Curcumin C³ Complex®

A versatile Phytonutrient

From

The Sami Sabinsa Group
Turmeric - The choice of millions

"IF MY FATE were such that I could have only one medicinal plant, I would choose turmeric. My choice would be the choice of millions before me, from emperors to peasants."

C. Leigh Broadhurst, Ph.D
USDA
Turmeric Plant
Curcuma longa

Herbaceous plant belonging to the family Zingiberaceae.

Useful parts are the underground rhizome and multi-branched extensions from the Rhizomes.

Spice and Natural color used globally in curries.........
Important constituents of *Curcuma longa*

- Curcumin
- Demethoxy curcumin
- Bisdemethoxy curcumin
- Turmerones
Chemical structures of Curcuminoids

CURCUMIN

(Diferuloyl methane)

DEMETHOXY CURCUMIN

(p-Hydroxy-cinnamoyl-feruloyl-methane)
Chemical structures of Curcuminoids

BISDEMETHOXY CURCUMIN
(\textit{pp}'-Dihydroxy-dicinnamoyl-methane)

ar-turmerone
Curcumin C³ Complex from Turmeric Rhizomes
The structure – activity relationship

1. Parahydroxyl groups - antioxidant activity
2. Keto groups - anti-inflammatory, anticancer, antimutagen
3. Double bonds - anti-inflammatory, anticancer, antimutagen
Primary pharmacological actions of Curcuminoids

- Antioxidant
- Anti-inflammatory
- Anti-carcinogenic
- Immunomodulatory
- Antimutagenic
- Anti-thrombotic
- Hepatoprotectant
- Antimicrobial
- Antiviral
- Antiparasitic
Antioxidant Potential
IN VITRO

The Rancimat Method measures the conductivity changes caused by formation of small free fatty acid molecules, when fats and oils undergo experimentally induced accelerated rancidity or oxidative changes.

Pure lard is used for the preparation of test samples containing 0.02% by weight of the antioxidant being tested.

-Contd.
Lipid peroxidation prevention by natural and synthetic antioxidants as measured by Rancimat Method

Research report no. 786, Sabinsa Corporation, 1995

Antioxidant index

1. BHT
2. Curcumin
3. BDMC
4. Curcumin C3 Complex
5. Grape Seed Extract
6. Pine Bark Extract
Antioxidant Profile – DPPH Scavenging

In the DPPH radical scavenging method, the ability of an antioxidant to bind the 1,1 diphenyl-2-picrylhydrazyl -radical (a very stable free radical species) is measured, using various concentrations of the selected antioxidants.

A compound with high antioxidant potential effectively traps this radical thereby preventing its propagation and the resultant chain reaction.
DPPH scavenging ability of Curcuminoids

Research Report No. 786, Sabinsa Corporation, 1995
Antioxidant Profile – ORAC value

The Oxygen Radical Absorbance Capacity (ORAC) assay depends on the free radical damage to a fluorescent probe through the change in its fluorescence intensity.

In the presence of antioxidant, the inhibition of free radical damage, which is reflected in the protection against the change of probe fluorescence, is a measure of its antioxidant capacity against the free radical.
ORAC value of Curcuminoids

Research Report No. 786, Sabinsa Corporation, 1995
Proposed antioxidant mechanisms

**PREVENTION** of free radical formation.

**INTERVENTION** whereby already preformed radicals are quenched by the Curcuminoids.
Anti-inflammatory Potential
Almost all of the degenerative diseases are driven by chronic subclinical inflammation.

Essentially, nearly every condition that walks into a doctor’s office is driven, at least in part, by inflammation.
The old view of the inflammation is that it represents the healing process. This is true to a certain extent; however when the inflammation becomes chronic, it becomes a disease.

