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Title: Efficacy of curcumin formulations in relation to systemic availability in the brain and different blood compartments in neuroinflammatory and AD models

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Abstract: Curcumin (Curc) exerts antioxidant, anti-inflammatory, chemopreventive and neuroprotective activities. Although Curc has demonstrated significant efficacy and safety in different disease models, its limited bioavailability continues to be highlighted as a major concern. Our goal was to improve Curc delivery to the blood and brain, by comparing different formulations including the use of phosphatidylcholine (PC), oil, other lipids or cyclodextrin. We also wanted to establish an oral formulation, which improved Curc efficacy in neuroinflammatory and Alzheimer's disease (AD) models. We found Curc micelles (with PC) significantly increased plasma (0.465 uM) and brain (2.059 uM) Curc delivery by acute gavage in mice. Curc dissolved in oil showed the highest Curc delivery (0.485 uM) to the red blood cell (RBC), which significantly correlated with the brain Curc delivery (2.518 uM), but did not result in detectable plasma Curc levels. This led us to develop a novel formulation of Curc (solid lipid curcumin microparticle, SLCP) with ratios of lipid and PC to optimize delivery of Curc to both the blood and brain. Our established LC/MS/MS method for measuring Curc and its metabolites in tissue, confirmed that SLCP delivered efficacious levels of Curc to the RBC (0.803 uM), which correlated with brain Curc levels (23.95 uM), unlike plasma levels, which did not correlate with brain Curc. We also used LPS injection to induce

neuroinflammation and synapse loss. Results showed that SLCP at 500 or 1000 ppm in chow prevented the loss of hippocampal synaptophysin (SY38) better than unformulated Curc and appeared to increase synaptic proteins above those of control animals (vehicle). Lipidated Curc formulation also significantly reduced GFAP (an astrocyte marker that is often elevated in inflammatory conditions) compared to LPS injected animal model mice. In 3 mouse AD models (3x Tg AD, Tg2576 and Tau Tg), SLCP corrected behavioral deficits (Morris Water Maze and Y-maze) and in a Tg rat model SLCP caused mobilization of Abeta into plasma and CSF and a trend for cognitive improvement. We also evaluated if RBC Curc levels can be used in Curc clinical trials as a marker for Curc delivery to the brain. Data from the ADRC (Mary S. Easton Center for Alzheimer's Disease Research at UCLA) Curc clinical trial study also showed higher RBC levels of Curc observed from the patients who absorbed Curc better, but no correlations were observed either with Abeta or other parameters of AD. In this Curc clinical trial patients received unformulated Curc. In the future, RBC Curc or whole blood Curc may be a useful tool to predict brain delivery of Curc in future rodent studies and human clinical trials.