Tianjin University of Traditional Chinese Medicine[1]; State Key Laboratory of Experimental Hematology[2], National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

Salidroside inhibits proliferation, migration and invasion of human pancreatic cancer PANC1 and SW1990 cells through the AKT and ERK signaling pathway

Li Yuetong[1], Li Shangzhu[2], Hu Qinglin[2], Huang Pingping[2,*]

Received May 28, 2020, accepted May 30, 2020

**Corresponding author: Prof. Huang Pingping, State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Tianjin, China huangpp66@aliyun.com;1046871902@qq.com*

Pharmazie 75: 385-388 (2020) *doi: 10.1691/ph.2020.0556*

Salidroside is the main compounds extracted from the Chinese medicine *Rhodiola rosea* and has many pharmacological effects, including anti-tumor effects. However, the role of salidroside in human pancreatic cancer remains poorly known. Thus, the focus of this study was to evaluate the inhibitory effect of purified salidroside on human pancreatic cancer cells and its underlying molecular mechanisms. PANC1 and SW1990 cells were incubated with various concentrations of salidroside, and CCK-8 assay, colony formation, apoptosis, migration and invasion, western blot were conducted. As a result, it was found that salidroside significantly inhibited pancreatic cancer cells viability, proliferation, migration and invasion, and also induced cell apoptosis. Furthermore, we also detected that salidroside inhibited pancreatic cancer cells by downregulating the AKT and ERK signaling pathways. In conclusion, these findings suggest that salidroside may be a promising candidate for the development of a therapy of human pancreatic cancer.

1. Introduction

Pancreatic cancer is one of the most fatal malignant tumors with apporcimately 459,000 new diagnoses in 2018 (Ferlay et al. 2019). Despite being the fifteenth most frequently occurring cancer worldwide, pancreatic cancer is the fourth most common cause of death due to cancer (Jia et al. 2019). The five-year survival rate of pancreatic cancer is only 9%, the lowest among all cancer patients in the United States (Siegel et al. 2019). Unlike in other cancer types, chemotherapy and radiation are only modestly effective against pancreatic cancer, causing significant toxicity but only marginal improvements in survival (He et al. 2015). Therefore, searching for innovative drugs with minimal side effects remains a top priority.

Rhodiola rosea is a traditional Chinese herbal medicine that is mainly distributed in the cold regions of the northern hemisphere (Zhang et al. 2014). Pharmacological studies have demonstrated that *R. rosea*'s biological properties should be mainly attributed to salidroside, which exerts several adaptogenic functions, such as neuroprotective action (Xu et al. 2019), ameliorates cognition (Palmeri et al. 2016), has anti-inflammatory (Wei et al. 2017), anti-depressant (Vasileva et al. 2018), anti-viral effects (Wang et al. 2009). Especially, salidroside has been found to exert anticancer functions in Wilms' tumor (Li et al. 2019), thyroid cancer (Shang et al. 2019), lung cancer (Ren et al. 2019), gastric cancer (Qi et al. 2018), ovarian cancer (Yu et al. 2018), colorectal cancer (Fan et al. 2018), breast cancer (Zhao et al. 2015), and bladder cancer (Liu et al. 2012). So far, however, there has been few research about salidroside inhibiting pancreatic cancer. Only one study reported that salidroside can ameliorate hypoxia-induced tumorigenesis of BxPC-3 cells (Chen et al. 2019). The potential role of salidroside against pancreatic cancer cell growth, promotion of apoptosis, inhibition of migration and invasion have not been fully clarified. More significantly, the mechanism by which salidroside inhibits pancreatic cancer cells remains largely unknown.

The purpose of this research was to investigate the potential of salidroside to inhibit pancreatic cancer cell proliferation, migration and invasion, promote apoptosis and to explore the underlying molecular mechanisms of anti-tumor.

