EFFECT OF NATURAL AND SYNTHETIC PCSK9 INHIBITORS ON ALZHEIMER'S DISEASE-RELATED PARAMETERS IN HUMAN CEREBRAL CELL MODELS

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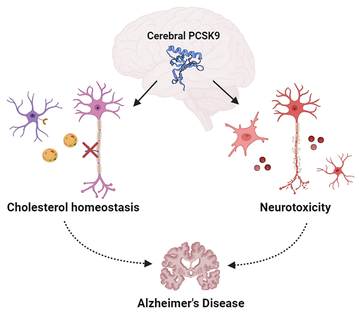
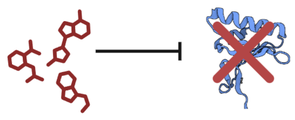


Brief representation of cerebral PCSK9 functions related to AD

BACKGROUND AND RATIONALE

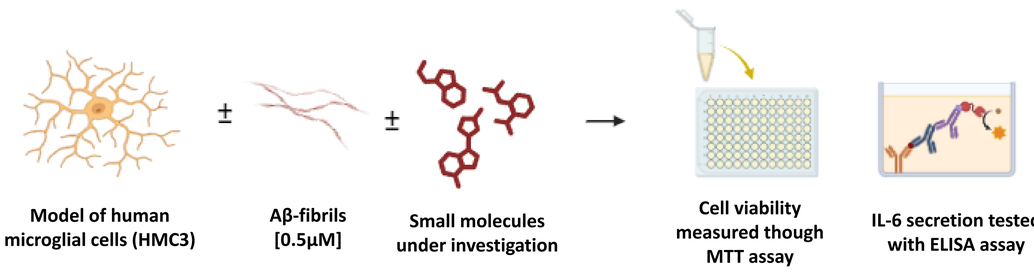
The proprotein convertase subtilisin/kexin 9 (**PCSK9**), beyond regulating plasma cholesterol, is **expressed** also in the **central nervous system** (CNS), where a pathogenetic role in AD has been postulated. **Elevated levels** of this **protein have been found in cerebrospinal fluid** and **frontal cortex of AD patients**[1,2]; *in vitro* experiments demonstrated that **PCSK9 reduces ApoE-mediated neuronal cholesterol uptake, exacerbates β-amyloid (Aβ) neurotoxicity** and **neuroinflammation**, corroborating its **involvement in AD**.[3] Moreover, **PCSK9 genetic deletion ameliorates cognitive performance** and **protects against Aβ deposition** and **neuroinflammation in 5XFAD mice**.[4]

AIM OF THE STUDY

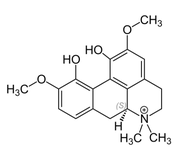


This research aims to further elucidate the **influence of PCSK9** on **neuroinflammation** and to investigate the **potential protective effect** of its **pharmacological inhibition** with **natural** and **newly-synthesized molecules**.

MATERIALS AND METHODS



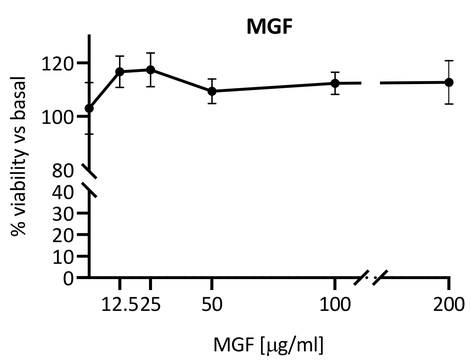
STUDY ON A NATURAL PCSK9 INHIBITOR: MAGNOFLORINE



Magnoflorine

Treatment with Magnoflorine (MGF), a plant-derived molecule and Berberine analogue, **did not affect microglial viability** at the concentrations tested (***Figure A***). **Aβ-fibrils reduced viability** (-28%; p<0.01) was **dose-dependently restored by Magnoflorine** at **200μg/ml** (p>0.05 vs basal condition, ***Figure B***). Furthermore, Magnoflorine at 100μg/ml significantly reduced **Aβ-triggered IL-6 release** (p>0.05 vs basal condition, ***Figure C***).

