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Piceatannol promotes apoptosis via up-regulation of microRNA-129 expression in colorectal cancer cell lines

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ABSTRACT

Piceatannol, a naturally occurring analog of resveratrol, has been confirmed as an antitumor agent by inhibiting proliferation, migration, and metastasis in diverse cancer. However, the effect and mechanisms of piceatannol on colorectal cancer (CRC) have not been well understood. This study aimed to test whether piceatannol could inhibit growth of CRC cells and reveal its underlying molecular mechanism.

MTT assay was used to detect the cell viability in HCT116 and HT29 cells. Flow cytometry analysis was employed to measure apoptosis of CRC cells. Bcl-2, Bax and caspase-3 levels were analyzed by Western blot and miR-129 levels were determined by real-time RT-PCR. Our study showed that piceatannol inhibited HCT116 and HT29 cells growth in a concentration- and time-dependent manner. Piceatannol induced apoptosis by promoting expression of miR-129, and then inhibiting expression of Bcl-2, an known target for miR-129. Moreover, knock down of miR-129 could reverse the reduction of cell viability induced by piceatannol in HCT116 and HT29 cells. Taken together, our study unraveled the ability of piceatannol to suppress colorectal cancer growth and elucidated the participation of miR-129 in the anti-cancer action of piceatannol. Our findings suggest that piceatannol can be considered to be a promising anticancer agent for CRC.

1. Introduction

Colorectal cancer (CRC) is one of the most common cancer related cause of death in the worldwide [1]. In general, the incidence of CRC is higher in economically developed countries than in developing countries [2]. While important efforts in the early detection and prevention of CRC are ongoing, approximate one-fifth of patients diagnosed with CRC will have evidence of distant spread at diagnosis [3], which is usually treated with surgery, frequently in combination with adjuvant chemotherapy. However, most patients are eventually resistant to chemotherapy, which results in subsequent recurrence and metastasis.

Increasing evidence supports that natural agents open up a novel avenue for treatment of cancers, especially by combining with conventional therapeutics [4]. Piceatannol (*trans*-3,4,3′,5′-tetrahydroxystilbene, also known as 3-hydroxyresveratrol or astringinine) is a naturally occurring polyphenol and an analog of the cancer chemopreventive agent resveratrol (*trans*-3,5,4′-trihydroxystilbene) [5]. It has been well documented that resveratrol inhibits growth and proliferation in various cancer cells via inducing apoptosis and cell cycle arrest [6,7]. Recent observations showed that piceatannol also could inhibit proliferation, migration, and metastasis of diverse cancers, such as breast cancer, prostate cancer, bladder cancer and so on [8–10]. However, limited studies have pay attention on the therapeutic effects and underlying mechanisms of piceatannol on colorectal cancer.

MicroRNAs (miRNAs) are a class of endogenous small non-coding RNAs with 18–22 nt in length. Mature miRNAs bind to the 3′-UTR of target mRNAs and repress translation of target mRNAs or induce degradation of target mRNAs [11]. Increasing evidence supports that miRNAs play indispensable roles in many biological processes involving in the pathogenesis of diverse cancer, such as proliferation, apoptosis and angiogenesis in lung cancer, breast cancer, ovarian cancer and so on [12–14]. And, kinds of miRNAs have been confirmed to participate in the initiation and progression of colorectal cancer [15,16]. Karaayvaz M et al. found that miR-129 promotes apoptosis by suppressing BCL2 protein

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expression in CRC [17]. However, whether miR-129 participates in the anti-cancer effects of piceatannol in unknown.

The primary objective of the present study was to elucidate the effects and underlying molecular mechanisms of the anti-cancer action of piceatannol. Considering the important roles of miR-129 and apoptosis in carcinogenesis, we investigated whether miR-129 contributes to the anti-cancer effect of piceatannol.

2. Materials and methods

2.1. Materials

Piceatannol (purity >99%) was purchased from Sigma–Aldrich, and was dissolved in ethanol to prepare a 100 mM stock solution which was stored at −20 °C in the dark.

