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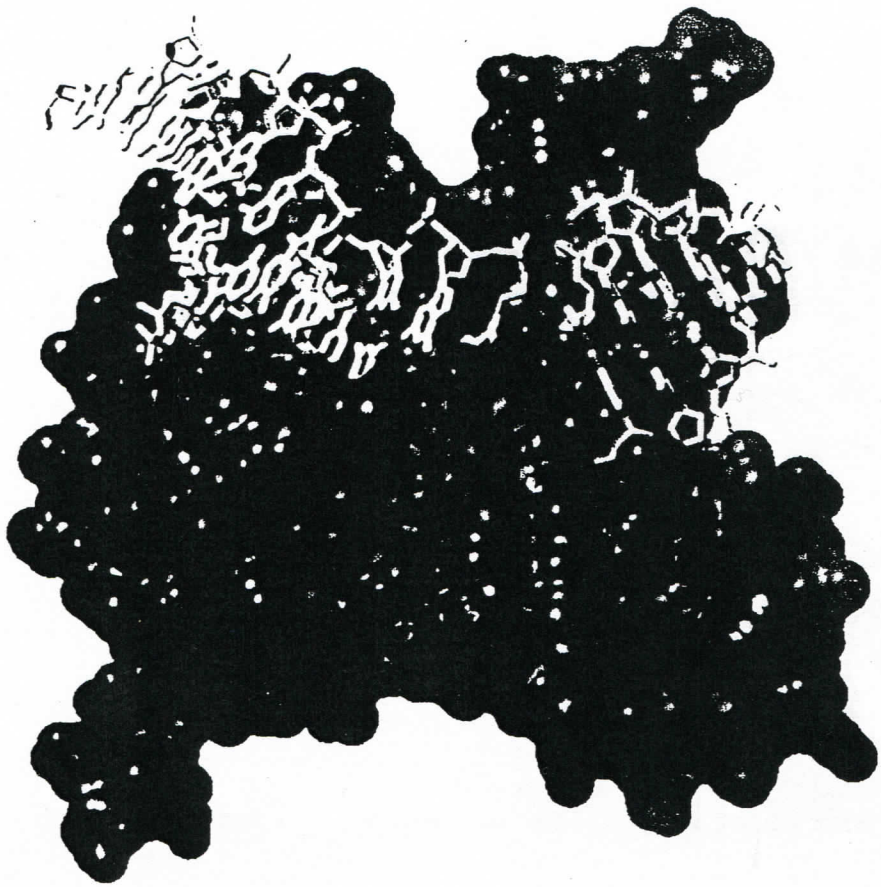

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ANTIPROLIFERATIVE AND APOPTOTIC EFFECTS OF NATURALLY OCCURRING PHENOLIC COMPOUNDS ON DIFFERENT CANCER CELL LINES

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Introduction: With the rapid advances in biomedical researches, there has been a growing interest in screening natural products for their potential use in disease prevention and treatment. One remarkable compound in this list is resveratrol (RV), which possesses a wide range of pharmacological properties and has been proposed as a cancer chemotherapeutic agent (1). The multifunctional activities of RV encouraged us to evaluate the in vitro cytostatic activity of phenolic compounds, isolated from Yucca schidigera (2) and Y. gloriosa (unpublished data), which contain the stilbene moiety related to RV.
Methods: Tested compounds were made up of a stilbene core linked via a γ-lactone ring to one (yuccaol 1, 10, A-D) or two (gloriosaol A-D) C15 moieties related to a flavonoid skeleton. Cancer cell lines: HepG2, U937, MOLT4. Proliferation assay: cells following 24 and 48h treatment were quantified by the acid phosphatase method (4). Cytotoxicity was determined by Lactate-DH leakage. Apoptosis was evaluated by flow cytometry by measuring the increase of hypodiploid elements (5) or the exposure of phosphatidylserine on plasma membrane (annexin V-propidium iodide).
Results: Among tested compounds, yuccaol D and gloriosaol 1, were found to be more effective than RV as cytostatic agents on both HepG2 and U937 cells.
However, differently from RV, these molecules appeared to cause cell death rather than unpaired cell-cycle progression. In particular, the measurement of LDH release, hypdiploidia induction and phosphatidylserine exposure indicated that these compounds exerted their effects by inducing both types of cell death, necrosis and apoptosis. As the promonocytic cell line, U937, resulted more susceptible than HepG2 cells to the cytotoxic effect of tested compounds, the apoptotic potential of the highly active compound gloriosaol 1 was further evaluated on MOLT4, a lymphoblastic leukemia cell line. The lower susceptibility of this p53 expressing cell line as compared to that of p53-null U937 cells, suggests that gloriosaol 1-induced apoptosis is not related to p53 activation.

References
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16.18

ROLE OF MITOCHONDRIA AND REACTIVE OXYGEN SPECIES IN THE DIFFERENTIATION PROCESS OF HUMAN MONOCYTE-DERIVED DENDRITIC CELLS

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Introduction: Dendritic cells (DC) are potent antigen presenting cells (APC) with a unique ability in inducing T and B cell response and immune tolerance (1). DC derive from bone marrow precursors and reside in an immature state in peripheral tissues where they exert a sentinel function for incoming antigens (Ag). Following an encounter with an Ag, DC undergo a maturation process that enhances their APC function and promotes their migration to the draining lymph nodes where they present processed Ag to naive T cells. Recent studies suggest a role for Reactive Oxygen Species (ROS) as essential second messengers for DC response to several physiological stimuli (2). It is well established that the basal production of cellular ROS is mainly due to the mitochondrial electron transport chain. Two sites of the mitochondrial respiratory chain, namely complex I and complex III, have been suggested to be the major source of ROS.
We are currently investigating the role of mitochondrial oxidative phosphorylation system in the differentiation and maturation processes of DC.
Materials and Methods: Human DC were generated from immuno-magnetically selected CD14+-monocytes and characterised by flow cytometry with anti-CD14, CD1a, MHC-II, CD83 and CCR7 monoclonal antibodies. Oxygen consumption was measured in a Rank Brothers oxygraph at 37° C. Cell viability was assessed by flow cytometry, using FITC-conjugated annexin V and propidium iodide.
Results: Our preliminary results show that i): the differentiation process of monocytes into dendritic cells is characterised by an increase of endogenous respiration, and ii) the presence of sub-saturating concentrations of the complex I inhibitor rotenone (180 nM) inhibits DC differentiation process. Accordingly, rotenone-treated cells showed an increased expression of CD14 (monocyte marker), a decreased expression of CD1a (marker of DC differentiation), and the presence of CCR7, a chemokine receptor involved in the trafficking and homing of DC to secondary lymphoid organs. Given the strategic localization of DC at the interface of innate and adaptive immunity, this study may provide the rational for the identification of new targets in the regulation of DC functions.

References
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