Exploring Marine Bioactive Compounds for targeting Novel Sphingolipid pathways: An In-silico approach

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Résumé

Sphingolipids are lipid mediators, which are categorized under the group of phospholipids. These are also known as lipid rafts, which play a significant role in signal transduction pathways. Some important metabolites are ceramides and sphingosine-1-phosphate (S1P), which are involved in various cellular processes including proliferation, apoptosis, cellular senescence, angiogenesis, and barrier protection. Imbalance in sphingolipid pathways leads to several diseases such as cancers, neurodegenerative diseases, inflammatory diseases, autoimmune disorders, and lysosomal storage disorders. Thus, there is a need for novel sphingolipid pathway modulators such as sphingosine kinase-1 blockers, ceramidase inhibitors etc. In recent times, marine natural products drug discovery has attracted considerable attention due to their unique chemical diversity and potential therapeutic considerations. Marine organisms such as algae, sponges, seagrasses, corals, tunicates, marine microorganisms etc., produce secondary metabolites that have proven activities including antioxidants, anti-inflammatory, neuroprotective, cardioprotective, immunomodulatory, antimicrobial effects etc. In this study, we have performed in-silico approaches such as molecular docking with high throughput virtual screening, standard precision, and extra precision for three proteins 4V24, 6MHM, and 8JHR which are involved in sphingolipid metabolism and the results were -16.186, -11.635, and -11.693 kcal/mol of each protein binding affinities with marine-based compounds. In addition, we carried out MM/GBSA for free binding energy calculations, Quantum mechanics with Density Functional Theory, ADME-T properties for drug-likeness, molecular dynamics etc. for all three proteins and to explore novel sphingolipid metabolism inhibitors by incorporating comprehensive marine natural products databases. The top common compounds for each of the three proteins include CMNPD18555 and CMNPD4741 respectively.

Mots-Clés: Marine natural products, drug discovery, molecular docking, sphingosine, ceramidase, CMNPD, seaweeds

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