

# Neurosupportive Effects of *Longvida*<sup>®</sup> Optimized Curcumin Shown in New Research

## Introduction

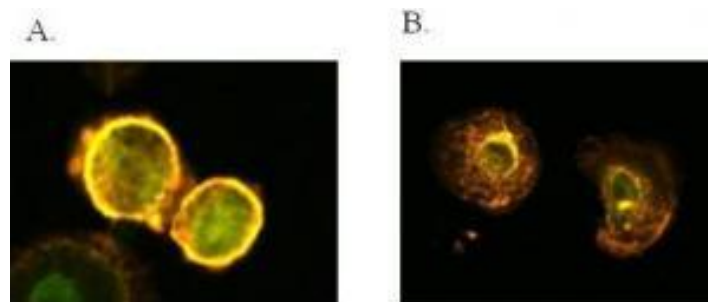
Alzheimer's disease (AD) involves a complex pathological cascade which is triggered by the accumulation of amyloid-beta and tau peptide aggregates. Multiple age-related causes contribute to peptide aggregation. These causes include aberrant cell signaling, lipid dysregulation, inflammatory and oxidative stress, and the normal ageing process. Together, these result in large-scale neuron death and loss of cognitive function.

## *A New Paradigm for Healthy Brain Ageing*

Based on the current understanding of neurodegenerative diseases, **a new paradigm for healthy brain ageing and neuroprotection is now emerging** which encompasses three primary aims: 1) reduction of oxidative damage; 2) reduction of inflammation caused by genetic predisposition and environmental and age-related stresses and 3) regulation of lipid and protein aggregates which accumulate as a result of ageing, inflammation and oxidation.

## Curcumin: The Ideal Amyloid-Binding Compound

At low concentrations, curcumin inhibits accumulation of amyloid beta peptide and formation of beta-amyloid fibrils, and disaggregates preformed fibrils in the central nervous system (Lim). The effective concentration of curcumin required to inhibit the formation, extension, and stabilization of amyloid fibrils is between 0.1 to 1 micromolar -- making curcumin an attractive therapeutic target for the treatment of Alzheimer's disease (AD).

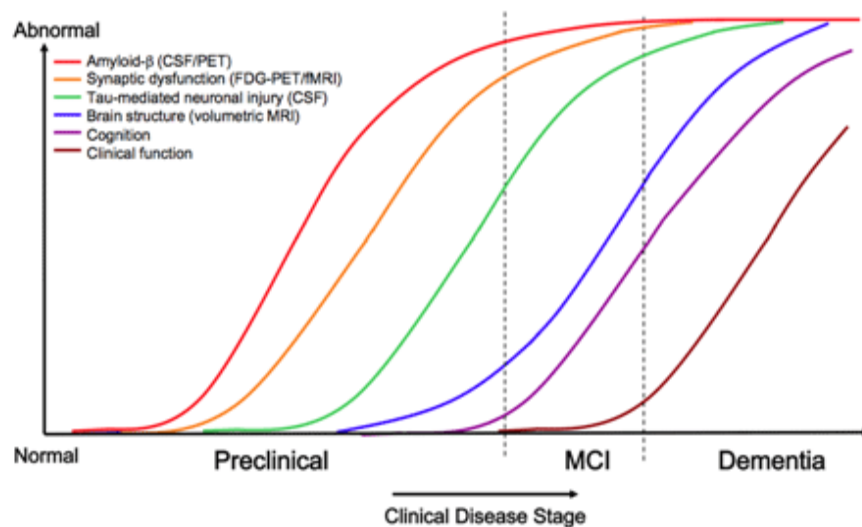


**Figure 1. Curcumin is an established binding agent of amyloid-beta.** Above: On left, curcumin fluoresces (A) at low concentrations during binding to amyloid beta, versus control (no curcumin B) on the right. (Ono 2004)

**Curcumin possesses most – if not all – the characteristics of an ‘ideal’ broad-spectrum neuroprotective agent** including anti-inflammatory, antioxidant, and anti-protein/anti-lipid aggregation activities, along with a strong safety profile.

## **Managing Amyloid-beta is Critical for Healthy Brain Ageing**

Blood levels of amyloid-beta are strongly associated with brain amyloid plaque deposits, which, as a primary risk factor for Alzheimer’s disease, kill brain cells *en masse* and prevent healthy brain ageing. **New research is revealing that amyloid and other deposits (such as tau) can begin to accumulate in the brain more than 20 years before signs of cognitive loss** (Figure 2). Thus, a decrease of amyloid-beta in healthy, middle-aged individuals could represent a clearance of amyloid from the brain and excretion from the body.



