ONCOLOGY

Effects of Extracts from Medicinal Plants on the Development of Metastatic Process

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The possibility of inhibiting metastases by preparations from plants growing in Siberia and Far East after removal of the tumor node was proven in experiments on animals with transplanted tumors. Plant preparations stimulated the antitumor resistance of the organism.

Key Words: *transplanted tumors; preparations of plant origin; antimetastatic activity; antitumor resistance*

An important characteristic of tumor cells is their capacity to metastatic growth. Dissemination of malignant cells in the body and their growth is an intricate multistaged process, depending, on the one hand, on the characteristics of these cells and the primary tumor node and on the other, on the host antitumor resistance [12]. Use of traditional methods (surgery, radio- and chemotherapy and their combinations) does not guarantee cure, and the results are largely determined by the development of the metastatic process. A promising approach to improving the efficiency of the known treatment methods is the use of drugs with antimetastatic activity, stimulating antitumor resistance. Preparations from medicinal plants, containing a wide spectrum of bioactive substances and stimulating homeostasis, seem to be promising in this respect.

We studied medicinal plants with the aim of creating on the basis of these plants preparations to be used in combined therapy of patients with malignant tumors. A system for selection of these preparations was developed.

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MATERIALS AND METHODS

The study was carried out on animals with transplanted tumors. Effects of the preparations on the course of tumor process (Ehrlich adenocarcinoma, Lewis lung carcinoma — LLC) and efficiency of cytostatic therapy [1,2] were evaluated during the stage of primary screening. Use of spontaneously metastasizing LLC helped to detect the drugs inhibiting both the tumor node growth and the dissemination process.

The efficiency of therapeutic measures was evaluated by the following parameters: tumor weigh, percentage of tumor growth inhibition (GI), number of metastases in the lungs and their area, incidence of tumor metastasizing. The index of metastases inhibition (IMI) indicated the severity of metastatic involvement, as its estimation required such parameters as the incidence of metastatic growth and number of metastatic nodes in the lungs:

$$IMI=\frac{(A_C\times B_C)-(A\times B)}{A_C\times B_C}\times 100\%,$$

where A_C and A represent incidence of metastases in the lungs of mice and B_C and B are the mean numbers

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of metastases in the lungs in control and experimental groups, respectively.

The severity of metastatic involvement was evaluated using the scale suggested by D. Tarin and J. E. Price [15], differentiating the severity of involvement by the number of metastases and their size. The following degrees of lung involvement were distinguished: low colonization potential (LCP): degree 1 (<10 nodes) and degree 2 (10-30 nodes); and high colonization potential (HCP): degree 3 (>30 nodes, no fused nodes), degree 4 (<100 nodes, fused nodes), and degree 5 (>100 nodes).

RESULTS

Screening evaluation of the effects of medicinal compositions prepared from 59 plant species on the course of tumor process and efficiency of chemotherapy was carried out. Experiments on mice with LLC showed antimetastatic activity of 19 plant extracts (Table 1), IMI of 18 of these plants surpassing 50% (*Bergenia pacifica*, *Phellodendron amurense*, *Empetrium nigrum*, *Angelica daurica*, *Calendula officinalis*, *Rhaponticum carthamoides*, *Lespedeza bicolorica*, *Cotton burdock*, *Hippophae rhamnoides L.*, *Abies sibiricus*, *Common plantain*, *Rhodiola rosea*, *Securinega suffruticosa*, *Glycirrhiza uralica*, *Chelidonium magnum*, *Scutellaria baikalensis*). The greater part of these plants inhibited the tumor node growth. Some extracts (from *Taraxacum officinalis Wigg*. and common aspen) did not modify the metastatic process when used alone, but potentiated the efficiency of cytostatic therapy (Table 1). IMI in mice with LLC treated with cyclophosphamide was 79%, while combination of the cytostatic with aspen bark extract led to an increase of this index to 96%. Similar results were observed with *Taraxacum* extract added to combined therapy (IMI=57% in mice treated with the cytostatic alone and 77% in those treated with cytostatic+extract).

