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Research

Polydatin inhibits the stemness and angiogenesis of gastric cancer cells by targeting down-regulation of HDAC7

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Received: 5 November 2024 / Accepted: 24 April 2025
Published online: 14 May 2025

Abstract
Gastric cancer (GC) is a prevalent malignancy of gastrointestinal tract with a high incidence worldwide. Polydatin, a bioactive compound in *Polygonum cuspidatum*, possesses antitumor effects. We aimed to study the role of polydatin in GC and its possible mechanism. HGC27 cells were treated with varying doses of polydatin, and cell viability was tested by CCK-8 assay. Colony formation assay and immunofluorescence staining of Ki67 were employed to evaluate the proliferation of HGC27 cells. Sphere formation assay was conducted to analyze the stemness of HGC27 cells and levels of genes related to stemness was tested by RT-qPCR and immunoblotting. Additionally, angiogenesis was assessed by performing tube formation assay and examining VEGF secretion. Then, histone deacetylase 7 (HDAC7) was upregulated in polydatin-treated HGC27 cells to explore the regulatory effect of polydatin on HDAC7. Results suggested that polydatin gradually reduced the viability and suppressed the proliferation of HGC27 cells with the increase of polydatin concentrations. Notably, polydatin dose-dependently decreased sphere formation in size, accompanied by downregulated SOX2 and OCT4 levels. Besides, the conditioned medium from polydatin treated HGC27 cells resulted in decreased VEGF secretion levels and tube formation capacities. Importantly, Super-PRED database and molecular docking predicted that HDAC7 was a downstream target that could combine with polydatin. Bioinformatics analysis indicated that HDAC7 expression was elevated in GC tissues and high HDAC7 expression predicted low prognosis. Moreover, polydatin downregulated HDAC7 expression in HGC27 cells. Particularly, HDAC7 upregulation blocked the influences of polydatin on proliferation, stemness and angiogenesis of HGC27 cells. Collectively, polydatin inhibits the stemness and angiogenesis of GC cells by targeting down-regulation of HDAC7.

Keywords Stemness · Angiogenesis · Polydatin · HDAC7 · Gastric cancer

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-02481-8.

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1 Introduction

Malignancies originating from digestive system are a prevalent type of cancer worldwide, with gastric cancer (GC) predominating [1]. In China, GC ranks fifth in terms of incidence among malignant tumors [2]. It has been estimated that more than 1 million new cases of GC are reported worldwide annually, of which about 40 per cent occur in China [3]. As the fifth leading cause of cancer-associated death in the world, GC poses a major threat to the health of individuals [4, 5]. In recent years, despite significant advancements in GC therapy, the clinical outcome of advanced GC is still unsatisfactory [6]. Therefore, there is a tremendous need to develop effective and reliable therapeutic drugs for GC treatment.

Cancer stem cells (CSCs) are a subpopulation of cancer cells with strong self-renewal and differentiation capacities, which are closely related to the development, metastasis and recurrence of a large number of malignancies including GC [7, 8]. In addition, angiogenesis is a pivotal event in tumorigenesis and progression and is essential for aggressive tumor growth and metastasis [9]. Inhibition of stemness and angiogenesis of GC cells has been developed as effective approaches for GC treatment [10, 11]. Polydatin, a biologically active compound initially separated from *Polygonum cuspidatum*, has been demonstrated to possess multiple excellent biomedical features [12]. In recent years, the antitumor effects of polydatin have garnered enormous concern [13]. It has been soundly evidenced that polydatin exerts inhibitory effects on colon cancer and hepatocellular carcinoma, two important digestive system malignancies [14, 15]. To date, the role of polydatin in GC, another tumor originating from digestive system, remains unclear. Of note, polydatin suppresses the malignant phenotypes and stemness of malignant phenotype cells [16]. Besides, a collection of studies has confirmed that polydatin shows an anti-angiogenic action and reduces the level of vascular endothelial growth factor (VEGF) in human umbilical vein endothelial cells (HUVECs) [17]. Super-PRED database and molecular docking showed the combination between polydatin and HDAC7. Histone deacetylase 7 (HDAC7), one of the 18 members in the HDACs family, has been associated with significant functions in a variety of physiological and pathological processes [18]. In recent years, HDAC7 has emerged as a promising treatment strategy for solid tumors [19]. Particularly, patients with high HDAC7 expression in GC tissues have shorter overall survival [20]. Of note, HDAC7 deficiency inhibits the growth, invasion and migration of GC cells [21]. Therefore, this study was designed to analyze the anti-cancer effect of polydatin on GC and its regulation on HDAC7.

In this work, human gastric cancer cell line HGC27 was exposed to varying concentrations of polydatin to investigate the regulation of polydatin on stemness and angiogenesis of GC cells. Further molecular docking and bioinformatics analysis were conducted to elucidate the downstream target that could be regulated by polydatin.

2 Materials and methods

2.1 Culturing cells and treatment

HGC27 cells and gastric epithelial cells-1 (GES-1) sourced from Cellverse (iCell) Bioscience (Shanghai, China) were grown in DMEM (Gibco, USA) and RPMI-1640 medium (Gibco, USA), respectively. These medium were augmented with 10% FBS (Gibco, USA). The conditions of normally growing cells were 37 °C, 95% air and 5% CO_2. HGC27 cells and GES-1 were exposed to 100, 200 and 300 μM polydatin (Sigma-Aldrich, St. Louis, MO, USA) for 72 h [22].

