Biomedical Data Mining

Extended Abstract

Molecular interaction studies of Deguelin and its derivatives with Cyclin D1 and Cyclin E in cancer cell signaling pathway: The computational approach

K Venkateswara Swamy

Abstract

Deguelin is a major active ingredient and principal component in several plants and it is a potential molecule to target proteins of cancer cell signaling pathway. As a complex natural extract, deguelin interacts with various molecular targets to exert its anti-tumor properties at nanomolar level. It induces cell apoptosis by blocking anti-apoptotic pathways, while inhibiting tumor cell multiplication and malignant transformation through p27-cyclin-E-pRb-E2F1- cell cycle control and HIF-1alphaVEGF antiangiogenic pathways. In silico studies of deguelin and its derivatives is performed to explore interactions with Cyclin D1 and Cyclin E to understand the molecular insights of derivatives with the receptors. Deguelin and its derivatives are minimized by Avogadro to achieve stable conformation. All docking simulation are performed with AutoDockVina and virtual screening of docked ligands are carried out based on binding energy and number of hydrogen bonds. Molecular dynamics (MD) and Simulation of Cyclin D1 and Cyclin E1 is performed for 100 ns and stable conformation is obtained at 78 ns and 19 ns respectively. Ligands thus obtained from docking studies may be probable target to inhibit cancer cell signaling pathways.

Introduction

In spite of extensive research on cancer and its cellular pathways, target identification and drug development, cancer still remains the major cause of death in economically developing and developed countries. Progression through the cell cycle checkpoints is regulated by complex interactions of cyclin and cyclin-dependent kinases (CDKs). One such cell cycle pathway, is well studied and has been shown to be abnormal in large number of tumors. The pRb/p16/cyclin D1 cell cycle control pathway as it is a part of CDK. CDKs contain two subunits, one is catalytic Cdk subunit and another is regulatory cyclin subunit that activate Cdk. Each phase of the cell cycle has a unique profile of cyclin-Cdk activity. Two types of cyclin-Cdks regulate the transportation of mammalian cells from quiescence into S phase of cell cycle: the D-type cyclins, which activates Cdk4/6, and cyclin E, which activates Cdk.

Cyclin D1 is an important regulator of cell cycle progression and can function as a transcriptional co-regulator. Cyclin D1 induction of cell migration is CDK-dependent function. Amplification or rearrangement of cyclin D1 gene-located on the chromosome 11q13, as well as overexpression of cyclin D1 protein has been described in a wide spectrum of human cancers such as squamous cell carcinomas of head and neck, esophagus, tongue and larynx and carcinomas of uterine cervix, astrocytoma's, non-small-cell lung cancers and soft tissue sarcomas. Apart from cyclin D1, cyclin E is also extensively studied in many cancers like carcinomas (breast, lung cervix, endometrium, and GI tract), lymphoma, leukemia, sarcomas and adrenocortical tumors. Cyclin E-CDK2 catalytic activity is required to down-regulate p27 protein. Forced expression of p27 Kip1 in proliferating cells arrests the cell cycle. CDK4 and CDK6, which is associated with cyclin D and CDK2 which associates with cyclin E, are rate limiting for progression through G1 and into S-phase of the vertebrate cell cycle. In contrast, cyclin E-Cdk2 deregulation leads to development of cancer.

K Venkateswara Swamy
Dr. D Y Patil Biotechnology and Bioinformatics Institute, India, E-mail: k.swamy@dpu.edu.in

Deguelin is a natural retinoid extracted from several plants species, including Derris trifoliata, Mundulea sericea and Tephrosin veogelii and has shown great potential as a cancer chemo-preventive and therapeutic agent for cancer. Research indicates that deguelin on animal models of mice, rat and mouse has effectively reduced the incidence of chemically induced skin tumors, mammary tumors, colonic aberrant crypt foci and pre-neoplastic lesion formation in mammary gland in organotypic culture. Deguelin induces apoptosis in association with the down regulation of cyclin D1, p21, pRb and regulates the G1/S and G2/M checkpoint. Cell cycle abnormalities are important feature of the procession of human cancers. Deguelin has been found to regulate cell cycle in colon cancer cells by stimulating p27 expression. Cyclin D1 and cyclin E is dramatically downregulated with treatment of deguelin.

