Tectorigenin suppresses the viability of gastric cancer cells *in vivo* and *in vitro*

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RESEARCH ARTICLE

Abstract

Gastric cancer is currently the 4th most common malignant tumor with a poor prognosis in 2022. New and effective drugs are needed to combat this disease to treat advanced gastric cancer. Tectorigenin (Tec) has a series of pharmacological activities, such as anti-inflammatory and anticancer. However, the effect of Tec on the progression of gastric cancer is unclear. In this study, we investigated the role of Tec in regulating cell viability, cell cycle, and tumor growth of gastric cancer. To detect the role of Tec in the progression of gastric cancer *in vitro* and in mice, we performed several *in vitro* assays such as MTT, colony formation, wound closure, transwell, Immunoblot assays, and *in vivo* tumor growth assays. Our data confirmed that Tec restrained the viability of gastric cancer cells at concentrations of 100, 200, and 300 μM. It also denied the motility of gastric cancer cells. Tec treatment also induced the cell cycle arrest of gastric cancer cells. Mechanically, Tec could suppress the activation of the PI3K/Akt pathway and stop gastric cancer progression. We, therefore, thought Tec could serve as a drug for treating gastric cancer.

Keywords: Apoptosis, cell cycle, gastric cancer, PI3K/Akt pathway, Tectorigenin (Tec)

Introduction

Gastric cancer is the 4th most common tumor and the third leading cause of cancer-related death in 2022(Shang, Zhao, Xu, Ma, & Su, 2023). It has also become China's second most lethal cancer (Y. Li *et al*., 2019). The overall therapeutic effect of gastric cancer is not ideal (Camilloni, Nati, Maggiolini, Romanelli, & Latina, 2021; W. Chen *et al*., 2023). The recurrence and metastasis of gastric cancer are the main causes of death, and it is also a complex pathological process caused by a series of change molecular. At the same time, the clinical treatment is still unsatisfactory (Ooki & Yamaguchi, 2022). In recent years, natural bioactive agents have attracted increasing attention in the fight against cancer due to the unique advantages of certain biological drugs, such as high anti-tumor efficacy and the ability to regulate the tumor microenvironment (Lan *et al*., 2022; Suh *et al*., 2023). The correlation between dietary components and the risk of stomach cancer and various protective and deleterious factors have been identified in our diet associated with gastric cancer (Sharma & Sageena, 2022). Diet and *helicobacter pylori* infection play a crucial role in gastric cancer progress. Other major etiological parameters for gastric cancer include alcohol use, smoking, previous gastric surgery, obesity, adenomatous polyps, pernicious anemia, chronic atrophic gastritis, and radiation exposure (Akbari *et al*., 2022). While diet is an important modifiable risk factor for gastric cancer, administration of some compounds can aid in preventing or treating this gastric cancer. In this regard, some epidemiological evidence demonstrated the links between

nutritional exposures and dietary components to gastric cancer. Adequate diet modification may play a key role in reducing the incidence of gastric cancers.

Tectorigenin, known as 5,7,4'-trihydroxy-6-methoxy-isoflavone, is a kind of isoflavone compound that exists in the rhizomes of the genus Iris and the genus Echinacea (J. Li *et al*., 2022). Modern medical research has found that Tectorigenin (Tec) has pharmacological activities like anti-inflammatory and anticancer abilities (J. Li, Yan, Ren, & Sang, 2023; Yang *et al*., 2020). For example, Tec can improve fatty liver disease by alleviating inflammation and regulating intestinal flora in mice (Y. Chen, Song, Peng, Ge, & Han, 2008). Tec induces G0/G1 cell cycle arrest by regulating cyclin expression, thus inhibiting glioblastoma proliferation (Yeh, Hsu, Chung, & Chen, 2020). Tec treatment can also effectively inhibit the production of TNF-α and IL-6 increased by PA (Q. Y. Li, Chen, Yan, Shi, & Zhong, 2015). The number of live HepG2 cells was decreased by treatment with Tec (Jiang *et al*., 2012). Tec inhibits the invasion of colon cancer cell Caco-2 by down-regulating NF-κB (Liu *et al*., 2019). Its effects on the progression of multiple types of tumors have been demonstrated. However, the role of Tec in gastric cancer is unclear.

