

Curcumin and Inflammatory Diseases: Learn About Its Potential Role in Prevention and Treatment

By Sharon Collison, MS, RD, LDN, CSSD

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The spice turmeric has been used for centuries not only to flavor, color, and preserve foods but also as a medicinal remedy, and it has been used for thousands of years in Ayurvedic medicine for the treatment of inflammatory disorders.^{1,2} Turmeric is derived from the plant *Curcuma longa*, a member of the ginger family, and its rhizome (root) is the most useful part for culinary and medicinal purposes. Turmeric contains three naturally occurring phytochemicals called curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin, though the terms “curcumin” and “curcuminoids” frequently are used interchangeably in the research literature. Curcumin is one of the principal healthful components of turmeric, comprising 2% to 5% of most turmeric preparations² and giving the spice its characteristic yellow color.

Increasingly, the anti-inflammatory properties of these curcuminoids have attracted the attention of researchers, who have gathered extensive evidence of curcumin’s positive impact on preventing and treating proinflammatory diseases.³ Curcumin is a nontoxic and highly promising natural anti-inflammatory compound that’s currently being administered in phase 2 and 3 clinical trials.¹

Inflammation and Disease

When the body experiences injury, irritation, or infection, an acute inflammatory response occurs to heal the affected tissue. However, when that acute response isn’t effective, the body elicits a chronic inflammatory response. Although acute inflammation has therapeutic potential, persistent low-level inflammation eventually can cause chronic diseases.

Chronic inflammation “is associated with the alteration of cell signaling pathways, which results in increased levels of inflammatory markers, lipid peroxides, and free radicals,”¹ causing cell damage and eventually leading to the clinical symptoms of disease. Recent research has demonstrated that chronic inflammation initiates and promotes many disease states, including obesity; diabetes; cardiovascular, neurodegenerative, and inflammatory bowel diseases; and certain types of cancers.⁴⁻⁷

Oxidative damage is a major contributor to the inflammatory response as well as the functional decline that’s characteristic of aging and diseases of aging.⁸ Immune system cells use free radicals such as reactive oxygen species and reactive nitrogen species to eliminate disease-causing viruses and bacteria. The excess production of free radicals results in a state of oxidative stress, which damages polyunsaturated fats in lipoproteins and cell membranes and

alters proteins such as DNA and RNA.^{9,10} This damage leads to impaired cell functions and an inflammatory response that contributes to cell damage, aging, and disease.

Chronic inflammation and oxidative stress result in increased serum levels of the transcription factor NF- κ B.¹¹⁻¹³ Transcription factors regulate gene expression within cells and ultimately control cell behavior. NF- κ B controls DNA transcription and can be activated by factors that trigger an inflammatory response, such as viral infections, oxidants, and antigens.¹⁴

The NF- κ B proinflammatory signaling pathway drives macrophages and neutrophils to respond to such pathogens as part of the immune response. Cell signaling pathways are the body's primary means of communication, directing and regulating all cellular activities. Incorrect regulation of NF- κ B has been linked to improper immune development, inflammatory and autoimmune diseases, viral infections, neurodegenerative diseases, and cancer.^{3,15}

NF- κ B increases the expression of many cytokines and enzymes that are active in these chronic inflammatory diseases. Cytokines are hormonelike proteins that act as signaling molecules to regulate immune responses and responses to infection, inflammation, and trauma. Some cytokines are anti-inflammatory and promote healing once the injury, infection, or foreign body has been destroyed. Other cytokines are proinflammatory, such as tumor necrosis factor–alpha (TNF-alpha) and interleukin-1 (IL-1), as well as IL-2, -6, -8, and -12, and initiate an inflammatory response that recruits lymphocytes to fight disease.

The release of proinflammatory cytokines into the bloodstream signals the liver to produce proteins such as acute phase reactants and cell adhesion molecules that respond to trauma or infection and serve as additional biomarkers of inflammation. Plasma concentrations of acute phase reactants either can increase (positive reactants) or decrease (negative reactants) during chronic inflammation. C-reactive protein (CRP), fibrinogen, and amyloid are examples of positive acute phase reactants that increase with inflammation; transferrin and albumin are negative phase reactants that decrease with inflammation.

Cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and lipoxygenase (LOX) are important enzymes that mediate inflammatory processes. Pathways that depend on COX and LOX enzymes synthesize lipid mediators involved in inflammation. Improper upregulation of these enzymes has been associated with the pathophysiology of inflammatory disorders and certain types of cancer.^{4,16} COX-2, for example, is responsible for the increased production of the prostanoids (arachidonic acid–derived prostaglandins and thromboxane) in inflammatory diseases,¹⁶ which results in inflammation and pain.

