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REPORT

What Is Nuclear Factor-Kappa Beta?

By Julius G. Goepf, MD



For the past seven years, Life Extension has published extensive articles about chronic inflammation and the numerous diseases it causes, such as cancer, athero-sclerosis, arthritis, dementia, and more.

In these articles, we showed how aging people over-express a molecule called nuclear factor-kappa beta, which then ignites a lethal inflammatory cascade throughout the body.

An abundance of new scientific studies has validated the multiple pathological effects inflicted by nuclear factor-kappa beta. Fortunately, scientists have discovered methods to safely suppress this insidious chronic inflammation-inducing agent. Aging humans are thus able to protect against a major cause of age-related disease.

In this article, we enlighten Life Extension members about what nuclear factor-kappa beta is and what can be done to suppress it.

Understanding the relationship between nuclear factor-kappa beta (NFkB) and inflammation is critical to maintaining your health and longevity. Over the last several years, scientists have gained new insights into how NFkB functions in the body. As a result, we are on the verge of finding ways to overcome our genetic predisposition toward degenerative conditions such as cancer, heart disease, arthritis, and even asthma.

Simply put, NFkB is a protein that acts as a switch to turn inflammation on and off in the body. Scientists describe NFkB as a "smoke sensor" that detects dangerous threats like free radicals and infectious agents. In response to these threats, NFkB "turns on" the genes that produce inflammation. As we age, NFkB expression in the body increases, provoking widespread chronic inflammation and setting the stage for diseases ranging from atherosclerosis and diabetes to Alzheimer's. The knowledge of this simple fact should motivate us to counteract NFkB's deleterious effects and thus guard against many of the diseases commonly associated with aging.

As we have reported over the last several years, inflammation is the key initiating factor in major degenerative diseases. In fact, some scientists estimate that inflammation underlies up to 98% of the diseases afflicting humans, including a vast array of seemingly different conditions such as cancer, heart disease, diabetes, and neurodegenerative disorders.¹

NFkB is an instigating factor that unleashes inflammatory responses in chronic disease conditions. For example, NFkB can signal our cells to continue to multiply long past their normal life span, which can promote cancer. Furthermore, NFkB can further spark the smoldering inflammation that damages joint tissues, thereby provoking crippling arthritic conditions. NFkB likewise plays a role in spurring inflammation in the nervous system, which can set the stage for the onset of various neurological disorders. Scientists believe that NFkB-induced inflammation in the airways may play a role in asthma.

RECENT FINDINGS ON NFkB AND DISEASE

In recent years, numerous studies have shed light on the disease-promoting effects of NFkB and the benefits of quieting its activity in the body. For instance, recent studies indicate that NFkB plays a role in the following conditions:

- **Autoimmune joint disease:** NFkB plays a crucial role in both rheumatoid arthritis and systemic lupus erythematosus, according to Spanish researchers.² These two autoimmune conditions are known to produce severe joint pain and deterioration, as well as other symptoms that dramatically impair quality of life. Effective therapies to block NFkB may positively modulate these disease processes.
- **Hepatitis C:** Infection with the hepatitis C virus is a growing cause of liver disease and liver cancer, and (unlike hepatitis B) there is no vaccine to protect against this deadly threat. In early 2006, Japanese scientists determined that NFkB

plays a key role in the process by which the hepatitis C virus leads to the proliferation of human liver cancer cells.³

- **Inflammatory bowel disease:** Crohn's disease is an inflammatory bowel disease associated with symptoms such as severe abdominal pain, diarrhea, weight loss, and rectal bleeding. Recently, scientists noted that therapies that improve the symptoms and pathological signs of Crohn's disease may work by decreasing levels of NFκB.⁴
- **Survival after heart attack:** The death of heart muscle due to a blocked coronary artery is known as a heart attack. If the heart cannot adequately repair itself after such an attack, a common result is heart failure, in which the heart muscle cannot pump enough blood to meet the body's needs. New findings from 2006 suggest that blocking NFκB may support cardiac muscle healing and prevent heart failure following heart attack.⁵
- **Prostate cancer:** Zinc has long been known for its role in supporting healthy prostate function. Research from 2006 suggests that NFκB may provide the link between zinc and protection against prostate cancer. Zinc supplementation suppresses NFκB's signaling effects, and researchers believe this may help prevent the metastasis of malignant prostate cancer cells.⁶
- **Diabetes:** Insulin resistance in muscle tissues is a key factor in type II diabetes. In a recent investigation, researchers studied the muscle tissue of people with type II diabetes and found signs of increased NFκB activity. Reducing NFκB through exercise training in these individuals led to improvements in blood sugar metabolism.⁷

The identification of NFκB as a critical "switch" that "turns on" inflammation has profound implications for both preventing and treating some of today's deadliest diseases. Clearly, NFκB is something we need to control if our goal is to lead a long and healthy life.

Fortunately, ongoing research continues to uncover a wealth of natural remedies that suppress NFκB's activity in the body. These remedies provide the foundation for safe, effective nutritional strategies to quell NFκB and disease-provoking inflammation, thus providing a formidable defense against a vast array of deadly diseases and against aging itself.

INTERACTING WITH DNA: HOW NFκB WORKS

Present in the interior portion (cytoplasm) of every cell, NFκB is normally bound to inhibitory proteins that keep it in an inactive state. When cells are exposed to infectious invaders or stressors such as free radicals or environmental toxins (like cigarette smoke), NFκB is activated. NFκB then travels to the cells' command center, known as the nucleus, where it binds with DNA to turn certain genes on or off. By interacting with more than 400 different genes, NFκB can thus activate the body's blueprints for inflammation.¹ These gene products are used to coordinate further inflammatory and immune responses in the body.

NFκB AND CANCER DEVELOPMENT

One of NFκB's most lethal functions is inducing cancer in our bodies. Scientists are finding that, in addition to its central role in producing inflammation, NFκB plays an equally prominent and related role in the development of cancer.

THREE STAGES OF CANCER DEVELOPMENT

Initiation: Cells become cancerous when their DNA is damaged by any of a host of factors, including various forms of radiation, oxidative stress, and specific toxins. Such DNA damage occurs over 3 million times per cell per day. Fortunately, because of cellular repair mechanisms, few of these mutations go on to produce cancer. Cells that survive with enough unrepaired DNA to potentially become cancerous are said to have become initiated.

Promotion: Even initiated cells rarely go on to become cancerous, because cells in most tissues have lost the ability to replicate themselves. The process of programmed cell death, or apoptosis, prevents potentially cancerous cells from passing damaged DNA along to future generations of cells. Unfortunately, under certain circumstances, cells regain the ability to replicate. Such "immortalized" cells are said to have undergone promotion, the second stage in cancer development.

