MOLECULAR DYNAMICS SIMULATION OF THE INTERACTION BETWEEN TNKS1/TNKS2 AND IWR1 INHIBITOR

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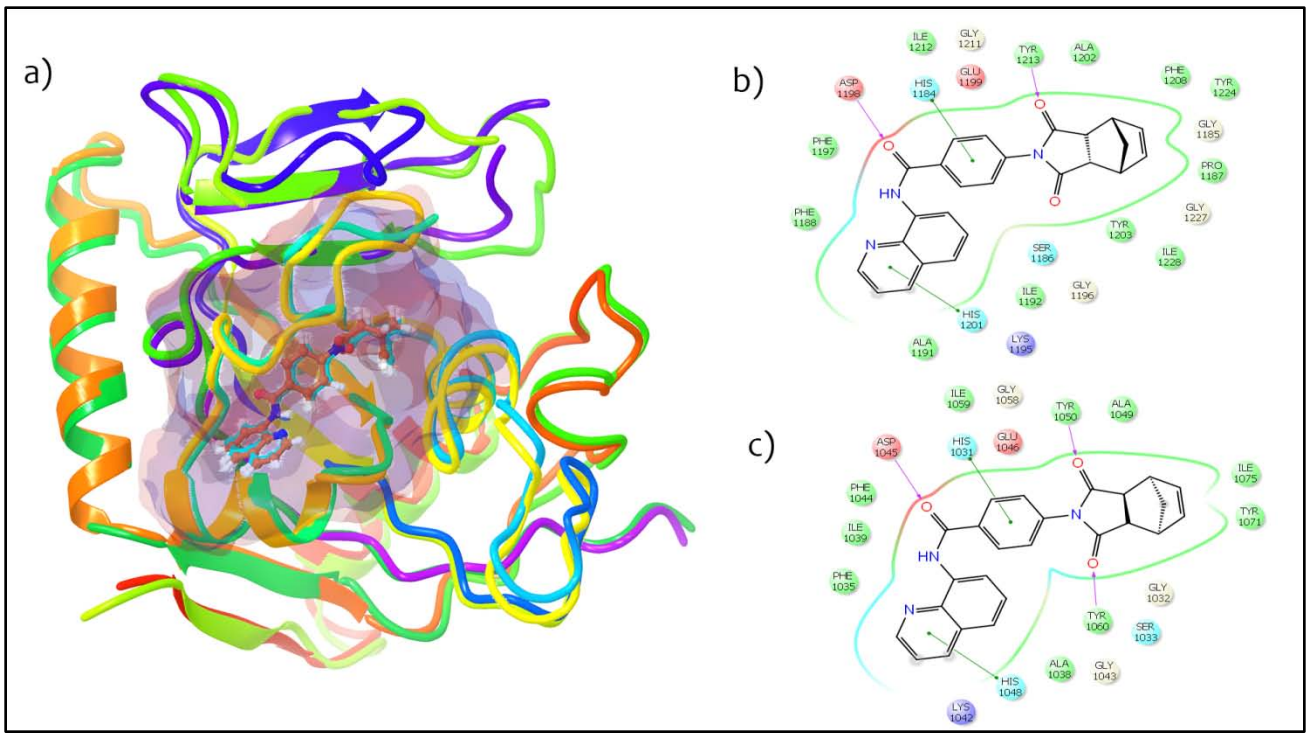
Abstract

Tankyrases (TNKS) belong to poly (ADP-ribose) polymerase (PARP) protein superfamily and plays a vital role in the Wnt/β-catenin signalling pathway. It is a potential target for therapeutic intervention against various cancers, heritable disease (cherubism) and implications in the replication of herpes simplex virus (HSV). The recent discovery of tankyrase' structure with IWR1 inhibitor has provided insights into the binding modes which are specific for tankyrase protein which will aid in the development of drugs that are specific for tankyrase protein. The current study investigates the molecular interactions between the induced pocket of TNKS1 and TNKS2 with IWR1 compound using computational approaches. Molecular docking analysis with IWR1 at the induced pocket of TNKS1 and TNKS2 were performed and the resulting protein-ligand complexes used for molecular dynamics (MD) simulation study for a time scale of 100 ns. Results revealed the stable binding of IWR1 at the induced pocket of TNKS1 and TNKS2. Apart from active site amino acids, π - π stack paring interactions were also crucial for the protein-ligand binding and stabilization of the complex. The conformational dynamics of the protein-ligand complex, as obtained from MD studies have been investigated and compared using principal component analysis (PCA). Further, energy-optimized pharmacophore mapping was performed and the resulting pharmacophore model contained a four (TNKS1-IWR1) and five (TNKS2-IWR1) featured sites. Based on the pharmacophoric sites, screening of Zinc natural product compound database was done and the results were interpreted.



a) Superimposition of docked poses of IWR1 compound with TNKS1 and TNKS2. The binding sites were colored based on the molecular surface representations for TNKS1 (blue) and TNKS2 (red), b) 2D representation of the interacting model of IWR1 complex with the TNKS1 protein and c) 2D representation of the interacting model of IWR1 complex with the TNKS2 protein.

Key words: Poly (ADP-ribose) polymerase, tankyrases, IWR1, molecular docking, molecular dynamics, E-pharmacophore mapping.

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