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REGULATORY EFFECTS OF *RUMEX OBTUSIFOLIUS* AND *HYPERICUM ALPESTRE* EXTRACTS ON THE QUANTITY OF IL-2 IN *IN VITRO* AND *IN VIVO* CANCER MODELS

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The increase in the incidence of cancer in Armenia and around the world is a serious problem, and the chemical interventions used in cancer therapy, which partially have a therapeutic effect, are often accompanied by the destruction of normal body cells. Therefore, it is necessary to search for new alternative treatments that will be highly effective and accompanied by a small number of side effects. From this point of view, several medicinal plants used in traditional medicine can be considered new, effective means of treating cancer, since they have an immunostimulating effect on individual parts of the human immune system. Considering all this, the work aimed to study the quantitative changes in the production of interleukin-2 in the blood and tumor of rats under the influence of plant extracts in an experimental model of DMBA (7,12-dimethylbenz[a]anthracene)-induced breast cancer, as well as cell cultures of breast cancer and lungs. We showed that *Hypericum alpestre* and *Rumex obtusifolius* extracts have a pronounced anticancer effect by increasing interleukin-2 (IL-2) levels in the blood and tumors of rats. They also brought quantitative changes in phosphoinositol-3-kinase (PI3K), which plays a key role in cancer development. This could be the basis for developing new anticancer or cancer-preventing drugs derived from more potent *H. alpestre* and *R. obtusifolius* herbs.

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Introduction. Herbal extracts and isolated phytochemicals have gained recognition as useful cancer treatments. Clinical studies have demonstrated the beneficial effects of herbal medicines on improving the quality and duration of life. Their role in immune system regulation in cancer patients when combined with classical chemotherapy agents was also shown [1]. Herbal extracts contain numerous active components that can affect different targets in the body, leading to pharmacodynamic reactions [2]. Diseases accompanied by inflammatory processes and related to the immune system have long been treated with herbal preparations that act as

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immunoregulators. Immunomodulators can be considered herbal medicines that alter the function of the immune system through dynamic regulation of the metabolic pathways of messenger molecules, cytokines, adhesion molecules, nitric oxide, hormones, neurotransmitters, etc. Data from the literature suggest that many of the immunological effects of herbs may be related to the modulation of cytokine synthesis and transport [3].

Cytokines are pleiotropic peptides and glycoproteins with multiple sources, targets, and functions [4]. These compounds play an important role in inflammatory processes, as well as in cell growth, differentiation, cell death, angiogenesis, development, and repair. Manipulation of cytokine activity holds promise in many diseases related to immune function, including asthma and cancer [5]. The goal of cancer immunotherapy is to restore an anticancer immune response in tumors by modifying immune cells (e.g., macrophage cells, T lymphocytes, dendritic cells) and the tumor microenvironment [6].

Interleukin-2 (IL-2) is a cytokine that is crucial in activating the immune system. It has been shown to mediate tumor regression in metastatic renal cell carcinoma and metastatic melanoma [7]. Complexation of IL-2 or IL-2 mutants with other common γ-chain cytokine family members known as "superkines" can promote unique and more powerful signaling effects on lymphocytes by activating multiple signaling complexes simultaneously. These superkines have shown positive anticancer effects on patients' life expectancy when used alone or combined with other anticancer immunotherapies, such as herbal extracts [8].

Herbal extracts or secondary metabolites isolated from them have been found to exhibit immunostimulatory or immunosuppressive effects in the tumor micro-environment [9]. *R. obtusifolius*, also known as broad-leaved dock, is a wild plant widely growing in Armenia and worldwide. This plant is known for its high pharmacological effects including homeostatic, anti-inflammatory, anti-allergic, antimicrobial, antioxidant, neuroprotective, and anti-cancer properties [10]. The anticancer activity of *R. obtusifolius* extract has been demonstrated in rat breast cancer models [11]. Plants of the genus *Hypericum* have high antidepressant, anti-viral, antibacterial, and neuroprotective properties. Chemical analysis has revealed the presence of various bioactive compounds such as tannins, petrodianthrones (hypericin, pseudohypericin), acylfluoroglycols (hyperforin) resins, anthocyanins, saponins, glycosides, hyperoside, vitamin C, rutin, nicotinic acid, carotene, choline etc., which contribute to its therapeutic potential in cancer treatment [11].

