INTISARI

Cisplatin masih menjadi *front-line* terapi kanker payudara, namun memiliki kekurangan seperti resistensi dan efek samping yang merugikan, seperti nefrotoksik. Ko-kemoterapi merupakan salah satu strategi terapi baru yang dikembangkan untuk mengatasi kanker. Penggunaan agen ko-kemoterapi diharapkan dapat meningkatkan sensitivitas, mengatasi resistensi, dan mengurangi efek samping obat. Pentagamavunon-1 (PGV-1) merupakan analog kurkumin yang terbukti efektif dalam menginduksi *cell cycle arrest* pada berbagai sel kanker. Galangin (3,5,7-*trihydroxyflavone*) adalah flavonoid yang juga dapat menginduksi *cell cycle arrest* pada sel kanker dan tak bersifat toksik pada sel normal. Induksi *cell cycle arrest* merupakan salah satu target terapi kanker yang dipengaruhi oleh beberapa protein dan jalur persinyalan. Penelitian ini bertujuan untuk mengevaluasi sinergisme dan potensi induksi *cell cycle arrest* dari *triple combination* PGV-1, galangin, dan cisplatin pada sel kanker payudara MCF-7. Evaluasi dilakukan melalui uji pendahuluan sitotoksik secara tunggal, dilanjutkan dengan uji sinergisme kombinasi dua senyawa, serta analisis *triple combination*. Penelitian ini juga bertujuan untuk mengidentifikasi target protein dan jalur persinyalan potensial yang terlibat dalam mekanisme kerja *triple combination* pada kanker payudara luminal secara bioinformatika. Efek sitotosik dianalisis dengan uji MTT, sinergisme kombinasi senyawa dievaluasi berdasarkan perhitungan nilai *Combination Index* (CI), analisis siklus sel secara *propidium iodide* (PI)-*flow cytometry*, sedangkan analisis bioinformatika dilakukan dengan menggunakan *database* dan *software* seperti *SwissTargetPrediction*, UALCAN, STRING, *ShinyGO*, *OncoLnc*, dan *Cytoscape*. Hasil sitotoksik tunggal menunjukkan bahwa nilai IC_{50} PGV-1, galangin, dan cisplatin berturut-turut sebesar 11,5 µM, 146,45 µM, dan 2,12 µM. Kombinasi dua senyawa yang menunjukkan sinergisme kuat adalah cisplatin dan PGV-1 (CI=0,16–0,45), dan sinergisme adalah cisplatin dan galangin (CI=0,65–0,66) bersamaan dengan PGV-1 dan galangin (CI=0,68–0,87). *Triple combination* menunjukkan sinergisme (CI=0,31–0,88) pada sel MCF-7. *Triple combination* meningkatkan populasi sel di fase SubG1, S, dan G2/M. Studi bioinformatika menunjukkan bahwa *triple combination* menarget protein MAPT dan TOP2A serta jalur persinyalan *PI3K/AKT*. Secara keseluruhan, *triple combination* PGV-1, galangin, dan cisplatin berpotensi untuk dikembangkan sebagai kandidat terapi kanker payudara melalui mekanisme induksi *cell cycle arrest*.

Kata Kunci: PGV-1, Galangin, *Triple Combination*, *Luminal Breast Cancer* (MCF-7), *Cell Cyle Arrest*

ABSTRACT

Cisplatin is still the front-line therapy for breast cancer, but it has drawbacks such as resistance and adverse side effects, such as nephrotoxicity. Co-chemotherapy is one of the new therapeutic strategies developed for cancer treatment. The use of a co-chemotherapy agent may enhance sensitivity, overcome resistance, and decrease the side effects of the drug. Pentagamavunon-1 (PGV-1), a curcumin analog, effectively induces cell cycle arrest in cancer cells. Galangin (3,5,7-*trihydroxyflavone*) is a flavonoid that can induce cell cycle arrest in cancer cells without toxic effects in normal cells. Induction of cell cycle arrest is one of the targets of cancer therapy influenced by several proteins and signalling pathways. This study aims to evaluate the synergism and cell cycle arrest induction potential of triple combination PGV-1, galangin, and cisplatin in MCF-7 cells. Evaluation was conducted through preliminary cytotoxic tests as a single agent, followed by synergism tests of two compounds, as well as analysis of triple combination. In addition, this study also aims to identify the potential protein target and signalling pathway involved in the mechanism of action of the triple combination in luminal breast cancer by bioinformatics. Cytotoxic effects were analyzed by the MTT test, the synergism of the combination compound was evaluated based on the calculation of the Combination Index (CI) value, cell cycle analysis was performed using propidium iodide (PI)-flow cytometry, meanwhile, bioinformatic analysis was done using several databases and software like SwissTargetPrediction, UALCAN, STRING, ShinyGO, OncoLnc, and Cytoscape. Single cytotoxic results showed that the IC_{50} values of PGV-1, galangin, and cisplatin were 11.5 μM, 146.45 μM, and 2.12 μM, respectively. The combination of two compounds that showed strong synergism was cisplatin and PGV-1 (CI: 0.16–0.45), and synergism was cisplatin and galangin (CI: 0.65-0.66), together with PGV-1 and galangin (CI: 0.68-0.87). Triple combination showed synergistic effect in MCF-7 cells (CI: 0.31-0.88). Triple combination enhances the cell population in the SubG1, S, and G2/M phases. Bioinformatics studies showed that the triple combination targets MAPT and TOP2A proteins and PI3K/AKT signaling pathways. Overall, the triple combination of PGV-1, galangin, and cisplatin has the potential to be developed as a candidate for breast cancer therapy through its mechanism of cell cycle arrest induction.

Keywords: PGV-1, Galangin, Triple Combination, Luminal Breast Cancer (MCF-7), Cell Cycle Arrest