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# Pycnogenol Modulated Myeloid-Derived Suppressor Cells in Murine Model of Breast Cancer

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## Abstract

***Background:*** Myeloid-derived suppressor cells (MDSCs) promote immune evasion and tumor progression in breast cancer. Pycnogenol®, a standardized extract from Pinus pinaster bark, possesses antioxidant and immunomodulatory properties, but its effect on MDSCs in cancer remains unclear. Therefore, the aim of this study was to evaluate the effect of Pycnogenol on MDSCs function and tumor progression in a mouse model of breast cancer.

**Methods:** Female BALB/c mice were inoculated with 4T1 mammary carcinoma cells and treated with Pycnogenol (50 mg/kg/day) for four weeks. MDSCs were isolated from tumor-bearing mice for analysis of nitric oxide (NO), reactive oxygen species (ROS), arginase activity, and gene expression (*Arg1, iNOS, S100A8, S100A9*). Tumor volume and survival were also assessed.

**Results:** Pycnogenol significantly reduced *Arg1* mRNA expression, NO production, and ROS levels in MDSCs. No significant changes were observed in arginase activity, *iNOS*, or *S100A8/A9* expression. Pycnogenol modestly delayed tumor growth and slightly extended survival, although these differences did not reach statistical significance.

**Conclusion:** Pycnogenol attenuates key immunosuppressive functions of MDSCs in breast cancer, suggesting its potential as a supportive immunomodulatory agent. Further investigation is warranted to explore its role in combination with immunotherapies.

**Keywords:** Breast Cancer, Immunomodulation, Pycnogenol, MDSCs, Natural Compounds, Tumor Microenvironment.

## Introduction

Breast cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, despite advances in early detection and treatment modalities (1). The tumor microenvironment (TME), which is composed of stromal cells, immune cells, and extracellular matrix components, plays a pivotal role in shaping tumor progression and

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immune evasion (2). Among the immune cells within the TME, myeloid-derived suppressor cells (MDSCs) have garnered considerable attention due to their ability to suppress T-cell activity, promote angiogenesis, and facilitate metastasis (3). These functions underscore the importance of studying MDSCs in the context of breast cancer.

In breast cancer, the accumulation of MDSCs is driven by various tumor-derived factors (4), including granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF) (5). These factors not only promote the expansion of MDSCs but also enhance their suppressive functions. For instance, MDSCs suppress T-cell responses through the production of reactive oxygen species (ROS), nitric oxide (NO), and arginase-1, creating a microenvironment conducive to tumor progression (6). Emerging evidence suggests that MDSCs are actively involved in promoting the metastatic potential of breast cancer cells. (7, 8). Overall, MDSCs represent a critical component of the immunosuppressive TME in breast cancer. Their multifaceted roles in immune evasion, tumor progression, and metastasis underscore the importance of studying these cells to advance our understanding of breast cancer biology and develop more effective therapies. Continued research in this area is essential to elucidate the complex interplay between MDSCs and other components of the TME and to translate these findings into clinical benefit.

Pycnogenol, a standardized extract derived from the bark of the French maritime pine tree (*Pinus pinaster*), has garnered attention for its diverse pharmacological properties, including antioxidant, anti-inflammatory, and immunomodulatory effects (9). The extract is a complex mixture of bioactive compounds, primarily consisting of procyanidins, flavonoids, and phenolic acids. These constituents may contribute to several of the biological activities attributed to Pycnogenol (10).

One of the hallmark features of Pycnogenol is its potent antioxidant activity, which arises from its ability to scavenge ROS and inhibit lipid peroxidation (11). This property is particularly relevant in the context of cancer, where oxidative stress plays a pivotal role in tumor initiation, progression, and immune evasion. By mitigating oxidative damage, Pycnogenol may help restore the balance of the tumor microenvironment and enhance antitumor immune responses (12, 13).

