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Cycloartenol attenuates cell motion and angiogenesis by regulating VEGFA/VEGFR2 signaling pathway in gastric cancer

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Abstract. Xiaotansanjiefang, a traditional Chinese medicine formula containing pinellia rhizomes, is investigated for anti-gastric cancer (GC) activity. Cycloartenol, a triterpenoid saponin from pinellia, exhibits emerging anti-tumor properties. This study evaluates its effects on GC cell migration, invasion, and angiogenesis. Cytotoxicity of cycloartenol (0–160 μM) was assessed in GC cells (AGS and MKN-45) and immortalized normal gastric epithelial cells (GES-1) *via* MTT assays. Colony formation, wound healing, and Transwell assays were conducted to assess proliferation, migration, and invasion. Angiogenesis was evaluated by HUVEC tube formation using conditioned media harvested from cycloartenol-treated GC cells. VEGFA and VEGFR2 protein levels were measured by Western blotting. Cycloartenol showed dose-dependent cytotoxicity in GC cells with minimal toxicity toward GES-1 cells, indicating selectivity. It suppressed colony formation, delayed wound closure, reduced invading cells, and inhibited HUVEC tube formation. Consistently, cycloartenol downregulated VEGFA and VEGFR2 expression in GC cells and HUVECs. In conclusion, cycloartenol selectively suppresses GC cell growth, migration, invasion, and angiogenesis through inactivation of the VEGFA/VEGFR2 pathway.

Key words: Angiogenesis — Cycloartenol — Gastric cancer — VEGFA — VEGFR2

Introduction

Gastric cancer (GC) is among the most lethal malignancies worldwide, ranking fifth in global incidence and fourth in cancer-related mortality (López et al. 2023; Hu et al. 2024). As a primary epithelial neoplasm arising from the gastric mucosa, GC is influenced by various risk factors, such as Helicobacter pylori infection, high-salt and processed-food diets, low intake of fresh fruits and vegetables, smoking, and advancing age (Yang et al. 2023). Despite advances in diagnosis and treatment, GC continues to impose a major global health burden, with nearly one million new cases diagnosed annually (Xia and Aadam 2022; Sundar et al. 2025).

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Traditional Chinese medicine (TCM) has garnered increasing scientific attention as a source of new or adjunctive therapeutic strategies for cancer (Chen et al. 2024; Liu et al. 2024; Sun et al. 2025). Xiaotansanjiefang, a classical TCM formula with over three decades of clinical use in China, is composed of 11 herbal ingredients: *Pinelliae* rhizoma (Ban-xia, 12.7%), Poria cocos (Fu-ling, 12.7%), *Rhizoma arisaematis* (Nan-xing, 12.7%), Galli gigerii endothelium corneum (Ji-nei-jin, 12.7%), *Aurantii fructus immaturus* (Zhi-shi, 8.5%), *Citri reticulatae viride pericarpium* (Chen-pi, 7.6%), Scolopendra (Wu-gong, 7.6%), *Fritillaria cirrhosae bulbus* (Bei-mu, 7.6%), *Semen vrassicae* (Bai-jie-zi, 7.6%), Licorice (Gan-cao, 5.1%), and Scorpio (Quan-xie, 5.1%) (Yan et al. 2014; Ye et al. 2022). Xiaotansanjiefang has shown efficacy in GC treatment in China (Ye et al. 2022). Earlier studies suggested its beneficial effects in patients with advanced stage GC (Yan et al. 2014). Furthermore, animal experiments revealed its ability to inhibit tumor growth

and suppress angiogenesis (Yan et al. 2014). These findings underscore the need to dissect its active constituents and underlying molecular mechanism. *Pinelliae* rhizome constitutes a pharmacologically critical component of this formula. Notably, its ethanol extract suppress growth of SGC7901 cells in a concentration-dependent manner, concomitant with intracellular acidification and extracellular alkalinization, which is phenomena linked to disrupted pH homeostasis and impaired tumor metabolism (Zhang et al. 2011). Cycloartenol, a triterpenoid isolated from pinellia rhizomes (Zheng et al. 2007), has demonstrated broad-spectrum anti-tumor activity effects (Niu et al. 2018). It induces cell cycle arrest and p38 MAPK-dependent apoptosis in glioma U87 cells (Niu et al. 2018). Nevertheless, the role of cycloartenol in GC cell malignancy remains unknown.

Given that Xiaotansanjiefang inhibits angiogenesis in GC and its bioactive triterpenoid constituent cycloartenol has anticancer potential, this study investigated the effects of cycloartenol on GC cell migration, invasion, and endothelial tube formation (a functional surrogate of angiogenesis). Angiogenesis enables tumors to access nutrients and carry out metabolic processes, which can ultimately promote tumor metastasis (Liu et al. 2023). *In vivo*, this process is initiated by tumor-secreted pro-angiogenic factors, most notably vascular endothelial growth factor A (VEGFA), which binds to its high-affinity receptor VEGFR2 on endothelial cells to trigger downstream signaling cascades governing proliferation, migration, and permeability (Rudno-Rudzińska et al. 2017). The VEGFA/VEGFR2 signaling is the dominant and most therapeutically validated driver of pathological angiogenesis across various malignancies, including GC (Zhang et al. 2019). For example, ACE2 suppresses breast cancer angiogenesis by inhibiting the VEGFA/VEGFR2/ERK signaling pathway (Zhang et al. 2019). Babao Dan suppresses VEGFA-induced angiogenesis by inhibiting the VEGFA/VEGFR2 pathway (Guan et al. 2021). Based on these findings, we hypothesized that cycloartenol exerts anti-metastatic effects in GC, at least in part, *via* the VEGFA/VEGFR2 signaling. This study advances mechanistic understanding of the anti-GC activity of cycloartenol and identifies its potential for future therapeutic exploitation.

