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Taraxasterol from edible plants inhibits breast cancer progression by targeting the miRNA-140-5p/OGT axis: Implications for functional food-based therapies

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Abstract

The second most frequent cause of tumor-related mortality in women is malignant breast cancer (BC). The exploration of new therapeutic agents and related mechanisms is crucial for BC research. Numerous investigations have demonstrated that taraxasterol (TAX) has antitumor effects, but the role of TAX in BC and the corresponding mechanisms are unknown. In this investigation, after treating BC cells with TAX, the proportion of apoptosis was measured using flow cytometry, the Transwell® was used to measure cell invasion, and the wound-healing assay was used to measure cell migration. It was discovered that TAX promoted the apoptosis of BC cells and inhibited BC cell migration and invasion. In addition, according to the results of *in vivo* tests, tumor growth was suppressed by TAX. Mechanistically, O-GlcNAc transferase (OGT) expression was indirectly reduced by TAX through the up-regulation of miRNA-140-5p expression. According to this theory, TAX blocks the growth and migration of BC by controlling the miRNA-140-5p/OGT axis.

Keywords: BC; growth; motility; miRNA-140-5p; OGT; taraxasterol

Introduction

Breast cancer (BC), being a primary contributor to cancer-related fatalities worldwide, is a cancer that predominantly impacts women and poses a grave risk to their healthy well-being. Survival proportion of patients is hindered by the hurdles of metastasis and recurrence in spite of the progress made in conventional treatment methods. These challenges highlight the pressing necessity to investigate therapies that can work alongside or improve the existing medical interventions.

Exploring the realm of natural healing substances is an exciting field that focuses on identifying bioactive compounds in food sources, such as fruits and vegetables, for potential medicinal use. These natural compounds commonly found in fruits and vegetables could serve as valuable supplementary treatments in prevention of cancer and therapy.

Bioactive compounds, such as polyphenols and flavonoids, have shown promise in influencing molecular pathways related to development and spread of cancer, including apoptosis and metastasis regulation. Taraxasterol (TAX) is a pentacyclic triterpenoid found in common edible plants such as dandelions that have exhibited anticancer properties in various research studies. Investigating TAX and similar plant-derived

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compounds could lead to the development of safer treatment options for BC patients that may help decrease the chances of recurrence and spread of cancer.

As our knowledge in the field of food science progresses ahead of time and research efforts intensify on the impact of diet and specific bioactive elements in preventing diseases such as cancer, it is gaining more attention nowadays. Therefore, it becomes increasingly crucial to search for foods and natural substances that can be incorporated into BC treatment plans to improve survival proportions and enhance patients' overall quality of life. Exploring these food-based compounds' health–food bonds could open up avenues for innovative approaches rooted in nutrition in the research and treatment of BC (Li *et al*., 2022).

Taraxasterol, a type of triterpenoid compound derived from the common dandelion plant belonging to the Asteraceae family, has been widely recognized for its various health benefits to humans. TAX has become increasingly popular in the field of food science for its numerous positive effects on health, such as reducing inflammation and oxidative stress as well as potential anticancer properties. This has led to a growing interest for incorporating such beneficial compounds found in edible plants into our diets for nutrition and maintaining good health. With the increasing fascination surrounding plant-based substances for improving health and well-being, TAX shows the potential to aid disease prevention and treatment. This is particularly significant when incorporating components into dietary strategies to address cancer, cardiovascular diseases, and metabolic disorders (Jiao *et al*., 2022). Previous studies have demonstrated that TAX has blocky effects on many tumors. TAX causes apoptosis, blocks HCC cell growth, and may be a candidate for therapeutic suppression (Bao *et al*., 2018). TAX contributes to the inactivation of the phosphatidylinositol 3-kinase–protein kinase B (PI3K-Akt) axis, thereby promoting melanoma cell apoptosis and suppressing melanoma cell motility (Liu *et al*., 2022).

MicroRNAs (miRNA) are non-coding RNAs discovered in eukaryotes that are essential in controlling gene activity after transcriptional processes occur within cells. These tiny RNA molecules have garnered interest in food science and medical research because of their capacity to regulate gene functioning and impact various biological activities, such as cancer development. Within the context of BC, miRNAs are linked to overseeing tumor expansion spread to parts of the body and the movement of cancerous cells. This makes them focal points for therapies to treat this type of cancer.

A significant group component is miRNA-140-5p that is known for its ability to hinder the advancement of BC by pinpointing certain oncogenes. Mirroring this is miRNA-140-5p's ability to reduce the expression of vascular endothelial growth factor A (VEGFA), a pivotal element in the angiogenesis essential for the proliferation and spread of tumors. Expression levels show a decrease in BC cells' proliferation proportion and movement capabilities while also impeding the formation of blood vessels within them, making it a potential target for innovative therapeutic strategies incorporating bioactive compounds found in food sources.

In the realm of food science exploration, miRNAs, such as miRNA-140-5p, and bioactive substances, such as TAX, may pave the way for dietary approaches to the management of BC through functional foods and nutraceutical products by incorporating phytochemicals that regulate miRNA levels—an intriguing fusion of nutritional and molecular oncology realms (Lu *et al*., 2017). O-GlcNAc transferase (OGT or O-linked N-acetylglucosaminyl transferase) is elevated in BC tissues, and its knockdown blocks BC growth, indicating the potential to act as a BC target (Barkovskaya *et al*., 2020).