This study found that Tec restrained the proliferation of gastric cancer cells in vivo and in vitro. In vitro experiments demonstrated that Tec inhibited the motility of gastric cancer cells, induced cell apoptosis and cell cycle arrest, and inhibited the PI3K/AKT pathway. Therefore, we thought Tec could be a promising drug for treating gastric cancer.

Materials and Methods

Cell culture and drug treatment

Human gastric cancer cell line AGS, MKN45, and normal gastric cell line GES-1 were purchased from the Chinese Academy of Sciences. AGS, as well as MKN45 cells, were cultured with the RPMI-1640 complete medium. After 12 hours of culture, cells were treated with Tec (Bought from Sigma) at concentrations of 0, 25, 50, 100, 200, or 300 μM for 24 h. Subsequently, the effect of Tec was verified for subsequent experiments.

Western blotting

Cells were lysed in a buffer containing 1% Triton X-100, 150 mM NaCl, and 50 mM Tris (pH 7.5). The BCA assay method was used for protein concentration determination, after which proteins were separated (20 μg/lane) by SDS-PAGE on 8% gels. Proteins were then transferred onto polyvinylidene difluoride membranes (MilliporeSigma), which were blocked at room temperature for 2 h in Tris-buffered saline containing 0.2% Tween 20 and 5% non-fat milk. Then the corresponding primary antibodies including PI3K (Abcam, ab302958; 1:1000), p-PI3K (ab278545; 1:500), AKT (ab8805; 1:1000), p-AKT (phospho-T308, ab38449; 1:1000), GAPDH (ab8245; 1:3000) were added, and then secondary antibodies were used for another incubation for 1 h. Proteins were visualized using an enhanced chemiluminescence detection reagent (Pierce; Thermo Fisher Scientific, Inc.) and were analyzed using ImageJ 9.0 software (National Institutes of Health).

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) *assay*

1000 cells / well AGS as well as MKN45 cells were plated into 96-well plates and maintained for 48 h. Cells were subsequently incubated with MTT for 4 h, washed with PBS, and dissolved with 150 μL DMSO. Then, the OD value was measured by a microplate reader at 490 nm wavelength (BD).

Colony formation assay

AGS and MKN45 cells were plated into the 6-well plates (500 cells per well) and maintained in media (10% FBS) for 14 days at 37°C. Then, the cells were fixed with PFA for 15 min and stained with 0.1% crystal violet for 20 min. Further, the cells were photographed using an Axio Observer fluorescence microscope and analyzed by ImageJ 9.0 software.

Transwell assay

BD Falcon inserts (BD Biosciences, Inc.) were used as upper chambers and 24-well plates as lower chambers. Cell culture inserts were coated with 50 μl Matrigel (1:4 diluted with serum-free medium) at 37°C for 30 min. Subsequently, Cells were placed in the upper chamber (serum-free medium), and a complete medium (with 10% FBS) was added to the lower chamber. Cells were incubated for 24 h at 37°C, after which invaded cells on the underside were fixed with 4% paraformaldehyde for 25 min at room temperature, stained with the crystal violet (2%) solution for 25 min at room temperature, and images were captured using a light microscope.

Wound-healing assay

Cells were plated onto glass coverslips until 100% confluent. A 10-μl pipette tip was used to create a scratch,

after which cells were washed twice with PBS to remove cell debris and cultured in serum-free media for another 24 h. Images of the wound were captured using a light microscope at 0 and 24 h to determine the extent of wound closure using ImageJ 9.0 software, and the wound healing percentage was calculated as follows: Healing area/total area.

Cell apoptosis and cell cycle assay

The cells treated with Tec at 0, 50, 100, and 200 μM concentrations for 24 h were washed with PBS. Subsequently, cells were fixed with 70% ethanol at −20°C for 2 h. Next, they were stained with PI and FITC Annexin V at 4°C, and the apoptosis rate was measured. For cell cycle assays, cells were stained with PI at 4°C for 20 min, and the cell cycle was assessed using a FACSCalibur flow cytometer and CellQuest Pro 5.1 (BD Biosciences, Inc.).