Materials and Methods

Cell culture

GC cell lines (AGS and MKN-45), normal human gastric epithelium cells (GES-1), and human umbilical vein endothelial cells (HUVECs) were purchased from Procell (Wuhan, China). Cells were maintained in RPMI-1640 medium (#R20161, OriLeaf, Shanghai, China) with 10% (v/v) fetal bovine serum (#F0193, Sigma Aldrich, St. Louis, USA), along with 100 U/ml penicillin and 100 μg/ml streptomycin (#516106, Millipore, Billerica, USA), under a humidified atmosphere containing 5% CO_2 at 37°C.

Cell treatment

To measure the cytotoxicity of cycloartenol, GES-1 and two GC cell lines were treated with 5, 10, 20, 40, 80, and 160 μM cycloartenol (#HY-N7255, purity ≥ 98%, MedChemExpress, Monmouth Junction, USA) for 24 h. For functional experiments, GC cell lines (MKN-45 and AGS) were exposed to cycloartenol at concentrations of 10, 20, and 40 μM for duration of 24 h. The dosages of cycloartenol and treatment time were identified according to a previous study (Niu et al. 2018), with some modifications.

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

Cell viability was measured using a MTT assay kit (#M1020, Solarbio, Beijing, China). GC cells (MKN-45 and AGS) and gastric epithelial cells (GES-1) were inoculated in 96-well plates for 12 h and subsequently exposed to varying concentrations of cycloartenol (5–160 μM). After 24 h of incubation, 100 μl of MTT solution (0.5 mg/ml) was added to each well and incubated for an additional 4 h. The supernatant was aspirated, and 100 μl of DMSO was added to solubilize the formazan crystals. A microplate reader (EXL800, BioTek Instruments, Winooski, USA) was used to determine the optical density at a wavelength of 570 nm. Cell viability was calculated as the ratio of mean absorbance in the treated group relative to the untreated group.

Colony formation assay

MKN-45 and AGS cells were seeded into 6-well plates (500 cells/well) and cultured for 48 h to allow adhesion. Next, cells were treated with three doses of cycloartenol (10, 20, or 40 μM) for 10 to 14 days. Following incubation, the colonies were fixed using 4% paraformaldehyde (#30525-89-4, Thermo Scientific, Waltham, USA) for 15 min and subsequently stained with a 0.1% crystal violet solution (#32675, Sigma Aldrich) for 30 min at room temperature. Finally, the number of colonies containing more than 50 cells was counted.

Transwell assay

Transwell assays were conducted to evaluate the invasive capacities of GC cells with or without cycloartenol (10, 20, or 40 μM) treatment. The upper chamber was pre-coated with Matrigel (#354248, Corning Incorporated, Corning, USA) diluted at a ratio of 1:8. Next, 3×10^4 cells suspended in serum-free medium were seeded into the upper chamber,

while 750 µl of medium containing 10% fetal bovine serum (#F0193, Sigma Aldrich) was placed in the lower chamber to stimulate cell movement across the membrane. Following 36 h of incubation, the chamber was retrieved, and the cells were fixed with 4% paraformaldehyde (#30525-89-4, Thermo Scientific) for 30 min. Noninvaded cells on the upper surface were removed using cotton swabs, and the invaded cells were stained with 0.1% crystal violet (#32675, Sigma Aldrich) for 20 min. The number of cells in five randomly selected microscopic fields was counted under 100× magnification.

Wound healing assay

GC cells with or without cycloartenol (10, 20, or 40 µM) treatment were seeded to 6-well plates (6×10^5 cells/well). When the cells became fully confluent, a wound was introduced into the monolayer using a 200 µl pipette tip, and any non-adherent cells were removed by washing with phosphate-buffered saline (#P1020, Solarbio). The remaining cells were then maintained in serum-free medium to minimize proliferation. Wound closure was quantified by capturing images at 0 and 24 h post-wounding, and the closure rate was calculated as the percentage reduction in wound area using ImageJ software.

To assess HUVEC migration, GC cells were treated with cycloartenol for 24 h, after which the conditioned medium was collected and applied as a chemoattractant in HUVEC migration assays. The remaining procedures were performed as previously described.

Tube formation assay

Tube formation assays were conducted to assess the effect of cycloartenol on GC cell angiogenesis. AGS and MKN-45 cells were treated with cycloartenol (10, 20, or 40 µM) for 24 h, and the conditioned medium was then harvested. HUVECs were incubated in endothelial cell medium supplemented with the conditioned medium. Subsequently, HUVECs were inoculated at a density of 6×10^5 cells *per* well onto 6-well plates pre-coated with Matrigel (#354248, Corning Incorporated). After 4 h of incubation, the cells were observed under phase-contrast microscopy and analyzed using ImageJ. The luminal structure was assessed based on the tube formation rate. The tube sprouting percentage was calculated as the ratio of the number of sprouted endothelial cells to total number of endothelial cells.

Western blotting

VEGFA and VEGFR2 protein levels in GC cells or HUVECs were analyzed using Western blotting. Cells were cultured in 25 cm^2 flasks (1×10^5 cells/ml) and exposed to cycloartenol (10–40 µM) for 24 h. Next, cells were lysed in RIPA buffer (#R0278, Sigma Aldrich) to extract total protein, and protein concentration was assessed utilizing a bicinchoninic acid assay kit (#C05-02001, Bioss, Beijing, China). The protein samples (50 µg) were loaded onto a 10% SDS-PAGE gel for electrophoretic separation and subsequently transferred to nitrocellulose membranes (#HATF85R, Millipore, Billerica, USA). Subsequently, the membranes were blocked with 5% (w/v) skimmed milk in TBST for 2 h at room temperature, followed by an overnight (16 h) incubation at 4°C with primary antibodies targeting VEGFA (#ab214424, 1:1,000, Abcam), VEGFR2 (#ab134191, 1:1,000, Abcam), and β-actin (#ab213262, 1:1,000, Abcam). After three washes (each lasting 30 min) at ambient temperature, the membranes were incubated with goat anti-rabbit secondary antibody (#ab205718, 1:2,000, Abcam) for 2 h. Protein bands were visualized using Super ECL Star reagent (Beyotime, Shanghai, China), and their intensities were quantified using Image Lab software (Beyotime).