Previous studies have shown that TAX up-regulates miR-140 expression (Xie *et al*., 2022). This research study has successfully proven the impact of TAX on the movement and development of BC cells, indicating its potential as a compound that possesses anticancer properties worth exploring further in the field of medical research and treatment. OGT was discovered as a *miRNA-140-5p* downstream target gene, confirming that TAX exerts its anti-BC effect by up-regulating miRNA-140-5p and then inhibiting the expression of OGT.

Methods

Cell culture

The BC cell lines MDA-MB-231 and MCF 7 were grown in Dulbeccos Modified Eagle Medium (DMEM) with 1% penicillin-streptomycin to prevent bacteria and 10% fetal calf serum (FS). These used BC cell lines were sourced from the American Type Culture Collection (ATCC) and serve as important tools in research on behavior of cancer cells, such as growth and response to treatments such as TAX.

Cell counting kit-8 (CCK8) assay

Cells were inoculated in 96-well plates (1×10^4 cells/well) and exposed to TAX for 24, 48, and 72 h; relevant reagents were added according to the instructions prescribed for CCK8 assay (10 μL). Optical density (OD) at 450 nm was calculated by an enzyme labeling instrument.

Clone formation assay

Breast cancer cells were placed in six well plates with 400 cells per plate and exposed to two varying amounts of TAX, that is, 2.5 μM and 5 μM, to observe how it impacts colony formation. The cells were left to grow for 2 weeks so that colonies could develop. Each colony indicates a group originating from one progenitor cell. After incubation, the cells were dyed with crystal violet to observe and measure the developed colonies. This test gives us an understanding of how TAX can limit the growth ability of BC cells and shows signs of its benefits in fighting cancer.

By inhibiting the formation of colonies in cancer cells over a period, TAX shows how it can help reduce their survival and growth. This highlights its effectiveness as a natural compound for preventing or treating cancer through dietary interventions.

Apoptosis rate assay

Breast cancer cells were treated with TAX (2.5 μM and 5 μM), digested with trypsin, and cell suspensions stained with membrane-bound protein V-FITC and PI apoptosis detection kit for 5 min in the dark. The proportion of apoptotic cells was examined using flow cytometry and the FlowJo software.

Wound healing assay

The cells were completely confluent into a monolayer of a medum. A 10-uL pipette tip was used to create scratches in a petri dish. The cell debris was then washed with phosphate-buffered saline (PBS) solution. This was the starting time (0 h), and the width of the wound was photographed and recorded using a microscope. A serum-free medium containing TAX was added to the culture dish, incubated for 24 h, and again recorded and photographed.

Transwell assay

After being cultivated, BC cells were introduced in the top chamber of Transwell®, and the lower chamber was supplemented with 10% PBS. A day later, polymethanol was used to fix the cells in the lower chamber stained with crystal violet. Following a PBS wash, pictures were taken using an inverted microscope, and cells passing through the lower chamber were counted.

Dual-Luciferase® Reporter (DLR) assay

To explore the relationship between miRNA-140-5p and 3' untranslated regions (UTRs) of human OGTs, both original version (wild type [WT]) and modified version (mutant [MUT]) of the OGT 3'UTRs were inserted into DLR vector to create a Dual-Luciferase gene plasid. HEK293 cells were placed in 24-well plates and transfected with either a mimic of miRNA-140-5p or a negative control mimic to study how miRNA-140-5p affects the expression of OGT gene regulation. After 24 h, the cells were transfected with a DLR plasmid containing either the wild type OGT or the mutant OGT gene fragment.

We measured luciferase activity using a DLR assay kit to quantify the signals that indicate miRNA binding to OGT 3'UTRs. If there is a decrease in luciferase activity in cells transfected with wild type OGT 3'UTRs plasmid, it suggests that miRNA successfully binds and suppresses OGT expression. This study offers evidence supporting how miRNA-140-5p down-regulates OGT and plays a crucial role in understanding the mechanism through which TAX demonstrates its anticancer properties via miRNA-140-5p-OGT pathway connection action. The cells were left to grow for 2 weeks to form colonies; each colony represents a group of cells originating from a single parent cell unit.

Real-time quantitative polymerase chain reaction (RT-qPCR)

TRIzol reagent was used to extract total nucleic acids (NA). Using the TaqMan miRNA reverse transcription kit, total RNA was reverse-transcribed into complementary DNA (cDNA). SYBR FAST qPCR kit was used to detect the mRNA expression of miRNA-140-5p quantitatively. Using U6 as an internal reference, the comparative CT method (2-ΔΔCt method) analyzed the results. The primer sequences are as follows: miRNA-140-5p, F: 5'-GAGTGTCAGTGGTTTTACCCT-3', R: 5'-GCAGG GTCCGAGGTATTC-3'; and U6, F: 5′-CTCGCTTCGGC AGCACA-3′, R: 5′-AACGCTTCACGAATTTGCGT-3′.

