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Cytotoxicity of Some Russian Ethnomedicinal Plants and Plant Compounds

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The cytotoxic action of crude ethanol extracts from 61 plant species used in Russian ethnomedicine for alleviating symptoms of diseases in cancer patients was studied on cultured human lymphoblastoid Raji cells. Extracts from *Chelidonium majus*, *Potentilla erecta*, *Chamaenerium angustfolium*, *Filipendula ulmaria* and *Inula helenium* possessed marked cytotoxicity, suppressing the growth of the cells at concentrations of 10 and 50 μg/mL. The cytotoxicity of purified active compounds from selected plant species was evaluated along with pharmaceutical antineoplastic drugs methotrexate, fluorouracil, cyclophosphamide and vinblastine. Sesquiterpene lactones helenin, telekin and artemisinin, aromatic polyacetylene capillin, and alkaloid preparation sanguirythrine suppressed cell growth at concentrations of 1–2 μg/mL, which exceeds the cytotoxicity of cyclophosphamide and fluorouracil. Copyright © 2005 John Wiley & Sons, Ltd.

Keywords: Russia traditional medicine; medicinal plants; cancer; cytotoxicity; lymphoblastoid Raji cells.

INTRODUCTION

Numerous plants were reputed in Russian ethnomedicine to alleviate the symptoms of diseases in cancer patients. The use of about 200 plant species for this purpose was reported (Balitskii and Vorontsova, 1982; Kuvaev *et al*., 1988; Ladynina, 1990, 1993; Rylkov *et al*., 1990). The characteristic features of the folk medicine were: a symptomatic approach to the selection of medicinal plants, the use of complex multicomponent phytopreparations versus individual plants and long-term courses of phytotherapy treatment ranging from months to years. Phytotherapeutics were taken as water infusions, decoctions or 40% ethanol extracts, with periodic changes in phytocompositions. Remarkably, there are no specific 'anticancer' plants in the folk medicine recipes. Each of the plants possesses a wide spectrum of therapeutic properties and is also employed for treatment of non-cancer patients. In particular, plants that stimulate bile excretion, possess diuretic, adaptogenic, analgesic and sedative properties were traditionally included in anticancer phytocompositions.

The results are presented of a comparative study of cytotoxicity of crude ethanol extracts from 61 plant species, and some purified secondary metabolic compounds from selected medicinal plants. Plants were studied common to Central Russia which were traditionally employed in phytotherapeutic anticancer compositions, and also some adaptogenic plants of Siberian and Far Eastern origin that were adopted in Russian ethnomedicine. Many of the species used in this work are currently employed by the official medicine (Muravieva, 1991; Mashkovskii, 2001). The cytotoxic activity of medicinal plants was estimated by the suppression of the growth of cultured human lymphoblastoid Raji cell line derived from Burkitt's lymphoma (Pulvertaft, 1964). To evaluate the cytotoxic efficiency of medicinal plants and plant compounds, the cytotoxicity of pharmaceutical antineoplastic drugs was measured in parallel experiments.

MATERIALS AND METHODS

Most of the plants used in this study were collected in the Moscow Region in the season recommended in the literature (Muravieva, 1991). Fruits of *Sophora japonica* L. were collected in Kerch, Crimea. Roots of *Scutellaria baicalensis* Georgi were collected by V. I. Bakaneva in Baikal Region, Siberia. *Acorus calamus* L., *Bergenia crassifolia* (L.) Fritsch., *Calendula officinalis* L., *Eleuterococcus senticosus* (Rupr. et Makino) Maxim., *Panax ginseng* C. A. May, *Peonia anomala* L., *Schisandra chinensis* (Turcz.) Baill. and *Valeriana officinalis* L. were from commercial sources. The plant material was dried (with the exception of *Chelidonium majus* L. and *Datura stramonium* L. which were extracted immediately after collection), and extracted with 40% ethanol at room temperature in the dark for 5–7 days.

The sesquiterpene lactones were isolated from plants collected in the Stavropol Region: artemisinin, from the aerial parts of *Artemisia annua* L.; β-santonin, from the aerial parts of *Artemisia maritima* L.; telekin, from the roots of *Telekia speciosa* (Schreb.) Baumb; helenin (40% alantolactone and 60% isoalantolactone), from the roots of *Inula helenium* L. as described (Konovalov, 1995). Sesquiterpene alcohol ledol was isolated from the aerial parts of *Ledum palustre* L. collected in Moscow Region (Konovalov, 1995). Aromatic polyacetylene capillin was isolated from the