Statistical analysis

Each experiment was conducted in triplicate. GraphPad Prism (version 8) was used for data analysis. Data are shown as the mean ± standard deviation. Due to the small sample size ($n = 3$ *per* group) and the inability to reliably assess normality, non-parametric tests were employed for all statistical analyses. Comparisons between two groups were made using the Mann-Whitney U test. For comparisons involving multiple groups, the Kruskal-Wallis test was first performed, followed by Dunn's *post hoc* test. A p value < 0.05 was considered statistically significant.

Results

Cycloartenol inhibits the proliferation of AGS and MKN-45 cells

MTT assays were performed to investigate the cytotoxicity of cycloartenol ($C_{30}H_{50}O$, Fig. 1A). Figure 1B showed that cycloartenol significantly reduced the viability of GC cells (AGS and MKN-45) with the increasing of doses, with no significant effect observed on the viability of normal gastric epithelial GES-1 cells. The results indicate that cycloartenol may be safe for potential GC treatment. Moreover, the number of GC cell colonies was markedly reduced following treatment with 10–40 µM cycloartenol (MKN-45: 174 ± 15, 132 ± 11, 85 ± 7; AGS: 155 ± 13, 105 ± 9, 75 ± 7) compared to the untreated group (MKN-45: 268 ± 22; AGS: 241 ± 21) (Fig. 1C). The findings suggest the inhibitory effects of cycloartenol on GC cell viability and proliferation.

Cycloartenol suppresses GC cell migration and invasion

Results from wound healing assays revealed that cycloartenol noticeably reduced the wound closure rate in a dose-dependent manner, with the most pronounced effect observed at 40 μM: wound closure was reduced to 36.15 ± 2.15% in MKN-45 cells and 27.12 ± 2.15% in AGS cells relative to the untreated control (set to 100%) (Fig. 2A,B). Moreover, Transwell assays demonstrated a decrease in the number of invaded cells following cycloartenol treatment compared to the untreated group (MKN-45: 264 ± 22; AGS: 284 ± 24) (Fig. 2C). Cycloartenol at the concentration of 40 μM most significantly lowered the cell number to 124 ± 11 and 114 ± 10 in MKN-45 and AGS cells (Fig. 2C). These results indicate the suppressive impact of cycloartenol on GC cell migration and invasion.

Cycloartenol inhibits the migration and angiogenesis of HUVECs

AGS and MKN-45 cells were treated with cycloartenol (10, 20, or 40 μM) for 24 h; the conditioned medium was collected