A



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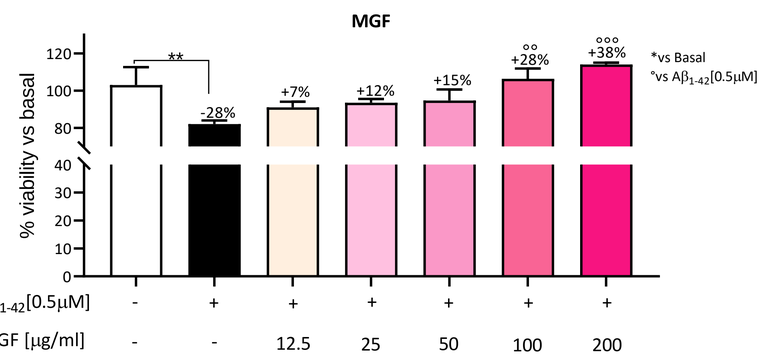

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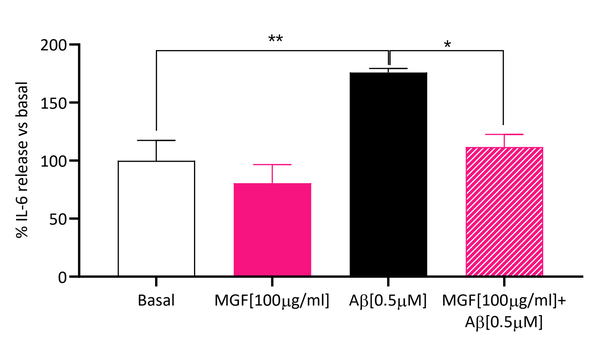
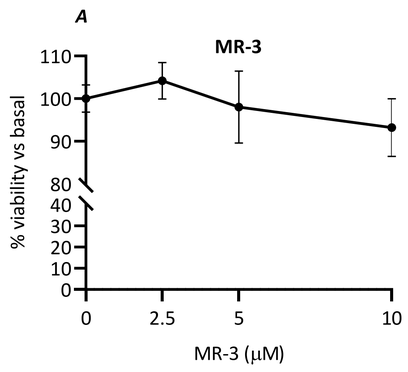


STUDY ON SYNTHETIC PCSK9 INHIBITORS: MR COMPUNDS

A



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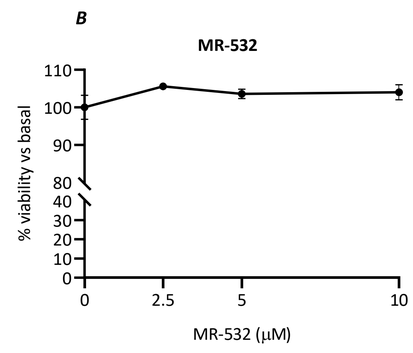

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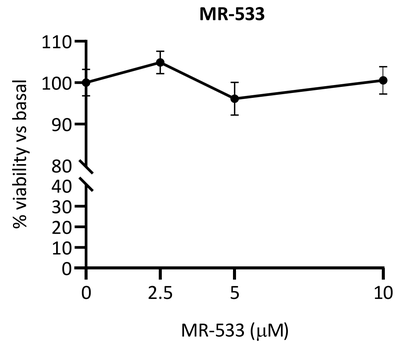

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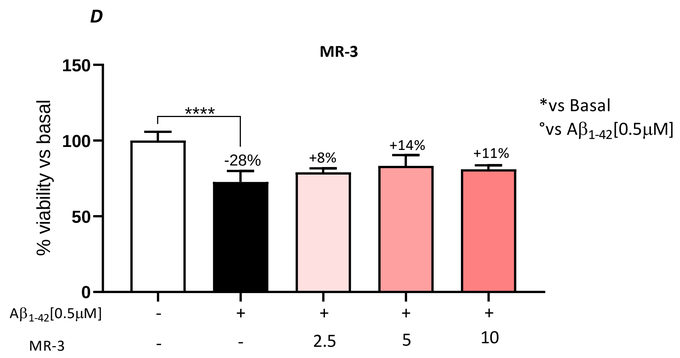

