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# Anti-proliferation of breast cancer cells with itraconazole: Hedgehog pathway inhibition induces apoptosis and autophagic cell death

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## Abstract

Itraconazole is a common antifungal which may have promise for treating various human cancers. We report that itraconazole was cytotoxic to MCF-7 and SKBR-3 breast cancer cell lines via apoptosis by altering mitochondria membrane potential, reducing BCL-2 expression and elevating caspase-3 activity. Itraconazole also induced autophagic cell death via LC3-II expression upregulation, P62/SQSTM1 degradation, autophagosome formation and increases in autophagic puncta. Itraconazole treatment inhibited hedgehog pathway key molecular expression, such as SHH and Gli1, resulting in promotion of apoptosis and autophagy. The anti-proliferation effect of itraconazole-induced apoptosis and autophagy via hedgehog pathway inhibition was confirmed with Gli1 inhibitor GANT61 and SHH siRNA, GANT61 and SHH siRNA synergistically enhanced cytotoxicity induced by itraconazole. A human xenograft nude mouse model corroborated the anti-breast cancer activity as

evidenced by reduced tumor size, and increased tumor tissue apoptosis and autophagy. Thus, itraconazole has a potent anti-breast cancer activity that may be improved when combined with hedgehog pathway inhibitors.

**Keywords:** Apoptosis; Autophagic cell death; Breast cancer; Hedgehog pathway; Itraconazole.



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