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Original Research Article

Effects of baicalin on the proliferation of extranodal NK/T-cell lymphoma cells and the sensitivity of the cells to the drug

Xiaohui Duan, Jianhong Wang, Yao Lv, Jing Liu, Shixiong Wang, Zhentian Wu, Binxuan Wang, Ming Lu, Na Yang, Xinwei Liu, Zheshen Lin, Yeye Li, Rong Liang*

Department of Hematology, Xijing Hospital, First Affiliated Hospital of Air Force Military Medical University, No. 127, Changle West Road, Xincheng District, Xi'an City, Shaanxi Province; Xi'an, Shaanxi 710032, China

For correspondence:* ***Email:* *lurongfen057665@126.com*

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Abstract

Purpose: *To evaluate the effect of baicalin on the proliferation of extranodal NK/T-cell lymphoma cells and the sensitivity of the cells to the drug.*
Methods: *Cell-counting-kit (CCK) assay was used to determine cell activity, while the antagonistic, superimposed and synergistic effects of drug combinations were investigated by coefficient of drug interaction (CDI). Cell proliferation was assessed using 5-ethynyl-2'- deoxyuridine (EdU) test. Flow cytometry was carried out to determine the apoptosis of studied extranodal NK/T-cell lymphoma cells. Furthermore, western-blot was used to evaluate the expression levels of BCL2, BAX, cleaved-caspase3 and caspase3 of the cells.*
Results: *Survival of SNK-6 and YTS cells decreased gradually in a concentration-dependent manner (r = -0.97 and -0.98). Cell viability at the same concentration diminished with time, but with increase in cisplatin concentration, cell viability at the same time point also decreased. At cisplatin concentrations of 5, 10, and 20 µmol/L, reduction in cell viability between the two groups were significantly different ($p < 0.001$). Furthermore, the proliferation of SNK-6 and YTS cells decreased with increasing baicalin concentrations while apoptosis of the cells increased with increasing baicalin concentration.*
Conclusion: *Baicalin inhibits the proliferation but promotes the apoptosis of SNK-6 and YTS cells. Cisplatin plus baicalin lowers cell proliferation rate and increase the apoptosis rate of both SNK-6 and YTS cells compared with baicalin or cisplatin alone. This drug combination should be further explored for its apoptosis potential in animal models.*

Keywords: *Baicalin, Proliferation, Extranodal NK/T-cell lymphoma cells, Drug sensitivity*

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INTRODUCTION

Extranodal NK/T cell lymphoma (ENKTCL) is a highly aggressive hematologic malignancy with geographic characteristics and an extremely low incidence (0.2 - 0.4 %) in the United States and Europe [1,2]. Extranodal NK/T cell lymphoma accounts for 22 % of peripheral T-cell

lymphomas (PTCLs) in Japan [3] and 30 % in China [4]. There is currently no standard chemotherapy regimen for the management of ENKTCL. Clinically, ENKTCL is managed by radiation +/- chemotherapy in stage I/II, and by chemotherapy +/- radiotherapy and autologous hematopoietic stem cell transplantation (ASCT) in stage III/IV [5]. Research has shown that radiotherapy provided an enrichment in the 5-year overall survival (OS) by 48 % in patients who received chemotherapy only [6]. Central nervous system recurrence has been frequently reported in patients with advanced ENKTCL after combined therapy of chemotherapy plus ASCT, resulting in a poor median duration of remission of only 15.2 months [7].

Currently, methylase or platinum-containing drug-based regimens are predominantly recommended [8]. However, drug-related toxicity and drug resistance after long-term medication severely compromise the therapeutic effect and long-term survival of patients.

