Effects of Coumarins on Haemopoietic Tumor Cell Lines *in Vitro* and Bone Marrow Cells *in Vivo*

K.H.A. Al-Jorany*

ABSTRACT

The antiproliferative and cytotoxic effects of closely related coumarins, including esculetin, scopoletin and umbelliferone against human T, B lymphoid, myeloid, erythroid and mastocytoma cell lines, were studied *in vitro*. Esculetin was found to inhibit, dose-dependently, the proliferation of most cell lines. Myeloblastic leukemia, KG-1, was the most sensitive to the effect of esculetin. The Lc 50 was 24.7 μM. Other cell lines were also susceptible to the effect of esculetin. CEM demonstrated an Lc 50 of 35.2 μM, and EBV-transformed cell lines demonstrated an Lc 50 of 41.7 and 46.9 μM. Some cell lines were quite resistant and include T-cell line Ke 37 and the erythroblastic leukemia K562. Interestingly, CTLL16, a crytotoxic normal T-cell line which is dependent on its growth on IL-2, did not show any appreciable cytotoxic effect to esculetin even when the cell had undergone 2 cycles of cell division.

Mastocytoma showed in vitro stimulation by esculetin at low concentrations and by scopletin and umbelliferone at high concentrations. *In vivo* studies indicated that esculetin, scopoletin and umbelliferone were potent inhibitors of bone marrow mitosis. The results were discussed based on available data relating the effects of esculetin on leukotrienes and leukotrienes role in cell growth.

INTRODUCTION

Coumarins are a class of compounds that include esculetin (a well-known inhibitor of lipoxygenase enzyme) (Sekiya, et al., 1982; Neichi et al., 1983; Panossian, 1984; Kimura, et al., 1985), scopoletin, umbelliferon and warfarin.

* Associate Professor, College of Medical Sciences, Applied Science University, Amman, 11931, Jordan. Received on 21/7/1997 and Accepted for Publication on 5/7/1998.

Warfarin is a well-known inhibitor of vitamin K epoxide reductase (Olson, 1984). Recently, additional studies of the effect of esculetin demonstrated its inhibition of human lymphocyte proliferation and human T cyctotoxic cell generation in vitro (Kabelitz and Al-Gorany, 1989), lymphoid and myeloid stem cell in vitro (Vore, et al., 1989), and GM-CFC clonal proliferation in vivo (Kozabik, et al., 1994).

Mammary tumor cell proliferation inhibition by esculetin was demonstrated in one study (Noguchi, et al., 1993) but not in another (Lee and Ip, 1992).

The contribution of lipoxygenase enzyme and its products leukotrienes to growth of rat and human giloma were also reported, and the involvement of esculetin inhibition to giloma growth was documented (Wilson, et al., 1989; Blomgren and Kling-Anderson, 1992). Besides its antiproliferative effects, the effects of esculetin were attributed to its inhibition, dose-dependently, to tyrosine kinase that involved in signal transduction and DNA synthesis (Huang, et al., 1993; Ondręy, et al., 1989).

In this study, the effects of closely related coumarins, namely, esculetin, scopoletin and umbelliferone on hemopoietic tumor cell lines *in vitro*, as well as the effects of the compounds on bone marrow proliferation *in vivo*, were evaluated.

MATERIALS AND METHODS

Coumarins

Esculetin (6,7-dihydroxycoumarin), scopoletin (7-hydroxy-6-methoxy coumarin), and umbelliferone (7-hydroxycoumarin) were purchased from Fluka AG (Switzerland). The structural formula is shown in (Fig. 1). MTT, a 3-(4, 5-dimethylthiazol-z-yl)- 2, 5- diphenyltetra-zolium bromide), was obtained from Sigma (Munich, FRG). Coumarins were dissolved in sterile saline solubilized with 0.1 N sodium hydroxide, filter

sterilized and further diluted to a working concentration in 2x strength RPM1-1640 medium. The solvent control was sterile saline, 0.1 N sodium hydroxide and 2x strength RPM1-1640 medium. It did not have any influence on cell viability.

Tumor Cell Lines

Tumor cell lines included human T cell, human B cell, human myeloid, in addition to mouse thymoma and mastocytoma. The lineage of these cell lines is shown in (Table 2). In addition, a non-tumor CTLL-16, a cytototxic T cell line that depends on Interleukin-2 (IL-2) for its growth, was included as a control. The cells were grown in the presence of 10 U/mL (IL-2).

Cell Culture

All tumor cell lines were routinely cultured in RPM1-1640 medium, supplemented with 10% heat inactivated fetal bovine serum, L-glutamine and antibiotics (Biochrom, Berlin, FRG). The cells were harvested from the exponential growth period; viability always exceeded 95%.

In order to check for a direct relationship between cell numbers and optical densities (ods) in the MTT-assay, an experiment that involved different cell numbers for each cell line and the degree of MTT-splitting was conducted.

