Unique Curcuminoids and Inflammation

Presented by Dr Robert Buist Ph.D
Unique Curcuminoids and Inflammation

What is Curcumin?

Turmeric

- Extracted from the roots of *Curcuma longa* plant
- Ground into a powder “curry spice” used in Asian cuisine
- Essentially a mixture of three related compounds
  - curcumin
  - demethoxycurcumin
  - bisdemethoxycurcumin
  collectively termed “curcuminoids”
  (curcumin being the most active)

Curcumin as an Antioxidant

Studies have shown that turmeric, as well as curcumin, has significant antioxidant activity (Shalini & Srinivas 1987, Soudamini et al 1992). Turmeric not only exerts direct free radical scavenging activity, it also appears to enhance the antioxidant activity of endogenous antioxidants, such as glutathione peroxidase, catalase and quinine reductase. Curcumin has been shown to induce phase II detoxifying enzymes (glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase and catalase) (Iqbal et al 2003). Additionally, its antioxidant effects are 10-fold more potent than ascorbic acid or resveratrol (Song et al 2001).

Curcumin has also been found to prevent protein glycosylation and lipid peroxidation caused by high glucose levels *in vitro* (Jain et al 2006) and to improve diabetic nephropathy (Srinivasan 2005). Turmeric has been shown to suppress cataract development and collagen cross-linking, promote wound healing, and lower blood lipids and glucose levels (Jain et al 2006).
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Strong Antioxidant

- Endogenous antioxidants
- Detoxification enzymes
- Wound healing
- HDL

- LDL, VLDL, Triglycerides
- Blood glucose
- Glycosylation (AGE’s)
- Lipid peroxidation
- Cataract development
- Collagen cross linking

Notes:
Curcumin is Hepatoprotective

Curcumin prevents carbon tetrachloride-induced liver injury both in vivo and in vitro (Deshpande et al 1998, Kang et al 2002), reverses aflatoxin-induced liver damage in experimental animals (Soni et al 1992) and effectively suppresses the hepatic microvascular inflammatory response to lipopolysaccharides in vivo (Lukita-Atmadja et al 2002). An ethanol soluble fraction of turmeric was shown to contain three antioxidant compounds, curcumin, demethoxycurcumin and bisdemethoxycurcumin, which exert similar hepatoprotective activity to silybin and silychristin in vitro (Song et al 2001). Several different mechanisms may contribute to turmeric’s hepatoprotective activity.

Curcumin has been shown to prevent lipoperoxidation of subcellular membranes in a dosage-dependent manner, due to an antioxidant mechanism (Quiles et al 1998) and turmeric may also protect the liver via inhibition of NF-kappa-B, which has been implicated in the pathogenesis of alcoholic liver disease.

Curcumin also blocked endotoxin-mediated activation of NF-kappa-B and suppressed the expression of cytokines, chemokines, COX-2, and iNOS in Kupffer cells (Nanji et al 2003).
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Hepatoprotective

- Protects against CC1₄ / Aflatoxin
- Protects against bacterial endotoxin and inflammation
- C3 Complex® Curcumin = Silybin/Silychristin
- Protects lipid peroxidation of cell membranes
- Blocks endotoxin-mediated activation of NF-κB and expression of cytokines, COX-

Notes:
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Comparative Antioxidant Activity of the Curcuminoids and Tetrahydrocurcuminoids in linoleic acid autoxidation model (determined by Thiocyanate method)

Improved Liver Function

In a recent rat study conducted to evaluate the effects of turmeric on the liver's ability to detoxify xenobiotic (toxic) chemicals, levels of two very important liver detoxification enzymes (UDP glucuronyl transferase and glutathione-S-transferase) were significantly elevated in rats fed turmeric as compared to controls. The researchers commented, "The results suggest that turmeric may increase detoxification systems in addition to its antioxidant properties...Turmeric used widely as a spice would probably mitigate the effects of several dietary carcinogens."

Curcumin has been shown to prevent colon cancer in numerous rodent studies. When researchers set up a study to analyze how curcumin works, they found that it inhibits free radical damage of fats (such as those found in cell membranes and cholesterol), prevents the formation of the inflammatory cyclooxygenase-2 (COX-2), and induces the formation of the primary liver detoxification enzyme, glutathione S-transferase (GST). When the rats were given curcumin for 14 days, the liver production of GST increased by 16%, and malondialdehyde (a marker of free radical damage) decreased by 36% when compared with controls. During this two week period, the researchers gave the rats carbon tetrachloride, a known carcinogen. In the rats not fed curcumin, markers of free radical damage to colon cells went up, but in the rats given turmeric, this increase was prevented by dietary curcumin.
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Activates Detoxification Enzymes

- Detoxifies xenobiotic chemicals
- Increases UDP Glucuronyl transferase
- Increases Glutathione-S-transferase
- Inactivates procarcinogens
- Decreases inflammatory COX-2

Mice 14 days on curcumin:

- GST 16%
- malondialdehyde 36%
- CCl₄ damage to colon cells

Notes:
The Absorption Question

Researchers compared giving turmeric in the diet versus injecting curcumin into the rats' colons. They found injecting curcumin resulted in more curcumin in the blood, but much less in the colon mucosa. They concluded, "The results show that curcumin mixed with the diet achieves drug levels in the colon and liver sufficient to explain the pharmacological activities observed and suggest that this mode of administration may be preferable for the chemoprevention of colon cancer." (Sharma RA et al 2001).

This may also indicate that one of the major absorption pathways to the liver is via the enterohepatic circulation and supports the use of dietary oils to increase the uptake of curcumin. Taking curcumin with hot watery food such as chicken broth, miso soup or Tom Yum hot asian soup, prior to ingestion, or taking with warm oily foods, such as curries and stir fries, increases bioavailability. Co-supplementation with piperine extracted from black pepper will increase absorption. However, due to its effects on drug metabolism, piperine should be taken cautiously (if at all) by individuals taking other medications.

