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Taraxasterol Inhibits Migration, Invasion, and Adhesion of Human Glioblastoma U87MG Cells through Downregulation of MMP-2 and MMP-9 Expression

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ABSTRACT

Background & Objective: Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor, characterized by extensive infiltration into surrounding brain tissue. Due to the limited efficacy of current therapeutic interventions, identifying novel compounds capable of suppressing GBM progression is a critical research priority. Taraxasterol, a pentacyclic triterpene extracted from *Taraxacum officinale*, has demonstrated anticancer activity in several tumor models. This study investigated the effects of taraxasterol on the migration, invasion, and adhesion of human U87MG glioblastoma cells and evaluated its impact on MMP-2 and MMP-9 expression.

Materials & Methods: U87MG cells were treated with escalating concentrations of taraxasterol (1–128 μ\muμM) over 24, 48, and 72 h. Cell viability was assessed using MTT, trypan blue exclusion, and LDH release assays. Cell migration, invasion, and adhesion were evaluated via wound-healing, Transwell, and adhesion assays, respectively. The mRNA expression levels of MMP-2 and MMP-9 were quantified using real-time PCR.

Results: Taraxasterol significantly reduced U87MG cell viability in a dose- and time-dependent manner. Treatment at the IC50 concentration markedly inhibited cell migration (~70%), invasion (>55%), and adhesion (~25%) compared with untreated controls ($p < 0.05$). Furthermore, taraxasterol significantly downregulated MMP-2 and MMP-9 mRNA expression levels, reducing their expression to approximately 25% and 30% of control values, respectively ($p < 0.01$).

Conclusion: Taraxasterol effectively suppresses the migratory, invasive, and adhesive properties of glioblastoma cells, potentially through the downregulation of MMP-2 and MMP-9 expression. Consequently, taraxasterol represents a promising candidate for the development of adjunctive therapeutic strategies aimed at limiting glioblastoma invasiveness.

Keywords: *Taraxasterol, Metastasis, Glioblastoma, cancer*

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1. Introduction

Glioblastoma multiforme (GBM) is recognized as the most prevalent and aggressive primary malignant tumor affecting the central nervous system (1). Despite progress in neurosurgery, radiotherapy, and chemotherapy, the outlook for GBM patients continues to be exceedingly grim, with a median survival rate of merely 12–15 months post-diagnosis (2). The high invasiveness and diffuse infiltration of GBM cells into the surrounding brain tissue make complete surgical resection almost impossible, resulting in frequent tumor recurrence (3). Therefore, identifying novel therapeutic agents capable of targeting GBM cell invasion and migration is an urgent priority.

Natural products and phytochemicals have long been considered a rich source of bioactive compounds with potential anti-cancer properties. In recent decades, plant-derived agents such as vincristine, paclitaxel, and camptothecin have become important components of modern chemotherapy (4). Compared with conventional cytotoxic drugs, herbal compounds often exhibit lower toxicity and multiple mechanisms of action, including antioxidant, anti-inflammatory, and anti-proliferative effects (5). *Taraxacum officinale* (commonly known as dandelion) is a medicinal herb belonging to the Asteraceae family, traditionally used for its diuretic,

hepatoprotective, and anti-inflammatory properties (6). Phytochemical studies have identified several active constituents in *T. officinale,* among which taraxasterol—a pentacyclic triterpene—has received increasing attention for its pharmacological potential (7). Taraxasterol exerts antioxidant, anti-inflammatory, and anti-tumor activities in various cancer cell lines, including hepatic, gastric, and prostate cancers (8).

One of the key mechanisms underlying tumor invasion and metastasis involves the breakdown of the extracellular matrix (ECM), which is facilitated by matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9 (9). Overexpression of these enzymes enhances GBM cell migration, invasion, and adhesion, thereby contributing to tumor progression and therapeutic resistance (10). Therefore, agents capable of modulating MMP expression and activity may represent a promising approach in GBM therapy. Given the reported anticancer properties of taraxasterol and the urgent need for novel therapies targeting GBM invasiveness, this study investigated the effects of taraxasterol on migration, invasion, and adhesion of human glioblastoma U87MG cells, as well as its influence on MMP-2 and MMP-9 gene expression.

2. Materials and Methods

2.1 Cell Line and Culture Conditions

The human glioblastoma cell line U87MG was obtained from the Pasteur Institute of Iran (Tehran, Iran). Cells were cultured in RPMI-1640 medium (Gibco, USA) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin solution. Cultures were maintained at 37 °C in a humidified incubator containing 5% CO_2 (11). Subculturing was performed when cell confluence reached approximately 80% using 0.25% trypsin–EDTA for cell detachment.

2.2 Preparation of Taraxasterol Solution

Taraxasterol (Sigma-Aldrich, USA) was dissolved in dimethyl sulfoxide (DMSO) to prepare a stock solution at a concentration of 10 mM, which was subsequently diluted with culture medium to obtain final working concentrations of 1, 2, 4, 8, 16, 32, 64, and 128 µ\muµM. The final concentration of DMSO in all treatment groups was maintained below 0.1% (v/v) to avoid solvent-induced cytotoxicity (v/v).

