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Shikonin derivatives trigger phenotype reprogramming of B16 mouse melanoma cells

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Shikonin is a naphthoquinone found in the roots of plants of the *Boraginaceae* family and is widely known for its numerous biological activities, including anticancer. In this study, the antitumor mode of action of shikonin derivatives isolated from the roots of *Onosma visianii* was investigated in mouse melanoma cell line B16. MTT and CV assays showed that six examined shikonins decreased B16 cell viability in a dose-dependent manner, with compounds 5 and 6 exhibiting the highest cytotoxic activity. This effect correlated with caspase-mediated apoptosis, which was detected by flow cytometry and fluorescence microscopy. In addition, CFSE staining revealed a strong blockage of cell division in response to treatment, with a more profound effect of compound 6. The altered cell morphology together with the loss of dividing potential upon exposure to both shikonins implied reprogramming of the B16 cell phenotype. The absence of melanogenesis enhancement coupled with an elevated level of myelin basic protein in response to treatment with both tested agents suggested that the cells transdifferentiated into a Schwann-like phenotype, with possible involvement of the autophagic process in this conversion. Differentiation of malignant cells has become favourable in cancer treatment, bearing in mind the phenomenon of apoptosis-induced proliferation. Hence, the specific antitumor mode of action of shikonin derivatives on melanoma *in vitro* shown here provides a good platform for new investigations of these promising natural compounds.

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