Suppression of the Nuclear Factor-κB Activation Pathway by Spice-Derived Phytochemicals

Reasoning for Seasoning

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ABSTRACT: The activation of nuclear transcription factor κB has now been linked with a variety of inflammatory diseases, including cancer, atherosclerosis, myocardial infarction, diabetes, allergy, asthma, arthritis, Crohn's disease, multiple sclerosis, Alzheimer's disease, osteoporosis, psoriasis, septic shock, and AIDS. Extensive research in the last few years has shown that the pathway that activates this transcription factor can be interrupted by phytochemicals derived from spices such as turmeric (curcumin), red pepper (capsaicin), cloves (eugenol), ginger (gingerol), cumin, anise, and fennel (anethol), basil and rosemary (ursolic acid), garlic (diallyl sulfide, *S*-allylmercaptocysteine, ajoene), and pomegranate (ellagic acid). For the first time, therefore, research provides "reasoning for seasoning."

KEYWORDS: NF-κB; TNF; inflammation

INTRODUCTION

Q: "by"? or "be thy food"?

Almost 25 centuries ago, Hippocrates remarked, "Let food be thy medicine and medicine by thy food." This differs little from our adage, "You are what you eat." Vasco da Gama, a Portuguese sailor, left for India almost 500 years ago in search of spices, and the route he used is called "the spice route." Why were spices so precious that he was willing to make this arduous journey? People of da Gama's time revered spices not just for their brilliant colors and taste but also for their medicinal value. The true medicinal value of spices, however, is only now beginning to be unveiled.

Nuclear transcription factor κB (NF-κB), discovered by David Baltimore in 1986, is a ubiquitous factor that resides in the cytoplasm but, when activated, is translocated to the nucleus, where it induces gene transcription. NF-κB is activated by free radicals, inflammatory stimuli, carcinogens, tumor promoters, endotoxin, γ radiation, ultraviolet (UV) light, and x-rays.[1] On activation, NF-κB induces the ex-

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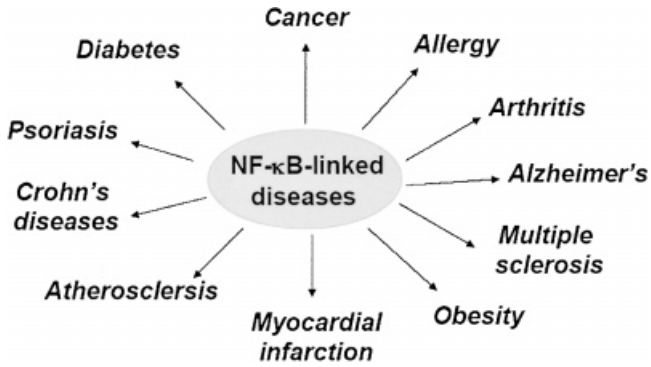

FIGURE 1. NF-κB-linked diseases.

pression of more than 200 genes that have been shown to suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemoresistance, radioresistance, and inflammation.[1–3] The activated form of NF-κB has been found to mediate cancer,[1,4,5] atherosclerosis,[6] myocardial infarction,[7] diabetes,[8] allergy,[9,10] asthma,[11] arthritis,[12] Crohn's disease,[13] multiple sclerosis,[14] Alzheimer's disease,[15,16] osteoporosis, psoriasis, septic shock, AIDS, and other inflammatory diseases.[17–19] That NF-κB has been linked to this wide variety of diseases is not too surprising because most diseases are caused by dysregulated inflammation.[20] Thus, agents that can suppress NF-κB activation, in principle, have the potential to prevent or delay the onset of or treat NF-κB-linked diseases (FIG. 1). This article describes, in brief, the components of spices that can suppress the NF-κB activation pathway (FIG. 2).