Progression: Even at this late stage, our bodies' defenses normally maintain control even over collections of initiated cells that have undergone promotion. The immune system constantly patrols the body looking for potentially cancerous cells. When it finds them, it destroys these trouble-making cells and mounts an offensive against similar cells found in other body areas. Cancerous tissue that has overcome these defenses is said to be in the final stage of cancer development, known as progression.

Since NFκB plays a role in all three stages of cancer development, understanding its actions as well as strategies to control its activity is crucial to both the prevention and adjuvant treatment of various cancers.

NFκB acts in each of the main phases of cancer development, which are known as initiation, promotion, and progression. NFκB

“switches on” genes that allow cells to become initiated, and once initiated, to have their growth promoted, and once promoted, to progress and invade healthy tissue.⁸ Successful cancers evade powerful repair and control mechanisms at each of the three distinct stages of cancer development.⁸ Since NFκB is involved in each of the three stages, it is critically important that we understand NFκB’s actions in our bodies and what we can do to better control them.

The NFκB system has emerged as the central actor in the link between inflammation and cancer. NFκB affects both malignant and non-malignant tumor cells. In malignant cells, it turns on genes that create resistance to apoptotic cell death and DNA damage, in effect promoting cancer development by rendering cells capable of reproducing, even when they are exposed to pharmaceutical anti-cancer agents. In non-malignant tumor cells, NFκB turns on genes that produce factors to stimulate blood vessel formation, in support of rapid tumor enlargement and progression. Finally, byproducts produced by NFκB stimulation can also damage DNA, thereby contributing to the very earliest stages of tumor initiation.⁸

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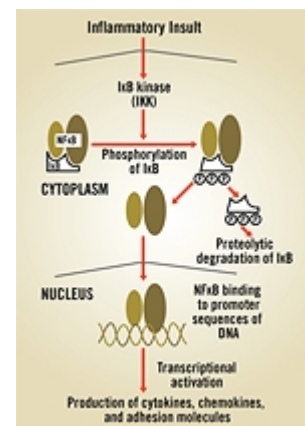
HOW INHIBITING NFkB HELPS FIGHT CANCER

Recent discoveries about NFkB confirm the deadly link between inflammation and cancer. It is well known that nutrients and drugs that reduce inflammation also help fight cancer.^{8,9} Some anti-inflammatory drugs, however, carry cardiovascular risk.^{10,11} Scientists hope that therapies that block NFkB may provide safe, effective action against both inflammation and cancer.

The ubiquitous presence of NFkB throughout the inflammation-cancer cycle suggests that the next breakthroughs in cancer treatment will likely center on the inhibition of NFkB and its actions. As scientists learn more about NFkB and the complex systems that regulate it, they also learn more about the wide array of substances that can inhibit its dangerous actions. For example, the anti-inflammatory drug ibuprofen inhibits not only the COX-2 enzyme but also NFkB,¹² and has a well-established safety record. This drug, as well as many natural inhibitors of NFkB, will therefore play an important role in controlling the inflammatory components of tumor formation and growth.

Because the NFkB factors are active in both the cancerous cells and inflammatory cells in tumors, nutrients or drugs that can inhibit NFkB show tremendous promise as anti-cancer or cancer-preventive agents.⁸ Scientists believe that the combination of NFkB inhibition with drugs or cytokines that induce cancer cell death has great promise in fighting cancer.¹³

Because the NFkB system is also involved in producing healthy immune responses, there are concerns about its long-term inhibition. While NFkB seems to be most profoundly involved in cancer at the stages of promotion and progression,^{8,14} it may be possible to use inhibitors for relatively short periods. Another potential use for such inhibitors would be in combination with chemotherapy or radiation treatments, as a means of controlling the associated inflammation and enhancing the effects of those treatments.⁸



How NFkB activation affects gene expression.

NFkB: LINKING INFLAMMATION AND CANCER

NFkB and Cancer Promotion

The impact of NFkB on inflammation and cancer is most prominent in the second stage of cancer development, in which cells with newly mutated DNA are promoted into “immortalized” cancer cells.⁸ Scientists have identified two general mechanisms by which NFkB acts to promote tumors.

In tissue cells that have become initiated because of DNA damage from toxins, radiation, or free radical attack, activated NFkB “switches on” genes that reduce apoptosis (programmed cell death). These “immortalized” cells can now reproduce in the unregulated fashion characteristic of cancer; that is, they have been promoted.¹⁵⁻¹⁷

On the other hand, NFkB activation in inflammatory cells results in increased production of cytokines and other growth factors that support the growth, replication, and invasion of the transformed cancerous cells.^{8,18,19} Such activated inflammatory cells also provide growing cancers with factors essential to new blood vessel formation, producing a life-sustaining environment for the deranged cancer tissue and further promoting its growth.⁸

Scientists now think of NFkB as the agent that links the processes of toxic damage and inflammation during the promotion phase of cancer development. Because of NFkB’s actions on DNA-damaged cancer cells, these cells are able to outlive their normal counterparts and multiply. Through its action on healthy (non-cancerous) inflammatory cells, NFkB creates an environment that favors cancerous tissue over healthy tissue, providing yet another “advantage” for the growing cancer.

NFkB and Tumor Progression

Inflammation is linked to cancer not only through tumor promotion, but also through supporting the similarly complex mechanisms of tumor progression.⁸ Once cancer cells have been promoted, NFkB stimulates production of inflammatory signals that support the cancer’s spread to other tissues, both locally (a process known as invasion) and at a distance (known as metastasis).⁸

Practically since the science of human cancer biology began, scientists have known that at the core of most solid tumors is a mass of dead, or necrotic, tissue. It is now clear that this necrotic tissue contributes to aggressive tumor growth, and once again, the connection is NFkB.⁸ Dying tumor cells rupture and release inflammatory mediators, leading to the activation of NFkB, which then “turns on” genes involved in rapid tumor growth and invasion. Once kindled by a small amount of necrosis, a tumor can roar to life like a forest fire from a smoldering ember. NFkB is the strong wind that fans the cancer’s destructive growth.

NUTRIENTS THAT INHIBIT NFkB

The search is on for safe, effective inhibitors of NFkB. One of the most exciting features of the explosion of NFkB research is that it sheds new light on the mechanisms of many familiar nutrients.



Health-conscious people are quite familiar with how antioxidants, vitamins, minerals, and essential nutrients such as omega-3 fatty acids can maintain health and prevent disease. It is becoming increasingly clear that many such compounds exert some of their beneficial effects through interactions with the NFkB system. Although the precise mechanisms vary, all of these agents work by inhibiting NFkB activation, thus preventing the expression of genes involved in inflammation and cancer development. Here we summarize familiar nutrients whose NFkB-related actions are now coming to light.

