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Original Research Article

Inhibition of Oral Carcinoma Cell Proliferation by miR-15b Carrying Pterostilbene and Related Mechanisms

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Abstract

Background: MicroRNA-15b (miR-15b) plays a cancer-suppressing role in various tumors, while sandalwood astragalus, as a natural antioxidant, has significant anti-cancer potential. However, the synergistic mechanism of miR-15b and Rosewood stilbene in oral cancer remains unclear.
Objectives: This study investigated the effects of miR-15b combined with Rosewood astragalus treatment on oral cancer KB cells.
Materials and Methods: Oral cancer KB cells were divided into the miR-15b mimics group, miR-15b inhibitor group, and negative control group, followed by measuring cell activities and B-cell lymphoma 2 (Bcl-2) expression.
Results: Transfection of miR-15b carrying pterostilbene mimic promoted overexpression of KB cell lines, inhibiting KB cell proliferation and increasing caspase-3 activity ($p < .05$). Overexpression of miR-15b carrying pterostilbene inhibited Bcl-2 expression ($p < .05$). However, transfection inhibitors significantly inhibited the expression of miR-15b carrying pterostilbene, promoting cell proliferation, upregulating Bcl-2, and inhibiting caspase-3. However, the changes in the expression of pterostilbene carried by miR-15b did not alter cell invasion ($p > .05$).
Conclusion: Pterostilbene carried by miR-15b downregulates Bcl-2 expression, increasing caspase-3 activity, promoting tumor cell apoptosis, and inhibiting the proliferation of oral cancer cells.

Keywords

Oral carcinoma, microRNA-15b carries pterostilbene, B-cell lymphoma 2, caspase-3, cell proliferation, cell apoptosis, cell invasion

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Introduction

Oral squamous carcinoma occupies more than 90% of all malignant tumors in the oral cavity and is one of the most frequent head and neck tumors. In recent years, the onset age of oral cancer has shown a trend of younger, and its early pathological features include oral mucosal leukoplakia and a rough surface (Chen et al., 2016; Choi et al., 2016). With the progression of the tumor, the lesion may develop into a papillary or ulcerative type, the latter of which is more common and often accompanied by lymph node metastasis (Hirko et al., 2021; Sun et al., 2022). Distal metastasis often occurs in advanced patients, which seriously affects the health and quality of life of patients (Chomik et al., 2015; Hu et al., 2016). Although chemotherapy is the primary treatment for oral cancer at present, due to individual differences, disease progression, clinical stages, symptoms, and immune status, the sensitivity and efficacy of chemotherapy vary greatly, and the prognosis of advanced patients is usually poor (He et al., 2016; Li et al., 2016).

MicroRNA (miRNA) is a class of small ribonucleic acid (RNA) molecules that play an important role in biological functions, and can affect body metabolism, growth, and development by regulating transcription factors, cell growth factors, and apoptosis genes (Gallach et al., 2014; Orang &

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Barzegari, 2014). Studies have shown that the role of miRNA in tumors is similar to that of oncogenes or tumor suppressor genes, which can affect tumors (Li et al., 2014; Mao et al., 2015). MicroRNA-15b (miR-15b) has a high homology with miR-15a. miR-15a is involved in a variety of tumors (Kim et al., 2014; Tewari et al., 2015). However, its specific mechanism in oral cancer remains unclear.

Pterostilbene, a stilbenoid compound extracted from plants such as blueberries, has strong antioxidant activity, which can fight oxidative stress, prevent and treat a variety of chronic diseases, and show potential in inhibiting tumor growth (Xu et al., 2021). Rosewood stilbene inhibits tumor cell activities by regulating reactive oxygen species (ROS) (He et al., 2024). Recently, miR-15b can carry Dalbergia and is expressed in a variety of tissues and organs (Kang et al., 2019), but its mechanism remains unclear.

