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RECEIVED 02 October 2025
ACCEPTED 28 October 2025
PUBLISHED 12 November 2025

CITATION
Kujawska M, Kreiner G and Teissedre P-L
(2025) Editorial: Brain aging,
neurodegeneration, and the role of natural
molecules in maintaining brain health.
Front. Neurosci. 19:1717873.
doi: 10.3389/fnins.2025.1717873

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Editorial: Brain aging, neurodegeneration, and the role of natural molecules in maintaining brain health

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KEYWORDS

brain aging, neurodegeneration, natural molecules, proteostasis, neuroinflammation, precision medicine, translational strategies

Editorial on the Research Topic

[Brain aging, neurodegeneration, and the role of natural molecules in maintaining brain health](#)

The demographic shift toward an aging global population has made brain health one of the most pressing scientific and public health challenges of our time. Neurodegenerative diseases such as Alzheimer's and Parkinson's impose an increasing burden on individuals and societies, while effective preventive or disease-modifying therapies remain elusive (Sabayan et al., 2023). This gap has fueled interest in natural molecules and nature-inspired derivatives as agents capable of reinforcing endogenous defense mechanisms, modulating proteostasis, and reducing neuroinflammation (Kujawska and Jodynis-Liebert, 2018; Babazadeh et al., 2023). By integrating advances in genetics, mechanistic neuroscience, and translational strategies, researchers are beginning to build a more coherent framework for preserving brain function across the lifespan (Nehmeh et al., 2024; Jiang et al., 2025).

A first theme concerns the link between inherited genetic variation and the vulnerability of cortical networks. Using a multimodal imaging-genetics approach, Kim et al. identified single nucleotide polymorphisms associated with cortical thinning and cognitive decline and showed that amyloid- β burden partially mediates these effects. The work highlights the convergence of immune-synaptic signaling pathways and cortical atrophy, underscoring the importance of stratifying patient cohorts not only by clinical phenotype but also by genotype and amyloid status (Kim et al.). Beyond methodological innovation, these findings indicate that genetic information may serve as an important factor to consider in the design of preventive or interventional trials, supporting therapeutic strategies that are better aligned with the biological context of vulnerability (Kim et al.; Nehmeh et al., 2024). Together, these findings suggest that molecular interventions may ultimately need to be guided by precision medicine principles, where genomic risk scores and amyloid imaging inform both trial inclusion and expected responsiveness.

Mechanistic insights into neuronal survival emerge in complementary fashion from the work of Wu et al., who disrupted the Sel1L-Hrd1 ER-associated degradation (ERAD) complex selectively in adult neurons. Loss of ERAD function destabilizes

endoplasmic reticulum homeostasis, triggers maladaptive unfolded protein responses, and leads to progressive hippocampal and cerebellar degeneration with behavioral manifestations of ataxia (Wu et al.). These findings establish ER proteostasis not merely as a biomarker of disease but as a prerequisite for neuronal viability.

Building on this mechanistic foundation, Kouchmeshky et al. introduced elloraxine, a selective retinoic acid receptor agonist with favorable stability compared to all-trans retinoic acid. In neuronal cultures, elloraxine mitigated excitotoxic injury, restored proteostasis, and modulated stress granule dynamics. While the data are preclinical, they illustrate how molecules inspired by endogenous signaling can reinforce resilience under conditions of synaptic stress and proteostatic challenge. Importantly, the study highlights the translational potential of receptor-specific retinoids, which may overcome the pharmacokinetic and safety limitations of earlier compounds (Kouchmeshky et al.). This line of work also connects to a broader literature indicating that retinoid signaling intersects with pathways of neuroinflammation and plasticity, making it a promising yet still underexplored therapeutic avenue (Mey and McCaffery, 2004; Kouchmeshky et al.).

A complementary translational avenue is offered by repurposed iron chelators. Fine et al. tested intranasal deferroxamine in the intracerebroventricular streptozotocin model of sporadic Alzheimer's disease. Low-dose treatment reversed deficits in spatial memory, prevented hippocampal neuronal loss, and attenuated neuroinflammatory and degenerative signatures at both the transcriptomic and cytokine levels. Higher doses were less effective, emphasizing the need for careful dose selection. The use of intranasal delivery to bypass the blood–brain barrier is particularly notable, as it opens a practical route for chronic administration of chelators and other molecules with limited systemic tolerability (Fine et al.).

