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Paeonol inhibits the proliferation of human colorectal carcinoma cells and synergic with chemotherapeutic agents

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Colorectal cancer is the third most common cancer in the world and the second leading cause of cancer-related deaths in the United States.[1] Surgical removal of the tumor supplemented with chemotherapeutic agents is a major treatment for it. However, most of the chemotherapeutics for colorectal carcinoma have great aversive effects, so it is indispensable for us to find a proper and natural therapeutic strategy for our patient. Paeonol (Pae) is a Chinese traditional herb, which has been shown to exhibit anti-pyretic, sedative, anti-inflammatory and anti-bacterial[2] activities. It was reported that Pae exhibited anti-tumor activity in multiple cancer cell lines. Gastric lavage with Pae could inhibit liver tumor growth in mice model.[3] Paeonol has been proven to suppress hepatocellular tumourigenesis in vitro.[4] However, little was known on the effect of Pae on colorectal cancer cells. We provided evidence here that Pae inhibited the growth of colorectal carcinoma cell line HT-29, which was also synergistic with certain chemotherapeutic drugs.

The current study was conducted at Renmin Hospital of Wuhan University in China, between September 2003 and September 2004. And the study was approved by our Hospital Ethics Committee. Human colorectal carcinoma cell lines HT-29 were purchased from Oncology Institute of the Zhongnan University. Paeonol was obtained from Shanghai first pharmaceutical factory while 5-fluoro-2,4(1H,3H)pyrimidinedione (5-FU) was from Xu Dong Hai Pu Pharmaceutical Co. Ltd, Shanghai, China, mitomycin C (MMC) from Tokyo Co., and diamminedichloroplatinum (c-DDP) from Qi Lu Pharmaceutical Co., Shandong, China. The in vitro growth rate of HT-29 cells treated with Pae, was measured by the methyl thiazolyl tetrazolium (MTT) method. Briefly, HT-29 cells (1×10^3 cells/well) were seeded in 96-well plates. We added Pae to these cells in the concentration of 0.024, 0.047, 0.094, 0.188, 0.376, 0.752, 1.504 $\mu mol.L^{-1}$, respectively. And one group of cells was added without Pae as blank control. Making sure that each group contained 5 slots. Then the cells were incubated in an incubator for 24, 48, 72 and 96 hours .We added 20 µl MTT to each slot 4 hours ahead of termination, abscised the culture solution, and added 200 µl dimethyl sulphoxide (DMSO) to each slot again. The absorbance value was measured at a wavelength of 570 nm with background subtraction at 650 nm by the use of spectrophotometer. Inhibitory rate = (1-Ae/Ac)×100%. We also observed HT-29 cells at Log phase that had been incubated with different concentrations of Pae under inverted microscope. The cells were also cultured on cover-slip and fixed by 10% formalin and stained with hematoxylin and eosin. Each experiment was performed at least 2 times and results are presented as the mean ± standard deviation. The *p* values were determined by unpaired t test by using the Statistical Program for Social Sciences analysis. We found out that Pae significantly inhibited the growth of the HT-29 cells at a concentration of 7.81- 250 mg/L in a dose-effect and time-effect pattern (**Figure 1**). Microscopically, the control cells proliferated faster with a larger size and brighter field than cells treated with Pae. Hematoxylin and eosin staining of the control cells showed blue nuclear staining without visible apoptotic body. Cells treated with Pae exhibited apoptotic cell in a concentration of 31.25-250 mg/L. Apoptotic cells were distinguished by

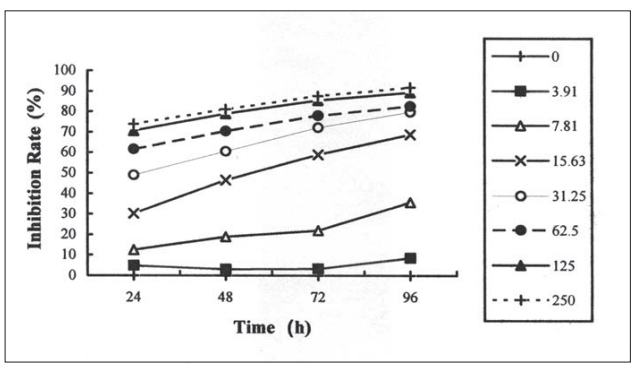

Figure 1 - The effect of paeonol to the proliferation of HT-29 cell.