Our previous studies established the potent anticancer properties of *H. alpestre* and *R. obtusifolius* ethanolic extracts in rat mammary carcinogenesis models [11]. This current research aimed to unravel the underlying mechanisms of their anticancer action. While previous reports highlighted the extracts' effects, the exact mechanisms remained unclear.

The study aimed to investigate the possible anticancer mechanisms of extracts of Armenian herbs, *H. alpestre* and *R. obtusifolius*, in in vitro cellular and in vivo an experimental rat model of breast cancer. We aimed to assess the quantitative change of interleukin-2 in the blood and tumor of rats in the experimental groups. Furthermore, possible mechanisms of the anticancer effect of these herbal extracts on different cancer cell lines were elucidated.

Materials and Methods.

Chemicals and Reagents. All chemicals and reagents were purchased from "Sigma-Aldrich GmbH" (Taufkirchen, Germany) and "Abcam" (UK).

Plant Material Collection, Identification, and Extraction. Aerial parts of *H. alpestre* subsp. polygonifolium (Rupr.) and seeds of *Rumex obtusifolius* Avet. & Takht. were collected from the Tavush Region of Armenia (1450–2700 *m* height above m. s. l.). Plant materials identification was done at the YSU Department of Botany and Mycology (Armenia) by Dr. Narine Zakaryan. Voucher specimens were deposited at the Herbarium at YSU. Extraction of dry plant material was done by maceration using ethanol (96%) with a ratio of 10:1 (solvent volume/plant mass). For *in vivo* studies working solutions of plant extracts were prepared by dissolving dry extracts in pure dimethyl sulfoxide (DMSO) [10]. For studies with cell cultures, 50 *mg* DW/*mL* crude ethanol extract was prepared as described earlier [11].

Cell Culture. A549 (human lung adenocarcinoma) cell line was provided by the Institute of Physiology after L.A. Orbeli RA NAS was maintained in Dulbecco's Modified Essential Medium (DMEM) supplemented with 10% fetal bovine serum and a mixture of penicillin and streptomycin. MCF-7 (Human breast cancer) cell line was obtained from the American Type Culture Collection (ATCC) and maintained in Eagle's minimal essential medium (EMEM) medium supplemented with L-glutamine (2 *mmol*/*L*), sodium pyruvate (200 *mg*/*L*), fetal bovine serum (100 *mL*/*L*), antibiotics (100 *U*/*mL* penicillin and 100 $\mu g/L$ streptomycin). The cells were grown at 37°C with 5% CO_2 and a humidified atmosphere in a CO_2 incubator (Biosan S-Bt Smart Biotherm) [12]. To assess IL-2 changes in cell medium, cells were cultured in a 24-well microplate with 50 000 cells per well in 450 μL of medium. The next day, 50 μL of plant extract was added. After 24 *h*, IL-2 quantity was determined in the cell medium.

Animals and Tumor Inhibition. The experiments including animal models were done on white laboratory female albino rats weighing 120–150 *g*. Rats were maintained on a 12 *h* light/12 *h* dark cycle. All animals were decapitated at 190 days (28 weeks after DMBA injection) under anesthesia. The rats were divided into 8 different groups with 8 rats in each group. Mammary carcinogenesis induction in rats was performed by a single subcutaneous injection of 1 *mL* of 25 *mg* DMBA (dissolved in soybean oil) into the 2nd and 3rd pairs of breasts at 60–65 days of age [13]. The effects of plant extracts, on DMBA-stimulated cancer were determined 60 days (8 weeks, tumor stabilization) and 190 days (28 weeks, end of experiment) after the latter injection. The doses of herbal extracts were selected according to literature data. After 196 days (28 weeks after DMBA induction) all animals were decapitated. Experimental rats were regularly monitored for food and water consumption, apparent signs of toxicity, weight loss, mortality, tumor numbers, and sizes. Blood samples were collected according to the method of Lee and Goossens [14].

Determination of IL-2 Level by ELISA. A Rat IL-2 ELISA kit was used for the determination of IL-2 quantity in serum, plasma, and cell culture. IL-2 levels in the blood plasma and tumors were determined using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions ("Sigma-Aldrich", Germany). Breast tumors (0.1 *g*) were homogenized in RIPA buffer (0.625% Nonidet P-40, 0.625% sodium deoxycholate, 6.25 *mM* sodium phosphate, and 1 *mM*

ethylene-diamine tetraacetic acid at pH 7.4) containing 10 *μg*/*mL* of a protease inhibitor cocktail ("Sigma-Aldrich", Germany). Homogenates were centrifuged at 12,000 *g* for 10 *min* at 4°C, the supernatant was separated, and a quantitative assessment of IL-2 in the supernatant was carried out using a RAT IL-2 ELISA kit (RAB0288, "Sigma-Aldrich", Germany) [10].

