

Eudesmane-Type Sesquiterpenes from *Laggera alata* Inhibiting Angiogenesis

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Abstract : Angiogenesis is the process of new blood vessel development. It has been recognized as a therapeutic target for blocking cancer growth four decades ago. Vascular sprouting is initiated by pro-angiogenic factors. Vascular endothelial cell growth factor (VEGF) plays a central role in angiogenic initiation, many patients with cancer or ocular neovascularization have been benefited from anti-VEGF therapy. Emerging approaches impacting in the later stages of vessel remodeling and maturation are expected to improve clinical efficacy. TIE receptor as well as the corresponding angiopoietin ligands, were identified as another endothelial cell specific receptor tyrosine kinase signaling system. Much efforts were made to reduce the activity of angiopoietin-TIE receptor axis. Two eudesmane-type sesquiterpenes from *laggera alata*, namely, 15-dihydrocotic acid and ilicic acid were found with strong anti-angiogenic properties in zebrafish model. Meanwhile, the mRNA expression levels of VEGFR2 and TIE2 pathway related genes were down-regulated in the sesquiterpenes treated zebrafish embryos. Besides, in human umbilical vein endothelial cells (HUVECs), the sesquiterpenes have the ability to inhibit VEGF-induced HUVECs proliferation and migration at non-toxic concentration. Moreover, angiopoietin-2 induced TIE2 phosphorylation was inhibited by the sesquiterpenes, the inhibitory effect was detected in angiopoietin-1 induced HUVECs proliferation as well. Thus, we hypothesized the anti-angiogenic activity of the compounds may via the inhibition of VEGF and TIE2 related pathways. How the compounds come into play as the pathways inhibitors need to be evaluated in the future.

Keywords : *Laggera alata*, eudesmane-type sesquiterpene, anti-angiogenesis, VEGF, angiopoietin, TIE2

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