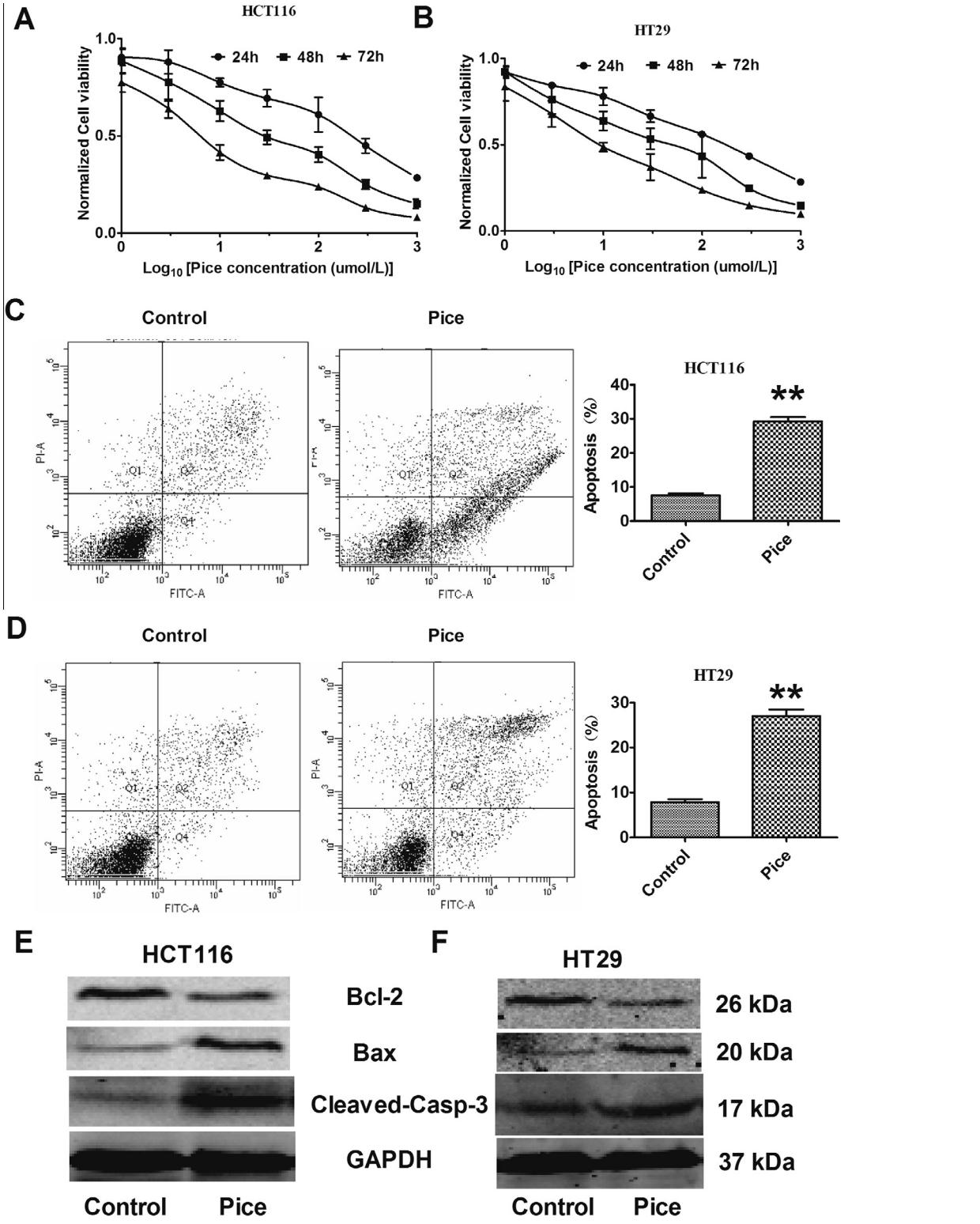

Fig. 1. Piceatannol induces apoptosis in CRC cells. Effects of different concentration of piceatannol on cell viability of HCT116 (A) and HT29 (B) cells. Piceatannol increases apoptosis of HCT116 (C) or HT29 (D) cells, as assessed by flow cytometry. Piceatannol causes dysregulation of Bcl-2 and Bax protein, and induces activation of caspase-3 in HCT116 (E) or HT29 (F) cells, as determined by Western blot. $n = 5$, $^{*}p < 0.05$ *vs.* Control.

