# Discovering a Path from Molecular Modeling to Alzheimer's Phytotherapeutics: Characterizing Novel GSK3ß Inhibitors in silico and in vitro

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The prevalence of Alzheimer's disease (AD), a multifactorial, neurodegenerative disease characterized by a decline in cognitive functions, is projected to double by 2060, underscoring a growing public health crisis. The dysregulation of glycogen synthase kinase-3ß (GSK3ß) accounts for various AD hallmarks. Medicinal herbs are considered multi-target drugs with minimal side effects, making them promising non-toxic GSK3ß inhibitors. Last year, using computational modeling, we predicted that five phytochemicals could be GSK3ß inhibitors. This year, we verified the inhibitors' binding abilities using ligand docking and characterized selected inhibitors' IC50 values using kinase assays. All five molecules demonstrated GSK3ß inhibition in silico, and we computed their physicochemical properties using SwissADME, where thymoquinone and undulatin were shown to be blood-brain barrier permeable. After in silico tests, we hypothesized that at least one of the two pure chemicals tested in vitro would inhibit GSK3ß. Luminescent kinase and ADP-Glo™ assays were performed to determine the activity of chlorogenic acid and thymoquinone. To determine the IC50 values, 4-parameter logistic regressions were applied to dose-response curves of each inhibitor's obtained luminescence from the ADP-Glo™ assays. The hypothesis was supported; both test inhibitors demonstrated GSK3ß inhibition. Our study reveals computational chemistry's effectiveness for in vitro experiments and highlights medicinal herbs as promising therapeutics for AD. Further experiments can characterize these inhibitors' kinetic parameters and create a selective, allosteric drug that minimizes side effects. With nearly 1 million new U.S. cases predicted annually, discovering an effective, non-toxic AD treatment is imperative.

**Awards Won:**
Fourth Award of $600