PROCEEDINGS OF THE YEREVAN STATE UNIVERSITY

Chemistry and Biology 2024, **58**(3), p. 197–206

Biology

MODULATION OF THE L-ARGININE METABOLIC PATHWAY IN HeLa CANCER CELLS THROUGH COMBINED TREATMENT WITH PATHWAY INHIBITORS AND HERBAL EXTRACTS

G. H. PETROSYAN *

Laboratory of Basic and Pathological Biochemistry,
Research Institute of Biology, YSU, Armenia

As the global population grows and ages, the incidence of cancer is rising. Cancer treatment remains one of the most significant biomedical challenges of modern medicine. Current treatment modalities, including surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy, have significantly improved survival rates for some cancers. However, substantial challenges persist across several fronts, which limit the efficacy and accessibility of cancer treatment.

In recent years, the integration of herbal preparations alongside conventional chemotherapy has gained growing attention in cancer treatment. The investigation into the synergistic potential of herbal extracts combined with chemotherapeutic agents is of particular interest, as it could enhance their therapeutic efficacy while reducing adverse effects.

This work aimed to evaluate the antitumor effect of plant extracts in the HeLa cancer cell line, study the possible mechanisms of action, and observe the effectiveness of the combined effect of plant extracts such as *Inula helenium* and *Alchemilla smirnovii* Juz. with chemical inhibitors of the arginase like L-NAME and nor-NOHA, targeting the metabolic pathways of nitric oxide synthase (NOS) and arginase. In our study, treatment with *Alchemilla smirnovi* Juz. resulted in a significant decrease in arginase activity compared to the control group. Similarly, treatment with *Inula helenium* also reduced arginase activity.

This combination aimed to enhance the cytotoxic impact on cancer cells, potentially offering an effective strategy for combating breast cancer. Based on the data, we can conclude that targeting arginine metabolism and using plant-derived compounds holds promise for developing novel anticancer therapies.

https://doi.org/10.46991/PYSUB.2024.58.3.197

***Keywords*:** cancer, cell lines, L-arginine metabolic pathway, arginase, NO, herbal extract.

Introduction. Nowadays cancer research helps understand why certain populations are more affected and how to address these disparities effectively. For advancing treatment options cancer research also leads to the development of new treatments, such as targeted therapies, immunotherapies, and personalized medicine. These advancements improve survival rates and the quality of life for cancer patients. By studying the mechanisms that drive cancer growth and spread, the investigation

* E-mail: gayanepetrosyan@ysu.am

of cancer biology can discover new targets for treatment, predict responses to therapy, and prevent resistance to current treatments [1].

An increasing number of studies in recent years demonstrate that two mammalian arginase isoforms, arginase 1 (ARG1) and arginase 2 (ARG2), are aberrantly upregulated in various types of cancers, and play crucial roles in the regulation of tumor growth and metastasis through various mechanisms such as regulating L-arginine metabolism, influencing tumor immune microenvironment, etc. Therefore, arginase receives increasing focus as an attractive target for cancer therapy [2].

Cancer is fundamentally a disease characterized by disrupted biochemical processes. One critical process involves cell signaling pathways regulating how cells communicate, grow, and divide. In cancer, these signaling pathways often become dysregulated due to gene mutations encoding signaling proteins [3]. This dysregulation leads to uncontrolled cell proliferation and enhanced survival. Many components of cell signaling pathways serve as biomarkers for cancer diagnosis, prognosis, and predicting treatment responses.

Tumor initiation and progression require the metabolic reprogramming of cancer cells. Cancer cells autonomously alter their flux through various metabolic pathways to meet the increased bioenergetic and biosynthetic demand and mitigate oxidative stress required for cancer cell proliferation and survival [4]. Arginine metabolism is highly compartmentalized due to the expression of enzymes involved in arginine metabolism in various cells. L-arginine is a multipurpose amino acid that also serves as a precursor for multiple metabolites, including polyamines and nitric oxide (NO), which have strong immunomodulatory properties. It is the substrate for four enzymes, several of which exist as multiple isoforms: NO synthases (NOSs), arginases (ARGs), glycine amidotransferase, and L-arginine decarboxylase. To encounter the enzymes involved in its metabolism, L-arginine must be transported through the plasma membrane *via* cationic amino acid transporters (CATs) and metabolized by NOS enzymes [5].