Low Blood Levels of Curcumin Effective

Interestingly, some studies have suggested that curcumin elicits systemic effects relevant to the chemoprevention of cancer in hepatic and mammary tissues of animals, despite attainment of very low levels of curcumin ($10^{-9}$ to $10^{-8}$ mol/L range) (Sharma R A et al 2001).

Also, lymphocyte glutathione-S-transferase activity, a potential surrogate biomarker of curcumin activity, was significantly decreased in patients taking 440mg/day despite the lack of measurable serum curcumin (Sharma RA et al 2001).
Absorption of Curcumin

- Low absorption
- Oral curcumin for gastrointestinal problems
- Hot oily foods for systemic absorption
- Active Enterohepatic absorption
- Sulphate and glucuronide conjugate metabolites
- Piperine from black pepper increases absorption
- Low blood levels $10^{-9} - 10^{-8}$ mol/l still effective

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Cholagogue and Hypolipidaemic

Turmeric extract or curcumin extract has shown dose dependent hypolipidaemic activity *in vivo* (Asai & Miyazawa 2001). One *in vivo* study suggests that curcumin may stimulate the conversion of cholesterol into bile acids, and therefore, increase the excretion of cholesterol (Srinivasan & Sambaiah 1991). A further study demonstrated that supplementation with turmeric reduces fatty streak development and oxidative stress (Quiles et al 2002). Oral curcumin has also been shown to stimulate contraction of the gall bladder and promote the flow of bile in healthy subjects (Rasyid & Lelo 1999).

Cardiovascular Protection

Curcumin may be able to prevent the oxidation of cholesterol and other polyunsaturated fatty acids in the body. Since oxidized cholesterol is what damages blood vessels and builds up in the plaques that can lead to heart attack or stroke, preventing the oxidation of new cholesterol may help to reduce the progression of atherosclerosis and diabetic heart disease.

![Effect of curcumin administration on serum Lipid peroxide in human volunteers](image)

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Curcumin blocks lipid peroxidation

- Prevents cholesterol oxidation
- Prevents LDL and VLDL oxidation
- Prevents polyunsaturated fatty acid oxidation
- Retards atherosclerosis and plaque formation
- Prevents stroke and heart attack

Notes:
In research published in the Indian Journal of Physiology and Pharmacology (Soni KB & Kuttan R 1992), when 10 healthy volunteers consumed 500 mg of curcumin per day for 7 days, not only did their blood levels of oxidized cholesterol drop by 33%, but their total cholesterol dropped 11.63%, and their HDL (good cholesterol) increased by 29%.

Soni & Kuttan (1992) report that curcumin can lower total cholesterol by:

A. Increasing the activity of liver microsomal cholesterol-7α-hydrolase and bile acid synthesis and thus cholesterol excretion
B. Increasing the flow of bile (curcumin is a cholagogue)
C. Up-regulating genes in liver cells, which increase the production of mRNA and associated proteins required for the construction of receptors for LDL cholesterol. With more LDL-receptors, liver cells are able to clear more LDL-cholesterol from the body

LDL-receptor mRNA increased sevenfold in liver cells treated with curcumin at a concentration of 10 microM, compared to untreated cells. (Liver cells were found to tolerate curcumin at levels of up to 12 microM for 24 hours). (Peschel D & Koerting R 2007). Meanwhile, the protective HDL cholesterol is increased.
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Oral Curcumin 500mg/day for 7 days (10 healthy volunteers)

- Reduction in Oxidized Cholesterol 33%
- Reduction in Total Cholesterol 12%
- Increase in HDL Cholesterol 29%

How does Curcumin lower Cholesterol?

- Increased conversion to bile salts
- Increased bile flow to intestines
- Increased LDL receptors and cholesterol clearance
- Increased production of HDL

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Management of Secondary Complications of Diabetes Mellitus

Sabsina’s website [www.curcuminoids.com/health](http://www.curcuminoids.com/health) provides numerous studies on the co-morbidity of diabetes and the beneficial effects of curcuminoids.

Nephropathy or kidney disease is one of the dangerous secondary complications induced by diabetes. In an animal model study, it was observed that dietary curcumin brought about significant inhibition in the progression of renal lesions. Curcumin fed at 0.5% level in the diet to streptozotocin-induced diabetic rats for eight weeks lessened renal damage and preserved the integrity and functions of the kidneys. The authors inferred that the beneficial effects of dietary curcumin on diabetic nephropathy is probably mediated through the hypolipidemic effects of curcumin.

Increased oxidative stress and high serum glucose levels have been postulated to contribute significantly to the accelerated accumulation of advanced glycation end products (AGEs) in diabetics. This results in cross-linking of collagen and the progression of the degenerative secondary complications of diabetes. Curcumin (200 mg/kg body wt, administered orally) was found to reduce the level of AGEs and the cross-linking of collagen in diabetic rats. The oxidative stress and accumulation of lipid peroxidation products in serum of diabetic rats was observed to reduce significantly on curcumin administration. This study confirmed the significance of free radicals in the accumulation of AGEs and cross-linking of collagen in diabetics and validated the use of curcumin for the inhibition of AGE-induced complications of diabetes mellitus.

