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Chronic Diseases Caused by Chronic Inflammation Require Chronic Treatment: Anti-inflammatory Role of Dietary Spices

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Abstract

Noncommunicable chronic diseases such as inflammatory bowel diseases, cancer, diabetes, obesity, and pulmonary, cardiovascular, and neurodegenerative diseases are becoming the leading cause of death throughout the world. Unhealthy diet, smoking, lack of exercise, stress, radiation exposure, and environmental pollution are among the common causes of chronic diseases. Most of these risk factors are closely linked to chronic inflammation, which leads to the development of various chronic diseases. Diets high in fruits, vegetables, legumes, fiber, and certain spices have been shown to suppress chronic inflammation and prevent the development of chronic diseases. In this review we discuss the evidence for the molecular basis of inflammation and how inflammation mediates most chronic diseases. We also present clinical and experimental models showing the molecular effects of selected spices and spice-derived nutraceuticals such as cardamonin, curcumin, capsaicin, gingerol, thymoquinone, and piperine on these inflammatory pathways and the potential role of nutraceuticals in preventing chronic diseases.

Keywords: Inflammation; Chronic diseases, Spices; Inflammatory pathways; Nutraceuticals

Introduction

Chronic diseases, defined as diseases of long duration and slow progression, include inflammatory bowel disease (IBD), heart disease, stroke, cancer, chronic respiratory diseases, neurological diseases, obesity, and diabetes. According to the U.S. Centers for Disease Control and Prevention, together these diseases account for 63% of all deaths worldwide and about 70% of all deaths (1.7 million each year) in the United States. The chief causes of these diseases are the changes in diet and lifestyle brought about by industrialization, economic development, urbanization, and market globalization, all of which have accelerated over the past 10 years. Most chronic diseases are preventable because they are linked to lifestyle. A modified diet, daily exercise, and avoiding tobacco can prolong life by preventing the occurrence of chronic diseases or improving the management of illnesses that do occur. Among these modifiable determinants of chronic diseases, nutrition may be the most influential, and scientific evidence increasingly supports the view that alterations in diet have strong effects on health throughout life [1].

Over the past few decades, studies have investigated the possible protective role of plant foods against chronic diseases. Several epidemiological studies have revealed that greater consumption of fruits and vegetables is associated with a lower risk of chronic diseases such as cancer [2]. The World Health Organization stated that diets high in fruits and vegetables may have a protective effect against many cancers. More specifically, intake of fruits and vegetables probably reduce the risk for colorectal, pancreatic, lung, oral, esophageal, and stomach cancers. Conversely, obesity, excess consumption of red and preserved meat, alcohol may be associated with an increased risk of cancer. (http://www.who.int/dietphysicalactivity).

Among the foods containing beneficial active compounds, spices have their own particular importance. Some common spices and their bioactive components are shown in Figure 1. In general, spices are consumed in the form of dried seed, fruit, root, bark, or vegetative substance. Spices usually are used in nutritionally insignificant quantities as a food additive for flavor or color or as a preservative. Spices also are sometimes eaten as vegetables or used for other purposes, such as medicine, religious rituals, cosmetics, or perfumery. In this review, we will discuss the link between inflammation and chronic diseases, the anti-inflammatory activities of some spices and spice-derived nutraceuticals, and the use of spices and spice-derived nutraceuticals in the prevention and treatment of chronic diseases.

Role of Inflammation in Chronic Disease

Inflammation is a response of the immune system to injury, irritation, or infection caused by invading pathogens, radiation exposure, very high or low temperatures, or autoimmune processes. Therefore, inflammation is a mechanism for removing damaged cells, irritants, or pathogens. Inflammation is considered to be beneficial when it is short term and under control within the immune system (acute inflammation). Inflammation that persists longer is known as chronic inflammation. This inflammation is characterized by the simultaneous destruction and healing of tissue [3].

The various factors known to induce chronic inflammatory responses also cause numerous chronic diseases. These factors include bacterial, viral, and parasitic infections (eg, *Helicobacter pylori*, Epstein-Barr virus, human immunodeficiency virus, flukes, schistosomes); chemical irritants (eg, tumor promoters such as phorbol ester 12-O-tetradecanoylphorbol-13-acetate, also known as phorbolmyristate acetate); andnondigestible particles (eg, asbestos, silica) [4,5]. Inflammation produces reactive oxygen species and reactive nitrogen species, which cause oxidative damage and further lead to chronic diseases [6]. Inflammation also recruits leukocytes that

secrete inflammatory cytokines and angiogenic factors to the site of tissue insult. These cytokines are required for proper wound healing and to stimulate epithelial cell proliferation; however, if uncontrolled these cytokines can lead to inflammatory disorders. All these inflammatory products have shown to be regulated by the nuclear transcription factor NF-κB, which is considered the master molecule of inflammation.

Figure 1: Anti-inflammatory spices and their bioactive molecules.

