Testing novel anti-oxidant compounds for neuroprotective effects in the treatment of Alzheimer's Disease

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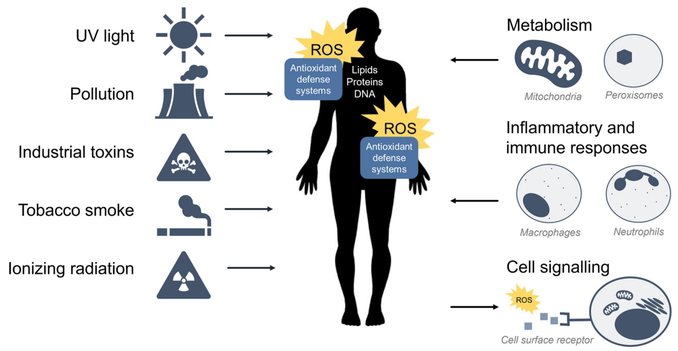
Alzheimer's disease is the fastest growing form of dementia in the world. Currently the origin of disease is unknown, however, there are distinct signs seen in patients with Alzheimer's disease (AD). Chronic neuroinflammation, increased ROS, dyshomeostasis of metal ions, Tau tangles, and mitochondrial dysfunction are well known to the pathogenesis and progression of this disease. In AD, neuronal cells abnormally cleave and process APP causes Aβ oligomers and plaques to form that disrupt synaptic signaling. These plaques lead to an increase in oxidative stress and neuroinflammation. These plaques overstimulate glutamate receptors causing an influx of Ca^{2+} ions. Elevated intracellular Ca^{2+} has been linked to the formation of Tau tangles. Tau tangles are associated with mental decline and activation from astrocytes and microglia that produce cytokines and ROS. In this study, we examined the antioxidant properties of the compound, **L2**, on TBHP induced oxidative stress in mice microglial cells (BV-2) and mice neuronal cells (HT-22 cells). We hypothesized that **L2** directly reduces oxidative damage caused by Alzheimer's Disease. DCFH-DA assay was utilized to test this hypothesis.

Background

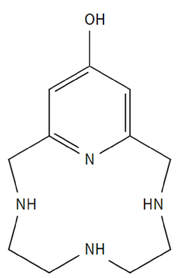
- Alzheimer's disease (AD) is the leading form of dementia worldwide
- About 1 in 9 adults over 65 have AD (11%)
- The cause of AD is currently unknown, however, Aβ plaques and hyperphosphorylated Tau Tangles are associated with the pathology of the disease
- Chronic neuroinflammation associated with the pathology leads to neuronal cell death and activation of an immune response producing inflammatory cytokines and ROS
- Cells have the innate ability to regulate intracellular ROS under normal conditions
- Although, when intracellular [ROS] is too high, the cell is unable to regulate and will undergo apoptosis



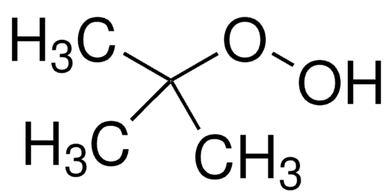
Oxidative Stress (Ngo & Duennwald, 2023)

Compounds used in this study

L2[1, 2, 3]