The specific objectives of this study were to investigate the impact of Pycnogenol on the function of MDSCs in a murine model of breast cancer. This includes examining the ability of Pycnogenol to modulate MDSC proliferation, differentiation, and immunosuppressive activity within the tumor microenvironment. Another objective is to evaluate the effects of Pycnogenol on tumor progression, including tumor growth following Pycnogenol treatment. The central hypothesis of this study is that Pycnogenol exerts immunomodulatory effects by targeting MDSCs within the tumor microenvironment, thereby reducing their immunosuppressive activity and contributing to enhanced antitumor immunity. It is further hypothesized that these effects translate into inhibited tumor progression and metastasis, highlighting the potential of Pycnogenol as an adjunctive therapeutic agent in breast cancer management.

## Materials and Methods

### *Tumor model*

Ten female BALB/c mice, aged 6–8 weeks and weighing 18-22 g, were selected for their immunocompetent profile and randomly assigned to two groups: a control group and a Pycnogenol-treated group. The 4T1 murine mammary carcinoma cell line, a model for triple-negative breast cancer (TNBC), was used due to its aggressive and metastatic nature. Cultured 4T1 cells ($1 \times 10^6$ viable cells) were orthotopically injected into the fourth mammary fat pad in 100 µL of sterile phosphate-buffered saline (PBS). Tumor growth was monitored with digital callipers, and volumes were calculated using the formula: (length × width$^2$)/2. All procedures complied

with institutional and national animal care guidelines and were approved by the Institutional Animal Care and Use Committee (IACUC) of Bam University of Medical Sciences.

### *Pycnogenol Treatment*

Pycnogenol was administered orally at a dosage of 50 mg/kg body weight, after being dissolved in sterile water. The treatment commenced one week after tumor cell implantation and continued daily for four weeks. This dosage was selected based on previous studies demonstrating its efficacy and safety in preclinical cancer models. Oral gavage was used to ensure precise delivery of the compound, and the treatment duration was chosen to cover the critical phases of tumor progression and immune modulation.

### *MDSC Isolation*

MDSCs were isolated from 4T1-bearing mice to evaluate their role in the tumor microenvironment. Single-cell suspensions were prepared from the spleens, tumors, and bone marrow of mice in the treated and untreated groups. The protocol for isolation involved the following steps:

Tissue Dissection and Digestion: Tissues were dissected aseptically and enzymatically digested using a mixture of collagenase (type IV, 1 mg/mL) and DNase I (0.1 mg/mL) in RPMI-1640 medium. Tumor tissues were incubated at 37 °C for 30 minutes with gentle agitation.

Filtration and cell collection: Digested tissues were filtered through a 70-μm cell strainer to obtain single-cell suspensions. Cells were washed with phosphate-buffered saline (PBS) and centrifuged at 300 × g for 5 minutes.

Density gradient centrifugation: Red blood cells were lysed using ACK lysis buffer, followed by density gradient centrifugation with Ficoll-Paque to enrich the mononuclear cells.

Magnetic Bead Separation: MDSCs were further purified using magnetic-activated cell sorting (MACS) with antibodies targeting the Gr1 and CD11b markers (Miltenyi Biotec). Purity was confirmed by flow cytometry, with more than 90% Gr1+CD11b+ cells considered acceptable.

### *Functional Assays*

Nitric Oxide (NO) production: Supernatants from MDSC cultures were collected, and NO levels were measured using the Griess reagent. Absorbance was recorded at 540 nm, and NO concentration was calculated using a sodium nitrite standard curve.

Arginase Activity: Arginase-1 activity in MDSCs was quantified using an arginase activity assay kit. Cells were lysed, and urea production from the hydrolysis of L-arginine was measured colorimetrically at 450 nm.

Reactive oxygen species (ROS) generation: ROS levels in MDSCs were determined using the fluorescent probe 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA). Fluorescence intensity was measured by flow cytometry. Flow cytometry was also used to characterize MDSCs. Cells were stained with fluorophore-conjugated antibodies specific to CD11b and Gr-1, which are markers that define MDSC subsets in mice. Data were acquired on a flow cytometer and analyzed using FlowJo software.

Gene expression analysis by real-time PCR: Total RNA was extracted from purified MDSCs using an RNA isolation kit, and cDNA was synthesized using reverse transcriptase. Gene expression levels of immunosuppressive markers, including S100A8, S100A9, Arg1, and iNOS, were quantified by quantitative real-time PCR (qPCR) using SYBR Green chemistry. Relative expression was normalized to β-actin, which was used as a housekeeping gene**,** and fold changes were calculated using the $2^{-\Delta\Delta Ct}$ method.