The transcription factor NF-κB is activated in response to a wide variety of stimuli such as stress (physical, psychological, mechanical, or chemical), tobacco, radiation, asbestos, dietary agents, environmental pollutants, obesity, and various infectious agents. NF-κB is activated by at least two separate pathways "canonical or classical" and "non-canonical or alternate". Canonical pathway is triggered by microbial products and proinflammatory cytokines such as TNF-α and IL-1, usually leading to activation of RelA (p65)- or cRel (p50/p105)- containing complexes while non-canonical or alternative pathway is activated by lymphotoxin β, CD40 ligand, B cell activating factor, and receptor activator of NF-κB ligand, resulting in activation of RelB/p52 complexes [7]. The NF-κB activation pathway typically involves activation of NF-κB inhibitor α (IκBα) kinase (known as IKK), leading to phosphorylation, ubiquitination, and degradation of IκBα, nuclear translocation of the p50 and p65 subunits of NF-κB, DNA binding and transcription of NF-κB target gene. Although canonical NF-κB activation is mediated through the activation of IKKβ, noncanonical activation involves IKKα [8]. Binding of NF-kB on target genes results in transcription of over 500 genes involved in inflammation, immunoregulation, growth regulation, carcinogenesis, and apoptosis [7]. The activation of NF-κB in various immune cells, including T cells, B cells, macrophages, dendritic cells, and neutrophils, leads to expression of proinflammatory cytokines. The activation of NF-κB has also been shown to production of proinflammatory cytokine and chemokine in disease tissue from patients [9]. Another study also showed that proinflammatory cytokine production in human atherosclerotic plaques is NF-κB-dependent [10]. Thus, NF-κB plays a crucial role in inflammation.

Besides NF-κB, STAT3 pathway is also known to contribute to the inflammatory microenvironment. STAT3 is activated by many cytokines and growth factors, including epidermal growth factor, platelet-derived growth factor, and IL-6, oncogenic proteins, such as Src and Ras as well as by numerous carcinogens, such as cigarette smoke and tumor promoters [11]. The activation of STAT3 is regulated by phosphorylation at its tyrosine residue at 705 by receptor and nonreceptor protein tyrosine kinases. The phosphorylation of STAT3 in the cytoplasm leads to its dimerization, translocation into the nucleus, and DNA binding which result in transcription of genes that regulate inflammation, cell proliferation, differentiation, and apoptosis [11]. In addition, phosphorylation at serine 727 has been implicated in the activation of STAT3 [12]. STAT3 promote inflammatory environment by regulating the expression of cytokines, chemokines and other mediators [13,14]. STAT3 is highly interconnected with NF-κB signaling and interacts with NF-κB. For example the pro-inflammatory cytokine IL-6, encoded by NF-κB target genes, is important for STAT3 activation. STAT3 and NF-κB also co-regulate numerous oncogenic and inflammatory genes [15]. These indicate that NF-κB and STAT3 alone or in combination produce inflammation and inflammatory microenvironment.

There is a strong association between chronic inflammatory conditions and chronic diseases. Chronic inflammation damages the cells of the brain, heart, arterial walls, and other anatomic structures; this damage leads to various inflammatory chronic diseases. Studies on the causes of inflammation at the molecular level showed that numerous biomarkers are involved in the process of inflammation. Many of these biomarkers—transcription factors such as NF-κB and STAT3; inflammatory cytokines and chemokines such as tumor necrosis factor-alpha (TNF)-α, interleukin (IL)-1, IL-6, IL-8, and MCP-1; inflammatory enzymes such as cyclooxygenase (COX)-2, 5-lipoxygenase (LOX), 12-LOX, and matrix metalloproteinases (MMPs);

and other factors such as prostate-specific antigen (PSA), C-reactive protein (CRP), adhesion molecules, vascular endothelial growth factor (VEGF), and TWIST are found common in most chronic diseases [16].

IBD is a group of inflammatory conditions of the colon and small intestine comprising in Crohn disease (CD) and ulcerative colitis (UC). IBD causes inflammation anywhere along the lining of digestive tract and often spreads deep into affected tissues. A number of cytokines/chemokines and their receptors have shown to be upregulated in patients with IBD. For example, the overproduction of various cytokines such as IL-2, IL-12, IL-18, IFN-γ, and TNF-α has been well documented in patients with CD [17,18]. A pilot study of 33 IBD patients (19 with CD and 14 with UC) and 33 matched healthy controls showed that cytokine and chemokine levels increased with disease severity [19]. Kader et al. [20] identified IBD serum biomarkers such as cytokines, growth factors, and soluble receptors in 65 patients with CD and 23 with UC; the researchers found that the levels of 4 cytokines [placental growth factor (PLGF), IL-7, IL-12p40, and TGF-β1] were significantly higher in patients with clinical remission than in those with active disease. Besides these, increased levels of NF-κB, myeloperoxidase, and fecal calprotectin were reported in healthy twins with IBD [21]. The association of STAT3 in IBD was also described in CD and UC populations [22]. These studies indicate that inflammatory transcription factors and cytokines are integral to IBD.