A previous study found that miR-30b inhibits cisplatin resistance in ENKTCL SNK-6 and YTS cell lines by targeting macrophage-derived chemokine (CCL22) [9]. This suggests a positive correlation between CCL22 and cisplatin resistance. Cisplatin is an important chemotherapy drug for ENKTCL. Recent studies have indicated enormous advantages of baicalin in the treatment of gastric cancer, esophageal cancer, breast cancer and other tumors [10-13]. Previous research has found that baicalin inhibits the growth of SNK-6 and YTS cells through the FOXO3/CCL22 signaling pathway [14]. However, the effects of baicalin enhancing chemotherapeutic drug sensitivity and its regulatory mechanism remain poorly understood. This study was performed to determine the role of baicalin in enhancing the antitumor effect and sensitizing effect of cisplatin.

EXPERIMENTAL

Reagents and instruments

Baicalin (crystalline powder, standard, HPL ≥ 98 %) was purchased from Yuanye Biotechnology Co. Human ENKTCL cell lines SNK-6 and YTS were provided by Shanghai Enzyme Research Technology Company. Cisplatin (DDP) was from Jiangsu Hausen Pharmaceutical Co., Ltd. BeyoClick™ EdU-488 cell proliferation assay kit and CO_2 cell culture chamber were from Thermo, USA. 0.25 % Trypsin (1×) from HyClone, USA. Cell culture dishes and culture flasks were from Guangzhou JITE Biofilter Co. Inverted fluorescence microscope was from Leica, Germany. High-speed frozen centrifuge was from Ohaus, USA. Flow cytometry was from Becton Dickinson, USA; Annexin V-FITC apoptosis kit was from Biyuntian (Shanghai) Biotechnology Co. Rabbit anti-GAPDH-loaded control polyclonal antibody (primary antibody), HRP-conjugated Affinipure goat anti-rabbit IgG (H + L) (secondary antibody), BCL2, BAX, cleaved-caspase3, caspase3 antibodies were from Proteintech, USA. RIPA cell lysis solution was from Bio-world, USA. BCA protein quantification kit was from Beijing BoaoTuoDa Technology Co.

CCK assay

To determine the optimal concentration and optimal duration of action of cisplatin, SNK-6 and YTS cell lines were incubated overnight in a 96-well plate, with 5000 cells/well, at 37 °C with 5 % CO_2. The supernatant was removed, and 1, 5, 10, and 20 μmol/L of cisplatin were added to the sample wells, while no drug was added to the control group. Five samples of each concentration were tested in 3 replicates, and each cell line was assayed at 24, 48, and 72 h after incubation. Each well was incubated with CCK8 reagent for 4 h. Absorbance at 450 nm was determined by enzyme marker. The cell activity of the controls, 10 μmol/L of baicalin, 20 μmol/L of baicalin, 10 μmol/L of cisplatin, 10 μmol/L of baicalin + 10 μmol/L of cisplatin, and 20 μmol/L of baicalin + 10 μmol/L of cisplatin were determined the CCK assay.

The cell activity (C) was calculated using Eq 1.

$$C = \{(At-Ab)/(Ac-Ab)\}100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

where At = absorbance of treated group, Ab = absorbance of blank group, and Ac = absorbance of control group.

Determination of the coefficient of drug interaction (CDI)

The CDI was employed to determine the antagonistic, superimposed, and synergistic effects of drug combinations. It was calculated using Eq 2.

$$CDI = ABI (A \times B) \quad \ldots\ldots\ldots\ldots\ldots (2)$$

where A or B is the ratio of cell survival in the single drug group to that in the control group, and AB is the ratio of cell survival in the combination group to that in the control group.

A CDI ≥ 1 indicates antagonism between drugs, 1 > CDI ≥ 0.7 indicates superposition between drugs, and CDI < 0.7 indicates significant

synergism between drugs [18]. The determinations were repeated thrice.

