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Original Research Article

Paeoniflorin Increases Prostaglandin-endoperoxide Synthase 2 to Reduce Inflammation and Inhibit Colon Cancer Tumor Growth

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Abstract

Background: Paeoniflorin, a principal bioactive component of Paeoniae Alba, inhibits liver, gastric, and lung cancers, but its precise role in colon cancer remains unclear.
Objectives: To explore the mechanism by which paeoniflorin inhibits colon cancer cell growth by regulating phosphoinositide 3-kinases–protein kinase B (PI3K–AKT) pathway and prostaglandin-endoper-oxide synthase 2 (PTGS2).
Materials and Methods: With 10 rats in the control group, another 40 rats were induced to develop a model of colon cancer, and they were divided into four groups: model group, PI3K–AKT inhibitor group, low-dose and high-dose paeoniflorin group. After treatment, the colon tissues were stained to observe the pathological change, and the Transwell chamber method and flow cytometry assessed the migration ability and apoptosis rate of colon cancer cells. Interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α levels were detected using enzyme-linked immunosorbent assay (ELISA), and reverse transcription quantitative polymerase chain reaction (RT-qPCR) determined the levels of PI3K, AKT, and prostaglandin-endoperoxide synthase 2 (PTGS2).
Results: Compared with healthy tissues in the control group, a tumor mass appeared in the model group, and the tumor in the PI3K–AKT inhibitor group was even larger than the model group, while the tumor was smaller in the compared paeoniflorin groups, especially the high-dose group. Importantly, PI3K–AKT inhibitor treatment elevated the number of invaded and migrated cells, while paeoniflorin treatment importantly suppressed colon cancer cell migration. PI3K–AKT pathway activity and the concentration of paeoniflorin can affect the apoptosis of colon cancer cells. Inhibiting the pathway decreased the apoptosis rate, while the addition of paeoniflorin dose-dependently induced apoptosis. Moreover, inhibition of PI3K–AKT resulted in an enhancement in IL-6 and TNF-α, but the contents were decreased in the presence of paeoniflorin. Paeoniflorin increased the expression of PI3K and AKT, as well as up-regulated PTGS2 expression; PI3K–AKT inhibitors decreased the expression of PI3K, AKT, and PTGS2.
Conclusion: Paeoniflorin decreases PI3K–AKT activity and promotes the expression of PTGS2 to attenuate inflammatory response, thereby inhibiting the proliferation of colon cancer tumors. Therefore, paeoniflorin may become a new medicinal material for colon cancer treatment.

Keywords

Paeoniflorin, PI3K–AKT pathway, PTGS2, inflammatory response, colon cancer

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Introduction

Colon cancer is cancer starting in the digestive tract, mainly caused by genetics and environmental factors (Benson et al., 2021). Nowadays, the prevalence of colon cancer in China keeps rising due to a hostile environment, diversification of diets, and the possible presence of chemical carcinogens in some foods (Chen & Shen, 2020). Degradation of cellular immune function and imbalance of related factors will trigger colon cancer, and may also be accompanied by an inflammatory response (Fabregas et al., 2022). With the rising incidence rate, the main treatment for colon cancer is surgery and chemotherapy. However, chemotherapy also damages other cells in the body while killing cancer cells, which causes many adverse reactions and even suppresses the immune

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function. Therefore, regimens should be adjusted when patients suffer from adverse reactions during treatment (Taniura et al., 2020). Therefore, current clinical research on colon cancer mainly focuses on finding a mild and effective treatment approach.

Phosphatidylinositol 3-kinase (PI3K), an enzyme in the body, is known to affect tumor cells by combining with other enzymes (Saahene et al., 2021). It participates in cell proliferation, differentiation, and apoptosis-related processes, and also undertakes various cellular functions, such as transporting glucose (Daniel et al., 2020). A combination of PI3K and its downstream protein kinase B (Akt) forms a signaling pathway, as Akt is a product of the proto-oncogene c-Akt and is regulated by PI3K. Akt is involved in PI3K-related signal-mediated processes (Uko et al., 2020). The PI3K–AKT pathway is noted to be related to the generation and proliferation of tumors. Its abnormality will not only cause malignant growth of cells but also may influence various cellular processes, such as the generation of tumor blood vessels and degradation of the extracellular matrix (Li & Gong, 2021). As a central component of the pathway, Akt can control nerve-related activities such as neuron survival, nerve and blood vessel reconstruction, and dendrite-related life activities (Hua et al., 2021).

