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THE REGULATION OF DEAMINATION OF ADENINE COMPOUNDS IN BREAST AND LIVER IN DMBA-INDUCED BREAST CANCER RATS TREATED BY *HYPERICUM ALPESTRE*

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Cancer treatment is an ongoing struggle around the world, and research into its treatment and prevention is constantly deepening. Unrestricted cell proliferation is a hallmark of cancer. In cell reproduction, the exchange of purine nucleotides is of great importance, because they are involved in the synthesis of DNA, which is necessary for the uninterrupted process of cell division. The activities of deamination enzymes of purine nucleotides, nucleosides, and nitrogenous bases are altered during cancer development both in tumor tissue and in other tissues and organs of diseased animals. From this point of view, it is of great interest to study the changes in the activity of purine metabolism, the first stage of which is deamination. The aim of this work was the study the deamination alterations of AMP, ADP, ATP, as well as adenine and adenosine in the liver and breast tissue homogenates in rats with 7,12-DMBA-induced breast cancer.

In the experimental model of rats, mammary cancer was induced by 7,12-DMBA, and further treatment was carried out with the *Hypericum alpestre*. In addition, we also observed the combined effect of *H. alpestre* extract and chemical inhibitors on the deamination of purine compounds.

Data show a significant elevation of the adenine compounds' deamination level in the breast cancer group treated with *H. alpestre* extract compared with rats with DMBA-induced breast cancer. During the development of breast cancer in rats, a significant reduction in deamination levels was observed in the liver homogenate. This reduction was compared with the group treated with *H. alpestre*, where deamination levels showed a notable increase. The levels of deamination of adenine compounds after the treatment with *H. alpestre* herb become very close to the values typical of the samples of healthy animals.

Thus, in conclusion, the mentioned herb's anticancer activity can be expressed by the elevation of the deamination levels of adenine compounds, and one of the molecular mechanisms of the anticancer effect can be the dysregulation of deamination of adenine compounds under the influence of the selected plant.

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***Keywords*:** deamination, purine, adenine compounds, herbal extract, DMBA-induced cancer.

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Introduction. Normal cells undergo a series of highly regulated physiological responses to provide necessary substrates for the basic cellular processes, while cancer cells are involved in a complex metabolic rearrangement characterized by an increase in energy production and biosynthetic processes to sustain cell growth and proliferation [1–3]. Purines are the most abundant metabolic substrates for all living organisms by providing essential components for DNA and RNA. Besides as building blocks for DNA and RNA, purines provide the necessary energy and cofactors to promote cell survival and proliferation. Thus, purines and their derivatives widely participate in biological processes, including immune responses and host–tumor interaction [4].

Notably, high concentrations of purine metabolites have been indicated in tumor cells, and this discovery favors the development of the earliest antitumor drugs (purine antimetabolites) to treat cancers by blocking DNA synthesis and halting cell growth [5]. Cancer cells are known to reprogram their metabolism to enhance nucleotide synthesis via *de novo* pathway to replenish the nucleotide pool in cells and thereby provide the starting materials for DNA synthesis. In this way, they ensure their growth and reproduction [5]. From this point of view, nucleotide salvage pathways may also play an important role, by which the degradation of nucleotides and nitrogenous bases does not proceed to completion. Still, degradation intermediates are re-engaged in nucleotide biosynthesis, saving material and energy, which can be extremely important in rapidly dividing and active cancer tissue [6]. However, the molecular events by which oncogenes and cancer suppressors modulate these metabolic pathways have not yet been fully elucidated.

The fight against cancer continues to be a global struggle, and curative and preventive therapies are constantly evolving. Medicinal herbs have been used and are used as the main source of cancer treatment in developing countries for many years. The natural anti-inflammatory properties of herbs and cytotoxic effects on cancer cells make them necessary in the fight against cancer [6]. Several herbs growing in Armenia have an important place among anti-cancer medicinal plants, in particular, *H. alpestre* [7]. Taking into account the anti-inflammatory properties of *H. alpestre*, this plant was used to clarify its effect on the deamination of adenine compounds and to confirm its possible anticancer value. Data also indicate that during the development of various types of cancer, high activity of the arginase and NO-synthase (NOS) enzymes is manifested. Therefore, to treat or at least suppress cancer, arginase, and NOS inhibitors are often used, in the presence of which the proliferation of cancer cells is suppressed and their apoptosis is stimulated [8]. From this perspective, the enzymes arginase and NOS are becoming an increasingly attractive target in cancer research, and chemical inhibitors of these enzymes are being used to treat cancer [9, 10].