Literature strongly recommends that there is a need to halt the chronic inflammation and its induction.
Today the study of inflammation has gone from the tissue levels deeper into the nuclear level. Cell-signaling molecules have been identified which stimulate the gene that induce the expression of the COX enzyme which in turn induce inflammation.
The Fires Within

Inflammation is the body’s first defense against infection, but when it goes awry, it can lead to heart attacks, colon cancer, Alzheimer’s and a host of other diseases.

Illustration for TIME by Brian Stawffer

By CHRISTINE GORMAN and ALICE PARK

What does a stubbed toe or a splinter in a finger have to do with your risk of developing Alzheimer’s disease, suffering a heart attack or succumbing to colon cancer? More than you might think. As scientists delve deeper into the fundamental causes of those and other illnesses, they are starting to see links to an age-old immunological defense mechanism called inflammation—the same biological process that turns the tissue around a splinter red and causes swelling in an injured toe. If they are right—and the evidence is starting to look pretty good—it could radically change doctors’ concept of what makes us sick. It could also prove a bonanza to pharmaceutical companies looking for new ways to keep us well.

Most of the time, inflammation is a lifesaver that enables our bodies to fend off various disease-causing bacteria, viruses and parasites. (Yes, even in the industrialized world, we are constantly bombarded by pathogens.) The instant any of these potentially deadly microbes slips into the body, inflammation maintains a defensive attack that lays waste to both invader and any tissue it may have infected. Then just as quickly, the process subsides and healing begins.

Every once in a while, however, the whole feverish production doesn’t shut down once. Sometimes the problem is a genetic predisposition; other times something like smoking or high blood pressure keeps the process going. In any event, inflammation becomes chronic rather than transitory. When that occurs, the body turns on itself—like an emery wheel, continuously picking a scab—while stinging with aches and pains to underlie a wide variety of diseases.

Suddenly, inflammation has become one of the hottest areas of medical research.
Nuclear factor Kappa B (NF-kB)

NF-kB is the “Big cheese” cell-signaling molecule for inflammation;

its activation induces the expression of COX-2, which leads to tissue inflammation.
What activates NF-κB?

**ROI inducers**
- Cytokines (TNF family, IL-1, IL-17, IL-18, EGF)
- Infection (bacterial/viral; e.g. HIV, EBV-LMP, HTLV1)
- Apoptosis-inducers
  - Chemotherapeutic agents & g-irradiation
- Endotoxin (LPS)

**Carcinogens** (e.g. TNF, CSC, DMBA)

**Tumor Promoters** (PMA)

**Stress** (pH, hypoxia, stress, heavy metals)

**Aggarwal BB, Cancer Cell, 2004**
NF-κB in Inflammation

NF-κB resides in the cytoplasm of the cell and is bound to its inhibitor.

Injuries and inflammatory stimuli, such as free radicals, release NF-κB from its inhibitor.

The free NF-κB, now moves into the nucleus and activates the genes responsible for expressing COX-2.

This leads to inflammation.
Stress and carcinogens activate NF-kB.

Chronic NF-kB activation mediates inflammation/carcinogenesis/tumorigenesis.

Inhibition of NF-kB activation suppresses inflammation/tumorigenesis.
Central dogma for most type of inflammations

- TNF/Carcinogens
  - NF-κB
    - COX-2
Drug-discovery from natural sources

There are 121 prescription drugs in use today, which come from 90 plant species. About 74% came from following folklore claims.


Approximately 25% of the drug prescription in the USA are compounds derived from plants and were discovered through scientific investigation of folklore claims.