ANTIOXIDANTS

Antioxidants are known to reduce inflammation and cancer risk. The identification of NFkB as the common link to both processes may serve to explain how these substances operate. Vitamins E and C have been shown to reduce inflammatory cytokine production that is a consequence of NFkB activation.²⁰

N-acetylcysteine inhibits NFkB, which is likely the mechanism by which it confers its health-promoting effects.²¹ S-adenosyl-methionine (SAME) exerts some of its powerful anti-inflammatory effects by reducing NFkB activation.²² The potent antioxidant lipoic acid binds to and inhibits NFkB in the cell’s nucleus.²³ Zinc may also exert its antioxidant effect by reducing NFkB activation.²⁴

ESSENTIAL FATTY ACIDS AND OTHER LIPIDS

The omega-3 fatty acids are also known to reduce inflammation and decrease the production of inflammatory cytokines. Evidence is emerging that these effects occur due to inhibition of NFkB activity by eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and other essential fatty acids in this class.²⁵⁻²⁷

EPA and DHA protect the eye’s retinal cells from oxidative damage. Moreover, these fatty acids may impair the overgrowth of blood vessel cells that occurs in several retinal diseases, by reducing the production of inflammatory cytokines, vascular growth factors, and adhesion molecules, all via the common pathway of NFkB inhibition.²⁸

ISOFLAVONES AND PHYTOESTROGENS

Soy isoflavones and other plant flavonoids are well-established modulators of the immune system’s inflammatory responses. These phytoestrogens (plant-derived, estrogen-like molecules) are known to help reduce the risk of certain hormone-dependent cancers, as well as the risk and severity of osteoporosis.²⁹ Researchers have shown that the isoflavone-induced inhibition of NFkB is the mechanism by which isoflavones reduce the invasiveness of breast cancer and increase programmed cell death in various human cancer cell lines.³⁰⁻³² Evidence also indicates that isoflavones may act by the same mechanism to inhibit bone loss in osteoporosis.³³

Some researchers have speculated that one of the reasons women live longer than men is related to the favorable effects of estrogen on up-regulating antioxidant genes often suppressed by NFkB, suggesting that the phytoestrogens might have similar effects in promoting longevity.³⁴

FROM GARDEN TO MEDICINE CHEST

Herbs and spices from around the world have long been sought for their pleasing flavors and healing qualities. Even today, these plant extracts are valued worldwide for promoting health and fighting disease. Scientists are discovering that many of these natural agents act through the universal mechanism of inhibiting the over-expression of NFkB.

Curcumin is a compound found in a number of South Asian spices, most prominently in turmeric, a component of curry seasoning.

Curcumin has well-established antioxidant and anti-inflammatory effects.^{35,36} The extent to which curcumin exerts these effects by inhibiting NFκB is becoming increasingly clear.³⁷ Curcumin acts directly within the cell's nucleus and also acts on substances that activate NFκB. For example, it binds iron and copper in brain tissue, reducing the activation of NFκB that is associated with the production of amyloid beta proteins in Alzheimer's disease.³⁵



Turmeric (*Curcuma longa*)

Strong evidence suggests that curcumin may fight the following inflammatory diseases:

- **Colitis.** Dietary curcumin supplements strongly suppressed NFκB activation in a rat model of colitis,³⁸ resulting in both decreased tissue wasting and colonic inflammation. When curcumin was given to experimental animals before the induction of colitis, there was reduced NFκB activation and less visible damage to the colon.³⁹ This effect was accompanied by reduced activity of several enzymes involved in inflammation in the gut.
- **Liver disease.** The development of alcoholic liver disease, resulting in chemical hepatitis and eventually cirrhosis, has recently been associated with NFκB-mediated gene expression. When laboratory rats were fed sufficient alcohol to produce alcoholic fatty liver with liver cell inflammation and necrosis, dietary curcumin inhibited NFκB activation, preventing both the microscopic and biochemical changes associated with alcoholic liver disease.⁴⁰ In an experimental model of non-alcoholic fatty liver degeneration (which induces substantial oxidative stress), investigators found that dietary curcumin significantly reduced inflammation and the release of inflammatory modulators through NFκB inhibition.⁴¹
- **Chronic neurodegenerative diseases.** NFκB-induced inflammation involving brain glial cells is thought to be one mechanism contributing to the formation of amyloid beta proteins, which are characteristic of Alzheimer's and other degenerative brain diseases.⁴² In several recent studies, curcumin has been shown to reduce the glial cell expression of inflammatory mediators.^{43,44} Curcumin likewise has been shown to reduce amyloid beta formation in animal models by inhibiting NFκB.^{45,46}
- **Arthritis.** Curcumin's inhibition of NFκB reduces the degenerative changes to arthritic joints.^{47,48} Just this year, curcumin was shown to enhance the anti-inflammatory effects of the COX-2 inhibitor drug celecoxib.⁴⁹ This is an important finding, since COX-2 inhibitors have adverse effects on the cardiovascular system. This caused scientists to propose that co-treatment with curcumin could reduce the dose of selective COX-2 inhibitors required to achieve significant relief from inflammation.
- **Cancer.** Curcumin has been found to suppress, retard, and even reverse cancer development at each stage of the disease.⁵⁰ By inhibiting NFκB, curcumin reduced expression of proteins needed by cancer cells for proliferation (the promotion stage) and for invasion and metastasis (the progression stage).⁵¹ Curcumin also reduces cancer progression by increasing cell death in cancer cells, thereby depriving them of the "immortality" they need to survive and invade other tissues.^{52,53} This has allowed curcumin to be effective in highly chemotherapy-resistant cancers;⁵⁴ it has also been shown to increase the effect of chemotherapy in animal models of advanced human cancer.⁵¹

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CURCUMIN: POTENT CANCER FIGHTER

Curcumin has been specifically evaluated against the following human cancer types:

Skin cancer. Curcumin has been hailed as one of the most promising agents in preventing “photocarcinogenesis,” or cancer caused by ultraviolet light.⁵⁵ Researchers have found that by inhibiting NFκB, curcumin dramatically increases the rate of cell death in human melanoma cells in culture.⁵⁶ The effect was both dose- and time-dependent, meaning that more curcumin exposure over a longer time increased the rate of cancer cell destruction. Virtually identical effects have been demonstrated in malignant squamous cell carcinoma of the head and neck.⁵⁷

Prostate cancer. Curcumin inhibits NFκB and sensitizes human prostate cancer cells to the lethal effects of tumor necrosis factor, which speeds up cell death⁵⁸ and reduces the ability of cancer cells to proliferate.⁵⁹ In a 2006 study, curcumin was also shown to decrease the invasiveness of prostate cancer cells, by reducing their production of certain protein-digesting enzymes that help the cancerous cells force their way between healthy cells in order to spread. This resulted in significantly fewer metastatic nodules in the experimental animals fed curcumin than in the controls.⁶⁰

Breast cancer. Primary breast cancers are treated using surgery, radiation, estrogen modulators, and chemotherapy. Curcumin functions via additional anti-cancer mechanisms. Through its effects on NFκB, curcumin enhances the programmed death of cells from human breast cancers⁶¹ and their lung metastases.⁵¹ In a 2005 study, curcumin also reduced cancer cells’ production of vascular growth factors, adhesion molecules, and other proteins required for sustaining the cells.⁵¹ This study also demonstrated that dietary administration of curcumin to laboratory animals decreased the incidence of cancer metastasis to the lung. These results have staggering implications for human use of curcumin as an adjunctive breast cancer treatment.