Chemosensitivity Testing

This was done according to Cole S.P.C. 1986, as follows: cells cultured in T-25 flasks (Nunce, Roskide, Denmark) were harvested by centrifugation, washed with RPM1 medium, resuspended in fresh medium, and counted; viability was assessed by Eosine- Y exclusion test. Cells were plated at 2 x 10^4 cells/ well in a volume of 100 µl, except for EBV-transformed cell lines that were plated at 3 x 10^4 cells/ well, using a 96-well flat bottom microtitration plate (Nunc, Roskilde, Denmark).

Chemicals, serially diluted with medium, were replicated at 100 µL onto plated cells. Controls included cells plus medium without chemicals and medium plus chemicals. All tests were done in quadruplicate, and incubation was for 3 days at 37°C in a humidified 5% CO_2 incubator. At the end of the incubation period, 100 µL fresh medium was added to each well and the plate was centrifuged using a 96-well plate holder at 1200 r.p.m for ten minutes. Then 200 µL of supernatants was removed from all wells and a 20 µL MTT (2.5 mg/mL phosphate buffered saline) was added to every well, followed by incubation for three hours at 37°C in a humidified CO_2 incubator. The MTT splitting reaction was stopped by adding 100 µL/ well 1N HCl: 1-propanol (1:24), followed by mixing to dissolve the blue crystals. Viabilities were assessed from ods values using Dynatech micro ELISA reader. The test wavelength was 570 µM, and the reference wavelength was 620 µM. The blank wells contained medium and MTT, and their ods values were always substracted from the test values.

Effects of Coumarins on Bone Marrow Cells *in Vivo*

Esculetin, scopoletin and umbelliferone were prepared in sterile saline at 200 and 400 µg/0.2 mL. Each chemical, at 200 and 400 µg/ 0.2 mL, was given to a group of 6 C_{57}/ BL mice. Mice test groups received 8 intraperitoneal injections every second day; control mice received sterile saline only. Mice test groups rested for 2 days before being sacrified. Mitosis was arrested by giving the mice 40 µg of animal colchicin per animal (Fluka, Switzerland). The mice were treated with colchicin for four hours. The bone marrow was obtained from femurs. The marrow was flushed with 5 mL saline and collected by centrifugation. Hypotonic shock, fixation, chromosome spreading, and staining were done essentially according to Andrew, et al., (1986). Mitosis was enumerated on stained slides by counting 500 cells. Percent dividing cells and percent inhibition were calculated by the formula:

$$\% \text{ dividing} = \frac{\text{Total dividing cells}}{\text{Total dividing cells + non dividing cells}} \times 100$$

$$\% \text{ inhibition} = \frac{\text{Number of dividing cells of control - Number of dividing cells of test}}{\text{Number of dividing cells of control}} \times 100$$

Statistical analysis was done using student t-test. (Milton, 1992).

RESULTS

The relationship of viable cell numbers and the degree of MTT-splitting

An experiment was performed to ensure a good relationship between viable numbers and the degree of MTT-splitting. The results indicated that there was a good linear relationship between the cell numbers and the degree of MTT-splitting (ods). The linear relationship covered 1560-10,000 cells (Data not shown).

Effect of Esculetin Pretreatment

EBV-Gieger cell lines were treated with esculetin for 6 hours at 125 and 250 μM. Esculetin did not show any cytotoxicity to the cell line (Table 1). Cells pretreated for 6 hours were washed out from the chemical, resumed their growth and showed normal growth.

Effect of Coumarins on Human Tumor T Cell Lines

The influence of esculetin, scopoletin and umbelliferone on three human tumor T cell lines and one mouse thymoma cell line is shown in (Fig. 2). A progressive depletion of viable cell numbers is evident for the four cell lines at 62 μM esculetin. However, scopoletin and umpileferon did not show any effect on Molt-4, CEM and Ke 37 cell lines, whereas they were slightly active against the mouse thymoma cell line BW5417.

The calculated lethal concentration fifty (Lc 50) for esculetin were 59.6, 35.2, 209.1 and 73.9 μM for Molt-4, CEM, Ke 37 and Thymoma 5417, respectively (Table 2).

Effect of Coumarins on Human Tumor B Cell Lines

As shown in (Fig. 3, a,b), esculetin, dose-dependently, was cytotoxic to two B cell lines, and the chemical was almost completely cytotoxic at 500 μM concentration. Scopoletin and umbelliferone did show cytotoxicity toward both B cell lines at higher chemical concentrations compared to controls.

Effect of Coumarins on Myeloid Tumor Cell Lines

Figures (3 and 4) show that esculetin has the same cytotoxic effect on myeloid tumor cell lines HL-60, KG-1 and the monoblastic tumor cell line U937. The calculated Lc50 were 60.1, 24.7 and 125 μM for HL-60, KG-1 and U937, respectively (Table 2). On the other hand, scopoletin and umbelliferone showed slight cytotoxic effects on these three cell lines.