Also, hyperlipidemia is often associated with diabetes and could induce cardiovascular problems. In earlier studies, curcumin was proven to be an effective hypolipidemic agent. One study validated the role of dietary curcumin in maintaining healthy serum cholesterol levels in diabetic rats. Streptozotocin-induced diabetic rats were maintained on 0.5% curcumin containing diet for 8 weeks. It was observed that the LDL-VLDL fraction and the serum levels of triglycerides and phospholipids was reduced by dietary curcumin in diabetic rats. In a parallel study employing a high cholesterol diet for the diabetic rats, curcumin exhibited lowering of cholesterol and phospholipid in treated animals as compared to curcumin-free controls. Liver cholesterol, triglycerides and phospholipid elevated under diabetic conditions were lowered by dietary curcumin, in both studies. Renal cholesterol and triglycerides elevated in diabetic rats, were similarly lowered by the curcumin in the diet. The authors observed that the enzyme activity of liver cholesterol-7a-hydroxylation was markedly higher in curcumin fed diabetic animals. This suggests that curcumin induces a higher rate of cholesterol catabolism, which may play a role in the prevention of cardiovascular disease.
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Curcumin in Diabetes (animal studies)

- Reduced lipid peroxidation
- Improved small blood vessel function in kidney
- Reduced lipoproteins LDL, VLDL and cholesterol
- Increased liver cholesterol-7α-hydroxylase
- Reduced AGE’s and collagen cross-linking*

* Diabetic vessels are high in cross-linked collagen with significant accumulation of AGE’s. This change in collagen biochemistry is associated with stiffening of blood vessel walls.

Notes:
Age-related cataractogenesis is a significant health problem worldwide and is also commonly found in diabetics. Oxidative stress has been suggested to be a common underlying mechanism of the formation of cataracts. If the antioxidant defenses of the ocular lens is enhanced, the formation of cataracts is delayed or prevented. A study was designed to test the efficacy of preventing cataractogenesis in an \textit{in vitro} rat model. Rats were maintained on a standard diet for 2 weeks, after which they were given a daily dose of corn oil alone or with 75 mg curcumin/kg body weight in corn oil for 14 days. Their lenses were removed and cultured for 72 hours \textit{in vitro} in the presence or absence of 100 microM of 4-hydroxy-2-nonenal, which is a highly electrophilic product of lipid peroxidation. The results of these studies showed that 4-HNE caused cultured lenses to become opaque, as indicated by the measurements of transmitted light intensity. However, the lenses from curcumin-treated rats were much more resistant to 4-HNE-induced opacification than were lenses from control animals fed curcumin-free diet.

Curcumin treatment was found to cause a significant induction of a glutathione S-transferase (GST) isozyme (rGST8-8) in rat lens epithelium. This enzyme is known to preferentially utilize 4-HNE. The authors suggest that the protective effect of curcumin may be mediated through the induction of this GST isozyme and that curcumin may be an effective protective agent against cataract formation induced by lipid peroxidation.

(http://www.curcuminoids.com/health.htm)
Curcumin Protective against Cataracts

- Animals fed corn oil daily for 2 weeks with/without 75mg/kg Curcumin
- Lenses removed and cultured 72 hours with/without 4-HNE caused cultured lens to become opaque
- Curcumin caused opacification resistance
- Curcumin induced Glutathione-S-transferase in lense epithelium
- Curcumin may protect against cataracts

Notes:
Curcumin as Anti-inflammatory Agent

Turmeric is a dual inhibitor of the arachidonic acid cascade. There has been studies examining the anti-inflammatory effects of curcumin. Curcumin has been shown to exert anti-inflammatory effects via phospholipase, lipo-oxygenase, COX-2, leukotrienes, thromboxane, PGs, NO, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1, IFN-inducible protein, TNF and IL-12 (Chainani-Wu 2003, Lantz et al 2005). The anti-inflammatory effect of curcumin was tested in adjuvant-induced chronic inflammation rats which found that curcumin significantly reduced C-reactive protein, TNF-alpha, IL-1 and NO, with no significant changes observed in PGE₂ and leukotriene B4 levels or lymphocyte proliferation (Banerjee et al 2003). Curcumin has also been shown to inhibit inflammation in experimental pancreatitis via inhibition of NF-kappa-B and activator protein-1 in two rat models (Gukovsky et al 2003).

In numerous studies, curcumin's anti-inflammatory effects have been shown to be comparable to the potent drugs hydrocortisone and the non-steroidal anti-inflammatory agents. Unlike these drugs such as, which are associated with significant toxic effects (ulcer formation, decreased white blood cell count, intestinal bleeding), curcumin produces no toxicity.
Curcumin Inhibits

Phospholipase A2
Lipoxygenase
Cyclooxygenase
COX-2
Leukotrienes (LTB4)
Thromboxanes (TXA2)
Prostaglandins (PGE2)

Also
Nitric Oxide
Collagenase
Elastase
TNF-alpha
IL-1,6,8,12
CRP

Notes:
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Inflammatory Bowel Disease

Curcumin may provide a more natural, well-tolerated, and effective treatment for inflammatory bowel disease (IBD) such as Crohn's and ulcerative colitis. In one study (Salh et al 2003), mice given an inflammatory agent that normally induces colitis. They were protected from colitis when curcumin was added to their diet five days beforehand. The mice receiving curcumin not only lost much less weight than the control animals, but when researchers checked their intestinal cell function, all the signs typical of colitis (mucosal ulceration, thickening of the intestinal wall, and the infiltration of inflammatory cells) were all much reduced. While the researchers are not yet sure exactly how curcumin achieves its protective effects, they think its benefits are the result of not only antioxidant activity, but also inhibition of a major cellular inflammatory agent called NF-kappa B. Curcumin has been found to attenuate experimental colitis in animal models through a mechanism correlated with the inhibition of NF- kappa-B (Salh et al 2003).

NF Kappa B Inhibition

The many and varied effects of curcumin may be partly associated with the inhibition of transcription factor nuclear factor-kappa beta (NF-kappa B) and induction of heat shock proteins. The list of diseases that have been shown to be associated with activation of NF-kappa B is lengthy and includes all of those listed below and many more.

