

# CURCUMINOIDS FROM *CURCUMA LONGA* IN DISEASE PREVENTION & TREATMENT

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## ACUTE vs. CHRONIC INFLAMMATION

The inflammatory cycle is often treated with a “band-aid” type approach to quell immediate pain. However it is inflammation as a lingering, rather than an acute process that is increasingly attracting attention. It is considered as the root-cause of many diseases that remain poorly understood or treated. Cardiovascular disease, a leading cause of mortality in the world, is no longer considered a disorder of lipid accumulation, but rather a disease process characterized by low-grade inflammation of the vascular lining (endothelial cells) and an inappropriate 'wound healing response' of the blood vessels. <sup>(1)</sup> Cancer is another chronic degenerative disease that is initiated and promoted by lingering inflammation often triggered by environmental or nutritional factors, i.e. carcinogen. <sup>(2)</sup> Similarly, the devastating neurodegenerative disorder, Alzheimer’s Disease (AD) is hypothesized as being caused by dysfunction of the immune system reacting to chronic inflammation of the central nervous system.<sup>(3)</sup>

A number of epidemiological and laboratory studies have demonstrated that individuals with the above cited diseases may have elevated serum levels of *cytokines* such as nuclear factor kappa beta (NF-kB), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), *cell adhesion molecules* such as intercellular adhesion molecule-1 and P-selectin, and *acute-phase proteins* such as C-reactive protein, fibrinogen and amyloid. Other studies have shown an over-expression of cyclooxygenase enzymes (COX 1 and COX 2). These changes may signal a chronic inflammatory process in an individual predisposed to a multitude of degenerative diseases and cancers.



*Curcuma longa illustration*



Although synthetic drugs effectively reduce inflammation and pain in both acute and chronic inflammatory conditions, they work in a very selective way that may be counterproductive to the purpose of treatment. Recent research reveals that selective COX-2 inhibitors (pharmaceutical) may induce metabolic imbalances that can result in the over production of toxic cytokines, TNF-alpha and certain interleukins that are involved in the inflammatory process. <sup>(4)</sup>

In the emerging trend to search for natural therapies, turmeric root, ginger root, rosemary leaves, green tea leaves and their active phytochemical constituents are reported to be effective COX-2 inhibitors that also inhibit the formation of inflammatory leukotrienes and toxic cytokines. These herbs do not irritate the gastrointestinal lining (mucosa) and have safe medicinal record spanning centuries. Furthermore, no adverse effects have been reported with these herbs in clinical studies performed to validate various therapeutic properties. In fact, many of these compounds are included on the so-called

GRAS list (generally recognized as safe) – which means that they are safe to use in daily nutrition. Based on the current body of scientific evidence, turmeric’s curcuminoids are considered the most promising food derived compound(s) to fight inflammation and related diseases [Table 1]. <sup>(5, 6)</sup>

Curcumin (chemically diferuloylmethane), and its derivatives demethoxycurcumin and bisdemethoxycurcumin, collectively known as curcuminoids, are responsible for the yellow pigment derived from the roots of the perennial herb turmeric (*Curcuma longa* L.) [Fig. 1]. The same ground, dried roots of turmeric, which have been used for centuries as a spice (curry), food preservative and a coloring agent, have been found to be a rich source of phenolic compounds (curcuminoids) with

**Comparison of Cancer Incidence in U.S. (Curcumin Non-Users) and India (Curcumin Users)**

Cancer	U.S.		India	
	Cases	Deaths	Cases	Deaths
Breast	660	160	79	41
Prostate	690	130	20	9
Colon/rectum	530	220	30	18
Lung	660	580	38	37
Head and neck SCC	140	44	153	103
Liver	41	44	12	13
Pancreas	108	103	8	8
Stomach	81	50	33	30
Melanoma	145	27	1.8	1
Testis	21	1	3	1
Bladder	202	43	15	11
Kidney	115	44	6	4
Brain, nervous system	65	47	19	14
Thyroid	55	5	12	3
Endometrial cancers	163	41	132	72
Ovary	76	50	20	12
Multiple myeloma	50	40	6	5
Leukemia	100	70	19	17
Non-Hodgkin's lymphoma	180	90	17	15
Hodgkin's disease	20	5	7	4