### *Statistical Analysis*

Statistical analyses were performed using GraphPad Prism software. Tumor growth data, MDSC frequencies, and other continuous variables were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. Non-parametric data were

analyzed using the Mann-Whitney U test or Kruskal-Wallis test as appropriate. Results are presented as mean ± standard deviation (SD). A *p*-value of less than 0.05 was considered statistically significant.

## Results

### *Survival and tumor size trends*

Survival rates were monitored daily over the study period (Fig. 1a). Mice were euthanized when tumor burden exceeded 1,000 mm³ or signs of significant distress were observed. The survival data, based on five mice per group, were recorded.

Tumor volume measurements were recorded throughout the study period and averaged for each group based on the number of surviving mice (Fig. 1b). The following tumor volume data (mean ± SD, in mm³) were calculated:

The Pycnogenol-treated group exhibited slightly prolonged survival compared to the control group, with differences becoming apparent by day 20. Complete mortality occurred by day 26 in the Pycnogenol-treated group, while the control group reached complete mortality by day 25. Kaplan-Meier survival curves were generated for both groups, and survival distributions were compared. While the Pycnogenol-treated group showed a mild improvement in survival compared to the control group, this difference did not reach statistical significance. This observation suggests a potential trend of extended survival with Pycnogenol treatment in this murine model of breast cancer.

### *MDSC evaluation results*

Impact of Pycnogenol on gene expression levels in MDSCs

To assess the effect of Pycnogenol on gene expression associated with immunosuppressive function, qRT-PCR was used to quantify the expression of Arg1, iNOS, S100A8, and S100A9 in isolated MDSCs from tumor-bearing mice (Fig. 2).

