CDK5

Cyclin-dependent kinase 5 (CDK5) is a proline-directed Serine/threonine-specific protein kinase vital for neuronal cell cycle arrest and differentiation. It activates by binding with p35 and p39 and is important for the functioning of the nervous system. A growing body of evidence suggests that CDK5 contributes to the onset and progression of neurodegeneration and tumorigenesis and represents itself as a potential therapeutic target. The research illustrates virtual screening of phytochemicals from the IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) library to search for potential inhibitors of CDK5. Initially, the compounds from the parent library were filtered out via their physicochemical properties following the Lipinski rule of five. Then sequentially, molecular docking-based virtual screening, PAINS filter, ADMET, PASS analysis, and molecular dynamics (MD) simulation were done using various computational tools to rule out adversities that can cause hindrances in the identification of potential inhibitors of CDK5. Finally, two compounds were selected via the extensive screening showing significant binding with CDK5 ATP-binding pocket and ultimately were selected as potent ATP-competitive inhibitors of CDK5. Finally, Atiya et al. propose that the elucidated compounds Desmodin and Isopongachromene can be used further in the drug discovery process and act as therapeutics in the medical industry to treat certain complex diseases, including cancer and neurodegeneration [1].

Cyclin dependent kinase 5 (CDK5) and ataxia telangiectasia mutated (ATM) are involved in normal human neurodevelopment and serves as a switch between neuronal survival and death.

The molecular mechanisms underlying CDK5-ATM-induced neuronal injury caused by intracerebral hemorrhage (ICH) remain unclear.

In a work, Wu et al. used rat ICH models and thrombin-induced cell models to investigate the potential role of CDK5-ATM signals. The findings revealed that CDK5 protein levels and kinase activities (p-histone H1 expression) were enforced in hematoma-surrounding neuron tissues following ICH. Besides, the expression of p25, p-ATM, and active caspase-3 protein was also upregulated after ICH. According to in vitro assays, the expression of CDK5, p-ATM, and active caspase-3 was all upregulated in cell viability-decreasing ICH cell models. However, blocking of either CDK5 or ATM suppressed the phosphorylation of ATM and the expression of active caspase-3, and attenuated the inhibition of neuronal survival. When p35/p25 was silenced, CDK5-ATM pathway was further inhibited, and cell viability was obviously ameliorated. In conclusion, this work suggested that ATM could be phosphorylated by CDK5 to induce the active caspase-3 and neuronal injury when intracerebral hemorrhage or ischemia occurred. Thus, the CDK5-AMT signal pathway has an important role in ICH process and may be a therapeutic target to prevent brain injury [2].

1)
Atiya A, Batra S, Mohammad T, Alorfi NM, Abdulmonem WA, Alhumaydhi FA, Ashraf GM, Baeesa SS, Elasbali AM, Shahwan M. Desmodin and isopongachromene as potential inhibitors of cyclin-dependent kinase 5: phytoconstituents targeting anticancer and neurological therapy. J Biomol Struct Dyn. 2022 Oct 2:1-11. doi: 10.1080/07391102.2022.2128877. Epub ahead of print. PMID: 36184739.
2)
Wu J, Zhang X, Yan Y, Tang Z, Sun X, Huo G, Liao Z. The Crucial Role of Cyclin-Dependent Kinase-5-Ataxia-Telangiectasia Mutated Axis in ICH-Induced Neuronal Injury of Rat Model. Mol Neurobiol. 2015 Nov 14. [Epub ahead of print] PubMed PMID: 26567107.