2.2. Patient samples

Cancer samples were obtained from CRC patients who underwent surgical resection of primary tumors, and control samples were obtained from resected adjacent tissues of colorectal cancer from the Second Affiliated Hospital of the Harbin Medical University under the procedures approved by the Ethnic Committee for Use of Human Samples of Harbin Medical University (Harbin, China).

2.3. Cell culture and treatments

Human colorectal cancer cell lines HCT116 and HT29 were purchased from Shanghai cell bank of Chinese Academy of Sciences (Shanghai, China). Cells were cultured in RPMI 1640 (Hyclone, USA) supplemented with 10% fetal bovine serum (Hyclone, USA) at 37 °C in a humidified atmosphere of 95% air and 5% CO_2. The cells treated with piceatannol were collected at 24 h and 48 h for further measurements.

2.4. MTT cell viability assay

HCT116 or HT29 cells were seeded in 96-well culture plates with 1×10^4 cells/well, and incubated at 37 °C with 5% CO_2. After treating with different concentrations of piceatannol, MTT assay (Amresco, Solon, USA) was performed. Briefly, 20 μl of MTT solution (5 mg/ml) was added to each well, and the cells were continuously incubated for 4 h. Formazan crystals were then dissolved in 150 μl DMSO. The optical density (OD) of the wells was measured with a microplate reader (BioTek, Richmond, USA) at 490 nm.

2.5. Cell apoptosis detection by flow cytometry

HCT116 or HT29 cells were collected after treatment, and then washed twice with PBS. The cells were resuspended in 500 μl binding buffer at a concentration of 10^6/ml and then mixed with 10 μl Annexin V (Bio-Science, Co. Ltd, Shanghai, China) for 10 min in the dark at room temperature (RT), followed by the addition of 5 μl PI (Bio-Science, Co. Ltd., Shanhai, China). After incubation at RT in the dark for 5 min, samples were analyzed by a FACS Aria flow cytometry (BD Biosciences, San Jose, CA, USA).

2.6. Transfection

Before transfection, HCT116 or HT29 cells were grown in 25 cm^2 cell culture flasks with 4 ml medium. The miRNA and lipofectamine 2000 (Invitrogen, Carlsbad, CA) were separately mixed with 500 μl of Opti-MEM ® I Reduced Serum Medium (Gibco, Grand Island, NY) for 5 min. Then, the two mixtures were combined and incubated for 20 min at room temperature (RT). The lipofectamine-miRNAs mixture was added to the cells, which were incubated at 37 °C for 36 h for further experiments.

2.7. Quantification of miR-129

Total RNA was extracted from HCT116 or HT29 cells by TRIZOI® Reagent (Invitrogen, USA) following the manufacturer's protocol. miR-129 levels were measured using the mirVanaTM qRT-PCR miRNA Detection Kit (Ambion, USA) as Liang et al. did [11]. Primers for real-time PCR were 5′-GGGGGCTTTTTGCGGTCTGG-3′ (miR-129 forward) and 5′-AGTGCGTGTCGTGGAGTC-3′ (miR-129 reverse). Variations in expression of miR-129 between different RNA samples were calculated after normalization to U6.

2.8. Western blot

For Western blot analysis, total protein samples were extracted from HCT116 or HT29 cells. Cells were lysed with RIPA lysis buffer (Beyotime, Jiangsu, China). 50 μg proteins were fractionated on a 15% SDS–polyacrylamide gel. After electrophoretically transferring to a Pure Nitrocellulose Blotting membrane, the blots were probed with primary antibodies. Rabbit polyclonal antibody for Bcl-2, Bax and caspase-3 were purchased from Santa Cruz Biotechnology.

