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Anti-Metastatic Potential of Hydroalcoholic Extract of *Pistacia Khinjuk* Leaves and Its Mechanism: An *in Vitro* Study

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ABSTRACT

Background & Objective: Metastasis represents the primary contributor to mortality associated with cancer. Traditionally, *Pistacia khinjuk* has been utilized for addressing various ailments. Considering the reported anticancer effects of *Pistacia Khinjuk*, this research seeks to explore the anti-metastatic properties of the hydroalcoholic extract derived from this indigenous Iranian herb on prostate and breast cancer cells.

Materials & Methods: Hydroalcoholic extract was prepared, and its cytotoxicity was tested. The extract's impact on the migration, invasion, and adhesion capabilities was analyzed. Matrix metalloproteinases-2 and -9 secretions were evaluated. Also, metastatic-related gene expression levels were assessed.

Results: After 24, 48, 72, and 96 hrs, the extract decreased the cancer cells viability in a concentration- and time-dependent manner. Notably, breast cancer cells demonstrated greater sensitivity to the extract's cytotoxic effects than prostate cancer cells. After 24 hrs of treatment with half-maximal inhibitory concentration, there was a significant reduction in the cell migration, invasion, and adhesion capabilities ($p<0.05$). Additionally, matrix metalloproteinases-2 and -9 levels were reduced. Also, the extract significantly decreased matrix metalloproteinases-2 and -9, urokinase, and urokinase receptorg genes expression ($p<0.05$). Conversely, tissue inhibitors of metalloproteinase-1 and -2 gene expression levels significantly increased ($p<0.05$).

Conclusion: Altogether, *Pistacia khinjuk* leaves hydroalcoholic extract had cytotoxic effects on breast and prostate cancer cells and reduced the metastasis potential.

Keywords: Metastasis, Hydroalcoholic Extract, *Pistacia Khinjuk*

1. Introduction

Metastasis serves as a distinguishing characteristic of cancer, setting it apart from benign tumors. While most cancers have the potential to metastasize, the extent varies among different types. This process is crucial in cancer staging systems, including the TNM classification, where metastasis categorizes the cancer as stage IV. Once metastasis occurs, the options for curative treatment are significantly diminished or often completely removed (1).

Matrix metalloproteinase (MMP) enzymes exhibit activity against the extracellular matrix (ECM) components. 16 MMP family members have been identified through cloning and sequencing efforts in humans. These proteinases share a common core of domain structures and are associated with tissue inhibitors of metalloproteinases (TIMPs). TIMPs inhibit MMPs by forming stable, non-covalent interactions with their active sites, thereby regulating tumor cell invasion and metastasis. Therapeutic strategies to disrupt specific MMP functions are beneficial in managing metastatic disease (2).

Urokinase, or urokinase-type plasminogen activator (uPA) enzyme found in the ECM of various tissues, and

its main physiological substrate is plasminogen. Plasmin activation initiates a proteolytic cascade that can lead to thrombolysis or ECM degradation and has been associated with cancer progression (3, 4). The urokinase receptor, also referred to as the surface plasminogen-activated receptor urokinase (uPAR) or CD87 (5) is essential in tissue remodeling processes such as the mammary glands dissolution and the healing of wounds in a healthy organism. For effective tissue remodeling, the existing tissue must be capable of being degraded. A key process in this degradation is the proteolytic cascade initiated by the plasminogen activation system (6).

The genus *Pistacia*, belonging to the Anacardiaceae family, includes about 600 species. In Iran, three wild species grow, including *Pistacia Atlantica*, *Pistacia Vera*, and *Pistacia Khinjuk* (7, 8). This family encompasses numerous plant species, several of which possess medicinal properties. Research indicates that Pistacia khinjuk's resin is utilized in treating digestive issues and dental pain, and serves as an astringent in traditional healing practices. Additionally, the fruit of *Pistacia khinjuk* is ingested for its health benefits (9).

Secondary metabolites in plants are organic substances that do not directly contribute to growth and reproduction. In contrast to primary metabolites, they are not as extensively distributed throughout the plant kingdom. Some secondary metabolites, such as alkaloids, terpenoids, and flavonoids, exhibit anti-cancer properties (10). Considering the reported anticancer effects of *Pistacia khinjuk* (11), this study seeks to explore the anti-metastatic properties of the hydroalcoholic extract derived from the leaves of the Pistacia Khinjuk species.

2. Materials and Methods

2.1 Extract preparation

Pistacia khinjuk leaves were gathered from the Kermanshah mountains in western Iran during the spring of 2023, and following a botanist's endorsement, its extract was subsequently prepared. The leaves were dried in the air and turned into powder. This powder (25 gr) was soaked with 70% ethanol solvent for three days with frequent agitation. Then, the mixture was filtered and completely dried with the help of a freeze dryer. The dry powder was stored at -20 ˚C (12). At the time of use, the extract was first dissolved in dimethyl sulfoxide (DMSO) and then in a culture medium. DMSO concentration in the final solution was 0.1%. DMSO is non-toxic in concentrations less than 1% (13).