Based on this, we explored the mechanism of miR-15b carrying Dantalostilbene in oral cancer cells. We hypothesized that miR-15b-carrying *Radix santalis* could inhibit oral cancer cell activities and promote apoptosis by regulating the expression of B-cell lymphoma 2 (Bcl-2) and caspase-3. We further verified this hypothesis by transfecting MiR-15b-carrying Dantalostilbene mimics and inhibitors and explored their potential application in oral cancer treatment.

Materials and Methods

Experimental Material

The oral cancer KB cell line used in this study was purchased from Shanghai Fuxiang Biotechnology Co., Ltd., No. CCL-17, with a STR identification certificate, was kept in our laboratory for a long time.

Oral Cancer KB Cell Culture and Grouping

KB cell line was cultured under 100% saturated humidity with 5% CO_2 at 37°C. Cells that grew in a layer of attachment were digested with 0.25% trypsin containing 10% fetal calf serum. To compare the effects of miR-15b-carrying mimics and inhibitors of sandalwood astragalus on the proliferation, apoptosis, and invasion of KB cells in oral cancer, non-specific effects were excluded by a negative control (NC) group. Density inoculation channels were reserved at a ratio of 1:2 and divided into the following four groups: miR-15b carrying pterostilbene inhibitor NC group, miR-15b carrying pterostilbene mimic group, miR-15b carrying pterostilbene mimic NC group, and miR-15b carrying pterostilbene inhibition dose group.

Transfection of miR-15b Carrying Pterostilbene Mimics and Transfection of miR-15b Carrying Pterostilbene Inhibitors Using Liposome Method

Cell transfection was performed according to the liposome construction method (Akbarzadeh et al., 2013).

miR-15b mimic group and miR-15b inhibitor group: miR-15b mimic group (Guangzhou Ruibo Biotechnology Co., Ltd., item No.: miR10000415-1-5), miR-15b inhibitors (Guangzhou Ruibo Biotechnology Co., Ltd., product number: miR20000415-1-5) were obtained by Lipofectamine™ 2000 (Invitrogen, USA, product number: 11668-019) transfected into KB cells at a concentration of 50 nM. Twenty-four hours after transfection, Rosewood stilbene (Sigma, USA, article number: P1499) was added to the final concentration of 10 μM, and the cells were cultured for 48 h.

miR-15b mimic NC group (mimic NC group) and miR-15b inhibitor NC group (inhibitor NC group): miR-15b mimic NC group (Guangzhou Ruibo Biotechnology Co., Ltd., article number: miRN000215-1-5) and the NC of miR-15b inhibitors (Guangzhou Ruibo Biotechnology Co., Ltd., No.: miRN00215-1-5) were transfected into KB cells by Lipofectamine™ 2000 at 50 nM. About 24 h after transfection, an equal volume of dimethyl sulfoxide (DMSO) (Sigma, USA, item number: D8418) was added as a solvent control, and the cells continued to be cultured for 48 h.

Real-time Polymerase Chain Reaction (PCR)

Total ribonucleic acid (RNA) was extracted, and complementary deoxyribonucleic acid (cDNA) double-stranded was prepared by real-time quantitative polymerase chain reaction (RT-qPCR). Real-time detection was done by RT-qPCR to determine relative levels (template: cDNA; internal reference: glyceraldehyde 3-phosphate dehydrogenase [GAPDH]). The primers are shown in Table 1.

3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) Detection of Effects of Cell Proliferation in Each Group

MTT method (Mosmann, 1983) detected cell proliferation. The KB cells were washed to remove residual media and cell debris. After washing, cells were resuspended in fresh α-MEM medium (Gibco, USA, item no. In 12571-063), the cell density was adjusted to 1×10^5 cells/mL, and inoculated. After 24 h, 20 μL MTT solution (5 mg/mL, Sigma, USA, article number: M2128) was added for 4 h. Subsequently, 150 μL of DMSO (Sigma, USA, article number: D8418) was added, and absorbance was determined at 570 nm using BioTek Synergy H1, USA. The absorbance value was calculated to determine the cell proliferation rate. The measurement was repeated three times.