Anti-Inflammatory Agents

Synthetic drugs such as NSAIDs traditionally are the first line of defense against acute and chronic inflammation and pain. NSAIDs are a family of COX-1 and -2 inhibitors used to reduce prostanoid synthesis, especially prostaglandin E₂, resulting in anti-inflammatory and antitumor activities.^{17,18} However, the side effects of long-term use of these drugs, including upper gastrointestinal complications and cardiovascular events, often outweigh the benefits.^{18,19} Efforts are under way to discover safer NSAIDs that inhibit the inflammatory process while reducing the side effects associated with long-term treatment.

Curcumin's Anti-Inflammatory Properties

Researchers have found that phytochemicals from natural foods, including spices and herbs, are safe and effective therapies to help reduce inflammation and prevent and treat disease. Phenolic compounds derived from botanic sources such as curcumin have demonstrated anti-inflammatory activity in vitro and in vivo.^{17,20,21}

Extensive clinical trials over the past several decades have addressed curcumin's pharmacokinetics, safety, and efficacy against many diseases in humans. However, research on curcumin accelerated much earlier when it was found to have not only anti-inflammatory properties but also cholesterol-lowering, antidiabetic, and antioxidant properties.²²⁻²⁴

Curcumin's anticancer activity was first discovered in the 1980s in both in vitro and in vivo studies.^{25,26} Once these studies demonstrated curcumin's role as a therapeutic agent for disease, research increased significantly. In 1995, it was discovered that curcumin inhibits NF-KB, pointing toward curcumin's potential as an effective and safe anti-inflammatory agent.²⁷

Curcumin also exerts a protective role against inflammatory diseases by scavenging free radicals and suppressing COX, LOX, iNOS, and other inflammatory mediators.^{1,4,5}

Research involving patients with various proinflammatory diseases, including neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune, and neoplastic diseases, has been encouraging.^{1,4,5} Curcumin also shows promise in the treatment of hepatic conditions such as liver fibrosis and cirrhosis, psoriasis, AIDS, burn pain, and wounds.^{4,28-31}

Obesity and Heart Disease

Extensive research in the last two decades has shown that obesity, a major risk factor for chronic diseases such as type 2 diabetes, atherosclerosis, and cancer, is a proinflammatory disease. Obesity and insulin resistance in patients suffering from type 2 diabetes are associated with chronic low-grade systemic inflammation, resulting in increased inflammatory markers.³¹ Adipose tissue is the main origin of this inflammatory response, and it's a major secretor of adipocytokines, especially adiponectin, an anti-inflammatory cytokine, and leptin, a proinflammatory cytokine. Either a reduced level of adiponectin or an increased level of leptin results in an elevated risk of atherosclerotic disease.³²

Abdominal obesity reflects the amount of adipose tissue in the body.³² Macrophages respond to increased fat cell mass by infiltrating adipose tissue,³³ secreting proinflammatory cytokines, including TNF-alpha, IL-6, and IL-1 beta. These, in turn, signal the liver to produce CRP and initiate inflammatory pathway signaling.^{31,34}

Evidence from cellular and animal studies supports the beneficial effects of curcumin on obesity and related metabolic disorders.³⁴⁻³⁶ Weisberg and colleagues demonstrated that treating genetically obese mice fed a high-fat diet with curcumin decreased NF-KB activation in the liver and decreased macrophage accumulation in adipose tissue. The curcumin-treated mice experienced increased adiponectin production by adipose tissue and decreased development of insulin resistance and hyperglycemia. They also had a small but significant

decrease in body weight and fat content despite either a maintenance or increase in total daily calories, suggesting that curcumin may have beneficial effects on body composition.³⁶

Shao and colleagues found similar results in a mouse study where curcumin significantly attenuated the effect of a high-fat diet on glucose tolerance, body weight and body fat gain, and the development of insulin resistance.³⁷

Although several studies have found that curcumin's antioxidant and anti-inflammatory effects reduce body weight, lower triglyceride synthesis, increase basal metabolic rate and fatty acid oxidation, and improve insulin sensitivity in animal models,³⁴⁻³⁷ human clinical trials are needed to verify such antiobesity benefits.³⁸

