Targeting pyruvate dehydrogenase kinase signalling in the development of effective cancer therapy: A combined computational and experimental approach

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Abstract

Pyruvate is irreversibly decarboxylated to acetyl coenzyme A by mitochondrial pyruvate dehydrogenase complex (PDC). Decarboxylation of pyruvate is considered a crucial step in cell metabolism and energetics. The cancer cells prefer aerobic glycolysis rather than mitochondrial oxidation of pyruvate. This attribute of cancer cells allows them to sustain under indefinite proliferation and growth. Pyruvate dehydrogenase kinases (PDKs) play critical roles in many diseases because they regulate PDC activity. Design and development of potential pyruvate dehydrogenase kinase 3 (PDK3) inhibitors have gained attention because of their possible therapeutic uses in cancer therapy. In the present study, the binding affinity of naturally occurring alkaloids, hordenine, vincamine, tryptamine, cinchonine, artemisinin and colcemid was measured with PDK3. The molecular docking and fluorescence binding studies suggested that all these compounds show a considerable binding affinity for PDK3 which was further complemented by isothermal titration calorimetric measurements. These compounds bind to PDK3 with an admirable binding affinity and forms numerous interactions with the residues of active site. Molecular dynamics simulation studies show the formation of a stable complex of PDK3-natural compounds. Our findings suggest that natural products could be implicated as a scaffold for designing potent anticancer molecules with PDK3 inhibitory potential. We propose to develop potential PDK3 inhibitors that may provide a better treatment for cancer resistance and other PDK3 related pathological complications.

Keywords: Kinase inhibitors, Anticancer therapy; pyruvate dehydrogenase kinase; MD simulation; Molecular docking; Drug design and discovery, Drug resistance

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