European Review for Medical and Pharmacological Sciences 2021; 25: 5349-5354

Multiple mechanisms of salidroside on anti-tumor effects

X.-P. WANG, D.-Y. YUAN, Y. TIAN, W.-H. LI

Department of Medicine, Xizang Minzu University, Xianyang, China

Abstract. – Salidroside, a kind of natural herb, has the advantages of a wide range of anti-tumor activities with low toxicity and high efficiency. A large number of studies have shown that salidroside can inhibit the proliferation of tumors in different ways and achieve the goal of treating tumors. After summary and analysis of the recent research on anti-tumor mechanisms of salidroside, it can be concluded that salidroside could suppress cancer proliferation by blocking cell cycle, promoting cell differentiation, inducing cell apoptosis or autophagy, and regulating the signal pathways of cancer cells.

Key Words:
Salidroside, Tumor, Cell cycle, Apoptosis, Autophagy, Differentiation.

Introduction

Research showed that the cancer incidence rate in China accounts for 22%, while the mortality rate accounts for 27% of global cancer[1]. In recent years, trying to find effective and low toxicity anti-tumor drugs has become an important field in basic and clinical research. Salidroside is the main effective component of the Chinese Tibetan herb, *Rhodiola sachalinensis*. It owns the functions of improving blood circulation and invigorating health effectively. The research showed that salidroside possesses the effects of immunity enhancement, hypoxia inhibition, and tumor treatment[2-4]. In recent years, with the advancement of molecular biology techniques, it is found that salidroside indeed plays multiple active roles in the treatment of tumors. Therefore, the following anti-tumor mechanisms of salidroside are summarized to provide a better basis for further investigation of cancer treatment.

Arresting Cancer Cell Cycle

The normal cells must have a complete cell cycle to proliferate. The cell cycle usually accompanies the downregulation of cyclin-dependent kinase 4 (CDK4), cyclin D1, and the upregulation of p27 (Kip1) and p21 (Cip1). These molecules participate in the regulation of G1-S-G2-M progression[5,6]. However, when some stimulators interfere with cell division, the cell could not pass through the G1/S and G2/M checkpoints. The cell proliferation has to be terminated[7,8].

Cancer cell growth also depends on the continuous progression of the cell cycle. During this process, cyclins and CDK are the most important key checkpoints[9]. Therefore, arresting the cell cycle is an important way to suppress cancer cell growth. The study found that salidroside inhibited the proliferation of gastric cancer SGC-7901 in the G2/M checkpoints by down-regulating the expression of cyclin B1[10]. Similarly, salidroside could suppress the growth of breast cancer cell lines MDA-MB-435 and MCF-7. The expression of cyclin B1 and Cdc2 was downregulated in the G1 phase, and the cell cycle was blocked in the G2 phase. The proliferation of breast cancer cells was inhibited[11]. Besides, salidroside can block the liver cancer cell cycle in the G0/G1 phase and demonstrate the effective anti-cancer function[12].

Inducing Apoptosis of Cancer Cells

Tumor growth depends on the ratio between cell proliferation and cell death. In addition to the roles of tumor oncogenes and anti-oncogenes, apoptosis-regulating genes also play important roles in the progression of tumors. Therefore, the imbalance of apoptosis is one of the mechanisms for tumor development[13-17]. The process of tumor cell apoptosis is the result of activating a series of genes. These apoptosis-regulating genes regulate and interact with each other. For example, caspases, a kind of apoptotic protease, can inhibit cell division and form apoptotic bodies. Then the apoptotic bodies are recognized and phagocytized finally by adjacent phagocytes or other cells. The process leads to the complete elimination of abnormal or dam-

Corresponding Author: Xiaoping Wang, MD; e-mail: wxpphd@aliyun.com

aged cells in the end. Anti-apoptosis genes, such as Bcl-2, mutant p53, both can inhibit apoptosis and promote the growth of tumor cells. On the contrary, the pro-apoptotic gene Bax participates in the process of tumor cell apoptosis. The research found that salidroside could induce apoptosis of adenoma cells by upregulating the expression of pro-apoptotic genes caspase-3 and caspase-8[18]. The study also showed that salidroside was able to inhibit the expression of anti-apoptosis gene Bcl-2 and increase the expression of caspase 3, caspase 8, and Bax in hepatocellular carcinoma. Salidroside induced apoptosis of cancer cells and suppressed the growth of liver cancer[19].

