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IN VITRO AND *IN VIVO* NEUROPROTECTIVE EFFECTS OF MAGNOFLORINE: POTENTIAL IMPLICATION FOR ALZHEIMER'S DISEASE

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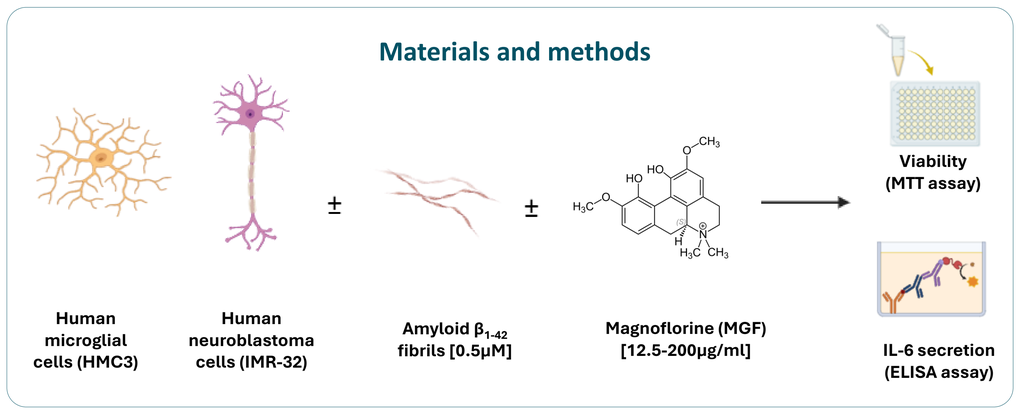
INTRODUCTION AND AIM OF THE STUDY

Magnoflorine (MGF), a plant-derived alkaloid, might be involved in **immune system modulation** and recent studies suggest its ability to reach the central nervous system, where it may positively impact **brain functions**.[1] Although some studies suggest an **antioxidant and anti-amnestic effect**, possibly impacting Alzheimer's disease (AD) features[2], MGF influence on immune and cerebral functions has not been clarified yet. The aim of the study is therefore to **evaluate MGF impact on AD parameters through *in vitro* and *in vivo* studies**.

IN VITRO STUDIES

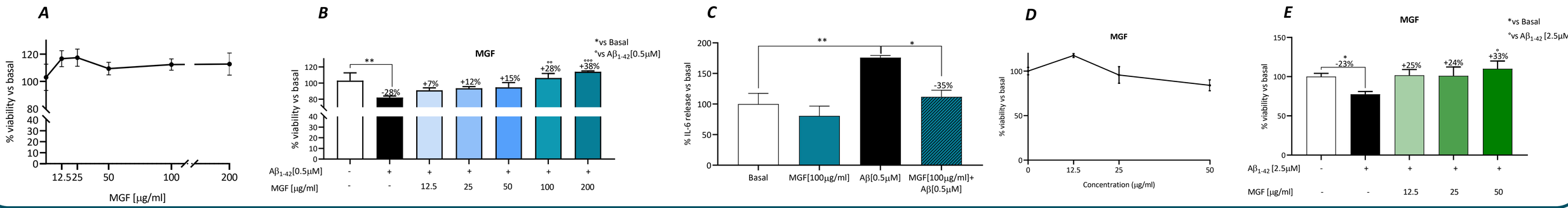
RESULTS I

Obtained results demonstrated that **MGF was nontoxic** at the concentrations tested on **HMC3** cells (***Figure A***). Moreover, **microglial viability**, which was significantly reduced after incubation with $A\beta_{1-42}$-fibrils (-28%; p<0.01), **was dose-dependently restored by MGF with a complete rescue** at the concentration of 100 µg/ml (p>0.05 vs basal, ***Figure B***). Furthermore, **MGF at 100 µg/ml reduced Aβ-induced IL-6 release** (-35%; p<0.05, ***Figure C***).