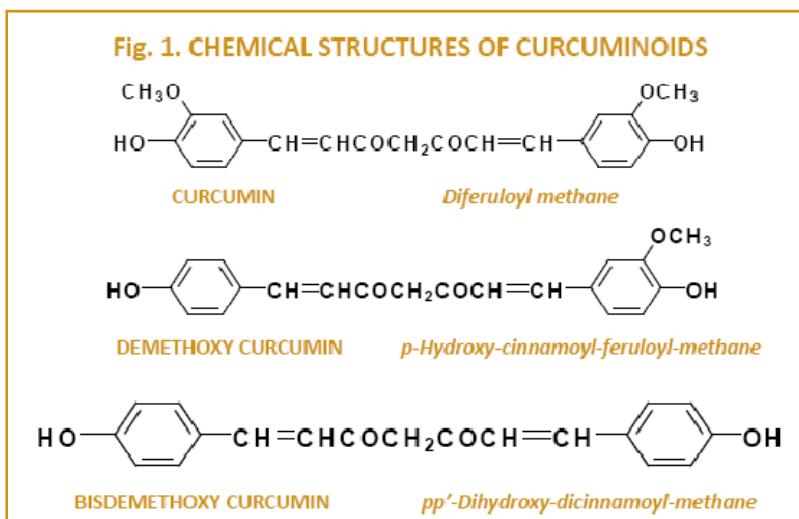
Showing cases per 1 million persons calculated on the basis of current consensus:  
Endometrial cancers include Cervix uteri and Corpus uteri.

GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0.  
IARC Cancer Base No. 5. Lyon, IARC Press, 2001.

**Table 1. Comparison of Cancer Incidence in U.S. and India**



versatile biological mechanisms.<sup>(6)</sup> In dietary supplement practice and in a growing body of scientific research, an extract of turmeric roots is being utilized that is standardized for a high purity of curcuminoids, e.g. 95% curcuminoids.<sup>(7-22)</sup>

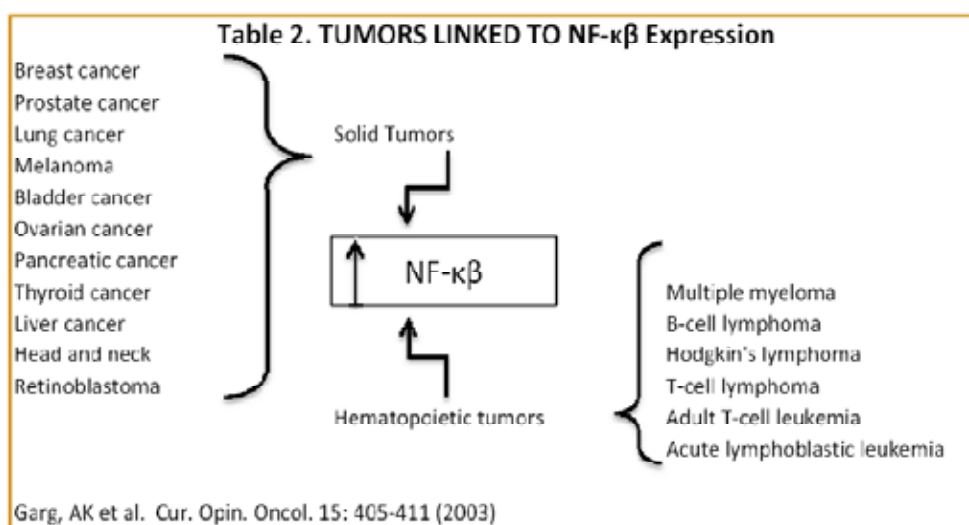


## CURCUMINOIDS IN TREATMENT OF CANCER: POTENTIAL MECHANISMS OF ACTION

In the last three years alone there have been several pioneering IND (Investigational New Drug) studies granted by the FDA and other NIH funded studies for the investigation of curcumin and its derivatives in the treatment of patients with cancer.<sup>(16, 17, 18)</sup> Some of the leading clinical research centers in the US, including MD Anderson Hospital in Houston, TX, are involved in pre-clinical and clinical research of the anti-cancer mechanism and application of curcuminoids in conditions including multiple myeloma, colon, pancreatic, breast, prostate, head and neck and respiratory tract cancers. These cancer conditions are either currently being studied in clinical experiments or considered next in line for systematic evaluation with curcuminoids therapy.