Epidemiological evidence points to a connection between inflammation and a predisposition for the development of cancer, ie, long-term inflammation leads to the development of dysplasia. Various pro-inflammatory biomarkers have been found to be elevated in several cancers. The pro-inflammatory biomarker STAT3 was found to be activated in 82% of patients with late-stage prostate cancer [23-25]. Another inflammatory transcription factor, NF-κB, was found in 60% of colorectal cancer patients [26]. Also, the overproduction of cytokines has shown to be associated with cancer-related fatigue [27].

Inflammation has also been shown to mediate cardiovascular diseases [28,29]. CRP, an acute-phase protein produced by the liver during bacterial infections and inflammation, was found to be a common marker for detecting cardiovascular and atherosclerotic diseases [30]. Inflammation is also a cause of autoimmune diseases such as rheumatoid arthritis, in which excess levels of cytokines such as TNF-α, IL-6, IL-1β, and IL-8 are often found [31]. Multiple sclerosis, another autoimmune disease, is caused by chronic inflammation in the central nervous system. Activated NF-κB is found in patients with multiple sclerosis [32]. Elevated levels of other cytokines such as IL-1α, IL-2, IL-4, IL-6, IL-10, IFN-γ, TGF-β1,TGF-β2, and TNF-α have also been found in frozen sections of central nervous system tissue from multiple sclerosis patients [33]. Similarly, cerebrospinal fluid samples from patients with Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, and schizophrenia have been shown to exhibit the overexpression of cytokines and NF-κB [34]. Likewise, in patients with diabetes, high levels of CRP, IL-6, IL-1, and TNF-α—along with abnormal expression of NF-κB—have been observed [35-37]. The studies listed above indicate mounting evidence of a stronger association between inflammation and chronic diseases than was once believed.

Role of Spices in Regulation of Inflammation

For centuries, spices available in nature have been used as medicines against inflammation. Numerous studies have shown that

some spices have great potential to inhibit chronic inflammation. Turmeric, one of the common spices used in daily life in Asian countries, has been used as a medicine against inflammation. The active component of turmeric, curcumin, is a potent inhibitor of inflammation. Studies on animal models have shown that curcumin is effective in preventing UC and inflammation. Over the past few decades, curcumin has been shown to inhibit myeloperoxidase, COX-1, COX-2, LOX, TNF-α, IFN-γ, iNOS, and NF-κB in patients with IBD [38].

Curcumin at concentrations of 0.5 and 20 μM inhibited pro-inflammatory cytokine (TNF-α, IL-1β, and IL-8) production induced by lipopolysaccharide (LPS) in lung inflammatory cells *ex vivo* [39]. Treatment with curcumin also inhibited the upregulation of COX-2 in ultraviolet B-irradiated HaCaT cells [40]. In one study, curcumin was found to inhibit the NF-κB activation induced by TNF in human myeloid ML-1a cells. Specifically, curcumin blocked phorbol ester- and hydrogen peroxide-mediated activation of NF-κB [41], indicating that curcumin inhibits free radical–induced inflammation. Another study found that the constitutive phosphorylation of STAT3 transcription factors was inhibited by curcumin treatment. In multiple myeloma cells, curcumin suppressed both constitutive and IL-6-induced STAT3 activation [42]. Treatment with curcumin also was shown to block the activation of AP-1 and NF-κB induced by IL-1α and TNF-α cytokines [43]. This study indicated that curcumin inhibits cytokine-induced inflammation by suppressing inflammatory pathways.

Capsaicin, a major ingredient of pepper, has been shown to inhibit NF-κB activation. Phorbol ester-induced activation of AP-1 was also abolished by capsaicin pretreatment [44]. Capsaicin inhibited constitutive and IL-6-induced STAT3 activation. The activation of JAK1 and c-Src, which are implicated in STAT3 activation, were also inhibited by capsaicin [45]. Capsaicin treatment in HepG2 cells resulted in a transient increase in the nuclear translocation of Nrf2, enhancing the binding of Nrf2 to the antioxidant response element (ARE) [46]. Thus, capsaicin inhibits inflammation by inhibiting different inflammatory pathways.

Nigella sativa (also known as black cumin), a plant commonly used in Ayurvedic medicine for more than 2,000 years, exhibits anticancer activity through its inhibition of the inflammatory pathway. The predominant bioactive component of *N. sativa*, thymoquinone, suppressed NF-κB activation, which was correlated with the inhibition of IκBα kinase activation and the direct binding of nuclear p65 to the DNA [47]. Thymoquinone also inhibited both constitutive and IL-6-induced STAT3 phosphorylation, which correlated with the inhibition of c-Src and JAK2 activation, in multiple myeloma cells [48]. This inhibition of inflammatory transcription factors indicates that thymoquinone has anti-inflammatory activities.

