Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol13Issue3abst158P.pdf

Anticancer Properties and Biological Evaluation of Novel Natural Alkaloid Jerantinine B

Natural products play a pivotal role in medicine especially in the cancer arena. Many drugs that are currently used in cancer chemotherapy originated from or were inspired by nature. In 2008, a seven novel Aspidosperma indole alkaloids have been isolated, jerantinine A–G, from a leaf of Malayan plants of the species *Tabernaemontana corymbosa*. Jerantinine B (JB) was one of these novel indole alkaloids and revealed profound in vitro anti-tumour activity. Our preliminary anti-proliferative assays revealed that JB and JB acetate significantly inhibited growth (GI_{50} 0.245 - 0.917 μM) and colony formation.

Mean ± SEM GI_{50} values (μM)		
	JB	**JBA**
MCF-7 (Breast carcinoma)	0.917±0.004	0.482±0.009
HCT 116 (Colon carcinoma)	0.682±0.026	0.362±0.006
A549 (Lung carcinoma)	0.701±0.010	0.547±0.092
MiaPaCa 2 (Pancreas carcinoma)	0.245±0.033	0.253±0.010

Flow cytometric assays were then employed to determine whether jerantinine B affected cell cycle progression. Stark cell cycle perturbation revealed i) profound G2/M cell cycle arrest (inferring inhibition of microtubule dynamics); ii) emergence of pre-G1 populations (indicative of apoptosis induction). Indeed, 1 μM JB comprehensively inhibited tubulin polymerisation; microtubule growth from tubulin seeds (dynamicity) was dose-dependently inhibited (IC_{50} 0.385 μM). Confocal microscopy exposed multipolar spindles within cells undergoing failed mitoses, aneuploidy and apoptotic morphology following treatment with JB. Dual annexin-V / PI staining, dose-dependent accumulation of cleaved-PARP and caspase 3/7 activation, in addition to reduced Bcl-2 and Mcl-1 expression confirmed dose- and time-dependent apoptosis. Furthermore, JB evoked significant increase in reactive oxygen species (ROS) production, which is plays an important role in stimulating release of pro-apoptotic factors from mitochondria and apoptosis induction. Polo-like kinase 1 (PLK1) activity, an oncogenic kinase possessing key functions during mitosis and validated as an anti-cancer therapeutic target, was dose-dependently inhibited by JB (IC_{50} 1.5 μM JB). Indeed, we had recent crystal structure studies determined JB acetate bound to the colchicine binding site to tubulin. Such promising data advocate further preclinical evaluation, in vivo testing and development of JB as a potential chemotherapeutic agent.