Curcumin

Natural inhibitor of NF-κB
Therapeutic potential of curcumin

- Cardiovascular diseases
- Cholesterol, platelet aggregation, inhibition of smooth muscle cell proliferation
- Multiple sclerosis
- Diabetes
- Nephrotoxicity
- Antioxidant
- Gall-stones formation
- Cataract formation
- Cardiotoxicity
- Wound healing
- Alzheimer disease
- Chemotherapeutic
- Chemopreventive
- Skin, liver, colon, stomach
- Antiflammatory
- Arthritis
- Lung fibrosis
- HIV replication
Different stages of cancer progression and its suppression by curcumin

Overexpression of
- Oncogenes
- HER2
- Growth factors (e.g.; EGF, PDGF, FGF)
- Growth factor receptors
- Survival factors (e.g.; Survivin, Bcl-2 and Bcl-xl)
- Cyclin D1
- Decoy receptor

Overexpression of
- Matrix metalloproteases
- Cyclooxygenase-2
- Adhesion molecules
- Chemokine
- TNF

Constitutive activation of transcription factors
- AP-1 & NF-kB

Normal cells  Tumor cells  Tumor growth  Tumor Metastasis

Transformation  Proliferation  Invasion

Curcumin Blocks

From Aggarwal B et al, Anticancer Research 23, 2003, 363-398
Curcumin helps fights diseases.....

So if we take care to reduce the NF-kB activity, we are protecting ourselves from a host of diseases, including Cancer.

Curcumin has a positive role in this.

Curcumin: A natural anti-inflammatory agent
*Indian J Pharmacol* | June 2005 | Vol 37 | Issue 3 | 141-147
(and references cited therein)
Inhibition of NF-kB can help prevent/delay the onset of the disease.

This is the basic premise on which NFkB-Zero™ has been developed.
Effect of curcuminoids application in patients with external cancerous lesions

* 62 Subject Study

Effect of turmeric administration on levels of urinary mutagens in smokers

Time elapse from turmeric administration 16 smokers + 6 non-smokers

Antithrombotic activity of curcumin

Dose dependent antithrombotic effect of curcumin and aspirin

Effect of curcuminoids on the hepatotoxicity produced by Aflatoxin B₁ (AFB) in ducklings

![Graph showing liver GPT activity under different treatment regimens: Normal, AFB, AFB + Curcuminoids.]

**Treatment regimens**

Soni et. al. (1992), Cancer Lett, 66, 115
Research

on

Curcumin C³ Complex®
Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials

Since the first article referring to the use of curcumin was published in “The Lancet in 1937”, more than 2,600 research studies using curcumin or turmeric have been published in English language journals.

This review article provides an overview of the extensive published literature on the use of curcumin as a therapy for malignant and inflammatory diseases and its potential use in the treatment of degenerative neurologic diseases, cystic fibrosis and cardiovascular diseases.

Strimpakos AS, Sharma RA., Antioxid Redox Signal. 2008 Mar; 10(3); 511-545
Department of Medicine, Royal Marsden Hospital, London, England
Curcumin C³ Complex® and Cancer Prevention

Curcumin and Cancer
Curcumin C³ Complex® and Cancer Prevention

M.D. Anderson Cancer Center is currently conducting numerous studies to determine the effects of curcumin, an extract of turmeric root, in fighting against several types of cancers.

Sabinsa Corporation's Curcumin C³ Complex® was named as the curcumin ingredient of choice by M.D. Anderson Cancer Center at the University of Texas.
Curcumin Analogues in Cancer Prevention

In a pre-clinical study, the authors investigated whether analogs of curcumin (Cur), such as demethoxy curcumin (DMC), bisdemethoxycurcumin (BDMC), tetrahydrocurcumin (THC) and turmerones, modulate inflammatory signaling and cell proliferation to the same extent as curcumin.

The results demonstrated that different analogs of curcumin present in turmeric exhibit variable anti-inflammatory and anti-proliferative activities.