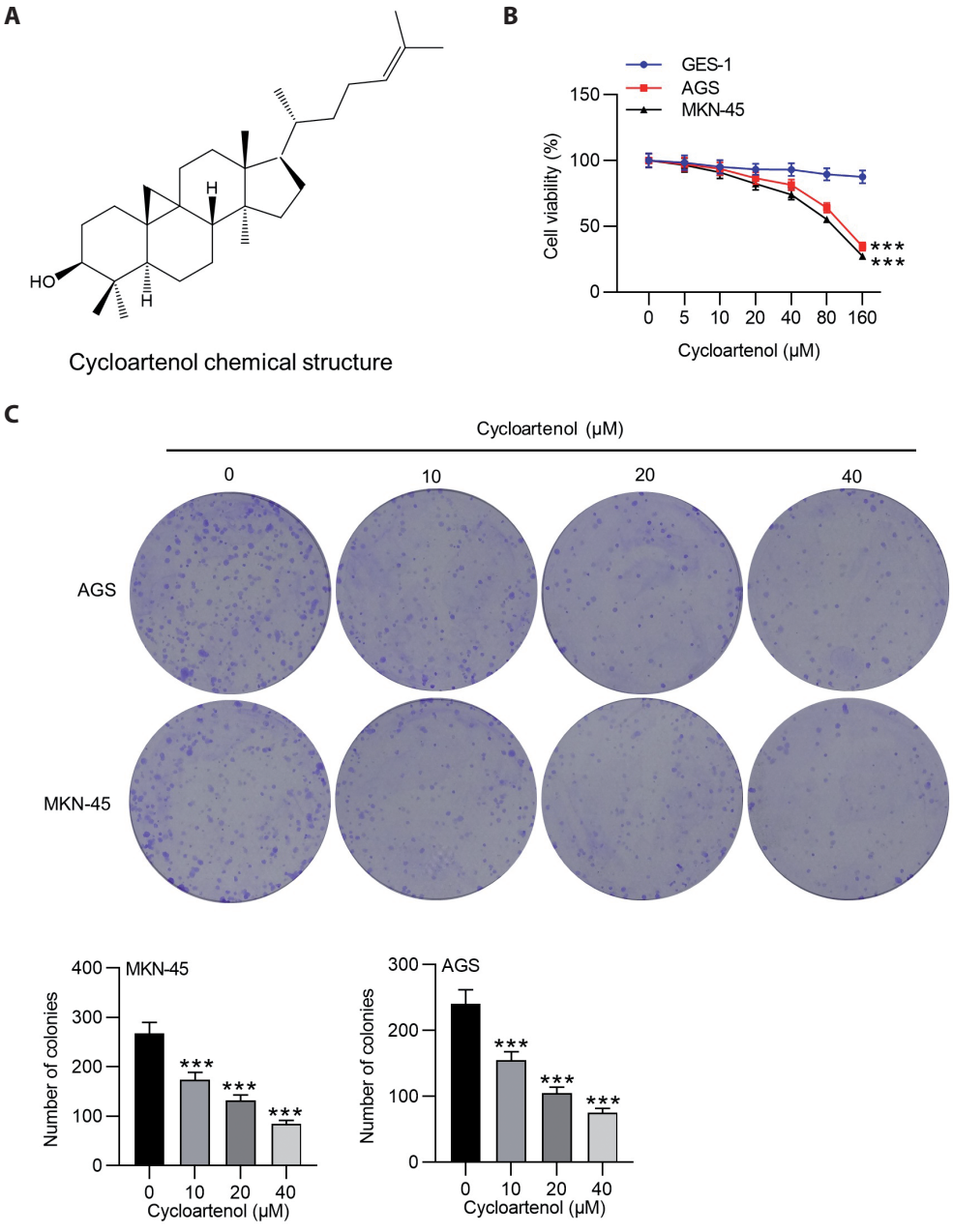

Figure 1. Suppressive effects of cycloartenol on GC cell viability and proliferation. **A.** Chemical structure of cycloartenol ($C_{30}H_{50}O$) was obtained from the MedChemExpress website (https://www.medchemexpress.cn/cycloartenol.html). **B.** MTT assays were conducted to measure the viability of GC cells (AGS and MKN-45) and normal gastric epithelial GES-1 cells treated with 0, 5, 10, 20, 40, 80, and 160 μM cycloartenol. $n = 3$. *** $p < 0.001$ *vs.* GES-1 group. **C.** Colony formation assays were performed to measure the proliferation of AGS and MKN-45 cells treated with 0, 10, 20, and 40 μM cycloartenol. $n = 3$. *** $p < 0.001$ *vs.* untreated control.

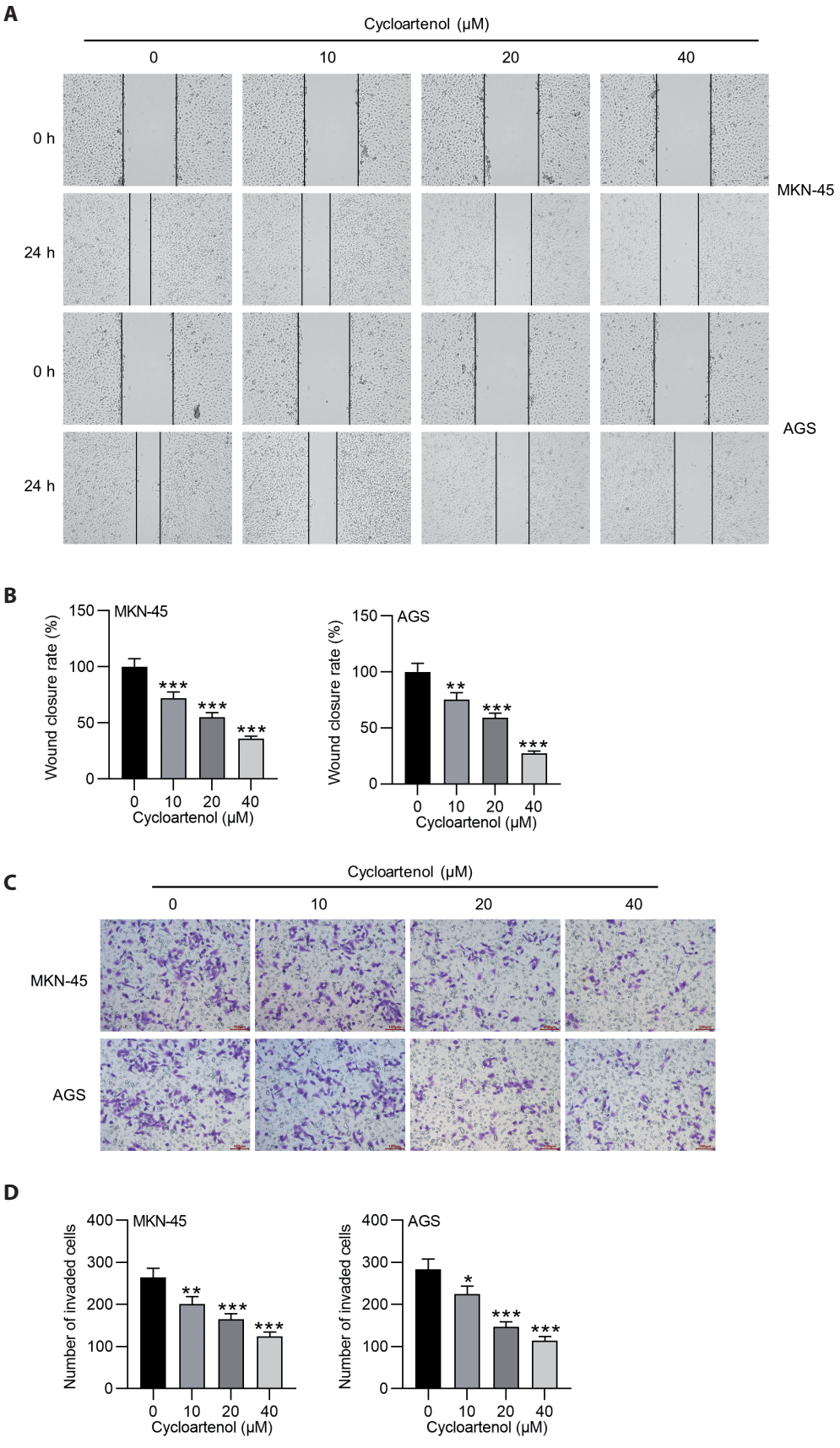

Figure 2. Effects of cycloartenol on GC cell migration and invasion. **A.** Wound healing assays were conducted to measure GC cell migration following treatment of 10–40 μM cycloartenol. **B.** Quantification of wound closure rate in MKN-45 and AGS cells. **C.** Transwell assays were performed to assess effects of cycloartenol on GC cell invasion. **D.** The number of invaded MKN-45 cells and that of AGS cells was calculated. $n = 3$. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs.* untreated control.