It should be noted that synthetic analogs of arginine are of great importance in anticancer therapy and are currently used as chemotherapy drugs [6]. For example, the NOS intermediate **N**-hydroxy-L-arginine (NOHA) is known as an arginase inhibitor. It has been successfully used in organ cultures of human prostate cancer to suppress arginase activity and, when combined with any NOS inhibitor, to restore tumor uptake reactivity by lymphocytes. The L-arginine derivative **N**-hydroxy-nor-L-arginine (nor-NOHA) has been shown to completely reverse polymorphonuclear (PMN) cell-associated T-cell suppression during purulent inflammation and restore normal airway responsiveness in an animal model of arginase-mediated asthma [7]. Nor-NOHA, as a non-competitive inhibitor with a high affinity for the anionic isoform of arginase (AII), can also prevent hyperammonemia that can arise from arginase inhibition [2]. The compound **N**-nitro-L-arginine methyl ester (L-NAME) is one of the most clinically advanced NOS inhibitors, with demonstrated efficacy in treating septic and cardiogenic shock, as well as for prophylactic purposes [8]. L-NAME also exhibits tumor-suppressive properties in various *in vivo* cancer models [9]. These observations form the basis for the preclinical evaluation of nor-NOHA and L-NAME in the treatment of breast cancer. The L-arginine metabolic

pathway is crucial in cancer biology, as it is involved in several key processes such as nitric oxide (NO) production [10]. NO is synthesized from L-arginine by nitric oxide synthase (NOS).

The flora of Armenia, though geographically limited, is characterized by a remarkable biodiversity. Despite this, it remains largely underexplored for its potential to yield novel biologically active compounds [11]. This gap presents a valuable opportunity to explore the anticancer properties of Armenian plant species, which could contribute to the development of new therapeutic strategies. Given the ongoing challenges in the treatment of breast cancer, which remains one of the most prevalent malignancies with limited effective therapeutic options, there is a critical need to identify novel agents or combinations of agents, both synthetic and natural, that possess potent anticancer activity [12]. This study aims to investigate the anticancer properties of *Inula helenium* and *Alchemilla smirnovii* Juz. to assess their potential as complementary treatments in breast cancer therapy.

We propose that the inhibition of arginase and NO synthase may exert an antitumor effect on cancer development by reducing the levels of polyamines and NO, which are precursors of cancer cell proliferation, metastasis, and tumor angiogenesis, respectively. Furthermore, given the significant potential of herbal extracts in future cancer treatments, we also investigated the possible anticancer mechanisms that can occur in HeLa cell lines under the influence of herbal extracts. *I. helenium* and *A. smirnovii* have shown the potential to enhance the efficacy of arginase and NO synthase inhibitors. To investigate the underlying mechanisms, we assessed the cytotoxic effects of L-NAME, and nor-NOHA and measured the quantitative changes in nitric oxide (NO), malondialdehyde (MDA) levels, changes of activity of arginase and NOS enzymes following their combined application with chemical inhibitors in HeLa cells.

Materials and Methods.

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

***Plant Material and Their Collection, Identification, and Extraction*.** The plants: *Inula helenium* (IH) (flower and leaf) and *Alchemilla smirnovii* Juz. (AS) (aerial parts) were harvested from the Tavush Region of Armenia (1450–1700 *m* above sea level). Plant parts were collected during the flowering period (June–July). Identification of plants was done at the Department of Botany and Mycology, Yerevan State University (Armenia) by Dr. Narine Zakaryan. Plant specimens were deposited to the Herbarium of YSU, where voucher numbers were given. 50 *mg* DW/*mL* plant crude extracts were prepared by maceration technique using pure ethanol (96%) at a 10:1 solvent-to-sample ratio (v/w) [13]. The percent yield of the extracts was determined earlier [14].