Inducing Differentiation of Cancer Cells

Inducing the differentiation of cancer cells does not directly kill cancer cells but prevents them from progression. Under the function of some differentiation inducers, cancer cells could be induced to develop into normal cells. At present, retinoic acid (RA) is the most widely used differentiation inducer in clinical practice. RA is used in the treatment of a variety of malignant tumors, such as acute leukemia, thyroid cancer, and breast cancer[20,21]. The studies showed that the initiation of cell differentiation was regulated by oncogenes, such as c-myc and p5[22,23]. As an oncogene, c-myc participates in the process of cancer proliferation, invasion, and migration. In transformed cells, the expression of c-myc gene is increasing, while in differentiated cells, the expression of c-myc gene is decreasing, and the ability of cell proliferation would be weakened. The research found that salidroside could cooperate with RA to downregulate c-myc expression, promote apoptosis of gastric cancer cells, and inhibit the growth of gastric cancer[24]. When hepatocellular cells were treated with different concentrations of salidroside, the cell DNA content was lower than that in the control group. Meanwhile, the expression of c-myc decreased with the increasing salidroside concentration. Morphological observation also showed that the volume of the hepatocellular cancer cells increased significantly with high expression of c-myc, especially for the enlarged and hyperchromatic nuclei. However, after treated with salidroside, the expression of c-myc was decreased, and the differentiation of HCC cells got better[25]. Therefore, salidroside can inhibit the expression of oncogene c-myc, and promote cancer cells to differentiate into normal cells, which could indeed induce differentiation of cancer cells.

Autophagy of Cancer Cells Induced by Salidroside

Autophagy refers to the process that cells phagocytize their own cytoplasm or organelles after receiving some stimulation. The process usually forms autophagy bodies via membrane encapsulation, and then autophagy bodies combine with lysosomes to form autophagic lysosomes. Finally, autophagic lysosomes complete their degradation under the reaction of proteolytic enzymes[26-28]. Autophagy activity occurs in a variety of human tumor cells. In recent years, many studies have shown that autophagy plays an important role in the development and progression of tumors[26-28]. Inducing or suppressing autophagy is likely to become an effective anti-cancer strategy. Autophagy is regulated by a series of autophagy-related genes (ATG)[29]. Becline 1 and LC3 are involved in the formation of autophagy, and their expression level is closely related to autophagy ability[30]. LC3 exists in the cytoplasm by way of unactivated form, LC3-I. When autophagy occurs, LC3-I would be transformed into LC3-II and combine with a lysosome to form an autophagic lysosome until it is degraded by lysosomal enzymes. Therefore, the expression of LC3-II can reflect the level of autophagy in cells. The study found that salidroside could induce autophagy in SW1353 cells by upregulating LC3-II and downregulating p62 expression[31]. Salidroside can also induce autophagy in colon cancer cells, possibly by increasing the expression of LC3-II and becline 1[32].

Regulating Cancer Cells Through Signaling Pathways

Salidroside can also inhibit cancer by regulating multiple signaling pathways[33-37]. The study showed that salidroside decreased MMP2 expression by downregulating the EGFR/JAK2/STAT3 signal transduction pathways in breast cancer cells, MDA-MB 231. Therefore, the migration, invasion, and angiogenesis of the breast cancer cells were suppressed[38]. Salidroside induced apoptosis of human colon cancer cells by inhibiting PI3K/Akt/mTOR pathway and promoted the expression of LC3-II and becline 1 to induce autophagy[39]. The research found that salidroside could inhibit the proliferation, migration, and invasion of colon cancer cell SW116. The mechanism is likely to be related to the downregulation of VEGF, VEGFR-2, MMP-2, and MMP-9 expression[40]. Salidroside also suppressed the proliferation, migration, and invasion of gastric cancer BGC-

823 cells by downregulating the activation of ROS-mediated Src-related signal pathways and decreasing the expression of HSP70[41].