Experimental design and treatment

Groups	Number of rats in each group	Experimental design	25 *mg*/*mL* oil per rat, DMBA	Treatment by *H. alpestre* and *R. obtusifolius* 2.4 *mg*/*kg*/day in 0.25 *mL* saline
I	8	control	–	–
II	10	DMBA (breast cancer)	on the 60th day, a single dose	–
III	8	normal control + saline	–	–
IV	8	hypericum control	–	administered for 8 weeks (after tumor development in the 8th week, every 4th day)
V	8	rumex control	–	administered for 8 weeks (after tumor development in the 8th week, every 4th day)
VI	8	DMBA + hypericum	on the 60th day, a single dose	administered for 8 weeks (after tumor development in the 8th week, every 4th day)
VII	8	DMBA + rumex	on the 60th day, a single dose	administered for 8 weeks (after tumor development in the 8th week, every 4th day)

Phospho-PI 3 Kinase p85 + Total In-Cell ELISA Assay. MCF-7 cells ($1.5 \cdot 10^4$ cells per well) were seeded in the 96-well plates treated for tissue culture. After 24 *h* incubation, the cell medium (180 *μL*) was refreshed and the cells were treated with 20 *μL* control or test compounds with the following final concentrations: phosphate-buffered saline (PBS), 1% ethanol solution (control, MCF7C cells), *H. alpestre* (0.5 *mg*/*mL*) and *R. obtusifolius* (0.25 *mg*/*mL*). The calculations during the seeding of the cells were done in a way to reach approximately 80% confluency at fixation time. After 24 *h* exposure, the medium was discarded and cells were fixed with 100 *μL* of 4% formaldehyde in PBS. Crystal Violet was used to stain the cells for normalizing readings in 450 *nm* for Phospho-PI 3 kinase p85 + Total. The measured OD450 readings were corrected for cell number by dividing the OD450 reading for a given well by the OD595 reading for that well. This relative cell number was then used to normalize each reading. Total and phospho-PI 3 kinase p85 were each assayed in triplicate using the phospho- and Total PI 3 Kinase p85 antibodies included in the PI3Kinase Kit. Levels of Phospho-PI 3 kinase p85 and Total PI3K were measured using an In-Cell ELISA kit (ab207484), according to the manufacturer's instructions.

***Statistical Analysis*.** The obtained results were presented as the mean values with standard errors (M±SD). Statistical analyses were performed using GraphPad Prism 8 software (San Diego, CA, USA), and a significance level of $p < 0.05$ was deemed statistically significant.

Results. To assess changes in cytokine production during cancer development, experiments were conducted both in vitro using A549 and MCF7 cell cultures and *in vivo* using a rat breast cancer model induced by DMBA (7,12-dimethylbenz[a]anthracene). In the initial phase of the experiments, the quantity of IL-2 was evaluated in the blood and tumor of rats with breast cancer who underwent treatment with ethanolic extracts of *H. alpestre* and *R. obtusifolius* herbs. Analyses of tumor tissue homogenates indicated that the DMBA+RO (DTRO) group (treatment group with *R. obtusifolius* extract) exhibited a 1.8-fold increase in interleukin-2 (IL-2) levels, while the DMBA+HA (DTHA) group (treatment group with *H. alpestre* extract) demonstrated a 1.4-fold decrease compared to the DMBA group. (Fig. 1, A). IL-2 level changes were also detected in blood samples. In the DMBA group, IL-2 levels decreased by 1.6 times compared to the healthy group (Fig. 1, B). The obtained data also indicated that in the DMBA+RO (DBRO) group, as well as in the HA treatment group (DMBA+HA (DBHA)), there was a noticeable increase in the quantity of IL-2, approximately 2.6-fold and 2.2-fold, respectively.

These findings suggest that *R. obtusifolius* and *H. alpestre* may have a positive impact on cancer treatment by enhancing cytokine levels within the tumor, potentially promoting immune cytotoxicity (Fig. 1, B).

