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Identification of Analogues to EGCG for the Inhibition of HPV E7: A Fundamental Insights through Structural Dynamics Study

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Abstract : High risk human papillomaviruses are highly associated with the carcinoma of the cervix and the other genital tumors. Cervical cancer develops through the multistep process in which increasingly severe premalignant dysplastic lesions called cervical intraepithelial neoplastic progress to invasive cancer. The oncoprotein E7 of human papillomavirus expressed in the lower epithelial layers drives the cells into S-phase creating an environment conducive for viral genome replication and cell proliferation. The replication of the virus occurs in the terminally differentiating epithelium and requires the activation of cellular DNA replication proteins. To date, no suitable drug molecule is available to treat HPV infection whereas identification of potential drug targets and development of novel anti-HPV chemotherapies with unique mode of actions are expected. Hence, our present study aimed to identify the potential inhibitors analogous to EGCG, a green tea molecule which is considered to be safe to use for mammalian systems. A 3D similarity search on the natural small molecule library from natural product database using EGCG identified 11 potential hits based on their similarity score. The structure based docking strategies were implemented in the potential hits and the key interacting residues of protein with compounds were identified through simulation studies and binding free energy calculations. The conformational changes between the apoprotein and the complex were analyzed with the simulation and the results demonstrated that the dynamical and structural effects observed in the protein were induced by the compounds and indicated the dominance to the oncoprotein. Overall, our study provides the basis for the structural insights of the identified potential hits and EGCG and hence, the analogous compounds identified can be potent inhibitors against the HPV 16 E7 oncoprotein.

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