2.2 Transfection

To upregulate HDAC7 expression, pcDNA3.1 containing HDAC7 (oe-HDAC7) and empty vector pcDNA3.1 (oe-NC) customized by Genechem (Shanghai, China) were introduced to HGC27 cells when the cultured cells reached 80% confluence. Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) was applied for implementing transfection. 48 h post-transfection, cells were harvested for subsequent assays.

2.3 Assay of cell viability

The un-transfected or transfected HGC27 cells were inoculated into 96-well plates for overnight cultivation at 37 °C. After 24, 48 and 72 h of varying doses of polydatin (100, 200 and 300 μM) stimulation, the viability of HGC27 cells was tested by adding 10 μl CCK-8 regent for additional 1 h culturing. The absorbance at 450 nm was examined applying a microplate reader (Bio-Rad, USA).

2.4 Colony formation experiment

HGC27 cells (1000 cells per well) propagated in cultured plates were subjected to treatment with various doses of polydatin (100, 200 and 300 μM) for two weeks. After that, the colonies were washed with PBS and preserved with 4% paraformaldehyde. Following fixation, 0.1% crystal violet was conducted for a period of 15 min. Images were photographed by virtue of a light microscope (Olympus).

2.5 Assessment of Ki67 expression

The treated HGC27 cells were immersed in 4% paraformaldehyde and permeabilized by 0.1% Triton X-100. Afterwards, 5% BSA was employed to block cells. The sections were cultivated with primary antibodies against Ki67 at 4 °C overnight. The next day, cells were probed with Alexa Fluor 488-linked second antibody, and the incubation was continued for 1.5 h. Counter staining of nuclei was performed by DAPI. Results were visualized and photographed with the adoption of a fluorescence microscope (Olympus).

2.6 Sphere formation assay

HGC27 cells (1000 cells per well) were grown in ultra-low-attachment 6-well plates, which were filled with serum-free DMEM that mixed with epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), B27 and insulin. The medium was changed every 3 days. Two weeks later, images of formed spheres were acquired by virtue of a light microscope (Olympus).

2.7 Detection of VEGF secretion

HUVECs (Cellverse (iCell) Bioscience, Shanghai, China) were grown under 5% CO_2 in DMEM mixed with 10% (FBS) at 37 °C. To analyze the levels of VEGF secretion in HGC27 cells, the media of HGC27 cells treated with varying doses of polydatin without or with oe-HDAC7 transfection were collected and used as conditioned medium (CM). A VEGF assay kit was executed for examining VEGF contents in CM. The absorption values were determined with a microplate reader (Bio-Rad, USA).

2.8 Tube formation assay

HUVECs (3×10^4 cells/well) were seeded in 96-well plates coated with Matrigel and cultivated in the CM obtained from the polydatin treated HGC27 cells. After 24 h, the formed tubules were observed and photographed through a light microscope (Olympus).

2.9 Reverse transcription-quantitative PCR (RT-qPCR)

After being prepared from HGC27 cells using TRIzol® reagent (Invitrogen, USA), total RNA was processed with the First Strand cDNA Synthesis Kit to produce cDNA. The template was amplified by qPCR using SYBR Green PCR Master Mix (Takara, Toyobo, Japan) on a ABI 7500 Real-Time PCR System. The $2^{-\Delta\Delta CT}$ equation was used for comparative quantitation [23]. Data were standardized to GAPDH expression.

HDAC7 Primer sequence:	F: 5′-GGCGGCCCTAGAAAGAACAG-3′
	R: 5′-CTTGGGCTTATAGCGCAGCTT-3′

HDAC7 Primer sequence:	F: 5′-GGCGGCCCTAGAAAGAACAG-3′
SOX2 Primer sequence:	F: 5′-GCCGAGTGGAAACTTTTGTCG-3′
	R: 5′-GGCAGCGTGTACTTATCCTTCT-3′
OCT4 Primer sequence:	F: 5′-CTGGGTTGATCCTCGGACCT-3′
	R: 5′-CCATCGGAGTTGCTCTCCA-3′
GAPDH Primer sequence:	F: 5′-GTTACCAGGGCTGCCTTCTC-3′
	R: 5′-ACCAGCTTCCCATTCTCAGC-3′

2.10 Immunoblotting

Proteins extracted from HGC27 cells utilizing RIPA lysis buffer was quantified based on the BCA method. The protein samples were then fractionated by SDS-PAGE and loaded onto PVDF membranes. After being sealed with 5% BSA, the protein bands were reacted with the designated primary antibodies at 4 °C overnight. The next day, these blots underwent incubation with HRP-labeled secondary antibody for 1.5 h. ECL (EMD Millipore) was used to visualize the complexes. The densitometric data was evaluated using ImageJ software.

2.11 Molecular docking and bioinformatics analysis

Super-PRED database (http://prediction.charite.de/) predicted the possible targets of polydatin. The combination between polydatin and HDAC7 was analyzed by molecular docking. In detail, after being downloaded from the Protein Data Bank (PDB) database (https://www.rcsb.org/), the crystal structure of HDAC7 (PDB ID: 3C0Z) was processed by PyMOL v2.2.0 software. The molecular docking between polydatin and HDAC7 was performed using Autodock 4.2. The minimum binding free energy was − 6.3 kcal/mol. Expression of HDAC7 in stomach adenocarcinoma (STAD) tissues ($n = 415$) and normal tissues ($n = 34$) was analyzed using UALCAN database (https://ualcan.path.uab.edu/). Additionally, Kaplan–Meier Plotter database (https://www.kmplot.com/analysis/) analyzed the correlation between HDAC7 expression in GC tissues and prognosis.