Table 1 - Paeonol synergizes with 3 chemotherapeutic drugs on the inhibition of HT-29 cell proliferation.

Items	A	Inhibition rate (%)
Control	1.073 ± 0.021	
Single Use		
Pae	0.871 ± 0.013	(18.826)*
5-FU	0.751±0.028	(30.002)*
MMC	0.749 ± 0.030	(30.151)*
DDP	0.745 ± 0.019	(30.569)*
Combined use		
Pae+5-FU	0.280 ± 0.009	(73.884)*†
Pae+MMC	0.373±0.025	(65.267)*†
Pae+DDP	0.497 ±0.018	(53.713)*†

Concentration of Pae - 7.81 mg/L, 5-FU - 10 mg/L, MMC - 0.5 mg/L, DDP - 10 mg/L. *p<0.01 ;†p<0.01, 5-FU - 5-fluoro-2,4(1H,3H)pyrimidinedione, MMC - mitomycin C, DDP - diamminedichloroplatinum, Pae - Paeonol, A - absorbance value by the use of spectrophotometer

nuclear condensation and fragmentation as well as deep nuclear staining. Furthermore, 7.81 ml/L of Pae was combined with or without one of 3 chemotherapeutic drugs (10 mg/L 5-FU, 0.5 mg/L MMC, or 10 mg/L c-DDP) to treat the cells. As a control, all drugs were also applied respectively. There was also a blank control. Forty-eight hours later, MTT assay was performed. We saw that low dose of Pae achieved a significantly synergistic effect with 5-FU, MMC or c-DDP in the inhibition of HT-29 cell growth (p<0.01). Paeonol had the most prominent synergistic effect with 5-FU (**Table 1**). Therefore, we came to the conclusion that, besides its direct anti-tumor activity, Pae might sensitize cancer cells to multiple chemotherapeutic drugs. Low dose of Pae (7.81 mg/L) could only inhibit HT-29 cell growth by 18.826%, whereas its combined use with 5-FU, MMC and c-DDP at a concretion of IC_{30}, achieved an inhibitory rate of 73.884%, 65.267% and 53.713%, respectively. The combined use of Pae with chemotherapeutic drugs was significant (p<0.01).

In conclusion, plant extract Pae possesses the anti-tumor and immunity-promoting activity with no apparent side effects. We are expecting that combined application of Pae in the clinical treatment of colorectal cancer with 5-FU would enhance the efficacy of the chemotherapeutic drug with less side effects due to a reduced dose.

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Household cardiovascular health education. ***A school–based approach***

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There is no doubt that control of risk factors is an effective strategy in primary prevention of cardiovascular disease. Lifestyle behaviors such as unhealthy diet and physical inactivity contribute significantly to the progression of cardiovascular disease.[1] Cardiovascular health promotion in children has the potential to reduce the risk of atherosclerosis in both the children and their families. Schools provide an excellent setting for introducing comprehensive health education and promotion as a public health approach to the general population. Furthermore, it is suggested that involvement of families in school- based programs is feasible and effective.[2]

Like many other countries, coronary heart disease (CHD) is the leading cause of mortality and morbidity in Iran.[3] The process of urbanization and corresponding lifestyle changes has been associated with increase in the prevalence of CHD. On the other hand, the population of Iran is relatively young. This provides an opportunity to prevent cardiovascular disorders since childhood. As many people in Iran still do not have enough information on cardiovascular risk factors, we performed this school-based educational intervention to investigate its effect on the improvement of cardiovascular health knowledge in targeted households. The study was carried out on ordinary households of 1000 fifth-grade boys and