Effect of Coumarins on an Erythroblastic Leukemia Cell Line

K562, an erthroblastic leukemia cell line, was the least affected by esculetin, even at high concentrations. The calculated lethal concentration fifty was 389.8 μM (Table 2). Scopoletin and umbelliferone did not show any effect on this tumor cell type. Likewise, scopoletin and umbelliferone were nontoxic (Figs. 3 and 4).

Effect of Coumarins on a Mastocytoma Cell Line

Figure (4) shows the effect of coumarins on a mastocytoma cell line. This cell line was stimulated at 15.625 μM esculetin. Increasing esculetin concentration showed dose-dependent cytotoxicity to this cell line. The Lc 50 value for esculetin was 67.5 μM. (Table 2). In addition, scopoletin and umbelliferone treatments were stimulatory for their growth, even at higher concentrations.

Effects of Esculetin on CTLL-16 Cytotoxic T-cell Line

Interestingly, esculetin did not show any appreciable cytotoxicity toward CTLL-16, cytotoxic T cell line, that is dependent on IL-2 for its growth (Table 3).

Inhibition of Bone Marrow Mitosis by Coumarins

Coumarins administered to $C_{57}BL$ mice were assessed for their cytotoxicity and/or inhibition of proliferating bone marrow cells. The three compounds produced inhibition of mitosis of bone marrow dividing cells.

Esculetin showed 68.28% inhibition at 200 µg toward treated mice. At 400 µg, however, the percent inhibition decreased to 62.23%.

Scopoletin treatment produced the same effect as esculetin. However, umbelliferone was much more inhibitory to bone marrow dividing cells. At 200 and 400 µg doses, the percent inhibition of mitotically active cells reached 73.23% and 75.71%, respectively. All the effects were statistically significant (Table 4).

DISCUSSION

Coumarins are natural chemical products (Lau Cam, 1978), which include esculetin. Esculetin proved to be a potent lipoxygenase enzyme inhibitor (Sekiya, et al., 1982; Neichi, et al., 1983). The contribution of the lipoxygenase enzyme to leukotriene's production is well demonstrated (Samuelsson, 1983) and lipoxygenase inhibition by esculetin will inhibit leukotriene's production (Kimura, et al., 1985). The fact that cell growth was shown to depend on leukotrienes rather than prostaglandins makes esculetin a good modulator of cell growth (Hata, et al., 1987).

In this study, coumarins, including esculetin, scopoletin and umbelliferone, which are structurally related, were evaluated for their *in vitro* and *in vivo* antiproliferative activities against a wide range of hemopoietic human and mouse tumor cell lines. As shown in (Table 1), esculetin did not have any direct cytotoxic effect during the six-hour treatment of cells. The recovery of control nontreated comparable growth after removal of esculetin was seen. The drop in viability after 24 hours of treatment might indicate that there is a prerequisite target for esculetin's effect.

In the latter experiment, (Figs. 2, 3 and 4) dealt with the effect of esculetin, scopoletin and umbelliferone on in vitro proliferating cells. It seems that esculetin was the most active cytotoxic compound towards proliferating cells. The most sensitive cell line to the cyotoxicity of esculetin was the human myeloblastic leukemia cell line KG-1, with the calculated Lc 50 of 24.7 µM. In this regard, it has been reported that esculetin inhibits lymphoid and myeloid stem cell proliferation (Vore, et al., 1989). This effect was attributed to the depletion of leukotriene B4 (LTB4). In addition, esculetin inhibits GM-CFC stem cell clonal proliferation, dose-dependently (Kozubik, et al., 1994). The efficient inhibition of KG-1 myeloblastic cell line in the present study may be due to the blocking of leukotrienes biosynthesis by esculetin. Nontheless, other cell lines, which include Molt-4, CEM, T cell lines, EBV-transformed B cell lines thymoma and mastocytoma, were also susceptible to the cytotoxic effect of esculetin (Table 2).

Most of these cell lines are lymphomas. It was shown that prostaglandin F2 (PGF_2) was inhibitory to some types of lymphoma (Phipps, et al., 1989). In another study, however, esculetin inhibited smooth muscle growth by its effect on decreasing PGE_2 (Huang, et al., 1993). The inhibition of these cell lines may be due to the fact that the inhibition of lipoxygenase will shuffle arachidonic acid to the production of PGF_2 at the expense of PGE_2, which might produce the effects seen among lymphoma inhibition. This notion requires further studies. The studies of the antiproliferative effect of esculetin demonstrated that rat mammary tumor cell line, TMT-081, was insensitive to esculetin (Lee, 1992), while in another study, a significant antiproliferative effect was seen in rat mammary carincoma (Noguchi, et al., 1993). This was attributed to a critical balance of the various eicosanoids within cells, which is important for cell proliferation and survival.