Cardamonin, a chalcone, has shown potent anti-inflammatory effects *in vitro* and *in vivo*. In a cellular model of inflammation, cardamonin inhibited the production of nitric oxide (NO) and prostaglandin E(2) (PGE(2)) and attenuated the expression of TNF-α, IL-6, IL-1β, inducible NO synthase (iNOS), and COX-2. Cardamonin also prevented the nuclear translocation of NF-κB. In a mouse model of endotoxin shock, cardamonin suppressed TNF-α, IL-6, and IL-1βsecretion in LPS-induced mouse blood serum [49].

Piperine, an alkaloid found in black pepper, inhibited cerebral ischemia-induced inflammation in Wistar rats. In same study, piperine also reduced the levels of pro-inflammatory cytokines IL-1β,

IL-6, and TNF-α in the ischemic rats and lowered the expression of COX-2, NOS-2, and NF-κB. Both cytosolic and nuclear NF-κB were downregulated in the ischemic rats [50]. Thus, piperine exhibits anti-inflammatory activities by suppressing cytokines and inflammatory transcription factors.

Ginger is known for its ethnobotanical applications as an anti-inflammatory agent. It has been found that [6] gingerol, an active component of ginger, inhibited the production of TNF-α, IL-1β, and IL-12 from LPS-stimulated macrophages [51]. In an *in vitro* study [6], gingerol and 6-shogaol, another active compound of ginger, inhibited MAPK and PI3K/Aktphosphorylation and NF-κB and STAT3 translocation [52].

Dietary zerumbone, a sesquiterpene phytochemical present in Asian ginger, can prevent inflammation, as observed in a mouse model of ultraviolet B–induced corneal damage. In the mice given dietary zerumbone, corneal damage was ameliorated by the inhibition of NF-κB activation and nuclear translocation; concomitant decreases in iNOS and TNF-α expression were also seen in these mice [53]. However, another report suggested that zerumbone induces the expression of IL-1α, IL-1β, IL-6, and tumor TNF-α in colorectal carcinoma cell lines, which implies that zerumbone increases the production of pro-inflammatory cytokines in cancerous tissues in the colon and that this biochemical property may cause side-effects [54].

Taken together, these reports from animal and *in vitro* studies have revealed that spices have a strong potential to inhibit inflammation. Spices and spice-derived nutraceuticals suppressed most, if not all, inflammatory biomarkers. The major biomarker of inflammation is NF-κB, which is inhibited by spice-derived nutraceuticals. The inhibition of inflammatory transcription factors is not restricted to NF-κB. Spice-derived nutraceuticals also inhibited cytokines and inflammatory enzymes. Some active components of spices also suppressed constitutive and inducible STAT3. Thus, the studies collectively suggest that spices could be used for targeting inflammatory molecules in the prevention and treatment of chronic diseases.

Clinical Aspects of Dietary Spices Against Chronic Diseases

Extensive preclinical studies over the past 3 decades have indicated curcumin's therapeutic potential against a wide range of human diseases [12]. These preclinical studies have formed a solid basis for evaluating curcumin's efficacy in clinical trials. Clinical studies have shown that co-administration of curcumin with conventional drugs is effective against IBD and well tolerated [38]. In one study of patients with ulcerative proctitis and CD, curcumin decreased the symptoms and inflammatory markers in all patients [55]. In another study of IBD patients, curcumin (360 mg 3 or 4 times/day for 3 months) significantly reduced clinical relapse. Curcumin inhibited major inflammatory mechanisms such as COX-2, LOX, TNF-α, IFN-γ, and NF-κB [56]; and thus it opens bright prospects for the treatment of IBD. In addition, curcumin has shown to be effective in maintenance therapy in patients with quiescent UC. In a randomized, double-blind study with 89 patients, those treated with curcumin (1 g twice daily) plus sulphasalazine or mesalazine for 6 months had a lower relapse rate than those treated with placebo plus sulphasalazine or mesalazine [57]. In a study of cultured *ex vivo* colonic mucosal biopsies and colonic myofibroblasts from children and adults with active IBD, curcumin reduced p38 MAPK activation, enhanced IL-10, and

reduced IL-1βlevel [58]. Thus curcumin holds promise as a novel therapy for patients with IBD.

