catechins, lycopene, capsaicin, bromelain, curcumin, [6]-gingerol, lupeol, ellagic acid, ursolic acid, limonene, indole-3-carbinol and dially sulfide (Figure 1). These agents can be used either alone or in combination with chemotherapy to treat the disease and some have entered clinical practice or are under clinical testing.

This review summarizes the studies regarding the effects of dietary natural agents on various cancers and provides comprehensive knowledge of the biological and molecular mechanisms underlying the promising cancer chemopreventive and anti-cancer activity driven by selected phytochemicals.

## 3. CANCER CHEMOPREVENTIVE PHYOCHEMICALS

### 3.1. Genistein a phytochemical in soy

Genistein found in enormous quantity in soy (*Glycine max*; Family-Leguminous), a plant compound having estrogen-like activity (a phytooestrogen), is currently of great interest for its implications as cancer chemopreventive/anti-cancer compound. It was first isolated in 1899 from the dyer's broom *Genista tinctoria*; hence, the chemical name derived from the generic name. Epidemiological data suggests that incidence rate of endometrial cancer, ovarian, breast and prostate cancer remains lowest in Asian nations, consuming diet rich in soy products (14- 18). Lu *et al* suggested that soya isoflavone increases the metabolism of endogenous estrogens into protective 2-hydroxylated estrogens in women which might play an important role in lowering 17 beta-estradiol levels along with the long-term risk for breast cancer (19, 20). Soy isoflavones are well known antioxidants because of their ability to act as free radical scavengers and thus prevent DNA damage (21). Genistein has been well studied and have shown to stimulate the activity of several antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase and reductase (22).

In *in-vitro* genistein arrests cells in G2/M phase (23, 24), induces apoptosis (24-27), regulate NF-kappa B activity (28), cause impairment in the signal transduction pathways Ras/MAPK/AP-1, MEK5/ERK5 (23, 29) and inhibit angiogenesis in cancer cells (30). Induction of apoptosis by soy isoflavones was evidenced by cleavage of caspase-3 and poly(ADP-ribose)polymerase (PARP) and downregulation of Bcl-2 and Bcl-XL expression in hepatoma cells after 24 h exposure (25). Genestein effects on suppression of cell adhesion and migration were evident by inhibiting the activity of NF-kappa B and AP-1, resulting in the suppresed of secretion of urokinase-type plasminogen activator (uPA) in breast cancer cells (29, 31). Genestein has also been reported to induce significant epigenetic changes to alter the dynamics of growth in breast cancer cells (32). Soy isoflavon genistein and daidzein independently modify cytokine production and play an imperative role in the reduction of ovarian cancer cell proliferation *via* an estrogen receptor (ER)-dependent pathway (33). DNA synthesis was significantly inhibited by genistein or daidzein in ovarian cancer cells whereas transforming growth factor (TGF)-AA1 production was significantly raised after incubation with both (33). In addition, approximately 20% inhibition of interleukin-6 (IL-6) synthesis by these two was noted. Gossner *et al* reported both apoptotic and autophagic cell death induction by genistein treatment. In this study genistein treatment resulted in caspase independent cell death with hallmarks of autophagy and inhibits glucose uptake and methyl pyruvate in ovarian cancer cells (26). Additionaly, reduced level of phosphorylated Akt was noted, which may contribute towards a mechanism to limit glucose utilization. Anti-apoptotic genes c-IAP1, Bcl-2, Bcl-xL, survivin and NF-kappa B DNA binding activity were all found to be significantly down regulated in the ovarian cancer cells primed with genistein and than treated with combination of genistein and cisplatin (34). Soy phytochemicals are also reported to inhibit the growth of androgen-sensitive (AR+) and -negative (AR-) prostate cancer cells (35) and synergized with radiation, via affecting APE1/Ref-1, NF-kappa B and HIF-1alpha, suggesting an AR-independent mechanism of prostate cancer prevention by soy

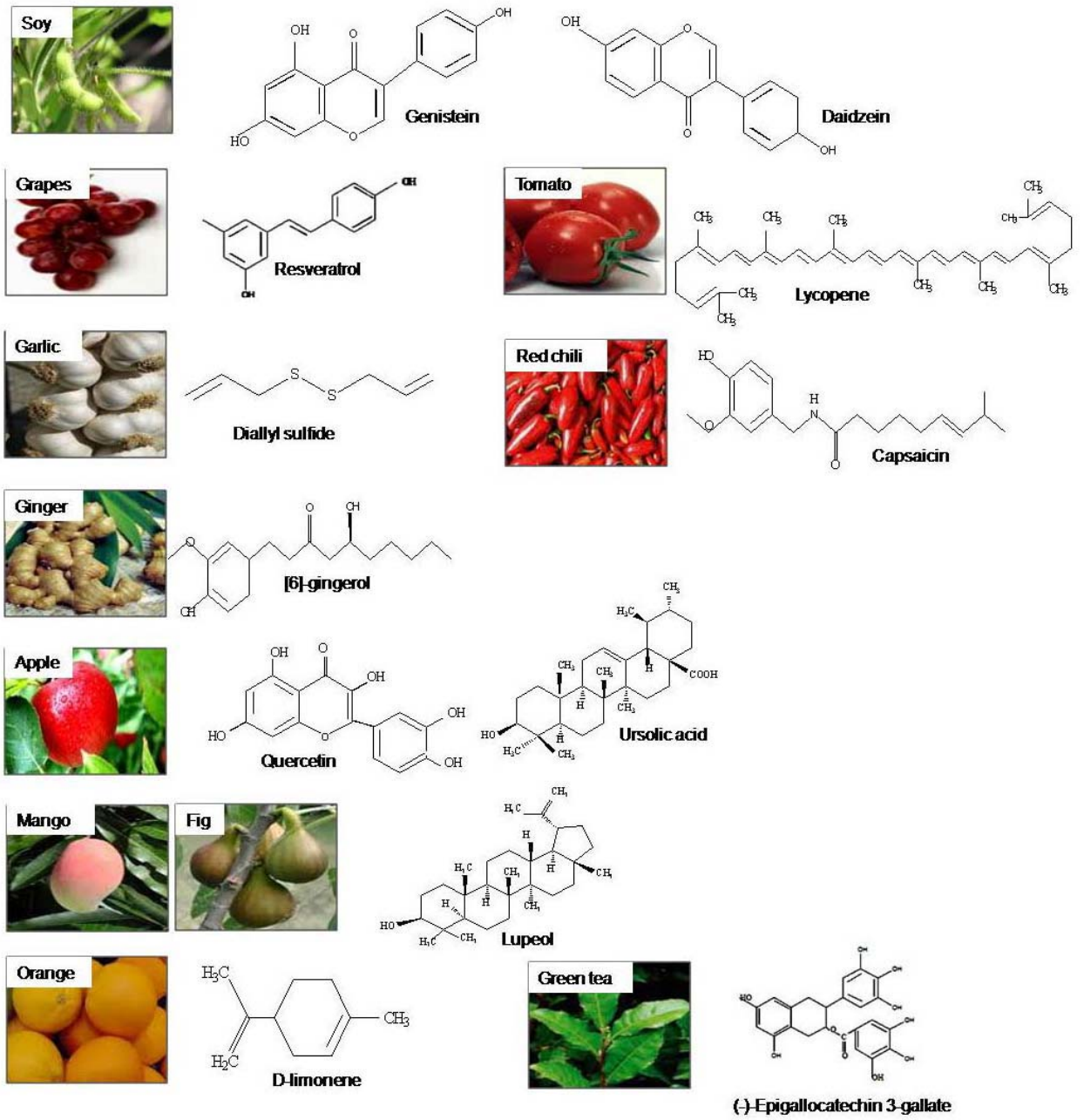


**Figure 1.** Structure of dietary phychemicals and their major source(s).

components. Involvements of soy isoflavone in modulation of androgen-regulated genes and pathways controlling cell cycle, metabolism and intracellular trafficking were determined by Rice *et al* (36). Genistein and daidzein dose dependently inhibited DHT-induced expression of the prostate androgen-regulated transcript (PART-1), a novel androgen-dependent prostate tumor marker (37).