2.3 Cell Viability Assay (MTT)

Cell viability was assessed using the MTT assay. Briefly, cells were seeded in 96-well plates and treated with various concentrations of taraxasterol for 24, 48, and 72 h. Following treatment, MTT solution was added, and the resulting formazan crystals were solubilized. The absorbance was measured using a microplate reader. The percentage of viable cells was calculated relative to untreated controls, and the half-maximal inhibitory concentration IC_{50} was determined using GraphPad Prism software version 6 (La Jolla, CA, USA) (12).

2.4 Trypan Blue Exclusion Assay

Cell viability and membrane integrity were further evaluated using the trypan blue exclusion technique. Cells were mixed with 0.4% trypan blue dye at a 1:1 (v/v) ratio and counted using a hemocytometer under an inverted microscope. Cells that took up the blue dye were counted as non-viable, whereas those excluding the dye were considered viable (13).

2.5 Lactate dehydrogenase (LDH) release assay

To evaluate plasma membrane damage and cellular cytotoxicity induced by taraxasterol, an LDH release assay was performed. Following incubation, cell culture supernatants were collected, and extracellular LDH activity was quantified using the LDH Cytotoxicity Detection Kit (Roche, Germany) in accordance with the manufacturer's instructions. Absorbance was measured at 490 nm with a reference wavelength of 630 nm using a microplate reader (14).

2.6 Migration Assay (Wound-Healing Test)

The effect of taraxasterol on cell migration was assessed using a scratch wound-healing assay. A straight scratch was made through the monolayer using a sterile 200-µL pipette tip. Detached cells were removed by washing with PBS, and fresh medium containing taraxasterol (at the IC_{50} concentration) was added. Images were captured at 0 and 24 hours after treatment using an inverted microscope, and the wound closure percentage was quantified using ImageJ software (12). The percentage of wound closure was calculated according to the following formula:

Wound closure (%) = [(A0 − At) / A0] × 100

where A0 represents the initial wound area at 0 h and at represents the wound area after 24 h.

2.7 Invasion Assay (Transwell Assay)

Cell invasion was assessed using Transwell chambers with an 8 µm pore size that were pre-coated with Matrigel. U87MG cells at a concentration of 1×10^5 cells/mL, suspended in serum-free medium, were introduced into the upper chamber, while the lower chamber contained medium with 10% FBS to serve as a chemoattractant. Cells were treated with or without taraxasterol for 24 h. Following incubation, non-invading cells on the upper surface of the membrane were gently removed with a cotton swab, and the invaded cells on the lower surface were fixed with methanol and stained with crystal violet. For quantitative analysis, the bound crystal violet was dissolved in 10% acetic acid, and the absorbance was measured at 560 nm using a microplate reader (12).

2.8 Adhesion Assay

For the purpose of adhesion analysis, 96-well plates were coated with fibronectin at a concentration of 10 µg/mL and incubated overnight at 4°C. U87MG cells, which had been pre-treated with taraxasterol at the IC_{50} concentration for 24 hours, were then seeded into the coated wells and allowed to incubate for 1 hour at 37°C. Non-adherent cells were eliminated by washing with PBS, while adherent cells were subsequently fixed and stained using 0.1% methylene blue. For the quantitative analysis, the bound dye was solubilized with 10% acetic acid, and the absorbance was measured at 560 nm with a microplate reader. The absorbance values were interpreted as being proportional to the number of adherent cells (12).

2.9 RNA Extraction and Real-Time PCR

Total RNA was extracted using TRIzol reagent (Invitrogen, USA) according to the manufacturer's instructions. Complementary DNA (cDNA) was synthesized from 1 µ\muµg of total RNA using a cDNA synthesis kit (Thermo Scientific, USA). Quantitative real-time PCR (qRT-PCR) was performed to measure the relative mRNA expression levels of *MMP-2* and *MMP-9*, with *GAPDH* serving as the internal reference control. Amplification was carried out using the SYBR Green Master Mix (Applied Biosystems), and the relative gene expression was determined using the $2^{-}\Delta\Delta Ct$ method **(12)**.

The primer sequences were as follows Table1.

Table 1. Primer sequences, annealing temperatures, and amplicon sizes of MMP-2, MMP-9, and GAPDH genes used in real-time PCR.

Gene	Forward	Reverse	Annealing temperature	Amplicon size
MMP-2	5′-TTGATGGCATCGCTCAGATC-3′	5′-GCTCCTGAATGCCCTTGAGA-3′	60 ˚ C	170 bp
MMP-9	5′-TGTACCGCTATGGTTACACTCG-3′	5′-GGCAGGGACAGTTGCTTCT-3′	60 ˚ C	140 bp
GAPDH	5′-GAAGGTGAAGGTCGGAGTC-3′	5′-GAAGATGGTGATGGGATTTC-3′	58 ˚ C	226 bp

2.10 Statistical Analysis

For quantitative real-time PCR analysis, each biological sample was analyzed in triplicate technical reactions. Statistical analysis was performed using biological replicates as independent values. All experiments were performed in triplicate and repeated at least three independent times. Data were expressed as mean ± standard deviation (SD). Statistical analyses were performed using SPSS version 22. Differences between groups were analyzed using one-way ANOVA followed by Tukey's post hoc test, with $p < 0.05$ considered statistically significant.