Curcuminoids act by inhibiting several processes that contribute to the survival, proliferation, invasion and metastasis of tumor cells.<sup>(23)</sup> Curcuminoids act by interfering with signaling mechanisms (critical for tumor growth), regulation of apoptosis (cell death), and tumor angiogenesis (new blood vessel formation which feeds tumors). Current research is designed to determine which of these fundamental processes in cancer development account for the clinical effects of curcumin and its derivatives.

Curcuminoids have significant immunomodulating and anti-inflammatory effects, in part due to the inhibition of cyclooxygenase type 2 enzyme (COX-2) and its subsequent arachidonic acid metabolism. <sup>(24, 25)</sup> Curcuminoids, like several other immunomodulators, inhibit the activation of the nuclear factor kappa-B (NF-κB) family of transcription factors that are known to be activated in a wide variety of solid tumors and leukemias. [Table 2] <sup>(26, 27, 28)</sup> The activation of NF-κB may shield tumor cells from apoptosis, or programmed cell death, promote tumor growth factors and those factors that facilitate invasion and metastasis of tumors. Curcuminoids block the NF-κB mediated gene expression responsible for the chain of events leading to tumor development, progression and expansion. A probable mechanism of curcuminoids seems to be blocking the degradation of the inhibitors of NF-κB. [Graph 1] <sup>(26)</sup> *In vitro*, curcuminoids induce apoptosis, and thus inhibit tumor growth in a broad range of tumor cells, including cell lines from colon, breast, prostate, squamous cell, renal cell, hepatocellular carcinomas, B and T-cell lymphomas, leukemias, melanoma and sarcoma cells. <sup>(29)</sup>



Curcuminoids also affect a signaling mechanism that involves expression and activation of certain growth factor receptors that promote tumor growth. For example, HER-2/neu is a member of the Epidermal Growth Factor Receptor family, which is over expressed in approximately 30% of breast cancer patients. HER-2/neu positive breast cancer cells, when exposed to curcumin, were found to have decreased expression of the HER-2 receptor. <sup>(29, 30, 31)</sup>

This ability makes curcumin a promising agent for combination with paclitaxel (Taxol). <sup>(29)</sup> Taxol is an alkaloid derived from the Pacific yew tree, and is used as first line chemotherapy in breast cancer. It induces the apoptosis (programmed cell death) of various breast tumor cell lines, but over expression

of HER2/neu may block these apoptotic effects and induce resistance to Taxol. Further, HER2/neu and Taxol can activate anti-apoptotic pathways through activation of NF kB. Thus, agents such as curcuminoids that can down-regulate NF kB activation and decrease HER2/neu over expression and other markers of tumorigenesis augment the therapeutic effects of Taxol against breast cancer.

Interestingly, curcuminoids may have a comparable mechanism of action to the drug therapy involving Herceptin for breast cancer patients with HER-2 receptor positive cancer cells. Herceptin is an antibody against HER-2 receptors; binding, blocking and inactivating those receptors. *In vitro*, the growth of breast cancer cells with multi-drug resistance (MDR) characteristics is inhibited by these turmeric phenolics; the stimulation of estrogen receptor (ER) positive cell lines by estrogenic pesticides is also inhibited by curcuminoids.<sup>(31, 32)</sup> Curcuminoids have also been found to inhibit epidermal growth factor receptor expression and/or activation in skin cancer cell lines as well as in androgen sensitive and androgen insensitive prostate cancer cell lines.<sup>(33)</sup>