Few studies have been conducted to evaluate curcumin's effect on obesity and heart disease in humans. Two small studies have been done to examine curcumin's effect on obesity-related parameters.^{39,40} One study examined curcumin's effect on HDL and LDL cholesterol. Twelve men taking 20 mg of curcumin per day for 30 days increased their HDL cholesterol and apolipoprotein A levels while decreasing their LDL cholesterol, apolipoprotein B, and apolipoprotein A/B levels. High levels of apolipoprotein B are related to heart disease, whereas apolipoprotein A is cardioprotective.³⁹

Ramirez and colleagues completed another study in adults with atherosclerosis in which 10 mg of curcumin was administered to 16 men and 14 women twice daily for 15 days.⁴⁰ Curcumin significantly lowered the levels of plasma fibrinogen, a major plasma protein coagulation factor, in both men and women. Fibrinogen, a classical positive acute-phase reactant, independently predicts coronary heart disease events.⁴¹

In a recent six-month randomized, double-blind, placebo-controlled clinical trial to evaluate curcumin's effects on risk factors for atherosclerosis in type 2 diabetes patients, participants were instructed to take three capsules with blinded labels containing either 250 mg of curcuminoid or a placebo twice per day (total of six capsules per day). The results showed that curcumin intervention significantly reduced pulse wave velocity (an atherosclerosis indicator), increased levels of serum adiponectin, and decreased levels of leptin, thus reducing the risk of atherosclerotic disease in patients with type 2 diabetes. At the last follow-up visit (six months after intervention), the authors noticed slight reductions in mean body weight, BMI, lipid profiles (total and LDL cholesterol), blood glucose profiles (fasting blood glucose and hemoglobin A1c [HbA1c]) and a slight increase in HDL cholesterol in the group of patients treated with curcumin but not in the placebo-treated group.³²

These in vitro, in vivo, and clinical studies support curcumin's anti-inflammatory and antioxidant effects on obesity, leading to outcomes such as weight loss, improved blood lipids, increased basal metabolic rate, increased fatty acid oxidation, increased energy expenditure, reduced risk of atherosclerosis, and improved insulin sensitivity. Thus, curcumin shows potential for addressing obesity and associated inflammation.³⁸

Type 2 Diabetes

Hyperglycemia, insulin resistance, and decreased insulin secretion characterize type 2 diabetes. Oxidative stress and inflammatory reactions have been found to play a crucial role in the occurrence and development of type 2 diabetes, resulting in insulin resistance, impaired insulin signaling, pancreatic beta cell dysfunction, and abnormal glucose and lipid metabolism, which cause elevated blood glucose.⁴² Hyperglycemia can lead to further oxidative stress, mainly through the increased production of mitochondrial free radicals.⁴² Oxidative stress associated with hyperglycemia impairs cellular function and alters vascular and neural function.⁴

Since antidiabetic agents alleviate, rather than cure, the disease, there's growing interest in complementary and alternative approaches, including herbal therapies.^{43,44} Curcumin appears to influence diabetes by stimulating the pancreas to produce and secrete insulin, interfering with dietary glucose absorption, causing insulin-sparing action, and exerting its antioxidant and anti-inflammatory properties.⁴ Curcumin also directly affects pancreatic beta cells, which could contribute to the hypoglycemic/antidiabetic effects.³⁴

Several studies have found that curcumin and curcuminoids can help regulate glucose and lipid metabolism in type 2 diabetes.^{21,42,45} Some of these studies also demonstrated that curcumin and curcuminoids can significantly improve glycemic control while also increasing the activity levels of antioxidant enzymes and scavenging free radicals.⁴² Research has shown that curcumin can reduce blood glucose and glycosylated HbA1c levels and inhibit the activity of inflammatory cytokines.^{36,46,47} Jain and colleagues reported that curcumin supplementation in diabetic rats lowered the production of inflammatory cytokines and decreased blood levels of TNF-alpha, IL-6, monocyte chemoattractant protein-1, glucose, and HbA1c.⁴⁶

A randomized, double-blind, placebo-controlled trial involving 240 prediabetic subjects investigated curcumin's effect on the progression of prediabetes to diabetes. Subjects were given capsules totaling 250 mg of curcuminoid or a placebo twice daily for nine months. Curcumin significantly reduced type 2 diabetes development; none of the 120 curcumin-treated subjects progressed to type 2 diabetes compared with a 16.4% progression rate in the placebo group. The curcumin-treated group showed significantly lower HbA1c levels and fasting and postprandial glucose levels, and increased levels of the anti-inflammatory cytokine adiponectin.⁴⁷