5-Ethynyl-2'- deoxyuridine (EDU) assay

The cells were divided into a control group, 10 μmol/L of baicalin group, 20 μmol/L of baicalin group, 10 μmol/L of cisplatin group, 10 μmol/L of baicalin + 10 μmol/L of cisplatin group, and 20 μmol/L of baicalin + 10 μmol/L of cisplatin group. Logarithmic phase cells were incubated overnight in an 18-well plate with 3×10^4 cells per well at 37 ℃, 5 % CO_2. The cells were then fixed with 4 % paraformaldehyde for 15 min at room temperature and re-stained with Hoechst reagent. Finally, the cell proliferation status was recorded using a fluorescent microscope. The ratio of EdU minus positive cells (rE-pC) was computed as shown in Eq 3.

rE-pC = {(rE-pC)/(H-sC)}100 …… (3)

where H = Hoechst cells, and sC = stained cells

Evaluation of apoptosis

The cells were divided into a control group, 10 μmol/L of baicalin group, 20 μmol/L of baicalin group, 10 μmol/L of cisplatin group, 10 μmol/L of baicalin + 10 μmol/L of cisplatin group, and 20 μmol/L of baicalin + 10 μmol/L of cisplatin group. After 24 h of drug treatment, the supernatant was collected, rinsed with PBS and used for apoptosis staining. Specifically, 195 μL of Annexin V-FITC conjugate was added to resuspend the cells and 5 μL of Annexin V-FITC was added and mixed, followed by 10 μL of propidium iodide staining solution and incubated in the dark for 20 min at room temperature, and apoptosis was measured by flow cytometry over 1 h.

Determination of expressions of BCL2, BAX, cleaved-caspase3 and caspase3

Total cellular protein was extracted by adding RIPA lysis buffer to each group of cells at logarithmic growth stage, and protein quantification was performed using BCA method. Absorbance values were measured at 562 nm and a standard curve was plotted from the absorbance values to determine the concentration of the sample to be measured. During gel electrophoresis, each well was sampled according to the concentration of BCA quantified for analysis, and 3 μL of marker was also added to the wells of the same gel as a reference. The PVDF membrane was transferred in an incubator with 5% skimmed milk powder. Primary antibodies were diluted with 5 % skimmed milk powder at the following ratios: 1:1000 dilution for Bcl2, 1:2000 dilution for Bax, 1:500 dilution for cleaved-caspase3, 1:5000 dilution for caspase3, with rabbit anti-human polyclonal antibody GAPDH as internal reference. The primary antibodies were incubated overnight at 4 ℃. The membrane was rinsed thrice with TBST buffer. The secondary antibody diluted with TBST buffer was incubated at room temperature for 1 h. The membrane was rinsed thrice with TBST buffer and soaked in ECL luminescence reagent, followed by the chemiluminescence apparatus to acquire the images. The membrane was scanned to compare the grayscale changes of each group. The experiment was repeated thrice.

Statistical analysis

Statistical analysis was done using SPSS 13.0 software, and GraphPad Prism 8 software was employed to plot graphics. Western blot image quantitative grayscale values were calculated using Image J software (v2.1.4.7). The measurement data were expressed as mean ± standard deviation (SD), and the Student's *t*-test was used to test the difference between the two groups. Count data were analyzed using chi-square test. All tests were 2-sided, with a significance level of 0.05.

RESULTS

Effect of baicalin on the proliferation of SNK-6 and YTS cells

The proliferation rates of SNK-6 and YTS cell lines after treatment with 5, 10, and 20 μmol/L baicalin, are reported in Figures 1 A and B. Survival of SNK-6 and YTS cells decreased gradually in a concentration-dependent manner (r = -0.97, and -0.98).

