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In vitro and *In vivo* Anticancer Activity of Semisynthetic Derivatives of Betulinic acid

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SUMMARY. **A-ring modifications of betulinic acid isolated from *Diospyros peregrina* was carried out and the chemically modified derivatives were characterized by spectroscopic methods. Chemically modified betulinic acid analogues were subjected to molecular docking studies on topoisomerase-1 and were evaluated for *in vitro* and *in vivo* anticancer activity. *In vitro* anticancer studies revealed that among semisynthetic derivatives of betulinic acid the 2- benzylidene derivatives BE-6 and BE-7 as the most active compounds against HeLa and MDA-MB-435 cell lines. Compounds BE-6 and BE-7 exhibited apoptosis-mediated cell death and caused cell cycle arrest at the G0/G1 phase of HeLa cells. The *in vivo* Ehrlich ascites carcinoma model further confirms the antitumor efficacy BE-6 and BE-7. Molecular docking studies reveal that introduction of benzylidene group in the second position of betulinic acid has improved the binding affinity to topoisomerase-1. Further, the anticancer property of betulinic acid derivatives was in agreement with molecular docking results.**

RESUMEN. Se llevaron a cabo modificaciones en el anillo A del ácido betulínico aislado de *Diospyros peregrina* y los derivados modificados químicamente se caracterizaron por métodos espectroscópicos. Los análogos de ácido betulínico modificados químicamente se sometieron a estudios de acoplamiento molecular a topoisomerasa-1 y se evaluaron para determinar la actividad anticáncer *in vitro* e *in vivo*. Los estudios anticancerígenos *in vitro* revelaron que, entre los derivados semisintéticos del ácido betulínico, los derivados de 2 bencilideno BE-6 y BE-7 son los compuestos más activos contra las líneas celulares HeLa y MDA-MB-435. Los compuestos BE-6 y BE-7 geeraron muerte celular mediada por apoptosis y causaron la detención del ciclo celular en la fase G0/G1 de las células HeLa. El modelo de carcinoma de ascitis Ehrlich *in vivo* confirma aún más la eficacia antitumoral BE-6 y BE-7. Los estudios de acoplamiento molecular revelan que la introducción del grupo bencilideno en la segunda posición del ácido betulínico ha mejorado la afinidad de unión a la topoisomerasa-1. Además, la propiedad anticancerígena de los derivados del ácido betulínico estaba de acuerdo con los resultados de acoplamiento molecular.

KEY WORDS: anticancer, betulinic acid, docking, Ehrlich's ascites, topoisomerase.

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