and used to supplement endothelial cell medium for HUVEC incubation. As shown by Figure 3A and B, cycloartenol treatment restrained the migration of HUVECs, as evidenced by decreases in wound closure rates compared to the control group. Figure 3C and D revealed that tube sprouting rate of HUVECs co-incubated with conditioned medium from cycloartenol-pretreated GC cells was significantly reduced ($p < 0.001$). In cycloartenol (40 μM) group, the percentages of

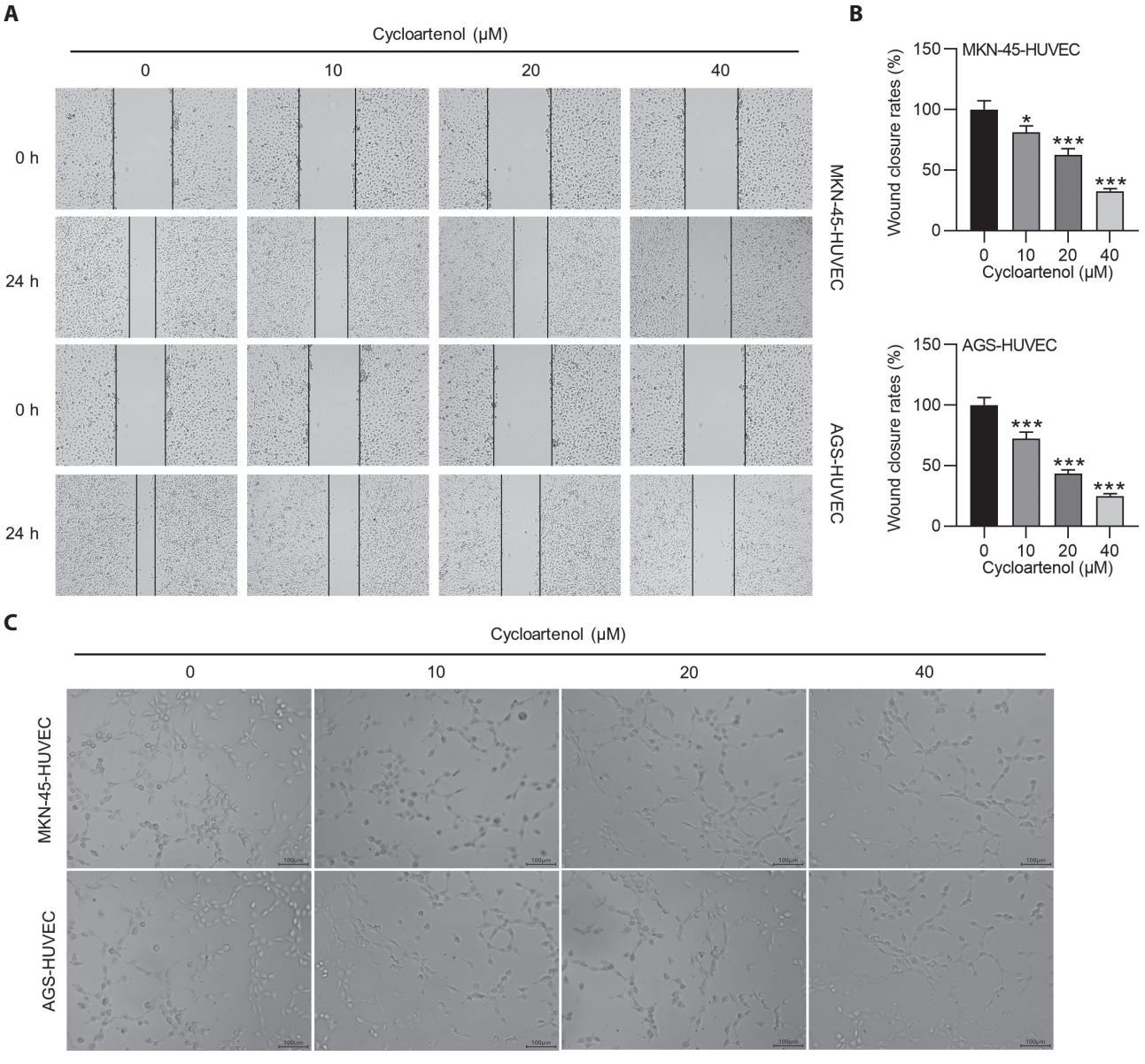

Figure 3. Effects of cycloartenol on HUVEC cell migration and invasion. **A.** Wound healing assays were conducted to assess the migration of HUVECs co-incubated with conditioned medium from cycloartenol-pretreated GC cells. **B.** Calculation of wound closure rates. **C.** Tube formation assays were conducted to measure the angiogenic ability of HUVECs co-incubated with conditioned medium from cycloartenol-pretreated GC cells. **D.** The percentage of tube formation was calculated as (number of sprouted cells / total number of cells) × 100. $n = 3$. * $p < 0.05$, *** $p < 0.001$ *vs.* untreated control.