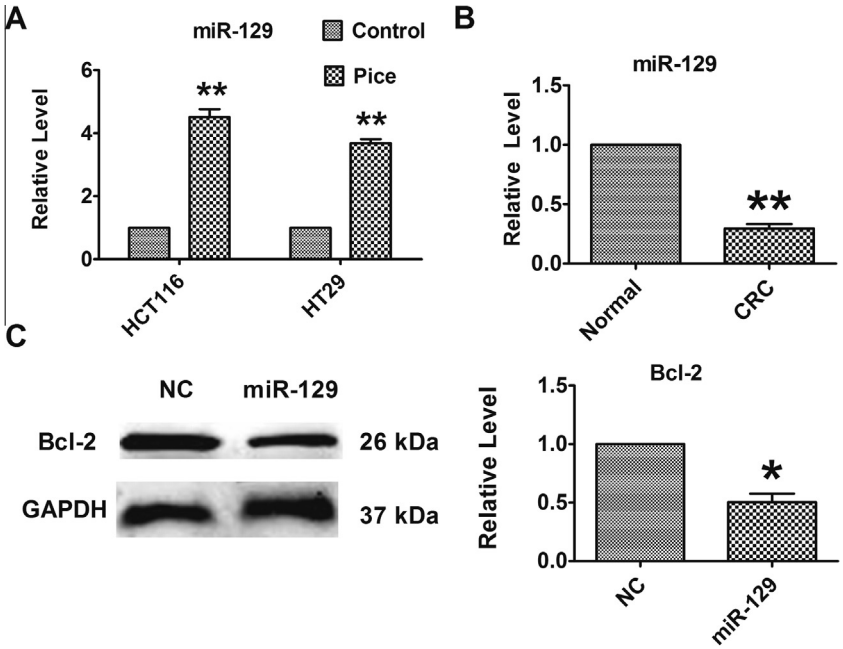

Fig. 2. Piceatannol promotes miR-129 expression in CRC cells. (A) Piceatannol increases miR-129 expression in HCT116 or HT29 cells. $n = 5$, $^{**}p < 0.050.01$ *vs.* Control. (B) miR-129 is down-regulated in colorectal cancer samples compared with normal samples, as measured by real-time PCR. $n = 10$, $^{**}p < 0.01$ *vs.* Normal. (C) Effects of miR-129 on the expression of Bcl-2 protein in HCT116 cells. $n = 5$, $^{*}p < 0.05$ *vs.* NC. NC: negative control.

Anti-GAPDH antibody (Kangchen, Shanghai, China) was used as an internal control. The immunoreactivity was detected using Odyssey Infrared Imaging System and analyzed using Odyssey software (Infrared Imaging System LI-COR Biosciences) [18].

2.9. Caspase-3 activity assay

CRC cells were lysed and centrifuged at 600*g* for 5 min and then lysed in 50 μl of ice-cold cell lysis buffer for 30 min. The lysates were centrifuged at 16,000*g* for 15 min at 4 °C. The fluorogenic substrates for Caspase-3 were labeled with the *p*-nitroaniline (*p*NA). The enzyme activity was determined by monitoring the fluorescence produced by free *p*NA using a spectrofluorophotometer (SHIMADZU Corporation, RF-5301PC, Kyoto, Japan) at 405 nm. Caspase-3 activity was expressed in micromoles *p*NA liberated as per minute per microgram of protein.

2.10. Statistical analysis

All data are presented as mean ± SEM. Student's *t* test was used for two group comparison and One-way ANOVA followed by Bonferroni test for multiple comparisons. A two-tailed $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Growth inhibition of CRC cells induced by piceatannol

To investigate the effect of piceatannol on the growth of colon cancer cells, HCT116 cells were treated with piceatannol at different concentration for 24, 48 and 72 h, and then the cells were analyzed by MTT Assay. As shown in the Fig. 1A, the growth of HCT116 cells was inhibited in a dose- and time-dependent manner with an IC_{50} (48 h) of ~25.29 μM. And, the growth inhibitory effect was also demonstrated in another colorectal cancer cell line HT29 with an IC_{50} (48 h) of ~38.73 μM (Fig. 1B). Therefore, we used piceatannol with the concentration of 30 μM for the following analysis.

