Curcumin for Cognition: Is It Just Hype, Based on Current Data?

Dear Editor:

It is with great interest that we read 2 recent complementary publications that explored the potential of curcumin to promote health through improved gastrointestinal function (1) and anti-inflammatory mechanisms (2). These articles are timely, following positive results in a trial investigating cognitive benefits of curcumin by Small et al. (3) suggesting larger trials are warranted to investigate the pleiotropic activity of bio-enhanced versions of curcumin as a therapeutic strategy in the management of age-related neurodegenerative diseases including Alzheimer disease (AD).

The multiple neurobiological mechanisms by which curcumin may exert health benefits, including those related to cognition, are currently receiving extensive investigation (see **Figure 1**) in an era when pharmaceutical trials have largely failed to arrest the symptoms of cognitive decline. The presence of the apoE ϵ4 allele is known to have multiple effects on AD risk; however, chronic low-grade inflammation, oxidative stress, and mitochondrial dysfunction have come into focus in the development of AD pathology centrally and peripherally (2, 4). Curcumin has been shown to act on cell-signaling transduction pathways in multiple tissues by inhibiting reactive oxygen species and NF-κB activity, resulting in a reduction in proinflammatory cytokines (4). Curcumin re-establishes antioxidant enzyme activity to reduce neuroinflammation, moderates the amyloidogenic pathway peripherally and centrally by binding with amyloid β (Aβ) to render it nontoxic, inhibits its aggregation, and de-establishes preformed Aβ aggregates in the brain (4, 5). Curcumin is also reported as a powerful iron chelator, which may reduce excessive iron accumulation in the brain that correlates with Aβ and contributes to mitochondrial decay during aging (4). Curcumin improves mitochondrial health through inducing mitochondrial biogenesis and mitophagy and inhibiting mitochondrial fission (4). Healthy mitochondria reduce Aβ aggregation and improve brain function through the promotion of healthy cell recycling (4).

The potential negative effects of gut-derived molecules on glia and the brain inflammatory cascade in neurodegenerative conditions are an emerging area of research, which may be modulated by curcumin's effects on the gut microbiota via the vagus nerve (6). Dysfunction of the microbiota–gut–brain axis has been shown to be associated with poorer cognitive performance and may serve as an early diagnostic in some neurodegenerative conditions. The article by Lopresti (1) argues curcumin's beneficial effects may be explained by its positive influence on the composition of the gut microbiota, ability to reduce low-grade inflammation in the gastrointestinal tract, and reductions in tight junction dysfunction. Curcumin has recently been shown to suppress inflammation by targeting the gut–brain axis in rats through the cholinergic anti-inflammatory pathway, reversing changes in gut microbiota diversity, and prolonging neurotransmitter action (6). Therefore, curcumin is a prime candidate to investigate further the interaction between diet and the microbiota–gut–brain axis to improve or delay symptoms of cognitive decline.

A range of curcumin formulations have been developed, with current investigators focusing on its potential for use in controlling symptoms associated with cognitive decline. The earliest curcumin trials demonstrated negligible effects, whereas more recent trials provided optimism perhaps due to the use of bio-enhanced forms of curcumin that reduce gastrointestinal stress. Use of a liposomal-encapsulated form (Longvida) and curcuminoid complex (Biocurcumax) has revealed the potential for curcumin to treat mood and cognition in healthy older adults (5, 7). However, the recent trial by Small et al. (3) revealed the most exciting results using a nanoparticle formulation (Theracurmin) twice daily for 18 mo in older individuals without dementia ($n = 21$). Compared with placebo, the curcumin group improved in measures of memory and attention and had less accumulation of Aβ and tau proteins in the amygdala and hypothalamus. However, because both groups increased their verbal memory score at 6 mo, there may have been an initial training effect observed, with the curcumin preventing cognitive decline over the final 12 mo compared with the placebo group. Overall, interpretation of curcumin trial data is limited by considerable variation in the studies and small sample sizes (range: 34–96).