3. Result

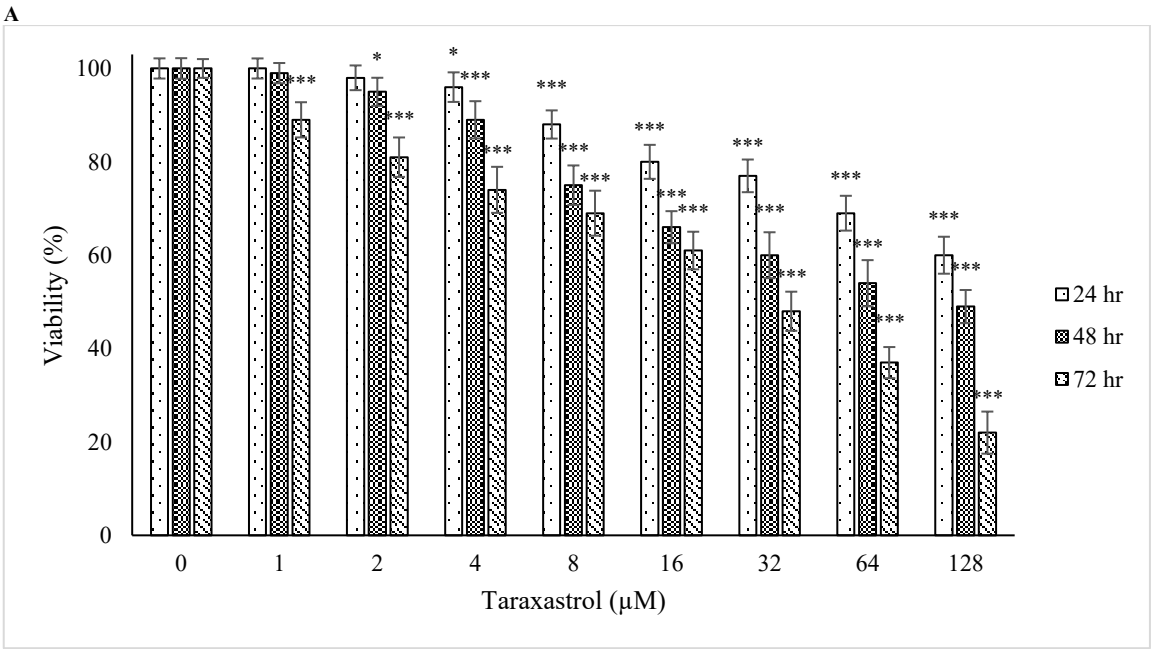
3.1 Effect of Taraxasterol on Cell Viability

The treatment of U87MG glioblastoma cells with escalating concentrations of taraxasterol (1–128 µM) over periods of 24, 48, and 72 hours led to a significant decrease in cell viability, which was both dose- and time-dependent (Figure 1 A). The findings from trypan blue staining corroborated the outcomes of the MTT assay (Figure 1 B). According to the results from the Trypan Blue assay, the IC50 values were determined to be 245.84, 73.37, and 17.96 µM, while the MTT assay yielded IC50 values of 148.65, 60.26, and 32.32 µM for the respective time points of 24, 48, and 72 hours. Taraxasterol Inhibits Migration of U87MG Cells

The wound-healing assay demonstrated that taraxasterol markedly suppressed the migratory capacity of U87MG cells. In untreated control cultures, the wound gap was nearly closed within 24 hours, whereas in taraxasterol-treated cells (IC_{50} concentration), only partial closure was observed (Figure 2). Quantitative analysis showed that the migration rate of treated cells was reduced by approximately 70% ($p < 0.01$). These findings indicate that taraxasterol effectively inhibits GBM cell motility.

3.2 LDH Release Assay

To confirm the cytotoxic effect of taraxasterol, LDH release was measured. As shown in Figure 1 C, treatment with taraxasterol significantly increased LDH release ($p < 0.05$). These results are consistent with the MTT assay findings, suggesting that taraxasterol induces cytotoxicity in U87MG cells both by reducing metabolic activity and disrupting membrane integrity.