2.12 Statistical analysis

Data calculated by GraphPad Prism 8 software (La Jolla, CA, USA) were expressed as mean ± standard deviation. Discrepancies among groups were evaluated applying one-way ANOVA combined with Tukey's post hoc test. A p value of less than 0.05 was set as statistically significant.

3 Results

3.1 Polydatin suppresses the proliferation of GC cells

Firstly, the effects of d various doses of polydatin on the viability of GES-1 and HGC27 cells were detected by CCK-8 assay. As presented in Fig. 1a, polydatin at 100, 200 and 300 μM had no significant effect on GES-1 cell viability. Conversely, the viability of HGC27 cells gradually reduced with the increase of polydatin concentrations. Afterwards, the HGC27 cell growth curve assay and colony formation experiments were conducted to evaluate the proliferation of HGC27 cells after stimulation with polydatin. It could be found from Fig. 1b, c that polydatin dose-dependently decreased the OD value and reduced colony forming ability as comparison to the control group. Consistently, the Ki67 fluorescence intensity was decreased in polydatin-treated groups, especially in the 300 μM polydatin group (Fig. 1d). Above results revealed that polydatin notably repressed GC cell growth and proliferation.

3.2 Polydatin inhibits the stemness and angiogenesis of GC cells

Next, a spheroid-formation experiment was applied for examining the stemness of GC cells. As depicted in Fig. 2a, relative to the control group, polydatin dose-dependently inhibited sphere formation in size. At the same time, RT-qPCR

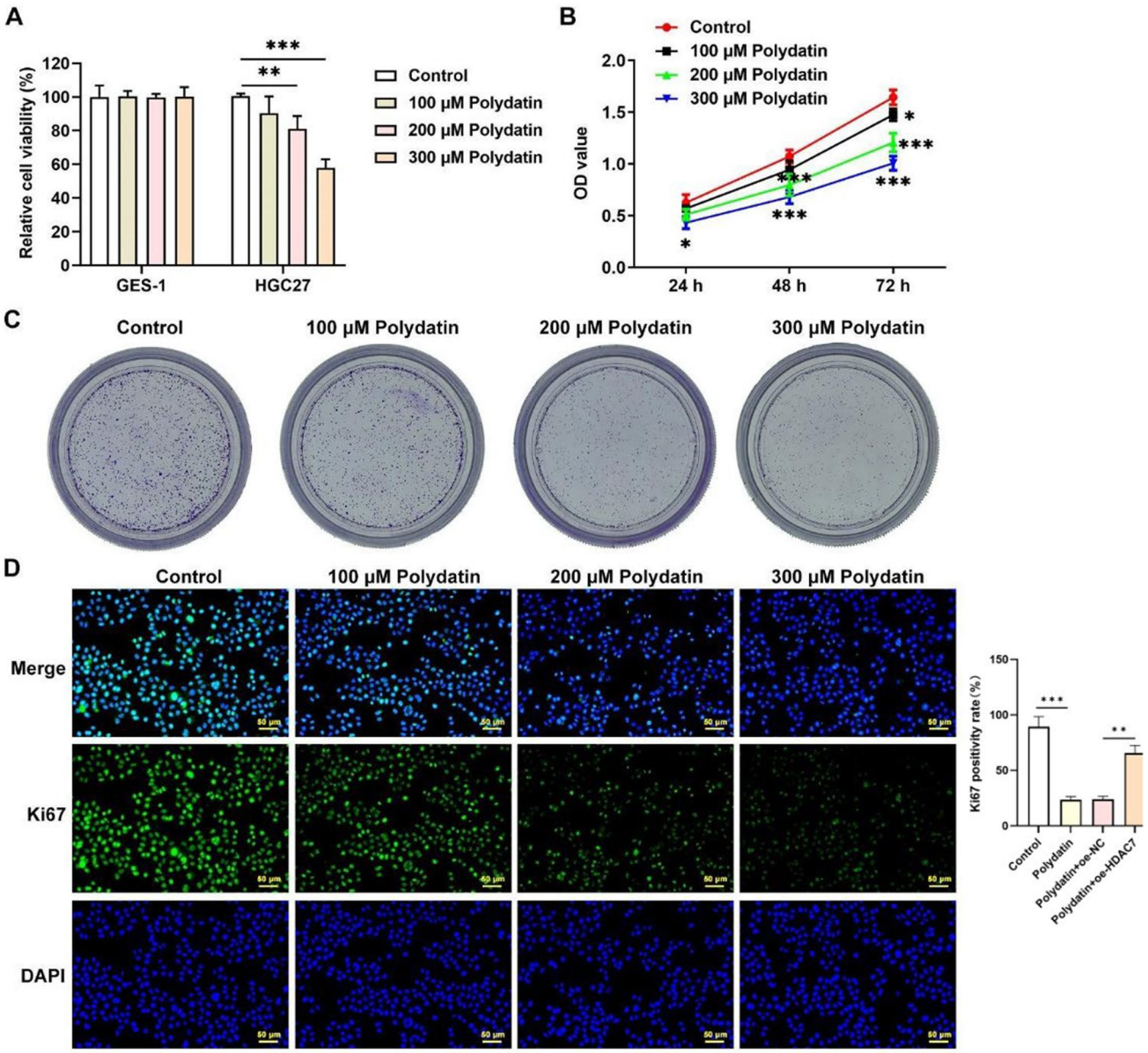


Fig. 1 Polydatin suppressed the proliferation of GC cells. **a** The viability of GES-1 and HGC27 cells treated with various dosages of polydatin was tested through CCK-8 assay. $^{**}p < 0.01$, $^{***}p < 0.001$. **b** CCK-8 assay evaluated the proliferation of HGC27 cells after treatment with polydatin for indicated time. $^{*}p < 0.05$, $^{***}p < 0.001$ versus control. **c** The ability of HGC27 cell proliferation was detected by virtue of colony formation assay. **d** Ki67 expression was assessed using immunofluorescence staining

and immunoblotting provided consistent evidences that polydatin prominently downregulated SOX2 and OCT4 mRNA and protein expression levels, which are two crucial markers of CSCs (Fig. 2b, c) [24]. Moreover, the CM obtained from polydatin treated HGC27 cells resulted in the decreased VEGF secretion levels and reduced tube formation capacities of HUVECs, and the most obvious effects were observed in the high dose group (Fig. 2d, e). These findings showed that polydatin inhibited the stemness and angiogenesis of GC cells.