Several *in-vivo* studies also documented the role of soy and its phyochemicals in cancer prevention. Researchers used chemical carcinogens induced mammary and prostate cancer model to test the effectiveness of soy isoflavones as chemopreventive agents. Genistein was found effective in reducing tumor multiplicity, but it reduced tumor incidence less efficiently. They further noted that tissue samples from genistein treated animals contained similar topo II and protein tyrosine kinase (PTK) activities as the control group (38). According to Murrill *et al* genistein (500 microg/g bwt) treatment during the prepubertal period can suppress the development of DMBA induced mammary cancer without significant toxicity to the endocrine/reproductive system (39). Prepubertal exposure of female rats to genistein (500 mg/kg) can reduce later breast cancer risk and its protective effects are associated

with persistent down regulation of erbB2, p-Akt, AIB1, and PCNA expression and with low activity of PTK in tumor (40). Anti-angiogenic effect of soy phytochemicals were noted by decreased microvascular density and plasma vascular endothelial growth factor (VEGF) and increased plasma endostatin levels (41). Soy phytochemicals inhibit experimental prostate tumor incidence, growth, weight and neovasculature in mice (42, 43). Besides of these genistin producing the greatest decrease in total serum testosterone and dihydrotestosterone level (43). Thus, soy and its phytochemicals treatment serve to alone or potentiate therapeutic agents designed to treat hormone dependent human cancer and needs further attention to their implementation in clinics.

### 3.2. Resveratrol a phytochemical in red grapes, peanuts and berries

Resveratrol (3,5,4-trihydroxystilbene) was first isolated in 1940 as a constituent of the roots of white hellebore (*Veratrum grandiflorum* O. Loes), but has since been found in various plants, including grapes, berries and peanuts.

Anti-cancer potential of resveratrol are well explored for its substantial activity against variors human cancers like ovarian, breast, prostate, skin, pancreatic and hepatic. The growth inhibitory effects of resveratrol in cancer cells are mediated by way of cells cycle blocked in S phase (44, 45), apoptosis induced by both mitochondrial and autophagocytic mode (46-49), modulation of signaling pathways such as PI3K/Akt, Raf/MEK/ERK kinase, ATM/ATR/Chk1/2/Cdc25C (44, 46, 50) and angiogenesis by inhibition of HIF-1alpha and VEGF expression (51, 52). Kueck and others suggested that it caused changes in glucose utilization comprises the mechanism which underlies resveratrol induced autophagocytosis (53). Moreover, resveratrol reduces the levels of pAkt and mTOR in ovarian cancer cells, two signals that increase glucose uptake and the rate limiting steps in glycolysis (53). Resveratrol doses can suppress proliferation of endometrial cancer cells through down regulation of EGF (54) and COX activity (55). Exposure of increasing concentrations of resveratrol (0-50 microM) resulted in increase in intracellular reactive oxygen species (ROS) and mitochondrial superoxide production, and a concomitant decrease in transmembrane potential (49). Significant alteration in viability, clonogenic survival, apoptosis and androgen stimulated growth was noted in LNCaP cells treated with 0-50 microM/L (24 h) resveratrol (50). Resveratrol reported to suppress EGFR-dependent ERK1/2 activation pathways stimulated by EGF and TPA in androgen-non-sensitive prostate cancer cells (56). Expressions of cyclin D1, E, and Cdk4 and activity of cyclin D1/Cdk4 kinase were reduced only in LNCaP cells and, cyclin B and Cdk1 expression and cyclin B/Cdk1 kinase activity were decreased in both LNCaP and PC-3 cells following exposure to resveratrol, suggests that resveratrol acts through different mechanisms depending upon the androgen status (47). Inhibition of tumor necrosis factor (TNF)-alpha mediated matrix metalloproteinase (MMP)-9 expression and invasion by resveratrol in hepatocellular carcinoma cells and was associated with the downregulation of the NF-kappa B pathway (57). Together with these, resveratrol adds to the growth inhibitory/anti-cancer activity of cisplatin and doxorubicin in cancer cells (58).

Dietary administration of resveratrol (10 ppm) reduced in incidence (45%) and multiplicity (55%) and extended latency period of DMBA induced mammary tumor development (59) along with suppression of the DMBA-induced COX-2, MMP-9 and NF-kappa B expression. Resveratrol (up to 150 microM) has antitumoral activity in androgen-sensitive and androgen-non-sensitive human prostate tumours by inhibiting survival pathways mediated by PI3K (60). Intraperitoneal administration of resveratrol retarded the growth of ovarian cancer cell xenograft and the expression of eukaryotic elongation factor 1A2 (eEF1A2), PCNA and CD-31 in athymic nude mice (61). Decrease in cell proliferation, insulin-like growth factor (IGF) -1, ERK1/2 activation and increase in tumor suppressor ER-beta, provide mechanistic basis for resveratrol's effect on prostate cancer in TRAMP mice (62). According to Seeni *et al* resveratrol induced downregulation of AR was associated with suppressed levels of androgen responsive glandular kallikrein 11 (Gk11) mRNA, known ortholog of prostate specific antigen (PSA) (63). Using a two-stage model of rat hepatocarcinogenesis preventive effects of resveratrol doses (50, 100 or 300 mg/kg body weight/day) was noted by Bishayee and Dhir in terms of reduced incidence, total number and multiplicity of visible hepatocyte nodules (64). Resveratrol also modulated the expression of Bax, Bcl-2 expression, with a concurrent increase in Bax/Bcl-2 ratio (Bishayee & Dhir 2009). Resveratrol dose dependently inhibited DEN-induced expressions of hepatic HSP70 and COX-2 and translocation of NF-kappa B p65 (65). In skin carcinogenesis model pretreatment of mouse skin with resveratrol significantly counteracted TPA-induced oxidative stress; modulate the expression of c-fos and TGF-beta 1, ERK, p38 MAPK and COX-2, and DNA binding of AP-1 (66, 67). Resveratrol suppressed phosphorylation and subsequent degradation of I kappa B alpha, thereby inhibiting activation of NF-kappa B in TPA-stimulated mouse skin tumors (68).

Besides these chemopreventive effects, resveratrol appears to exhibit therapeutic effects against cancer. Limited data in humans revealed that resveratrol is pharmacologically quite safe (69). Currently, structural analogues of resveratrol with improved bioavailability are being pursued as potential therapeutic agents for cancer further clinical studies are warranted to establish resveratrol and its analogues to cancer prevention.

### 3.3. Epigallocatechin gallate a green tea polyphenol

Tea (*Camellia sinensis,* Family-Theaceae) contains the active ingredient polyphenol, which has a subgroup known as catechins. Catechins are powerful antioxidants. Epigallocatechin-3-gallate (EGCG), a green tea polyphenol (GTP) has been of interest as possible therapeutic agents; its benefits in terms of cancer chemoprevention have been well investigated primarily through *in-vitro* and *in-vivo* studies and now is in clinical

trials. Abundant epidemiological data have indicated decreased cancer occurrence in people who regularly drink green tea. Initial interest in a potential preventative effect of green tea on prostate cancer stemmed from the epidemiological observation of the low incidence of prostate cancer among Japanese and Chinese populations with a high dietary intake of green tea (70). Several epidemiological studies have demonstrated that those who regularly consume tea have a lower incidence of prostate cancer (71, 72). Green tea catechins are safe and very effective for treating premalignant lesions before prostate cancer develops (73). August *et al.* showed green tea causes a significant reduction in prostaglandin (PG) - $E_2$ synthesis in rectal mucosa of human volunteers and suggesed that active compounds in tea potntialy inhibit cycloxygenases activity (74). Green tea drinkers had a 51% lower risk of chronic gastritis related to *H. pylori* than non-drinkers in a Chinese population (75). Recently, results from Australian study revealed that green tea consumption reduces the risk of ovarian cancer (76). A prospective cohort study with over 8,000 individuals revealed that the daily consumption of green tea resulted in delayed cancer onset and a follow-up study of breast cancer patients found that stages I and II breast cancer patients experienced a lower recurrence rate and longer disease-free period (77).