An important anti-cancer mechanism of curcuminoids is restriction of vital blood supply to the rapidly growing tumor.<sup>(34, 35)</sup> *In vitro*, these compounds inhibit the blood vessel endothelial and smooth muscle cell growth and proliferation, which is the basis for inhibition of angiogenesis (new blood vessel formation). Curcuminoids also inhibit new vessel formation induced by growth factors, such as fibroblast growth factor-2 (FGF-2).<sup>(34)</sup> Furthermore, curcuminoids inhibit the production of vascular endothelial growth factor (VEGF) in human melanoma cells.<sup>(36)</sup> The anti-angiogenic effect of turmeric compounds can be explained due to the aforementioned selective COX-2 inhibition with curcuminoids. COX-2 enzyme activity may contribute to tumor growth (inhibition of apoptosis) along with increased production of the new vessel growth factors (VEGF, FGF) and the formation of new blood vessels. An *in vivo* study showed tumor regression in response to cyclooxygenase inhibitors in experimental models of human colon, prostate, gastric, lung and certain types of head and neck tumors. In *in vitro* experiments cyclooxygenase inhibitors inhibited the growth of human pancreatic, liver and breast cancer cell lines.

## PRE-CLINICAL AND CLINICAL TRIALS IN CANCER

While there are still limited human trials involving curcuminoids, in animal models curcuminoids prevent tumor formation in genetically predisposed animals, i.e. animals prone to develop precancerous multiple intestinal adenomas, a model for the human condition known as Familial Adenomatous Polyposis (FAP).<sup>(37, 38)</sup> Dietary enrichment with curcuminoids inhibited polyp growth in these animals by over 60%. A study with human subjects is currently underway evaluating the effects of curcuminoids on cellular proliferation, apoptosis and COX-2 expression and activity in the colorectal mucosa of subjects with a history of sporadic adenomatous polyps.<sup>(Badmaev Personal communication, 2008)</sup> Curcuminoids have also been successfully tested in several other intervention trials.<sup>(7, 15, 17, 18, 19, 21)</sup> In one study, mice inoculated with melanoma cells responded to dietary curcumin intervention with a reduction in the number of lung tumor nodules by 90%, as compared to sham fed controls. In a dose-escalation study 15 patients with advanced colorectal cancer refractory to standard chemotherapy received curcuminoids in doses between 0.45 and 3.6 g daily for up to 4 months.<sup>(7)</sup> Three biomarkers of the potential activity of curcuminoids were translated from preclinical models and measured in patient blood leukocytes: glutathione S-transferase activity (GST), levels of M1G, and prostaglandin E2 (PGE2) production induced *ex vivo*. Dose-limiting toxicity was not observed. A daily dose of 3.6 gm curcuminoids resulted in a significant decrease in PGE2 production in the blood samples, while showing no effect on GST and M1G formation. In conclusion of this study, a daily oral dose of 3.6 gm of curcuminoids is advocated for Phase II evaluation in the prevention or treatment of colorectal cancer. PGE2 production in blood and target tissue may indicate biological activity. It should be noted that other studies indicate the anti-cancer mechanism of curcuminoids as related to induction of GST enzymes, inhibition of PGE2 production, or suppression of oxidative genetic material damage (DNA adduct (M1G) formation).

Pancreatic cancer remains one of the most fatal and short-prognosis cancers, with few available treatments for the disease. The only drugs approved by the Food and Drug Administration that are currently available for treatment are gemcitabine and erlotinib. Both of these drugs elicit responses in only a small percentage of patients (less than 10%), and their effect on survival is measured in weeks. Many studies have shown that nuclear transcription factor- $\kappa$ B (NF- $\kappa$ B) is activated in experimental model of pancreatic cancer. The preclinical studies have shown that curcuminoids

suppress NF- $\kappa$ B activation and the growth of human pancreatic cancer xenografts in mice. Phase I human clinical trials of curcuminoids have shown that curcuminoids are safe at doses up to 8 g/day. <sup>(39)</sup> Subsequently the phase II clinical trial was undertaken to determine whether orally administered curcuminoids have biological activity in patients with advanced pancreatic cancer. <sup>(40)</sup>