3.3 Polydatin directly targets HDAC7 and downregulates HDAC7 expression in GC cells

The downstream targets that could combine with polydatin were predicated by Super-PRED database and analyzed by molecular docking. We found that HDAC7 bound to polydatin and the 3D diagram of binding between them was showed in Fig. 3a. Then, HDAC7 expression in STAD tissues was examined with the adoption of UALCAN database. When compared with the normal group, remarkably elevated HDAC7 expression was discovered in the primary tumor tissues

Fig. 2 Polydatin inhibited the stemness and angiogenesis of GC cells. **a** Sphere formation experiment was exploited for examining the sphere-forming capacity of HGC27 cells. **b** RT-qPCR was employed to detect SOX2 and OCT4 mRNA expression in HGC27 cells. **c** Immunoblotting was employed to estimated SOX2 and OCT4 levels in HGC27 cells. **d** VEGF secretion in the corresponding conditioned medium from HGC27 cells was monitored by means of a kit. **e** The capacity of tube formation of HUVECs cultured in the corresponding conditioned medium from HGC27 cells was evaluated. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

(Fig. 3b). Additionally, analysis from Kaplan–Meier Plotter database indicated that high expression of HDAC7 predicted low prognosis (Fig. 3c). Immunoblotting demonstrated that HGC27 cells treated with polydatin exhibited notably down-regulated HDAC7 level, and the most pronounced reduction was found in 300 μM polydatin group (Fig. 3d). Overall, above data suggested that polydatin directly targeted suppression of HDAC7 expression in GC cells.

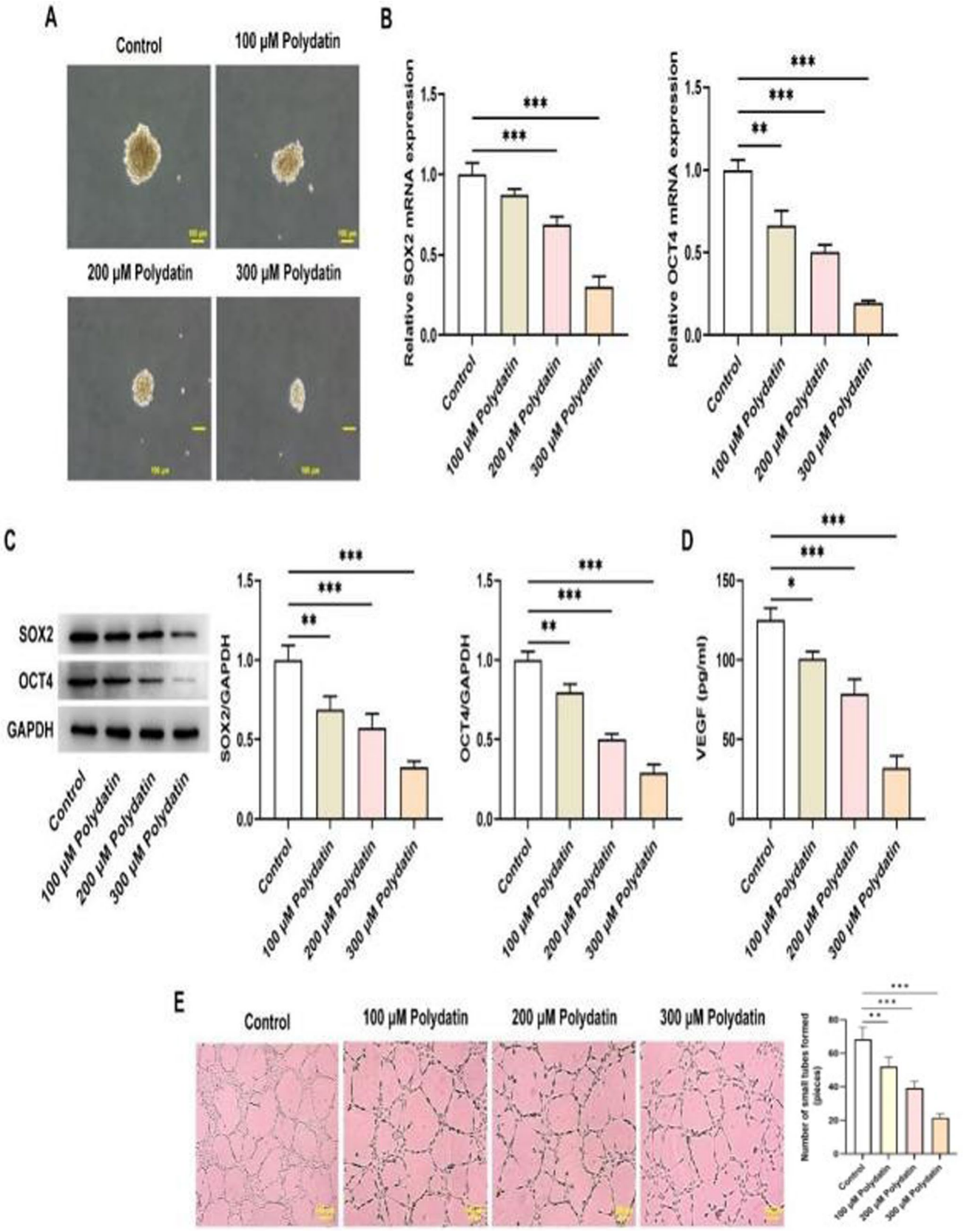
3.4 HDAC7 upregulation blocks the influences of polydatin on proliferation, stemness and angiogenesis of GC cells