Thus, targeting purine metabolism may serve as a potential cancer treatment modality. We aim to investigate the anticancer effects of the plant extract and arginase and NOS enzyme inhibitors: Nw-hydroxy-nor-L-arginine (nor-NOHA) which inhibits arginase and suppresses tumor growth in a dose-dependent manner, and N-nitro-L-arginine-methylene ether (L-NAME), which is a Ca^{2+}-dependent non-selective inhibitor of NOS.

Materials and Methods.

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

***Animals and Tumor Induction*.** The experimental procedures involving animals were conducted following the guidelines outlined in Directive 2010/63/EU [11]. Ethical approval was obtained from the Armenian National Center of Bioethics. Female albino rats weighing between 120–150 *g*. were randomly distributed into 5 groups, with each group comprising eight individuals (except for the DMBA group, which had 10 individuals) as detailed in Table. The animals underwent a one-week acclimatization period before the experiment. They were housed in cages with a total area of 3500 cm^2, in a temperature-controlled room set at 25℃, with a 12-hour light/12-hour dark cycle and relative humidity of 50–55%. The animals were maintained under constant environmental and nutritional conditions (Animal Care house, YSU, Faculty of Biology). To initiate the development of breast cancer in rats, a solitary dose of 25 *mg* of 7,12-DMBA, dissolved in 1 *mL* of soy oil, was administered via subcutaneous injection into the 2nd set of mammary glands [12]. The chemical carcinogen was administrated at the age of 60–65 days. Following 28 weeks of DMBA administration, the rats were compassionately euthanized.

***Tumor Inhibition Study*.** The experimental design and treatment scheme are shown in Table. The experimental rats were regularly monitored for food and water consumption, the apparent signs of toxicity, weight loss, or mortality. Intraperitoneal injections of the *H. alpestre* extract, nor-NOHA, and L-NAME were performed according to Directive 2010/63/EU. All the animals were sacrificed after 190 days (28 weeks after administration by DMBA).

Experimental design and treatment

Groups	Experimental design	Number of rats in each group	25 *mg*/*mL* oil per rat, 7,12-DMBA	Treatment by *H. alpestre* 2.4 *mg*/*kg*/day in 0.25 *mL* saline	Treatment by nor-NOHA (3 *mg*/*kg*/day) and L-NAME (30 *mg*/*kg*/day) in 0.25 *mL* saline
1	DMBA (breast cancer)	10	on the 60th day, a single dose	–	–
2	normal control + Saline	8	–	–	–
3	DMBA+ *H. alpestre*	8	on the 60th day, a single dose	administered for 8 weeks (after tumors development in the 8th week, every 4th day)	–
4	DMBA + nor-NOHA + *H. alpestre*	8	on the 60th day, a single dose	administered for 8 weeks (after tumors development in the 8th week, every 4th day)	
5	DMBA + *L*-NAME + *H. alpestre*	8	on the 60th day, a single dose	administered for 8 weeks (after tumors development in the 8th week, every 4th day)	

Preparation of H. alpestre Extract. Plants were deposited to the Herbarium of YSU, voucher specimen serial number was given. Plant crude extracts are prepared by maceration technique using methanol (98%) and ethanol (96%) at a 10:1

solvent-to-sample ratio (v/w) [7]. The stock solutions of the samples for *in vivo* assay have been prepared by dissolving crude dried extracts in pure dimethyl sulfoxide (DMSO) ("Sigma-Aldrich").

Determination of the Intensity of Deamination of Adenine Compounds in Rat's Breast and Liver Homogenate. The intensity of deamination of adenine compounds (adenine, adenosine, adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP)) was determined in rat breast and liver homogenates according to the quantity of ammonia measured by Berthelot's indophenol reaction [13]. The resulting coloring intensity was measured with a spectrophotometer GENESIS 10S UV-VIS ("Thermo Fisher Scientific Inc.", USA) at a wavelength of 640 *nm*.

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

Results and Discussion.

Investigation of Deamination Intensity of Adenine Compounds in the Breast. The tissue homogenate of breast cancer exhibits a relatively high rate of deamination for adenine compounds, except for ADP, which shows negligible deamination activity. Adenine and adenosine demonstrate an approximately equal intensity of deamination, twice as high as the deamination rate observed for AMP and ATP (Fig. 1).

