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Plants Against Cancer: A Review on Natural Phytochemicals in Preventing and Treating Cancers and Their Druggability

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Abstract

Cancer remains to be one of the leading causes of death in the United States and around the world. The advent of modern drug-targeted therapies has undeniably improved cancer patients' cares. However, advanced metastasized cancer remains untreatable. Hence, continued searching for a safer and more effective **chemoprevention** and treatment is clearly needed for the improvement of the efficiency and to lower the treatment cost for cancer care. Cancer chemoprevention with natural phytochemical compounds is an emerging strategy to **prevent, impede**, delay, or cure cancer. This review summarizes the latest research in cancer chemoprevention and treatment using the bioactive components from natural plants. Relevant molecular mechanisms involved in the pharmacological effects of these phytochemicals are discussed. Pharmaceutical developmental challenges and opportunities in bringing the phytochemicals into the market are also explored. The authors wish to expand this research area not only for their scientific soundness, but also for their potential druggability.

Keywords

anti-cancer; chemoprevention; druggability; mechanism; natural compounds; pathway; phytochemical

1. Introduction

Natural plants have been used to prevent and to treat various diseases for thousands of years. The **ancient** Chinese emperor, the Red Emperor, or *Shen Nung*, compiled the first medicinal herbal **literature**, *Pentsao* in 2,800 BC [1]. In dealing with diseases, prevention is considered a superior approach. As illustrated by the *Huang-Di Nei-Jing*, a manuscript believed being written by the ancient Chinese emperor, the Yellow Emperor, "The Saint treats those ill-to-be rather than those being ill, and **cares for** those in **normality** rather than

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those in chaos. Drug a disease after it's developed, or quench a chaos after it's evident, is same as dig a well when in thirsty, or casting a sword in a battle — Is that somewhat late?"

There are excellent **sources** of bioactive components exerting their health beneficial effects, and very often, **these sources** are materials for gourmet food consumptions. Certain bioactive components from the plants have been confirmed for their anti-cancer activities. There is an estimate that approximately 50-60% of cancer patients in the United States utilize agents derived from different parts of plants or nutrients (complementary and alternative medicine), exclusively or concomitantly with traditional therapeutic regimen such as chemotherapy and/or radiation therapy [2]. These include curcumin from tumeric, genistein from soybean, tea polyphenols from green tea, resveratrol from grapes, sulforaphane from broccoli, isothiocyanates from cruciferous vegetables, silymarin from milk thistle, diallyl sulfide from garlic, lycopene from tomato, rosmarinic acid **from rosemary**, apigenin from parsley, and gingerol from gingers, just to name a few.

Various review articles summarized natural phytochemicals and their anti-cancer effects. In recent years, some of these reviews touched the general overview for the bioactive aspect for phytochemical compounds [3-12], or specific compounds such as Vitamin E from plant oil [13-15], boron-rich natural compound [16], hydroxytyrosol from virgin olive oil [17], resveratrol from grapes [18], phytoestrogens most notably from soybean [19, 20], or EGCG from green tea polyphenols [21], while the others are more specific for certain cancers, e.g., colorectal cancer [22, 23], breast cancer [14, 24], head and neck cancer [25], pancreatic cancer [26], prostate cancer [27], or protein targets and pathway mechanisms, such as Nrf2 [28], COX-2 [29], PLK1 [30], angiogenesis [31]. In this review, we will provide a comprehensive summary for the current status of the research and challenges in this area [32].

2. Phytochemicals used as cancer chemopreventive and treatment agents

2.1 Apigenin from parsley

Apigenin is a flavone present in vegetables such as parsley, celery, chamomile [33], and Egyptian plant *Moringa peregrina* [34]. It demonstrates cytotoxic activities against breast cancer cell lines (MCF 7), colon cell line (HCT 116), and its cytotoxic activity is comparable to that of doxorubicin.[34]. Apigenin is also being considered as a mediator for chemoprevention in the cancerous process and induces a process of autophagia but may induce resistance against chemotherapy [35]. It induces apoptosis in human colon cancer cells [36, 37], reduces azoxymethane (AOM) induced aberrant crypt foci (ACF) formation in male Sprague-Dawley rats, and increases apoptosis which may contribute to the colon cancer prevention [38]. Apigenin affects leptin/leptin receptor pathway, and induces cell apoptosis in lung adenocarcinoma cell line [39]. It also increases melanogenesis in B16 cells by activating the p38 MAPK pathway at least partially and suggests that apigenin or its derivatives may potentially be used for treating hypopigmentation disorders [40]. Apigenin has been shown to be one of the beneficial compounds in various stages of carcinogenesis. In a recent review by Clere *et al*, the preventive and therapeutic effects of Apigenin and other flavonoids was summarized to facilitate the extrapolation from animal studies to human [41].

2.2 Curcumin from turmeric

Curcumin (diferuloylmethane) is the major components of popular Indian spice turmeric, *Curcuma longa L.*, a member of the ginger family. Its anti-cancer effects have been studied for colon cancer, breast cancer [42], lung metastases, and brain tumor [43].

Curcumin's anticancer effect is attributed to its ability to induce apoptosis in cancer cells without cytotoxic effects on healthy cells, which is very attractive to cancer research scientists. Curcumin interferes with NF- κ B [44], which connects with inflammatory diseases including cancer [45]. Curcumin was able to dissociate raptor from mTOR, inhibit mTOR complex I and might represent a new class of mTOR inhibitor [46]. Ravindran *et al* suggested that curcumin modulates 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-IAP1), 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) [47]. Curcumin inhibits p65 and cell invasion by downregulation of COX-2 and MMP-2 expression [48]; by suppression of gene expression of EGFR and modulation of Akt/mTOR signaling, and inhibition of cell growth [49, 50]. It has also been reported that curcumin suppresses p38 mitogen-activated protein kinase (MAPK) activation, reduces IL-1 beta and matrix metalloproteinase-3, and enhances IL-10 in the mucosa of children and adults with inflammatory bowel disease [51]. Epstein and co-workers had a thorough review on *in vitro*, animal and clinical studies [52]. In that review, curcumin is cited as non-toxic to human subjects at a high oral dose of up to 12 g/day, and it has anti-inflammatory, antioxidant and anti-cancer properties, however, under some circumstances, its effects can be contradictory as the first clinical trial failed to show benefit, which may be due to an unexpected lack of cognitive decline in placebo group [52]. In our lab, curcumin was studied for modulating AP-1 in human colon HT-29 cancer cell line and was found increasing AP-1-luciferase activity dose-dependently from 1 to 25 μ M, and the expression of endogenous cyclin D1 protein was well correlated with those of AP-1-luciferase assay [53]. It inhibited NF- κ B stimulator lipopolysaccharide (LPS)-induced inflammation, reduced LPS-induced I κ B phosphorylation, and potently inhibited cell growth in MTS assay. Caspase-3 activity was also induced by curcumin [54]. Among our other studies, Affymetrix mouse genome 430 array (45K) was used to analyze mouse liver and intestine mRNA after oral dose of curcumin at 1,000 mg/kg. Our results showed that 822 (664 induced and 158 suppressed) and 222 (154 induced and 68 suppressed) genes in **the liver and small intestine**, respectively, were curcumin-regulated Nrf2 dependent, which can be classified as ubiquitination and proteolysis, electron transport, detoxification, transport, apoptosis and cell cycle control, cell adhesion, kinase and phosphatase, and transcription factor [55]. Another study from our lab found curcumin inhibited the phosphorylation of Akt, mTOR, and their downstream substrate in human prostate cancer PC-3 cells concentration- and time-dependently. And the inhibition of Akt/mTOR signaling by curcumin resulted from calyculin A-sensitive protein phosphatase-dependent dephosphorylation [56]. We have also investigated combination of curcumin with sulforaphane [57], with PUFA [58], with PEITC in inhibiting the growth of human PC-3 prostate xenografts in immunodeficient mice [59] and in inhibiting EGFR signaling in

human prostate cancer PC-3 cells [60] and these studies demonstrated various levels of synergistic effects.

2.3 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.* [2]. In a recent review article, saffron is listed as a potential **agent** for a novel anti-cancer drug against hepatocellular carcinoma [2, 61, 62]. Saffron and its ethanolic extracts are also reported for **the studies on** human lung cancer [63, 64], pancreatic cancer cell line [65], skin carcinoma [66], colorectal cancer cells [67], and breast cancer [68]. Its applications **and mechanism** of actions are reviewed by Bathaie and Mousavi [69], and more recently, by Gutheil and Reed [2]. Yet, it has been concluded that the exact mechanism of action is still not clear. In general, crocetin affects the growth of cancer cells by inhibiting nucleic acid synthesis, enhancing anti-oxidative system, inducing apoptosis and hindering growth factor signaling pathways [2]. Nam's study has shown that crocetin is effective for the inhibition of LPS-induced nitric oxide release, for the reduction of the produced TNF- α , IL-1 β , and intracellular reactive oxygen species, for the activation of NF- κ B, and blockage of the effect of LPS on hippocampal cell death [70]. Although some studies beyond those mentioned above are successfully conducted, more thorough understanding of the mechanism on crocetin and its effects are needed.

2.4 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. It possesses antioxidant and radical-scavenging effects which may reduce the risk of cancer. It is reported to inhibit cell proliferation, and iNOS and COX-2 gene expression in colon cancer cells [71]. Another study shows that cyanidin-3-glucoside (C3G) attenuated the benzo[a]pyrene-7,8-diol-9,10-epoxide-induced activation of AP-1 and NF- κ B and phosphorylation of MEK, MKK4, Akt, and MAPKs, blocked the activation of the Fyn kinase signaling pathway, which may contributed to its chemopreventive potential [72]. C3G blocks ethanol-induced activation of the ErbB2/cSrc/FAK pathway in breast cancer cells and may prevent/reduce ethanol-induced breast cancer metastasis.[73] Cyanidin-3-O-glucoside, cyanidin-3-O-rutinoside, and the ethanol extract of their source of freeze-dried black raspberries selectively caused significant growth inhibition and induction of apoptosis in a highly tumorigenic rat esophagus cell line (RE-149 DHD) but not in a weakly tumorigenic line (RE-149) [74]. Cyanidin markedly inhibited UVB-induced COX-2 expression and PGE2 secretion in the epidermal skin cell line by suppressing NF- κ B and AP-1 which are regulated by MAPK. In that study, MKK-4, MEK1 and Raf-1 are targets of cyanidin for the suppression of UVB-induced COX-2 expression [75]. Cyanidin-3-galactoside and cyanidin-3-glucoside are found to be BCRP substrates, and cyanidin, cyanidin-3,5-diglucoside, and cyanidin-3-rutinoside are potential BCRP inhibitors but their effects on MDR1 were weak [76]. This finding may be helpful for the further development of these compounds for clinical studies and may explain their pharmacokinetic performance *in vivo*.