NF-kappa B is a transcription factor pivotal in the regulation of inflammatory genes and is also closely associated with the heat shock response, which is a cellular defence mechanism that confers broad protection against various cytotoxic stimuli. Inhibition of NF-kappa B may reduce inflammation and protect cells against damage (Chang 2001).
Curcumin and Inflammatory Bowel Disease

Experimental Colitis in Animals fed curcumin for 5 days

- Decreased mucosal ulceration
- Decreased thickening of intestinal wall
- Decreased infiltration of inflammatory cells
- Decreased weight loss

Curcumin in Ulcerative Colitis

Relapse rate in 82 ulcerative colitis patients in remission on sulfasalazine was only 4.7% when they took 1000mg curcumin twice daily.
(Controls relapse rate 15.1%)


Notes:
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Relief for Rheumatoid Arthritis

Numerous clinical studies have substantiated that curcumin exerts very powerful antioxidant effects. As an antioxidant, curcumin is able to neutralize free radicals which cause great amounts of damage to healthy cells and cell membranes. This is important in many diseases, such as arthritis, where free radicals are responsible for the painful joint inflammation and eventual damage to the joints. In a recent study of patients with rheumatoid arthritis, curcumin was compared to phenylbutazone and produced comparable improvements in shortened duration of morning stiffness, lengthened walking time, and reduced joint swelling.

Chemical Structure of 3 curcuminoids

CURCUMIN

DEMETHOXY CURCUMIN

BISDEMETHOXY CURCUMIN

(Diferuloyl methane)

(p-Hydroxy-cinnamoyl-feruloyl-methane )

(pp’-Dihydroxy-dicinnamoyl-methane)
Cartilage Degradation and Protection

Role of IL-1β and TNF-α in arthritis both inflammatory IL-1β - mediates cartilage destruction

- activates matrix metalloproteinases
- degrades resident collagen fibrils in cartilage
- induces chondrocyte apoptosis
- increases inflammatory cytokines PGE₂, NO

Notes:
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Curcumin protects human chondrocytes

Interleukin 1beta (IL-1beta) and TNF alpha are pro-inflammatory cytokines that play a key role in mediating cartilage degradation in osteoarticular disorders such as osteoarthritis (OA) and rheumatoid arthritis (RA). Both IL-1beta and TNF-alpha can launch inflammation but it is the IL-1beta that drives cartilage and bone destruction. At the cellular level, the IL-1beta activates matrix degrading enzymes in chondrocytes, down-regulates expression of matrix components, degrades resident collagen fibrils in the cartilage and induces chondrocyte apoptosis (Raymond L et al). Curcumin has recently been shown to antagonize the pro-inflammatory effects of cytokines in chondrocytes and other cells. To test the hypothesis that curcumin also protects chondrocytes from morphological alterations induced by IL-1beta, human articular chondrocytes were pre-treated with 10 ng/ml IL-1beta alone for 30 min before being co-treated with IL-1beta and 50 microM curcumin for 5, 15 or 30 min, respectively (Kurz B, 2005).

Transmission electron microscopy of chondrocytes stimulated with IL-1beta revealed early degenerative changes which were relieved by curcumin co-treatment. The suppression of collagen type II and beta1-integrin synthesis by IL-1beta was inhibited by curcumin. Additionally, curcumin antagonized IL-1beta-induced caspase-3 activation in a time-dependent manner. This study clearly demonstrates that curcumin exerts anti-apoptotic and anti-catabolic effects on IL-1beta-stimulated articular chondrocytes. Therefore curcumin may have a novel therapeutic potential as an adjunct nutraceutical chondroprotective agent for treating OA and related osteoarticular disorders (Kurz, B 2005).

The Chemical Structure of Curcuminoids

1. Para hydroxyl groups – Antioxidant activity
2. Keto groups – Anti-inflammatory, anti-cancer, antimutagen activities
3. Double bonds – Anti-inflammatory, anti-cancer, antimutagen activities
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Curcumin Dampens Effects of Inflammatory Cytokines in Chondrocytes

- IL-1β induces degenerative changes in human condrocytes \textit{in vitro}

- Curcumin blocks IL-1β induced:
  - A. suppression of collagen type II
  - B. suppression of beta 1-integrin
  - C. caspase-3 activation
  - D. chondrocyte apoptosis

\textit{Combines well with Chondrosamine and Omega-3 fish oils for treatment of Rheumatoid Arthritis and Osteoarthritis}

Notes:
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Cancer Prevention

Curcumin's antioxidant actions enable it to protect the colon cells from free radicals that can damage cellular DNA—a significant benefit particularly in the colon where cell turnover is quite rapid, occurring approximately every three days. Because of their frequent replication, mutations in the DNA of colon cells can result in the formation of cancerous cells much more quickly. Curcumin may also help the body to destroy mutated cancer cells, so they cannot spread through the body and cause more harm. A primary way in which curcumin does so is by enhancing liver function. Epidemiological data suggest that curcumin reduces the rate of colorectal cancer (Hergenhahn et al 2002) and curcumin has wide-ranging chemopreventive activity in preclinical carcinogenic models (Plummer et al 2001), most notably for gastrointestinal cancers (Ireson et al 2001). To date, however, there are no controlled trials to attest to turmeric’s efficacy in cancer treatment or prevention. In a phase I human study, curcumin taken orally for 3 months at a starting dose of 500 mg/day was found to produce histological improvement in cases of bladder cancer, oral leucoplakia, intestinal metaplasia of the stomach, cervical intraepithelial neoplasm and Bowen’s disease (Cheng et al 2001).