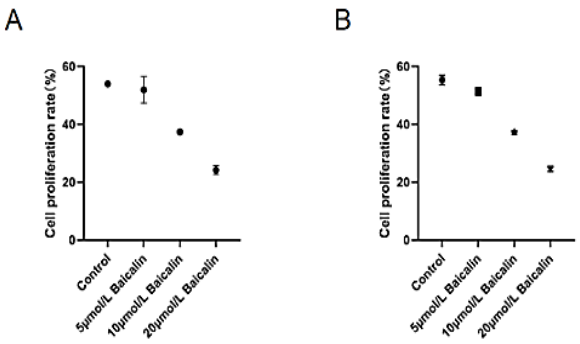

Figure 1: Effects of different concentrations of baicalin on the proliferation of SNK-6 and YTS cells by EdU immunostaining

Effect of cisplatin on the proliferation of SNK-6 and YTS cells

Cisplatin at different concentrations (1, 5, 10, and 20 μmol/L) was applied to ENKTCL cell lines SNK-6 and YTS, and the cell viability after 24, 48, and 72 h diminished with time, while with an increase in cisplatin concentration, the cell viability at the same time point also decreased. No statistical difference was found in cell viability for both SNK-6 and YTS cell lines when the cisplatin concentration was 1 μmol/L in comparison with the control group. When the cisplatin concentrations were 5, 10, and 20 μmol/L, the two groups exhibited a significantly different reduction of cell viability ($p < 0.001$). The IC_{50} of cisplatin was 15.9 μmol/L in the SNK-6 cell line while its IC_{50} was 10.87 μmol/L in the YTS cell line. Given the above data, a cisplatin concentration of 10 μmol/L was chosen for subsequent experiments.

Effect of baicalin on cisplatin sensitivity

Proliferation of cisplatin and CDI values

As shown in Table 1, after 48 h of treatment, when baicalin concentration was 10 μmol/L and cisplatin concentration was 10 μmol/L, the CDI value was less than 0.7 when the two drugs were co-administered, indicating a significant synergistic effect between the drugs. When baicalin concentration was 20 μmol/L and cisplatin concentration was 10 μmol/L, the CDI values were greater than 0.7 and less than 1, suggesting that with the increase of baicalin drug concentration, the combination between drugs predominantly showed a superimposed effect.

Inhibition of SNK-6 and YTS cell growth by cisplatin

The inhibitory effect of baicalin and cisplatin on the proliferation of SNK-6 and YTS cells was found under fluorescence microscopy (Figure 2 A and C). The proliferation rates of SNK-6 and YTS cell lines after treatment are shown in Figures 2 B and D. All groups were statistically different from the control group ($p < 0.0001$), and the proliferation rates of both SNK-6 and YTS cells gradually decreased with increasing baicalin concentration. The proliferation rates of SNK-6 and YTS cells were lower in both drug and single-drug groups than with either the 10 μmol/L baicalin + 10 μmol/L cisplatin group or the 20 μmol/L baicalin + 10 μmol/L cisplatin group or compared to the groups with equivalent concentrations of baicalin or cisplatin alone ($p < 0.0001$). The same results were obtained when the viability of each group of cells was determined using the CCK method (Figures 3 A and B).

Cisplatin-promoted SNK-6 and YTS cell apoptosis

Apoptosis was determined using flow assay, and the apoptosis rates of SNK-6 and YTS cell lines after treatment is reported in Figures 4 A and B, respectively. All groups were statistically different from the control group ($p < 0.0001$). The apoptosis rate of both SNK-6 and YTS cells gradually increased with increasing baicalin concentration. The apoptosis rates of SNK-6 and YTS cells were significantly higher in the 10 μmol/L of baicalin + 10 μmol/L of cisplatin and 20 μmol/L of baicalin + 10 μmol/L of cisplatin groups than in the respective equivalent concentrations of baicalin or cisplatin alone ($p < 0.0001$) (Figures 4 C and D).

