Cancer and Inflammation: The emerging role of botanical compounds in targeting proinflammatory pathways, with particular attention to the NF-κB signaling pathway

By Donald Yance

All chronic conditions such as cardiovascular disease and cancer have a strong and persistent link with chronic inflammation. Inflammation promotes the production of free radicals, which is a contributing factor to the onset of cancer.[1,2]

Although inflammation is an essential response to injury or infection, chronic inflammation is harmful and causes tissue damage. Cancer and inflammation come together from both sides; inflammation causes and promotes cancer, and cancer ("Cancer Energy") creates inflammation. In fact, cancer cells play an active part in stimulating bone marrow-derived cells (BMDCs) to create a microenvironment—the "pre-metastatic niche"—that is favorable for growth and metastasis. One of the primary ways they are able to do this is by upregulating inflammatory pathways. The ability of metastatic cancer cells to stimulate production of interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNFa) is central to this process.[3,4]

Cancer cells are genetically diverse, evolving, and becoming "smarter". They contain a range of mutations, which include both "drivers" that actively promote cancer and "passengers" that may not confer a selective advantage to a growing tumor, but are nonetheless commonly found either assisting the driver(s), or resulting because they happen to be with the driver(s).[5]

One such driver is the transcription protein, **Nuclear Factor-kappa Beta (NF-κB),** a major inducer of inflammation, as well as multiple other pathways to cancer development, growth, invasion, and resistance. Botanicals and their active compounds are effective "multi-taskers" that can suppress chronic inflammation, perhaps specifically suppressing one pathway, but most likely by regulating and gently moving multiple pathways—both drivers and passengers. For example, in cancer, often a mutation in the tumor suppressor gene, **PTEN** (phosphatase and tensin homologue), is the likely driver that activates NF-κB.[6,7]

The multi-factorial mechanistic nature of cancer calls for the development of multifunctional therapeutic tools, i.e., combining the structural features of a single compound that blocks Epidermal Growth Factor Receptor (EGFR), determined from pathology tests that include EGFR, KRAS, BRAFF, and the tumor suppressor gene, **PTEN**, with a combination of plant extracts and plant compounds to enable interaction with multiple altered pathogenetic pathways.

Phytocompounds that enhance PTEN expression and/or inhibit PTEN mutation include quercetin, resveratrol, and various **isoflavones,** often referred to as phytoestrogens.[8,9,10]

An ever-growing body of evidence is pointing to and validating that the mediation and inhibition of NF-κB and its companion effectors including PTEN mutations and upstream pathways, including COX-2, suggest plant-based medicines and their active compounds can and should play an important role in cancer prevention and treatment protocols.

A new horizon in chemoprevention research is the recent discovery of molecular links

between inflammation and cancer. Components of the cell-signaling network, especially those that converge on the redox-sensitive transcription factor, NF-κB, have been implicated in the pathogenesis of many inflammation-associated disorders.

How to use and integrate this information into clinical practice

Within the Eclectic Triphastic Medical System (ETMS) targeting such pathways with phytonutrients often involves the use of super-concentrates and falls under Branch III of the ETMS. Branch III assesses and targets the biological terrain in terms of the modern scientific understanding of the molecular biology of cancer, as well as the pharmacological influences of natural compounds on cancer at the molecular and genomic level. At the same time, it recognizes that the cancer energy (tumor) interacts with and affects both the individual (Branch I) and their relationship to their environment (Branch II). This "hybrid" interactive characterization of Branch III as biological terrain is therefore much more than the interface of molecular biology of plants and of cancer at a molecular level, it is also simultaneously a redefinition of traditional herbal medicine and a methodology for refining the botanical elements in oncology protocols. It is the driving force of ETMS therapeutics in clinical practice. This revisiting of herbal medicine is unique to the ETMS and makes it possible to incorporate botanicals seamlessly and synergistically with modern oncology in precise, scientifically-guided, but until now largely unexplored ways.

Dietary Medicine: a potent way to modulate inflammation

The first step to reducing systemic inflammation is to implement a diet that encourages optimal health, creating an internal environment, or terrain, that mediates inflammation and/or stabilizes gene behavior. In the implementation of the ETMS, the goal regarding diet is to outline and balance it out for individuals based on these areas: geographic location, season, energetic type (deficiency/excess, Yin/Yang, organ systems weakness, etc.), traditional diet (ethnic background, taste preferences), chronic and/or acute condition(s) or disease, nutrigenomics (diet-gene interaction), lifestyle (work/exercise), and environmental influences (toxic exposure).