Inhibits Cancer Cell Growth and Metastases

Other epidemiological studies have linked the frequent use of turmeric to lower rates of breast, prostate, lung and colon cancer; laboratory experiments have shown curcumin can prevent tumours from forming; and research conducted at the University of Texas by Dr Bharat Aggarwal (2005), suggests that even when breast cancer is already present, curcumin can help slow the spread of breast cancer cells to the lungs in mice.

Currently, there is no effective therapy for metastatic breast cancer after surgery, radiation, and chemotherapy that has been used against the primary tumor. Chemotherapeutic agents activate NF-κB for cell survival, proliferation, invasion and metastasis. Curcumin has been shown to suppress the NF-κB so may reduce further tumor formation.
Curcumin in Cancer Prevention

- Blocks carcinogen-induced colon, skin, liver carcinogenesis
- Induces apoptosis in melanoma and BCCs
- Inhibits oncogenes and transcription factors
- Inhibits proliferating cells via protein kinases and phosphorylase kinase
- Exhibits anti-metastatic action in melanoma cells
- Inhibits metalloproteinases
- Enhances cytotoxicity of chemotherapeutic drugs
- Inhibits production of inflammatory cytokines

Notes:
This activation of NF-κB with long term use of chemotherapy is problem with chemotherapeutic agents in general:

“Paclitaxel, which is a microtubule-stabilizing anti-tumour agent, vinblastine and vincristine, which are microtubule-depolymerizing agents, and daunomycin and doxorubicin, which are drugs that intercalate into DNA and inhibit RNA synthesis, all could induce NF-kappa B. Although these drugs are structurally and functionally dissimilar, they share a common property, which is activation of protein kinase C. Thus, since these drugs have effects other than interfering with microtubule assembly, it is possible that they induce NF-kappa B by mechanisms distinct from microtubule-associated mechanisms. As demonstrated, one such potential mechanism is through the increased activity of protein kinase C” (Kumuda C et al)

Dr Aggarwal hypothesized that curcumin would potentiate the effect of chemotherapy in advanced breast cancer and inhibit lung metastasis. In order to confirm this he injected human breast cancer cells into mice, and the resulting tumours were removed to simulate a mastectomy.

The mice were then divided into four groups. One group received no further treatment and served as a control. A second group was given the cancer drug paclitaxel (Taxol); the third got curcumin, and the fourth was given both Taxol and curcumin.

After five weeks, only half the mice in the curcumin-only group and just 28% of those in the curcumin plus Taxol group had evidence of breast cancer that had spread to the lungs.

But 75% of the mice that got Taxol alone and 96% of the control group developed lung tumours.
Most chemotherapeutic agents activate NF kappa B. Curcumin suppresses it.

<table>
<thead>
<tr>
<th>Tumours linked to</th>
<th>NF-kB Expression</th>
<th>Hematopoietic tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Breast</td>
<td>- Colon</td>
<td>- Multiple myeloma</td>
</tr>
<tr>
<td>- Liver</td>
<td>- Retinoblastoma</td>
<td>- B-cell lymphoma</td>
</tr>
<tr>
<td>- Prostate</td>
<td>- Bladder</td>
<td>- Hodgkins lymphoma</td>
</tr>
<tr>
<td>- Head and neck</td>
<td>- Ovarian</td>
<td>- T-cell lymphoma</td>
</tr>
<tr>
<td>- Lung</td>
<td>- Pancreatic</td>
<td>- Adult T-cell lymphoma</td>
</tr>
<tr>
<td>- Melanoma</td>
<td>- Thyroid</td>
<td>- Acute lymphoblastic leukaemia</td>
</tr>
</tbody>
</table>

Notes:
Aggarwal published these results in Clin Cancer Research, September 2005. Curcumin is a pharmacologically safe compound, which has a therapeutic potential in preventing breast cancer metastasis possibly through suppression of NF-κB and NF-κB–regulated gene products.

How did curcumin help? "Curcumin acts against transcription factors, which are like a master switch," said Aggarwal. "Transcription factors regulate all the genes needed for tumours to form. When we turn them off, we shut down some genes that are involved in the growth and invasion of cancer cells."
## Metastasis in Animals Receiving Taxol or Curcumin (5 weeks)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage with metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>96</td>
</tr>
<tr>
<td>Paclitaxel (TAXOL)</td>
<td>75</td>
</tr>
<tr>
<td>Curcumin</td>
<td>50</td>
</tr>
<tr>
<td>Curcumin Plus TAXOL</td>
<td>28</td>
</tr>
</tbody>
</table>

### Notes:
Aggarwal says “we have not found a single cancer on which curcumin does not work”. Prof Aggarwal’s hypothesis is that most cancers exhibit activated NF-kB which in turn promotes the proliferation and metastasis of tumours. Blocking of NF-kB suppresses the formation of tumours.

In another laboratory study of human non-Hodgkin’s lymphoma cells published in *Biochemical Pharmacology* (Shishodia S et al 2005), again the University of Texas researchers showed that curcumin inhibits the activation of NF-kB, and hence signals to the genes to produce a slew of inflammatory molecules (including TNF, COX-2 and IL-6) that promote cancer cell growth. In addition, curcumin was found to suppress cancer cell proliferation and to induce cell cycle arrest and apoptosis (cell suicide) in the lung cancer cells. Early phase I clinical trials at the University of Texas are now also looking into curcumin’s chemopreventive and therapeutic properties against multiple myeloma and pancreatic cancer, and other research groups are investigating curcumin’s ability to prevent oral cancer.

**Curcumin and Colon Cancer**

Research published in the August 2006 issue of *Clinical Gastroenterology and Hepatology* by Cruz-Correa et al shows that curcumin and quercitin reduce both the size and number of precancerous lesions in the human intestinal tract. Five patients with an inherited form of precancerous polyps in the lower bowel known as familial adenomatous polyposis (FAP) were treated with regular doses of curcumin and quercetin over an average of six months. The average number of polyps decreased by 60.4%, and the average size of the polyps that did develop were reduced by 50.9%.

