

Virtual screening, molecular docking, MD simulation, MMPBSA, and DFT analysis of marine drugs in search of molecules effective against KRAS mutation

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Marine bioactive compounds have been showing diversified bioactivities such as antifungal, antimicrobial, anticancer, and antiviral. Mutations of KRAS G12C and G12D protooncogenes are responsible for colorectal, lung, and pancreatic cancers. KRAS G12C and G12D inhibitors sotorasib, MRTX 1133, and adagrasib showed good anticancer potential. In this research, we have screened 2000 marine bioactive compounds from marine database and 1699 molecules show highest probability as drug like structure. Selected marine compounds have been molecular docked against KRAS G12C and G12D using sotorasib and MRTX 1133 as standard structures. In case of KRAS G12C inhibition, Halenaquinone, xestoquinone, halenaquinol, and sotorasib show good docking scores of -11.7 kcal/mol, -11.6 kcal/mol, 11.5 kcal/mol, and -9.1 kcal/mol, respectively. In case of KRAS G12D inhibition Pseudane V, 1,6,10-trihydroxy-8-methyltracene-5,12-dione, Methylaplysinopsine, and MRTX 1133 show good docking scores of -11.0 kcal/mol, -9.9 kcal/mol, and 9.7 kcal/mol, and -10.2 kcal/mol, respectively. MD simulation and MMPBSA analysis data show that RMSD, RMSF, SASA, Rg and hydrogen bond analysis reflect the structural integrity and stability of drug-receptor complex. FMO analysis shows that Xestoquinone and 1,6,10-trihydroxy-8-methyltracene-5,12-dione represent soft molecules effective against KRAS G12C and G12D, respectively. This research confirmed the potential of marine ecosystem in the management of cancer by targeting KRAS mutations.

Keywords: Marine bioactive compounds, KRAS, Molecular docking, MD simulation, DFT