2.5 Diindolylmethane (DIM) /Indole-3-carbinol (I3C) from Brassica vegetables

Indole-3-carbinol (I3C) is found in *Brassica* vegetables, 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 and therapy for years [77] 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/PI3K/Akt signaling pathway, at least partially [78]. I3C and DIM demonstrated exceptional anti-cancer effects against hormone responsive cancers like breast, prostate and ovarian cancers [79]. In a recent study, it is concluded that DIM rather than I3C is the active agent in cell culture studies [80].

DIM showed anti-cancer properties and is currently in clinical trials for various forms of cancers. DIM **transduces** signaling via aryl hydrocarbon (Ah) receptor, NF- κ B/Wnt/Akt/mTOR pathways, impinging on cell cycle arrest, modulated key CYP enzymes, altering angiogenesis, invasion, metastasis and epigenetic behavior of cancer cells [81]. DIM, along with I3C were found to induce Nrf2-mediated phase II drug metabolizing (GSTm2, UGT1A1, and NQO1) and antioxidant (HO-1 and SOD1) genes and also shown synergism with isothiocyanates, such phenethyl isothiocyanate (PEITC) and sulforaphane (SFN) [82]. Lubet *et al* found that I3C **acts** as AhR agonist in mammary cancers while DIM does not, and DIM is not analogous to I3C in exerting their anticarcinogenesis effects [83]. DIM and I3C may act more effectively at earlier stage of prostate carcinogenesis and likely through a combination of effects on steroid hormones and/or xenobiotic metabolism pathway [84].

2.6 Epigallocatechin gallate from green tea

EGCG is the most abundant catechin compounds in green tea. Increasing evidences show that EGCG can be beneficial in treating brain [85], prostate [86], cervical [87], **and** bladder [88] cancers. Yang *et al* reviewed tea and cancer prevention on molecular mechanisms, molecular targets and human relevance of tea constituents [89-91]. Among numerous mechanism studies, EGCG binds and inhibits the anti-apoptotic protein Bcl-xl [92], a protein involved in both cancer cell and normal cell survival [93]. EGCG suppressed AOM-induced colonic premalignant lesions in mice [94], interfered with EGFR signaling [95], and inhibited hepatocyte growth factor-induced cell proliferation in human colon cancer cells [96]. EGCG has shown inhibition of mitogen-activated protein kinases (MAPK), cyclin-dependent kinases, growth factor-related cell signaling, activation of activator protein 1 and NF- κ B, topoisomerase I and matrix metalloproteinases. In human, the pharmacological concentration are typically at least 10 μ mol/L [91].

Our lab studied EGCG induced stress signals in HT-29 human colon adenocarcinoma cells and found that EGCG inhibited HT-29 cell growth with an IC₅₀ of approximately 100 μ M, and the dose levels higher than that showed apparent nuclear condensation and fragmentation, and the study concluded that EGCG caused damage to mitochondria and JNK mediated EGCG-induced apoptotic cell death [97]. EGCG was also found to increase

AP-1 luciferase activity dose-dependently up to 100 μ M [53], reduce LPS-induced I κ B alpha phosphorylation [54]. Additional study in our group demonstrated that combining sulforaphane and EGCG exerted synergistic effects in HT-29 AP-1 human colon carcinoma cells [98]. To investigate possible Nrf2-mediation, EGCG were orally dosed to C57BL/6J and C57BL/6J/Nrf2(-/-) mice. The liver and small intestine were analyzed using Affymetrix mouse genome 430 2.0 array. Gene expression showed that 671 Nrf2-dependent and 256 Nrf2-independent genes were regulated by EGCG in liver, and 228 Nrf2-dependent and 98 Nrf2-independent genes are regulated by EGCG in intestine. This study pointed out that the EGCG chemopreventive effects may be mediated by Nrf2, at least partially [99].

2.7 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 [100-102]. Fisetin has been found to alleviate aging effects in the yeast or fruit fly [103, 104], exert anti-inflammatory effect in LPS-induced acute pulmonary inflammation and anti-carcinogenesis effects in HCT-116 human colon cancer cells [105, 106]. Fisetin is also a potent antioxidant and modulates protein kinase and lipid kinase pathways [107]. Fisetin, along with other flavonoids such as luteolin, quercetin, galangin and EGCG, induced 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 [108] and reduced hydrogen peroxide (H₂O₂)-induced cell death [109]. A recent study by Khan *et al* found dual inhibition of PI3K/Akt and mTOR signaling in human non-small cell lung cancer cells by fisetin [110]. Fisetin inhibited Wnt signaling through the modulation of beta-catenin expression, transcriptional activity and of the subsequent expression of Wnt target genes [111]. Other studies found fisetin decreased cell viability with G1-phase arrest and disrupted Wnt/ β -catenin signaling [112], exhibited an inhibitory effect on the abilities of adhesion, migration, and invasion, and significantly decreased the nuclear levels of nuclear factor kappa B (NF- κ B) and activator protein-1 (AP-1) [113]. 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 [114].

2.8 Genistein from soybean

Genistein is an isoflavone originates from a number of plants such as lupine, fava beans, soybeans, kudzu, and psoralea, *Flemingia vestita*, and coffee. Functioning as antioxidant and anthelmintic, genistein has been found to have antiangiogenic effects (blocking formation of new blood vessels), and may block the uncontrolled cell growth associated with cancer, most likely by inhibiting the enzymes that regulate cell division and cell survival (growth factors). Genistein's activity was chiefly functioned as a tyrosine kinase inhibitor by inhibiting DNA topoisomerase II [115, 116]. *In vitro* and *in vivo* studies show that genistein has been found to be useful in treating leukemia [117-120].

Estrogen receptors are over-expressed in around 70% of breast cancer cases (ER-positive). Binding of estrogen to the ER stimulates proliferation of mammary cells, with the resulting

increase in cell division and DNA replication. Estrogen metabolism produces genotoxic waste, which may cause disruption of cell cycle, apoptosis, DNA repair, and forms tumor. Genistein can compete with 17β -estradiol (estrogen) to bind to estrogen receptor and shows higher affinity towards estrogen receptor β than towards estrogen receptor α [121], where estrogen receptor functions as a DNA-binding transcription factor that regulates gene expression. Genistein was confirmed to increase the rate of growth of some estrogen receptor in breast cancer and the rate of proliferation of estrogen-dependent breast cancer when not co-treated with an estrogen antagonist [122, 123]. In colon cancer, genistein is thought to contribute to reduced colonic inflammation in 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis [124]. Our lab previously investigated genistein and found that genistein possibly involved in JNK pathway in inducing AP-1 activity [125].

2.9 Gingerol from gingers

Gingerol is the active component of fresh ginger with distinctive spiciness. Gingerol has been studied for its anticancerous effects for the tumors in colon [126], breast and ovarian [127, 128], and pancreas [129]. A recent review by Oyagbemi *et al* summarized the mechanisms in the therapeutic effects of gingerol [130]. In short, gingerol has demonstrated antioxidant, anti-inflammation, and antitumor promoting properties, decreases iNOS and TNF-alpha expression via suppression of $\text{I}\kappa\text{B}\alpha$ phosphorylation and NF- κB nuclear translocation [130]. Treating K562 cells and MOLT4 cells with gingerol, the ROS levels were significantly higher than control groups, inducing apoptosis of leukemia cells by mitochondrial pathway [131]. 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 6-shogaol further regulated urokinase-type plasminogen activity [132]. Topical application of 6-shogaol, another active component from ginger is more effective than 6-gingerol and curcumin in inhibiting 12-O-tetradecanoylphorbol 13-acetate (TPA)-induced transcription of iNOS and COX-2 mRNA expression in mouse skin, which may justify further *in vitro* and *in vivo* studies [133].

2.10 Kaempferol from tea, broccoli, grapefruit

Kaempferol is a natural flavonol isolated from tea, broccoli, Witch-hazel, grapefruit, Brussels sprouts, apples, etc [134]. Kaempferol has been studied for pancreatic cancer [135], and lung cancer [136]. It has been investigated for its antiangiogenic, anticancer, and radical scavenging effects [137] [138]. Kaempferol, displayed moderate cytostatic activity of 24.8 – 64.7 μM in the cell lines of PC3, HeLa and K562 human cancer cells [139]. To *et al* studied kaempferol as aryl hydrocarbon receptor (AhR) antagonist showing inhibition of ABCG2 upregulation, thereby reversing the ABCG2-mediated multi-drug resistance, which may be useful for esophageal cancer treatment [140]. Luo *et al* found that kaempferol induces apoptosis in ovarian cancer cells through the activation of p53 in the intrinsic pathway [141]. Yang *et al* reported that kaempferol inhibited quinone reductase 2 with an IC (50) value of 33.6 μM for NF- κB activity [142]. In a study by Niestroy *et al*, kaempferol was studied on benzo[a]pyrene (BaP) mediated effects on Caco-2 cells on concerted effects on the expression of AhR and Nrf2 pathway components [143]. In that study, BaP, quercetin and kaempferol activated Nrf2 pathway by induction of Nrf2, and its target genes NQO1, GSTP1, GSTA1, and GCLC. However, in spite of their own induction potential for Nrf2,

both quercetin and kaempferol counteract the effects of BaP on expression of AhR, AhRR, Nrf2, GSTP1 and NQO1 [143].

Kaempferol showed very low bioavailability of approximately 2% in earlier study [144]. Using Madin-Darby canine kidney (MDCK) cell monolayers, kaempferol was shown to be a breast cancer resistance protein (Bcrp, Abcg2) inhibitor and may also be a Bcrp substrate, which may represent one possible mechanism for the low bioavailability of kaempferol [145].

2.11 Lycopene from tomato

Lycopene is a bright red pigment and phytochemical from tomatoes, red carrots, watermelons, and red papayas. It demonstrates antioxidant activity and chemopreventive effects in many studies, especially for prostate cancer. Poorly soluble in water, lycopene has high solubility in organic solvents. Its anti-cancer property is attributed to activating cancer preventive enzymes such as phase II detoxification enzymes [146]. Lycopene was found to inhibit human cancer cell proliferation, and to suppress insulin-like growth factor-I-stimulated growth. This may open new avenues for lycopene study on the role of the prevention or treatment of endometrial cancer and other tumors [147]. Lycopene also possesses inhibitory effects on breast and endometrial cancer cells [148], prostate cancer cells [146], and colon cancer cells [149]. However, in a study conducted by Erdman and group using xenograft prostate tumors into rats, it was found that the tumors grew more slowly in those given whole dried tomato powder but not in those given lycopene, which may indicate that lycopene may be an important component in tomato but not the only component in tomato that actively suppressing the growth of the prostate cancer [150].