Tea polyphenols are persuasive inhibitors of cell growth and proliferation as well as inducer of proapoptotic effects, on various cell types. The anticancer activity of EGCG is mediated by inhibition of uPA, one of the most frequently overexpressed enzymes in human cancers (78). Dong and coworkers recognized that EGCG can inhibit protein kinase C and thus control cell division. In addition, EGCG inhibited EGF or TPA-induced cell transformation, AP-1 transcriptional activity and DNA binding activity (79). Nam *et al.* suggested that EGCG potently and specifically inhibits the chymotrypsin-like but not trypsin-like activity of the proteasome (80). Inhibition of the chymotrypsin-like activity of the proteasome has been associated with induction of tumor cell apoptosis. Modulation of beta-catenin and Akt activities by GTP/EGCG caused apoptosis (81). EGCG has been shown to inhibit NF-kappa B activity (82) which is a specific target for cleavage by caspases during EGCG-mediated apoptosis (83). The treatment of EGCG (10-40 micromol/L) to NHEK cells before UVB exposure was shown to inhibit UVB-induced $H_2O_2$ production concomitant with the inhibition of UVB-induced phosphorylation of ERK1/2, JNK, and p38 proteins (82). EGCG (10-20 microg/mL) has also been shown to inhibit EGFR (84) and COX-2 (85, 86) activity in cancer cells. Green tea extract and EGCG significantly inhibited hypoxia- and serum-induced HIF-1 alpha protein accumulation in human cervical carcinoma and hepatoma cells (87). A novel anti-angiogenesis application of EGCG in cancer chemoprevention was explained by Tang *et al* in year 2007 (88). EGCG inhibited ephrin-A1-mediated endothelial migration and angiogenesis along with ephrin-A1mediated phosphorylation of EphA2 and ERK-1/2. Decrease in VEGF receptor phosphorylation and inhibition of binding to its receptor as are also major contributor of anti-angiogenic effects of EGCG (89). The signal transduction pathways of VEGF, including autophosphorylation of VEGFR-1 and -2, phosphorylation of ERK1/2 and expression of the early growth response factor-1 was also significantly inhibited in EGCG (5-50 micromol/L)-pretreated HUAEC cells (90). In breast cancer cells EGCG inhibits VEGF production by inhibiting the constitutive activation of STAT 3 and NF-kappa B (91). In a study EGCG seems to hamper the migration or invasion of cancer cells via suppressing the activation of EGFR-related protein (Erb) B2/ErbB3/protein kinase B (92).

Studies have been conducted to understand the *in-vivo* mechanisms of tumor inhibition by tea. Lu *et al.* showed that green tea enhances UV-induced apoptosis and p53 and p21waf1-positive cells in SKH-1 mice skin (93). Administration of green tea as drinking water induces apoptosis in lung adenomas developed in A/J mice after exposure to NNK (94). GTP inhibit cell growth, induce apoptosis and caused marked inhibition of MMP-2 and -9 in prostate of TRAMP mice (95, 96). GTP treatment also resulted in substantial reduction in the levels of IGF-I and increase in the levels of IGF binding protein (IGFBP) -3 in TRAMP mice (Adhami *et al* 2004).

In clinical cases EGCG delivered in the form of capsule (200 mg p.o. for 12 weeks) has been reported to be effective in the patients with human papilloma virus (HPV) infected cervical lesions (97). The antineoplastic effects of green tea were seen in patients with androgen-independent prostate carcinoma (98). In conclusion, positive responses observed in phase II and phase III clinical trials along with exciting preclinical data indicate that ways and means to take EGCG "from bench to real-life situations" are on the horizon more information from clinics will establish this compound as an chemopreventive mean.

### 3.4. Phytochemicals in apple fruit

Apples (*Malus domestica*, Rosaceae), a rich source of nutrient as well as non-nutrient components, contain high levels of polyphenols and other phytochemicals. Main structural classes of its constituents include hydroxycinnamic acids, dihydrochalcones, flavonols (quercetin and quercetin glycosides), flanan-3-ols (epi-catechins), and oligomeric procyanidins, as well as triterpenoids (ursolic acid) in apple peel and anthocyanins in red apples, all are strong antioxidants. Epidemiological observations indicate that regular consumption of one or more apples a day may reduce the risk for lung and colon cancer (8, 99).

In prelimnary findings apple and its components have been shown to influence multiple mechanisms relevant for cancer prevention including potent antimutagenic, antioxidant and anti-inflammatory activities, modulation of carcinogen metabolism and signal transduction pathways along with anti-proliferative and apoptosis inducing capability. Apple polyphenols reduced cellular ROS level and oxidative DNA at 24 h of incubation (100) and enhances expression of GST T2 (101, 102) in human colon cells. A mechanistic study by Ding *et al* showed that pretreatment with apple peel extract inhibited AP-1 transactivation induced by UVB irradiation or TPA in

JB6 cells and AP-1-luciferase reporter activity in transgenic mice appears to be mediated by the inhibition of ERK(s) and JNK activity (103). Apple juice constituents, the proanthocyanidins B1 and B2, quercetin-3-glc (isoquercitrin) and quercetin-3-gal were found to possess substantial EGFR-inhibitory properties (104). In breast cancer cells, anti-proliferative activities of apple phytochemical were due to its effects on G1/S transit via cyclin D1 and Cdk4 proteins (105). Apple extract (2.5 and 5 mg/ml) have shown the capabilities of inhibiting TNF-alpha induced NF-kappa B activation in MCF-7 cells by inhibiting the proteasomal activities instead of IKK activation (106). Recently it was reported that apple peel extract also consists strong antioxidant and antiproliferative effects against cancer cells and researchers suggested that apple peels should not be discarded from the diet (107, 108).

The chemopreventive prospectives of apple and its constituents are well investigated in various studies. Apple has been shown to prevent skin (103), mammary (109-111), liver (112) and colon (113, 114) carcinogenesis in animal models. Apple procyanidins have chemopreventive properties against colon cancer, via modulation of intracellular signalling pathways and trigger apoptosis (114, 115). Dietary supplemention of 20% apple pectin exerts stronger bacteriostatical action on *Staphylococcus aureus*, *S. faecalis*, *Pseudomonas aeruginosa* and *Escherichia coli* along with significant decrease in incidence of colon tumor and $PGE_2$ level in distal colonic mucosa (116). Fecal beta-glucuronidase activities, a key enzyme for the activation of dimethylhydrazine metabolism to carcinogens in the colonic lumen, were also significantly lower in pectin supplemented group than those in control group (116, 117). The expression of PCNA, cyclin D1, and Bcl-2 decreased, and Bax expression and apoptosis increased with increasing doses apple extracts in DMBA-initiated mammary cancers in rats. (111).

### 3.5. Lycopene a phytochemical in tomato fruits

Phytochemical lycopene is a bright red carotene and carotenoid pigment, majorly present in tomatoes (*Solanum lycopersicum*; Family-Solanaceae). Other red fruits and vegetables, such as red carrots, watermelons and papayas are also the source of lycopene. As lycopene has potent antioxidant potential and accordingly has been evaluated for anticancer effects. Several epidemiological studies indicate that tomato consumption, lycopene intake, and serum lycopene levels (118-123) are associated with decreased risk of gastrointestinal, breast, cervical and prostate cancer. Giovannucci *et al* evaluated men in the Health Professionals Follow-Up-Study and found a moderate benefit for lycopene and a somewhat stronger benefit for tomato sauce (124). Ingestion of tomato paste (50 g/d for 10 weeks) and lycopene (15 mg/d for 6-month) significantly reduced mean plasma PSA levels in patients with benign prostate hyperplasia (125, 126).

Various mechanisms have been proposed to explain the inhibitory effects of lycopene, including modulation of phase I and II enzymes (127), cell cycle arrest via IGF-1 signaling (128, 129), enhancement of gap-junction communication (130), induction of apoptosis (131), inhibition PI3K dependent survival (132), and neoplastic cell transformation (133). It has potential effect on expression of the uPA receptor (uPAR) and gap junctional protein connexin 43 thus inhibiting proliferation and invasion of prostate cancer cells (134). In addition, lycopene protect prostate cells from ROS and block IGF-mediated cellular proliferation. Prostate cancer cells incubation with sera from men who consumed purified lycopene (16 mg/d) led to significant up-regulation of IGFBP-3, c-fos, and uPAR compared with sera collected after placebo consumption (135).