White peony root, a kind of traditional Chinese herbal medicine made from the roots and branches of Paeoniae Alba, the monoterpene glycosides extracted from the roots of peony plants have immune regulation, anti-depression, anti-thrombosis, and other potent effects, and also play an important role in anti-inflammatory, anti-tumor, and the protection of liver cells. In addition, they can further inhibit the agglutination factors in the blood by inhibiting platelets. It exhibits analgesic and antipyretic activity, harmonizing the liver and spleen, evacuating clots formed by blood stagnation, relieving swelling and pain, and reducing rubella caused by rising blood temperature. Compared with ginseng for tonifying Qi, white peony root is mainly used to tonify blood (Chen et al., 2021; Wang, Peng, et al., 2021). Evidence has shown that it has refreshing and calming, memory-improving, anti-fatigue, anti-radiation, and anti-inflammatory properties, and it can regulate nerve-related endocrine processes (Wu et al., 2023). In recent years, research on the peony has identified a main active ingredient, paeoniflorin, found in Paeoniae Alba. Paeoniflorin is a monoterpene glycoside compound capable of inhibiting inflammatory response, protecting the liver, promoting immune regulation, and protecting nerves and relieving damage caused by chemotherapy (Zhang & Wei, 2020). Paeoniflorin also has a significant inhibitory effect on tumor cells, such as liver cancer, gastric cancer, and lung cancer cells. Besides, paeoniflorin can also improve the therapeutic effect of chemotherapy drugs by changing the drug resistance of some gastric cancer cells and sensitivity to chemotherapy (Wang, Feng, et al., 2021; Zhou, Liu, et al., 2021). Studies have found that paeoniflorin can affect the PI3K–AKT pathway, but the specific mechanism and its possible role in colon cancer are still unclear. Therefore, this article aimed at investigating the mechanism underlying the protective role of paeoniflorin in colon cancer and its interaction with the PI3K–AKT pathway and prostaglandin-endoperoxide synthase 2 (PTGS2). This study, for the first time, reveals the molecular mechanism by which paeoniflorin inhibits the growth of colon cancer through the PI3K–AKT/PTGS2 axis, providing a new drug target and theoretical basis for the treatment of colon cancer.

Materials and Methods

Experimental Reagents, Instruments, and Animals

Reagents and Instruments

1,2-Dimethylhydrazine (DMH) was obtained from Sigma-Aldrich Co., Ltd, paeoniflorin (purity: >98%, batch number: 110736-202145; Xi'an Shennong Bio), extracted from the root of the peony family plant, with immune-regulatory, anti-depressant, anti-thrombotic, and other potent effects; and PI3K–AKT inhibitor LY294002 from Shanghai Zeye Biotechnology Co., Ltd. Other reagents included eosin-hematoxylin (Biolab, Beijing); fetal bovine serum (FBS) (Shenyou Precision, Co., Ltd); phosphate-buffered saline (PBS) (Nanjing Senbega Biotechnology); Dulbecco's modified Eagle's medium (DMEM) medium (Shanghai Yuanpei Co., Ltd); PI staining solution (Wuxi Puhe Biotechnology Co., Ltd); flow cytometry (Jinan Hao Noble Medical Equipment); tumor necrosis factor (TNF)-α and interleukin (IL)-6 enzyme-linked immunosorbent assay (ELISA) kits (Wuhan Elite, Co. Ltd); gel imaging analysis system (Shandong Kangjian Biotechnology Co., Ltd).

Animals

Fifty male mice (8 weeks old, 26 g) were purchased and raised. With 10 mice selected as the control group, the remaining 40 were used to induce the construction of colon cancer models through DMH.

Methods

Establishment of Colon Cancer Model

DMH, an indirect carcinogen, was used in the model construction of this study. Before use, DMH needed to be configured and was mixed with saline. The prepared solution was adjusted with 4% NaOH to keep the pH consistent with that in the mouse, and then filtered to sterilize. The prepared DMH solution was injected into the subcutaneous tissue of the neck and back of mice in the experimental group at 25 mg/kg, and normal saline was administered in the control group every week for 12 weeks. When mice exhibit the following manifestations, the model construction is considered successful: (a) histopathological observation shows tumor formation; (b) the levels of tumor markers significantly increased; (c) weight loss and morphological changes of the colon in mice.