Cervical cancer. One of the best-known examples of virally induced human cancer is cervical cancer, which is often caused by infection with human papillomavirus. In 2006, curcumin was shown to inhibit the expression of viral cancer genes (initiation), while also down-regulating inflammatory mediators that cervical cells produce under the influence of NFκB during cancer promotion.⁶²

Colon cancer. Although colon cancer is a major cause of death in Western countries, many scientists believe that dietary modification could reduce its impact by as much as 90%.⁶³ Animals with colorectal cancer showed a reduction in their tumor burden when fed curcumin.⁶⁴ Human colon cancer cells in culture are inhibited by curcumin,⁶⁵ and their death is markedly enhanced by curcumin.⁶⁶ Both effects appear to be mediated by NFκB inhibition and related effects on tumor survival genes. Curcumin was also recently found to markedly enhance the anti-tumor effectiveness of the COX-2 inhibitor drug celecoxib.⁶⁷

Lung cancer. Curcumin down-regulates NFκB activation caused by cigarette smoke in human lung cells⁶⁸ and reduces the expression of genes required for tumor promotion and progression of human non-small cell lung cancers.⁶⁹ Curcumin also induces cell death in multiple human lung cancer cell lines.⁷⁰

Blood malignancies. Leukemia and multiple myeloma, two cancers of the immune system cells in the blood, are known to be highly dependent on NFκB activity,⁷¹ which makes them natural targets for curcumin treatment. Multiple myeloma cells treated with curcumin showed down-regulation of several gene products required for proliferation, and demonstrated arrested growth and increased cell death.⁷¹ In one type of human leukemia cell, curcumin inhibited expression of a variety of NFκB-dependent genes needed for both tumor initiation and progression.⁷² In adult T-cell leukemia, curcumin prevented the growth of virus-infected cells, but not of normal blood immune system cells.⁷³ Curcumin also stopped cell replication and induced cell death by inhibiting NFκB. These results are promising as a means of suppressing this currently incurable form of leukemia.

Human studies are rapidly catching up with these exciting laboratory findings about curcumin. Phase I (safety and tolerability) trials among patients with high-risk cancers or pre-cancerous conditions have demonstrated that curcumin is absorbed after oral dosing and that humans can tolerate up to 8000 mg per day for up to four months without toxicity.^{74,75} The scientists who authored these studies have recommended further phase II studies of curcumin for the prevention or treatment of various cancers.

Licorice root extracts are among the oldest remedies in Chinese medicine, and have long been used for their anti-inflammatory, anti-viral, anti-ulcer, and cancer-preventive properties.^{76,77} More recently, scientists discovered that a major component of licorice

inhibited NFkB and protected rat liver cells from alcohol toxicity.⁷⁸ Another licorice extract inhibited NFkB activation and decreased production of a pro-inflammatory cytokine in human colon cells that had been exposed to an inflammatory challenge.⁷⁹ These results elegantly demonstrate how NFkB inhibition can interrupt the inflammatory cycle by which cytokines stimulate the production of still more cytokines. Glabridin, another licorice root extract, produces similar anti-inflammatory effects by inhibiting NFkB.⁸⁰

Capsaicin, the main ingredient in red pepper, has both anti-inflammatory and anti-cancer effects.⁸¹⁻⁸³ Red pepper compounds have long been used to manage inflammatory joint conditions.³⁷ Capsaicin inhibits the induction of two inflammation-provoking enzymes in stimulated macrophage immune cells.⁸² This effect is attributable to its inhibition of NFkB activation.⁸³ Capsaicin also induces cell death in many cancers by modulating NFkB.⁸¹ Like curcumin, capsaicin inhibits the growth of adult T-cell leukemia cells by impairing NFkB activation.⁸⁴ Capsaicin further impairs cancer progression by reducing levels of vascular endothelial growth factor, thus depriving growing cancers of nutrients.⁸⁵

Clove extract (eugenol) inhibits NFkB-mediated expression of inflammatory cytokines.^{86,87} Like capsaicin, eugenol inhibits NFkB activation in stimulated macrophage immune cells,⁸⁷ reducing their synthesis of COX-2 and inflammatory cytokines.⁸⁶ Oil of cloves has been used in dental care for centuries, and eugenol is now widely used to promote healing and prevent excessive inflammation after root canal surgery.^{88,89}

Ginger extracts exert anti-inflammatory activity and stimulate cancer cell death by inhibiting NFkB.⁹⁰⁻⁹² Ginger reduces expression of the key inflammatory enzymes COX-1 and COX-2.⁹³ Topical application of ginger extract inhibits skin inflammation in a mouse model⁹² by inhibiting NFkB.⁹¹ A ginger extract was shown to enhance tumor cell death and down-regulate production of tumor invasion factors by preventing activation of NFkB.⁹⁰

Basil and rosemary extracts, which contain ursolic acid, reduce cancer cell proliferation and tumor progression through NFkB inhibition.⁹⁴⁻⁹⁶ By inactivating NFkB, ursolic acid prevents initiated cells from reproducing and also triggers tumor cell death.⁹⁵ This compound further down-regulates molecules that are required for tumor invasion and metastasis.⁹⁶ Ursolic acid works through its effects on NFkB to induce resting macrophage immune cells, and thus to participate in tumor cell destruction in the early stages of cancer.⁹⁷ Ursolic acid derivatives that inhibit NFkB have been shown to suppress pro-inflammatory enzyme expression in mouse models of inflammation.⁹⁸ This effect has been associated with reduced cardiac fibrosis (scar tissue) in the heart tissue of diabetic mice.⁹⁴