Most agents derived from spices have antioxidant and anti-inflammatory activities. Shobana and Naidu[21] examined the antioxidant activities of commonly used spices, including garlic, ginger, onion, mint, cloves, cinnamon, and pepper. Among the spices tested, cloves exhibited the greatest antioxidant activity and onion showed the least. The relative antioxidant activities decreased in the following order: cloves, cinnamon, pepper, ginger, garlic, mint, and onion. The antioxidant activities of spice extracts were retained even after boiling for 30 min at 100°C, indicating that the spice constituents were resistant to thermal denaturation. The antioxidant activities of these dietary spices suggest that, besides imparting flavor to foods, they possess potential health benefits.

TURMERIC

The medicinal use of turmeric (also called curry) goes back almost 5,000 years in *ayurvedic* (science of long-life) medicine as an anti-inflammatory agent. Extensive research within the last century has indicated that curcumin, the active component in turmeric, can prevent different cancers (chemoprevention),[22] decrease blood cholesterol, suppress myocardial infarction, improve arthritis-associated symptoms,

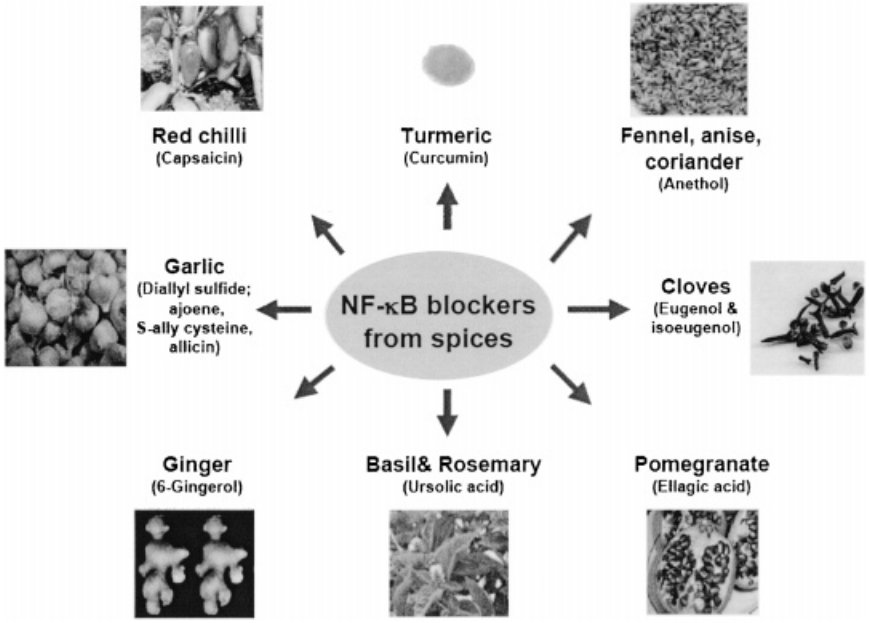

FIGURE 2. Suppression of NF-κB by spice polyphenols.

treat Crohn's disease, suppress psoriasis, and prevent Alzheimer's disease (for references, see Aggarwal *et al.*[22]). We showed that curcumin is a potent blocker of NF-κB activation[23] through the inhibition of IκB kinase (IKK),[24] a kinase that is needed for NF-κB activation. We also showed that curcumin downregulates cyclin D1,[25] a gene overexpressed in various tumors and proliferating control cells; suppresses the proliferation of various tumor cells, including prostate,[26] breast,[27] acute myelogenous leukemia,[28] and multiple myeloma;[29] and induces apoptosis. More recently, we have shown that curcumin can prevent osteoclastogenesis,[30] a process closely associated with bone loss. Curcumin also can suppress cigarette smoke-induced carcinogenesis[31] and the expression of cell surface adhesion molecules.[32] The activity of curcumin against psoriasis is believed to be mediated through the inhibition of phosphorylase kinase.[33] Other effects of curcumin were recently reviewed elsewhere.[34]

RED CHILI

Red chili, whose active component is capsaicin, determines the "hotness" or "spiciness" of food. Capsaicin has been shown to induce apoptosis in the nerve endings and thus induce "anesthesia" or numbness. It is used in the treatment of certain kinds of headache and pain. Because it selectively induces apoptosis of tumor cells,[35] its potential as an anticancer agent has been suggested.[36] We have shown that

capsaicin can suppress NF-κB activation by suppressing the degradation of IκBα, an inhibitor of NF-κB.[37]

