Polyphenols as Natural, Dual Action Therapeutics for Alzheimer's Disease

by

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Alzheimer’s disease (AD), the most common form of dementia, is characterized by extracellular plaques in the brain created when monomeric amyloid-β (Aβ) protein aggregates into fibrillar structures. Soluble Aβ aggregates, including oligomers, that form along the reaction pathway are believed to be the primary pathogenic species and have been shown to increase the production of reactive oxygen species (ROS). This upregulation of ROS is one suggested contributing factor of Aβ aggregate cytotoxicity and has proven capable of mediating cell signaling associated with Aβ aggregate-induced cellular responses.

Polyphenols have been suggested as a complimentary AD therapeutic based on epidemiological evidence that polyphenol-rich diets correlate with a reduced incidence of AD. Polyphenols have demonstrated the ability to inhibit Aβ aggregation thereby neutralizing the protein’s damaging effects. Additionally, polyphenols may counteract Aβ aggregate-induced cellular responses by neutralizing ROS through their antioxidant properties. This study sought to identify polyphenols that can reduce Aβ oligomer-induced cellular responses by 1) altering oligomer formation via changing oligomer size distribution and/or modulating oligomer conformation and 2) exerting antioxidant capabilities. The ability of polyphenols to function as dual-action therapeutics for AD by acting through both mechanisms was also explored.

Many of the studied polyphenols exhibited the ability to alter oligomer formation by both reducing the amount of 25 – 250 kDa oligomers formed and by changing oligomer surface hydrophobicity. Key polyphenol structural elements were identified that dictate the polyphenol’s ability to alter oligomer formation, providing insights into the optimum inhibitor structure.
Additionally, these polyphenol-induced changes in Aβ oligomer size distribution and structure resulted in lowered cellular responses, including both intracellular ROS and caspase activation. Polyphenols also exhibited strong antioxidant capabilities, and thus many polyphenols were able to reduce intracellular ROS and caspase activation induced by native Aβ oligomers. These findings demonstrate that polyphenols can attenuate oligomer-induced cellular responses even without altering oligomer formation. Studies also investigated by which mechanism each polyphenol primarily reduces oligomer-induced cellular responses and identified the polyphenol kaempferol as a potential dual-action therapeutic exhibiting synergy between the two mechanisms. Combined, these studies identify several promising polyphenols for use as natural therapeutics for AD.