2.2 Cell culture

The MCF-7 breast cancer and LNCap prostate cancer cell lines were cultured as previously described at a temperature of 37 ˚C with 5% CO2 and 95% humidity (14).

2.3 MTT test

The cancer cells were plated in 96-well plates and allowed to incubate overnight. Subsequently, the cells were exposed to varying concentrations of the extract at 800, 400, 200, 100, 50, 25, 12.5, and 6.25 µg/ml, as well as docetaxel at concentrations of 20, 10, 5, 2.5, 1.25, and 0.62 ng/ml (Standard chemotherapy drug). Control cells received a culture medium. The MTT assay was conducted following the previously established protocol (14).

2.4 Migration assay

Following a 24-hour treatment with the extract's half-maximal inhibitory concentration (IC50), cells were cultured in 6-well plates and incubated overnight. A sterile yellow tip was used to create a scratch in the center of each well. The wells were subsequently washed three times with phosphate-buffered saline (PBS), and a culture medium was added to each well. The wells were photographed at the time of scratching, and the resulting images were analyzed using TScratch software. Control cells were provided with a culture medium.

2.5 Invasion assay

In this experiment, the cells that had been pretreated with the IC50 concentration of the extract for 24 hours and Cell Biolabs CytoSelect™ cell invasion assay kit were utilized following the instructions.

2.6 Adhesion assay

The wells of a six-well plate were subjected to treatment with a matrigel solution at a concentration of 5 mg/ml and permitted to dry at ambient temperature for one hour. Subsequently, the cells were pre-treated with the IC50 concentration of the extract for 24 hours. Control cells were maintained in a culture medium. After 6 hours, each well underwent three washes with PBS, then fixation of the remaining cells using a 4% paraformaldehyde solution and staining with a 5% crystal violet solution. The dye was solubilized in 70% ethanol to quantify the number of adhered cells, and the absorbance was recorded (570 nm). The adhesion capacity was assessed by comparing the absorbance values of the treatment cells against those of the control cells.

2.7 The enzyme-linked immunosorbent assay (ELISA)

Cells were subjected to treatment with the IC50 concentration of the extract for 24 hours. Subsequently, the RayBio® Human MMP-2 ELISA and the RayBio® Human MMP-9 ELISA Kits were employed to assess the secretion of MMP-2 and MMP-9, following the provided protocols.

2.8 Molecular analysis

Gene expression analysis was performed following the methodology established in prior research (15). Briefly, RNA was extracted, and its purity and concentration were tested. Complementary DNA (cDNA) was generated, and Real-time PCR was conducted. The data analysis was conducted using the comparative CT method, and the fold change was determined through the $2^{-\Delta Ct}$ calculation.

2.9 Statistical analysis

One-way ANOVA Tukey post hoc test was hired for data analysis (using SPSS 16, SPSS Inc., Chicago, IL). The findings were expressed as mean ± standard error, with a significance threshold at $p < 0.05$.

3. Results

3.1 The effects on cell viability

Pistacia Khinjuk leaves extract diminished breast and prostate cancer cell viability in a manner dependent on both concentration and duration compared to control cells (Figure 1 A and B). The IC50 values of extract in prostate cancer cells were 1188.17, 408.02, 87.33, and 31.66 µg/ml, and in breast cancer cells were 1078.61, 326.57, 81.85 and 28.66 µg/ml for 24, 48, 72 and 96 hr, respectively. Also, the IC50s of docetaxel in prostate cancer cells were 18.64, 8.19, 3.87, and 1.85 µg/ml, and in breast cancer cells were 17.23, 6.45, 3.60, and 2.19 µg/ml for 24, 48, 72 and 96 hr, respectively.

3.2 The effects on the migration ability of cells

Following a 24-hour treatment, the migratory capacity of the cells was reduced by 61% and 70% in prostate and breast cancer cells compared to control cells. This decrease was significant ($p<0.05$) (Figures 2 and 3).

3.3 The effects on the invasion ability of cells

The cell invasion showed a 59% and 66% decrease after 24 hrs treatment with extract in prostate and breast cancer cells compared to control cells. This decrease was significant ($p<0.05$) (Figures 4 and 5).

3.4 The effects on the adhesion ability of cells

After extract treatment, the cells' adhesion ability was reduced by 35% and 38% compared to control cells in prostate and breast cancer cells, respectively. This decrease was significant ($p<0.05$) (Figures 6 and 7).

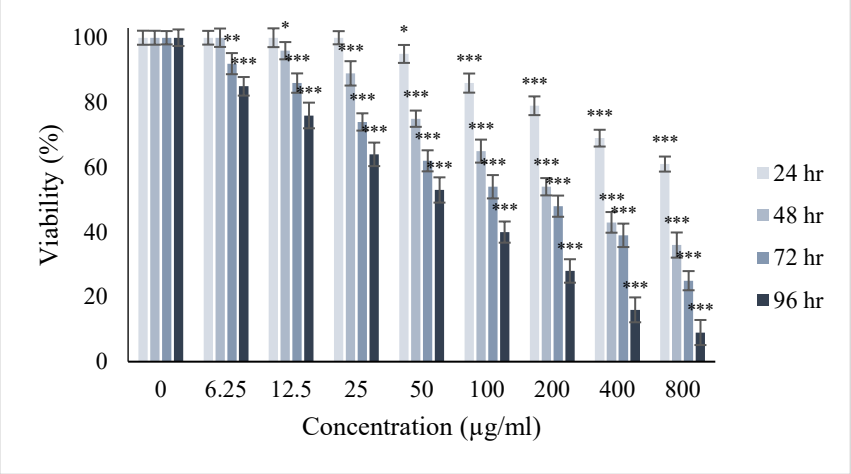
3.5 The effects on MMPs secretion

The secretion of MMP-2 and MMP-9 enzymes showed a significant decrease after 24 hrs treatment in prostate and breast cancer cells compared to control cells ($p<0.05$) (Figure 8).