Interestingly, esculetin, which proved to be a potent cytotoxic compound for most cell lines studied, did not show any appreciable cytotoxicity for CTLL-16, a cytotoxic T-cell line that depends on IL-2 for its growth. Whether IL-2 bypassed the inhibitory effect of esculetin remains to be known by further studies.

Other findings in this study indicated that scopoletin and umbelliferone were less effective as cytotoxic compounds *in vitro*. However, these two compounds proved to be potent in inhibiting cell proliferation *in vivo*. Mice that were treated with these two compounds showed a very significant decrease in mitotically active cells, and inhibition of mitosis was very pronounced (Table 4). Scopoletin (7-hydroxy, 6-methoxy coumarin) and umbelliferone (7-hydroxy coumarin) (Fig. 1), which were ineffective as cytotoxic compounds in vitro, must have undergone biotransformation *in vivo* to more active compounds. It was reported by Huang, et al. (1993) that C-6 and C-7 adjacent phenolic groups are necessary for antiproliferative effects of coumarins. The acquisition of C-6 hydroxyl group instead of 6-methoxy for scopoletin and the addition of 6-hydroxyl group to umbelliferone are possibilities. Other changes may be possible too. It has also been reported that coumarins undergo biotransformation in vivo (Legrum and Netter, 1980).

Another interesting finding includes the stimulatory effect of esculetin on mastocytoma at narrow ranges of concentrations (15.62 and 31.25 μM) and the stimulatory effects of scopoletin and umbelliferone to this cell type at higher concentrations (Fig. 4a). The biochemical basis of the stimulatory effects needs further investigation.

From the findings present in this report and the known mechanisms of esculetin-mediated inhibition of cell growth which includes depletion of leukotrienes (Ondrey, et al., 1989; Vore, et al., 1989; Wilson, et al., 1989; Rose and Connlly, 1990), and tyrosine kinase inhibition (Huang, et al., 1993), the exact nature of coumarins effect on cell proliferation remains to be seen.

Table 1. Effect of esculetin pretreatment on the viability of the human B cell line EBV-Gieger.

Esculetin Conc.	Esculetin treatment time (hours)	
(μM)	6	24
0	0.28 ± 0.05	0.08 ± 0.00
125	0.28 ± 0.05	0.06 ± 0.00
250	0.284± 0.01	0.022 ± 0.09

EBV-Gieger cell line was cultured at $3x10^4$ cells/well and treated with esculetin for the times indicated. The chemical was removed by washing and the cells were resuspended in the medium and allowed to grow for 3 days. Viability was assessed by MTT-assay. Numbers represent the OD mean values for triplicates ± SD.

Table 2. Calculated lethal concentration fifty (Lc 50) for the different haematopoietic cell lines.

Tumor cell line	Lc 50 (μM)
Human tumor T cell lines:	
Molt-4	59.6
CEM	35.2
Ke37	209.1
Human EBV-Transformed Cell lines:	
EBV-Gieger	41.7
EBV-Varweller	46.9
Human myeloid cell lines	
Monoblastic Leukemia U-937	125.0
Myeloblastic Leukemia KG-1	24.7
Promyelcytic Leukemia HL-60	60.1
Human Erythroblastic Leukemia K-562	389.8
Mouse leukemic cell lines:	
Thymoma BW 5417	73.9
Mastomytoma P 815	67.5
Normal Cell line:	
CTLL-16	257.0

Lc 50 values were derived from computer generated linear regression data of cytotoxicity dose response curves. Conditions of growth, MTT-assay, were as indicated in the text.

Table 3. Effect of esculetin treatment on CTLL-16 T-cell line.

Esculetin (μM)	CTLL-16 viability
0	0.28 ± 0.05
0.25	0.26 ± 0.04
0.5	0.25 ± 0.03
1	0.24 ± 0.03
2	0.24 ± 0.03
4	0.24 ± 0.03
8	0.25 ± 0.03
16	0.24 ± 0.03
32	0.22 ± 0.03
64	0.20 ± 0.02
128	0.20 ± 0.02
256	0.16 ± 0.01

▪ Viability was assessed by MTT-assay. Numbers represent O.D mean values of triplicates ± SD.

Table 4. Inhibition of bone marrow mitosis by coumarins.

Treatment (μM)	% Dividing Cells	% Inhibition
Esculetin		
200	3.79 ± 0.12 ($p < 0.05$)	68.28
400	4.52 ± 0.76 ($p < 0.05$)	62.23
Scopoletin		
200	4.37 ± 0.38 ($p < 0.05$)	63.42
400	3.78 ± 0.17 ($p < 0.02$)	68.39
Umbelliferone		
200	3.20 ± 0.18 ($p < 0.02$)	73.23
400	2.90 ± 0.10 ($p < 0.001$)	75.71
Control	11.96 ± 0.02	

Values derived form 6 replicate treatments.