Garlic has now been shown to exert its anti-inflammatory and immunomodulatory effects by inhibiting NFkB.^{37,99} Garlic extracts lowered NFkB activity by up to 41% in human blood and kidney cells that had been exposed to an inflammation-provoking challenge, thus reducing the expression of certain cytokines.¹⁰⁰ These effects may be linked to the observation that a garlic compound inhibits damage to endothelial cells lining blood vessels and reduces atherosclerotic changes.¹⁰¹ Garlic's inhibition of NFkB leads to reduced production of chemicals that cause lipid peroxidation, and this could provide further protection from atherosclerosis.¹⁰² NFkB inhibition is credited for garlic's ability to protect liver cells from auto-immune damage in an animal model,¹⁰³ as well as induce cell death in leukemia.¹⁰⁴



Pomegranate fruit extract protects cells against the effects of ultraviolet B radiation by inhibiting ultraviolet light-stimulated NFkB activation.¹⁰⁵ Pomegranate fruit extract also prevented chemically induced skin cancers in mice through NFkB-mediated effects on both cancer initiation and promotion.¹⁰⁶ Blockade of NFkB by pomegranate fruit extract has shown promise in osteoarthritis by inhibiting the production of protein-digesting enzymes and inflammatory cytokines.¹⁰⁷ Pomegranate wine reduced the activation of NFkB in vascular endothelial cells by inflammatory mediators or biomechanical stresses,¹⁰⁸ thus protecting against atherosclerosis.¹⁰⁹

SUMMARY

Scientists have discovered that by controlling our DNA, nuclear factor-kappa beta (NFkB) plays a central role in determining our health and longevity. By integrating signals of inflammation, NFkB appears to be the common link between such diverse conditions as heart disease, cancer, and arthritis.

Agents that control NFkB's influence within the human body—such as omega-3 fatty acids, phytoestrogens, curcumin, garlic, licorice, ginger, rosemary, and pomegranate—hold great promise in fighting many diverse diseases and in promoting long and healthy lives.

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NFkB-Mediated Diseases:

The activation of NFkB has been linked with a wide variety of diseases in humans. Below is a partial list of disorders that scientists have linked with NFkB:

- Aging
- Headaches
- Pain
- Cardiac hypertrophy
- Type I diabetes
- Type II diabetes
- Elevated cholesterol
- Atherosclerosis
- Heart disease
- Chronic heart failure
- Angina pectoris
- Cancer
- Alzheimer's disease
- Pulmonary disease
- Kidney disease
- Gut diseases
- Skin diseases
- Sleep apnea
- Asthma
- Arthritis
- Crohn's disease
- Ocular allergy
- Appendicitis
- Pancreatitis
- Periodontitis
- Sepsis.

Source: Ahn KS, Aggarwal BB. Transcription Factor NF- κ B: A Sensor for Smoke and Stress Signals. *Ann N Y Acad Sci.* 2005 Nov;1056:218-33.

References

1. Ahn KS, Aggarwal BB. Transcription Factor NF- κ B: A Sensor for Smoke and Stress Signals. *Ann N Y Acad Sci.* 2005 Nov;1056:218-33.
2. Orozco G, Sanchez E, Collado MD, et al. Analysis of the functional NFKB1 promoter polymorphism in rheumatoid arthritis and systemic lupus erythematosus. *Tissue Antigens.* 2005 Feb;65(2):183-6.
3. Sato Y, Kato J, Takimoto R, et al. Hepatitis C virus core protein promotes proliferation of human hepatoma cells through enhancement of transforming growth factor- α expression via activation of NF- κ B. *Gut.* 2006 Mar 31;[Epub ahead of print].
4. Di Sabatino A, Morera R, Ciccocioppo R, et al. Oral butyrate for mildly to moderately active Crohn's disease. *Alimen Pharmacol Ther.* 2005 Nov 1;22(9):789-94.
5. Kawano S, Kubota T, Monden Y, et al. Blockade of NF- κ B improves cardiac function and survival after myocardial infarction. *Am J Physiol Heart Circ Physiol.* 2006 Apr 21;[Epub ahead of print].
6. Uzzo RG, Crispen PL, Golovine K, Makhov P, Horwitz EM, Kolenko VM. Diverse effects of zinc on NF- κ B and AP-1 transcription factors: implications for prostate cancer progression. *Carcinogenesis.* 2006 Apr 10;[Epub ahead of print].
7. Sriwijitkamol A, Christ-Roberts C, Berria R, et al. Reduced skeletal muscle inhibitor of kappaB content is associated with insulin resistance in subjects with type 2 diabetes: reversal by exercise training. *Diabetes.* 2006 Mar;55(3):760-7.

8. Karin M, Greten FR. NF-kappaB: linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol.* 2005 Oct;5(10):749-59.
9. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med.* 2000 Jun 29;342(26):1946-52.
10. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med.* 2005 Mar 17;352(11):1092-102.
11. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med.* 2005 Mar 17;352(11):1071-80.
12. Karin M, Yamamoto Y, Wang QM. The IKK NF-kappa B system: a treasure trove for drug development. *Nat Rev Drug Discov.* 2004 Jan;3(1):17-26.
13. Li Q, Verma IM. NF-kappaB regulation in the immune system. *Nat Rev Immunol.* 2002 Oct;2(10):725-34.
14. Karin M, Cao Y, Greten FR, Li ZW. NF-kappaB in cancer: from innocent bystander to major culprit. *Nat Rev Cancer.* 2002 Apr;2(4):301-10.
15. Maeda S, Kamata H, Luo JL, Leffert H, Karin M. IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. *Cell.* 2005 Jul 1;121(7):977-90.
16. Kamata H, Honda S, Maeda S, et al. Reactive oxygen species promote TNFalpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases. *Cell.* 2005 Mar 11;120(5):649-61.
17. Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. *Nat Rev Immunol.* 2004 Aug;4(8):641-8.
18. Becker C, Fantini MC, Schramm C, et al. TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. *Immunity.* 2004 Oct;21(4):491-501.
19. Greten FR, Eckmann L, Greten TF, et al. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell.* 2004 Aug 6;118(3):285-96.
20. Grimble RF. Effect of antioxidative vitamins on immune function with clinical applications. *Int J Vitam Nutr Res.* 1997;67(5):312-20.
21. Lee JY, Je JH, Jung KJ, Yu BP, Chung HY. Induction of endothelial iNOS by 4-hydroxyhexenal through NF-kappaB activation. *Free Radic Biol Med.* 2004 Aug 15;37(4):539-48.
22. Majano PL, Garcia-Monzon C, Garcia-Trevijano ER, et al. S-Adenosylmethionine modulates inducible nitric oxide synthase gene expression in rat liver and isolated hepatocytes. *J Hepatol.* 2001 Dec;35(6):692-9.
23. Lee HA, Hughes DA. Alpha-lipoic acid modulates NF-kappaB activity in human monocytic cells by direct interaction with DNA. *Exp Gerontol.* 2002 Jan;37(2-3):401-10.
24. Prasad AS, Bao B, Beck FW, Kucuk O, Sarkar FH. Antioxidant effect of zinc in humans. *Free Radic Biol Med.* 2004 Oct 15;37(8):1182-90.
25. Zhao G, Etherton TD, Martin KR, et al. Anti-inflammatory effects of polyunsaturated fatty acids in THP-1 cells. *Biochem Biophys Res Commun.* 2005 Oct 28;336(3):909-17.
26. Jia Y, Turek JJ. Altered NF-kappaB gene expression and collagen formation induced by polyunsaturated fatty acids. *J Nutr Biochem.* 2005 Aug;16(8):500-6.
27. Li H, Ruan XZ, Powis SH, et al. EPA and DHA reduce LPS-induced inflammation responses in HK-2 cells: evidence for a PPAR-gamma-dependent mechanism. *Kidney Int.* 2005 Mar;67(3):867-74.
28. SanGiovanni JP, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina.