Twenty-five patients (13 men, 12 women; aged 43-77) with histologically confirmed pancreatic cancer and a Karnofsky performance score greater than 60 were enrolled in the phase II trial, which was conducted at the University Of Texas M. D. Anderson Cancer Center in Houston, Texas. The patients ingested 8 g of curcuminoids in capsule form (1 capsule = 0.5 gm curcuminoids) daily for up to 18 months. The chemotherapy or radiotherapy was excluded. Disease staging, a physical examination, and blood sampling were performed at baseline and at 4 and 8 weeks. Blood samples were used to measure the following values: cytokine concentrations (interleukin-6, -8, -10, and interleukin-1 receptor antagonist), carcinoembryonic antigen concentrations, and peripheral blood mononuclear cell expression of NF- $\kappa$ B and cyclooxygenase-2 (COX-2). The adverse events were assessed on the basis of the National Cancer Institute Expanded Common Toxicity Criteria, and tumor response was evaluated on the basis of the Response Evaluation Criteria in Solid Tumors.

Twenty-four patients were available for the toxicity evaluation, and 21 patients were available for evaluation of the response to treatment with curcuminoids. Two of the 21 patients exhibited a favorable response to curcuminoids. Pancreatic cancer remained stable in 1 of these patients for greater than 18 months. "Marked" tumor regression (73%) and significant ( $p < 0.05$ ) increases in serum interleukin-6, -8, and -10 and in interleukin-1 receptor agonist were observed in the other patient. NF- $\kappa$ B activation decreased with curcuminoids treatment, but not significantly compared with the healthy controls. COX-2 expression decreased significantly ( $p < 0.03$ ) with curcumin treatment. Carcinoembryonic antigen concentrations decreased gradually over 1 year in 1 patient, which indicated an improvement in cancer status. Circulating concentrations of curcumin in blood serum were low (concentrations of curcumin peaked at 22-41 ng/mL), which indicated poor oral bioavailability of curcuminoids. No treatment-related toxicity was observed. The results of this study indicate that oral curcuminoids is tolerated well at doses of 8 g/d for up to 18 months and may result in therapeutic activity in some patients with pancreatic cancer.



Another study performed at the Department of Oncology, Rambam Medical Center, Haifa, Israel was undertaken to evaluate feasibility and efficacy of gemcitabine in combination with curcuminoids in patients with advanced pancreatic cancer. <sup>(41)</sup> Patients received 8 grams of curcumin by mouth daily concurrently with gemcitabine 1000 mg/m<sup>2</sup> IV weekly x 3 out of 4 weeks. Time to tumor progression was the primary endpoint and toxicity profile the main secondary endpoint. Seventeen patients (10 male, 7 female, aged 54-78) were enrolled for the study. Six patients had locally advanced tumor and 11 patients had metastatic disease, all in the liver. Patients received a median of 2 cycles of gemcitabine. Five patients discontinued curcumin after few days to 2 weeks due to intractable abdominal fullness or pain. One patient died due to unrelated to the treatment event. In the 11 patients curcumin and gemcitabine were delivered concomitantly for a period of 1 to 12 months. Dose of curcumin was reduced to 4 gram/day in 3 of the patients because of abdominal discomfort. One patient out of the 11 evaluable patients had partial response (7 months), 4 had stable disease (2, 3, 6 and 12 months) and 6 had tumor progression. Time to tumor progression was 1 to 12 months (median 2) and overall survival 1 to 24 months (median 6). These preliminary results suggest that a combination of gemcitabine and curcumin for patients with advanced pancreatic cancer is feasible. However, daily oral dose of curcumin should be less than 8 grams per day.

The potential role of curcuminoids in plasma cell dyscrasias/paraproteinaemia is currently undergoing clinical trials at St George Hospital, Australia. Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS) are typified by a serum M-protein value of <30g/L, fewer than 10% plasma cells in the bone marrow, no or a small amount of M protein in the urine, and absence of lytic bone lesions, anemia, hypercalcemia or renal insufficiency related to the plasma-cell proliferative process. <sup>(19)</sup> While MGUS occurs in association with a variety of diseases, it can also precede the onset of multiple myeloma. There is no current treatment for these patients. Management includes the regular clinical observation for changes in clinical and immunochemical status at 4 – 6 month intervals.

