FACULTY OF MEDICINE AND HEALTH SCIENCES

MUHAMMADIYAH UNIVERSITY OF MAKASSAR

Khadijah Zumratul Rabbani[1], Dito Anurogo[2]. Juliani Ibrahim[3], Ferdinan[4]

[1]Student of Faculty of Medicine and Health Sciences Muhammadiyah University of Makassar, Class of 2022/Email: khadijahzr35@med.unismuh.ac.id

[2]Lecturer of Faculty of Medicine and Health Sciences Muhammadiyah University of Makassar

[3]Lecturer of Faculty of Medicine and Health Sciences Muhammadiyah University of Makassar

[4]Lecturer of Departement of Al-Islam Kemuhammadiyahan Faculty of Medicine and Health Sciences Muhammadiyah University of Makassar.

"MOLECULAR DOCKING OF FLAVONOIDS FROM CARICA PAPAYA LEAVES WITH PPARα AS A POTENTIAL TARGET FOR DYSLIPIDEMIA THERAPY"

ABSTRACT

Background: Dyslipidemia is a major risk factor for cardiovascular disease. The nuclear receptor PPARα is known to play an important role in the regulation of lipid metabolism and is a major target in the development of dyslipidemia therapy. Flavonoid compounds have potential as natural modulators of PPARα, but computational studies that systematically compare their interaction potential are still limited. **Objective:** This study aimed to evaluate the potential of five flavonoid compounds (quercetin, kaempferol, luteolin, apigenin, and isorhamnetin) as PPARα ligands in silico, and to compare them with the reference ligand fenofibric acid. **Methods:** Molecular docking simulations were performed using Pyrx software with the AutoDock Vina algorithm. The target protein, PPARα (PDB ID: 6LX4), was prepared through structure optimization and Gasteiger charge addition. The docking procedure was validated by re-docking fenofibric acid against its crystal structure. The main parameters analyzed included the binding affinity value and the ligand-residue interaction pattern in the active site. **Key results:** Re-docking validation yielded an RMSD value of 1.263 Å, demonstrating the reliability of the method. Fenofibric acid exhibited the highest affinity (–9.4 kcal/mol) and interacted with the key residue HIS A:440 as well as a network of hydrophobic residues. Among flavonoids, apigenin showed the strongest predicted affinity (–8.5 kcal/mol), followed by luteolin (–8.4 kcal/mol) and quercetin (–8.3 kcal/mol). Apigenin and kaempferol exhibited (relatively weak) interactions with residue HIS A:440, while luteolin, quercetin, and isorhamnetin bound via alternative residue patterns, such as SER A:280 and THR A:279. **Interpretation:** These results indicate that flavonoids, especially apigenin, have the potential to interact with the active site of PPARα. The interaction with residue HIS A:440 showed a similar binding mode to the reference ligands, although the interaction strength was lower. Differences in

binding patterns of other flavonoids suggest the possibility of different modulation modes, which cannot be interpreted as direct functional activation. **Limitations:** this study is static and computational. The affinity values of the docking results do not represent direct evidence of agonistic activity, and differences in scores between flavonoids are within the uncertainty limits of the docking method. **Validation plan:** to further evaluate the biological implications, further studies are needed in the form of molecular dynamics simulations to assess the stability of the ligand-receptor complex and in vitro functional assays, such as reporter gene assays in cell systems expressing PPARα.

Keywords: PPARα, dyslipidemia, *Carica papaya* leaves

FAKULTAS KEDOKTERAN DAN ILMU KESEHATAN

UNIVERSITAS MUHAMMADIYAH MAKASSAR

Khadijah Zumratul Rabbani[1], Dito Anurogo[2]. Juliani Ibrahim[3], Ferdinan[4]

[1]Mahasiswa Fakultas Kedokteran dan Ilmu Kesehatan Universitas Muhammadiyah Makassar, Angkatan 2022/email: khadijahzr35@med.unismuh.ac.id

[2]Dosen Fakultas Kedokteran dan Ilmu Kesehatan Universitas Muhammadiyah Makassar

[3]Dosen Fakultas Kedokteran dan Ilmu Kesehatan Universitas Muhammadiyah Makassar

[4]Dosen Departemen Al-Islam Kemuhammadiyahan Fakultas Kedokteran dan Ilmu Kesehatan Universitas Muhammadiyah Makassar.

