doi 10.18699/bgrs2024-3.2-20

Structure-guided identification of Baicalin exhibiting anti-Alzheimer's effects via CLK1 inhibition

Khan S., Hassan M.I., Islam A.*

Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi, India
** aislam@jmi.ac.in*

Key words: Alzheimer's disease; kinase inhibition; CDC2-like kinase 1; hyperphosphorylation; structure-guided drug discovery

Motivation and Aim: Alzheimer's disease (AD) is a rapidly increasing neurodegenerative disorder, projected to affect 78 million people by 2050 [1]. Current treatments provide only modest symptomatic relief [2]. Tau protein hyperphosphorylation is a key pathological feature of AD, and evidence suggests that targeting tau phosphorylation through the inhibition of protein kinases, particularly CLK1 (CDC2-like kinase 1), could reduce tau aggregation and neuronal death [3]. This study aims to investigate the potential of Baicalin as a CLK1 inhibitor, offering a novel therapeutic approach for AD and other tauopathies.
Methods and Algorithms: We employed structure-based molecular docking to predict the binding affinity of Baicalin to CLK1. Molecular dynamics simulations were conducted to analyze the stability and interactions of the Baicalin-CLK1 complex. Fluorescence spectroscopy was used to confirm the binding mechanism. Additionally, a kinase inhibition assay was performed to determine the inhibitory potential of Baicalin on CLK1, quantified by IC50 values.
Results: Our molecular docking studies revealed a strong binding affinity of Baicalin to CLK1. Molecular dynamics simulations confirmed the stability of the Baicalin-CLK1 complex. Fluorescence spectroscopy validated the binding interactions between Baicalin and CLK1. The kinase inhibition assay demonstrated that Baicalin significantly inhibits CLK1 activity, with an IC50 value of 12.04 μM.
Conclusion: Baicalin exhibits significant potential as a CLK1 inhibitor, effectively reducing CLK1 activity in vitro. These findings position Baicalin as a promising lead molecule for developing specific CLK1 inhibitors, offering a novel therapeutic strategy for AD and other tauopathies. Further research and clinical trials are necessary to validate these findings and explore the therapeutic efficacy of Baicalin *in vivo*.
Funding: Sumaiya Khan acknowledges the DST INSPIRE Fellowship with reference number: IF220384.

References

1. Li X. et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2019. *Front Aging Neurosci*. 2022;14:937486. doi 10.3389/fnagi.2022.937486
2. Khan S. et al. Nature's toolbox against tau aggregation: An updated review of current research. *Ageing Res Rev*. 2023;87:101924. doi 10.1016/j.arr.2023.101924
3. Jain P. et al. Human CDC2-like kinase 1 (CLK1): A novel target for Alzheimer's disease. *Curr Drug Targets.* 2014;15(5):539-550. doi 10.2174/1389450115666140226112321