Transwell Chamber Detection of Cell Invasion Impact in Each Group

Cells containing SDF-1α (1×10^5 cells/mL) were inoculated into the lower chamber and incubated for 12 h. After the supernatant was discarded, 150 μL of DMSO (Sigma, USA,

Table 1. Primer Sequences.

Gene	Forward Primer 5′-3′	Reverse Primer 5′-3′
GAPDH	AGTACCAGTCTGTTGCTGG	TAATAGACCCGGATGTCTGGT
miR-15b	CTTATCTCTGTGTGGAACTT	CCTCTCAGCG CTCACAGCTTG
BCL-2	CTCTGTCTCCCACAGAAG	TTACCTCGCATGGGGTAATT

Note: BCL-2: B-cell lymphoma 2; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; miR-15b: MicroRNA-15b.

article number: D8418) was added, and absorbance was determined at 565 nm. After absorbing floating color, absorbance was detected at 565 nm. Cell migration was observed and photographed under a conventional microscope. The measurement was repeated three times.

Flow Cytometry Was Used to Detect the Effect of Apoptosis

The cells of each group were cultured according to 1×10^5/mL, 200 µL were inoculated into 6-well plates, and AnnexinV-fluorescein isothiocyanate (FITC) and propidium iodide (PI) solution were added to measure apoptosis by flow cytometry for 15 min. The measurement was repeated three times.

Caspase-3 Activity Detection

Transfected cells were seeded at 1×10^3 cells/well (200 µL). After 4 h, the cells were transferred to Dulbecco's modified Eagle medium (DMEM) containing 10% caspase-3 for 1 h. The caspase-3 kit was used to detect cell growth and draw a growth curve.

Western Blot

Protein was extracted and determined using the bicinchoninic acid (BCA) method. A monoclonal antibody (1:400) probe was used overnight, washed with tris-buffered saline with Tween (TBST), and a 1:500 secondary antibody probe was used for 1 h. Then it was irradiated with a luminescent agent, and protein expression was calculated using ImageJ software (internal reference: GAPDH) for grayscale processing.

Statistical Analysis

All experimental data were expressed as mean ± SD and analyzed using SPSS 21.0 software (IBM, USA). To verify data normal distribution and homogeneity of variance, Shapiro–Wilk test and Levene test were first performed. A one-way analysis of variance (ANOVA) was used for comparison between groups, and the *F*-test assessed the significance. For the groups with significant differences, the least significant difference (LSD) method was further used for pairwise comparison. Non-parametric tests (such as the Kruskal–Wallis test) are used to analyze data that do not conform to normal distribution or have uneven variances. $p < .05$ refers to a difference. In all analyses, appropriate testing methods are selected according to the experimental design to ensure the scientific reliability of the results.

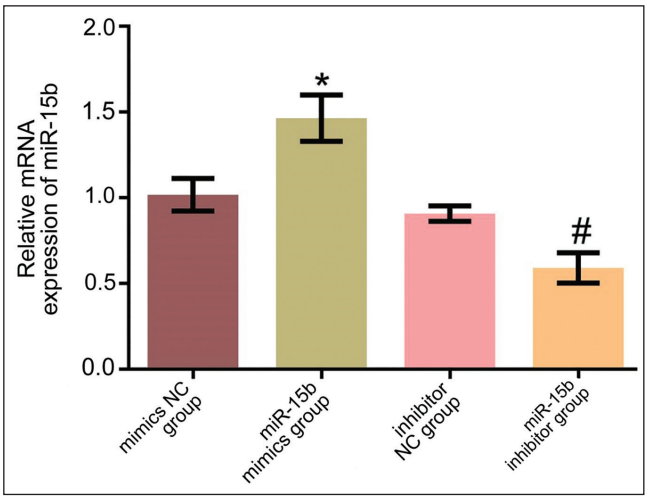


Figure 1. MicroRNA-15b (miR-15b) Expression in KB Cells.