3.6 The effects on gene expression

After 24 hrs treatment, the expression of MMP-2 and MMP-9 significantly reduced, and the expression of TIMP-1 and TIMP-2 significantly increased in both cell lines compared to control cells ($p<0.05$). The extract did not significantly influence uPA and uPAR expression levels in prostate cancer cells; however, a notable reduction in their expression was observed in breast cancer cells ($p<0.05$) (Figure 9).

A



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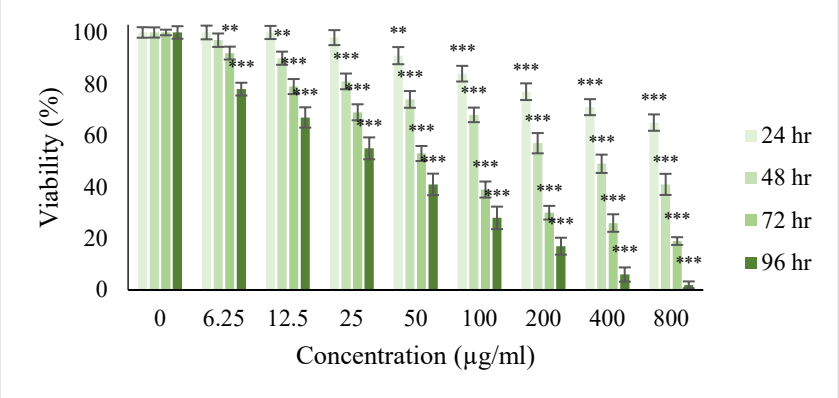

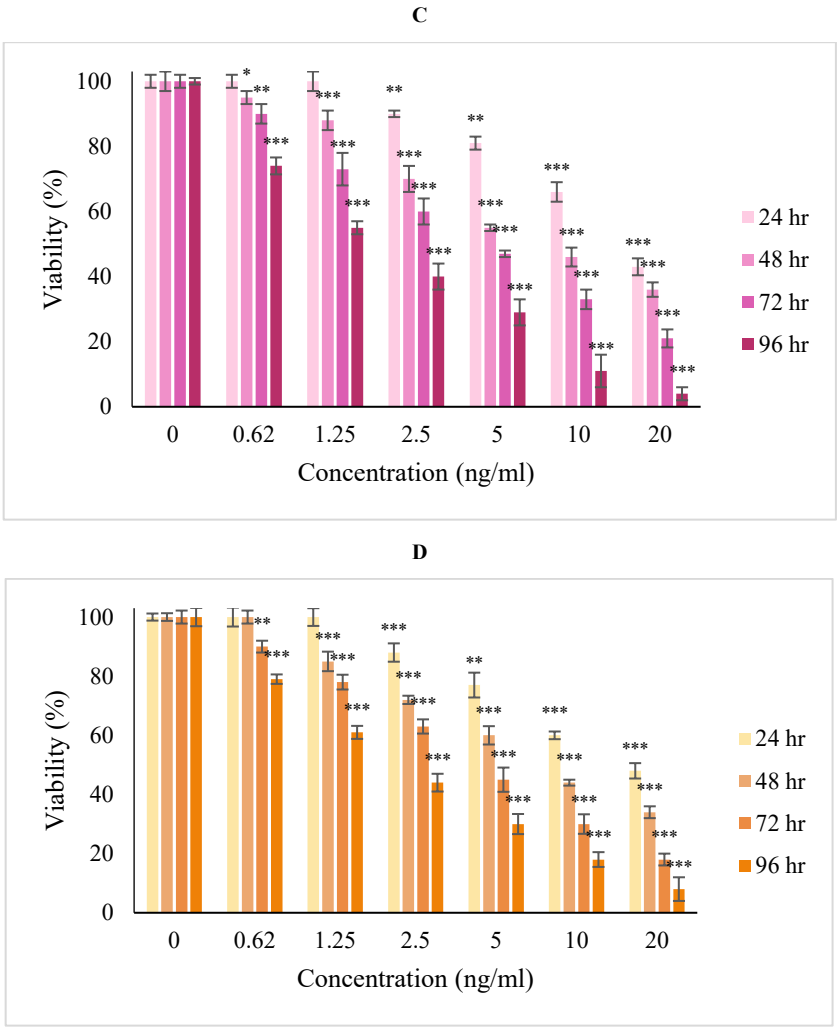

Figure 1. The effect of Pistacia Khinjuk extract on the viability of (A) prostate and (B) breast cancer cells and docetaxel on the viability of (C) prostate and (D) breast cancer cells. Asterisks denote statistical significance levels: * indicates $p<0.05$, ** indicates $p<0.01$, and *** indicates $p<0.001$ in comparison to the control group.