FAP runs in families and is characterized by the development of hundreds of polyps (colorectal adenomas) and, eventually, colon cancer. Recently, nonsteroidal anti-inflammatory drugs (NSAIDs such as aspirin, ibuprofen) have been used to treat some patients with this condition, but these drugs often produce significant side effects, including gastrointestinal ulcerations and bleeding, according to lead researcher Francis M. Giardiello, M.D., at the Division of Gastroenterology, Johns Hopkins University.
Curcumin and Cancer

“Most cancers exhibit activated NF-κB which in turn promotes the proliferation and metastasis of tumours. Blocking of NF-κB suppresses tumour formation ……we have not found a single cancer on which curcumin does not work.”

Dr Bharat Aggarwal

Notes:
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Previous observational studies in populations that consume large amounts of curry, as well as animal research, have strongly suggested that curcumin might be effective in preventing and/or treating cancer in the lower intestine. Similarly, quercetin, an anti-oxidant flavonoid found in a variety of foods including onions, green tea and red wine, has been shown to inhibit growth of colon cancer cell lines in humans and abnormal colorectal cells in animals.

In this study, a decrease in polyp number was observed in four of five patients at three months and four of four patients at six months. Each patient received curcumin (480 mg) and quercetin (20 mg) orally 3 times a day for 6 months. Although the amount of quercetin was similar to what many people consume daily, the curcumin consumed was more than would be provided in a typical diet because turmeric only contains on average 3-5 % curcumin by weight.

While simply consuming curry and onions may not have as dramatic an effect as was produced in this study, this research clearly demonstrates that liberal use of turmeric and onions can play a protective role against the development of colorectal cancer.

Curcumin/Cruciferous vegetables and Prostate Cancer
Prostate cancer is possibly the second leading cause of cancer death in Australian men but is a rare occurrence among men in India, whose low risk is attributed to a diet rich in brassica family vegetables and turmeric.

Researchers have tested turmeric, along with phenethyl isothiocyanate, a phytochemical abundant in cruciferous vegetables including cauliflower, cabbage, broccoli, Brussels sprouts, kale, kohlrabi and turnips.

When tested singly, both phenethyl isothiocyanate and curcumin greatly retarded the growth of human prostate cancer cells implanted in immune-deficient mice. In mice with well-established prostate cancer tumours, neither phenethyl isothiocyanate nor curcumin by itself had a protective effect, but when combined, they significantly reduced both tumour growth and the ability of the prostate cancer cells to spread (metastasize) in the test animals.
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Curcumin in cancer

Treatment of 5 Patients with Bowel Polyps with Curcumin and Quercitin

- 5 patients took 480mg curcumin and 20mg quercetin 3 times daily for 6 months
- Number of polyps decreased 60.4%
- Size of polyps decreased 50.9%

* Polyps returned when one patient discontinued therapy after 3 months but regressed when recommenced the therapy.

Rationale for combining specific vegetables for their phytonutrient content:

- Colorectal cancer – turmeric (curcumin) and onions (quercetin)
- Prostate cancer – turmeric (curcumin) & caulifower (isothiocyanate)

Notes:
Unique Curcuminoids and Inflammation

The researchers believe the combination of cruciferous vegetables and curcumin could be an effective therapy not only to prevent prostate cancer, but to inhibit the spread of established prostate cancers.

Best of all, this combination—cauliflower spiced with turmeric—is absolutely delicious! For protection against prostate cancer, cut cauliflower florets in quarters and let sit for 5-10 minutes; this allows time for the production of phenethyl isothiocyanates, which form when cruciferous vegetables are cut, but stops when they are heated. Then sprinkle with turmeric, and sauté on medium heat in a few tablespoons of vegetable or chicken broth for 5 minutes. Remove from the heat and top with olive oil, sea salt and pepper to taste.

Reducing Risk of Childhood Leukemia

Research presented (Nagabhushan M 2006) at a recent conference on childhood leukemia, held in London, provides evidence that eating foods spiced with turmeric could reduce the risk of developing childhood leukemia. The incidence of this cancer has risen dramatically during the 20th century, mainly in children under age five, among whom the risk has increased by more than 50% cent since 1950 alone. Modern environmental and lifestyle factors are thought to play a major role in this increase.

Childhood leukemia is much lower in Asia than Western countries, which may be due to differences in diet, one of which, the frequent use of turmeric, which has been investigated in a series of studies over the last 20 years by Prof. Moolky Nagabhushan from the Loyola University Medical Centre, Chicago, IL.

"Some of the known risk factors that contribute to the high incidence of childhood leukemia are the interaction of many lifestyle and environmental factors. These include prenatal or postnatal exposure to radiation, benzene, environmental pollutants and alkylating chemotherapy drugs. Our studies show that turmeric— and its colouring principle, curcumin—in the diet mitigate the effects of some of these risk factors" (Nagabhushan, 2004).

Nagabhushan has shown that the curcumin in turmeric can:
A. Inhibit the mutagenicity of polycyclic aromatic hydrocarbons (PAHs) (carcinogenic chemicals created by the burning of carbon based fuels including cigarette smoke)
B. Inhibit radiation-induced chromosome damage
C. Prevent the formation of harmful heterocyclic amines and nitroso compounds, which may result in the body when certain processed foods are consumed, such as processed meat products that contain nitrosamines
D. Irreversibly inhibit the multiplication of leukemia cells in a cell culture
Childhood Leukemia on the Rise
due mainly to pre- and post-natal environmental factors.

