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Identification of hordenine as a potential inhibitor of pyruvate dehydrogenase kinase 3

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Design and development of potential pyruvate dehydrogenase kinase 3 (PDK3) inhibitors has gained attention because of their possible therapeutic uses in lung cancer therapy. In the present study, the binding affinity of naturally occurring alkaloids, hordenine, vincamine, tryptamine, cinchonine, and colcemid was measured with PDK3. Molecular docking and fluorescence binding studies suggested that all these compounds show considerable binding affinity for PDK3. Among them, the affinity of hordenine to the PDK3 was excellent (K=106 M-1) which was further complemented by isothermal titration calorimetric measurements. Molecular docking study shows that hordenine binds in the active site pocket of PDK3 and forms a significant number of non-covalent interactions with functionally important residues. All-atom molecular dynamics (MD) simulation study suggested that the PDK3-hordenine complex is stabilized throughout the trajectory of 100ns and leads to fewer conformational changes. Enzyme inhibition studies showed that hordenine significantly inhibits the activity of PDK3 with an IC50 value of 5.4 µM. Furthermore, hordenine inhibited the proliferation of human lung cancer cells (A549 and H1299) with admirable IC50 value. In summary, our findings provide the basis for the therapeutic implication of hordenine and its derivatives in lung cancer and PDK3-related diseases after required in vivo validation.

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