Paeonol Exerts Anti-angiogenic and Anti-metastatic Activities through Downmodulation of Akt Activation and Inactivation of Matrix Metalloproteinases

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Paeonol (2’-hydroxy-4’-methoxyacetophenone) is known to possess anti-inflammatory and anti-proliferative activities. Recently there is evidence that anti-inflammatory agents may be useful in the setting of angiogenesis-related diseases. Thus in the present study the anti-angiogenic activity of paeonol and its mechanism were investigated in vitro and in vivo. Paeonol significantly inhibited proliferation of basic fibroblast growth factor (bFGF)-stimulated human umbilical vein endothelial cells (HUVECs). Paeonol also significantly inhibited migration and tube formation of bFGF-stimulated HUVECs in vitro. In addition, paeonol significantly suppressed neovessel formation on bFGF-treated chick chorioallantoic membrane (CAM) and disrupted bFGF-induced neovascularization in Matrigel plug assay in vivo. Furthermore, paeonol downregulated Akt phosphorylation in bFGF-stimulated HUVECs and reduced expression of matrix metalloproteinases-2 and -9 in HT1080 human fibrosarcoma cells. The Akt inhibitor LY294002 synergistically potentiated paeonol-induced inactivation of Akt and vascular endothelial growth factor in bFGF-treated HUVECs. Taken together, these findings suggest that paeonol can be a potent suppressor of angiogenesis and metastasis partially through inhibition of Akt signaling pathway and matrix metalloproteinase activity.

Key words paeonol; basic fibroblast growth factor; human umbilical vein endothelial cell; angiogenesis; Akt

Recently, many chemopreventive agents have been developed from medicinal plants, rich sources of phytochemicals.¹ Paeonol is a major phenolic component isolated from the root of Paeonia suffruticosa Andr., Moutan Cortex, which has been frequently used for treatment of blood stasis and inflammation as a folk remedy.² Paeonol was reported to have anti-inflammatory³ and analgesic⁴ effects through the suppression of tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and prostaglandin E₂ (PGE₂) production in a rat model of carrageenan-evoked thermal hyperalgesia. Paeonol is also known to exhibit anticancer activity against esophageal carcinoma, hepatocellular carcinoma, colorectal carcinoma, and leukemia.⁵–¹⁰ Even though there is evidence that angiogenesis mediates tumor development and metastasis, the anti-angiogenic mechanism of paeonol was not examined until now. Recent studies have suggested that anti-inflammatory agents exert substantial protective effects on tumor promotion by blocking expression of matrix metalloproteinases (MMPs) such as MMP-2 (72 kDa) and MMP-9 (92 kDa).¹¹ MMPs have been implicated in primary and metastatic tumor growth and angiogenesis, and may contribute to tumor promotion.¹²,¹³ Selected inhibition of MMPs thus represents another important strategy for cancer prevention or treatment.¹³,¹⁴

Basic fibroblast growth factor (bFGF) is an angiogenic growth factor that induces endothelial cell replication, migration, and extracellular proteolysis similarly to vascular endothelial growth factor (VEGF).¹⁵–¹⁷ Besides, bFGF has autocrine activities on angiogenesis at all stages.¹⁸–²⁰ and promotes angiogenesis both by a direct effect on endothelial cells and indirectly by upregulating VEGF in endothelial cells.²¹,²² Despite previous evidence gained of anti-inflammatory and anti-tumor effects of paeonol, the anti-angiogenic and anti-metastatic mechanism of paeonol was not investigated until now. Thus in the present study we evaluated anti-angiogenic and anti-metastatic activities in in vitro angiogenesis-related experiments, chick chorioallantoic membrane (CAM) assay, and Matrigel plug assay and elucidated the molecular mechanism in in bFGF-treated human umbilical vein endothelial cells (HUVECs).