Notes: miR-15b expression levels in KB cells transfected with miR-15b mimic, inhibitor, and their respective negative controls (NC). Data are presented as mean ± standard deviation (SD) ($n = 3$). *$p < .05$ compared to mimic NC group; #$p < .05$ compared to inhibitor NC group.

Results

MiR-15b Expression in KB Cells

As shown in Figure 1, compared with the control group, the expression of miR-15b in the miR-15b mimic group was significantly upregulated ($p < .05$). However, miR-15b was downregulated in the miR-15b inhibitor group ($p < .05$).

KB Cell Proliferation and miR-15b

Combined treatment of miR-15b simulant and Radix astragali significantly inhibited KB cells' proliferation ($p < .05$), while the combined treatment of miR-15b inhibitor and Radix astragali promoted KB cell proliferation ($p < .05$). The cell proliferation of the NC group was not different from that of the untreated group ($p > .05$) (Figure 2).

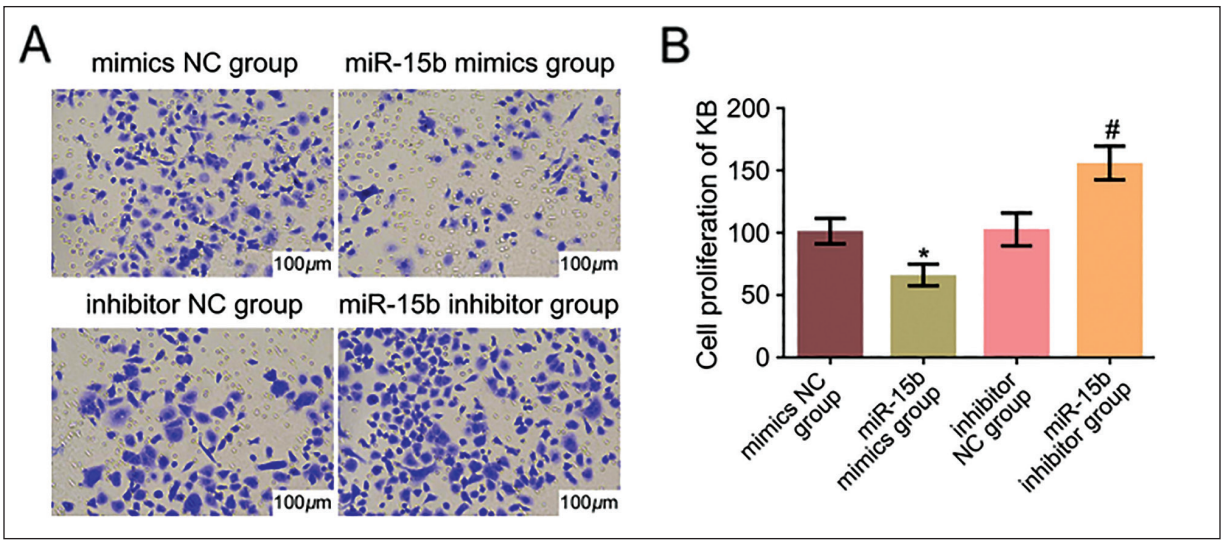


Figure 2. Effect of MicroRNA-15b (MiR-15b) and Pterostilbene on KB Cell Proliferation.

Notes: (A) Representative images of KB cell proliferation in each group. (B) Quantitative analysis of cell proliferation. Data are presented as mean ± standard deviation (SD) (n = 3). *p < .05 compared to mimic negative controls (NC) group; #p < .05 compared to inhibitor NC group. Scale bar: 100 μm.