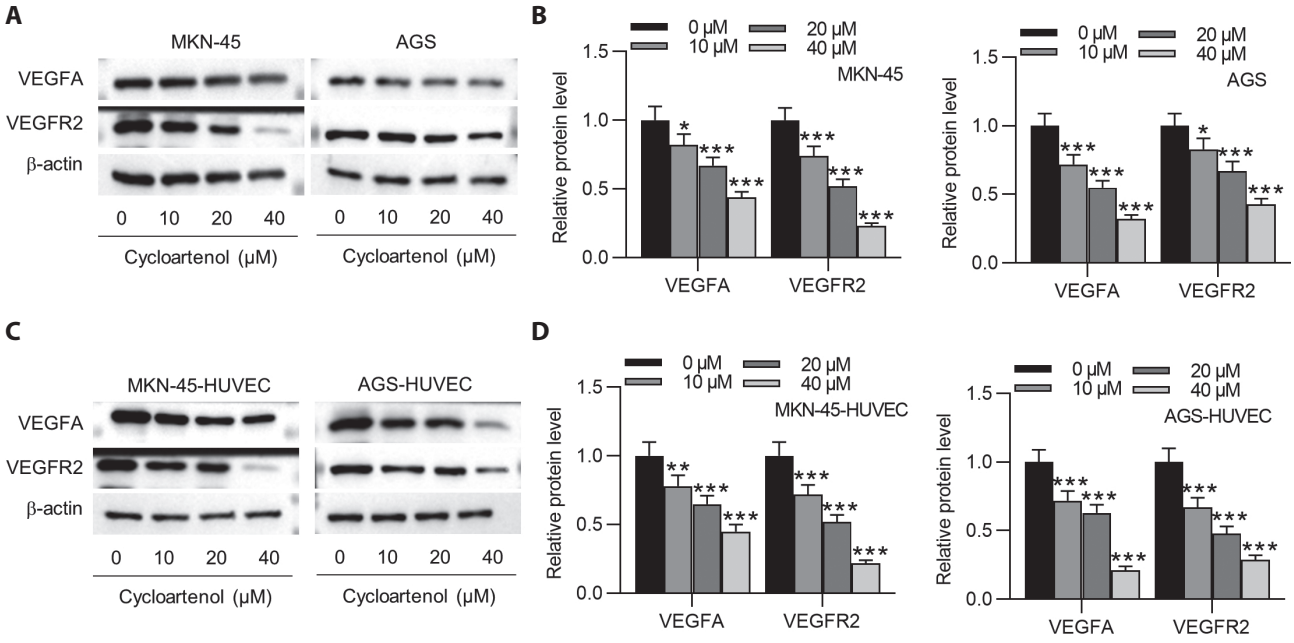

Figure 4. Cycloartenol regulates the VEGFA/VEGFR2 signaling in GC cells. **A.** Western blotting was performed to measure protein levels of VEGFA and VEGFR2 in MKN-45 and AGS cells treated with various doses of cycloartenol. **B.** Relative protein levels of VEGFA and VEGFR2 in GC cells were calculated, with normalization to β-actin. **C.** Protein levels of VEGFA and VEGFR2 in HUVECs co-incubated with conditioned medium from cycloartenol-pretreated GC cells were measured by Western blotting. **D.** Quantification of VEGFA and VEGFR2 in HUVECs (MKN-45) and HUVECs (AGS). $n = 3$. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs.* untreated control.

tube formation in HUVECs (MKN-45) and HUVECs (AGS) were reduced to 36.12 ± 3.22% and 42.3 ± 3.89%, compared to control groups (100 ± 6.25% and 100 ± 6.28%) (Fig. 3C,D). These results indicate the suppressive effects of cycloartenol on HUVEC migration and angiogenesis.

Cycloartenol inactivates the VEGFA/VEGFR2 signaling in GC cells and HUVECs

Given the critical roles of VEGFA and VEGFR2 in angiogenesis and tumor growth (Hou et al. 2021; Chen et al. 2023), we investigated whether cycloartenol suppresses the VEGFA/VEGFR2 signaling axis in GC cells. As shown by Figure 4A–D, protein levels of VEGFA and VEGFR2 were dose-dependently reduced by cycloartenol in GC cells and HUVECs co-incubated with GC cell-conditioned medium. The finding suggests the inhibitory effect of cycloartenol on the VEGFA/VEGFR2 pathway in GC.

Discussion

Recent studies have identified many plant-derived components with anti-GC activity (Tang et al. 2023). For example, solanine, a steroidal glycoalkaloid from Solanum species, suppresses GC cell growth by inhibiting AAMDC/Sesn2 pathway-mediated autophagy (Tang et al. 2023). Triptonoterpene, isolated from Celastrus orbiculatus Thunb, exerts its anti-cancer effect by obstructing GC cell migration, invasion, and epithelial mesenchymal transition (Wang et al. 2022). Consistent with these findings, this study demonstrated that cycloartenol inhibited GC cell proliferation, migration, invasion, and angiogenesis by inactivating the VEGFA/VEGFR2 signaling pathway. This effect aligns with previous evidence revealing the anti-proliferative activity of cycloartenol in glioma cells (Niu et al. 2018).

Tumor angiogenesis, defined as the formation of new blood vessels within solid tumors, supplies nutrients and oxygen to support tumor growth, survival, and metastatic dissemination (Zhang et al. 2019). This process occurs during tumor progression and plays a crucial role in tumor metastasis (Carmeliet and Jain 2011; Giubelan et al. 2023). Upon stimulation by pro-angiogenic molecules released from tumors, such as VEGFs, basic fibroblast growth factors, and matrix metalloproteinases, the blood vessel network expands rapidly and invades adjacent tissues (Herrera-Vargas et al. 2021; Wasik et al. 2024). To date, anti-angiogenic therapies have primarily focused on inhibiting the VEGF/VEGFR signaling pathway to disrupt oxygen and nutrient delivery to the tumor site (Mei et al. 2023; Wang et al. 2023). Among angiogenic factors, VEGFA serves as a powerful stimulator of blood vessel formation. VEGFs must bind to their

corresponding receptor (VEGFR) to initiate downstream signaling cascades that ultimately promote endothelial cell proliferation and migration (Hu et al. 2018; Savage et al. 2019). VEGFR2, a transmembrane glycoprotein, acts as the primary receptor for VEGFA and mediates its downstream angiogenic effects, including endothelial cell survival, invasion, tube formation, and sprouting (Dong et al. 2025). In line with these mechanisms, our findings demonstrated that cycloartenol not only inhibited GC cell growth and migration but also downregulated protein levels of pro-angiogenic factors (VEGFA and VEGFR2).