In vivo tumor growth assay

6-8 weeks-old female nude mice were bought from Beijing Vital River (Beijing, China). AGS cells were treated with the Tec (15 mg/kg) for 24 h for tumor growth assay. About 1×10^6 cells were implanted into athymic nude mice (6 mice in each group), and the tumor size and weight were monitored every 4 days until 24 days. All animal experiments were approved by the Ethics Committee of Huanggang Central Hospital, affiliated with Changjiang University, for the use of animals and conducted by the National Institutes of Health Laboratory Animal Care and Use Guidelines (Approval No. 2020-179).

Statistics

Data were analyzed using GraphPad 8.0 software (GraphPad Software, Inc.). Error bars represent mean ± SD, and in vitro experiments were repeated three times. The unpaired Student's t-test was used to determine the statistical significance between the two groups. $p < 0.05$ was thought to be significant.

Results

Tec treatment restrained the proliferation of gastric cancer cells

To confirm the role of Tec in the progression of gastric cancer in vitro and in mice, we performed several assays, such as MTT, colony formation, wound closure, transwell, immunoblot, and tumor growth in mice assays. To evaluate the effects of Tec on gastric cancer cell proliferation, we first detected its effects on the viability of AGS as well as MKN45 cells at the concentrations of 25, 50, 100, 200, and 300 μM for 24 h via MTT assays. The molecular formula of Tec is shown in Figure 1A. Interestingly, we noticed Tec treatment decreased the OD value in the AGS, MKN45, as well as normal gastric GES-1 cells (Figure 1B). We further performed the colony formation assays and the data showed Tec treatment decreased the colony numbers at the high concentration (Figure 1C). Therefore, Tec treatment restrained gastric cancer cell proliferation.

Tec suppressed the motility of gastric cancer cells

Then, we investigated the effects of Tec on the migration and invasion of gastric cancer cell line AGS and MKN45. Through wound healing assays, AGS and MKN45 cells were treated with Tec for 24 h at 0, 50, 100, and 200 μM concentrations. We found that Tec treatment suppressed the migration of AGS as well as MKN45 cells (Figure 2A). Similarly, transwell assay also confirmed that Tec treatment restrained the invasion of AGS as well as MKN45 cells, with the decrease of invasive cell numbers (Figure 2B). Therefore, Tec suppressed the migration as well as invasion of gastric cancer cells.

The treatment of Tec stimulated apoptosis and cell cycle arrest in gastric cancer cells

Interestingly, we further performed FCM assays to detect the effects of Tec on the cell cycle and the apoptosis of AGS and MKN45 cells. We noticed that Tec treatment at the concentration of 50, 100, and 200 μM for 24 h stimulated the apoptosis of AGS and MKN45 cells, with an increased percentage of apoptosis cells (Figure 3A). The data further confirmed that Tec treatment at the concentration of 50, 100, 200 μM for 24 h increased the cells at G1 phase and decreased the cells at G2 phase, suggesting the cell cycle was arrested at G1 phase (Figure 3B). Consistently, immunoblot assays also confirmed the decreased cyclin D1 as well as the increased p21 and cleaved caspase 3 expression upon Tec treatment at the concentration of 50, 100, 200 μM (Figure 3C,D). Therefore, Tec stimulated apoptosis and induced cell cycle arrest in gastric cancer cells.

Tec suppressed the PI3K/Akt pathway in gastric cancer cells

A previous study suggested that Tec could mediate the PI3K/Akt pathway, which affected the progression of tumor cells (Yao *et al*., 2021). We, therefore, detected