Since interest in lycopene is relatively recent, there have only been a few animal studies on the role of lycopene in preventing or treating cancer. Supplementing a semipurified diet with extremely low levels of pure lycopene significantly inhibited of spontaneous mammary tumor development (136). Together with this lycopene treatment reduced the growth of brain (137), lung (138), urinary bladder (139), and colon (140) cancer in laboratory animals. Protective effects of it have also been reported in formation of aberrant colon crypt (141, 142) and hepatic preneoplasia (143). Experimentally it reduces PSA level (144) and high concentration of lycopene in prostate tissues resulted in nearly three-fold increase in apoptosis (145). Campbell and collegues illustrated that short term intake of tomato carotenoids significantly alters androgen status in F344 rats (146).

### 3.6. Lupeol a phytochemical in mango fruit

Lupeol also known as fagarsterol [Lup-20(29)-en-3β-ol], a diet-based triterpene, is the principal constituent of mango fruit (*Mangifera indica*; Family-Anacardiaceae) and others e.g. olive, strawberry, grapes, figs etc. has been reported to possess a wide range of medicinal properties that include strong anti-oxidant, anti-mutagenic, and anti-inflammatory effects.

Several *in-vitro* studies provide insight into the mechanism of action of lupeol and suggest that it is a multi-target agent with immense anti-inflammatory potential targeting several key molecular pathways which involve COX-2, NF-kappa B, survivin/cFLIP, K-ras, PI3K/Akt and Wnt/beta-catenin in cancer cells. Lupeol is reported to activate apoptotic machinery by means of both Fas signaling (147, 148) and mitochondrial mode (149-151). Its treatment in 451Lu melanoma cells caused G(1)-S phase cell cycle arrest and decreased the expression of protein cyclin D1, D2, and Cdk2; and increased the expression of p21 (151). *In-vitro* lupeol inhibits the tumorigenicity of androgen-sensitive prostate cancer cells with a concomitant decrease in serum PSA levels under *in- vivo* conditions (147). It reduces the proliferative and clonogenic potential of androgen-sensitive as well as androgen-insensitive prostate cancer cells by modulating beta-catenin signaling pathway (152). The treatment of cells with a combination of anti-Fas monoclonal antibody and lupeol resulted in higher cell death when compared with alone (147). Employing a focused microarray of human prostate cancer associated genes, Saleem *et al* found that lupeol

significantly modulates the expression level of proliferation and survival associated genes such as ErbB2, TIMP-3, cyclin D1 and MMP-2, which are known to either regulate or act as downstream target of beta-catenin signaling (153). In addition lupeol induced growth inhibition of prosate cancer cells is an outcome of disruption of microtubule assembly through simultaneous effect on stathmin, cFLIP, and survivin molecules (152).

Lupeol potential in prevention of cancer are proved by *in vivo* studies. Lupeol treatment inhibits head and neck cancer in a mouse tumor xenograft model and exerted a synergistic effect with cisplatin (154). Lupeol-induced G2/M-phase arrest was mediated through inhibition of the cyclin-B-regulated signaling pathway involving p53, p21/WAF1, Cdc25C, Cdc2, cyclin-B and Plk-1 in skin cancer model (155, 156). Lupeol/mango pulp extract supplementation resulted in inhibition of prostate enlargement in testosterone-treated animals (157). Thus, lupeol could be a potential agent against cancer; further in-depth studies are warranted to allow the therapeutic application of this phytochemical.

### 3.7. Phytochemicals in ginger

Besides its food-additive functions ginger (*Zingiber officinale*; Family-Zingiberaceae) has a history of medicinal use for the treatment of a variety of human ailments including cancer. Ginger contains several non-volatile pungent principles viz. gingerols, paradols, shogaols and zingerone, which majorly account for its health beneficial effects. All these have been reported to possess strong anti-inflammatory, anti-oxidant and anti-angiogenic activities. These potentials are considered to be major contributor of cancer chemopreventive potential of ginger in prostate, urothelial, skin, lung, colorectal, gastric, and breast cancer.

Cancer preventive effects of ginger phytochemicals are mediated through ROS generation (158, 159), cell-cycle arrest in G1 phase (160-162); upregulation of p53 and Bax and down-regulation survivin, Bcl-2, Bcl-X(L) and caspases activation (158, 159, 163-165), cytochrome-c release, DNA fragmentation (165) and inhibition of MAPK, NF-kappa B and AKT/mTOR signalling pathways (162, 166-168). According to Pan *et al* [6]-shogaol down-regulates inflammatory iNOS and COX-2 gene expression through inhibiting the activation of NF-kappa B and interfering with the activation PI3K/Akt/IκB kinases IKK and MAPK (165). [6]-gingerol is reported to inhibits neoplastic transformation (169) and modulates secretion of angiogenic factors such as IL-8 and VEGF-induced capillary like tube formation (170, 171). Bode *et al* provide the evidence that [6]-gingerol treatment inhibited EGF-induced AP-1 DNA binding activity in mouse epidermal JB6 cells (169). Lee *et al* proved anti-tumorigenic effects of [6]-gingerol in human colorectal cancer cells through the up-regulation of NSAID-activated gene-1 (NAG-1), down-regulation of cyclin D1 and degradation of beta-catenin (161).

Above and beyond of these, ginger potential in skin cancer prevention is well explored by the researchers. Ethanolic extract of ginger is reported to have anti-tumor promoting effects in a mouse skin tumorigenesis model (172). Topical application of [6]-gingerol or [6]-paradol prior to each TPA treatment attenuated the mouse skin papillomagenesis initiated by DMBA and also significantly inhibited the inflammation, TNF-alpha production and activation of epidermal ODC activity (173, 174). According to Kim *et al* (166) topical application of [6]-gingerol inhibited PMA-induced COX-2 expression in mouse skin by suppression of NF-kappa B. Togetherly, it was found to suppress I kappa B alpha degradation and translocation of p65 to nuclear by blocking of upstream kinase p38 MAPK (166, 175). [6]-gingerol is an effective therapeutic agent providing protection against UVB-induced skin disorders (176). Pre-treatment with [6]-gingerol reduced UVB-induced intracellular ROS levels, activation of caspase-3, -8, -9, Fas expression, and COX-2 transactivation. In same study, topical application of [6]-gingerol (30 microM) prior to UVB irradiation of hairless mice, also inhibited the induction of COX-2 mRNA and protein, as well as NF-kappa B translocation. Topical application of [6]-paradol inhibited TPA-induced ear edema and $H_2O_2$ production and myeloperoxidase activity in the dorsal skin of mice (177).

### 3.8. Capsaicin a phytochemical in chili pepper

In the countries where diets are traditionally high in chili pepper (*Capsicum annuum L.*; Family-Solanaceae), the cancer death rates for people are significantly lower than they are in countries with less chili pepper consumption. Capsaicin, (a homovanillic acid; N-vanillyl-8-methyl-α-nonenamide) is a principal pungent ingredient of hot and red chili peppers, has been shown to detoxify a broad range of chemical carcinogens and subjected to extensive experimental and clinical investigations, due to its well-known pharmacologic properties.