Grouping and Treatment

Experimental groups were divided into four groups: model group, PI3K–AKT inhibitor (LY294002) group, low-dose group, and high-dose paeoniflorin group (n = 10, each group) in which the mice received intraperitoneal injection of LY294002 or 20 mg/kg and 100 mg/kg of paeoniflorin solution every day for a week, respectively.

Hematoxylin Staining

One week after treatment, the mice were anesthetized and sacrificed, and the colon tissues were dissected and removed. The tissues were fixed with 10% formaldehyde solution, dehydrated, and embedded in paraffin. Red-hematoxylin (HE) was used for staining, and the tissues were then placed under a microscope for observation.

Culture of Colon Cancer Cells

Colon cancer cells extracted from rectal cancer tissue were cultured in DMEM high-glucose medium containing 10% FBS.

Detection of Cell Migration Ability

Matrigel was placed in a 4°C refrigerator to melt for 12 h and then transferred to culture medium to dilute (1:8). A 40 μL sample was placed into each upper chamber in a 37°C incubator for 0.5 h. Colon cancer cells were inoculated into DMEM/F12 medium (containing 1% FBS) to make the number of cells 2×10^5/mL, and then inoculated into the upper chamber (100 μL/well). A 500 μL of DMEM/F12 medium was added to the lower chamber, and then stored for 48 h. After storage, the 24-well plate was taken out and washed with PBS to absorb the remainder of the culture medium. The cells were fixed with 4% tissue cell fixative for 0.5 h and then placed on the table to wait for air-drying, followed by 30-min dyeing with crystal violet (0.1%). After successful staining, a cotton swab was used to gently wipe off the tumor cells and Matrigel that had not yet invaded in the upper chamber, then washed with PBS three times. The swab was placed upside down under a microscope to observe and count the invaded cells three times.

Detection of Cell Apoptosis Rate

Cells (10^6) were added to the culture medium (1–2 mL) containing calf serum and centrifuged for 5 min at 2,000 rpm. With the supernatant removed, PBS was added to remake the cell suspension, and the sample was then centrifuged twice. After centrifugation, the cells were suspended and mixed well with 5 μL Annexin V-FITC and 5 μL PI for 15 min, and the apoptosis rate was measured by flow cytometry.

Enzyme-linked Immunosorbent Assay

ELISA was conducted in accordance with the instructions of the TNF-α (Catalog # KHC3011, Thermo Fisher Scientific) and IL-6 (Catalog # EH2IL6, Thermo Fisher Scientific) ELISA kits. The enzyme label strip was added to a 100 μL sample for 120 min incubation and washed four times after culturing. Then the sample was incubated with 100 μL of biotin antibody working solution (1:250) at 25°C for 1 h. After incubation, the working solution was sucked off, and the sample was washed and then mixed with the enzyme-binding working solution (1:100) for 30 min. After washing, the sample was incubated with 50 μL of chromogenic solution for 10 min, followed by the addition of 50 μL of stop solution and immediate measurement of the absorbance value (OD) at 450 nm. TNF-α and IL-6 levels were calculated according to the standard curve.

Reverse Transcription Quantitative Polymerase Chain Reaction

RNA was extracted for RT-qPCR with a 10 μL reaction system in a PCR machine. The expressions were calculated using $2^{-\Delta\Delta CT}$. Primer sequences for PI3K, AKT, and PTGS2 are shown in Table 1.

Western Blot

Cells were inoculated onto a 6-well plate (1×10^5 cells/well). After culturing for 1 day, cells were lysed to obtain protein. Then, the protein obtained was separated by electrophoresis using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to the polyvinylidene fluoride (PVDF) membrane. After blocking, washed the membrane with tris-buffered saline with Tween 20 (TBST). Dilute the rabbit-derived polyclonal antibodies (PI3K, AKT, PTGS2) at a ratio of 1:1,000 and probe at 4°C for 1 day and incubate with secondary antibody (1:5,000) for 2 h. The membrane was placed in enhanced chemiluminescence (ECL) reagent for color development, then photographed with a gel imaging system, and the image was quantitatively analyzed using

Table 1. Primer Sequences of Reverse Transcription Quantitative Polymerase Chain Reaction (RT-qPCR).