HGC27 cells were transfected with oe-HDAC7 and notably elevated HDAC7 mRNA and protein levels were found in the oe-HDAC7 group (Fig. 4a, b). Subsequently, the transfected HGC27 cells were exposed to 300 μM polydatin. As displayed in Fig. 4c, relative to the Polydatin + oe-NC group, enforced HDAC7 expression markedly increased HDAC7 level in HGC27 cells (Fig. 4c). Importantly, the capacity of HGC27 cell proliferation was elevated by oe-HDAC7 transfection, as evidenced by the increased OD value, raised colonies and enhanced Ki67 fluorescence intensity (Fig. 4d–f). Moreover, by contrast with the Polydatin + oe-NC group, remarkably augmented sphere formation in size as well as obvious upregulation in SOX2 and OCT4 mRNA and protein expression levels were observed in the Polydatin + oe-HDAC7 group (Fig. 5a–c). Furthermore, the CM obtained from HDAC7-overexpressed HGC27 cells with polydatin exposure led to the increased VEGF secretion level and elevated tube formation capacities of HUVECs (Fig. 5d, e). To sum up, HDAC7 re-expression abrogated the influences of polydatin on proliferation, stemness and angiogenesis of GC cells.

4 Discussion

As a prevalent malignancy of the gastrointestinal tract, GC has the 5th highest incidence in the world [4]. Currently, the alternative options for GC are lacking, which are usually characterized by poor efficacy and high cost. Chinese herbs has gradually attracted the attention of a wide range of researchers due to its unique efficacy of, low toxicity, minimal side effects and high efficiency [25, 26]. There is no doubt that Chinese herbs are important modality in complementary and alternative medicine. As a natural stilbene commonly found in food, polydatin exhibits excellent ant-cancer effects in multiple tumors [27–29]. Nevertheless, the effect of polydatin on GC is less well studied. In this work, we assessed the role of polydatin in GC by exposing HGC27 cells to varying doses of polydatin. We demonstrated that polydatin repressed the stemness and angiogenesis of GC cells, which might be attributed to the targeted inhibition of HDAC7.

The tumor microenvironment (TME), a highly dynamic cellular environment, is composed of multiple elements, such as immune and inflammatory cells, cancer-associated fibroblasts, nearby stromal tissue, and tumor blood vessels [30, 31]. CSCs are a subpopulation of tumor cells with stem-like properties to self-renewal and differentiation, which are implicated in tumor development, metastasis and recurrence [32]. CSCs are intricately interconnected with their environment. They can alter the TME by releasing signaling molecules, enhancing angiogenesis and assisting metastasis. In contrast, cells within the TME and the factors they secrete can enhance the self-renewal and stemness of CSCs, stimulate angiogenesis, attract immune cells, and promote tumor metastasis [33]. As reported, gastric cancer CSCs (GCSCs) are first identified in 2007 [34]. Since then, a large body of literature have suggested that targeting GCSCs may be an effective approach for GC treatment [35–37]. Studies have attached great importance of Chinese herbs to regulate the stemness of GC cells. For instances, Tanshinone IIA, Cinobufacini and 4-Bromo-Resveratrol have been confirmed to repress the stemness of GC cells [38–40]. SOX2 and OCT4, two essential transcriptional regulators maintaining embryonic stem cell properties, have been demonstrated to be upregulated in CSCs and can serve as markers of CSCs [41, 42]. Importantly, notably high SOX2 and OCT4 levels have been discovered in GC tissues and cells [43, 44]. The inflammation and metastatic potential associated with the TME can be counteracted by Polydatin [45]. Polydatin radiosensitizes lung cancer while preventing radiation injuries by modulating tumor-infiltrating B cells [46]. It is noteworthy that polydatin suppresses the malignant phenotypes and stemness of malignant phenotype cells [16]. Polydatin enhances the radiosensitivity via facilitating apoptosis of colorectal cancer stem cells [47]. In this study, polydatin dose-dependently inhibited sphere formation and


A
Control
100 μM Polydatin
200 μM Polydatin
300 μM Polydatin
B
Relative SOX2 mRNA expression
Relative OCT4 mRNA expression
Control
100 μM Polydatin
200 μM Polydatin
300 μM Polydatin
C
SOX2
OCT4
GAPDH
SOX2/GAPDH
OCT4/GAPDH
D
VEGF (pg/ml)
E
Number of small tubes formed (pieces)

