In silico High-Throughput Identification of Novel Dual Amyloid Beta and Tau Aggregation Inhibitors for Alzheimer's Disease Treatments

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Alzheimer's disease (AD) is characterized by toxic aggregates formed by amyloid beta (AB) and tau, which kill memory and learning neurons. With only symptomatic treatments for mild-moderate stages and the ineffectiveness of the first disease-modifying drug, Aducanumab, the identification of a functioning treatment is pressing. This study identified safe, bioactive, dual AB and tau aggregation inhibitors: drugs that bind with the aggregation regions of both proteins—AB's N-terminal and tau's PHF6 segment—to stabilize them, inhibit further aggregation, and slow AD's progression. Phase I conducted two molecular docking screenings of 646 structurally-diverse, FDA-approved, bioactive drugs docked on an (i) AB fibril and (ii) tau paired helical filament. AB aggregation inhibitors were selected by comparing drug complexes with Curcumin, an AB aggregation inhibitor whose low bioactivity prevents its effectiveness. Tau aggregation inhibitors were selected by the same manner, but by comparison to Purpurin, a non-FDA-approved tau aggregation inhibitor. Phase II identified dual inhibitors by analyzing interacting amino acid residues of the aggregation inhibitors from each screening. Finally, Phase III developed an algorithm to assess the Blood-Brain Barrier (BBB) penetrability of each dual inhibitor. Clofazimine, Paliperidone, and Risperidone were identified as FDA-approved, bioactive, BBB-penetrable, dual inhibitors. Clofazimine was 5.81 times more potent than Curcumin and Purpurin, while Paliperidone interacted with the most residues in both aggregation regions—100% more than Curcumin and 50% more than Purpurin. Further indications of drug strength come from hydrogen and hydrophobic interactions. Verifying these results can lead to a promising AD treatment.

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