***Cell Culture*.** HeLa (human cervical carcinoma) cells have been maintained in Dulbecco's Modified Essential Medium (DMEM) supplemented with 10% Bovine serum and 1×Pen/Strep. Cells have been seeded in tissue culture-treated plates at a maximum density of 2×10^5 cells/cm^2. The cells have been propagated at 37°C in an atmosphere of 5% CO_2 in a CO_2 incubator (Biosan S-Bt Smart Biotherm, Latvia).

MTT Cytotoxicity Assay. The MTT test [15] was performed to assess the inhibition of growth of HeLa cells exposed for 4 *h*, 24 *h*, or 72 *h* to different concentrations (0.5, 0.25, and 0.125 *mg* DW/*mL*) of IH, AS extracts, and inhibitors (L-NAME-14 *mM*, nor-NOHA-0.5 *mM*). Treatments were performed as three technical replicates. Three independent replicates of each treatment were performed. Cytotoxicity was expressed as percent growth inhibition of cells exposed to tested plant extract compared to control cells treated with the appropriate volume of solvent only (1% ethanol in the final mixture), whose growth was regarded as 100%.

Treatment of Cells with Chemotherapeutic Agents and Herbal Extracts for Determination of Arginase, NOS, and NO Changes. HeLa cells were seeded in 24-well (5×10^4 cells per well) plates and incubated for 24 *h*. After incubation, the medium in wells (450 μL) was refreshed. The cells were treated with 50 μL control or test compounds with the following final concentrations: PBS, 1% ethanol (Control, HeLa), L-NAME (14 *mM*), nor-NOHA (0.5 *mM*), *Alchemila smirnovii* Juz. (0.125 and 0.25*mg*/*mL*), and *Inula Helenium* (0.125 and 0.25 *mg*/*mL*). After 24 *h* incubation, the supernatant without cells was discarded. Cells from each group were collected (trypsinized, neutralized, centrifuged), lysed on ice with Lysis buffer, collected in a centrifuge tube, and further lysed for 10 *min*. After centrifugation at 13000×*g* for 10 *min* at 4°C, the supernatant was collected. The levels of Nitrite anions, Arginase, NOS, and NO were quantified according to the methods described below.

Measurement NO Quantity. NO levels in the medium of cell cultures were determined as nitrite anions. For measurement Griess assay was used as described before for each 100 μL sample was added 100 μL Griess reagent. The supernatants were transferred to the tubes containing pellets of cadmium and incubated at room temperature for 12 *h* to convert nitrate to nitrite. The samples' absorbance was measured at λ = 550 *nm* and the NO quantity was calculated based on a standard curve prepared with $NaNO_2$ [16].

Malondialdehyde (MDA) Assay. MDA quantity in the cell culture medium was determined with a colorimetric assay using the Ohkawa thiobarbituric acid-malondialdehyde method [17].

Determination of Arginase Activity. The modified Diacetyl Monoxime colorimetric method was employed to assess the arginase activity in cell lysates.

Determination of NOS Activity. Nitric oxide synthase activity (μmol citrulline/ *mg* protein) in cell lysates was measured by the conversion of L-arginine to L-citrulline. All assays were performed in duplicate on aliquoted samples (to avoid freezing/thawing cycles). The results were normalized for protein content.

Statistical Analysis. The obtained results were presented as the mean values with standard deviation (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 and Discussion.

Cytotoxic Properties of Plant Extracts and Chemotherapeutic Compounds. In our previous study, we demonstrated that the herbal extracts of *I. helenium* and *A. smirnovii* Juz. exhibited significant cytotoxic effects. Based on these findings, in the first stage of this work sub-inhibitory concentrations of 0.25 *mg*/*mL* and 0.125 *mg*/*mL* were selected for combination with chemical inhibitors. Additionally,

the inhibitors nor-NOHA and L-NAME were evaluated using cytotoxicity assays, and their sub-inhibitory concentrations were determined for long-term studies (Fig. 1, A and B).

