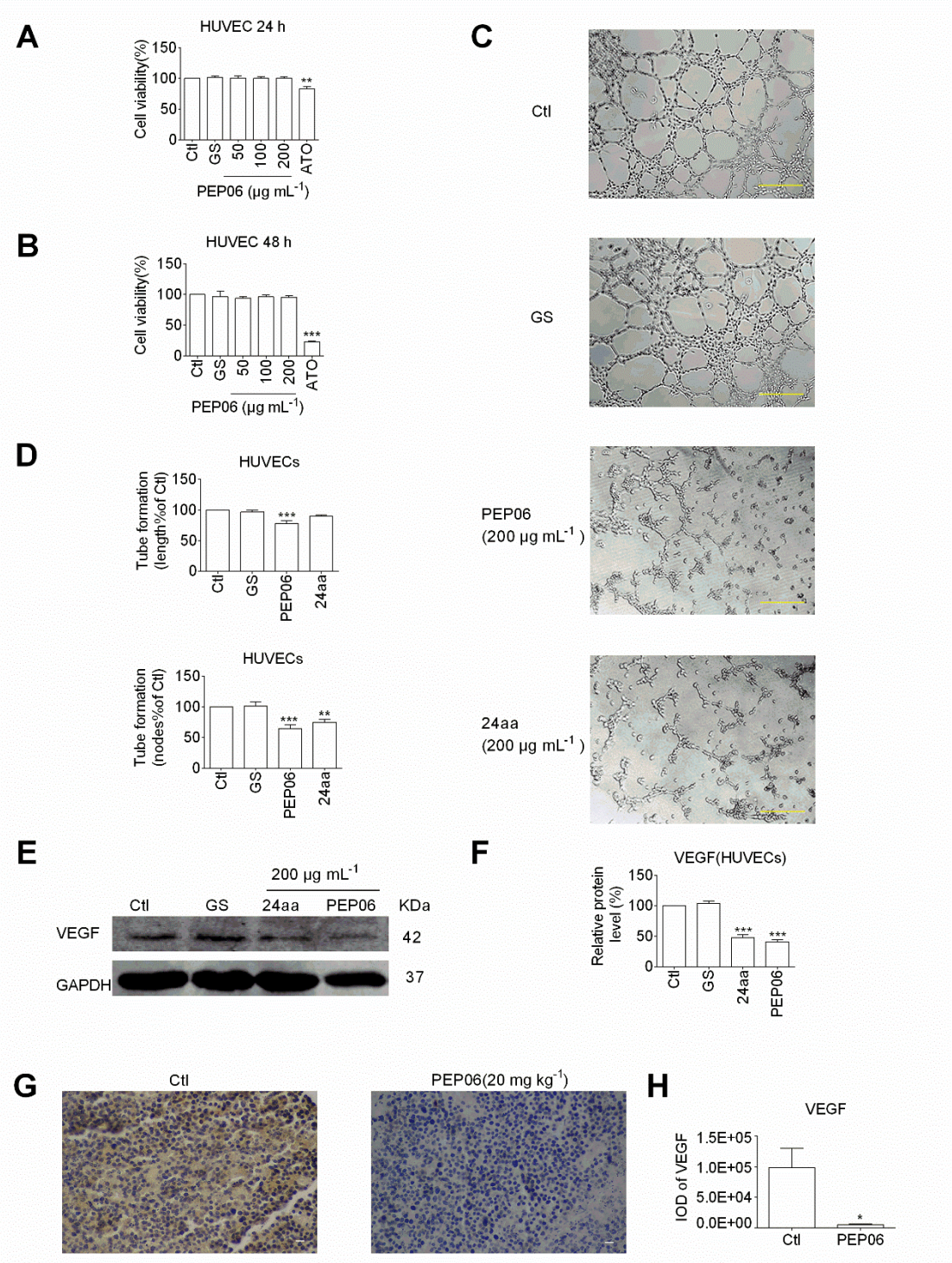

Fig. S1. The anti-angiogenic property of PEP06.