Regulation of apoptosis-related proteins in cisplatin SNK-6 and YTS cells

In SNK-6 cell lines, the expression of Bcl-2 anti-apoptotic proteins was decreased ($p < 0.01$) and the expression of Bax pro-apoptotic proteins was increased ($p < 0.05$) in the 10 μmol/L of baicalin + 10 μmol/L of cisplatin group compared with the 10 μmol/L of cisplatin group. The expression of cleaved caspase3 protein was significantly higher ($p < 0.0001$), and only cleaved caspase3 protein expression was higher in the 10 μmol/L of baicalin + 10 μmol/L of cisplatin group versus the 10 μmol/L baicalin alone group ($p < 0.01$). The expression levels of Bcl-2 anti-apoptotic protein in the 20 μmol/L baicalin + 10 μmol/L cisplatin group were not significantly changed compared with either the 10 μmol/L cisplatin group alone or the 20 μmol/L baicalin group alone, and the expression levels of Bax pro-apoptotic protein in the 20 μmol/L baicalin + 10 μmol/L cisplatin group were increased compared with the 10 μmol/L cisplatin group alone ($P < 0.01$).

Table 1: Dual drug interaction coefficients of baicalin and cisplatin at different concentrations

Cell	baicalin	Cisplatin	Comb (%)	CDI
SNK-6	10μmol/L (52%)	10μmol/L (45%)	35	0.67
SNK-6	20μmol/L (48%)	10μmol/L (45%)	27	0.80
YTS	10μmol/L (53%)	10μmol/L (48%)	37	0.69
YTS	20μmol/L (49%)	10μmol/L (48%)	28	0.84

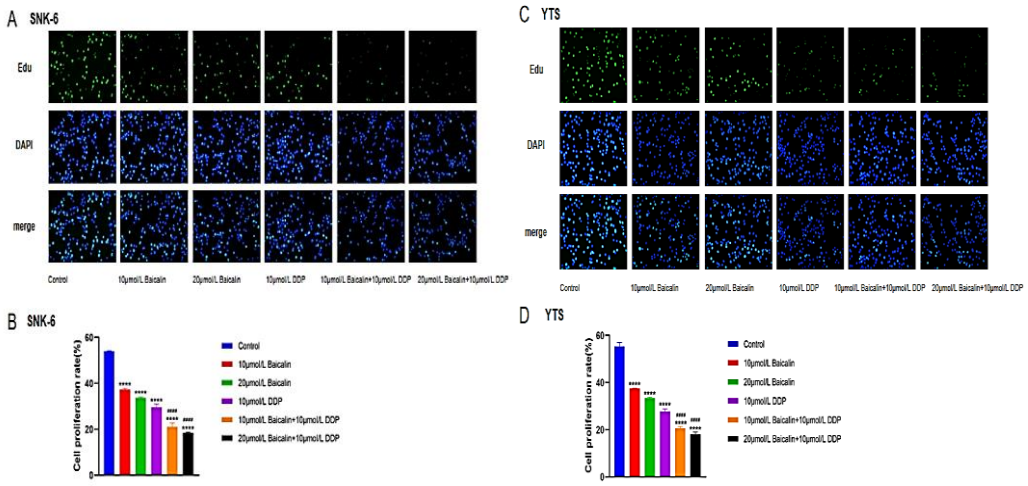

Figure 2: Effects of different concentrations of baicalin and cisplatin on cell proliferation. The cell proliferation capacities of (A and B) SNK-6 and (C and D) YTS. ($p < 0.05$) versus control

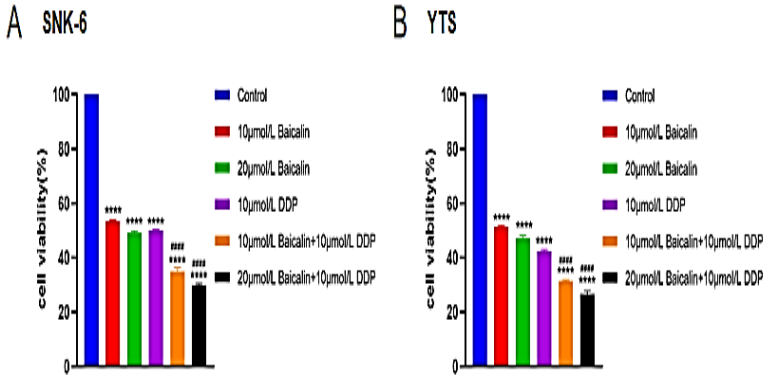

Figure 3: Cell proliferation ability was measured using CCK-8 assay (A-B)

