

## REPORT

### Can Curcumin Prevent Alzheimer's Disease?

By John C. Martin

*Curcumin has long been prized in traditional Chinese and Indian medicine as a natural remedy for a variety of ailments. In modern research laboratories, curcumin's ability to scavenge free radicals and suppress inflammatory cytokines has impressed scientists who are seeking ways to prevent and treat Alzheimer's disease and other neurodegenerative disorders.*

Alzheimer's disease was discovered in 1907 by Dr. Alois Alzheimer, a German medical researcher who described a unique and destructive pathology in his patients' brains.<sup>1</sup> Today as then, Alzheimer's is a ravaging illness that robs its victims not only of their health, but also of their relationships with family and friends. Alzheimer's is also a burgeoning disease that affects more than 4 million Americans, a number that has doubled in the past 25 years. The disease is expected to continue its devastating surge over the next several decades.<sup>2</sup>



No cure exists for Alzheimer's, and the drugs currently available to treat the disease address only its symptoms, and with only limited effectiveness. Medical experts believe that therapeutic intervention that could postpone the onset or progression of Alzheimer's—even by as little as two years—would dramatically reduce the number of cases over the next 50 years.<sup>3</sup> A growing body of evidence suggests that a promising therapeutic modality may already be available. This remedy is most commonly found not in a biochemical laboratory, but rather in the kitchen spice rack: the perennial herb known around the world as turmeric.



Curcumin is the active compound in turmeric powder.

#### From Ancient Healing to Modern Medicine

A plant cultivated mostly in Asia, turmeric (*Curcuma longa*) is a member of the ginger family.<sup>4</sup> Its root and rhizome, or underground stem, are ground into a powder and used as a spice in various food preparations. Turmeric is the seasoning that gives curry powder its yellow color.

In addition to its uses as a spice, turmeric has been used therapeutically over the centuries in different parts of the world. Turmeric is rich in its active compound, curcumin, which is widely prescribed in Indian medicine as a potent remedy for liver disorders, rheumatism, diabetic wounds, runny nose, cough, and sinusitis.<sup>5</sup> Traditional Chinese medicine uses curcumin as a treatment for diseases associated with abdominal pain, and it is used in ancient Hindu medicine as a treatment for sprains and swelling.<sup>5</sup>

While the therapeutic use of this treasured spice has been commonplace throughout history, emerging medical research has begun to elucidate curcumin's beneficial effects for a range of diseases and conditions. Much of the recent science has focused on its effects against cancer, both therapeutically and prophylactically.<sup>6</sup> Curcumin's potential apparently stems from its ability to suppress the proliferation of a wide variety of tumor cells and to inhibit harmful molecules and enzymes, as well as its antioxidant and anti-inflammatory properties. Some studies have even suggested that curcumin can inhibit cancer metastasis.<sup>6</sup>

In research studies, curcumin has shown potential activity against cataract formation,<sup>7</sup> liver injury,<sup>8</sup> and the resultant damage from heart attack<sup>9</sup> and stroke.<sup>10</sup> More important, curcumin's anti-inflammatory effects and apparent effectiveness in keeping Alzheimer's disease at bay are attracting the notice of more and more medical researchers.

#### Alzheimer's and Its Risk Factors

Alzheimer's disease is considered a form of dementia, a brain disorder that seriously affects a person's ability to carry out daily activities. Alzheimer's is the most common form of dementia in people over the age of 65.<sup>11</sup> Symptoms typically appear after age 60, with some early-onset forms of the disease linked to a specific genetic defect.

Alzheimer's disease primarily involves the parts of the brain that control thought, memory, and language. Its causes are still essentially unknown, and no cure exists. Alzheimer's evolves slowly. At first, its only symptom may be mild forgetfulness. As the disease progresses, more serious symptoms arise, such as forgetting how to carry out simple tasks like combing one's hair or brushing one's teeth. People with Alzheimer's disease eventually require comprehensive care.<sup>11</sup>



Turmeric plant

There is probably no one specific cause of Alzheimer's disease; instead, several factors are likely to affect each person differently. Age is a common denominator in the disease, with the incidence of Alzheimer's doubling every five years in people over age 65. Family history also plays an important role, as Alzheimer's disease with a familial component can occur between the ages of 30 and 60. In older people, however, no obvious family pattern has been noted.<sup>11</sup> Other genes that may be centrally involved in the onset and progression of Alzheimer's remain to be discovered.