29. Dijsselbloem N, Vanden BW, De NA, Haegeman G. Soy isoflavone phyto-pharmaceuticals in interleukin-6 affections. Multi-purpose nutraceuticals at the crossroad of hormone replacement, anti-cancer and anti-inflammatory therapy. *Biochem Pharmacol.* 2004 Sep 15;68(6):1171-85.
30. Kang JS, Yoon YD, Han MH, et al. Estrogen receptor-independent inhibition of tumor necrosis factor-alpha gene expression by phytoestrogen equol is mediated by blocking nuclear factor-kappaB activation in mouse macrophages. *Biochem Pharmacol.* 2005 Dec 19;71(1-2):136-43.
31. Li Y, Ahmed F, Ali S, et al. Inactivation of nuclear factor kappaB by soy isoflavone genistein contributes to increased apoptosis induced by chemotherapeutic agents in human cancer cells. *Cancer Res.* 2005 Aug 1;65(15):6934-42.
32. Valachovicova T, Slivova V, Bergman H, Shuherk J, Sliva D. Soy isoflavones suppress invasiveness of breast cancer cells by the inhibition of NF-kappaB/AP-1-dependent and -independent pathways. *Int J Oncol.* 2004 Nov;25(5):1389-95.
33. Jimi E, Ghosh S. Role of nuclear factor-kappaB in the immune system and bone. *Immunol Rev.* 2005 Dec;208:80-7.
34. Vina J, Borrás C, Gambini J, Sastre J, Pallardo FV. Why females live longer than males? Importance of the upregulation of longevity-associated genes by oestrogenic compounds. *FEBS Lett.* 2005 May 9;579(12):2541-5.
35. Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. *J Alzheimers Dis.* 2004 Aug;6(4):367-77.
36. Holt PR, Katz S, Kirshoff R. Curcumin therapy in inflammatory bowel disease: a pilot study. *Dig Dis Sci.* 2005 Nov;50(11):2191-3.
37. Aggarwal BB, Shishodia S. Suppression of the nuclear factor-kappaB activation pathway by spice-derived phytochemicals: reasoning for seasoning. *Ann NY Acad Sci.* 2004 Dec;1030:434-41.
38. Jian YT, Mai GF, Wang JD, et al. Preventive and therapeutic effects of NF-kappaB inhibitor curcumin in rats colitis induced by trinitrobenzene sulfonic acid. *World J Gastroenterol.* 2005 Mar 28;11(12):1747-52.
39. Salh B, Assi K, Templeman V, et al. Curcumin attenuates DNB-induced murine colitis. *Am J Physiol Gastrointest Liver Physiol.* 2003 Jul;285(1):G235-43.
40. Nanji AA, Jokelainen K, Tipoe GL, et al. Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-kappa B-dependent genes. *Am J Physiol Gastrointest Liver Physiol.* 2003 Feb;284(2):G321-7.
41. Leclercq IA, Farrell GC, Sempoux C, dela PA, Horsmans Y. Curcumin inhibits NF-kappaB activation and reduces the severity of experimental steatohepatitis in mice. *J Hepatol.* 2004 Dec;41(6):926-34.
42. Cole GM, Morihara T, Lim GP, et al. NSAID and Antioxidant Prevention of Alzheimer's Disease: Lessons from In Vitro and Animal Models. *Ann NY Acad Sci.* 2004 Dec;1035:68-84.
43. Kang G, Kong PJ, Yuh YJ, 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.* 2004 Mar;94(3):325-8.
44. Witek-Zawada B, Koj A. Regulation of expression of stromelysin-1 by proinflammatory cytokines in mouse brain astrocytes. *J Physiol Pharmacol.* 2003 Dec;54(4):489-96.
45. Yang F, Lim GP, Begum AN, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. *J Biol Chem.* 2005 Feb 18;280(7):5892-901.
46. Giri RK, Rajagopal V, Kalra VK. Curcumin, the active constituent of turmeric, inhibits amyloid peptide-induced cytochemokine gene expression and CCR5-mediated chemotaxis of THP-1 monocytes by modulating early growth response-1 transcription factor. *J Neurochem.* 2004 Dec;91(5):1199-210.
47. Shakibaei M, Schulze-Tanzil G, John T, Mobasheri A. Curcumin protects human chondrocytes from IL-1beta-induced inhibition of collagen type II and beta1-integrin expression and activation of caspase-3: an immunomorphological study. *Ann*