**Figure 2. Amyloid-beta and tau begins to accumulate many years before cognitive function declines.** Progression of Brain Ageing, Criteria for Preclinical Alzheimer’s Disease, International Conference on Alzheimer’s Disease, September 25, 2010.

## **The Key Limitation of Curcumin**

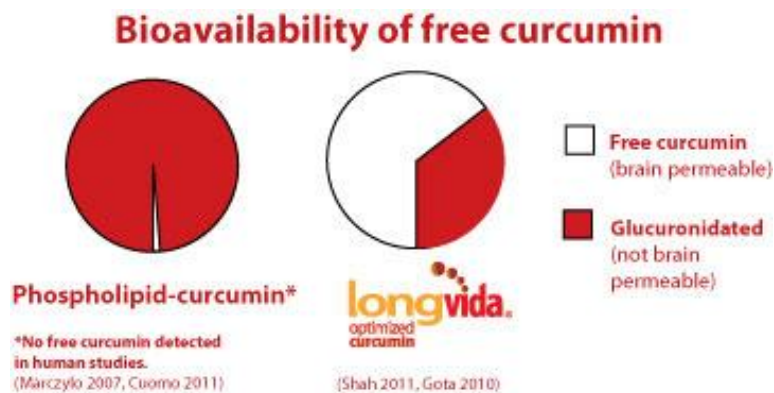
In the current clinical use of curcumin, a critical factor is overlooked: **curcumin has limited bioavailability**. Hundreds of published studies in animal and cell culture show curcumin’s potential efficacy in a variety of disease models, but at high doses often impractical for human use. Further, several failures of curcumin to fulfill its promise in clinical studies fuel the common belief that curcumin’s poor bioavailability prevents its practical ability for use as a neurotherapeutic compound (Baum 2007, Baum 2008).

Even with ‘enhanced-bioavailability’ formulations, curcumin has *only* been detected after oral dosage in its inactive *glucuronide conjugate* form (Baum 2007 and 2008, Cuomo, Kanai, Lao,

Marczylo). As curcumin glucuronide, curcumin is not able to cross the blood-brain barrier at significant levels.

**“There have been** two 6-month studies with an ‘enhanced’ curcumin using a dosage of 2-4 grams per day that resulted only in high glucuronidated curcumin in blood; free curcumin levels were below 0.02 uM and too low for the target dose range,” says Dr. Greg Cole Ph.D., Professor of Medicine and Neurology at UCLA. “Neither trial showed clinical efficacy and there was no impact on inflammation or oxidative damage markers in CSF. We hypothesize that this is because blood levels of free curcumin were too low.” (Baum 2007, Baum 2008)

However, a new technology has advanced the curcumin state of the art, and may be the key to unlocking its brain-optimizing power: **Solid-Lipid Curcumin Particle (SLCP™) Technology.**

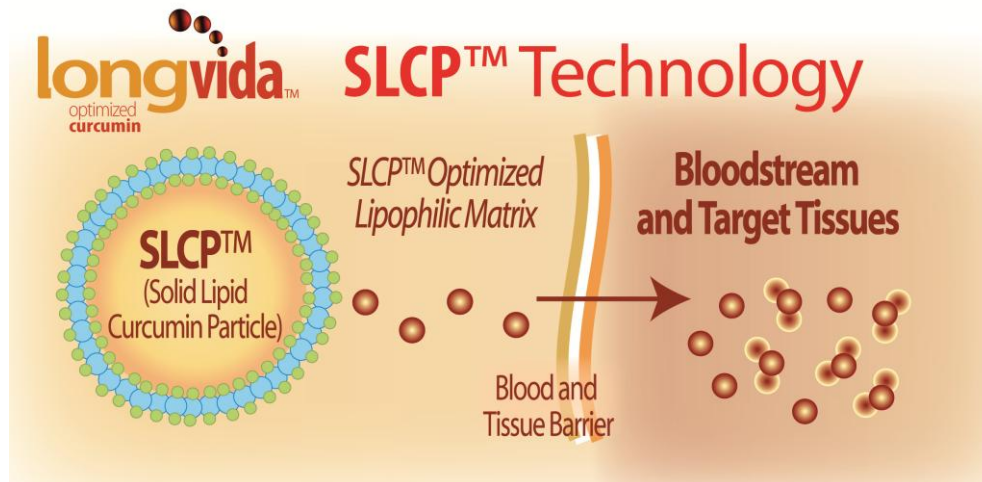


**Figure 3. The fraction of free curcumin in plasma is significantly higher from Longvida® made with SLCP™ Technology than for unformulated curcumin or phospholipid-curcumin.**

