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Mechanisms of phytonutrient modulation of Cyclooxygenase-2 (COX-2) and inflammation related to cancer

Shreena J. Desai, **Ben Prickril**, and **Avraham Rasooly**

Office of Cancer Complementary and Alternative Medicine, National Cancer Institute, Rockville, MD 20850

Abstract

The link between chronic inflammation and cancer involves cytokines and mediators of inflammatory pathways. Cyclooxygenase-2 (COX-2), a key enzyme in fatty acid metabolism, is upregulated during both inflammation and cancer. COX-2 ιs induced by proinflammatory cytokines at the site of inflammation and enhanced COX-2-induced synthesis of prostaglandins stimulates cancer cell proliferation, promotes angiogenesis, inhibits apoptosis and increases metastatic potential. As a result COX-2 inhibitors are a subject of intense research interest toward potential clinical applications.

Epidemiological studies highlight the potential benefits of diets rich in phytonutrients for cancer prevention. Plants contain numerous phytonutrient secondary metabolites shown to modulate COX-2. Studies have shown that these metabolites, some of which are used in traditional medicine, can reduce inflammation and carcinogenesis.

This review describes the molecular mechanisms by which phytonutrients modulate inflammation, including studies of carotenoids, phenolic compounds and fatty acids targeting various inflammation-related molecules and pathways associated with cancer. Examples of pathways include those of COX-2, MEKK, MAPK, pro-inflammatory cytokines, and transcription factors like NF-κB. Such phytonutrient modulation of COX-2 and inflammation continue to be explored for applications in the prevention and treatment of cancer.

Keywords

COX2; inflammation; cancer; phytonutrient; modulation

INTRODUCTION

Phytonutrients are plant nutrients with specific biological activities with potential benefits to human health, including disease prevention. Among these activities, modulation of inflammation is an essential element of cancer. Cancer patients are among the most frequent users of complementary and alternative medicine (CAM) therapies, including phytonutrients, with about 40% of individuals undergoing cancer treatment using some form

*Address correspondence to: Dr. Avraham Rasooly, NIH/NCI, 9609 Medical Center Drive, Rockville, MD 20850, Phone: (301) 240-276-6186 rasoolya@mail.nih.gov.

of CAM (1). Out of these 40% the most common reasons for using CAM include helping patients feel better or reducing symptoms or side effects, and support of conventional biomedicine (2). Other uses include treating or reducing the risk of disease recurrence, mitigating adverse effects of chemotherapy and radiation, and improving overall health, quality of life, and well-being (3). Among the many uses of CAM for cancer, anti-inflammatory applications are perhaps the most important. Inflammation is closely linked to cancer, and reducing or eliminating inflammation may lead to better strategies for cancer prevention and therapy (4).

Individuals with a previous or current diagnosis of cancer are more likely to use CAM than the general population It is also important to note that CAM as understood in industrialized countries in the West is somewhat distinct from developing countries or regions where these practices are often considered neither complementary nor alternative, but a common and widespread medical practice.

The use of CAM therapies has been studied in many different cancer populations. One of the most popular of these therapies is the use of natural dietary supplements and herbs. A cross-sectional study of adult patients diagnosed with thoracic malignancies conducted by the researchers at Roswell Park Cancer Institute and the State University of New York at Buffalo concluded that the prevalence of CAM use among patients in this study was similar to that of the general U.S. population. The most commonly reported types of CAM included vitamins and minerals (38%), dietary supplements such as omega fatty acids (24.1%), and herbs (13.9%) (5) (6).

Regarding the effectiveness of phytonutrients in cancer prevention, several meta-analyses suggest a statistically significant association between high flavonoid intake and reduced risk of developing lung cancer (7). Similarly, meta-analysis of prospective studies of breast cancer suggests that soy isoflavone intake is associated with a reduction in breast cancer incidence within Asian but not Western populations, and in postmenopausal but not in premenopausal women (8). Another meta-analysis examined soy food consumption in Asia, the United States and Canada, and suggested a protective effect of dietary genistein and daidzein against prostate cancer (9). Protective effects were also reported for green tea against breast (10, 11), ovarian (12, 13), prostate (14, 15), gastric (16), lung (17) and liver cancers (6). However, there are many mixed reports regarding green tea (18–20). In general, the literature is inconclusive concerning intake of natural products and risk of tumor development, with some studies showing a benefit while others report questionable or even harmful associations depending on cancer type and the type of natural product (8). For example, no association between tea consumption and risk of gastric (21, 22), ovarian (23–25) or colon (26) cancer was reported. In addition it should be noted that several natural compounds (such as Curcumin or phenolic compounds) may have multiple functions and are considered Panassay Interference Compounds (PAINS) that have been observed to show activity in multiple types of assays by interfering with the assay readout rather than through specific compound/target interactions (27–29). However, despite inconsistencies regarding PAINS issues and potential effectiveness in population studies, on the molecular level as described in this manuscript, many phytonutrients have been shown to modulate COX-2 and the immune response, mainly *in vitro*.

1. COX-2 PROMOTES CARCINOGENESIS

COX exists in two isoforms: COX-1 and COX-2 (Figure 1). COX-1 is present normally in tissues and has housekeeping functions, while COX-2 is expressed at low levels in normal cells in response to physical, biological, chemical, or UV light stimuli (30). COX-2 catalyzes the conversion of free arachidonic acid to prostaglandins, and COX-1-derived products drive the initial phase of acute inflammation with COX-2 upregulation occurring within several hours (31). COX-2 is an enzyme that is released at the site of tissue injury to produce a hormone-like substance called prostaglandin E2 (PGE2) that stimulates pain and inflammation. COX-2 derived prostaglandin can promote tumor growth by binding its receptors and activating signaling pathways which control cell proliferation (32) promote angiogenesis (33, 34), inhibit apoptosis and increase metastatic potential (35). In breast cancer cells COX-2 expression alters extracellular matrix structure and function and numbers of cancer associated fibroblasts (36). The role of the COX-2 pathway in creating an immunosuppressive microenvironment, and in initiation and progression of Wilms' tumor, was discussed recently (37). Cox-2 is also associated with the transformation of normal stroma into a 'reactive' stromal phenotype. PPARγ, COX-2 and p-IkB-α have important roles in this stromal remodeling (38). Elevated COX-2 expression is exhibited in various cancers including gastric, hepatic, esophageal, pancreatic, head and neck, lung, breast, bladder, cervical, endometrial, skin, and colorectal cancers when compared with nonmalignant tissue (39).

COX-2 is induced by inflammatory stimuli such as bacterial endotoxin and cytokines, and is the molecular target for analgesic and anti-inflammatory drugs. Mechanistically, increased COX-2 decreases the intracellular levels of free arachidonic acid, thereby preventing apoptosis and facilitating the growth of cancer cells (40). COX-2 inhibitors are designed to block COX-2 enzyme activity and relieve pain. Phospholipids transform to arachidonic acid in response to tissue injury and are then further transformed to PGE2 through COX enzymes. Cyclooxygenase donates two oxygen molecules to arachidonic acid to form PGG2 by peroxidation, which is then reduced to PGH2 in a committed step. Ultimately PGE2s and other prostaglandins are formed through activation of PGE synthase (41). COX-2 is inducible (Figure 1) and is elevated when there is tissue damage. Notably, COX-2 overexpression is correlated with high levels of intracellular telomerase - a vital reverse transcriptase enzyme associated with increased cell proliferation and lessened apoptosis (42). The continuous overexpression of COX-2 could initiate and promote carcinogenesis by: (1) increasing production of reactive oxygen species that are carcinogenic (mutagenesis); (2) increasing production of PGE2 and other factors that strongly promote cell proliferation (mitogenesis); (3) stimulation of VEGF and PDGF by PGE2 resulting in the formation of blood vessels (angiogenesis); (4) increasing production of metalloproteinases, thus enhancing invasive potential (metastasis); (5) decreasing bioavailable arachidonic acid pools, thereby reducing cell differentiation and apoptosis (anti-apoptosis); and (6) inhibiting proliferation of B and T lymphocytes, particularly natural killer T cells, thus limiting anti-neoplastic activity (immunosuppression) reviewed in (43).

2. ROLE OF INFLAMMATION IN CANCER

Cancer and inflammation are related by epidemiology, histopathology, inflammatory profiles, and the efficacy of anti-inflammatory drugs in prophylaxis (44). Inflammation is a pathophysiological manifestation of numerous diseases. The development of unregulated cellular processes is a result of the onset of chronic inflammatory diseases and may lead to cancer. During non-pathological inflammation, platelets release several immunological mediators that regulate vascular permeability and help in clot formation. These factors induce the release of chemotactic molecules such as growth factors and interleukin 1β (IL1β), while neutrophils and monocytes are concurrently recruited to the site of inflammation. These cells are the sources for reactive oxygen species (ROS) and PGEs as well as cytokines. All serve as inflammatory markers for the immunological response. PGE_2 is a vasodilator and has been demonstrated to induce angiogenesis and growth of epithelial and endothelial cells. COXs are key enzymes for production of prostanoids implicated in inflammation, and can stimulate tumor cell proliferation, promote angiogenesis, and suppress apoptosis. The mechanisms by which prostaglandins promote cancer formation include suppression of the immune system, stimulation of cell growth and inhibition of apoptosis. COX-2 is induced by inflammatory stimuli such as bacterial endotoxin and cytokines, and is the molecular target for analgesic and anti-inflammatory drugs and natural products (Figure 2). Phytonutrients such as fatty acids, phenolic compounds, carotenoids and flavonoids are reported to have an effect on COX-2. The pro-inflammatory transcription factor nuclear factor kappa B (NF-κB) and COX-2 pathways studies showed fast activation of NF-κB, most likely triggered by DNA damage in the irradiated cells, followed by upregulation of p38 MAPK and COX-2 in the irradiated and surrounding, non-irradiated, areas of the 3D cultures (45) It was shown that prostate cancer downregulated SIRP-α modulates apoptosis and proliferation through p38-MAPK/NF-κB/COX-2 signaling. (46)

There are many uses of anti-inflammatory agents. For example, synthetic drugs and natural herbs have been used to target and suppress dysregulated pathways that could lead to chronic inflammation and carcinogenesis. Anti-inflammatory phytochemicals or synthetic compounds for chemoprevention of almost any cancer including colon cancer(47), breast cancer (48), lung cancer (49), prostate cancer (50) were described. Many molecules of natural origin, semi-synthesis and synthesis with anti-inflammatory and anticancer utilities were reviewed recently (51, 52).

The active constituents of natural compounds are being studied more extensively due to their potential in the treatment and prevention of cancer (41) and compared to many drugs they have fewer side effects.

3. COX-2 REGULATORY PATHWAYS

Acute inflammation initiates a cascade of cytokines and chemokines that attract immune and non-immune cells to infiltrate disrupted and damaged tissue. The model of COX-2 regulation and induction by proinflammatory cytokines, stimulation of cell proliferation, increase of metastatic potential, and effect on apoptosis and inflammation is shown in Figure 2.

Pro-inflammatory signals include cytokines TNF-α and IL-1, UV radiation, carcinogens, tumor promoter (TPA), lipid mediators and other factors. These signals (Figure 2) stimulate COX-2 transcription via activation of mitogen-activated protein kinase kinase kinase (MEKK), mitogen-activated protein kinase kinase (MAPKK), mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), activator protein 1 (AP-1), p300 and IκB kinase (IKK)-κB/NF-κB-mediated signaling pathways regulating COX-2 transcription. Here we address two main arachidonic acid regulatory pathways, the NF-κB regulation of COX-2 transcription and the MAPK pathway.

3.1 NF-κB regulation of COX-2 transcription:

The NF-κB family of transcription factors is a key regulator of immune development, immune responses, inflammation, and cancer. The promoter regions of COX-2 contain consensus sequences for NF-κB (53) and the NF-κB signaling system, including those governing interactions between NF-κB dimers and IκB regulators. These play key roles in COX-2 transcription and inflammation activated by external stimuli including LPS, infectious agents, free radicals, and cytokine stimuli such as trauma, viruses, UV radiation, free radicals, TNF-α and IL-1β. These signals, along with peroxisome proliferator-activated receptor-γ (PPARG), turn on specific genes that lead to the production of inflammatory cytokines (54). The NF-κB binds to the inhibitory kappa B (IκB) kinase forming the NF-κB-IκB complex. Pro-inflammatory stimuli activate the complex containing the NF-κB essential modulator (NEMO) and IκB kinase (IKK)1/2. IKK1/2 phosphorylates IκBs by IKK signalosome complex. After IκB has been phosphorylated it is ubiquitinated and degraded by 26S proteosome (55–57) and the resulting free NF-κB translocates to the nucleus where it binds to the promoter κB sites of pro-inflammatory genes. These include iNOS, COX-2, IL-1β, IL-6, and TNF-α (58–60), and activate gene expression (61, 62) to induce expression (63). A negative feedback prevents overproduction of cyclopentenone prostaglandins (cyPG) which can directly inhibit NF-κB activity by preventing phosphorylation and degradation of the NF-κB inhibitor IκBα (64). Alternatively, the cyPG metabolite PGA_1 inhibits TNF-α–induced phosphorylation of IκBα-NF-κB DNA binding and prevents NF-κB transactivation and continued nuclear accumulation of NF-κB (65)

3.2 MAPK pathway regulation of COX-2:

MAPK signaling pathways include extracellular signal-regulated kinase 1/2 (ERK1/2), p38, BMK1, and c-Jun N-terminal kinase (JNK) (66). These pathways are involved in LPS-induced iNOS and COX-2 expression in activated macrophages (Figure 2). Furthermore, MAPKs play essential roles in the activation of NF-κB (67). IL-1β up-regulated the COX-2 expression through the activation of the p38 MAPK pathway (68, 69). IL-6 induces ERK1/2 activation (70). TNF-α and Ras are also involved in MAPK pathway activation. There are two main MAPKKs that are known to specifically activate p38 (α, β, γ, δ): MKK3 and MKK6. Activation occurs via dual phosphorylation of their Thr–Gly–Tyr motif which causes conformational changes that alter the alignment of the two kinase halves (N-terminal and C-terminal domains) of the folded protein and enhance access to substrate to increase enzymatic activity. MKK4 and MKK7 are involved with JNK activation (71). The diverse range of MEKKs (MAP3K) also participate in p38 activation. Overexpression of these MEKKs leads to activation of both p38 and JNK pathways - one reason why these two

pathways are often co-activated. In addition to the pro-inflammatory cytokines activated by p38, expression of intracellular enzymes such as iNOS (a regulator of oxidation) and VCAM-1 (an adherent protein) produce other downstream effects in COX-2 induction. P38α is thought to be the main isoform involved in mediating cytokine production associated with COX-2 activation (72). P38 and JNK both activate phosphorylation of ATF-2, which allows its heterodimerization or homodimerization with AP-1 transcription factor and consequently association with COX-2 induction (73, 74).

4. CONVENTIONAL COX-2 INHIBITORS

COX-2 inhibitors work by directly inhibiting the synthesis of prostaglandins, which are fatty acid derivatives located all over the body having inflammation and immune response effects.

Synthetic COX-2 inhibitors (Figure 1) have been around for decades and have been effective in blocking the COX-2 pathway in inflammation either selectively or non-selectively. The first-generation of nonsteroidal anti-inflammatory drugs (NSAIDs) were nonselective COX inhibitors such as aspirin which demonstrate a similar affinity for COX-1 and COX-2 and irreversibly block the target enzyme by acetylation at Ser530 (COX-1 nomenclature). Other nonselective NSAIDs act as competitive COX inhibitors that displace AA from the active site of the enzyme (75). These include diclofenac, indomethacin, ketoprofen, naproxen, ibuprofen, phenylbutazone, and meclofenamate. However, prolonged use of these inhibitors produces negative gastrointestinal side-effects such as ulcers, membrane mucus degradation, and pore formation in the gastric lining (76). This led researchers to investigate selective COX-2 inhibitors to limit these side-effects, and in 1998 the first selective COX-2 inhibitor, celecoxib (Celebrex), was approved by the FDA (77). Several months later, rofecoxib (Vioxx) and valdecoxib (Bextra) were also approved (78). These NSAIDS were designed to block the COX-2 enzyme that produces inflammatory prostacyclin, PGI_2, while still allowing production of gastrointestinal protective prostaglandins and platelet-derived thromboxane, TXA_2. The use of non-selective inhibitors decreased as these new selective drugs grew in popularity. However, in 2004 there was a global withdrawal of Vioxx (79) because studies determined that there was a doubling of the risk of serious thromboembolic events, including myocardial infarction, that could occur 18 months after use This drug selectively allowed COX-1 to continue to produce platelet synthesis of thromboxane, but at the same time it selectively inhibited COX-2 production of prostacyclin, which has effects that oppose those of thromboxane.

Recently a new class of peptide derivatives was recognized as the highest selective COX-2 inhibitor with a COX-2 selectivity index of >500 (80). Ultimately, these drugs had a high risk of producing thrombotic cardiovascular events, and showed little improvement in preventing gastrointestinal ulcers (81). Three large randomized control trials designed to test the efficacy of different COX-2 inhibitors for a variety of indications confirmed the cardiovascular toxicity (82–84). Understanding the implications of these drugs spurred researchers to study the use of natural herbs and dietary supplements to mitigate side effects and find treatments that do not increase the risk of other complications already present in cancer patients.

5. PHYTONUTRIENTS MODULATION OF COX-2 EXPRESSION

Phytonutrients are secondary metabolites found in plants, and are known for their antibacterial, antioxidant and radical scavenging properties (85). More than 5000 individual phytochemicals have been identified in fruits, vegetables, and grains, and the additive and synergistic effects of phytochemicals in fruits and vegetables are responsible for these potent antioxidant and anticancer activities. The benefits of a diet rich in fruits and vegetables can be attributed to the complex mixture of phytochemicals present in whole foods (86). Inhibition of COX-2 is one of the many proposed mechanisms by which dietary phytochemicals may prevent cancer (86). The main phytonutrients shown to modulate COX-2 commonly present in human diet and their main plant sources are listed in Table 1.