There are multiple registered clinical trials investigating bio-enhanced versions of curcumin to address cognitive decline. The trial described by Kuszewski et al. (2) represents a novel investigation of Longvida curcumin coadministered with an anti-inflammatory nutraceutical, omega-3 fish oil (500 mg DHA and 100 mg EPA; ACTRN12616000732482). The assessment of cerebral circulatory function, C-reactive protein, and inflammatory cytokines in this trial will provide valuable data on the peripheral response to curcumin relative to cognitive function and evaluate a potential anti-inflammatory synergistic effect with fish oil (8). However, recent large and long-term trials of DHA-rich fish oil did not prevent cognitive decline (9, 10), which has been proposed to be due to dosage or DHA-to-EPA ratios, or possible oxidation during storage. However, a lack of effect may also be due to unchecked gut dysbiosis or fat malabsorption in participants before enrolment, and the possibility that ω-3 FAs may oxidize centrally in the presence of neuroinflammation (8). Therefore, controlling for gut health in older adults before group assignments may be insightful. However, there is a

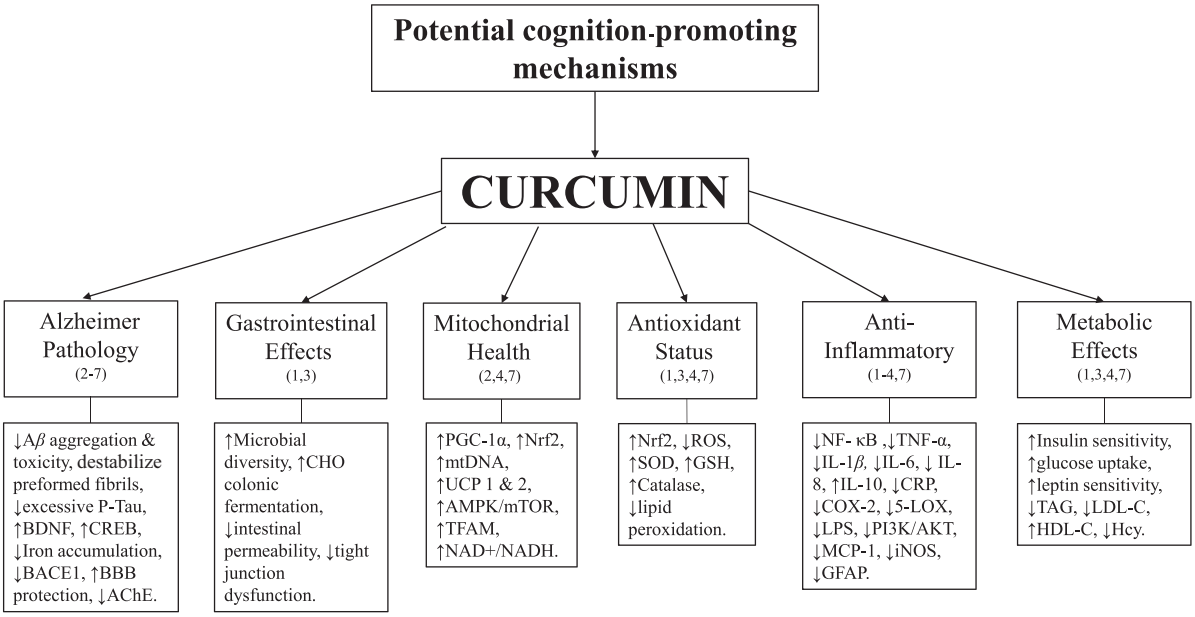

FIGURE 1 Potential and proposed mechanisms by which curcumin may promote cognitive performance. AChE, acetylcholinesterase; AKT, protein kinase B; AMPK, 5′ AMP-activated protein kinase; Aβ, amyloid β; BACE1, β-secretase 1; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CHO, carbohydrate; COX-2, cyclooxygenase-2; CREB, cAMP response element binding protein; CRP, C-reactive protein; GFAP, glial fibrillary acidic protein; GSH, reduced glutathione; Hcy, homocysteine; HDL-C, HDL cholesterol; iNOS, nitric oxide synthase; LDL-C, LDL cholesterol; MCP-1, monocyte chemoattractant protein 1; mtDNA, mitochondrial DNA; mTOR, mechanistic target of rapamycin; NADH, NAD hydride; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1; PI3K, phosphatidylinositol 3-kinase; P-tau, phosphorylated-tau; ROS, reactive oxygen species; SOD, superoxide dismutase; TAG, triacylglyceride; TFAM, transcription factor A, mitochondrial; UCP, uncoupling protein; 5-LOX, 5-lipoxygenase.