Many studies have indicated that curcumin can attenuate several complications of diabetes, mainly through its antioxidant and anti-inflammatory activities.^{21,42,45} For instance, diabetic neuropathy, a microvascular problem that occurs mostly because of oxidative damage and inflammation, was shown to improve after curcumin administration.⁴⁸

Many studies also have demonstrated that curcumin can reduce both neuropathic and inflammatory pain, most likely through its inhibitory action on inflammatory cytokines and free radicals.⁴⁵ Curcumin also improved complications such as diabetic retinopathy, nephropathy, and cardiomyopathy.^{45,49-52}

Alzheimer's Disease

The pathogenesis of Alzheimer's disease (AD) involves neuroinflammation induced by free radical production and oxidative damage^{1,3,4,53} and the formation and accumulation of beta-amyloid plaques, or fibrils, in the brain. Amyloid fibrils are formed by normally soluble proteins, which assemble to form insoluble fibers. High expression of beta-amyloid plaques, along with neuroinflammation, is associated with the loss of neurons and synapses that affects neuronal function in patients with AD.⁵⁴

Because current treatments for AD and other neurodegenerative diseases, including Parkinson's and Huntington's, can cause severe side effects,⁵⁵ there's strong interest in alternative approaches. Because of its antioxidant and anti-inflammatory effects as well as its ability to inhibit protein aggregation, curcumin has the potential to help reduce oxidative damage, prevent mitochondrial and cellular dysfunction, and counteract neurodegeneration.⁵³

In a large population-based study of 1,010 elderly Asians without dementia, subjects who consumed curcumin-rich curry occasionally, often, or very often scored significantly better on the Mini-Mental State Examination (MMSE), an established measure of cognitive function, than did those who never or rarely consumed curry.⁵⁶

Substantial in vitro data indicate that curcumin has antioxidant, anti-inflammatory, and anti-beta-amyloid protein activity. In addition, studies in animal models of AD indicate a direct effect from curcumin in decreasing AD's amyloid pathology.^{57,58} These findings suggest that curcumin may be one of the most promising compounds for the development of AD therapies.⁵⁹

Several in vivo preclinical studies and cell culture and animal models also support curcumin's neuroprotective potential and suggest a role for this compound in the prevention and reversal of degenerative diseases such as AD and Parkinson's.⁶⁰⁻⁶²

Clinical trials, however, haven't been as promising. Two independent clinical trials concluded that curcumin wasn't effective at reducing cognitive decline.^{63,64} One, a six-month randomized, placebo-controlled, double-blind, clinical pilot study in Hong Kong, involved 34 participants with AD who were randomly assigned to receive curcumin at two different doses (1 or 4 g) or a placebo. MMSE scores didn't improve in the curcumin group. However, the curcumin group showed increased plasma levels of vitamin E and increased serum beta-amyloid 40 compared with the placebo group, suggesting that curcumin could disaggregate beta-amyloid deposits in the brain and release them for circulation and disposal.⁶³

Despite the results of these clinical trials, it's too soon to conclude that there's a lack of effectiveness regarding curcumin and AD.⁵⁵ A recently published review of studies summarizing the effects of curcumin and curcuminoids in AD concluded that the different components of a curcuminoid mixture showed different biological activities with varied efficacy and potency, and that a curcuminoid mixture may offer better therapeutic potential in AD compared with pure curcumin.⁶⁵

Two other clinical studies involving AD patients remain active⁵⁵: a phase 2 study in India using 2 g/day of curcumin and an early intervention study conducted in the United States with a

combination of 5.4 g of curcumin and bioperine, a natural product derived from black pepper that's thought to increase curcumin's bioavailability. These studies are directed to evaluate the efficacy, safety, and tolerability of curcumin in moderate AD.

Although clinical trials to date haven't shown curcumin to be therapeutic in patients with AD, its success as part of in vitro and animal studies and the current progress with its improved bioavailability combined with the knowledge that curcumin, even at the highest doses, didn't cause adverse effects warrant further clinical studies.

Arthritis

Osteoarthritis (OA), one of the most common types of arthritis, results in joint degradation, including articular cartilage and subchondral bone. It's a chronic condition in which cartilage breaks down, causing the bones to rub against each other and resulting in stiffness, pain, and loss of joint movement.

Rheumatoid arthritis (RA) is an autoimmune disease that results in a chronic, systemic inflammatory disorder that may affect many tissues and organs but principally attacks flexible (synovial) joints.