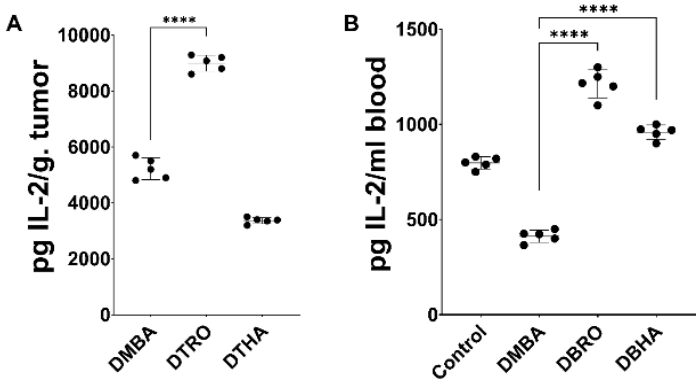

Fig. 1. Changes in the quantity of IL-2 in the tumor (A. DTRO group – DMBA + *R. obtusifolius*, DTHA group – DMBA + *H. alpestre*) and blood (B. DBRO group – DMBA + *R. obtusifolius*, DBHA group – DMBA + *H. alpestre*) of rats with breast cancer under the influence of *R. obtusifolius* and *H. alpestre* (0.25 *mg* DW/*mL*); $n = 5$, $p < 0.05$.

In the second phase of the research, we assessed the changes in the quantity of IL-2 in the A549 lung cancer cell under the influence of *R. obtusifolius* and *H. alpestre* herbal extracts. As a positive control, we employed the chemotherapeutic drug 5-fluorouracil (5-FU). The results revealed that, when compared to the control group, the application of the chemotherapeutic drug led to a three-fold increase in the quantity of IL-2. Conversely, no statistically significant changes in IL-2 levels were observed in the RO (cells treated with *R. obtusifolius* extract) and HA (cells treated with *H. alpestre* extract) treatment groups when compared with the control

group. However, both the RO and HA treatment groups exhibited a decrease in the quantity of IL-2 when compared to the 5-FU group, with a similar reduction of approximately 1.4-fold in both cases (Fig. 2, A). For a general understanding of the mechanism of IL-2 action, we evaluated the change in the levels of total (Total PI3K) and phosphorylated (p85-PI3K) phosphoinositol-3-kinase in the MCF-7 breast cancer cell line under the influence of *H. alpestre* and *R. obtusifolius* herbs. The obtained results indicated that significant changes in the Total PI3K levels were not observed in almost all cases. However, in the case of p85-PI3K (its active form), a decreased quantity was observed compared to the control group. Specifically, under the influence of *R. obtusifolius* and *H. alpestre* extracts, the p85-PI3K levels decreased by approximately 1.3 and 1.6 times, respectively (Fig. 2, B).

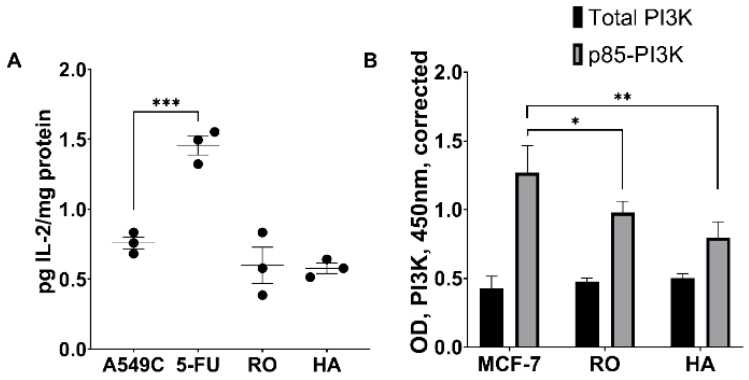

Fig. 2. A) Change of IL-2 levels expressed per mg of protein under *H. alpestre* (HA) and *R. obtusifolius* (RO) extracts (0.25 *mg* DW/*mL*) in A549 cells. B) Change of quantity of total (Total PI3K) and phosphorylated phosphoinositol-3-kinases (p85-PI3K) under the influence of *R. obtusifolius* and *H. alpestre* (0.25 *mg* DW/*mL*) on MCF-7 breast cancer cell line; $n = 3$, $p < 0.05$.