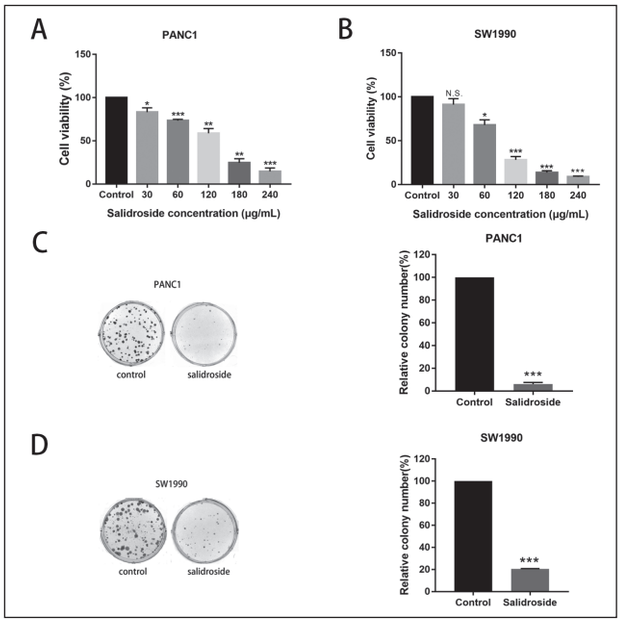

Fig. 1: Salidroside inhibited the proliferation of pancreatic cancer cells .PANC1 (A) and SW1990 (B) cells were treated with 30, 60, 120, 180, 240 μg/mL of salidroside for 48 h, and non-treated cells were acted as control. Cell viability was detected by CCK-8 assay. (C) Cell colony formation was detected by staining with crystal violet in PANC1 cells. (D) Cell colony formation was detected by staining with crystal violet in SW1990 cells. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

2. Investigations and results

2.1. Salidroside inhibited cell proliferation of PANC1 and SW1990 cells

PANC1 and SW1990 cells were treated with various concentrations of salidroside (0, 30, 60, 120, 180, 240 μg/mL) for 48 h. The viability of cells was determined by CCK-8 assay. As demonstrated in Fig. 1 A and B, the viability of PANC1 and SW1990 cells was reduced gradually with increase in the salidroside treatment concentration. Compared with the control group, salidroside significantly inhibited both PANC1 and SW1990 cells at the concentration of 120 μg/mL, but 30 μg/mL of salidroside had no obvious inhibitory effect on SW1990 cells. Based on the above results, salidroside was used for the subsequent experiments in a concentration of 120 μg/mL.

Next, we undertook a colony formation experiment to further observe the effect of 120 μg/mL of salidroside on cell proliferation. As shown in Fig 1 C and D, salidroside significantly reduced the colony formation of both PANC1 and SW1990 cells.

2.2. Salidroside induced cell apoptosis of PANC1 and SW1990 cells

We performed flow cytometey to assess the effect of salidroside on the apoptosis of PANC1 and SW1990 cells. The results, as shown in Fig. 2, indicated that the number of early and late apoptotic cells increased significantly after salidroside treatment for 48 h.

Furthermore, we detected the expressions of apoptosis-related proteins by western blot. The western blot analysis showed that salidroside caused the decrease of the expression of anti-apoptotic protein Bcl-2 in both PANC1 and SW1990 cells. Correspondingly, the expression of pro-apoptotic protein Bax increased in the saldroside-treated group (Fig. 3). Compared with the control group, the bcl-2/bax ratio in the drug-administered group was significantly lower.