The roles of inflammatory cytokines and chemokines (special types of cytokines that direct the migration of white blood cells to infected or damaged tissues), inflammatory enzymes, and cell adhesion molecules in the pathogenesis of arthritis are well documented. NF-KB has been shown to regulate almost all of the mediators of inflammation linked with arthritis.³

NSAIDs such as celecoxib (Celebrex) are efficient anti-inflammatory agents frequently used to treat OA but, as noted previously, they can have negative side effects.^{3,66} Lev-Ari and colleagues conducted a study to determine whether a lower and safer concentration of celecoxib in combination with curcumin would be effective for treating OA. Curcumin augmented the inhibition of OA cell growth and enhanced celecoxib's induction of apoptosis. This synergistic effect of curcumin and celecoxib was mediated through inhibition of COX-2 activity. The authors noted that the results of this study support the use of celecoxib at lower and safer concentrations and may pave the way for a novel combination treatment of arthritis.⁶⁶

In a clinical study on curcumin's effects on OA, 50 patients were given Meriva, a proprietary formulation of 200 mg of curcumin blended with lecithin, daily for three months. OA signs and symptoms plus mobility and inflammatory status were evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC), walking performance, and CRP measurement, respectively. Meriva treatment decreased the global WOMAC score by 58%, extended walking distance from 76 to 332 meters, and decreased CRP levels from 168 ± 18 to 11.3 ± 4.1 mg/L.⁶⁷

In another study of 45 patients diagnosed with RA, 500 mg of curcumin and 50 mg of diclofenac sodium alone or in combination were administered to three groups of patients. Diclofenac, the current standard of care for patients with RA, is an NSAID used to relieve pain, tenderness, swelling, and stiffness. Study results showed that the curcumin group had the best

improvement of the overall Disease Activity Score and American College of Rheumatology scores (tests used in clinical practice and clinical trials to evaluate symptoms of RA and disease progression) of all three groups.⁶⁸

By inhibiting COX-2 and reducing arthritis pain and swelling, curcumin's role in the treatment of OA and RA shows promise.

Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, are debilitating immune disorders involving chronic inflammation of the digestive tract that results in severe abdominal cramping and diarrhea.

Two of the main treatments for mild to moderate IBD are the anti-inflammatory medications sulfasalazine (Azulfidine) and mesalamine, which work by inhibiting the COX and LOX pathways and the inflammatory process. Unfortunately, these medications frequently produce side effects such as nausea, headache, diarrhea, and abdominal pain.⁶⁹

Two independent researchers have found that in rats with IBD colitis, the expression of NF-KB activation and proinflammatory cytokines in colonic mucosa was suppressed in the curcumin-treated groups.^{70,71} Since curcumin has shown efficacy as an anti-inflammatory without significant side effects, many studies have been conducted to evaluate its potential in patients with IBD.^{72,73}

Holt and colleagues conducted a pilot study in people with IBD to determine whether the dosage of routine medications given to suppress disease symptoms could be reduced with curcumin coadministration. Five patients with ulcerative colitis each were given 550 mg of curcumin twice daily for one month and then 550 mg three times daily for another month. Five patients with Crohn's disease each were given 360 mg of curcumin three times per day for one month and then four times per day for two months. Of the 10 patients, nine showed immunological and symptomatic improvement at the study's conclusion. Curcumin reduced the inflammatory response in four of five ulcerative colitis patients and four of five Crohn's disease patients. In fact, four of the five patients with ulcerative colitis were able to decrease or eliminate their medications. These subjects reported improvement in clinical symptoms, including more formed stools, less frequent bowel movements, and decreased abdominal pain/cramping.⁷⁴

In a multicenter, double-blind, placebo-controlled clinical trial, 89 patients with ulcerative colitis were randomized to receive curcumin (1 g twice daily) or a placebo for six months. Both groups also received sulfasalazine or mesalamine. There were significant improvements in the curcumin group but not in the placebo group, showing that curcumin significantly suppressed the morbidity associated with active ulcerative colitis. Relapse rate was significantly lower in the curcumin group over the placebo group.^{72,75}

The research results to date support further exploration of curcumin's efficacy for treating patients with IBD. Clinical studies of curcumin for patients with active IBD are needed in large cohorts using a wide range of dosages and long follow-up times.⁷² Furthermore, large clinical

trials on patients with active IBD are needed with curcumin not only as a monotherapy but also as an adjuvant to the commonly used medications to evaluate its beneficial effects.⁷⁶ Several clinical trials currently are being conducted.