5.1 Carotenoid modulation of COX-2

Carotenoids are pigments found in chloroplasts and chromoplasts of plants and some other photosynthetic organisms. There are over 600 known carotenoids divided into two classes: xanthophylls (contain oxygen) and carotenes (contain no oxygen), all produced from 8 isoprene molecules and containing 40 carbon atoms. In general, carotenoids absorb wavelengths in the range of 400-550 nanometers. Their main roles in plants and algae are to absorb light for photosynthesis, to protect chlorophyll from photodegradation and to act as antioxidants. Chlorophyll and the carotenoid pigments bixin, lycopene, and β-carotene were tested for inhibition of COX-1 and COX-2 and showed a dose-dependent growth inhibition of cancer cell lines (breast, colon, stomach, central nervous system, and lung tumor cells) (87). Astaxanthin (AST) and lutein are other carotenoids that have been found to inhibit COX-2 (40)

5.1.1. β-carotene: β-carotene is a red-orange pigment and is a member of the family of carotenoids found in fruit, vegetables, and whole grains. β-carotene provides about 50% of the vitamin A requirement in humans. Evidence from epidemiological studies indicates that a high dietary intake of foods rich in β-carotene is associated with a low risk for colon neoplasias, and in combination with selenium and vitamin E, it has a significant protective effect on gastrointestinal cancer (88).

COX-2 inhibition: The suppression of COX-2 by β-carotene may represent a molecular mechanism by which this compound acts as an antitumor agent in colon carcinogenesis (89). Structural modeling and simulation studies of human COX-1 have shown that β-carotene is the most selective inhibitor of COX-1 (90). The evidence for protective effects of β-carotene against colon cancer was demonstrated in animal models as well as in cultured cells.

COX-2 inhibitory mechanism: - LS-174 is a human colon adenocarcinoma cancer cell line that expresses ErbB3 and ErbB4 transmembrane receptor tyrosine kinases. When the ligand heregulin binds these receptors in *in vitro* experiments, cells are activated COX-2 and produce PGE2 (91). Consequently, cell proliferation, invasion, and differentiation of malignant cells can occur (92). β-carotene decreased the expression of COX-2 but not COX-1 in the LS-174 cells, indicating a specific effect. β-carotene also had an inhibitory effect on ERK1 and ERK2, which are members of the mitogen-activated protein kinase

super family that mediate cell proliferation and apoptosis signaling pathways. Generally ERK phosphorylates and activates transcription factors like NF-κB, IL-6, and IL-1β, which can in turn further induce COX-2 expression. The β-carotene COX-2 inhibition activity was accompanied by ERK inhibition. Another finding in this study was the dose-dependent decrease in ROS production, which is directly related to COX-2 decrease because ROS production depends on the peroxidase function of COX. These two findings provide valuable information regarding the chemo-preventive and anti-proliferative effects of β-carotene in down regulating the COX-2 pathway (88).

5.1.2 Zeaxanthin: Anti-inflammatory activity of carotenoid meso-zeaxanthin (MZ) was demonstrated in Balb/c mice. In macrophages, LPS-stimulated mRNA expression of various inflammatory mediator genes like COX-2, TNF-α, and iNOS were down-regulated by MZ administration (93). Pigments (bixin, lycopene, β-carotene, and chlorophyll) inhibited COX-1 and COX-2 and showed a dose-dependent growth inhibition of cancer cell lines (breast, colon, stomach, central nervous system, and lung tumor cells) (87)

5.1.3. Astaxanthin (AST): Astaxanthin is a carotenoid pigment that contains two xanthophylls, yellow and brown pigments. These pigments have potent anti-oxidant potential by regulating ROS production and decreasing oxidative stress. Both these xanthophylls are also able to decrease NF-κB expression, and inhibit COX-2 activity to stimulate apoptosis in colon and pancreas adenocarcinomas (94). AST is abundant in crustaceans, trout, salmon, and the microalgae species, Haematococcus pluvialis and Chlorella vulgaris. It has been found to protect against oxidation of essential polyunsaturated fatty acids (PUFAS) and against UV light radiation (94). In animal studies, Astaxanthin anti-dermatitic effects were associated with inhibition of the expression of COX-2 and NF-κB activity, as well as release of TNF-α, IL-1β, IL-6, and IgE.(95). Colon cancers induced in rats with dimethyl hydrazine (DMH), a powerful colon carcinogen, showed an increase in COX-2 expression. AST decreased expression of COX-2 in rats compared to DMH. A combination of AST and DMH decreased expression of COX-2 compared to DMH alone. Thus AST significantly inhibits the expression of COX-2. AST had the same effects of inhibition on NF-κB as well (40). AST inhibited the expression or formation of nitric oxide (NO), iNOS, and COX-2 in lipopolysaccharide (LPS)-stimulated BV-2 microglial cells. AST also suppressed the protein levels of iNOS and COX-2 in LPS-stimulated BV2 microglial cells. The marine AST possesses powerful biological antioxidant, anti-inflammatory, and anti-cancer properties; inhibits colitis and colitis-associated colon carcinogenesis in mice via modulation of COX-2, NF-κB, and the inflammatory cytokines IL-1β, IL-6 (96). Similarly, in induced rat colon carcinogenesis, AST inhibits tumor invasion by decreasing extracellular matrix production and induces apoptosis in experimental rat colon carcinogenesis by modulating the expressions of ERK-2, NF-κB and COX-2 (97)

5.1.4 Lutein: Lutein is the second most abundant carotenoid in human serum and is obtained through food sources such as dark, leafy green vegetables, and in microalgae, Chlorella pyrenoidosa and Haematococcus pluvialis. Like AST, lutein is able to quench single oxygen molecules by acting as a free radical scavenger and exerts cytoprotective effects due to the properties of its xanthophyll moieties. A study done with deoxynivalenol

(DON), which affects cells of the esophagus and GI tract and is prevalent in esophageal and colon cancers, demonstrated decreased COX-2 and NF-κB expression when treated with lutein. Although COX-2 expression was not completely inhibited, pre-treatment of HT-29 colon cancer cells with DON substantially decreased COX-2 activity. This result may be attributed to the down-regulatory effect lutein also has on NF-κB activation (98).

Lutein significantly reduced several skin inflammatory responses: the increased expression of IL-6 from LPS-treated macrophages, upregulation of COX-2 from IFN- γ and TNF-α treated HaCaT cells, and the enhanced MMP-9 levels in UV-irradiated keratinocytes (99). Lutein inhibited the activation of redox-sensitive AP-1 pathway by suppressing the activation of p38 and c-Jun-N-terminal kinase (JNK). Evaluation of the radical and ROS scavenging activities further revealed that lutein was able to act as a strong anti-oxidant (99).

5.1.5 Lycopene: Lycopene is the most abundant carotenoid in tomatoes and has been demonstrated to inhibit *in vivo* and *in vitro* pro-inflammatory gene expression by scavenging reactive oxygen species ROS. Other dietary sources of lycopene include rosehips, watermelon, papaya, guava, and grapefruit. Populations that consume diets rich in lycopene exhibit a lower risk for lung cancer (100). Lycopene is very reactive towards free radical species and oxygen because it has a high number of conjugated double bonds that are able to quench oxygen singlets. The cancer preventive effect of lycopene is achieved by its ability to induce apoptosis, modulate cytokine expression, and interfere with cell signaling critical to carcinogenesis (100). Lycopene has been shown to significantly inhibit COX-2 expression (53). It induces apoptosis in immortalized fibroblasts exposed to tobacco. This effect was associated with inhibition of smoke condensate -induced expression of COX-2 and hsp90 (101). Lycopene rich extract from red guava (*Psidium guajava L.*) display anti-inflammatory and antioxidant profiles by reducing COX-2 and NF-κB, the suggestive hallmarks of acute inflammatory response in mice (102). Anti-neuroinflammatory effects of lycopene through the MP-activated protein kinase (AMPK) pathway was observed in LPS-induced COX-2 expression in mouse and rat cultured microglia (103). Consumption of lycopene inhibits the growth and progression of colon cancer in a mouse xenograft model and the chemopreventive effects of lycopene were associated with suppression of COX-2, PGE2, and phosphorylated ERK1/2 proteins (104).

Lycopene decrease of PGE2 was correlated with the reduction in COX-2 mRNA (103) and protein expression. COX-2 inhibition occurred at the transcriptional level from the inhibition of NF-κB activation (53). Lycopene and fish oil synergistically inhibited tumor growth and progression in a mouse xenograft model of colon cancer through suppression of COX-2, MMP-7, MMP-9, and PGE2 (105) However, intervention with lycopene or fish oil did not significantly change IGF-1 and COX-2 gene expression in the normal prostate microenvironment in men with low-burden prostate cancer (106).

5.2. Phenolic compounds modulation of COX-2

Natural phenolic compounds including phenolic acids, flavonoids, tannins, stilbenes, curcuminoids, coumarins, lignans, and quinones are produced by plants for protection against stress, for structural integrity and scaffolding support, and for repelling

microorganisms. The potential chemopreventive properties of phenolic compounds include their antioxidant, anticarcinogenic, antimutagenic, and anti-inflammatory effects. They induce apoptosis by arresting the cell cycle, regulating carcinogen metabolism and oncogenetic expression, inhibiting DNA binding and cell proliferation, and differenting and blocking signaling pathways (107).

The numerous plant polyphenols may have synergetic effects. For example, in postmenopausal women obesity is a risk factor for the development of estrogen-driven hormone receptor-positive breast cancer. This obesity-induced inflammation of CLS (crown-like structures formed from necrotic adipocytes) associated with NF-κB activation, elevated levels of proinflammatory mediators: TNF-α, IL-1β, and COX-2, and increased aromatase expression. Aromatase (CYP19A1) is the key enzyme of the cytochrome P450 superfamily that catalyzes the last step of estrogen biosynthesis from androgens. In a mouse model, several polyphenols: resveratrol, curcumin, and epigallocatechin gallate (EGCG), blocked induced CLS (108). Similarly, antioxidant polyphenols from virgin olive oil (oleuropein and hydroxytyrosol) and red wine (resveratrol and quercetin) reduce inflammatory angiogenesis in cultured endothelial cells associated with the inhibition of the specific activator of Protein Kinase C (PKC) Phorbol Myristate Acetate (PMA) which induced COX-2 and the activation of NF-κB (109) (110). Tumor metastasis is correlated with matrix metalloproteinases (MMPs) and proteolytic degradation of the extracellular matrix. Expression of these proteins is regulated by cytokines and PMA. Resveratrol inhibits PMA induced MMP-9 mRNA expression. Curcumin and resveratrol synergistically stimulate p21 and regulate COX-2 by maintaining adequate zinc levels during lung carcinogenesis (111).

Typical phenolic acid compounds and flavonoids that possess antioxidant activity were studied extensively for their antioxidant, anti-inflammatory, and anti-carcinogenic properties. However, it was suggested that the multiple functions of phenolic compounds are non-specific, and may be considered as Panassay Interference Compounds (PAINS) [(27)], a factor which should be considered in studying these phenolic compounds.

5.2.1. Curcumin: Curcumin, the yellow pigment in turmeric, is the active ingredient derived from the rhizomes of the perennial herb, *Curcuma longa* (112), and has been used for centuries in traditional medicines and cooking of India.

Curcumin pharmacoactivity: The active ingredient, curcuminoid, is used medicinally to treat a variety of conditions involving inflammation. Curcumin has been shown to have anti-carcinogenic, anti-inflammatory, apoptotic, and preventative effects in gastrointestinal diseases such as colitis (113). Increased levels of COX-2 mRNA and proteins have been found in studies of Irritable Bowel Disease, IBD (114). Colonic mucosal epithelium inflammatory cell concentrations of TNF-a are higher in patients with IBD due to an impaired intestinal barrier, resulting in a pre-disposition to colorectal cancer (115). Curcumin is known to exhibit potent anti-proliferative and apoptosis-inducing activities in colon cancer HT-29 cell lines. The apoptotic effects occur through activation of AMPK, and the consequent inhibition of Akt, and COX-2 proteins, while other mechanisms utilize p21, p27, cdk, and p53 to regulate the cell cycle and induce apoptosis (113). Curcumin caused the condensation of chromatin in HT-29 cells, which is a marker of its pro-apoptic effects (113).

Co-treatment of curcumin with the COX-2 inhibitor Celecoxib synergistically inhibited growth of colon cancer cells (116). The anti-oxidant role of curcumin is due to donation of its hydrogen atom to a lipid peroxyl radical, thereby forming a lipid hydroperoxide, interrupting the radical chain reaction. However, the efficacy of curcumin as a cancer chemopreventive agent is limited by its chemical and metabolic instability (117). Non-enzymatic degradation has been described to yield vanillin, ferulic acid, and feruloylmethane. However, oxidation to a reactive quinone methide is the mechanistic basis of many phenolic anti-cancer drugs. Therefore, it is possible that the oxidative transformation of curcumin, a prominent but previously unrecognized reaction, contributes to its cancer chemopreventive activity (117).

Curcumin inhibition of NF-κB: The effects of curcumin the arachidonic acid (AA) pathway was reviewed recently (118). Curcumin inhibited arachidonic acid metabolism by down-regulating COX-2 expression (119) through the inhibition of NF-κB. Curcumin downregulates the constitutive activity of NF-κB and induces apoptosis in mouse melanoma cells (120). It was seen that nuclear NF-κB expression was inhibited by curcumin and treatment with curcumin inhibited the expression of COX-2 (121). In human bronchial and non-small cell lung carcinoma cell lines, curcumin was reported to down–regulate cigarette smoke–induced NF-κB activation through inhibition of IκBα in human lung epithelial cells. The inhibition of NF-κB activation correlated with suppression of cigarette smoke-induced NF-κB dependent COX-2 and MMP-9 expression (122). Novel synthetic curcumin analogs were used as potent anti-angiogenic agents in colorectal cancer, inhibiting tumor growth in mice by inhibition of NF-κB. This led to decreased transcription and expression of HIF-1α, and COX-2 (121). Curcumin may prevent alcohol and tobacco-induced carcinogenesis by regulating pathways involving NF-κB, COX-2 and AKT/MTOR (34). Combination of curcumin and melatonin leads to an enhanced inhibition of cell proliferation in bladder cancer cells. It was shown that a combinational treatment enhanced the repression of nuclear translocation of NF-κB and its binding on COX-2 promoter via inhibition of IKK-beta activity, resulting in inhibition of COX-2 expression (123). Curcumin because of its broad activities has been classified as both a PAINS (panassay interference compounds) and an IMPS (invalid metabolic panaceas) candidate (27, 28) however this designation was questioned(124).

Curcumin inhibition of cytokines: Although curcumin decreases COX-2 expression it also increases PGE_2 levels, and through negative feedback decreases levels of TNF-α, IFN-g, and iNOS. These molecules are highly expressed in IBD and colon cancer inflammation, so inhibition is considered chemo-preventive (115). Curcumin also inhibits TNF-α induced COX-2 expression by suppressing IκB kinase (IKK) signaling complex that phosphorylates IκB (125). The inhibition of TNF-α induced expression of the calcium-dependent phospholipase A2 (PLA2). Cytosolic phospholipase A2 (cPLA2) catalyzes the release of arachidonic acid involved in inflammation from membrane phospholipids by targeting MAPK/NF-κB/p300-mediated pathway (126). Curcumin inhibits IFN-α-induced activations of NF-κB and COX-2 in lung cancer cells (127), inhibits down-regulated expression of LPS-induced COX-2 by inhibiting MAPK/NF-κB/AP-1 pathway (128–130), and inhibits tobacco

and other carcinogen-induced cPLA2 expression (131) (127). The PAINS factor described above should be considered in studying curcumin.

5.2.2 Resveratrol (RSVL): RSVL is a Stilbenoid, a polyphenolic phytoalexin phytoestrogen synthesized by plants in response to pathogens. It is found in grape skin, red wine, cranberries, mulberries, and peanuts. The trans form of the molecule is a biologically active compound and a potent anti-oxidant having anti-inflammatory and anti-cancer effects. RSVL inhibits proliferation and induces apoptosis in human colon cancer cells, which showed significantly lower COX-2 and prostaglandin receptor expression [117]. Wine polyphenols (tannic acid, gallic acid, quercetin, and resveratrol) exert anti-neoplastic effects on androgen resistant PC-3 cell line through the inhibition of the transcriptional activity of COX-2 promoter mediated by NF-κB (132). Resveratrol inhibits glioma cell growth via targeting oncogenic microRNAs and multiple signaling pathways (133). Resveratrol inhibits the proliferation of breast cancer cell lines by tristetraprolin (TTP) upregulation, which is associated with downregulation of COX-2 and VEGF and upregulation of iNOS (134). In a mouse model, (135) resveratrol suppresses the NF-κB activation and expression of cyclin D1, COX-2, ICAM-1, MMP-9. RSVL significantly inhibits the expression of COX-2 and NF-κB either *in vitro* or *in vivo*. The suppressive effect of RSVL on COX-2 is also suggested as one of the molecular mechanisms responsible for its anti-glioma activity (133). The anti-gliomal effect of RSVL included decrease the expression of EGFR, MMP-9 NF-κB, PCNA, COX-2, and VEGF. In a study with colon epithelial cells, RSVL used in a concentration 20 times lower than 5-aminosalicylic acid, was able to significantly reduce NO and PGE2 production, iNOS and COX-2 expression, and ROS formation induced by the cytokine challenge (136). To improve the potency of RSVL, a study compared different analogues of resveratrol and it was found that RSVL and RSVL-2 (not RSVL-3) inhibit COX-2 mediated production of PGE2 *in vitro* and *in vivo* in a dose-dependent manner (137). The synergistic combination of doxorubicin and RSVL significantly decreased the wound healing and clonogenic potential of breast cancer cells. Chronic inflammation is associated with high expression of NF-κB and COX-2, the combination treatment was also found to combinatorial treatment caused down regulation of COX-2 and NF-κB transcripts by ~42 and ~23 folds inhibiting the inflammatory response (138).

Mechanism of resveratrol inhibition of COX-2: Resveratrol suppresses the expression of TNF-α, IL-6, IL-8 and COX-2 through a decrease in the intracellular levels of Ca2+ and ERK 1/2, as well as activation of NF-κB (139). Decreasing NF-κB activity then inhibits COX-2 and prostaglandin synthesis in colon cancer. In addition, it was shown that RSVL directly binds to COX-2 and that this binding is absolutely required for resveratrol's inhibition of HT-29 colon cancer cell colony growth (137). Curcumin and resveratrol synergistically stimulate p21 and regulate COX-2 by maintaining adequate zinc levels during lung carcinogenesis(111). It was showed that RSVL inhibits the activation of NF-κB in breast cancer cells and dietary administration in rats bearing mammary tumors inhibits tumor growth and decreases the expression of NF-κB, COX-2 and MMP-9 in tumor tissues (140). In human ovarian cells, RSVL and ceramide, a lipid component of sphingomyelin in cell membranes, converge on an endocytosis-requiring, ERK1/2-dependent signal transduction pathway and induce COX expression as an essential molecular antecedent for

subsequent p53-dependent apoptosis (141). In human intestinal cells, Caco-2 cells treated with lipopolysaccharide (LPS), RSVL modulated NF-κB activation, which resulted in downregulation of PGE2 production and COX-2 expression [127].