2.12 Phenethyl Isothiocyanate (PEITC) from cruciferous vegetable

PEITC, along with sulforaphane from cruciferous vegetables, such as watercress, broccoli, cabbage, etc., have been studied for induction of apoptosis in cell lines. PEITC has shown very strong potency against melanoma. It has been intensively studied for chemoprevention against breast cancer cells [151, 152], non-small cell lung cancer [153], cervical cancer [154, 155], osteogenic sarcoma U-2 OS [156], prostate cancer [157-159], and myeloma cell lines [160]. PEITC induces apoptosis in some cell lines that are resistant to some currently used chemotherapeutic drugs.

PEITC induced apoptosis in highly metastatic human non-small cell lung cancer L9981 cells via Caspase-3 activation, leading to cell cycle arrest at the G2/M phase by modulation of cyclin B1 expression, where MAPK/AP-1 pathway was the target [153]. *In vitro* and *in vivo* data support that PEITC, as well as sulforaphane, induced G2/M cell cycle arrest, apoptosis of cell death of myeloma cells [160]. In cervical cancer cells, PEITC was found to increase the expression of the death receptors (DR4 and DR5), cleaved caspase-3, induced caspase-8 and truncated BID, down-regulated the ERK1/2 and MEK phosphorylation while maintaining the expression of JNK and phospho-p38 MAPK [154]. PEITC was also studied for cytotoxicity in a human liver hepatoma cell line (HepG2-C8) along with I3C, DIM, and sulforaphane, and it turned out that PEITC was more toxic than I3C and DIM [82]. In human prostate cancer DU 145 cells, PEITC induced apoptosis mediated by the activation of

caspase-8, -9, and -3-dependent pathways [161]. PEITC induced substantial increase in the activation of caspase-3, -8, -9, cleavage and degradation of PARP, and apoptosis dose- and time-dependently, accompanied by the caspase-independent downregulation of Mcl-1, Akt inactivation, and activation of JNK [162]. Using human osteogenic sarcoma U-2 OS cells, PEITC, along with benzyl isothiocyanates (BITC), caused growth inhibition, inhibited cell cycle regulatory proteins, promoted Chk1 and p53, induced apoptosis and poly(ADP-ribose)polymerase (PARP) cleavage [156]. Wang *et al* found that cells with mutant p53 are more sensitive to cytotoxicity induced by PEITC than those with wild-type protein, which may be a novel target for cancer chemoprevention [163].

2.13 Resveratrol from grapes

Resveratrol is a natural phenol and can be found in the red grapes skin, peanuts and in other fruits. Jang *et al* reported cancer chemopreventive activity of resveratrol [164]. In that study, resveratrol was found to 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. However, poor oral bioavailability [165] caused by rapid metabolism limited its effectiveness in animal cancer models and in human studies [166, 167]. However, with direct contact, resveratrol has demonstrated anti-carcinogenesis effects in skin tumor [168, 169] and gastrointestinal tract tumor, such as N-nitrosomethylbenzylamine (NMBA)-induced esophageal tumors in rats [170]. Resveratrol was found to inhibit metastasis via reducing hypoxia inducible factor-1 α and MMP-9 expression in colon cancer cells [171]; to suppress dextran sulfate sodium (DSS) – induced colitis through downregulation of p38, prostaglandin E synthase-1, iNOS, and COX-2 in mice [172]; to inhibit Wnt signaling and beta-catenin localization in colon-derived cells [173]. Another study found that resveratrol at a concentration of 10 μ M or more induces apoptosis in normal cells as well as cancer cells which demonstrated a potential cytotoxic effect on normal cells [174].

Our lab studied resveratrol's modulation of AP-1 in human colon HT-29 cancer cell line and reported that resveratrol increased AP-1-luciferase activity dose-dependently and induced cell death in a dose-dependent manner [53]. Resveratrol increased activation of LPS-induced NF- κ B-luciferase activity at lower dose, but inhibited activation at higher dose, reduced LPS-induced I κ B alpha phosphorylation, and induced caspase-3 activation [54]. Our another toxicogenomics study of resveratrol in rat liver showed that at the high doses (3 gm/kg/day for 28 days) the modulation of liver genes may implicate the potential toxicity [175].

2.14 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. Rosemary extracts play important roles in anti-inflammation, anti-tumor, and anti-proliferation in various *in vitro* and *in vivo* studies. Study in Ls174-T human colon carcinoma cells found that rosmarinic acid inhibits migration, adhesion, and invasion dose-dependently [176]. In another study, rosmarinic acid may inhibit bone metastasis from breast carcinoma mainly via the pathway of the NF- κ B and by simultaneous suppression of

interleukin-8 (IL-8) [177]. Moon *et al* investigated TNF- α mediated anti-cancer therapy mechanism. In human leukemia U938 cells, rosmarinic acid significantly sensitized TNF- α -induced apoptosis through the suppression of NF- κ B and reactive oxygen species (ROS), and suppressed NF- κ B activation through inhibition of phosphorylation and degradation of I κ B α . [178]. Rosmarinic acid reduced 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 promoter activity and protein levels in colon cancer HT-29 cells, repressed binding of the activator protein-1 (AP-1) in a nonmalignant breast epithelial cell line (MCF10A), and antagonized the stimulatory effects of TPA on COX-2 protein expression [179].

2.15 Sulforaphane from cruciferous vegetables

Sulforaphane is an organosulfur compound obtained from cruciferous vegetables such as broccoli, Brussels sprouts and cabbages. The enzyme myrosinase in GI tract transforms glucoraphanin into sulforaphane upon damage to the plant such as from chewing. Broccoli sprouts and cauliflower sprouts are rich in glucoraphanin.

Sulforaphane has shown 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. Sulforaphane downregulated the Wnt/beta-catenin self-renewal pathway in breast cancer stem cells [180]; protected skin against UV radiation damage [181], and inhibited histone deacetylase (HDAC) activity [182]. In *Apc*^(Min/+) mice, sulforaphane reduced the number of polyps by inhibiting Akt, ERK signaling, COX-2, and cyclin D1 protein expression [183] and also inhibited cancer cell growth by inducing apoptosis in SW620 cells [184]. In a recent study, sulforaphane induced cytotoxicity and lysosome- and mitochondria-dependent cell death in colon cancer cells 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 [185].

In our lab, sulforaphane has been studied for its chemoprevention activities and its involvement in anti-inflammation. 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 [53]. Sulforaphane also strongly inhibited LPS-induced NF- κ B-luciferase activations. In MTS assay, sulforaphane potently inhibited cell growth and induced caspase-3 activity [54]. In HepG2 human hepatoma cells, sulforaphane strongly induced Nrf2 protein expression and ARE-mediated transcription activation, retarded degradation of Nrf2 through inhibiting Keap1, and activated transcriptional expression of antioxidant enzyme HO-1 [186]. In human prostate cancer PC-3 cells, sulforaphane suppressed NF- κ B and NF- κ B-regulated gene expression through I κ B-alpha, and IKK pathway [187]. Sulforaphane was found to be unable to disrupt the cytosolic distribution of Nrf2 zip which indicates that the importance of Keap1 retention as a key rate-limiting step in Nrf2 activation [188]. Study in HepG2 cells also found that transcriptional activation of Nrf2/ARE is critical in sulforaphane-mediated induction of HO-1, which can be modulated in part by the blockade of p38 MAPK signaling pathway. In addition, p38 MAPK can phosphorylate Nrf2 and enhances the association between Nrf2 and Keap1 proteins, thereby potentially inhibiting Nrf2 translocation into nuclear to initiate antioxidant gene transcription [189]. Pretreatment of sulforaphane in primary peritoneal macrophages of wild

type mice potentially inhibited LPS-stimulated mRNA expression, protein expression of TNF- α , IL-1 β , COX-2 and iNOS. HO-1 expression was significantly augmented as well. The anti-inflammatory effects were attenuated in Nrf2 ($-/-$) primary peritoneal macrophages and therefore, the anti-inflammatory activity was mainly exerted by Nrf2 pathway in mouse peritoneal macrophages [190].

In the liver of C57BL/6J and C57BL/6J/Nrf2($-/-$) mice, sulforaphane induced Nrf2-dependent detoxification phase I, II drug metabolizing enzymes and phase III transporters, using Affymetrix 39K oligonucleotide microarray. This study indicates that sulforaphane increases the expression of genes through the Nrf2 signaling pathway that directly detoxify exogenous toxins/carcinogens or endogenous reactive oxygen species, and genes involved in the recognition and repair/removal of damaged proteins [191]. In the Apc^{Min/+} mice, when fed with SFN supplemented diet, the mice developed significantly less and smaller polyps with higher apoptotic and lower proliferative indices in their small intestine in a dose-dependent manner. SFN also found to suppress the expression of phosphorylated c-Jun N-terminal kinase (p-JNK), phosphorylated extracellular signal-regulated kinases (p-ERK) and phosphorylated-Akt (p-Akt). However, the biomarkers of the Wnt pathway, beta-catenin and cyclin-D1 were unaffected by sulforaphane treatment. This study also found that a diet of 3 to 30 nmol/g is required to prevent or retard adenoma formation in the Apc^{Min/+} gastrointestinal tract [192]. In our another study, sulforaphane was found to inhibit 7,12-dimethylbenz(a)anthracene-induced skin tumorigenesis in C57BL/6 mice mediated by Nrf2 [193]. In Apc^{Min/+} mice, the effects of sulforaphane on the gene expression profile in small intestinal polyps were studied using Affymetrix microarray. While SFN is a strong phase II drug metabolizing enzyme inducer, apoptosis genes MBD4, TNFR-7 and TNF (ligand)-11 were up-regulated, cell growth and maintenance genes, pro-survival genes cyclin-D2, integrin-beta1 and Wnt-9A were down-regulated, where the predicted phase II genes were less modulated. Genes potentially involved in colorectal carcinogenesis, 15-LOX was found increased and COX-2 decreased [194]. In C57BL/6J wild type and C57BL/6J/Nrf2($-/-$) knock-out mice, UVB exposure (300mJ/cm²) resulted in skin inflammation in both groups, however, WT mice returned to basal level to a greater extent; and mice treated with sulforaphane restored sunburn cells by 8 days but KO mice did not, which indicates functional Nrf2 confers a protective effect against UVB-induced inflammation, and sulforaphane mediates photoprotective effects in the mice [195].