Cancer

Regularly consuming turmeric has been suggested as a possible factor contributing to lower cancer rates (colorectal, liver, pancreatic, lung, breast, uterine, ovarian, prostate, bladder, kidney, renal, brain, non-Hodgkin lymphoma, and leukemia) in India compared with those in Western countries.^{77,78} However, without quantitative data, a cause-and-effect relationship between turmeric consumption and cancer incidence can't be assumed.⁷⁹

Epidemiological studies have identified chronic infections and inflammation as major risk factors for various types of cancer.⁸⁰ Most risk factors for cancer, including tobacco use, obesity, alcohol consumption, infections, stress, food carcinogens, and environmental pollutants, have been shown to be components of a proinflammatory lifestyle that leads to tumorigenesis.⁸¹ In fact, inflammation is involved in most stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis.⁸⁰

The mixture of cytokines and proinflammatory mediators that are produced in tumor cells play an important role in tumor development and progression. NF-KB activation leads to the expression of inflammatory enzymes and mediators, including COX-2, LOX-2, iNOS, cell adhesion molecules, and inflammatory cytokines, especially TNF-alpha and chemokines.⁸¹

Recently, biochemical and animal studies revealed that the activation and interaction between NF-KB and STAT3, another transcription factor, are major factors linking inflammation to cancer.^{80,82} In fact, most carcinogens activate NF-KB and STAT3 pathways.⁸³ Both NF-KB and STAT3 are overactivated and locked in an "on" position in human cancer.⁸¹

Since the dysregulation of multiple cell signaling pathways causes cancer, the new generation of anticancer drugs is designed to modulate multiple targets.⁸⁴ Many spices have been found to target multiple cellular signaling pathways in tumorigenesis.⁸¹ By modulating multiple targets, such as transcription factors like NF-KB and STAT3, growth factor receptors, kinases, and inflammatory mediators, curcumin inhibits several processes that contribute to cancer cell survival, proliferation, invasion, and metastasis.^{81,84} And because of its multitargeting activities, curcumin has been found to be effective against many cancer types in human clinical trials.²¹

A clinical trial of 62 patients with external cancerous lesions conducted in 1987 first demonstrated curcumin's anticancer activities in humans. Topical curcumin was found to produce substantial symptomatic relief as evidenced by reductions in smell, itching, lesion size, and pain.²⁶

In a phase 1 dose-escalation clinical trial, 15 patients with advanced colorectal cancer took 0.45, 0.9, 1.8, or 3.6 g of curcumin once daily for up to four months. Toxic effects weren't observed, suggesting good tolerability of curcumin. The highest daily dose (3.6 g) significantly lowered the levels of the inflammatory biomarker prostaglandin E2. The authors recommended

a daily oral dose of 3.6 g of curcumin for phase 2 evaluation in the prevention or treatment of cancers outside the gastrointestinal tract.⁸⁵

In another study of patients with colorectal cancer, presurgical curcumin administration (360 mg three times daily) for 10 to 30 days increased body weight, decreased serum TNF-alpha levels, increased the number of apoptotic cells, and enhanced the expression of p53, a known tumor suppressor, in tumor tissue. The study concluded that curcumin may be therapeutic in patients with colorectal cancer.⁸⁶

In a clinical trial evaluating curcumin's effect in 29 multiple myeloma patients, the treatment group took curcumin at doses of 2, 4, 6, 8, or 12 g/day alone or in combination with bioperine (10 mg) for 12 weeks. Curcumin and bioperine were well tolerated, with no significant adverse events. Results showed that curcumin downregulated the activation of NF-KB and STAT3, and suppressed COX-2 expression.⁸⁷ These observations support curcumin's potential for treating multiple myeloma.

In another clinical trial, 25 patients with pancreatic cancer were given 8 g of curcumin per day, with restaging (the process of finding out how much cancer there is in a person's body and where it's located) every two months. The majority of the patients showed downregulation of NF-KB and COX-2 after treatment with curcumin, but this downregulation didn't result in a clinical response in many patients.⁸⁸

Since poor bioavailability may be a reason for the lack of a clinical response, the authors concluded that the development of liposomal curcumin for clinical trials in cancer patients is a worthwhile strategy, since this curcumin formulation may provide more consistent blood levels with better pharmacologic effect. The study was first human trial to report that curcumin can downregulate the expression of these inflammatory molecules, and that oral curcumin is well tolerated at doses of 8 g/day for up to 18 months.⁸⁸