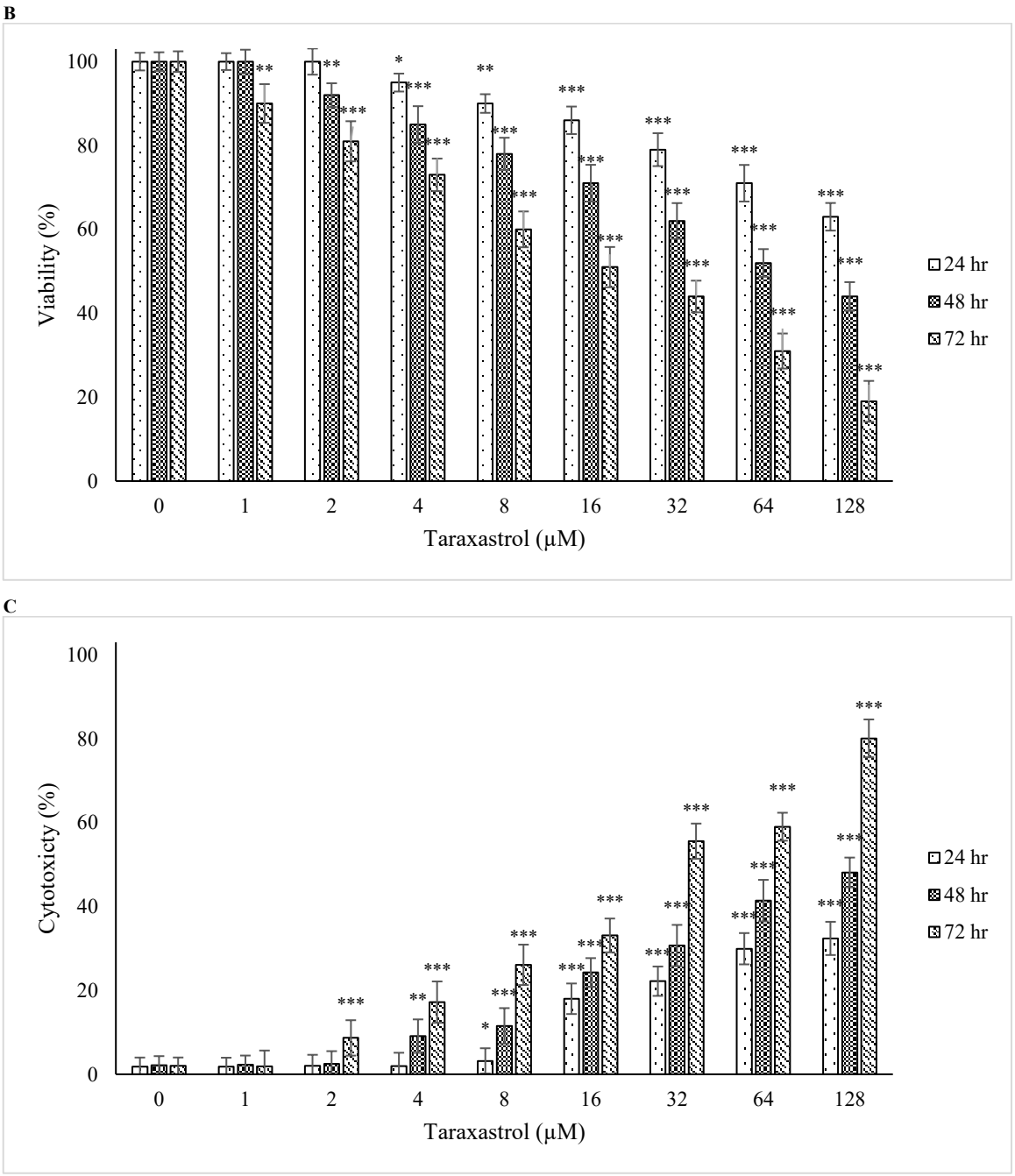
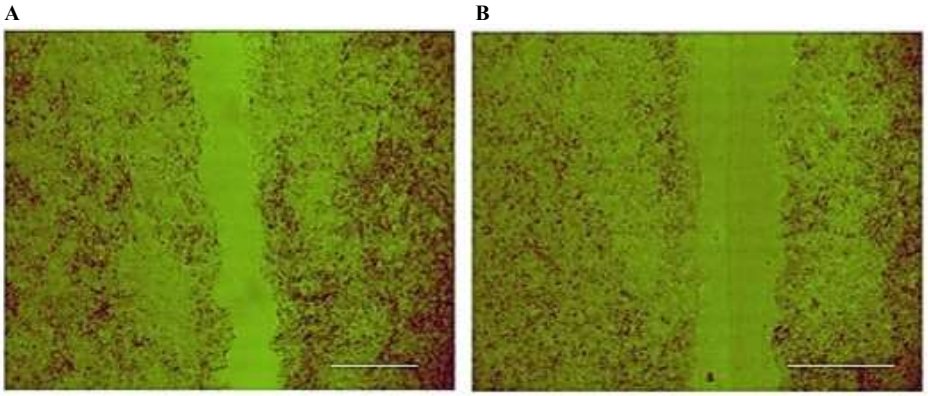


Figure 1. Cytotoxic effects of taraxasterol on U87MG glioblastoma cell viability. Cell viability was evaluated after 24, 48, and 72 hours of treatment using (A) MTT assay, (B) trypan blue exclusion test, and (C) lactate dehydrogenase (LDH) release assay. Control cells received drug-free medium. (*p < 0.05, **p < 0.01, ***p < 0.001 vs. control). **(Prepared by Authors, 2026)**.