Conclusions

Salidroside, as a kind of traditional herb, possesses the advantages of low toxicity and multiple anti-cancer effects. Salidroside plays an important role by way of a variety of mechanisms, that is, inducing autophagy of cancer cells, inducing cancer cells to differentiate into normal cells, enhancing immune reaction to kill cancer, and blocking the cancer cell cycle to inhibit their proliferation. Recent studies further verified that salidroside suppressed the growth of cancers by regulating signal pathways (Figure 1, Table I). Nevertheless, the detailed mechanisms for salidroside still need further investigation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Financial Disclosure

This work is supported by the Key Scientific Research Program of Xizang Minzu University and Xizang Autonomous Region (No. 20MDT02, XZ202101ZR0074G), Scientific Research Program Funded by Shaanxi Provincial Education Department (No. 18JS031), the Scientific Research Program of Shaanxi Administration of Traditional Chinese Medicine (No. 15-SCJH001, JCPT001), and the Natural Science Basic Research Plan in Shaanxi Province of China (No. 2016JM8023, 2020JM-590).

Table I. Mechanisms of salidroside against different cancers[10-58].

Cancer types	Mechanisms
Liver cancer	Decreases the expression of Notch1 genes, MMP and Bcl-2 mRNA Increases the expression of BAX and caspase-3 mRNA
Gastric cancer	Decreases the expression of ROS-mediated signaling pathway, HSP70 and PKC-α
Colorectal cancer	Decreases the expression of PI3K/Akt/mTOR signaling, JAK2/STAT3 signaling, VEGF/VEGFR-2, MMP-2 and MMP-9 Increases the expression of LC3B and Becline-1
Lung cancer	Decreases the expression of HIF-1α, Foxp3, TGF-β1, MEK, ERK1/2 signaling and the ratio of CD4+ CD25+ regulatory T cells
Breast cancer	Decreases the expression of CDK4, STAT3 signaling and Bcl-2 Increases the expression of p27Kip1, p21Cip1 and caspase-9
Ovarian cancer	Increases the expression of p53, p21Cip1/Waf1 and p16INK4a, BAX and BAD Decreases the expression of Bcl-2 and XIAP Enhances activity of macrophages and T/B lymphocytes
Cervical cancer	Decreases the expression of Eag1 and IMP3 Increases the expression of caspase-9/-3
Renal cancer	Decreases the expression of JAK2/STAT3 signaling
Bladder cancer	Inhibits the expression of mTOR pathway and 4EBP1 phosphorylation Enhances AMPK-α phosphorylation, BAX and caspase-9/-3 expression
Skin cancer	Inhibits the expression of NF-κB signaling and TNF-α, IL-1β, IL-18, IL-6, COX2 and TGF-β1 release
Gliomas	Decreases the expression of Wnt/β-chain signaling pathway and enhances anti-oxidative stress response
Fibrosarcomas	Increases the expression of TIMP-2, E-cadherin and PKC Decreases the expression of β1-integrin from connexins

Notes: AMPK, adenosine monophosphate-activated protein kinase; BAD, B-cell lymphoma-2-associated death promoter protein; BAX, B-cell lymphoma-2-associated X protein; Bcl-2, B-cell lymphoma-2; CDK 4, cyclin-dependent protein kinase 4; COX 2, cyclooxygenase 2; Eag1, ether-a-go-go potassium channel 1; 4EBP1, 4E-binding protein 1; ERK1/2, extracellular signal-regulated protein kinase1/2; HIF-1α, Hypoxia-inducible factor-1α; HSP70, heat-shock protein 70; IL, interleukin; IMP3, insulin-like growth factor IImRNA-binding protein; JAK2, Janus kinase 2; LC3B, microtubule-associated protein 1A/1B light chain 3 B; MEK, mitogen-activated extracellular signal-regulated protein kinase; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-kappa B; PKC-α, protein kinase C-α; ROS, reactive oxygen species; STAT 3, signal transducers and activators of transcription 3; TGF-β1, transforming growth factor-β1; TIMP-2, tissue inhibitor of metalloproteinases-2; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor 2; XIAP, X-linked inhibitor of apoptosis protein.