Sulforaphane demonstrated synergistic effects when combined with EGCG in HT-29 AP-1 human colon carcinoma cells [98], or with dibenzoylmethane in Apc^{Min/+} mice for reducing intestinal adenomas [183], 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 [57].

After fed with dietary broccoli sprouts for 16 weeks, TRAMP mice were sacrificed and analyzed for sulforaphane and sulforaphane-GSH conjugate in the prostate tumor. TRAMP mice with high broccoli diet showed significant retardation of prostate tumor growth and elevated expression levels of Nrf2, HO-1, cleaved-Caspase-3, cleaved-PARP and Bax proteins and decreased expression levels of Keap1 and Bcl-xL proteins; and the Akt and its downstream kinase and target proteins such as mTOR, 4E-BP1 and cyclin D1 were also

reduced. All of these indicate that sulforaphane has significant inhibitory effects on prostate tumorigenesis [196].

Many other laboratories have been very active in the research on sulforaphane. There are currently eighteen clinical studies registered with clinicaltrials.gov and sulforaphane is a promising compound for its druggability.

2.16 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 [197]. This group of phytochemicals are sub-classified into cucurbitanes, dammaranes, ergostanes, friedelanes, lanostanes, limonoids, lupanes, oleananes, tirucallanes, ursanes [14], and the list is still growing. The diversity and regulation of terpenoids are appreciated by Tholl review [198]. Various *in vitro* and *in vivo* studies have been conducted for chemoprevention and therapy of breast cancer [14], and pancreatic cancer [199] 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-1 β , NF- κ B, IKK α / β , cyclin D1, cyclin A, cyclin B1, ER α protein and mRNA, HER2 phosphorylation, caveolin-1, Akt, JAK1, STAT 3, Bcl2, c-Jun, c-Fos, JNK, mTOR, blocking cell cycle at G1, G1-S, G2-M, etc [14].

Through these studies, triterpenoids have been shown to possess pleiotropic mode of effects for cancers in *in vitro* and *in vivo* models. More studies are needed to validate their promises in their chemopreventive and anti-cancer activities in clinical stage.

2.17 Vitamin D from mushroom

After exposed to ultraviolet B light, vertebrate can generate Vitamin D in their skins. Light exposed mushroom could also be an excellent source of Vitamin D. Vitamin D has been involved in breast cancer [200], colon cancer [201], ovarian cancer [202], and pancreatic cancer [203]. The mechanism is still not quite clear. However, vitamin D receptor (VDR) appears playing an important role. For example, women with mutations in the VDR gene had an increased risk of breast cancer and VDR may be a mediator of breast cancer risk which could represent a target for cancer prevention efforts [204].

Two physiologically relevant Vitamin Ds are vitamin D2 (ergocalciferol) and D3 (cholecalciferol). D3 is produced after exposure to ultraviolet B light from the sun or artificial sources. Numerous studies have linked vitamin D and cancer but opposite conclusion were also presented by the conflicting study results. Vitamin D's anti-cancer effect may be mediated via vitamin D receptors (VDR) in cancer cells [200]. Increased risk of breast cancer has been linked with the polymorphisms of VDR gene [204]. Kovalenko *et al* using VDR KO and WT mice and showed that low diet vitamin D or VDR deletion provided a prostate environment that is permissive to early pro-carcinogenic events that enhance prostate cancer risk [205]. Stefanska *et al* reported that vitamin D3 possess high efficacy in the reduction of PTEN promoter methylation and it was associated with PTEN induction as well as DNA methyltransferase down-regulation and p21 up-regulation after

treatments with vitamin D3, suggesting a complex regulation of the DNA methylation machinery [206]. However, a literature conducted through June 2010, Hypovitaminosis D seems to be associated with a worse prognosis in some cancers, but vitamin D supplementation failed to demonstrate a benefit in prostate cancer patients and the available evidence is insufficient to recommend vitamin D supplementation in cancer patients in clinical practice [207]. And study also suggested that genetic polymorphisms in vitamin D-related genes do not play a major role in breast cancer risk in Chinese women [208]. Therefore, vitamin D's skin cancer and prostate cancer prevention are still inconclusive [209, 210].

2.18 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 many foods including wheat germ oil, sunflower oil, and safflower oils. Alphatocopherol is the most bioactive form of vitamin E that stops the production of reactive oxygen species when fat undergoes oxidation. There are reports that both tocopherols and tocotrienols have anti-tumor effects due to their antioxidant properties, and tocotrienols show stronger bioactivity and both show antiproliferative, proapoptotic and COX-2 inhibiting effects in *in vitro* studies [211]. Review by Viola *et al* discussed the hypomethylated forms of tocotrienols in their high *in vitro* and *in vivo* metabolism and their potency in cytoprotection, cancer prevention and even chemotherapeutic effects [13]. Chen *et al* reported that vitamin E supplementation could evidently inhibit or reverse the cytotoxic effects of cigarette smoke extract in a dose- and time-dependent manner in mouse embryonic lung cells [212]. A recent review by Nesaretnam and Meganathan linked tocotrienols and their roles in inflammation and cancer, and in this review, mechanism of the cellular signaling pathways of NF- κ B, STAT3, and COX-2 were discussed [213]. In a meta-analysis and meta-regression study, although vitamin A, dietary vitamin E, and total vitamin E intake all reduced breast cancer risk significantly when data from all studies were pooled, the results became non-significant when data from cohort studies were pooled [214].

Tocotrienols are members of the vitamin E family. Unlike tocopherols, tocotrienols possess an unsaturated isoprenoid side chain that confers superior anti-cancer properties and they inhibit AKT and ERK activation and suppress pancreatic cancer cell proliferation by suppressing the ErbB2 pathway [215]. In pancreatic cancer cell lines, tocotrienols selectively inhibit the HMG-CoA reductase pathway through posttranslational degradation and suppress the activity of transcription factor NF- κ B. γ - and δ -tocotrienol treatment of cells reduced the activation of ERK MAP kinase and that of its downstream mediator ribosomal protein S6 kinase (RSK) in addition to suppressing the activation of protein kinase AKT. Tocotrienols reduced apoptosis in pancreatic cancer cells through the suppression of vital cell survival and proliferative signaling pathways such as those mediated by the PI3-kinase/AKT and ERK/MAP kinases via downregulation of Her2/ErbB2 expression [215]. Sylvester *et al* discussed the approach to combine tocotrienols with agents that have complementary anticancer mechanisms of action to achieve synergistic anticancer response, e.g., combination with traditional cancer chemotherapy, with statins, with receptor tyrosine kinase inhibitors, and with COX-2 inhibitors [216].

3. Mechanisms involved in cancer chemoprevention and treatment

3.1 Apoptosis mechanism initiated by phytochemicals

Apoptosis pathways are very important in cancer related therapies. In fact, many phytochemicals were originally used as anti-inflammatory or anti-viral reagents and, while the understanding of cancer mechanism deepens, their anti-tumor activities, such as targeting apoptosis pathways in cancer are recognized and utilized [217, 218]. Li-Weber summarized apoptosis pathways in cancer by traditional Chinese medicine (TCM) based on practical experiences [217].

Apoptosis is the process of programmed cell death that may occur in multicellular organisms. The process includes blebbing, cell shrinkage, and nuclear fragmentation. In cancer, insufficient apoptosis results in uncontrolled cell proliferation. The apoptosis mechanism involves several signal transduction pathways. Apoptotic proteins may form membrane pores and cause mitochondrial swelling and increase the permeability of the mitochondrial membrane and leak out the apoptotic effectors [219]. Small mitochondrial-derived activator of caspases (SMACs) are released from the mitochondrial into cytosol, bind to inhibitor of apoptosis proteins (IAPs), deactivate IAPs and prevent them from arresting the apoptotic process. Caspases, which carry out the cell degradation and are normally suppressed by IAPs, proceed for cell apoptosis process [220]. Due to the formation of mitochondrial apoptosis-induced channel (MAC) in the outer mitochondrial membrane, cytochrome c is released from mitochondria and binds with apoptotic protease activating factor-1 (Apaf-1) and ATP, which then binds to pro-caspase-9 to create a protein complex apoptosome and cleaves pro-caspase and release active form of caspase-9, which in turn activates the effector caspase-3 [221]. Bcl-2 family proteins regulate MAC and Mitochondrial Outer Membrane Permeabilization Pore (MOMP) where pro-apoptotic Bax and/or Bak form the pore, and anti-apoptotic Bcl-2, Bcl-xL or Mcl-1 inhibit the formation of the pore [222].

Tumor Necrosis Factor (TNF), a cytokine mainly produced by activated macrophages, is the major mediator of binary hipaloptic apoptosis. When TNF binds with its receptor, cell survival and inflammatory responses are initiated. Fas ligand (FasL) is a transmembrane protein of the TNF family. The interaction of FasL and Fas receptor (Apo-1 or CD95) forms death-inducing signaling complex (DISC), which contains the Fas-associated death domain protein (FADD) , caspase-8, and caspase-10 [223].

In mammalian cells, a balance between pro-apoptotic (BAX, BID, BAK, or BAD) and anti-apoptotic (Bcl-Xl and Bcl-2) proteins of the Bcl-2 family is established and maintained. Caspase activator such as cytochrome c and SMAC can be released from within the mitochondrial membrane when the membrane is permeable after the pro-apoptotic homodimers are formed in the outer-membrane of the mitochondrion. Inhibitor caspases, such as caspase 8, 10, 9, 2 require binding to certain oligomeric adaptor protein; and effector caspases, such as caspases 3, 7, 6, are activated by the active initiator caspase via proteolytic cleavage and degradation of a host of intracellular proteins to further the cell death process. Some of the cancer and phytochemical related apoptosis mechanisms are discussed in more detail in the following sections.

