Pharmacological Reports
2011, 63, 1500–1517
ISSN 1734-1140

Oleanolic acid derivative methyl 3,11-dioxoolean-12-en-28-olate targets multidrug resistance related to ABCB1

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Abstract:
Multidrug resistance (MDR) in leukemia patients is a great incentive to the development of new drugs. In a search for potential multidrug resistance modulators we tested a group of oleanolic acid (OA) analogues modified at C-3, C-11, C-12 and C-28 using an experimental model consisting of three human acute lymphoblastic leukemia cell lines (CCRF-CEM and the multidrug resistant sublines CCRF-VCR1000 and CCRF-ADR5000).
The most effective compound, methyl 3,11-dioxoolean-12-en-28-olate (DIOXOL) was more potent in cell viability inhibition than its precursor – OA, and showed similar or even higher activity in the drug resistant than in the wild-type cells. Resistance factor (RF) values obtained for CCRF-VCR1000 and CCRF-ADR-5000 cells using MTT assay were 0.7 and 0.8 (24 h of treatment) and after 72 h of treatment 0.9 and 1.1, respectively. Moreover, 5 μM DIOXOL significantly reduced the expression of the *ABCB1* gene in MDR cells by around 30%, and also decreased the level of P-gp protein. Compared to untreated control cells, DIOXOL treatment resulted in a significant P-gp decrease (30% in CCRF-ADR5000 and 50% in CCRF-VCR1000), that was detected by western blot and confirmed by flow cytometry analysis. Moreover, DIOXOL (at 10 μM) significantly inhibited P-gp transport function by more than twofold comparing to control, untreated cells that was demonstrated using rhodamine 123-based functional test. The compound exhibited synergistic activity with ABCB1 substrate – adriamycin in CCRF-VCR1000 cells, indicating partial but significant MDR reversing ability.

Key words:
multidrug resistance, P-gp, oleanolic acid derivatives, acute lymphoblastic leukemia cells, chemotherapy