Drug Repurposing Menargetkan Non-Structural Protein 3 dan Non-Structural Protein 13 SARS-CoV-2 Menggunakan Pemodelan Farmakofor = Drug Repurposing against SARS-CoV-2 Non-Structural Protein 3 and Non-Structural Protein 13 through Pharmacophore Modeling Approach

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Abstrak

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) merupakan agen penyebab Coronavirus Disease 2019 (COVID-19) yang telah menginfeksi hampir dua ratus juta orang dan menyebabkan hampir empat juta kematian di dunia. Saat ini, belum ada obat yang spesifik ditemukan untuk virus ini. Drug repurposing merupakan salah satu alternatif strategi pengembangan obat di masa pandemi. Pada penelitian ini, non-structural protein 3 (NSP3) dan non-structural protein 13 (NSP13) SARS-CoV-2, yang mengkode papain-like protease dan helikase, terpilih sebagai target potensial yang berperan penting dalam replikasi virus. Drug repurposing berbasis pemodelan farmakofor dilakukan menggunakan program LigandScout. Ligan kokristal NSP3 dan NSP13 SARS-CoV-2 dari Protein Data Bank dipilih sebagai training set. Sebelumnya, sekuens protein disejajarkan dengan Clustal Omega dan interaksi protein-ligan diidentifikasi dengan Protein-Ligand Interaction Profiler. Model farmakofor divalidasi menggunakan test set yang terdiri dari ligan terpilih sebagai senyawa aktif dan decoy dari A Database of Useful Decoys-Enhanced sebagai senyawa inaktif. Model farmakofor NSP3 pada akhirnya tidak terbentuk karena sedikitnya ligan yang tersedia. Model farmakofor NSP13 yang memiliki satu cincin aromatik (AR), satu daerah hidrofobik (H), satu akseptor ikatan hidrogen (HBA), dan satu donor ikatan hidrogen (HBD) dengan penambahan feature tolerance sebesar 0,15 Å dan feature weight sebesar 0,1 pada fitur AR, H, dan HBA menghasilkan nilai AUC100%, EF1%, EF5%, sensitivitas, dan spesifisitas sebesar 0,83; 21,2; 8,8; 0,792; dan 0,790. Model ini digunakan sebagai kueri penapisan terhadap obat yang telah disetujui FDA dari The Binding Database. Ticarcillin, sulfisoxazole, lacosamide, sulfathiazole, cefaclor, penicillin G, cephalexin, carbenicillin, atenolol, dan tolazoline diperoleh sebagai senyawa kandidat dengan pharmacophore-fit score tertinggi. .....Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causal agent of Coronavirus Disease 2019 (COVID-19), has infected almost two hundred millions of people and caused nearly four millions of deaths worldwide. Currently, no treatment has been identified to be effective against the virus. In the outbreak, drug repurposing emerges as a promising strategy to develop efficient therapeutics. This study selected SARS-CoV-2 non-structural protein 3 (NSP3) and non-structural protein 13 (NSP13), that encodes papain-like protease and helicase, respectively, as potential targets based on their crucial role in virus replication. Drug repurposing was carried out by LigandScout pharmacophore modeling using SARS-CoV-2 NSP3 and NSP13 co-crystallized ligands from Protein Data Bank as training set. Prior to that, crystal structures were aligned by Clustal Omega and analyzed by Protein-Ligand Interaction Profiler for interaction profiling. Generated pharmacophore model was validated by a test set consisting of above-mentioned ligands as actives and A Database of Useful Decoys-Enhanced decoys as inactives. Unfortunately, NSP3 model cannot be generated due to insufficient ligands. NSP13 model that has one aromatic ring (AR), one hydrophobic area (H), one hydrogen bond acceptor (HBA), and one hydrogen bond

donor (HBD) features with 0,15 Å feature tolerance and 0,1 feature weight additions on AR, H, and HBA resulted AUC100%, EF1%, EF5%, sensitivity, and specificity of 0,83; 21,2; 8,8; 0,792; and 0,790. This model was chosen for screening against FDA-approved drugs from The Binding Database. Ticarcillin, sulfisoxazole, lacosamide, sulfathiazole, cefaclor, penicillin G, cephalexin, carbenicillin, atenolol, and tolazoline were obtained as hits with the highest pharmacophore-fit score.