PROCEEDINGS OF THE YEREVAN STATE UNIVERSITY

Chemistry and Biology 2025, **59**(3), p. 113–121

Biology

ALTERATIONS IN ARGINASE ACTIVITY, NITRIC OXIDE, AND MDA LEVELS IN BONE MARROW DURING DMBA-INDUCED BREAST CANCER IN RATS

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This study investigates the therapeutic potential of herbal extracts to mitigate bone marrow damage during DMBA-induced breast cancer and its treatment in rats. Untreated tumor-bearing rats showed elevated arginase activity and malondialdehyde (MDA) levels with reduced nitric oxide (NO) bioavailability. Treatment with herbal extract combined with the arginase inhibitor nor-NOHA, significantly reduced MDA and restored NO levels, demonstrating antioxidant and protective effects on the bone marrow. Conversely, combining a NOS inhibitor (L-NAME) with herbal extract exacerbated oxidative damage. The findings support using specific phytotherapeutics as adjuvants to conventional cancer therapy to maintain bone marrow integrity.

https://doi.org/10.46991/PYSUB.2025.59.3.113

***Keywords*:** breast cancer, bone marrow, malondialdehyde, 5-fluorouracil, L-NAME, nor-NOHA, 5-FU, arginase, nitric oxide.

Introduction. Breast cancer remains one of the most frequently diagnosed malignancies in women and continues to be a leading cause of cancer-related mortality worldwide. While chemotherapy, particularly agents like 5-fluorouracil (5-FU), has contributed significantly to improving patient outcomes, it often comes with systemic side effects, including adverse impacts on the bone marrow – the primary site of hematopoiesis and a known niche for metastatic cancer cell colonization. Chemotherapy-induced alterations in the bone marrow microenvironment may contribute not only to hematologic dysfunction but also to conditions that promote tumor progression and metastasis [1].

Among the key biochemical factors affected by cancer and its treatment are arginase activity, nitric oxide (NO) levels, and malondialdehyde (MDA) concentration. Arginase, which hydrolyzes L-arginine to urea and ornithine, competes with nitric oxide synthase (NOS) for its shared substrate [2]. Its overexpression has been implicated in immunosuppression and tumor advancement [3, 4], while its

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inhibition, for instance with nor-NOHA, has been shown to restore T-cell activity and suppress tumor growth [3]. NO itself has a dual role in cancer biology: low levels may facilitate angiogenesis and tumor survival, whereas higher concentrations may have tumoricidal effects [5]. Inhibiting NOS with agents such as L-NAME allows for a better understanding of NO's complex function in the tumor-bearing microenvironment. In parallel, MDA is a well-established marker of lipid peroxidation and oxidative stress, often elevated in malignancies and correlated with DNA damage, immune escape, and reduced response to therapy [6].

In recent years, interest in phytotherapy – the use of medicinal plant-derived compounds in treatment – has grown substantially. These natural agents are known for their potential anti-inflammatory, antioxidant, and anticancer effects [7]. In the present study, we explored the potential benefits of three plant extracts: *Inula helenium*, traditionally used in herbal medicine and rich in sesquiterpene lactones like alantolactone, which exhibit anticancer activity [8]; *Alchemilla smirnovii* Juz., a member of the Rosaceae family, valued for its antioxidant polyphenols and potential tissue-repair properties; and *Rumex obtusifolius*, known in folk medicine for its detoxifying and anti-inflammatory actions, with emerging evidence pointing to anticancer and cytoprotective effects [9, 10].

The current study aims to evaluate changes in arginase activity, nitrite ion concentration (as a proxy for NO levels), and MDA levels in the bone marrow of DMBA-induced breast cancer-bearing rats following various treatment regimens. These included monotherapies with 5-FU or the individual plant extracts, as well as combinations involving 5-FU, L-NAME (LN), or nor-NOHA (NN) with the plant extracts. By correlating biochemical alterations in the bone marrow with tumor size and weight, we seek to understand the relationship between arginine metabolism, oxidative stress, and tumor progression. Furthermore, this work provides insight into the possible protective or synergistic effects of herbal extracts when combined with conventional or targeted therapies. Previous work by our group has demonstrated the value of similar biomarkers in cancer models [11, 12] and this investigation builds upon that foundation with a focus on the underexplored bone marrow niche.

Materials and Methods.

