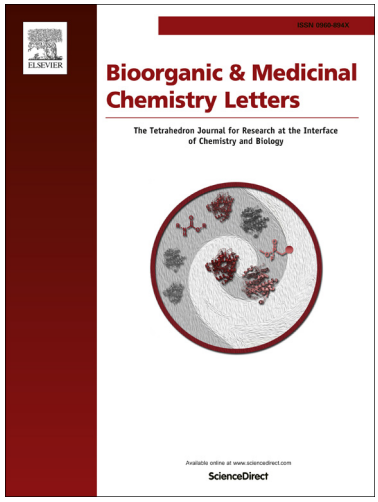

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Naturally occurring polyphenolic inhibitors of Amyloid Beta aggregation

Quentin I. Churches[a], Joanne Caine[a], Kate Cavanagh[b], V. Chandana Epa[a], Lynne Waddington[a], C. Elisabet Tranberg[b], Adam G. Meyer[b], Jose N. Varghese[a], Victor Streltsov[a], Peter J. Duggan[b,c]

[a] *CSIRO Materials Science and Engineering, 343 Royal Parade, Parkville,Victoria, 3052, Australia*
[b] *CSIRO Materials Science and Engineering, Bag 10, Clayton South, Victoria, 3169, Australia*
[c] *School of Chemical and Physical Sciences, Flinders University, Adelaide, SA 5042, Australia*

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ABSTRACT

Alzheimer's disease is the most common neurodegenerative disease and is one of the main causes of death in developed countries. Consumption of foods rich in polyphenolics is strongly correlated with reduced incidence of Alzheimer's disease. Our study has investigated the biological activity of previously untested polyphenolic compounds in preventing Amyloid β aggregation. The anti-aggregatory potential of these compounds was assessed using the Thioflavin-T assay, transmission electron microscopy, dynamic light scattering and size exclusion chromatography. Two structurally related compounds, luteolin and transilitin were identified as potent inhibitors of Aβ fibril formation. Computational docking studies with an X-ray derived oligomeric structure offer a rationale for the inhibitory activity observed and may facilitate development of improved inhibitors of Aβ aggregation and toxicity.

Alzheimer's Disease(AD) is the most common form of dementia affecting the elderly population and is characterized by gradual memory loss, behavioral change and by the formation of cerebral plaques formed by deposition of amyloid-beta (Aβ) protein. The amyloid cascade hypothesis is the most widely accepted explanation of the overall disease pathology.[1] Aggregation of the Aβ monomer into oligomeric and larger insoluble aggregates has been strongly implicated in AD pathology and the neurotoxicity observed with this disease.[2–4] The pathogenesis of the disease is poorly understood and the cause of the disease a subject of much debate.

Sufferers of AD are growing in number and yet there are currently no disease-modifying treatments for Alzheimer's disease, resulting in an urgent need for improved treatment options for AD. A common therapeutic strategy is based on seeking small molecule compounds to modulate the biosynthesis or inhibit the aggregation of Aβ, which according to the amyloid cascade hypothesis should result in a therapeutic outcome. The consumption of foods and beverages rich in naturally occurring polyphenolics has been correlated with a delay in the onset of AD in the elderly.[5,6] Given these epidemiological results, seemingly correlated to the presence of these naturally occurring compounds, there has been much interest in the therapeutic potential of polyphenolics.

Polyphenolic compounds have the known beneficial properties of radical scavenging, antioxidant activity and can attenuate metal induced toxic effects.[7,8] Indeed, the results of many studies seem to indicate that certain polyphenolics may exert their neuroprotective effect through multiple pharmacological pathways.[9–13] However their primary neuroprotective effect is thought to be derived from their amyloid inhibitory properties.[14–18]

Previously, we have demonstrated the use of reduced carboxymethylated κ-Casein as an economical alternative to Aβ assays in screening for anti-aggregatory potential of polyphenolic compounds.[19] As there are many naturally occurring polyphenolics with as-yet unstudied bioactivity, we wished to investigate the therapeutic potential of this rich class of compounds in Alzheimer's disease. In this study, we sought to extend this work and examine structurally related analogues, seeking compounds with improved anti-aggregatory activity.

In our previous study on protein aggregation inhibition,[19] some observations were made on the activity of polyphenolic compounds and their corresponding anti-aggregatory properties. Both the number of hydroxy groups and the positioning of these groups on the polyphenolic structure is important, however there is no clear understanding of the link between phenol positional substitution and corresponding anti-aggregatory activity.[17,19] The importance of inhibitor hydroxylation is likely to correlate with hydrogen bonding which facilitates binding of the hydroxylated inhibitor with the amide rich backbone of the peptide.[14,15] Once formed, this bound species may either stabilize Aβ monomers or small oligomers, or perhaps divert the aggregation pathway of Aβ, as has been proposed as the mechanism of action of the