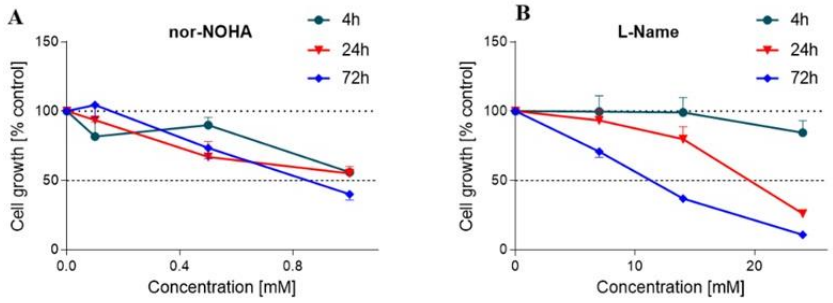


Fig. 1. The cytotoxic effects of nor-NOHA-0.5 *mM* and L-NAME-14 *mM* after 4 *h*, 24 *h*, and 72 *h* of treatment in the HeLa cell line, $n = 3$, $p < 0.05$.

During this research previously studied plants (with concentrations of 0.25 *mg*/*mL*) were selected and their synergistic effect with inhibitors (nor-NOHA--0.5 *mM* and L-NAME-14 *mM*) was assessed on the HeLa cell line. The results showed that after 24 *h* of treatment *I. helenium* combined with nor-NOHA had a high synergistic effect.

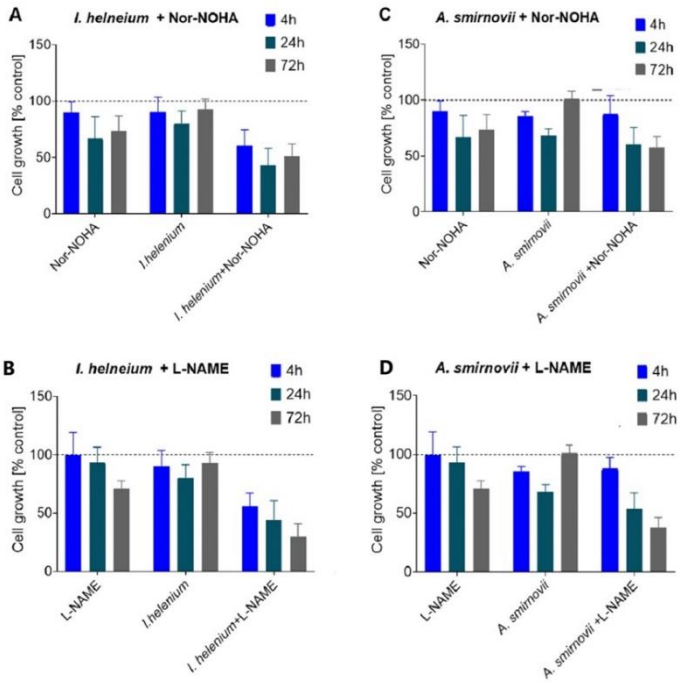


Fig. 2. The cytotoxic effects of the *I. helenium* and combination of *A. smironovii* Juz. herbal extract 0.25 *mg*/DW*mL* with nor-NOHA-0.5 *mM*, L-NAME-14 *mM*, $n = 3$, $p < 0{,}05$.

The cytotoxic effect was about 60%. (Fig. 2, A). As for L-NAME, a high cytotoxic effect was observed in combination with both herbs after 24 *h* and 72 *h* of treatment (Fig. 2, B and D). At the 24th hour, the cytotoxic effect of Inula + L-NAME was observed by approximately 60% growth reduction (Fig. 2, B), and Alchemilla + nor-NOHA had approximately 50% growth reduction (Fig. 2, C).