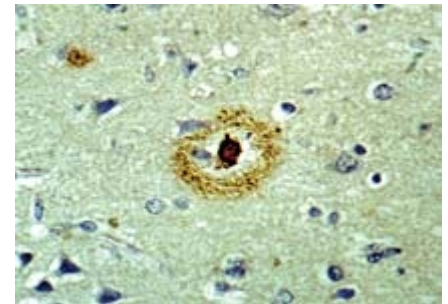
One recently discovered risk factor is the presence of a protein known as apolipoprotein E, which normally helps carry cholesterol in the blood. This molecule has three forms, and while one form helps protect people from Alzheimer's disease, scientists have found another form that can do just the opposite.<sup>12</sup>

Alzheimer's disease is characterized by two key abnormalities in the brain: amyloid plaques and neurofibrillary tangles. Amyloid plaques are clumps of a protein known as beta amyloid. They are found in the tissue between nerve cells in the brain, along with degenerating bits of neurons and other cells.<sup>13</sup>

Neurofibrillary tangles, largely comprising a protein called tau, are bundles of twisted filaments found within neurons. In healthy individuals, the tau protein augments the function of microtubules (part of the cell's structural support) and delivers various substances throughout them. In Alzheimer's sufferers, tau's function is transformed abnormally so that it twists into pairs of helical filaments that collect in tangles. When this occurs, the microtubules do not function correctly and disintegrate. The resulting collapse of the neurons' transport system eventually impairs communication between nerve cells, and causes them to die.<sup>13</sup>

### Targeting Destructive Plaques and Cells

Studies suggest curcumin helps to avert the insidious evolution of amyloid beta plaques in the brain. Building on previous research examining the inhibitory effects of certain compounds on beta amyloid formation, investigators have studied the effects of curcumin and rosmarinic acid, a phenolic compound that has been shown to possess anti-inflammatory and antioxidant properties. In one study, researchers compared the effects of curcumin and rosmarinic acid on the formation, extension, and destabilization of beta amyloid fibrils.<sup>14</sup> They found that both curcumin and rosmarinic acid inhibited the formation and extension of beta amyloid fibrils, and also destabilized beta amyloid plaques that had already formed.<sup>14</sup> Although the mechanism by which curcumin exerted these effects is not known, the Japanese study team notes that curcumin "could be a key molecule for the development of therapeutics for Alzheimer's disease."<sup>14</sup>



Alzheimer's disease. Senile plaque with labeling of the A $\beta$  amyloid protein. Histological section of a cerebral cortex.

In another in-vitro study, researchers studied the action of curcumin against the abnormal growth and proliferation of neuroglial cells, which provide mechanical and physical support for, as well as electrical insulation between, neurons in the brain.<sup>15</sup> In Alzheimer's disease, a condition known as gliosis can occur, characterized by the rapid proliferation of neuroglia. Alzheimer's disease is also marked by astrogliosis, an abnormal proliferation of astrocytes near neurodegenerative lesions. Astrocytes are the largest and most numerous neuroglial cells in the central nervous system.

In this study, researchers at the University of California, Berkeley, infused various doses of curcumin into rat glioma cells, which are malignant tumors of neuroglial origin. The researchers concluded: "Curcumin inhibited neuroglial proliferation, with the degree of inhibition correlated directly with the curcumin concentration."<sup>15</sup>

Amyloid plaques are known to cause oxidative damage in the brains of Alzheimer's sufferers. Free radicals generated by beta amyloid and other factors, such as mitochondrial abnormalities in cells, inadequate energy supply, inflammation, or abnormal changes in natural antioxidant defenses, may play a role in the pathophysiology of Alzheimer's disease. Substances with antioxidant properties, such as curcumin, may therefore offer biochemical support in this condition.

"Treatment with antioxidants is a promising approach for slowing disease progression to the extent that oxidative damage may be responsible for the cognitive and functional decline observed in Alzheimer's disease," wrote researchers at the University of California, San Diego.<sup>16</sup>

In another theory of how curcumin provides its advantageous effects against oxidative damage, medical experts speculate that curcumin induces a heat-shock response in the brain.<sup>17</sup> Heat-shock proteins serve as a prophylaxis against stress exerted on cells.

## Impressive Pre-clinical Research Evidence

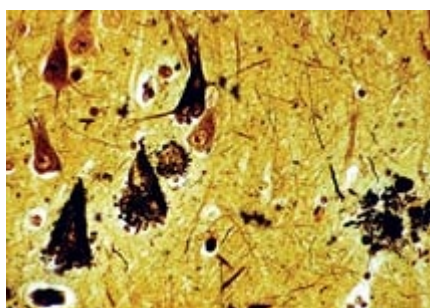
Observation of curcumin's benefits is not limited to in-vitro studies. Promising studies in animals have also been published. Scientists tested the effects of curcumin against damage induced by beta amyloid in rats, and compared the results with the protective effects of ibuprofen, a common non-steroidal anti-inflammatory drug (NSAID).<sup>18</sup> Some clinical trials have indicated that NSAIDs may help prevent the onset of Alzheimer's disease as a result of their anti-inflammatory properties.<sup>19,20</sup>

In a pre-clinical trial involving 22 rodents, researchers gave the rats a beta amyloid amino acid, which resulted in oxidative damage, loss of synaptophysin (a protein involved in brain synapses), and widespread amyloid deposits. When both ibuprofen and curcumin were then introduced into the rats' diets after this cerebral damage had occurred, only curcumin suppressed both the oxidative damage and continual synaptophysin loss.<sup>18</sup> Both interventions reduced levels of microglia—small glial cells in that brain that serve as support structures for neurons—in the cortical layers.<sup>18</sup>