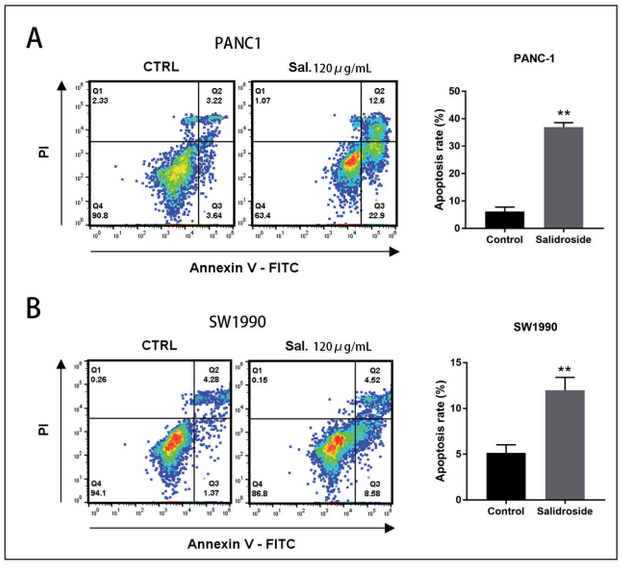

Fig. 2: Salidroside promoted PANC1 and SW1990 cell apoptosis. (A) PANC1 cells were treated with salidroside (120 μg/mL) for 48h, and non-treated cells were acted as control. Percentage of apoptosis was determined by flow cytometry. (B) SW1990 cells were treated with salidroside (120 μg/mL) for 48 h. Percentage of apoptosis was determined by flow cytometry. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

2.3. Salidroside inhibited cell migration and invasion of PANC1 and SW1990 cells

Cell migration and invasion are closely related to the metastasis of cancer, which is an important cause for the high mortality of pancreatic cancer. In order to assess the effect of salidroside on the migration and invasion of PANC1 and SW1990 cells, a transwell assay was performed with Cell Culture Inserts and Matrigel. As can be seen from Fig. 4, salidroside effectively inhibited PANC1 and SW1990 cells migration compared with the control group. Matrigel was used to mimic the basement membrane *in vivo* to study the invasive ability of cells. The results showed that salidroside further promoted the inhibitory effects of the invasion of PANC1 and SW1990 cells.

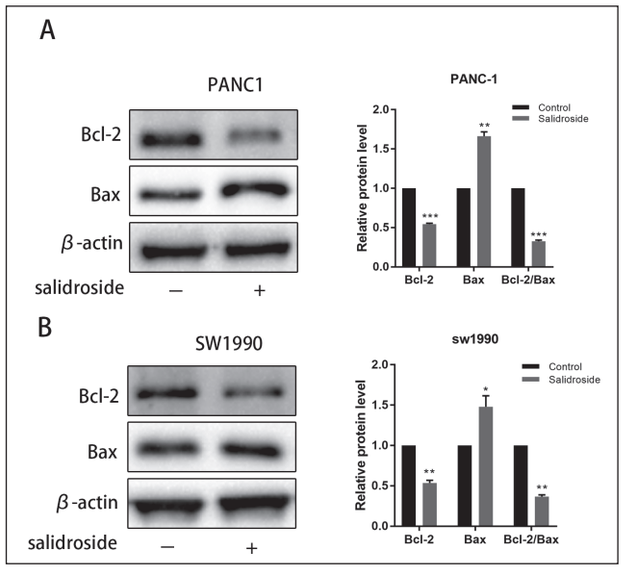

Fig. 3: Salidroside affected the expression of apoptosis-related proteins in pancreatic cancer cells. (A) The protein levels of Bcl-2 and Bax were detected by western blot assay in PANC1 cells. Quantitative analysis of protein expression was carried out with GraphPad Prism 7. (B) The protein levels of Bcl-2 and Bax were detected by western blot assay in SW1990 cells. Quantitative analysis of protein expression was carried out with GraphPad Prism 7. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

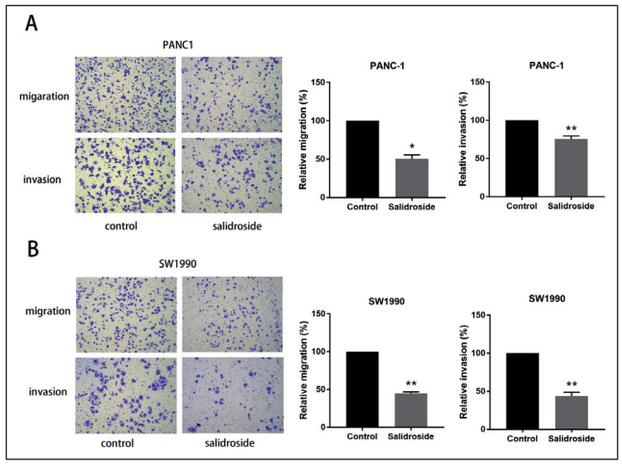

Fig. 4: Salidroside inhibited the migration and invasion of PANC1 and SW1990 cells. PANC1 (A) and SW1990 (B) were treated with salidroside (120 μg/mL) for 48 h, and non-treated cells were acted as control. Cell migration and invasion were detected by transwell assay. Quantitative analysis of cell migration and invasion rate was carried out with GraphPad Prism 7. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

