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Taspine derivatives inhibited tumor angiogenesis by targeting EphrinB2 and regulating its signaling players

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Introduction: The Eph receptor tyrosine kinases and their plasma-membrane-anchored Ephrin ligands play a pivotal role in angiogenesis, cell proliferation and migration in many different cell types and tissues[1]. EphrinB2 ligand expressed in various tumor cells is related to its high vascularity.EphrinB2 is a transmembrane subclass ligand and its reverse signaling is mediated by the EphrinB2 cytoplasmic domain, which contains a PDZ binding motif that can interact with signaling molecules [2,3]. So, regulation of EphrinB2 signaling might be useful to simultaneously interfere with the function of VEGFR2 and VEGFR3 which act together during angiogenesis[4].Taspine isolated from *Radix et RhizomaLeonticis* was a kind of aporphines alkaloid. The aim of this study is to investigate the action of taspine derivatives which inhibit tumor angiogenesis by targeting EphrinB2 and regulating its pathway.

Methods: Over-expressed Ephrin B2 cells, non-small lung carcinoma cell line A549, NCI-H1299 and NCI-H460 were used to study the cell proliferation, which was used to screen active compounds from taspine derivatives. The cell membrane chromatography (CMC) and binging assay were used to confirm the target. The biological activities of screened active compound were evaluated by cell assays and angiogenesis model of CAM *in vivo* and TMA *in vitro*. In addition, EphrinB2 expression and signaling players were investigated by Western Blotting.

Results: The cell proliferation results indicated that No.1822, No.T27 and No.T9among the taspine derivatives showed good inhibition on over-expressed EphrinB2 cells and lung cancer cells. At the same time, No.1822could act on EphrinB2 cell membrane stationary phase and interact on EphrinB2. The cell binging assay exerted the consistent result of No.1822 with CMC. Angiogenesis models *in intro* and *in vivo* showed the obvious inhibition on the angiogenesis treated by No.1822.The obtained data of western blotting indicated No.1822inhibitedEphrinB2expression and PDZ protein PICK1. Accordingly, it was associated with the down-regulation of PI3K/AKT/mTOR and MAPK signal pathway molecules, such as Akt, mTOR, Erk1/2, PLCγ, etc.

Conclusions: No.1822, a taspine derivative, showed good retention activity on EphrinB2CMC stationary phase and could target EphrinB2, and regulate PI3K/AKT/mTOR and MAPK signal pathway, which contributed to its inhibition on tumor angiogenesis.

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Biography:

Dr. Yanmin Zhang is a professor of School of Pharmacy, Health Science Center, Xi'an Jiaotong University of China, member of Chinese Pharmaceutical Association. Yanmin Zhang received his B.S. in chemistry and Ph.D. in pharmaceutical analysis. He began his independent career in 1999. He is currently the director of molecular pharmacology program and a full professor at school of Pharmacy of Xi'an Jiaotong University, and assistant research scientist in the Biodesign Institute of Arizona State University, USA. Research interests in the Yanmin Zhang Group are at the interface of pharmacy and biology focused on screening and activity evaluation of small molecular drug for antitumor, studies of molecular mechanism of bioactive natural products and drug process analysis *in vivo*. He has published more than 100 papers including *CDDs, Sci Rep, JCMM, Cancer Lett*, et al. and holden 21 patents.