MATERIALS AND METHODS

Materials Paeonol (2-hydroxy 4-methoxy acetophenone, see Fig. 1), Drabkin reagent kit 525, heparin, and gelatin were purchased from Sigma Chemical (St. Louis, MO, U.S.A.). Recombinant human bFGF was purchased from R&D Systems (Minneapolis, MN, U.S.A.). M199, fetal bovine serum (FBS), and antibiotic-antimycotic were bought from Gibco (Grand Island, NY, U.S.A.). 5-Bromo-2’-deoxyuridine (BrdU) colorimetric assay kit was purchased from Roche (Stahnhofer, Mannheim); Thermaxan coverslips were from Nunc (Naperville, IL, U.S.A.), and growth factor-reduced Matrigel from Becton Dickinson (San Jose, CA, U.S.A.). Forty-eight-well microchemotaxis chambers and polyester membrane (12 μm pores) were from Neuro Probe, Inc. (Cabin John, MD, U.S.A.). Antibody to phospho-extra-cellular signal-regulated kinase (ERK) was obtained from Promega (Madison, WI, U.S.A.); antibody to VEGF was ob-
tained from Santa Cruz Biotech (Santa Cruz, CA, U.S.A.), and antibody to phospho-Akt was from New England Biolabs. LY294002 was obtained from Calbiochem (San Diego, CA, U.S.A.).

**Cell Culture** HUVECs were isolated from fresh human umbilical cord veins according to a published protocol and cultured in M199 supplemented with 20% heat-inactivated FBS, 3 ng/ml bFGF, 5 units/ml heparin, and 100 units/ml antibiotic-antibiotic-antimycotic in 0.1% gelatin-coated flasks. HUVECs were used in three to six passages. HT1080 (human fibrosarcoma) cells were grown in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with penicillin/streptomycin and 10% FBS. All cells were grown at 37 °C in a humidified atmosphere containing 5% CO₂.

**Proliferation Assay** Proliferation assay was performed using a 5-bromo-2’-deoxyuridine (BrdU) colorimetric assay kit as described by the manufacturer’s protocols. HUVECs (5×10⁴ cells/well) were seeded onto 0.1% gelatin-coated 96-well plates and incubated in a humidified incubator for 24 h. After starving in M199 containing 5% heat-inactivated FBS for 6 h, the cells were exposed to various concentrations of paeonol in the presence or absence of bFGF (10 ng/ml) and assayed by BrdU incorporation assay. After 48 h incubation at 37 °C, 10 µl of BrdU was added to each well, and incubated at 37 °C for 6 h. The cells were fixed and incubated with anti-BrdU then detected by the substrate reaction. The reaction was stopped by addition of 25 µl of 1 × H₂SO₄, the absorbance was then measured by microplate reader (Molecular Devices Co., U.S.A.) at 450—690 nm.

**Migration Assay** Migration assay was performed using modified 48-well microchemotaxis chambers (Nuero Probe, Inc., Cabin John, MD, U.S.A.). Briefly, polyester membrane (12-µm pores) (Nuero Probe, Inc., Cabin John, MD, U.S.A.) was coated with 0.2% gelatin for 30 min then dried. The lower chamber was filled with 30 µl of M199 containing 0.2% BAS (control medium) in the presence or absence of bFGF (10 ng/ml). The coated membrane and upper chamber were placed over the lower chamber. HUVECs (4×10⁴ cells/well) and various concentrations of paeonol were loaded onto the upper chamber wells. After incubation at 37 °C for 2 h in 5% CO₂ incubator, the membrane was fixed with Diff-Quick fixative and stained with Diff-Quick Solution I and II (DADE Behring Inc., Newark, DE, U.S.A.). Non-migrating cells on the upper surface of the membrane were wiped off with a swab and the migrated cells to the lower surface were randomly photographed under an Axiovert S 100 light microscope (Carl Zeiss, Inc., U.S.A.) at ×100 magnification and counted.

**Tube Formation Assay** *In vitro* differentiation assay of HUVECs into capillary-like tubes was performed using growth factor-reduced Matrigel as described previously. HUVECs (1×10⁵) were seeded onto growth factor-reduced Matrigel-coated 24-well plates and various concentrations of paeonol added in M199 with 1% FBS, 10 ng/ml bFGF, and 5 units/ml heparin. After 18 h, randomly chosen fields were photographed under an Axiovert S 100 light microscope (Carl Zeiss, Inc., U.S.A.) at ×100 magnification and formed tubes counted.

