Alzheimer’s disease (AD) is the most common form of neurodegenerative disease. Nationally, AD is the 6th leading cause of death and the only top 10 killer of Americans that cannot be slowed, cured, or prevented. AD is characterized by the deposition of extracellular plaques of aggregated amyloid-β protein (Aβ). Aβ originates from the amyloid precursor protein (APP), a transmembrane protein that is cleaved to form a short and inert protein fragment called Aβ. However, Aβ undergoes a nucleation process wherein aggregates from soluble oligomers to insoluble fibrils are formed. While uncertainty remains as to the exact mechanism, studies have associated Aβ aggregates with an increase in reactive oxygen species (ROS), potentially explaining their toxicity. Unfortunately, current AD treatments target disease symptoms and not the underlying cause.

Epidemiological studies have correlated particular diets with a reduced incidence of AD. Most of these diets are rich in fruits and vegetables and previous studies have identified many potential biochemical sources. Some, such as polyphenols, are of interest because of both their ability to interfere with Aβ aggregation and their ability to attenuate Aβ-induced intracellular ROS. Enhanced understanding of how biochemical can modulate aggregation can lead to the development of new AD therapeutics. This study explores the modulation of Aβ aggregation, either through 1) the use of small molecule modulators or 2) targeting a structural motif embedded in Aβ’s primary sequence.

First, this study explored the mechanistic effects of both olive-derived phenylethanoids and soy-derived isoflavones (SIFs) on Aβ aggregation and toxicity. While both groups effect aggregation, this did not attenuate toxicity. Next, antioxidant capacity was investigated. While phenylethanoids were good antioxidants, SIFs, contrary to previously studied results, were not. Further results indicate some SIFs activate intracellular antioxidant processes such as catalase, a hydrogen peroxide metabolizing enzyme. Neither SIFs nor phenylethanoids effect toxicity as a result of their antioxidant capacity. Ultimately, the strength of both groups was in their ability to act through both anti-aggregation and antioxidant mechanisms simultaneously. Moreover, tyrosol, a phenylethanoid, and genistein, a SIF, had a synergistic effects on Aβ toxicity.

This study also explored ways in which aggregation could be altered using the Aβ protein primary sequence. Amyloid proteins have a conserved glycine zipper motif (GxxxG), which previous studies have shown to be important in oligomer formation and cellular interaction. Results indicate that zipper motif extension increase aggregation propensity and decrease aggregate size. Conversely, removal of a single zipper repeat has a deleterious effect on aggregation, and when aggregates form, they are wispy aggregates that lack many of the morphological features of traditional Aβ aggregates.

From modulation of aggregation propensity to targeting toxicity, there are many viable routes to control Aβ. This study identified several promising ways to regulate Aβ aggregation: phenylethanoids that successfully shift aggregate equilibrium but their ultimate potential stems from their antioxidant capacity and dual action inhibition; SIFs which modulate aggregation and ameliorate toxicity through an array of mechanisms; and, finally, targeting the glycine zipper, which yielded dramatic effects on protein aggregation.