Sandur SK, Aggarwal BB et al, Carcinogenesis. 2007 Aug; 28(8); 1765-1773
Curcuminoids and their analogues on production of cellular ROS and GSH

Sandur SK, Aggarwal BB et al, Carcinogenesis. 2007 Aug; 28(8); 1765-1773
## Comparison of Cancer Incidence -1
### U.S [curcumin non-users] vs. India [curcumin users]

<table>
<thead>
<tr>
<th>Cancer</th>
<th>US</th>
<th></th>
<th>India</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
<td>Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>Breast</td>
<td>600</td>
<td>160</td>
<td>79</td>
<td>41</td>
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<tr>
<td>Prostate</td>
<td>690</td>
<td>130</td>
<td>20</td>
<td>9</td>
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<tr>
<td>Colon/Rectum</td>
<td>530</td>
<td>220</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Lung</td>
<td>660</td>
<td>580</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Head and Neck SCC</td>
<td>140</td>
<td>44</td>
<td>153</td>
<td>103</td>
</tr>
<tr>
<td>Liver</td>
<td>44</td>
<td>41</td>
<td>13</td>
<td>12</td>
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<tr>
<td>Pancreas</td>
<td>108</td>
<td>103</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Stomach</td>
<td>81</td>
<td>50</td>
<td>33</td>
<td>30</td>
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<tr>
<td>Melanoma</td>
<td>145</td>
<td>27</td>
<td>1.8</td>
<td>1</td>
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<tr>
<td>Testis</td>
<td>21</td>
<td>1</td>
<td>3</td>
<td>1</td>
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</table>

Showing cases per 1 million persons calculated on the basis of current consensus:  
## Comparison of Cancer Incidence -2
U.S [curcumin non-users] vs. India [curcumin users]

<table>
<thead>
<tr>
<th>Cancer</th>
<th>US Cases</th>
<th>US Deaths</th>
<th>India Cases</th>
<th>India Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>202</td>
<td>43</td>
<td>15</td>
<td>11</td>
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<tr>
<td>Kidney</td>
<td>115</td>
<td>44</td>
<td>6</td>
<td>4</td>
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<tr>
<td>Brain, Nervous Systems</td>
<td>65</td>
<td>47</td>
<td>19</td>
<td>14</td>
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<tr>
<td>Thyroid</td>
<td>55</td>
<td>5</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Endometrial Cancer</td>
<td>163</td>
<td>41</td>
<td>132</td>
<td>72</td>
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<tr>
<td>Ovary</td>
<td>76</td>
<td>50</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Multiple Myelome</td>
<td>50</td>
<td>40</td>
<td>6</td>
<td>5</td>
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<tr>
<td>Leukemia</td>
<td>100</td>
<td>70</td>
<td>19</td>
<td>17</td>
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<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>180</td>
<td>90</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>20</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Showing cases per 1 million persons calculated on the basis of current consensus:

Endometrial cancers include Cervix, Uteri and Corpus uteri

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>Diabetic Nephropathy</td>
<td>Lichen planus</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Oral cancer</td>
</tr>
<tr>
<td>COPD [Lung inflammation]</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>Head and Neck Cancer</td>
</tr>
</tbody>
</table>
Curcumin Bioavailability enhanced by Bioperine®

Serum concentration of curcumin in healthy volunteers (n=8) after administration of curcumin with and without Bioperine.
Sabinsa Corporation is currently working with a US based, research oriented Pharmaceutical company to effect studies with Curcumin in the form of nanosomes and liposomes in patients with various forms of cancer, particularly pancreatic cancer.

Nano-liposomes can act as both encapsulation and delivery systems with new and exciting applications, particularly in the pioneering of anti-aging research.
Standing out in the crowd...

Dedicated Curcumin Facility

Never again worry about the pungent yellow turmeric stains left at your manufacturing facilities. Sabinsa Corporation has developed novel approaches in retaining the biological activity of Curcumin while simultaneously addressing formulation challenges and product safety criteria's. We utilize the right equipment and right expertise to bring together a complete and economical solution for manufacturing Curcumin capsules and tablets without any production hassles. Our dedicated Curcumin facility and capabilities allows us to precisely tailor solutions to meet our customer's individual needs. Giving you the competitive edge to stand out in the crowd.

To learn more, visit us at www.sabinsa.com/manufacturing

Sabinsa Manufacturing
A division of Sabinsa Corporation

Thank You