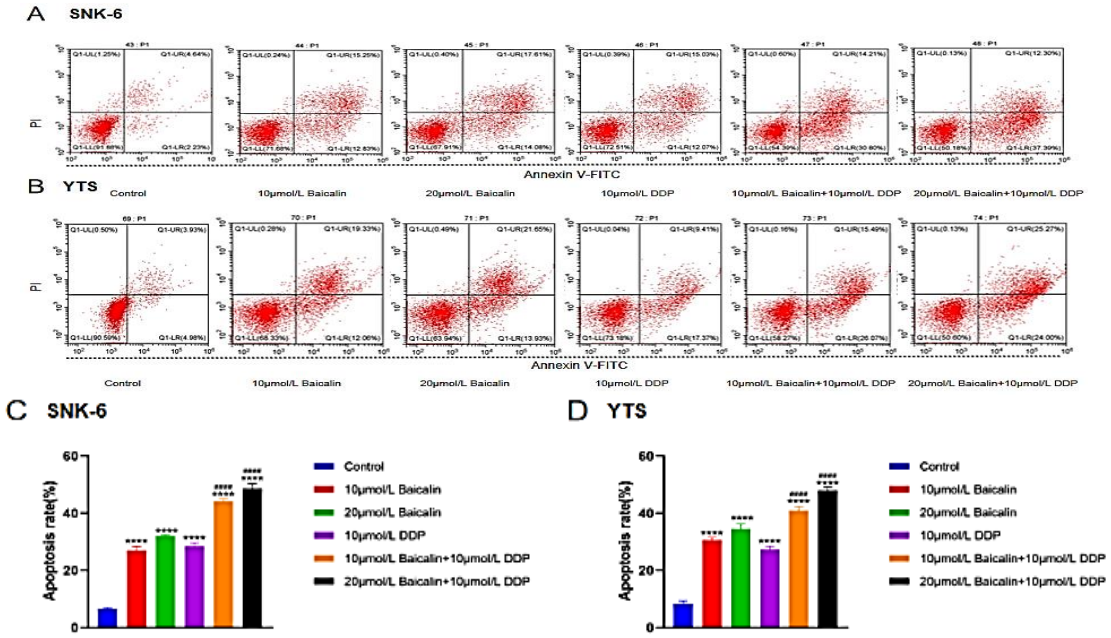

Figure 4: SNK6 cells and YTS cells were stained with Annexin-V FITC and PI to be measured apoptosis. Apoptotic cells are presented in the right-lower (early apoptosis) and right-upper (late apoptosis) quadrants of the plots (A & B). Comparison of apoptosis rate between single drug and combined drug (C & D)