Nutrigenomics

Until recently, nutrition research concentrated on nutrient deficiencies and impairment of health. The advent of genomics—scientific information about the composition and functions of genomes—has created unprecedented opportunities for increasing our understanding of how nutrients modulate gene and protein expression, and ultimately influence cellular and organismal metabolism. The diverse tissue and organ-specific effects of bioactive dietary components include gene-expression patterns (transcription); organization of the chromatin (epigenome); protein-expression patterns, including posttranslational modifications (proteome); as well as metabolite profiles (metabolome).[11]

Nutrigenomics is the application of the science of genomics to study diet-gene interactions in and identify dietetic components' beneficial or detrimental health effects.[12] Human diets of plant origin contain many hundreds of compounds which cannot be considered nutrients, but appear to play a role in the maintenance of health. Nutrigenomics also examines the effects of specific

dietary chemicals, often called phytonutrients, and/or nutraceuticals. In some cases where the disease process is at least partially understood, elements of protection can be related to a single compound or structurally related group of compounds in the diet. Some of the bioactive components of food, spices, and beverages of special interest include the following groups: polyphenols, phytoestrogens, saponins, terpenoids, isothiocyanates, phytosterols, phytates, and omega-3 fatty acids.[13]

Phytonutrients as pleotrophic cancer suppressing agents

As research is expanding that links cancer initiation, promotion, progression, angiogenesis, and metastasis to inflammatory events, a key new approach to cancer within Branch III of the ETMS is the modulation of the inflammatory cascade using botanical medicine. A wide variety of chemopreventive and chemoprotective phytonutrients, or whole plant extracts, can alter or correct undesired cellular functions/responses caused by abnormal proinflammatory signal transmissions, many of which are mediated by NF-κB. These same natural agents are capable of modulating both lipoxygenase (LOX) and cyclooxygenase (COX), and can significantly advance the efficacy of cancer therapy and prevention.[14]

These phytonutrients act as pleotrophic cancer suppressing agents, being able to produce multiple beneficial, synergistic effects to both suppress cancer and enhance and instill efficient cell behavior. Modulation of cellular signaling with concentrated phytonutrients targets chronic inflammatory responses, hence providing a rational and pragmatic strategy in molecular target-based chemoprevention, cell-protection, and cancer treatment. Many of these same compounds also are capable of inducing phase-2 detoxifying or antioxidant genes, representing yet another important cellular defense in response to oxidative and electrophilic insults, as well as inflammation. Many redox-allostatic-regulating phytonutrients derived from dietary (often common spices or teas) and medicinal plants, such as medicinal mushrooms, have been found to activate this particular redox-sensitive transcription factor, thereby potentiating the cellular antioxidant or detoxification capacity.[15]

Nutrigenomics is giving us an increased understanding of how nutrition and botanical medicine influence metabolic pathways and homeostatic/allostatic impact, how this regulation is disturbed in the early phases of diet-related cancers, and the extent to which specific genotypes contribute to cancer. The food we consume can either turn on cancer-related genes or turn them off. Certain phytonutrients found in large doses in particular foods can also maintain genes that inhibit cancer and other diseases that often go awry as we age. Nutrigenomics will lead to evidence-based dietary intervention strategies for restoring health and fitness and toward preventing diet-related disease.

Eating a diet rich in rancid and/or oxidized omega-6 fatty acids and refined sugars encourages inflammation and cancer growth, while eating a balanced diet with unrefined omega 6s and omega 3s, avoiding refined sugar, and being sure to have enough co-factors including magnesium, zinc, and B-6, can inhibit cancer-related inflammation and growth. For example, zinc deficiency, common in cancer patients, induces vascular proinflammatory parameters associated with NF-κB and Peroxisome Proliferator-activated Receptor (PPAR) signaling.[16] Linoleic acid is an essential fatty acid and is the metabolic precursor of arachidonic acid, which

is also an n-6 fatty acid and the substrate for the cyclooxygenase (COX) and lipoxygenase (LOX) families of enzymes.[17] There are two COX proteins. The constitutive isoform is COX-1, which is expressed in most normal tissues and is responsible for the synthesis of prostaglandins required for essential physiological functions. In contrast, COX-2 is not detectable in most normal tissues, with exception of the kidneys where it is constitutively expressed; it can be induced by phorbol esters, cytokines, and growth factors, including TGF-beta1 and bFGF, and has been associated with all cancer processes.[18]

Conversely, eating a diet rich in omega-3 fatty acids in the form of cold water fish, rich in EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), as well as flax seeds (alpha linolenic acid) and foods rich in healthy omega 6s, and in particular GLA (gamma linonenic acid), can reduce inflammation in cancer, downregulate growth factors such as HER-2/neu, and suppress cancer growth.[19]

Gamma-linolenic acid (GLA), the essential omega-6 fat that is found in evening primrose, black currant seed, borage oil, and pine seed oil, can inhibit the action of the cancer gene Her-2/neu. This gene is overexpressed in almost 30 percent of all breast cancers, and made them highly lethal until the discovery of specific Her-2/neu antagonists. When cancer cells that over-express the Her-2/neu gene are treated with GLA, it not only helps suppress the cancer-causing gene, but also causes up to a 40-fold increase in response to the drug Herceptin (trastuzumab), which is used as part of breast cancer treatment for tumors that overexpress the Her-2/neu gene.[20]