Lack of effects of PEP06 on viability of HUVEC cells. Relative or percent cell viability was determined by MTT assay with the OD values from the PEP06 groups normalized to those from the control groups. The measurements were taken 24 h or 48 h after PEP06 treatment. Lack of effect of different concentrations of PEP06 (50, 100,

and 200 μg mL^{-1}) on viability in HUVECs at 24 h **(A)** and 48 h **(B)** after treatment. Glucose solution was used as a vehicle control and ATO (5 nM) was employed as a positive control. *P<0.05 by one-way ANOVA; Dunnett for comparison with controls (Ctl). **(C)** Representative photomicrographs of tubule formation in the control, vehicle, PEP06-treated and 24aa-treated groups were shown. Cells were plated in 24-well plates previously coated with Matrigel and incubated for 6 h at 37°C in the absence of 200 μg mL^{-1} peptides. Scale bar: 50 μm. **(D)** Tubular structures were counted. PEP06 inhibited HUVEC tubule formation with a greater efficacy than 24aa. **'**Percentage (%) of control' is the mean length of tube or mean number of nodes formed as a proportion of that in the control group. ** P<0.01; ***, P<0.001 by one-way ANOVA; Dunnett for comparison with controls (Ctl). **(E)** HUVECs were treated with a concentration of 200 μg mL^{-1} PEP06 or 24aa for 24 h and subjected to Western blot analysis with anti-VEGF antibody. **(F)** Western blot analysis showed that the level of VEGF was significantly decreased by both PEP06 and 24aa. PEP06 produced stringer inhibitory effects on VEGF expression than 24aa in HUVECs. The values of protein band densities were normalized to those of control group. Averaged values (mean ± SEM, n=5) of Western blot band density normalized to the internal control GAPDH and to the data obtained from the Ctl groups. ** P<0.01; *** P<0.001 by one-way ANOVA; Dunnett for comparison with controls (Ctl). **(G)** PEP06 significantly inhibited tumour vessels in LOVO tumour xenografts. Paraffin sections of LOVO tumour tissue were tested by immunohistochemical analysis with anti-VEGF antibody. Representative tumour vasculature (brown) from vehicle- or PEP06-treated mice (20 mg kg^{-1}) was shown. Scale bar: 50 μm. **(H)** The Integral Optical Density (IOD) of VEGF was calculated by IPP. *P<0.05, by unpaired t test: compared with Ctl.