Western-blot analysis

Cells were broken down using radioimmunoprecipitation assay (RIPA) lysis buffer on ice for 30 min. Tissue samples were frozen quickly in nitrogen, components were crunched, and RIPA lysis buffer was applied on ice for 30 min. The resulting lysed sample was spun down to collect supernatant. We used a bicinchoninic acid assay (BCA) kit to gauge protein concentration. To separate proteins effectively, we employed the sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) method. The protein band transfer was done on a polyvinylidene fluoride (PVDF) membrane. Then, it is treated with primary and secondary antibodies accordingly. Details of antibodies are as follows: OGT, 1:1000 dilution (Catalog No. ab96718; Abcam, Cambridge, UK); and β-actin, 1:1000 dilution (Catalog #4967; Cell Signaling, USA).

Xenograft tumor experiments

Shanghai Jihui Experimental Animal Breeding Co. Ltd. (Shanghai, China) provided 10 nude mice, split into two groups: the TAX group (n = 5) and the control group (n = 5); mice were injected with subcutaneous MDA-MB-231 (5×10^6 cells). Nude mice in the TAX group were administered TAX (10 mg/kg) every day. The mass and volume of tumor were measured every 7 days. Evaluation of solid tumors was done according to Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines. All procedures performed in the study involving animals were in accordance with the standards of the Ethics Committee of Zhejiang Cancer Hospital (Approval No. 2023-06-013). At the end of the experiment, the animals were executed using the decapitation method.

Statistical analysis

The statistical analysis was conducted using SPSS 22.0, and the Student's *t*-test was employed to compare both groups. One-way ANOVA compared data between several groups, and the Bonferroni post hoc test was also conducted; $p < 0.05$ was deemed statistically significant. The data were distributed normally.

Results

TAX promotes BC cell apoptosis

Taraxasterol in varying concentrations was added to MDA-MB-231 and MCF-7 cells to observe cell viability. It was found that 10- and 20-μM TAX significantly inhibited cell viability, indicating that these two concentrations of TAX ar e cytotoxic (Figure 1A). Next, CCK8 cell line was used to measure the effects of 2.5 and 5-μM TAX on cell proliferation at various time points. The outcomes demonstrated that TAX slowed the proliferation of BC cells (Figure 1B). Cell proliferation was observed through a colony formation experiment, and the findings demonstrated a substantial decrease in the number of crystal violets in the TAX group (Figure 1C). Using flow cytometry, cell apoptosis was identified, and the findings indicated a substantial rise in the proportion of TAX

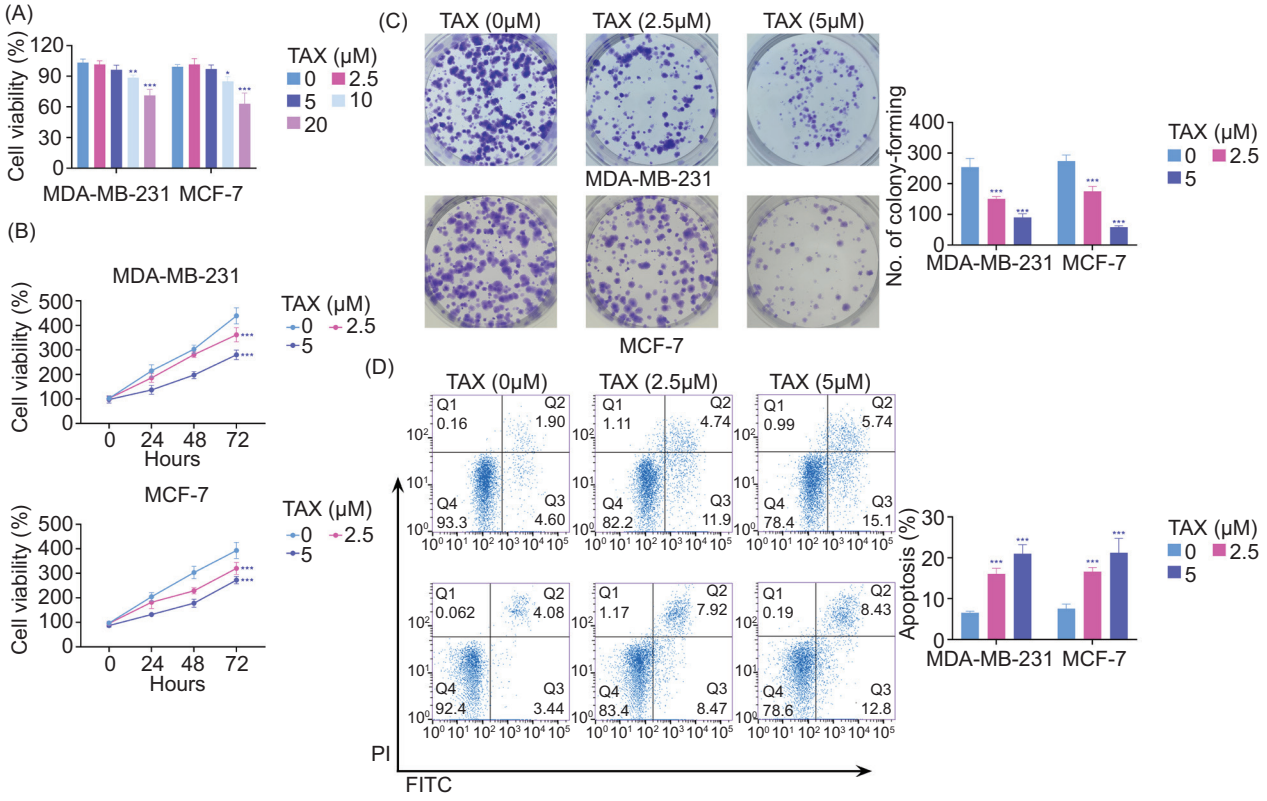

Figure 1. Taraxasterol (TAX) promotes BC cell apoptosis. (A) CCK8 assay detects effects of TAX on the viability of BC cells; (B) CCK8 detects cell viability of TAX at different time points; (C) effect of TAX on BC cell growth detected by clone formation assay. (D) Effect of TAX on apoptosis rate of BC cells detected by flow cytometry. vs. TAX (0 μM), *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