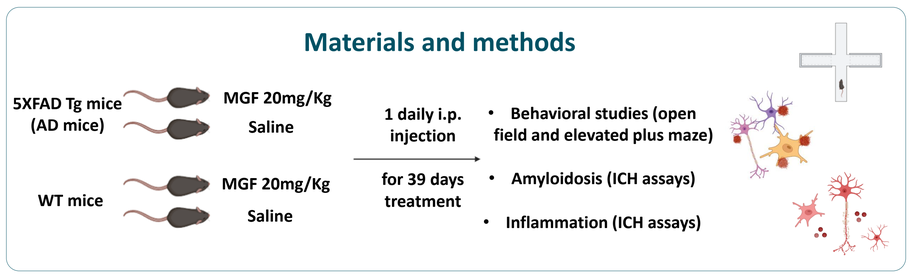


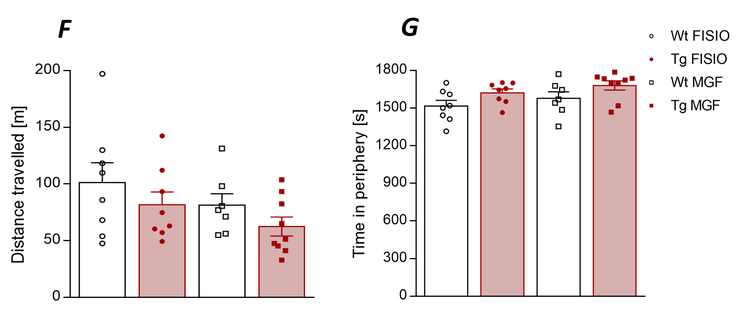
RESULTS II

MGF was tested also on neuroblastoma cells **IMR-32** and it showed **absence of toxicity** up to a concentration of 50µg/ml (***Figure D***). Similarly to what we observed in microglial cells, $A\beta_{1-42}$-fibrils incubation induced a significant reduction of **neuronal viability** (-23%; p<0.05) which **was dose-dependently renewed by MGF treatment, leading to a complete restoration** at the highest concentration (p>0.05 vs basal, ***Figure E***).



IN VIVO STUDIES



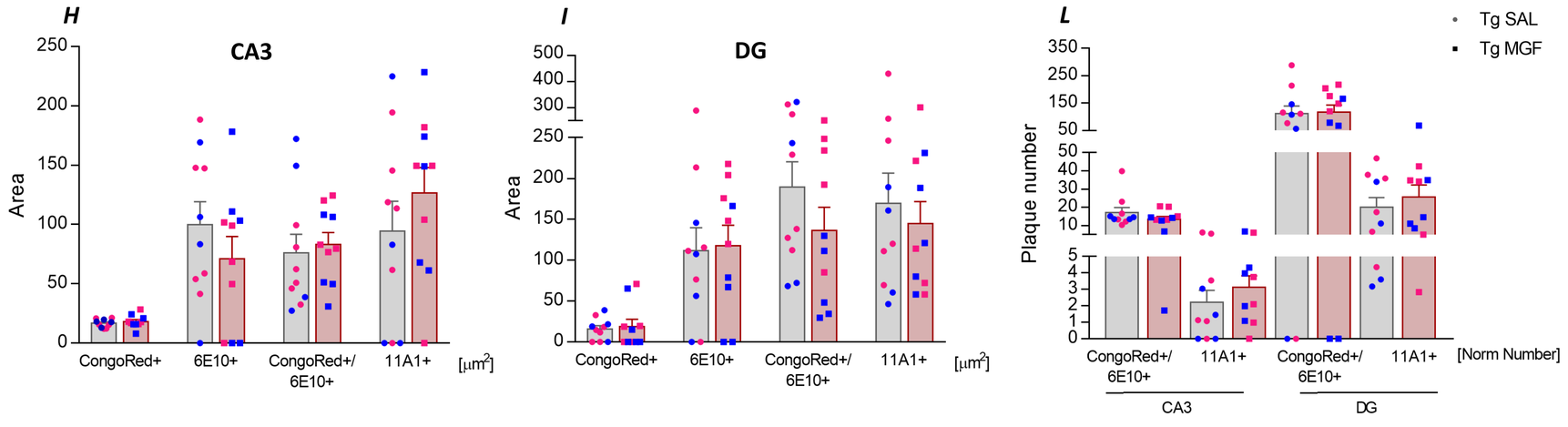


RESULTS III

MGF *in vivo* treatment did not show **any alteration of animal behaviour**, since there were no differences among the group treatment both **in terms of distance travelled** during open field test (p>0.05, ***Figure F***) **and time spent in periphery** in elevated plus maze test (p>0.05, ***Figure G***).