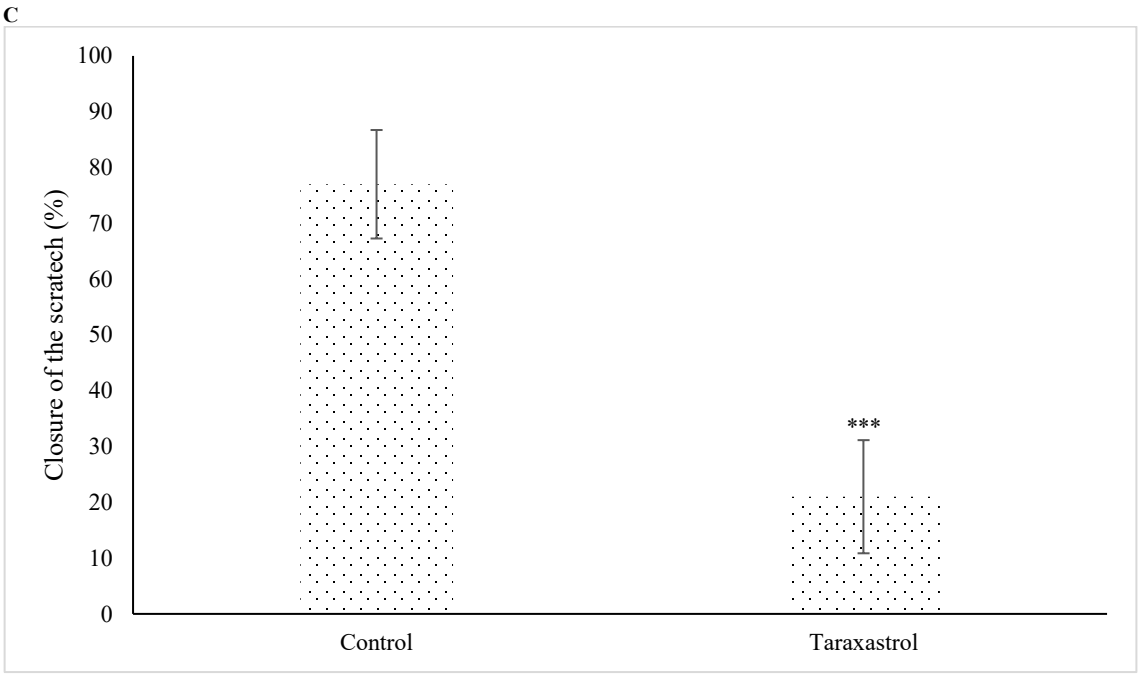


Figure 2. Inhibitory effect of taraxasterol on migration of U87MG cells (wound-healing assay). Representative images of (A) control and (B) taraxasterol-treated cells after 24 h, and (C) quantification of wound closure percentage (***p < 0.001 vs. control). Scale bar: 200 µm. **(Prepared by Authors, 2026)**.

3.3 Inhibitory Effect of Taraxasterol on Cell Invasion

The invasion assay revealed a significant reduction in the number of invaded cells following taraxasterol treatment (Figure 3). Compared with the control group, the number of invading cells decreased by more than 55% after 24 hours of exposure to taraxasterol ($p < 0.01$). Microscopic observation confirmed fewer cells penetrating the Matrigel-coated membrane in the treated group, supporting the anti-invasive activity of taraxasterol on glioblastoma cells.

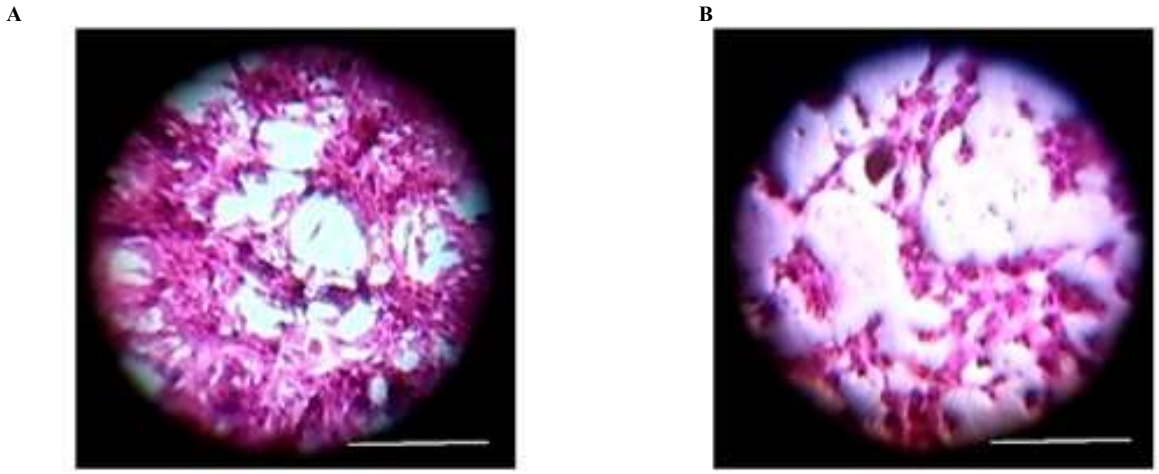
3.4 Taraxasterol Suppresses Cell Adhesion

Taraxasterol significantly reduced the adhesion of U87MG cells to fibronectin-coated surfaces. The number of adherent cells in the treated group was significantly lower (by ~25%) than that of untreated controls ($p < 0.05$) (Figure 4). This result suggests that taraxasterol interferes with cell–matrix interactions, which are critical for tumor cell colonization and metastasis.

3.5 Downregulation of MMP-2 and MMP-9 Gene Expression

Taraxasterol treatment caused a substantial decrease in the mRNA expression levels of MMP-2 and MMP-9 in U87MG cells (Figure 5).