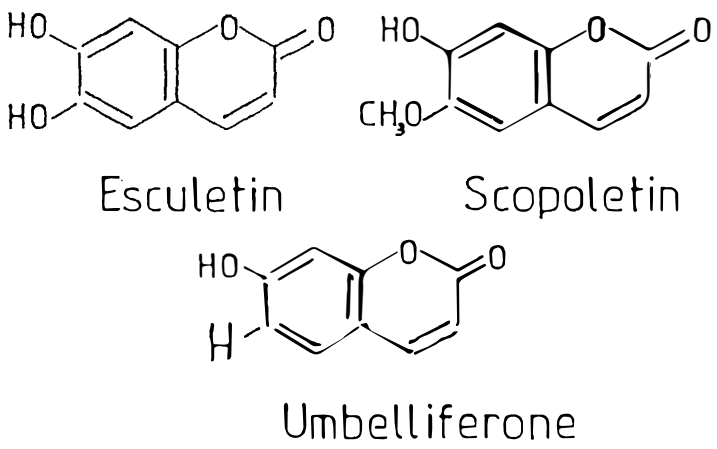

Figure 1: The structural formulae of closely related coumarins: esculetin, scopoletin and umbelliferone.

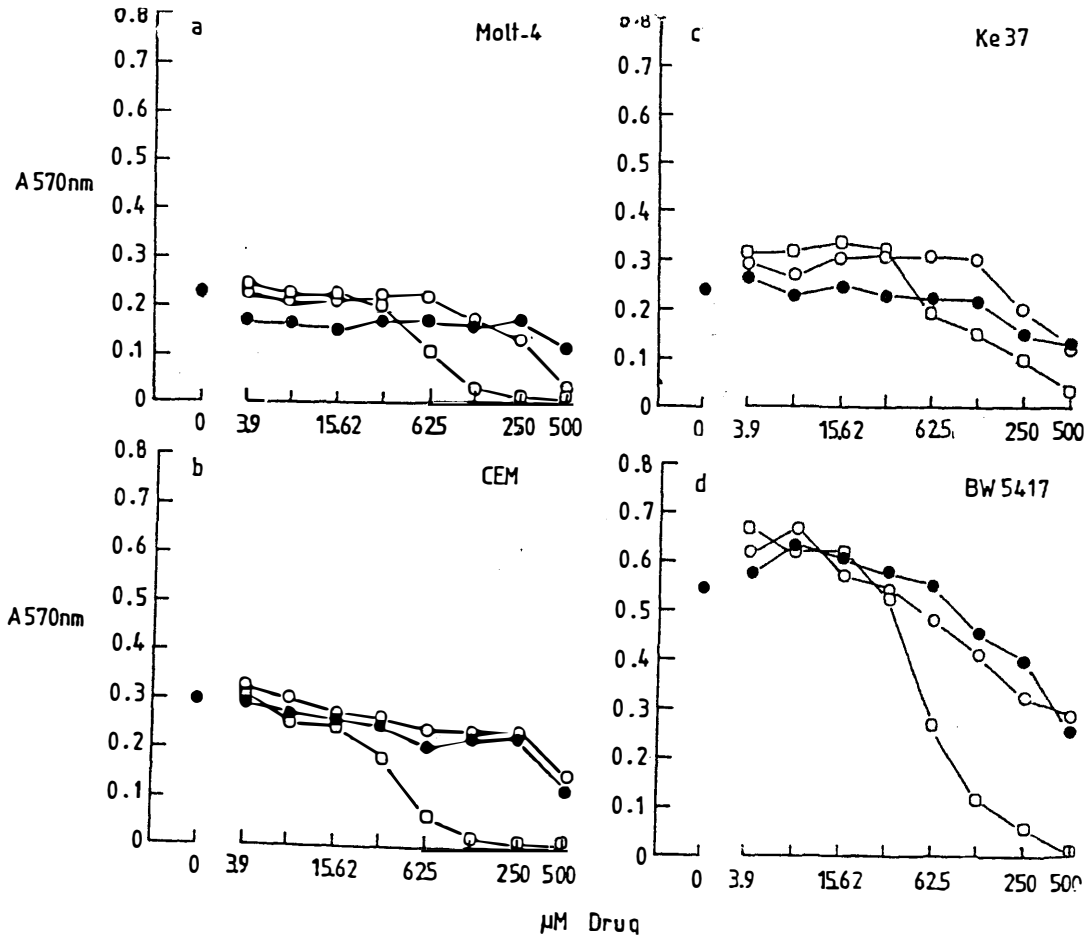

Figure 2: Effects of umbelliferon (•), scopoletin (o) and esculetin (□) on the growth of: a-Molt-4, b-CEM, c-Ke 37, d-BW 5417 thymoma after 72 h continuous exposure to the three compounds. Point represents the mean of three determinations. Bars that represent SDs of means were omitted for clarity.

