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AD0157, a pyrrolidinedione fungal metabolite, inhibits angiogenesis by targeting the Akt signaling pathway

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In the course of a screening program for the inhibitors of angiogenesis from marine sources, AD0157, a pyrrolidinedione fungal metabolite, was selected for its angiosupressive properties. AD0157 inhibited the growth of endothelial and tumor cells in culture in the micromolar range. Our results show that subtoxic doses of this compound inhibit certain functions of endothelial cells, namely, differentiation, migration and proteolytic capability. Inhibition of the mentioned essential steps of *in vitro* angiogenesis is in agreement with the observed antiangiogenic activity, substantiated by using two *in vivo* angiogenesis models, the chorioallantoic membrane and the zebrafish embryo neovascularization assays, and by the *ex vivo* mouse aortic ring assay. Our data indicate that AD0157 induces apoptosis in endothelial cells through chromatin condensation, DNA fragmentation, increases in the subG1 peak and caspase activation. The data shown here altogether indicate for the first time that AD0157 displays antiangiogenic effects, both *in vitro* and *in vivo*, that are exerted partly by targeting the Akt signaling pathway in activated endothelial cells. The fact that these effects are carried out at lower concentrations than those required for other inhibitors of angiogenesis makes AD0157 a new promising drug candidate for further evaluation in the treatment of cancer and other angiogenesis-related pathologies. [Our experimental work is supported by grant P12-CTS-1507 (Andalusian Government and FEDER) and funds from group BIO-267 (Andalusian Government). The "CIBER de Enfermedades Raras" is an initiative from the ISCIII (Spain). This communication has the support of a travel grant "Universidad de Málaga. Campus de Excelencia Internacional Andalucía Tech"].