group's cell apoptosis (Figure 1D). To sum up, to differing degrees, proliferation was inhibited by TAX (2.5 μM and 5 μM), while the apoptosis was promoted by TAX. TAX blocks BC cell motility.

In this study, BC cells were exposed to different concentration of TAX to check how it affected their ability to move around and spread out in the body. Researchers used scratch test to observe cell movement and Transwell invasion test to measure how well the cells could invade tissues (Figures 2A and 2B). The findings indicated that both concentrations of TAX (2.5 μ m and 5 μ m) inhibited the migration and invasion of BC cells.

The results indicate that TAX not only inhibits the growth of BC cells and encourages cell death but also successfully prevents cell movement and infiltration, supporting its possible function as a beneficial substance with anti-spreading qualities in BC therapy. This strengthens the concept that TAX obtained from plants could be analyzed as a useful component for its anticancer benefits.

TAX regulates miRNA-140-5p/OGT pathway

In order to study how TAX affects the expression of miRNA-140-5p and OGT in BC cells, a series of molecular

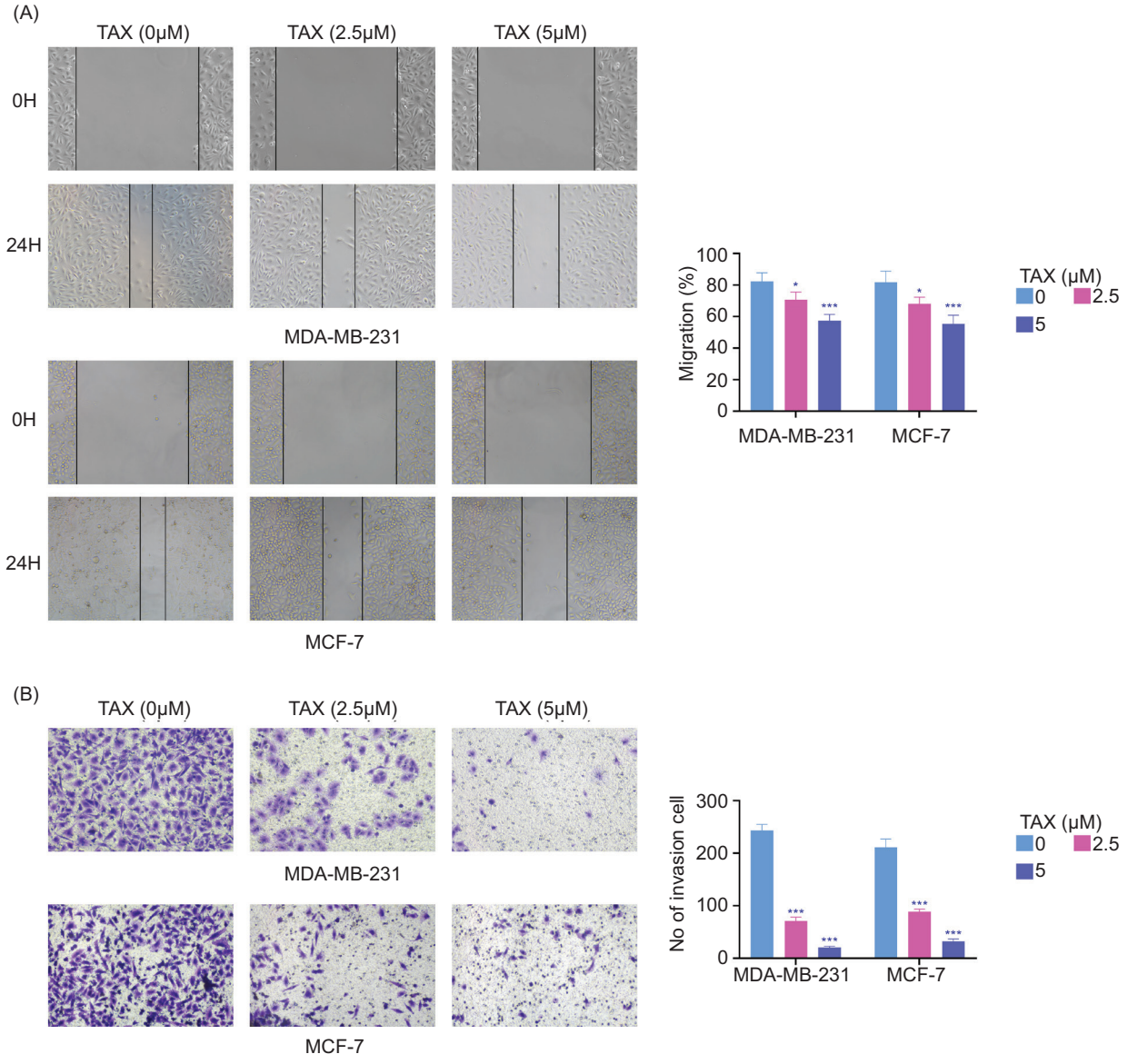

Figure 2. Taraxasterol (TAX) blocks BC cell motility. (A) Effect of TAX on the migration of BC cells detected by scratch assay; (B) Transwell assay to detect the effect of TAX on BC cell invasion. vs. TAX (0 μM), *$p < 0.05$, ***$p < 0.001$.