2.4. Salidroside downregulated AKT and ERK signal pathway

To explore the molecular mechanism of salidroside in the treatment of pancreatic cancer, we examined the key signaling molecules of AKT and ERK signaling pathway by Western blotting. As we know, AKT plays a critical role in controlling survival and

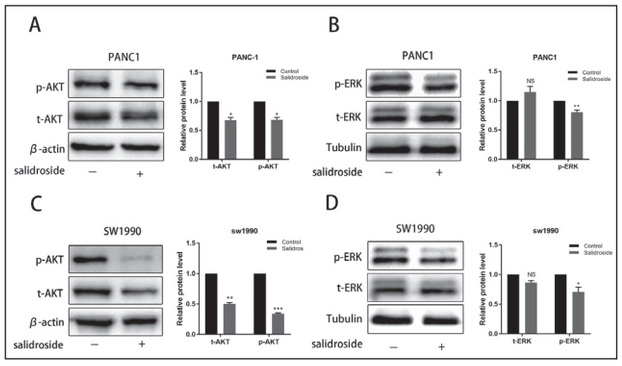

Fig. 5: Salidroside deactivated AKT and ERK signal pathway in PANC1 and SW1990 cells. PANC1 and SW1990 were treated with salidroside (120 μg/mL) for 48 h. (A) and (B) The protein levels of total and phosphorylation AKT and ERK were determined by western blot assay in PANC1 cells. (C) and (D) The protein levels of total and phosphorylation AKT and ERK were determined by western blot assay in SW1990 cells. Quantitative analysis of protein expression was carried out with GraphPad Prism 7. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

apoptosis. ERKs regulate cell proliferation, differentiation and survival, and their signaling pathways mediate and amplify signals during tumor invasion and metastasis. Therefore, we evaluated the effects of salidroside on total and phosphorylation levels of AKT and ERK. The results of western blot analyses are presented in Fig. 5. Salidroside not only caused a decrease in phosphorylated AKT levels, but also caused a decrease in total AKT. Correspondingly, salidroside also downregulated the levels of phosphorylated ERK, and there was no significant change in total ERK levels. Together, results indicated that salidroside treated pancreatic cancer by blocking AKT and ERK signal pathway.

3. Discussion

Plant-derived anticancer drugs play a significant role in the prevention and treatment of cancer because of their availability, and relatively low toxicity compared to chemotherapy (Gali et al. 2015). Classic examples of plant-derived anticancer drugs are paclitaxel, the Vinca alkaloids, vincristine, camptothecin, etoposide, and also *Rhodiola rosea*. Salidroside has shown some anticancer activity in a variety of cancers. Consistent with previous reports, our present study found that salidroside exhibited the ability to inhibit proliferation of pancreatic cancer cells, promoted apoptosis, and inhibited migration and invasion. In addition, it was also found that the molecular mechanism by which salidroside inhibited pancreatic cancer may be through deactivate the AKT and ERK signaling pathway.

Dysregulated cell proliferation is a hallmark of cancer development. Therefore, the inhibition of tumor growth is an important target for the prevention of tumor progression. A previous study has shown that salidroside had an inhibitory effect on the cell viability of renal cell carcinoma A498 and 786-0 cells. In addition, salidroside was demonstrated to inhibit A498 and 786-0 cells cell colony formation, and this effect was concentration-dependent (Lv et al. 2016). Similarly, our data suggested that salidroside significantly showed antigrowth activity in PANC1 and SW1990 cells as cell viability and colony formation capacity were reduced.