Genes	Forward Primer (5′-3′)	Downstream Primers (5′-3′)
PI3K	AGCTGGACCTCAACATCACC	TCCATGTCGTAGCCGTAGTG
AKT	CCTGAGCTGAAGGACCAAGA	GGTGCCACCACACATACAAA
PTGS2	TGCACTATGGTTACAAAAGCG	CTCCATGGTGGTGAAGTGTT
GAPDH	AGGTCGGTGTGAACGGATTTG	GGGGTCGTTGATGGCAACA

Note: GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; PTGS2: Prostaglandin-endoperoxide synthase 2.

ImageJ14.0 software, with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as the internal reference.

Statistical Analysis

Data were analyzed with SPSS 21.0 and GraphPad Prism. The calculated data were displayed as mean ± standard deviation (SD) and assessed by the *F* test and the least significant difference (LSD) method. $p < .05$ indicates a significant difference.

Results

Histopathological Observation of Mouse Colon Cancer

The cell morphology of the tumor mass appeared in the model group, and the tumor mass of the LY294002 group was larger than that of the model group. However, paeoniflorin groups had no obvious tumors. And the mass in the high-dose group was smaller, as shown in Figure 1.

Paeoniflorin Inhibits Cell Migration

The number of migrated cells in the LY294002 group was larger than that of the model group (Figure 2). The treatment with paeoniflorin suppressed colon cell migration, decreasing the number of migrated and invaded cells in a concentration-dependent manner (Figure 3).

Paeoniflorin Promotes Cell Apoptosis

As shown in Figure 4, the PI3K–AKT inhibitor decreased the apoptosis rate of colon cancer cells in the LY294002 group, compared with the model group. Meanwhile, we detected an elevated apoptosis rate in the paeoniflorin groups, with a higher apoptosis rate in the high-dose group.

Paeoniflorin Reduces Interleukin-6 and Tumor Necrosis Factor-α Expression in Colon Cancer Cells

To further assess paeoniflorin's role in colon cancer, we checked the levels of inflammatory factors. The results

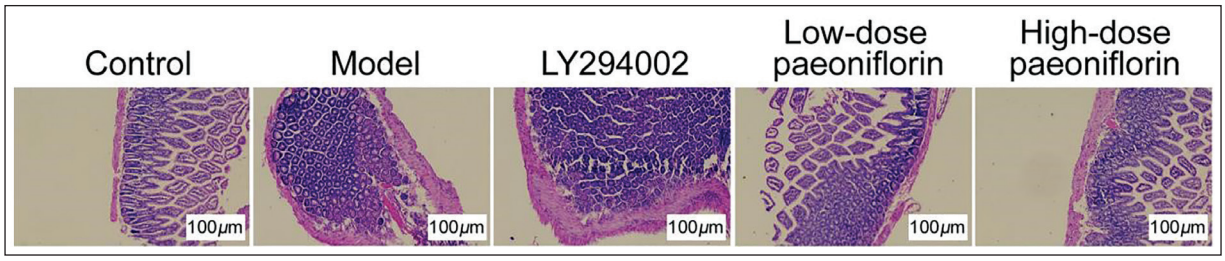


Figure 1. Pathological Observation of Colon Cancer Tissue (400×).