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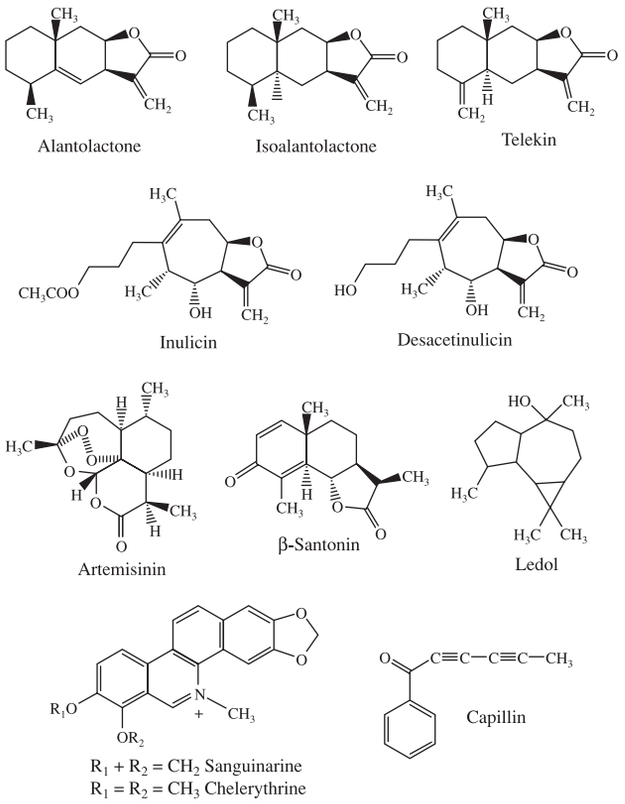

Figure 1. Structural formulas of tested compounds.

aerial parts of *Artemisia scoparia* Waldst. et Kit as described (Konovalova *et al*., 1989). Structures of isolated compounds were identified by UV, IR and NMR spectrometry using Specord M-40, Specord IR-75 (Karl Zeiss, Iena, Germany) and NMR-spectrometer HA-100D (Varian), correspondingly. The identity of the isolated compounds was confirmed by the melting temperature test using the corresponding reference compounds. Inulicin and desacetinulicin from the aerial parts of *Inula japonica* Thunb. and sanguirythrine (equimolar mix of benzophenanthridine alkaloids sanguinarine and chelerythrine from aerial parts of *Macleaya microcarpa* (Maxim.) Fedde) were generous gifts from Dr O. A. Konovalova and Dr L. D. Shipulina (All-Russian Medicinal and Aromatic Plants Research Institute, Moscow). The purity of isolated individual compounds was 95%–99%. Structural formulas for the compounds tested are presented in Fig. 1.

The cytotoxicity of crude plant extracts and purified compounds was tested on human lymphoblastoid Raji cells grown on DMEM medium in the presence of 5% fetal bovine serum (Serva) at 5% CO_2 and 37 °C. Pharmaceutical antineoplastic drugs methotrexate, fluorouracil, cyclophosphamide (Minmedprom) and vinblastine (Richter) were used as reference compounds. The tested substances were solubilized in dimethyl sulphoxide or ethanol immediately prior to experiments. Plant extracts and the tested substances were introduced into the medium simultaneously with inoculation of the cells, and the final cell density was determined after 72 h of cultivation. Cultures containing appropriate solvents were used as controls. The final concentration of ethanol or dimethyl sulphoxide in cell culture media did not exceed 0.2%, a concentration that did not affect growth of the cells.

RESULTS AND DISCUSSION

Cytotoxicity of crude plant extracts

The cytotoxic activities of extracts from different medicinal plants varied greatly. Data for the 24 most active plant species are presented in Table 1. Most of these plants contain alkaloids, sesquiterpene lactones and other terpenoids, tannins and coumarins. The greater celandine *Chelidonium majus*, the meadowsweet *Filipendula ulmaria*, the fireweed *Chamaenerium angustfolium*, the elecampane *Inula helenium* and *Potentilla erecta* displayed the highest cytotoxicity, completely suppressing the cell growth at concentrations of 10 and 50 μg/mL. Extracts from some of the tested plants (*Filipendula ulmaria*, *Potentilla erecta*, *Rumex confertus*, *Juniperus communis*, *Rhodiola rosea* and *Hyoscyamus niger*) disrupted the processes of cytokinesis in addition to growth suppression, which led to the formation of giant polyploid cells.