Apoptosis is an active process involving the activation, expression and regulation of a range of genes. Impaired apoptosis plays a central role in cancer development and limits the efficacy of conventional cytotoxic therapies (Adams et al. 2018). The proteins of the Bcl-2 family represent a critical checkpoint in major apoptotic signal transduction cascades. Bcl-2 proteins that have been discovered so far can be divided into two categories according to their functions. One is to inhibit apoptosis like Bcl-2, and the other is to promote apoptosis, such as Bax. In addition, apoptotic cell death is typically determined by the ratio of Bcl-2/Bax (Yang et al. 1996). Yu Yu et al. (2018) found that salidroside could induce Bcl-2 and Bax expression, and decreased the ratio of Bcl-2/Bax. Similarly, out study demonstrated that salidroside inhibited pancreatic cancer cells by downregulating Bcl-2 and upregulating Bax. In addition, the ratio of Bcl-2/Bax was significantly reduced after treatment with salidroside. These results further supported the suggestion that salidroside promotes the apoptosis of pancreatic cancer cells.

Invasion and migration of tumor cells are significantly correlated with the degree of malignancy and prognosis of the tumor. Invasion and migration are important for pancreatic cancer metastasis, especially hematological dissemination (Ren et al. 2018). So far, several studies have shown that salidroside inhibits the migration of various tumors. Sun et al. (2012) confirmed that salidroside can significantly reduce the wound closure area of HT1080 cells and inhibit HT1080 cells from invading the matrigel-coated membrane. Researchers treated colon cancer cells SW1116 with salidroside at different concentrations (10, 20, 50 g/ml) and found that salidroside was indeed involved in the migration and invasion of human colon cancer cells (Sun et al. 2015). Consistent with these findings, our results indicated that salidroside can effectively inhibit the migration and invasion of pancreatic cancer PANC1 and SW1990 cells.

Akt, also known as Akt protein kinase B (PKB), is a serine/threonine-specific protein that plays an important role in many cellular processes such as glucose metabolism, apoptosis, cell proliferation transcription and cell migration. The AKT pathway regulates the proliferation and survival of tumor cells, and its abnormal activity cannot only cause malignant transformation of cells, but also cause migration of cells of cancers (Linton et al. 2019). Downregulation of the AKT pathway can inhibit the proliferation and migration of various tumor cells, such as cervical cancer (Liu et al. 2016). Extracellular regulated protein kinases (ERK) include ERK1 and ERK2. Phosphorylation-activated erk1/2 is translocated from cytoplasm to nucleus, and is involved in various biological reactions such as cell proliferation and differentiation, apoptosis (Maik et al. 2019). ERK plays a mediating and amplifying role in tumor invasion and metastasis, and over-activation of ERK can be found in many human cancers, such as oral cancer, pancreatic cancer, etc (Neuzillet et al. 2013). Previous studies have shown that the occurrence of pancreatic cancer involves multiple signaling pathways, including Akt and ERK (Li et al. 2019). Several reports have demonstrated that salidroside significantly suppressed the AKT and ERK signal pathway in human lung cancer cells (Ren et al. 2019) and gastric cancer cells (Qi et al. 2018). Consistent with previous studies, our results suggested that salidroside inhibited pancreatic cancer cells by downregulating the AKT and ERK signaling pathways. Interestingly, our results indicated that salidroside not only downregulated phosphorylated AKT levels in pancreatic cancer cells, but also downregulated total AKT levels.

In summary, the findings of the present study provided evidence that salidroside significantly inhibited pancreatic cancer cells proliferation, migration and invasion, and induced apoptosis *in vitro*. Furthermore, salidroside treatment significantly deactivated AKT and ERK signal pathways, which may contribute to the inhibition of tumor growth. Thus, salidroside may be a promising natural compound for the chemotherapy of human pancreatic cancer.

4. Experimental

4.1. Materials

Salidroside (purity≥98%) was purchased from Solarbio (Beijing, China). DMEM and RPMI 1640 culture medium were obtained from HyClone Laboratories, USA. Phosphate buffer saline (PBS), fetal bovine serum (FBS), bovine serum albumin (BSA) were obtained from Thermo Fisher Scientific, USA. Annexin V-FITC/PI apotosis detection kit was obtained from BD Biosciences, USA. Transwell co-culture chamber and matrigel were obtained from Corning, USA. Antibodies Bcl-2, Bax, Akt, Phospho-Akt (Ser473), Erk1/2, Phospho- Erk1/2 Antibody, β-actin, β-tublin were obtained from Cell Signaling Technology, USA.