**CAM Assay** *In vivo* angiogenic activity was assayed using CAMs as described previously. Paeonol and bFGF (100 ng) were loaded onto 1/4 piece of thermonox disks (Nunc, Naperville, IL, U.S.A.). Dried thermonox disk was applied to the CAMs of 10-d-old chick embryos. After 72 h incubation, a fat emulsion was injected under the CAMs for better visualization of the blood vessels and the number of newly formed blood vessels around the loaded disk was counted. The experiment was repeated twice and 15 eggs were used for each test sample.

**Matrigel Plug Assay** Matrigel plug assay was performed as described previously. Briefly, 6-week-old C57BL/6 mice were subcutaneously injected with 0.5 ml of growth factor-reduced Matrigel containing paeonol, bFGF (300 ng/mouse), and heparin (5 U). Seven days later, mice were sacrificed and the Matrigel plugs removed and photographed. To quantify the formation of blood vessels, the amount of hemoglobin (Hb) was measured by Drabkin reagent kit 525.

**Western Blot Analysis** After treatment with paeonol (125, 250, 500 µg/ml), the cells were washed twice in phosphate buffered saline (PBS) and suspended in a lysis buffer (50 mM Tris, pH 8.0, 150 mM NaCl, 0.1% sodium dodecyl sulfate (SDS), 0.5% sodium deoxycholate, 1% NP-40, 100 µg/ml phenylsulfonyl fluoride, 2 µg/ml aprotinin, 1 µg/ml pepstatin, and 10 µg/ml leupeptin). The cells were placed on ice for 30 min. The supernatant was collected after centrifugation at 15000 g at 40°C for 20 min. The protein concentration was determined by Bio-Rad protein assay reagents (Bio-Rad Lab, Hercules, CA, U.S.A.) with bovine serum albumin (BSA) (Sigma) as the standard. The whole lysates (20 µg) were resolved on a 7.5% SDS-polyacrylamide gel, transferred to an immobilon polyvinylidene difuride membrane (Amersham, Arlington Heights, IL, U.S.A.), and probed with the phospho-Akt, phospho-ERK, ERK, Akt, and VEGF antibodies. The blots were then developed using an enhanced chemiluminescence (ECL) kit (Amersham).

**Gelatin Zymographic Assay for MMPs** MMP2 and MMP9 enzymatic activities were assayed by gelatin zymography. HT1080 cells were plated on 6-well dishes and grown to 90% confluence in 2 ml of growth medium. The cells were maintained in serum-free media and treated with various concentrations of paeonol for 24 h. Conditioned medium was collected and concentrated at 10000×g for 30 min in a SpeedVac concentrator (Savant, E-C Instruments, Niantic, CT, U.S.A.). The protein concentration was measured using BCA protein assay reagents. Equal amounts of conditioned media were mixed with nonreducing sample buffer, incubated for 15 min at room temperature, then electrophoresed on 10% SDS-polyacrylamide gel electrophoresis (PAGE) gels containing 1 mg/ml gelatin. After electrophoresis, the gels were washed with 2.5% Triton X-100 twice for 30 min, rinsed three times for 30 min with a 50 mM Tris–HCl buffer (pH 7.6) containing 5 mM CaCl₂, 0.02% Brij-35, and 0.2% sodium azide, then incubated at 37 °C overnight. The gels were stained with 0.5% Coomassie brilliant blue R-250 solution containing 10% acetic acid and 20% methanol for 30 min, then destained with 7.5% acetic acid solution containing 10% methanol. Areas of gelatinase activity were detected as clear bands against the blue-stained gelatin background.

**Statistical Analysis** All data are presented as means ± standard deviation (S.D.) for *in vitro* data or standard error (S.E.) for *in vivo* data. Statistically significant differences be-
RESULTS

**Paeonol Inhibits bFGF-Induced Proliferation of HUVECs**

Paeonol with the chemical structure shown in Fig. 1 did not show any cytotoxicity against normal human endothelial cells up to the concentration of 500 μg/ml by a trypan blue dye exclusion test (data not shown), indicating that it is not toxic in physiological conditions. Thus we used non-toxic concentrations (125—500 μg/ml) in our angiogenesis-related experiment. To determine the anti-angiogenic activity of paeonol, proliferation assay was performed using HUVECs stimulated by 10 ng/ml bFGF. Proliferation of bFGF-treated HUVECs was 4-fold higher compared with untreated control, whereas paeonol significantly inhibited bFGF-induced proliferation of HUVECs in a dose-dependent manner (Fig. 2).