The model of surgical removal of the tumor most adequately reflects clinical conditions, when the main tumor node is eliminated as a result of surgery. After

TABLE 1. Effects of Medicinal Plant Extracts on LLC Growth and Metastases in Mice

Plant	Tumor process development		Efficiency of cyclophosphamide therapy			
			IMI, %		GI, %	
	IMI, %	GI, %	CP	CP+ preparation	CP	CP+ preparation
Bergenia pacifica	33-96	13-47	96	99	16	39
Phellodendron amurense	51	32	No data			
Black grape	0-34	6-24	27	53	21	23
Empetrum nigrum	29-78	3-35	99	100	72	77
Angelica daurica	49-83	—				
Calendula officinalis	56	45	66	73	73	42
Rhaponticum carthamoides	12-81	4-22	97	100	71	60
Lezpedeza bicolorica	88	—				
Cotton burdock	17-63	3-38	99	100	72	77
Macleya microcarpa	37	31	No data			
Hippophae rhamnoides L.	64-89	14-16	76	99	41	59
Taraxacum officinalis	4	11	57	77	21	30
Common aspen	—	—	79	96	16	23
Juglans mandschurica	61	33	89	99	76	64
Abies sibirica	56-79	—	No data			
Common plantain	52-97	30-48	91	100	12	73
Rhodiola rosea	96-97	38-47	78	100	70	90
Securinega suffriticosa	7-79	—	No data			
Glycirrhiza uralica	51	—	97	100	33	30
Chelidonium magnum	58-72	16-22	57	99	90	95
Scutellaria baikalensis	51-97	35-50	84	100	41	46

Note. CP: cyclophosphamide.

TABLE 2. Effects of Plant Extracts on LLC Metastases in Mice after Removal of Tumor Node (Tumor Transplanted Subcutaneously) (*M*±*m*)

Plant	IMI+stimulation, %		Incidence of metastases, %			Number of metastatic nodes in the lungs per animal		
	T	T+P	C	T	T+P	C	T	T+P
Tumor in hind paw pad								
Common plantain	+299	100	25	47	0^+	0.25±0.13	0.53±0.17	0
Lespedeza bicolorica	92	98	57	31*	20*	3.9±2.8	0.5±0.2	0.2±0.1
Rhodiola rosea	38	100	57	36*	0^+	2.1±0.3	0.7±0.2	0
Scutellaria baikalensis	38	100	57	36*	0^+	11.9±0.7	11.6±0.2	0
Tumor under back skin								
Rhaponticum carthamoides	33	81	88	100	55**	9.8±2.6	5.8±2.1	2.9±1.0*
Taraxacum officinalis	61	92	100	88	67	34.4±7.5	15.3±5.8*	4.1±1.0
Common aspen	35	83	82	75	53	9.5±2.8	6.7±1.9	2.5±1.2*
Hippophae rhamnoides	+18	74	100	100	89	21.8±3.4	25.6±5.3	$6.3±2.3^+$
Scutellaria baikalensis	*41*	72	*100*	*100*	*86*	*9.3±1.6*	*7.4±1.3*	*4.1±0.8**
glycirrham (*Glycirrhiza glabra* preparation)	53	75	100	94	94	52.4±7.1	26.4±7.4	$14.2±3.6^+$

Note. C: control group; T: mice in which tumor node was removed; T+P: operated mice treated with plant extract. *$p<0.05$ *vs.* control group, $^+p<0.05$ *vs.* operated animals.

development of metastases (days 9-16 after transplantation subcutaneously or into the hind paw pad) the main tumor node was removed under ether narcosis in mice with LLC. The treatment started 1 hour before the surgery.

Leuzea, *Lespedeza*, *Hippophae rhamnoides*, *Taraxacum*, *Aspen*, *Rhodiola rosea*, and *Scutellaria baikalensis* extracts, plantain preparation, and glycirrham prepared from *Glycirrhiza glabra* exhibited high antimetastatic activity under these conditions (Table 2).