## **The Breakthrough: Clinical Proof**

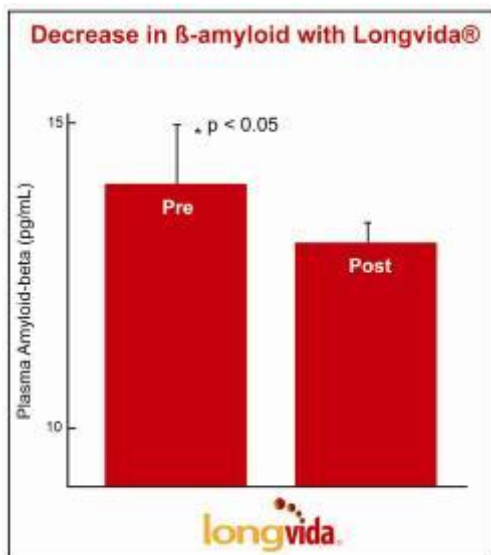
Longvida®, based on patent-pending **SLCP™ Technology** developed by the University of California – Los Angeles (UCLA), has shown the capability to reach therapeutic levels of *free* (unconjugated) curcumin at manageable doses in more than a dozen pharmacokinetic trials (Figure 4).

**With SLCP™, only one small daily dose required for fast improvement in a diverse number of biomarkers key for healthy brain ageing.** In recently published research, a single dose of just 40mg curcumin led to blood concentrations of *free* curcumin reaching the target anti-amyloid level of 0.1 micromolar (Shah).



**Figure 4. SLCP™ Technology addresses the three key limitations to curcumin bioavailability: 1) solubility, 2) permeability and 3) stability after oral ingestion.**

These therapeutic blood levels from Longvida have resulted in significant results in placebo-controlled clinical trials. In fact, a significant **8% decrease in plasma amyloid-beta** was observed after just 80mg curcumin daily for 30 days (Figure 5) (Disilvestro)



**Figure 5. Longvida 30-day dosing led to significant reduction in plasma beta-amyloid.**

### **Lipid Regulation: A Critical Key for Healthy Brain Ageing**

Triglyceride levels are also related to healthy brain ageing and Alzheimer’s disease (Razay 2007). **Apolipoprotein (ApoE4), whose function is to transport and eliminate triglycerides, represents one of the most malfunctioning of all ApoE genotypes, and has been associated**

with amyloid deposition in meta-analyses (Sudlow 2006) The genetic predisposition for ApoE4 is also the largest known genetic risk factor for developing late-onset Alzheimer's disease.

Likewise, **plasma triglyceride levels** are strongly correlated with plasma amyloid-beta levels in human populations (Fujiwara). Elevated plasma triglycerides precede amyloid-beta deposits in Alzheimer's disease models, suggesting that reduction of triglycerides, correlated to a decrease in amyloid-beta, supports healthy brain ageing, and may prevent Alzheimer's disease (Burgess).

**Cholesterol** also induces the production of amyloid-beta. As a primary cardiovascular risk factor, cholesterol is associated with healthy levels of brain deposits (Fujiwara). Circulating levels of total cholesterol are strongly correlated with ApoE genotype and plasma triglyceride levels. Statin therapy, which reliably reduces total cholesterol and targets inflammation, is considered a potential treatment for Alzheimer's disease (Sparks).

After 30 days of SLCP™ based Longvida, a significant **14% reduction in plasma triglycerides was observed** ( $p < 0.05$ ). This coincided with a trend for **decrease of total cholesterol** (DiSilvestro)

**Soluble intercellular cell adhesion molecule 1 (sICAM-1)** is associated with elevated levels of amyloid deposits in humans (Esmailzadeh). sICAM-1 is strongly associated with hyperlipidemia and dysfunctional endothelial and vascular function. **Elevated plasma levels of sICAM-1 have also been observed as a possible risk factor for Alzheimer's and cerebrovascular diseases** (Frohman, Nielsen). Likewise, increased sICAM in both healthy and Alzheimer's humans was highly correlated with decrease blood flow in the brain ( $p < 0.001$ ) (Janciauskiene).

30 days of Longvida dosing led to a significant **14% reduction in sICAM-1** ( $p < 0.05$ ) vs **placebo** (DiSilvestro)

## **Anti-inflammatory Activity of Curcumin**

Curcumin blocks many steps in the inflammatory cascade, including C-reactive protein, activator protein-1 (AP-1) transcription, activation of nuclear factor-kappaB, iNOS, and JNK. Likewise, curcumin may represent one of the few compounds which safely addresses neuroinflammation.

