ECMC-P 2025 Conference

The 1st International Electronic Conference on Medicinal Chemistry and Pharmaceutics

01–30 November 2025 | Online

MDPI

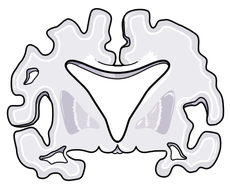
Fiscalin-Based Compounds as Multifunctional Agents Against Alzheimer's Pathology: Addressing Amyloid Toxicity, Iron Overload, and Cholinergic Deficits

Inês Costa[1,2,3], Daniel José Barbosa[4,5], Maria Emília Sousa[3,6] and Renata Silva[1,2]

[1]UCIBIO – Unidade de Biociências Moleculares Aplicadas, Laboratório de Toxicologia, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto (FFUP), Rua de Jorge Viterbo Ferreira, 228, 4050-313, Porto, Portugal; [2]Laboratório Associado i4HB – Instituto de Saúde e Bioeconomia, FFUP, Rua de Jorge Viterbo Ferreira, 228, 4050-313, Porto, Portugal; [3]CIIMAR – Centro Interdisciplinar de Investigação Marinha e Ambiental, Terminal de Cruzeiros do Porto de Leixões, Matosinhos, Portugal; [4]Laboratório Associado i4HB – Instituto de Saúde e Bioeconomia, Instituto Universitário de Ciências da Saúde – CESPU, Rua Central de Gandra, 4585-116, Gandra, Portugal; [5]UCIBIO – Unidade de Biociências Moleculares Aplicadas, Laboratório de Investigação em Toxicologia Translacional, Instituto Universitário de Ciências da Saúde (1H-TOXRUN, IUCS-CESPU), Rua Central de Gandra, 4585-116, Gandra, Portugal; [6]Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, FFUP, Rua de Jorge Viterbo Ferreira, 228, 4050-313, Porto, Portugal.

INTRODUCTION & AIM

Alzheimer's disease



Most common age-related dementia characterized by [1, 2]:

- intracellular **accumulation of amyloid-beta (Aβ) peptides**
- **hyperphosphorylation of Tau protein**
- **oxidative stress**
- **reduced acetylcholine (ACh) levels.**

Although significant progress has been made in Alzheimer's disease research, **the development of effective and durable treatments capable of altering the disease's course remains a major challenge.**

Fiscalin derivatives have been intensely studied and shown to exhibit diverse biological activities, including neuroprotective effects [3].

The main aim of this work was to evaluate the **cytotoxicity** and potential **neuroprotective effects** of **6 newly synthesized fiscalin derivatives, as well as their ability to inhibit acetylcholinesterase (AChE,** the enzyme responsible for acetylcholine degradation).

METHODS

In vitro model: **SH-SY5Y cells** differentiated into a **cholinergic phenotype**

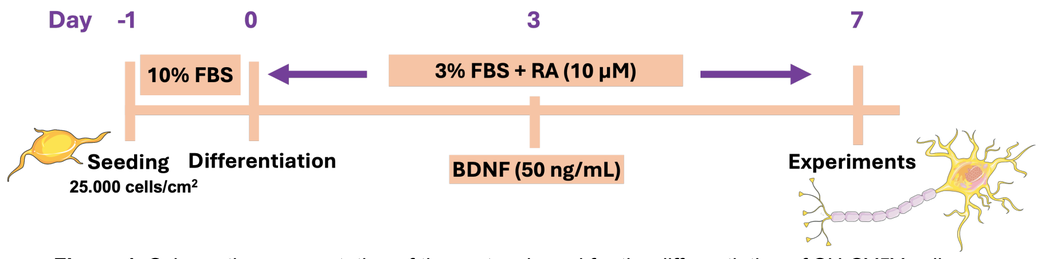


Figure 1. Schematic representation of the protocol used for the differentiation of SH-SY5Y cells.