***Chemicals and Reagents*.** All chemicals used in the research were purchased from Sigma-Aldrich.

***Collection and Extraction of Plant Material*.** The *Rumex obtusifolius* (RO), *Inula helenium* (IH), and *Alchemilla smirnovii* Juz. (AS) were harvested from the Tavush Region of Armenia (1400–1600 *m* height above mean sea level) according to the protocol described before [12]. Dr. Narine Zakaryan identified plant material at the YSU Department of Botany and Mycology. Plant materials were deposited at the Herbarium of YSU.

***Animals and Experimental Groups*.** The experimental procedures involving animals were conducted following the guidelines outlined in Directive 2010/63/EU [13]. Ethical approval was obtained from the Armenian National Center of Bioethics. Female albino rats weighing between 120 *g* and 150 *g* were randomly distributed into 8 groups, with each group comprising eight animals, except for the DMBA group (dimethylbenz(a)anthracene, cancer group), which had 10 animals.

Following 28 weeks of DMBA administration, the rats were euthanized by isoflurane using a precision vaporizer with an induction chamber and waste gas scavenger (RWD Life Science). Isoflurane was administered slowly up to 5% until respiratory arrest occurred. Animals were monitored for the cessation of respiration and remained in the euthanasia chamber for an additional 60 *s* after respiration had ceased.

The animals underwent a 1-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°C, with a 12 *h* light/12 *h* 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 induce breast cancer in rats, a single dosage of 25 *mg* of 7,12-DMBA dissolved in 1 *mL* of soy oil was administered subcutaneously into the 2^{nd} set of mammary glands [11]. The chemical carcinogen was administered when the rats were aged between 60 and 65 days. The tumor was first detected by touch, and its size was subsequently measured and monitored regularly.

The laboratory personnel conducted daily health monitoring and tumor measurements. The body weights of the animals were monitored weekly throughout the entire experiment.

The selection of plant extract concentrations was based on *in vitro* findings and information available in the literature from similar studies involving other plant extracts.

NO Quantity Measurement. The levels of NO in the blood plasma were quantified by measuring nitrite ions using the Griess assay [6]. Briefly, 100 μL of plasma samples were combined with 100 μL of Griess reactant. Subsequently, the supernatant obtained was transferred to tubes with cadmium pellets and left to incubate at room temperature for 12 *h*, facilitating the conversion of nitrate to nitrite. The absorbance was measured at a wavelength of 550 *nm* (a standard curve constructed using $NaNO_2$).

Arginase Activity. The modified Diacetyl Monoxime colorimetric method was employed to assess the arginase activity in blood plasma. The enzyme activity was quantified as the amount of urea formed per second, measured in micromoles [14].

Isolation of the Bone Marrow, Cell Counting, and Fixation. The rats were euthanized by isoflurane using a precision vaporizer with an induction chamber and waste gas scavenger (RWD Life Science). Isoflurane was administered slowly up to 5% until respiratory arrest occurred. Animals were monitored for the cessation of respiration and remained in the euthanasia chamber for an additional 60 *s* after respiration had ceased. Bone marrow cells were extracted from the femur of the rats as described before [15]. After isolation, the bone marrow cells were resuspended in 25 *mL* of DMEM and centrifuged for 5 *min* at 1500 *rpm*. The supernatant was removed, and the pellet was additionally resuspended in 2 *mL* of DMEM. The cell suspension was afterward lysed in Radio-Immunoprecipitation Assay (RIPA) lysis buffer (Biovision) and proceeded with the experimental protocol for further analysis.

Statistics. The findings are depicted as the mean values ± standard deviation. Statistical analyses were performed using GraphPad Prism 10 software, and a significance level of $p < 0.05$ was deemed statistically significant.

Results and Discussion.

Evaluation of the Arginase Activity in the Bone Marrow of the DMBA-induced Breast Cancer Rat Model.

Changes of the Arginase Enzyme in the Bone Marrow after the Treatment with the Plant Extract and Chemotherapy Combination. Arginase enzymes, particularly arginase 1 and arginase 2, play a critical role in the bone marrow by regulating L-arginine metabolism. Through the hydrolysis of L-arginine into urea and ornithine, arginase activity influences several key processes within the bone marrow microenvironment. One of the primary effects of arginase is the depletion of L-arginine, which is essential for T-cell proliferation and function. This depletion leads to immunosuppression, a mechanism frequently exploited by myeloid-derived suppressor cells, especially in pathological conditions such as cancer, chronic inflammation, and autoimmune diseases. In this study, we evaluate the changes in arginase enzyme in the bone marrow after the administration.