Extracts from the majority of the tested plant species exerted moderate to low growth-inhibiting action at concentrations of 50 and 200 μg/mL (listed in order of decreasing cytotoxicity, species that caused formation of polyploid cells are indicated with an asterisk): *Allium cepa* L.*, *Allium sativum* L.*, *Inonotus obliquus* (Pers.) Pil.*, *Populus balsamifera* L. (buds), *Hypericum perforatum* L. (herb, flowers)*, *Valeriana officinalis* L. (roots), *Bidens tripartita* L. (herb), *Convolvulus arvensis* L. (herb, flowers), *Schisandra chinensis* (Turcz.) Baill. (fruits), *Eleuterococcus senticosus* (Rupr. et Makino) Maxim. (roots)*, *Plantago major* L. (herb, flovers), *Panax ginseng* C. A. May (roots), *Scutellaria baicalensis* Georgi (roots), *Centaurium erythraea* Rafn. (herb, flowers), *Artemisia vulgaris* L. (herb), *Artemisia absinthium* L. (herb), *Aloe arborescens* Mill. (leaves), *Acorus calamus* L. (roots), *Utrica dioica* L. (herb), *Plantago lanceolata* L. (herb, flowers), *Achillea millefolium* L. (herb, flowers), *Aesculus hippocastanum* L. (flowers), *Datura stramonium* L. (herb, flowers), *Mentha piperita* L. (herb, flowers), *Calendula officinalis* L. (flowers), *Betonica officinalis* L. (herb, flowers) and *Galium verum* L. (herb, flowers).

Extracts from the following species displayed very low cytotoxicity and did not suppress the growth of cells at concentrations up to 200 μg/mL: *Sophora japonica* L. (fruits), *Viburnum opulus* L. (fruits), *Fumaria officinalis* L. (herb, flowers), *Melilotus officinalis* Desr. (herb, flowers), *Arctium lappa* L. (roots), *Taraxacum officinale* Web. (roots), *Sorbus aucuparia* L. (fruits), *Equisetum arvense* L. (herb), *Cichorium intybus* L. (roots), *Gnaphalium uliginosum* L. (herb) and *Capsella bursa pastoris* L. (herb).

Comparison of our results with data from the literature shows that the cytotoxic action of medicinal plants in culture does not always correlate with their antineoplastic properties *in vivo*. In cases where such a correlation does exist it is suggested that cytotoxicity contributes to antineoplastic properties. Antineoplasic action on laboratory animals with interwisted tumors was reported for the following species that displayed marked cytotoxic activity in our experiments: *Chelidonium majus* (Balitskii and Vorontsova, 1982; Amosova *et al*., 1991), *Filipendula ulmaria* (Bespalov *et al*., 1992a,b,c; Peresunko *et al*., 1993), *Chamaenerium*

Table 1. The effect of crude ethanol (40%) extracts from some Russian medicinal plants on the growth of human lymphoblastoid Raji cells in culture (final cell density, % to control)

Plant species	Part of plant	Active compounds	Extract concentration in the medium, μg/mL		
			10	50	200
Chelidonium majus L.	Herb, flowers	Alkaloids	29 ± 5	0	0
Potentilla erecta (L.) Raeusch.	Roots	Tannins, triterpenoid saponins	30 ± 6[a]	2 ± 2[a]	0
Chamaenerium angustfolium (L.) Scop.	Flowerheads	Tannins	51 ± 5	1 ± 1	0
Filipendula ulmaria (L.) Maxim.	Flowers	Salicylates, tannins	53 ± 5	0	0
	Roots		93 ± 6	19 ± 5[a]	0
Inula helenium L.	Roots	Sesquiterpene lactones	60 ± 5	0	0
Rumex confertus Willd.	Roots	Anthraglycosides, tannins	55 ± 7[a]	10 ± 4[a]	0
Juniperus communis L.	Fruits	Terpenoids	88 ± 8[a]	7 ± 4[a]	3 ± 3[a]
Juglans regia L.	Nut partitions	Tannins	77 ± 6	9 ± 5	0
Paeonia anomala L.	Roots	Paeonol, iridoids, salicylates	79 ± 6	11 ± 4	3 ± 2
Salvia verticillata L.	Herb, flowers	Terpenoids	52 ± 6	23 ± 6	0
Rhodiola rosea L.	Roots	Phenylpropanoids, tannins	69 ± 5	25 ± 5[a]	0
Filipendula hexapetala Gilib.	Flowers	Not known	85 ± 8	38 ± 7	0
Salvia officinalis L.	Herb, flowers	Terpenoids	87 ± 9	35 ± 10	0
Agrimonia eupatoria L.	Herb, flowers	Coumarins, terpenoids, tannins	91 ± 5	43 ± 11	0
Betula pendula Roth.	Buds	Sesquiterpenoids	72 ± 6	37 ± 6	5 ± 3
Ledum palustre L.	Herb	Terpenoids, sesquiterpene alcohols	102 ± 5	43 ± 9	1 ± 1
Origanum vulgare L.	Herb, flowers	Phenols, terpenoids	93 ± 6	65 ± 6	0
Angelica archangelica L.	Roots	Coumarins	95 ± 5	65 ± 5	0
Bergenia crassifolia L.	Roots	Tannins	71 ± 12	65 ± 8	1 ± 1
	Leaves		77 ± 3	49 ± 8	18 ± 4
Hyoscyamus niger L.	Herb, flowers	Alkaloids	92 ± 6	72 ± 5[a]	0
Thymus serpyllum L.	Herb, flowers	Terpenoids, phenols	79 ± 6	56 ± 5	4 ± 3
Matricaria recutita L.	Flowers	Sesquiterpenoids	85 ± 5	75 ± 5	1 ± 1
Tanacetum vulgare L.	Herb, flowers	Terpenoids	88 ± 11	77 ± 6	3 ± 2
Veronica chamaedrys L.	Roots	Saponins, tannins	85 ± 8	87 ± 16	0

