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Poster 50

Dual-action breakthrough: Fiscalin derivatives targeting amyloid burden and acetylcholinesterase for Alzheimer's therapy

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Abstract

Background: Alzheimer's disease (AD) is the most common age-related dementia, characterized by neurodegeneration associated with the accumulation of amyloid-beta (Aβ) peptides and hyperphosphorylated Tau, mitochondrial dysfunction, and oxidative stress, among other pathological features [1]. Moreover, reduced acetylcholine levels contribute to the cognitive impairment and memory deficits characteristic of the disease. With life expectancy increasing globally and the current treatments providing only symptomatic relief, AD prevalence is projected to more than triple by 2050 [2]. Therefore, the development of novel compounds targeting these mechanisms could help restore brain function or slow disease progression. In this regard, fiscalins, a class of valine-derived alkaloids with an indolyl and tricyclic anthranilic acid core, have previously demonstrated neuroprotective, antimicrobial, and anticancer properties, making them promising candidates for further investigation in AD treatment [3]. **Objective:** The main objective of this work was to evaluate the cytotoxicity and neuroprotective effects of six synthetic fiscalin derivatives (Figure 1), and their ability to inhibit acetylcholinesterase (AChE), the enzyme that degrades acetylcholine, using SH-SY5Y cells differentiated into a cholinergic phenotype. **Methods:** The cytotoxicity of the compounds (0–50 μM) was assessed after 24 h of exposure by the neutral red uptake and MTT reduction assays, to select non-cytotoxic concentrations. Neuroprotection was further tested against β-amyloid peptide (Aβ; 50 μM), assessing cell viability by the MTT reduction assay after 24 h of exposure in the absence or presence of fiscalin derivatives (10 and 25 μM). Additionally, compounds' ability to inhibit AChE activity was evaluated using Ellman's assay. **Results:** All the tested compounds were non-cytotoxic for concentrations up to 25 μM. Three of the six tested fiscalin derivatives significantly reduced Aβ-induced cell death, while five compounds significantly reduced AChE activity, when compared with control cells. **Conclusions:** These findings highlight the potential of these compounds to counteract Aβ toxicity and reduce AChE activity, two critical features of AD. Nevertheless, further studies are needed to elucidate their neuroprotective mechanism(s).

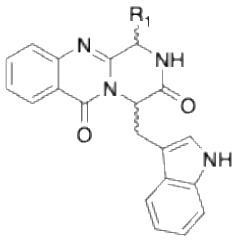

Figure 1. Chemical structure of fiscalin derivatives.

Keywords: Alzheimer's disease; fiscalin derivatives; β-amyloid; acetylcholinesterase activity

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