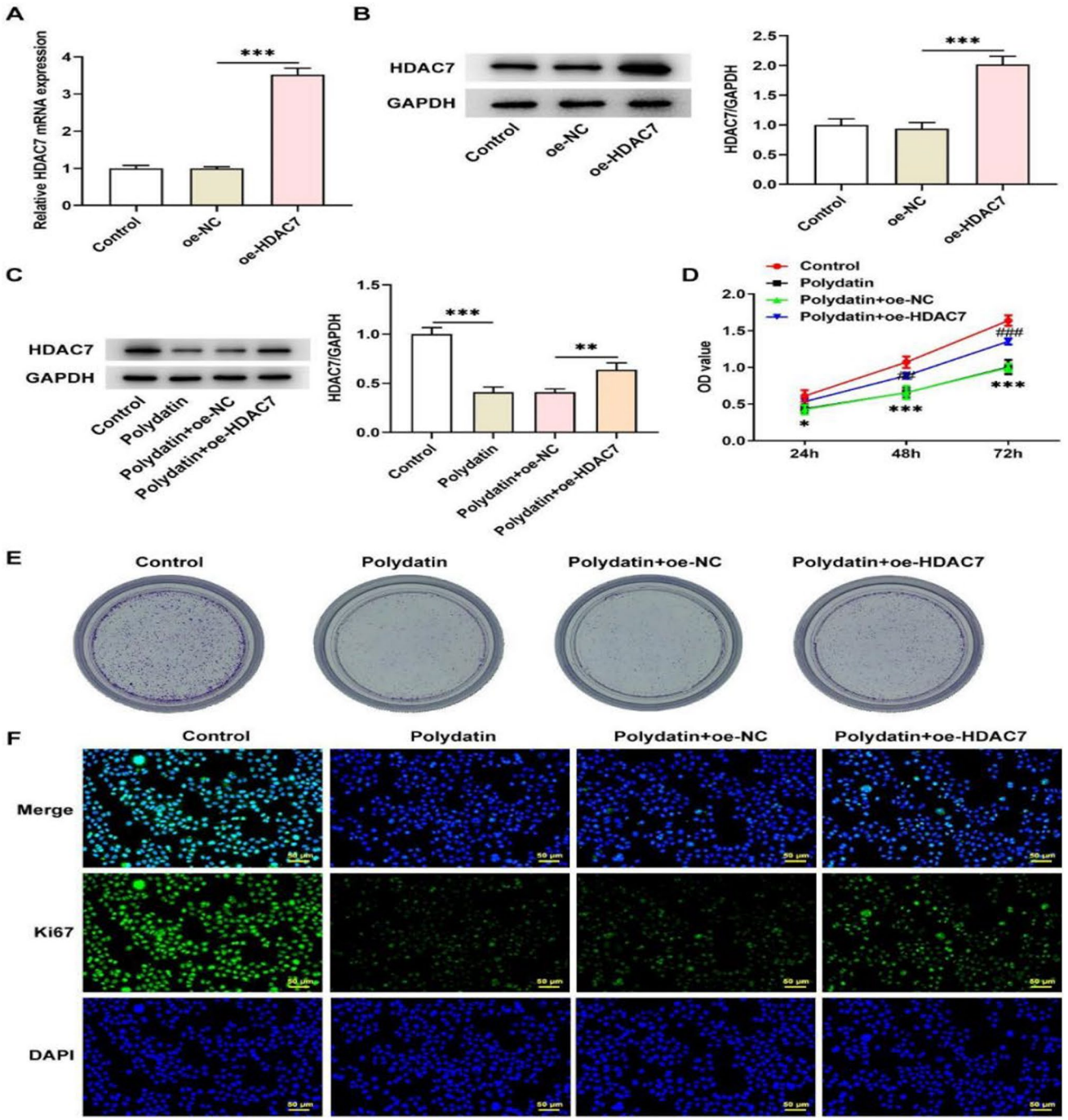


Fig. 3 Polydatin directly targeted HDAC7 and downregulated HDAC7 expression in GC cells. **a** The 3D diagram of binding between polydatin and HDAC7 was analyzed through molecular docking. **b** HDAC7 expression in STAD tissues was examined with the adoption of UALCAN database. **c** Kaplan–Meier Plotter database analyzed the correlation between HDAC7 expression in GC tissues and prognosis. **d** Immunoblotting was employed to estimated HDAC7 level in polydatin-treated HGC27 cells. $^{**}p < 0.01$, $^{***}p < 0.001$

downregulated SOX2 and OCT4 levels in HGC27 cells, suggesting a potential inhibitory effect of polynaringin on the stemness of GC cells.

Angiogenesis is one of the key factors supporting tumor growth and development by providing oxygen and nutrients to tumor cells [48]. Inhibition of cancer angiogenesis has emerged as a new anti-tumor strategy [49]. VEGF, first identified as a vascular permeability factor, is indispensable for angiogenesis. It can be released by tumor cells during the development of tumors and promotes vascular leakage [50]. A growing body of laboratory work has discovered the importance

