POTENSI BORNEOL DALAM MENINGKATKAN SENSITIVITAS KANKER PAYUDARA HER2+ RESISTEN LAPATINIB TERHADAP LAPATINIB: STUDI BIOINFORMATIKA DAN *IN VITRO*

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INTISARI

Resistensi lapatinib pada kanker payudara HER2+ (LR-HER2+) dapat disebabkan karena adanya mutasi pada jalur kompensatori, seperti PI3K/Akt/mTOR dan MAPK. Borneol diketahui mampu menghambat jalur tersebut pada sel glioma, serta mampu menurunkan ekspresi protein anti-apoptosis Bcl-2, Bcl-XL, dan Mcl-1 pada sel hepatocellular carcinoma. Studi ini dilakukan untuk eksplorasi target gen potensial dari borneol (PTGBs) untuk meningkatkan sensitivitas LR-HER2+ terhadap lapatinib melalui pendekatan bioinformatik dan validasi in vitro.

Data diperoleh dari basis data bioinformatika seperti GEO, BindingDB, SEA, SwissTargetPrediction, ChEMBL, STITCH, dan GeneCards. Gen hasil irisan antara target gen borneol dan gen yang berperan dalam regulasi lapatinib dianalisis melalui GO dan KEGG menggunakan DAVID. Kemudian, 10 gen dengan nilai interaksi tertinggi dipilih melalui pembentukan interaksi protein-protein (PPI) dan seleksi hub gen menggunakan STRING dan Cytoscape. Validasi invitro dilakukan melalui uji MTT, analisis siklus sel, dan qPCR.

Hasil uji MTT menunjukkan IC_{50} borneol dan lapatinib terhadap LR-HCC1954 adalah 67.389 μM and 5.917 μM secara berurutan, serta kombinasi 25 μM borneol dan 0.25 μM lapatinib menunjukkan penurunan viabilitas sel yang signifikan. Selain itu, analisis siklus sel menunjukkan adanya penghentian siklus sel pada fase S dan G2/M, serta penurunan populasi pada fase G0/G1. Hasil tersebut juga didukung oleh penurunan ekspresi *CDKN1A*, *PCNA*, dan *DHFR*, serta peningkatan *CCND1* akibat paparan borneol. Borneol juga meningkatkan ekspresi *BAX* dan *CASP8*. Validasi qPCR mengidentifikasi 7 gen hub utama dari 10 PTGB teratas. Borneol dan kombinasinya dengan lapatinib terbukti mampu menurunkan ekspresi mRNA dari *ERBB2*, *ICAM1*, dan *PTGS2*, serta meningkatkan ekspresi *GSK3B*, *PTPRC*, *AGTR1*, dan *CXCR4*. Temuan ini konsisten dengan hasil analisis KEGG yang menunjukkan bahwa PI3K/Akt/NF-κB, Ras, dan Wnt jalur target dari borneol pada LR-HER2+.

Kata kunci: Borneol, kanker payudara, resistensi lapatinib, bioinformatika, in vitro

THE POTENTIAL OF BORNEOL TO IMPROVE THE SENSITIVITY OF LAPATINIB-RESISTANT HER2+ BREAST CANCER AGAINST LAPATINIB: A BIOINFORMATICS AND IN VITRO STUDIES THESIS

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ABSTRACT

Lapatinib-resistant HER2+ breast cancer (LR-HER2+) can be caused by mutations in compensatory pathways such as PI3K/Akt/mTOR and MAPK. Borneol is known to inhibit these pathways in glioma cells and reduce the expression of anti-apoptotic proteins Bcl-2, Bcl-XL, and Mcl-1 in hepatocellular carcinoma cells. This study explored the potential target genes of borneol (PTGBs) to increase the sensitivity of LR-HER2+ against lapatinib through bioinformatics approaches and in vitro validation.

Data were obtained from GEO, BindingDB, SEA, SwissTargetPrediction, ChEMBL, STITCH, and GeneCards databases. The overlapping genes between borneol target genes and lapatinib regulating genes underwent functional enrichment analysis via GO and KEGG pathways using the DAVID. The top ten PTGBs were selected based on protein interaction (PPI) analysis and hub gene selection using STRING and Cytoscape. In vitro validation was performed through MTT assay, cell cycle analysis, and qPCR.

MTT assay showed that IC_{50} of borneol and lapatinib against LR-HCC1954 were 67.389 μM and 5.917 μM, respectively. The combination of 25 μM borneol and 0.25 μM lapatinib significantly decreased cell viability. Cell cycle analysis showed an increase in the S and G2/M phases and a decrease in the G0/G1 phase, indicating S and G2M phase cell cycle arrest. These results were supported by a decrease in the expression of *CDKN1A*, *PCNA*, and *DHFR*, and an increase in *CCND1* by borneol. Borneol also increased the expression of *BAX* and *CASP8*. The qPCR validation identified 7 major hub genes from the top 10 PTGBs obtained from bioinformatics studies. Borneol and its combination decreased the mRNA expression of *ERBB2*, *ICAM1*, and *PTGS2*, also increased *GSK3B*, *PTPRC*, *AGTR1*, and *CXCR4*. These findings are consistent with KEGG analysis, which showed that the PI3K/Akt/NF-κB, Ras, and Wnt pathways are the main targets of borneol in overcoming LR-HER2+.

Key words: Borneol, breast cancer, Lapatinib resistance, bioinformatics, in vitro