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Decrease of Cyclophosphamide Haematotoxicity by *Rhodiola rosea* Root Extract in Mice with Ehrlich and Lewis Transplantable Tumours

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BIOLOGICAL RESPONSE MODIFIERS may decrease haematotoxicity during cancer chemotherapy [1]. Many such modifiers are of natural origin [2]. One such is *Rhodiola rosea* root extract (RRRE), used in Siberian folk medicine for many diseases, including cancer [3]. Our aim was to study the effect of RRRE on neoplastic and normal haemapoietic cell precursors of mice with Ehrlich ascites tumour (EAT) and Lewis lung carcinoma (3LL) treated with cyclophosphamide 100 mg/kg. RRRE 0.5 ml/kg was given orally daily from 2–8 days after EAT and 3LL transplantation (7 doses). We evaluated the numbers of leucocytes and myelokariocytes, weight of tumours and extent of metastases in mice with 3LL, and relative number of viable EAT cells. Neoplastic (0.3×10^5) and haemapoietic (0.5×10^6) elements were placed in diffusion chambers and implanted intraperitoneally in syngenaic mice [4]. Colonies were counted on the 5th day.

Cyclophosphamide suppressed the growth of both tumours to 31–39% ($P < 0.05$) and extent of metastases of 3LL to 18%. Corresponding figures for RRRE were 19–27% and 16% ($P < 0.05$). However, while cyclophosphamide inhibited the numbers of leucocytes and myelokariocytes to 40–50% ($P < 0.05$) and 20–25%, respectively, RRRE had no effect on these indices. In combination, RRRE increased by 36% the antimetastatic activity of cyclophosphamide ($P < 0.05$) and enhanced the number of leucocytes and myelokariocytes by 30% ($P < 0.05$) and 16–18%, respectively.

Cyclophosphamide inhibited the proliferation of all the clonogenic cells assessed (Table 1); RRRE inhibited only tumour cells. The combination resulted in summation of these effects, and complete abrogation of the haematotoxicity of cyclophosphamide.

The results indicate that RRRE selectively inhibited the proliferation of tumour-disseminating elements, enhanced the antimetastatic and antitumour activities of cyclophosphamide, and decreased its haematotoxicity. This effect could be linked to different actions of RRRE on the clonogenic elements of both tissues.

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Table 1. Effect of RRRE and cyclophosphamide on colony-forming activity of myelokariocytes and cells of EAT and 3LL mice tumours (% of control)

	CFA of tumour cells		CFA of myelokariocytes	
	EAT	3LL	EAT	3LL
Control	100	100	100	100
Cyclophosphamide	53.6*	52.6*	47.5*	42.9*
RRRE	67.9*	63.2*	103.8	104.2
RRRE + cyclophosphamide	43.4†	42.1	105.0†	124.3†

CFA = colony-forming activity.
* Statistically significant difference from non-injected (control) mice.
† Statistically significant difference from mice injected with cyclophosphamide.

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In vitro Interaction between Retinoids and Cytokines in Human Myeloid Leukaemia Cells

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PECK AND BOLLAG [1] reported that interferon-beta (INF-β) has no potentiating effect on retinoid-induced differentiation of human HL-60 and U937 cells after only 2 days of incubation. Previously, Ho [2] showed a significant synergistic anticellular effect between INF-β and tretinoin in U937 cells, but only after 4 and not 2 days of incubation. I have studied the effect of IFN-β with and without tretinoin on U937 cells.

U937 cells were cultured at 10^5 ml in 24-well plates containing RPMI 1640 supplemented with l-glutamine and 10% fetal calf serum for 4 days at 37°C in a humidified incubator in 7.5% CO_2. Recombinant human INF-β_2 (interleukin 6, IL-6) was added at 1–1000 U/ml either alone or with tretinoin at 1–100 nmol/l. After 4 days, viable cells were counted by trypan blue exclusion, and differentiation was assessed by nitroblue tetrazolium dye reduction; at least 500 cells were scored for positivity. IC_{50} was the concentration of tretinoin inducing either 50% inhibition of

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