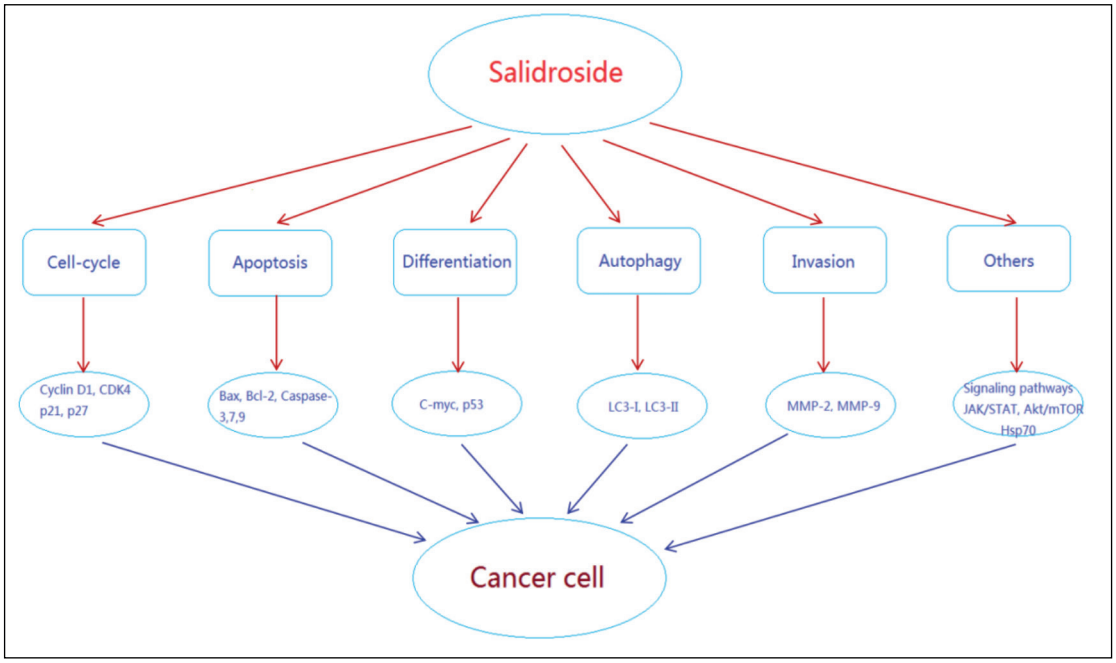

Figure 1. Mechanisms of salidroside against tumor. Salidroside plays multiple roles in inhibiting the proliferation of cancer cells, including inducing autophagy of cancer cells, inducing cancer cells to differentiate into normal cells, enhancing immunity to kill cancer cells, and blocking the cancer cell cycle. It is verified that the anti-cancer mechanism of salidroside involved the regulation of the signal pathways.