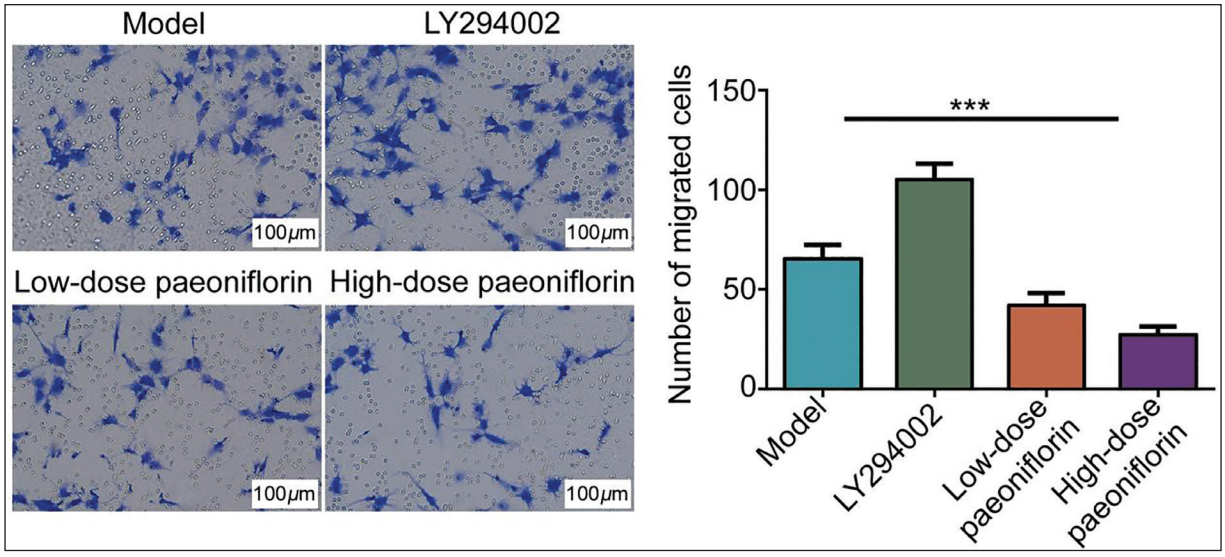


Figure 2. Transwell Migration Assay Analysis of Cell Migration Ability in Each Group (n = 3 ×50 μm).

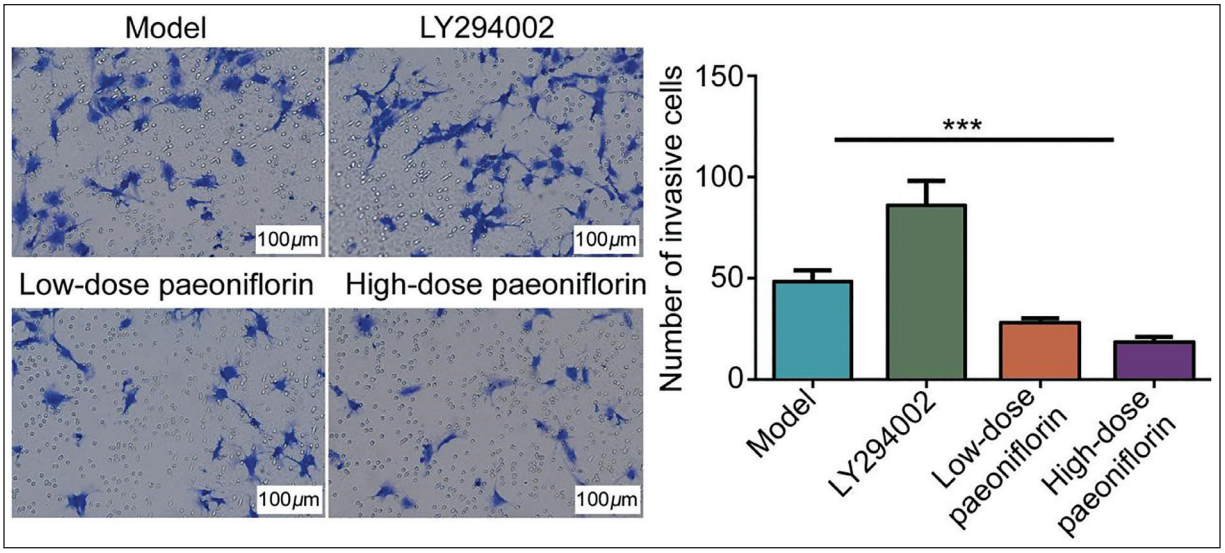


Figure 3. Effects of Paeoniflorin on Cell Invasion and Migration (n = 3).

Note: (A) The number of invasive cells in each group; (B) the number of migrated cells in each group.

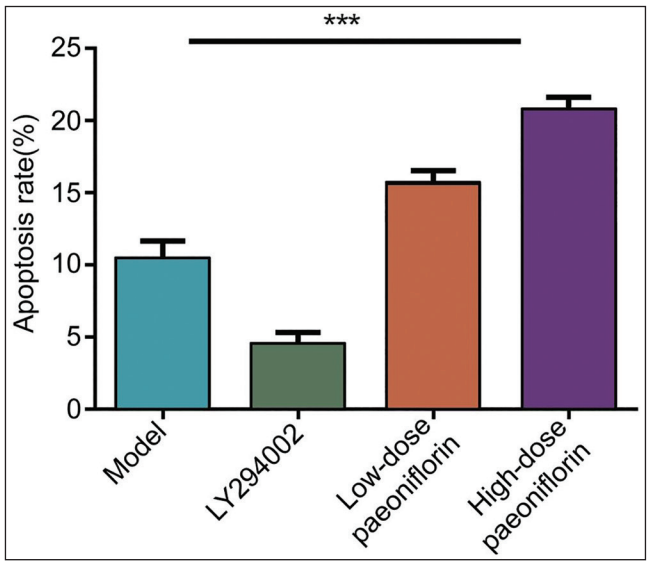


Figure 4. Effects of Paeoniflorin on Apoptotic Rate of Cells (n = 3).