Spice-derived nutraceuticals also have been studied in cancer treatment. Our group has shown that 8 g of curcumin is safe and well tolerated and that it downregulated the expression of NF-κB, COX-2, and phosphorylated STAT3 in peripheral blood mononuclear cells from pancreatic cancer patients [59]. Another single-blind, randomized, placebo-controlled study evaluated the effects of oral curcumin with piperine on pain and oxidative stress biomarkers in 25 patients with tropical pancreatitis [60]. Curcumin-piperine therapy produced significantly reduced the erythrocyte malondialdehyde levels compared with curcumin plus placebo and a significant increase in GSH levels but without improvement in pain. The authors of this study concluded that curcumin with piperine may reverse lipid peroxidation in patients who have tropical pancreatitis [60]. In a phase II clinical trial of patients with advanced pancreatic cancer, 8 g of curcumin per day orally inhibited the expression of NF–κB, COX-2, and pSTAT3 in peripheral blood mononuclear cells. Clinical biological activity was seen in 2 patients, and 1 patient had stable disease for more than 18 months. Interestingly, 1 additional patient had a brief, but marked, tumor regression accompanied by significant increases in serum cytokine levels (IL-6, IL-8, IL-10, and IL-1 receptor antagonists). The study concluded that oral curcumin, despite limited absorption, was well tolerated and demonstrated biological activity in some patients [59].

Curcumin has demonstrated potential against colorectal cancer in numerous clinical trials. In 1 study, in 15 patients with advanced, treatment-refractory colorectal cancer received 440 mg of *Curcuma* extract containing 36 mg of curcumin for 29 days, resulting in a 59% decrease in lymphocytic glutathione S-transferase activity. Leukocytic DNA damage was constant within each patient and unaffected by treatment. The researchers observed no dose-limiting toxicities and reported that the *Curcuma* extract was well tolerated [61]. In a study of 15 patients with advanced, treatment-refractory colorectal cancer, a daily dose of 3.6 g of curcumin caused 62% and 57% decreases in inducible prostaglandin E2 production in blood samples taken 1 hour after the dose administered on days 1 and 29, respectively [62]. Curcumin in combination with quercetin suppresses adenomas in patients with familial adenomatous polyposis [63]. Five patients with familial adenomatous polyposis received curcumin (480 mg) and quercetin (20 mg) orally 3 times a day. After 6 months of treatment, the number and size of the patients' polyps were reduced with no significant toxicity [63].

In patients with breast or prostate cancer, curcuminwas found to be well tolerated. The maximum tolerated dose of curcumin was found to be 8 g per day, whereas the recommended dose was 6 g per day for 7 consecutive days every 3 weeks when combined with a standard dose of docetaxel [64]. In a randomized, double-blind, controlled study, 85 men who underwent prostate biopsies were given soy isoflavones and curcumin. In the patient group with baseline PSA values greater than10ng/mL, PSA levels decreased among those who received isoflavones and curcumin [65]. Another study investigated the safety, tolerability, and clinical efficacy of curcumin in 29 patients with asymptomatic, relapsed, or plateau-phase multiple myeloma. Oral curcumin (2, 4, 6, 8, or 12 g/day in 2 divided doses) was well tolerated and significantly downregulated the constitutive activation of NF–κB and STAT3; curcumin also inhibited the expression of COX-2 in most patients [66].

Curcumin has shown effectiveness in patients with other chronic inflammatory diseases. The signs and symptoms of osteoarthritis were decreased in patients who received 200 mg of curcumin (present in Meriva). Curcumin inhibited serum inflammatory biomarkers such as IL-1β, IL-6, soluble CD40 ligand, soluble vascular cell adhesion molecule-1, and erythrocyte sedimentation [67]. In a randomized, double-blind, placebo-controlled clinical trial, curcumin delayed the development of type 2 diabetes in a prediabetes population [68]. A total of 240 participants received curcumin (1.5 g/day) or placebo. After 9 months of treatment, 16.4% of participants in the placebo group were diagnosed with diabetes, but no participants treated with curcumin developed diabetes. The authors of this study concluded that the curcumin might be beneficial in a prediabetes population [68].

Fenugreek seeds (*Trigonella foenum-graecum*) have been shown to improve blood glucose and the serum lipid profile in insulin-dependent (type 1) diabetic patients. In patients who ate a fenugreek diet, fasting blood sugar was significantly reduced, glucose tolerance improved, and 24-hour urinary glucose excretion was reduced by 54%. Also, levels of total cholesterol, LDL and VLDL cholesterol, and triglycerides in the serum were significantly reduced [69]. An inverse relationship between the risk of gallbladder cancer and the amount of vegetables (including fenugreek) consumed was observed in 153 patients with gallbladder cancer and 153 controls with gallstone disease [70]. In a double-blind, placebo-controlled study conducted in 50 patients with Parkinson disease, fenugreek capsules (300 mg, twice daily) had an excellent safety and tolerability profile. Thus, it has been concluded that fenugreek can be useful in the management of Parkinson disease [71].