A course of injections of the plantain preparation, extracts of *Rhodiola rosea* and *Scutellaria baikalensis* to mice after removal of the paw with the tumor suppressed the dissemination process completely: no metastases were found in the lungs (Table 2). *Lespedeza bicolorica* extract, which previously showed high antimetastatic activity, caused no appreciable changes in the metastatic process in this case.

Rhaponticum carthamoides extract exhibited a pronounced antimetastatic effect: IMI increased 2.5 times in comparison with operated animals (Table 2). After removal of subcutaneously transplanted tumor the metastases were detected in all mice, while in animals treated with this preparation the incidence of metastases in the lungs was only 55%. Decrease in the incidence of metastases was paralleled by a 2-fold reduction of their mean number and a 4.2 times decrease of their area (Fig. 1).

Injection of extract from sea buckthorn bark and sprouts to operated animals led to an appreciable inhibition of the process dissemination: 78% mice had LCP (degree 1 of lung involvement) *vs.* 12.5% ($p<0.001$) in the group of operated animals (10% in the control). The number of metastases was 4.1 times less and area of metastatic involvement 10.4 times less, IMI being 74%, while removal of the tumor did not influence the metastatic process (Table 2; Fig. 1). Due to treatment with sea buckthorn extract, the number of animals with relapses reduced to 11% *vs.* 38% in the group of operated animals receiving no therapy.

Treatment of animals with glycirrham and extracts from common aspen, *Scutellaria baikalensis*, and dandelion led to a marked increase in IMI and a significant decrease in the number of metastatic nodes and their area (Table 2; Fig. 1).

Treatment with aspen bark extract did not change the number of mice with relapses emerging at the site of removed tumors (47% in the surgery and 47% in the surgery+aspen group) and led to a 1.9 times decrease of their weights in comparison with operated animals (1.8±0.3 g in the surgery and 0.9±0.2 g in the surgery+aspen group; $p<0.05$).

The tumor capacity to metastasizing was appreciably modified under the effect of glycirrham and dandelion extract. Many animals in the control group

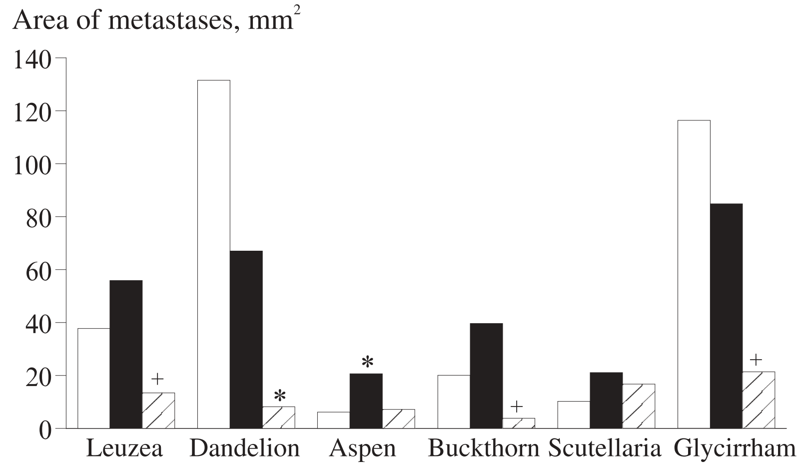

Fig. 1. Effects of plant extracts on metastasizing of Lewis lung carcinoma in mice after removal of tumor node (tumor transplanted subcutaneously). Light bars: control group; dark bars: animals in which tumors were removed; cross-hatched bars: operated animals treated with plant preparation. *$p<0.05$ *vs.* control group; $^{+}p<0.05$ *vs.* operated animals.

without surgery had high colonization potential (Fig. 2): degree 3 and some even degrees 4 and 5. High colonization potential was much more rare after removal of the tumor node, the treatment with plant preparations resulting in low colonization potential in the majority of animals (Tables 1, 2; Fig. 2).