4.2. Cell culture

Human pancreatic cancer cell line PANC1 and SW1990 were purchased from American Type Culture Collection (Manassas, USA) and cultured in DMEM and RPMI 1640 medium supplemented with 10% fetal bovine serum, respectively, in a humidified incubator at 37 °C with 5% CO_2. Salidroside with different concentrations (range from 30-240 μg/mL) was used to treat PANC1 and SW1990 for 48 h.

4.3. Cell viability assay

PANC1 and SW1990 cells were seeded in sterile 96-well plates at a density of 4000/well and allowed to adhere. Then cells were treated with salidroside solutions in a concentration range of 30-240 μg/mL. After 48 h treatment, the cultures were subjected to 10 μl/well of CCK-8 solution and were incubated for 2 h at 37 °C with 5% CO_2. The optical density (OD) values were quantified by a Multifunctional microplate detector (Symergy HT; USA) at 450 nm. The experiments were performed with three replicates for each condition.

4.4. Colony formation assay

PANC1 and SW1990 cells were seeded in 6-well plates at a density of 500 cells per well and cultured for 24 h. Then, these two cell lines were treated with (120 μg/mL) or without salidroside for 48 h. The medium was then discarded, the cells were washed in PBS and incubated in complete medium for another 10 days. The colonies were stained with 20% ethanol solution containing 0.25% crystal violet for 15 min followed by washing with PBS for three times. The visible colonies were counted and normalized to control cells.

4.5. Cell apoptosis assay

Cell apoptosis assay was performed by using Annexin V-FITC/PI apotosis detection kit according to the manufacturer's protocol. Briefly, cells were treated with 120 μg/mL salidroside for 48 h and 1×10^5 cells were collected and resuspended in 100 μl binding buffer. Then, the cells were stained with 5 μl of Annexin V-FITC and 5 μl of PI. After reaction for 10 min at room temperature in the dark, 400 μl of binding buffer were added, and samples were analyzed in a BriCyte E6 flow cytometer to quantify early apoptotic cells (Annexin V+/PI -).

4.6. Migration and invasion assay

Migration and invasion assays were performed in a 24-wells Transwell co-culture chamber with 8 μm pore size (Corning, USA). For the migration assay, PANC1 and SW1990 cells ($3*10^5$/ml) with or without salidroside (120 μg/mL) were re-suspended in serum-free medium, then 200 μl of cells were added to the upper chamber and 600 μl of complete medium containing 10% FBS were added to the lower chamber. After 24 h incubation at 37 °C according to the manufacturer's protocol, the cells in the upper chamber were gently wiped off with a cotton swab and washed with PBS. The invaded cells left at the bottom of chambers were fixed with methanol for 30 min at room temperature followed by staining with 0.25% crystal violet for 10 min. The numbers of the migratory cells were counted in three random visual fields for each chamber using an upright microscope (Carl Zeiss Microscopy GmbH, Germany) equipped with a digital camera.

For the invasion assay, the upper inserts were covered with 100 μl/well diluted Matrigel and incubated at 37 °C for 2 h to facilitate gel formation. Then cells were added to the upper chambers with 200 μl of serum-free medium. The subsequent steps were the same as in the migration experiment described above.

4.7. Western blot

The proteins used for western blot were extracted by using RIPA lysis buffer and total protein concentrations were quantified using the Enhanced BCA Protein Assay Kit. Equal amounts of protein were separated on 8 or 12% SDS-PAGE followed by transferring to a polyvinylidene difluoride (PVDF) membrane. After blocking with 5% milk in Tris-buffered Saline with 0.1% Tween for 1 h at room temperature, the membrane was incubated with primary antibodies at 4 °C overnight. The following primary antibodies were used to detect the proteins: Bcl-2 Mouse Monoclonal antibody (1:1000; CST), Bax Antibody (1:1000; CST), Akt Antibody (1:1000; CST), Phospho-Akt (Ser473) Antibody (1:1000; CST), Erk1/2 Antibody (1:1000; CST), Phospho-Erk1/2 Antibody (1:1000; CST) , β-actin antibody (1:5000; Proteintech), β-tublin antibody (1:5000; Proteintech). After being washed with TBST for three times, the membrane was incubated with the goat anti-rabbit and anti-mouse immunoglobulin G conjugated to horseradish peroxidase antibody (1:5000; Proteintech) as the secondary antibodies at 37 °C for 1 h. After rinsing, the blottings were visualized for bands with an ECL Kit (Thermo, USA) and quantified by Image Lab software (Bio-Rad).