3.2 ATP-dependent chromatin remodeling

Chromatin remodeling is the enzyme-assisted movement of nucleosomes on DNA. Chromatin is a condensed and often inaccessible structure where genomic DNA is packaged through histone and non-histone proteins. When DNA damage occurs, efficient and accurate repair of DNA damage ensures genome stability and prevents damage development which could lead to cancer or cell death [224]. Activating DNA damage response (DDR) enables the cells to utilize post-translation histone modifications and ATP-dependent chromatin remodeling to modulate chromatin structure and increase the accessibility of the repair machinery to lesions embedded in chromatin [225]. Chromatin remodeling utilizes the energy of ATP to disrupt nucleosome DNA contacts, move nucleosomes along DNA, and remove or exchange nucleosomes such that DNA repair can be accomplished. Via ATP hydrolysis, the chromatin structure of a number of large multi-protein complexes (200 kDa – 2 MDa) can be enzymatically modulated [226]. Several chromatin remodeling complexes are involved in the process: switch/sucrose non-fermentable (SWI/SNF) family containing either the brahma (BRM) or brahma-related gene 1 (BRG1) ATPase which slide and eject nucleosomes, imitation switch (ISWI) complexes containing SNF2H or SNF2L ATPase and mediate nucleosome sliding and histone displacement, inositol requiring 80 (INO80) chromatin remodeling factors containing INO80 ATPase or related SWR1-like factors such as the p400 ATPase which features long insertion in the middle of the conserved ATPase domain, and chromodomain helicase DNA-binding protein (CHD) family members containing two tandemly arranged chromodomains (CDs) on the N-terminus of their ATPase which are involved in binding methylated histone tails as well as DNA and can slide and eject histones and have both activatory and inhibitory roles in transcription regulation [225, 227]. An ATPase which is capable of DNA translocation moves nucleosomes such that transcription factors can access to DNA [228]. Luijsterburg and van Attikum recently linked chromatin and the DNA damage response with the cancer [225]. Hargreaves and Crabtree reviewed the genetics, genomics and mechanisms of ATP-dependent chromatin remodeling [229].

While many cancer cells have defects in one or more aspects of the DDR, such cells may be more vulnerable to cancer therapies that aim at targeting the tumor-related DDR defects [230].

3.3 Cyclooxygenases-2 (COX-2)

Cyclooxygenases are bi-functional membrane-bound enzymes related to the formation of prostanoids, which are oxygenated C18 to C22 compounds derived from ω -3 and ω -6 fatty acids [231]. While COX-1 in general is involved in housekeeping functions and is constitutively and stably expressed in cells and in tissues, and COX-3 which appears expressed only in some specific tissues including brain and spinal cord [232, 233], COX-2 is normally low in most cells but is constitutively elevated in 80-90% of colorectal and other cancers [234, 235]. This may due to the cross-talk between several mediator of inflammation, such as interleukins and cytokines (i.e., IL-1, IL-6 and TNF- α) [236]. For this reason and also that COX-2 expression in colorectal cancers association with larger tumor size and poor survival [237], COX-2 is therefore proposed to be a nutritional target for colon cancer prevention [238].

Since COX-2 is one of the pro-inflammatory mediators which may be induced at the very early stage of carcinogenesis, the prevention of its aberrant expression could translate to prevention of the formation of cancer because of its insurgence [29, 239]. The cultured murine macrophages, RAW 264.7, or primary macrophages collected from mice then stimulated with LPS/IFN γ are common models of acute inflammation [58, 240]. COX-2, due to its promoter contains a number of upstream regulatory sequences specific for binding with a variety of transcription factors, such as NF- κ B, SP-1 transcription factor, activator protein-1 (AP-1), etc [241]. and these transcription factors are pleiotropic and being the final executors for a myriad of intracellular signaling pathways [29], which make the COX-2 transcriptional regulation highly complicated. Cerella *et al* reviewed COX-2 expression and modulation during transcriptional, post-transcriptional, and post-translational stages and its modulation by selected natural compounds [29].

3.4 DNA methylation - epigenetics

DNA methylation is a process that a methyl group is added to the 5 position of the cytosine pyrimidine ring or the number 6 nitrogen of the adenine purine ring. DNA methylation can be inherited when cells divide. DNA methylation typically occurs at CpG sites, where a cytosine and guanine are separated by a phosphate in the linear sequence of bases along its length in adult somatic tissue. According to studies, between 60% and 90% of all CpGs are methylated in mammals [242]. Unmethylated CpG are present in the 5' regulatory regions of many genes. In cancer developmental process, gene promoter CpG islands acquire abnormal hypermethylation, result in transcriptional silencing and are inherited by daughter cells following cell division. Hypomethylation of CpG sites is associated with the over-expression of oncogenes within cancer cells. On the other hand, methylation of CpG sites within the promoters of genes can lead to their silencing in cancer. Therefore, hypermethylation becomes the target for epigenetic therapy [243].

In addition, methylated DNA can bind with methyl-CpG-binding domain proteins (MBDs), and form compact yet inactive heterochromatin which also causes gene silencing. It is known that for hypermethylated genes in cancer, methyl-CpG-binding domain protein 2 (MBD2) mediates the transcription gene silencing.

3.5 Hedgehog signaling pathway

The hedgehog signaling pathway provides instructions to the cells to be developed properly into different parts based on the different concentrations of hedgehog signaling proteins at a specific time. Activation of the hedgehog pathway has been implicated in the cancers in various organs, including brain, lung, prostate, and skin. It is shown that abnormal activation of the pathway may give rise to cancer through transformation of adult stem cells into cancer stem cells and researcher are studying specific inhibitors of hedgehog signaling in an effort to devise an efficient therapy for a wide range of cancer [244].

In vertebrate cells, sonic hedgehog (SHH) contains a ~20 kDa N-terminal signaling domain (SHH-N) and a ~25 kDa C-terminal domain with unknown signaling role. When SHH binds to the Patched-1 (PTCH1) receptor, the downstream protein Smoothened (SMO) inhibited by PTCH1 is activated and leads to the activation of the GLI transcription factors [245]. The

activated GLI accumulates in the nucleus and controls the transcription of hedgehog target genes. Activation of the hedgehog pathway leads to the increases of angiogenic factors, cyclins, anti-apoptotic genes and the decreases of apoptotic genes, such as Fas [246-248].

Sarkar [249], Marini [250], and Gupta[251] recently reviewed Hedgehog signaling as a target pathway for cancer treatment. Thus far, modulating SMO, PTCH[252] and Gli3(5E1) [253] are the approaches to regulate the hedgehog pathway in the search of hedgehog antagonist for solid tumor, and Gli1 siRNA has been used to inhibit cell growth and promote apoptosis in prostate cancer [254].

3.6 Histone modification - epigenetics

Each chromosome consists of 146 base-pairs of duplex DNA wrapped around a histone octamer while chromosomes form chromatin and are compartmentalized in the nucleus to form a highly intricate packaging, DNA is accessible for critical cellular processes such as transcription, replication, recombination, and repairs. Histones are highly alkaline proteins in cell nuclei that package and order the DNA into structural units – chromasomes. Histones act as spools around DNA winds to allow the compaction to fit the large genomes inside cell nuclei. Histone modifications include acetylation, methylation, phosphorylation and ubiquitylation of different tails [225, 255]. Through histone modification, an activation or repression of the gene transcription will be resulted. For example, methylated DNA binds to MBD proteins then recruits additional proteins to the locus such as histone deacetylases and other chromatin remodeling proteins that can modify histone to form compact inactive heterochromatin.

3.7 microRNAs (miRNA)

miRNAs receive greater attention in cancer research in recent years and their regulation by natural phytochemicals becomes an emerging field in chemoprevention and chemotherapy research [256]. miRNAs are small conserved non-coding RNA molecules that post-transcriptionally regulate gene expression by targeting the 3' untranslated region of specific messenger RNAs for degradation or translational repression [257]. miRNAs serve as post-transcriptional regulators that binds to complementary sequences on one or more messenger RNA transcripts [258]. In animals, miRNA can be fully or partially complementary to the miRNA target so that one miRNA could target many different sites on the same mRNA or on many different mRNAs. In this manner, relatively small changes in miRNA expression can lead to modest changes in the levels of multiple proteins and collectively can add up to qualitative or quantitative physiological changes [259].

Most miRNA genes are found in intergenic regions or in anti-sense orientation to genes and contain their own miRNA gene promoter and regulatory units [260]. miRNA appears to bind to messenger RNA before it can be translated to proteins that switch genes on and off [261]. miRNA are transcribed as a huge double-stranded primary transcript (pri-miR) by RNA polymerase II. Subsequently, nuclear enzymes, Drosha (ribonuclease III) and Pasha convert this precursor into a double-stranded miRNA precursor of ~70 nucleotide (pre-miR) which is then transported into the cytoplasm by a mechanism involving protein Exportin 5. The pre-miR is processed into the 22-nucleotide double-stranded miRNA by dicer enzyme. The

duplex is then unwinded into two strands, the passenger strand which is degraded, and the guide strand which is incorporated into the RNA-induced silencing complex (RISC). RISC incorporated with miRNA is able to bind to the 3' untranslated region (UTR) of target mRNAs and causes a block of translation or mRNA degradation depending on the level of complementarity [257, 258, 262]. While miRNA plays an important role in regulating cellular differentiation and proliferation, its misregulation is linked to cancer and can be tumor suppressor and inducer oncogenes. Studies show that miRNA deficiencies or excesses have been correlated to cancer and other diseases. Excess c-Myc, a protein with mutated forms implicated in several cancers, shows that miRNA has an effect on the development of cancer.[263]

Over-expression of miRNAs down-regulates tumor suppressors and contributes to tumor formation by stimulating proliferation, angiogenesis, and invasion, and acting as oncogenes. However, miRNAs can also down-regulate different proteins with oncogenic activity or acting as tumor suppressor [264]. Therefore, identifying specific miRNA regulators could be a viable approach in searching and developing cancer prevention and treatment agents.

3.8 NF- κ B pathway

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) is linked to cancer development and many other diseases. NF- κ B is a family of rapid-acting primary transcription factors, and their presence in cells are in a state of inactive and do not require new protein synthesis to be activated, like c-Jun, STATs. This allows NF- κ B to be a first responder to harmful cellular stimuli. Reactive oxygen species (ROS), TNF alpha, IL-1 beta, lipopolysaccharide (LPS) are some examples of NF- κ B inducers.

In the basal condition, the NF- κ B dimmers are sequestered in the cytoplasm by a family of I κ Bs, whose ankyrin repeat domains mask the nuclear localization signals (NLS) of NF- κ B. There are five proteins in the mammalian NF- κ B family: NF- κ B1 (p50), NF- κ B2(p52), RELA(p65), RELB, c-REL. When stimulated, I κ Bs are modified by ubiquitination via I κ B kinases (IKK) and leads to their degradation. NF- κ B is then freed to enter the nucleus where it can turn on the expression of specific genes that have DNA-Binding sites for NF- κ B nearby. The NF- κ B turns on expression of its own repressor, I κ Balpha, which in turn reinhibits NF- κ B and forms an auto feedback loop, which results in oscillating levels of NF- κ B activity [265]. In tumor cells, NF- κ B is activated, while blocking NF- κ B can cause tumor cells to stop proliferating, to die or become more sensitive to the action of anti-tumor agents [266].