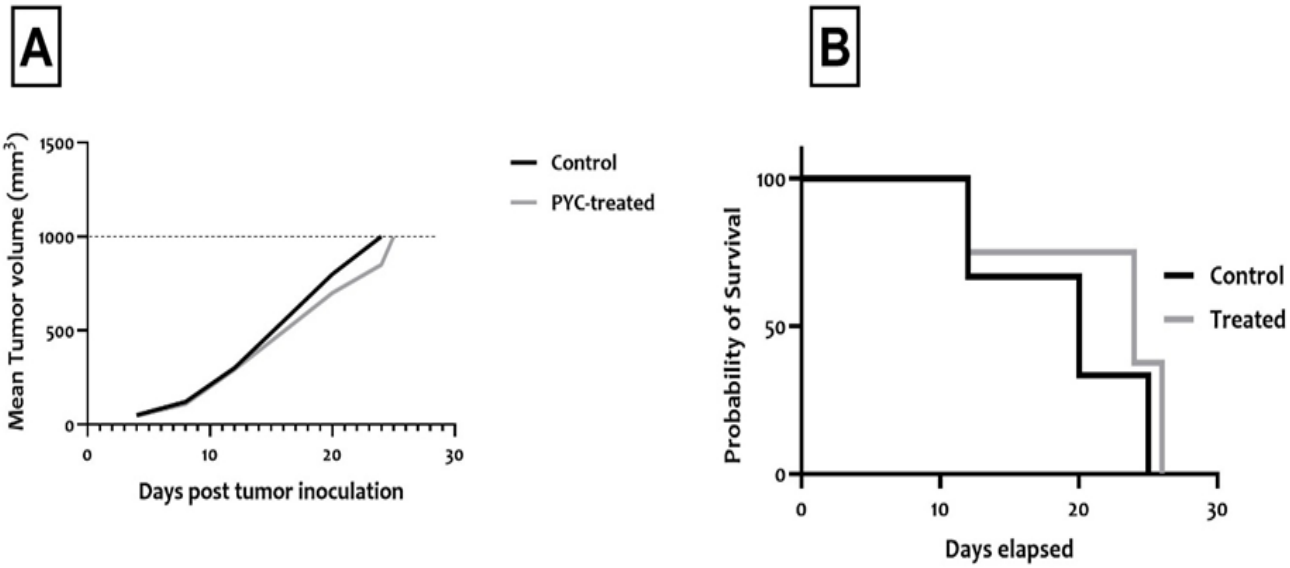


**Fig. 1.** Pycnogenol reduces tumor progression and improves survival in 4T1 breast cancer model. (A) Tumor growth curves showing mean tumor volume (mm³) in control and Pycnogenol-treated mice over time. Pycnogenol treatment moderately slowed tumor progression compared to the control group. (B) Kaplan–Meier survival analysis demonstrating a trend toward improved survival in Pycnogenol-treated mice, though the difference was not statistically significant. *Data represent mean ± SD; *p< 0.05 considered significant; n = 5 per group.* *Tumor volume reached the ethical endpoint limit of 1,000 mm³.