demonstrated IL-6 and TNF-α levels were related to PI3K–AKT activity and the concentration of paeoniflorin. Their levels in the LY294002 group were higher than those of the model group, while those of the paeoniflorin groups were lower, still exceeding those of the control group. Additionally, high-dose paeoniflorin obtained lower levels of the inflammatory factors, as shown in Figure 5.

Paeoniflorin Upregulates PI3K/AKT and PTGS2 mRNA Expression

Compared with the control and model groups, the LY294002 group had lower gene expression of PI3K/AKT and PTGS2. PI3K/AKT and PTGS2 mRNA expressions was restored by administration of paeoniflorin, but the levels were lower than those in the control group. With the increase in concentration, gene expression levels increased, as shown in Figure 6.

Paeoniflorin Increases PI3K/AKT and PTGS2 Protein Expression

Using GAPDH as the internal reference protein, PI3K/AKT and PTGS2 protein levels were reduced in the model group (Figure 7). Treatment with paeoniflorin dose-dependently elevated their levels, while their expressions were decreased in the LY294002 group, as shown in Figure 8.

Discussion

As one of the malignant tumors, colon cancer has a high detection rate and high mortality rate, seriously endangering the lives and health of Chinese residents (Angell et al., 2020). The occurrence of colon cancer is accompanied by the occurrence of an inflammatory response, and tumor necrosis factor, an important cytokine, is related to early inflammatory response (Luoma et al., 2020; Schmitt & Greten, 2021). Petersen and Pedersen (2005) found that the increase in the concentration of the inflammatory factor IL-6 indicates severe infection and inflammatory response, so the levels of these factors are important indicators for assessing the condition. China is rich in resources of traditional Chinese medicine. Research on traditional Chinese medicine has found that some effective monomers contained in traditional Chinese medicine can inhibit the progression of tumor cells; extracting effective monomers is one of the effective ways to produce new anti-cancer drugs (Yao et al., 2021). Paeoniae Alba

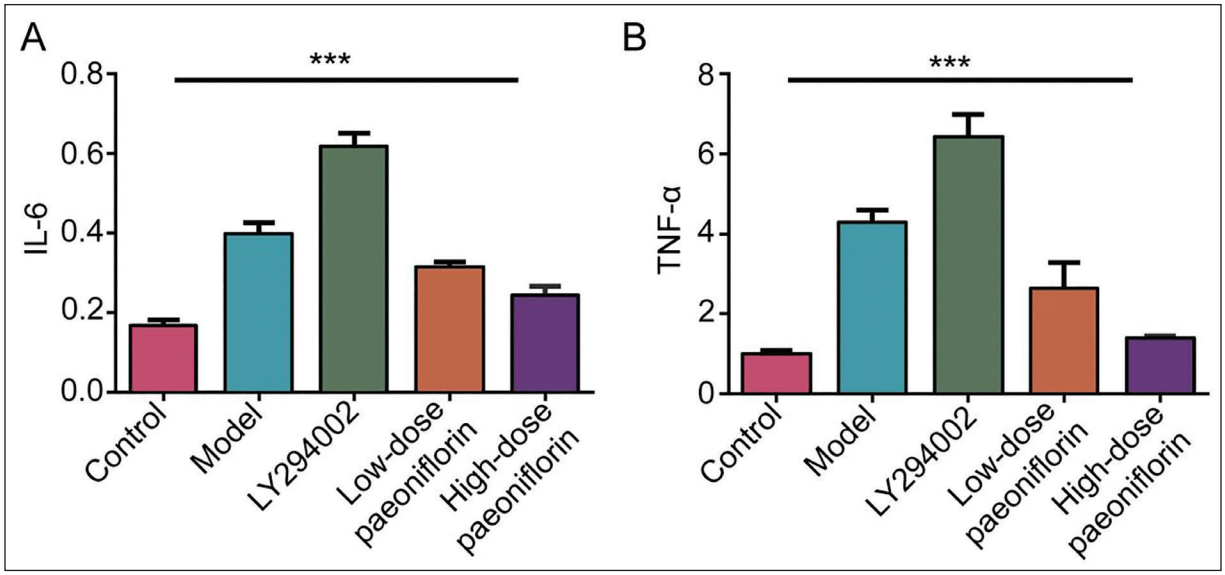


Figure 5. Effects of Paeoniflorin on Levels of Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-α (n = 3).