3.9 Nrf2 pathway

Nuclear factor (erythroid-derived 2)-like 2 (Nrf2, or NFE2L2) is a transcription factor that regulates antioxidant responses [267]. Since oxidative stress can result in cancer, Nrf2 pathway is important in cancer chemoprevention and cancer therapy studies.

Nrf2 is a basic leucine zipper (bZIP) transcription factor that is distinct from the other bZIP families, such as JUN and FOS [268]. Under unstressed condition, Nrf2 is tethered in the cytoplasm by the Kelch like-ECH-associated protein 1 (Keap1) [269]. Oxidative or other electrophonic stress disrupts critical cysteine residues in Keap1 and releases Nrf2 to

translocate into the nucleus. There, Nrf2 heterodimerizes with small Maf proteins and binds to the anti-oxidant response element (ARE) in the promoter region of many antioxidative genes and initiate their transcription [270]. The cytoprotective proteins include phase II drug metabolism enzymes, such as NAD(P)H-quinone oxidoreductase 1 (NQO1); heme oxygenase-1 (HO-1), glutathione S-transferase (GST), UDP-glucuronosyltransferase (UGT), or phase III transporters, such as multidrug resistance-associated proteins (MRPs) [271-276]. Figure 1 illustrates the chemopreventive agents dissociating Keap1 from Nrf2, resulting in induction of Phase II genes, followed by translating the genes to proteins for chemoprevention effects. Nrf2 has been extensively discussed and a recent review by Keum provides an up-to-date review of this signal pathway [277].

3.10 PI3 kinase pathway

Phosphatidylinositol 3-kinases (PI3Ks) are a family of enzymes involved in cell growth, proliferation, differentiation, survival and intracellular trafficking. They are intracellular signal transducer enzymes and exert their functions by phosphorylating the 3 position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns) [278].

Activated PI3-k produces PtdIns(3,4,5)P3 and PtdIns(3,4)P2, which are bound by AKT. AKT translocation to the plasma membrane due to that of the PtdIns(3,4,5)P3 and PtdIns(3,4)P2 are restricted to plasma membrane. In the same fashion, the pleckstrin homology domain of the phosphoinositide-dependent protein kinase 1 (PDK1) binds to PtdIns(3,4,5)P3 and PtdIns(3,4)P2, translocates to plasma membrane as well. Due to the colocalization of activated PDK1 and AKT, AKT is phosphorylated by PDK1 on threonine 308, leading to partial activation of AKT. AKT is fully activated upon phosphorylation of serine 473 by the TORC2 complex of the mTOR protein kinase. In many cancers, PI-3k P110alpha is mutated, which causes the kinase to be active, and its antagonist PTEN is absent. Therefore, PI-3k activity contributes significantly to the cellular transformation and the cancer development. Inhibition of PI-3k became a therapeutic strategy for suppressing cancer development [279].

3.11 Plk1 expression

Polo-like kinase 1 (Plk1) is an enzyme consists of 603 amino acids. Besides the N-terminus kinase domain, two conserved polo-box regions of 30 amino acids at the C-terminus can regulate the kinase activity for auto-inhibition and sub-cellular localization [280]. Plk1 is an early trigger for the G2/M transition. It is a proto-oncogene and is overexpressed in tumor cells. Plk1 is believed to drive cell cycle progression, an oncogenic property. In nude mice, tumor cells have been detected for Plk1 overexpression [281]. Plk1 appears to be involved in the tumor suppressor p53 related pathways [282]. A recent review focused on Plk1, a key regulator of mitosis, and its potential role in non-small cell lung cancer (NSCLC) anticancer therapy [283].

3.12 Poly-ADP-ribosylation

Poly(ADP-ribosylation) is a post-translational modification of nuclear proteins that converts β -NAD(+) into ADP-ribose. During the process, poly(ADP-ribose) polymerase (PARP) enzyme is responsible for polymer synthesis to bind to nuclear acceptor proteins with the

liberation of nicotinamide and protons, and poly(ADP-ribose)glycohydrolase (PARG) enzyme regulates poly(ADP-ribose) turnover for polymer degradation to free ADP-ribose and AMP. The most abundant PARP, PARP1, is a 113kDa zinc-finger protein with a modular structure composed of the N-terminal DNA binding domain (DBD) essential for the recognition of DNA breaks and the C-terminal catalytic domain required for the conversion from NAD(+) to ADP-ribose. Poly(ADP-ribosylation) plays an important role in many basic processes such as DNA replication, repair, and transcription while in sensing and repairing DNA damage [284]. PARP normally acts as a pro-survival factor, due to its role in DNA repair; yet, under massive DNA damage or stress conditions, PARP drives cells to necrosis [285]. However, over-activation of PARP causes NAD depletion and consequent necrosis followed by inflammatory condition. Therefore, inhibition of PARP could be protective in cancer therapy, and inactivation of poly(ADP-ribosylation) could be utilized to limit cellular injury and attenuate the inflammation.[285] Recently, many efforts have been showing promising results through utilizing poly(ADP-ribosylation) pathway by using novel PARP inhibitors, as summarized by Giansanti *et al* [285].

Besides, PARP has been reported to interact with NF- κ B by PARP-1 acetylation. After acetylation, NF- κ B interacts with other proteins, binds DNA and activates the gene transcription for inflammation, cell proliferation, differentiation, and death, and regulates the production of pro-inflammatory cytokines, such as TNF α , MIP1 α , IL-1, and IFN γ , as well as iNOS [286-288].

3.13 Tumor angiogenesis inhibition

Angiogenesis is the physiological process involving the growth of new blood vessels from pre-existing vessels. It is a fundamental step in the transition of tumors from a dormant to a malignant state, leading to the use of angiogenesis inhibitors.

Tumor induces blood vessel growth by secreting various growth factors, such as vascular endothelial growth factor (VEGF), which induce capillary growth into the tumor. In normal cells, protein kinase G (PKG) limits beta-catenin, which solicits angiogenesis. Angiogenesis is also a required step for the spread of tumor (metastasis). Therefore, using specific compounds that inhibits or reduce the creation of new blood vessels may help to combat tumor, which requires an abundance of oxygen and nutrients to proliferate. The fibroblast growth factor (FGF) is a family of mostly single chain peptides [289]. FGF-1 stimulates the proliferation and differentiation of all cell types, e.g., endothelial cells and smooth muscle cells that are necessary for building arterial vessel, where VEGF drives the formation of new capillaries [290]. VEGF causes a series of signaling cascade in endothelial cells. Binding to VEGF receptor-2 (VEGFR-2) initiates tyrosine kinase signaling cascade that stimulates the production of factors which stimulate vessel permeability by producing NO, proliferation/survival, migration and finally differentiation into mature blood vessels. In normal cells, anti-VEGF enzyme protein kinase G (PKG) limits beta-catenin, which solicits angiogenesis. In cancer cells, it was found that cancer cells stop producing PKG [291].

3.14 STAT 3 pathway

Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that mediates the expression of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis. It is activated through phosphorylation of tyrosine 705 and serine 727 in response to cytokines and growth factors such as interferons, epidermal growth factor, by receptor-associated kinases and then form homo- or heterodimers that translocate to the cell nucleus. While GTPase RAC1 appears to bind and regulate STAT3, PIAS3 protein is a specific inhibitor of this protein. In cancer cells, constitutive STAT3 activation is associated with poor prognosis and has anti-apoptotic and proliferative effects [292].

3.15 Wnt pathway

Wnt proteins are not only involved in normal physiological process in adult animals, but also play roles in embryogenesis and cancer [293]. They consist of a group of secreted lipid-modified (palmitoylation) signaling proteins of 350-400 amino acids in length [294], which carry a conserved pattern of 23-24 cysteine residues on which palmitoylation occurs on a cysteine residue [295]. These proteins activate various pathways (Wnt, β -catenin, cadherin, etc.) in the cell including canonical and noncanonical Wnt pathways, and exert their important roles in embryonic development, cell differentiation, and cell polarity generation [296]. In canonical Wnt pathway, the Wnt proteins bind to cell-surface receptors of the Frizzled family, cause the receptor to activate Dishevelled (DSH) family proteins and ultimately change the amount of β -catenin that reaches the nucleus. DSH complex inhibits a second complex of other proteins such as axin, GSK-3 and APC which normally promotes the proteolytic degradation of the β -catenin. The β -catenin destruction inhibition allows cytoplasmic β -catenin stabilization and entering the nucleus to interact with TCF/LEF family transcription factors to promote specific gene expression. Therefore, modifications of Wnt, APC, axin, and TCF are associated with carcinogenesis. For example, an APC deficiency or mutations to β -catenin that prevent its degradation can cause excessive stem cell renewal and proliferation, predisposing the cells to the formation of tumors [297]. Non-steroidal anti-inflammatory drugs (NSAIDs) that interfere β -catenin signaling have been shown to prevent colorectal cancer [298]. Other strategies in treating cancer cells include using monoclonal antibodies against Wnt proteins to induce apoptosis [299].

3.16 Other mechanisms

Besides the mechanisms listed above, there are many other mechanisms not discussed. For example, the extra-virgin olive oil may target the human epidermal growth factor receptor (HER2) in breast cancer prevention [300], resveratrol may reduce hypoxia-induced factor-1 α and MMP-9 expression in colon cancer cells [171], lycopene may alter mevalonate pathway and inactivate Ras signaling [301], and those in other recent reviews [302, 303]. Interested reader may find the references by searching related database.

4. Development Challenges, Opportunities, and Druggability

Many natural dietary phytochemicals have been selected for epidemiological, preclinical, and early clinical studies for cancer prevention and treatment. These compounds typically

involve multiple signaling transduction pathways. They themselves or their synthetic analogues have profoundly guided continuing research to bring them into the market. However, there are many developmental challenges that have to be overcome before their druggability is fully established. Currently, there are 675 anti-cancer clinical studies registered with www.clinicaltrials.gov (accessed Feb. 27, 2012) involving dietary supplements with various statuses ranging from active, completed, terminated, or unknown. The following natural plants and agents are in the clinical trials for anti-carcinogenesis: ashwagandha, brassica, ginseng, tomato-soy juice, red and white wine; curcumin, DIM, **genistein**, I3C, **lutein**, PEITC, **quercetin**, and sulforaphane [304].