In cell culture studies, capsaicin has been found to selectively suppress the growth of various human tumor cells (178- 183). Capsaicin induced the accumulation of cells in G1 phase, inhibited proliferation, induced ROS generation and induced apoptosis, as indicated by caspase activation, PARP cleavage, and down-regulation of tNOX and Bcl-2 (181, 184-187). Capsaicin is a novel modulator of the EGFR/HER-2 pathway in both ER-positive and -negative breast cancer cells (187). Furthermore, capsaicin-induced apoptotic cell death in HT-29 colon cancer cells was associated with the PPAR-gamma pathway (188). It was also found that capsaicin could enhance the transcripts of two proto-oncogenes (c-myc and c-Ha-ras) and tumor suppressor gene p53 in cancer cells (182). Kang *et al* suggested that red pepper had differential effect between normal and transformed cells by selective induction of apoptosis in H-ras-transformed cells but not in their normal cell counterparts (189). Along with these, TPA-stimulated activation of NF-kappa B and AP-1 in cultured HL-60 cells was suppressed by capsaicin (190). The effect of capsaicin and its analogue, resiniferatoxin, on the activation of NF-kappa B induced by different agents including TNF has been investigated by Singh *et al* (191). The pretreatment of human myeloid cells with capsaicin blocked TNF-mediated activation of NF-kappa B and degradation of I kappa B

alpha. Capsaicin has been also been reported to inhibit activation of NF-kappa B mediated by ROIs endogenously generated via the NAD(P)H:quinine oxidoreductase system in malignant melanoma cells (192). Capsaicin induced the degradation of Tax and up-regulation of I kappa B alpha, is responsible for decrease of NF-kappa B/p65 DNA binding activity (181). The effect of this vanilloid on the STAT3 pathway was also investigated. It was found that capsaicin can inhibit constitutive activation of STAT3 in multiple melanoma cells, with a minimal effect on STAT5 (184). The activation of JAK1 and c-Src, implicated in STAT3 activation, were also inhibited by this vanilloid, with no effect on ERK1/2 activation. In addition, down-regulation of the expression of the STAT3-regulated gene products such as cyclin D1, Bcl-2, Bcl-xL, survivin and VEGF was also documented (184). Furthermore, capsaicin significantly inhibited the migration of melanoma cells (193) through the inhibition of the PI3-K/Akt/Rac1 signal pathway.

Capsaicin act as potent antioxidant, as revealed by attenuation of oxidative damage or lipid peroxidation LPO in experimental animals (194-195). It exerted protective effects against ethanol induced gastric mucosal injury in rats (196). Ethanol induced haemorrhagic erosion, LPO and myeloperoxidase activity in rats were ameliorated by intragastric capsaicin treatment, which was associated with suppression of COX-2 activity (197). Capsaicin inhibited TPA promoted mouse skin papillomagenesis (198). Topical application of capsaicin to dorsal skin of female ICR mice strongly suppressed TPA-stimulated activation of NF-kappa B and AP-1 activity (199). When administered intraperitoneally, capsaicin inhibited the growth of human multiple myeloma xenograft tumors in male athymic nu/nu mice (184). In pancreatic tumors model capsaicin treated group demonstrated increased apoptosis, which was related to the activation of JNK and increased cytosolic protein expression of Bax, cytochrome c, AIF and cleaved caspase-3, as compared with controls (200). Capsaicin potently inhibited the development of pre-neoplastic breast lesions by up to 80% without evidence of toxicity and suggested as a novel modulator of the EGFR/HER-2 pathway in both ER-positive and -negative breast cancer (187). Capsaicin (10 mg/kg b wt) altered the levels of cytochromes (P450, b5), activities of phase I biotransformation enzymes (NADPH-cytochrome P450 reductase, NADH-cytochrome b5 reductase and epoxide hydrolase), phase II enzymes (GST, UDP-glucuronyl transferase and DT-diaphorase), and the levels of serum tumor markers in B(a)P induced lung cancer tissues (201).

### 3.9. Bromelain a phytochemical in pineapple

The medicinal qualities of pineapple (*Ananas comosus*; Family-Bromeliaceae) are recognized in several native cultures. These qualities are attributed to bromelain (a 95% mixture of sulphur-containing proteolytic enzymes) derived from pineapple stem, has been known chemically since 1876 for its medicinal potential. Medicinal qualities of bromelain include anti-inflammatory, anti-thrombotic, fibrinolytic and anti-cancer functions (202). Existing evidence suggests that bromelain acts by affecting multiple cellular and molecular targets include: interference with growth of malignant cells; inhibition of platelet aggregation; fibrinolytic activity; and anti-inflammatory action. These biological functions of bromelain have therapeutic values in modulating tumor growth, inflammatory changes, and enhancement of drugs absorption (203).

Bromelain in doses of over 1000 mg/day when combined with chemotherapeutic agents such as 5-FU and vincristine resulted in tumor regression (204). Bromelain, in both the active and inactive forms with or without proteolytic and anti-coagulant properties, has shown to possess dose dependent anti-metastatic properties in Lewis lung cancer cells implanted in mice (205, 206). Another study shows that incubation of sarcoma L-1 cells with bromelaine significantly reduced their tumorigenic/metastatic capacities in animals (207). From our laboratory anti-tumor-initiating competence of bromelain in two-stage mouse skin tumorigenesis model was reported (208, 209). Studies showed that bromelain application delayed the onset of skin tumorigenesis, reduced the number and volume of tumors and resulted in upregulation of p53 and Bax and activation of caspase -3 and -9 with concomitant decrease in Bcl-2 level. A marked inhibition in COX-2 expression and ERK1/2, MAPK, Akt and NF-kappa B activity was recorded by bromelain (209).

In human use of oral doses of bromelain in cancer patients was first reported in 1972. Patients with ovarian and breast tumors were given 600 mg of bromelain daily upto 6 months to several years, reported resolution of some of the cancerous masses and a decrease in metastasis at makeable levels (204). The use of bromelain also has been suggested for adjuvant therapy of malignant diseases. Results of a study conducted by Eckert *et al* to evaluate the immunological effects of bromelain on breast cancer patients revealed that orally applied bromelain stimulates the deficient monocytic cytotoxicity of mammary tumor patients (210).

### 3.10. Curcumin a phytochemical in turmeric

Curcumin is a component of the culinary spice turmeric (*Curcuma longa;* Family-Zingiberaceae), which is often used in curry powder. This active ingredient was first isolated in 1842 by Vogel. In 1910, Milobedzka determined that the structure was diferuloylmethane, and this compound was first synthesized in 1918 by Lampe and cocrystallized with 5-LOX by Skrzypczak-Jankun and collegues (211). Extensive research over the last five decades has indicated that this polyphenol beneficial in all stages of carcinogenesis.

The anti-cancer potential of curcumin stems from its ability i) to suppress proliferation of a wide variety of tumor cells ii) to down-regulate transcription factors iii) to down-regulate the expression of COX-2, LOX, iNOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules, and cyclin D1, iv) to down-regulate growth factor receptors such as EGFR and HER2, and v) to inhibit the activity of c-Jun, PTK, and protein serine/threonine kinases (212-214). Curcumin, a well known inhibitor to AP-1 and NF-kappa B activity and was shown to increase

apoptosis in cancer cells (214-216). It could efficiently suppress NF-kappa B activation induced by TNF, phorbol ester and $H_2O_2$ through suppression of I kappa B alpha degradation (217). NF- kappa B reporter activity induced by TNFR1, TNFR2, NF-kappa B inducing kinase, IKK, and the p65 subunit of NF- kappa B was suppressed by curcumin too. Along with these TNF-induced NF- kappa B regulated gene products which involved in cellular proliferation (COX-2, cyclin D1, c-myc), anti-apoptosis (IAP1, IAP2, XIAP, Bcl-2, Bcl-xL, Bfl-1/A1, TRAF1, cFLIP) and metastasis (VEGF, MMP-9, ICAM-1) were also down regulated by curcumin. A study by Huang *et al* suggested that curcumin suppresses TPA-responsive element-binding activity of c-Jun/AP-1, as major description for the anti-cancer effect of this chemopreventive agent (218). Wang *et al* provided the first insight that the Notch-1 signaling pathway is associated with NF- kappa B activity during curcumin-induced growth inhibition and apoptosis in cancer cells (219). Inhibition of IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation in cancer cells was reported by curcumin (220). Squires *et al* suggested that curcumin has several different molecular targets within the MAPK and Akt/PI3K/PKB signalling pathways that could contribute to inhibition of proliferation and induction of apoptosis (221). Treatment of bladder cancer cell with curcumin (10-25 microM/L) resulted in inhibition of growth, induction of apoptosis and decreased expression of survivin, VEGF and VEGFR-1 (222). The possible use of curcumin in the management of human papilloma virus (HPV) associated tumors is reported via downregulation of viral E 6 and E7 oncogenes, prevention of NF- kappa B and AP-1 translocation and modulation of apoptosis (214). Results of the study revealed that the cytotoxic activity of curcumin was selectively more in HPV infected cells compared to non-HPV infected cells via apoptosis and selective inhibition of viral oncogenes in cervical cancer cells. Gao *et al* suggested a potential use of curcumin to sensitize cells for TRAIL-mediated immunotherapy (223). The combined treatment of curcumin and TRAIL enhanced accumulation of glioma cells (U87MG cells) in sub-G1 phase of cell cycle and induced the cleavage of procaspases-3, -8, -9 and release of cytochrome-c from mitochondria.