Resveratrol induction of programmed cell death (apoptosis): In addition to RSVL activation of p53-dependent apoptosis (142), resveratrol induces apoptosis by several mechanisms related to COX-2 based on activation of important signal transducing proteins:

i. In ovarian cancer cells the extracellular signal-regulated kinases (ERKs) 1 and 2 in cancer cells, causes nuclear accumulation of the enzyme COX-2 and of the oncogene suppressor protein, p53 (143). The inducible COX-2 forms a nuclear complex with pERK1/2, pSer-15 p53 and SUMO-1 in RSVL-treated ovarian cancer cells. ERK1/2 activation is essential for RSVL-induced nuclear complexing of nucleoproteins in RSVL-treated cells. The inducible COX-2 associated with SUMO-1 transports into the nucleus and forms a complex with phosphorylated p53, phosphorylated ERK1/2 and p300. These processes are activated ERK1/2 and COX-2 dependent. The inducible nuclear-accumulated COX-2 potentiates RSVL-induced p53-dependent apoptosis.

ii. Resveratrol suppresses induced transformation of human breast epithelial cells by blocking IκB kinase β-NF-κB signaling. RSVL suppressed the natural estrogen metabolite 4-OHE_2 induced activation of IκB kinaseβ (IKKβ) and the phosphorylation of IκBα. Consequently, NF-κB DNA binding activity and COX-2 expression was also suppressed (144).

iii. Pro-apoptotic action of RSVL in cancer cells includes causing inducible COX-2 to accumulate in the nucleus where it complexes with pERK1/2 and induces p53 apoptosis(145)

5.2.3 Ferulic acid (FA):

The antioxidant Ferulic acid, is a phenolic acid compound (mono-phenolic phenylpropanoid) ubiquitous in plants, abundant in fruits and vegetables, and can be derived from rice bran. It possesses potent antioxidant and chemo-preventive properties seen in skin tumor studies.

Ferulic acid modulation of COX-2: IκBα is a suppressive factor protein of NF-κB (146), and treatment of RAW264.7 murine macrophage cell line with FA was shown to lead to IκBα breakdown. Thus, this had an inhibitory effect on NF-κB activation. The disruption of NF-κB nuclear migration through IκBα degradation is the main mechanism through which FA exerts its downstream effects on the COX-2 pathway (146). Ferulic acid isomers possess an even greater direct effect on COX-2 inhibition due to their retained phenolic, anti-inflammatory functions as opposed to pure FA (147). Ferulic acid is the major phenolic acid in Adlay bran ethanolic extract (ABE-Ea), which was used in colon carcinogenesis rat animal model study (148). ABE-Ea suppresses DMH-induced pre-neoplastic lesions of the colon and COX-2 expression was significantly suppressed in all colon tissue receiving the ABE-Ea. This indicates that ABE-Ea delayed carcinogenesis by suppressing chronic inflammation, which may be attributed to FA (148). In the tumor cell proliferation assay, antioxidant ferulic and caffeic acids showed excellent growth inhibition of various cancer

cells. In gastric cancer cell COX enzyme inhibitory assays, ferulic and caffeic acid esters significantly inhibited both COX-1 and COX-2 enzymes (149).

Anti-inflammatory role of Ferulic acid: Protection against radiation-induced oxidative stress was studied in murine model. FA significantly ameliorated the radiation induced inflammatory response of phosphorylation of IKKα/β and IκBα, and consequent nuclear translocation of NF-κB. FA also prevented the increase of COX-2 protein, iNOS-2 gene expression, lipid peroxidation in liver, and the increase of serum TNF-α and IL-6 (150).

Ferulic acid protective functions: UV radiation generates oxidative stress on the skin creating photo damage through the generation of free radical oxygens that oxidize macromolecules. This cascade can result in skin cancer and photo-aging cellular transformation. Vitamin C is the predominant antioxidant in the skin and protects the fluids of the body (151). Since the human body cannot produce its own vitamin C because of human gene mutation, humans must obtain this vitamin from diet and/or supplements (152). Vitamin E protects the lipid phase of the skin including the stratum corneum and cell membranes (153). Both these vitamins protect each other and increase overall effectiveness by acting synergistically (154). The incorporation of FA moieties provided more than 90% increased stability for L-ascorbic acid and 100% for a-tocopherol (155). Ferulic acid provides protection against vitamin C degradation (156) and prevents UV-induced thymine dimer formation that is characteristic of the oxidative DNA modifications that are responsible for carcinogenesis (156).

5.3 Plant Flavonoid modulation of COX-2

Flavonoids are plant polyphenolic compounds made up of flavonols, flavonones, flavanols, flavan-3-ols, and isoflavones (157). Epidemiological studies suggest dietary intake of flavonoids may reduce the risk of tumors of the breast, colon, lung, prostate, and pancreas (158).

5.3.1. Epigallocatechin gallate (EGCG): Tea is a major dietary source of flavonoids

of which the flavan-3-ols catechins are the most common in dry tea leaves with green tea having a higher concentration than black tea. EGCG is the major biologically active polyphenolic flavan-3-ols flavonoid constituent in green tea. Green tea extract attenuates lipid peroxidation and PGE2 accumulation by decreasing COX-2 activity (159) and it has been studied for its chemo-preventive potency because it possesses anti-inflammatory and anti-oxidant properties. EGCG decreases the protein and mRNA expression levels of COX-2 and the mRNA expression of inflammatory cytokines: TNF-α, IFN-γ, IL-6, IL-12, and IL-18, in the colonic mucosa (160).

EGCG regulatory modulation activities: EGCG activity has been studied *in vivo* and *in vitro*:

i. EGFR Modulation: EGFR modulation was studied in murine models in colitis and colon cancer. Colorectal carcinoma is marked by overexpression of epidermal growth factor receptor (EGFR) which exists on the cell surface. Generally, the binding of a ligand to this protein induces the tyrosine kinase auto-

phosphorylation cascade and leads to cell proliferation, angiogenesis, inhibition of apoptosis, and migration and adhesion of cells. Mutations involving EGFR lead to its constant activation and uncontrolled cell division, making it a target for cancer treatment. *In vitro* studies have demonstrated that EGCG inhibits human colorectal carcinoma cell growth and induces apoptosis via COX-2 inhibition (94).

ii. ROS induced HT-29 cells pre-treated with EGCG, significantly reduce cancer cell growth compared to those cells not treated with EGCG. Therefore, EGCG possesses growth-inhibitory effects on proliferation of these ROS induced HT-29 cells (161)

iii. EGCG inhibited COX-2 and other cell survival proteins in prostrate tumor tissue. EGCG inhibited cell migration or invasion in melanoma cells, which was associated with a reduction in the levels of COX-2, PGE_2 and PGE_2 receptors (EP2 and EP4) (162).

iv. VEGF modulation: EGCG reversed the upregulation of HIF-1α, VEGF, COX-2, p-Akt, p-ERK, and vimentin protein levels and reversed the downregulation of p53 and β-catenin protein in non-small cell lung cancer (163).

v. EGCG improved efficacy of cisplatin treatment in HeLa cells by regulating NF-κB, p65, COX-2, p-Akt, and p-mTOR pathways (164).

vi. Combinations of curcumin, EGCG, and lovastatin were able to suppress esophageal cancer cell growth *in vitro* and in nude mouse xenografts. These drugs also inhibited phosphorylated ERK1/2, c-Jun, and COX-2 expression (165).

vii. EGCG, a major green tea catechin, has the ability to inhibit melanoma cell invasion/migration, an essential step of metastasis, by targeting the endogenous expression of COX-2, PGE-2 receptors, and epithelial-to-mesenchymal transition (162).

viii. EGCG treatment of colon cancer cells resulted in a strong activation of AMPK and an inhibition of COX-2 expression (166).

Mechanism of EGCG activities: Several studies focus on the mechanism of EGCG activity:

i. The mechanism by which EGCG downregulates EGFR is through COX-2 inhibition. EGCG stimulates AMPK, which reduces NF-κB activity and consequently inhibits COX-2 expression. As a result, there is a decrease in PGE2 synthesis, which induces apoptosis of the HT-29 adenocarcinoma colon cells. In human melanoma cell line, EGCG inhibits COX-2 by inactivation of PGE_2/EP_2 receptor/cAMP mediated activation of PI3K/AKT pathway (167).

ii. In ROS induced HT-29 cells, free radical expression via hydrogen peroxide treatment of HT-29 cells, increased COX-2 expression. Treatment with EGCG on the other hand, reduces COX-2 expression and decreases levels of PGE2s. To

determine the role AMPK plays in suppressing COX-2 and PGE2 expression, HT-29 cells were treated with an AMPK activator, AICAR. It was found that AICAR significantly reduces COX-2 and PGE2 expression (161).

iii. Low dose H2O2 is known to activate cell signaling to induce cell proliferation. In the presence of EGCG, these proliferative effects are attenuated and accompanied by AMPK activation, decreased COX-2 and PGE2 expression, and p53 induction. (161).

iv. EGCG significantly inhibits constitutive COX-2 mRNA, and the effect of EGCG on COX-2 expression results in decreased COX-2 promoter activity via inhibition of NF-κB activation (168).

v. EGCG-induced COX-2 expression through protein kinase C activation and p38 MAPK in immortalized astroglial line and normal astrocyte cells (169).

However, there are many mixed reports regarding green tea including insufficient evidence to support green tea as a treatment or preventative agent for lung cancer. Green tea (18–20)

5.3.2 Quercetin: The flavonol quercetin, is a polyphenolic antioxidant constituent found abundant in many fruits and vegetables. Modulation of COX-2 is a mechanism by which this flavonoid is thought to interfere with carcinogenesis. Quercetin could partially inhibit COX-2 enzyme by binding to subunit A which has peroxidase activity and serves as a source of Reactive Oxygen Species (170). It reduced PGE2 levels in studies done with HCA-7 cells and HCEC cells. The actual dose-dependency and efficacy of treatment with the different flavonoids varies with cell line type and duration of incubation (171).

Mechanisms of anti-inflammatory role of Quercetin: Quercetin suppresses early colon carcinogenesis in rats through downregulation of COX-1 and COX-2 expression. It attenuates TNF-α induced NF-κB activation, which is accompanied by reduced COX-2 levels (172). Quercetin also reduces the production of other inflammatory factors associated with TNF-α, COX-2, and IL-6, which play crucial roles in cancer cell metastasis (173).

Quercetin protects mouse liver against inflammation due to its anti-oxidant activity and its ability to modulate the TLR2/TLR4 and MAPK/NF-κB signaling pathway. Quercetin significantly decreases cytochrome P450 2E1 (CYP2E1) expression and production of iNOS, IL-1β, COX-2, and NO in livers of CCl4-treated mouse suggesting that quercetin protects mouse liver from damage by inhibition of TLR2/4 and MAP, which in turn inactivates NF-κB (174).

In rat abberant crypt foci formation, quercetin lowers the proliferative index of pre-neoplastic lesions and increases the proportion of apoptotic colonocytes. It also tends to suppress transcript levels of COX-1 and COX-2 [160].

Quercetin is a component of ethyl acetate fraction (Tn-EE-BF) prepared from the seed of T. nucifera. It displays anti-inflammatory activity through suppression of the production of NO and PGE2 and mRNA expression of iNOS, TNF-α, and COX-2. Analysis of transcription factors and upstream signaling mechanisms reveal that Tn-EE-BF diminishes the activation

of NF-κB and AP-1 via blockade of Src, Syk, and IRAK. Arctigenin, amentoflavone, and quercetin may be the active components with these anti-inflammatory activities (175). Quercetin metabolites display potent COX enzyme inhibition, and their inhibitory potency is significantly higher than that of the parent molecule in human colorectal cancer cell line (176).

Quercetin suppression of tumorigenesis: Quercetin suppression of tumorigenesis includes: inhibition of migration and invasion, and suppression of cell proliferation and angiogenesis.

Quercetin inhibits migration and invasion of human oral cancer cells through inhibition of NF-κB and down-regulation of PKC, iNOS and COX-2, by blocking the MAPK signaling, which results in suppression of MMP-2/9 pathways (177). Similarly, quercetin inhibits invasion, migration, and signaling molecules involved in cell survival and proliferation of prostate cancer cell line by downregulating urokinase-type plasminogen activator (uPA), a serine protease that is involved in cancer progression, and EGF, EGFR mRNA expressions. Quercetin inhibits cell survival factor B-catenin, NF-κB, and proliferative signaling molecule expression such as p-EGF-R, N-Ras, Raf-1, c.Fos c.Jun and p-c.Jun (178). Quercetin suppresses the migratory and invasive capacity of Caco-2 cells and expression of metastasis-related proteins of the mitochondrial membrane.

It suppresses cell proliferation and increases the fraction of floating apoptotic cells of human oesophageal adenocarcinoma cell line. COX-2 mRNA expression was suppressed by quercetin and the synthetic COX-2 (179).

Quercetin suppresses COX-2 mRNA and protein expression and angiogenesis through inactivation of p300, a co-activator of COX-2 promoter (180). Mechanistically, quercetin considerably inhibits the binding of the trans-activators CREB2, C-Jun, C/EBPβ, and NF-κB and blocks the recruitment of p300 to COX-2 promoter. Moreover, quercetin effectively inhibits p300 histone acetyltransferase (HAT) activity, thereby attenuating the p300-mediated acetylation of NF-κB (180). Anticarcinogenic action of quercetin is associated with the downregulation of the expression of PI3K, PKC, COX-2, and ROS. Additionally, quercetin enhances the expression of p53 apoptotic factor and associated BAX gene expression in HepG2 cells suggesting that it elicits anticarcinogenic action by upregulation of p53- mediated apoptosis in HepG2 cells via downregulation of ROS, PKC, PI3K and COX-2 (181).

Protective role of Quercetin: The protective effect of quercetin against arsenite-induced COX-2 expression includes targeting PI3K in rat liver epithelial cells (182). Quercetin directly binds with PI3K to inhibit PI3K activity.

Protection against UV radiation; quercetin-loaded nanoparticles can significantly block UVB irradiation induced COX-2 expression and NF-κB activation in Hacat cell line. Treatment of mice with quercetin-loaded NPs also attenuates UVB irradiation-associated macroscopic and histopathological changes in mice skin (183).

Anti-cancer effect of quercetin; quercetin activates AMPK in breast cancer cell lines and colon cancer cells, and this activation of AMPK seems to be closely related to decrease in COX-2 expression (184) suggesting that AMPK is crucial to the anti-cancer effect of quercetin and that the AMPK/COX-2 signaling pathway is important in quercetin-mediated cancer control.

5.3.3 Genistein: Epidemiological studies suggest that Asian women have a lower incidence of breast cancer compared with Western women, and **soya** consumption has been suggested as a contributory factor (185). Genistein is a natural isoflavone found in soybeans, which has been studied for its chemo-preventive and chemotherapeutic nutritional potential.

Genistein suppression of tumorigenesis: Genistein has been shown to decrease proliferation *in vitro* of prostrate, breast, lung, colon, and ovarian cancer and it shows promise for human gastric cancer cell line BGC-823 (186). It was suggested that genistein inhibits TPA-induced COX-2 expression in breast epithelial cells by blocking ERK-mediated phosphorylation of p65 (187) Genistein inhibits cell proliferation and induces apoptosis in a dose and time-dependent manner in the BGC-823 gastric cancer cells (188). Genistein inhibits hepatocellular carcinoma cell migration by reversing the epithelial-mesenchymal transition and suppressing COX-2 expression (189).

Genistein modulation of COX-2: Genistein suppresses the production of COX-2 protein levels and NF-κB DNA binding activity is reduced in a dose-dependent manner (188). Like other isoflavones, genistein has been identified as an angiogenesis inhibitor. In order to determine the actual mechanism by which COX-2 is down regulated, the effect of genistein on prostaglandin-endoperoxide synthase-2, PTGS2, which catalyzes the first rate-limiting step in the conversion of arachidonic acid to prostaglandins, was studied. NF-κB is responsible for the regulation of PTGS2 gene expression and promoter activity (190); therefore genistein's ability to interfere with NF-κB activation provides good evidence that it affects COX-2 downstream (188). Genistein inhibits TPA-induced COX-2 expression and transcriptional activity of NF-κB in MCF10A human breast epithelial cells by blocking ERK-mediated phosphorylation of p65/RelA in human mammary epithelial cells (187). Genistein inhibits COX-2 expression in MCF-7 breast cancer cells, which could be the mechanism underlying the reduction of breast carcinogenesis in Asian women. It was suggested that such COX-2 inhibition might have important implications in the chemopreventive application of soya isoflavones and that he mechanism of COX-2 expression inhibition in breast cells may be comparable to that in colon cells (185). It was demonstrated that combination of 5-fluorouracil and genistein exert a novel chemotherapeutic effect in colon cancers through inhibition of AMPK/COX-2 expression (191).

5.3.4. Tricin: Tricin, a major flavonoid constituent of rice bran, oats, barley, and wheat, is a potential chemo-preventive agent consumed by more than half of the world's population. Other health benefits include its antioxidant effects, inhibition of lipid peroxidation, anti-viral, immunomodulatory, anti-tubercular, anti-ulcerogenic, anti-mutagenic, and anti-

inflammatory effects (192). Such tumor suppressive properties of brown rice, in particular its tricin phyonutrient, have been studied in human derived colon and breast cancer cells (193).

Tricin modulation of COX 2: Tricin was found to inhibit COX-2 enzymes *in vivo* in Apc^{Min} mouse and *in vitro* in intact colon cells (194). Tricin given to mice through diet, significantly decreased COX-2 expression and PGE2 production in human colon epithelial cells. Another study investigated the same effects of tricin in HCA-7 cells and induced HCEC cells, and found it to significantly down-regulate COX-2 protein expression and decrease PGE2 levels moderately (171). These results suggest the adenoma suppressing activity of tricin exerted in part through COX-2 inhibition.