Relative to control cells, MMP-2 and MMP-9 expression levels were reduced to approximately 25% and 30%, respectively ($p < 0.01$).



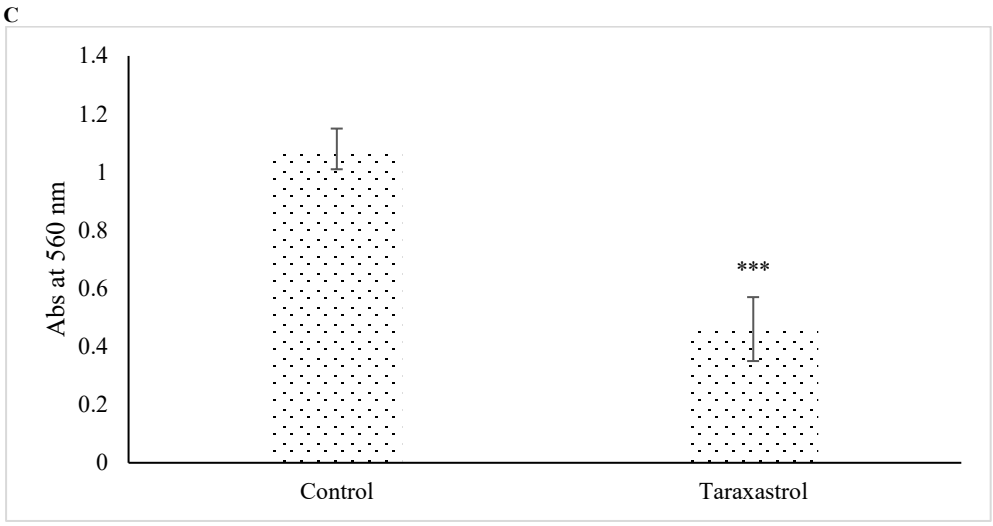


Figure 3. Effect of taraxasterol on invasion ability of U87MG glioblastoma cells (Transwell assay). Representative micrographs of (A) control and (B) taraxasterol-treated cells stained with crystal violet after 24 h. (C) Quantitative analysis of invaded cells based on absorbance at 560 nm. (***p < 0.001 vs. control). Scale bar: 100 µm. **(Prepared by Authors, 2026)**.