3.2. Piceatannol induces apoptosis in cultured CRC cells

To detect whether the reduction of cell viability was associated with cell apoptosis, flow cytometry assay was applied to detect the

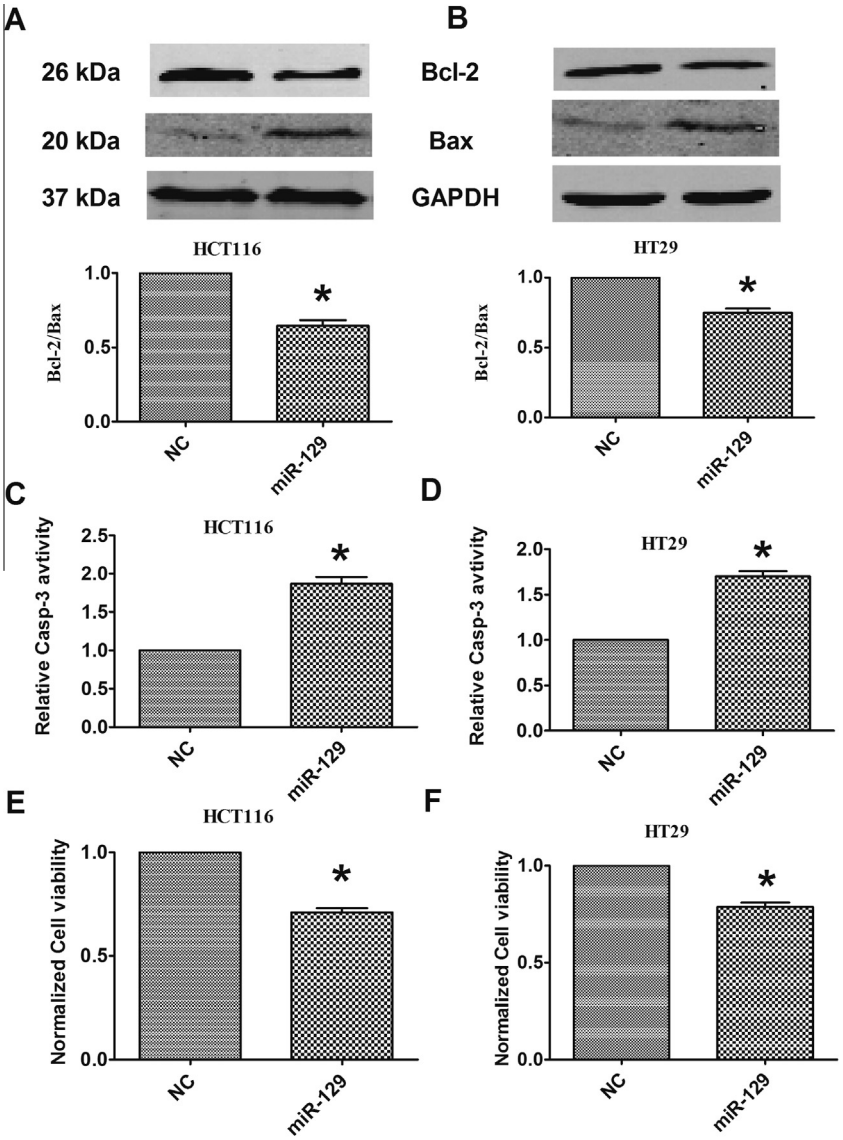

Fig. 3. Overexpression of miR-129 induces apoptosis in CRC cells. Forced expression of miR-129 induces dysregulation of Bcl-2 and Bax protein expression in HCT116 (A) or HT29 (B) cells. Overexpression of miR-129 increases caspase-3 activity in HCT116 (C) or HT29 (D) cells, and inhibits cell viability in HCT116 (E) or HT29 (F) cells. $n = 5$, $^{*}p < 0.05$ *vs.* NC.

apoptotic rate of HCT116 and HT29 cells treated with piceatannol. As shown in Fig. 1C and D, compared with the control group, apoptosis was markedly increased in HCT116 and HT29 cells after treating with 30 μM piceatannol for 48 h. Both caspase-dependent and -independent pathways are known to be involved in the process of apoptosis. We tested whether the apoptosis of CRC cells caused by piceatannol was associated with the activation of caspase-3. To address this question, Western blot were used to examine the expression changes of caspase-3 protein. And, we found that the activated caspase-3 (cleaved-caspase-3) was markedly increased in the cells incubated with piceatannol, which was along with dysregulation of Bcl-2 and Bax protein in activated apoptotic pathway (Fig. 1E and F). These results suggest that the piceatannol could induce apoptosis in CRC cells by caspase-dependent process.