4.1 Study approaches

Applying phytochemicals to cancer chemoprevention encounters an immediate challenge, that is, how to prove their effect on human. As it is neither realistic nor feasible to design a clinical study to prove that suppression of tumor in subjects is due to taking a phytochemical for a long period of time, e.g., 30 years as cancer takes long time to initiate, to promote, and to progress. Modern biotechnology provides an alternative approach: surrogate biomarkers. Through innovative discovery research, such biomarkers can be effectively used to predict, and to describe a lesion and to implement the treatment protocol, provided that the biomarkers are thoroughly validated, qualitatively and ideally, quantitatively.

Animal studies may be the more practical chemoprevention research approach. Typically, efficacy of the chemopreventive agents is established in nude mice first, then to better understand the underlying molecular mechanisms, autochthonous, germ-line transgenic and knockout animals may be used for such purpose [305]. Many animal models including transgenic animal models have been well established to facilitate the researches in phytochemicals. For example, transgenic adenocarcinoma of mouse prostate (TRAMP) mice are genetically modified animal model for prostatic intraepithelial neoplasia that has been used to study prostate cancer chemoprevention over the past years [306]. Our lab has successfully conducted in vivo pharmacodynamic study of indole-3-carbinol [307], curcumin [308], mixed tocotrienols [309], dibenzoylmethane [310], broccoli sprouts [196], and γ -tocopherol-enriched mixed tocopherol [311]. Knockout rodent are another **tool** to elucidate the role of a specific biomarker. However, it is necessary to understand that most cancers are multi-factorial during its initiation, promotion, or progression and involve multiple internal and external factors. Yet, knocking out a gene that exerts pleiotropic effects or is central to the development of several cancers presents an invaluable model that offers a mechanistic approach to cancer development and its chemoprevention. Nrf2 has been shown to regulate the expression of more than 200 genes. Therefore, Nrf2 knockout mice have been used to study the role of this transcript factor in the detoxifying and antioxidant genes. Our lab used Nrf2 knockout mice and studied possible links between Nrf2 and anti-inflammation effects using sulforaphane, docosahexaenoic acid and eicosapentaenoic acid among others [190, 240, 312]. Cross-breeding to obtain double or triple knockout mice may also be helpful to elucidate the underlying mechanisms. Thus, due to the significant relevance and potential application to cancer chemoprevention research, animal model undoubtedly will play a pivotal role to develop new chemopreventive phytochemicals or its synthetic analogues.

4.2 Chemical entity considerations

The chemical structures of the phytochemicals are now well understood and yet some of their physical/chemical properties are not documented in literatures. Table 1 summarized the most studied phytochemicals for their structures, and physical chemical properties predicted by ACD/Labs software version 11.0. These data are provided for prediction purpose and always need to be verified in the experiments. However, to enhance the druggability of phytochemical, additional studies and drug developmental diligence are necessary to further characterize their physical and chemical properties, e.g., to understand the chemicals' degradation routes under different stability storage conditions so as to establish the products' shelf life.

Potency has been one of the challenges the phytochemical researches are facing. Medicinal scientists now use these phytochemicals as lead compounds to synthesize their analogues based on the ever-enriching structure-property relationships. For example, although curcumin has been shown to be an effective chemopreventive compound, its synthesis analogue, EF24 demonstrated ~ 10-fold greater potency over its natural form [313].

4.3 Biopharmaceutics considerations

Bioavailability is another challenge needs to be overcome for many phytochemicals. Another example of curcumin is that it shows low bioavailability in earlier studies. To improve that, nanotechnology, liposomes, micelles, various coating materials, and phospholipid complexes have been applied to increase its water solubility and to enhance its bioavailability [314]. Genistein has limited bioavailability in earlier studies. Cohen *et al* studied the effect of complexation of genistein with high-amylose corn starch and achieved twice as high in genistein concentration in the plasma versus controls [315].

Phytochemicals' crystal structures, **polymorphism**, amorphism, appropriate salt selection, excipient comparability, etc. should be considered so as to develop a robust phytochemical drug. The physical forms of a phytochemical may impact the solubility in various physiological conditions, absorption, variation in pharmacokinetic performance, product content consistency in large scale manufacturing, drug stability, degradation product formation and pathway during product storage. Clas summarized the importance and quantification approaches in characterizing the crystal form of the drug substance during drug development [316].

Most drug products or nutrition supplements in oral dosage forms are tested *in vitro* using United States Pharmacopeia (USP) Apparatus I or II to analyze the percent dissolved values of the drug active ingredients in selected biorelevant dissolution media at a few sampling time points. The dissolution test not only evaluates their potential bioavailability *in vivo*, but also serves as a means to monitor the quality of the drug product after it is manufactured. It is possible to establish a dissolution *in vitro in vivo* correlation by applying relevant mathematical algorithm with software such as WinNonlin® or GastroPlus™. Soh and Heng updated the *in vitro* dissolution techniques of pharmaceutical solids recently [317].

4.4 Bioavailability of orally dosed phytochemicals

Phytochemicals are naturally originated and many are components of daily foods. Therefore, though not exclusively, studies have been emphasized on oral administration for the phytochemicals. Dosing via oral route may show low bioavailability due to excessive metabolism by Phase I and Phase II drug metabolism enzymes (DME). This may hamper the phytochemicals from being available for absorption and distribution in the body. Phase I drug metabolism enzymes include mostly cytochrome P450 and can be found in most tissues of the body. They are involved in oxidation, reduction, or hydrolysis to increase the polarity of a drug. An important aspect of phytochemicals is their ability to impact CYP enzymes. Famous examples include grapefruit juice inhibit CYP3A4 mediated metabolism of certain drugs and cause the increased bioavailability of the drug and potential toxicity [318]. Other phytochemical related examples include watercress inhibites CYP2E1 which may complicate the absorption of some drugs [319]. Therefore, phytochemicals have to be studied for food effects.

Phase II drug metabolizing enzymes include conjugating enzymes for glucuronidation, sulfation to increase the water solubility and excreatability of a drug. Excessive metabolism by Phase II DMEs may also relate to a drug's poor bioavailability. Recent book chapter by Tompkins *et al* on liver drug metabolism and bioavailability had an excellent discussion on this topic [320].

4.5 Toxicity considerations

Although phytochemicals are extracted from natural plants and are generally considered non-toxic, they can exert their toxicities to the animal or human systems at certain situation (drug-drug interaction) and concentration, which impede their application in the clinical studies and further application in chemoprevention and treatment. This involves another major challenge: the controversy of the effects of the natural compounds. This controversy may be due to synergistic effects existing in natural compounds when consumed as a whole rather than a single extracted compound. Lambert *et al* analyzed benefits *vs* risks on possible controversy over dietary polyphenols [321]. Some of the antioxidant activities of the natural compounds demonstrated *in vitro* studies are not reproducible *in vivo*. Even in some occasions, natural phytochemicals demonstrate hepatic and gastrointestinal toxicities, e.g., by green tea polyphenols (EGCG) at high doses [321-323]. Therefore, a thorough understanding of the compounds and their pharmacological effects are essential for natural phytochemicals' drugability and their transition from bench top to patients' bedside.

4.6 Regulatory considerations

An unavoidable question on phytochemical drugability is regulatory considerations. Thus far, many phytochemicals are sold as dietary supplements in the market, which are governed by relatively liberal regulations of the health authority (i.e., FDA) compared to those of prescription drugs. FDA defines drug as: articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and articles (other than food) intended to affect the structure or any function of the body of man or other animals. (FD&C Act section 201(g)(1)) (www.fda.gov). To be considered as a drug, the therapeutic claims need to be studied and be approved by the health authority. In the contrast, a dietary supplement is

available to consumers under the provisions of Dietary Supplement Health and Education Act of 1994, for which the FDA has the burden of proving a dietary supplement is harmful rather than requiring the manufacturer prove that the supplement is safe. Collins and colleagues reviewed the clinically relevant differences between dietary supplement and prescription formulations of omega-3 fatty acids in the context of legislative and regulatory issues [324]. The prescription omega-3 (P-OM3, LOVAZA®), was approved as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (> 500 mg/dL) hypertriglyceridemia. Backed by 23 clinical studies, LOVAZA® won FDA's approval in 2004.

5. 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. Through the extensive mechanistic studies, we have observed robust chemopreventive effects by some of the phytochemicals. 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 regimens. Natural dietary phytochemicals have been and will continue to be a promising and active research area in the near future.

Abbreviations

ABCG2	ATP-binding cassette sub-family G member 2
ACF	aberrant crypt foci
Ah	aryl hydrocarbon
ALP	alkaline phosphatase
AMPK	AMP-activated protein kinase
AOM	azoxymethane
AP-1	activator protein 1
Apaf-1	apoptotic protease activating factor-1
ARE	antioxidant response element
BaP	benzo[a]pyrene
Bcl-2	B-cell lymphoma 2
BCRP	breast cancer resistance protein
BITC	benzyl isothiocyanates
BRCA1	breast cancer type 1 susceptibility protein 1
C3G	cyaniding-3-O-glucoside

CD	chromodomain
CDK4	cyclin-dependent kinase 4
CHD	chromodomain helicase DNA-binding protein
COX-2	cyclooxygenase-2
CYP	cytochrome P450
DDR	DNA damage response
DHC	dihydrochalcone
DISC	death-inducing signaling complex
DIM	diindolylmethane
DR	death receptor
DSH	Dishevelled
DSS	dextran sulfate sodium
EGCG	epigallocatechin gallate
EGFR	epidermal growth factor receptor
ER	estrogen receptor
ERK	extracellular signal-regulated kinases
FAK	focal adhesion kinase
FoxM1	Forkhead box protein M1
GAPDH	glyceraldehydes 3-phosphate dehydrogenase
GCLC	glutamate-cysteine ligase catalytic subunit
GSH	glutathione
GSTm2	glutathione S-transferase Mu 2
HDAC	histone deacetylase
HER2	human epidermal growth factor receptor
HO-1	hemeoxygenase-1
HSP	heat shock protein
HTRF	homogenous time resolved fluorescence
HUVEC	human umbilical vein endothelial cells
I3C	indole-3-carbinol
IAP	inhibitor of apoptosis proteins
IC50	half maximal inhibitory concentration
IFN	interferon