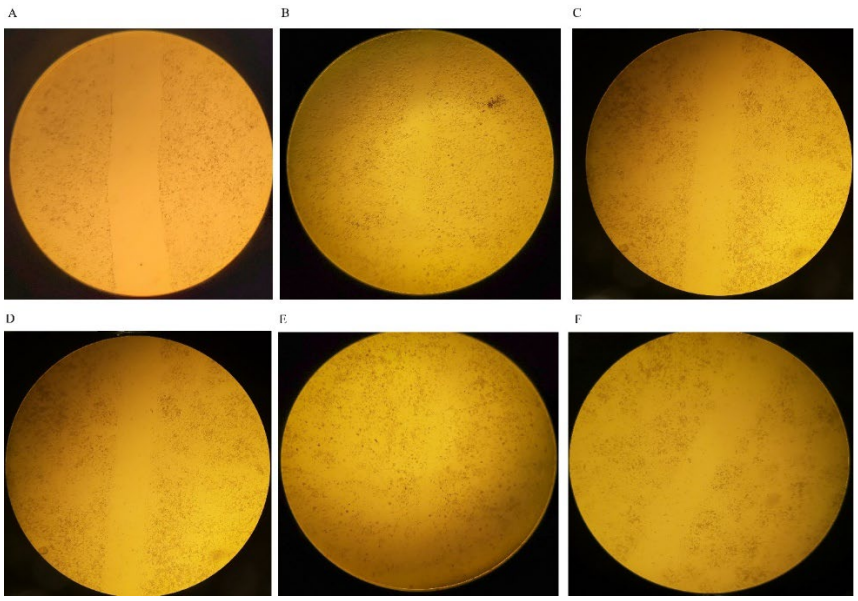

Figure 2. The effect of Pistacia Khinjuk extract on the migration ability of prostate and breast cancer cells. (A) zero control, (B) control after 24 hrs, (C) treatment after 24 hrs for prostate and (D) zero control, (E) control after 24 hrs, (F) treatment after 24 hrs for breast cancer cells.

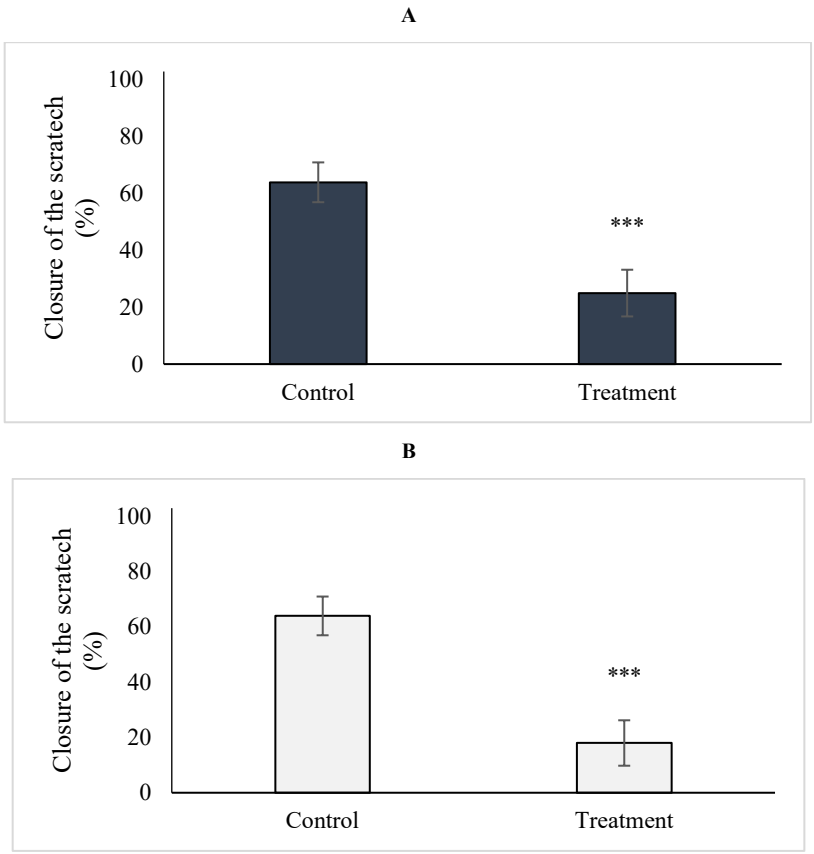

Figure 3. The effect of Pistacia Khinjuk extract on the migration ability of (A) prostate and (B) breast cancer cells. Asterisks denote statistical significance levels: *** indicates $p<0.001$ in comparison to the control group.