The results indicate antimetastatic activity of *Rhaponticum carthamoides*, *Hippophae rhamnoides*, *Taraxacum officinalis*, *Aspen*, *Rhodiola rosea*, *Scutellaria baikalensis* extracts, plantain preparation, and glycirrham. Previous experiments showed that these plant preparations improved antitumor resistance of animals and the efficiency of cytostatic therapy [3,7-9].

It is well known that surgical resection of the tumor, emotional painful stress, and cytostatic therapy often involve stimulation of metastatic process, particularly in multiple-modality treatment, so stressful for the patient. Some scientists regard the tumor as a stress factor causing marked changes in the homeostasis and forming the strained status with phase-wise changes in the neuroendocrine system activity. The neurohormonal mechanisms of stress reactions play an important role in the development of metastatic process, in regulation of the primary tumor necrosis, status of the inner vascular surface, hemostasis and immunity systems. A promising approache to improving the antitumor resistance and suppressing the metastatic process can be drug correction of the neurohormonal changes developing after surgical removal of the tumor.

Our studies aimed at evaluation of the effects of extracts from *Rhaponticum carthamoides*, *Hippophae rhamnoides*, *Taraxacum officinalis*, *Common aspen*, *Rhodiola rosea*, *Scutellaria baikalensis*, and plantain preparation on the development of acute stress reaction, caused by hanging of animals by the cervical fold, demonstrated antistress activity of all these preparations.

Study of the effects of *Rhodiola rosea*, *Scutellaria baikalensis*, and *Hippophae rhamnoides* extracts on

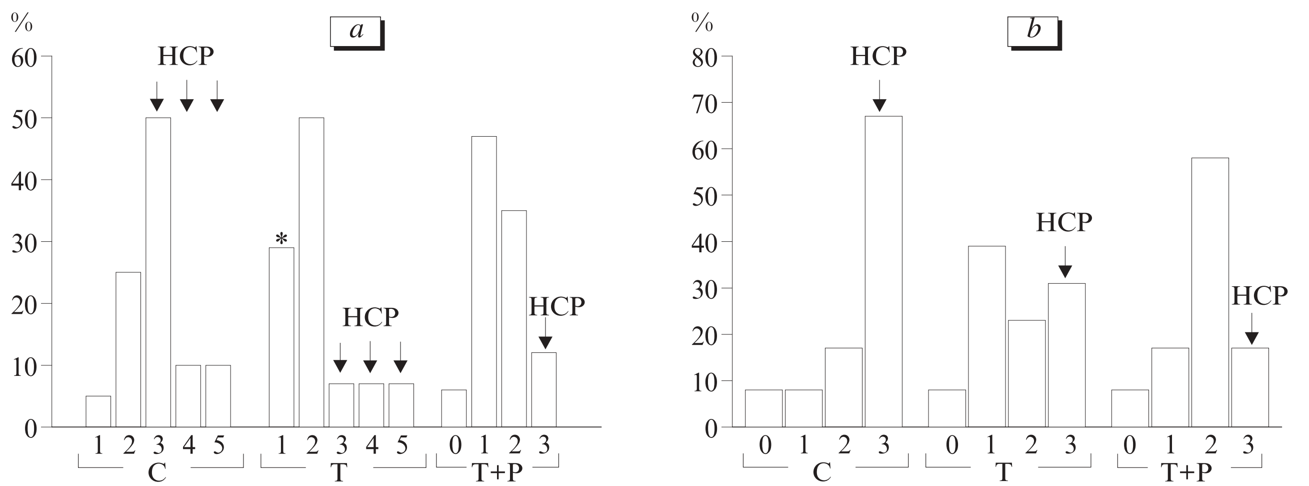

Fig 2. Effects of glycirrham (*a*) and dandelion extract (*b*) on metastatic involvement of the lungs in mice with Lewis lung carcinoma after removal of tumor node (tumor transplanted subcutaneously). C: control group; T: animals in which tumor was removed; T+P: operated animals treated with plant preparation. HCP: high colonization potential (metastatic involvement of the lungs, shown with arrows). 0-5) degree. Abscissa: groups of animals. Ordinate: degree of metastatic involvement of the lungs (number of animals in percent).

