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Identification of Potent and Selective SIRT7 Anti-Cancer Inhibitor via Structure-Based Virtual Screening and Molecular Dynamics Simulation

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Abstract : Background: Computational medicinal chemistry approaches are used for designing and identifying new drug-like molecules, predicting properties and pharmacological activities, and optimizing lead compounds in drug development. SIRT7, a nicotinamide adenine dinucleotide (NAD+)-dependent deacylase which regulates aging, is an emerging target for cancer therapy with mounting evidence that SIRT7 downregulation plays important roles in reversing cancer phenotypes and suppressing tumor growth. Activation or altered expression of SIRT7 is associated with the progression and invasion of various cancers, including liver, breast, gastric, prostate, and non-small cell lung cancer. Objectives: The goal of this work was to identify potent and selective bioactive candidate inhibitors of SIRT7 by in silico screening of small molecule compounds obtained from Nigella sativa (N. sativa). Methods: SIRT7 structure was retrieved from The Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB), and its active site was identified using CASTp and metaPocket. Molecular docking simulation was performed with PyRx 0.8 virtual screening software. Drug-likeness properties were tested using SwissADME and pkCSM. In silico toxicity was evaluated by Osiris Property Explorer. Bioactivity was predicted by Molinspiration software. Antitumor activity was screened for Prediction of Activity Spectra for Substances (PASS) using Way2Drug web server. Molecular dynamics (MD) simulation was carried out by Desmond v3.6 package. Results: A total of 159 bioactive compounds from the N. Sativa were screened against the SIRT7 enzyme. Five bioactive compounds: chrysin (CID:5281607), pinocembrin (CID:68071), nigellidine (CID:136828302), nigellicine (CID:11402337), and epicatechin (CID:72276) were identified as potent SIRT7 anti-cancer candidates after docking score evaluation and applying Lipinski's Rule of Five. Finally, MD simulation identified Chrysin as the top SIRT7 anti-cancer candidate molecule. Conclusion: Chrysin, which shows a potential inhibitory effect against SIRT7, can act as a possible anti-cancer drug candidate. This inhibitor warrants further evaluation to check its pharmacokinetics and pharmacodynamics properties both in vitro and in vivo.

Keywords : SIRT7, antitumor, molecular docking, molecular dynamics simulation
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