As well protective potential of curcumin in chemical carcinogenesis is supported by several animal studies. Curcumin alleviate TPA-induced skin tumor promotion along with epidermal ODC activity and mRNA expression (224). It also attenuates oxidative DNA damage in mouse epidermis (225). When applied topically on the dorsal side of mouse skin significantly inhibited epidermal COX and lipoxygenase (226) and inhibited expression of proto-oncogenes such as c-fos, c-Jun and c-myc (227). F344 rats fed with curcumin in the diet exhibited reduced catalytic activities of phospholipase $A_2$ and phospholipase C gamma 1 that are involved in arachidonic acid release from cellular phospholipid (228). These pleiotropic effects of curcumin appear to be mediated at least in part through inhibition of transcription factors (229). Lee *et al* reported that both 1% and 5% w/w dietary curcumin exerted physiological changes in lung tissues by significantly decreasing LPS-induced TNF-alpha production in lungs, only 5% dietary curcumin significantly improved survival of mice after irradiation and decreased radiation-induced lung fibrosis (230).

As curcumin have diverse anti-cancer activities that lead to inhibition of cancer cell and tumor growth, induction of apoptosis, and anti-angiogenic responses. In several systems, curcumin has also been described as a potent anti-oxidant and anti-inflammatory agent. The compound has been found to be pharmacologically safe: human clinical trials indicated no dose-limiting toxicity when administered at doses up to 10 g/day (231).

### 3.11. Indole-3-carbinol a phytochemical in cruciferous vegetables

Several studies have shown that frequent consumption of cruciferous vegetables is associated with a decreased risk for cancer. Indole-3-carbinol (I3C; autolysis product of glucosinolates) is produced by members of this family and particularly bu members of the genus Brassica (e.g. cabbage, radishes, cauliflower, broccoli, Brussels sprouts and daikon), is well investigated for cancer chemoprevention studies. Michoud *et al* found that men who ate two or more half-cup servings of broccoli per week had a 44 % lower incidence of bladder cancer compared to men who ate less than one serving per week (232). In an epidemiological study researchers recorded 259 cases of lung cancer during the study's follow-up period and found that the men with detectable amounts of isothiocyanate from broccoli in their bodies had a 36% lower risk of developing lung cancer over a 10-year period (233). Initial clinical trials in women have shown that I3C is a promising agent against cervical and breast cancers (234-236).

*In vitro*, I3C has been shown to suppress the proliferation, induce cell cycle in G1 phase and apoptosis in human breast, cervical and prostate cancer cells (237-241). It has been reported to up-regulate CDK inhibitors including p21WAF1/CIP1 (p21) and p27(Kip1) and to down-regulate CDK6 levels and activity. I3C also reported to inhibit the hyperphosphorylation of the Rb protein (239). These all responses have been reported in both ER negative (BT20, MDA-MB-231 and BT539) and positive (MCF-7, 734B and BT474) human breast cancer cells, as well as in prostate cancer cells (238, 239, 242, 243) in dose- and time-dependent manner. In skin cancer cells I3C induces phosphorylation of p53 at Ser 15 and induces caspase-8 mediated apoptosis via the Fas death receptor (244). I3C modulates the apoptosis by inhibiting the activation of NF-kappa B, which brings about the significant down-regulation of anti-apoptotic Bcl-2 and its related gene Bcl-$X_L$ (245). Treatment of highly tumorigenic MDA-MB-231 human breast cancer cells with I3C directly inhibited the extracellular elastase-dependent cleavage of membrane-associated CD40 (a member of the TNF receptor superfamily) as a part of its anti-cancer mechanism (246). It has also been reported to activate ATM signaling pathway to stimulate p53 phosphorylation and disruption of the p53-MDM2 interaction, which releases p53 to induce the p21 Cdk inhibitor and a G1 cell cycle arrest in mammary cancer cells (247). A dose-dependent depression in the estrogen

activated ER alpha signaling and transcriptional activity occurs when I3C is added to cells at 10-125 microM (248). In yet another study I3C at 10 microM concentration can markedly modify the phosphorylation of ER alpha and adding 50 microM of I3C can completely abrogate ER phosphorylation in MCF-7 cells (249). The expression and function of ER alpha and ER beta can be uncoupled by I3C with a key cellular consequence being a significantly higher ER beta: ER alpha ratio that is generally highly associated with anti-proliferative status of human breast cancer cells (250). In LNCaP prostate carcinoma cells I3C treatment subdued the production of PSA (251) by down regulation in expression of PSA transcripts and protein as well as PSA promoter activity (252). Recently researchers uncovered a critical role for the GATA3 transcription factor in this indole regulated cascade and implicated I3C as a novel anti-cancer agent in cancers that coexpress ER alpha, GATA3, and Aryl hydrocarbon receptor (AhR) (253). Hung and Chang suggest that I3C inhibits MMP-2 expression by blocking the ERK/Sp1-mediated gene transcription to attenuate migration and invasion of breast cancer cells (254). Along with these I3C is also capable to retard the development of multidrug resistance (MDR) in cancer cells. This response may relate to suppression in the expression of MDR-1 gene transcript P-glycoprotein (P-gp) (255, 256). Dietary I3C (300–500 mg/kg/day) significantly alleviated the resistance to the anti-cancer drugs such as doxorubicin or vinblastine (256).

*In-vivo*, I3C was found to be a potent chemopreventive agent for hormone dependent cancer (257, 258). Numerous studies have indicated that I3C also has a strong hepatoprotective activity against various carcinogens (259, 260). These effects are mediated through its ability to induce apoptosis, inhibit DNA-carcinogen adduct formation, and suppress free-radical production, stimulate 2-hydroxylation of estradiol, inhibit invasion and angiogenesis. A study by Qi *et al* show that dietary I3C increased PTEN expression in the cervical epithelium of the transgenic mouse, an observation that suggests that PTEN upregulation by I3C is one possible mechanism by which I3C inhibits development of cervical cancer (261). Horn *et al* demonstrated that I3C treatment (250 mg/kg body weight) for 4 or 10 days significantly increased rat liver and mammary mRNA for CYP1A1 and CYP2B1/2 compared with controls (262). I3C inhibit lung adenoma induced by tobacco smoke carcinogens in A/J mice. Analyses of cell proliferation and apoptosis markers revealed that I3C (1, 10, 30, 71, and 112 microM/g), reduced the number of Ki-67-positive cells and expression of PCNA, p-Akt, and p-BAD and increased cleavage of PARP, suggesting that the lung tumor inhibitory effects of I3C were mediated, at least partly, through inhibition of cell proliferation and induction of apoptosis (263). I3C (70 microM/g diet) decreased multiplicities of tumors on the surface of the lung, carcinoma incidence, and size (as well as adenoma with cellular pleomorphism (264). I kappa B alpha degradation, NF-kappa B activation, expression of COX-2, p-Akt and fatty acid synthase and activates caspase-3 and PARP cleavage. Prepubertal I3C treatment appeared to provide an insignificant protection against MNU-induced mammary carcinogenesis (265).