the hormonal and metabolic status of rats during development of the adaptation syndrome (in functional dexamethasone and ACTH tests) showed that these extracts modified the neuroendocrine function by modulating the production of glucocorticoids and the hypothalamus sensitivity to regulatory factors in stressed animals [5,6,13]. On the other hand, the study of the hormonal status of rats with Pliss lymphosarcoma showed a decrease in the level of 11-hydroxycorticosteroids (11-HOCS) under the effect of *Rhodiola rosea* extract and plantain preparation in animals with the tumor treated with a cytostatic [4,5]. These data suggest that inhibition of the metastatic process after removal of the tumor is due to the effects of *Rhodiola rosea*, S*cutellaria baikalensis*, *Hippophae rhamnoides* extracts and plantain preparation on the pituitary-adrenal function.

The impact of stress associated with the surgical trauma on the tumor metastasizing and the effects of plant preparations on this process was evaluated on the test laparotomy model. The surgery was carried out on rats with subcutaneously transplanted Pliss lymphosarcoma. Plantain preparation was used as a stress-relief remedy.

The intervention led to an increase in the incidence of metastases to 84% *vs.* 33% in non-operated animals ($p<0.001$). A 1.5 times increase of plasma 11-HOCS level was observed 24 h after the surgery (20.9±1.6 µg% in the control and 31.1±5.3 µg% in the surgery groups; $p<0.05$). Increase of hormone release in stress stimulated the metastatic process. A single dose of plantain preparation 1 h before the intervention prevented the increase in the hormone level (21.5±2.2 µg%). At the end of experiment the intensity of dissemination process decreased appreciably in animals treated with plantain preparation: the incidence of metastases was 50% and the primary tumor growth was inhibited significantly (by 30%). The pituitary-adrenal function remained moderately elevated after treatment with the preparation (11-HOCS level in intact animals being 14.3±1.4 µg%), and tumor dissemination was suppressed under these conditions. It seems that a certain elevation of the hormone level under the effect of a plant preparation prevents the exhaustion of the neuroendocrine mechanisms essential for the formation of antitumor resistance.

The stimulatory effect of stress on the development of metastases is realized, among other things, through systems mediating the nonspecific antitumor resistance, the effects of stress factors on the functional activity of immunocompetent cells being particularly significant. Increase of the corticosteroid level as a result of stress reaction causes suppression of the natural killer (NK) cell activity, playing an important role in antitumor resistance. Increase of NK activity can be a perspective approach to prevention of stress-induced disorders in the antitumor immunity system.

Evaluation of the effects of extract from sea buckthorn bark and sprouts on NK functional activity showed that in intact animals a single dose of this preparation caused an increase of splenic NK cytotoxic activity [11]. As cell count of the spleen did not change, presumably, the migration and proliferative processes did not play the key role in this phenomenon, and the increase in NK activity was due to accelerated maturing of a new generation of killers from precursor cells. A course of treatment with this preparation led to an increase in the splenic NK cytotoxic activity and in the cell count of the organ. It seems that in this case the cytotoxicity increased at the expense of increase in the number of splenocytes as well, which can be a result of cell redistribution and migration under the effect of the extract. Injection of the extract to mice with LLC resulted in attenuation of the signs of exhaustion of NK cytotoxic function, decrease of the tumor-stimulating activity of peritoneal macrophages, and normalization of the TNF level. Combined use of the extract with the cytostatic stimulated cytotoxic activity of NK, which remained high at late terms of tumor development [11].