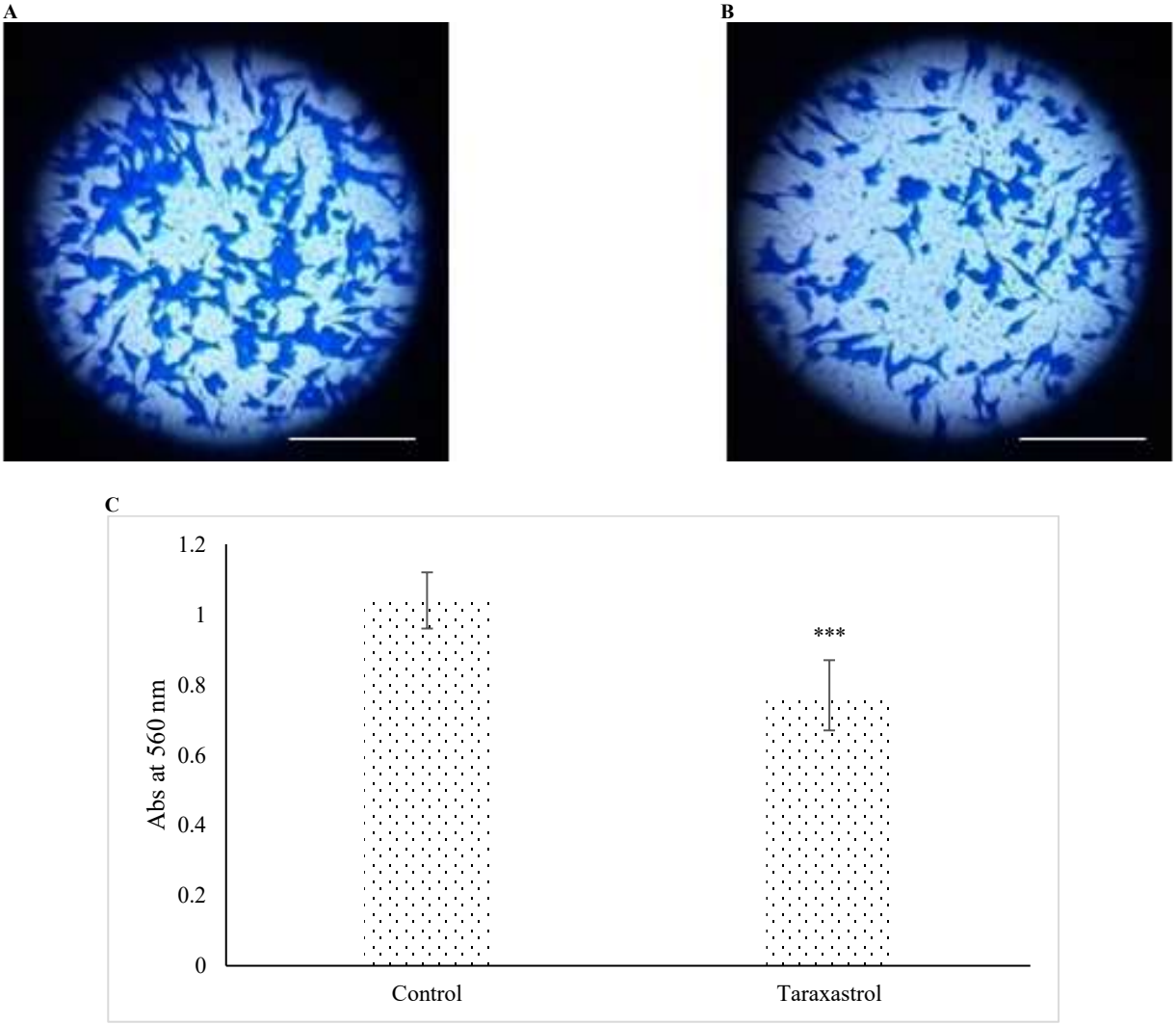


Figure 4. Effect of taraxasterol on cell adhesion of U87MG glioblastoma cells. Representative images of (A) control and (B) taraxasterol-treated cells after 1 h incubation on fibronectin-coated wells. (C) Quantitative measurement of adherent cells determined by crystal violet absorbance at 660 nm. (***p < 0.001 vs. control). Scale bar: 100 µm. **(Prepared by Authors, 2026)**.

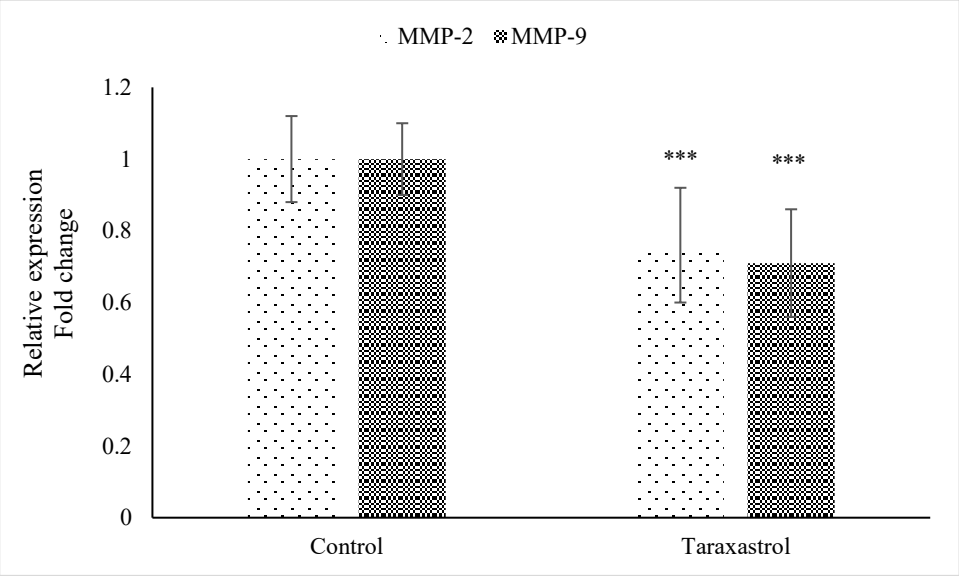


Figure 5. Effect of taraxasterol on MMP-2 and MMP-9 mRNA expression in U87MG cells. Relative mRNA expression levels were analyzed by real-time PCR using GAPDH as internal control (***p < 0.001 vs. control). **(Prepared by Authors, 2026)**.

4. Discussion

In the present study, we demonstrated that taraxasterol significantly attenuated the migratory, invasive, and adhesive capacities of U87MG glioblastoma cells, accompanied by a marked reduction in MMP-2 and MMP-9 mRNA expression. These findings suggest that taraxasterol may suppress the metastatic behavior of glioblastoma cells by modulating extracellular matrix (ECM)-degrading enzymes.

The highly invasive nature of glioblastoma multiforme (GBM) is a primary driver of poor prognosis and therapeutic resistance. This process is largely mediated by the degradation of the ECM by matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which facilitate tumor cell migration and infiltration into adjacent brain tissue **(15,16)**. Elevated expression of these gelatinases correlates with advanced tumor grade, recurrence, and reduced survival in GBM patients **(17,18)**. Furthermore, resistance to radiation and chemotherapy has been linked to increased MMP-9 expression **(19)**, highlighting the potential of targeting these enzymes as a therapeutic strategy **(19)**.

Our results are consistent with existing literature regarding the anti-invasive effects of plant-derived compounds. Taraxasterol, a pentacyclic triterpene, has previously been reported to inhibit tumor progression in various cancer models, including liver, lung, bladder, and prostate cancers **(20-24)**.

Moreover, the anti-metastatic properties of taraxasterol have been corroborated in other cancer models, notably in prostate cancer. In a study by Movahhed et al. (2023), taraxasterol treatment of PC3 prostate cancer cells resulted in marked reductions in cell migration, invasion, and adhesion (by approximately 76%, 56%, and 74%, respectively), alongside the downregulation of MMP-2 and MMP-9 gene expression and diminished gelatinase activity, as demonstrated by zymography **(8)**. These findings in a different tumor context reinforce the hypothesis that taraxasterol exerts a generalized anti-invasive action across cancer types via the suppression of matrix metalloproteinases. The consistency between our observations in glioblastoma cells and the data from prostate cancer strengthens the plausibility that taraxasterol targets conserved pathways involved in tumor cell motility and ECM degradation.

