ABSTRACT

Trastuzumab resistance poses a challenge in the treatment of HER2+ breast cancer, necessitating the exploration of combination therapies to overcome it. Honokiol has been observed to have broad anticancer activity. This research aims to identify the effect of honokiol in increasing trastuzumab sensitivity in trastuzumab-resistant HER2+ breast cancer cells and to discover the most potential target hub-gene for honokiol in HER2+ breast cancer.

Trastuzumab Resistant HCC1954 (TR-HCC1954) was obtained after trastuzumab resistance induction with significantly higher cell viability compared to parental HCC1954 indicating successful trastuzumab resistance induction. Honokiol shows cytotoxicity to parental and TR-HCC1954 with an IC_{50} of 41.05 and 69.61 μM respectively. Additionally, combination of honokiol and trastuzumab yield significant differences of cytotoxicity in TR-HCC1954 at 25 μM and 400 μg/mL; 50 μM and 400 μg/mL; and 50 μM and 800 μg/mL respectively indicating an increase in trastuzumab sensitivity by honokiol. This result was validated using bioinformatics analysis which shows honokiol might target potential hub-genes in HER2+ breast cancer major pathways such as *AKT1, ESR1, VEGFA, MYC, EGFR, IL6, CCND1, TNF,* and *STAT3* to increase trastuzumab sensitivity. In conclusion, honokiol might help overcome the trastuzumab resistance by affecting various other pathways that can't be targeted by trastuzumab.

Keywords: *Honokiol, Trastuzumab resistance, HER2+ breast cancer, Cytotoxicity assay, Hub-genes*