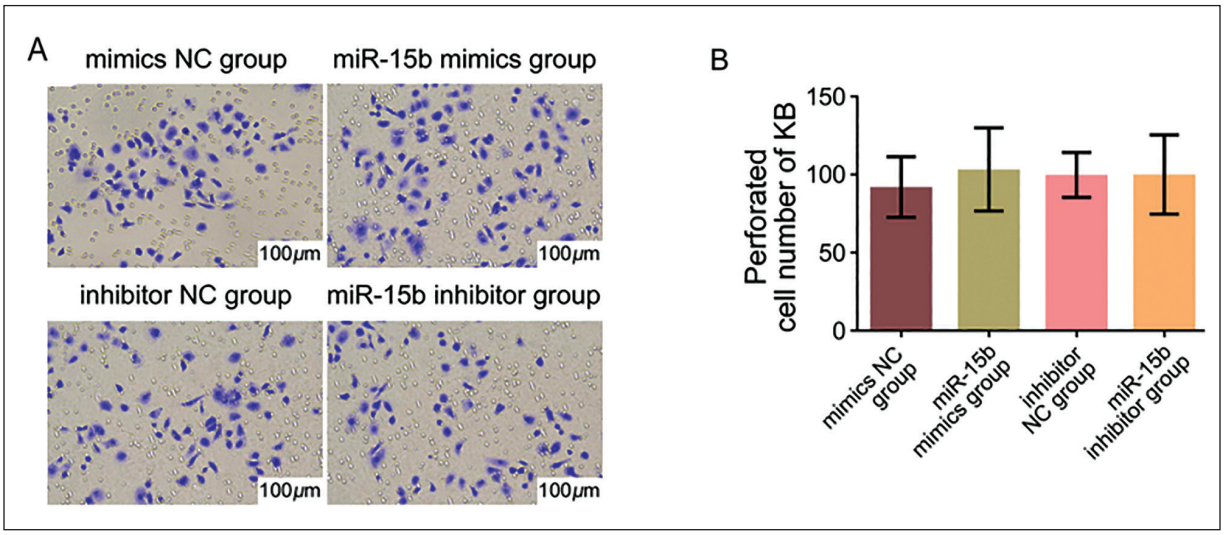


Figure 3. Effect of MicroRNA-15b (MiR-15b) and Pterostilbene on KB Cell Invasion.

Notes: (A) Representative images of KB cell invasion in each group; (B) Quantitative analysis of cell invasion. Data are presented as mean ± standard deviation (SD) (n = 3). *p < .05 compared to mimic negative controls (NC) group; #p < .05 compared to inhibitor NC group. Scale bar: 100 μm.

MiR-15b and KB Cell Invasion

Combined treatment of miR-15b simulant and Radix astragali did not affect the invasion ability of KB cells (p > .05), and the combined treatment of miR-15b inhibitor and Radix astragali did not significantly change the invasion ability of KB cells (p > .05). The cell invasion ability of the NC group was not different from that of the untreated group (p > .05). These results indicate that the combined effects of miR-15b and Radix astragali mainly affect cell proliferation but have little impact on cell invasion (Figure 3).

MiR-15b and KB Cell Apoptosis

The apoptosis rate of KB cells was significantly increased in the combination of miR-15b mimics and Rosewood. In contrast, the combination of miR-15b inhibitors and Rosewood significantly inhibited the apoptosis of the cells (Figure 4A). The results of caspase-3 activity detection showed that combined treatment with miR-15b mimics significantly increased caspase-3 activity in KB cells (p < .05), while combined treatment with miR-15b inhibitors significantly inhibited caspase-3 activity (p < .05). The caspase-3 activity of the NC group was