[a] Formation of giant polyploid cells.

angustfolium (Pukhalskaya *et al*., 1975; Syrkin and Konyaeva, 1984), *Rhodiola rosea* (Dementyeva and Yaryomenko, 1987) and *Bergenia crassifolia* (Amosova *et al*., 1994).

A number of species that are traditionally employed in anticancer phytocompositions did not demonstrate significant cytotoxic activity against lymphoblastoid cells in our experiments. Many of these plants (*Achillea millefolium*, *Arctium lappa*, *Artemisia absinthium*, *A. vulgaris*, *Calendula officinalis*, *Gnaphalium uliginosum*, *Inonotus obliquus*, *Plantago major*, *P. lanceolata*, *Taraxacum officinale*, *Untica dioica* and others) demonstrated the ability to reduce the growth of interwisted tumors, to suppress the formation of metastases, to potentate the effect of synthetic anticancer drugs and to alleviate their side-effects in *in vivo* experiments on laboratory animals (Kuroda *et al*., 1976; Balitskii and Vorontsova, 1982; Reahovskaya *et al*., 1989; Ratakhina and Pashinsky, 1990; Gribel and Pashinsky, 1991; Amosova *et al*., 1991, 1994; Bespalov *et al*., 1992a). This observation may indicate selectivity of the above mentioned plants against different types of tumors. Alternatively, the anticancer properties of these plants may not be due to their toxicity or to direct suppression of the cell division, and could be mediated through different mechanisms.

Low cytotoxicity *in vitro* was also displayed by plants with the adaptogenic mode of action, such as *Panax ginseng*, *Eleuterococcus senticosus*, *Schisandra chinensis* and *Scutellaria baicalensis*, whose antineoplastic action on laboratory animals with interwisted tumors and chemically induced neoplasia is mediated through stimulation of the immune system and non-specific resistance of the organism (Yun *et al*., 1983; Dementyeva and Yaryomenko, 1987; Bespalov *et al*., 1992a,b; Bakuridze *et al*., 1993; Razina *et al*., 1993). However, the *in vivo* efficiency of phytotherapeutic treatment of cancer is generally low, compared with synthetic antineoplastic drugs. In the majority of studies on laboratory animals, crude phytotherapeutics delayed cancer development, but did not provide complete recovery. Cytotoxicity of the plants *in vitro* does not correlate with their toxicity *in vivo*. The non-toxic plants *Chamaenerium angustfolium*, *Filipendula ulmaria*, *Iinula helenium* and *Potentilla erecta* displayed the same high cytotoxicity as the poisonous *Chelidonium majus*, while the poisonous plants *Datura stramonium* and *Convolvulus arvensis* did not possess significant cytotoxicity. The use of poisonous plants is generally avoided in traditional practice.

Cytotoxicity of purified plant compounds and pharmaceutical antineoplastic drugs

The active components were isolated from selected plant species and tested for cytotoxicity on cultured lymphoblastoid cells. Sesquiterpene lactones helenin (*Inula helenium*), telekin (*Telekia speciosa*) and artemisinin (*Artemisia annua*) displayed marked cytotoxic action and effectively suppressed the growth of cells at concentrations of 1–2 μg/mL (Fig. 2A).