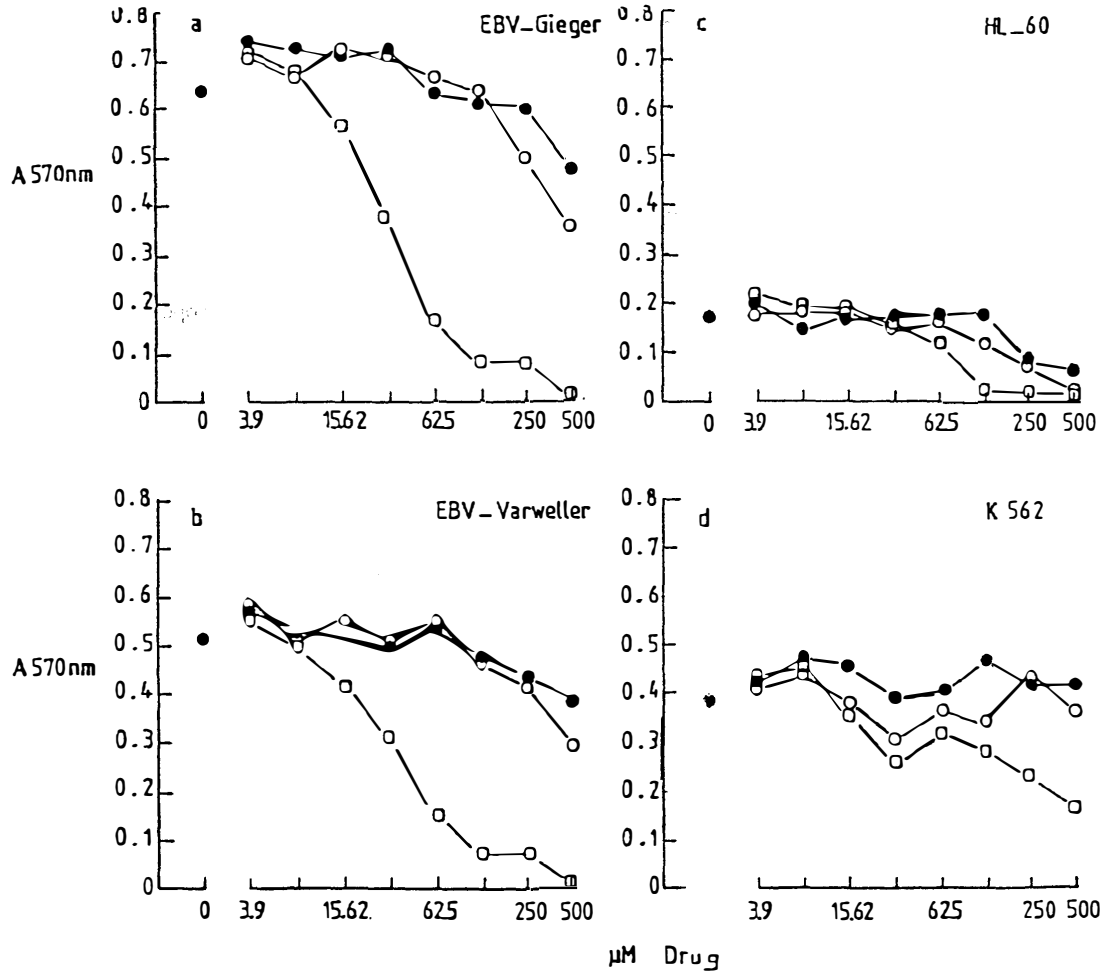

Figure 3: Effects of umbelliferon (•), scopoletin (o) and esculetin (□) on the growth of: a-EBV-Gieger, b-EBV-Varweller, c-HL-60, promyelocytic leukemia cell line, d-K562 erythroblastic cell line after 72 h continuous exposure to the three compounds. Point represents the mean of three determinations. Bars that represent SDs of means were omitted for clarity.