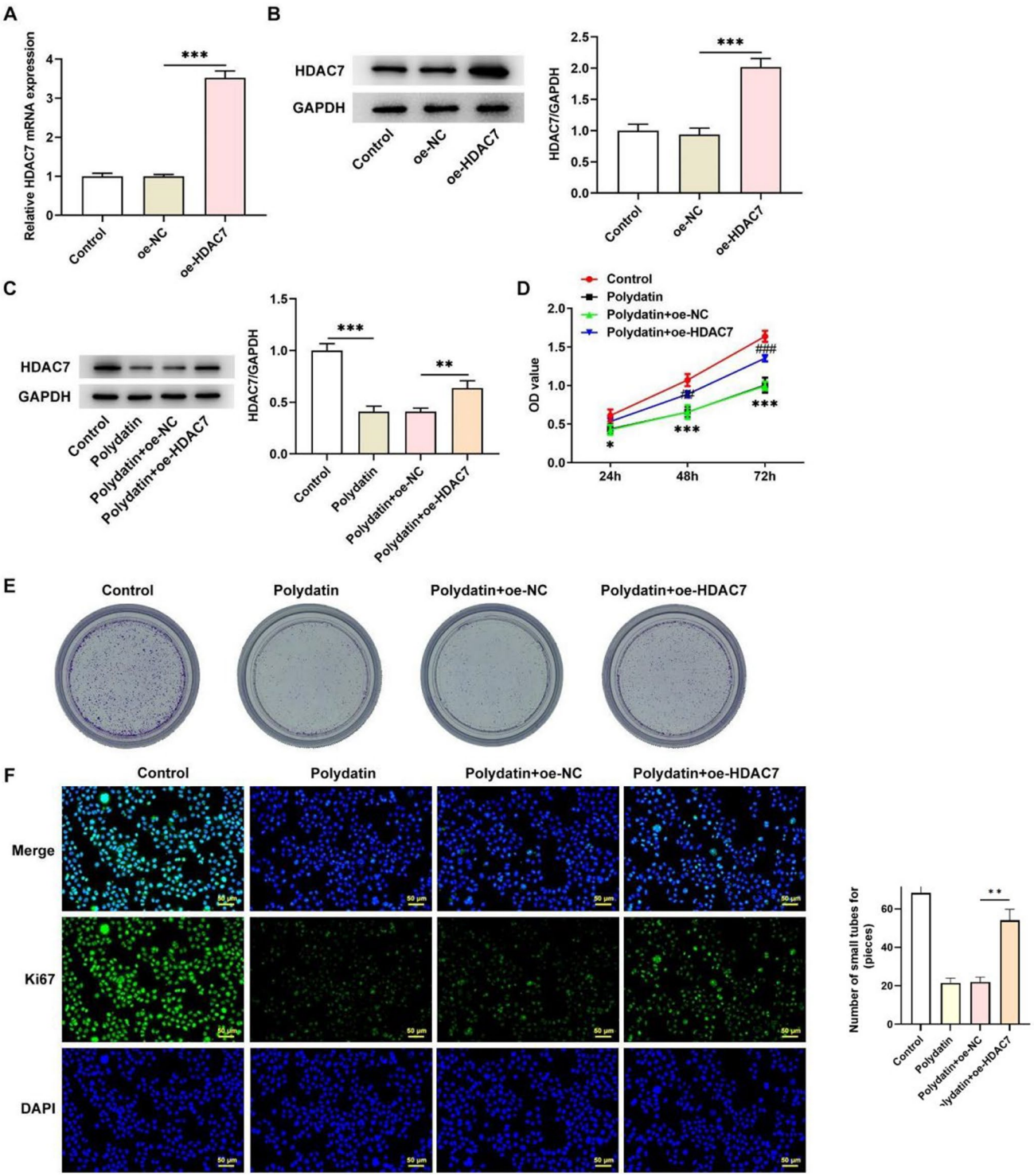


Fig. 4 HDAC7 upregulation blocked the influences of polydatin on proliferation, of GC cells. **a** RT-qPCR and **b** immunoblotting were executed for evaluating HDAC7 levels in HGC27 cells after transfection. **c** Immunoblotting analyzed HDAC7 expression in HDAC7-overexpreesed HGC27 cells with polydatin treatment. $^{**}p < 0.01$, $^{***}p < 0.001$. **d** CCK-8 assay evaluated the proliferation of HGC27 cells. $^{*}p < 0.05$, $^{***}p < 0.001$ versus control; $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ versus Polydatin + oe-NC. **e** The ability of HGC27 cell proliferation was detected by virtue of colony formation assay. **f** Ki67 expression was assessed using immunofluorescence staining

of Chinese herbs in inhibiting angiogenesis in GC [51, 52]. In particular, polydatin shows an anti-angiogenic action and