Taken together, these studies not only establish ER proteostasis as a prerequisite for neuronal survival but also provide a mechanistic support for therapeutic approaches aimed at sustaining proteostasis, suggesting that interventions targeting stress granules, protein clearance, or retinoid pathways may derive part of their efficacy from stabilizing ER function. At the same time, rigorous dose-finding and long-term evaluation will be essential to define the therapeutic window and safety profile of such agents (Jiang et al., 2025).

The contributions in this Research Topic outline a coherent translational arc. Genetic risk factors set the stage for vulnerability; proteostatic networks in the endoplasmic reticulum determine neuronal survival, and nature-inspired interventions, whether receptor-selective retinoids or repurposed chelators, offer strategies to restore resilience.

The convergence of these dimensions underscores the need for interdisciplinary research that bridges scales—from genomic

risk to molecular targets to functional outcomes. Equally critical will be the development of regulatory frameworks capable of accommodating nutraceuticals, repurposed drugs, and synthetic derivatives of natural molecules, ensuring that promising leads can be tested in well-designed clinical trials (Kakoti et al., 2022; Qiao et al., 2023; Feldman et al., 2024; Jiang et al., 2025).

In conclusion, the articles collected here demonstrate how complementary approaches can be integrated into a forward-looking strategy for preserving brain health across aging. By linking genetics, mechanistic insight, and translational intervention, this Research Topic emphasizes the value of sustained collaboration across disciplines and sectors. Future progress is likely to require genetics-informed patient selection, robust mechanistic endpoints, and pragmatic delivery routes that together can accelerate the safe and effective deployment of natural molecules and their derivatives to protect the aging brain.

Author contributions

MK: Writing – original draft. GK: Writing – review & editing. P-LT: Writing – review & editing.

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References

- Babazadeh, A., Vahed, F. M., Liu, Q., Siddiqui, S. A., Kharazmi, M. S., and Jafari, S. M. (2023). Natural bioactive molecules as neuromedicines for the treatment/prevention of neurodegenerative diseases. *ACS Omega* 8, 3667–3683. doi: 10.1021/acsomega.2c06098

- Feldman, H. H., Cummings, J. L., Boxer, A. L., Staffaroni, A. M., Knopman, D. S., Sukoff Rizzo, S. J., et al. (2024). A framework for translating tauopathy therapeutics: drug discovery to clinical trials. *Alzheimers Dement.* 20, 8129–8152. doi: 10.1002/alz.14250
- Jiang, Q., Liu, J., Huang, S., Wang, X.-Y., Chen, X., Liu, G.-H., et al. (2025). Antiageing strategy for neurodegenerative diseases: from mechanisms to clinical advances. *Sig. Transd. Targeted Ther.* 10:76. doi: 10.1038/s41392-025-02145-7
- Kakoti, B. B., Bezbaruah, R., and Ahmed, N. (2022). Therapeutic drug repositioning with special emphasis on neurodegenerative diseases: threats and issues. *Front. Pharmacol.* 13:1007315. doi: 10.3389/fphar.2022.1007315
- Kujawska, M., and Jodynis-Liebert, J. (2018). Polyphenols in Parkinson's disease: a systematic review of *in vivo* studies. *Nutrients* 10:642. doi: 10.3390/nu10050642
- Mey, J., and Mc Caffery, P. (2004). Retinoic acid signaling in the nervous system of adult vertebrates. *Neuroscientist* 10, 409–421. doi: 10.1177/1073858404263520
- Nehmeh, B., Rebehmed, J., Nehmeh, R., Taleb, R., and Akoury, E. (2024). Unlocking therapeutic frontiers: harnessing artificial intelligence in drug discovery for neurodegenerative diseases. *Drug Discov. Today* 29:104216. doi: 10.1016/j.drudis.2024.104216
- Qiao, J., Wang, C., Chen, Y., Yu, S., Liu, Y., Yu, S., et al. (2023). Herbal/natural compounds resist hallmarks of brain aging: from molecular mechanisms to therapeutic strategies. *Antioxidants* 12:920. doi: 10.3390/antiox12040920
- Sabayan, B., Doyle, S., Rost, N. S., Sorond, F. A., Lakshminarayan, K., and Launer, L. J. (2023). The role of population-level preventive care for brain health in ageing. *Lancet Healthy Longev.* 4, e274–e283. doi: 10.1016/S2666-7568(23)00051-X