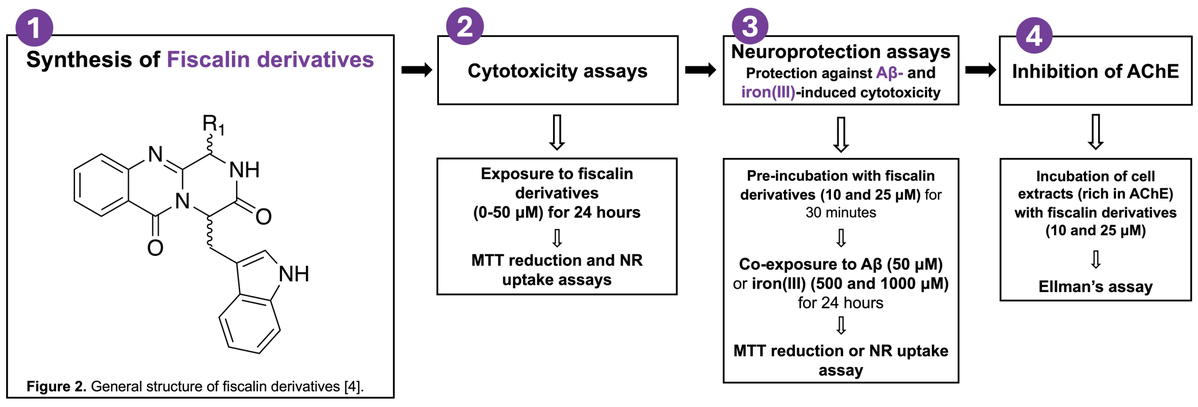


Figure 2. General structure of fiscalin derivatives [4].

CONCLUSION

All tested fiscalins were non-cytotoxic at concentrations **up to 25 µM**.

Three (1a, 1b and 3) derivatives significantly **reduced Aβ-induced cell death**, and **five** (1a, 1b, 1c, 2a and 3) counteracted **iron(III)-induced cytotoxicity**.

Five fiscalin derivatives (1a, 1b, 2a, 2b and 3) significantly **inhibited AChE activity**.

These findings suggest that fiscalin derivatives may counteract Aβ and iron(III) toxicity, and reduce AChE activity - **key therapeutic targets in AD**.
Nonetheless, **further studies are required to elucidate their underlying neuroprotective mechanisms**.

REFERENCES

1. Khan, S. et al. Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease. Curr Neuropharmacol 2020, 18, 1106-1125, doi:10.2174/1570159x18666200528142429.
2. Monteiro, A.R. et al. Alzheimer's Disease: Insights and New Prospects in Disease Pathophysiology, Biomarkers and Disease-Modifying Drugs. Biochem Pharmacol 2023, 211, 115522, doi:10.1016/j.bcp.2023.115522.
3. Barreiro, S. et al. Fiscalin Derivatives as Potential Neuroprotective Agents. Pharmaceutics 2022, 14, doi:10.3390/pharmaceutics14071456.
4. Long, S. et al. Antitumor Activity of Quinazolinone Alkaloids Inspired by Marine Natural Products. Marine Drugs 2018, 16, 261, doi: 10.3390/md16080261

RESULTS & DISCUSSION

Compounds' safety profile: NR uptake assay

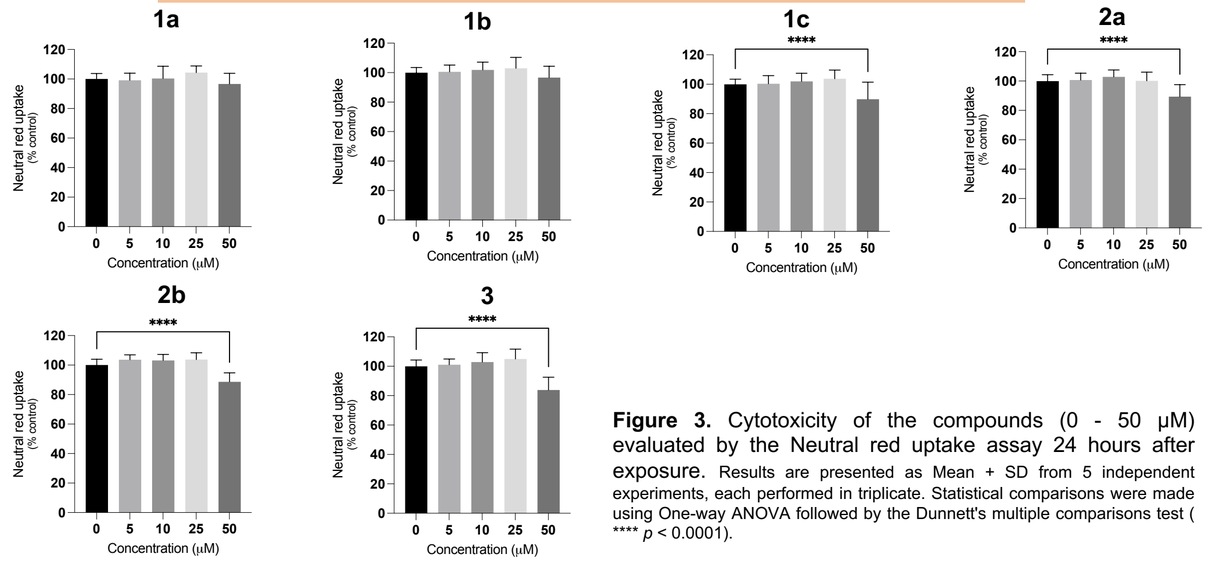


Figure 3. Cytotoxicity of the compounds (0 - 50 µM) evaluated by the Neutral red uptake assay 24 hours after exposure. Results are presented as Mean + SD from 5 independent experiments, each performed in triplicate. Statistical comparisons were made using One-way ANOVA followed by the Dunnett's multiple comparisons test (**** $p < 0.0001$).