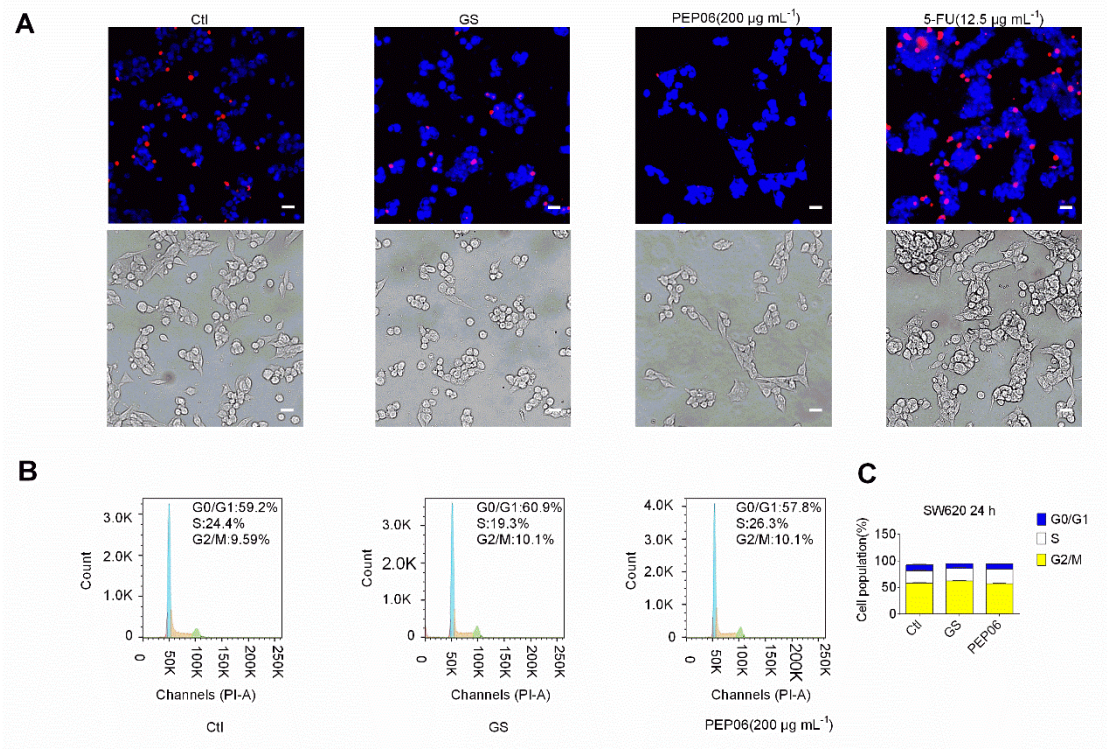

Fig. S2. Lack of effects of PEP06 on cell apoptosis and cell cycle on SW620 cells. **(A)** SW620 cells were treated with 5% GS, 200 μg mL^{-1} PEP06, 12.5 μg mL^{-1} 5-FU (positive control) for 24 h and then stained with the TUNEL assay. PEP06-treated cells showed no more TUNEL-positive cells (red fluorescence) in comparison to Ctl cells. Scale bar: 50 μm. **(B)** Cell cycle analysis in SW620 cells after treated with 200 μg mL^{-1} PEP06 for 24 h by flow cytometry, showing the average percentage of cells in G0/G1, S and G2/M phase. **(C)** There was no significant effect of each cell population in the presence of PEP06. Averaged data (mean ± SEM, n=5) of cell population in PI-A channels.