References

1) Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond) 2019; 39: 22.
2) Chen M, Hui C, Chang Y, Wu P, Fu Y, Xu X, Fan R, Xu C, Chen Y, Wang L, Huang X. Salidroside exerts protective effects against chronic hypoxia-induced pulmonary arterial hypertension via AMPKα1-dependent pathways. Am J Transl Res 2016; 8: 12-27.
3) Li Y, Pham V, Bui M, Song L, Wu C, Walia A, Uchio E, Smith-Liu F, Zi X. Rhodiola rosea L.: an herb with anti-stress, anti-aging, and immunostimulating properties for cancer chemoprevention. Curr Pharmacol Rep 2017; 3: 384-395.
4) Shi X, Zhao W, Yang Y, Wu S, Lv B. Salidroside could enhance the cytotoxic effect of L-OHP on colorectal cancer cells. Mol Med Rep 2018; 17: 51-58.
5) Tachibana KE, Gonzalez MA, Coleman N. Cell-cycle-dependent regulation of DNA replication and its relevance to cancer pathology. J Pathol 2005; 205: 123-129.
6) Rastogi N, Mishra DP. Therapeutic targeting of cancer cell cycle using proteasome inhibitors. Cell Div 2012; 7: 26.
7) Abril-Rodriguez G, Ribas A. SnapShot: Immune Checkpoint Inhibitors. Cancer Cell 2017; 31: 848.
8) Doğan Şiğva ZÖ, Balci Okcanoğlu T, Biray Avci Ç, Yilmaz Süslüer S, Kayabaşi Ç, Turna B, Dodurga Y, Nazli O, Gündüz C. Investigation of the synergistic effects of paclitaxel and herbal substances and endemic plant extracts on cell cycle and apoptosis signal pathways in prostate cancer cell lines. Gene 2019; 687: 261-271.
9) Yang P, Yin K, Zhong D, Liao Q, Li K. Inhibition of osteosarcoma cell progression by MacroH2Avia the downregulation of cyclin D and cyclin dependent kinase genes. Mol Med Rep 2015; 11: 1905-1910.
10) Sun AQ, Ju XL. Advances in Research on Anticancer Properties of Salidroside. Chin J Integr Med 2021; 27: 153-160.
11) Hu X, Lin S, Yu D, Qiu S, Zhang X, Ruhuan Mei. A preliminary study: the anti-proliferation effect of salidroside on different human cancer cell lines. Cell Biol Toxicol 2010; 26: 499-507.
12) Ding SY, Wang MT, Dai DF, Peng JL, Wu WL. Salidroside induces apoptosis and triggers endoplasmic reticulum stress in human hepatocellular carcinoma. Biochem Biophys Res Commun 2020; 527: 1057-1063.
13) Ye L, Jia Y, Ji KE, Sanders AJ, Xue K, Ji JF, Mason MD, Jiang WG. Traditional Chinese medicine in the prevention and treatment of cancer and cancer metastasis. Oncol Lett 2015; 10: 1240-1250.
14) Gui D, Cui Z, Zhang L, Yu C, Yao D, Xu M, Chen M, Wu P, Li G, Wang L, Huang X. Salidroside attenuates hypoxia-induced pulmonary arterial

smooth muscle cell proliferation and apoptosis resistance by upregulating autophagy through the AMPK-mTOR-ULK1 pathway. BMC Pulm Med 2017; 17: 191.

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

16) Pistritto G, Trisciuoglio D, Ceci C, Garufi A, D'Orazi G. Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. Aging (Albany NY) 2016; 8: 603-619.

17) Mortezaee K, Salehi E, Mirtavoos-Mahyari H, Motevaseli E, Najafi M, Farhood B, Rosengren RJ, Sahebkar A. Mechanisms of apoptosis modulation by curcumin: Implications for cancer therapy. J Cell Physiol 2019; 234: 12537-12550.

18) Tang C, Zhao CC, Yi H, Geng ZJ, Wu XY, Zhang Y, Liu Y, Fan G. Traditional Tibetan Medicine in Cancer Therapy by Targeting Apoptosis Pathways. Front Pharmacol 2020; 11: 976.

19) Lu L, Liu S, Dong Q, Xin Y. Salidroside suppresses the metastasis of hepatocellular carcinoma cells by inhibiting the activation of the Notch1 signaling pathway. Mol Med Rep 2019; 19: 4964-4972.

20) Taibi G, Gueli MC, Nicotra CM, Cocciadiferro L, Carruba G. Retinol oxidation to retinoic acid in human thyroid glandular cells. J Enzyme Inhib Med Chem 2014; 29: 796-803.

21) Kogai T, Schultz JJ, Johnson LS, Huang M, Brent GA. Retinoic acid induces sodium/iodide symporter gene expression and radioiodide uptake in the MCF-7 breast cancer cell line. Proc Natl Acad Sci USA 2000; 97: 8519-8524.

22) Ouyang JF, Lou J, Yan C, Ren ZH, Qiao HX, Hong DS. In-vitro promoted differentiation of mesenchymal stem cells towards hepatocytes induced by salidroside. J Pharm Pharmacol 2010; 62: 530-538.

23) Bertout JA, Majmundar AJ, Gordan JD, Lam JC, Ditsworth D, Keith B, Brown EJ, Nathanson KL, Simon MC. HIF2alpha inhibition promotes P53 pathway activity, tumor cell death, and radiation responses. Proc Natl Acad Sci USA. 2009; 106: 14391-14396.

24) Chen ZM, Wu Q, Chen YQ, Su WJ. Regulation of cell cycle by retinoic acid in gastric cancer cells. Shi Yan Sheng Wu Xue Bao 1999; 32: 135-140.