Moreover, a recent study on triple-negative breast cancer (TNBC) cells has provided further evidence of the anti-tumor potential of taraxasterol. Abdolmaleki et al. (2023) demonstrated that taraxasterol treatment of MDA-MB-231 cells significantly reduced cell viability over 24 to 96 h, with IC50 ~439 µM at 24 h to ~27.9 µM at 96 h, while also inducing apoptosis. Importantly, taraxasterol suppressed the gene expression of *AKT1*, *mTOR*, and β\betaβ-catenin, while increasing *PTEN* expression, indicating the involvement of the AKT/mTOR/β\betaβ-catenin pathway in its mechanism of action **(23)**. This study in a different cancer type reinforces the possibility that taraxasterol may exert broad anti-invasive and anti-proliferative effects via the modulation of key signaling pathways. In the context of glioblastoma, such modulation of AKT/mTOR/β\betaβ-catenin (or its upstream regulators) might also contribute to the downregulation of MMP-2/MMP-9 and the suppression of migration and invasion.

While the exact molecular mechanism remains to be fully elucidated, growing evidence indicates that taraxasterol has the potential to influence various intracellular signaling pathways linked to cancer progression, including NF-κB, STAT3, PI3K/Akt, and MAPK **(7)**. In GBM, these pathways are known to regulate MMP transcription, cell motility, and invasion **(24,25)**. Therefore, the suppression of MMP-2 and MMP-9

expression observed in our study may result from the inhibition of one or more of these signaling cascades.

Specifically, we demonstrated that taraxasterol significantly attenuated the migratory, invasive, and adhesive capacities of U87MG glioblastoma cells, accompanied by a marked reduction in MMP-2 and MMP-9 mRNA expression. The simultaneous inhibition of these cellular processes suggests that taraxasterol interferes with multiple stages of glioblastoma cell dissemination. Furthermore, the downregulation of MMP-2 and MMP-9 provides a plausible molecular explanation for the observed reduction in invasive behavior, as these enzymes play essential roles in extracellular matrix (ECM) degradation and tumor cell infiltration. To confirm this hypothesis and identify the precise targets, further studies employing Western blotting and specific pathway inhibitors are required.

Consistent with our findings, previous studies have demonstrated that natural triterpenoid compounds can suppress cancer cell migration and invasion through the modulation of MMP expression and associated signaling pathways **(26)**. Taraxasterol, in particular, has been reported to inhibit proliferation, migration, and invasion across various cancer models, partly via the regulation of apoptosis-associated and metastasis-related pathways **(8)**. Furthermore, studies in glioblastoma models have emphasized the critical role of MMP-2 and MMP-9 in driving the highly invasive phenotype of GBM cells, supporting the relevance of targeting these enzymes as a potential therapeutic strategy **(27)**. Consequently, our findings extend these observations by suggesting that taraxasterol may represent a promising candidate for limiting GBM invasiveness through the suppression of mechanisms related to extracellular matrix (ECM) remodeling.

Despite these promising insights, several limitations of the current study should be acknowledged. First, we assessed only the mRNA expression levels of MMPs; therefore, confirming these findings at the protein level via Western blotting or evaluating enzymatic activity through gelatin zymography is warranted. Second, this study was conducted using a single cell line (U87MG), necessitating validation in additional glioblastoma cell lines or patient-derived models to ensure broader applicability. Finally, the absence of *in vivo* studies limits the direct translation of these findings to clinical settings. Future research should prioritize the use of animal models and explore the potential synergistic effects of taraxasterol in combination with standard-of-care therapies, such as temozolomide.

5. Conclusion

Taken together, our findings demonstrate that taraxasterol effectively inhibits glioblastoma cell migration, invasion, and adhesion, likely through the downregulation of MMP-2 and MMP-9. These results suggest that taraxasterol may serve as a promising adjunctive therapeutic agent for glioblastoma, warranting further molecular and *in vivo* investigations.

6. Declarations

6.1 Acknowledgments

We would like to express our sincere gratitude to Kermanshah University of Medical Sciences for its financial support.

6.2 Ethical Considerations

The study was approved by the Ethics Committee of Kermanshah University of Medical Sciences (IR.KUMS.REC.1399.1158).

6.3 Authors' Contributions

Conceptualization, resources, supervision, and funding acquisition, I. R.; methodology, investigation, and writing—review and editing, S. B. M.; software and writing—original draft preparation, M. S. M.; validation, C. J.; formal analysis and data curation.

6.4 Conflict of Interest

The authors declare no conflict of interest.

6.5 Fund or Financial Support

This research was funded by Kermanshah University of Medical Sciences, grant number 4000704.

6.6 Using Artificial Intelligence Tools (AI Tools)

Artificial intelligence (AI) was used solely for language editing, proofreading, and improving the manuscript's clarity, grammar, and readability. No modifications were made to the original data, statistical analyses, results, figures, or graphical representations.

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