Compounds' safety profile: MTT reduction assay

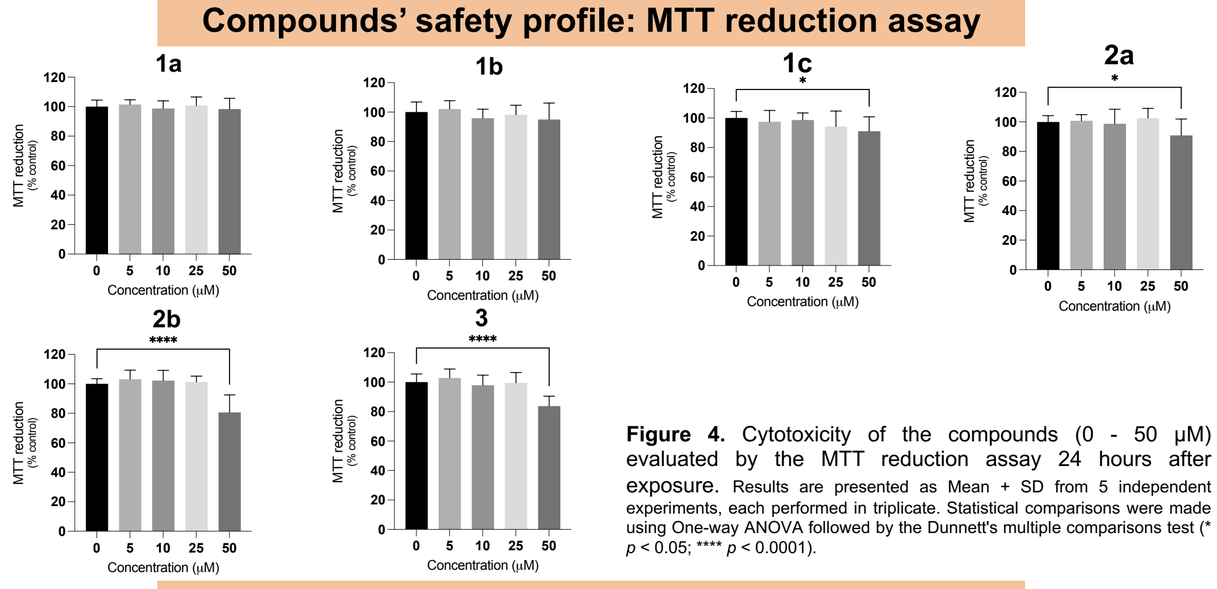


Figure 4. Cytotoxicity of the compounds (0 - 50 µM) evaluated by the MTT reduction assay 24 hours after exposure. Results are presented as Mean + SD from 5 independent experiments, each performed in triplicate. Statistical comparisons were made using One-way ANOVA followed by the Dunnett's multiple comparisons test (* $p < 0.05$; **** $p < 0.0001$).

Protective effects against Aβ-induced cytotoxicity

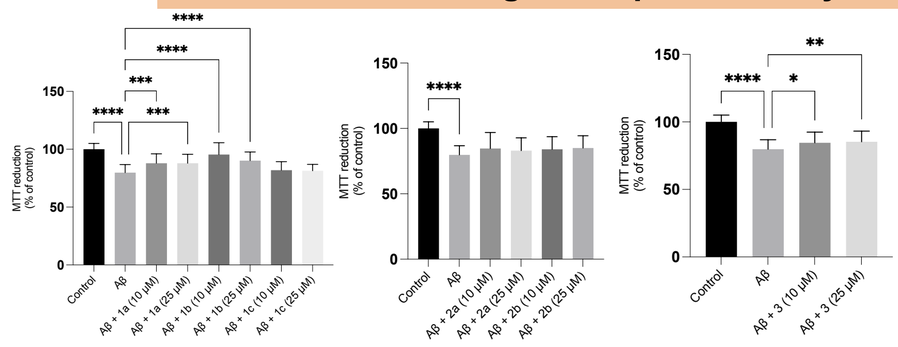


Figure 5. Protective effects of fiscalin derivatives (10 and 25 µM) against Aβ-induced cytotoxicity, evaluated by the MTT reduction assay, 24 hours after exposure to the aggressor (50 µM) in the presence or absence of the compounds. Results are presented as Mean + SD from 4 independent experiments, each performed in triplicate. Statistical comparisons were made using One-way ANOVA followed by the Dunnett's multiple comparisons test (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$).