In a single blind randomised control pilot study, curcuminoids or placebo was administered orally, 2 grams twice daily to a cohort of 26 MGUS patients. A 5-30% decrease in serum paraprotein concentrations occurred in MGUS patients after only one week of therapy compared to stable or increased paraprotein concentrations in controls. Serum paraprotein levels continued to remain

suppressed after 3 months of “active” curcumin therapy. A double-blind, randomised, cross-over controlled trial is currently underway.

## **CURCUMINOIDS CLINICAL TRIAL IN PSORIASIS**

Psoriasis is a chronic inflammatory skin condition classified as autoimmune disorder which affects approximately 1-3% of the population world-wide and about 5.5 million people in the USA. There is a need for safe, inexpensive, and effective psoriasis therapies, especially since 95% of patients are willing to try new treatments. Curcuminoids have been successfully used to treat psoriasis based on anecdotal reports. A strong scientific rationale suggests that curcuminoids may in fact be promising for the treatment of psoriasis. In vitro and animal studies have demonstrated the inhibitory effect of curcuminoids on immune pathways critical to the pathophysiology of psoriasis such as NFκB (Nuclear factor kappa B) and downstream, inflammatory gene products such as Th-1 type cytokines (i.e., TNF-α, IFN γ).

Based on the physiological effects of curcumin and the positive anecdotal reports of its benefit for psoriasis an open label, clinical trial to assess the safety and efficacy of oral curcuminoids in the treatment of chronic psoriasis vulgaris was conducted in the Department of Dermatology Department at the University of Pennsylvania School of Medicine as well as the Department of Dermatology at the University of Rochester, Rochester, NY. <sup>(42)</sup>

The study sought to determine the safety and efficacy of oral curcuminoids in patients with plaque psoriasis receiving 4.5 g/day of oral curcuminoids for the first 12 weeks followed by a 4 week observation period after discontinuing the study drug. End points included improvement in Physicians Global Assessment score, Psoriasis Area and Severity Index score, and safety end points throughout the study. The intention-to-treat analysis response rate was 16.7%. There were no study-related adverse events that necessitated participant withdrawal. The response rate was low and possibly caused by a placebo effect or the natural history of psoriasis. Large placebo-controlled studies are necessary before recommending oral curcuminoids as a psoriasis treatment.

## CURCUMINOIDS IN PREVENTION AND TREATMENT OF NEURODEGENERATIVE CONDITIONS

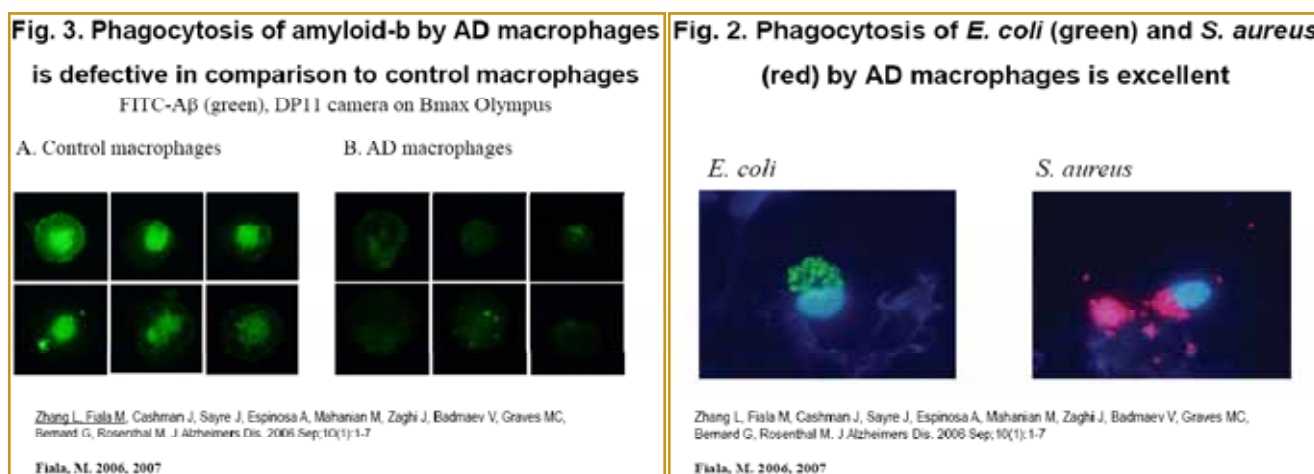
Aging can be described as a decline in function and performance of body organs and systems, which enhances the likelihood of wear-and-tear damage, inflammation and pain. One of the most challenging fields in anti-aging medicine is the management and treatment of chronic degenerative conditions as exemplified by Alzheimer's disease. This disease is increasingly seen as a defective response to the aging immune system. <sup>(3)</sup>