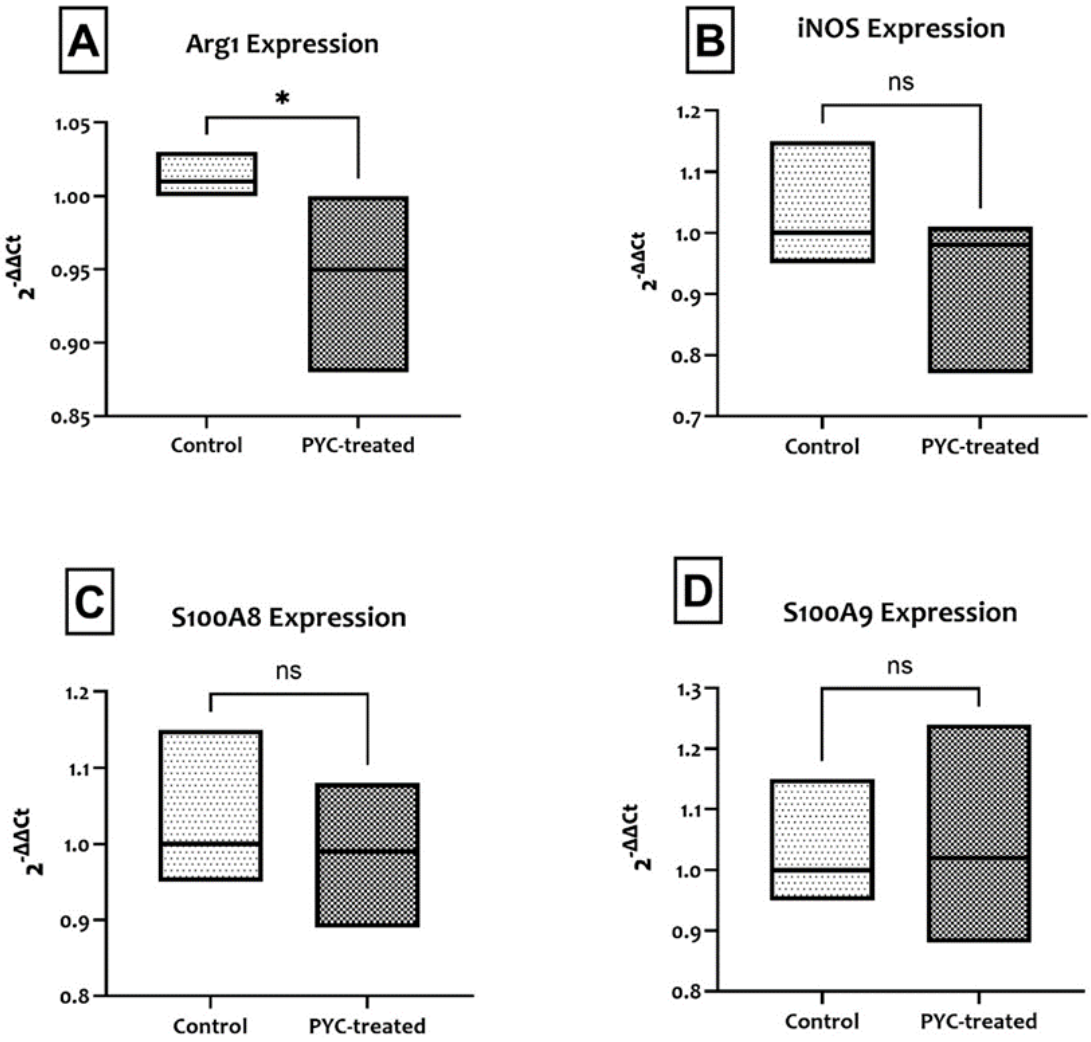


**Fig. 2.** Pycnogenol modulates MDSC suppressive functions in tumor-bearing mice. (A) Relative expression of Arg1 mRNA in isolated MDSCs was significantly reduced in the Pycnogenol-treated group compared to controls. (B) Arginase enzymatic activity in MDSC lysates showed a decreasing trend but did not reach statistical significance. (C) iNOS mRNA levels were modestly lower in Pycnogenol-treated MDSCs without reaching significance. (D) Nitric oxide (NO) production, measured by the Griess assay, was significantly reduced following Pycnogenol treatment. (E) ROS levels, assessed via DCFH-DA fluorescence and expressed as mean fluorescence intensity (MFI), were also significantly reduced in the treated group. *Data represent mean ± SD from n = 5 mice per group. *p< 0.05, ns: not significant.*

Administration of Pycnogenol significantly decreased Arg1 mRNA expression levels compared with those in the untreated control group ($p< 0.05$), indicating its potential to modulate the immunosuppressive activity in MDSCs.

Although there was a reduction in iNOS mRNA expression in the Pycnogenol-treated group compared with the control group, this difference was not statistically significant ($p> 0.05$).

Expression levels of S100A8 and S100A9 genes showed no statistically significant changes between Pycnogenol-treated and control groups ($p> 0.05$), suggesting a minimal or selective regulatory effect of Pycnogenol on these inflammatory mediators.

### *Effects of Pycnogenol on MDSC Functional Activity*

Functional assays were performed to evaluate whether Pycnogenol treatment affected the immunosuppressive functions of MDSCs (Fig. 3).

Arginase enzymatic activity showed a trend toward reduction in MDSCs from Pycnogenol-

treated mice; however, this was not statistically significant ($p > 0.05$).

Pycnogenol significantly reduced NO production in cultured MDSCs isolated from treated mice compared with the control group ($p < 0.05$).

Similarly, ROS generation, another critical factor in MDSC-mediated immunosuppression, was significantly reduced in the Pycnogenol-treated group ($p< 0.05$).

