Novel antitumor agent Jerantinine B mediates apoptotic cell death through c-Jun/JNK pathway and ROS in leukaemic cell lines

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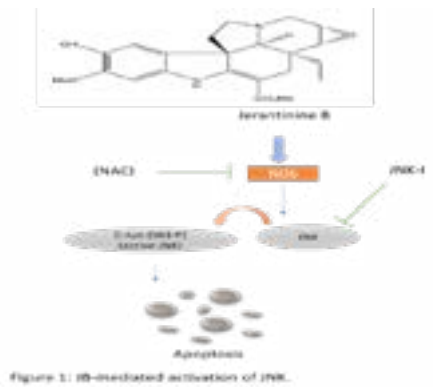
Statement of the Problem: Acute myeloid leukaemia (AML) is a complex malignancy associated with genetic, epigenetic, and phenotypic heterogeneity. Chemoresistance and relapse are the major challenges in AML treatment. Activation of JNK pathway was demonstrated to be a vital step for the chemotherapy agent, anthracycline, to induce apoptosis in AML cells and defects in JNK-activation contributes to AML chemoresistance. Jerantinine B is a novel aspidosperma alkaloid isolated from the leaf extract of Tabernaemontana corymbosa. Preliminary screens established that JB possess *in vitro* anticancer activities against various human derived solid cancer cell lines but, the effect on AML was unknown.

Aim: The purpose of this study was to demonstrate whether this novel agent provide potential effective targeting of AML cells.

Methodology: Following determination of JB cytotoxicity in AML cell lines and patient samples, flow cytometry and immunoblotting was used for further experiments to explore the mechanism of action of JB.

Findings: JB exhibited significant inhibition of growth and colony formation of AML cell lines accompanied by an induction of apoptosis in a time and dose-dependent manner. JB IC50 dose at early time point (4 hrs) resulted in strong expression of both total and phosphorylated c-Jun (S63) protein and significant increases in reactive oxygen species (ROS) level (P≤0.01.) Co-treatment with a ROS scavenger, N-acetylcysteine (NAC), in JB-treated HL60 cells significantly reduced JB-induced ROS (P=0.031) and reversed JB-mediated c-Jun/JNK activation and subsequent cell apoptosis. This suggests that JB-mediated intracellular oxidative stress acts as signal for c-Jun/JNK-induced death in HL60 cells. Furthermore, JB caused cell cycle perturbation, Polo-like kinase 1 (PLK1) inhibition (evidenced by phosphorylation of phospho-histone H3 (pHH3)) and up-regulation of apoptotic markers including active caspase 3 and cleaved PARP (p≤0.02). These findings indicate that JB appears to be a potential chemotherapeutic agent in AML and its continued development is recommended.



Recent Publications

1. Lagadinou E D, Ziros P G, Tsopra O A, Dimas K, Kokkinou D, Thanopoulou E, Karakantza M, Pantazis P, Spyridonidis A and Zoumbos N C (2008) c-Jun N-terminal kinase activation failure is a new mechanism of anthracycline resistance in acute myeloid leukemia. Leukemia, 22:1899-908.
2. Lim K H, Hiraku O, Komiyama K and Kam T S (2008) Jerantinines A-G, cytotoxic Aspidosperma alkaloids from Tabernaemontana corymbosa. J Nat Prod, 71:1591-4.
3. Qazzaz M E, Raja V J, Lim K H, Kam T S, Lee J B, Gershkovich P and Bradshaw T D (2016) *In vitro* anticancer properties and biological evaluation of novel natural alkaloid jerantinine B. Cancer Lett, 370:185-97.

Biography

Hayaa Alhuthali is a haematology scientist at university of Nottingham (CSB, City Hospital). She is in last year of her PhD, which focuses on studying response of AML to novel therapeutic drug and explores mechanisms of drug action. She has Skills in cell culture, molecular biology, immunoblotting, flow cytometry, cell cycle analysis and cell signaling

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