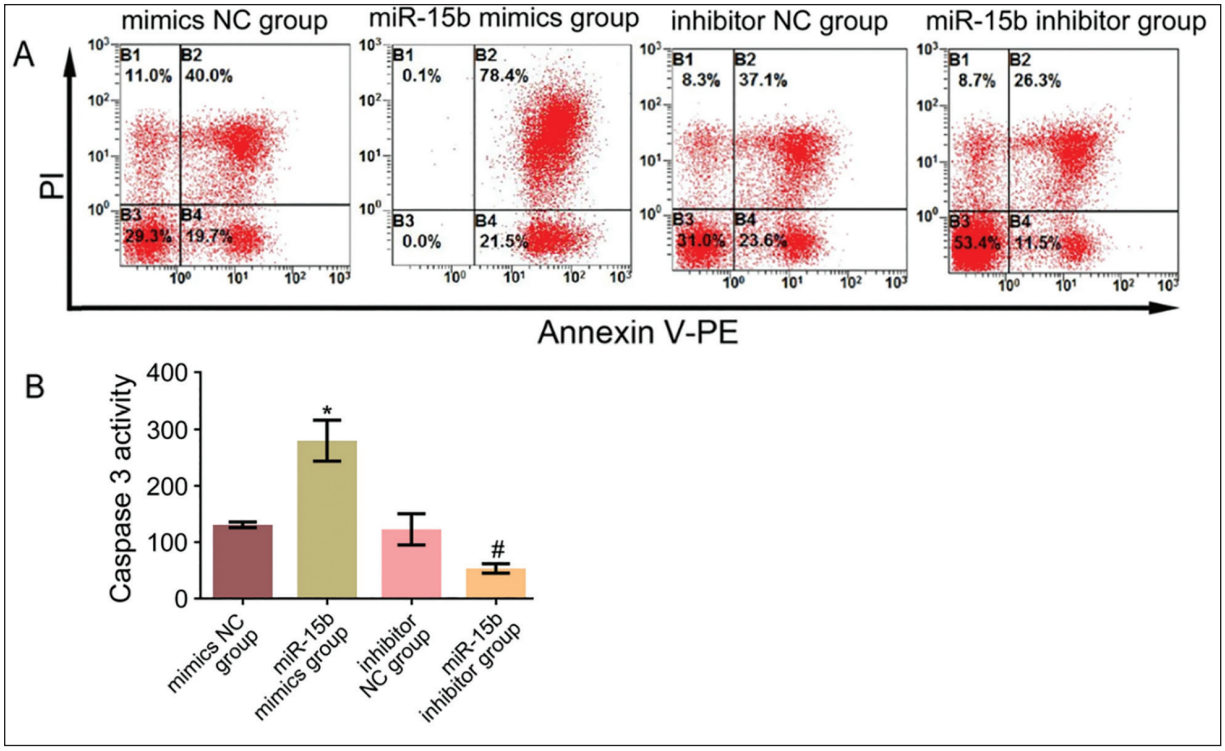


Figure 4. Effects of MicroRNA-15b (miR-15b) and *Radix astragalus* on Apoptosis of KB Cells.

Notes: (A) The representative images of KB cell apoptosis in each group; (B) caspase-3 activity of KB cells with miR-15b carries pterostilbene expression. *$p < .05$ compared to mimics negative controls (NC) group; #$p < .05$ compared to inhibitor NC group.

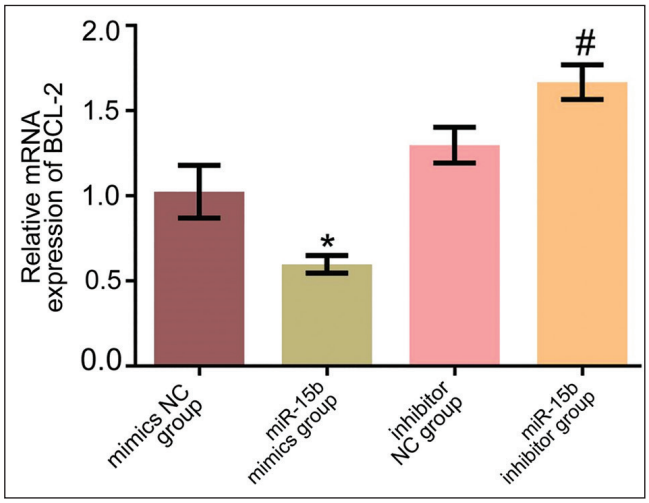


Figure 5. B-cell Lymphoma 2 (Bcl-2) Messenger Ribonucleic Acid (mRNA) Level in KB Cells.

