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Hederagenin from *Sapindus saponaria* L. fruits as a template for the development of new antitumor compounds

Diego Rodríguez-Hernández[1], Antonio J. Demuner[1], Luiz C. A. Barbosa[1,2], Ricardo M. Montanari[1], René Csuk[3], Lucie Heller[3]

[1]Universidade Federal de Viçosa, Viçosa, Brazil; [2]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [3]Martin-Luther-University Halle-Wittenberg, Germany.

(diego.hernandez@ufv.br)

Abstract:

Natural products have been used to treat human diseases for thousands of years. The results of these treatments has been by and large middling, but during the last decades natural products have been used as model for the development of new drugs, including selective anti-cancer active substances. Within the plethora of natural products, the triterpenoic acids are considered amongst the most promising candidates as scaffolds for anti-cancer drug development [1].Among the many sources of bioactive natural products are the fruits of *S. saponaria* L., (Sapindaceae), popularly known in Brazil as "sabão-de-soldado" (soldier soap).These fruits accumulate in its pericarps great quantity of saponins with the aglycone hederagenin. This study, a series of novel esters and amides substituted derivatives have been synthesized at C-28 starting from hederagenin, in an attempt to develop potent antitumor agents. Firstly, hederagenin was isolated from pericarp of *S. saponaria* L. Subsequently it was transformed into corresponding esters (**1-23**) at position C-28, by its reaction with alkyl bromide in the presence of finely grounded K_2CO_3. Thus, following this general procedure [2], alkyl esters were obtained with yields ranging between 35-90%. In addition, the hederagenin was also converted into several amides (**26-31**) by its reaction with primary amines in the presence of TBTU and DIPEA in excellent yields [3].The structures of all derivatives were confirmed by MS, IR, ^{1}H NMR and ^{13}C NMR. The compounds were screened for antitumor activity in a panel of six human cancer cell lines by an SRB assay. The pharmacological results showed that a conversion of hederagenin into esters and amides resulted in an increase of cytotoxicity. As shown for all different human cancer cell lines, alkyl and benzyl esters and alkyl amides (**1-30**) possess a higher cytotoxicity than hederagenin. However, activity is decreased for 1-ethylmorpholinyl amide (**31**). The amides carrying an ethylpiperidinyl (**28**) and ethylpyrrolidinyl (**29**) moiety were the most active derivative for all cells tested, showing IC_{50} values ranging between 1.3-6.5 µM for **28** and values between 1.1-3.9 µM for **29**. This corresponds to an approximately 30 times higher cytotoxicity than hederagenin. In addition the esters carrying a benzyl (**1**) or an *ortho*-nitrobenzyl (**18**) group were the most active among all esters derivatives for the cells lines tested, showing IC_{50} values between 7.0-9.7 µM for **1** and 6.1-8.4 µM for **18**. These results revealed that compounds **1** and **18** are approximately 20 times more active than hederagenin.

Keywords:

hederagenin derivatives, SRB assay, *Sapindus saponaria*

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