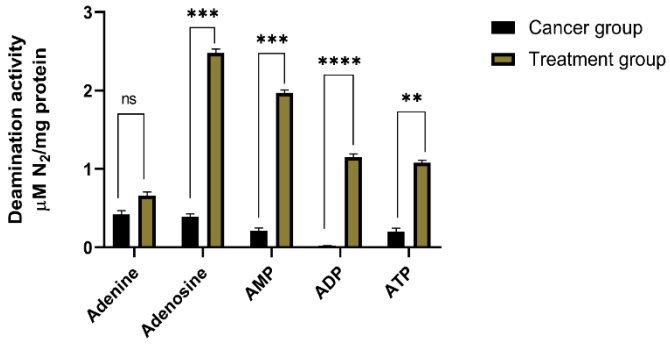

Fig. 1. Deamination intensity in adenine, adenosine, AMP, ADP, ATP of breast homogenate in cancer and treatment groups treated with the extract of the *H. alpestre*; *n*=8.
* – $p < 0.05$;
** – $p < 0.01$;
*** – $p < 0.001$;
**** – $p < 0.0001$.

Based on the data we can conclude, that the breast cancer tissue homogenate exhibits a notable level of adenine compound deamination, except for ADP, which displayed minimal deamination activity. Notably, adenine and adenosine demonstrated nearly equal rates of deamination, approximately two-fold higher than the deamination observed in AMP and ATP nucleotides (Fig. 1).

We compared the results of adenine compound deamination with data obtained from the breast. The obtained data can be explained by the fact that in rapidly growing and proliferating cancer cells, there is a constant demand for the synthesis of nucleic acids, which, in turn, necessitates the biosynthesis of nucleotides. Two interconnected pathways contribute to fulfilling this nucleotide requirement. Firstly, there is continuous *de novo* synthesis, which involves the catabolism of nucleotides in the cell into low-molecular-weight end products.

Literature data also support the notion that this pathway of nucleotide synthesis predominates in various types of cancer cells [14].

Since the initial step in nucleotide catabolism is deamination, adenine compounds undergo deamination in rat mammary carcinoma cells, with the potential for further degradation [5]. The low levels of deamination of adenine compounds in breast tumor homogenates indicate that the intensity of catabolism of these compounds decreased, as a result of cancer development (Fig. 1). Since the catabolism of adenine compounds provides a substrate for de novo synthesis of nucleotides, the reduction in the intensity of catabolism compared to herb-treated animals may lead to a lack of starting materials for DNA synthesis and thus to suppression of DNA synthesis in cancer cells. Most likely, the synthesis of nucleotides necessary for DNA synthesis in cancer cells is compensated by nitrogenous bases and nucleotide salvage pathways. It should also be noted that the decrease in the deamination of ATP and ADP in cancer cells is due to their energetic role because fast-growing cancer cells have a high energy demand. ATP and ADP in this case do not undergo catabolism but are hydrolyzed, supplying the energy necessary for cell growth. ATP acts as a universal source of energy, and ADP as an alternative source [1]. Therefore, the deamination of ADP, the intensity of which is almost the same in the cells treated with the herb as that of ATP, is manifested only as a trace activity in cancer cells (Fig. 1).

Relatively low levels of deamination are observed for adenine nucleotides, specifically AMP and ATP, while only trace deamination activity is detected for ADP (Fig. 1). This pattern can be attributed to the high energy demand experienced by rapidly growing cancer cells. In the case of animals treated with the herb *H. alpestre*, the significant increase in the intensity of deamination of adenine compounds, particularly adenosine, and AMP, suggests that catabolic reactions of adenine compounds start to prevail in regenerating cells during the recovery process.

Assessing Adenine Compound Deamination Intensity in the Liver Homogenate. The onset of cancer in the body leads to a reconfiguration of the functioning of all organ systems, and disruptions in the normal operation of these systems are inevitable [15]. Therefore, it is important to elucidate the biochemical status of other organ systems in the body during the development of cancer in any organ or tissue. The significance of this issue is heightened by the common use of non-selective cytostatic antitumor chemotherapy drugs in cancer treatment, which can lead to side effects in cells of various tissues and organs throughout the body. Notably, liver and brain cells are particularly susceptible to these adverse effects. It is crucial to assess the risk of liver damage and the potential for recovery during cancer development and potential treatment. Our data for the intensity of deamination of adenine compounds in liver homogenate obtained from rats with breast cancer are shown in Fig. 2.