possibility that the combination of curcumin and fish oil may work synergistically to provide measurable cognitive benefits through curcumin's influence on intestinal microbiota composition (1) and the ability of curcumin to boost brain DHA concentrations (8). Moreover, curcumin has not been investigated in combination with other promising antineuroinflammatory compounds or flavanols that can cross the blood–brain barrier such as β-hydroxybutyrate and fisetin. Healthy fiber-rich dietary patterns such as the Mediterranean diet are associated with a lower prevalence of AD, and co-ingestion of curcumin as part of a polyphenol-rich diet could plausibly enhance curcumin's activity and biological properties.

The current availability of more bioavailable and tolerable curcumin formulations may serve to establish the therapeutic potential of curcumin in the prevention, treatment, and delay of cognitive decline. Larger long-term controlled trials of curcumin are required, which measure inflammatory and dementia-related biomarkers, and the mediating effects on the microbiota–gut–brain axis in order to assess its potential efficacy as a mode of treatment.

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References

1. Lopresti AL. The problem of curcumin and its bioavailability: could its gastrointestinal influence contribute to its overall health-enhancing effects? Adv Nutr 2018;9(1):41–50.
2. Kuszewski JC, Wong RHX, Howe PRC. Can curcumin counteract cognitive decline? Clinical trial evidence and rationale for combining ω-3 fatty acids with curcumin. Adv Nutr 2018;9(2):105–13.

3. Small GW, Siddarth P, Li Z, Miller KJ, Ercoli L, Emerson ND, Martinez J, Wong K-P, Liu J, Merrill DA, et al. Memory and brain amyloid and tau effects of a bioavailable form of curcumin in non-demented adults: a double-blind, placebo-controlled 18-month trial. Am J Geriatr Psychiatry 2018;26(3):266–77.
4. de Oliveira MR, Jardim FR, Setzer WN, Nabavi SM, Nabavi SF. Curcumin, mitochondrial biogenesis, and mitophagy: exploring recent data and indicating future needs. Biotechnol Adv 2016;34(5):813–26.
5. Rainey-Smith SR, Brown BM, Sohrabi HR, Shah T, Goozee KG, Gupta VB, Martins RN. Curcumin and cognition: a randomised, placebo-controlled, double-blind study of community-dwelling older adults. Br J Nutr 2016;115(12):2106–13.
6. Dou Y, Luo J, Wu X, Wei Z, Tong B, Yu J, Wang T, Zhang X, Yang Y, Yuan X, et al. Curcumin attenuates collagen-induced inflammatory response through the "gut-brain axis". J Neuroinflammation 2018;15(1):6.
7. Cox KH, Pipingas A, Scholey AB. Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. J Psychopharmacol 2015;29(5):642–51.
8. D'Cunha NM, McKune AJ, Panagiotakos DB, Georgousopoulou EN, Thomas J, Mellor DD, Naumovski N. Evaluation of dietary and lifestyle changes as modifiers of S100β levels in Alzheimer's disease. Nutr Neurosci 2017:1–18.
9. Danthiir V, Hosking DE, Nettelbeck T, Vincent AD, Wilson C, O'Callaghan N, Calvaresi E, Clifton P, Wittert GA. An 18-mo randomized, double-blind, placebo-controlled trial of DHA-rich fish oil to prevent age-related cognitive decline in cognitively normal older adults. Am J Clin Nutr 2018;107(5):754–62.
10. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, Bories L, Cufi MN, Dantoine T, Dartigues JF, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol 2017;16(5):377–89.

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