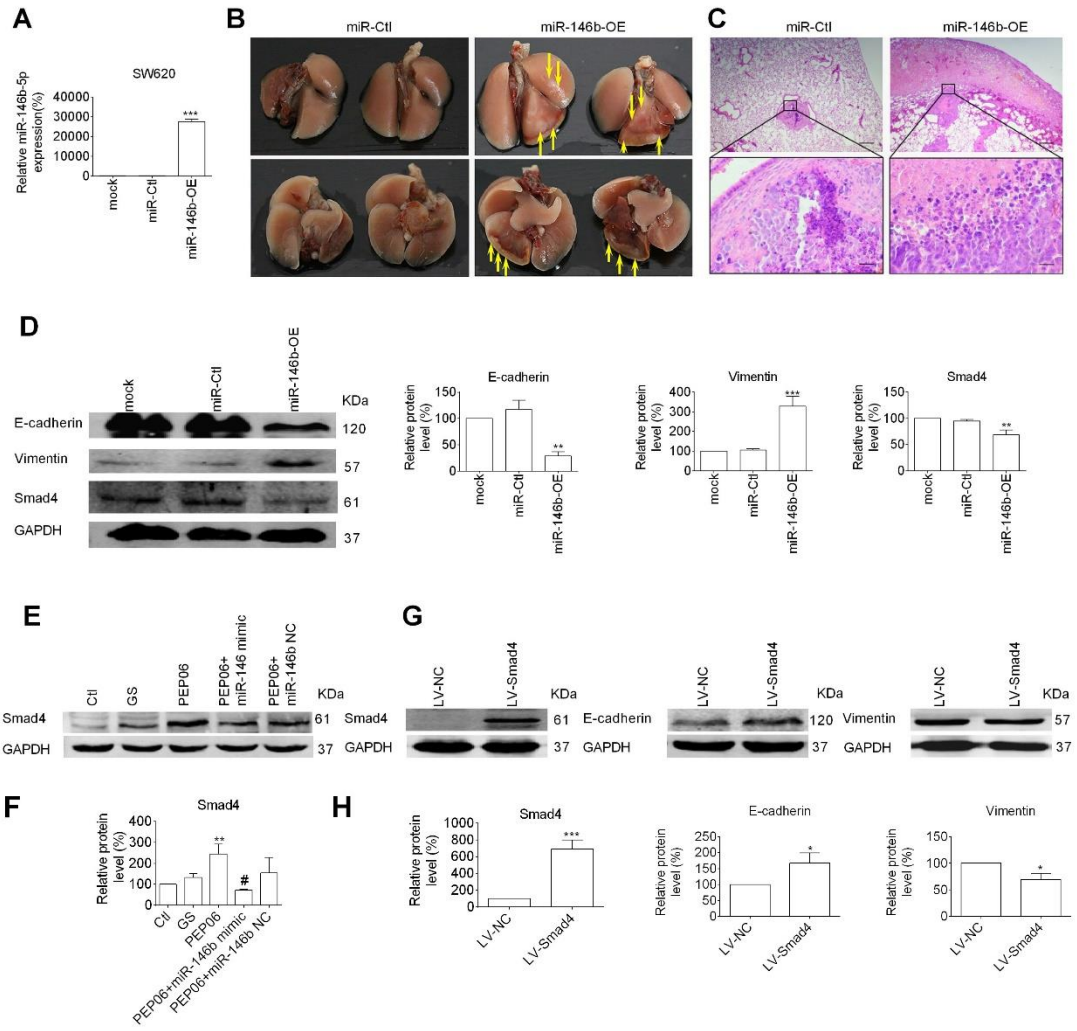

Fig. S3. MiR-146b-5p re-expression partly abrogates the tumour suppressive effect of PEP06 in CRC. (A) Successful construction of stable expression of miR-146b-5p in SW620. SW620 cells (mock), SW620 cells that stably expressing control lentiviral plasmid (miR-Ctl), and miR-146b-5p lentiviral plasmid (miR-146b-OE) were analysed by qRT-PCR. RNU6 was used as an internal control. Data (mean ± SEM) were from five independent experiments. ***P<0.001 by one-way ANOVA, Dunnett: compared with mock. **(B)** The SW620 cells stably expressing miR-146b-5p (miR-146-OE) and negative control (miR-Ctl) were injected intravenous on the tails of BALB/c mice and the lungs of the mice were dissected at Day 40. The miR-146-OE group induced pulmonary metastasis in 6 out of 8 mice (6/8), including 3 cases visible metastatic nodules in the lungs and 3 cases of microscopic nodules. However, miR-Ctl group induced pulmonary metastasis in 1 cases of microscopic nodules out of

8 mice (1/8). n=8, use one as example. **(C)** Representative H & E-stained sections of the lung tissues collected from the miR-Ctl and miR-146b-OE groups. Scale bar: 50 μm (upper), 500 μm (lower). **(D)** Forced expression of miR-146b-5p through stably transfection cell sublines decreased E-cadherin protein levels and Smad4 protein levels, and increased vimentin levels compared with the blank control group by western blot analysis. Averaged values (mean ± SEM, n=5) of Western blot band density normalized to the internal control GAPDH and to the data obtained from the mock groups. $^{**}P<0.01$, $^{***}P<0.001$ by one-way ANOVA, Dunnett: compared with mock. **(E)** The expression of Smad4 was elevated by PEP06 and was abrogated in partial by miR-146b-5p mimic. **(F)**Averaged values (mean ± SEM, n=5) of western blot band density normalized to the internal control GAPDH and to the data obtained from the Ctl groups. $^{**}P<0.01$ by one-way ANOVA, Dunnett: compared with Ctl; $\#P<0.05$, by unpaired t test: compared with the PEP06 group. **(G)** Western blot analysis of Smad4 and EMT-related markers in the Smad4 rescue experiments in miR-146b-5p stable overexpressing SW620 cells. **(H)** Smad4 and E-cadherin were upregulated and vimentin was downregulated after Smad4 overexpression. Averaged values (mean ± SEM, n=5) of Western blot band density normalized to the internal control GAPDH and to the data obtained from the LV-NC groups. $^{*}P<0.05$, $^{***}P<0.001$ by one-way ANOVA, Dunnett: compared with LV-NC.

Table S1. Oligonucleotide and primer sequences.

Name	Sequence (5'-3')
has-miR-146b-5p mimic (sense)	UGAGAACUGAAUUCCAUAGGCU
NC	UUCUCCGAACGUGUCACGUTT
has-miR-146b-5p inhibitor	AGCCUAUGGAAUUCAGUUCUCA
microRNA inhibitor N.C	CAGUACUUUUGUGUAGUACAA
miR-146b-5p RT	GTCGTATCCAGTGCGTGTCGTGGAGTCGG
	CAATTGCACTGGATACGACAGCCTATG
miR-146b-5p F	GGGCGGTGAGAACTGAATT
miR-146b-5p R	CAGTGCGTGTCGTGGAGT
U6 F	CTCGCTTCGGCAGCACA
U6 R	AACGCTTCACGAATTTGCGT

All primers correspond to *homo sapiens*.