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In silico identification of natural product inhibitors of HMG-CoA reductase

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Coronary heart diseases such as hypercholesterolemia along with cancer and AIDS are the most studied diseases in the world. Inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase) which is the rate determining enzyme in the cholesterol synthesizing mevalonate pathway has been proven to control serum cholesterol levels. At present, statins have been extensively used as a medication to lower the serum cholesterol level. They have HMG CoA like moiety hence act as competitive reversible inhibitors. It has been found that the use of statins results in certain side effects. Since hypercholesterolemia is a chronic condition needing lifelong therapy, the use of natural product-based drugs can be more beneficial. Therefore, in this study, natural product compounds isolated from various plants that are used as drugs for hypercholesterolemia in ayurvedic medicine have been investigated for their inhibitor activity against the enzyme applying molecular docking and molecular dynamics. HMG CoA reductase is a tightly associated tetramer with a bipartite active site. The crystal structure of HMG CoA reductase (PDB ID: 3CCZ) was retrieved from the RCSB PDB database. For the initial model, only chains A and B were retained while the remaining chains and all other non-standard residues were removed using Chimera. The stability of the model was investigated through a 100 ns molecular dynamic simulation. Subsequently, selected compounds were docked to the enzyme using the Autodock Vina algorithm in PyRx software. Several commercially available statins were considered as references. The complex with the highest negative binding affinity was studied with a 100 ns molecular dynamic simulation. Results revealed that reference molecules showed binding affinities ranging from -6.4 to -8.2 kcal/mol. Several natural product ligands show comparable binding affinities (>7.0 kcal/mol) to the references and show drug likeliness. Coclaurine emerge as a promising candidate for further studies making a stable complex, stabilized after 25 ns from the start of the simulation with the highest negative binding affinity of -7.6 kcal/mol with two significant hydrogen bonds and showing drug likeliness.

Keywords: Hypercholesterolemia, Natural product inhibitors, *in-silico* study

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A Computational Study of Cyclin-dependent Kinases 1 (CDK1) butyrolactone I complex and the Role of Mg Ion in the Active Site

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Cyclin-dependent kinases (CDK) 1, 2, 4, and 6 are the protein kinases that play a pivotal role in the cell cycle regulating of all eukaryotic organisms by phosphorylating proteins needed during the cell division cycle. Phosphorylation of protein kinase requires the assistance of a divalent metal ion, usually Mg^{2+} ion to facilitate the transfer of a phosphate group onto a particular residue (serine, threonine, or tyrosine) in a substrate. However, only CDK1 is required for the successful completion of the M-phase of the cell cycle. Therefore, inhibition of CDK1 is emerging as a drugable target for diseases caused by unregulated cell proliferation. Butyrolactone I is a