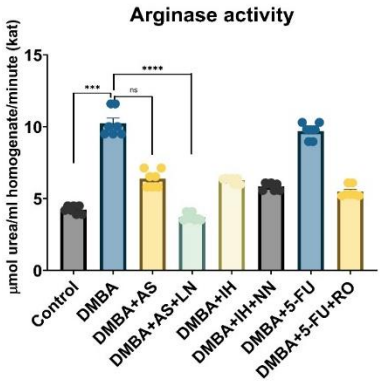

Fig. 1. Evaluation of the arginase activity in the bone marrow. Each independent experiment includes 7 rats with three repetitions per sample.

In our study, arginase activity was found to be elevated in the cancer group, consistent with its known role in promoting immunosuppression and altering the bone marrow microenvironment during tumor progression. In all treatment groups, arginase activity decreased compared to the cancer group, except in the group treated solely with 5-fluorouracil (5-FU), where arginase activity remained elevated. Interestingly, when 5-FU was combined with *Rumex obtusifolius* extract, arginase activity decreased significantly and approached levels observed in the healthy control group. The most pronounced reduction in arginase activity was observed in the DMBA+AS+LN group, which received a combination of *Alchemilla smirnovii* Juz. extract and a NOS inhibitor. This result is somewhat unexpected, as the NOS inhibitor would typically reduce nitric oxide production and redirect L-arginine toward arginase, potentially increasing its activity. However, this anticipated effect was not observed, suggesting that the plant extract may have had a dominant suppressive effect on arginase expression or activity, or that other regulatory mechanisms were involved.

Furthermore, both the group treated with *Inula helenium* alone and the group treated with Inula helenium combined with the NOS inhibitor Nor-NOHA showed a reduction in arginase activity compared to the cancer group. However, no significant difference was observed between these two groups, indicating that *Inula helenium*

may exert its effect independently of NOS inhibition. Arginase-mediated depletion of L-arginine likely contributes to T-cell dysfunction and impaired anti-tumor immunity, facilitating tumor survival and growth. Interestingly, treatment with our selected interventions led to a significant reduction in arginase activity. This decrease suggests a reversal of the immunosuppressive and dysregulated hematopoietic environment typically observed in cancer. Lower arginase activity may reflect restored L-arginine availability, improved T-cell responsiveness, and normalized bone marrow function. Overall, these findings highlight the potential of targeting arginase as part of a therapeutic strategy to modulate the tumor-associated bone marrow niche and enhance anti-cancer immune responses.

Evaluation of the Nitrite Ion Level in the Bone Marrow of the DMBA-induced Breast Cancer Rat Model. Several studies have demonstrated that NO levels can be dysregulated in the bone marrow during cancer progression. In hematological malignancies such as acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), significantly lower levels of nitrite – the stable end product of NO – have been detected in both plasma and bone marrow, suggesting reduced NOS activity and impaired NO production in the bone marrow micro-environment [16]. This reduction may contribute to immune suppression and altered hematopoiesis in leukemic conditions.

In contrast, studies investigating solid tumors, including breast cancer, have reported elevated serum NO levels, particularly in advanced disease stages [17]. However, NO levels tend to decline following chemotherapy, indicating dynamic regulation of NO during cancer treatment. While direct evidence of decreased NO specifically in the bone marrow in breast cancer models is limited, the increased arginase activity observed in tumor-associated myeloid-derived suppressor cells (MDSCs) supports a mechanism of reduced NO synthesis due to substrate competition for L-arginine [18]. This arginase-driven pathway may lead to NO downregulation in the bone marrow microenvironment during breast cancer progression.

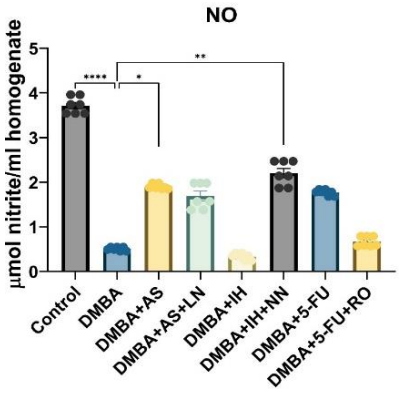

Fig. 2. Evaluation of the nitrite ion level in the bone marrow. Each independent experiment includes 7 rats with three repetitions per sample.