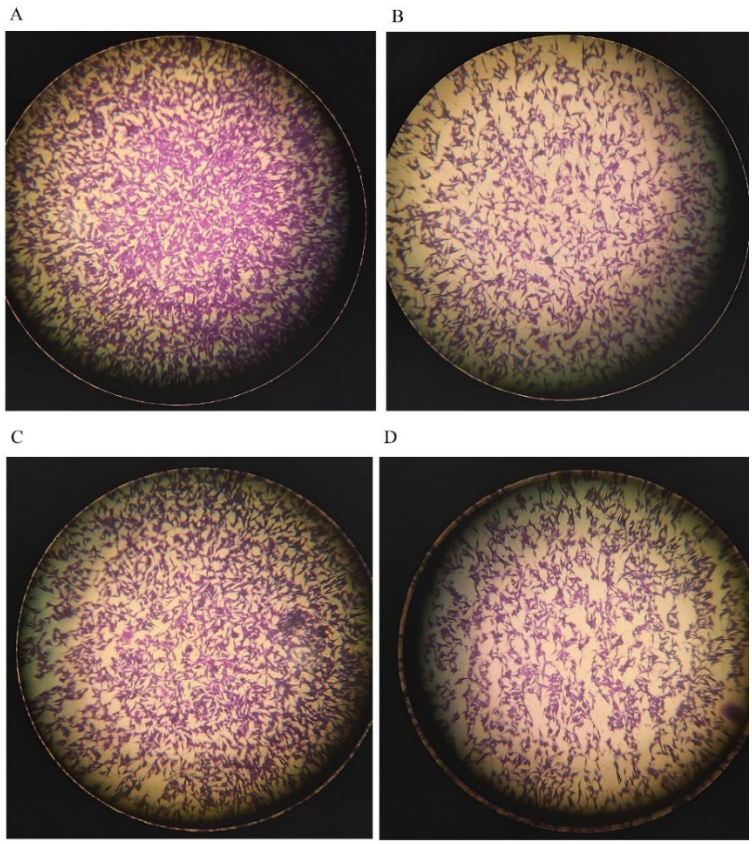

Figure 4. The effect of Pistacia Khinjuk extract on the invasion ability of prostate and breast cancer cells. (A) control, (B) treatment after 24 hrs for prostate and (C) control, and (D) treatment after 24 hrs for breast cancer cells.

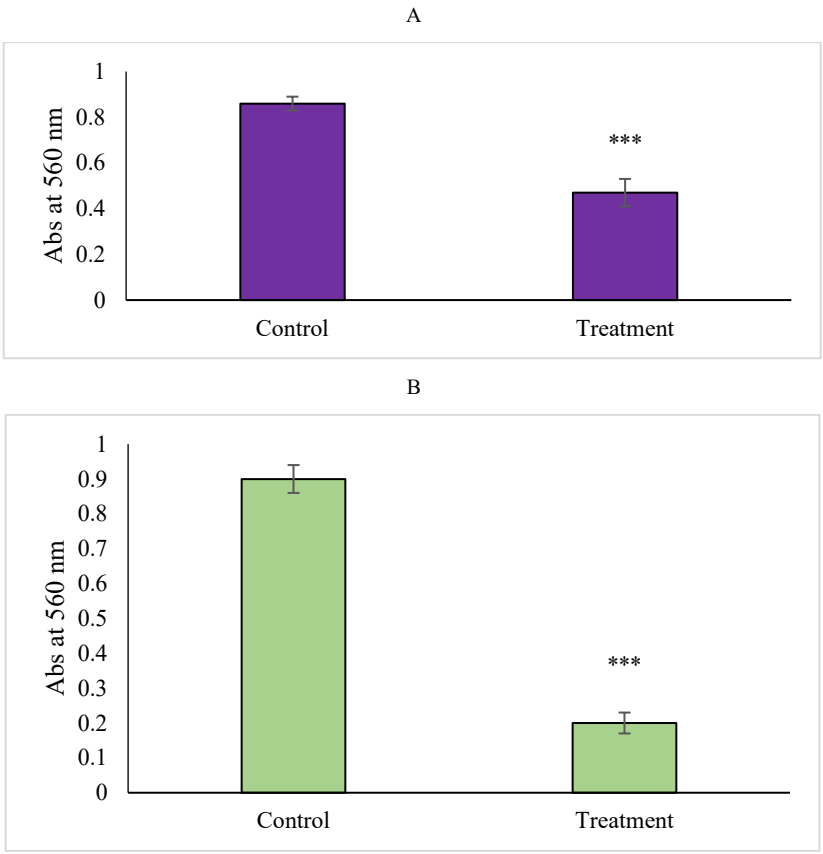

Figure 5. The effect of Pistacia Khinjuk extract on the invasion ability of (A) prostate and (B) breast cancer cells. Asterisks denote statistical significance levels: *** indicates $p<0.001$ in comparison to the control group.

