Mechanisms and active compounds in the cognitive effects of Centella asiatica

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Contact information of lead PI
Country

USA

Title of project or programme

Mechanisms and active compounds in the cognitive effects of Centella asiatica

Source of funding information

NIH (NIA)

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€ 2,018,763.30

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01/08/2014

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3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Gotu kola, Water, Herb, Tg2576, madecassic acid

Research Abstract
DESCRIPTION (provided by applicant): Centella asiatica (L.) Urban herb (CA), is a medhya-rasayana (nerve rejuvenating) herb from the Ayurvedic tradition, used as a memory enhancer

and nerve tonic. Studies in humans, and numerous rodent models, support CA's ability to improve memory and learning. In our preliminary studies, CA water extract (CAW), reversed learning deficits in aged Tg2576 mice, a model of Alzheimer's disease (AD) with high beta amyloid (A?) plaque burden. This was not accompanied by changes in brain A? levels, suggesting that CAW attenuates the toxic effects of A? rather than altering its formation or deposition. This conclusion is supported by data from the MC65 human neuroblastoma cell line, where CAW prevented cell death caused by intracellular A? accumulation, again without altering A? levels. The active compounds responsible for this effect appear to be other than CA's well known triterpenes (asiatic acid, madecassic acid and their glycosides), since we observed robust activity in both the Tg2576 mouse and MC65 cell models despite the absence of these compounds in CAW. The triterpene compounds were also inactive when tested in MC65 cells. CAW is, instead, rich in phenolic compounds including caffeoylquinic acids, suggesting an important therapeutic role for these, and inadequately studied components of CA. Despite clear evidence of a cognitive enhancing effect of CA, there has been no systematic investigation of CA's active components, their biochemical mechanism(s) of action, and effective doses required for cognitive improvement. The goal of the present study is to explore in detail, the mechanisms by which CAW protects neurons from A? toxicity, identify the critical active compounds, and determine therapeutic plasma levels of these substances. Specific Aim 1 is to determine the mechanism(s) by which CAW attenuates A? toxicity in MC65 cells, using both targeted and unbiased approaches. Target mechanisms to be investigated are effects on anti-oxidant status, calcium homeostasis and mitochondrial function. The unbiased approach will utilize metabolomics technology to identify changes induced by A?, and explore attenuation of these changes by CAW. Specific Aim 2 is to isolate and identify active compounds in CAW responsible for attenuation of A? neurotoxicity in MC65 cells and primary cortical neurons in vitro, and to explore synergistic interactions and mechanisms of these compounds. In Specific Aim 3 the Tg2576 mouse model and wild type controls will be used to validate in vivo, the mechanisms and active compounds of CAW, identified, in vitro, in Aims 1 and 2. The therapeutic plasma levels of these compounds will be determined through a dose response study of CAW. The mechanisms to be explored in this study are relevant to age- related decline in neuronal health and cognition in general, and are not limited to those associated with A? toxicity. A successful outcome to this study will support the development of a standardized CA product containing appropriate levels of active compounds, with defined mechanisms of action, and target therapeutic plasma levels, all of which will lead directly to clinical trials of CA in humans with age-related cognitive decline.

Lay Summary
PUBLIC HEALTH RELEVANCE: This project will explore the mechanisms and active compounds underlying the ability of the herb, Centella asiatica, to improve cognitive function. Results from this study will lead to the development of standardized products of Centella asiatica which can be used in clinical trials of the herb as a treatment for cognitive decline in te elderly. The study may also provide insights into the therapeutic potential of this herb in other degenerative conditions associated with aging.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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