Abstrak

STUDI POTENSI SENYAWA FLAVONOID TERPRENILASI TERHADAP RESEPTOR ALK DAN RET MELALUI PENDEKATAN *MOLECULAR DOCKING*

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Latar Belakang: *Anaplastic lymphoma kinase* (ALK) dan *rearranged during transfection* (RET) merupakan keluarga tirosin kinase yang teridentifikasi pada subset *non-small cell lung cancer* (NSCLC). Penggunaan obat inhibitor ALK dan RET pada jangka panjang seringkali mengembangkan mutasi resistensi dan menimbulkan permasalahan klinis dalam terapi NSCLC, sehingga upaya pencarian kandidat inhibitor baru perlu dikembangkan untuk mengoptimalkan terapi NSCLC. Flavonoid terprenilasi sebagai metabolit sekunder alami dilaporkan memiliki aktivitas antikanker karena sifat lipofilisitas yang tinggi dan afinitas yang baik dengan protein targetnya. Penelitian ini bertujuan untuk mengevaluasi potensi interaksi senyawa flavonoid terprenilasi dengan protein ALK dan RET melalui pendekatan *molecular docking*.

Metodologi: Penelitian ini dilakukan secara *in silico* yang terdiri tahap skrining *drug likeness* dan toksisitas senyawa flavonoid terprenilasi. Senyawa yang lolos kriteria kemudian dilakukan preparasi untuk selanjutnya ditambatkan pada protein ALK dan RET. Hasil kemudian dianalisis interaksi antara ligan dan protein, serta dibandingkan dengan kontrol positif.

Hasil Penelitian: Hasil skrining *drug likeness* dan toksisitas diperoleh enam senyawa kandidat terbaik, yaitu senyawa xanthoangelol D, derricidine, xanthoangelol J, lespeol, TB2, dan TB3. Hasil *molecular docking* terhadap protein ALK diperoleh nilai *binding affinity* berkisar antara -6,6 hingga -8,3 kkal/mol, yang menunjukkan pengikatan lebih lemah dibandingkan kontrol positifnya (-10,9 kkal/mol). Hasil penambatan pada protein RET berkisar antara -7,7 hingga -9,3 kkal/mol, yang menunjukkan pengikatan lebih baik dibandingkan kontrol positifnya (-5,8 kkal/mol).

Kesimpulan: Keenam senyawa flavonoid terprenilasi memiliki afinitas pengikatan yang lebih kuat terhadap protein RET dibandingkan ALK, serta berpotensi dikembangkan sebagai kandidat inhibitor RET yang lebih selektif pada NSCLC.

Kata kunci: Flavonoid terprenilasi, ALK, RET, NSCLC, antikanker, penambatan molekuler.

Abstract

STUDY OF THE POTENTIAL OF PRENYLATED FLAVONOID COMPOUNDS AGAINST ALK AND RET RECEPTORS USING A MOLECULAR DOCKING APPROACH

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Background: Anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET) are members of the tyrosine kinase family that are identified in a subset of non-small cell lung cancer (NSCLC). Long-term use of ALK and RET inhibitor leads to the development of resistance mutations, causing clinical problems in NSCLC therapy. Therefore, efforts to find new inhibitor candidates are required to optimize NSCLC treatment. Prenylated flavonoids, as natural secondary metabolites, have been reported to exhibit anticancer activity due to high lipophilicity and strong affinity for target proteins. This study aims to evaluate the interaction potential of prenylated flavonoid compounds with ALK and RET proteins using a molecular docking approach.

Methodology: This study involved drug-likeness screening and toxicity evaluation of prenylated flavonoid compounds. The compounds that met the screening criteria were prepared for binding studies with ALK and RET proteins. The results were analyzed for ligand-protein interactions and compared to positive controls.

Results: Drug likeness and toxicity screening identified six best candidate compounds, namely xanthoangelol D, derricidine, xanthoangelol J, lespeol, TB2, and TB3. Molecular docking against the ALK protein produced binding affinity values ranging from -6.6 to -8.3 kcal/mol, indicating weaker binding than the positive control (-10.9 kcal/mol). In contrast, docking against the RET protein resulted values ranging from -7.7 to -9.3 kcal/mol, indicating stronger binding than the positive control (-5.8 kcal/mol).

Conclusion: The six prenylated flavonoid compounds exhibited stronger binding affinity toward the RET protein than toward ALK, indicating their potential to be developed as more selective RET inhibitor candidates for NSCLC.

Keywords: Prenylated flavonoids, ALK, RET, NSCLC, anticancer, molecular docking.