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Evaluation of binding and inhibition mechanism of dietary phytochemicals with human kinase and its implication to human health

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Kinase are important enzymes of signalling, has recently gained attention as a potential drug target due to its involvement in various types of cancers and other inflammatory diseases. In the present study, we have investigated binding affinity of various dietary phytochemicals including, ursolic acid, capsaicin, DL-α tocopherol acetate, quercetin, vanillin, citral, ellagic acid, limonin and simvastatin with sphingosine kinase 1 (SPhK1) and pyruvate dehydrogenase kinase 3 (PDK3) towards implications in anticancer therapy. Docking studies revealed that all these compounds bind to the active site cavity located in the kinase domain with varying affinities. *In silico* observations were further corroborated with fluorescence binding and isothermal titration calorimetric measurements. Among all compounds, quercetin, ellagic acid and capsaicin bind to these kinaseswith an excellent affinity. ATPase inhibition assay was conducted for ellagic acid, quercetin and capsaicin further revealed a significant inhibition in the activity of SphK1 and PDK3 with the IC_{50} values in micromolar range. Binding mechanism of quercetin and ellagic acid was assessed by molecular docking and molecular dynamics simulation studies for 100 ns in detail. We found that quercetin and ellagic acid act as lipid substrate competitive inhibitor, and it interacts with important residues of active-site pocket through hydrogen bonds and various other stabilizing interactions. Quercetin and ellagic acid form a stable complex with PDK3 and SphK1 without inducing any significant conformational shift in the protein structure. In conclusion, this study indicates that quercetin, ellagic acid and capsaicin act as potent inhibitors of SphK1 and PDK3; being quercetin as the best inhibitor by interacting directly with the substrate binding pocket. Hence, targeting SphK1 and PDK3 by these natural compounds can be a smart therapeutic approach to manage the clinical manifestations of cancer and other SphK1 and PDK3 associated diseases.

Keywords: Sphingosine kinase 1;Phytochemicals; Pyruvate dehydrogenase kinase 3; Anticancer therapy; Kinase inhibitor; MD simulation; Molecular docking; Drug design and discovery