Note: *$p < .05$ compared to mimics negative controls (NC) group; #$p < .05$ compared to inhibitor NC group.

not different from that of the untreated group ($p > .05$) (Figure 4B). miR-15b and *Radix astragalus* promote apoptosis of tumor cells by regulating caspase-3 activity.

Effects of miR-15b and Rosewood Stilbene on Bcl-2 Expression

Combining miR-15b simulant and *Radix santalis* significantly downregulated Bcl-2 in KB cells ($p < .05$). However, the combination of miR-15b inhibitor and Radix astragali significantly upregulated Bcl-2 ($p < .05$). Bcl-2 levels in the NC group were not different from those in the untreated group ($p > .05$). These results suggest that miR-15b and Rosewood stilbene inhibit tumor cell survival by regulating Bcl-2 expression (Figures 5 and 6).

Discussion

Due to the abundant distribution of vessels and lymph tissues in the oral cavity, oral carcinoma is predisposed to early metastasis, causing rapid progression and a lower survival rate (Lee et al., 2015). The identification of effective molecular markers is thus of great importance for evaluating treatment strategy, efficacy, and prognosis of patients for individualized treatment. It can also help to optimize the treatment methodology in clinics, thus providing new insights for cancer treatment (Suzuki et al., 2016).

miRNAs can regulate the expression of cell growth factors, transcription factors, and so on, at post-transcriptional levels (Zhang et al., 2015). miRNAs regulate gene expression

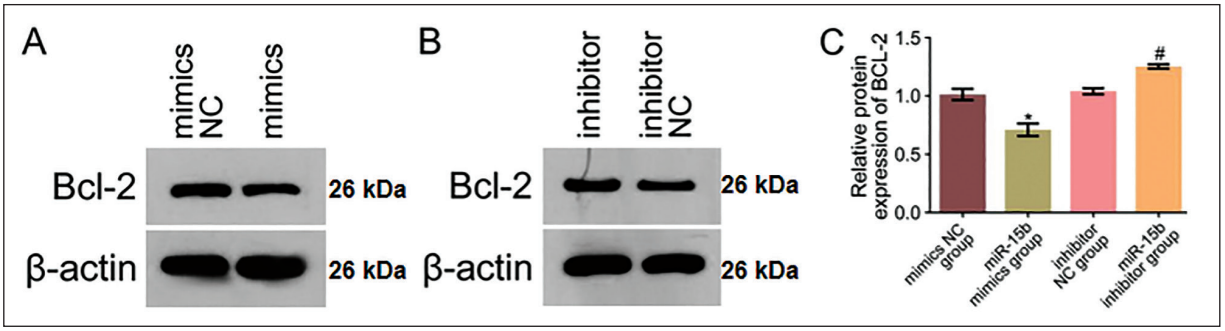


Figure 6. Western Blotting Bands of B-cell Lymphoma 2 (Bcl-2) Protein.

Notes: (A) MicroRNA-15b (miR-15b) carries pterostilbene mimics transfection and negative controls (NC) groups; (B) miR-15b inhibitor transfection and NC groups; (C) Effects of miR-15b carrying pterostilbene on Bcl-2 protein expression level in KB cells. *$p < .05$ compared to mimics NC group; #$p < .05$ compared to inhibitor NC group. mRNA: Messenger ribonucleic acid.