3.3. Piceatannol promotes expression of miR-129

It has reported that miR-129 could promote apoptosis and enhance chemosensitivity to 5-fluorouracil in CRC [17]. Thus, we assumed that piceatannol induces the apoptosis of CRC cells by upregulating expression of miR-129. The level of miR-129 was determined by real-time RT-PCR after treating with piceatannol in HCT116 or HT29 cells for 48 h. Fig. 2A showed that piceatannol increased the level of miR-129 both in HCT116 and HT29 cells. Further experiments confirmed that miR-129 was decreased in the patients of colorectal cancer (Fig. 2B). And, forced expression of miR-129 by transfection markedly reduced the level of Bcl-2 protein, an known target for miR-129 (Fig. 2C).

3.4. miR-129 mediates proapoptotic effects of piceatannol

To confirm the role of miR-129 in the process of apoptosis, we transfected miR-129 mimics into CRC cells. Our data showed that forced expression of miR-129 induced the reduction of Bcl-2 and increased Bax in HCT116 and HT29 cells (Fig. 3A and B). And, overexpression of miR-129 increased caspase-3 activity both in HCT116 and HT29 cells (Fig. 3C and D). Meanwhile, transfection of miR-129 into CRC cells inhibited the cell viability (Fig. 3E and F). These data indicating that miR-129 could induce apoptosis in CRC cells.

To examine whether the up-regulation of miR-129 contributes to the piceatannol-induced apoptosis in CRC cells, we knocked down the expression of miR-129 by transfection of its specific inhibitor AMO-129, and then observed the alteration of piceatannol-induced apoptosis in CRC cells. As shown in Fig. 4A and B, AMO-129 reversed the dysregulation of Bcl-2 and Bax caused by piceatannol in HCT116 and HT29 cells. Moreover, AMO-129 restored the reduction of cell viability induced by piceatannol (Fig. 4C and D), indicating that the elevation of miR-129 is involved in the process of piceatannol-induced apoptosis in CRC cells.

4. Discussion

In the present study, we demonstrated that piceatannol could inhibit the growth of colorectal cancer cell in a dose- and time-dependent manner. The piceatannol promoted the expression of miR-129, then caused down-regulation of Bcl-2, up-regulation of Bax and activation of caspase-3, and finally induced the apoptosis in CRC cells. More importantly, we found that overexpression of