The aging immune system becomes progressively less efficient in dealing with inflammation. This is because both innate and adaptive (acquired during life-time) immune responses show age-related changes that could be decisive for healthy aging and survival. Natural or innate immunity is particularly important in the aging process and is based on foot soldier-type cells called macrophages, which are crucial for defense against microbes and removal of cellular and metabolic debris. Innate immunity is our first line of defense. It functions due to a macrophages' ability to recognize a pattern of a pathogenic (harmful) molecule through a code system called pathogen-associated molecular patterns (PAMPs). These potentially harmful molecules, e.g. amyloid protein, when recognized by macrophages, trigger responses that also guide an appropriate adaptive immune response. The interaction between the innate and adaptive immune systems is critical for the clinical outcome of a pathogen molecule challenge to an organism. A harmonious response to the challenge of a pathogen molecule changes with aging and may lead to a defective or misguided response of macrophages – a difference between macrophages contributing to the body injury or to the healing process.

In Alzheimer's disease (AD), there is increasing evidence supporting a role for macrophages and the dependent innate immunity system in disease origins and progression. <sup>(3)</sup> Brain amyloidosis is hypothesized to be a crucial pathogenic mechanism in the AD brain and many investigators of AD pathogenesis believe that accumulation of amyloid- $\beta$  ( $A\beta$ ) is toxic to neurons. The immune system of patients with AD is generally poorly responsive to  $A\beta$ . The amyloid hypothesis of AD has increased interest in developing therapies that promote clearance of brain amyloidosis by macrophages leading to a novel strategy of immunotherapy with  $A\beta$  vaccine, or antibodies against the amyloid protein. It was established that the anti- $A\beta$  antibodies were sufficient for reducing  $A\beta$  in the brain, and that

these reductions were accompanied by improvement in cognitive function in animal models of AD. Importantly, since the 1990's macrophages have been considered as perpetrators of inflammatory damage in neurodegenerative diseases, in parallel with cardiovascular disorders. Consequently, anti-inflammatory therapies with different drugs and nutritional compounds have been tested with positive, but also negative results. <sup>(22)</sup>