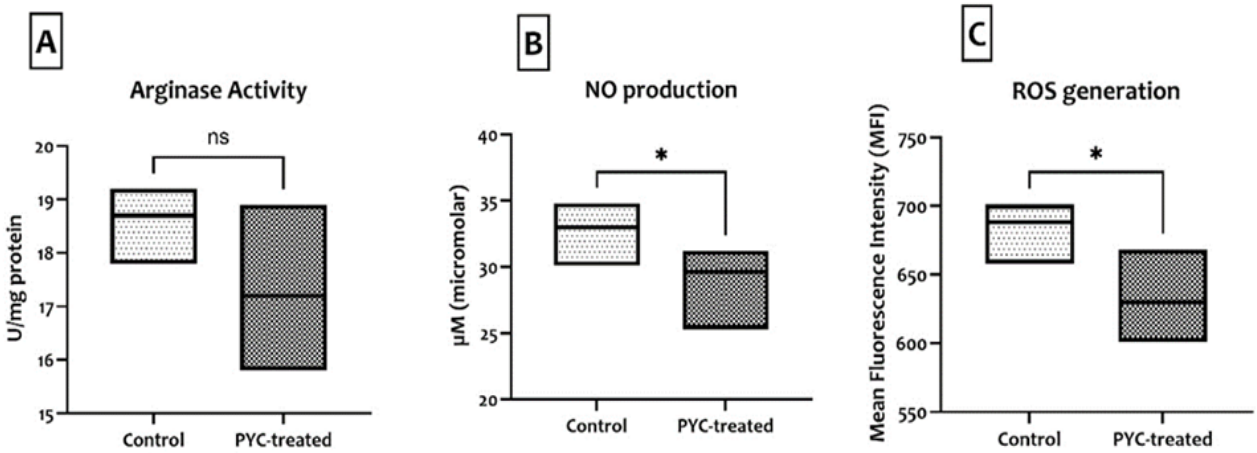


**Fig. 3.** Expression of S100A8 and S100A9 in MDSCs is not significantly affected by Pycnogenol. (A) qRT-PCR analysis of S100A8 gene expression in MDSCs showed no significant difference between Pycnogenol-treated and control groups. (B) S100A9 gene expression levels were also unchanged by treatment. *Data are presented as $2^{-\Delta\Delta Ct}$ values normalized to β-actin and shown as mean ± SD. ns: not significant; n = 5 per group.*

## Discussion

Myeloid-derived suppressor cells (MDSCs) are key orchestrators of immunosuppression in breast cancer, accumulating in the TME and draining lymphoid organs where they potently inhibit T-cell and NK-cell responses. (14-16). In our 4T1 murine breast cancer model, Pycnogenol treatment specifically attenuated several of these immunosuppressive pathways in MDSCs: Arg1 expression was significantly reduced, and MDSCs from treated mice produced markedly lower levels of NO and ROS compared to controls. These changes suggest that Pycnogenol renders MDSCs less immunosuppressive, potentially preserving T-cell activity in the TME. This is in line with the extract's known anti-inflammatory and antioxidant properties (17).

Pycnogenol (a French maritime pine bark extract rich in procyanidins) is a potent scavenger of ROS and reactive nitrogen species and has been shown to suppress inflammatory gene expression. For example, in vitro studies demonstrate that Pycnogenol can dose- dependently inhibit NF- κB/AP-1 activation in activated immune cells, leading to lower iNOS expression and NO output (18). Our findings extend this knowledge to the tumor setting, indicating that Pycnogenol's antioxidative action can modulate pathologic myeloid cells and potentially alleviate MDSC-induced immune suppression.

Interestingly, not all immunosuppressive markers were altered by Pycnogenol in our study. We observed no significant change in iNOS gene expression in MDSCs, despite the reduction in nitrite/NO levels. One interpretation is that Pycnogenol may diminish NO bioavailability by direct scavenging or interfering with the co-factors of NO production, rather than through the transcriptional downregulation of iNOS (15, 18). A similar pattern was reported with other natural compounds: icariin (a flavonol from Epimedium) and its derivative both significantly reduced NO and ROS levels in 4T1 MDSCs in vivo while failing to inhibit arginase activity (19).

In our study, S100A8/A9 expression in MDSCs was also unchanged by Pycnogenol.

S100A8/A9 (calprotectin) are damage-associated molecular pattern proteins that help recruit and activate MDSCs via TLR4/RAGE signaling. The lack of S100A8/A9 modulation suggests that Pycnogenol did not markedly impact the upstream inflammatory signals driving MDSC accumulation. In other words, Pycnogenol functionally reprogrammed MDSCs (dampening Arg1/ROS/NO output) without significantly altering their presence or myeloid differentiation state (20).

Notably, the pattern of immune changes induced by Pycnogenol, the lowering of Arg1 and ROS/NO production, maps onto the known dichotomy of MDSC subsets (21). Polymorphonuclear MDSCs (PMN-MDSCs, granulocytic) primarily use Arg1 and ROS to suppress T cells and are largely iNOS-independent, whereas monocytic MDSCs rely more on iNOS-derived NO and immunosuppressive cytokines (IL-10, TGF-β) (14, 16). The selective impact of Pycnogenol on Arg1 and ROS (with minimal effect on iNOS) suggests it may preferentially diminish the suppressive functions of granulocytic MDSCs.