Tricin modulation of inflammatory responses: Tricin suppresses the expression of the inflammatory mediators IL-6 and NO (195) and it reduces inflammatory responses through down-regulation of NF-κB and STAT3 pathways. It modulates the p38 MAPK and PI3K/Akt pathways to prevent inflammation (196). Tricin significantly inhibits the release of TNF-α (195) and its actions are comparable to other specific pathway blockers like ERK inhibitor, JNK inhibitor, and p38 inhibitor (196). Combination treatment of tricin and PI3K/Akt inhibitor showed increased activation of COX-2 and TNF-α (197). Tricin alone or in combination treatment with other inhibitors shows significantly greater inhibition of COX-2 activation and TNF-α levels (196). It was suggested that PI3K activation is essential for the anti-inflammatory effect of tricin. Studies conducted on human cells reveal the protective effect of tricin against endothelial dysfunction associated with LPS induced inflammation. It blocks the TLR4 signaling-mediated activation of cytosolic phospholipase A2 (cPLA2), which is confirmed by specific inhibition of COX-2 (198), and inhibits the activation of pro-inflammatory mediators like TNF-α, IFN-γ, and MCP-1 by modulating NF-κB and MAPK signaling pathways (196).

Incubation of polyphenols with the cancer cell line HCA–7 and lipopolysaccharide (LPS) stimulated primary monocytes, supporting the hypothesis that polyphenols including genistein can effect COX–2 expression and activity *in vitro* In comparison with pharmaceutical COX inhibitors, polyphenols are about 100 to 1000-fold less potent in the monocyte assay. Food polyphenols including genistein fail to cause a biologically relevant reduction of COX-2 activity in mice (199) and did not decrease plasma or tissue prostaglandin levels, suggesting that despite their moderate potency *in vitro*, an effect of polyphenols on COX–2 during acute inflammation is unlikely even if a high ingested doses(199)

5.4. Fatty acids modulation of COX-2

Fatty acids are carboxylic acids with long aliphatic saturated) or unsaturated chains with 4-28 carbons. Fatty acids can influence inflammation through cell surface and intracellular receptors that control inflammatory cell signaling and gene expression. Modifications of inflammatory cell membrane fatty acids can modify cell signaling leading to altered gene expression. The exposure of inflammatory cells to different types of fatty acids can influence their function and has the potential to modify inflammatory processes (200, 201).

Several long chain fatty acids [stearic acid, oleic acid, linoleic acid, α-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and derivatives of the flavonoid Quercetin-3-*O*-glucoside (Q3G) are considered mediators and regulators of inflammation (200, 201). It was shown that saturated fatty acids (SFAs), but not unsaturated fatty acids (UFAs), induce NF-κB activation and expression of COX-2 and other inflammatory markers (202), while polyunsaturated fatty acids (PUFAs), have been associated with inhibition of COX-2, decreased inflammation, and the prevention of tumorigenesis. Omega-3 (ω-3)-PUFAs include the essential fatty acid α-linolenic acid (ALA) and its metabolites eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ω-3 PUFAs display multiple anti-tumor actions and alpha-linoleic acid (ALA 18:3 ω-3); The omega-3 polyunsaturated fatty acids prevented colitis-associated carcinogenesis through blocking dissociation of beta-catenin complex, inhibiting COX-2 through repressing NF-κB, and inducing 15-prostaglandin dehydrogenase (203).

Eicosapentaenoic acid (EPA 20:5, ω-3) and docosahexaenoic acid (DHA 22:6, ω-3) may exert inhibitory cancer action (204).

5.4.1 Polyunsaturated fatty acids (PUFAS): PUFAS (e.g. from tree nuts and legume seeds) have long shown promise for treatment of many pathologies. They exert their beneficial functions through the modulation of peroxisome proliferator-activated receptor gamma (PPARG), which has anti-inflammatory effects. PUFAS bind to PPARG with a higher affinity than saturated or monounsaturated fatty acids. Ultimately, this regulation lends itself to the inhibition of COX-2 and eventually apoptosis of cancer cells.

Mechanisms for COX-2 Modulation: The down-regulation of the COX-2 and PGE2 pathway gives PUFAS their anti-angiogenic properties (94). Both *in vitro* and *in vivo* studies have confirmed the inhibition of COX-2 expression by (n-3) PUFAS including EPA and DHA. Another mechanism by which COX-2 is suppressed is through inhibition of iNOS expression (205, 206). PUFAS obtained from a fish oil diet combined with quercetin (flavonoid) treatment demonstrates significant reduction in the colonic pro-inflammatory cytokine, TNF-α. When this effect was compared separately with both treatments, a difference was not observed suggesting that both PUFAS and quercetin treatment has a synergistic inhibitory effect (205, 206). PUFAs down-regulate the expression of COX-2 in human colon cancer cells (207). The consumption of ω-3-PUFAs is associated with a reduced risk of CRC (208). In mice, EPA-FFA diets dramatically suppress the number of colonic polyps and in both the small intestine and colon, the mucosal arachidonic acid is replaced leading to a significant reduction in COX-2 expression and beta-catenin nuclear translocation. Moreover, with EPA-FFA treatment, there is significant decrease in cell proliferation throughout the intestine with an increase in apoptosis (208). In a case-control study of 466 men diagnosed with aggressive prostate cancer, dietary long-chain ω-3-PUFAs appear protective for aggressive prostate cancer. This effect is modified by the COX-2 SNP rs4648310 (209).

5.4.2 Alpha-linoleic acid (ALA): Seed oils are the richest sources of ALA, which is an essential fatty acid that must be provided through dietary intake. It is reported to have beneficial cardiovascular-protective, anti-cancer, anti-inflammatory, and antioxidant effects.

It is the precursor to long chain ω-3 fatty acids and is found in vegetable and seed oils such as flax and walnuts, as well as in beans, legumes, grains, and leafy vegetables. In animal studies, it was shown that increased dietary levels of alpha-linoleic acid inhibit mammary tumor growth and metastasis (210).

Mechanisms of ALA COX 2 modulation: ALA is known to suppress cytokines IL-6, IL-8, and TNF-α, which are involved in the inflammatory process (30). Dietary intake of ALA decreases COX-2 expression, increases apoptosis in hepatoma cells, and decreases MCF-7 breast tumor growth (211). ω -3 and ω -6 PUFAS suppress expression of fatty acid synthetase, which is generally overexpressed in tumor and liver tissue and induces apoptosis. A diet enriched in ALA induces significant changes in the fatty acid composition of whole hepatoma lipids and is correlated with a decrease in arachidonate content in carcinogenic liver cells. These observations were made in rats fed a linseed (LS) diet enriched with linoleic and **α**-linolenic acids. Transcriptional modulation of the COX-2 encoding gene is cell specific. In the liver, COX-2 expression is regulated by the family of CCAAT enhancer binding protein (C/EBP) transcription factors. C/EBP-a, induces growth arrest and differentiation and negatively modulates COX-2 expression while C/EBP-b positively modulates COX-2 expression. The mRNA level of isoform C/EBP-b, was measured in rats fed different diets. The rats that consumed a diet specifically enriched with linoleic and **α**-linolenic acid (LS) had lower C/EBP-b mRNA levels compared to those on the control diet (211), which means that COX-2 expression was suppressed. Tumor-bearing rats fed supplemental oils rich in ALA, resulted in a 2.3-fold decrease in tumor mass, a 3.0-fold decrease in cell proliferation, and a 20% reduction in COX-2 expression (212).

6. DISCUSSION AND FUTURE DIRECTIONS:

The potential utility of the research on phytonutrient modulation of COX-2 and inflammation related to cancer is to identify new natural COX-2 inhibitors for cancer treatment needed to overcome the limitations of current COX-2 inhibitors. In general, there has been a steady increase in the basic studies of natural products as adjuvant therapeutic options to traditional cancer treatments. The application of such studies to cancer prevention is demonstrated by the use of clinical chemotherapeutic drugs such as paclitaxel, vincristine, and podophyllotoxin. Plant sourced derivatives such as etoposide are also used as anti-cancer agents. The goal of these studies is to isolate these bioactive compounds to determine and better understand the pharmacological properties of these phytonutrients. Polypharmacological targeting of complex pathways of inflammation and cancer may be superior to single targeted approaches. These compounds can act synergistically or provide an effective therapeutic index or reduced toxicity to traditionally used anti-inflammatory agents (213), this raise an important question; what is the impact of having several compounds administered in the diet in combinations? The impact of having several compounds administered in the diet in varying combinations must account for the shift in drug development from the use of mono-agents to multi-targeted agents. Most if not all diseases involve a complex, multi-faceted network of signaling pathways and defective genes or molecules. In discussing the effect of a single protein, it is important to keep a perspective of the interplay of numerous proteins in the pathogenesis of cancer. There may

be one major signaling pathway of a given disease, but many collateral proteins feed into this defined pathway leading to multifaceted presentation of the disease. Genomic sequencing results revealed that a lung tumor carried more than 23,000 mutations and that a smoker develops one mutation for every 15 cigarettes smoked. Out of the 25,431 human genes, about 3,000 genes have been linked with over 150 cell signaling pathways. However, only 350 genes are directly linked to a specific cancer; for example, the Philadelphia chromosome is directly linked to CML. Thus targeting a single gene or single protein does not seem to provide the most benefit, especially when viewing inflammation as a systemic and multi-factorial dysregulation of cell-signaling. (213)

Perhaps the ideal drug or treatment is one whose efficacy is not based on a single target, but instead focuses on rebalancing several proteins that contribute to pathogenesis of inflammation and cancer. In a short-term treatment, single-targeted chemo agents may prove beneficial. However, in the long-term, inflammation may persist, along with the degree of involvement of multiple signaling pathways and tissues. Thus advancement in targeting cancer from multiple signaling pathways can provide more efficacious treatment and better understanding of the mechanisms of pathogenesis of disease. (214)

In laboratory studies the carotenoid, phenolic compound and fatty acid phytochemicals highlighted in this review have been shown to have notable effects on COX-2, which is upregulated during both inflammation and cancer via cancer related pathways, while it is impossible to confirm directly that these phytochemicals have similar *in vivo* pharmacological effects in humans in the absence of complex clinical testing, active constituents of herbs have long been used in medicines around the world, and the importance of phytonutrients for human health is supported by epidemiological studies (215). Studies also suggest that a high intake of fruits and vegetables contributes to good health (216) and appears to be protective for many health conditions, including cancer (217–222). A meta-analysis of nutritional studies included prospective studies as well as four case-control studies involving 5,073 lung cancer cases and 237,981 controls. The study results suggest health benefits, including a statistically significant association between high flavonoid intake and reduced risk of developing lung cancer. An increase in flavonoid intake of 20 mg/day was associated with a 10% decreased risk of developing lung cancer (7). Another group carried out a meta-analysis of 14 prospective studies of breast cancer incidence and 4 prospective studies of disease recurrence and concluded that soy isoflavone intake was associated with a reduction in breast cancer incidence in Asian but not in Western populations, and in postmenopausal but not in premenopausal women. A 16% reduction in breast cancer recurrence was reported for the highest intake of isoflavones in postmenopausal women (8). Similarly, a meta-analysis of eight case-control and five cohort studies examined soy food consumption in Japan, China, Taiwan, United States, and Canada, finding a protective effect of dietary genistein and daidzein against prostate cancer (9). Moreover, many phytonutrients used in traditional medicine, including those described here, have been shown in *in vitro* and in animal studies to reduce inflammation.

While evidence of anti-inflammatory effects and decreased risk of certain cancers may suggest therapeutic potential, there are many gaps in what is known about phytonutrient COX-2 modulation across all cancers. A review of data from epidemiological and preclinical

studies of the potential benefits of a flavonoid-based diet for cancer prevention alludes to this disconnect and posits that more research needs to be done. For example, studies of tea, a major dietary source of flavonoids, have produced evidence for a protective effect of tea consumption on certain, but not all cancers. Protective effects of green tea were reported against breast (10, 11), ovarian (12, 13), prostate (14, 15), gastric (16), lung (17) and liver (6) cancer, while no association between tea consumption and risk of gastric (21, 22), ovarian (23–25) and colon (26) cancer was reported.

In some cases, there is a disconnect between the large body of molecular and mechanistic research on phytonutrients modulation of inflammation and cancer carried out in cell culture or animal models versus those carried out in humans. For example, epidemiologic studies show a correlation between the dietary intake of food polyphenols and beneficial health effects, but *in vitro* studies support the anti-inflammatory potential of polyphenols for COX modulation, as demonstrated by stimulation of primary monocytes by incubation of polyphenols with cultured cancer cells. This supports the hypothesis that polyphenols can affect COX–2 expression and activity *in vitro.* However, other studies suggest that food polyphenols do not cause biologically relevant reduction of COX-2 activity (199). From this one can conclude that an effect of polyphenols on COX–2 during acute inflammation is unlikely despite moderate potency *in vitro*, even when high doses of polyphenols are ingested. Similarly, there are several mixed reports regarding green tea including insufficient evidence to support green tea as a treatment or preventative agent for lung cancer. Green tea (18–20). Such conflicting reports regarding the anticancer effectiveness of natural products may point to a potential inherent limitation to data interpretation regarding anti-cancer activity arise from several factors, including methodological variation and the difficulty of assessing activities to specific components of complex mixtures of phytonutrients. Other confounding factors include plant diversity, genetic variability, phenotypic variability between plants (growth conditions, time of harvest, presence of growth factors, etc.), mode of propagation or even how the natural product is prepared and consumed. For example, it was shown that interaction between EGCG and flavonols of green tea might form complexes during thermal treatment (19) and that the temperature of green tea when consumed, affects the risk of gastric cancer (20). Most studies that are limited to a relatively small range of phytonutrients such as carotenoids or polyphenols may not allow researchers to identify associations between these phytonutrients and cancer due to the complexity, breadth, diversity and synergies of natural products present in food. In addition, the effects seen in epidemiological studies are difficult to translate from in vitro studies due to effects of duration and dose of phytonutrient intake (treatment), as well as effects of variation between acute and chronic inflammation it may not be sufficient to utilize the pure “active ingredient” of a natural product in order to obtain the full effect reported in epidemiological studies due to synergies within the complex of components of natural products contributing to therapeutic function. The concept of synergy is based on the idea that using a whole plant containing a group of chemicals working together is more beneficial than using a single compound to achieve a specific effect (223). The challenge is that while the in vitro studies we describe can identify mechanisms of phytonutrient modulation of COX-2 and inflammation related to cancer (which may be supported by epidemiology and “holistic”

population data), in the absence of clinical testing and clinical therapeutic determination our observations remain subject to the issues of material complexity discussed above.

An additional challenge is that some natural compounds (such as curcumin or phenolic compounds) may function non-specifically as PAINS (27–29), for example as reactive chemicals rather than discriminating drugs. PAINS non-specific activity may include interference with other proteins in addition to the intended target, giving false readouts in a variety of ways. These may include functioning as chelators and trapping toxic or reactive metals which then give rise to signals, or coating a protein. Other possibilities include sequestration of metal ions essential to a protein's function, catalyzing non-specific reactions, or where phytonutrients themselves are fluorescent or strongly colored resulting in false optical signals. Such factors should be considered in studying phytonutrient compounds having multiple functions.

Another factor contributing to inconsistency is plant variability, complexity and research uniformity. To overcome this challenge, better genetic identification analysis of the plant material may be needed using "standard" plant material from plant genebank collections for research, standardization of plant growth to reduce phenotypic variability between plants and amore in vitro studies on plant compound synergies. To overcome the challenge of multiple non-specific PAINS activities, there is a need to consider these activities when analyzing the data, and to develop *in vitro* and *in vivo* assays to identify and characterize PAINS activities of the compounds tested.

On the molecular level, phytonutrients were shown to play an important role in inflammation, modulation of COX-2, and cancer prevention. A central challenge for the use of phytonutrients in the fields of cancer nutrition and CAM will be resolving the tension between the reductionist focus of molecular studies on individual phytonutrients and the more holistic approaches focusing on food habits and the relationship between diet and health.

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REFERENCES:

1. Horneber M, Bueschel G, Dennert G, Less D, Ritter E, et al.: How Many Cancer Patients Use Complementary and Alternative Medicine: A Systematic Review and Metaanalysis. Integrative Cancer Therapies 11, 187–203, 2012. doi: 10.1177/1534735411423920 [PubMed: 22019489]
2. Bishop FL, Prescott P, Chan YK, Saville J, von Elm E, et al.: Prevalence of Complementary Medicine Use in Pediatric Cancer: A Systematic Review. Pediatrics 125, 768–776, 2010. doi: 10.1542/peds.2009-1775 [PubMed: 20308209]
3. Perlman A, Lontok O, Huhmann M, Parrott JS, Simmons LA, et al.: Prevalence and correlates of postdiagnosis initiation of complementary and alternative medicine among patients at a comprehensive cancer center. J Oncol Pract 9, 34–41, 2013. doi: 10.1200/JOP.2012.000634 [PubMed: 23633969]
4. Rayburn ER, Ezell SJ, Zhang R: Anti-Inflammatory Agents for Cancer Therapy. Mol Cell Pharmacol 1, 29–43, 2009. doi: 10.4255/mcpharmacol.09.05 [PubMed: 20333321]

