

INTISARI

Triple-negative breast cancer (TNBC) merupakan subtype kanker payudara yang sangat agresif, invasif, dan memiliki kemampuan metastasis yang sangat tinggi. Pengobatan TNBC menggunakan obat kemoterapi komersil menimbulkan efek samping dan tidak efektif mencegah metastasis. Senyawa analog kurkumin Pentagamavunon-1 (PGV-1) diketahui memiliki aktivitas antikanker, tetapi efektivitasnya masih perlu ditingkatkan. Senyawa dari bahan alam, contohnya asam ursolat (AU) diketahui memiliki aktivitas antimigrasi sehingga diharapkan mampu meningkatkan efektivitas PGV-1. Posisi AU sebagai senyawa antikanker payudara dipetakan melalui studi bibliometrik. Efek perubahan aktivitas seluler pada sel model setelah pemberian PGV-1 dan AU dievaluasi dengan CCK-8 *assay* untuk meninjau viabilitas sel dan *scratch wound healing assay* untuk mengamati migrasi sel. Prediksi protein target PGV-1 dan AU pada TNBC dianalisis dengan studi bioinformatika, lalu interaksi molekulernya disimulasikan dengan *molecular docking*. Studi bibliometrik menunjukkan bahwa AU banyak diteliti sebagai agen antikanker, termasuk salah satunya untuk mencegah migrasi sel pada kanker payudara. Viabilitas sel 4T1 sebagai model TNBC menurun setelah pemberian PGV-1 dan AU dengan IC_{50} berturut-turut $2,57 \pm 0,91 \mu\text{M}$ dan $14,21 \pm 8,28 \mu\text{M}$. Penambahan $10 \mu\text{M}$ AU secara signifikan meningkatkan efek sitotoksik $1 \mu\text{M}$ PGV-1 pada sel 4T1. Pengkombinasian AU dengan PGV-1 secara umum cenderung menghambat migrasi sel 4T1 setelah inkubasi 24 jam. Secara molekuler, PGV-1 dan AU berinteraksi dengan ADAM17 dengan skor afinitas sebesar $-10,1 \text{ kcal/mol}$ dan $-7,2 \text{ kcal/mol}$. Selain itu, PGV-1 dan AU dapat berinteraksi dengan BACE1 dengan skor afinitas $-9,6 \text{ kcal/mol}$ dan $-9,1 \text{ kcal/mol}$. ADAM17 berperan dalam inisiasi migrasi sel melalui aktivasi jalur NF κ B dan MAPK3. BACE1 berperan dalam memediasi TME dan NET sehingga memfasilitasi terjadinya migrasi sel. Dengan demikian, penghambatan kedua jenis protein tersebut dapat mencegah terjadinya migrasi sel. Meskipun penelitian lanjutan diperlukan, penelitian ini membuktikan bahwa AU berpotensi dalam meningkatkan efektivitas PGV-1 melalui aktivitas antimigrasi.

Kata kunci: Asam ursolat; Kombinasi; Migrasi; PGV-1; TNBC

ABSTRACT

Triple-negative breast cancer (TNBC) is a highly aggressive, invasive subtype of breast cancer with a very high metastatic ability. Treatment of TNBC using commercial chemotherapy drugs causes side effects and is ineffective in preventing metastasis. The curcumin analog Pentagamavunon-1 (PGV-1) is known to have anticancer activity, but its efficacy still needs to be improved. Natural compounds, such as ursolic acid (AU), are known to have anti-migratory activity and are therefore expected to enhance the efficacy of PGV-1. The role of AU as an anti-breast cancer compound was mapped through a bibliometric study. The effects of cellular activity changes in model cells after PGV-1 and AU administrations were evaluated using the CCK-8 assay to assess cell viability and the scratch wound healing assay to observe cell migration. The predicted target proteins of PGV-1 and AU in TNBC were analyzed using bioinformatics studies, and their molecular interactions were simulated using molecular docking. The bibliometric study showed that AU has been extensively studied as an anticancer agent, including for preventing cell migration in breast cancer. The viability of 4T1 cells, a TNBC model, decreased after administration of PGV-1 and AU with IC_{50} values of $2.57 \pm 0.91 \mu\text{M}$ and $14.21 \pm 8.28 \mu\text{M}$, respectively. The addition of $10 \mu\text{M}$ AU significantly enhanced the cytotoxic effect of $1 \mu\text{M}$ PGV-1 on 4T1 cells. The combination of AU with PGV-1 generally tended to inhibit 4T1 cell migration after 24-hour incubation. At the molecular level, PGV-1 and AU interact with ADAM17 with affinity scores of -10.1 kcal/mol and -7.2 kcal/mol , respectively. Additionally, PGV-1 and AU can interact with BACE1 with affinity scores of -9.6 kcal/mol and -9.1 kcal/mol , respectively. ADAM17 plays a role in initiating cell migration through the activation of the NF κ B and MAPK3 pathways. BACE1 mediates the TME and NET, thereby facilitating cell migration. Thus, inhibiting these two proteins can prevent cell migration. Although further research is needed, this study demonstrates that AU has the potential to enhance the efficacy of PGV-1 through its anti-migratory activity.

Keyword: Ursolic acid; Combination; Migration; PGV-1; TNBC