"MOLECULAR DOCKING SENYAWA FLAVONOID DAUN *CARICA PAPAYA* TERHADAP PPARα SEBAGAI TARGET POTENSIAL TERAPI DISLIPIDEMIA"

ABSTRAK

Latar Belakang: Dislipidemia merupakan faktor risiko utama penyakit kardiovaskular. Reseptor nuklir PPARα diketahui berperan penting dalam regulasi metabolisme lipid dan menjadi target utama dalam pengembangan terapi dislipidemia. Senyawa flavonoid memiliki potensi sebagai modulator alami PPARα, namun studi komputasional yang secara sistematis membandingkan potensi interaksinya masih terbatas. **Tujuan:** Penelitian ini bertujuan untuk mengevaluasi potensi lima senyawa flavonoid (quercetin, kaempferol, luteolin, apigenin, dan isorhamnetin) sebagai ligan PPARα secara *in silico*, serta membandingkannya dengan ligan pembanding asam fenofibrate. **Metode:** Simulasi docking molekuler dilakukan menggunakan perangkat lunak Pyrx dengan algoritma AutoDock Vina. Protein target berupa PPARα (PDB ID: 6LX4) dipreparasi melalui optimasi struktur dan penambahan muatan Gasteiger. Prosedur docking divalidasi melalui re-docking fenofibric acid terhadap struktur kristalnya. Parameter utama yang dianalisis meliputi nilai afinitas pengikatan (*binding affinity*) dan pola interaksi ligan–residu pada situs aktif. **Hasil Utama:** Validasi re-docking menghasilkan nilai RMSD sebesar 1.263 Å, menunjukkan reliabilitas metode. Fenofibric acid menunjukkan afinitas tertinggi (–9,4 kcal/mol) dan berinteraksi dengan residu kunci HIS A:440 serta jaringan residu hidrofobik. Di antara flavonoid, apigenin menunjukkan prediksi afinitas terkuat (–8,5 kcal/mol), diikuti luteolin (–8,4 kcal/mol) dan quercetin (–8,3 kcal/mol). Apigenin dan kaempferol menunjukkan interaksi (relatif lemah) dengan residu HIS A:440, sedangkan luteolin, quercetin, dan isorhamnetin berikatan melalui pola residu alternatif, seperti SER A:280 dan THR A:279. **Interpretasi:** Hasil ini mengindikasikan bahwa flavonoid, khususnya apigenin, memiliki potensi untuk berinteraksi dengan situs aktif PPARα. Interaksi dengan residu HIS A:440

menunjukkan kemiripan mode ikatan dengan ligan pembanding, meskipun kekuatan interaksinya lebih rendah. Perbedaan pola pengikatan pada flavonoid lain mengisyaratkan kemungkinan mode modulasi yang berbeda, yang tidak dapat diinterpretasikan sebagai aktivasi fungsional secara langsung. **Keterbatasan:** Studi ini bersifat statis dan berbasis komputasi. Nilai afinitas hasil docking tidak merepresentasikan bukti langsung aktivitas agonistik, dan perbedaan skor antar flavonoid berada dalam batas ketidakpastian metode docking. **Rencana Validasi:** Untuk mengevaluasi implikasi biologis lebih lanjut, diperlukan studi lanjutan berupa simulasi dinamika molekuler untuk menilai stabilitas kompleks ligan–reseptor serta uji fungsional *in vitro*, seperti *reporter gene assay* pada sistem sel yang mengekspresikan PPARα.

Kata Kunci: PPARα, dyslipidemia, daun *Carica papaya*