In vitro, in vivo, animal, and human clinical studies support curcumin's clinical therapeutic potential for cancer patients.^{25,26,89-92} Some of the leading clinical research centers in the United States are involved in preclinical and clinical research of the anticancer mechanism and application of curcuminoids in cancer treatment. Many clinical trials already have been completed that support curcumin's safety and efficacy in patients with multiple myeloma, colorectal, pancreatic, breast, prostate, lung, and head and neck cancers.²¹ This research supports curcumin's potential to prevent and treat various cancers.⁹³

Bioavailability

As discussed, one drawback to the therapeutic use of curcumin is its poor bioavailability.^{3,21,80,93-95} The main limitation for using curcumin-based formulations is its poor solubility and fast metabolism, resulting in poor absorption from the gastrointestinal tract and limiting therapeutic effectiveness.⁹⁵ With oral doses, most of the curcumin is excreted in feces, and only traces appear in the blood. Since curcumin's limited bioavailability weakens its effectiveness in vivo, improving bioavailability is of the utmost importance.

Several strategies have been explored to improve curcumin's bioavailability, such as modulation of the delivery system and medium of curcumin administration (nanoparticles, liposomes, micelles, and phospholipid complexes), blocking of metabolic pathways by administering curcumin with other agents (adjuvants), and conjugation and structural modifications of curcumin.^{93,94}

The roles of adjuvants, or substances added to block curcumin metabolism, resulting in increased absorption, are of great interest.^{94,95} Piperine is a popular adjuvant in clinical application.⁹⁶ One study, for example, found that "in humans receiving a dose of 2 g of curcumin, serum levels either have been undetectable or very low, but using piperine as an adjuvant was associated with a 2,000% increase in curcumin's bioavailability."⁹⁶ Other adjuvants, such as quercetin, genistein and eugenol, also show promise in improving curcumin's uptake and bioavailability.⁹⁴

In addition, many scientists are focusing on structurally modifying curcumin to improve its bioavailability.⁹⁴ Many patented formulas are being developed and used in clinical trials. For example, the patented curcumin formula Meriva resulted in total curcuminoid absorption 29-fold higher than an unformulated curcuminoid mixture.^{21,97,98} In addition, since curcumin is of low molecular weight and highly lipophilic, it's possible that it may be absorbed more easily through a transdermal rather than an oral route.³⁶

With the fast pace at which new synthetic curcuminoids and their delivery systems are being patented and disclosed, the development of a more bioavailable curcumin product is likely.^{94,95}

Safety

Human clinical trials have established curcumin's safety, tolerability, and nontoxicity at high doses.^{32,68,85,88} However, some investigators have reported undesired adverse effects at higher doses. Some human studies have shown that curcumin at doses ranging from 0.9 to 3.6 g/day for one to four months resulted in nausea and diarrhea.⁸⁵ In a recent clinical trial of 240 subjects who were instructed to take three blinded-label capsules twice per day either of curcumin (1.5 g of total curcuminoids) or placebo continuously for six months, curcumin was well tolerated with few adverse effects: One subject reported a hot flash, two subjects reported constipation, and one reported nausea.³²

Based on a review of clinical trials to date, curcumin is considered to be safe and well tolerated at doses up to 8 g/day.^{1,99} As a result of this research, the FDA has approved curcumin as a Generally Recognized as Safe compound. However, dose levels that elicit desirable vs. undesirable effects need to be determined in order for curcumin to be useful as a preventive or therapeutic drug.

Clinical Recommendations

More than 1 billion people regularly consume curcumin as part of their diets.⁴ In India, the average dietary intake of turmeric by 60-kg individuals (roughly 132 lbs) is approximately 2 to 2.5 g/day which provides 60 to 100 mg of curcumin daily.¹⁰⁰

According to one study, 1,500 mg of turmeric per day has biological activity.⁷⁸ The University of Maryland Medical Center suggests 1 to 3 g of dried, powdered turmeric root per day is needed to gain health benefits.¹⁰¹ However, there's no clear recommendation for curcumin dosage.