In a second group of rats infused with beta amyloid, dietary curcumin prevented spatial memory problems as shown in the Morris Water Maze exercise, a sensitive test used to assess spatial memory, in which rats must locate a hidden escape platform. These rats also showed lower levels of beta amyloid after curcumin was introduced in their diet. "Because of its low side-effect profile and long history of safe use, curcumin may find clinical application for Alzheimer's disease prevention," the study team concluded.<sup>18</sup>

Additional pre-clinical studies echo these findings.<sup>21</sup> In a 2001 study, UCLA researchers fed groups of mice one of two different doses of curcumin (160 or 5,000 parts per million) as part of their normal diet. The researchers wanted to determine how each dose affected inflammation, oxidative damage, and cerebral plaque levels. Both doses of the spice were effective. Curcumin lowered levels of oxidized proteins and the proinflammatory cytokine known as interleukin-1 beta, which were previously elevated in the brains of the mice. Interestingly, only low-dose curcumin lowered levels of an inflammatory biological marker, glial fibrillary acidic protein, by as much as 16%. Amyloid plaques were also reduced in the rodents' brains by up to 50%. Microgliosis was also suppressed when rats were fed curcumin, though only in neuronal layers and not in proximity to plaques.<sup>21</sup>

The researchers concluded that curcumin "is a promising agent" as a prophylactic therapy against Alzheimer's and possibly other brain disorders such as Parkinson's disease.<sup>21</sup>



Photomicrograph: histological section of the cerebral cortex of a patient with Alzheimer's disease. Apparent are three neurofibrillary (tau protein) tangles (left) and one beta amyloid plaque (right). Both are considered the signature lesions of this disease.

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#### The Curcumin Advantage

Even if NSAIDs are proven as effective as curcumin as a prophylaxis for Alzheimer's disease, researchers are not heralding these anti-inflammatory drugs in the long-term struggle against Alzheimer's. The reason for their reticence is simple: NSAIDs have potentially lethal side effects. According to the UCLA research team, "A principal limitation precluding widespread NSAID use for prevention of Alzheimer's disease is gastrointestinal and occasional liver and kidney toxicity caused by inhibiting cyclooxygenase-1 [an enzyme that protects the stomach lining]. Side-effect issues could be overcome using alternative anti-inflammatory drugs directed against different inflammatory targets."<sup>21</sup>



One such anti-inflammatory agent, they postulated, is curcumin, which may offer powerful protection for humans as well as mice. Curcumin's antioxidant effects are central to its promise, as scientists have determined that the pathology of Alzheimer's involves oxidative damage that correlates directly with the beta amyloid deposits that typically characterize the disease.<sup>22</sup> In this vicious cycle, oxidative stress promotes the production of beta amyloid in the brain, and increasing levels of beta amyloid inflict greater levels of oxidative damage.

#### Mystery Waiting to Be Solved

Although curcumin shows great promise as an agent for preventing Alzheimer's disease, many questions remain to be answered. Scientists still are not completely certain of curcumin's mechanism of action against neuronal plaques, though they do know that it inhibits many of the body's inflammatory mediators. In fact, studies have found that curcumin retards the action of molecules such as phospholipase, lipoxygenase, cyclooxygenase-2 (COX-2), leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, tumor necrosis factor, and interleukin-12.<sup>23</sup>

Recent research suggests that oxidation caused by free radicals in the brain sparks neuronal toxicity, not only in Alzheimer's disease but possibly in other neurodegenerative disorders such as Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.<sup>24</sup> These disorders likewise have been associated at the molecular level with free-radical-induced mutation, oxidative enzyme impairment, and mitochondrial dysfunction.<sup>24</sup>



Some experts believe an antioxidant molecule known as glutathione plays a central role in the evolutionary events in the brain that lead to oxidation. "[Glutathione] plays multiple roles in the nervous system, including free radical scavenger, redox modulator of ionotropic receptor activity, and possible neurotransmitter," wrote investigators from the University of British Columbia in 1997.<sup>25</sup>

Other experts have noted that brain cell abnormalities, specifically in the cells' mitochondria, may contribute to the abnormal production of free radicals in the brain.<sup>25</sup> Abnormal mitochondrial function leads to dysfunction of cytochrome-c oxidase, a necessary mitochondrial enzyme that in turn may contribute to the abnormal production of free radicals, thus causing levels of beta amyloid to increase. As the vicious cycle continues, beta amyloid attracts even more free radicals.

"The free radical hypothesis can account for the vastly heterogeneous nature of Alzheimer's disease and the fact that both genetic and nongenetic causes are involved," wrote one expert. "Such general considerations suggest that free radicals are involved in many age-related pathologies, specifically in Alzheimer's disease and all neurodegenerative diseases."<sup>26</sup>

The inflammation and destructive oxidation inherent in Alzheimer's are why antioxidants like curcumin may be so effective in preventing progression of the disease. By its very nature, curcumin fends off free radicals, preventing their destructive effects in the illness's very earliest stages. Antioxidants not only target free radicals in the brain, but also possess powerful anti-inflammatory mechanisms, another reason why curcumin may be efficacious against Alzheimer's disease.<sup>27</sup> These dual mechanisms of protection against inflammation and oxidative damage make curcumin a particularly promising natural agent in fighting the ravages of aging and degenerative diseases.

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