Note: (A) Intracellular IL-6 concentration in each group; (B) intracellular TNF-α concentration in each group.

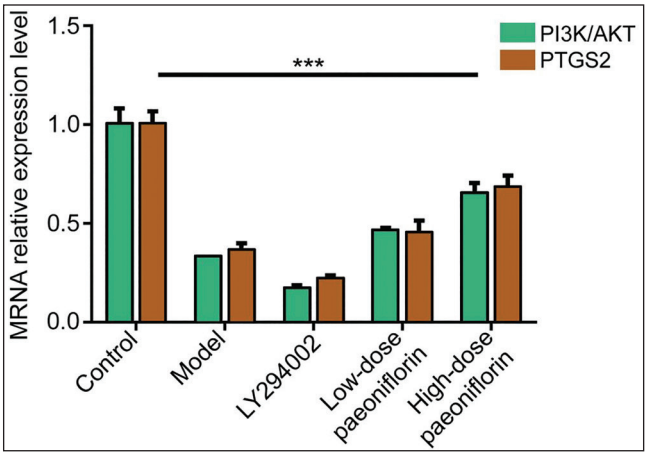


Figure 6. PI3K, AKT, and Prostaglandin-endoperoxide Synthase 2 (PTGS2) mRNA Expression Levels (n = 3). RNA Was Isolated from Cells After Different Treatments, and the mRNA levels of PI3K, AKT, and PTGS2 Were Measured.

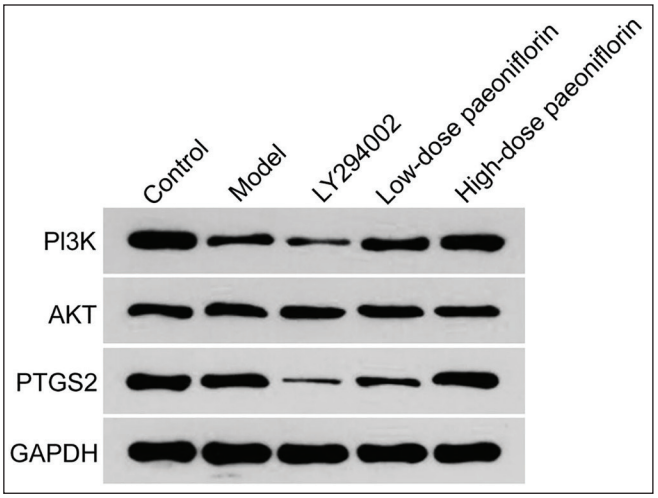


Figure 7. Protein Expression Chart of PI3K/AKT and Prostaglandin-endoperoxide Synthase 2 (PTGS2) in Each Group (n = 3).

is a kind of traditional Chinese medicine, and paeoniflorin is its effective monomer with anti-inflammation, antioxidation, and anti-depression activities (Yan et al., 2022). The study found that the number of tumor masses metastasized from the lungs in mice was significantly reduced after treatment with paeoniflorin, which confirmed that paeoniflorin can inhibit transplanted tumor growth in mice (Tang et al., 2021). Paeoniflorin can not only reduce TNF-α and IL-6 levels but also inhibit the development of tumors. Zhou, Chang, et al. (2021) noted that various signal transduction pathways can regulate the inflammatory response; inflammation and oxygen deficiency will increase the PI3K/AKT activity. The pathway is activated by a conformational change in the dimer of the PI3K protein, which is caused by the binding of growth factors containing phosphorylated tyrosine residues (Xu et al., 2020). Similarly, the production of PIP3 is due to the activation of PI3K. PIP3 can stimulate the phosphorylation of Ser308 in the Akt protein by binding to Akt and PDK1, thereby effectively promoting the activation of Akt (Wang et al., 2022). The activation of Akt will further affect its downstream target proteins to regulate the growth and development of cells (Tsai et al., 2022).