Oral capsaicin has been reported to substantially reduce oral mucositis pain from cancer therapy [72]. A 12-week double-blind, placebo-controlled randomized study of capsaicin cream (0.075%) in the treatment of chronic distal painful polyneuropathy found no evidence of superior efficacy of capsaicin cream [73]. In contrast, another study showed that after 8 weeks of treatment, patients treated with capsaicin cream had an average pain reduction of 53% versus 17% for those treated with placebo [74]. In a double-blind, randomized, controlled trial of 100 patients with mild to moderate knee osteoarthritis, 0.0125% capsaicin gel was reported be effective [75]. Thus, capsaicin reduces pain in patients with chronic diseases.

Piperine has been reported to enhance the oral bioavailability of other supplements and drugs. In one study, piperine (20 mg) was administered along with phenytoin in human volunteers, and samples collected 12 hours later showed that piperine significantly increased the mean plasma concentration of phenytoin [76]. In a placebo-controlled pilot study, 8 healthy adult males were randomly assigned to receive nevirapine (200 mg) alone or with piperine (20 mg). The levels of nevirapine were higher in blood of individuals treated with nevirapine and piperine than in those treated with nevirapine alone, providing evidence that piperine enhanced the bioavailability of nevirapine [77].

Ginger has also great potential against inflammatory diseases. In a pilot trial, 20 people at increased risk for colorectal cancer were given of ginger (2 g) or placebo daily for 28 days. Differences between the 2 groups in levels of biomarkers for cell proliferation, apoptosis, and differentiation in colorectal epithelial cells with normal appearance indicated that ginger may reduce proliferation, increase apoptosis, and increase differentiation [78]. Another study in patients with acute respiratory distress syndrome, diet enriched with ginger showed lower serum levels of inflammatory cytokines IL-1, IL-6, and TNF-α [79].

Cinnamon's effects on blood glucose were identified in a meta-analysis of clinical trials, which found that consuming whole cinnamon or as cinnamon extract significantly reduced fasting blood glucose levels in people with type 2 diabetes or prediabetes [80]. The studies described above show than various spices act against inflammation *in vitro*, in animal models, and in patients.

Role of Dietary Spices in Preventing Chronic Diseases

Because spices have chemical properties that reduce inflammation, the occurrence of some chronic diseases can be prevented by increasing the consumption of spices (Figure 2). For example, differences in spice consumption could be the reason the occurrence of cancer in India, where spices are used routinely, is much lower than in the United States [81].
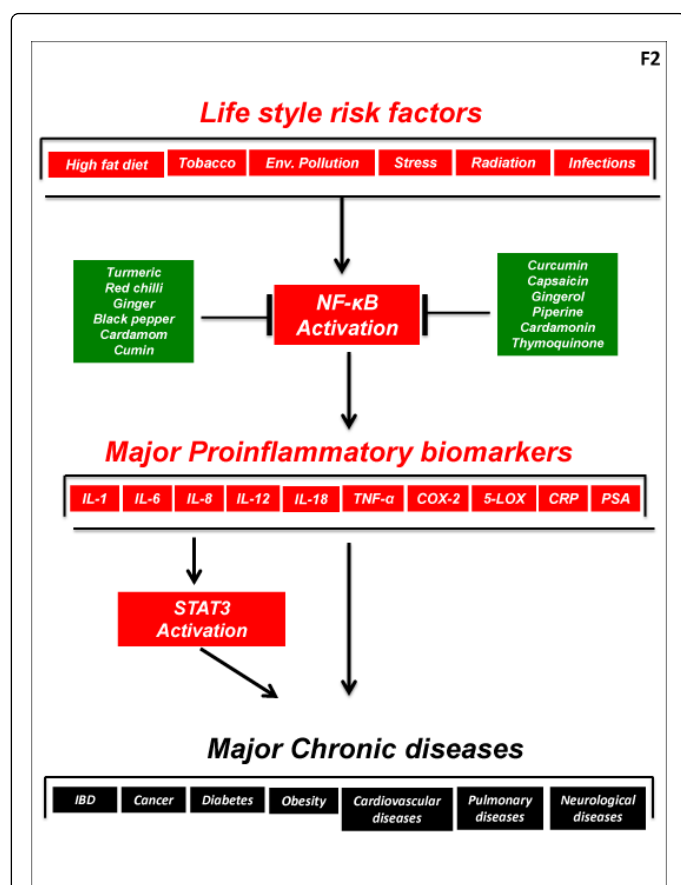

Figure 2: An intimate relationship of inflammation and chronic diseases and the role of spices and spice-derived nutraceuticals in their treatment. Life style risk factors such as high fat diet, tobacco, environmental pollution, stress, radiation and infection induce inflammation through activation of inflammatory transcription factors including NF-κB. NF-κB further activates various proinflammatory cytokines including interleukins, TNF-α, COX-2, 5-LOX, CRP and PSA. Interleukins, specifically IL-6, activates another transcription factor STAT3. Persistent activation of NF-κB and STAT3 leads to development of various chronic diseases. However, dietary spices could prevent development of chronic diseases by blocking activation of proinflammatory transcription factors and cytokines.