Fig. 2, a shows the intensity of adenine and adenosine deaminases within the liver homogenate of cancer and treatment groups of rats including a control group of rats (healthy rats), a DMBA-induced cancer group, and a treatment group consisting of three different treatment models. The first model is DMBA+*H. alpestre* extract, the second is L-NAME+*H. alpestre*, combines L-NAME, a chemical inhibitor of NOS, with *H. alpestre* herbal extract, the third treatment group is nor-NOHA+

H. alpestre employs nor-NOHA as a chemical inhibitor for arginase, in combination with *H. alpestre* herbal extract.

Fig. 2, b shows the changes in deamination of AMP, ADP, and ATP in the same group as mentioned above. Notably, the plant used remains consistent across all treatment groups.

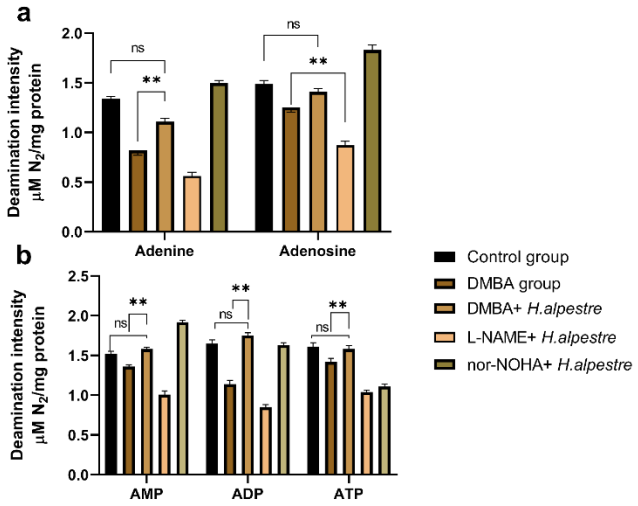

Fig. 2. Deamination of adenine compounds in liver homogenate of different experimental groups; $n = 8$.
* – $p < 0.05$;
** – $p < 0.01$;
*** – $p < 0.001$;
**** – $p < 0.0001$.

During the induction of breast cancer by DMBA in the rats, noticeable changes in the deamination of adenine compounds occur also in the liver homogenate. Thus, in the liver homogenate of DMBA-induced cancer rats, the catabolism of all adenine compounds is suppressed and the most significant effect was recorded for adenine. So the deamination intensity of adenine was decreased by 38.8%, in the case of adenosine – by 16%, and in the case of AMP – by 10.5% in the case of ADP – by 30.9%, and in the case of ATP – by 11.8% ($p < 0.001$).

As indicated by the obtained data (Fig. 2), following the administration of *H. alpestre* extract to animals with breast cancer, a consistent trend of increased deamination strength in adenine compounds is observed. In some cases, this increase significantly surpasses the levels seen in healthy animals, particularly in the cases of AMP and ADP. Thus, it can be concluded that the treatment with *H. alpestre* promotes the recovery of catabolic processes in the liver homogenate of rats.

In the combined treatment of cancer with chemical inhibitors and *H. alpestre*, we observed an increase in the strength of deamination of adenine compounds (Fig. 2). Importantly, this increase was more pronounced than when the herb was administered alone, and in terms of these indicators, animals treated with the combination of nor-NOHA and *H. alpestre* even suppressed healthy animals. The only exception was ATP, where deamination intensity was lower in both healthy and *H. alpestre*-treated rats. It can be assumed that ATP catabolism is relatively suppressed in the liver of treated animals, leading to increased hydrolysis to meet energy requirements. As for other adenine compounds, their catabolism is enhanced, and the *de novo* pathway of nucleotide synthesis regains dominance [16].

In the case of combined treatment with L-NAME and *H. alpestre*, the intensity of deamination of adenine compounds in the liver of animals with breast cancer

decreases for all the considered compounds, in comparison with cancer animals. Thus, during this combined treatment, the catabolism of adenine compounds, the initial stage of which is deamination, is suppressed. It can be inferred that nucleotide salvage pathways become more significant in this context. Since the nucleotide salvage pathway is vital for both DNA repair and replication in cancer cells, targeting enzymes in this pathway is a strategy in cancer therapy. Inhibitors of these enzymes can lead to nucleotide depletion, thereby impairing DNA repair and replication in cancer cells, potentially leading to their death [17].