tests were conducted. A PCR test (Figure 3A) was used to measure the levels of miRNA-140-5p. A Western blot test (Figure 3B) assessed OGT protein levels. The outcomes indicated that treatment with TAX led to an increase in miRNA-140-5p expression while notably decreasing OGT levels in BC cells.

To delve deeper to understand connection between miRNA-140-5p and OGT, we used the database to anticipate the potential genes targeted by miRNA-140-5p and pinpointed OGT as a probable target (as shown in Figure 3C). This relationship was validated through a DLR test (Figure 3D), confirming that miRNA-140-5p directly interacts with OGT 3'UTR section to regulate its expression level.

To gather proof, BC cells received a miRNA mimic of miR-140-5 and examined its impact on OGT expression. The findings revealed a decrease in OGT protein levels in cells that carried the excess of miR-140-5 (Figure 3e).

In order to explore the influence of TAX on OGT via miRNA-140-5p, cells treated with TAX were subjected to a knockdown sequence of miRNA-140-5p. Reduced miRNA-140-5p reversed the suppressing impact of TAX on OGT protein levels. This confirmed that TAX influenced OGT expression through miRNA-140-5p (see Figure 3F).

The results demonstrated that TAX operated against cancer by boosting the expression of miRNA-140-5p, which inhibited OGT—a key factor in the growth and movement of BC cells. This emphasized the use of TAX as a natural substance aimed at certain molecular pathways in BC treatment.

Overexpression of OGT reverses blocking effect of TAX on BC progression

In order to investigate whether the compounded TAX hinders the advancement of BC by targeting OGT, BC