at the post-transcriptional level, thereby directly affecting the body's metabolism, growth, and development (Sivanantham et al., 2016). Pterostilbene is a stilbene compound obtained from blueberries and has several pharmacological properties. Pterostilbene inhibits the production of ROS and can fight against various free radicals. miR-15b carrying pterostilbene can be expressed in various important tissues and organs such as the heart, liver, and kidneys. Its expression and distribution lack tissue specificity (Zerp et al., 2015). The transcription of miR-15b carrying pterostilbene mimic can promote its overexpression in oral cancer cells and inhibit cell proliferation. Transfection-related inhibitors can reduce the expression of miR-15b carrying pterostilbene and promote the proliferation of oral cancer cells. Overexpression or silencing of miR-15b carrying pterostilbene did not affect tumor cell invasion. Bcl-2 is a target gene for miR-15 family. Abnormal proliferation of tumor cells causes the formation and development of tumors. Tumor cells proliferate too fast, and tumor cell death is reduced, making it challenging to control tumor progression, in which apoptosis plays a role that cannot be ignored. Apoptosis is a way of regulating the body's homeostasis. It delays the occurrence of tumors by inhibiting excessive tumor growth. When cells initiate the apoptosis program, it can promote activation of the apoptosis family. If caspase-3 activity is upregulated, tumor cell apoptosis can be induced (Yang et al., 2015). When Bcl-2 is overexpressed, damaged cells will not undergo apoptosis and will progress to tumors under the influence of related genes, including proliferation and growth inhibitory genes (Yang et al., 2016). However, it has not been confirmed whether pterostilbene carried by miR-15b can regulate the proliferation of oral cancer cells through the target gene Bcl-2. This study confirmed that transfection of miR-15b carrying pterostilbene mimic and overexpression of miR-15b carrying pterostilbene significantly inhibited Bcl-2 expression and increased caspase-3 activity. On the other hand, transfection inhibitors significantly downregulated miR-15b carrying pterostilbene in oral cancer cells. These results confirm that, during the development of oral cancer, miR-15b carrying pterostilbene can play a regulatory role in pathogenesis. In addition to directly regulating Bcl-2 expression, miR-15b and Radix astragali may enhance the inhibitory effect on tumor cells through synergistic interaction. As a natural antioxidant, Rosewood stilbene can induce tumor cell apoptosis by inhibiting ROS production and regulating apoptosis-related signaling. miR-15b further enhanced the proapoptotic effect of Radix astragali by directly targeting anti-apoptotic genes such as Bcl-2. Therefore, the mechanism by which miR-15b inhibits the survival of tumor cells by regulating Bcl-2 is worthy of further investigation.

Conclusion

In this study, the combination of miR-15b and *Radix santalis* significantly inhibited oral cancer KB cell activities by downregulating Bcl-2 and upregulating caspase-3 activity. These results not only reveal the synergistic mechanism of miR-15b and Radix astragali in inhibiting oral cancer cells but also provide targets for treating oral cancer. However, the combined treatment of miR-15b and Radix astragali may synergistically inhibit the survival and proliferation of tumor cells through multi-target and multi-pathway. However, this study is still a basic study at the cellular level, and its specific pharmacological effects have not been verified in animal experiments; further exploration is still needed.

Abbreviations

AMPK: AMP-activated protein kinase; ANOVA: Analysis of variance; BCA: Bicinchoninic acid; Bcl-2; B-cell lymphoma 2; CO_2: Carbon dioxide; COX-2: Cyclooxygenase-2; DMEM: Dulbecco's modified Eagle medium; DMSO: Dimethyl sulfoxide; ELISA: Enzyme linked immunosorbent assay; ERK: Extracellular signal-regulated kinase; FITC: Fluorescein isothiocyanate; FNDC5: Fibronectin-type III domain containing 5; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; IL-6: Interleukin-6; iNOS: Inducible nitric oxide synthase; LSD: Least significant difference; miR/miRNA: MicroRNA; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide;

mTOR: Mammalian target of rapamycin; NC: Negative control; NF-κB: Nuclear factor kappa B; PCR: Polymerase chain reaction; PI: Propidium iodide; PI3K/AKT: Phosphatidylinositol 3-kinase/protein kinase B; ROS: Reactive oxygen species; RT-qPCR: Real-time quantitative polymerase chain reaction; SDF-1α: Stromal cell-derived factor 1 alpha; SIRT1: Sirtuin 1; SREBP: Sterol regulatory element-binding protein; STR: Short tandem repeat; TBST: Tris-buffered saline with Tween; TNF-α: Tumor necrosis factor-alpha.

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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 The First Affiliated Hospital of Hubei University of Science and Technology.

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Informed Consent

Not applicable.

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