Fish, and omega-3 fatty acids from fish inhibit cancer and are important nutritional compounds in treatment protocols. Mechanisms accounting for fish oil's anti-tumor effects include reduced levels of PGE(2) and inducible nitric oxide synthase, as well as an increased lipid peroxidation, or translation inhibition with subsequent cell cycle arrest. Further, EPA is capable of downregulating the production and effect of a number of mediators of inflammation associated with cancer cachexia, such as IL-1, IL-6, TNF-alpha and proteolysis-inducing factor.[21]

Olive oil is an integral ingredient of the "Mediterranean diet" and accumulating evidence suggests that it may have a potential role in lowering the risk of several types of cancers. A number of epidemiological studies have linked consumption of olive oil with a reduced risk of cancer and researchers are increasingly investigating this association.[22]

One of the best overall diets for the control of cancer-related inflammation, and general inhibition of cancer, heart disease, and neurological disease is the Mediterranean diet. The Mediterranean diet includes locally grown wild vegetables, as well other common vegetables, such as cabbage, leafy and root vegetables, bitter greens including arugula, radicchio, endive, mushrooms, tomatoes and other fruiting vegetables, grapes and berries, fish, a moderate intake of hard cheeses, grains, and plenty of olive oil. Olive oil has been shown to suppress HER-2/neu in HER-2/neu-positive breast cancer.[23]

Olive oil contains a high amount of omega 9 fatty acids (oleic acid) and important phenols which have been shown to inhibit colon cancer.[24] It also contains 0.2-0.7% squalene, a triterpene compound that has demonstrated chemopreventive activity by inhibiting ras farnesylation, modulation of carcinogen activation, and anti-oxidative activities.[25,26]

Men between the ages of 70 and 90 eating a Mediterranean diet have consistently lower rates of all cancers by 50%, but in particular, stomach, colorectal, breast, and prostate cancer, as well as cancer of the esophagus, pancreas, and liver than men in the wealthier industrial North East US. There is a 50% reduction in heart disease associated with adherence to this diet as well.[27] Older men in the USA who eat more than two servings a day of any dark green and deep yellow vegetable have a lower rate of heart disease, according to the US Department of Agriculture. They had up to a 70 percent lower risk of cancer than men who eat less than one serving a day.[28]

Once one gains a good understanding of the general concepts of eating well for cancer prevention and treatment, the next step is to personalize the diet with regard to nutritional status, age, body composition, work and physical activities, the type of cancer, blood and organ systems' status, with additional consideration of the genotype and energetic-type. Energetic-typing can be applied to the person as well as the food. For example, a person with a "cold" constitution may benefit from adding warming foods with aromatic spices like ginger, cardamom, cinnamon, and pepper. During the summer an individual with signs of excess "heat" may benefit from fresh watermelon or cucumber juice. Diet is foundational to cancer prevention and treatment.

It is important to outline a diet rich in a diversity of important plant compounds and add a supplement program that includes them in concentrated forms, including concentrated extracts of turmeric (*Curcuma l.*- 95% curcuminoids, 75% curcumin), green tea (*Camellia s.*- 95% polyphenols, 60% catechins), grape seed/skin (*Vitis v.*– 95% OPCs in the seed and 30% total polyphenols in the skin), Japanese Knotweed (*Polygonum c.*- 20% resveratrol), Ginger (*Zingiber off.*-5% gingerols), rosemary (*Rosemarinus off.*- 6% carnosic acid, 1% rosemarinic acid, 1.5% ursolic acid). All of these compounds have demonstrated broad-spectrum, multi-targeting, anti-cancer effects, as well as disease-preventive, health-promoting benefits.

NF-κB plays a significant role in the regulation of numerous important processes in relation to cancer including immune response, inflammatory response (NF-κB activates immune/inflammatory responses, while glucocorticoids reduce immune/inflammatory responses), apoptosis (suppression of NF-κB leads to an increase cancer-cell apoptosis), and cell proliferation (NF-κB is involved in the induction of a cell cycle gene, cyclin D1, which is involved in the activation of G1/S transition within the cell cycle).[29]

NF-κB modulation is an important target for cancer prevention and treatment. NF-κB protein is a transcription factor whose upregulation has been found to be associated with almost every kind of cancer.[30] Its activation depends on the phosphorylation and subsequent degradation of I-κB proteins.[31] When NF-κB is activated, I-κB is degraded such that the heterodimer is translocated to the nucleus, binds the DNA, and activates the gene. The NF-κB and p53 pathways together play crucial roles in most human cancers in which hyperactivation of NF-κB and inactivation of p53 is a common occurrence. Inhibition of NF-κB and activation of p53 (a major tumor suppressor gene) promotes apoptosis in cancer cells.[32]