Conclusion. Based on the data we can conclude that the development of breast cancer in rats leads to noticeable changes in the deamination of adenine compounds in breast cancer tissue and liver homogenate. Specifically, catabolism of adenine compounds is suppressed, which can lead to a decrease of nucleotides *de novo* synthesis in cancer. The treatment of cancer with *H. alpestre* extract appears to promote the recovery of catabolic processes in the breast and liver of rats and leads to an increase in the deamination intensity of adenine compounds (Fig. 3).

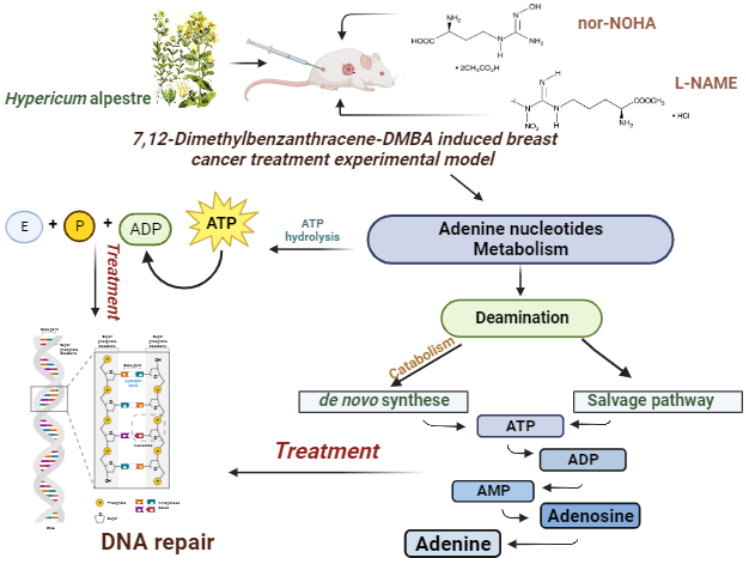

Fig. 3. Possible mechanism of DNA repair and adenine cycle in DMBA-induced breast cancer treatment experimental model of rats.

Combined treatment with chemical inhibitors (nor-NOHA) and *H. alpestre* leads to a lower intensity of ATP catabolism, leading to increased hydrolysis of ATP to meet energy requirements. L-NAME and *H. alpestre* combined treatment of cancer animals leads to a decrease in adenine compound catabolism, possibly leading to a greater reliance on nucleotide salvage pathways.

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HYPERICUM ALPESTRE ԲՈՒԺՄԱՆ ԸՆԹԱՑՔՈՒՄ ԱԴԵՆԻՆԱՅԻՆ ՄԻԱՑՈՒԹՅՈՒՆՆԵՐԻ ԴԵԱՄԻՆԱՑՄԱՆ ԿԱՐԳԱՎՈՐՈՒՄԸ 7,12-DMBA-ՈՎ ԱՌԱՋԱՑԱԾ ՔԱՂՑԿԵՂՈՎ ՀԻՎԱՆԴ ԱՌՆԵՏՆԵՐԻ ԿՐԾՔԱԳԵՂՁՈՒՄ ԵՎ ԼՅԱՐԴՈՒՄ

Քաղցկեղի բուժմանն ուղղված պայքարը շարունակվում է ամբողջ աշխարհում: Քաղցկեղին բնորոշ է բջիջների անսահմանափակ բաժանումը: Բջիջների վերարտադրության տեսանկյունից պուրինային նուկլեոտիդների փոխանակությունը մեծ նշանակություն ունի, քանի որ դրանք մասնակցում են բջիջների բաժանման շարունակական գործընթացի համար անհրաժեշտ ԴՆԹ-ի սինթեզին: Այս տեսանկյունից մեծ հետաքրքրություն են ներկայացնում պուրինային միացությունների նյութափոխանակային փոփոխությունները, որոնց առաջին փուլը դեզամինացումն է: Նուկլեոտիդները, նուկլեոզիդները և ազոտային հիմքերը դեզամինացնող ֆերմենտների ակտիվությունները փոփոխվում են քաղցկեղի զարգացման ընթացքում՝ ինչպես ուռուցքային հյուսվածքում, այնպես էլ այլ հյուսվածքներում և օրգաններում:

Մեր աշխատանքի նպատակն է եղել ուսումնասիրել ԱՄՖ-ի, ԱԿՖ-ի, ԱԵՖ-ի, ինչպես նաև՝ ադենինի և ադենոզինի դեզամինացման փոփոխությունները՝ ԴՄԲԱ-ով (7,12-դիմեթիլբենզատրացենով) հարուցված կրծքագեղձի քաղցկեղով հիվանդ առնետների լյարդի և կրծքագեղձի հոմոգենատներում: Բուժումը իրականացվել է *H. alpestre* դեղաբույսով: Դիտարկվել է նաև *H. alpestre* բույսի լուծամզվածքի և նյութափոխանակային արգելակիչների համակցված ազդեցությունը պուրինային միացությունների դեզամինացման վրա:

Տվյալները ցույց են տվել ադենինային միացությունների դեզամինացման մակարդակի զգալի աճ կրծքագեղձի քաղցկեղով հիվանդ առնետների խմբում, որոնք բուժվել են *H. alpestre* դեղաբույսով՝ համեմատած կրծքագեղձի քաղցկեղով հիվանդ առնետների: Կրծքագեղձի քաղցկեղով առնետների լյարդի հոմոգենատներում դիտվել է դեզամինացման մակարդակի կտրուկ նվազում հիվանդության զարգացման ընթացքում՝ համեմատած *H. alpestre*-ով բուժվող խմբի հետ, որտեղ դեզամինացման մակարդակը զգալիորեն աճել է՝ մոտենալով ստուգիչ խմբի առողջ կենդանիներին բնորոշ մակարդակին:

Այսպիսով, նշված բույսի հակաուռուցքային ակտիվության մեխանիզմներից մեկը կարող է լինել ադենինային միացությունների դեզամինացման մակարդակի բարձրացումը:

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РЕГУЛЯЦИЯ ДЕЗАМИНИРОВАНИЯ АДЕНИНОВЫХ СОЕДИНЕНИЙ В МОЛОЧНОЙ ЖЕЛЕЗЕ И ПЕЧЕНИ КРЫС С 7,12-ДМБА-ИНДУЦИРОВАННЫМ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ, ПОД ВЛИЯНИЕМ ЛЕЧЕНИЯ С *HYPERICUM ALPESTRE*

Борьба с раком продолжается во всем мире, и исследования в области его лечения и профилактики постоянно углубляются. Неограниченная

пролиферация клеток является отличительной чертой рака. В размножении клеток большое значение имеет обмен пуриновых нуклеотидов, поскольку они участвуют в синтезе ДНК, необходимой для непрерывного процесса деления клеток. Активность ферментов дезаминирования пуриновых нуклеотидов, нуклеозидов и азотистых оснований изменяется при развитии рака как в опухолевой ткани, так и в других тканях и органах больных животных. С этой точки зрения большой интерес представляет изучение изменений активности пуринового обмена, первой стадией которого является дезаминирование.

Целью работы было изучение изменений дезаминирования АМФ, АДФ, АТФ, а также аденина и аденозина в гомогенатах тканей печени и молочной железы у крыс с 7,12-ДМБА-индуцированным раком молочной железы. На экспериментальной модели крыс рак молочной железы индуцировали 7,12-ДМБА, а дальнейшее лечение проводили экстрактом растения *H. alpestre*. Кроме того, мы также наблюдали совместное действие экстракта *H. alpestre* и химических ингибиторов на дезаминирование пуриновых соединений.

Данные показывают значительное повышение уровня дезаминирования адениновых соединений в группе крыс, больных раком молочной железы и получавших экстракт травы *H. alpestre*, по сравнению с нелеченными крысами. При развитии рака молочной железы у крыс наблюдалось значительное снижение уровня дезаминирования в гомогенате печени. Это снижение сравнивали с группой, получавшей *H. alpestre*, где уровни дезаминирования показали заметное увеличение. Уровни дезаминирования адениновых соединений после обработки экстрактом *H. alpestre* стали очень близкими к значениям, характерным для проб здоровых животных.

Таким образом, противораковая активность упомянутой травы может выражаться в повышении уровня дезаминирования адениновых соединений, и одним из молекулярных механизмов противоракового действия может быть нарушение регуляции дезаминирования адениновых соединений под влиянием *H. alpestre*.