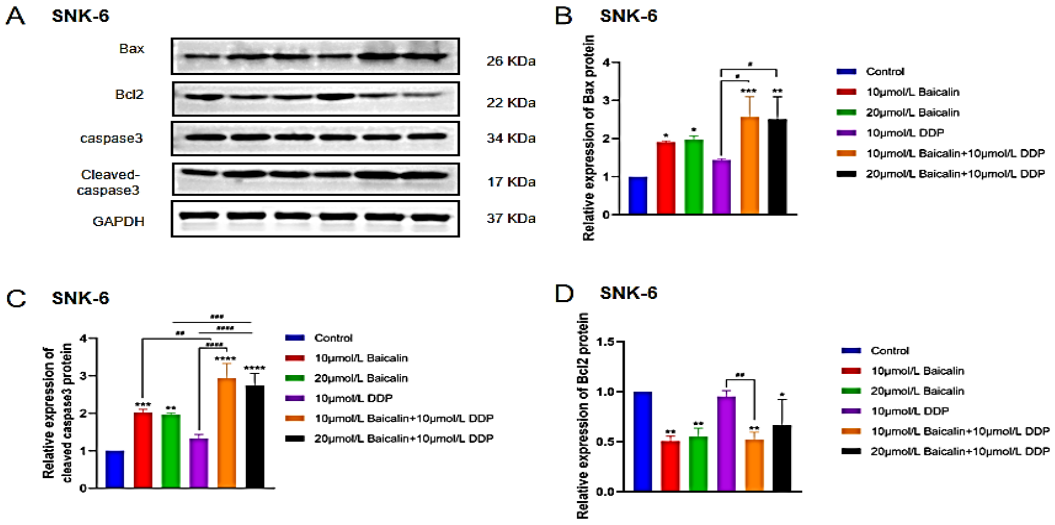

Figure 5: Effect of combined drugs on the expressions of apoptosis-related proteins in SNK-6 cells

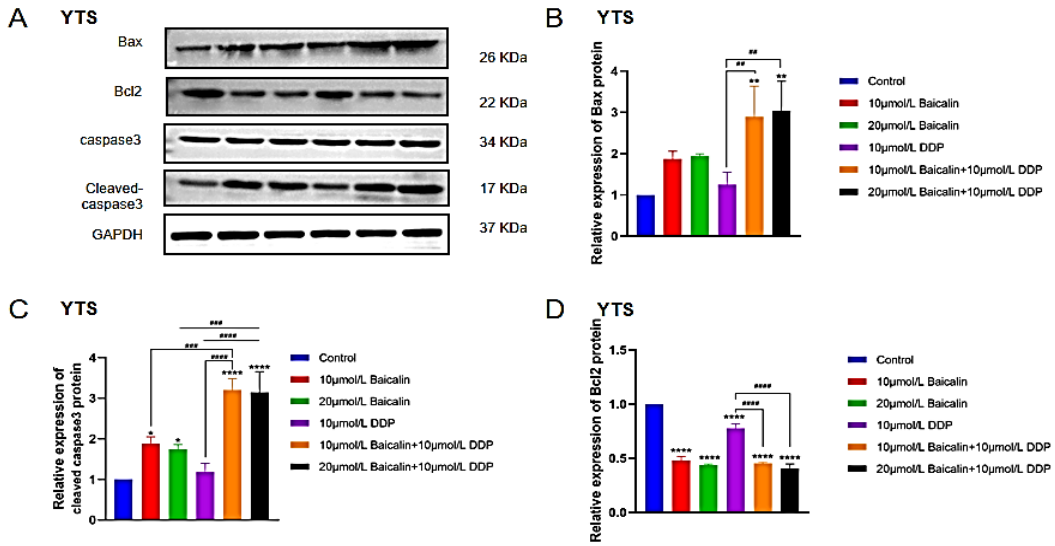

Figure 6: Effect of combined drugs on the expression of apoptosis-related proteins in YTS cells

No significant changes were observed compared to the 20 μmol/L of the baicalin group, and the expression of cleaved caspase3 protein was higher in both groups compared to the single drug group ($p < 0.001$) (Figures 5 A - D). In YTS cell lines, the expression levels of Bcl-2 anti-apoptotic protein were lower ($p < 0.0001$) while Bax pro-apoptotic protein expression was significantly higher ($p < 0.01$) in the 10 μmol/L of baicalin + 10 μmol/L of cisplatin and 20 μmol/L of baicalin + 10 μmol/L of cisplatin groups than in the 10 μmol/L cisplatin group alone, and the expressions of cleaved caspase3 protein was higher ($p < 0.0001$). The expressions of Bcl-2 anti-apoptotic protein and Bax pro-apoptotic protein were not different in the 10 μmol/L of baicalin + 10 μmol/L of cisplatin and 20 μmol/L of baicalin + 10 μmol/L of cisplatin groups compared with groups with equivalent doses of baicalin, but the expression of cleaved caspase3 protein was elevated ($p < 0.001$) (Figures 6 A - D).