5. Bismark RS, Chen HB, Dy GK, Gage-Bouchard EA, Mahoney MC: Complementary and alternative medicine use among patients with thoracic malignancies. Supportive Care in Cancer 22, 1857–1866, 2014. doi: 10.1007/s00520-014-2144-0 [PubMed: 24554203]
6. Sing MF, Yang WS, Gao S, Gao J, Xiang YB: Epidemiological studies of the association between tea drinking and primary liver cancer: a meta-analysis. European Journal of Cancer Prevention 20, 157–165, 2011. doi: 10.1097/CEJ.0b013e3283447497 [PubMed: 21403523]
7. Tang NP, Zhou B, Wang B, Yu RB, Ma J: Flavonoids intake and risk of lung cancer: a meta-analysis. Jpn J Clin Oncol 39, 352–9, 2009. doi: 10.1093/jjco/hyp028 [PubMed: 19351659]
8. Dong JY, Qin LQ: Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. Breast Cancer Res Treat 125, 315–23, 2011. doi: 10.1007/s10549-010-1270-8 [PubMed: 21113655]
9. Hwang YW, Kim SY, Jee SH, Kim YN, Nam CM: Soy food consumption and risk of prostate cancer: a meta-analysis of observational studies. Nutr Cancer 61, 598–606, 2009. doi: 10.1080/01635580902825639 [PubMed: 19838933]
10. Sun CL, Yuan JM, Koh WP, Yu MC: Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. Carcinogenesis 27, 1310–5, 2006. doi: 10.1093/carcin/bgi276 [PubMed: 16311246]
11. Seely D, Mills EJ, Wu P, Verma S, Guyatt GH: The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: a systematic review and meta-analysis. Integr Cancer Ther 4, 144–55, 2005. doi: 10.1177/1534735405276420 [PubMed: 15911927]
12. Nagle CM, Olsen CM, Bain CJ, Whiteman DC, Green AC, et al.: Tea consumption and risk of ovarian cancer. Cancer Causes Control 21, 1485–91, 2010. doi: 10.1007/s10552-010-9577-7 [PubMed: 20490647]
13. Butler LM, Wu AH: Green and black tea in relation to gynecologic cancers. Mol Nutr Food Res 55, 931–40, 2011. doi: 10.1002/mnfr.201100058 [PubMed: 21595018]
14. Boehm K, Borrelli F, Ernst E, Habacher G, Hung SK, et al.: Green tea (Camellia sinensis) for the prevention of cancer. Cochrane Database Syst Rev, CD005004, 2009. doi: 10.1002/14651858.CD005004.pub2 [PubMed: 19588362]
15. Zheng J, Yang B, Huang T, Yu Y, Yang J, et al.: Green tea and black tea consumption and prostate cancer risk: an exploratory meta-analysis of observational studies. Nutr Cancer 63, 663–72, 2011. doi: 10.1080/01635581.2011.570895 [PubMed: 21667398]
16. Kang H, Rha SY, Oh KW, Nam CM: Green tea consumption and stomach cancer risk: a meta-analysis. Epidemiol Health 32, e2010001, 2010. doi: 10.4178/epih/e2010001 [PubMed: 21191454]
17. Tang N, Wu Y, Zhou B, Wang B, Yu R: Green tea, black tea consumption and risk of lung cancer: a meta-analysis. Lung Cancer 65, 274–83, 2009. doi: 10.1016/j.lungcan.2008.12.002 [PubMed: 19128856]
18. Fritz H, Seely D, Kennedy DA, Fernandes R, Cooley K, et al.: Green tea and lung cancer: a systematic review. Integr Cancer Ther 12, 7–24, 2013. doi: 10.1177/1534735412442378 [PubMed: 22532034]
19. Dai QY, He YY, Ho CT, Wang J, Wang SJ, et al.: Effect of interaction of epigallocatechin gallate and flavonols on color alteration of simulative green tea infusion after thermal treatment. Journal of Food Science and Technology-Mysore 54, 2919–2928, 2017. doi: 10.1007/s13197-017-2730-5
20. Deandrea S, Foschi R, Galeone C, La Vecchia C, Negri E, et al.: Is temperature an effect modifier of the association between green tea intake and gastric cancer risk? European Journal of Cancer Prevention 19, 18–22, 2010. doi: 10.1097/CEJ.0b013e328330eb1a [PubMed: 19864955]
21. Zhou Y, Li N, Zhuang W, Liu G, Wu T, et al.: Green tea and gastric cancer risk: meta-analysis of epidemiologic studies. Asia Pac J Clin Nutr 17, 159–65, 2008 [PubMed: 18364341]
22. Myung SK, Bae WK, Oh SM, Kim Y, Ju W, et al.: Green tea consumption and risk of stomach cancer: a meta-analysis of epidemiologic studies. Int J Cancer 124, 670–7, 2009. doi: 10.1002/ijc.23880 [PubMed: 18973231]
23. Braem MG, Onland-Moret NC, Schouten LJ, Tjonneland A, Hansen L, et al.: Coffee and tea consumption and the risk of ovarian cancer: a prospective cohort study and updated meta-analysis. Am J Clin Nutr 95, 1172–81, 2012. doi: 10.3945/ajcn.111.026393 [PubMed: 22440851]

24. Zhou B, Yang L, Wang L, Shi Y, Zhu H, et al.: The association of tea consumption with ovarian cancer risk: A metaanalysis. Am J Obstet Gynecol 197, 594 e1–6, 2007. doi: 10.1016/j.ajog.2007.05.027 [PubMed: 17905170]
25. Steevens J, Schouten LJ, Verhage BA, Goldbohm RA, van den Brandt PA: Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis. Br J Cancer 97, 1291–4, 2007. doi: 10.1038/sj.bjc.6604008 [PubMed: 17923877]
26. Sun CL, Yuan JM, Koh WP, Yu MC: Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies. Carcinogenesis 27, 1301–9, 2006. doi: 10.1093/carcin/bgl024 [PubMed: 16638787]
27. Baell J, Walters MA: Chemistry: Chemical con artists foil drug discovery. Nature 513, 481–3, 2014. doi: 10.1038/513481a [PubMed: 25254460]
28. Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, et al.: The Essential Medicinal Chemistry of Curcumin. J Med Chem 60, 1620–1637, 2017. doi: 10.1021/acs.jmedchem.6b00975 [PubMed: 28074653]
29. Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, et al.: Curcumin May (Not) Defy Science. Acs Medicinal Chemistry Letters 8, 467–470, 2017. doi: 10.1021/acsmedchemlett.7b00139 [PubMed: 28523093]
30. Kim KB, Nam YA, Kim HS, Hayes AW, Lee BM: alpha-Linolenic acid: Nutraceutical, pharmacological and toxicological evaluation. Food Chem Toxicol, 2014. doi: S0278-6915(14)00243-9 [pii] 10.1016/j.fct.2014.05.009
31. Smyth EM, Grosser T, Wang M, Yu Y, FitzGerald GA: Prostanoids in health and disease. J Lipid Res 50 Suppl, S423–8, 2009. doi: 10.1194/jlr.R800094-JLR200 [PubMed: 19095631]
32. Sheng H, Shao J, Washington MK, DuBois RN: Prostaglandin E2 increases growth and motility of colorectal carcinoma cells. J Biol Chem 276, 18075–81, 2001. doi: 10.1074/jbc.M009689200 [PubMed: 11278548]
33. Ben-Av P, Crofford LJ, Wilder RL, Hla T: Induction of vascular endothelial growth factor expression in synovial fibroblasts by prostaglandin E and interleukin-1: a potential mechanism for inflammatory angiogenesis. FEBS Lett 372, 83–7, 1995 [PubMed: 7556649]
34. Tsuji S, Kawano S, Tsujii M, Michida T, Masuda E, et al.: [Mucosal microcirculation and angiogenesis in gastrointestinal tract]. Nihon Rinsho 56, 2247–52, 1998 [PubMed: 9780700]
35. Kakiuchi Y, Tsuji S, Tsujii M, Murata H, Kawai N, et al.: Cyclooxygenase-2 activity altered the cell-surface carbohydrate antigens on colon cancer cells and enhanced liver metastasis. Cancer Res 62, 1567–72, 2002 [PubMed: 11888937]
36. Krishnamachary B, Stasinopoulos I, Kakkad S, Penet MF, Jacob D, et al.: Breast cancer cell cyclooxygenase-2 expression alters extracellular matrix structure and function and numbers of cancer associated fibroblasts. Oncotarget 8, 17981–17994, 2017. doi: 10.18632/oncotarget.14912 [PubMed: 28152501]
37. Maturu P, Jones D, Ruteshouser EC, Hu Q, Reynolds JM, et al.: Role of Cyclooxygenase-2 Pathway in Creating an Immunosuppressive Microenvironment and in Initiation and Progression of Wilms' Tumor. Neoplasia 19, 237–249, 2017. doi: 10.1016/j.neo.2016.07.009 [PubMed: 28254151]
38. Vandoros GP, Konstantinopoulos PA, Sotiropoulou-Bonikou G, Kominea A, Papachristou GI, et al.: PPAR-gamma is expressed and NF-KB pathway is activated and correlates positively with COX-2 expression in stromal myofibroblasts surrounding colon adenocarcinomas. Journal of Cancer Research and Clinical Oncology 132, 76–84, 2006. doi: 10.1007/s00432-005-0042-z [PubMed: 16215757]
39. Koki AT, Masferrer JL: Celecoxib: a specific COX-2 inhibitor with anticancer properties. Cancer Control 9, 28–35, 2002 [PubMed: 11965228]
40. Nagendraprabhu P, Sudhandiran G: Astaxanthin inhibits tumor invasion by decreasing extracellular matrix production and induces apoptosis in experimental rat colon carcinogenesis by modulating the expressions of ERK-2, NFkB and COX-2. Invest New Drugs 29, 207–24, 2011. doi: 10.1007/s10637-009-9342-5 [PubMed: 19876598]

41. Murakami A, Ohigashi H: Targeting NOX, INOS and COX-2 in inflammatory cells: Chemoprevention using food phytochemicals. International Journal of Cancer 121, 2357–2363, 2007. doi: 10.1002/ijc.23161 [PubMed: 17893865]
42. Harris RE, Beebe-Donk J, Alshafie GA: Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. Bmc Cancer 6, 2006. doi: Artn 27 10.1186/1471-2407-6-27
43. Harris RE, Casto BC, Harris ZM: Cyclooxygenase-2 and the inflammogenesis of breast cancer. World J Clin Oncol 5, 677–92, 2014. doi: 10.5306/wjco.v5.i4.677 [PubMed: 25302170]
44. Rakoff-Nahoum S: Why cancer and inflammation? Yale J Biol Med 79, 123–30, 2006 [PubMed: 17940622]
45. Acheva A, Schettino G, Prise KM: Pro-inflammatory Signaling in a 3D Organotypic Skin Model after Low LET Irradiation-NF-kappaB, COX-2 Activation, and Impact on Cell Differentiation. Front Immunol 8, 82, 2017. doi: 10.3389/fimmu.2017.00082 [PubMed: 28239377]
46. Yao C, Li G, Cai M, Qian YY, Wang LQ, et al.: Prostate cancer downregulated SIRP-alpha modulates apoptosis and proliferation through p38-MAPK/NF-kappa B/COX-2 signaling. Oncology Letters 13, 4995–5001, 2017. doi: 10.3892/ol.2017.6070 [PubMed: 28588738]
47. Madka V, Rao CV: Anti-inflammatory Phytochemicals for Chemoprevention of Colon Cancer. Current Cancer Drug Targets 13, 542–557, 2013 [PubMed: 23597198]
48. Yiannakopoulou EC: Interaction of Salicylates and the Other Nonsteroidal Anti-Inflammatory Agents With Breast Cancer Endocrine Treatment Systematic Review. American Journal of Clinical Oncology-Cancer Clinical Trials 38, 641–644, 2015. doi: 10.1097/Coc.0000000000000166
49. Conte E, Fagone E, Fruciano M, Gili E, Iemmolo M, et al.: Anti-inflammatory and antifibrotic effects of resveratrol in the lung. Histology and Histopathology 30, 523–529, 2015. doi: 10.14670/Hh-30.523 [PubMed: 25515609]
50. Wang X, Lin YW, Wu J, Zhu Y, Xu XL, et al.: Meta-analysis of nonsteroidal anti-inflammatory drug intake and prostate cancer risk. World Journal of Surgical Oncology 12, 2014. doi: Artn 304 10.1186/1477-7819-12-304
51. Lourenco AM, Ferreira LM, Branco PS: Molecules of Natural Origin, Semi-synthesis and Synthesis with Anti-Inflammatory and Anticancer Utilities. Current Pharmaceutical Design 18, 3979–4046, 2012 [PubMed: 22632756]
52. Orlikova B, Legrand N, Panning J, Dicato M, Diederich M: Anti-Inflammatory and Anticancer Drugs from Nature. Advances in Nutrition and Cancer 159, 123–143, 2014. doi: 10.1007/978-3-642-38007-5_8
53. De Stefano D, Maiuri MC, Simeon V, Grassia G, Soscia A, et al.: Lycopene, quercetin and tyrosol prevent macrophage activation induced by gliadin and IFN-gamma. Eur J Pharmacol 566, 192–9, 2007. doi: S0014-2999(07)00417-7 [pii] 10.1016/j.ejphar.2007.03.051 [PubMed: 17477920]
54. Venturini CM, Isakson P, Needleman P: Non-steroidal anti-inflammatory drug-induced renal failure: a brief review of the role of cyclo-oxygenase isoforms. Curr Opin Nephrol Hypertens 7, 79–82, 1998 [PubMed: 9442367]
55. Hoffmann A, Levchenko A, Scott ML, Baltimore D: The IkappaB-NF-kappaB signaling module: temporal control and selective gene activation. Science 298, 1241–5, 2002. doi: 10.1126/science.1071914 [PubMed: 12424381]
56. Liu F, Xia Y, Parker AS, Verma IM: IKK biology. Immunol Rev 246, 239–53, 2012. doi: 10.1111/j.1600-065X.2012.01107.x [PubMed: 22435559]
57. Basak S, Hoffmann A: Crosstalk via the NF-kappa B signaling system. Cytokine & Growth Factor Reviews 19, 187–197, 2008. doi: 10.1016/j.cytogfr.2008.04.005 [PubMed: 18515173]
58. Karin M, Ben-Neriah Y: Phosphorylation meets ubiquitination: The control of NF-kappa B activity. Annual Review of Immunology 18, 621-+, 2000. doi: 10.1146/annurev.immunol.18.1.621
59. Ben-Neriah Y: Regulatory functions of ubiquitination in the immune system. Nature Immunology 3, 20–26, 2002. doi: 10.1038/ni0102-20 [PubMed: 11753406]
60. Lappas M, Permezel M, Georgiou HM, Rice GE: Nuclear factor kappa B regulation of proinflammatory cytokines in human gestational tissues in vitro. Biology of Reproduction 67, 668–673, 2002. doi: 10.1095/biolreprod67.2.668 [PubMed: 12135912]

61. Alves BN, Tsui R, Almaden J, Shokhirev MN, Davis-Turak J, et al.: I kappa B epsilon Is a Key Regulator of B Cell Expansion by Providing Negative Feedback on cRel and RelA in a Stimulus-Specific Manner. Journal of Immunology 192, 3121–3132, 2014. doi: 10.4049/jimmunol.1302351
62. Escoubet-Lozach L, Benner C, Kaikkonen MU, Lozach J, Heinz S, et al.: Mechanisms Establishing TLR4-Responsive Activation States of Inflammatory Response Genes. Plos Genetics 7, 2011. doi: ARTN e1002401 10.1371/journal.pgen.1002401
63. Wong MM, Fish EN: Chemokines: attractive mediators of the immune response. Seminars in Immunology 15, 5–14, 2003. doi: 10.1016/S1044-5323(02)00123-9 [PubMed: 12495636]
64. Rossi A, Kapahi P, Natoli G, Takahashi T, Chen Y, et al.: Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of I kappa B kinase. Nature 403, 103–108, 2000 [PubMed: 10638762]
65. Yamamoto Y, Gaynor RB: Therapeutic potential of inhibition of the NF-kappa B pathway in the treatment of inflammation and cancer. Journal of Clinical Investigation 107, 135–142, 2001. doi: 10.1172/Jci11914 [PubMed: 11160126]
66. Johnson GL, Lapadat R: Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science 298, 1911–1912, 2002. doi: 10.1126/science.1072682 [PubMed: 12471242]
67. Carter AB, Knudtson KL, Monick MM, Hunninghake GW: The p38 mitogen-activated protein kinase is required for NF-kappa B-dependent gene expression - The role of TATA-binding protein (TBP). Journal of Biological Chemistry 274, 30858–30863, 1999. doi: 10.1074/jbc.274.43.30858 [PubMed: 10521478]
68. Huang F, Cao J, Liu Q, Zou Y, Li H, et al.: MAPK/ERK signal pathway involved expression of COX-2 and VEGF by IL-1beta induced in human endometriosis stromal cells in vitro. Int J Clin Exp Pathol 6, 2129–36, 2013 [PubMed: 24133591]
69. Di Mari JF, Saada JI, Mifflin RC, Valentich JD, Powell DW: HETEs enhance IL-1-mediated COX-2 expression via augmentation of message stability in human colonic myofibroblasts. American Journal of Physiology-Gastrointestinal and Liver Physiology 293, G719–G728, 2007. doi: 10.1152/ajpgi.00117.2007 [PubMed: 17640979]
70. Pei XY, Dai Y, Tenorio S, Lu J, Harada H, et al.: MEK1/2 inhibitors potentiate UCN-01 lethality in human multiple myeloma cells through a Bim-dependent mechanism. Blood 110, 2092–2101, 2007. doi: 10.1182/blood-2007-04-083204 [PubMed: 17540843]
71. Cuenda A, Rousseau S: P38 MAP-Kinases pathway regulation, function and role in human diseases. Biochimica Et Biophysica Acta-Molecular Cell Research 1773, 1358–1375, 2007. doi: 10.1016/j.bbamcr2007.03.010
72. Zarubin T, Han JH: Activation and signaling of the p38 MAP kinase pathway. Cell Research 15, 11–18, 2005. doi: 10.1038/sj.cr.7290257 [PubMed: 15686620]
73. Lopez-Bergami P, Lau E, Ronai Z: Emerging roles of ATF2 and the dynamic AP1 network in cancer (vol 10, pg 65, 2010). Nature Reviews Cancer 10, 379–379, 2010. doi: 10.1038/nrc2846
74. Lopez-Bergami P, Lau E, Ronai Z: OPINION Emerging roles of ATF2 and the dynamic AP1 network in cancer. Nature Reviews Cancer 10, 65–76, 2010. doi: 10.1038/nrc2681 [PubMed: 20029425]
75. Simmons DL, Botting RM, Hla T: Cyclooxygenase isozymes: The biology of prostaglandin synthesis and inhibition. Pharmacological Reviews 56, 387–437, 2004. doi: 10.1124/pr.56.3.3 [PubMed: 15317910]
76. Maroon JC, Bost JW, Borden MK, Lorenz KM, Ross NA: Natural antiinflammatory agents for pain relief in athletes. Neurosurg Focus 21, E11, 2006
77. Burton TM. Monsanto arthritis-pain drug, Celebrex, surpasses Viagra's early sales success, 1999.
78. Ehrich EW, Dallob A, De Lepeleire I, Van Hecken A, Riendeau D, et al.: Characterization of rofecoxib as a cyclooxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. Clinical Pharmacology & Therapeutics 65, 336–347, 1999. doi: 10.1016/S0009-9236(99)70113-X [PubMed: 10096266]
79. Boyles S Vioxx, Celebrex Were Overused, Study Shows 3/4 of Users Had Little Need for Cox-2 Inhibitors, 2005.