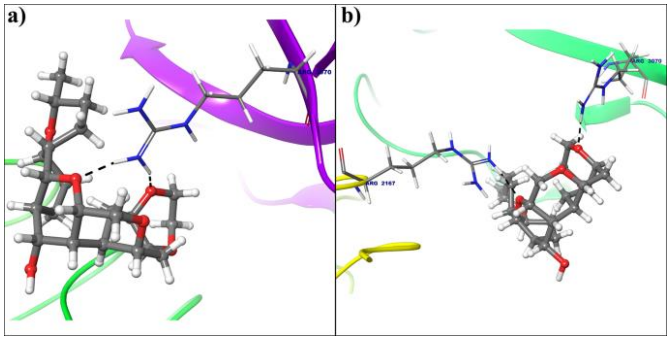
Thus, in the light of the reports stated above, it is evident that deguelin has shown promising chemopreventive and therapeutic activities in diverse types of cancer. Our study shows that, interaction of deguelin and its derivatives with cyclin D1 and cyclin E, to understand molecular insights in to cell cycle arrest. The effectiveness of deguelin can be enhanced through designing its derivatives by applying advanced computational approaches like molecular modeling, docking, dynamics and simulation for initial screening of leads. Molecular Docking calculates the binding energy, which is crucial to interpret the biological activity of ligand molecules. Molecular dynamic simulation (MDS) is a computer simulation technique, used to monitor and evaluate the physical movements of atoms and molecules. MDS permitted us to measure flexibility, rigidity and secondary structure prediction in terms of gain or loss during the simulation time. At different time step of simulation, conformational flexibility of a receptor alter its interaction with ligand, because convergence of amino acid pattern.

Results and Discussion

Virtual screening and energy minimization PubChem database is searched to obtain compounds having structural similarity with deguelin. The search showed 181 compounds to have 95% **similarity with** deguelin. Deguelin and its 181 derivatives are energy minimized using Steepest Descent method and Universal Force Field (UFF) and all the minimized compounds are subjected to the docking calculations with cyclin D1 and cyclin E receptor.

Sequence analysis

Cyclin D1 crystal structure [PDB ID: 2W96 (Resolution: 2.30A°), 2W99 (Resolution: 2.80A°), 2W9Z (Resolution: 2.45A°) and 2W9F (Resolution: 2.85A°)] are downloaded and Multiple Sequence Alignment (MSA) is performed. It is observed that the inhibitory site residues are conserved in all the structures. The alignment shows that except for residue number 169, all others residues are identical (Fig. 1). Asp169Ala mutation is observed among three structures (2W96 to 2W99 and 2W9Z). Apart from existing structures another mutation absorbed at same position Asp169Phe in 2W96 and 2W9F.



Conclusion

The present research describes the result of screening and identification of potent anti-cancerous deguelin and its derivatives, targeted towards a key receptors namely cyclin D1 and cyclin E in cell signaling pathway. Screening of deguelin derivatives from PubChem database revealed 181 derivatives through molecular property filter. The potency and efficacy of

the successfully screened deguelin derivatives were further analyzed by performing molecular docking analysis. It was noticed that 24 derivatives were docked successfully with cyclin D1 and 5 derivatives with cyclin E receptor. Among them Deg-32, Deg-40 and Deg-49 were ranked higher as compared to deguelin as the most potent inhibitor. The calculated binding free energy of deguelin is notably weaker towards cyclin E receptor than cyclin D1. The result of MD simulation revealed least RMSD values for cyclin D1 and cyclin E as a stable conformation at solvent system and the docking validation was done after simulation with dynamically stable conformation suggesting that Deg-32 shows more affinity towards stable conformation of cyclin D1 and cyclin E. Thus, the present work makes a foundation for the development of Deg-32 as a potent anti-cancerous drug acting to inhibition of cyclin D1 and cyclin E.

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K Venkateswara Swamy
Dr. D Y Patil Biotechnology and Bioinformatics Institute, India, E-mail: k.swamy@dpu.edu.in