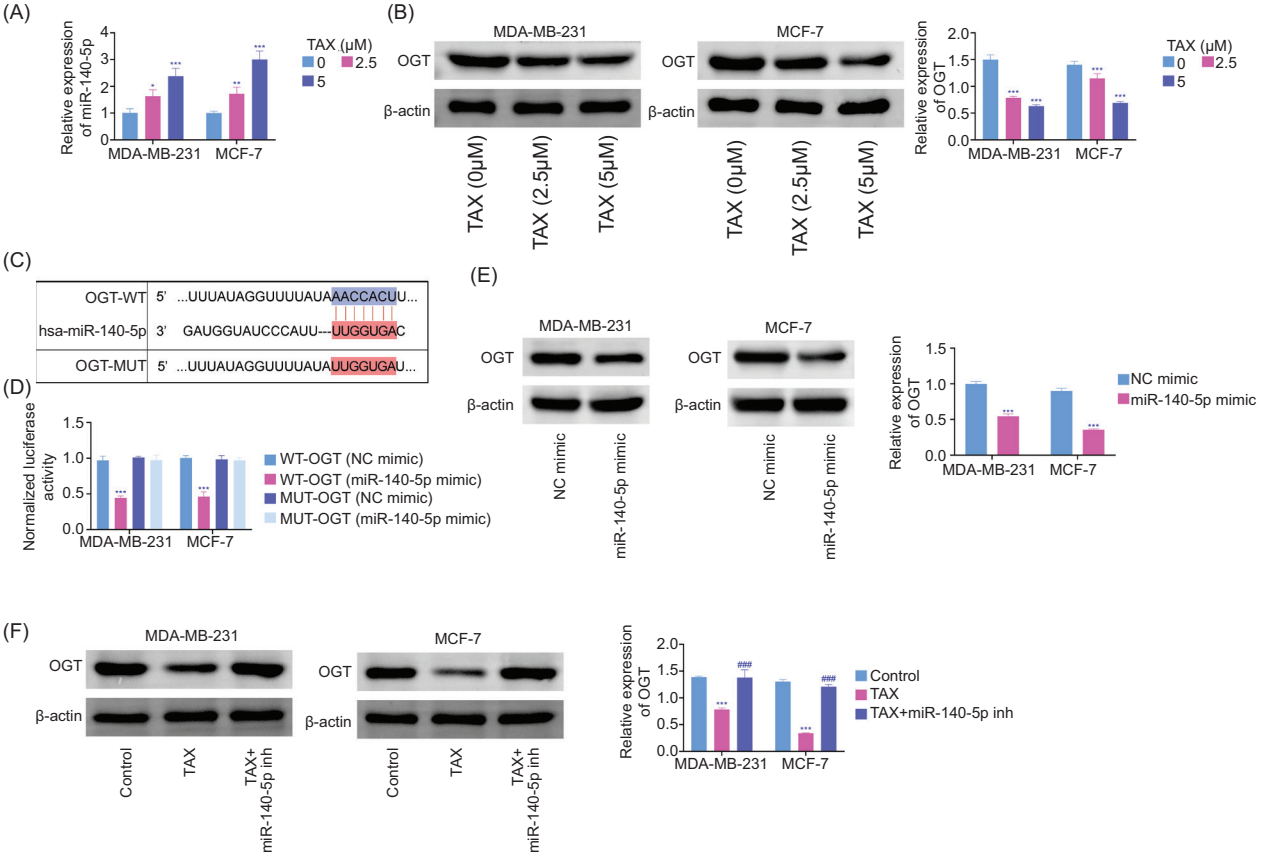

Figure 3. TAX stimulates miRNA-140-5p/OGT axis. (A) qPCR of the effect of TAX on miR-140 5p; (B) effect of TAX on OGT in BC cells detected by Western blot analysis; (C) TargetScan database predicts the presence of binding sites for miRNA-140-5p and GT; (D) DLR assay validates the relationship between miRNA-140-5p and GT; (E) Western blot analysis detects OGT in BC cells transfected with miR-140 5p; (F) TAX regulation of OGT protein expression through miRNA-140-5p confirmed by rescue assay. vs. TAX (0 μM), ***$p < 0.001$; vs. wild type OGT(NC mimic), ***$p < 0.001$; vs. control, ***$p < 0.001$; vs. TAX, ###$p < 0.001$.

cells were exposed to TAX and then genetically modified to reintroduce OGT expression levels within the cells. Researchers then tested cell viability and movement abilities and observed cell invasion using specialized assays (Figures 4A–4D). The findings revealed that reintroducing OGT negated the impact of TAX on the growth and mobility of BC cells.

The results proposed that inhibiting OGT is a way in which TAX hinders the growth and spread of BC cells. Effectively restoring OGT expression enabled the cells to resume their capacity to proliferate and move around again. This solidly supports the idea that TAX works against cancer mainly by controlling OGT, further emphasizing the declaration that TAX as a treatment targets OGT to halt advancement of BC.

TAX blocks BC growth *in vivo*

In order to create a xenograft model and study how TAX affects tumor development in BC, researchers first implanted BC cells into mice. Then, they injected TAX to the mice with tumors while monitoring progress of tumor growth over time. The findings showed that treatment with TAX notably decreased tumor weight and size while effectively impeding the growth of BC tumors in living organisms (Figure 5A).