4.8. Statistical analysis

Each experiment was performed at least three times and results are shown as means±SEM. Data were analyzed by a Student's *t* test using the SPSS v.11.0 software program (IBM SPSS, Chicago,IL, USA). Experimental data was presented as the means±SD using GraphPad Prism 7, and $P<0.05$ was considered statistically significant.

Acknowledgements: This research was funded by CAMS Innovation Fund for Medical Science (Grant number: 2017-I2M-1-016).

Conflicts of interest: None declared.

References

Adams JM, Cory S (2018) The BCL-2 arbiters of apoptosis and their growing role as cancer targets. Cell Death Differ 25: 27–36.

Chen X, Kou Y, Lu Y, Pu Y (2019) Salidroside ameliorated hypoxia-induced tumorigenesis of BxPC-3 cells via downregulating hypoxia-inducible factor (HIF)-1α and LOXL2. J Cel Biochem 121: 165–173.

Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, Znaor A, Bray F (2019) Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 144: 1941–1953.

Fan XJ, Wang Y, Wang L, Zhu MY (2016) Salidroside induces apoptosis and autophagy in human colorectal cancer cells through inhibition of PI3K/Akt/mTOR pathway. Oncol Rep 36: 3559–3567.

Gali H, Hmadi R, Kareh M, Tohme R, Darwiche N (2015) Cell death mechanisms of plant-derived anticancer drugs: beyond apoptosis. Apoptosis 20: 1531–1562.

He WG, Zhao H, Chan WY, Lopez D, Shroff RT, Giordano SH (2015) Underuse of surgical resection among elderly patients with early-stage pancreatic cancer. Surgery 158: 1226–1234.

Jia XY, Du PL, Wu KS, Xu ZX, Fang JY, Xu XL, Lin K (2018) Pancreatic cancer mortality in China: characteristics and prediction. Pancreas 47: 233–237.

Li H, Huang DL, Hang SY (2019) Salidroside inhibits the growth, migration and invasion of Wilms' tumor cells through down-regulation of miR-891b. Life Sci 222: 60–68.

Liu ZB, Li XS, Simoneau AR, Jafari M, Zi XL (2012) Rhodiola rosea extracts and salidroside decrease the growth of bladder cancer cell lines via inhibition of the mTOR pathway and induction of autophagy. Mol Carcinogen 51: 257–267.

Lv C, Huang Y, Liu ZX, Yu D, Bai ZM (2016) Salidroside reduces renal cell carcinoma proliferation by inhibiting JAK2/STAT3 signaling. Cancer Biomarkers A 17: 41–47.

Linton MF, Moslehi JJ, Babaev VR (2019) Akt signaling in macrophage polarization, survival, and atherosclerosis. Int J Mol Sci 20: 2703–2712.

Liu JN, Sun YP, Zhang HR, Ji DX, Wu F, Tian HH, Liu K, Zhang Y, Wu BH, Zhang GY (2016) Theanine from tea and its semi-synthetic derivative TBrC suppress human cervical cancer growth and migration by inhibiting EGFR/Met-Akt/NF-κB signaling. Eur J Pharmacol 791: 297–307.

Li W, Wang Z, Xiao X, Han L, Wu Z, Ma QY, Cao L (2019) Curcumin attenuates hyperglycemia-driven EGF-induced invasive and migratory abilities of pancreatic cancer via suppression of the ERK and AKT pathways. Oncol Rep 41: 650–658.