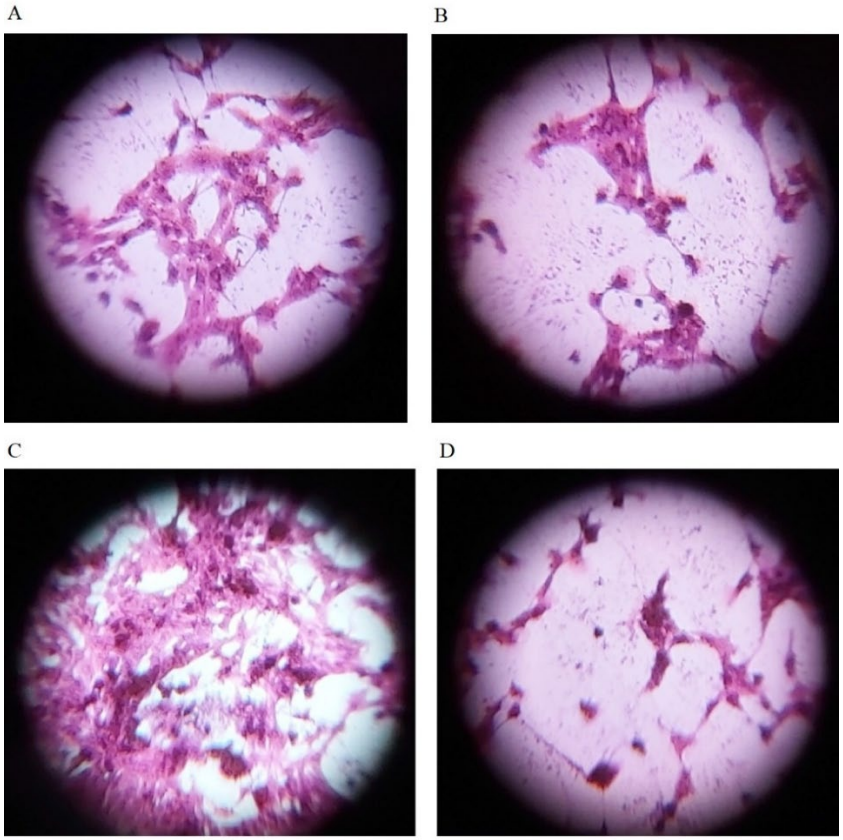

Figure 6. The effect of Pistacia Khinjuk extract on the adhesion ability of prostate and breast cancer cells. (A) control, (B) treatment after 24 hrs for prostate and (C) control, and (D) treatment after 24 hrs for breast cancer cells.

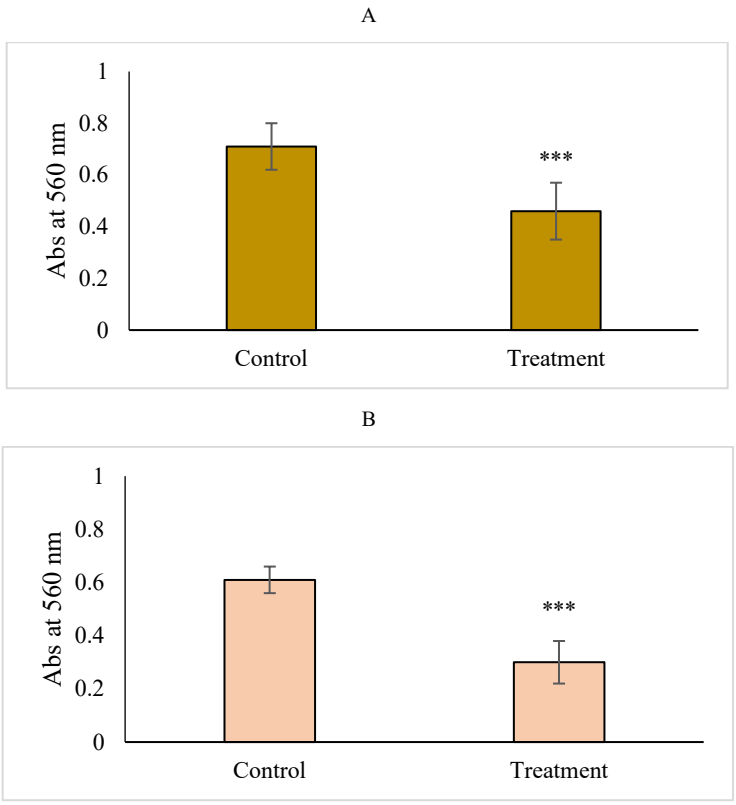

Figure 7. The effect of Pistacia Khinjuk extract on the adhesion ability of (A) prostate and (B) breast cancer cells. Asterisks denote statistical significance levels: *** indicates $p<0.001$ in comparison to the control group.