The limitations of this study include the absence of animal experiments and deeper exploration of molecular mechanisms. Future studies employing xenograft mouse models are warranted to further validate the anti-cancer property of cycloartenol in GC. In addition, further experiments are required to determine the safe dosages of cycloartenol for animal models and clinical applications. Whether cycloartenol directly or indirectly regulates VEGFA and VEGFR2 also merits further investigation. Given the complexity of mechanisms involved in cancer progression, additional studies are needed to elucidate whether cycloartenol inhibits the malignant behavior of GC cells by modulating signaling pathways such as MAPK and PI3K.

In conclusion, this study demonstrates the anti-cancer potential of cycloartenol by attenuating GC cell motility and angiogenesis through inactivation of the VEGFA/VEGFR2 pathway. This is the first study to report the anti-angiogenic properties of cycloartenol in GC cells, highlighting its potential as a promising therapeutic candidate for GC in clinical settings.

Conflicts of interest. The authors declare that they have no competing interests.

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Authors' contributions. CC conceived and designed the experiments. CC, GH and ZF analyzed the data. CC, GH and ZF drafted the manuscript. All authors agreed to be accountable for all aspects of the work. All authors have read and approved the final manuscript.

Data availability statement. The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

References

Carmeliet P, Jain RK (2011): Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases. Nat Rev Drug Discov **10,** 417-427 https://doi.org/10.1038/nrd3455

Chen L, Xie X, Wang T, Xu L, Zhai Z, Wu H, Deng L, Lu Q, Chen Z, Yang X, et al. (2023): ARL13B promotes angiogenesis and glioma growth by activating VEGFA-VEGFR2 signaling. Neuro Oncol **25,** 871-885 https://doi.org/10.1093/neuonc/noac245

Chen Z, Yu T, Wang Y, Li J, Zhang B, Zhou L (2024): Mechanistic insights into the role of traditional Chinese medicine in treating gastric cancer. Front Oncol **14,** 1443686 https://doi.org/10.3389/fonc.2024.1443686

Dong F, Zhou P, Kong F, Cao S, Pan X, Cai S, Chen X, Wang S, Li N, He B, et al. (2025): PCDH17 induces colorectal cancer metastasis by destroying the vascular endothelial barrier. Cell Death Dis **16,** 36 https://doi.org/10.1038/s41419-025-07355-z

Giubelan A, Stancu MI, Honţaru SO, Mălăescu GD, Badea-Voiculescu O, Firoiu C, Mogoantă S (2023): Tumor angiogenesis in gastric cancer. Rom J Morphol Embryol **64,** 311-318 https://doi.org/10.47162/RJME.64.3.03

Guan JH, Cao ZY, Guan B, Wei LH, Peng J, Chen YQ, Sferra TJ, Sankararaman S, Zhan ZX, Lin JM (2021): Effect of Babao Dan on angiogenesis of gastric cancer in vitro by regulating VEGFA/VEGFR2 signaling pathway. Transl Cancer Res **10,** 953-965 https://doi.org/10.21037/tcr-20-2559

Herrera-Vargas AK, García-Rodríguez E, Olea-Flores M, Mendoza-Catalán MA, Flores-Alfaro E, Navarro-Tito N (2021): Pro-angiogenic activity and vasculogenic mimicry in the tumor microenvironment by leptin in cancer. Cytokine Growth Factor Rev **62,** 23-41 https://doi.org/10.1016/j.cytogfr.2021.10.006

Hou JP, Men XB, Yang LY, Han EK, Han CQ, Liu LB (2021): Circ-CCT3 Acts as a sponge of miR-613 to promote tumor growth of pancreatic cancer through regulating VEGFA/VEGFR2 signaling. Balkan Med J **38,** 229-238 https://doi.org/10.5152/balkanmedj.2021.21145

Hu J, Cao J, Huang S, Chen Y (2024): ITGAX promotes gastric cancer progression via epithelial-mesenchymal transition pathway. Front Pharmacol **15,** 1536478 https://doi.org/10.3389/fphar.2024.1536478

Hu S, Liu Y, You T, Zhu L (2018): Semaphorin 7A promotes VEGFA/VEGFR2-mediated angiogenesis and intraplaque neovascularization in ApoE(-/-) mice. Front Physiol **9,** 1718 https://doi.org/10.3389/fphys.2018.01718

Liu Y, Yu X, Shen H, Hong Y, Hu G, Niu W, Ge J, Xuan J, Qin JJ, Li Q (2024): Mechanisms of traditional Chinese medicine in the treatment and prevention of gastric cancer. Phytomedicine **135,** 156003 https://doi.org/10.1016/j.phymed.2024.156003

Liu ZL, Chen HH, Zheng LL, Sun LP, Shi L (2023): Angiogenic signaling pathways and anti-angiogenic therapy for cancer. Signal Transduct Target Ther **8,** 198 https://doi.org/10.1038/s41392-023-01460-1