**Paeonol Inhibits bFGF-Induced Cell Migration**

To assess the effect of paeonol on endothelial cell migration, the effect of paeonol on migratory activity was evaluated in bFGF-treated HUVECs. Cells in bFGF-treated control exhibited 23-fold more migratory activity than untreated control (Figs. 3A, B). However, paeonol from 125 μg/ml significantly inhibited the migration of bFGF-induced HUVECs (Figs. 3C—E) in a dose-dependent manner (Fig. 3F).

**Paeonol Inhibits bFGF-Induced Tube Formation of HUVECs**

To examine the effect of paeonol on differentiation of endothelial cells, HUVECs were plated on growth factor-reduced Matrigel then treated with paeonol in the presence or absence of bFGF. As shown in Figs. 4A—D, paeonol clearly suppressed bFGF-induced HUVEC tube formation. Paeonol significantly inhibited tube formation of bFGF-induced HUVECs to 24.6%, 50%, and 56.8% of bFGF control at 125, 250, and 500 μg/ml, respectively (Fig. 4E).

**Paeonol Inhibits bFGF-Induced Angiogenesis in CAM and Matrigel Plug Assays**

To confirm in vitro antiangiogenic activity of paeonol, CAM assay was performed in vivo. New blood vessels in bFGF-treated control were formed 2.6-fold compared with the untreated control (Figs. 5A, B). In contrast, treatment with paeonol at doses of 0.8 and 1.6 μg/egg significantly inhibited bFGF-induced neovascularization by 47% and 61%, respectively, in CAMs without any sign of thrombosis and hemorrhage (Figs. 5C—E). Consistently, in Matrigel plug assay, as shown in Fig. 6A, pale color was detected on the surface of Matrigel plugs of the untreated group and dark red color indicating abundant angiogenesis was seen in Matrigel plugs of the bFGF-treated group, whereas light yellowish color was observed in bFGF- and paeonol-treated group. To quantify the relative angiogenesis, the amount of hemoglobin (Hb) was indirectly measured. The vessels were abundantly filled with intact red blood cells (RBCs), indicating the formation of a functional vasculature inside the Matrigel via VEGF induced angiogenesis. Hemoglobin content of bFGF treated control increased to 17.5 ± 1.5 g/dl compared with 5.4 ± 0.44 g/dl in untreated control. However, paeonol at 50 μg significantly inhibited the Hb levels to 8.2 ± 1.1 g/dl (Fig. 6B).

**Paeonol Suppresses bFGF-Induced Akt Phosphoryla-
tion But Not ERK Phosphorylation in HUVECs

To elucidate the molecular mechanism of paeonol, Western blotting was performed. As shown in Fig. 7A, bFGF induced phosphorylation of Akt in HUVECs, whereas the phosphorylation was downregulated in a concentration-dependent manner by paeonol. However, unexpectedly the expression of ERK was slightly upregulated at concentrations of 250 and 500 mg/ml of paeonol compared with bFGF-treated control. To confirm the role of AKT pathway in the anti-angiogenic effect of paeonol, Akt inhibitor study using LY294002 was undertaken. As shown in Fig. 7B, LY294002 synergistically potentiated paeonol-induced inactivation of Akt and VEGF in bFGF-treated HUVECs, suggesting that suppression of the Akt pathway plays a critical role in anti-angiogenic activity of paeonol.

Paeonol Suppresses MMP-2 and MMP-9 Enzymatic Activities

Extracellular matrix breakdown is vital to cellular invasion, indicating that matrix-degrading proteinases are essential for tumor cell metastasis. Metastatic HT1080 fibrosarcoma cells constitutively secrete high levels of MMP-2 and MMP9. To clarify whether activities of MMPs are involved in anti-metastatic activity by paeonol, we evaluated the effects of paeonol on MMP-9 and MMP-2 activities with the use of gelatin and fibrin zymography. As shown in Figs. 7C and D, the gelatinolytic activity of MMP-9 and MMP-2 was constitutively activated in HT1080 cells, whereas paeonol suppressed MMP-9 and MMP-2 enzymatic activities in HT1080 cells in a dose-dependent manner.