NF-κB suppression leads to a reduction in the activity of many other cancer proinflammatory pathways including COX-2, which like NF-κB and several LOX pathways,

is upregulated in practically all cancers. Expression of several NF-κB-regulated genes such as Bcl-2, cIAP, survivin, and TRAF function by blocking the apoptosis pathway, thus immortalizing cancer cells.[33]

Why target NF-κB in cancer? NF-κB has emerged has a major target in cancer because the signaling pathway being activated in the cytoplasm regulates genes involved in cancer cell survival, proliferation, and angiogenesis. NF-κB is hyperactive in many human cancers, including the most aggressive such as pancreatic cancer, accordingly raising cancer cells' resistance to chemotherapy drugs and chemoradiation.[35]

Inflammatory cytokines including the TNF family, interleukins such as IL-1, IL-17, and IL-18 activate NF-κB transcription factors. Downregulation of TNF-a, therefore, will also suppress NF-κB activation.[36]

Oxidative damage activates transcription factors including NF-κB: Increased formation of reactive oxygen species (ROS) and the oxidative damage they do in the cells can contribute to the process of carcinogenesis either through direct genotoxic effects or indirectly by way of signaling pathway modifications leading to altered gene expression.[37] ROS-induced modulations of these pathways can activate transcriptional factors such as AP-1, HIF-1, p53, and NF-κB, among others, that control the expression of genes, the protein products of which participate in complex signal transduction, and thus contribute to and maintain cell transformation to the malignant phenotype.[38]

The range of cellular processes under redox regulation is extensive and includes both the proliferative and apoptotic pathways. Control of the cellular redox environment is therefore essential for normal physiological function, imbalances being characteristic of many pathological states. Oxidative stress is particularly prevalent in cancer, where many malignant cell types possess an abnormal redox metabolism involving downregulation of antioxidant enzymes and impaired mitochondrial function.[39]

NF-κB increases survival of cancer cells and protects them from chemotherapy. A recent study found that suppressing NF-κB significantly increased the effectiveness of gemcitabine against pancreatic cancer cells.[40] Another indicated that NF-κB is strongly overexpressed in chronic lymphocytic leukemia (CLL) and acute myelogenous leukemia.[41] Inhibition of NF-κB in CLL with fludarabine had an enhanced effect even in patients with fludarabine resistance.[42] Inhibition of NF-κB resensitizes lymphoma cells to rituximab (Rituxan®) in formerly rituximab-resistant B-cell lymphoma.[43]

NF-κB mediates HER2 overexpression in Radiation-Adaptive Resistance. The molecular mechanisms governing acquired tumor resistance during radiotherapy remain somewhat unclear. In breast cancer patients, overexpression of HER2 (human epidermal growth factor receptor 2) is correlated with aggressive tumor growth and increased recurrence. HER2 expression can be induced by radiation in breast cancer cells with a low basal level of HER2. Furthermore, HER2-postive tumors occur at a much higher frequency in recurrent invasive breast cancer (59%) compared to the primary tumors (41%). Upregulation of both HER2/neu and NF-κB causes radiation-induced adaptive resistance in breast cancer cells. NF-κB appears

to mediate HER2 overexpression and inhibition of both HER2 and NF-κB can re-sensitize resistant cell lines to radiation.[44]

Why target NF-κB with botanical and dietary medicine? Plants have played a significant role in maintaining human health and improving the quality of human life for thousands of years. The many valuable components of foods, seasonings, beverages, cosmetics, dyes, and medicines from plants have served humans well. In traditional foods and herbs, a wide variety of active phytochemicals including the flavonoids, terpenoids, lignans, sulfides, polyphenolics, carotenoids, coumarins, saponins, plant sterols, and curcuminoids have been recently researched and found to possess important actions in health promotion and cancer prevention.

Because deregulation of NF-κB (and IkB) phosphorylation is a hallmark of chronic inflammatory disease and cancer, targeting these activated signaling pathways with botanicals and botanical compounds represents a most promising therapeutic tool. It is one of the many targets to focus on in an approach to cancer.[45]

NF-κB is a good target for various botanical compounds. Curcumin and resveratrol are two that act to suppress cancer in part by reducing NF-κB, with multiple positive effects including the reactivation of apoptosis and inhibition of tumor cell proliferation, stabilization of genes involved in tumor initiation, promotion, and metastasis, as all these functions are, at least in part, regulated by NF-κB. Alteration within the tumor reduces chemoresistance, thereby potentiating chemotherapy. (The cancer energy microenvironment induces NF-κB activation, which increases resistance to chemotherapeutic agents.)

NF-κB Causes Resistance to Apoptosis: Overexpression of NF-κB, together with TNF-a, COX-2, and LOX-5 is frequent in cancer. Often these pathways are linked together and one pathway upregulates the other, e.g., TNF→NF-κB→Cycloxygenase-2.