25) Xie F, Ouyang X, Jiang M. Reverse effects of salidroside on expression of c-myc in SMMC-7721 cell line in vitro. Xi Nan Guo Fang Yi Yao 2006; 12: 130-131.

26) Li T, Xu K, Liu Y. Anticancer effect of salidroside reduces viability through autophagy/PI3K/Akt and MMP-9 signaling pathways in human bladder cancer cells. Oncol Lett 2018; 16: 3162-3168.

27) Liu Z, Li X, Anne R. Simoneau, Mahtab Jafari, Xiaolin Zi. Rhodiola rosea extracts and salidroside decrease the growth of bladder cancer cell lines via inhibition of the mTOR pathway and induction of autophagy. Mol Carcinog. Mol Carcinog 2012; 51: 257-267.

28) Klionsky DJ. Autophagy: from phenomenology to molecular understanding in less than a decade. Nat Rev Mol Cell Biol 2007; 8: 931-937.

29) Mujumdar N, Mackenzie TN, Dudeja V, Chugh R, Antonoff MB, Borja-Cacho D, Sangwan V, Dawra R, Vickers SM, Saluja AK. Triptolide induces cell death in pancreatic cancer cells by apoptotic and autophagic pathways. Int J Cancer 2010; 139: 598-608.

30) Noda T, Yoshimori T. Molecular basis of canonical and bactericidal autophagy. Int Immunol 2009; 21: 1199-1204.

31) Zeng W, Xiao T, Cai A, Cai W, Liu H, Liu J, Li J, Tan M, Xie L, Liu Y, Yang X, Long Y. Inhibiting ROS-TFEB-Dependent Autophagy Enhances Salidroside-Induced Apoptosis in Human Chondrosarcoma Cells. Cell Physiol Biochem 2017; 43: 1487-1502.

32) Li H, Chen C. Inhibition of autophagy enhances synergistic effects of Salidroside and anti-tumor agents against colorectal cancer. BMC Complement Altern Med 2017; 17: 538.

33) Huang L, Huang Z, Lin W, Wang L, Zhu X, Chen X, Yang S, Lv C. Salidroside suppresses the growth and invasion of human osteosarcoma cell lines MG63 and U2OS in vitro by inhibiting the JAK2/STAT3 signaling pathway. Int J Oncol 2019; 54: 1969-1980.

34) Qin Y, Liu H, Li M, Zhai D, Tang Y, Yang L, Qiao K, Yang J, Zhong W, Zhang Q, Liu Y, Yang G, Sun T, Yang C. Salidroside improves the hypoxic tumor microenvironment and reverses the drug resistance of platinum drugs via HIF-1α signaling pathway. EBioMedicine 2018; 38: 25-36.

35) Chen X, Wu Y, Yang T, Wei M, Wang Y, Deng X, Shen C, Li W, Zhang H, Xu W, Gou L, Zeng Y, Zhang Y, Wang Z, Yang J. Salidroside alleviates cachexia symptoms in mouse models of cancer cachexia via activating mTOR signaling. J Cachexia Sarcopenia Muscle 2016; 7: 225-232.

36) Shang H, Wang S, Yao J, Guo C, Dong J, Liao L. Salidroside inhibits migration and invasion of poorly differentiated thyroid cancer cells. Thorac Cancer 2019; 10: 1469-1478.

37) Chen X, Kou Y, Lu Y, Pu Y. Salidroside ameliorated hypoxia-induced tumorigenesis of BxPC-3 cells via downregulating hypoxia-inducible factor (HIF)-1α and LOXL2. J Cell Biochem 2020; 121: 165-173.

38) Kang DY, Sp N, Kim DH, Joung YH, Lee HG, Park YM, Yang YM. Salidroside inhibits migration, invasion and angiogenesis of MDA-MB 231 TNBC cells by regulating EGFR/Jak2/STAT3 signaling via MMP2. Int J Oncol 2018; 53: 877-885.

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

40) He H, Chang X, Gao J, Zhu L, Miao M, Yan T. Salidroside Mitigates Sepsis-Induced Myocarditis in Rats by Regulating IGF-1/PI3K/Akt/GSK-3βSignaling. Inflammation 2015; 38: 2178-2184.