The 4T1 tumors are known to induce a large granulocytic MDSC population, which is characterized by high Arg1 and ROS activity (14). By quenching ROS and downregulating Arg1 in these cells, Pycnogenol could relieve the oxidative and nutrient-depletion stress on T cells. Reduced ROS and peroxynitrite would be expected to prevent the nitration of T-cell receptors and chemokines, thereby preserving T-cell migration and antigen recognition (15, 16). Likewise, lower Arg1 expression may improve local L-arginine availability, supporting T-cell proliferative capacity and CD3ζ chain re-expression. These mechanistic interpretations align with evidence that scavenging MDSC-derived radicals can restore T-cell function: the ROS scavenger N-acetylcysteine (NAC) and the NO scavenger PTIO both abrogate MDSC immunosuppressive effects and reinvigorate cytotoxic T lymphocytes in tumor models (15, 16).

There are several limitations in our study that temper the interpretation of Pycnogenol's effects and should be addressed by future research. First, the antitumor efficacy we observed (delayed tumor growth and slight survival extension) did not reach statistical significance. This could be due to a limited sample size, as our study was powered primarily to detect changes in immune cell readouts rather than survival. With only modest improvements in median survival, a larger cohort might be necessary to determine whether Pycnogenol confers a real survival benefit or if the trend we saw was incidental. It is also possible that the 4T1 model – being highly aggressive and metastatic – requires a stronger intervention or multi-agent therapy to significantly prolong survival. MDSC modulation alone may not be sufficient to tip the balance in such a model, especially if other immunosuppressive mechanisms (e.g. regulatory T cells, tumor-associated macrophages) remain active. Future studies could use a less aggressive tumor or an adjuvant setting (post-surgical model of 4T1) to see if Pycnogenol can reduce metastatic burden or prevent relapse, endpoints that might be more sensitive to partial immunomodulation.

Secondly, we have an incomplete picture of how Pycnogenol impacted the tumor immune microenvironment beyond the MDSC compartment. We quantified MDSC suppressive factors ex vivo, but we did not directly measure tumor-infiltrating lymphocyte populations, activation status, or the functional readouts of T cells in vivo (such as cytokine production or cytotoxicity).

Another limitation relates to dosing and scheduling. We used a single dosing regimen for Pycnogenol based on prior tolerance studies. It remains unknown whether a higher dose or more frequent dosing could produce stronger effects on MDSCs or tumor growth – a dose-response assessment is warranted. Since Pycnogenol is a mixture of active

constituents, its pharmacokinetics in mice (e.g. half-life of active polyphenols, tissue penetration) could influence efficacy. Future work might include measuring Pycnogenol metabolite levels in plasma or tumor tissue to correlate with biological effect, or isolating specific fractions of Pycnogenol to identify which components are most responsible for the MDSC-modulating activity.

Finally, our focus was on the Arg1/NO/ROS axis, but MDSCs deploy other suppressive mechanisms we did not measure – e.g. production of immunosuppressive cytokines like IL-10 and TGF-β, expression of checkpoint ligands like PD-L1, or the induction of regulatory T cells. In future studies, it would be valuable to see if Pycnogenol has any effect on these aspects.

In conclusion, our study provides a proof-of-concept that Pycnogenol can modulate the immunosuppressive functions of MDSCs in a breast cancer model, chiefly by curbing Arg1 expression and radical production. These changes, while not sufficient on their own to significantly halt tumor progression, highlight the potential of targeting redox and metabolic aspects of MDSC biology as part of a broader immunotherapeutic strategy. Pycnogenol's effects dovetail with known MDSC-targeted treatments and natural compounds, and it stands out as a well-tolerated agent that could be readily combined with existing cancer therapies.

## Ethics

The study protocol was approved by the Ethics Committee for Biomedical Research of Bam University of Medical Sciences, Bam, Iran, with ethics code IR-B-1401-57.

## Conflict of interest

The authors declare that they have no competing interests. Pycnogenol® was provided as a gift by Horphag Research, which had no role in the design, execution, analysis, or publication of this study.

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## Authors' Contributions

**AGS** and **JGN** conceptualized and designed the study. **GS** and **HG** contributed to the methodology, data interpretation, and critical review of the manuscript. **MHM** and **SN** conducted animal experiments and performed sample collection. **RVG** and **ASJ** carried out gene expression and flow cytometry assays. **NP** and **JGN** performed data analysis, statistical evaluation, and visualization. **JGN** supervised the entire project and was the major contributor to writing and revising the manuscript. All authors read and approved the final manuscript.

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