80. Ahmaditaba MA, Shahosseini S, Daraei B, Zarghi A, Houshdar Tehrani MH: Design, Synthesis, and Biological Evaluation of New Peptide Analogues as Selective COX-2 Inhibitors. Arch Pharm (Weinheim) 350, 2017. doi: 10.1002/ardp.201700158
81. FitzGerald GA: Coxibs and cardiovascular disease. New England Journal of Medicine 351, 1709–1711, 2004. doi: 10.1056/NEJMp048288 [PubMed: 15470192]
82. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, et al.: Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. New England Journal of Medicine 352, 1092–1102, 2005. doi: 10.1056/NEJMoa050493 [PubMed: 15713943]
83. Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, et al.: Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. New England Journal of Medicine 352, 1081–1091, 2005. doi: 10.1056/NEJMoa050330 [PubMed: 15713945]
84. Solomon SD, McMurray JJV, Pfeffer MA, Wittes J, Fowler R, et al.: Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. New England Journal of Medicine 352, 1071–1080, 2005. doi: 10.1056/NEJMoa050405 [PubMed: 15713944]
85. Kaur C, Kapoor HC: Antioxidants in fruits and vegetables - the millennium's health. International Journal of Food Science and Technology 36, 703–725, 2001. doi: 10.1046/j.1365-2621.2001.00513.x
86. Liu RH: Potential synergy of phytochemicals in cancer prevention: Mechanism of action. Journal of Nutrition 134, 3479s–3485s, 2004 [PubMed: 15570057]
87. Reddy MK, Alexander-Lindo RL, Nair MG: Relative inhibition of lipid peroxidation, cyclooxygenase enzymes, and human tumor cell proliferation by natural food colors. Journal of Agricultural and Food Chemistry 53, 9268–9273, 2005. doi: 10.1021/jf051399j [PubMed: 16277432]
88. Palozza P, Serini S, Maggiano N, Tringali G, Navarra P, et al.: beta-Carotene downregulates the steady-state and heregulin-alpha-induced COX-2 pathways in colon cancer cells. J Nutr 135, 129–36, 2005. doi: 135/1/129 [pii] [PubMed: 15623844]
89. Palozza P, Serini S, Maggiano N, Tringali G, Navarra P, et al.: beta-carotene downregulates the steady-state and heregulin-alpha-induced COX-2 pathways in colon canter cells. Journal of Nutrition 135, 129–136, 2005 [PubMed: 15623844]
90. Singh S, Pandey VP, Naaz H, Singh P, Dwivedi UN: Structural modeling and simulation studies of human cyclooxygenase (COX) isozymes with selected terpenes: Implications in drug designing and development. Computers in Biology and Medicine 43, 744–750, 2013. doi: 10.1016/j.compbiomed.2013.02.019 [PubMed: 23668350]
91. Wang SC, Lien HC, Xia WY, Chen IF, Lo HW, et al.: Binding at and transactivation of the COX-2 promoter by nuclear tyrosine kinase receptor ErbB-2. Cancer Cell 6, 251–261, 2004. doi: 10.1016/j.ccr.2004.07.012 [PubMed: 15380516]
92. Breuleux M: Role of heregulin in human cancer. Cellular and Molecular Life Sciences 64, 2358–2377, 2007. doi: 10.1007/s00018-007-7120-0 [PubMed: 17530167]
93. Firdous AP, Kuttan G, Kuttan R: Anti-inflammatory potential of carotenoid meso-zeaxanthin and its mode of action. Pharmaceutical Biology 53, 961–967, 2015. doi: 10.3109/13880209.2014.950673 [PubMed: 25739325]
94. Talero E, Avila-Roman J, Motilva V: Chemoprevention with phytonutrients and microalgae products in chronic inflammation and colon cancer. Curr Pharm Des 18, 3939–65, 2012. doi: CPD-EPUB-20120522-17 [pii] [PubMed: 22632755]
95. Park JH, Yeo IJ, Han JH, Suh JW, Lee HP, et al.: Anti-inflammatory effect of Astaxanthin in phthalic anhydride-induced atopic dermatitis animal model. Exp Dermatol, 2017. doi: 10.1111/exd.13437
96. Yasui Y, Hosokawa M, Mikami N, Miyashita K, Tanaka T: Dietary astaxanthin inhibits colitis and colitis-associated colon carcinogenesis in mice via modulation of the inflammatory cytokines. Chemico-Biological Interactions 193, 79–87, 2011. doi: 10.1016/j.cbi.2011.05.006 [PubMed: 21621527]
97. Nagendraprabhu P, Sudhandiran G: Astaxanthin inhibits tumor invasion by decreasing extracellular matrix production and induces apoptosis in experimental rat colon carcinogenesis by modulating

the expressions of ERK-2, NFkB and COX-2. Investigational New Drugs 29, 207–224, 2011. doi: 10.1007/s10637-009-9342-5 [PubMed: 19876598]

98. Krishnaswamy R, Devaraj SN, Padma VV: Lutein protects HT-29 cells against Deoxynivalenol-induced oxidative stress and apoptosis: prevention of NF-kappaB nuclear localization and down regulation of NF-kappaB and Cyclo-Oxygenase-2 expression. Free Radic Biol Med 49, 50–60, 2010. doi: S0891-5849(10)00190-5 [pii] 10.1016/j.freeradbiomed.2010.03.016 [PubMed: 20347963]
99. Oh J, Kim JH, Park JG, Yi YS, Park KW, et al.: Radical Scavenging Activity-Based and AP-1-Targeted Anti-Inflammatory Effects of Lutein in Macrophage-Like and Skin Keratinocytic Cells. Mediators of Inflammation, 2013. doi: Artn 787042 10.1155/2013/787042
100. Palozza P, Parrone N, Catalano A, Simone R: Tomato lycopene and inflammatory cascade: basic interactions and clinical implications. Curr Med Chem 17, 2547–63, 2010. doi: BSP/CMC/E-Pub/ 150 [pii] [PubMed: 20491642]
101. Palozza P, Sheriff A, Serini S, Boninsegna A, Maggiano N, et al.: Lycopene induces apoptosis in immortalized fibroblasts exposed to tobacco smoke condensate through arresting cell cycle and down-regulating cyclin D1, pAKT and pBad. Apoptosis 10, 1445–56, 2005. doi: 10.1007/s10495-005-1393-2 [PubMed: 16215689]
102. Vasconcelos AG, Amorim A, Dos Santos RC, Souza JMT, de Souza LKM, et al.: Lycopene rich extract from red guava (Psidium guajava L.) displays anti-inflammatory and antioxidant profile by reducing suggestive hallmarks of acute inflammatory response in mice. Food Res Int 99, 959–968, 2017. doi: 10.1016/j.foodres.2017.01.017 [PubMed: 28847433]
103. Lin HY, Huang BR, Yeh WL, Lee CH, Huang SS, et al.: Antineuroinflammatory effects of lycopene via activation of adenosine monophosphate-activated protein kinase-alpha 1/heme oxygenase-1 pathways. Neurobiology of Aging 35, 191–202, 2014. doi: 10.1016/j.neurobiolaging.2013.06.020 [PubMed: 23906616]
104. Tang FY, Pai MH, Wang XD: Consumption of lycopene inhibits the growth and progression of colon cancer in a mouse xenograft model. J Agric Food Chem 59, 9011–21, 2011. doi: 10.1021/jf2017644 [PubMed: 21744871]
105. Tang FY, Pai MH, Kuo YH, Wang XD: Concomitant consumption of lycopene and fish oil inhibits tumor growth and progression in a mouse xenograft model of colon cancer. Mol Nutr Food Res 56, 1520–31, 2012. doi: 10.1002/mnfr.201200098 [PubMed: 22961879]
106. Chan JM, Weinberg V, Magbanua MJ, Sosa E, Simko J, et al.: Nutritional supplements, COX-2 and IGF-1 expression in men on active surveillance for prostate cancer. Cancer Causes & Control 22, 141–150, 2011. doi: 10.1007/s10552-010-9684-5 [PubMed: 21103921]
107. Huang WY, Cai YZ, Zhang Y: Natural phenolic compounds from medicinal herbs and dietary plants: potential use for cancer prevention. Nutr Cancer 62, 1–20, 2010. doi: 10.1080/01635580903191585 [PubMed: 20043255]
108. Subbaramaiah K, Sue E, Bhardwaj P, Du B, Hudis CA, et al.: Dietary polyphenols suppress elevated levels of proinflammatory mediators and aromatase in the mammary gland of obese mice. Cancer Prev Res (Phila) 6, 886–97, 2013. doi: 10.1158/1940-6207.CAPR-13-0140 [PubMed: 23880231]
109. Scoditti E, Calabriso N, Massaro M, Pellegrino M, Storelli C, et al.: Mediterranean diet polyphenols reduce inflammatory angiogenesis through MMP-9 and COX-2 inhibition in human vascular endothelial cells: A potentially protective mechanism in atherosclerotic vascular disease and cancer. Archives of Biochemistry and Biophysics 527, 81–89, 2012. doi: 10.1016/j.abb.2012.05.003 [PubMed: 22595400]
110. Woo JH, Lim JH, Kim YH, Suh SI, Min DS, et al.: Resveratrol inhibits phorbol myristate acetate-induced matrix metalloproteinase-9 expression by inhibiting JNK and PKC delta signal transduction. Oncogene 23, 1845–53, 2004. doi: 10.1038/sj.onc.1207307 [PubMed: 14661062]
111. Malhotra A, Nair P, Dhawan DK: Curcumin and resveratrol synergistically stimulate p21 and regulate cox-2 by maintaining adequate zinc levels during lung carcinogenesis. European Journal of Cancer Prevention 20, 411–416, 2011. doi: 10.1097/CEJ.0b013e3283481d71 [PubMed: 21633290]
112. Sharma RA, Gescher AJ, Steward WP: Curcumin: The story so far. European Journal of Cancer 41, 1955–1968, 2005. doi: 10.1016/j.ejca.2005.05.009 [PubMed: 16081279]

113. Lee YK, Park SY, Kim YM, Park OJ: Regulatory Effect of the AMPK-COX-2 Signaling Pathway in Curcumin-Induced Apoptosis in HT-29 Colon Cancer Cells. Natural Compounds and Their Role in Apoptotic Cell Signaling Pathways 1171, 489–494, 2009. doi: 10.1111/j.1749-6632.2009.04699.x

114. Jiang H, Deng CS, Zhang M, Xia J: Curcumin-attenuated trinitrobenzene sulphonic acid induces chronic colitis by inhibiting expression of cyclooxygenase-2. World Journal of Gastroenterology 12, 3848–3853, 2006 [PubMed: 16804969]

115. Gibson PR: Increased gut permeability in Crohn's disease: is TNF the link? Gut 53, 1724–1725, 2004. doi: 10.1136/gut.2004.047092 [PubMed: 15542502]

116. Chun KS, Keum YS, Han SS, Song YS, Kim SH, et al.: Curcumin inhibits phorbol ester-induced expression of cyclooxygenase-2 in mouse skin through suppression of extracellular signal-regulated kinase activity and NF-kappa B activation. Carcinogenesis 24, 1515–1524, 2003. doi: 10.1093/carcin/bgg107 [PubMed: 12844482]

117. Griesser M, Pistis V, Suzuki T, Tejera N, Pratt DA, et al.: Autoxidative and Cyclooxygenase-2 Catalyzed Transformation of the Dietary Chemopreventive Agent Curcumin. Journal of Biological Chemistry 286, 1114–1124, 2011. doi: 10.1074/jbc.M110.178806 [PubMed: 21071447]

118. Yarla NS, Bishayee A, Sethi G, Reddanna P, Kalle AM, et al.: Targeting arachidonic acid pathway by natural products for cancer prevention and therapy. Semin Cancer Biol, 2016. doi: 10.1016/j.semcancer.2016.02.001

119. Hong J, Bose M, Ju J, Ryu JH, Chen X, et al.: Modulation of arachidonic acid metabolism by curcumin and related beta-diketone derivatives: effects on cytosolic phospholipase A(2), cyclooxygenases and 5-lipoxygenase. Carcinogenesis 25, 1671–9, 2004. doi: 10.1093/carcin/bgh165 [PubMed: 15073046]

120. Marin YE, Wall BA, Wang S, Namkoong J, Martino JJ, et al.: Curcumin downregulates the constitutive activity of NF-kappaB and induces apoptosis in novel mouse melanoma cells. Melanoma Res 17, 274–83, 2007. doi: 10.1097/CMR.0b013e3282ed3d0e [PubMed: 17885582]

121. Rajitha B, Nagaraju GP, Shaib WL, Alese OB, Snyder JP, et al.: Novel synthetic curcumin analogs as potent antiangiogenic agents in colorectal cancer. Mol Carcinog, 2016. doi: 10.1002/mc.22492

122. Shishodia S, Potdar P, Gairola CG, Aggarwal BB: Curcumin (diferuloylmethane) down-regulates cigarette smoke-induced NF-kappa B activation through inhibition of I kappa B alpha kinase in human lung epithelial cells: correlation with suppression of COX-2, MMP-9 and cyclin D1. Carcinogenesis 24, 1269–1279, 2003. doi: 10.1093/carcin/bgg078 [PubMed: 12807725]

123. Shrestha S, Zhu J, Wang Q, Du X, Liu F, et al.: Melatonin potentiates the antitumor effect of curcumin by inhibiting IKKbeta/NF-kappaB/COX-2 signaling pathway. Int J Oncol 51, 1249–1260, 2017. doi: 10.3892/ijo.2017.4097 [PubMed: 28849163]

124. Bahadori F, Demiray M: A Realistic View on "The Essential Medicinal Chemistry of Curcumin". ACS Med Chem Lett 8, 893–896, 2017. doi: 10.1021/acsmedchemlett.7b00284 [PubMed: 28947929]

125. Plummer SM, Holloway KA, Manson MM, Munks RJ, Kaptein A, et al.: Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex. Oncogene 18, 6013–20, 1999. doi: 10.1038/sj.onc.1202980 [PubMed: 10557090]

126. Lee CW, Lin CC, Lee IT, Lee HC, Yang CM: Activation and induction of cytosolic phospholipase A2 by TNF-alpha mediated through Nox2, MAPKs, NF-kappaB, and p300 in human tracheal smooth muscle cells. J Cell Physiol 226, 2103–14, 2011. doi: 10.1002/jcp.22537 [PubMed: 21520062]

127. Lee KW, Kim JH, Lee HJ, Surh YJ: Curcumin inhibits phorbol ester-induced up-regulation of cyclooxygenase-2 and matrix metalloproteinase-9 by blocking ERK1/2 phosphorylation and NF-kappaB transcriptional activity in MCF10A human breast epithelial cells. Antioxid Redox Signal 7, 1612–20, 2005. doi: 10.1089/ars.2005.7.1612 [PubMed: 16356124]

128. Guimaraes MR, Leite FR, Spolidorio LC, Kirkwood KL, Rossa C, Jr.: Curcumin abrogates LPS-induced pro-inflammatory cytokines in RAW 264.7 macrophages. Evidence for novel

mechanisms involving SOCS-1, -3 and p38 MAPK. Arch Oral Biol 58, 1309–17, 2013. doi: 10.1016/j.archoralbio.2013.07.005 [PubMed: 24011306]

129. Kang G, Kong PJ, Yuh YJ, Lim SY, Yim SV, et al.: Curcumin suppresses lipopolysaccharide-induced cyclooxygenase-2 expression by inhibiting activator protein 1 and nuclear factor kappab bindings in BV2 microglial cells. J Pharmacol Sci 94, 325–8, 2004 [PubMed: 15037818]
130. Shah VO, Ferguson JE, Hunsaker LA, Deck LM, Vander Jagt DL: Natural products inhibit LPS-induced activation of pro-inflammatory cytokines in peripheral blood mononuclear cells. Nat Prod Res 24, 1177–88, 2010. doi: 10.1080/14786410903112680 [PubMed: 20582811]
131. Cheng SE, Luo SF, Jou MJ, Lin CC, Kou YR, et al.: Cigarette smoke extract induces cytosolic phospholipase A2 expression via NADPH oxidase, MAPKs, AP-1, and NF-kappaB in human tracheal smooth muscle cells. Free Radic Biol Med 46, 948–60, 2009 [PubMed: 19280714]
132. Ferruelo A, de Las Heras MM, Redondo C, Ramon de Fata F, Romero I, et al.: Wine polyphenols exert antineoplasic effect on androgen resistant PC-3 cell line through the inhibition of the transcriptional activity of COX-2 promoter mediated by NF-kbeta. Actas Urol Esp 38, 429–37, 2014. doi: 10.1016/j.acuro.2014.02.017 [PubMed: 24836925]
133. Wang GX, Dai F, Yu K, Jia ZF, Zhang AL, et al.: Resveratrol inhibits glioma cell growth via targeting oncogenic microRNAs and multiple signaling pathways. International Journal of Oncology 46, 1739–1747, 2015. doi: 10.3892/ijo.2015.2863 [PubMed: 25646654]
134. Li C, Tang C, He G: Tristetraprolin: a novel mediator of the anticancer properties of resveratrol. Genet Mol Res 15, 2016. doi: 10.4238/gmr.15027213
135. Harikumar KB, Kunnumakkara AB, Sethi G, Diagaradjane P, Anand P, et al.: Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine in vitro and in orthotopic mouse model of human pancreatic cancer. International Journal of Cancer 127, 257–268, 2010. doi: 10.1002/ijc.25041 [PubMed: 19908231]
136. Serra D, Rufino AT, Mendes AF, Almeida LM, Dinis TCP: Resveratrol Modulates Cytokine-Induced JAK/STAT Activation More Efficiently than 5-Aminosalicylic Acid: An In Vitro Approach. Plos One 9, 2014. doi: ARTN e109048 10.1371/journal.pone.0109048
137. Zykova TA, Zhu F, Zhai XH, Ma WY, Ermakova SP, et al.: Resveratrol directly targets COX-2 to inhibit carcinogenesis. Molecular Carcinogenesis 47, 797–805, 2008. doi: 10.1002/mc.20437 [PubMed: 18381589]
138. Rai G, Mishra S, Suman S, Shukla Y: Resveratrol improves the anticancer effects of doxorubicin in vitro and in vivo models: A mechanistic insight. Phytomedicine 23, 233–42, 2016. doi: 10.1016/j.phymed.2015.12.020 [PubMed: 26969377]
139. Kang OH, Jang HJ, Chae HS, Oh YC, Choi JG, et al.: Anti-inflammatory mechanisms of resveratrol in activated HMC-1 cells: Pivotal roles of NF-kappa B and MAPK. Pharmacological Research 59, 330–337, 2009. doi: 10.1016/j.phrs.2009.01.009 [PubMed: 19416633]
140. Banerjee S, Bueso-Ramos C, Aggarwal BB: Suppression of 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in rats by resveratrol: Role of nuclear factor-kappa B, cyclooxygenase 2, and matrix metalloprotease 9. Cancer Research 62, 4945–4954, 2002 [PubMed: 12208745]
141. Lin HY, Delmas D, Vang O, Hsieh TC, Lin S, et al.: Mechanisms of ceramide-induced COX-2-dependent apoptosis in human ovarian cancer OVCAR-3 cells partially overlapped with resveratrol. J Cell Biochem 114, 1940–54, 2013. doi: 10.1002/jcb.24539 [PubMed: 23495037]
142. Huang CS, Ma WY, Goranson A, Dong ZG: Resveratrol suppresses cell transformation and induces apoptosis through a p53-dependent pathway. Carcinogenesis 20, 237–242, 1999. doi: 10.1093/carcin/20.2.237 [PubMed: 10069459]
143. Lin C, Crawford DR, Lin S, Hwang J, Sebuyira A, et al.: Inducible COX-2-dependent apoptosis in human ovarian cancer cells. Carcinogenesis 32, 19–26, 2011. doi: 10.1093/carcin/bgq212 [PubMed: 21187340]
144. Park SA, Na HK, Surh YJ: Resveratrol suppresses 4-hydroxyestradiol-induced transformation of human breast epithelial cells by blocking I kappa B kinase beta-NF-kappa B signalling. Free Radical Research 46, 1051–1057, 2012. doi: 10.3109/10715762.2012.671940 [PubMed: 22571807]

