

ABSTRAK

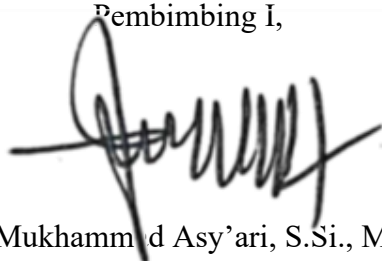
Inflamasi kronis merupakan kondisi patologis yang ditandai oleh aktivasi mediator inflamasi secara persisten, salah satunya melalui pelepasan *tumor necrosis factor- α* (TNF- α) yang dikatalisis oleh enzim *A Disintegrin and Metalloproteinase 17* (ADAM17). Karena perannya dalam regulasi TNF- α , ADAM17 menjadi target penting dalam pengembangan agen anti-inflamasi. Penelitian ini bertujuan mengevaluasi potensi senyawa terkait punicalagin sebagai inhibitor alami ADAM17 dengan marimastat sebagai inhibitor pembanding melalui pendekatan *in-silico* dan *in-vitro*. Analisis *in silico* menunjukkan bahwa seluruh senyawa terkait punicalagin diprediksi mampu berinteraksi kuat dan stabil dengan sisi aktif ADAM17, dengan energi interaksi berkisar antara -117,93 hingga -235,47 kJ/mol. Hasil skrining mengidentifikasi asam galat sebagai senyawa dengan energi interaksi terbaik (-235,47 kJ/mol), diikuti punicalin (-225,87 kJ/mol) dan punicalagin (-206,40 kJ/mol), sedangkan asam galat menunjukkan energi interaksi sebesar -139,51 kJ/mol. Marimastat sebagai inhibitor referensi memiliki energi interaksi paling kuat (-245,58 kJ/mol). Uji aktivitas enzim menunjukkan bahwa punicalagin dan asam galat menghambat aktivitas ADAM17 masing-masing sebesar 93,76% dan 76,69% pada konsentrasi 12,5 μ M, sedangkan marimastat menghasilkan inhibisi 90,37% pada 0,1 μ M. Nilai IC_{50} marimastat, punicalagin, dan asam galat berturut-turut sebesar 0,0075 μ M, 0,0689 μ M, dan diprediksi <0,004 μ M terhadap sisi aktif ADAM17. Analisis *molecular dynamics*, mekanika kuantum, dan spektroskopi UV-Vis mengonfirmasi kestabilan interaksi serta perubahan profil elektronik senyawa. Secara keseluruhan, integrasi hasil *in-silico* dan *in-vitro* menunjukkan bahwa marimastat, punicalagin dan asam galat diprediksi memiliki potensi sebagai inhibitor ADAM17 dengan kecenderungan mekanisme inhibisi kompetitif, non-kompetitif, dan campuran.

Kata Kunci: TNF- α ; Senyawa terkait punicalagin; Inhibitor ADAM17; Pendekatan komputasi molekuler; Uji aktivitas enzim *in vitro*

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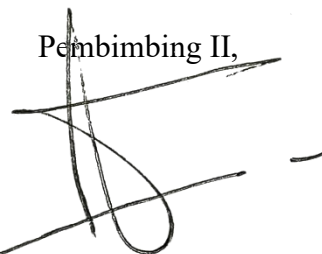
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ABSTRACT

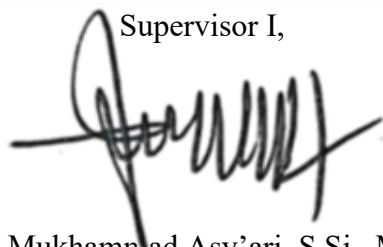
Chronic inflammation is a pathological condition characterized by the persistent activation of inflammatory mediators, including the release of tumor necrosis factor-alpha (TNF- α), which is catalyzed by A Disintegrin and Metalloproteinase 17 (ADAM17). Due to its crucial role in TNF- α regulation, ADAM17 has emerged as an important target for the development of anti-inflammatory agents. This study aimed to evaluate the potential of punicalagin-related compounds as natural ADAM17 inhibitors, using marimastat as a reference inhibitor through integrated in silico and in vitro approaches. In silico analyses revealed that all punicalagin-related compounds interacted strongly and stably with ADAM17 catalytic site, exhibiting interaction energies ranging from -117,93 to -235,47 kJ/mol. Screening results identified gallagic acid as the most promising compound with an interaction energy of -235,47 kJ/mol, followed by punicalin (-225,87 kJ/mol) and punicalagin (-206,40 kJ/mol), while gallic acid showed an interaction energy of -139,51 kJ/mol. Marimastat exhibited the strongest interaction energy (-245,58 kJ/mol). Enzymatic assays demonstrated that punicalagin and gallic acid inhibited ADAM17 activity by 93,76% and 76,69%, respectively, at 12,5 μ M, whereas marimastat achieved 90,37% inhibition at 0,1 μ M. The IC_{50} values toward ADAM17 catalytic site of marimastat and punicalagin were 0,0075 μ M and 0,0689 μ M, respectively, while gallic acid was predicted to have an IC_{50} below 0,004 μ M. Molecular dynamics, quantum mechanical calculations, and UV-Vis spectroscopy confirmed stable protein-bioactive interactions and electronic profile changes. Overall, the integrated in silico and in vitro findings suggest that marimastat, punicalagin and gallic acid are promising ADAM17 inhibitors with competitive, non-competitive, and mixed inhibitory mechanisms.

Keywords: TNF- α ; Punicalagin-related compounds; ADAM17 inhibitor; Computational molecular approaches; In vitro enzyme assay

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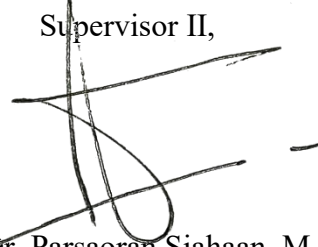
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