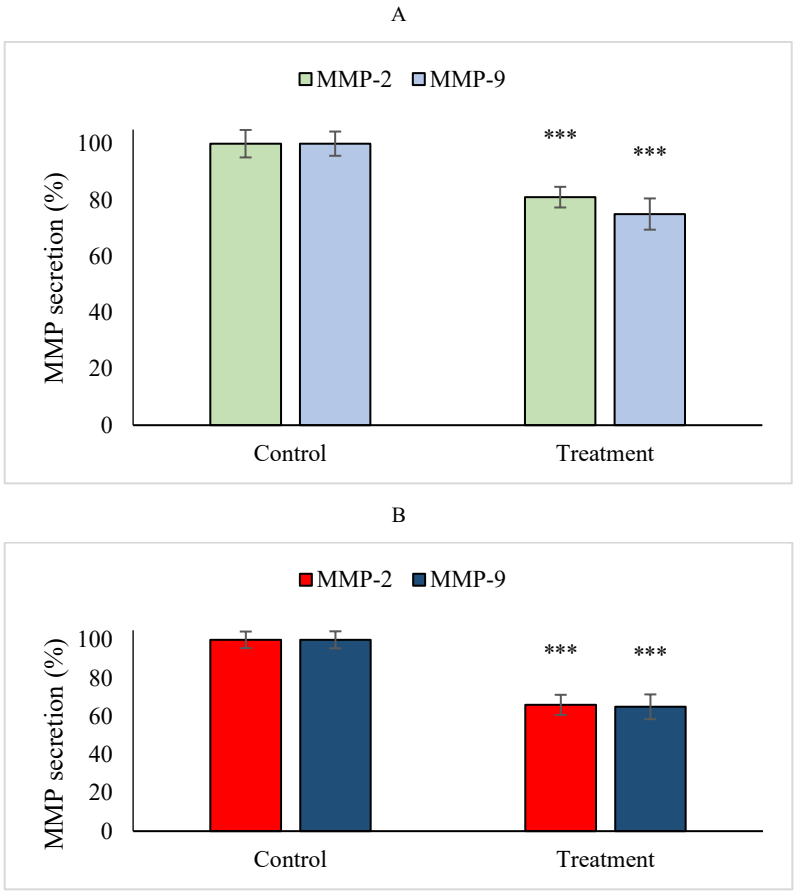

Figure 8. The effect of Pistacia Khinjuk extract on the MMP-2 and MMP-9 secretion in (A) prostate and (B) breast cancer cells. Asterisks denote statistical significance levels: *** indicates $p<0.001$ in comparison to the control group.

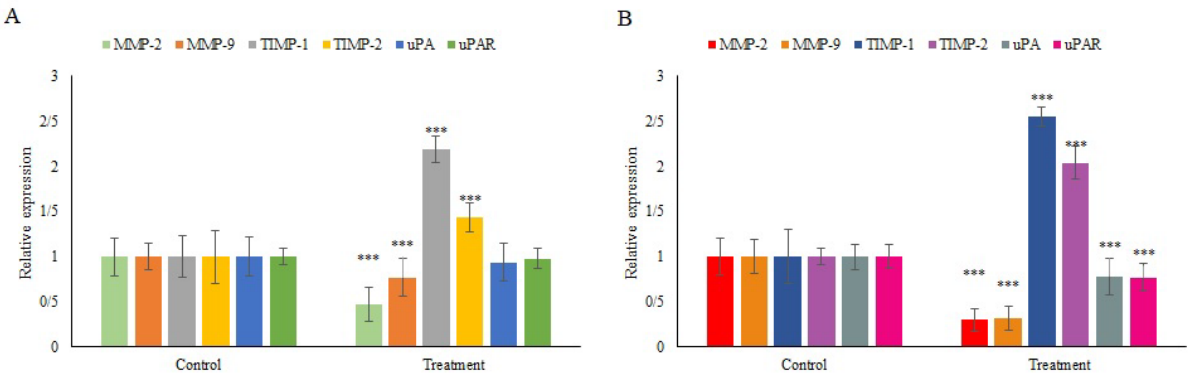

Figure 9. The effect of Pistacia Khinjuk extract on the MMP-2, MMP-9, TIPM-1, TIMP-2, uPA, and uPAR expression in (A) prostate and (B) breast cancer cells. Asterisks denote statistical significance levels: *** indicates $p<0.001$ in comparison to the control group.

4. Discussion

There is an ongoing need for innovative cancer therapies. The scientific community is increasingly focusing on naturally-derived compounds due to their potential for reduced toxicity compared to existing treatments. The plant kingdom generates naturally occurring secondary metabolites currently being studied for their anticancer properties, contributing to the creation of novel clinical drugs.

Here, the cytotoxic properties of the hydroalcoholic extract derived from *Pistacia Khinjuk* leaves were examined. Data showed that in breast cancer cells, the IC50 of the extract was 1078.61, 326.57, 81.85, and 28.66 µM/ml for 24, 48, 72, and 96 hrs. In prostate cancer cells, the IC50 of the extract was 1188.17, 408.02, 87.33, and 31.66 µg/ml for 24, 48, 72, and 96 hrs. The lower IC50 values in breast cancer cells indicate the greater sensitivity to the toxicity caused by the extract. The IC50 values of the extract were in the µM range, and those of docetaxel were in the nM range. The results showed that although docetaxel has more cytotoxic effects, the toxicity of the extract is also significant.

Over sixty percent of the anticancer agents are from natural sources such as plants, marine organisms, and microorganisms. The secondary metabolites found in plants exhibit a range of biological activities, including anticancer properties. *Pistacia lentiscus* extract analysis using GC-MS revealed a composition of 4% sesquiterpenes, whereas prior research on *Pistacia khinjuk Stocks* and *Pistacia chinensis Bunge* reported monoterpene alcohol levels of 16% and 8%, respectively **(9)**. The studies showed that the main components of the essential oil of *Pistacia khinjuk* include β-pinene, pinene, germacrene B, beta-caryophyllene, myrcene, and spathulenol **(16)**. The essential oil derived from *Pistacia Khinjuk* fruit analysis revealed that its primary constituents are phellandrene, α-pinene, and limonene **(17)**. Additionally, the leaves of *Pistacia Khinjuk* have been noted for their antioxidant and antimicrobial properties **(18)**.