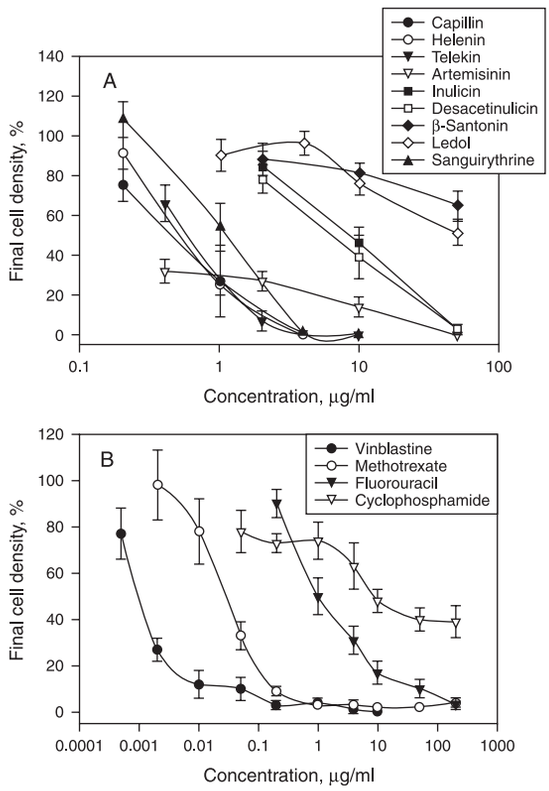

Figure 2. The effect of plant secondary metabolic compounds (A) and pharmaceutical antineoplastic drugs (B) on the growth of human lymphoblastoid Raji cells in culture.

Similar activity was displayed by aromatic polyacetylene capillin (*A. scoparia*) and sanguirythrine (equimolar mix of benzophenanthridine alkaloids sanguinarine and chelerythrine from *Macleaya microcarpa*, that are also major cytotoxic constituents of *Chelidonium majus*). Sesquiterpene lactones inulicin, desacetinulicin (*Inula japonica*) and β-santonin (*Artemisia maritima*) were less active and suppressed the cell growth at a concentration range of 2–50 μg/mL. Sesquiterpenoid alcohol ledol (*Ledum palustre*) showed low growth-inhibiting activity at relatively high concentrations (10–50 μg/mL).

The effect of pharmaceutical drugs on the growth of lymphoblastoid cells is shown in Fig. 2B. It is seen that vinblastine efficiently suppressed the growth of the cells at a concentration of 0.002 μg/mL and higher. Vinblastine also displayed marked mitotoxic activity and caused formation of giant polyploid cells at all effective concentrations. Methotrexate caused dose-dependent suppression of the cell growth at a concentration range of 0.01–1 μg/mL. At the same time, even high concentrations of methotrexate (up to 200 μg/mL) did not cause complete cell lethality, which indicates the presence of drug-resistant clones in the cell population. Fluorouracil and cyclophosphamide suppressed the growth of cells at concentrations of 0.2–200 μg/mL. The relative efficiency of the tested pharmaceutical drugs in our experiments correlated with their therapeutic doses (Mashkovskii, 2001).

It is seen from comparison of the data in Table 1 and Fig. 3 that crude extracts from only five plant species (*Chelidonium majus*, *Inula helenium*, *Chamaenerium angustfolium*, *Filipendula ulmaria* and *Potentilla erecta*) displayed activity comparable to that of fluorouracil. In contrast, the cytotoxic activity of purified active compounds of *Chelidonium majus* (sanguirythrine) and *Inula helenium* (helenin) exceeded that of cyclophosphamide and fluorouracil and approached the activity of methotrexate. Capillin, telekin and artemisinin possessed similarly high activity. The ability to induce apoptosis and to interfere with key components of the regulation and signal transduction pathways of mammalian cells was demonstrated for some of the plant compounds used in this study. There is experimental evidence that sanguinarine and chelerythrine induce apoptosis in different mammalian cells through the mitochondrial pathway (Chan *et al*., 2003; Adhami *et al*., 2003), while alantolactone induces apoptosis in leukemia T-cells (Dirsch *et al*., 2001). Chelerythrine is a potent and selective antagonist of protein kinase C, which acts as a receptor for tumor-promoting phorbol ethers (Herbert *et al*., 1990). Hypericin and pseudohypericin (aromatic polycyclic diones from *Hypericum perforatum* that show antiproliferative activity against mammalian cells) also possess the ability to specifically inhibit protein kinase C (Takahashi *et al*., 1989). Emodin from *Aloe arborescens* acts as a competitive inhibitor of casein kinase CK2 (Battistutta *et al*., 2000). These observations provide new insights into possible mechanisms of suppression of tumor growth by anticancer phytopreparations. Novel agents that could specifically affect the function of the cellular enzymes involved in cell signaling, regulation and apoptosis may be found among the diverse plant secondary metabolic compounds, especially those displaying high cytotoxic/cytostatic activity.

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