Curcumin has displayed a protective role in mouse models of IBD and in human UC by reducing neutrophil infiltration and levels of inflammatory molecules. In rat model of IBD, treatment with curcumin decreased levels of inflammatory molecules indicating, curcumin could be effective in the prevention and treatment of IBD [82]. Another preclinical study showed that curcumin interfered with inflammation in colonic epithelial cells by inhibiting chemokine expression neutrophil chemotaxis and chemokinesis, which results in the prevention of IBD [83]. Besides these, curcumin as well as cyclodextin-conjugated curcumin decreased the degree of colitis caused by the administration of dextran sodium sulfate (DSS) [84,85]. In primary cultures of human intestinal microvascular endothelial cells, curcumin inhibited the expression of VCAM-1, Akt, p38 MAPK, and NF-κB and thus may have a therapeutic role against endothelial activation in IBD [86].

Curcumin may have therapeutic potential, as it was found to be associated with the suppression of inflammatory cytokines and enzymes, transcription factors, and gene products linked with cell survival, proliferation, invasion, and angiogenesis. Curcumin exhibited anticancer activities in *in vitro* and in animal models of cancer. Several phase I and phase II clinical trials have indicated that curcumin is safe [87].

Numerous lines of evidence suggest that curcumin mediates cardioprotective effects through diverse mechanisms. Several studies have suggested that curcumin protects the heart from ischemia/reperfusion injury [88,89]. Venkatesan [90] showed that curcumin also decreased acute adriamycin-induced myocardial toxicity in rats. In preclinical studies of diabetes, curcumin can lower levels of blood glucose, raise pancreatic β-cells' antioxidant status, and facilitate PPAR-γ activation [91]. Curcumin can also induce hypoglycemia in rats with streptozotocin-induced diabetes [92]. The most likely mechanism for this action is that curcumin inhibits cholesterol, induces antioxidant and scavenge free radicals.

Capsaicin also has shown chemopreventive and chemoprotective effects [93]. In a mouse model, topical capsaicin was shown to inhibit skin tumors induced by phorbol 12-myristate 13-acetate [44]. In a study of 29 normotensive and 13 hypertensive people with alopecia, capsaicin and isoflavone reduced arterial blood pressure; this likely resulted from elevated levels of serum IGF-I [94]. Capsaicin has also been found to be protective against stress-induced neurological impairment. In an animal model, capsaicin administered at 10 mg/kg 1 hour before the introduction of stress mitigated stress-induced cognitive and Alzheimer disease-like pathological alterations [95]. In other animal studies, capsaicin had preventive effects against neonatal hypoxic-ischemic brain injury [95], epileptogenesis [96], and diabetic neuropathy [97]; it also reduced toxin-induced neuroparalytic effects in neuromuscular junctions [98].

Cardamonin has shown potential against several cancer types, such as colorectal and gastric cancers, sarcoma, and multiple myeloma. Cardamonin inhibited the proliferation, invasion, and angiogenesis of cancer cells [99,100]. Cardamonin also suppressed bone loss, which often occurs in multiple myeloma, breast cancer, and prostate cancer patients [101]. Cardamonin also enhances cell death of colorectal cancer cells induced by TRAIL through induction of ROS-CHOP-mediated death receptor as well as suppression of decoy receptor and cell survival proteins [102]. Beside this, cardamonin exhibits cardioprotective effects. It induced relaxation of phenylephrine-preconstricted mesenteric arteries in a rat model [103]. In a study of fructose-induced diabetes in rats, cardamonin reduced insulin

resistance and smooth muscle hyperplasia of the major vessels [104]. Cardamonin has been shown to act against systemic hypertension by inhibiting I(Ca(L)) and stimulating K(Ca)1.1 current [105]. Recently, thymoquinone was shown to prevent and ameliorate colonic inflammation in a mouse model of IBD. Treatment of mice with thymoquinone ameliorated of DSS-induced colitis by lowering colonic myeloperoxidase activity and malondialdehyde levels and raising glutathione levels [106]. A rat model showed that pretreatment for 3 days with 10 mg/kg of thymoquinone completely prevented acetic acid-induced colitis, while 500 mg/kg of sulfasalazine provided less protection [107].

Thymoquinone has been shown to inhibit proliferation in several cancer cell lines and to inhibit angiogenesis and tumor growth *in vitro* and *in vivo* [47,108]. Thymoquinone also reduced diabetes-related inflammation and protected β cells [109]. In a study of rats with streptozotocin-induced diabetes, thymoquinone protected the kidneys against oxidative stress [110]. Thymoquinone may protect neurons against toxicity and apoptosis. In a rat study, thymoquinone ameliorated ethanol-induced neurotoxicity in the primary cortical neurons, indicating its potential as a treatment against neonatal alcohol exposure [111]. Cinnamaldehyde, a compound in cinnamon, has shown activity against several chronic diseases. For example, cinnamaldehyde inhibits proliferation and induces apoptosis in cancer cells [112]. The compound also exhibits antidiabetic, antioxidant, and hypolipidemic activity [113] and acts as a vasorelaxant on isolated rat aorta [114].