Evaluation of Change of Arginase and NOS Activity, and Quantity of NO and MDA. In cancer, NO can play both pro-tumorigenic and anti-tumorigenic roles depending on its concentration and the tumor microenvironment. It influences angiogenesis, apoptosis, and immune response. Another pathway where L-arginine is involved is polyamine synthesis. It is well known that L-arginine is also a precursor for polyamines, essential for cell proliferation, and implicated in cancer growth and progression.

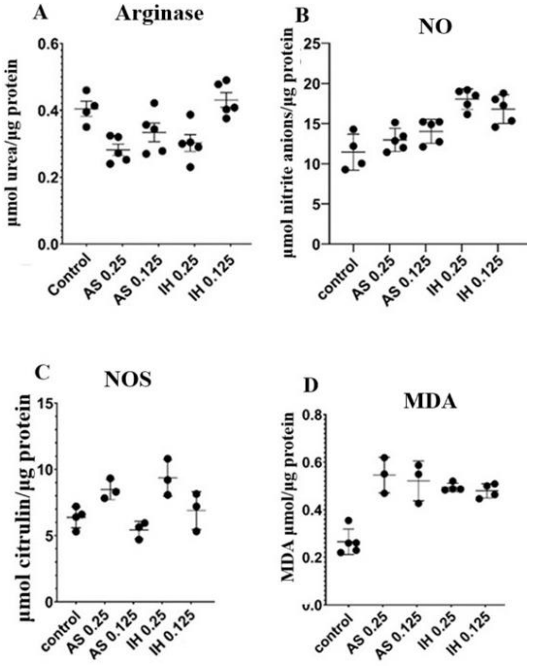


Fig. 3. The changes of activity of arginase (n = 5, $p < 0.05$) and NOS (n = 4, $p < 0.05$) enzymes, and the quantitative change of NO (n = 5, $p < 0.05$) and MDA (n = 5, $p < 0.05$) on HeLa cell lines, after treatment with herbal extracts of *Inula helenium* and *Alchemilla smirnovii* Juz.:
A – the arginase activity, *µmol* urea/*µg* protein;
B – NO quantity, *µmol* anions/*µg* protein;
C – NOS activity, *µmol* citrulline/*µg* protein;
D – MDA quantity, *µmol* MDA/*µg* protein.

The enzyme arginase competes with NOS for L-arginine, converting it to ornithine and urea. High arginase activity is often seen in cancer cells and can promote tumor growth by depleting L-arginine and limiting NO production, thereby suppressing immune responses. From this point of view, it is of great importance for us to understand what changes can occur in HeLa cell lines when they are exposed to herbal extracts.

Therefore, we investigated the changes in the activity of Arginase and NOS, and measured the quantity of NO and MDA, to understand the possible anticancer mechanisms with the influence of *I. hellenium* and *A. smirnovii* Juz. herbal extract. In studying the molecular mechanisms of plant influence on the L-arginine metabolic pathway, the herbal concentrations of 0.25 *mg*/*mL* and 0.125 *mg*/*mL* were chosen for their potential biological activity, particularly their role in modulating cancer-related processes.

In our study, as shown in Fig. 3, A, treatment with *A. smirnovii* Juz. (AS) at concentrations of 0.25 *mg*/*mL* and 0.125 *mg*/*mL* resulted in a significant decrease in arginase activity compared to the control group ($p < 0.05$). Similarly, treatment with *Inula helenium* (IH) at a concentration of 0.25 *mg*/*mL* also reduced arginase activity ($p < 0.05$); however, no significant changes were observed at the IH concentration of 0.125 *mg*/*mL*.

Fig. 3, C illustrates the changes in NOS activity. In the AS-treated group at 0.25 *mg*/*mL*, NOS activity was 1.3-fold higher than that of the control group ($p < 0.05$). Conversely, at 0.125 *mg*/*mL* AS, NOS activity was 1.18-fold lower than in the control group, though this change was not statistically significant ($p > 0.05$). In comparison to the control group, the IH-treated group at 0.25 *mg*/*mL* exhibited a 1.72-fold increase in NOS activity ($p < 0.05$), whereas, at 0.125 *mg*/*mL* IH, NOS activity remained comparable to the control, with a value of 6.5 units.