DISCUSSION

Extranodal NK/T cell lymphoma belongs to aggressive NHL with high malignancy, rapid clinical progression, dismal long-term prognosis, and unpromising survival outcomes. Currently, radiotherapy, chemotherapy, and combination radiotherapy are the mainstays for early-limited ENKTCL [15]. Recent research found a significantly higher overall remission rate of anti-PD-1 monoclonal antibody plus cidabendiamide regimen versus cidabendiamide regimen (73.3 vs 45.5 %) and a longer mOS of only 3.7 months longer than that of patients treated with ChT [16]. This result suggests that despite the addition of new agents such as immune checkpoint inhibitor drugs, the efficacy remains unsatisfactory.

Chemotherapy resistance remains one of the main causes of treatment failure in ENKTCL, as this type of lymphoma is prone to resistance to conventional chemotherapy [17]. In-depth studies on the molecular mechanisms of multidrug resistance in ENKTCL are still required.

Evidence has confirmed that CCL22 overexpression increases ENKTCL cell line SNK-6 cell activity and decreases Caspase-3 activity, and miR-30b inhibits cisplatin resistance in human NKTCL SNK-6 and YTS cells by targeting CCL22, suggesting a positive correlation between CCL22 and drug resistance [9]. In a subsequent study, it was found that baicalin at different concentrations inhibited the proliferation and promoted the apoptosis of ENKTCL cell lines SNK-6 and YTS and that FOXO3 expression was upregulated and CCL22 expression was downregulated after baicalin treatment. In comparison with the negative control group, the expression of FOXO3 protein was decreased while that of CCL22 protein increased in the FOXO3 siRNA interference plasmid transfection group; the expression of apoptosis-inhibiting-related proteins increased, and the apoptosis rate significantly decreased. In CCL22 pcDNA transfected SNK-6 cell line, the expression of CCL22 protein increased significantly in the transfected group, FOXO3 protein expression showed no significant changes, and the apoptosis rate decreased significantly, suggesting that baicalin regulated the molecular mechanism of apoptosis in ENKTCL cells through FOXO3-mediated regulation of CCL22 [14].

As previously reported, baicalin reduces cisplatin resistance in lung cancer by downregulating MARK2 and p-Akt [18]. Baicalin enhances the sensitivity of lung cancer cells to cisplatin by attenuating XRCC-1-mediated DNA repair. It enhances the effects of cisplatin, triggers DNA damage, upregulates Bax, and downregulates Bcl-2 and Cyclin D1 in A549/DPP cells [19,20]. Cisplatin is one of the major members of ENKTCL chemotherapy, and resistance to cisplatin is inevitable in patients in clinical practice, especially after several cycles of treatment. However, the effect of baicalin on the suppressed proliferation and promotion of apoptosis of cisplatin NKTCL SNK-6 and YTS cell lines in ENKTCL cells and its molecular mechanism remains poorly understood.

The current study found that baicalin inhibited the proliferation and promoted apoptosis of SNK-6 and YTS cells. Co-administration of cisplatin and baicalin significantly reduced the proliferation rate and increased the apoptosis rate of SNK-6 and YTS cells compared with the respective equal concentrations of baicalin or cisplatin alone, and the cell viability was also decreased.

CONCLUSION

These results indicate that baicalin and cisplatin inhibit the proliferation of NKTCL SNK-6 and YTS cells, promote NKTCL SNK-6 and YTS cell apoptosis, and enhance the anti-tumor effect of cisplatin at appropriate doses and incubation times. The findings also show that baicalin enhances the down-regulation of anti-apoptotic protein expression and up-regulation of pro-apoptotic protein expression of cisplatin, and specifically kills CPT1A-expressing tumor cells. However, baicalin-cisplatin combination should be further explored for its anti-proliferative and apoptosis potential in animal models.

DECLARATIONS

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None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Xiaohui Duan and Jianhong Wang contributed equally to this work.

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