48. Banerjee M, Tripathi LM, Srivastava VM, Puri A, Shukla R. Modulation of inflammatory mediators by ibuprofen and curcumin treatment during chronic inflammation in rat. *Immunopharmacol Immunotoxicol*. 2003 May;25(2):213-24.
49. Lev-Ari S, Strier L, Kazanov D, et al. Curcumin synergistically potentiates the growth-inhibitory and pro-apoptotic effects of celecoxib in osteoarthritis synovial adherent cells. *Rheumatology (Oxford)*. 2006 Feb;45(2):171-7.
50. Duvoix A, Blasius R, Delhalle S, et al. Chemopreventive and therapeutic effects of curcumin. *Cancer Lett*. 2005 Jun 8;223(2):181-90.
51. Aggarwal BB, Shishodia S, Takada Y, et al. Curcumin suppresses the paclitaxel-induced nuclear factor-kappaB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. *Clin Cancer Res*. 2005 Oct 15;11(20):7490-8.
52. Thomas RK, Sos ML, Zander T, et al. Inhibition of nuclear translocation of nuclear factor-kappaB despite lack of functional I kappa B alpha protein overcomes multiple defects in apoptosis signaling in human B-cell malignancies. *Clin Cancer Res*. 2005 Nov 15;11(22):8186-94.
53. Aggarwal S, Ichikawa H, Takada Y, et al. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of I kappa B alpha kinase and Akt activation. *Mol Pharmacol*. 2006 Jan;69(1):195-206.
54. Kim K, Ryu K, Ko Y, Park C. Effects of nuclear factor-kappaB inhibitors and its implication on natural killer T-cell lymphoma cells. *Br J Haematol*. 2005 Oct;131(1):59-66.
55. Baliga MS, Katiyar SK. Chemoprevention of photocarcinogenesis by selected dietary botanicals. *Photochem Photobiol Sci*. 2006 Feb;5(2):243-53.
56. Bush JA, Cheung KJ, Jr., Li G. Curcumin induces apoptosis in human melanoma cells through a Fas receptor/caspase-8 pathway independent of p53. *Exp Cell Res*. 2001 Dec 10;271(2):305-14.
57. LoTempio MM, Veena MS, Steele HL, et al. Curcumin suppresses growth of head and neck squamous cell carcinoma. *Clin Cancer Res*. 2005 Oct 1;11(19 Pt 1):6994-7002.
58. Deeb D, Jiang H, Gao X, et al. Curcumin sensitizes prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L by inhibiting nuclear factor-kappaB through suppression of I kappa B alpha phosphorylation. *Mol Cancer Ther*. 2004 Jul;3(7):803-12.
59. Kumar AP, Garcia GE, Ghosh R, et al. 4-Hydroxy-3-methoxybenzoic acid methyl ester: a curcumin derivative targets Akt/NF kappa B cell survival signaling pathway: potential for prostate cancer management. *Neoplasia*. 2003 May;5(3):255-66.
60. Hong JH, Ahn KS, Bae E, Jeon SS, Choi HY. The effects of curcumin on the invasiveness of prostate cancer in vitro and in vivo. *Prostate Cancer Prostatic Dis*. 2006 Jan 3.
61. Ramachandran C, Rodriguez S, Ramachandran R, et al. Expression profiles of apoptotic genes induced by curcumin in human breast cancer and mammary epithelial cell lines. *Anticancer Res*. 2005 Sep;25(5):3293-302.
62. Divya CS, Pillai MR. Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. *Mol Carcinog*. 2006 May;45(5):320-32.
63. Plummer SM, Holloway KA, Manson MM, 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*. 1999 Oct 28;18(44):6013-20.
64. Garcea G, Berry DP, Jones DJ, et al. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. *Cancer Epidemiol Biomarkers Prev*. 2005 Jan;14(1):120-5.
65. Chen A, Xu J, Johnson AC. Curcumin inhibits human colon cancer cell growth by suppressing gene expression of epidermal growth factor receptor through reducing the activity of the transcription factor Egr-1. *Oncogene*. 2006 Jan 12;25(2):278-87.

66. Jung EM, Lim JH, Lee TJ, et al. Curcumin sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through reactive oxygen species-mediated upregulation of death receptor 5 (DR5). *Carcinogenesis*. 2005 Nov;26(11):1905-13.
67. Lev-Ari S, Strier L, Kazanov D, et al. Celecoxib and curcumin synergistically inhibit the growth of colorectal cancer cells. *Clin Cancer Res*. 2005 Sep 15;11(18):6738-44.
68. Shishodia S, Potdar P, Gairola CG, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates cigarette smoke-induced NF-kappaB 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*. 2003 Jul;24(7):1269-79.
69. Lee J, Im YH, Jung HH, et al. Curcumin inhibits interferon-alpha induced NF-kappaB and COX-2 in human A549 non-small cell lung cancer cells. *Biochem Biophys Res Commun*. 2005 Aug 26;334(2):313-8.
70. Radhakrishna PG, Srivastava AS, Hassanein TI, Chauhan DP, Carrier E. Induction of apoptosis in human lung cancer cells by curcumin. *Cancer Lett*. 2004 May 28;208(2):163-70.
71. Bharti AC, Donato N, Singh S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and I kappa B alpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. *Blood*. 2003 Feb 1;101(3):1053-62.
72. Han SS, Keum YS, Seo HJ, Surh YJ. Curcumin suppresses activation of NF-kappaB and AP-1 induced by phorbol ester in cultured human promyelocytic leukemia cells. *J Biochem Mol Biol*. 2002 May 31;35(3):337-42.
73. Tomita M, Kawakami H, Uchihara JN, et al. Curcumin (diferuloylmethane) inhibits constitutive active NF-kappaB, leading to suppression of cell growth of human T-cell leukemia virus type I-infected T-cell lines and primary adult T-cell leukemia cells. *Int J Cancer*. 2006 Feb 1;118(3):765-72.
74. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res*. 2001 Jul;21(4B):2895-900.
75. Sharma RA, Euden SA, Platton SL, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res*. 2004 Oct 15;10(20):6847-54.
76. Wang ZY, Nixon DW. Licorice and cancer. *Nutr Cancer*. 2001;39(1):1-11.
77. Shibata S. A drug over the millennia: pharmacognosy, chemistry, and pharmacology of licorice. *Yakugaku Zasshi*. 2000 Oct;120(10):849-62.
78. Wang JY, Guo JS, Li H, Liu SL, Zern MA. Inhibitory effect of glycyrrhizin on NF-kappaB binding activity in CCl4- plus ethanol-induced liver cirrhosis in rats. *Liver*. 1998 Jun;18(3):180-5.
79. Kang OH, Kim JA, Choi YA, et al. Inhibition of interleukin-8 production in the human colonic epithelial cell line HT-29 by 18 beta-glycyrrhetic acid. *Int J Mol Med*. 2005 Jun;15(6):981-5.
80. Kang JS, Yoon YD, Cho IJ, et al. Glabridin, an isoflavan from licorice root, inhibits inducible nitric-oxide synthase expression and improves survival of mice in experimental model of septic shock. *J Pharmacol Exp Ther*. 2005 Mar;312(3):1187-94.
81. Lee YS, Kang YS, Lee JS, Nicolova S, Kim JA. Involvement of NADPH oxidase-mediated generation of reactive oxygen species in the apoptotic cell death by capsaicin in HepG2 human hepatoma cells. *Free Radic Res*. 2004 Apr;38(4):405-12.
82. Chen CW, Lee ST, Wu WT, et al. Signal transduction for inhibition of inducible nitric oxide synthase and cyclooxygenase-2 induction by capsaicin and related analogs in macrophages. *Br J Pharmacol*. 2003 Nov;140(6):1077-87.
83. Kim CS, Kawada T, Kim BS, et al. Capsaicin exhibits anti-inflammatory property by inhibiting I kappa B-alpha degradation in LPS-stimulated peritoneal macrophages. *Cell Signal*. 2003 Mar;15(3):299-306.
84. Zhang J, Nagasaki M, Tanaka Y, Morikawa S. Capsaicin inhibits growth of adult T-cell leukemia cells. *Leuk Res*. 2003 Mar;27(3):275-83.