Role for curcumin:

- Inhibits mutagenicity of polycyclic aromatic hydrocarbons including cigarette smoke, and carcinogens (PAH)
- Inhibits radiation-induced chromosomal damage (including computers, mobile phones, high-tension cables)
- Prevents formation of nitrosamines and other food-based carcinogens
- Inhibits multiplication of leukemia cells in cell culture

Notes:
Protection against Alzheimer's Disease

Growing evidence suggests that turmeric may afford protection against neurodegenerative diseases. Epidemiological studies show that in elderly Indian populations, among whose diet turmeric is a common spice, levels of neurological diseases such as Alzheimer's are very low. Concurrently, experimental research conducted recently found that curcumin does appear to slow the progression of Alzheimer's in mice. Preliminary studies in mice also suggest that curcumin may block the progression of multiple sclerosis. While it is still unclear how it may afford protection against this degenerative condition, one theory is that it may interrupt the production of IL-2, which can play a key role in the destruction of the myelin sheath that serves to protect most nerves in the body.

A number of studies have suggested that curcumin protects against Alzheimer's disease by turning on a gene that codes for the production of specific endogenous antioxidants. A study published in the *Italian Journal of Biochemistry* (Calabrese V et al 2003) discussed curcumin's role in the induction of the the heme oxygenase pathway, a protective system that, when triggered in brain tissue, causes the production of the potent antioxidant bilirubin, which protects the brain against oxidative (free radical) injury. Such oxidation is thought to be a major factor in aging and to be responsible for neurodegenerative disorders including dementias like Alzheimer's disease. Another study conducted jointly by an Italian and U.S. team and presented at the American Physiological Society's 2004 annual conference in Washington, DC, confirmed that curcumin strongly induces expression of the gene, called hemeoxygenase-1 (HO-1) in astrocytes from the hippocampal region of the brain.
Unique Curcuminoids and Inflammation

Curcumin and Alzheimer’s Disease

- Alzheimer’s Disease very low in India
- Curcumin induces expression of gene hemeoxygenase-1 in the hippocampal region of the brain to form bilirubin (a powerful antioxidant)
- Prevents oxidation - a major factor in neurodegenerative disorders

Notes:
Unique Curcuminoids and Inflammation

Curcumin Crosses Blood-Brain Barrier

Research conducted at UCLA and published in the Journal of Biological Chemistry (Yang F 2004), which has been confirmed by further research published in the Journal of Agricultural and Food Chemistry (Balasubramanian K 2006), provides insight into the mechanisms behind curcumin's protective effects against Alzheimer's disease.

Alzheimer's disease results when a protein fragment called amyloid-β accumulates in brain cells, producing oxidative stress and inflammation, and forming plaques between neurons that disrupt brain function.

Amyloid is a general term for protein fragments that the body produces normally. Amyloid-β is a protein fragment snipped from another protein called amyloid precursor protein (APP). In a healthy brain, these protein fragments are broken down and eliminated. In Alzheimer's disease, the fragments accumulate, forming hard, insoluble plaques between brain cells.

The UCLA researchers first conducted in vitro studies in which curcumin was shown to inhibit amyloid-β aggregation and to dissolve amyloid fibrils more effectively than the anti-inflammatory drugs ibuprofen and naproxen. Then, using live mice, the researchers found that curcumin crosses the blood brain barrier and binds to small amyloid-β species. Once bound to curcumin, the amyloid-β protein fragments can no longer clump together to form plaques. Curcumin not only binds to amyloid-β, but also has anti-inflammatory and antioxidant properties, supplying additional protection to brain cells. It also has a unique immune boosting function when it comes to brain macrophages.
A role for Curcumin in Alzheimer’s Disease

- Mechanism for Alzheimer’s is unclear
- Build-up of plaque from amyloid β deposits is a (factor) in Alzheimer’s
- Curcumin inhibits amyloid β aggregation
- Curcumin crosses blood-brain barrier
- Curcumin supplies antioxidant antiinflammatory protection to brain cells

Notes:
Unique Curcuminoids and Inflammation

Bisdemethoxycurcumin and Amyloid Plaque Clearance

One of the most active of the curcuminoids is bisdemethoxycurcumin. It boosts the activity of the immune system in Alzheimer's patients, helping them to clear the amyloid \( \beta \) plaques characteristic of the disease.

In healthy patients, macrophages engulf and destroy abnormal cells and suspected pathogens, and efficiently clear amyloid \( \beta \), but macrophage activity is suppressed in Alzheimer's patients. (Zhang L et al, 2006).

Using blood samples from Alzheimer's patients, Drs. Milan Fiala and John Cashman (2007) have shown that bisdemethoxycurcumin boosts macrophage activity to normal levels, helping to clear amyloid \( \beta \). Fiala and Cashman also observed that bisdemethoxycurcumin was more effective in promoting the clearance of amyloid beta in some patients' blood than others, hinting at a genetic element. Further study revealed the genes involved are MGAT III and Toll-like receptors, which are also responsible for a number of other key immune functions.

Bisdemethoxycurcumin enhances the transcription of these genes, correcting the immune defects seen in Alzheimer's patients. (Fiala M et al 2007)

Chemical Structure of 3 curcuminoids

\[
\text{CURCUMIN (Diferuloyl methane)}
\]

\[
\text{DEMETHOXY CURCUMIN (p-Hydroxy-cinnamoyl-feruloyl-methane)}
\]

\[
\text{BISDEMETHOXY CURCUMIN (pp'-Dihydroxy-dicinnamoyl-methane)}
\]
Bisdemethoxycurcumin Boosts Macrophages

- Macrophages clear amyloid β in healthy persons
- Macrophage activity is suppressed in Alzheimer’s patients
- Bisdemethoxycurcumin boosts macrophage activity in 50% Alzheimer’s patients (genetic defect?)
- Younger patients respond better
- Bisdemethoxycurcumin enhances transcription of genes, correcting immune defects of patients

Notes:
Help for Cystic Fibrosis Sufferers
According to an animal study published in *Science* (Egan ME et al 2004), Curcumin may correct the most common expression of the genetic defect that is responsible for cystic fibrosis. Cystic fibrosis, a fatal disease that attacks the lungs with a thick mucus, causing life-threatening infections, afflicts increasing numbers of children and young adults, who rarely survive beyond 30 years of age. The mucus also damages the pancreas, thus interfering with the body-ability to digest and absorb nutrients.