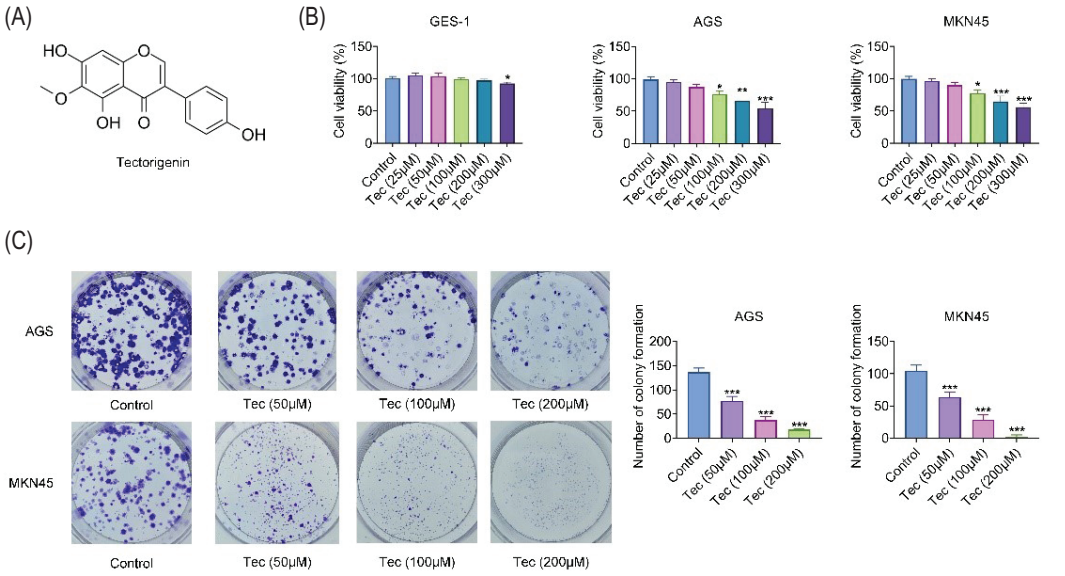

Figure 1. Tec treatment restrained the proliferation of gastric cancer cells. (A) The molecular formula of Tec. (B) MTT assays showed the effects of Tec on the OD value at 490 nm wavelength at the concentration of 25, 50, 100, 200, and 300 μM for 24 h in AGS, MKN-45, and GES-1 cells. The assays were performed three times. (C) Colony formation assays showed the effects of Tec on the viability of AGS cells at the concentrations of 50, 100, and 200 μM for 24 h. The colony number was quantified. The assays were performed three times. Data were represented as mean ± SD. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