IL-1β	interleukin-1 beta
IL-6	interleukin-6
IKK	I κ B kinase
iNOS	inducible nitric oxide synthase
JNK	c-Jun N-terminal kinases
LNCaP	lymph node carcinoma of the prostate
LPO	lipid peroxidation
LPS	lipopolysaccharide
MAC	mitochondrial apoptosis-induced channel
MAPK	mitogen-activated protein kinase
MBD4	methyl-CpG-binding domain protein 4
Mcl-1	myeloid cell leukemia sequence 1
MDCK	Madin-Darby canine kidney
Mitf	microphthalmia-associated transcription factor
MKK	mitogen-activated protein kinase kinase
MMP	matrix metalloproteinase
MNU	N-methyl nitrosourea
MOMPP	mitochondrial outer membrane permeabilization pore
mTOR	mammalian target of rapamycin
NF-κB	Nuclear factor-kappa-B
NQO1	NAD(P) dehydrogenase (quinone 1)
Nrf2	nuclear factor-erythroid 2-related factor 2
PARP	poly (ADP-ribose) polymerase
PCa	prostate cancer
PCNA	proliferating cell nuclear antigen
PEITC	phenyl isothiocyanate
PGE	prostaglandin E
PI3K	phosphoinositide 3-kinase
PKG	protein kinase G
PLK1	polo-like kinase 1
PTEN	phosphatase and tension homolog
PUFA	polyunsaturated fatty acids

q-PCR	quantitative real time-polymerase chain reaction
RISC	RNA-induced silencing complex
ROS	reactive oxygen species
RPE	retinal pigment epithelial
RT-PCR	reverse transcription polymerase chain reaction
SFN	sulforaphane
SHH	sonic hedgehog
SOD1	superoxide dismutase 1
SMAC	small mitochondrial-derived activator of caspases
SMRT	silencing mediator of retinoid and thyroid-hormone receptors
STAT	signal transducer and activator of transcription
TCF	T-cell factor
TIMP	tissue inhibitor of metalloproteinases
TNBS	2,4,6-trinitrobenzenesulfonic acid
TNF-α	tumor necrosis factor alpha
TRAMP	transgenic adenocarcinoma of mouse prostate
TUNEL	terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1
u-PA	urokinase-type plasminogen activator
UVB	ultraviolet B
VDR	vitamin D receptor
VEGF	vascular endothelial growth factor
XIAP	X-linked inhibitor of apoptosis protein

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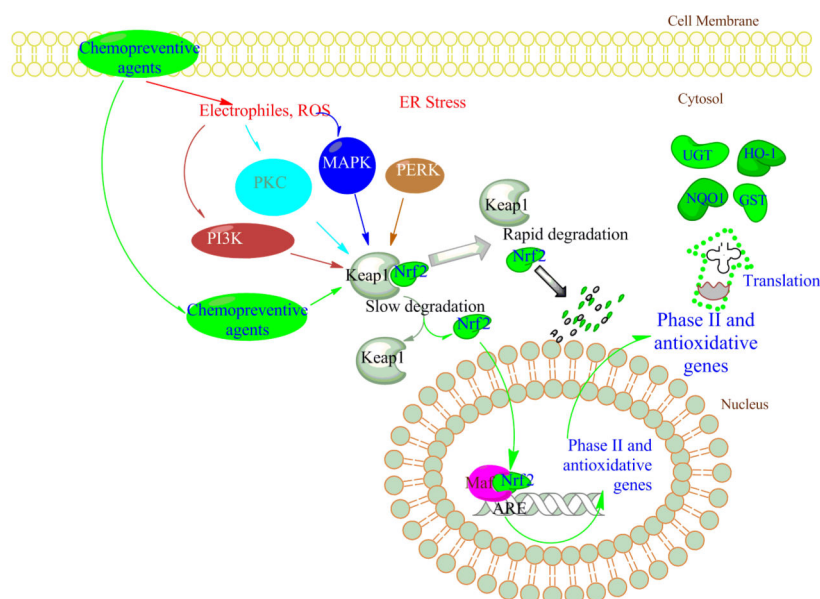

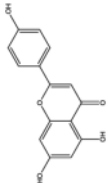

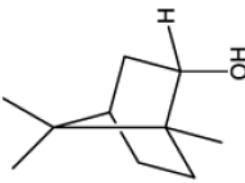





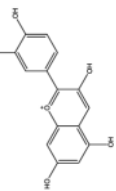

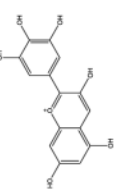




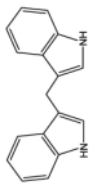

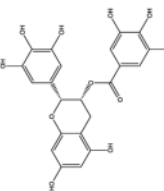

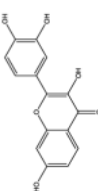

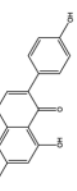


Figure 1. Regulation of Nrf2-mediated gene transcription by phytochemicals. Under homeostatic condition, Nrf2 is retained in the cytoplasm by Keap1 protein. Chemopreventive phytochemicals interact directly with the cysteine residues of Keap1 to trigger the release Nrf2 from the complex. Chemopreventive agent-generated electrophiles or reactive oxygen species can activate a wide variety of kinase signaling pathways, including PI3K, PKC, MAPK, all of which can trigger the release and translocation of Nrf2 from cytosol to nuclear.


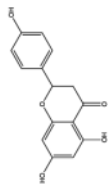

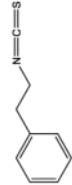

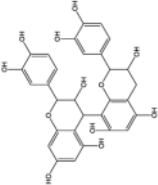

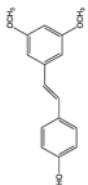

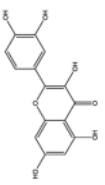
Table 1


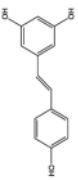





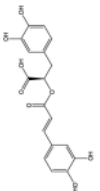

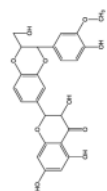
Phytochemicals, their sources, structures, and the predicted pKa, solubility in water, and logP using ACD/Labs software



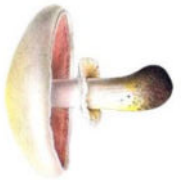
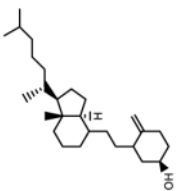



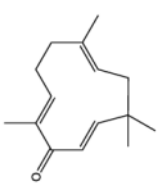
Compound	Source from Plant	Structure	pKa	Solubility	logP
Apigenin			10.42; 7.75; 6.53	pH 2, 0.27 mg/mL; pH 5.5, 0.3 mg/mL; pH 6.5, 0.66 mg/mL; pH 7.4, 4.15 mg/mL; pH 10, 1000 mg/mL	2.13
Borneol	Parsley 		15.36	4.97 mg/mL	2.55
Carotene	 Carrots		NA	Not soluble (<0.01 mg/mL)	14.76

Compound	Source from Plant	Structure	pKa	Solubility	logP
Curcumin			10.03 9.72 8.35	pH 2, 0.32 mg/mL; pH 5.5, 0.32 mg/mL; pH 6.5, 0.33 mg/mL; pH 7.4, 0.37 mg/mL; pH 10, 98.91 mg/mL	2.64
Cyanidin			12.99	Can not calculate	Not shown
Delphinidin			15.57	Can not calculate	Not shown
					

Compound	Source from Plant	Structure	pKa	Solubility	logP
3,3'-Diindolyl methane (DIM)	 Brussel sprouts		18, 16.91, -1.49, -3.1	0.02 mg/mL	3.88, 37
Epigallocatechin gallate (EGCG)	 Green tea leaves			pH 2, 0.85 mg/mL; pH 5.5, 0.86 mg/mL; pH 6.5, 0.9 mg/mL; pH 7.4, 1.24 mg/mL pH 10, 1000 mg/mL	0.64
Fisetin	 Strawberries		13.03, 9.93, 9.1, 6.83	pH 2, 0.16 mg/mL; pH 5.5, 0.16 mg/mL; pH 6.5, 0.22 mg/mL; pH 7.4, 0.68 mg/mL; pH 10, 1000 mg/mL	1.97
Genistein	 Soybean		9.66, 7.72, 6.51	pH 2, 0.12 mg/mL; pH 5.5, 0.13 mg/mL; pH 6.5, 0.29 mg/mL; pH 7.4, 1.79 mg/mL; pH 10, 1000 mg/mL	3.11
Lycopene	 Tomatoes				

Compound	Source from Plant	Structure	pKa	Solubility	logP
Naringenin	 Grapefruit and orange skin		N/A 9.69, 8.5, 7.52	Not soluble (<0.01 mg/mL) pH 2, 0.08 mg/mL; pH 5.5, 0.08 mg/mL; pH 6.5, 0.10 mg/mL; pH 7.4, 0.21 mg/mL pH 10, 1000 mg/mL	14.53 2.63
Phenyl isothiocyanates (PEITC)	 Watercress		N/A	0.07 mg/mL	3.47
Proanthocyanidin	 Berries		Various	Under pH 7.4, 0.10 mg/mL pH 10, 21.02 mg/mL	0.98
Pterostilbene	 Blue berries		9.96	Under pH 7.4, 0.07 mg/mL pH 10, 0.15 mg/mL	4.06
Quercetin	 Onions		13.03, 9.94, 8.74, 7.54, 6.31	pH 2, 0.23 mg/mL; pH 5.5, 0.28 mg/mL; pH 6.5, 0.7 mg/mL; pH 7.4, 5.42 mg/mL; pH 10, 1000 mg/mL	1.99

Compound	Source from Plant	Structure	pKa	Solubility	logP
Resveratrol	 Grapes		10.79, 10.02, 9.22	Under pH 7.4, 0.02 mg/mL; pH 10, 0.33 mg/mL	3.02
Retinoic Acid	 Carrots		4.73	pH 2, 0.01 mg/mL; pH 5.5, 0.04 mg/mL; pH 6.5, 0.38 mg/mL; pH 7.4, 2.76 mg/mL; pH 10, 34.67 mg/mL	6.26
Retinol	 Carrots		14.09	Not soluble (<0.01 mg/mL)	6.08
Rosmarinic Acid	 Rosemary		12.65, 12.33, 9.77, 9.33, 2.78	pH 2, 2.82 mg/mL; Above pH 5.5, 1000 mg/mL	0.87
Siibinin	 Milk thistle		14.1, 11.81, 9.72, 8.31, 7.39	pH 7.4, not soluble (< 0.01 mg/mL); pH 10, 19.13 mg/mL	4.23

Compound	Source from Plant	Structure	pKa	Solubility	logP
Sulforaphane			N/A	10.92 mg/mL	0.41
Vitamin D3			15	Not soluble from pH 1-12	10.03
Vitamin E					
Zerumbone			11.4	Not soluble (<0.01 mg/mL)	10.96
			N/A	0.29 mg/mL	4.17