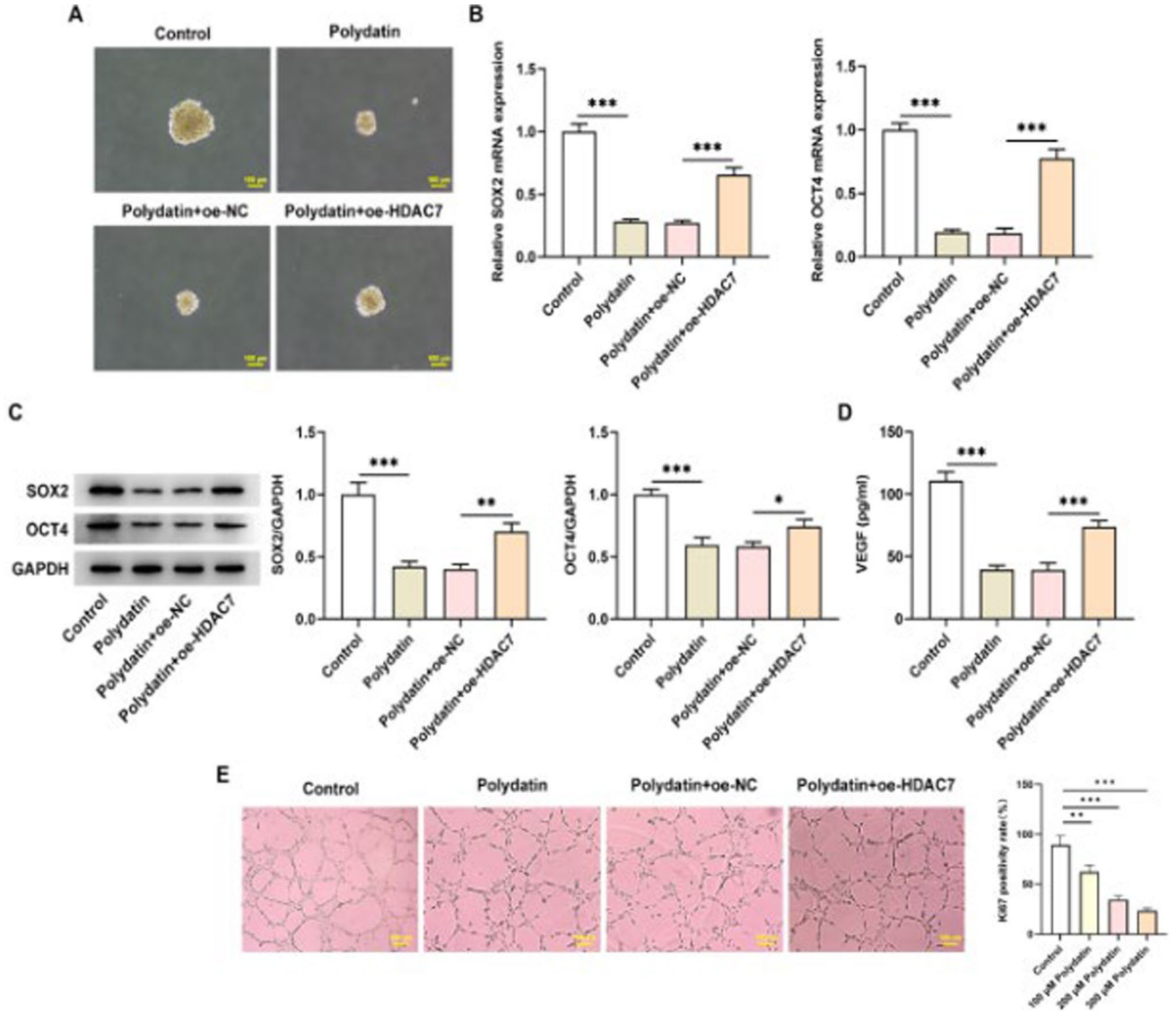


Fig. 5 HDAC7 upregulation abolished the influences of polydatin on stemness and angiogenesis of GC cells. **a** Sphere formation experiment was exploited for examining the sphere-forming capacity of HDAC7-overexpreesed HGC27 cells with polydatin treatment. **b** RT-qPCR was employed to detect SOX2 and OCT4 mRNA expression in HGC27 cells. **c** Immunoblotting was employed to estimated SOX2 and OCT4 levels in HGC27 cells. **d** VEGF secretion in the corresponding conditioned medium from HGC27 cells was monitored by means of a kit. **e** The capacity of tube formation of HUVECs cultured in the corresponding conditioned medium from HGC27 cells was evaluated. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

reduces the level of VEGF in HUVECs [17]. In terms of ovarian cancer, polydatin dose-dependent inhibits the secretion of VEGF in ovarian cancer cells [53]. Our current study confirmed that polydatin decreased VEGF secretion and reduced tube formation capacities of HUVECs, indicating the antiangiogenic effect of polydatin on GC cells.

Super-PRED database and molecular docking showed the combination between polydatin and HDAC7. HDAC7, a member of the histone deacetylase family, is believed to be involved in the development of a variety of cancers [19, 54, 55]. HDAC7-mediated control of TME maintains proliferative and stemness competence of human mammary epithelial cells [45]. The presence of HDAC7 blocks the induction of key genes for macrophage function, such as immune, inflammatory and defense responses [56]. A study conducted by Yu et al. suggested that patients with high HDAC7 expression in gastric cancer tissues have shorter overall survival [20]. In addition, HDAC7 deficiency attenuates the growth, invasion and migration of GC cells [21]. Our results provided consistent evidences that HDAC7 was remarkably elevated in the primary GC tissues and high HDAC7 expression predicted low prognosis. Importantly, a previous research has proven that interference with HDAC7 inhibits the stemness of liver cancer stem cells, as evidenced by downregulated SOX2 and OCT4

expression [57]. HDAC7 has been regarded as a key step in angiogenesis, and HDAC7 knockdown serves as a angiogenesis switch to elevate antiangiogenic genes in non-small cell lung cancer [58, 59]. As reported, HDAC7 contributes to cancer progression via regulating VEGF expression [60]. Mei et al. demonstrated that HDAC7 positively regulates VEGF expression in non-small cell lung cancer [61]. In this work, we found that HDAC7 levels were decreased in a dose-dependent fashion by polydatin in HGC27 cells. Further HDAC7 upregulation blocked the influences of polydatin on proliferation, stemness and angiogenesis of HGC27 cells, revealing that polydatin inhibits the stemness and angiogenesis of GC cells by targeted inhibition of HDAC7.

5 Conclusion

Taken together, we can tentatively conclude that polydatin inhibits the stemness and angiogenesis of GC cells. The above anti-GC effects of polydatin may be achieved by targeted inhibition of HDAC7. Our results might be potential neoadjuvant chemotherapy or an alternative strategy for treating GC patients.

Author contributions Jialin Zhou and Peng Dai contributed to the conception and design of this study. Jialin Zhou and Fucun Zheng analyzed the data and drafted the manuscript. Peng Dai contributed to make the figures and edit the manuscript. All author participated in the experiments. All authors read and approved the final manuscript.

Funding This work was supported by Wuhan Vocational College of Software and Engineering College-level Project (CXTD2024004 and H20230078).

Data availability All the data obtained during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Competing interests The authors declare no competing interests.

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