145. Lin HY, Tang HY, Davis FB, Davis PJ: Resveratrol and apoptosis. Resveratrol and Health 1215, 79–88, 2011. doi: 10.1111/j.1749-6632.2010.05846.x

146. Murakami A, Nakamura Y, Koshimizu K, Takahashi D, Matsumoto K, et al.: FA15, a hydrophobic derivative of ferulic acid, suppresses inflammatory responses and skin tumor promotion: comparison with ferulic acid. Cancer Lett 180, 121–9, 2002. doi: S0304383501008588 [pii] [PubMed: 12175542]

147. Hirata A, Murakami Y, Atsumi T, Shoji M, Ogiwara T, et al.: Ferulic acid dimer inhibits lipopolysaccharide-stimulated cyclooxygenase-2 expression in macrophages. In Vivo 19, 849–853, 2005 [PubMed: 16097437]

148. Chung CP, Hsu HY, Huang DW, Hsu HH, Lin JT, et al.: Ethyl Acetate Fraction of Adlay Bran Ethanolic Extract Inhibits Oncogene Expression and Suppresses DMH-Induced Preneoplastic Lesions of the Colon in F344 Rats through an Anti-inflammatory Pathway. Journal of Agricultural and Food Chemistry 58, 7616–7623, 2010. doi: 10.1021/jf101084e [PubMed: 20536243]

149. Jayaprakasam B, Vanisree M, Zhang YJ, Dewitt DL, Nair MG: Impact of alkyl esters of caffeic and ferulic acids on tumor cell proliferation, cyclooxygenase enzyme, and lipid peroxidation. Journal of Agricultural and Food Chemistry 54, 5375–5381, 2006. doi: 10.1021/jf060899p [PubMed: 16848520]

150. Das U, Manna K, Sinha M, Datta S, Das DK, et al.: Role of Ferulic Acid in the Amelioration of Ionizing Radiation Induced Inflammation: A Murine Model. Plos One 9, 2014. doi: ARTN e97599 10.1371/journal.pone.0097599

151. Shindo Y, Witt E, Han D, Epstein W, Packer L: Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. J Invest Dermatol 102, 122–4, 1994 [PubMed: 8288904]

152. Nishikimi M, Fukuyama R, Minoshima S, Shimizu N, Yagi K: Cloning and Chromosomal Mapping of the Human Nonfunctional Gene for L-Gulono-Gamma-Lactone Oxidase, the Enzyme for L-Ascorbic-Acid Biosynthesis Missing in Man. Journal of Biological Chemistry 269, 13685–13688, 1994 [PubMed: 8175804]

153. Thiele JJ: Oxidative targets in the stratum corneum. Skin Pharmacology and Applied Skin Physiology 14, 87–91, 2001. doi: 10.1159/000056395

154. Pinnell SR, Yang H, Omar M, Monteiro-Riviere N, DeBuys HV, et al.: Topical L-ascorbic acid: percutaneous absorption studies. Dermatol Surg 27, 137–42, 2001 [PubMed: 11207686]

155. Zielinski JE, Pinnell S. Stabilized ascorbic acid compositions and methods thereof, 2004.

156. Lin JY, Selim MA, Shea CR, Grichnik JM, Omar MM, et al.: UV photoprotection by combination topical antioxidants vitamin C and vitamin E. J Am Acad Dermatol 48, 866–74, 2003. doi: 10.1067/mjd.2003.425 [PubMed: 12789176]

157. Fajardo AM, Piazza GA: Chemoprevention in gastrointestinal physiology and disease. Anti-inflammatory approaches for colorectal cancer chemoprevention. Am J Physiol Gastrointest Liver Physiol 309, G59–70, 2015. doi: 10.1152/ajpgi.00101.2014 [PubMed: 26021807]

158. Romagnolo DF, Selmin OI: Flavonoids and cancer prevention: a review of the evidence. J Nutr Gerontol Geriatr 31, 206–38, 2012. doi: 10.1080/21551197.2012.702534 [PubMed: 22888839]

159. Chung MY, Mah E, Masterjohn C, Noh SK, Park HJ, et al.: Green Tea Lowers Hepatic COX-2 and Prostaglandin E2 in Rats with Dietary Fat-Induced Nonalcoholic Steatohepatitis. J Med Food 18, 648–55, 2015. doi: 10.1089/jmf.2014.0048 [PubMed: 25453513]

160. Shirakami Y, Shimizu M, Tsurumi H, Hara Y, Tanaka T, et al.: EGCG and Polyphenon E attenuate inflammation-related mouse colon carcinogenesis induced by AOM plus DDS. Mol Med Rep 1, 355–61, 2008 [PubMed: 21479417]

161. Park IJ, Lee YK, Hwang JT, Kwon DY, Ha J, et al.: Green tea catechin controls apoptosis in colon cancer cells by attenuation of H2O2-stimulated COX-2 expression via the AMPK signaling pathway at low-dose H2O2. Ann N Y Acad Sci 1171, 538–44, 2009. doi: 10.1111/j.1749-6632.2009.04698.x [PubMed: 19723101]

162. Singh T, Katiyar SK: Green Tea Catechins Reduce Invasive Potential of Human Melanoma Cells by Targeting COX-2, PGE(2) Receptors and Epithelial-to-Mesenchymal Transition. Plos One 6, 2011. doi: ARTN e25224 10.1371/journal.pone.0025224

163. Shi J, Liu F, Zhang W, Liu X, Lin B, et al.: Epigallocatechin-3-gallate inhibits nicotine-induced migration and invasion by the suppression of angiogenesis and epithelial-mesenchymal transition in non-small cell lung cancer cells. Oncol Rep 33, 2972–80, 2015. doi: 10.3892/or.2015.3889 [PubMed: 25845434]

164. Kilic U, Sahin K, Tuzcu M, Basak N, Orhan C, et al.: Enhancement of Cisplatin sensitivity in human cervical cancer: epigallocatechin-3-gallate. Front Nutr 1, 28, 2014. doi: 10.3389/fnut.2014.00028 [PubMed: 25988128]

165. Ye F, Zhang GH, Guan BX, Xu XC: Suppression of esophageal cancer cell growth using curcumin, (-)-epigallocatechin-3-gallate and lovastatin. World Journal of Gastroenterology 18, 126–135, 2012. doi: 10.3748/wjg.v18.i2.126 [PubMed: 22253518]

166. Hwang JT, Ha J, Park IJ, Lee SK, Baik HW, et al.: Apoptotic effect of EGCG in HT-29 colon cancer cells via AMPK signal pathway. Cancer Lett 247, 115–21, 2007. doi: 10.1016/j.canlet.2006.03.030 [PubMed: 16797120]

167. Singh T, Katiyar SK: Green tea polyphenol, (-)-epigallocatechin-3-gallate, induces toxicity in human skin cancer cells by targeting beta-catenin signaling. Toxicology and Applied Pharmacology 273, 418–424, 2013. doi: 10.1016/j.taap.2013.09.021 [PubMed: 24096034]

168. Peng G, Dixon DA, Muga SJ, Smith TJ, Wargovich MJ: Green tea polyphenol (-)-epigallocatechin-3-gallate inhibits cyclooxygenase-2 expression in colon carcinogenesis. Mol Carcinog 45, 309–19, 2006. doi: 10.1002/mc.20166 [PubMed: 16508969]

169. Kim SY, Ahn BH, Min KJ, Lee YH, Joe EH, et al.: Phospholipase D isozymes mediate epigallocatechin gallate-induced cyclooxygenase-2 expression in astrocyte cells. J Biol Chem 279, 38125–33, 2004. doi: 10.1074/jbc.M402085200 [PubMed: 15210717]

170. Raja SB, Rajendiran V, Kasinathan NK, P A, Venkatabalasubramanian S, et al.: Differential cytotoxic activity of Quercetin on colonic cancer cells depends on ROS generation through COX-2 expression. Food Chem Toxicol 106, 92–106, 2017. doi: 10.1016/j.fct.2017.05.006 [PubMed: 28479391]

171. Al-Fayez M, Cai H, Tunstall R, Steward WP, Gescher AJ: Differential modulation of cyclooxygenase-mediated prostaglandin production by the putative cancer chemopreventive flavonoids tricin, apigenin and quercetin. Cancer Chemother Pharmacol 58, 816–25, 2006. doi: 10.1007/s00280-006-0228-3 [PubMed: 16552572]

172. Granado-Serrano AB, Martin MA, Bravo L, Goya L, Ramos S: Quercetin Attenuates TNF-Induced Inflammation in Hepatic Cells by Inhibiting the NF-kappa B Pathway. Nutrition and Cancer-an International Journal 64, 588–598, 2012. doi: 10.1080/01635581.2012.661513

173. Han MY, Song YC, Zhang XD: Quercetin Suppresses the Migration and Invasion in Human Colon Cancer Caco-2 Cells Through Regulating Toll-like Receptor 4/Nuclear Factor-kappa B Pathway. Pharmacognosy Magazine 12, S237–S244, 2016. doi: 10.4103/0973-1296.182154 [PubMed: 27279714]

174. Ma JQ, Li Z, Xie WR, Liu CM, Liu SS: Quercetin protects mouse liver against CCl4-induced inflammation by the TLR2/4 and MAPK/NF-kappa B pathway. International Immunopharmacology 28, 531–539, 2015. doi: 10.1016/j.intimp.2015.06.036 [PubMed: 26218279]

175. Kim SH, Park JG, Hong YD, Kim E, Baik KS, et al.: Src/Syk/IRAK1-targeted anti-inflammatory action of Torreya nucifera butanol fraction in lipopolysaccharide-activated RAW264.7 cells. J Ethnopharmacol 188, 167–76, 2016. doi: 10.1016/j.jep.2016.05.008 [PubMed: 27178629]

176. Jones DJL, Lamb JH, Verschoyle RD, Howells LM, Butterworth M, et al.: Characterisation of metabolites of the putative cancer chemopreventive agent quercetin and their effect on cyclo-oxygenase activity. British Journal of Cancer 91, 1213–1219, 2004. doi: 10.1038/sj.bjc.6602091 [PubMed: 15292928]

177. Lai WW, Hsu SC, Chueh FS, Chen YY, Yang JS, et al.: Quercetin Inhibits Migration and Invasion of SAS Human Oral Cancer Cells through Inhibition of NF-kappa B and Matrix Metalloproteinase-2/-9 Signaling Pathways. Anticancer Research 33, 1941–1950, 2013 [PubMed: 23645742]

178. Senthilkumar K, Arunkumar R, Elumalai P, Sharmila G, Gunadharini DN, et al.: Quercetin inhibits invasion, migration and signalling molecules involved in cell survival and proliferation of

prostate cancer cell line (PC-3). Cell Biochemistry and Function 29, 87–95, 2011. doi: 10.1002/cbf.1725 [PubMed: 21308698]

179. Cheong E, Ivory K, Doleman J, Parker ML, Rhodes M, et al.: Synthetic and naturally occurring COX-2 inhibitors suppress proliferation in a human oesophageal adenocarcinoma cell line (OE33) by inducing apoptosis and cell cycle arrest. Carcinogenesis 25, 1945–1952, 2004. doi: 10.1093/carcin/bgh184 [PubMed: 15155531]
180. Xiao XS, Shi DB, Liu LQ, Wang JS, Xie XM, et al.: Quercetin Suppresses Cyclooxygenase-2 Expression and Angiogenesis through Inactivation of P300 Signaling. Plos One 6, 2011. doi: ARTN e22934 10.1371/journal.pone.0022934
181. Maurya AK, Vinayak M: Anticarcinogenic action of quercetin by downregulation of phosphatidylinositol 3-kinase (PI3K) and protein kinase C (PKC) via induction of p53 in hepatocellular carcinoma (HepG2) cell line. Mol Biol Rep 42, 1419–29, 2015. doi: 10.1007/s11033-015-3921-7 [PubMed: 26311153]
182. Lee KM, Hwang MK, Lee DE, Lee KW, Lee HJ: Protective Effect of Quercetin against Arsenite-Induced COX-2 Expression by Targeting PI3K in Rat Liver Epithelial Cells. Journal of Agricultural and Food Chemistry 58, 5815–5820, 2010. doi: 10.1021/jf903698s [PubMed: 20377179]
183. Zhu X, Zeng X, Zhang X, Cao W, Wang Y, et al.: The effects of quercetin-loaded PLGA-TPGS nanoparticles on ultraviolet B-induced skin damages in vivo. Nanomedicine 12, 623–32, 2016. doi: 10.1016/j.nano.2015.10.016 [PubMed: 26656634]
184. Lee YK, Park SY, Kim YM, Lee WS, Park OJ: AMP kinase/cyclooxygenase-2 pathway regulates proliferation and apoptosis of cancer cells treated with quercetin. Experimental and Molecular Medicine 41, 201–207, 2009. doi: 10.3858/emm.2009.41.3.023 [PubMed: 19293639]
185. Lau TY, Leung LK: Soya isoflavones suppress phorbol 12-myristate 13-acetate-induced COX-2 expression in MCF-7 cells. British Journal of Nutrition 96, 169–176, 2006. doi: 10.1079/Bjn20061639 [PubMed: 16870006]
186. Shon YH, Park SD, Nam KS: Effective chemopreventive activity of genistein against human breast cancer cells. J Biochem Mol Biol 39, 448–51, 2006 [PubMed: 16889690]
187. Chung MH, Kim DH, Na HK, Kim JH, Kim HN, et al.: Genistein inhibits phorbol ester-induced NF-kappaB transcriptional activity and COX-2 expression by blocking the phosphorylation of p65/RelA in human mammary epithelial cells. Mutat Res 768, 74–83, 2014. doi: 10.1016/j.mrfmmm.2014.04.003 [PubMed: 24742714]
188. Li YS, Wu LP, Li KH, Liu YP, Xiang R, et al.: Involvement of nuclear factor kappaB (NF-kappaB) in the downregulation of cyclooxygenase-2 (COX-2) by genistein in gastric cancer cells. J Int Med Res 39, 2141–50, 2011 [PubMed: 22289529]
189. Dai W, Wang F, He L, Lin C, Wu S, et al.: Genistein inhibits hepatocellular carcinoma cell migration by reversing the epithelial-mesenchymal transition: partial mediation by the transcription factor NFAT1. Mol Carcinog 54, 301–11, 2015. doi: 10.1002/mc.22100 [PubMed: 24243709]
190. Sarkar D, Saha P, Gamre S, Bhattacharjee S, Hariharan C, et al.: Anti-inflammatory effect of allylpyrocatechol in LPS-induced macrophages is mediated by suppression of iNOS and COX-2 via the NF-kappa B pathway. International Immunopharmacology 8, 1264–1271, 2008. doi: 10.1016/j.intimp.2008.05.003 [PubMed: 18602073]
191. Hwang JT, Ha J, Park OJ: Combination of 5-fluorouracil and genistein induces apoptosis synergistically in chemo-resistant cancer cells through the modulation of AMPK and COX-2 signaling pathways. Biochemical and Biophysical Research Communications 332, 433–440, 2005. doi: 10.1016/j.bbrc.2005.04.143 [PubMed: 15896711]
192. Zhou JM, Ibrahim RK: Tricin-a potential multifunctional nutraceutical. Phytochemistry Reviews 9, 413–424, 2010. doi: 10.1007/s11101-009-9161-5
193. Hudson EA, Dinh PA, Kokubun T, Simmonds MSJ, Gescher A: Characterization of potentially chemopreventive phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells. Cancer Epidemiology Biomarkers & Prevention 9, 1163–1170, 2000
194. Cai H, Al-Fayez M, Tunstall RG, Platton S, Greaves P, et al.: The rice bran constituent tricin potently inhibits cyclooxygenase enzymes and interferes with intestinal carcinogenesis in

ApcMin mice. Mol Cancer Ther 4, 1287–92, 2005. doi: 4/9/1287 [pii] 10.1158/1535-7163.MCT-05-0165 [PubMed: 16170019]