Piperine has been found to be effective against IBD alone or in combination with other natural products. In one study, piperinein combination with tea polyphenol inhibited DSS-induced colitis. Mice treated with the combination had reduced levels of histological damage to the colon and lipid peroxidation; the colon tissue had a decreased level of myeloperoxidase (a marker for neutrophil accumulation) and higher levels of superoxide dismutase and glutathione peroxidase (antioxidant enzymes) [115]. Piperine combined with a hydroalcoholic extract of *Amaranthusroxburghianus* and piperine had effects against UC that were comparable to those of prednisolone [116]. Recently, a combination of the polyphenols, quercetin and piperine, which was encapsulated into reconstituted oil bodies, was shown to protect against DSS-induced colitis and weight loss [117].

Piperine inhibited the growth of 4T1 mammary carcinoma cells in vitro and lung metastases in mice [118]. Co-administration of piperine also improved the antitumor efficacy of the chemotherapeutic agent docetaxel in a mouse xenograft model of castration-resistant prostate cancer [119] and of 5-fluorouracil in *in vitro* and *in vivo* models [120]. In mice with alloxan-induced diabetes, piperine lowered blood glucose levels at subacute doses but raised blood glucose levels at high doses [121]. Piperine was also shown protection against corticosterone-induced neurotoxicity in cultured rat pheochromocytoma cells [122]. In another study, piperine was shown to protect against epilepsy-associated depression; this antidepressant activity was likely due to piperine's activity as a monoamine oxidase inhibitor and its neuroprotective properties [123].

Ginger has been shown to ameliorate UC. In a rat model, ginger extract reduced the effects of acetic acid-induced UC [124]. In support, Hsiang et al. [125] showed that ginger extract and gingerone reduced the effects of 2,4,6-trinitrobenzene sulphonic acid-induced colitis by inhibiting NF-κB activity and IL-1β signaling. Furthermore, ginger volatile oil found to reduce colitis symptoms in a rat model by decreasing the colon weight/length ratio, ulcer severity, ulcer area, and ulcer index with a concomitant decrease in the inflammation induced by acetic acid [126]. [6]-Gingerol has demonstrated antioxidant, anti-inflammatory, and anticancer properties. In a preclinical study of hepatocellular carcinoma, [6]-Gingerol and [6]-shogaol inhibited invasion and metastasis through multiple molecular mechanisms [52]. The antitumor potential of [6]-gingerol was demonstrated when it prevented skin tumor growth and induced apoptosis in a mouse model [127]. It has also been shown that crude ginger extract and gingerol each reduced joint swelling in an animal model of rheumatoid arthritis [128]. The neuroprotective effect of [6]-gingerol was demonstrated in SH-SY5Y cells when pretreatment with the compound protected against cytotoxicity and apoptosis [129]. In a study of arsenic-intoxicated mice, [6]-gingerol had an anti-hyperglycemic effect and improved insulin signaling [130].

Zerumbone has been found to be effective against colitis. In a study mouse model, oral zerumbone lowered the DSS-induced levels of IL-1β, TNF-α and PGE(2) and suppressed colitis [131]. Zerumbonewas also shown to suppress tumor growth and induce apoptosis in various cancer cell lines. In a mouse model of skin cancer, zerumbone inhibited both tumor initiation and promotion through its antioxidant inducing nature and activation of phase II drug metabolizing enzymes along with attenuation of proinflammatory molecules [132]. A mouse model of colon cancer demonstrated that zerumbone prevented tumorigenesis and that this effect was mediated through its modulation of antiproliferative mechanisms, apoptosis, and inflammatory molecules [133]. These studies indicate zerumbone's potential against chronic diseases such as cancer.

Conclusion

Spices have been used as traditional medicine against chronic diseases for thousands of years. Numerous preclinical study results suggest that spices and spice-derived nutraceuticals are associated with a decreased risk of inflammation-regulated chronic diseases. More clinical trials are needed to strengthen this preclinical evidence. Because chronic diseases require a long time to manifest, structuring such clinical trials will be difficult. However, to validate the importance of spices in daily life, long-term prospective epidemiology studies and well-controlled clinical trials of spices are needed. The Dietary Approaches to Stop Hypertension (DASH) diet, which features high intakes of spices, fruits, vegetables, legumes, and nuts; moderate amounts of low-fat dairy products; low amounts of animal protein and sweets; and sodium reduction, is recommended because the DASH diet diet has a potential to prevent cancer. Until further evidence is available, we recommend increasing the amount of inexpensive, nontoxic nutraceuticals such as spices in the daily diet to help prevent the occurrence of chronic diseases.

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