The possibility of increasing the splenic NK cytotoxic activity by the plantain preparation was demonstrated in experiments on mice with LLC: the cytotoxic index increased 1.7 and 1.6 times at effector/target cell ratio of 50:1 and 25:1, respectively. Expression of the cytotoxicity in lythic units demonstrated a still more important difference between the control and experimental groups: the cytotoxic activity of NK increased 2.8 times as a result of the plantain preparation injection. Moreover, treatment with the preparation promoted an increase in the cytotoxicity of peritoneal macrophages towards target cells. Analysis of the NK and macrophage cytotoxicity in mice with LLC treated with cyclophosphamide showed a decrease of the cytostatic immunosuppressive effect as a result of treatment with the plantain preparation.

Studies on animals with transplanted tumors showed that extracts from *Scutellaria baikalensis* and *Rhodiola rosea* and plantain preparation stimulated the functional activity of neutrophils and lymph node cells. In addition to an appreciable improvement of the cytostatic treatment efficiency, these plant preparations attenuated its immunosuppressive effect [4].

The complex of disorders in the blood clotting system regulation plays an important role in the dissemination process. Our studies showed that the development of Pliss lymphosarcoma in rats is associated with disorders in the platelet hemostasis, manifesting by both decrease and increase of the platelet aggregation capacity. A high direct correlation be-

TABLE 3. Chemical Composition and Pharmacological Activity of Extracts from Medicinal Plants*

Plant	Chemical composition	Antistress activity	Pharmacological characteristics	
			published data	our findings
Medicinal plants and preparations from them allowed for medical use				
Rhaponticum carthamoides (officinal preparation: liquid extract from leuzea)	Tarry and tanning substances, alkaloids, ecdisteroids, volatile oil, carotene, ascorbic acid, lignanes	+	Tonic effect, increase of working capacity, stimulation of CNS	Decrease of hematotoxicity of cytostatics, antiulcerative effect
Taraxacum officinalis	*Triterpenoids, bitter glycosides, inulin, resins, sugars*	+	Stimulation of secretion of the digestive glands	Decrease of the cytostatic hematotoxicity
Plantain major (officinal preparation: plantain juice)	Flavonoids, saponins, aucubin, bitter, mucous, and tanning substances, phytoncides, vitamins K and C	+	Antiulcerative and antiinflammatory effects	Decrease of hematotoxicity in cytostatic and radiotherapy, stimulation of immunocompetent cells activity, decrease of the cytostatics gastrotoxicity, normalization of 11-HOCS level in stress, suppression of proliferative activity *in vitro*
Rhodiola rosea (officinal preparation: liquid extract of rhodiola)	Flavonoids, glycosides, phenols, organic acids, essential oils, tanning agents	+	Stimulatory adaptogenic effect	Decrease of the cytostatic hematotoxicity, stimulation of immunocompetent cell activity, decrease of the cytostatic gastrotoxicity, normalization of 11-HOCS level in stress
Scutellaria baikalensis (extract from root)	Flavonoids, tanning substances, pyrocatechines, starch	+	Hypotensive, sedative, antiallergic, nootropic effects	Decrease of the cytostatic hematotoxicity, stimulation of immunocompetent cell activity, regulation of blood clotting system, analgesic and antiulcerative effects
Glycirrham (preparation from *Glycirrhiza glabra*)	Monosubstituted ammonium salt of glycirrhizic acid	No data	Antiinflammatory effect, stimulation of the adrenal cortex	Decrease of the cytostatics hematotoxicity
Preparations at the stage of preclinical studies				
Lespedeza bicolorica (extract from over-ground parts)	Flavonoids, ascorbic and phenolcarbonic acids, alkaloids	+	Hypoazothemic and diuretic effects	Antiulcerative effect
Aspen (bark extract)	Tanning substances, glycosides, phenolglycosides, flavonoids, phenol acids, coumarines, essential oil, phytoncides	+	Antihelminthic effect	Analgesic and antiulcerative effects
Hippophae rhamnoides (extract from bark and sprouts)	Alkaloids, coumarines, triterpenoids, serotonin, tanning substances, carotenoids	+	Antitumor effect of extract from bark	Stimulation of immunocompetent cell activity, analgesic and antiulcerative effects

tween the functional activity of platelets and severity of metastatic involvement was detected. In addition to the antitumor and antimetastatic activity, *Scutellaria baikalensis* extract normalized the shifted parameters of platelet hemostasis irrespective of the direction of their changes [10].