Maik G, Hacohen A, Seger R (2019) Nuclear ERK: mechanism of translocation, substrates, and role in cancer. Int J Mol Sci 20: 1194–1208.

Neuzillet C, Hammel P, Tijeras A, Couvelard A, Raymond E (2013) Targeting the Ras-ERK pathway in pancreatic adenocarcinoma. Cancer Metastasis Rev 32: 147–162.

Palmeri A, Mammana L, Tropea MR, Gulisano W, Puzzo D (2016) Salidroside, a bioactive compound of Rhodiola rosea, ameliorates memory and emotional behavior in adult mice. J Alzheimers Dis 52: 65–75.

Qi ZL, Tang T, Sheng LL, Ma YF, Liu YH, Yan L, Qi SM, Ling LF, Zhang Y (2018) Salidroside inhibits the proliferation and migration of gastric cancer cells via suppression of Src-associated signaling pathway activation and heat shock protein 70 expression. Mol Med Rep 18: 147–156.

Ren M, Xu W, Xu T (2019) Salidroside represses proliferation, migration and invasion of human lung cancer cells through AKT and MEK/ERK signal pathway. Artif Cells Nanomed Biotechnol 47: 1014–1021.

Ren B, Cui M, Yang G, Wang HY, Feng MY, You L, Zhao YP (2018) Tumor microenvironment participates in metastasis of pancreatic cancer. Mol Cancer 17: 108–117.

Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA Cancer J Clin 69: 7–34.

Shang HX, Wang SN, Yao JM, Guo CC, Dong JJ, Liao L (2019) Salidroside inhibits migration and invasion of poorly differentiated thyroid cancer cells. Thoracic Cancer 10: 1469–1478.

Sun C, Wang ZH, Zheng QS, Zhang H (2012) Salidroside inhibits migration and invasion of human fibrosarcoma HT1080 cells. Phytomedicine 19: 355–363.

Sun K, Xia HW, Xia RL (2015) Anticancer effect of salidroside on colon cancer through inhibiting JAK2/STAT3 signaling pathway. Int J Clin Exp Pathol 8: 615–621.

Vasileva LV, Saracheva KE, Ivanovska MV, Petrova AP, Marchev AS, Georgiev ML, Murdjeva MA, Getova DP (2018) Antidepressant-like effect of salidroside and curcumin on the immunoreactivity of rats subjected to a chronic mild stress model. Food Chem Toxicol 121: 604–611.

Wang HB, Ding YY, Zhou J, Sun XL, Wang SW (2009) The in vitro and in vivo antiviral effects of salidroside from Rhodiola rosea L. against coxsackievirus B3. Phytomedicine 16: 146–155.

Wei YC, Hong HM, Zhang XQ, Lai WF, Wang YZ, Chu KD, Brown J, Hong GZ, Chen LD (2017) Salidroside inhibits inflammation through PI3K/Akt/HIF signaling after focal cerebral ischemia in rats. Inflammation 40: 1297–1309.

Xu N, Huang F, Jian CD, Qin L, Lu F, Wang YM, Zhang Z, Zhang Q (2019) Neuroprotective effect of salidroside against central nervous system inflammation-induced cognitive deficits: A pivotal role of sirtuin 1-dependent Nrf-2/HO-1/NF-κB pathway. Phytother Res 33: 1438–1447.

Yu G, Li N, Zhao Y, Wang W, Feng XL (2018) Salidroside induces apoptosis in human ovarian cancer SKOV3 and A2780 cells through the p53 signaling pathway. Oncol Lett 15: 6513–6518.

Yang E, Korsmeyer SJ (1996) Molecular thanatopsis: a discourse on the BCL2 family and cell death. Blood 88: 386–401.

Zhang JQ, Meng SY, Allen GA, Wen J, Rao GY (2014) Rapid radiation and dispersal out of the Qinghai-Tibetan Plateau of an alpine plant lineage Rhodiola (Crassulaceae). Mol Phylogenet Evol 77: 147–158.

Zhao G, Shi AP, Fan ZM, Du Y (2015) Salidroside inhibits the growth of human breast cancer in vitro and in vivo. Oncol Rep 33: 2553–2560.