**C-reactive Protein (CRP)** is a pro-inflammatory marker highly correlated with healthy levels of amyloid-beta deposits and cognitive function in meta-analyses (Kuo). In the DiSilvestro study, an **11% reduction in CRP** (significant from baseline) was observed.

**Nitric oxide (NO)** causes an increase in blood flow due to vasodilation effects, and its dysfunction is related to a pro-inflammatory state. **Subjects taking Longvida experienced a 37% increase in plasma levels of nitric oxide**, suggesting that Longvida may cerebrovascular function and blood flow (DiSilvestro).

## **Healthy Brain Ageing -- Managing Physiological and Oxidative Stress**

**Salivary amylase and cortisol** are established markers for physiological and emotional stress. The impact of stress on healthy ageing and cognition is well known. (Chida, Kivimaki) Stress and anxiety are also correlated with increased amyloid-beta and may represent important risk factors for Alzheimer's disease. In the Disilvestro study, a **significant improvement in salivary amylase** was observed ( $p < 0.01$ ), suggesting the treatment may help to alleviate the effects of physiological stress.

**Catalase** is an antioxidant enzyme that binds with high affinity to amyloid-beta (Milton 1999). Catalase is also responsible for eliminating peroxide radicals, which increase the toxicity of beta-amyloid (Behl). Further, reduced levels of circulating plasma catalase in humans are associated with cognitive impairment, beta-amyloid plaque formation, and Alzheimer's disease (Torres). A **72% improvement in catalase** was observed in subjects taking Longvida ( $p < 0.01$ ) (Disilvestro).

**Glutathione peroxidase (GPx)**, like catalase, is an endogenous antioxidant enzyme which eliminates amyloid toxicity-attenuating peroxides. GPx also works to block synthesis of pro-inflammatory COX2 and prostaglandins, critical factors in the maintenance of healthy levels of brain deposits. In humans with cognitive dysfunction, GPx is decreased (Torres). A trend for **increase of glutathione peroxidase** was also observed ( $p = 0.11$ ), in addition to a significant **24% increase in total antioxidant status**. Together, these results indicate a broad-spectrum positive influence on key markers for physiological and oxidative stress.

**“I think what was interesting** about this study is that we saw a number of effects, not just one thing,” said Dr. Robert DiSilvestro, Ph.D, Professor at Ohio State and independent collaborator on the study. “The kinds of effects we saw for the intervention could conceivably help people of different ages and health status.”

### **A Note On Safety**

Curcumin has a long history of use. It is an approved food additive and coloring by the U.S. FDA and equivalent global health agencies, and has undergone hundreds of studies supporting its safety during continuous dosing. However, long-term safety studies should be performed and published in peer review on 'enhanced' forms of curcumin to understand whether increased absorption is safe.

**“If you go high enough in dosing** with more bioavailable curcumin, you may be able to produce some toxic effects. This should be expected of any drug with any real potency,” says Dr. Cole. “All of the new formulations claiming higher bioavailability will need to produce toxicology data.”

**Longvida was recently determined to be Generally Recognized as Safe (GRAS) by an independent, internationally recognized panel of scientists (Thomas).** The safety determination, conducted by an independent, internationally recognized expert panel of scientists, is based on more than a dozen clinical, preclinical and safety studies on Longvida®, along with scores of supporting studies on curcumin by a number of government and university research groups.

In a published 90-day subchronic toxicity study included in the GRAS assessment, Longvida® showed no toxicity at 720 mg/kg body weight/day, the highest dose tested (Dadhaniya). This dose is 100 times the dosage range recommended for human use, after adjusting for body weight. Longvida® adheres to the most stringent global standards for impurities, and contains no piperine, crude lecithin, volatile oils, gluten, sugar, salt, artificial preservatives or additives.

## **Conclusion**

**A new model for neuroprotection is now emerging** which defines the requirements for a safe, efficacious dosage form of curcumin – and one which results in threshold blood levels of free curcumin. Three primary aims for this model include addressing age-related dysregulation of proteins (e.g. amyloid-beta) and lipids, along with inflammation and oxidative/physiological stress.

**Curcumin-based dosage forms that are able to overcome the critical problem of glucuronidation, and reach therapeutic levels of curcumin in its free form may fulfill a critical need for safe, effective neuroprotective agents.**

As a result, a ***diverse range of effects*** has been observed in recent clinical research on a low-dose curcumin formulation of curcumin (Longvida® Optimized Curcumin) that is a prime candidate for neuroprotective and neurotherapeutic development. The effects of this formulation are wide-ranging, and include ***relatively fast onset of anti-amyloid, anti-inflammatory, and antioxidant effects***. Future research will determine how cognitive function relates to changes in these critical biomarkers associated with healthy brain ageing.

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