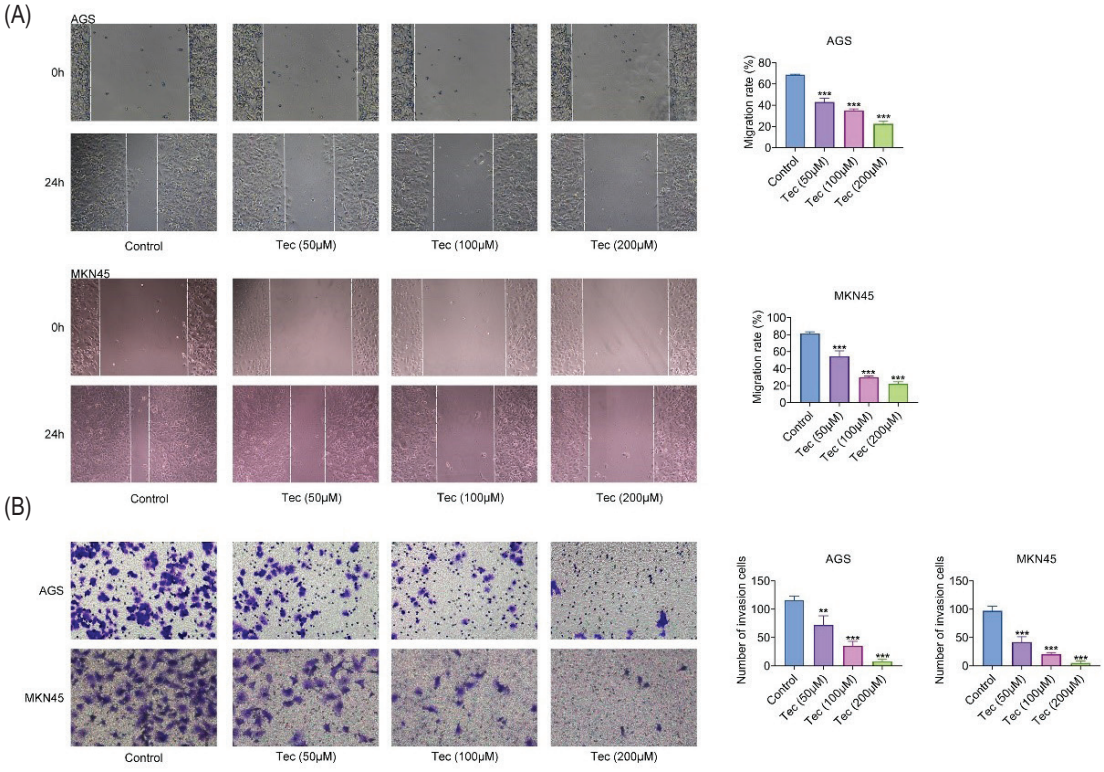

Figure 2. Tec suppressed the motility of gastric cancer cells. (A) Wound closure assays showed the effects of Tec on the migration of AGS cells at the concentration of 50, 100, and 200 μM for 24 h in AGS (up) as well as MKN45 cells (down). The wound width was measured. The assays were performed three times. (B) Transwell assays showed the effects of Tec on the invasion of AGS cells at the concentration of 50, 100, and 200 μM for 24 h in AGS as well as MKN45 cells. The invasive cell number was counted. The assays were performed three times. Data were represented as mean ± SD. ** $p<0.01$, *** $p<0.001$.