Under acidic conditions, I3C is converted to a series of oligomeric products among which 3,3'-diindolylmethane (DIM) is a major component, thought to be responsible for some biological effects. DIM-induced cell proliferation inhibition and apoptosis induction are partly mediated through the down-regulation of Akt/FOXO3a/GSK-3 beta/beta-catenin/NF-kappa B/AR signaling in hormone referactory cancers (266, 267). DIM at concentrations >50 microM induces CYP1A1 gene expression in breast cancer cells (268). Along with these increased the activation of caspase-3, -7, -8, and -9 and enhanced PARP cleavage in cancer cells (269). Garikapaty *et al* demonstrate that DIM is a potent anti-proliferative agent compared to I3C in the hormone independent prostate cancer cells (DU-145) (270). Results of the study revealed that the effect was mediated by cell cycle arrest in G1 phase with concurrent inhibition of cyclin D1, Cdk4, and Cdk6 and Akt/PI3 kinase signal transduction. DIM, a ligand of AhR, was found to inhibit estrogen-induced responses in ER-positive MCF-7 cells at concentrations ranging from 10 to 50 microM (268, 271). Treatment of MCF-7 cells with DIM (1 microM) down-regulated ER alpha mRNA (3 fold) when compared with untreated cells (272, 273). DIM can stimulate the phosphorylation of ER, which not only activates ER but also the accompanied nuclear cofactors including SRC-1 and CREB (274). DIM also exhibited potent estrogen-independent ER agonist activity at a concentration of 10 microM, and this was accompanied by a strong inhibition of endometrial tumor cell growth and the induction of TGF-alpha-responsive gene expression (275). Rahman *et al* clearly suggest that inhibition of Akt/NF-kappa B signaling by bioactive-DIM leads to chemosensitization of breast cancer cells to Taxotere, which may contribute to increased growth inhibition and apoptosis in breast cancer cells (276). DIM also reported to inhibit the development of human breast tumor in a xenograft model and to provide evidence for the anti-angiogenic properties of this dietary indole (277). Fares *et al* indicated that the DIM agent is not toxic and has an in-vivo preventive effect against the development of prostate cancer in a mouse model (237). Kim *et al* demonstrated that DIM profoundly inhibits the lung metastasis of 4T1 cells, which was accompanied by reduced levels of MMP (2 and 9), adhesion molecules (TIMP-1, and VCAM-1), and pro-inflammatory cytokines (IL-1 beta, IL-6 and TNF-alpha) (278).

### 3.12. D-limonene a phytochemical in citrus fruits

Fruits from Citrus species (Family-Rutaceae) have been widely used as a source of traditional medicines; the peel of the fruit is a more abundant source of bioactive compounds one of them is D-limonene. D-limonene (1-methyl-4-(1-methylethenyl) cyclohexane), one of the most common terpenes in nature which comprises >90% of orange peel oil, has chemopreventive activity against cancers. Many epidemiologic studies have shown a relationship between citrus fruits and cancer chemoprevention. Tuyns reported a protective effect of citrus fruits on esophageal cancer in 1983 (279). Including esophageal cancer positive role of citrus fruit have also been reported in thyroid, pancreatic, lung, prostate, renal, stomach and colon cancer. Based on epidemiological

results from Italy and France, high consumption of citrus fruits (>60 g/day) protected against esophageal cancer (280, 281). Moreover, a dose-response relationship was observed between higher citrus peel in the diet and reduced risk of skin cell carcinoma (282).

In a study the anti-proliferative activity of limonoids was found in high concentrations, against a series of human cancer cell lines i. e. leukemia (HL-60), ovary (SKOV-3), cervix (HeLa), stomach (NCI-SNU-1), liver (Hep G2), and breast (MCF-7) (283). It also inhibits tumor cell proliferation, acceleration of the rate of tumor cell death and/or induction of tumor cell differentiation. In addition, D-limonene inhibits protein isoprenylation, as many prenylated proteins regulate cell growth and/or transformation. Impairment of prenylation of one or more of these proteins might account for the anti-tumor activity of D-limonene (284). It was found that D-limonene attenuates gastric cancer through increasing apoptosis, while decreasing DNA synthesis and ornithine decarboxylase activity of cancer cells (285, 286). D-limonene has been shown to enhance gastrointestinal uridine 5'-diphospho-glucuronosyltransferase (UGT) activity in rats (287).

Limonene has been shown to inhibit the development of spontaneous neoplasms in mice receiving 1200 mg/kg orally (NTP 1990). Dietary limonene also reduces the incidence of lymphomas in $p53^{-/-}$ mice (288). Furthermore, when administered either in pure form or as orange peel oil, limonene inhibits the development of chemically induced rodent mammary (289-292), skin (293), liver (294), lung and forestomach (295, 296) cancers. The chemopreventive effects of limonene are evident in initiation phase of DMBA induced cancer (290) and promotion phase of both DMBA and NMU induced cancers (290, 291) in rat mammary carcinogenesis models. Dietary limonene also inhibits the development of *ras* oncogene induced mammary carcinomas in rats (297). The development of azoxymethane induced aberrant crypt foci in the colon of rats was significantly reduced by 0.5% limonene at both initiation and post-initiation stages (298). Topical application of limonin exhibited 60% reduction in tumor burden in DMBA-induced buccal pouch epidermoid carcinomas (299). Chemopreventive doses of dietary limonene was able to induce cytochrome 2B1 and 2C (300, 301) and epoxide hydratase as well (301). D-limonene inhibits hepatocarcinogenesis via inhibition of cell proliferation, enhancement of apoptosis, and blockage of oncogene expression (302, 303). While experimental and epidemiological reports are of enough to propose limonene as cancer chemotherapeutic agent, larger, more comprehensive molecular mechanistic studies are necessary to confirm its effectiveness as a potential agent for human application.

### 3.13. Diallyl sulfide a phytochemical in garlic

Garlic (Allium sativum L. fam. Alliaceae) is one of the most investigated, best selling herbal remedies and is commonly used as a spice in food. It holds an exclusive position in history and was renowned for its therapeutic prospectives in various diseases together with cancer. Organosulpher compounds (diallyl sulfide, diallyl disulfide, and diallyl trisulfide) extracted from crushed garlic by steam distillation, have been reported to provide the anti-cancer activity. As early as 1550 B.C., Egyptians had realized the effects of garlic as a remedy for a variety of diseases (304). Nowadays, health benefits of garlic appear to be true. Anti-cancer properties of garlic were first described by Weisberger and Pensky in 1958 (305). They reported an inhibitory effect of a garlic extract on cancer cell growth both *in vitro* and *in vivo* (305). Epidemiologic findings suggested that protection against stomach and colon cancers may be related to consumption of raw/cooked garlic (306, 307). A reduced risk of prostate cancer with an increased intake of garlic was also evidenced (308, 309). Several intensive studies have been carried out to verify chemopreventive and anti-carcinogenic effects of garlic, and to explain mechanisms of its action.

Diallyl sulfide (DAS) inhibit carcinogen activation, boost phase II detoxifying processes, cause cell cycle arrest mostly in G2/M phase, stimulate the mitochondrial apoptotic pathway, increase acetylation of histones, influence gap-junctional intercellular communication and participate in the development of MDR. The sulphur compounds of garlic inhibit cell proliferation, modulate cell cycle activity and interfere with hormone action in cancer cells (310-313). Allicin has been shown to inhibit the proliferation of human mammary, endometrial and colon cancer cells (313).

Consumption of garlic and related sulfur compounds by laboratory animals reduced carcinogen-induced tumors as evidenced by a number of studies (314-319). In these studies DAS has reportedly modulated activities of cytochrome P450 isozymes, blocked carcinogen activation, DNA adduct formation and facilitated carcinogen detoxification through increased activities of GST, epoxide hydrolase, and UGT as well as through induction of glutathione peroxidase. DAS also inhibited development of colon carcinoma, esophagus carcinomas, pulmonary adenomas and forestomach tumors in rodents, when administered prior to carcinogen exposure (295, 320-322). DAS administration following DEN and 2-AAF exposure led to the restoration of enzymic activity of ATPase, G-6-Pase and AlkPase, suggestive of its protective role in hepatocarcinogenesis (323). DAS protect against B(a)P induced tumorigenesis in mice via induction of QR (enzyme capable of detoxifying activated quinone metabolites of B(a)P) (324).

