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Brusatol downregulate HER1 signalling pathway via NRF2-mediated inhibition leading to reduced breast cancer proliferation

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Brusatol enhances the increased inhibition of cell growth breast cancer through targeting NRF2 function, although the exact mechanism of this inhibition is still not fully studied. The HER1 is one of the members of EGFR family which regulate the normal cellular proliferation, maintenance and determining the cancer initiation and progression. These receptors dimerize upon ligand binding, leading to activation of their tyrosine kinase domain. This subsequently led to the phosphorylation of their tyrosine residues in the intracellular domain. Nuclear factor (NRF2) is a transcription factor that regulates the expression of a battery of many genes including cytoprotective and detoxifying genes. Overexpression of both HER1 and NRF2 are reported in breast cancer and studies have implicated both NRF2 and HER family in resistance of numerous cancers to chemotherapeutic agents. In this study, we demonstrated that brusatol inhibited the NRF2 activity, which led to downregulation of HER1 protein expression and decreased cell growth of PEO4 and SKOV3 cells. Additional investigation revealed that brusatol could lead to transcriptional inhibition of HER1 promoter activity by inhibiting the NRF2 activity in the HER1 promoter region. Furthermore, inhibition of NRF2 led to increase in ROS level and depletion of total glutathione in all the cell lines. Taken together, these data suggest that brusatol may inhibit the cell growth of breast cancer cells through NRF2-mediated downregulation of HER1 expression and could be a novel avenue brusatol induced NRF2 inhibition, which lead to inhibition of breast cancer cell growth.