Discussion. In our previous research works we showed potent anticancer properties of *H. alpestre a*nd *R. obtusifolius* extracts in both *in vitro* and *in vivo* models [10, 11]. Particularly, *H. alpestre* ethanolic extract alone and in combination with chemotherapeutic agents showed pro-/antioxidant, antiproliferative, anti-angiogenic, and cytotoxic properties. In another research, *R. obtusifolius* extracts demonstrated a significant cytotoxic effect on the human colon (HT29) and breast cancer (MCF-7) cell lines. A combination of *R. obtusifolius* extracts with the arginase and nitric oxide synthase inhibitors exhibited potent anticancer properties in the *in vivo* rat mammary carcinogenesis model [10]. However, the exact mechanism that underlies the anticancer action of these plant extracts was not elucidated in earlier reports. In this research, we tried to find out possible mechanisms and cellular targets. We hypothesized phytochemicals contained in the extract of RO and HA can act as immunomodulators and play a pivotal role in preventing cancer development as well as can be used in immunotherapy. Therefore, we assessed IL-2 changes in cancer cells and animal cancer models. The obtained results confirmed our speculations. Although *in vitro* studies showed that they did not have a direct effect on the quantitative regulation of IL-2 in cells, *in vivo* experiments proved that this model was able to increase the amount of IL-2 in the blood and tumor of rats, which may

be the result of activation some other mechanisms, thus showing an immunostimulatory effect. Under the influence of *H. alpestre* and *R. obtusifolius* extract or/and tested chemotherapeutic agents, an increment in the amount of IL-2 was observed. Both extracts also act as inhibitors of PI3K. The inhibition of PI3K contributes to the immune system, particularly by increasing the number of T-killer cells in both the tumor microenvironment and blood plasma. Finally, this inhibition can boost immune cytotoxicity, preventing cancer cell invasion and metastasis (Fig. 3) [15].

Specialized T cells known as regulatory T cells (or Tregs) emerge in the thymus [16]. There are several different types of Tregs, including specialized subsets of $CD4^+$, $CD8^+$, double negative $CD3^+CD4{-}CD8{-}$ T cells, and NKT cells [17]. Modulating the PI3K pathway using drugs or genetic manipulation has revealed the importance of signaling components in regulating Treg development and function, maintaining the balance between Tregs and conventional $CD4^+$ T cells, and controlling the distinct metabolic requirements of different $CD4^+$ T cell subsets [18]. Moreover, inhibition of PI3K signaling can enhance the function of CD8 T cells. The high level of $CD8^+$ T cell shows that treated tumors also contained T cell memory cells, evidence of increased tumor NK cell accumulation and cytolytic biomarkers and intratumorally IFNγ production [19].

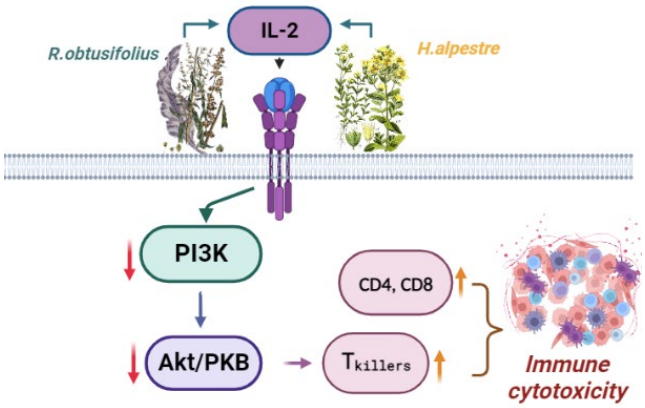

Fig. 3. Possible anticancer mechanism of *H. alpestre* and *R. obtusifolius* ethanol extract through changes in IL-2 levels mediated by the phosphoinositol-3 kinase pathway.

The changes in p85-PI3K levels after treatment with RO and HA plant extract indicate that their anticancer effect can be due to the regulation of the PI3K/AKT signaling pathway, which is a loop in mammalian cells that controls cell growth, migration, proliferation, and metabolism and plays a direct role in signaling downstream from activating receptors, including 2B4 and KIR receptors [20].

Conclusion. In conclusion, our research revealed that anticancer activity of *H. alpestre* and *R. obtusifolius* plant extract can be due to increment in IL-2 levels blood and tumor of experimental rats with breast cancer, coupled with the inhibition of the PI3K/AKT signaling pathway. It suggests that these extracts may function as immunomodulators, enhancing immune responses and potentially serving as candidates for immunotherapy. Understanding these immune pathways could pave the way for novel cancer prevention strategies.