Fig. 4. Paeonol Inhibits bFGF-Induced Tube Formation of HUVECs

HUVECs were plated on growth factor-reduced Matrigel and treated with paeonol in the presence of bFGF. After incubation for 18 h, cells were observed under microscope (×100 magnification) and photographed. (A) bFGF treated control, (B) 125 μg/ml of paeonol with bFGF, (C) 250 μg/ml of paeonol with bFGF, and (D) 500 μg/ml of paeonol with bFGF. (E) The number of tube formation per field was counted. All data are presented as means±S.D. of three experiments. Statistically significant differences between control and sample groups were calculated by Student’s t-test. **p<0.01 and ***p<0.001 versus bFGF control.

Fig. 5. Paeonol Inhibits bFGF-Induced Angiogenesis in CAM Assay

Paeonol with bFGF was loaded on CAMs of 10-d-old fertilized chicken eggs. After 72h incubation, a fat emulsion was injected into the CAMs for better visualization of the blood vessels. Thermanox and surrounding CAMs were photographed. (A) Un-treated control, (B) bFGF-treated control, (C) 0.8 μg of paeonol with bFGF, and (D) 1.6 μg of paeonol with bFGF. (E) The number of newly formed blood vessels per field was counted. All data are presented as means±S.D., n=15. Statistically significant differences between control and sample groups were calculated by Student’s t-test. **p<0.01 versus unstimulated control; **p<0.01 and ***p<0.001 versus bFGF control.

Fig. 6. Paeonol Inhibits bFGF-Induced Angiogenesis in Matrigel Plug Assay

C57BL/6 mice were subcutaneously injected with 0.5 ml of Matrigel containing paeonol, bFGF (300 ng), and heparin (10 unit/ml). (A) After 7 d, the Matrigel plugs were removed and photographed. (B) Hemoglobin content of the plugs was measured as an indicator of functional angiogenesis. All data are presented as mean±S.E., n=7. Statistically significant differences between control and sample groups were calculated by Student’s t-test. *p<0.05 versus untreated control; *p<0.05 versus bFGF control.
Angiogenesis is the process of forming new capillary blood vessels from preexisting ones. Because angiogenesis plays a vital role in the development of cancer, it has been reported that inflammation and angiogenesis are closely linked processes. Also, aspirin is known to prevent certain types of cancer such as lung, colon, and breast cancers through anti-angiogenic process. To evaluate the anti-angiogenic effects of paeonol with anti-inflammatory activities in HT1080 Cells

In the present study, paeonol significantly inhibited essential angiogenesis processes such as proliferation and migration in a dose-dependent manner in bFGF-stimulated HUVECs under pathological angiogenic condition, indicating that paeonol can inhibit the early processes of angiogenesis. Stimulation of HUVECs seeded on Matrigel by angiogenic activator bFGF can promote differentiation to form capillary-like tubes. Thus the inhibitory effect of paeonol on tube formation in bFGF-treated HUVECs suggests that paeonol can suppress angiogenesis via differentiation inhibition of human endothelial cells.

