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Petchicine, a novel human DNMT enzyme inhibitor isolated from Sri Lankan medicinal plant: An *in-silico* approach

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The genetic information of humans has been regulating by various epigenetic mechanisms, which are stable and reversible. DNA methyltransferase (DNMT) is an enzyme that methylates the fifth carbon of the cytosine residue in DNA. Therefore, the methylated DNA interacts with the chromatins through the methyl-binding proteins, which leads to a cancer state. Many recent studies prove that inhibition of DNMT contributes to control cancer growth. Therefore, DNMT inhibitors have been considered as developed anticancer agents. The studies on the inhibition of the DNMT enzyme are an up-and-coming developing area for cancer therapy. Azacitidine is an approved DNMT inhibitor by the Food and Drug Administration. This work focuses on studying the impact of Azacitidine on the stability of the DNMT through computational techniques and, by performing the comparative study, suggest a new potent compound to inhibit the DNMT enzyme. These techniques can be used to investigate atomic-level descriptions of drug binding sites and how the DNMT inhibitors change the enzyme's active site. The crystal structure of the DNMT enzyme was downloaded from the Protein Data Bank, and the structure of Azacitidine was optimized by CBS-QB3 method using the G09W package. The non-toxic new compounds, Petchicine and Ouregidione, were obtained from the Sri Lanka flora database. The docking studies followed by molecular dynamics simulation were carried out to perform trajectory analysis. The results of RMSD, Rg, and hydrogen bond analysis are used to compare the behavior of the DNMT-Petchicine and DNMT-Ouregidione with the DNMT-Azacitidine complex in the aqueous environment. The results reveal that all the DNMT-inhibitor complexes attain a stable conformation during the simulation time. However, the results clearly show that the new compound Petchicine is more effective than the reference inhibitor Azacitidine; therefore, further investigations on Petchicine in future clinical trials would yield more promising results in the treatment of epigenetically caused cancer.

Keywords: Epigenetic modification, DNA methyltransferase, Azacitidine, Sri Lanka flora database

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