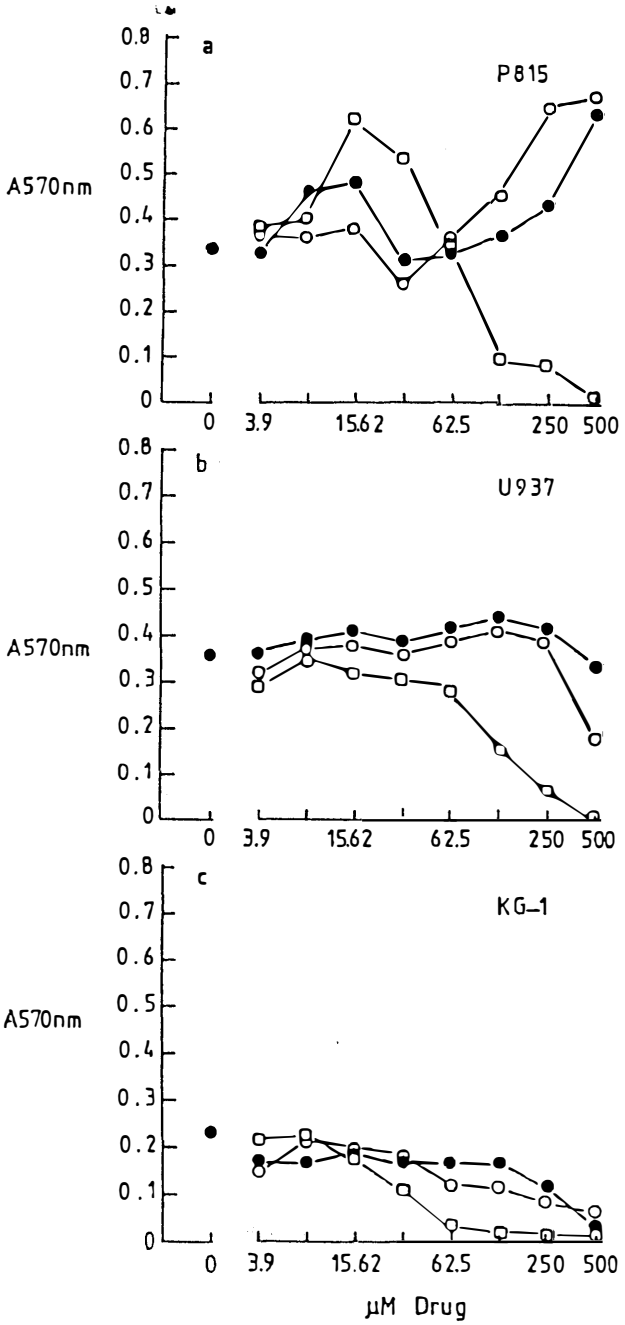

Figure 4: Effects of umbelliferon (•), scopoletin (o) and esculetin (□) on the growth of: a-Mastocytoma, b-human monoblastic cell line U 973, and c-human myeloblastic cell line KG1 after 72 h continuous exposure to the three compounds. Point represents the mean of three determinations. Bars that represent SDs of means were omitted for clarity.

REFERENCES

Andrew, J.H., G.M. Wadhwa, and A.D. Perris. 1986. In Vitro Administration of Interleukin-2 Stimulates Mitosis in Thymus and Bone Marrow. *Eur. J. Immuno,* 16: 1171–1174.

Blomgren, H., and G. Kling-Anderson. 1992. Growth Inhibition of Human Malignant Glioma Cells in Vitro by Agents which Interfere with Biosynthesis of Eicosanoids. *Anticancer. Res.,* 12: 981–986.

Cole, S.P.C. 1986. Rapid Chemosensitivity Testing of Human Tumor Cells using MTT Assay. *Cancer Chemotherapy and Pharmacology,* 17: 259–263.

Hata, S., et al., 1987. Synthesis of Sterols and 5-Lipoxygenase Products are Required for G1-S Phase Transition of Interleukin-2 Dependent Lymphocyte Proliferation. Microbio. *Immuno.*, 31: 1231–1244.

Huang, H.C., et al., 1993. Antiproliferative Effects of Esculetin on Vascular Smooth Muscle Cell: Possible Role of Signal Transduction Pathways. *Eur. J. Pharmacol,* 237: 39–44.

Kabelitz, D., and K.H. Al-Gorany. 1989. Esculetin Inhibits T Cell Activation Without Suppressing IL-2 Production or IL-2 Receptor Expression. *Immunol. Lett,* 20: 241–245.

Kimura, Y., et al., 1985. Inhibition of the Formation of 5-hydroxy-6, 8, 11, 14-eicosatetraenoic Acid from Arachidonic Acid in Polymorphonuclear Leukocytes by Various Coumarins. *Biochemica et Biophysca Acta*, 834: 224–229.

Kozubik, A., et al., 1994. Effects of Drugs Inhibiting Prostaglandin or Leukotriene Biosynthesis on Post Irriadiation Haematopoiesis in Mouse. *Int. J. Radiat. Biol.,* 65: 369–377.

Lau Cam, C.A. 1978. Thin Layer Chromatography of Coumarins of Medicinal and Phytochemical Interests on Buffered Layers. *J. Chromatogr,* 151: 391–395.

Lee, P.P., and M.M. Ip. 1992. Regulation of Proliferation of Rat Mammary Tumor Cell by Inhibitor of Cyclooxygenase and Lipoxygenase. *Prostaglandins-Leukotessent-Fat-Acids,* 45: 21–31.

