Epigallocatechin 3-Gallate: A Natural Therapeutic Agent in Alzheimer's Disease Targeting the CDK5 and CRMP2 Pathway

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Alzheimer’s Disease is a neurodegenerative disorder characterized by the hyperphosphorylation of Tau and collapsin response mediator protein-2 (CRMP2), a newly identified and understudied biomarker. Hyperphosphorylation of these proteins is caused by deregulated cyclin-dependent kinase-5 (CDK5) protein function. This increased phosphorylation activity leads to neurofibrillary tangles, partially composed of hyperphosphorylated CRMP2, that cause a loss in neuronal synaptic communication. Thus, CRMP2 and CDK5 are potential targets to alleviate the impacts of Alzheimer’s Disease. However, there is a lack of consensus on the molecular basis of Alzheimer’s, leading to inadequate treatment. Epigallocatechin-3 gallate (EGCG), a green tea catechin, has neuroprotective properties against inflammation of neural tissue and is an emerging medicinal herb with promising results. Microscale thermophoresis was performed to understand binding affinities, and kinase assays and western blotting were utilized to understand phosphorylation patterns of CDK5 in the presence of CRMP2 and EGCG. Mass spectrometry was performed to validate CRMP2’s phosphorylation sites, and computational docking was conducted to elucidate protein conformations and EGCG binding regions. It was concluded that CDK5 and CRMP2 have a strong binding affinity that is disrupted by EGCG, which is an uncompetitive inhibitor. EGCG’s efficacy in reducing CDK5-induced phosphorylation was heightened in the presence of CDK5 and CRMP2. Computational models corroborated wet lab results to reveal CDK5’s interaction with CRMP2’s C-terminus and EGCG’s binding pockets in CRMP2 and CDK5. Overall, it was concluded that the CDK5 and CRMP2 interaction is impacted by the EGCG, through its role as an uncompetitive inhibitor.

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