195. Kim KM, Kim YS, Lim JY, Min SJ, Ko HC, et al.: Intestinal anti-inflammatory activity of Sasa quelpaertensis leaf extract by suppressing lipopolysaccharide-stimulated inflammatory mediators in intestinal epithelial Caco-2 cells co-cultured with RAW 264.7 macrophage cells. Nutrition Research and Practice 9, 3–10, 2015. doi: 10.4162/nrp.2015.9.1.3 [PubMed: 25671061]
196. Shalini V, Pushpan CK, Sindhu G, Jayalekshmy A, Helen A: Tricin, flavonoid from Njavara reduces inflammatory responses in hPBMCs by modulating the p38MAPK and PI3K/Akt pathways and prevents inflammation associated endothelial dysfunction in HUVECs. Immunobiology 221, 137–144, 2016. doi: 10.1016/j.imbio.2015.09.016 [PubMed: 26514297]
197. Shalini V, Pushpan CK, G S, A J, A H: Tricin, flavonoid from Njavara reduces inflammatory responses in hPBMCs by modulating the p38MAPK and PI3K/Akt pathways and prevents inflammation associated endothelial dysfunction in HUVECs. Immunobiology 221, 137–44, 2016. doi: 10.1016/j.imbio.2015.09.016 [PubMed: 26514297]
198. Shalini V, Jayalekshmi A, Helen A: Mechanism of anti-inflammatory effect of tricin, a flavonoid isolated from Njavara rice bran in LPS induced hPBMCs and carrageenan induced rats. Molecular Immunology 66, 229–239, 2015. doi: 10.1016/j.molimm.2015.03.004 [PubMed: 25839778]
199. Willenberg I, Meschede AK, Gueler F, Jang MS, Shushakova N, et al.: Food Polyphenols Fail to Cause a Biologically Relevant Reduction of COX-2 Activity. Plos One 10, 2015. doi: ARTN e0139147 10.1371/journal.pone.0139147
200. Calder PC: Long-chain n-3 fatty acids and inflammation: potential application in surgical and trauma patients. Braz J Med Biol Res 36, 433–46, 2003 [PubMed: 12700820]
201. Calder PC: Long-chain fatty acids and inflammation. Proc Nutr Soc 71, 284–9, 2012. doi: 10.1017/S0029665112000067 [PubMed: 22369781]
202. Lee JY, Sohn KH, Rhee SH, Hwang D: Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. Journal of Biological Chemistry 276, 16683–16689, 2001. doi: 10.1074/jbc.M011695200 [PubMed: 11278967]
203. Han YM, Jeong M, Park JM, Kim MY, Go EJ, et al.: The omega-3 polyunsaturated fatty acids prevented colitis-associated carcinogenesis through blocking dissociation of beta-catenin complex, inhibiting COX-2 through repressing NF-kappaB, and inducing 15-prostaglandin dehydrogenase. Oncotarget 7, 63583–63595, 2016. doi: 10.18632/oncotarget.11544 [PubMed: 27566583]
204. Vara-Messler M, Buccellati C, Pustina L, Folco G, Rovati GE, et al.: A potential role of PUFAs and COXIBs in cancer chemoprevention. Prostaglandins & Other Lipid Mediators 120, 97–102, 2015. doi: 10.1016/j.prostaglandins.2015.04.003 [PubMed: 25908304]
205. Camuesco D, Comalada M, Concha A, Nieto A, Sierra S, et al.: Intestinal anti-inflammatory activity of combined quercitrin and dietary olive oil supplemented with fish oil, rich in EPA and DHA (n-3) polyunsaturated fatty acids, in rats with DSS-induced colitis. Clin Nutr 25, 466–76, 2006. doi: S0261-5614(06)00003-3 [pii] 10.1016/j.clnu.2005.12.009 [PubMed: 16698151]
206. Camuesco D, Galvez J, Nieto A, Comalada M, Rodriguez-Cabezas ME, et al.: Dietary olive oil supplemented with fish oil, rich in EPA and DHA (n-3) polyunsaturated fatty acids, attenuates colonic inflammation in rats with DSS-induced colitis. J Nutr 135, 687–94, 2005 doi: 135/4/687 [pii] [PubMed: 15795419]
207. Zhang C, Yu H, Ni X, Shen S, Das UN: Growth inhibitory effect of polyunsaturated fatty acids (PUFAs) on colon cancer cells via their growth inhibitory metabolites and fatty acid composition changes. PLoS One 10, e0123256, 2015. doi: 10.1371/journal.pone.0123256 [PubMed: 25886460]
208. Fini L, Piazzi G, Ceccarelli C, Daoud Y, Belluzzi A, et al.: Highly Purified Eicosapentaenoic Acid as Free Fatty Acids Strongly Suppresses Polyps in Apc(Min/+) Mice. Clinical Cancer Research 16, 5703–5711, 2010. doi: 10.1158/1078-0432.Ccr-10-1990 [PubMed: 21030497]
209. Fradet V, Cheng I, Casey G, Witte JS: Dietary omega-3 fatty acids, cyclooxygenase-2 genetic variation, and aggressive prostate cancer risk. Clin Cancer Res 15, 2559–66, 2009. doi: 10.1158/1078-0432.CCR-08-2503 [PubMed: 19318492]

210. Vara-Messler M, Pasqualini ME, Comba A, Silva R, Buccellati C, et al.: Increased dietary levels of alpha-linoleic acid inhibit mammary tumor growth and metastasis. Eur J Nutr 56, 509–519, 2017. doi: 10.1007/s00394-015-1096-6 [PubMed: 26582578]

211. Vecchini A, Ceccarelli V, Susta F, Caligiana P, Orvietani P, et al.: Dietary alpha-linolenic acid reduces COX-2 expression and induces apoptosis of hepatoma cells. J Lipid Res 45, 308–16, 2004. doi: 10.1194/jlr.M300396-JLR200 M300396-JLR200 [pii] [PubMed: 14563831]

212. Schiessel DL, Yamazaki RK, Kryczyk M, Coelho I, Yamaguchi AA, et al.: alpha-Linolenic Fatty Acid Supplementation Decreases Tumor Growth and Cachexia Parameters in Walker 256 Tumor-Bearing Rats. Nutr Cancer 67, 839–46, 2015. doi: 10.1080/01635581.2015.1043021 [PubMed: 26011096]

213. Gullett NP, Ruhul Amin AR, Bayraktar S, Pezzuto JM, Shin DM, et al.: Cancer prevention with natural compounds. Semin Oncol 37, 258–81, 2010. doi: 10.1053/j.seminoncol.2010.06.014 [PubMed: 20709209]

214. Mencher SK, Wang LG: Promiscuous drugs compared to selective drugs (promiscuity can be a virtue). BMC Clin Pharmacol 5, 3, 2005. doi: 10.1186/1472-6904-5-3 [PubMed: 15854222]

215. Riboli E, Norat T: Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am J Clin Nutr 78, 559S–569S, 2003 [PubMed: 12936950]

216. Eikenberry N, Smith C: Healthful eating: perceptions, motivations, barriers, and promoters in low-income Minnesota communities. J Am Diet Assoc 104, 1158–61, 2004. doi: 10.1016/j.jada.2004.04.023 [PubMed: 15215777]

217. Cox BD, Whichelow MJ, Prevost AT: Seasonal consumption of salad vegetables and fresh fruit in relation to the development of cardiovascular disease and cancer. Public Health Nutr 3, 19–29, 2000 [PubMed: 10786720]

218. van't Veer P, Jansen MC, Klerk M, Kok FJ: Fruits and vegetables in the prevention of cancer and cardiovascular disease. Public Health Nutr 3, 103–7, 2000 [PubMed: 10786730]

219. Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, et al.: Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. Lancet 361, 1496–1501, 2003. doi: 10.1016/S0140-6736(03)13174-1 [PubMed: 12737858]

220. Sandoval M, Font R, Manos M, Dicenta M, Quintana MJ, et al.: The role of vegetable and fruit consumption on survival and other habits following the diagnosis of oral cancer: a prospective study in Spain. International Journal of Oral and Maxillofacial Surgery 38, 31–39, 2009. doi: 10.1016/j.ijom.2008.09.004 [PubMed: 18951763]

221. Pavia M, Pileggi C, Nobile CGA, Angelillo IF: Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. American Journal of Clinical Nutrition 83, 1126–1134, 2006 [PubMed: 16685056]

222. Michels KB, Giovannucci E, Chan AT, Singhania R, Fuchs CS, et al.: Fruit and vegetable consumption and colorectal adenomas in the nurses' health study. Cancer Research 66, 3942–3953, 2006. doi: 10.1158/0008-5472.Can-05-3637 [PubMed: 16585224]

223. Malongane F, McGaw LJ, Mudau FN: The synergistic potential of various teas, herbs and therapeutic drugs in health improvement: a review. J Sci Food Agric, 2017. doi: 10.1002/jsfa.8472

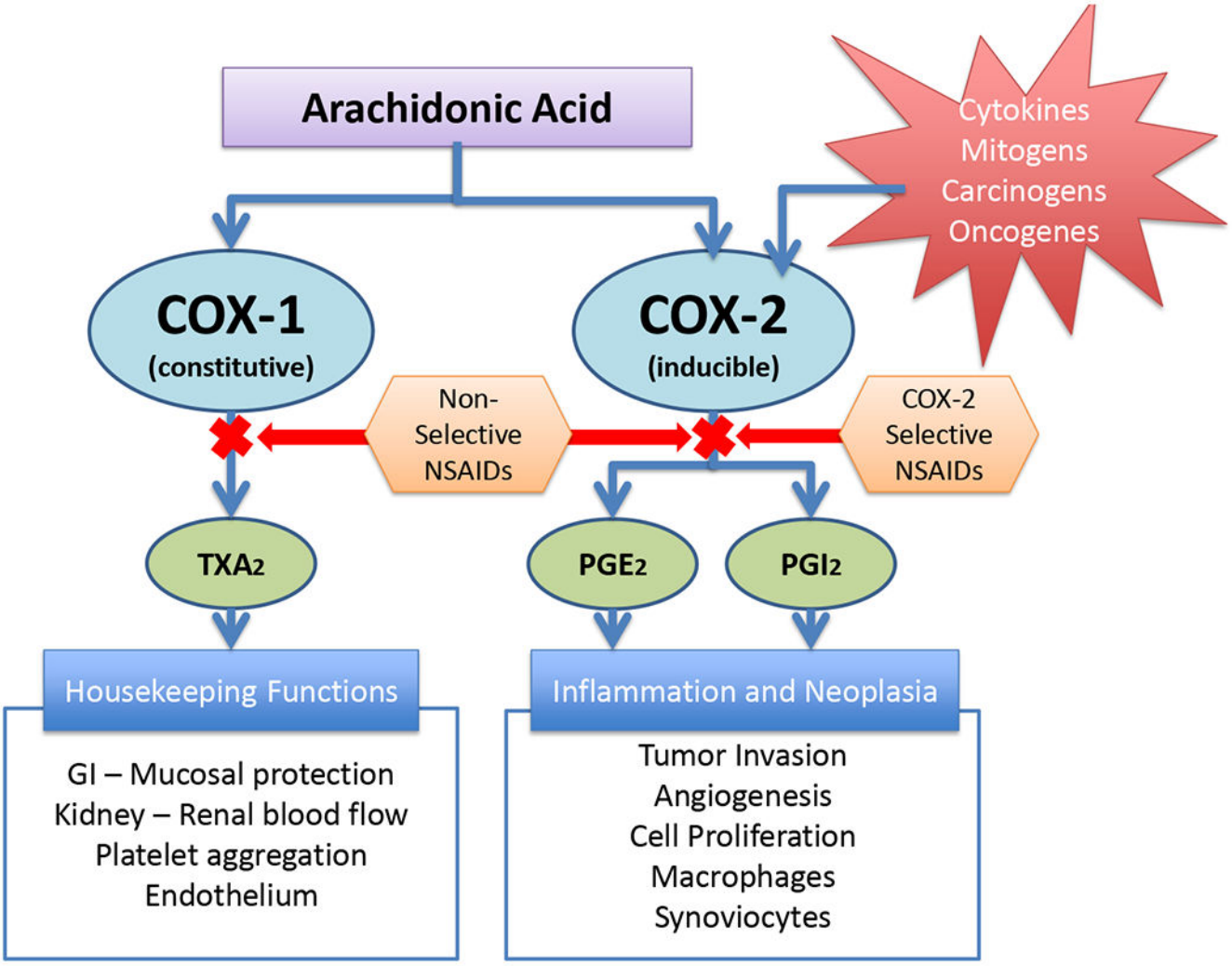

Figure 1:
A model for COX biosynthesis and function. COX-1: cyclooxygenase-1; COX-2: cyclooxygenase 2; TXA2: thromboxane A2; PGE2: prostaglandin E2; PGI2: prostaglandin I2 (prostacyclin); GI: gastrointestinal.

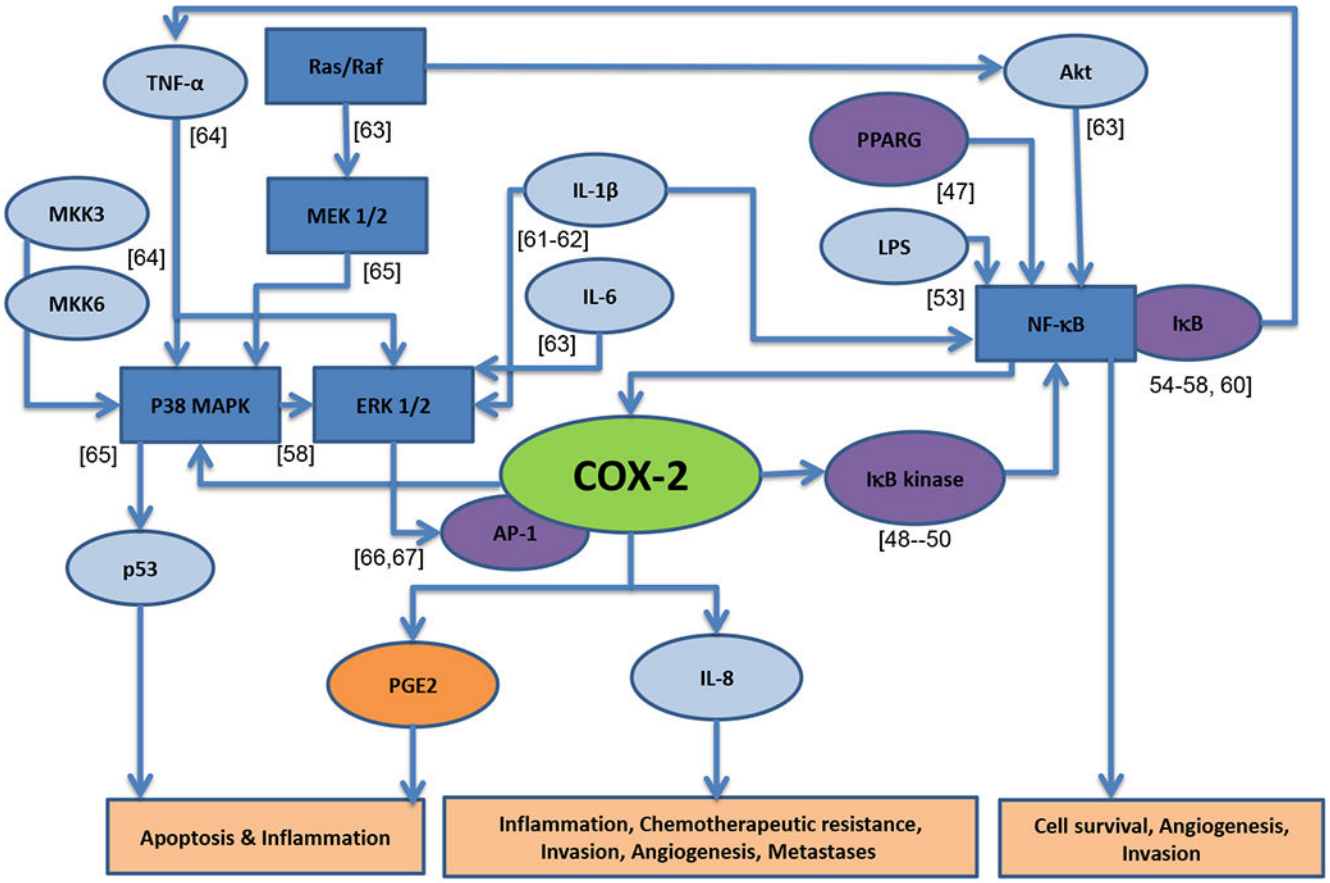

Figure 2: Model of COX-2: induction by proinflammatory cytokines, stimulation of cell proliferation, increase of metastatic potential, and effect on apoptosis and inflammation.

Akt: protein kinase B; AP-1: activator protein-1; COX-2: cyclooxygenase-2; ERK 1/2: extracellular signal–regulated kinases 1/2; IκB: inhibitor of κB (kinase); IL: interleukin; LPS: lipopolysaccharideMEK 1/2: mitogen activated protein kinase kinase 1/2; MKK3 (6): mitogen-activated protein kinase kinase 3 (6); NF-kB: nuclear factor-κB (kinase); P38 MAPK: P38 mitogen-activated protein kinases; p53: p53 oncogene; PGE2: prostaglandin E2; PPARG: Peroxisome proliferator-activated receptor-γ; ; Ras/Raf: mitogen-activated protein kinase (MAPK) cascade; TNF-α: tumor necrosis factor-α;

= key signaling protein as it pertains to target protein

= target protein

= key transcription regulatory proteins of signaling protein

= prostaglandins

= cytokines and inflammatory proteins

= physiological effect

TABLE 1:

Phytonutrients shown to modulate COX-2 Commonly Present in Human Diet

Phytonutrients	Main Compounds used in CAM	Major plant food sources
Carotenoid	β-carotene	Spices (Paprika, Cayenne, Chili), Sweet Potato (Baked), Dark Green Leafy Vegetables (Spinach, Cooked), Kale (Frozen, Cooked), Carrots (Cooked), Cos or Romaine Lettuce
	Astaxanthin	Red-pigmented vegetables and fruits such as Carrots, Red peppers, Radishes, Mangoes Blueberries Cranberry and in Green Algae
	Lutein	Leafy greens like spinach, kale, Lettuce, Basil, Squash, Broccoli, Brussels Sprouts, Leek, Asparagus, Green peas
	Lycopene	Guavas, Watermelon, Tomatoes (cooked), Papaya, Grapefruit, Sweet Red Peppers (Cooked)
Phenolic compound	Curcumin	Turmeric (ingredient in curry powders)
	Resveratrol	Red Grapes, Berries, Peanuts
	Ferulic acid	Coffee, spinach, asparagus, carrots tomato, whole Grains apples, pears, pineapples, citric fruits, dry dates, cabbage, olive, peanuts.
Flavonoid	Epigallocatechin gallate (EGCG)	White, Green and Black Teas, Carob Flour, Apple skin, Onion, Pecans Filberts or Hazelnuts, raw cranberries and pistachios
	Quercetin	Capers, Lovage leaves, Red onion, Berries, Leafy green veggies, including spinach, kale,Apples, Red grapes, Peppers. Dark cherries and berries (blueberries, bilberries, blackberries and others), Tomatoes, Cruciferous veggies, including broccoli, cabbage and sprouts Citrus fruits
	Genistein	Lupin, fava beans, soybeans, kudzu, and psoralea and in in the medicinal plants, Flemingia vestita and F. macrophylla, and coffee
	Tricin	Cereal grains, such as wheat, rice, barley, oat and maize and also a bamboo,
Fatty acids	Polyunsaturated fatty acids (PUFAS)	Walnuts, Sunflower seeds, Flax seeds. Flax oil, Corn oil Soybean oil, Safflower oil
	Alpha-linoleic acid (ALA)	Flaxseeds, flaxseed oil, Canola (rapeseed) oil, Soybeans and soybean oil, Pumpkin seeds and pumpkin seed oil, Perilla seed oil, Tofu, Walnuts and walnut oil