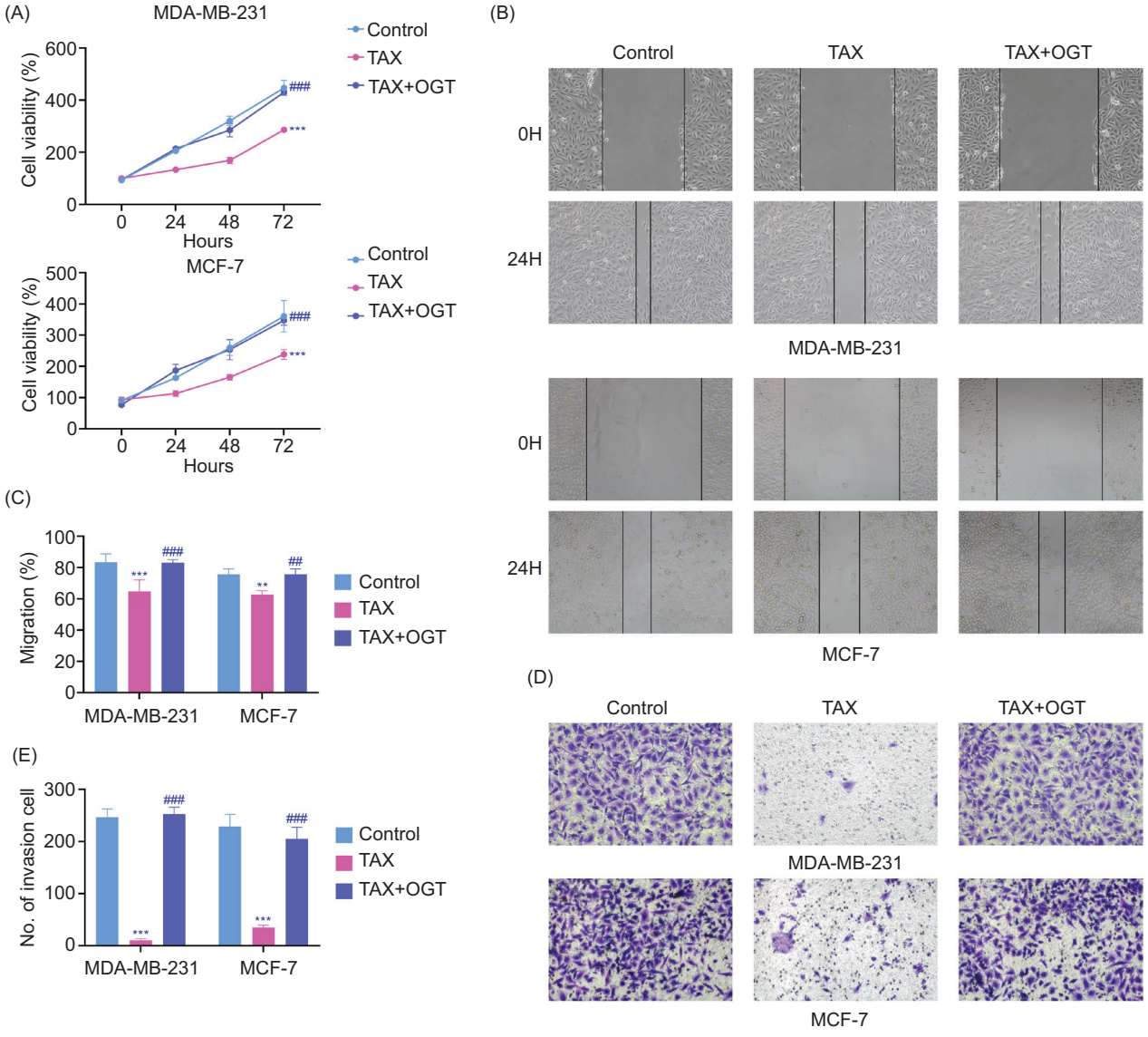

Figure 4. OGT overexpression reverses the blocking effect of TAX on BC progression. (A) OGT overexpression reverses the blocking effect of TAX on BC cell viability; (B) OGT overexpression reverses the blocking effect of TAX on BC cell migration; (C) quantification of cell migration; (d) quantification of the number of cell invasions. vs. control, **$p < 0.01$, ***$p < 0.001$; vs. TAX, $^{\#\#}p < 0.01$,$^{\#\#\#}p < 0.001$.

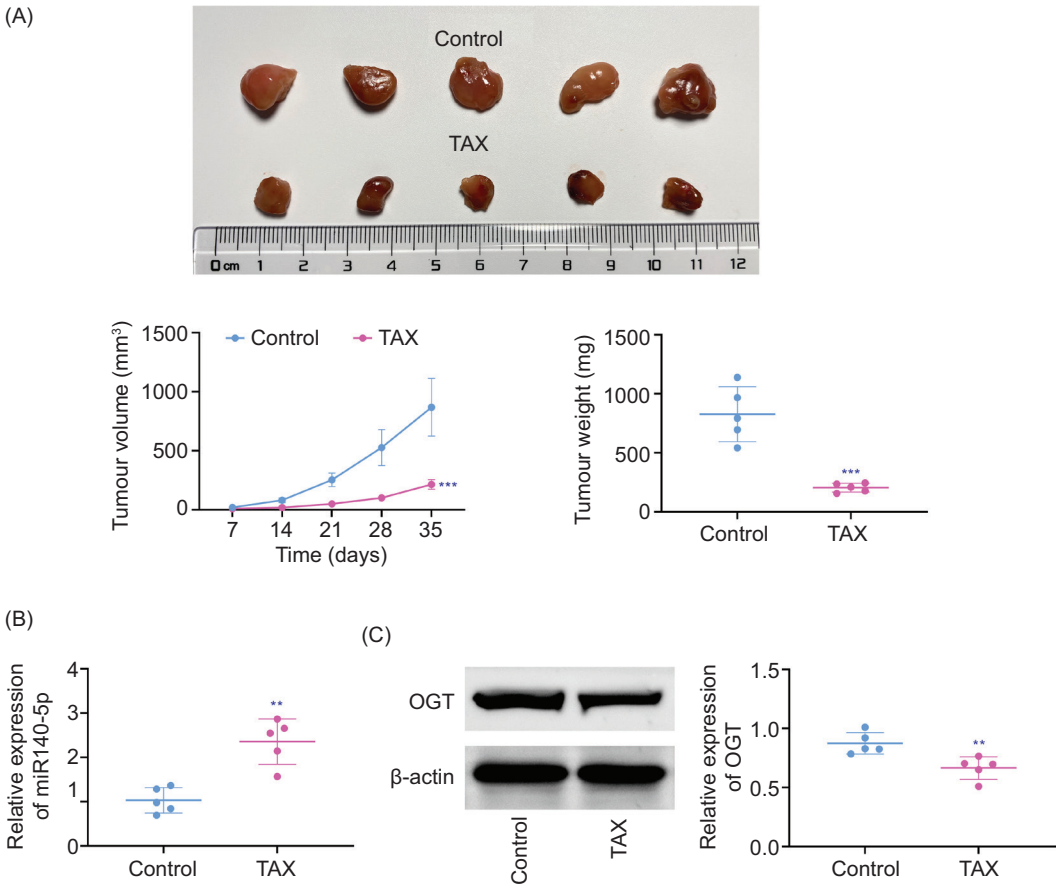

Figure 5. TAX blocks BC growth *in vivo*. (A) Tumor mass and volume; (B) detection of miRNA-140-5p in tumors of nude mice; (C) Western blot assay for the detection of OGT in tumors of nude mice. vs. control, **$p < 0.01$, ***$p < 0.001$.

Examination of tumor tissue unveiled a better comprehension of how TAX impacts tumor growth mechanism. The PCR test findings highlighted a reduced level of miR-140-5p expression in tumor samples (as depicted in Figure 5B). In contrast, Western blot analysis showed increased OGT levels in untreated tumor samples (Figure 5C). The results indicated that TAX opposed tumor growth by boosting miRNA-140-5p and hampered the activation of OGT, a critical protein linked to advancement of cancer.

The control of miRNA-140-5p by TAX highlights its ability as a natural compound that can slow down the growth of BC by focusing on critical biological pathways.

This real-life study validates that TAX hinders the growth of BC tumors by influencing the miRNA-140-5p/OGT pathway. This supports considering TAX as a remedy sourced from edible plants for treatment of cancer.