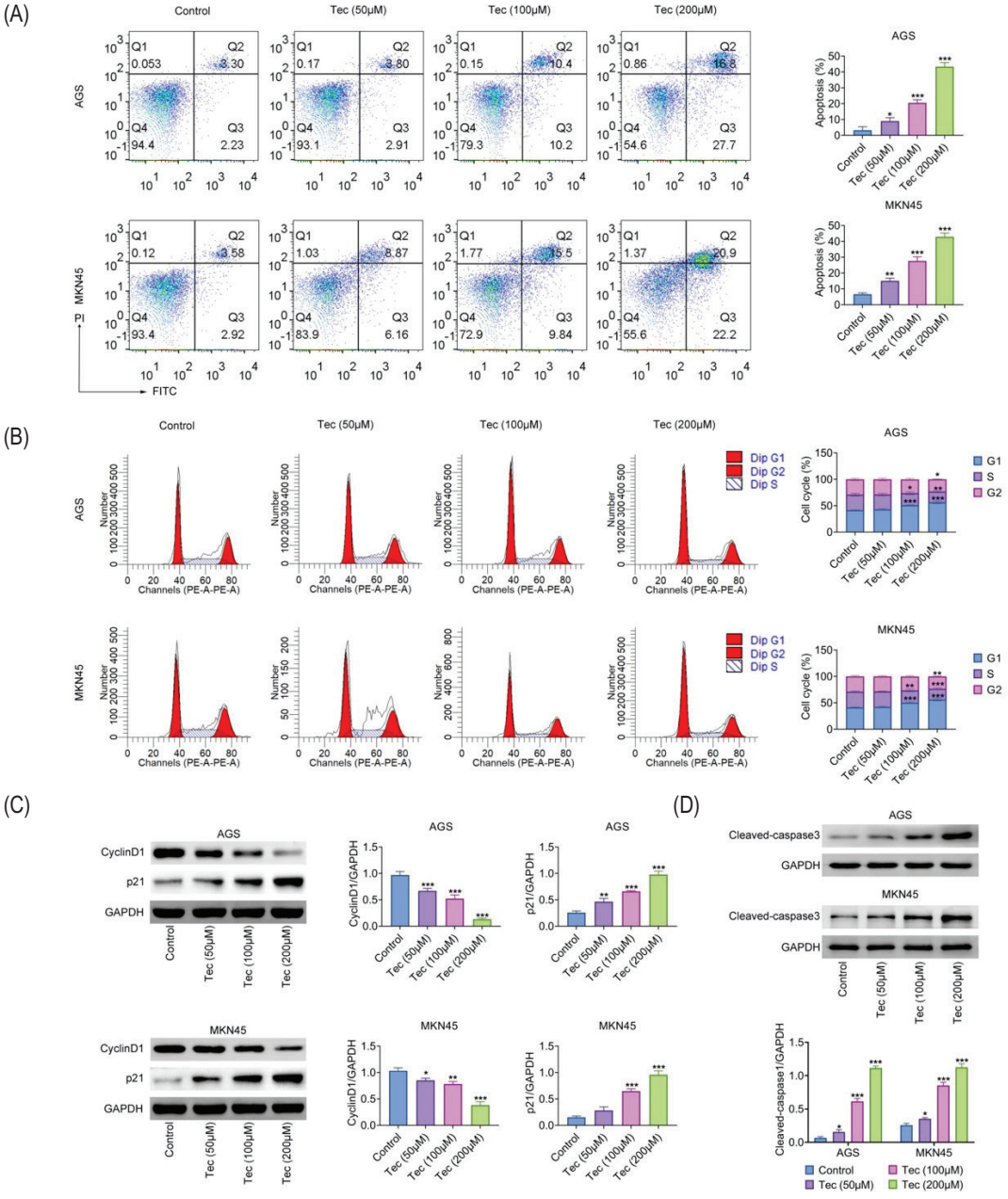

Figure 3. The treatment of Tec stimulated apoptosis and cell cycle arrest in gastric cancer cells. (A) FCM assays showed the effects of Tec on the apoptosis of AGS cells at the concentration of 50, 100, and 200 μM for 24 h in AGS as well as MKN45 cells. The percentage of apoptosis cells was shown. The assays were performed three times. (B) FCM assays showed the effects of Tec on the cell cycle at the concentration of 50, 100, and 200 μM for 24 h in AGS and MKN45 cells. The assays were performed three times. (C) Immunoblot assays showed the effects of Tec on the expression of indicated proteins at the concentration of 50, 100, and 200 μM for 24 h in AGS as well as MKN45 cells. The cells at different phases were shown. The assays were performed three times. (D) The expression of cleaved caspase 3 in AGS as well as MKN45 cells. Data were represented as mean ± SD. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

the effects of Tec on the PI3K/Akt pathway in AGS and MKN45 cells. Through Immunoblot assays, we found that Tec treatment decreased the phosphorylation levels of PI3K as well as Akt in AGS and MKN45 cells, suggesting the suppression of this pathway (Figure 4). Therefore, Tec suppressed the activation of the PI3K/Akt pathway in gastric cancer cells.

Tec suppressed tumor growth of gastric cancer cells in mice

Then, we detected the effects of Tec on gastric cancer growth in mice. AGS cells treated with Tec for 24 h were injected into the back of nude mice. We found that tumor volume and tumor weight were decreased by Tec