To confirm in vitro antiangiogenic activity of paeonol, CAM assay and Matrigel plug assay, which have been widely adopted as in vivo angiogenesis models, were carried out. Consistently with in vitro data, paeonol effectively disrupted new embryonic blood vessel formation in bFGF-treated CAM and Matrigel plugs without side effects such as thrombosis and hemorrhage, which implies anti-angiogenic efficacy of paeonol without harmful toxicity. There is accumulating evidence that the Akt pathway is closely involved in angiogenesis via activation of proliferation. Western blotting revealed that paeonol downregulated bFGF-induced activation of Akt in a concentration-dependent manner, suggesting that paeonol can suppress angiogenesis via regulation of Akt pathway. In addition, expression of ERK was slightly upregulated only at concentrations of 250 and 500 μg/ml of paeonol compared with the bFGF-induced control. However, extracellular signals often result in simultaneous activation or independent survival modules of both ERK and Akt pathways, although ERK and Akt are both survival proteins. Thus our data show different effects of paeonol on Akt and ERK pathways, suggesting that paeonol-induced anti-angiogenic activity may be partially via the phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway rather than ras/ERK pathway. We also performed Akt inhibitor study to confirm the antiangiogenic activity of paeonol, CAM assay and Matrigel plug assay, which have been widely adopted as in vivo angiogenesis models, were carried out. Consistently with in vitro data, paeonol effectively disrupted new embryonic blood vessel formation in bFGF-treated CAM and Matrigel plugs without side effects such as thrombosis and hemorrhage, which implies anti-angiogenic efficacy of paeonol without harmful toxicity. There is accumulating evidence that the Akt pathway is closely involved in angiogenesis via activation of proliferation. Western blotting revealed that paeonol downregulated bFGF-induced activation of Akt in a concentration-dependent manner, suggesting that paeonol can suppress angiogenesis via regulation of Akt pathway. In addition, expression of ERK was slightly upregulated only at concentrations of 250 and 500 μg/ml of paeonol compared with the bFGF-induced control. However, extracellular signals often result in simultaneous activation or independent survival modules of both ERK and Akt pathways, although ERK and Akt are both survival proteins. Thus our data show different effects of paeonol on Akt and ERK pathways, suggesting that paeonol-induced anti-angiogenic activity may be partially via the phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway rather than ras/ERK pathway. We also performed Akt inhibitor study to confirm the antiangiogenic activity of paeonol, CAM assay and Matrigel plug assay, which have been widely adopted as in vivo angiogenesis models, were carried out. Consistently with in vitro data, paeonol effectively disrupted new embryonic blood vessel formation in bFGF-treated CAM and Matrigel plugs without side effects such as thrombosis and hemorrhage, which implies anti-angiogenic efficacy of paeonol without harmful toxicity. There is accumulating evidence that the Akt pathway is closely involved in angiogenesis via activation of proliferation. Western blotting revealed that the Akt inhibitor LY294002 synergistically potentiated paeonol-induced inactivation of Akt and VEGF in bFGF-treated HUVECs, suggesting a critical role of Akt pathway in paeonol-induced anti-angiogenic activity.

Many studies have revealed that upregulation of MMPs is associated with invasion and metastasis of tumors. There is substantial evidence of MMP overexpression in metastasis. We demonstrated for the first time that paeonol markedly decreased MMP-9 and MMP-2 activities. The inhibitory effect of paeonol on proteinases activity suggests its anti-metastatic potential. However, in vivo animal study is required to confirm the anti-angiogenic and anti-metastatic activities of paeonol in the near future.

In summary, paeonol can exert anti-angiogenic activity by inhibition of proliferation, migration, and tube formation of bFGF-treated HUVECs in vitro and also suppressed new vessel formation in bFGF-treated CAM and Matrigel in vivo. Furthermore, paeonol downregulated Akt expression in bFGF-treated HUVECs and dramatically downregulated by bFGF, endothelial cells begin to form new capillary vessels in the following sequential steps such as degradation of basement membrane (BM) and extracellular matrix (ECM) by proteases, endothelial cell proliferation and migration, formation of capillary tubes, and maturation of the neovasculature.

**DISCUSSION**

The structure of paeonol (C₉H₁₀O₃) is similar to aspirin (C₉H₈O₄), a nonsteroidal anti-inflammatory drug. The beneficial effects of aspirin are well established in the various fields such as cardiovascular disease and inflammation. It has been reported that inflammation and angiogenesis are closely linked processes. Also, aspirin is known to prevent certain types of cancer such as lung, colon, and breast cancers through anti-angiogenic process. To evaluate the anti-angiogenic effects of paeonol with anti-inflammatory activity, in vitro and in vivo angiogenesis experiments were performed.

Angiogenesis is the process of forming new capillary blood vessels from preexisting ones. Because angiogenesis plays a vital role in the development of cancer, the process of angiogenesis might be a good target for cancer therapy. Actually, angiogenesis inhibitors such as bevacizumab, thalidomide, lenalidomide, sorafenib, and sunitinib have recently been approved by the U.S. Food and Drug Administration (FDA) for the treatment of cancer.

Members of the FGF family have an important role in angiogenesis and mediate cellular events such as cell proliferation, migration, and differentiation. Under proper stimulation...
MMP-9 and MMP-2 activities. Overall, these findings demonstrate that paeonol may be a potent cancer chemopreventive agent with anti-angiogenic and anti-metastatic activities.

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