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Brucine, an indole alkaloid from Strychnos nux-vomica exerts antiangiogenic and antitumor activity by targeting vascular endothelial growth factor receptor 2-mediated angiogenesis

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Angiogenesis blockade has been shown to be an effective strategy in inhibiting tumor growth and metastasis. Considering anti-angiogenesis therapy is to target endothelial cells that support tumor growth rather than cancer cells themselves, VEGFR-2 has become an important therapeutic target for cancer anti-angiogenesis therapy. Preliminary reports suggest that brucine possesses anti-tumor activity. However, its roles in tumor angiogenesis and the involved molecular mechanism are still unknown to make a firm conclusion before implementing it into the clinical practice. Therefore, we examined its anti-angiogenic effects and mechanisms *in vitro* and *in vivo*. Human umbilical vein endothelial cells (HUVECs) were treated with or without VEGF and different concentrations of brucine, then tested for cell viability, migration, tube formation and apoptosis. The role of VEGFR2-mediated signaling pathway in brucine-inhibited angiogenesis was evaluated using quantitative real-time PCR (qRT-PCR) and Western blotting. *In vivo* antiangiogenic activity was determined using sponge implant angiogenesis assay and antitumor activity was evaluated against Ehrlich ascites carcinoma tumor. Tumor volume, cell viability, anti-angiogenic and anti-inflammatory factors were determined. Immunohistochemistry analysis for CD-31, P-VEGFR2, P-Akt, and P-Erk was also performed. One-way analysis of variance (ANOVA) was used to determine the statistical significance of the difference between means. Brucine significantly inhibited a series of VEGF-induced angiogenesis processes including proliferation, migration, and tube formation in HUVECs and inhibited neovascularization in sponge implant angiogenesis assay and tumor growth *in vivo* via suppressing VEGF-induced phosphorylation of VEGFR2. Brucine inhibited VEGFR-2 tyrosine kinase activity (IC_{50}=21.34 μM) and further inhibited angiogenesis via inhibition of VEGFR2-mediated signaling with the involvement of some key kinases such as c-Src, FAK, ERK, AKT, mTOR and S6K and induction of apoptosis. Brucine acts as a potent VEGFR2 kinase inhibitor, and exerts the anti-angiogenic activity at least in part through VEGFR2-mediated signaling pathway.

Biography

Sarita Saraswati is a Distinguished Researcher at Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia. She obtained her Ph.D. in Pharmacy at University of Delhi, India in 2011. She has 16 peer reviewed publications to date, serves on editorial board of several journals and is a reviewer for several journals including *Food and Chemical Toxicology, Microvascular Research, Experimental Biology and Medicine's, Journal of Cancer Research and Experimental Oncology*. She has participated and presented research papers in international conferences at held at Germany, France and Saudi Arabia. She has educated and trained technicians, graduate students from academics as well as from industry in various aspects of research including teaching specific techniques in cancer biology, Molecular Biology, and Bioinformatics. She is a member of various national and international societies and recipient of various awards. Her research focusses on tumor angiogenesis and hepatocellular carcinoma. Her Research Interests includes Tumor-induced angiogenesis and metastasis; Regulation and function of angiogenic growth factors; Angiogenesis and the immune system; Apoptosis.

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