COX-2 inhibiting drugs and cancer: Drugs developed for inflammatory diseases have been found to be useful against cancer – most often as synergist or to potentiate other drug therapies. NF-κB activation increases COX-2 expression. The COX-2 inhibitor Celebrex can suppress cancer and enhance the cancer-suppressing effects of Her 1 (EGFR)- or 2-inhibiting drugs such as lapatinib (Tykerb®) and Herceptin®, as well as chemotherapy. Curcumin and omega-3 fatty acids have been found to enhance the COX-2 suppressive effects of celebrex, while reducing toxicity.[46] Recent studies showed that in pancreatic cancer cells curcumin synergistically potentiated the capacity of Celebrex to actively inhibit cell growth.[47,48]

NF-κB inhibition with phytoceutical compounds: Many botanical compounds are potent downregulators of cancer-induced NF-κB. Some of these botanical compounds include:

Curcuminoids (Curcumin) in Turmeric: All three stages of carcinogenesis, initiation, promotion and progression, have shown to be inhibited by curcumin, in part by inhibition of NF-κB, which is controlled by the proteasome-mediated proteolytic degradation pathway.[49]

In three different multiple myeloma studies, curcumin showed very positive anti-cancer effects.

One showed that when multiple myeloma cells were mixed with curcumin it caused downregulation of NF-κB activity, keeping the multiple myeloma cells from replicating and inducing apoptosis in those that remained.[50] In another, cell survival and proliferation in human multiple myeloma was inhibited by curcumin wherein one of the predominant mechanisms was via the suppression of NF-κB.[51] The third concluded that Curcumin is a potent inhibitor of IL-6 and STAT3, and this mechanism is involved in its suppressive effects against human multiple myeloma.[52]

Additionally, curcumin has been shown to inhibit mitogen activated protein kinase (MAPK) and NF-κB, which caused a dose-dependent induction of apoptosis in human colon cancer cells.[53]
(though some things are in such general use, they are no longer spelled out, such as K-RAS)
The recommended dose of curcumin is between 2000 and 4000 mg/day in combination with other herbal concentrates like piperine (black pepper extract), along with fatty acids (EPA/DHA/GLA) and bromelain, which contribute to enhanced absorption and a synergistic effect.

As noted previously, curcumin potentiates the antitumor effects of gemcitabine in pancreatic cancer by suppressing proliferation, angiogenesis, NF-κB, and NF-κB-regulated gene products. A small human trial showed that oral curcumin in doses up to 8 grams/day is well tolerated and, despite its limited absorption, has biological activity in some patients with pancreatic cancer.[54]

Curcumin inhibits head and neck cancer by downregulating NF-κB.[55] Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing p21 (WAF1/CIP1) expressions and suppressing NF-κB activation.[56] Curcumin inhibits VEGF-mediated angiogenesis in human intestinal microvascular endothelial cells through COX-2, NF-κB and MAPK inhibition.[57] Curcumin blocks TNF-a from activating NF-κB at multiple sites.[58,59]

Curcumin: Inducible Nitric oxide synthase and NF-κB: Inducible nitric oxide synthase (iNOS) contributes to enhanced microvascular permeability and density in response to proinflammatory mediators and VEGF. Curcumin scavenges nitric oxide free radicals, effectively inhibiting iNOS and COX-2, causing a downregulation of NF-κB activation, thereby reducing vascular flow and tumor permeability, minimizing tumor growth.[60,61] Resveratrol inhibits cancer-related inflammation and suppresses cancer angiogenesis by the same mechanism.[62]

Stilbenes: Stilbenes are naturally occurring phytochemical compounds produced in leaves and sapwood that work as stress metabolites in response to fungal attack.[63,64] Although known as plant defense compounds, these phytochemicals have an enormous diversity of effects on human biological and cellular processes. Many stilbenes such as resveratrol activate the sirtuin enzyme present within our genes which are responsible for preserving the lives of cells. Several stilbenes, including resveratrol, have been shown to extend the lifespan of yeasts, roundworms, and mice.[65,66] Stilbenes may additionally modulate cellular lifespan by inhibiting the insulin-signaling pathway, which occurs independently of its activation of SirT1 histone deacetylase.67

The mechanisms by which stilbenes are potent mediators of inflammation is through their effectively downgrading the signaling pathway of NF-κB activation, which results in an inhibition of prostaglandin production, synthesis and release of proinflammatory mediators, modification of eicosanoid synthesis, inhibition of cytokines, and inhibition of inducible iNOS, COX-1, COX-2, and AP-1.[68]

Resveratrol: Resveratrol is a natural product occurring in the skins of grapes and various other plants, including peanuts and *Polygonum cuspidum* (Japanese knotweed). It is an immune-enhancing cytokine that protects the plant from fungal or other pathogenic attack. Resveratrol has been shown to have anti-inflammatory, anti-oxidant, cardiovascular cell repair, gene stabilization and regulation, phytoestrogenic, and anti-tumor activities. Resveratrol also posseses cancer-inhibiting actions through its growth-inhibitory effects thought to be mediated mainly through cell-cycle arrest induced by upregulation of p21, p27, p53, and Bax, and downregulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-xL, and claps.[69-71]