FENNEL AND ANISE

Fennel (*Foeniculum vulgare*) and anise (*Pimpinella anisum*) are plants that have been used as estrogenic agents for millennia. Specifically, they are reputed to increase milk secretion, promote menstruation, facilitate birth, alleviate the symptoms of the male climacteric, and increase libido. The main constituent of the essential oils of fennel and anise, anethol, was considered to be the active estrogenic agent, but further research suggests that the actual pharmacologically active agents are polymers of anethol, such as dianethol and photoanethol.[38,39] Anethol has been shown to block both inflammation and carcinogenesis. It has been shown to have antioxidant and anti-inflammatory activities. We have shown that anethole can suppress NF-κB activation through the inhibition of IκBα degradation.[40,41]

CLOVES

Both the anti-inflammatory and antioxidant activities of cloves are well established. The active components in cloves are eugenol and isoeugenol. We have shown that these compounds can suppress NF-κB activation by suppressing IκBα degradation.[41] Murakami *et al.*[42] found that bis-eugenol, but not eugenol, inhibited the degradation of IκBα and inhibited the expression of inflammatory cytokines at both the gene and protein levels.

GINGER

This spice is used for the treatment of nausea associated with motion or chemotherapy[43] and of ulcers.[44] The active component, gingerol, has been shown to exhibit chemopreventive potential.[45] Gingerol also inhibits the enzymes nitric oxide synthase and cyclooxygenase (COX-2), which are known to be regulated through NF-κB.[46] Because gingerol can suppress platelet aggregation, synthetic gingerol analogues, designed to have greater potencies as platelet aggregation inhibitors similar to aspirin, have potential value in cardiovascular disease.[47]

BASIL

The chemopreventive activity of "holy basil" has been described. Ursolic acid, a triterpenoid derived from basil and rosemary, was found to suppress NF-κB activation through the inhibition of IKK; this leads to the suppression of cyclin D1, COX-2, and matrix metalloproteinase-9.[48]

GARLIC

Garlic (*Allium sativum*) is used as a spice in many different cuisines. It is also used for the prevention and treatment of many diseases, especially diseases of the

gastrointestinal tract. Diallyl sulfide, a thioether found in garlic, has been linked to the prevention of cancer. Diallyl sulfide was found to suppress tumorigenesis, in part through inhibition of the cytochrome P450 IIE1 isoform responsible for the activation of carcinogens. The organosulfur compound ajoene, a constituent of garlic, has been shown to induce apoptosis in a leukemic cell line as well as in blood cells of a leukemic patient.[49] The garlic compound *S*-allyl cysteine (SAC) has been shown to reduce oxidant load in cells involved in the atherogenic process and to block NF-κB activation.[50,51] This suppression of NF-κB may make SAC useful for the prevention of atherosclerosis. Garlic may indeed promote an anti-inflammatory environment by cytokine modulation in human blood that leads to an overall inhibition of NF-κB activity in the surrounding tissue.[52]

POMEGRANATE

Dried pomegranate (*Punica granatum*) seeds are widely used as a spice in cooking. The pomegranate juice flavonoids have been found to inhibit low-density lipoprotein oxidation and cardiovascular diseases in atherosclerotic mice and in humans.[53] Pomegranate juice consumption has been found to inhibit the activity of serum angiotensin-converting enzyme and to reduce systolic blood pressure.[54] Recent findings show that pomegranate can suppress NF-κB activation through a novel mechanism in vascular endothelial cells.[55]

CONCLUSIONS

This mini-review clearly demonstrates that a large number of spice-derived phytochemicals can mediate therapeutic effects, possibly through suppression of the NF-κB activation pathway.[56] Future research may use these phytochemicals in the design of better blockers of NF-κB. However, manipulation of these compounds may increase their side effects. These possibilities provide the real "reasoning for seasoning."

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