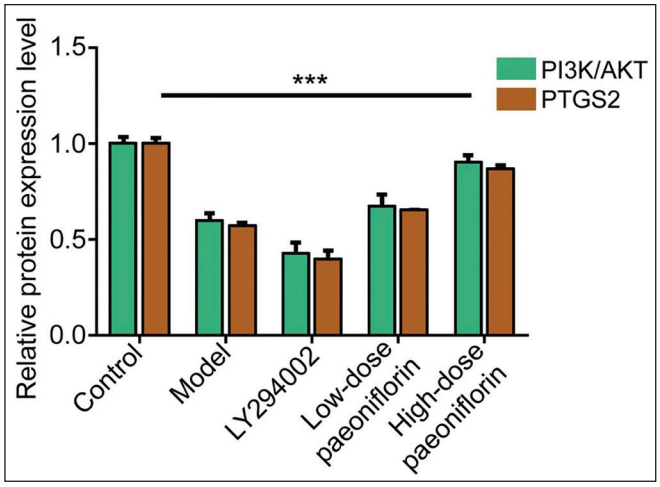


Figure 8. The Relative Protein Content of PI3K/AKT and Prostaglandin-endoperoxide Synthase 2 (PTGS2) in Each Group (n = 3). Protein Was Isolated from Cells After Different Treatments, and the Protein Levels of PI3K, AKT, and PTGS2 Were Measured.

We found that paeoniflorin dose-dependently elevated the apoptosis rate of colon cancer cells, inducing tumor cell apoptosis. The HE staining results supported that the tumor mass almost disappeared upon paeoniflorin treatment, while inhibition of the PI3K–AKT pathway reversely enhanced tumor growth in the LY294002 group.

It can be observed that both PI3K–AKT and paeoniflorin are associated with colon cancer cells. Blockage of the PI3K–AKT pathway will lead to further expansion of tumor cells, while paeoniflorin can inhibit the growth of colon cancer. Inhibiting PI3K–AKT activity increased the invasion and migration of colon cancer cells, but the presence of paeoniflorin suppressed the malignant characteristics of cancer cells. Statistical analysis was performed on the apoptosis data measured by flow cytometry, and confirmed the statistically significant difference ($p < .05$). It can be found that the effect of paeoniflorin on colon cancer cells is dosage-dependent, and the apoptosis rate can reach more than 30% with a high concentration of paeoniflorin. At the same time, the PI3K–AKT activity can also affect the apoptosis of colon cancer cells as well as inflammation. IL-6 and TNF-α decreased with the increase of paeoniflorin concentration; the PI3K–AKT inhibitor increased IL-6 and TNF-α content. This suggests that paeoniflorin alleviates inflammatory response, thereby inhibiting the proliferation of cancer cells, and the blockage of the PI3K–AKT pathway will promote inflammatory response. On the other hand, by detecting the mRNA and protein levels of PI3K, AKT, and PTGS2 in each group, we found that paeoniflorin treatment increased their levels and the PI3K–AKT pathway decreased them, while the levels of the LY294002 group were lower than those of the model group. This shows that paeoniflorin dose-dependently promotes PI3K, AKT, and PTGS2 levels, and the expression of PTGS2 will decrease after LY294002 suppresses the expression of PI3K and AKT. Additionally, our study focused on *in vitro* exploration; however, more mouse models are needed to verify whether *in vivo* studies will yield consistent conclusions.

Conclusion

Taken altogether, paeoniflorin can suppress colon cancer cell growth through promoting PI3K–AKT signaling activity and increasing PTGS2 expression. Then, paeoniflorin combined with PTGS2 reduces the content of inflammatory factors and attenuates the inflammatory response. However, this study also has certain shortcomings: (a) the experiment was only conducted in a mouse model, lacking clinical data support; (b) the influence of paeoniflorin on other signaling pathways was not explored. The safety and toxicity of long-term medication need to be further evaluated. Therefore, further research is still needed in the future to clarify its role and mechanism.

Abbreviations

PI3K–AKT: Phosphoinositide 3-kinases-protein kinase B; PTGS2: Prostaglandin-endoper-oxide synthase 2.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the ethics committee of Taizhou People's Hospital and the ethics committee of The Second Affiliated Hospital of Nanjing University of Chinese Medicine.

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Informed Consent

Not applicable.

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