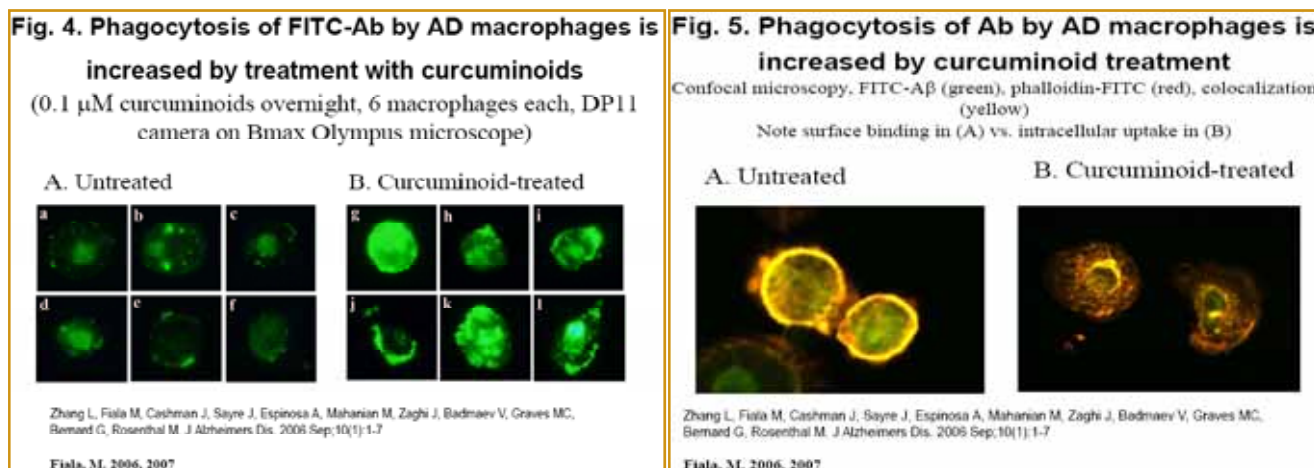
Recently a group of researchers from UCLA have tested a hypothesis that curcuminoids, which have epidemiologic and experimental rationale for use in AD, may improve the innate immune system and increase amyloid clearance from the brain of patients with sporadic Alzheimer's disease. <sup>(9)</sup> Macrophages of a majority of AD patients do not ingest (phagocytose), and do not efficiently clear amyloid from the brain, although they phagocytose bacteria. [Fig. 2 and Fig. 3]



In contrast, macrophages of normal subjects phagocytose amyloid. Upon amyloid stimulation, macrophages of normal subjects accelerate synthesis of molecules which participate in the previously discussed system of pathogen recognition, specifically MGAT3 (beta-1,4-mannosyl-glycoprotein 4-N-acetylglucosaminyltransferase) and Toll like receptors (TLRs), whereas mononuclear cells of AD patients generally down-regulate these genes. Defective phagocytosis of the amyloid may be related to suppression of these pathogen recognition molecules. In mononuclear (macrophage-like) cells isolated from peripheral blood in AD patients, curcuminoids, especially bisdemethoxycurcumin, may enhance defective phagocytosis of amyloid [Fig. 4 and Fig. 5] while restoring synthesis critical for



phagocytic function molecules, MGAT3 and TLRs. <sup>(10)</sup> Therefore curcuminoids may provide a novel approach to AD immunotherapy which is safer than the recently suggested vaccine therapy.



## CURCUMINOIDS CLINICAL USE, SAFETY AND PHARMACOKINETICS

Current clinical experience indicates that oral supplementation of curcuminoids is tolerated without toxicity at doses of up to 8 gm daily for up to 12 months. <sup>(7, 16, 18, 19)</sup> Curcuminoids are poorly absorbed from the gastrointestinal tract, with low nanogram levels of circulating curcuminoids detected in the plasma. <sup>(43)</sup> Nonetheless, biological activity is beyond question, with indices of inflammation like NF-κB and COX-2 suppressed by oral administration of curcuminoids as well as clinical improvement in the treated condition. <sup>(7, 16, 17, 18, 19, 20)</sup> Preclinical data suggests that curcumin can be more effective if higher levels of exposure are achieved. As hydrophobic and lipophilic compounds, curcuminoids cannot be given directly intravenously but can be encapsulated in a liposome for intravenous administration. <sup>(44)</sup> This method would theoretically achieve higher circulating levels of curcuminoids. Another possibility under consideration involves a nano-emulsion form of curcuminoids to bypass the gastrointestinal barrier to achieve higher plasma concentrations. <sup>(Badmaev personal communication 2008)</sup>

It is now well established that curcumin exists in rodent and human plasma largely in conjugated forms with the glucuronide conjugate present in much greater abundance than the sulfate conjugate. <sup>(45, 46)</sup> However, even plasma concentrations of curcumin released from conjugated forms are surprisingly low. Interestingly there is little evidence for the biological activity of curcumin conjugates, e.g. against malignant cell growth. <sup>(45)</sup> Possibly there are other forms of conjugated curcuminoids or derivatives of curcuminoids that can better explain their biological activity and provide future formulae for more effective clinical application.

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