Resveratrol also inhibits inflammatory processes by regulating many upstream protein kinases.[72-76] Other mechanisms contributing to resveratrol's anti-cancer effects include cellular and hepatic detoxification, anti-invasion, and cancer-induced angiogenesis.[77-81] In acute myeloid leukemia resveratrol has been shown to block interleukin-1β-induced activation of NF-κB, causing S-phase arrest and inducing apoptosis, thereby inhibiting the proliferation of leukemic cells.[82]

Pterostilbene (from *Pterocarpus marsupium*): Pterocarpus species have been used for their medicinal properties for millenia in Ayurveda. The heartwood is used as an astringent and in the treatment of inflammation and diabetes. Many animal studies have demonstrated that pterocarpus extract, at 5% pterostilbene, can reverse damaged beta cells and actually repopulate the islets, and promote restoration of normal insulin secretion.[83-88] Pterpcarpus extract augments glucose uptake by modulating targets like Glut-4, PPARγ, and PI3 kinase.[89]

COX-2 inhibition: In healthy human volunteers, pterostilbene extract selectively reduced COX-2 and its activity.[90] A cell culture study found it a potent inhibitor of COX-2 as well as iNOS.91 In another study it reduced Bcl-2- and superoxide dismutase 2-dependent mechanism.[92] Another cancer inhibiting action of pterostilbene includes a reinforcement and recovery effect on gap-junctional intercellular communication (GJIC).[93]

Proanthocyanidins from grape seed extract: Proanthocyanidins are a class of naturally occurring phenolic compounds widely found in fruits, vegetables, nuts, seeds, flowers, and bark. Proanthocyanidins from different sources, specifically from grape seeds (*Vitis vinifera*), suppress cancer through multiple molecular targets, such as NF-κB, mitogen-activated protein kinases, PI3K/Akt, caspases, cytokines, angiogenesis, and cell cycle regulatory proteins and other checkpoints.[94] A number of studies have shown that grapeseed proanthocyanidins (GSPs) exert their anti-cancer effects through the suppression of NF-κB.[95]

Epigallocatechin-3-gallate (EGCG), related catechins, and other compounds in green tea extract: The polyphenolic fraction contains four main catechins: epicatechin (EC), epicatechin-

3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG), the latter being the highest concentration and the most researched compound in green tea extract (GTE) (The recommended dose according to the ETMS is an extract of 95% total polyphenols and 40-50% EGCG that has not had the caffeine removed). As in the cases of curcumin and resveratrol, there has been and continues to be an enormous amount of supportive data demonstrating profound cancer-suppressing effects as well as overall health benefits from GTE.[96,97]

Parthenolide in feverfew (*Tanacetum parthenium L*): Most of the research attributed to feverfew's anti-inflammatory properties are attributed to the sesquiterpene lactone of parthenolide, which hinders the inflammatory process.[98] The antitumor activity of parthenolide is believed to be due to inhibition of NF-κB and STAT-3 binding to the DNA, reduction in MAPK and AP-1 activity, and diminished generation of reactive oxygen species.[99] What is particularly exciting is that this feverfew extract has been shown to destroy myeloid leukemia at the stem-cell level via the inhibition of NF-κB activity.[100] Parthenolide has been shown to increase the sensitivity of cancers with constitutively active NF-κB to chemotherapeutic drugs. The suppression of NF-κB activation and sustained JNK activation contribute to the sensitization effect of parthenolide to TNF-alpha-mediated cell death in human cancer cells.[101]

Ginsenosides in Ginseng: There are several species of ginseng, which include *Panax ginseng* (Korean ginseng), *Panax quinquefolius l.* (American ginseng), and *Panax notoginseng* (Sanchi ginseng).[102] The active compounds in ginseng that suppress inflammation and cancer are a group of triterpenoid saponins collectively called the *Ginsenosides.* Ginsenosides contain the same multicyclic cyclopentanophenanthrene ring that corticosteroids are built from, and inhibit cancer in part by suppressing proinflammatory pathways including NF-κB and COX-2: Ginseng acts as an anti-inflammatory molecule that targets many of the key players in the inflammation-to-cancer sequence.[103]

In a study using experimental sepsis, panax ginseng extract showed inhibition of the p38 MAPK pathway and NF-κB in vitro, and inhibition of proinflammatory cytokines in vivo.[104]