Protective effects against iron(III)-induced cytotoxicity

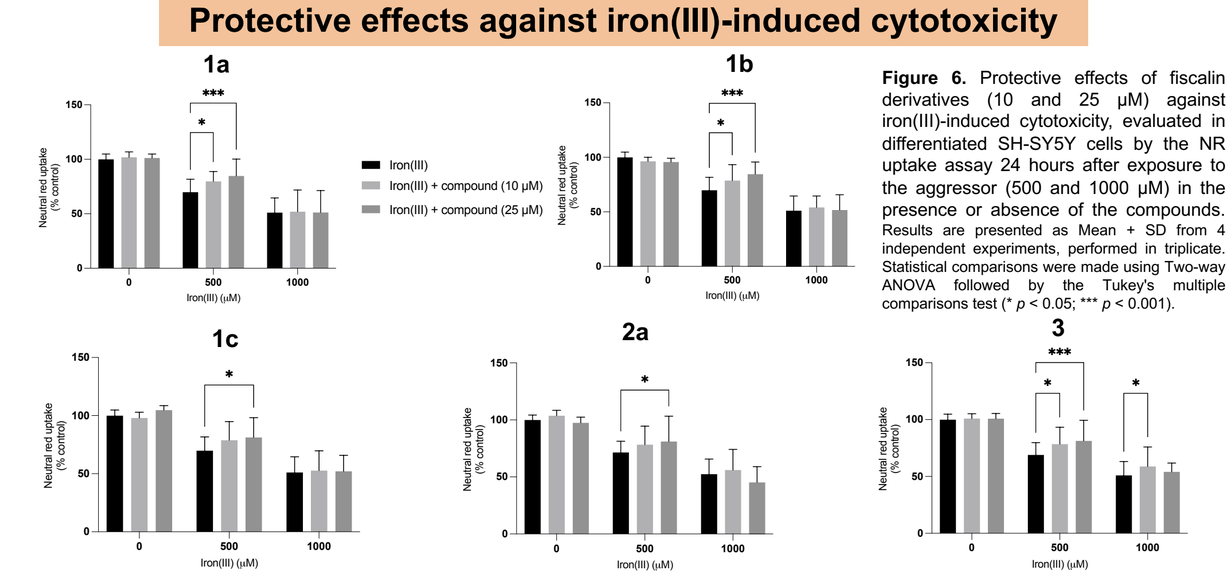


Figure 6. Protective effects of fiscalin derivatives (10 and 25 µM) against iron(III)-induced cytotoxicity, evaluated in differentiated SH-SY5Y cells by the NR uptake assay 24 hours after exposure to the aggressor (500 and 1000 µM) in the presence or absence of the compounds. Results are presented as Mean + SD from 4 independent experiments, performed in triplicate. Statistical comparisons were made using Two-way ANOVA followed by the Tukey's multiple comparisons test (* $p < 0.05$; *** $p < 0.001$).

Inhibition of AChE activity: Ellman's assay

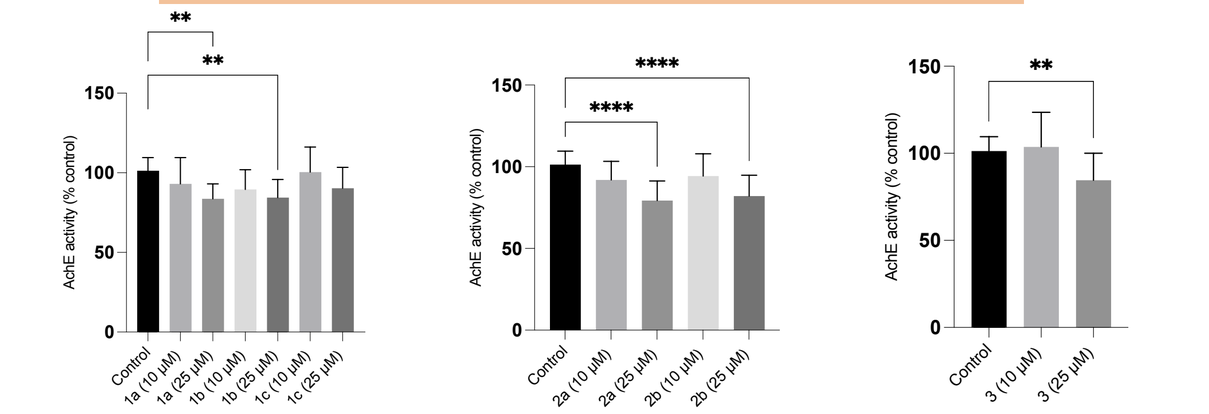


Figure 7. Direct effects of fiscalin derivatives (10 and 25 µM) on AChE activity, evaluated using the Ellman's assay. Results are presented as Mean + SD from 9 independent experiments, performed in duplicate. Statistical comparisons were made using One-way ANOVA followed by the Dunnett's multiple comparisons test (** $p < 0.01$; **** $p < 0.0001$).