Inhibition of the Amyloid Processing Pathway by Micronutrients: A Systematic Genome-Wide Chemical Repositioning Approach to Counteract Alzheimer's Pathology

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A primary neuropathological hallmark of Alzheimer's disease (AD) is the overabundant extracellular aggregation of the amyloid-beta (aβ) peptide 1-42 as amyloid plaques. Prior research suggests that micronutrients may be ideal AD inhibitors. A novel bioinformatics approach was utilized to identify lead chemicals and micronutrients capable of inhibiting AD pathology, with concurrent biochemical experiments. The piloted profile-based approach involves systematic chemical repositioning framework, using genome-wide data extracted from the LINCS1000 database. Using matrix evaluation techniques, the gene-profile signatures of 866 FDA-approved drugs and micronutrients, inclusive of AD-specific drugs, were mapped and ranked based on their statistical relevance to AD gene-profiles. Various micronutrients were among top-ranked drugs, some outperforming the leading drug treatment for AD-associated memory loss, donepezil. The potential of micronutrients as therapeutic targets was further demonstrated through analyzation of target pathways, using the Ingenuity Pathway Analysis software. Results from the pathway analyses suggest that a variety of micronutrients share ≥50 significant (p≤.005) canonical pathways with AD. Chemicals in spices displaying the Amyloid Processing pathway overlap were studied in vitro using circular dichroism, to monitor their effects on the rapidly aggregating aβ 1-42 peptide. Samples containing tartaric acid, acetic acid and anethole aggregated 3.3, 4.6, and 9.9%, whereas, curcumin and capsaicin appeared to reverse aggregation by 28 and 15%, respectively, compared to a fully aggregated control sample. This study demonstrated a novel chemical repositioning approach for identifying drugs and micronutrients with high affinity for inhibiting AD neuropathology.

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