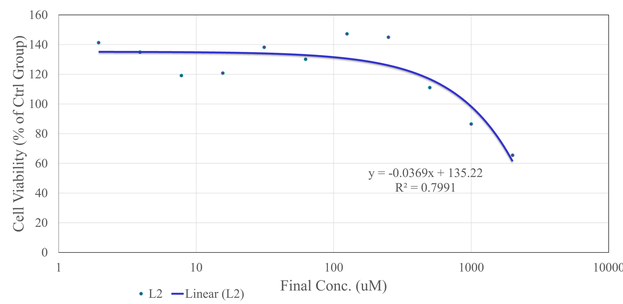


TBHP

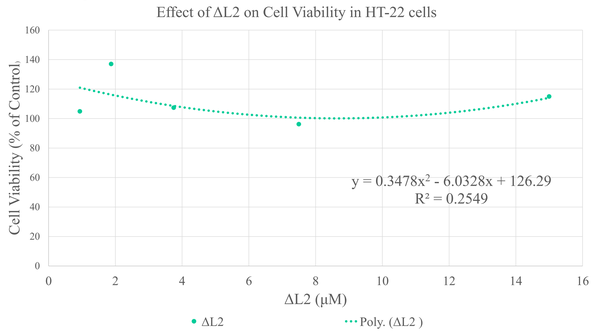


Results

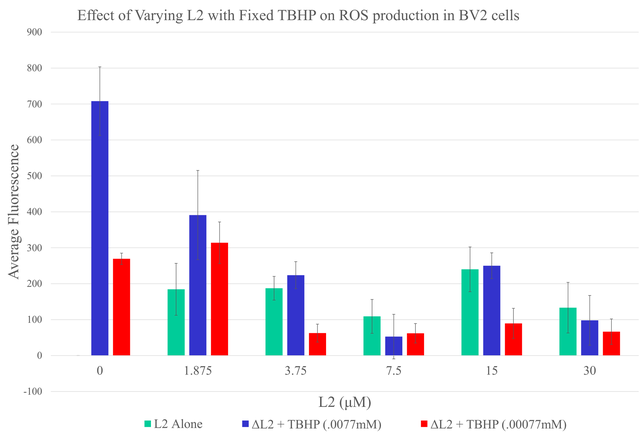
I. Cytotoxicity of L2 in BV-2 mouse microglial cells



II. Cytotoxicity of L2 in HT-22 mouse neuronal cells

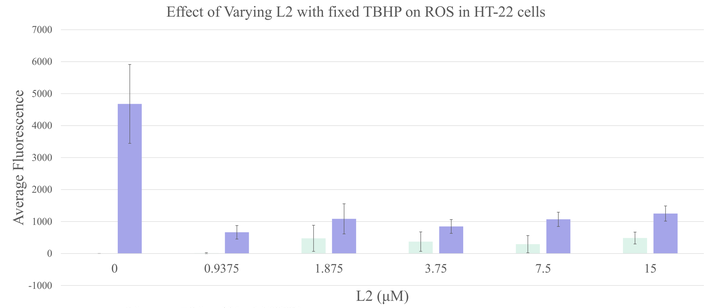


III. Effect of L2 on TBHP-induced ROS production in BV-2 cells



Results

IV. Effect of L2 on TBHP-induced ROS production in HT-22 cells



Conclusions

L2, a novel anti-oxidant compound was shown to display low cytotoxicity in BV-2 cells and HT-22 cells respectively.

L2 significantly reduces TBHP induced ROS in a dose dependent manner in both BV-2 and HT-22 cell lines.

L2 has potential Therapeutic effects for treating Alzheimer's type Dementia.

Bibliography

1. Alzheimer's Association. (2025). *Alzheimer's disease facts and figures*. https://www.alz.org/alzheimers-dementia/facts-figures
2. Johnston, H. M., Pota, K., Barnett, M. M., Kinsinger, O., Braden, P., Schwartz, T. M., Hoffer, E., Sadagopan, N., Nguyen, N., Yu, Y., Gonzalez, P., Tircsó, G., Wu, H., Akkaraju, G., Chumley, M. J., & Green, K. N. (2019). Enhancement of the Antioxidant Activity and Neurotherapeutic Features through Pyridol Addition to Tetraazamacrocyclic Molecules. *Inorganic chemistry*, *58*(24), 16771–16784. https://doi.org/10.1021/acs.inorgchem.9b02932
3. Liu, J., Chang, L., Song, Y., Li, H., & Wu, Y. (2019). The Role of NMDA Receptors in Alzheimer's Disease. *Frontiers in neuroscience*, *13*, 43. https://doi.org/10.3389/fnins.2019.00043
4. Park, M. W., Cha, H. W., Kim, J., Kim, J. H., Yang, H., Yoon, S., Boonpraman, N., Yi, S. S., Yoo, I. D., & Moon, J. S. (2021). NOX4 promotes ferroptosis of astrocytes by oxidative stress-induced lipid peroxidation via the impairment of mitochondrial metabolism in Alzheimer's diseases. *Redox biology*, *41*, 101947. https://doi.org/10.1016/j.redox.2021.101947
5. Toru Tanaka, Sachiyo Ohashi, Akihiko Takashima, Shunsuke Kobayashi, Effect of calcium ions on the aggregation of highly phosphorylated tau, Biochemistry and Biophysics Reports, Volume 40, 2024, 101887, ISSN 2405-5808, https://doi.org/10.1016/j.bbrep.2024.101887
6. Ngo, V., & Duennwald, M. L. (2023, February 1). *Nrf2 and oxidative stress*. *Encyclopedia*. https://encyclopedia.pub/entry/40684

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