

Amala Soumyanath, PhD and Joseph Quinn MD
Oregon Health and Science University
Portland, Oregon

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Safety and Target Engagement of *Centella asiatica* in Cognitive Impairment

This phase 1 study will evaluate whether a plant-based product is safe and active in individuals with mild cognitive impairment. It will test this extract as a potential therapy to prevent or slow cognitive decline.

Background

Centella asiatica is a popular plant-based dietary supplement sold in the U.S. as “gotu kola” with potential to be developed into a botanical drug. The herb reportedly enhances memory and cognitive function, although little is known about how it does so.

Dr. Amala Soumyanath and neurologist Dr Joseph Quinn in collaboration with neuroscientists and analytical experts, are studying the potential use of *Centella asiatica* for neurological diseases, including Alzheimer's. Their research has shown that administration of *Centella asiatica* extract improves cognition in aged mice and in genetically engineered Alzheimer's-like mice. In addition, Dr. Soumyanath and colleagues administered *Centella asiatica* extract to mouse and human brain cells grown in laboratory dishes to study its biological mechanisms and they believe that *Centella asiatica* reduces oxidative stress (or damage from toxic molecules called reactive oxygen radicals) and increases the function of mitochondria, components of cells that generate energy, in these models. Since oxidative stress and mitochondrial dysfunction appear to play a role in Alzheimer's and mild cognitive impairment (MCI, a subtle decline in memory that may precede Alzheimer's), the *Centella* extract may be able to positively impact biology relevant to Alzheimer's. Dr. Soumyanath and colleagues will study whether *Centella asiatica* affects oxidative stress and mitochondria in individuals treated with the extract, as the basis for future research examining its effects on cognition.

Research Plan

The researchers will conduct a Phase I clinical study to explore the safety and biological activity of *Centella asiatica* in individuals with MCI or mild Alzheimer's. They will recruit 48 individuals aged 65-85 years diagnosed with MCI or mild Alzheimer's. They will randomly assign half to take

Centella asiatica and half to take a placebo (not the actual Centella extract but an inactive substance that has no known risk for the participant). Neither the individuals nor the investigators will know to which treatment participants have been assigned until completion of the study. The individuals will take either *Centella* extract or a placebo for six weeks, with evaluations throughout the study.

Dr. Soumyanath and colleagues will use a specialized brain scan technique called magnetic resonance spectroscopic imaging (^1H -MRSI and ^{31}P -MRSI) to measure levels of specific molecules in the brain that indicate healthy nerve cells and their mitochondrial activity. In addition, the research team will measure levels of molecules suggestive of oxidative stress in participants' urine. Finally, the researchers will study the safety and tolerability of *Centella* extract and investigate any negative side effects.

Impact

The ultimate goal of Dr. Soumyanath and colleagues is to produce a therapeutic from *Centella asiatica* for use in MCI and Alzheimer's. This study will move forward this potential compound that has been implicated in past studies as being a potential therapy of interest. If successful, this study will lead to a larger and longer Phase II efficacy study of *Centella asiatica*'s effects on cognition in individuals with MCI and Alzheimer's.