López MJ, Carbajal J, Alfaro AL, Saravia LG, Zanabria D, Araujo JM, Quispe L, Zevallos A, Buleje JL, Cho CE, et al. (2023): Characteristics of gastric cancer around the world. Crit Rev Oncol Hematol **181,** 103841 https://doi.org/10.1016/j.critrevonc.2022.103841

Mei C, Gong W, Wang X, Lv Y, Zhang Y, Wu S, Zhu C (2023): Anti-angiogenic therapy in ovarian cancer: Current understandings

and prospects of precision medicine. Front Pharmacol **14,** 1147717
https://doi.org/10.3389/fphar.2023.1147717

Niu H, Li X, Yang A, Jin Z, Wang X, Wang Q, Yu C, Wei Z, Dou C (2018): Cycloartenol exerts anti-proliferative effects on glioma U87 cells via induction of cell cycle arrest and p38 MAPK-mediated apoptosis. J Buon **23,** 1840-1845

Rudno-Rudzińska J, Kielan W, Frejlich E, Kotulski K, Hap W, Kurnol K, Dzierżek P, Zawadzki M, Hałoń A (2017): A review on Eph/ephrin, angiogenesis and lymphangiogenesis in gastric, colorectal and pancreatic cancers. Chin J Cancer Res **29,** 303-312
https://doi.org/10.21147/j.issn.1000-9604.2017.04.03

Savage AM, Kurusamy S, Chen Y, Jiang Z, Chhabria K, MacDonald RB, Kim HR, Wilson HL, van Eeden FJM, Armesilla AL, et al. (2019): tmem33 is essential for VEGF-mediated endothelial calcium oscillations and angiogenesis. Nat Commun **10,** 732
https://doi.org/10.1038/s41467-019-08590-7

Sun S, Yu W, Zhang G, Li X, Song L, Lv Y, Chen Y (2025): Potential mechanism of traditional Chinese medicine intervention in gastric cancer: targeted regulation of autophagy. Front Pharmacol **16,** 1548672
https://doi.org/10.3389/fphar.2025.1548672

Sundar R, Nakayama I, Markar SR, Shitara K, van Laarhoven HWM, Janjigian YY, Smyth EC (2025): Gastric cancer. Lancet **405,** 2087-2102
https://doi.org/10.1016/S0140-6736(25)00052-2

Tang X, Guo Y, Zhang S, Wang X, Teng Y, Jin Q, Jin Q, Shen W, Wang R (2023): Solanine represses gastric cancer growth by mediating autophagy through AAMDC/MYC/ATF4/Sesn2 signaling pathway. Drug Des Devel Ther **17,** 389-402
https://doi.org/10.2147/DDDT.S389764

Wang H, Luo Y, Hu Y, Feng X, Feng J, Chu Z, Ou S, Dai X, Wang X, Liu Y (2022): Triptonoterpene, a natural product from Celastrus orbiculatus Thunb, has biological activity against the metastasis of gastric cancer cells. Molecules **27,** 8005
https://doi.org/10.3390/molecules27228005

Wang L, Liu WQ, Broussy S, Han B, Fang H (2023): Recent advances of anti-angiogenic inhibitors targeting VEGF/VEGFR axis. Front Pharmacol **14,** 1307860
https://doi.org/10.3389/fphar.2023.1307860

Wasik A, Podhorska-Okolow M, Dziegiel P, Piotrowska A, Kulus MJ, Kmiecik A, Ratajczak-Wielgomas K (2024): Correlation between periostin expression and pro-angiogenic factors in non-small-cell lung carcinoma. Cells **13,** 1406
https://doi.org/10.3390/cells13171406

Xia JY, Aadam AA (2022): Advances in screening and detection of gastric cancer. J Surg Oncol **125,** 1104-1109
https://doi.org/10.1002/jso.26844

Yan B, Liu L, Zhao Y, Xiu LJ, Sun DZ, Liu X, Lu Y, Shi J, Zhang YC, Li YJ, et al. (2014): Xiaotan Sanjie decoction attenuates tumor angiogenesis by manipulating Notch-1-regulated proliferation of gastric cancer stem-like cells. World J Gastroenterol **20,** 13105-13118
https://doi.org/10.3748/wjg.v20.i36.13105

Yang WJ, Zhao HP, Yu Y, Wang JH, Guo L, Liu JY, Pu J, Lv J (2023): Updates on global epidemiology, risk and prognostic factors of gastric cancer. World J Gastroenterol **29,** 2452-2468
https://doi.org/10.3748/wjg.v29.i16.2452

Ye M, Du J, Wang X, Xiu L, Liu X, Gu Y, Pei B, Sun D, Yue X (2022): Xiaotansanjiefang inhibits the viability of colorectal cancer cells via Jagged 1/Notch 3/Snail signaling pathway. Environ Toxicol **37,** 2957-2964
https://doi.org/10.1002/tox.23651

Zhang CA, Wu F, Mao ZJ, Wei Z, Li YJ, Wei PK (2011): Effects of ethanol extract of Rhizome Pinelliae Preparata on intracellular pH value of human gastric adenocarcinoma cells. Zhong Xi Yi Jie He Xue Bao **9,** 894-900
https://doi.org/10.3736/jcim20110812

Zhang Q, Lu S, Li T, Yu L, Zhang Y, Zeng H, Qian X, Bi J, Lin Y (2019): ACE2 inhibits breast cancer angiogenesis via suppressing the VEGFa/VEGFR2/ERK pathway. J Exp Clin Cancer Res **38,** 173
https://doi.org/10.1186/s13046-019-1156-5

Zheng XB, Chen KL, Yin WZ, Zhang WF (2007): Analysis of lipid compounds of high-yielded rhizoma pinelliae growing in the west of Hubei province by gas chromatography-mass spectrometry. Zhong Yao Cai **30,** 665-667

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