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Հ. Գ. ՋԱՎՐՈՒՇՅԱՆ, Մ. Մ. ԳԻՆՈՎՅԱՆ, Ն. Վ. ԱՎԹԱՆԴԻԼՅԱՆ

RUMEX OBTUSIFOLIUS ԵՎ *HYPERICUM ALPESTRE* ԴԵՂԱԲՈՒՅՍԵՐԻ ԿԱՐԳԱՎՈՐՈՂ ԱԶԴԵՑՈՒԹՅՈՒՆԸ ԻԼ-2-Ի ՔԱՆԱԿԱԿԱՆ ՓՈՓՈԽՈՒԹՅԱՆ ՎՐԱ ՔԱՂՑԿԵՂԻ *IN VITRO* ԵՎ *IN VIVO* ՄՈԴԵԼՆԵՐՈՒՄ

Քաղցկեղի աճող դեպքերը Հայաստանում և ամբողջ աշխարհում հանդիսանում են լուրջ խնդիր, իսկ քիմիաթերապևտիկ միջոցները, որոնք օգտագործվում են քաղցկեղի բուժման թերապիայում՝ հաճախ ուղեկցվում են օրգանիզմի նորմալ բջիջների ոչնացմամբ: Այդ պատճառով պետք է գտնել նոր և այլընտրանքային բուժման մեթոդներ, որոնք կունենան բարձր արդյունավետություն և կուղեկցվեն քիչ կողմնակի ազդեցություններով: Այս տեսանկյունից՝ ավանդական բժշկության մեջ օգտագործվող մի շարք դեղաբույսեր կարելի է դիտարկել որպես քաղցկեղի բուժման նոր, արդյունավետ միջոցներ, քանի որ դրանք կարող են ունենալ իմունախթանիչ ազդեցություն: Աշխատանքի նպատակն է ուսումնասիրել ինտերլեյկին-2 (ԻԼ-2) իմունախթանիչի արտադրության քանակական փոփոխությունը առնետների արյան և ուռուցքի մեջ՝ բույսերի լուծամզվածքների ազդեցությամբ՝ ԴՄԲԱ-ով (7,12-դիմեթիլբեզանտրացեն) խթանված առնետի կրծքագեղձի քաղցկեղի փորձարարական մոդելում, ինչպես նաև մարդու թոքի քաղցկեղի և կրծքագեղձի քաղցկեղի բջջային կուլտուրաներում: Արդյունքները ցույց են տվել, որ մեր կողմից կիրառված բույսերը՝ *Hypericum alpestre, Rumex obtusifolius* ունեն լավ

արտահայտված հակաքաղցկեղային ազդեցություն, որը դրսևորվել է առնետների արյան և ուռուցքի մեջ IL-2 քանակության աճով, որի պատասխանատուներից մեկը քաղցկեղի զարգացման գործընթացքում առանցքային դեր ունեցող ֆոսֆոինոզիտոլ-3-կինազի ընդհանուր և ֆոսֆորիլացված տեսակների քանակների նվազումն է: Այս ամենը հիմք կարող է հանդիսանալ նոր բուժական առավել արդյունավետ, բնական հումքով դեղամիջոցների ստացման համար:

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РЕГУЛИРУЮЩЕЕ ВЛИЯНИЕ *RUMEX OBTUSIFOLIUS* И *HYPERICUM ALPESTRE* НА КОЛИЧЕСТВО IL-2 В МОДЕЛЯХ РАКА *IN VITRO* И *IN VIVO*

Рост заболеваемости раком в Армении и во всем мире является серьезной проблемой, а химиотерапевтические вмешательства, которые используются в терапии рака и частично оказывают терапевтический эффект, часто сопровождаются разрушением нормальных клеток организма. Поэтому необходимо найти новые альтернативные методы лечения, которые будут высокоэффективны и сопровождатся небольшим количеством побочных эффектов. С этой точки зрения ряд трав, используемых в народной медицине, можно рассматривать как новые, эффективные средства лечения рака, поскольку они оказывают иммуностимулирующее действие на отдельные компоненты иммунной системы человека. Учитывая все это, целью работы было изучение количественного изменения продукции интерлейкина-2 (ИЛ-2) в крови и опухолях крыс под влиянием растительных экстрактов на экспериментальной модели ДМБА (7,12-диметилбезантрацен)-индуцированного рака молочной железы, а также в культуре клеток рака молочной железы и легких. Нами было показано, что используемые растения *Hypericum alpestre* и *Rumex obtusifolius* обладают хорошо выраженным противораковым действием, повышая количество ИЛ-2 в крови и опухолях крыс, а также снижая количество общей и фосфорилированной фосфоинозитол-3-киназы, которая играет ключевую роль в развитии рака. Все это может стать основой для получения новых лечебных препаратов из более эффективного природного сырья.