Researchers now know that cystic fibrosis is caused by mutations in the gene that encodes for a protein (the transmembrane conductance regulator or CFTR). The CFTR protein is responsible for traveling to the cell-surface and creating channels through which chloride ions can leave the cell. When the protein is abnormally shaped because of a faulty gene, this cannot happen, so chloride builds up in the cells, which in turn, leads to mucus production.

The most common mutation, which is called DeltaF508, results in the production of the misfolded CFTR protein.

About 70% of mutations observed in CF patients result from deletion of three base pairs in CFTR's nucleotide sequence. This deletion causes loss of the amino acid phenylalanine located at position 508 in the protein; therefore, this mutation is referred to as delta F508 or F508.

With normal CFTR, once the protein is synthesized, it is transported to the endoplasmic reticulum (ER) and Golgi apparatus for additional processing before being integrated into the cell membrane. When a CFTR protein with the delta F508 mutation reaches the ER, the quality-control mechanism of this cellular component recognizes that the protein is folded incorrectly and marks the defective protein for degradation. As a result, delta F508 never reaches the cell membrane.
Cystic Fibrosis (CF) Defect Corrected with Curcumin

- CF due to a genetic deletion Delta F508
- A misfolded protein CFTR is produced
- CFTR travels to cell-surface creating channels for chloride ions to leave cell
- Defective CFTR never reaches the surface - it is degraded
- Curcumin corrects defect to yield CFTR of normal appearance and function (by acting as a chemical ‘chaperone’)

Notes:
When mice with this DeltaF508 defect were given curcumin in doses that, on a weight-per-weight basis, would be well-tolerated by humans, curcumin corrected this defect, resulting in a DeltaF508 protein with normal appearance and function. In addition, the Yale scientists studying curcumin have shown that it can inhibit the release of calcium, thus allowing mutated CTFR to exit cells via the calcium channels, which also helps stop the chloride-driven build up of mucus. Specialists in the treatment of cystic fibrosis caution, however, that patients should not self-medicate with dietary supplements containing curcumin, until the correct doses are known and any adverse interactions identified with the numerous prescription drugs taken by cystic fibrosis sufferers.

Curcumin in Asthma?

Finally, Dr Vladimir Badmaev from Sabinsa is completing a Curcumin C3 complexR trial on patients with chronic obstructive pulmonary disease which is also caused by a longstanding asthma. The possible role of curcuminoids in prevention and treatment of asthma is highlighted in two papers. The first by Kobyashi et al. indicates that curcumin can interfere with the mechanism of lung inflammation and destructive remodeling.

They examined the effect of curcumin on the production of interleukin (IL-2, IL-5), granulocyte macrophage-colony stimulating factor (GM-CSF), and IL-4 by lymphocytes from atopic asthmatics in response to house dust mites, (Dermatophagoides farinea: Df) in order to clarify a potential application for allergic diseases. Curcumin inhibited Df-induced lymphocyte proliferation and production of IL-2. Exogenous IL-2 reconstituted the proliferative responsiveness of lymphocytes to Df in the presence of curcumin. Furthermore, curcumin inhibited IL-5, GM-CSF, and IL-4 production in a concentration-dependent manner.

These results indicate that curcumin may have a potential effect on controlling allergic diseases through inhibiting the production of cytokines affecting eosinophil function and IgE synthesis. (Kobayashi T et al)
Curcumin and Asthma

- Curcumin inhibits dust mite-induced cytokine production in atopic asthmatics in a dose-dependent manner
- Hence may affect eosinophil function and IgE synthesis
- Curcumin may restore corticosteroid sensitivity in asthma and chronic obstructive pulmonary disease by boosting enzyme HDAC-2 activity

Notes:
Unique Curcuminoids and Inflammation

The second paper indicates that curcuminoids can be used in restoring activity of steroids in patients who have become resistant to corticosteroid therapy. Insensitivity to corticosteroid treatment in inflammatory conditions, such as asthma and chronic obstructive pulmonary disease, present considerable management problems and cost burdens to health services.

Oxidative stress is a major component of chronic inflammation and can have a significant suppressive effect on corticosteroid efficacy. Recent advances in the understanding of both the mechanisms of corticosteroid action and corticosteroid insensitivity have provided hope for a therapeutic strategy of restoring corticosteroid sensitivity. The enzyme histone deacetylase 2 (HDAC-2) plays a pivotal role in corticosteroid action and has reduced many cases of steroid insensitivity. Moreover, it has shown that oxidative stress can be responsible for this reduction in HDAC-2 activity. Two structurally different compounds, the caffeine related, theophylline, and the polyphenol, curcumin have both been shown to restore HDAC activity, thereby restoring corticosteroid function (Marwick JA et al)
Unique Curcuminoids and Inflammation

**Helicobacter pylori eradication**
- Curcumin is bactericidal with anti-adhesive properties for *H. pylori*

**Psoriasis**
- Curcumin decreases phosphorylase kinase which involves the migration and proliferation of cells
- Down regulates proinflammatory cytokines.

**Antimicrobial**
- Food preservative, antifungal (aspergillus/aflatoxin), antiprotozoan (Giardia), antimalaria (inhibits growth of chloroquine-resistant *Plasmodium falciparum*)

**Notes:**
Unique Curcuminoids and Inflammation

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