85. Patel PS, Yang S, Li A, Varney ML, Singh RK. Capsaicin regulates vascular endothelial cell growth factor expression by modulation of hypoxia inducing factor-1alpha in human malignant melanoma cells. *J Cancer Res Clin Oncol*. 2002 Sep;128(9):461-8.
86. Murakami Y, Shoji M, Hirata A, et al. Dehydrodiisoeugenol, an isoeugenol dimer, inhibits lipopolysaccharide-stimulated nuclear factor kappa B activation and cyclooxygenase-2 expression in macrophages. *Arch Biochem Biophys*. 2005 Feb 15;434(2):326-32.
87. Murakami Y, Shoji M, Hanazawa S, Tanaka S, Fujisawa S. Preventive effect of bis-eugenol, a eugenol ortho dimer, on lipopolysaccharide-stimulated nuclear factor kappa B activation and inflammatory cytokine expression in macrophages. *Biochem Pharmacol*. 2003 Sep 15;66(6):1061-6.
88. Ozalp N, Saroglu I, Sonmez H. Evaluation of various root canal filling materials in primary molar pulpectomies: an in vivo study. *Am J Dent*. 2005 Dec;18(6):347-50.
89. Damle SG, Nadkarni UM. Calcium hydroxide and zinc oxide eugenol as root canal filling materials in primary molars: a comparative study. *Aust Endod J*. 2005 Dec;31(3):114-9.
90. Takada Y, Murakami A, Aggarwal BB. Zerumbone abolishes NF-kappaB and IkappaBalpha kinase activation leading to suppression of antiapoptotic and metastatic gene expression, upregulation of apoptosis, and downregulation of invasion. *Oncogene*. 2005 Oct 20;24(46):6957-69.
91. Kim SO, Kundu JK, Shin YK, et al. [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-kappaB in phorbol ester-stimulated mouse skin. *Oncogene*. 2005 Apr 7;24(15):2558-67.
92. Kim SO, Chun KS, Kundu JK, Surh YJ. Inhibitory effects of [6]-gingerol on PMA-induced COX-2 expression and activation of NF-kappaB and p38 MAPK in mouse skin. *Biofactors*. 2004;21(1-4):27-31.
93. Grzanna R, Lindmark L, Frondoza CG. Ginger—an herbal medicinal product with broad anti-inflammatory actions. *J Med Food*. 2005;8(2):125-32.
94. Huang TH, Yang Q, Harada M, et al. Pomegranate flower extract diminishes cardiac fibrosis in Zucker diabetic fatty rats: modulation of cardiac endothelin-1 and nuclear factor-kappaB pathways. *J Cardiovasc Pharmacol*. 2005 Dec;46(6):856-62.
95. Hsu YL, Kuo PL, Lin CC. Proliferative inhibition, cell-cycle dysregulation, and induction of apoptosis by ursolic acid in human non-small cell lung cancer A549 cells. *Life Sci*. 2004 Sep 24;75(19):2303-16.
96. Shishodia S, Majumdar S, Banerjee S, Aggarwal BB. Ursolic acid inhibits nuclear factor-kappaB activation induced by carcinogenic agents through suppression of IkappaBalpha kinase and p65 phosphorylation: correlation with down-regulation of cyclooxygenase 2, matrix metalloproteinase 9, and cyclin D1. *Cancer Res*. 2003 Aug 1;63(15):4375-83.
97. You HJ, Choi CY, Kim JY, et al. Ursolic acid enhances nitric oxide and tumor necrosis factor-alpha production via nuclear factor-kappaB activation in the resting macrophages. *FEBS Lett*. 2001 Dec 7;509(2):156-60.
98. Suh N, Honda T, Finlay HJ, et al. Novel triterpenoids suppress inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX-2) in mouse macrophages. *Cancer Res*. 1998 Feb 15;58(4):717-23.
99. Geng Z, Rong Y, Lau BH. S-allyl cysteine inhibits activation of nuclear factor kappa B in human T cells. *Free Radic Biol Med*. 1997;23(2):345-50.
100. Keiss HP, Dirsch VM, Hartung T, et al. Garlic (*Allium sativum* L.) modulates cytokine expression in lipopolysaccharide-activated human blood thereby inhibiting NF-kappaB activity. *J Nutr*. 2003 Jul;133(7):2171-5.
101. Ho SE, Ide N, Lau BH. S-allyl cysteine reduces oxidant load in cells involved in the atherogenic process. *Phytomedicine*. 2001 Jan;8(1):39-46.
102. Ide N, Lau BH. Garlic compounds minimize intracellular oxidative stress and inhibit nuclear factor-kappa b activation. *J Nutr*. 2001 Mar;131(3s):1020S-6S.
103. Bruck R, Aeed H, Brazovsky E, Noor T, Hershkoviz R. Allicin, the active component of garlic, prevents immune-mediated,

concanavalin A-induced hepatic injury in mice. *Liver Int.* 2005 Jun;25(3):613-21.

104. Dirsch VM, Antlsperger DS, Hentze H, Vollmar AM. Ajoene, an experimental anti-leukemic drug: mechanism of cell death. *Leukemia.* 2002 Jan;16(1):74-83.

105. Afaq F, Malik A, Syed D, et al. Pomegranate fruit extract modulates UV-B-mediated phosphorylation of mitogen-activated protein kinases and activation of nuclear factor kappa B in normal human epidermal keratinocytes paragraph sign. *Photochem Photobiol.* 2005 Jan;81(1):38-45.

106. Afaq F, Saleem M, Krueger CG, Reed JD, Mukhtar H. Anthocyanin- and hydrolyzable tannin-rich pomegranate fruit extract modulates MAPK and NF-kappaB pathways and inhibits skin tumorigenesis in CD-1 mice. *Int J Cancer.* 2005 Jan 20;113(3):423-33.

107. Ahmed S, Wang N, Hafeez BB, Cheruvu VK, Haqqi TM. Punica granatum L. extract inhibits IL-1beta-induced expression of matrix metalloproteinases by inhibiting the activation of MAP kinases and NF-kappaB in human chondrocytes in vitro. *J Nutr.* 2005 Sep;135(9):2096-102.

108. Schubert SY, Neeman I, Resnick N. A novel mechanism for the inhibition of NF-kappaB activation in vascular endothelial cells by natural antioxidants. *FASEB J.* 2002 Dec;16(14):1931-3.

109. Tzima E, Irani-Tehrani M, Kiosses WB, et al. A mechanosensory complex that mediates the endothelial cell response to fluid shear stress. *Nature.* 2005 Sep 15;437(7057):426-31.

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