Fig. 2 illustrates a significant reduction in nitrite ion levels in the bone marrow of the DMBA-induced cancer group that did not receive any treatment, indicating suppressed NO production in the tumor environment. In contrast, all treatment groups demonstrated varying degrees of nitrite ion restoration. The most notable

increase was observed in the DMBA+IH+NN group. This group received nor-NOHA, a known arginase inhibitor, which likely diverted the available L-arginine substrate toward nitric oxide synthase, resulting in elevated NO production and consequently higher nitrite ion levels.

Interestingly, in the group treated with *Inula helenium* alone, without the arginase inhibitor, nitrite ion levels were even lower than those in the untreated cancer group. This suggests that *Inula helenium*, in the absence of arginase inhibition, may not enhance NO production and could potentially downregulate NOS activity or arginine availability.

In the 5-FU-treated group, nitrite ion levels were moderately elevated, suggesting partial restoration of NO synthesis, possibly due to reduced tumor burden or immune modulation. However, the 5-FU+*Rumex obtusifolius* combination group exhibited persistently low nitrite ion levels, comparable to or even lower than the untreated DMBA group. This unexpected result may point to a potential interaction between 5-FU and *Rumex obtusifolius* that interferes with NOS activity or L-arginine metabolism.

Evaluation of the MDA Level in the Bone Marrow of the DMBA-induced Breast Cancer Rat Model. Increased MDA levels, a marker of lipid peroxidation and oxidative stress, have been observed in various malignancies, including hematologic cancers and bone tumors. Elevated serum MDA has been reported in patients with acute and chronic myeloid leukemia, reflecting enhanced oxidative damage in the bone marrow microenvironment [19].

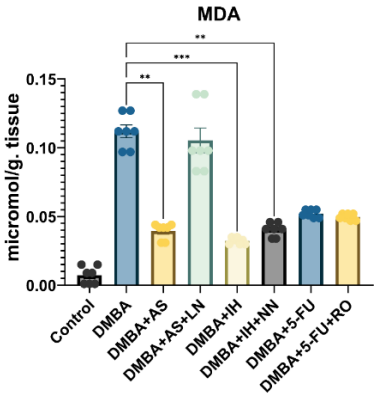

Fig. 3. Evaluation of the MDA level in the bone marrow. Each independent experiment includes 7 rats with three repetitions per sample.

As shown in Fig. 3, MDA levels, an indicator of lipid peroxidation and oxidative stress, were significantly elevated in the DMBA-induced cancer group compared to healthy controls. Treatment with most experimental agents led to a reduction in MDA levels, indicating attenuation of lipid peroxidation. The most pronounced reduction was observed in the group treated solely with *Inula helenium* extract, suggesting the strong antioxidant potential of this phytocompound. A similarly significant decrease was seen in the group treated with *Inula helenium* in combination with nor-NOHA, an arginase inhibitor. The reduction in MDA in this group may be attributed to the inhibition of arginase, which increases L-arginine availability for NOS. This promotes NO production, which is known to exert vasoprotective and antioxidant effects, thereby reducing oxidative damage [18, 20].

Interestingly, in the group treated with *A. smirnovii* extract was combined with L-NAME, a NOS inhibitor, MDA levels remained high, comparable to the untreated cancer group. L-NAME likely reduced NO production by inhibiting NOS, potentially leading to NOS uncoupling, superoxide production, and subsequent enhancement of oxidative stress and lipid peroxidation. While *A. smirnovii* extract alone did not induce a similar increase in MDA levels, the combined effect with L-NAME suggests that arginine diversion to arginase activity (due to NOS inhibition) and possible interactions with the phytocompound may exacerbate oxidative processes.