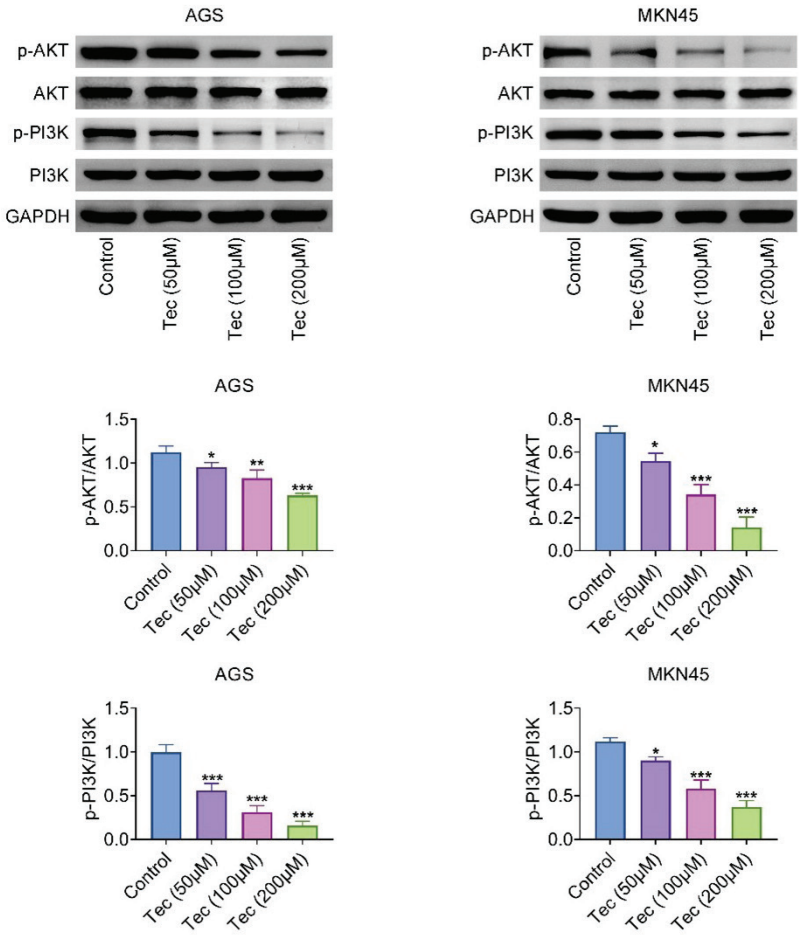

Figure 4. Tec suppressed the PI3K/Akt pathway in gastric cancer cells. Immunoblot assays showed the effects of Tec on the phosphorylation of PI3K and AKT and total expression of PI3K and AKT in AGS and MKN45 cells at the concentration of 50, 100, and 200 μM for 24 h. The assays were performed three times. Data were represented as mean ± SD. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

treatment at the concentration of 15 mg/kg after 2 weeks (Figure 5A). However, we found there was no difference in body weight between Tec treatment and control group, suggesting that Tec did not affect the status of mice (Figure 5B). Therefore, Tec suppressed tumor growth of gastric cancer cells in mice.

Discussion

Drug treatment is one of the most commonly used methods for treating gastric cancer, mainly when gastric cancer develops to the advanced stage, and most patients will be treated with drugs (Yamamoto *et al.*, 2023). The commonly used drugs for treating gastric cancer include fluorouracil, platinum-based, taxoid, irinotecan, and anthracyclines (Zhao *et al.*, 2022). When some standard chemotherapeutic drugs do not work, targeted and precise therapy drugs may work. At present, the prognosis of advanced gastric cancer is poor. Chemotherapy resistance is also a complex problem (Ooki & Yamaguchi, 2022). In recent years, the antitumor mechanism of natural active substances has been widely recognized, and related drugs are increasingly applied in clinical practice, which also has excellent prospects for treating advanced gastric cancer (Hu, Wang, Wang, & Xie, 2023). Through a series of experiments, we noticed that Tec could serve as a drug for treating gastric cancer.

Tec mainly treats acute hepatitis (Y. Chen *et al.*, 2008). It is an essential ingredient in a folk remedy for liver cirrhosis (Wang *et al.*, 2020). Tectorigenin could also mediate the adipogenic differentiation and adipocytokines secretion via PPARγ and IKK/NF-κB pathway (Li *et al.*, 2015). Tec alleviated intrahepatic cholestasis by suppressing hepatic inflammation and bile accumulation by mediating the PPARγ pathway (Xiang *et al.*, 2021). Tec also mediates the motility and apoptosis in dexamethasone-stimulated airway epithelial cells via activating miR-222-3p (Qian, Xiao, & Li, 2021). Here, we noticed that Tec inhibited gastric cancer cell proliferation. In vitro experiments demonstrated that Tec