Levels of NO were measured in both control and herbal-treated HeLa cell groups (Fig. 3, B). To evaluate the induction of oxidative stress and elucidate the anticancer potential of the plant extracts by targeting multiple cellular components, MDA levels were also quantified. MDA serves as an indicator of lipid peroxidation, which is typically elevated in tumors due to increased reactive oxygen species (ROS) levels. The quantitative analysis revealed that, compared to the control group, all concentrations of the selected plant extracts resulted in increased MDA levels (Fig. 3, D). This increase suggests enhanced lipid peroxidation, potentially contributing to the anticancer effects of the plant extracts by inducing oxidative stress in cancer cells.

Conclusion. These results confirm that NOS and arginase are potential therapeutic targets in oncology. By studying the metabolism of arginine and its critical role in cancer progression, it is possible to use inhibitors of arginase metabolic pathways, such as L-NAME and nor-NOHA, nitric oxide synthase (NOS) and arginase inhibitors, in combination with plant extracts to achieve a cytotoxic effect against cancer cells. Based on the data, we can conclude that targeting arginine metabolism and using plant-derived compounds holds promise for developing novel anticancer therapies.

This work was supported by the Science Committee of the MESCS RA, in the frames of the research project No.23LCG-1F010.

Received 19.11.2024
Reviewed 03.12.2024
Accepted 15.12.2024

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Գ. Հ. ՊԵՏՐՈՍՅԱՆ

ԱՐԳԻՆԻՆԻ ՆՅՈՒԹԱՓՈԽԱՆԱԿԱՅԻՆ ՈՒՂՈՒ ՓՈՓՈԽՈՒԹՅԱՆ ԴԻՏԱՐԿՈՒՄԸ HeLa ՔԱՂՑԿԵՂԱՅԻՆ ԲՋԻՋՆԵՐՈՒՄ ԱՐԳԵԼԱԿԻՉՆԵՐԻ ԵՎ ԴԵՂԱԲՈՒՅՍԵՐԻ ԼՈՒԾԱՄՋՎԱԾՔՆԵՐԻ ՀԱՄԱԿՑՄԱՄԲ ԵՎ ԹԻՐԱԽԱՅԻՆ ԱԶԴԵՑՈՒԹՅԱՄԲ

Վերջին տարիներին բնակչության քանակի աճին զուգընթաց մեծանում է նաև քաղցկեղով հիվանդների թիվը: Այս հիվանդության բուժումը շարունակում է մնալ ժամանակակից բժշկության ամենակարևոր մարտահրավերներից մեկը:

Չնայած ուռուցքաբանության ոլորտում տասնամյակների հետազոտություններին և առաջընթացին, քաղցկեղը շարունակում է մնալ հիվանդության և մահացության հիմնական պատճառն ամբողջ աշխարհում: Բուժման ներկայիս եղանակները, ներառյալ վիրահատական միջամտությունը, ճառագայթային թերապիան, քիմիաթերապիան, թիրախային թերապիան և իմունոթերապիան, զգալիորեն բարելավել են քաղցկեղի որոշ տեսակների բուժման ելքը: Այնուամենայնիվ, էական մարտահրավերները պահպանվում են և սահմանափակում են քաղցկեղի բուժման արդյունավետությունն ու հասանելիությունը:

Վերջին տարիներին քաղցկեղի բուժման մեջ դասական քիմիաթերապիայի հետ մեկտեղ բուսական լուծամզվածքների ինտեգրումը մեծ ուշադրություն է արժանացել: Այս տեսակետից առանձնահատուկ հետաքրքրություն է ներկայացնում քիմիաթերապևտիկ նյութերի և բուսական լուծամզվածքների սիներգետիկ ներուժի ուսումնասիրությունը, որը կարող է բարձրացնել դասական թերապևտիկ դեղորայքի արդյունավետությունը՝ միաժամանակ նվազեցնելով անբարենպաստ կողմնակի ազդեցությունները:

Այս աշխատանքի նպատակն է՝ գնահատել բուսական լուծամզվածքների հակաուռուցքային ազդեցությունը HeLa քաղցկեղի բջջային գծում, ուսումնասիրել ազդման հնարավոր մեխանիզմները և դիտարկել բույսերի էքստրակտների, մասնավորապես՝ *Inula helenium* ու *Alchemila sminovi* Juz. դեղաբույսերի և արգինազի քիմիական արգելակիչների, ինչպիսիք են L-NAME-ը և nor-NOHA-ն, համատեղ ազդեցության արդյունավետությունը՝ ուղղված ազոտի օքսիդ սինթազի (NOS) և արգինազի նյութափոխանակային ուղիների կարգավորմանը: Մեր ուսումնասիրության ընթացքում *Alchemilla smirnovi* Juz.-ով բուժումը հանգեցրեց արգինազի ակտիվության զգալի նվազմանը՝ համեմատած ստուգիչ խմբի հետ: Նմանապես, *Inula helenium*-ով բուժումը ևս նվազեցրեց արգինազի ակտիվությունը: Այս համակցումները նպատակ ունեն ուժեղացնել քաղցկեղի բջիջների վրա ցիտոտոքսիկ ազդեցությունը, որի արդյունքում հնարավոր է առաջարկել քաղցկեղի դեմ պայքարի արդյունավետ ռազմավարություն:

Ստացված տվյալների հիման վրա մենք կարող ենք եզրակացնել, որ արգինինի նյութափոխանակության թիրախավորումը բուսական ծագում ունեցող միացությունների հետ համատեղ ունի խոստումնալից հեռանկարներ հակաքաղցկեղային թերապիայի մեջ:

Г. О. ПЕТРОСЯН

НАБЛЮДЕНИЕ ИЗМЕНЕНИЯ МЕТАБОЛИЧЕСКОГО ПУТИ АРГИНИНА В РАКОВЫХ КЛЕТКАХ HeLa ПУТЕМ КОМБИНИРОВАННОГО И НАПРАВЛЕННОГО ВОЗДЕЙСТВИЯ ИНГИБИТОРОВ И РАСТИТЕЛЬНЫХ ЭКСТРАКТОВ

В последние годы вместе с ростом населения увеличивается и число онкологических больных. Лечение этого заболевания остается одной из важнейших задач современной медицины.

Несмотря на десятилетия исследований и достижений в области онкологии, рак остается ведущей причиной болезней и смертности во всем мире. Современные методы лечения, включая хирургическое вмешательство, лучевую терапию, химиотерапию, таргетную терапию и иммунотерапию, значительно улучшили результаты лечения некоторых типов рака. Однако остаются серьезные проблемы, которые ограничивают эффективность и доступность лечения рака.

В последние годы большое внимание уделяется интеграции растительных экстрактов с классической химиотерапией в лечение рака. С этой точки зрения особый интерес представляет исследование синергетического потенциала химиотерапевтических средств и лечебных средств на основе трав, совместимость которых может повысить эффективность классических терапевтических препаратов при одновременном снижении побочных эффектов.

Цель данной работы – оценить противоопухолевый эффект экстрактов трав на линии раковых клеток HeLa, изучить возможные механизмы действия и наблюдать эффект растительных экстрактов, а именно *Inula helenium* и *Alchemila sminovi* Juz., а также химических ингибиторов аргиназы, таких как как L-NAME и nor-NOHA, комбинированного действия, направленного на метаболические пути синтазы оксида азота (NOS) и аргиназы. В нашем исследовании лечение с помощью *A. Smirnovi* Juz. привело к значительному снижению активности аргиназы по сравнению с контрольной группой. Аналогично, лечение с помощью *I. helenium* также снизило активность аргиназы. Данная комбинация направлена на усиление цитотоксического действия на раковые клетки, в результате чего можно предложить эффективную противораковую стратегию.

На основании полученных данных можно сделать вывод, что воздействие на метаболизм аргинина в сочетании с соединениями растительного происхождения имеет многообещающие перспективы в противораковой терапии.