INTISARI

Terapi tertaget kanker payudara belum mengatasi kanker jenis *triple negative breast cancer* (TNBC) karena mempunyai tingkat proliferasi yang tinggi, rekurensi dan resisten agen kemoterapi, sehingga pengobatan ko-kemoterapi perlu dikembangkan. Studi ini meneliti bahan alam sintetik derivat kalkon, *p*-Hidroksi *m*-Metoksi-Kalkon (*p*H*m*MK) atau 3-(4'-hidroksi-3'-metoksifenil)-1-fenil-2-propen-1-on, baik tunggal dan kombinasinya dengan Doksorubisin (DOX) untuk diketahui potensi dan mekanisme aksinya sebagai agen anti kanker payudara pada sel T47D dan MCF-7 meliputi sitotoksisitas, penghambatan daur sel, pemacuan apoptosis dan penghambatan resistensi.

Uji sitotoksisitas *p*H*m*MK dan kombinasinya dengan DOX menggunakan MTT [3-(4,5-dimethylthiazol-2-il)-2.5-diphenyltetrazolium bromide] *assay* untuk menentukan potensi sitotoksik berdasar IC_{50}-nya, serta nilai *combination index* (CI)-nya. Penetapan hambatan daur sel, pacuan apoptosis dan ekspresi P-gp dianalisis dengan *flow cytometry* sedangkan ekspresi protein regulator daur sel, apoptosis, dan resistensi diamati dengan immunositokimia menggunakan antibodi monoklonal masing-masing.

Hasil penelitian menunjukkan bahwa *p*H*m*MK bersifat sitotoksik pada sel T47D dan MCF-7 dengan IC_{50} berturut-turut 48 dan 40 μM, sedangkan DOX menunjukkan nilai IC_{50} sebesar 84 nM pada sel T47D dan 6 μM pada MCF-7. Kombinasi *p*H*m*MK-DOX menunjukkan efek sinergi kuat pada sel T47D dan sinergi pada MCF-7. Pemberian *p*H*m*MK menyebabkan akumulasi sel pada fase G2/M pada sel T47D, serta G2/M dan S pada sel MCF-7. Kombinasi *p*H*m*MK-DOX menyebabkan akumulasi G2/M dan S pada sel T47D serta G2/M pada MCF-7. *p*H*m*MK dan kombinasi *p*H*m*MK-DOX menurunkan ekspresi cyclin B. Peningkatan apoptosis akibat pemberian *p*H*m*MK dan kombinasi *p*H*m*MK-DOX berupa penurunan ekspresi Bcl-2, peningkatan ekspresi Bax, *c*-Caspase-3 (sel T47D), *c*-Caspase-9 (sel MCF-7) dan *c*-PARP. *p*H*m*MK juga terbukti menurunkan resistensi DOX berdasarkan penurunan ekspresi P-gp pada sel MCF-7.

Kesimpulan dari penelitian ini bahwa *p*H*m*MK berpotensi sebagai anti kanker payudara; dan berpotensi memberikan efek sinergi dengan DOX pada hambatan proliferasi, hambatan daur sel pada fase G2/M dan S; serta peningkatan apoptosis dan menurunkan resistensi DOX.

Kata kunci : *p*-hidroksi-*m*-metoksi-kalkon, antikanker, mekanisme aksi, ko-kemoterapi, T47D dan MCF-7.

ABSTRACT

Targeted therapy has been unsuccesfulled to treat breast cancer of which triple negative breast cancer (TNBC)-type that has a high rate of proliferation, recurrence and chemotherapeutic resistance. Therefore co-chemotherapeutic treatment needs to be developed. This study explored the potencies as well as the mechanisms of action of a synthetic natural substance of chalcone derivate of *p*-Hydroxy-*m*-Methoxy-Chalcone (*p*H*m*MC) or 3- (4'-hydroxy-3'-methoxyphenyl) -1-phenyl-2-propen-1-one, either as a single treatment or a combination with Doxorubicin (DOX) against breast cancer on T47D and MCF-7 cells covering the cytotoxicity, the proliferative cell inhibition, apoptotic induction and resistance inhibition.

The MTT [3-(4,5-dimethylthiazol-2-il)-2.5-dipheniltetrazolium bromide] assay was carried out to determine the cytotoxic potencies (IC_{50}) and the *combination index* (CI) of the *p*H*m*MK and its combination. The cell cycle inhibition, apoptotic induction and expression of P-gp were observed using flow cytometry; while the expressions of regulator proteins of cell cycle, apoptosis, and resistance were observed by immunocytochemistry using respective monoclonal antibodies.

The results showed that *p*H*m*MC performed cytotoxic effect to T47D and MCF-7 cells with IC_{50} values of 48 and 40 μM respectively, whereas DOX gave IC_{50} values of 84 nM in T47D cells and 6 μM in MCF-7 cells. The combination of *p*H*m*MC-DOX gave a strong synergistic effect on T47D cells and synergistic effect on MCF-7 cells. *p*H*m*MC caused cell accumulation on the G2/M phase in T47D cells, and on the G2/M and S phases in MCF-7 cells. The combination of *p*H*m*MC-DOX caused cell accumulation on the G2/M and S phases in T47D cells, and on the G2/M phase in MCF-7 cells. The *p*H*m*MC and *p*H*m*MC-DOX decreased the cyclin B expression. Due to the *p*H*m*MC and its combination treatments, an apoptosis induction was observed through decreasing expression of Bcl-2, increasing Bax, c-Caspase-3 (T47D cells), c-Caspase-9 (MCF-7 cells), and c-PARP expressions. It was showed that *p*H*m*MC decreased DOX resistance through the decreasing of P-gP expression in MCF-7 cells.

It was concluded that *p*H*m*MC has a potency as anti-breast cancer; and it gives potential synergistic effects with DOX on proliferative inhibiton, cell cycle arrest at G2/M and S, as well as apoptotic induction; and decreasing of DOX resistance.

Keywords: *p*-Hydroxy-*m*-Methoxy-Chalcone, anticancer, mechanism of action, co-chemotherapy, T47D and MCF-7 cells.