Penggunaan Kembali Obat Menargetkan 3-Chymotrypsin-Like Protease SARS-CoV-2 menggunakan Pemodelan Farmakofor = Drug Repurposing Targeting SARS-CoV-2 3-Chymotrypsin-Like Protease with Pharmacophore Modelling

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Abstrak

Coronavirus Disease (COVID-19) merupakan pandemik penyakit global yang menyerang sistem pernapasan. Proses penemuan dan pengembangan obat baru untuk menanggulangi tingkat keparahan COVID-19 membutuhkan waktu yang lama. Mengingat banyaknya korban dalam pandemik ini, peneliti mencoba strategi menggunakan kembali obat (drug repurposing) yang telah disetujui FDA (Food and Drug Administration). Enzim 3CLpro (3-Chymotrypsin-Like Protease) berperan penting dalam replikasi dan transkripsi SARS-CoV-2. Penggunaan kembali obat dilakukan dengan pendekatan in silico menggunakan penapisan virtual berbasis farmakofor dari 95 ligan 3CLpro SARS-CoV-2 sebagai training set terhadap 1.328 molekul obat dari Pangkalan Data Obat FDA-approved dari BindingDB. Pembentukan model farmakofor, optimasi, dan penapisan virtual berbasis farmakofor dilakukan menggunakan LigandScout dan divalidasi dengan senyawa decoys dari A Directory of Useful Decoys: Enhanced (DUD-E). Metode tersebut divalidasi dengan nilai AUC100%, EF1%, EF5%, sensitivitas, dan spesifisitas. Optimasi model farmakofor yang digunakan untuk penapisan virtual menghasilkan tiga buah fitur farmakofor, yaitu Aromatic Ring (AR), Hydrogen Bond Acceptor (HBA), dan Hydrophobic (H). Senyawa kandidat (hits) yang memiliki kecocokan fitur farmakofor dengan ligan 3CLpro SARS-CoV-2 yaitu omeprazole, lansoprazole, docetaxel, silodosin, pyrvinium pamoate, ritonavir, mefloquine HCl, delavirdine mesylate, indapamide, dan lacosamide. Senyawa kandidat (hits) yang didapatkan berpotensi memiliki aktivitas terhadap 3CLpro SARS-CoV-2 sehingga dapat digunakan dalam pengobatan COVID-19.

.....Coronavirus Disease (COVID-19) is a pandemic disease that attacks the respiratory system. The process of discovering and developing new drugs to cure the severity of COVID-19 could take long time. The strategy is to use drug repurposing on FDA-approved drugs. 3CLpro (3-Chymotrypsin-Like Protease) is an enzyme that plays an important role in the replication and transcription of SARS-CoV-2. Drug repurposing was carried out with in silico approach using pharmacophore-based virtual screening of 95 ligands of SARS-CoV-2 3CLpro as training set, screened on 1.328 drug molecules from FDA-approved Drug Database from BindingDB. Pharmacophore model, its optimization, and its virtual screening were performed using LigandScout and validated with decoys from DUD-E (A Directory of Useful Decoys: Enhanced). The method was validated with AUC100%, EF1%, EF5%, sensitivity, and specificity. The optimization of pharmacophore model resulted in three pharmacophore features, which are Aromatic Ring (AR), Hydrogen Bond Acceptor (HBA), and Hydrophobic (H). Hits compounds that matched the pharmacophore features of SARS-CoV-2 3CLpro ligands are omeprazole, lansoprazole, docetaxel, silodosin, pyrvinium pamoate, ritonavir, mefloquine HCl, delavirdine mesylate, indapamide, and lacosamide. These hits compounds are potentially active against SARS-CoV-2 3CLpro and can be repurposed for COVID-19 treatment.