An evaluation of the anti-inflammatory as well as anti-tumor promoting effects of Rg_3, a major ginsenoside derived from heat-processed (red) ginseng, was performed on animals. Rg_3 pretreatment significantly inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ornithine decarboxylase (a cancer-activating kinase) activity and 7,12-dimethylbenz[a]anthracene-initiated papilloma formation. In another experiment, Rg_3 pretreatment abrogated the expression of COX-2. Rg_3 also inhibited the TPA-induced activation of the transcription factor, NF-κB in animals and cultured human pro-myelocytic leukemia (HL-60) cells. Moreover, Rg_3 exerted potent inhibitory effects on the activation of another transcription factor, AP-1 that is responsible for c-jun and c-fos oncogenic transactivation.[105]

Ginsenosides showed anti-inflammatory effects by inhibiting TPA-induced COX-2 expression, as well, contributing to its anti-tumor promoting effects on skin carcinogenesis in mice.[106] Pre-treatment with ginsenosides inhibited TPA-induced epidermal NF-κB DNA binding in mouse skin, which appeared to be mediated by blocking phosphorylation and subsequent degradation of IkappaBalpha (IKB-a).[107]

Panax notoginseng (*Panax pseudoginseng*), also called Tienchi ginseng, is a close relative of Panax Ginseng. Traditional Chinese medicine (TCM) practitioners have called notoginseng "the miracle root for the preservation of life." It is different from Panax ginseng and has been used for different medicinal purposes including pain relief. Panax notoginseng, although used to stop bleeding, is one of the best herbs to promote bloodflow and inhibit platelet aggregation and thrombosis. Panax Notoginseng possesses potent anti-inflammatory and anti-tumor effects by downregulating NF-κB and TNF-a.[108]

Reishi powdered extract: Reishi's (*Ganoderma lucidum*) Mandarin name, "Ling Zhi" is literally translated "spiritual mushroom," and has been used in Traditional Chinese Medicine for at least 2,000 years. It is known to increase longevity and was highly reagarded as an elixir of immortality. The Reishi Mushroom contains compounds including polysaccharides, polysaccharide peptides, nucleosides, triterpenoids, alkaloids, and compound structures yet to be identified, all contributing to an immune-modulating effect referred to as Host Defense Potentiators (HDP).[109]

Reishi is one of the main herbs used in fu-zheng therapy in China to offset the side effects of chemotherapy and radiation therapy. Fu zheng supports the root of the person and literally means to "normalize the center." Other herbs commonly used in fu-zheng therapy are kidney, spleen, and blood vitalizing, and include astragalus, millettia, panax ginseng, schisandra, lycium, ligusticum, salvia, he shou wu, cordyceps, atractylodis, Rehmannia, and licorice. Fu-zheng herbal therapy was used as an adjuvant to chemotherapy to treat 112 patients with non-Hodgkin's lymphoma and resulted in five-year survival rate twice as high as a group not receiving any fu-zheng herbs.[110]

Reishi Powdered Extract (RPE) inhibits NF-κB: RPE is a two-part extract of reishi that contains a minimum of **10% polysaccharides** and **4% triterpenes** (which are believed to be responsible for the anti-inflammatory anti-cancer actions of reishi). RPE has shown to inhibit NF-κB and AP-1, which resulted in the inhibition of expression of urokinase-type plasminogen activator (uPA) and its receptor, uPAR. RPE also suppressed cell adhesion and cell migration of highly invasive breast and prostate cancer cells, suggesting its potency to reduce tumor invasiveness. RPE extract inhibited active NF-κB, demonstrating strong inhibition of cancer cell migration.[111]

Glycyrrhizic acid: Licorice (*Glycyrrhiza glabra* & other species) increases overall vitality while it moderates and harmonizes the characteristics of other plants, to bring a multi-component formula together energetically. In TCM it is considered, because of this action, to be a synergist and is used in many classic formulas as a supporting and harmonizing agent. It possesses anti-inflammatory and anti-cancer actions.[112] Licorice extract has been shown to suppress the activities of LOX-5 and COX-2, key enzymes in the formation of proinflammatory eicosanoids from arachidonic acid (AA), and NF-κB. With regard to the properties of dual COX-2/LOX-5 inhibitors, licorice extract possesses anti-inflammatory activity devoid of the most troublesome gastric side effects seen for drugs used as COX-2 inhibitors.[113]
(by the way, there are no pharmaceutical dual cox-2/lox-5 inhibitors, though they'd love to find one)

Ursolic Acid (Holy basil and Rosemary): Ursolic acid, a triterpenoid compound, is found in holy basil (*Ocimum sanctum*), which is also called "Tulsi" and is considered an adaptogen and a sacred plant. Ursolic acid is also found in sage, rosemary, apples, prunes, and cranberries. It inhibits cancer through multiple mechanisms, including downregulating NF-κB. Holy basil and rosemary contain a number of synergistic compounds such as carnosol, ursolic acid, rosmarinic acid, apigenin, eugenol, cirsilineol, and cirsimaritin, all of which have shown potent redox/anti-oxidant enhancement, as well as COX-2 inhibitory effects.[114]