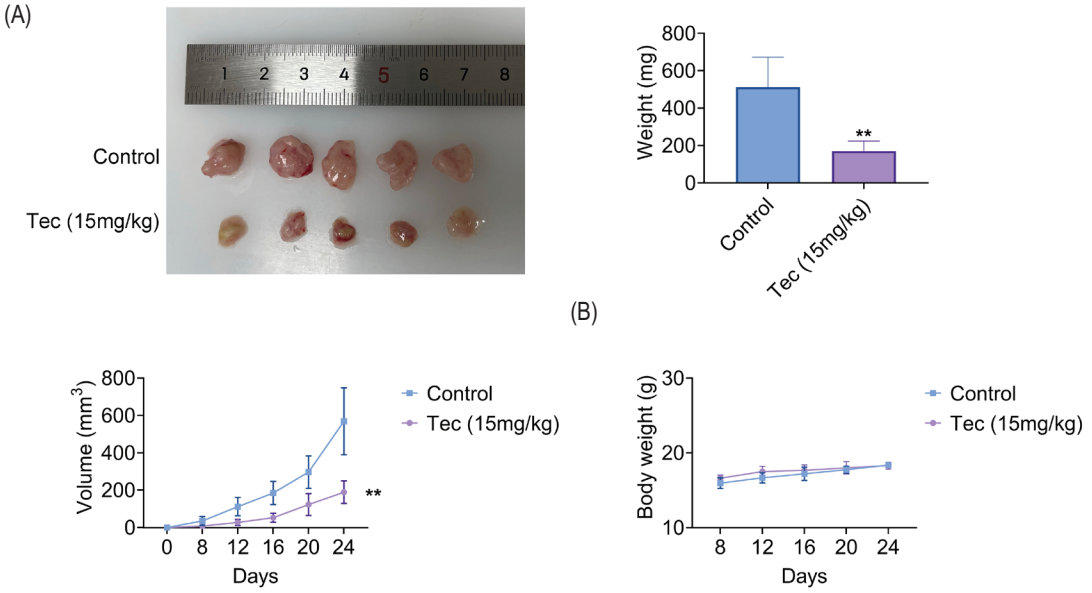

Figure 5. Tec suppressed tumor growth of gastric cancer cells in mice. (A) Tumor formation assays (6 mice in each group) showed the tumor from mice in Tec and control groups every 4 days until 24 days. The tumor growth curves and weight were calculated and analyzed. (B). The body weight in each group was shown. Data were represented as mean ± SD. *$p<0.05$, **$p<0.01$.

inhibited the motility of gastric cancer cells, similar to the results of previously reported studies.

Tec plays a crucial role in combating tumor progression. Tec could ablate the inflammation-induced EMT in a human lung carcinoma co-culture model, suggesting the anti-tumor activity of Tec (Qian *et al*., 2021). Tec could also suppress glioblastoma cell proliferation by stimulating G0/G1 cell cycle arrest (Yeh *et al*., 2020). Previous studies have demonstrated that Tec has the effect of inhibiting tumor cell proliferation. Two kinds of tumor cells were treated with Tec in the MTT assay. The three compounds inhibited the growth of human gastric cancer cells (BGC) and human lymphoid leukemia cells (HL-60) at concentrations of 10 μg/ml and 100 μg/ml. Tec inhibited the invasion of colon cancer cell Caco-2 by down-regulating NF-κB (Liu *et al*., 2019). Here, we also noticed that Tec inhibited gastric cancer cell growth *in vivo* and *in vitro* by affecting the cell cycle and inhibiting the activation of the PI3K/AKT pathway. We thought it could serve as a drug for treating gastric cancer. However, a high concentration of Tec treatment also suppressed the proliferation of normal cell lines (Data not shown). They suggested that a high Tec concentration had some toxicity for both normal and tumor cells. In the in vivo assays, 15 mg/kg Tec was also safe. We found no difference in body weight between the Tec treatment and control group, suggesting that Tec did not affect the status of mice. Next, we should consider the *In vivo* safety profile, like lipid profile and blood serum basic test, to perform the subsequent studies. Therefore, we should use the low concentration of Tec in the subsequent studies.

Conclusion

The *in-vitro* and *in-vivo* models confirmed that Tec inhibited gastric cancer cell proliferation. More experiments demonstrated that Tec inhibited the motility of gastric cancer cells, induced cell apoptosis, and G1 phase arrest, and inhibited the activation of the PI3K/AKT axis. Therefore, Tec could serve as a drug for gastric cancer treatment.

Animal Ethics approval

Ethical approval was obtained from the Huanggang Central Hospital Ethics Committee affiliated with Changjiang University (Approval No.2020-179).

Authors Contribution

Conceptualization, Wenchong Song; methodology, Wenchong Song; software, Weiwei Lv validation, Wenchong Song and Weiwei Lv.; formal analysis, Wenchong Song.; investigation, Wenchong Song.; resources, Weiwei Lv; data curation, Weiwei Lv.; writing—original draft preparation, Wenchong Song.; writing—review and editing, Guanglin Wang; visualization, Guanglin Wang; supervision, Weiwei Lv; project

administration, Guanglin Wang All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

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

Competing interests

The authors state that there are no conflict of interest to declare.

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