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 galagat 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 μM, sedangkan marimastat menghasilkan inhibisi 90,37% pada 0,1 μM. Nilai IC_{50} marimastat, punicalagin, dan asam galat berturut-turut sebesar 0,0075 μM, 0,0689 μM, dan diprediksi <0,004 μM 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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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 μM, whereas marimastat achieved 90,37% inhibition at 0,1 μM. The IC_{50} values toward ADAM17 catalytic site of marimastat and punicalagin were 0,0075 μM and 0,0689 μM, respectively, while gallic acid was predicted to have an IC_{50} below 0,004 μM. 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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