41) Qi Z, Tang T, Sheng L, Ma Y, Liu Y, Yan L, Qi S, Ling L, Zhang Y. 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 2018; 18: 147-156.

42) Hu XL, Zhang XQ, Qiu SF, Yu DH, Lin SX. Salidroside induces cell-cycle arrest and apoptosis in human breast cancer cells. Biochem Biophys Res Commun 2010; 398: 62-67.

43) Seo WG, Pae HO, Oh GS, Kim NY, Kwon TO, Shin MK, Chai KY, Chung HT. The aqueous extract of Rhodiola sachalinensis root enhances the expression of inducible nitric oxide synthase gene in RAW264.7 macrophages. J Ethnopharmacol 2001; 76: 119-123.

44) Zhang Y, Dong TR, Ni JH. The Study of Salidroside on Inhibition of Cervical Cancer HeLa Cells Proliferation. J Int Obstet Gynecol 2017; 44: 396-398.

45) Zhang LX, Wang T, Niu CQ. Effect and significance of salidroside on Eagl expression in mouse cervical cancer xenograft. Chongqing Med (Chin) 2017; 46: 3470-3476.

46) Gao J, Luo W, Wang Q. Effect of salidroside on proliferation and IMP3 expression of cervical cancer Siha cells. Chongqing Med (Chin) 2016; 45: 3849-3851.

47) Shi XM, Zhao W, Yang YB, Wu SC, Lv BN. Salidroside could enhance the cytotoxic effect of L-OHP on colorectal cancer cells. Mol Med Rep 2018; 17: 51-58.

48) Wang J, Li JZ, Lu AX, Zhang KF, Li BJ. Anticancer effect of salidroside on A549 lung cancer cells through inhibition of oxidative stress and phospho-p38 expression. Oncol Lett 2014; 7: 1159-1164.

49) Ren M, Xu WJ, Xu T. Salidroside represses proliferation, migration and invasion of human lung cancer cells through AKT and MEK/ERK signal pathway. Artif Cell Nanomed Biotech 2019; 47: 1014-1021.

50) Li B, Qu DH, Wang ZG. Salidroside decrease expression of hypoxia-inducible factor-1α in cultured human lung cancer cells. Afr J Pharm Pharmacol 2012; 6: 2526-2530.

51) Zhang M, Zhao YL, Sun FY. Inhibitory effect of sachalin rhodiola rhizome extract on CD4+ CD25+ regulatory T cells in xenograft tumors of Lewis lung cancer bearing mice. Chin J Cancer Biother 2013; 20: 444-448.

52) Yan W, Li K, Buhe A. Salidroside inhibits the proliferation and migration of gastric carcinoma cells and tumor growth via the activation of ERS-dependent autophagy and apoptosis. Royal Soci Chem 2019; 9: 25655-25666.

53) Liu MW, Su MX, Zhang W, Zhang LM, Wang YH. Rhodiola rosea suppresses thymus T-lymphocyte apoptosis by downregulating tumor necrosis factor-α-induced protein 8-like-2 in septic rats. Int J Mol Med 2015; 36: 386-398.

54) Zhang YS, Yao YY, Wang HJ, Guo YQ, Zhang H, Chen L. Effects of salidroside on glioma formation and growth inhibition together with improvement of tumor microenvironment. Chin J Cancer Res 2013; 25: 520.

55) Mora MC, Bassa LM, Wong KE, Tirabassi MV, Arenas RB, Schneider SS. Rhodiola crenulata inhibits Wnt/ β-catenin signaling in glioblastoma. J Surg Res 2015; 197: 247-255.

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

57) Lv C, Huang Y, Liu ZX, Yu D, Bai ZM. Salidroside reduces renal cell carcinoma proliferation by inhibiting JAK2/STAT3 signaling. Cancer Biomark 2016; 17: 41-47.

58) Kong Y, Xu SP. Salidroside prevents skin carcinogenesis induced by DMBA/TPA in a mouse model through suppression of inflammation and promotion of apoptosis. Oncol Rep 2018; 39: 2513-2526.