Carnosol acts as antioxidant and anticarcinogen, and is a potent modulator of NF-κB. Carnosol has shown to inhibit cancer-inducing NF-κB, iNOS, and MAPK activity.[115] Rosemary extract and basil also contain a water-soluble compound, rosmarinic acid, which has shown to downregulate COX-2 and suppress colon cancer.[116]

Ursolic acid is able to inhibit several key steps of angiogenesis in vitro, including endothelial cell proliferation, migration, and differentiation. At the same time, it seems to stimulate other key steps of angiogenesis, such as extracellular matrix degradation by MMP-2 and urokinase. Ursolic acid exerts an antiproliferative effect through the inhibition of tyrosine kinase enzymes.[117]

CAPE: Caffeic acid phenethyl ester (CAPE) is most often derived from honeybee propolis, which has been used as a folk medicine and has several proven biological activities, most notably as a potent inhibitor of cancer-inducing NF-κB.[118,119] Animal studies have demonstrated that CAPE suppresses cancer by inhibiting NF-κB activation and angiogenesis. In one study CAPE inhibited cell invasion by 47.8% but also decreased expression of vascular endothelial growth factor (VEGF) and of MMP-2 and MMP-9.[120]

Betulinic acid, a pentacyclic lupane-type triterpene, from Chaga (*Inonotus obliquus*): Chaga has been used in Eastern Europe, especially in Russia, as a folk medicine since the 16th century for treating cancer. Betulinic acid, a main compound found in Chaga powdered extract, is a selective inhibitor and inducer of apoptosis of many cancers (and HIV), including human melanoma. NF-κB inhibition has shown to be one of the many mechanisms through which betulinic acid suppresses melanoma and other cancers.[121]

Diindylmethane (DIM) and the bioactive form of Indole-3-carbinol (13C): I3C, found in cruciferous (Brassica) vegetables (such as cabbage, cauliflower, and brussels spouts), are known as a promoters of healthier estrogen metabolism by preventing the receptor binding of "stronger" more stimulating estrogens, and improves the hepatic detoxification of estrogens and estrogen-mimicking xenoestrogens, promoting the 2-hydroxylation pathway instead of the 16-hydroxylation pathway.[122] However, DIM and I3C exhibit anti-tumor effects through multiple mechanisms, including gene expression modulation, growth-factor suppression, and the inhibition of NF-κB activation.[123]

Magnolol (from *Magnolia officinalis*): The pleasant fragrance within the bark of the medicinal plant, *Magnolia officinalis*, is primarily due to the presence of two biphenol compounds, **magnolol** and **honokiol.** Magnolol and honokiol have been shown to suppress COX-2, induce apoptosis in cancer cells, and inhibit metastasis.[124-126] Magnolol suppresses inflammation by

inhibiting NF-κB activation and NF-κB regulated gene expression by inhibiting IkappaB kinase activation. Magnolol also downregulates NF-κB-regulated inflammatory gene products inducible nitric oxide synthase (iNOS), the production of inflammatory cytokines interleukin-8 and TNF-α in THP-1 cells (type of cancer cell line?), the formation of prostaglandin E2, and the artherosclerosis mediators monocyte chemotactic protein-1 (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1).[127]

Honokiol is the most important researched bioactive constituent within the bark of Magnolia. Numerous animal studies have demonstrated honokiol to act as an anti-stress agent and a potent suppressor of oxidative damage and cancer.[128] Honokiol strongly inhibited various inflammatory responses, such as: (i) the upregulation of nitric oxide (NO), prostaglandin E2 and TNF-alpha production and costimulatory molecule CD80 induced by lipopolysaccharide (LPS).[129]

Indirubin, a 3, 2' bisindole isomer of indigo: Indirubin, a minor constituent of the indigo plant, possesses potent anti-cancer effects mediated in part through the suppression of the NF-κB activation pathway.[130] A 1980 clinical study reported that indirubin induced complete remission of chronic myelocytic leukemia in 26% and partial remission in 33%. Studies have shown that indirubin or its derivatives act by inhibiting excessive signaling of the cyclin-dependent kinases, STAT 3 metabolic pathways, and NF-κB.[131] DIM enhances the growth inhibition effect of indirubin on human prostate cancer cells by the induction of apoptosis.[132]

Conclusion

NF-κB activation mediates inflammation related to cancer development, growth, and invasion. Inhibition of NF-κB with phytocompounds is an effective and safe way to suppress cancer growth. As modern science continues to investigate these and other plant compounds for cancer, it is becoming increasingly apparent that the science of plant medicines is developing a rational framework for the integration of botanical medicine into mainstream cancer treatments.

"For years I never knew whether the twilight was the ending of the day or the beginning of the night. And then suddenly one day I understood that this did not matter at all. For time is but a circle and there can be no beginning and no ending. And this is how I came to know that birth and death are one. And it is neither the coming or going that is of consequence. What is of consequence is the beauty that one gathers in this interlude called life" – W.O. Abbott

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