Discussion

Taraxasterol, a single unit of a triterpenoid derived from dandelions, is found to possess anticancer characteristics according to the studies conducted in the past. One way TAX demonstrates its effectiveness is by hampering the activity of the Wnt/β-catenin signaling pathway. A vital factor is movement of cancer cells and transition from epithelial to mesenchymal cells (EMT). EMT refers to the process where epithelial cells acquire ability to migrate and invade tissues and play a crucial role in spreading of cancer. TAX is discovered to lower the movement of thyroid cancer cells and block EMT by affecting the Wnt/β catenin pathway. This suggests that TAX could be a natural treatment for stopping the spreading and metastasizing of cancer.

TAX's control of this pathway underscores its significance as a substance that can be investigated not just in relation to thyroid cancer but also in various forms of cancer treatment options derived from edible plants in a natural manner (Zhu *et al.*, 2021). TAX also enhances the radiosensitivity of bladder cancer cells (Wang *et al.*, 2024) and blocks metastasis of prostate cancer cells (Movahhed *et al.*, 2023). In this study on BC, it was found that when BC cells were treated with TAX, an increase in cell death (apoptosis) was observed.

Moreover, TAX successfully hindered the development and movement of BC cells. These results indicate that TAX, a natural compound sourced from dandelions, displays strong anticancer characteristics by addressing various facets of cancer advancement, such as tumor growth. This demonstrates the promise of TAX as a treatment for BC when integrated into a holistic approach to manage cancer through functional foods. Numerous studies revealed that miRNA-140-5p blocks the growth of tumors. A decrease in miRNA-140-5p expression was observed in gastric cancer tissues, and transfection of miRNA-140-5p suppressed gastric cancer cell growth and motility (Fang *et al*., 2017). Down-regulation of miRNA-140-5p was observed in nephroblastoma tissues and was involved in tumor cell functions (Liu *et al*., 2019). In addition, in BC, miRNA-140-5p operated as a tumor suppressant. BC cell growth was blocked by overexpression of miRNA-140-5p, which also retarded tumor growth (Hou *et al*., 2022). This investigation verified that TAX could upregulate the expression of miRNA-140-5p.

miRNAs, which are RNA molecules in cells that play an important role in cancer advancement by reducing the activity of specific genes involved in tumor growth and spread development pathway, are shown to have an impact on BC. For instance, take miRNA 543; it has been demonstrated to slow down BC progression by targeting and suppressing *VCAN* gene expression (Li *et al*., 2021). In a distinctive manner, miRNA 152 can impede BC proliferation and spread by lowering ROCK1 protein levels (Maimaitiming *et al*., 2020).

The research indicated that the TargetScan website anticipated the connection between miRNA-140-5p and OGT, pinpointing *OGT* as its potential target gene. The control of the *OGT* gene by miRNA-140-5p established a mechanistic correlation between miRNA functioning and advancement of BC, emphasizing the prospective utility of miRNA-140-5p as a treatment target to impede *OGT*-driven tumor development and movement in BC patients.

O-GlcNAc transferase, an enzyme that transcriptionally alters proteins by attaching OGlcNAc sugars and affecting different cellular functions, has gained attention in cancer research because of its connection with development and progress of tumor. In studies concerning cell carcinoma, it is observed that elevated levels of OGT are linked to poorer survival proportions among patients (Kalantzakos *et al*., 2021). In BC, research demonstrates that increased OGT levels contribute to enhancing the ability of cancer cells to invade surrounding tissues. miRNA, known as miRNA-24, is observed to hinder the invasion of BC cells by preventing OGT activity; this inhibitory impact was overturned upon the re-expression of OGT as demonstrated by (Liu *et al*., 2017).

The current study confirmed that miRNA-140-5p negatively impacted OGT expression, and found TAX to indirectly inhibit OGT by boosting miRNA-140-5p levels through the effect of naturally derived compound from dandelion, that is, TAX. This affirmed the suppressive ability of TAX on OGT expression, leading to an antitumor impact. In BC, this implies that TAX blocks the development and movement of BC cells by elevating miRNA-140-5p, which then reduces its target *OGT* gene.

Conclusions

This study confirmed that TAX blocks growth and migration of BC. TAX's blocking effect on BC could be because it increased miRNA-140-5p, and the target *OGT* gene has less manifestation when miRNA-140-5p is expressed. TAX suppresses tumor growth in BC by lowering *OGT* expression.

Some limitations to this study included its basic structure, and usage of only two types of BC cells in the experiment. However, it didn't mean that it had no inhibitory effects on other BC cells. The focus of future research must be on whether TAX has an inhibitory effect on other aspects of BC stemness, glycolysis, etc., and whether TAX can regulate other miRNAs to inhibit BC.

Availability of Data and Materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Competing Interests

The authors stated that there was no conflict of interest to declare.

Ethics Approval

Ethical approval was obtained from the Ethics Committee of Zhejiang Cancer Hospital (Approval No.2023-06-013).

Author Contributions

Yanjun Hu designed the study, completed the experiment and supervised data collection. Jiefei Mao analyzed and interpreted the data. Yanjun Hu and Jiefei Mao prepared the manuscript for publication and reviewed its draft. Both authors read and approved the manuscript.

Conflict of Interest

The authors state that there are no conflicts of interest to disclose.

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