Extracts from *Hippophae rhamnoides*, *Scutellaria baikalensis*, and common aspen exhibited analgesic activity in mice with convulsions induced by injection of acetic acid. The capacity of plant preparations to reduce pain sensitivity after removal of the tumor can alleviate the severity of surgery stress.

Inhibition of the metastatic process under the effect of extracts of *Hippophae rhamnoides*, *Rhodiola rosea*, *Scutellaria baikalensis*, and plantain preparation can be due to their effects on the neuroendocrine and immune systems and on the blood clotting system. Moreover, extracts from *Hippophae rhamnoides*, *Rhodiola rosea*, *Scutellaria baikalensis*, *Rhaponticum carthamoides*, *Taraxacum officinalis*, and common aspen, plantain preparation and glycirrham potentiated the efficiency of cytostatic therapy [1,2,7-9]. All these preparations, except the aspen extract, attenuated the toxic effects of cytostatics (Table 3).

Analysis of chemical composition of the plants has shown that they contain flavonoids and tanning agents (Table 3). The effects of flavonoids are variegated: they exhibit antioxidant, spasmolytic, antiinflammatory, antiulcerative, wound-healing, antitumor, anticarcinogenic, estrogenic, and diuretic effects. The effects of these substances on tumor process is attributed to their capacity to reduce the activities of cytoplasmatic and mitochondrial ATPases, as a result of which a deficit of ADP and inorganic phosphorus is created in the cells. As antioxidants, substances of this group are very important for normal metabolism in the cell. Cell membrane lipid peroxidation ia associated with the formation of toxic products and disorders in the metabolic processes in the cell, which can lead to cell death [20].

Scutellaria baikalensis contains flavonoids baikalin, baikalein, vagonin, and scutelarin. Baikalein is characterized by anticoagulant effects, prevents fibrinogen transformation into fibrin, suppresses arachidonic acid metabolism, leading to decrease of thromboxane, which participates in the platelet aggregation process. Baikalein is involved in calcium ion metabolism, exhibits antibacterial and cytotoxic effects (*in vitro* towards leukemia L1210 cells) [14]. Tanning agents possess styptic, bactericidal, antiinflammatory, antitumorous effects and extinguish free radical reactions.

Rhaponticum carthamoides, *Lespedeza bicolorica*, and *Hippophae rhamnoides* contain alkaloids. Many substances belonging to this group are highly valuable drugs, for example, atropine, platiphylline, quinine, papaverine, morphine, *etc.*, or serve as sources for their synthesis. They possess a wide spectrum of pharmacological activities. Alkaloid-based drugs, possessing cytostatic activity, are used in oncology (vinblastin and vincristin, etoposide and teniposide, colchicine and colchamine). Serotonin obtained from sea buckthorn bark (5-hydroxytriptamine) was reported to possess antitumor effect (modifies the oxygen status of normal and tumor tissues, causes spasm of tumor vessels and inflammatory changes in them, which results in suppression of energy processes in tumor tissue).

Hence, numerous bioactive substances contained in medicinal plants from which the studied preparations were derived suggests their variegated and numerous effects. Extracts from *Rhaponticum carthamoides*, *Hippophae rhamnoides*, *Taraxacum officinalis*, *Common aspen*, *Rhodiola rosea*, *Scutellaria baikalensis*, plantain preparation, and glycirrham inhibit metastases after removal of the tumor node. Antimetastatic activity of extracts from *Hippophae rhamnoides*, *Rhodiola rosea*, *Scutellaria baikalensis*, and plantain preparation is explained by their effect on the neuroendocrine and immune systems, which leads to increase of antitumor resistance.

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