## 4. PROSPECTIVE

In light of above findings it is now possible to propose that the cancer chemopreventive activities of dietary phytochemicals induces direct impact on cancer cells along with their micro-environment, as well as in the modulation of various molecular pathways (Figure 2). The reduction in cancer incidence that might be expected from improved nutrition, through general public awareness, could have many benefits including a reduction in human suffering, health care costs and increased opportunities to design health food. This would provide new industries for

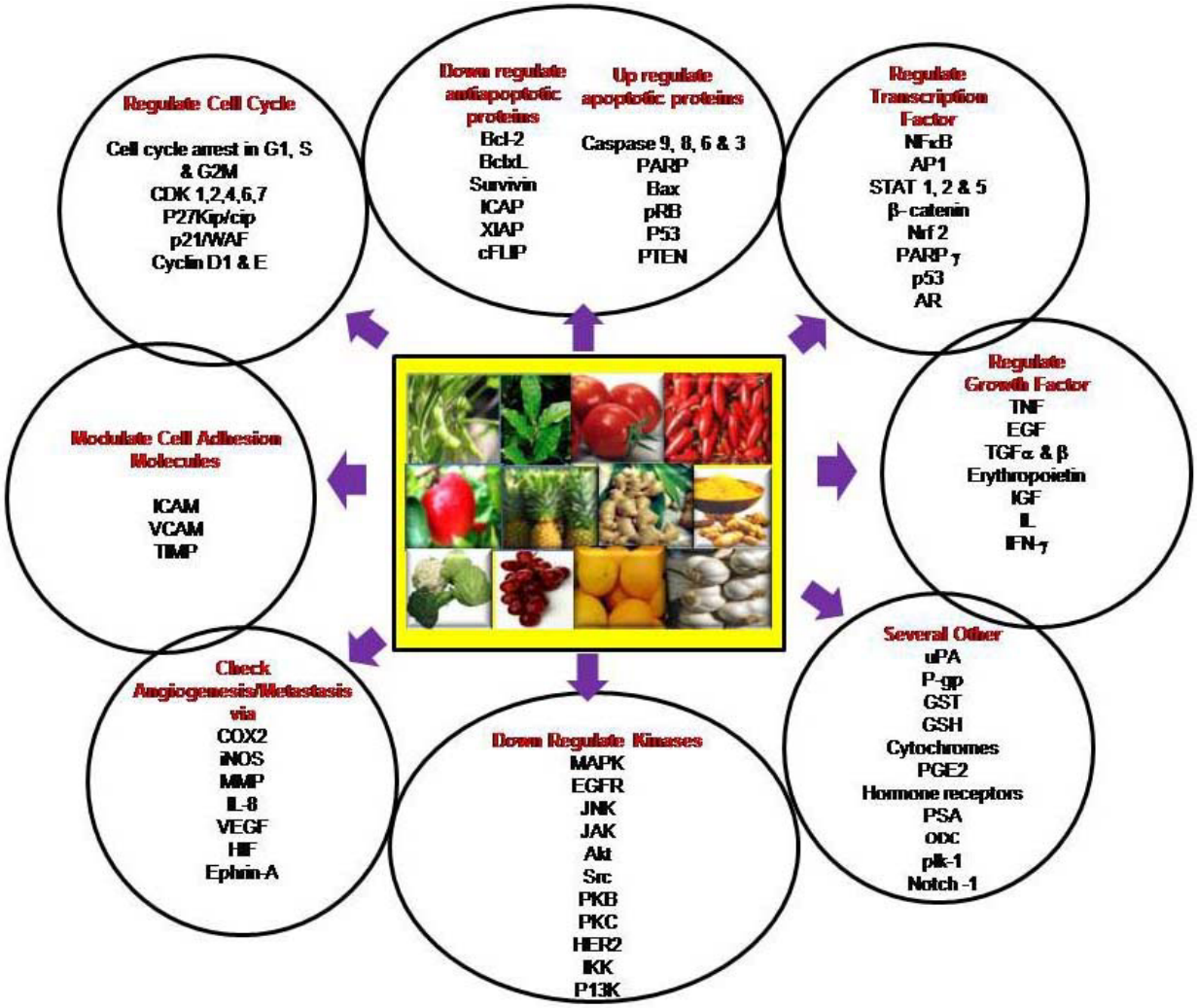


**Figure 2.** Cancer chemopreventive mechanisms exerted by selected dietary phychemicals.

processing of these products into human acceptable forms and to strenghthen the fight against cancer. Evidences suggest beneficial impact of complementary and alternative medicine to prevent or alleviate common illnesses are at niche, and these medicines are also popular in cancer treatment. Therefore, prevention of cancer through dietary intervention become not only important potential chemopreventive, but also therapeutic. Thus, change in dietary behavior, such as increasing consumption of fruits, vegetables and whole grains and related amendment in lifestyles is a practical strategy for notably reducing the incidence of cancer.

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**Abbreviations:** 7-12-dimethylbenz[a]anthracene: DMBA, 2-Acetylaminofluorene: 2-AAF, activator protein 1: AP-1, amplified in breast cancer 1: AIB1, androgen receptor: AR, apoptosis-inducing factor: AIF, Apurinic / apyrimidinic endonuclease: APE1 or Ref1, aryl hydrocarbon receptor: AhR, ataxia telangiectasia mutated protein: ATM, benzo[a]pyrene: B[a]P, cellular FLICE-inhibitory protein: c-FLIP, cyclic adenosine monophosphate response element-binding protein: CREB, cyclin- dependent kinase: CDK, Cyclooxygenase: COX, dihydrotestosterone: DHT, EGFR-related protein: Erb, ephrin type-A receptor 2: EphA2, epidermal growth factor: EGF, epidermal growth factor receptor: EGFR, estrogen receptor: ER, eukaryotic translation elongation factor 1 alpha 2: eEF1A2, extracellular signal-regulated kinase: ERK, forkhead box O3: FOXO3, glandular kallikrein 11: Gk11, glutathione S-transferases: GST, glycogen synthase kinase-3: GSK-3, human epidermal growth factor receptor: HER2, hypoxia-inducible factor: HIF, human papilloma virus: HPV, IGF binding protein 3: IGFBP-3, inducible nitric oxide synthase: iNOS, inhibitor of apoptosis: IAP, insulin-like growth factor: IGF, inter-cellular adhesion molecule: ICAM, interleukin (IL), janus kinase: JAK, jun N-terminal kinase: JNK, lipid peroxidation: LPO, mitogen-activated protein kinases: MAPK, mammalian target of rapamycin: mTOR, matrix metalloproteinase: MMP, multidrug resistance: MDR, NF-kappa B inducing kinase: NIK, nitrosomethylurea: NMU, NSAID-activated gene-1: NAG-1, nuclear factor-kappa B (NF-kappa B), ornithine

decarboxylase: ODC, peroxisome proliferators-activated receptor-gamma: PPAR-gamma, P-glycoprotein: P-gp, phosphatase and tensin homolog: PTEN, phosphoinositide 3-kinase: PI3K, poly (ADP-ribose) polymerase: PARP, proliferating cell nuclear antigen: PCNA, prostaglandine: PG, prostate androgen-regulated transcript: PART-1, prostate-specific antigen: PSA, protein kinase B: PKB, protein tyrosine kinase: PTK, reactive oxygen species: ROS, steroid receptor coactivator-1: Src-1, tissue inhibitor of MMP: TIMP, TNF receptor: TNFR, TNF receptor-associated factor 1: TRAF 1, TNF-related apoptosis-inducing ligand: TRAIL, transforming growth factor: TGF, tumor necrosis factor: TNF, tumor-associated nicotinamide adenine dinucleotide hydride oxidase activity: tNOX, uridine 5'-diphospho-glucuronosyltransferase: UGT, urokinase-type plasminogen activator: uPA, vascular cell adhesion molecule: VCAM, vascular endothelial growth factor: VEGF, X chromosome-linked IAP: XIAP

**Key Words:** Phytochemicals, Cancer, Chemoprevention, Anti-Carcinogenic, Review

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