Studi In Silico Aktivitas Metabolit Sekunder Invertebrata Laut Indonesia terhadap Penghambatan Transmembrane Protease Serine 2 dan Protein Spike SARS-CoV-2 Varian Omicron = In Silico Study of Secondary Metabolite Activity of Indonesian Marine Invertebrates on Inhibition of Transmembrane Protease Serine 2 and Spike Protein of SARS-CoV-2 Omicron Variant

Haviani Rizka Nurcahyaningtyas, author

Abstrak

Pandemi yang disebabkan oleh SARS-CoV-2 telah memicu situasi darurat kesehatan di seluruh dunia. Varian Omicron yang menyebar dengan cepat semakin mendesak pencarian terapi yang tepat untuk menghindari infeksi yang lebih berat. TMPRSS2 manusia dan protein spike SARS-CoV-2 varian Omicron diidentifikasi sebagai protein target melalui penapisan secara komputasi. Metode yang digunakan adalah penapisan virtual berbasis struktural; analisis prediksi absorption, distribution, metabolism, excretion, dan toxicity (ADMET); dan simulasi dinamika molekuler. Ligan uji yang digunakan adalah senyawa metabolit sekunder invertebrata laut Indonesia. Camostat dan nafamostat (ko-kristal) digunakan sebagai ligan pembanding terhadap penghambatan TMPRSS2 sedangkan mefloquine ligan pembanding terhadap Protein Spike. Berdasarkan hasil penambatan molekul, acanthomanzamine C (-9,75 kkal/mol) dan cortistatin G (-9,39 kkal/mol) memiliki aktivitas yang lebih baik terhadap penghambatan TMPRSS2 dibandingkan dengan camostat (-8,25 kkal/mol) dan nafamostat (-6,52 kkal/mol). Sebagai inhibitor protein spike SARS-CoV-2 varian Omicron, acanthomanzamine C (-9,19 kkal/mol) dan cortistatin J (-8,89 kkal/mol) juga menunjukkan penghambatan yang lebih baik dibandingkan dengan mefloquine (-6,34 kkal/mol). Ligan uji tersebut juga telah memenuhi seluruh kriteria ADMET yang ditetapkan. Dari hasil analisis simulasi dinamika molekuler menunjukkan pengikatan yang stabil senyawa ligan uji terhadap protein target setelah simulasi berjalan 60 nanodetik dan memiliki energi ikatan bebas MMGBSA dan MMPBSA yang lebih baik dibandingkan ligan pembanding diantaranya TMPRSS2–acanthomanzamine C (-28,2067; -24,6639 kkal/mol), TMPRSS2–cortistatin G (-29,9908; -24,8869 kkal/mol), protein spike–acanthomanzamine C (-45,1414; -27,8749 kkal/mol), dan protein spike–cortistatin J (-37,8537; -35,6439 kkal/mol). Hasil penelitian ini menunjukkan bahwa acanthomanzamine C, cortistatin G, dan cortistatin J merupakan senyawa hits sebagai kandidat terapi untuk infeksi SARS-CoV-2.

.....The pandemic caused by SARS-CoV-2 has triggered a global health emergency. The rapid spread of the Omicron variant has further intensified the urgency to search for appropriate therapies to prevent severe infections. The human TMPRSS2 and spike protein of the SARS-CoV-2 Omicron variant were identified as the target proteins through computational screening. The methods used are structure-based virtual screening; absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis; and molecular dynamics simulation. Bioactive marine invertebrates from Indonesia were employed as test ligands. Camostat and nafamostat (co-crystal) were utilized as reference ligands against TMPRSS2, whereas mefloquine was used as a reference ligand against spike protein. Following a molecular docking, acanthomanzamine C (-9,75 kcal/mol) and cortistatin G (-9,39 kcal/mol) had better activity against TMPRSS2 inhibition compared to camostat (-8,25 kcal/mol) and nafamostat (-6,52 kcal/mol). As inhibitors of spike protein of SARS-CoV-2

Omicron variant, acanthomanzamine C (-9,19 kcal/mol) and cortistatin J (-8,89 kcal/mol) also showed better inhibition compared to mefloquine (-6,34 kcal/mol). The test ligands have also met all the established ADMET criteria. The results of the molecular dynamics analysis showed stable binding of the test ligands to the target proteins after the initial 60 nanoseconds and had free binding energies of MMGBSA/MMPBSA that were better than the comparison ligands, including TMPRSS2–acanthomanzamine C (-28,2067; -24,6639 kcal/mol), TMPRSS2–cortistatin G (-29,9908; -24,8869 kcal/mol), spike protein–acanthomanzamine C (-45,1414; -27,8749 kcal/mol), and spike protein–cortistatin J (-37,8537; -35,6439 kcal/mol). These results indicate that acanthomanzamine C, cortistatin G, and cortistatin J are hits compounds as candidate therapies for SARS-CoV-2 infection.