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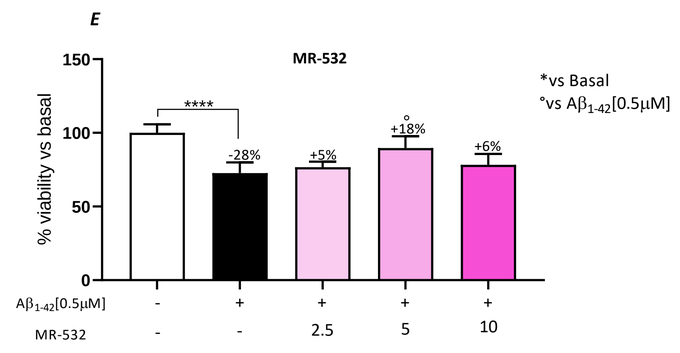

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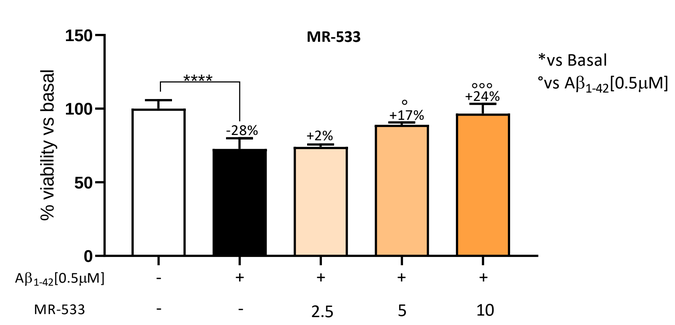
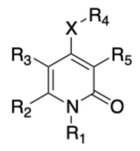
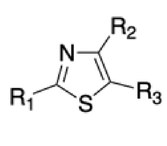




2-pyridone derivatives



Amino-thiazole derivatives

Compound ID	Cell viability inhibition IC_{50}(μM)	PCSK9 inhibition IC_{50} (μM)
MR-3	32.4	1.7
MR-532	35.7	5.7
MR-533	>50	6.1

Table 1 Cytotoxicity and efficacy of compounds in HepG2 cells

MR-3, MR-532 and **MR-533** – with proven PCSK9 inhibition activity on hepatoma cells (HepG2, ***Table 1***) - **did not show sign of cytotoxicity** at all concentrations tested (***Figure A, B, C***). **Microglial viability**, significantly **reduced after incubation with Aβ-fibrils** (-28%; p<0.0001), **was dose-dependently restored by all three synthetic PCSK9 inhibitors** (***Figure D, E, F***), **with the most evident effect for MR-533 at 10μM** (p>0.05 vs basal condition, ***Figure F***).

G

MR-532 and MR-533 at 10μM reduced IL-6 microglial release under basal conditions (-60%, p<0.01; -32%, ns, respectively), while MR-3 increased its secretion (p<0.0001, ***Figure G***).

CONCLUSIONS

PCSK9 pharmacological inhibition plays a protective role on Aβ-induced neurotoxicity suggesting a **neuroprotective effect**. In addition, **PCSK9 inhibitors carry out a pivotal function in the modulation of neuroinflammation**, potentially opening the way for the development of new approaches in the treatment of AD.

REFERENCES
1. Zimetti, Francesca et al. *Journal of Alzheimer's disease*(2017); 2.Picard C, et al. *PLoS One*. 2019; 3. Papotti, Bianca et al. *International journal of molecular sciences* (2022); 4. Vilella A, et al., *Brain Behav Immun*., 2024

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