Until research supports more specific recommendations for therapeutic curcumin intake, RDs can educate their patients on how to include turmeric in everyday cooking to try to reap some of its related health benefits. Both whole and ground dried turmeric are readily available in the spice section of most grocery stores. However, the curcumin content of turmeric and curry powders varies considerably. Turmeric powder has the highest curcumin concentration (averaging 3.14% by weight).⁷⁹

Turmeric is an important ingredient in curry mixes, chutney, and mustard pickles, but relatively small amounts of curcumin are present in curry powder samples.⁷⁹ Consuming curcumin with meals increases its absorption, especially with fatty foods such as olive oil, avocado, fish oil, and seeds.¹⁰²

With its earthy flavor and a hint of ginger, turmeric gives poultry and seafood a warm color and accents its natural flavor. It also goes well with rice, lentil, and vegetable dishes and can enhance the flavor of soups and stews. It can be added to vinaigrettes and to oil or butter for color and flavor; used with onion powder, garlic powder, cayenne pepper, or bouillon cubes; or included as part of a traditional Indian beverage of milk, turmeric powder, and sugar to taste.⁷⁸ However, it should be added gradually since its flavor grows more pronounced during cooking and using too much at one time could ruin a dish.

In Conclusion

Evidence continues to mount in support of curcumin's role in inhibiting the inflammatory process and, thus, inflammatory diseases. Additional research is needed to improve bioavailability and determine specific recommendations for curcumin intake. In the meantime, RDs can encourage their patients to incorporate turmeric in everyday food preparation and recipes to boost color and flavor while helping to fight inflammation.

— *Sharon Collison, MS, RD, LDN, CSSD, is a dietitian in a private practice and a freelance writer in Newark, Delaware.*

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Examination

1. Which of the following statements best describes the relationship between disease and NF-KB?

- A. Viral infections reduce the presence of NF-KB.
- B. NF-KB increases the transcription of inflammatory mediators.
- C. NF-KB increases the transcription of anti-inflammatory cytokines.
- D. NF-KB reduces the expression of cyclooxygenase-2 (COX-2).

2. In which of the following ways does curcumin act on adipose tissue?

- A. It promotes macrophage infiltration.
- B. It promotes NF-KB activation.
- C. It increases the expression of tumor necrosis factor–alpha (TNF-alpha).
- D. It increases the expression of adiponectin.

3. Curcumin exerts its anti-inflammatory effects through which of the following mechanisms?

- A. Increasing free radical production.
- B. Suppressing and activating lipoxygenase (LOX).
- C. Suppressing LOX, COX, and inducible nitric oxide synthase (iNOS).
- D. Activating LOX and iNOS.

4. Which of the following results were found as part of in vivo studies involving daily curcumin doses of 10 to 20 mg?

- A. Decreased HDL cholesterol.
- B. Increased LDL cholesterol.
- C. Increased apolipoprotein A and decreased apolipoprotein A/B.
- D. Increased plasma fibrinogen.

5. Curcumin has been shown to do which of the following in clinical trials?

- A. Reduce cognitive decline in patients with Alzheimer's disease.
- B. Decrease morning stiffness and joint swelling in patients with rheumatoid arthritis.
- C. Increase inflammatory cytokines in cancer patients.
- D. Increase the expression of COX-2 and LOX in cancer patients.

6. Results from a clinical trial that evaluated curcumin's effect on risk factors for atherosclerosis in patients with type 2 diabetes found which of the following to be true?

- A. Decreased leptin in the curcumin group vs. the placebo group.
- B. Increased pulse wave velocity in the curcumin group vs. the placebo group.
- C. Decreased levels of adiponectin in the curcumin group vs. the placebo group.
- D. Normal hemoglobin A1c levels in the curcumin group vs. the placebo group.

7. Based on this course, which of the following statements is true regarding curcumin absorption and bioavailability?

- A. Curcumin is highly soluble in water.
- B. Consuming curcumin with dietary fat results in increased absorption.
- C. Curcumin is metabolized slowly, resulting in reduced absorption.
- D. Consuming curcumin on an empty stomach increases its absorption.

8. In what way does curcumin affect cancer cells?

- A. It interferes with cell signaling mechanisms for tumorigenesis.
- B. It increases tumor angiogenesis.
- C. It prevents cancer cell apoptosis.
- D. It promotes metastasis.

9. In patients with colorectal cancer, curcumin has been found to do which of the following?

- A. Decrease body weight.
- B. Increase TNF-alpha.
- C. Decrease number of apoptotic cells.
- D. Enhance expression of p53.

10. Which of the following is an appropriate recommendation for curcumin consumption?

- A. Use curry powder to season foods since curry is the best source of curcumin.
- B. Consume curcumin with a low-fat meal.
- C. Use curcumin supplements for disease prevention.
- D. Use turmeric frequently in cooking since turmeric is the best source of curcumin.