

Computational study of ginkgolide B and P2X7 receptor interactions in neuroinflammatory pathways

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Neurodegenerative diseases represent an increasing global health burden and are characterized by progressive physical and cognitive decline. A central contributor to their pathogenesis is neuroinflammation, mediated by activated microglia. Upon stimulation, microglia release pro-inflammatory mediators, including IL-1 β , TNF- α , iNOS, and COX-2, contributing to neuronal dysfunction and cell death. The P2X7 receptor plays a pivotal role in regulating this inflammatory cascade and has emerged as a promising therapeutic target. However, the molecular interactions between Ginkgolide B and the P2X7 receptor remain poorly understood. Therefore, this study aimed to investigate the binding mechanism of Ginkgolide B towards the P2X7 receptor using computational approaches. The three-dimensional structure of the P2X7 receptor was generated using SWISS-MODEL and analyzed using binding site prediction tools, including COACH-D, Prank Web, and Protein Plus, to identify functionally relevant residues. A membrane bound receptor system was constructed using CHARMM-GUI, followed by a 200 ns molecular dynamics simulation using NAMD to assess structural stability of the wild-type receptor. Ginkgolide B was optimized using density functional theory at the B3LYP/6-31G(d) level and parameterized through CHARMM-GUI. The optimized ligand was subjected to blind molecular docking using PyRx to identify potential binding regions within the receptor. Docking results revealed binding energies ranging from -7.5 to -7.9 kcal/mol, indicating favorable

ligand receptor interactions. Targeted docking within the most favorable binding pocket further refined ligand positioning and interaction profiles. The best-binding pose exhibited hydrogen bond interactions with ASN100 and SER59, together with van der Waals interactions involving ILE58 and VAL321. These residues are located within functionally relevant receptor regions contribute to ligand stabilization. The interaction pattern suggests that Ginkgolide B associate with regions of the P2X7 receptor involved in receptor function and modulation. Overall, this study provides computational evidence supporting Ginkgolide B as a potential lead compound for further investigation targeting P2X7 receptor-mediated neuroinflammation in neurodegenerative disorders.

Keywords:

Neuroinflammation, P2X7 receptor, Ginkgolide B, molecular docking, molecular dynamics.

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