Conclusion. This study highlights the pivotal role of arginine metabolism and oxidative stress in the bone marrow microenvironment during DMBA-induced breast cancer progression. Elevated arginase activity and lipid peroxidation (MDA) were associated with decreased NO bioavailability in untreated cancer-bearing rats, contributing to a pro-oxidant state. Treatment with *Inula helenium* herbal extract, particularly when combined with the arginase inhibitor nor-NOHA, effectively reduced oxidative damage and restored NO levels, underscoring the therapeutic potential of targeting arginase-NOS balance. In contrast, NOS inhibition via L-NAME in combination with *A. smirnovii* extract exacerbated lipid peroxidation, revealing the delicate equilibrium between NO synthesis and oxidative stress. Additionally, while 5-FU, as a classical chemotherapy agent, demonstrated antitumor activity, it also induced adverse effects in the bone marrow, as evidenced by oxidative stress markers. Importantly, combining 5-FU with *Rumex obtusifolius* herbal extract mitigated these detrimental effects, suggesting improved therapeutic efficacy and bone marrow protection. These data support further exploration of phytotherapeutic agents alongside conventional chemotherapies to modulate the bone marrow microenvironment, potentially limiting tumor progression and improving treatment outcomes in breast cancer.

Received 03.11.2025
Reviewed 08.12.2025
Accepted 11.12.2025

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Ա. Ա. ՄԿՐՏՉՅԱՆ, Հ. Գ. ՋԱՎՐՈՒՇՅԱՆ

ԱՐԳԻՆԱԶԻ ԱԿՏԻՎՈՒԹՅԱՆ, ԱԶՈՏԻ ՕՔՍԻԴԻ ԵՎ ՄԵԱ-Ի ՔԱՆԱԿԱԿԱՆ ՓՈՓՈԽՈՒԹՅԱՆ ԳՆԱՀԱՏՈՒՄԸ ԴՄԲԱ-ԻՆԴՈՒՑՎԱԾ ԿՐԾՔԱԳԵՂՁԻ ՔԱՂՑԿԵՂՈՎ ԱՌՆԵՏՆԵՐԻ ՈՍԿՐԱԾՈՒԾՈՒՄ

Այս աշխատանքում ուսումնասիրվում է բուսական լուծամզվածքների բուժական ներուժը՝ մեղմելու առնետների մոտ DMBA-ով խթանված կրծքագեղձի քաղցկեղի բուժման ընթացքում ոսկրածուծի վնասումը: Բուժում չստացած ուռուցք կրող առնետների մոտ գրանցվել է արգինազի բարձր ակտիվություն և մալոնդիալդեհիդի (MDA) բարձր մակարդակ՝ ազոտի օքսիդի (NO) ցածր կենսամատչելիության պայմաններում: Բուժումը բուսական լուծամզվածքի և արգինազի արգելակիչ nor-NOHA-ի համակցությամբ զգալիորեն նվազեցրել է MDA-ի մակարդակը և վերականգնել NO-ի մակարդակը, ցուցաբերելով հակաօքսիդանտային և պաշտպանիչ ազդեցություն ոսկրածուծի վրա: Ընդհակառակը, NOS արգելակչի (L-NAME) և բուսական լուծամզվածքի համակցումը դրսևորել է օքսիդանտային ազդեցություն: Արդյունքները հաստատում են, որ ֆիտոթերապևտիկ միջոցները կարող են օգտագործվել որպես օժանդակ միջոցներ ավանդական քաղցկեղային բուժման հետ՝ ոսկրածուծի ամբողջականությունը պահպանելու համար:

С. М. ОГАННИСЯН, А. С. АКОБЯН, А. Н. АКОБЯН,
А. А. МКРТЧЯН, А. Г. ДЖАВРУШЯН

ИЗМЕНЕНИЯ АКТИВНОСТИ АРГИНАЗЫ, УРОВНЕЙ ОКСИДА АЗОТА И МДА В КОСТНОМ МОЗГЕ КРЫС ПРИ ДМБА-ИНДУЦИРОВАННОМ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ

В данном исследовании изучался терапевтический потенциал растительных экстрактов для смягчения повреждения костного мозга во время лечения DMBA-индуцированного рака молочной железы у крыс. У животных, не получавших лечение, наблюдались повышенные активность аргиназы и уровень малондиальдегида (МДА) наряду со сниженной биодоступностью оксида азота. Лечение экстрактом в сочетании с ингибитором аргиназы nor-NOHA значительно снизило МДА и восстановило уровни оксида азота, демонстрируя антиоксидантное и защитное действие на костный мозг. Напротив, комбинация ингибитора NOS (L-NAME) с растительным экстрактом усугубляла окислительное повреждение. Полученные данные подтверждают использование специфических фитотерапевтических экстрактов в качестве вспомогательных средств к традиционной терапии рака для сохранения целостности костного мозга.