

# Uji In Silico dan In Vitro Penghambatan Ekstrak Senyawa Herbal terhadap Aktivitas Papain-Like Protease (PLpro) Rekombinan dari SARS-CoV-2 = In Silico dan In Vitro Assay of Herbal Extract Chemicals Against the Activity of Recombinant SARS-CoV-2 Papain-Like Protease (PLpro)

Fairuz Andini Fatiningtyas, author

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## Abstrak

COVID-19 yang disebabkan oleh virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) menjadi pandemi di seluruh dunia pada 2020 hingga 2022. Dari agen terapi yang direkomendasikan, nirmatrelvir dan ritonavir aktif bekerja langsung menargetkan virus. Kemudian berkembang berbagai peluang pengembangan obat yang menargetkan virus secara langsung, dan salah satu target yang menarik adalah papain-like protease (PLpro), yaitu protein yang berperan penting dalam replikasi virus. Beberapa bahan alam yang berpotensi diteliti aktivitas penghambatannya terhadap PLpro adalah bunga telang (*Clitoria ternatea*), daun belimbing manis (*Averrhoa carambola* L.), dan jamblang (*Syzygium cumini*). Tujuan dari penelitian ini ialah memprediksi aktivitas penghambatan PLpro kandungan bunga telang (*Clitoria ternatea*), daun belimbing manis (*Averrhoa carambola* L.), dan jamblang (*Syzygium cumini*) yang dilakukan dengan metode penambatan molekul (molecular docking) secara in silico, dan dilanjutkan dengan uji in vitro. Metode penambatan molekul divalidasi dengan metode redocking dan didapatkan nilai RMSD 0,728 Å yang berarti metode valid (RMSD<2,0 Å). Uji penambatan molekul ketiga tanaman tersebut menunjukkan hasil adanya kandungan senyawa yang berpotensi untuk menghambat aktivitas PLpro. Ligan dengan nilai afinitas ikatan ternegatif dari masing-masing tanaman adalah asam folat (jamblang) dengan nilai -8,3 kcal/mol; petunidin 3-glucoside (telang) dengan nilai -7,1 kcal/mol; dan (-)-Epicatechin 3-O-gallate (belimbing manis) dengan nilai -8,6 kcal/mol. Hasil uji in silico dikonfirmasi dengan uji in vitro yang dilakukan dengan fluorescence-based inhibitory assay menggunakan PLpro sebagai protein target, substrat Z-RLRGG-AMC, serta inhibitor kontrol GRL0617. Hasil uji in vitro mendapatkan nilai IC<sub>50</sub> GRL0617 3,38 M. Ekstrak herbal dengan persentase inhibisi terbaik adalah ekstrak tunggal jamblang dengan nilai 66,10%.

.....COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus became the cause of the global pandemic from 2020 until 2022. Among currently recommended therapeutic agents, nirmatrelvir and ritonavir actively works by directly targeting the virus. This leads to various opportunities for developing drugs that acts directly on the structure of the virus. One interesting target for such drugs is the papain-like protease (PLpro) which is a protein that plays a significant role in viral replication. Several natural sources which has potential for their inhibitory activity against PLpro to be studied are butterfly pea (*Clitoria ternatea*), star fruit (*Averrhoa carambola* L.) and Java plum (*Syzygium cumini*). This study aimed to predict the inhibitory activity against PLpro possessed by the chemical contents of butterfly pea (*Clitoria ternatea*), star fruit (*Averrhoa carambola* L.) and Java plum (*Syzygium cumini*) through molecular docking and in vitro assay. Prediction of inhibitory activity against PLpro was done using molecular docking. The molecular docking method was validated using redocking method and RMSD score of 0.728 Å was received. This indicated that the docking method was valid (RMSD<2.0 Å). Molecular docking result showed that all three plants contain chemicals that have potential to inhibit PLpro activity. Ligands with the

lowest binding affinity from each plant are folic acid (Java plum) with a score of -8.3 kcal/mol; petunidin 3-glucoside (butterfly pea) with -7.1 kcal/mol; and (-)-Epicatechin 3-O-gallate (star fruit) with -8.6 kcal/mol. Results from in silico study were then confirmed through in vitro assay using fluorescence-based inhibitory assay using PLpro as target protein, Z-RLRGG-ACM as the substrate and GRL0617 as the control inhibitor. IC<sub>50</sub> concentration result of GRL0617 was 3,38 M. Herbal extract with the best inhibition percentage was found to be Java plum with an inhibition percentage of 66.10%.