Many research has been done to evaluate the biological effects *Pistacia* genus. The majority of these studies have demonstrated significant anticancer activity. For example, the extract of *Pistacia chinensis Bunge* exhibited considerable antitumor effects. Additionally, the crude stem extract was found to inhibit MCF-7 cell viability. Furthermore, its ethyl acetate and chloroform fractions inhibited MCF-7 cell line proliferation **(19)**.

The *Pistacia atlantica* galls essential oil has demonstrated moderate cytotoxic effects against mycobacteria in C3A and Vero monkey kidney cell lines **(20)**. Research indicates that *Pistacia atlantica* fruit extract triggers apoptosis without causing significant necrosis in cancer cell lines **(21)**. Furthermore, the bark extract of Pistacia vera demonstrated an inhibitory effect on angiogenesis in vitro **(22)**.

A study was done to test the anti-tumor properties of stem, fruit, and outer covering extract of *Pistacia vera* on prostate cancer and breast cancer cells. These extracts inhibited the proliferation of cells even at a low dosage **(23)**. Furthermore, the methanolic extract from the leaves of *Pistacia lentiscus* demonstrated significant cytotoxic activity **(24)**. Khan and Mukhtar **(25)** revealed that *Pistacia lentiscus* extract effectively inhibited angiogenesis.

A study was conducted to examine the plant extract of *Pistacia Khinjuk* cultivated under controlled laboratory conditions. The findings revealed that ethanol extracts, particularly those derived from the roots, exhibited significant cytotoxic activity. Notably, the root samples demonstrated superior cytotoxic effects. The extracts from the root displayed enhanced cytotoxicity against the cancer cell lines. Furthermore, it was concluded that the male genotype and root parts'

root extracts were more potent and advantageous regarding cytotoxic activity (26).

Metastasis and invasion of tumors represent the leading cause of mortality among cancer patients. Consequently, formulating a strategy to mitigate this invasion could significantly lower cancer-related fatalities (27). Despite the recent proliferation of research on natural anticancer agents, there has been a notable lack of emphasis on their potential to impede cancer metastasis (28).

Our research findings indicated that following a 24-hour treatment with the extract, there was a notable reduction in the cell's migration, invasion, and adhesion capabilities compared to the control group.

ECM and the basement membrane serve as a physical barrier that inhibits the invasion of tumor cells. ECM degradation by MMP enzymes promoting cancer invasion. Notably, MMP-2 and MMP-9 are essential in this process (29). Consequently, diminishing the production and secretion of MMPs can hinder the metastatic potential (30). Our findings indicated that the extract significantly reduced the secretion of both MMP-2 and MMP-9. The significance of phytochemicals remains largely untapped despite accumulating evidence of their capacity to inhibit MMPs. Synthetic MMP inhibitors have undergone phase III trials, but the results are unsatisfactory. This may be because they are only cytotoxic rather than cytostatic and lack specificity. Disappointments of synthetic inhibitors have triggered the research toward searching for new agents from natural resources. So, basic research on this issue is important (31).

The findings of our research indicated that following a 24-hour treatment with the extract, there was a reduction in the expression levels of MMP-2 and MMP-9 genes in both cancer cells. Conversely, TIMP-1 and TIMP-2 mRNA expression increased, while uPA and uPAR mRNA expression decreased.

In cancerous cells, the activities of MMP-2 and MMP-9 are regulated by TIMP-1 and TIMP-2. Consequently, reducing MMP or enhancing TIMP activities may diminish the invasion of cancer cells (32). Additionally, uPA contributes to the degradation of ECM and directly promotes tumor cell invasion. The uPAR receptor concentrates the activity of uPA at the cell membrane, thereby modulating the proteolytic processing of cell surface-associated plasminogen by uPA (33).

5. Conclusion

The hydroalcoholic extract derived from *Pistacia Khinjuk* leaves exhibited cytotoxic properties against breast and prostate cancer cells, diminishing their metastatic potential and altering the mRNA expression of genes associated with the metastasis pathway. Consequently, further investigations utilizing animal models (in vivo studies) are suggested.

6. Declarations

6.1 Acknowledgments

The authors express their gratitude to Kermanshah University of Medical Sciences.

6.2 Ethical Considerations

Not applicable.

6.3 Authors' Contributions

F. K.; Designed experiments and supervised the research. I. R.; Analyzed data. M.P; wrote the manuscript. M. Zh. And A. G.; Performed the cell culture experiments. E. R. and R. T.; Done gene expression. All authors read and approved the final manuscript.

6.4 Conflict of Interest

The authors declare that there are no conflicts of interest.

6.5 Fund or Financial Support

This research received financial backing from Kermanshah University of Medical Sciences under Grant Numbers 4010256 and 4020186.

6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

6.7 Availability of Data and Material

The data and materials can be obtained from the corresponding author upon request.

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