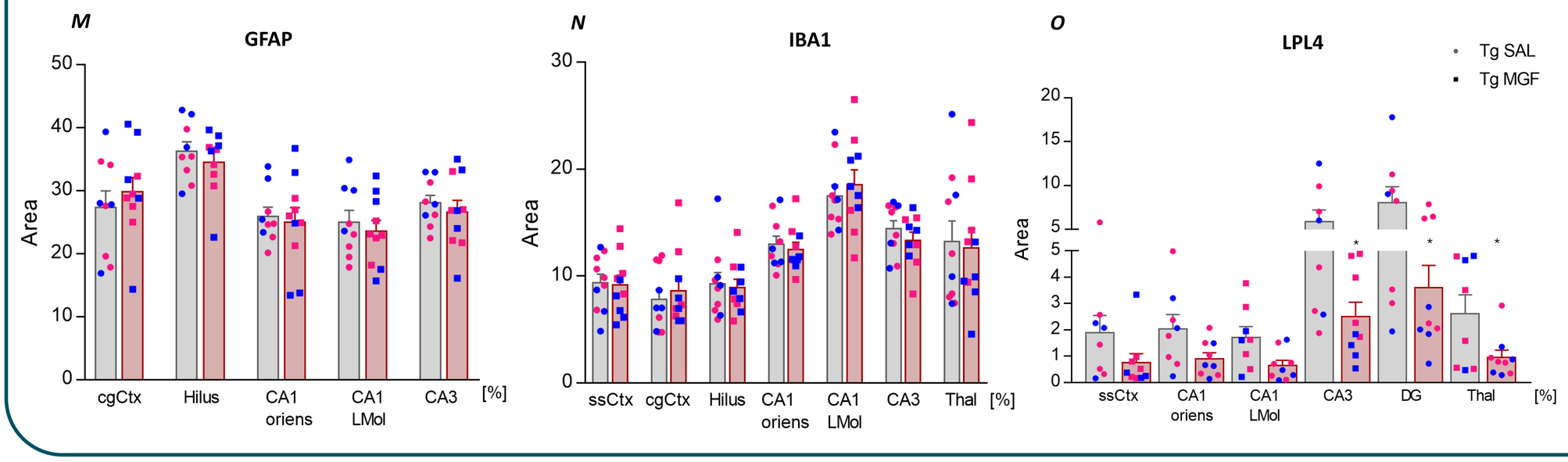
RESULTS IV

Analysing 5XFAD mice brain through immunohistochemistry assays, it resulted that **MGF treatment did not affect Aβ plaque composition and burden** in terms of amyloid plaque area (p>0.05; ***Figure H*** and ***I***), as well as in the number of plaques in the subfield CA3 of hippocampus and the dentate gyrus (DG) (p>0.05; ***Figure L***).



RESULTS V

GFAP and IBA1 immunoreactivity was unaltered in MGF treated mice (***Figure M*** and ***N***); while it **showed a significant reduction of LPL4 immunoreactivity in all brain regions analysed**, particularly in the CA3 subfield of the hippocampus (p<0.05), in the DG (p<0.05) and in the thalamus (p<0.05, ***Figure O***), suggesting an **involvement in inflammatory process and lipid homeostasis**.



CONCLUSIONS

Our results showed a **neuroprotective effect of MGF as it positively affects cell viability and reduces Aβ-induced inflammation *in vitro***. Consistently, *in vivo* data confirmed **MGF anti-inflammatory effects through the modulation of LPL4**, suggesting a possible involvement in the **modulation of cerebral immune-metabolic response**.

REFERENCES
[1]Zhao, Feng et al. "Magnoflorine Alleviates "M1" Polarized Macrophage-Induced Intervertebral Disc Degeneration Through Repressing the HMGB1/Myd88/NF-κB Pathway and NLRP3 Inflammasome." *Frontiers in pharmacology* (2021);
[2]Zhong, Lili et al. "Magnoflorine improves cognitive deficits and pathology of Alzheimer's disease via inhibiting of JNK signaling pathway." *Phytomedicine : international journal of phytotherapy and phytopharmacology* vol. 112 (2023)

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