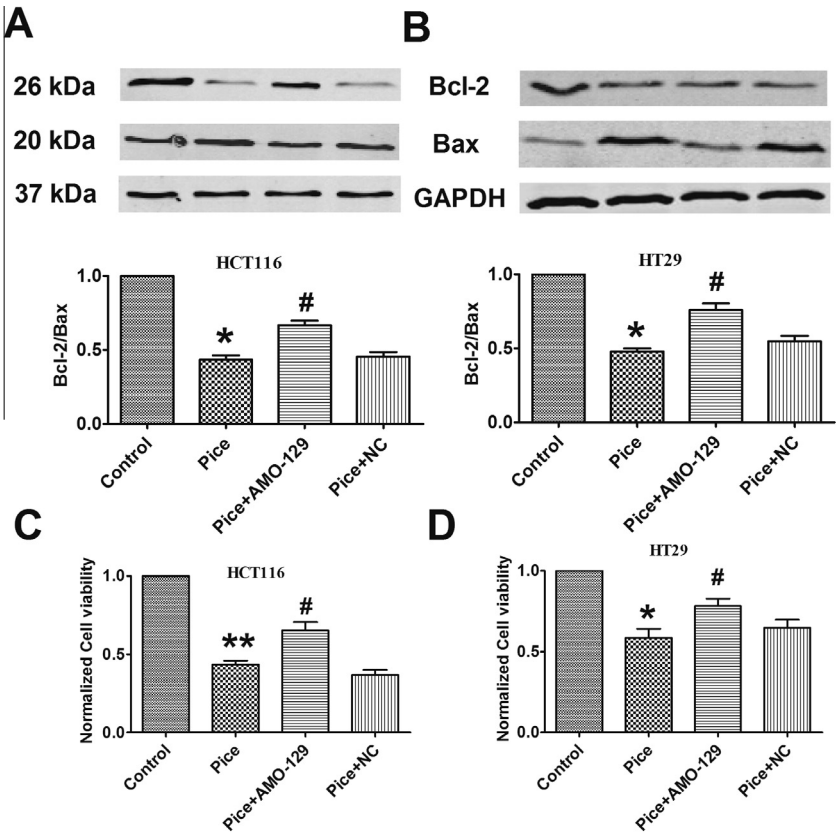

Fig. 4. Knock down of miR-129 alleviates the pro-apoptotic effects of piceatannol in CRC cells. Inhibition of miR-129 reverses dysregulation of Bcl-2 and Bax protein caused by piceatannol in HCT116 (A) or HT29 (B) cells. Knock down of miR-129 mitigates the reduction of cell viability induced by piceatannol in HCT116 (C) or HT29 (D) cell. $n = 5$, $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* Control; $^{\#}p < 0.05$ *vs.* Pice. AMO-129: miR-129 inhibitor.

miR-129 induces apoptosis in CRC cells, and knock down of miR-129 could alleviates the proapoptotic action of piceatannol. Taken together, our work revealed the proapoptotic effects of piceatannol in CRC cells and uncovered the participation of miR-129 in this process. And, our studies indicate that piceatannol could be a novel agent for treatment of CRC.

Several reports have demonstrated that resveratrol could inhibit cancer cell growth [6,19–21]. More evidences have found that piceatannol, a natural analog of resveratrol, induced apoptosis and cell cycle arrest in DU145 cells [9,22,23]. And, a study from Kwon GT et al. showed that piceatannol inhibits migration and invasion of prostate cancer cells [24], which indicate the potential therapeutic effects of piceatannol on prostate cancer. In addition, piceatannol had been confirmed as an anti-tumor agent in leukemia cells [25,26]. However, little attention has been paid to the effects of piceatannol in CRC. Wolter F et al. found that piceatannol inhibits progression of colorectal cancer cells through inhibiting the S phase of the cell cycle [5]. Our data reinforce this anti-tumor action of piceatannol by showing that the ability of piceatannol to inhibit CRC cells growth by at least partially inducing an caspase-3-dependent apoptosis, suggesting that piceatannol could be used for the treatment of colorectal cancer.

Recent experimental studies have revealed that colorectal cancer is controlled by diverse miRNAs, such as miR-574, miR-26a, miR-17 and so on [16,27,28]. Lin PL et al. found that miR-21 promoted progression of colorectal cancer through modulating nuclear translocation of β-catenin [29]. A study performed by Fang L et al. showed that overexpression of miR-17–5p caused chemotherapeutic drug resistance and tumour metastasis of colorectal cancer by repressing PTEN expression [28]. Increasing evidence supports that miRNAs are involved in the anti-cancer action of various agents, such as arsenic trioxide, resveratrol, matrine and so on [11,30,31]. However, it is unknown whether miRNAs mediated the anti-cancer effect of piceatannol.

A variety of studies have demonstrated that miR-129 participated in the progression of kinds of cancers [32,33]. For example, miR-129 inhibited cell migration by targeting BDKRB2 in gastric cancer [32]. Huang YW and his colleagues found that the expression of miR-129 was lost in primary endometrial tumors, and restoration of miR-129 by cell transfection led to decrease SOX4 expression and reduced proliferation of cancer cells [34]. Recently, miR-129 has been confirmed to promote apoptosis and enhance chemosensitivity to 5-fluorouracil by regulating the anti-apoptotic BCl-2 in colorectal cancer [17]. Our data showed that piceatannol promoted the expression to miR-129, which mediated the pro-apoptotic effect of piceatannol in CRC cells.

Interestingly, our work revealed that miR-129 is a novel mechanism by which piceatannol produces anti-cancer effects. However, emerging reports showed that other miRNAs also contribute to the initiation and progression of CRC. Maybe this is the reason why the dysregulation of Bcl2 and Bax were not fully recovered when we knocked down of miR-129 before treating with piceatannol in CRC cells. Examining the roles of other miRNAs in piceatannol-induced growth inhibition in CRC cells warrants our future research.

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