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Cladosporol A inhibits HT-29 cell proliferation through inactivation of the b-catenin/TCF pathway mediated by a PPARc-dependent mechanism

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Cladosporol A, a secondary metabolite from *Cladosporium tenuissimum*, has recently been shown to exhibit antiproliferative properties in various human colon cancer derived cell lines through modulation of gene expression of several cell cycle gatekeepers. Specifically, we demonstrated that cladosporol A induces inhibition of cell proliferation by the upregulation of p21waf1/cip1 gene expression mediated by an Sp1-dependent, p53-independent mechanism. To obtain these effects, a functional PPARg is required, indicating that the drug acts as a natural ligand of the receptor. In this work, we report that exposure of HT-29 cells to cladosporol A causes reduced expression and nuclear distribution of b-catenin, a key molecule involved in the carcinogenesis of various tissues, including colon. This result well correlates with a decrease of c-MYC and cyclin D1, two recognized targets of the b-catenin/TCF pathway and a simultaneous increase of E-cadherin expression. E-cadherin is involved in cell-cell and cell-extracellular matrix interactions and is a well-recognized gene target of PPARg because a PPRE motif is contained in its promoter region.

On the basis of these results, we propose that, acting as a new PPARg-ligand, cladosporol A inhibits cell migration and hence the metastatic potential, and inhibits cell proliferation through regulation of p21waf1/cip1, cyclin D1, cyclin E, CDK2, CDK4 expression. On the other hand, it inhibits the b-catenin/TCF pathway and transcription of its target genes, among which c-myc oncogene.