Legrum, W., and K.J. Netter. 1980. Characterization of Coumarin Metabolism by Liver Microsomes from Cobalt-Pretreated Mice. *Xenobiotica*, 10: 271–279.

Milton, J.S. 1992. *Statistical Methods in the Biological and Health Sciences.* McGraw-Hill International.

Neichi, T., Y. Koshihara, and S. Murota. 1983. Inhibition Effect of Esculetin on 5-lipoxygenase and Leukotriene Biosynthesis. *Biochemica et Biophysica Acta,* 753: 130–132.

Noguchi, M., et al., 1993. Influence of Esculetin on Incidence, Proliferation, and Cell Kinetics of Mammary Carcinoma Induced by 7, 12-dimethylbenz[a] Anthracene in Rats on High-and-low Fat Diets. *Jpn. J. Cancer. Res.,* 84: 1010–1014.

Olson, R.E. 1984. The Function and Metabolism of Vitamin K. *Anna. Rev. Nutr.,* 4: 281–337.

Ondrey, F., J.E. Harris, and K.M. Anderson. 1989. Inhibition of U937 Eicosanoid and DNA Synthesis by 5, 8, 11, 14-eicosatetraynoic Acid, an Inhibitor of Arachidonic Acid Metabolism and its Partial Reversal by Leukotriene C4. *Cancer. Res.,* 49: 1138–1142.

Panossian, A.G. 1984. Inhibition of Arachidonic Acid 5-lipoxygenase of Human Polymorphonuclear Leukocytes by Esculetin. *Biomedica et Biochemica Acta,* 43: 1351–1355.

Phipps, R.P., et al., 1989. E-series Prostaglandins are Potent Growth Inhibitors for some Lymphoma. *Eur. J. Immunol,* 19: 995–1001.

Rose, D.P., and J.M. Connoly. 1990. Effects of Fatty Acids and Inhibitors of Eicosanoids on the Growth of a Human Breast Cancer Cell Line in Culture. *Cancer. Res.,* 50: 7139–7144.

Samuelsson, B. 1983. Leukotriene Mediators of Immediate Hypersensitivity Reactions and Inflammation. *Science,* 220: 568-575.

Sekiya, K., H. Okuda, and S. Arichi. 1982. Selective Inhibition of Platelets Lipoxygenase by Esculetin. *Biochemica et Biophysica Acta,* 713: 86–72.

Vore, S.J., et al., 1989. Regulation of Murine Hematopoiesis by Arachidonic Acid Metabolites. *Int. J. Immunopharmacol,* 11: 435–442.

Wilson, D.E., et al. 1989. Effect of Nordihydroguaiaretic Acid on Cultured Rat and Human Glioma Cell Proliferation. *J. Neurosurg,* 7: 551–557.

تأثيرات الكومارينات على السلاسل المختلفة للخلايا الدموية السرطانية خارج الجسم الحي ونمو خلايا نقي العظم داخل الجسم الحي

خضر حسن علي الجوراني*

ملخص

اختبرت التأثيرات المضادة السامة للخلايا لبعض المركبات الكومارينية، الاسكولتين والسكوبولتين والامبليرفيرون تجاه سلاسل الخلايا الانسانية السرطانية اللمفاوية التائية والبائية والنقوية والحمر اضافة الى سلالة البدينة السرطانية من الفأر وسلالة خلايا CTTL-16 خارج الجسم الحي.

وجد ان الاسكولتين كان ساماً ومثبطاً لنمو معظم سلاسل الخلايا السرطانية اعتماداً على جرعته. وكانت سلاسل الخلايا السرطانية الأرومة النقوية اشد الخلايا تأثراً بالاسكولتين، وقد بلغ التركيز القاتل لهذه الخلايا 24.7 مايكرومول. وتراوحت شدة قتل الاسكولتين لانواع سلاسل الخلايا الاخرى ما بين الشديد والمتوسط، في حين كانت شدة قتل الاسكولتين لسلالة الخلايا التائية Ke37 والحمر قليلة.

والملفت للنظر، أن سلالة الخلايا غير السرطانية CTLL-16 التائية المنشأ والمعتمدة على الانترليوكين في نموها قد قاومت الفعل السام للاسكولتين. اما سلالة الخلايا البدينة فقد تحفز نموها بفعل الاسكولتين في التراكيز العليا.

اثبتت نتائج الدراسة داخل جسم الفأر ان المركبات لها فعل مثبط لانقسام خلايا نقي العظم. ونوقشت النتائج في ضوء النتائج المتوفرة لهذه المركبات وفعلها في تثبيط تخليق ليوكوترينات الخلايا ودور الليوكوترينات في النمو الخلوي.

---

* أستاذ مشارك، قسم التحاليل الطبية، جامعة العلوم التطبيقية، عمان، 11931، الأردن. تاريخ استلام البحث 21/5/1997 وتاريخ قبوله 5/7/1998.