DOI: 10.53469/jcmp.2025.07(01).22

Research Progress on the Pharmacological Effects and Clinical Application of Erigeron Brevicapas in the Treatment of Malignant Tumors

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Abstract: ***To investigate the pharmacological action and clinical application of Breviscapus and its derivatives in the treatment of malignant tumors, and to provide reference for further research and clinical application of breviscapus and its derivatives in the treatment of malignant tumors. In China National Knowledge Network (CNKI), WanfangDate Data Knowledge Platform and PubMed database with "Breviscapine", "Pharmacology", "Oncology", "Breviscapine", "scutellain", "Pharmacology", "Tumor" and so on as keywords, Relevant literatures published from May 2000 to August 2022 were retrieved to sort out and summarize the pharmacological effects and clinical applications of calendula breviscapus in tumor therapy.***

Keywords: Breviscapus, Tumor, Pharmacology, Clinical effect**.**

1. Introduction

Cancer poses a serious threat to human life and health. According to the World Health Organization (WHO) statistics in 2019, among 183 countries worldwide, cancer is the first or second leading cause of death before the age of 70 in 112 countries, ranking third or fourth in the causes of death before the age of 70 in another 23 countries. Cancer increasingly stands out as a major cause of death and increasingly becomes a significant barrier to extending life expectancy [1]. Common cancers worldwide include breast cancer, lung cancer, colorectal cancer, prostate cancer, stomach cancer, and liver cancer. It is estimated that by 2040, the number of new cancer cases globally will reach 28.4 million, an increase of 47% compared to 2020. The number of cases in lower and middle-developed countries has increased the most, with rises of 95% and 64% respectively [2]. At present, the situation of prevention and treatment of malignant tumors is very severe. Therefore, finding safe and effective methods for preventing and treating cancer has become an important issue. Existing treatment methods for malignant tumors mainly include surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy, etc. However, the current treatment methods are not as effective as expected, have significant side effects, and the probability of recurrence and metastasis after treatment of malignant tumors is high [3]. Compared with other anti-tumor therapies, traditional Chinese medicine, as a representative of traditional medicine, has characteristics of multi-targets and multi-pathways, fewer side effects, and low cost, and has become a research hotspot in the prevention and treatment of malignant tumors.

With the advent of artemisinin, the pharmacological research and clinical application of natural medicines have become increasingly extensive. Currently, it is estimated that there are about 70, 000 plant-based medicines that have been proven to have medicinal value [4]. Erigeron breviscapus, also known as breviscapine, or Dongju, is recorded in "Yunnan Chinese Herbal Medicine" as having a sweet taste and warm nature. It has the effects of dispersing cold, relieving exterior symptoms, alleviating pain, and relaxing muscles and tendons. It can be used in the treatment of diseases such as traumatic injuries, malaria, cerebral thrombosis, cerebral hemorrhage, and rheumatic arthritis [5]. Scutellarin is the extract from the dried whole plant of Erigeron breviscapus (Vant.) Hand-Mazz. The main active ingredient is scutellarin (Bre), primarily composed of scutellarein - 4′, 5, 6 - trihydroxyflavone- 7-glucuronide (accounting for over 95%), and also includes a small amount of scutellarin A (apigenin-7-O-glucuronide) [6]. Previous studies [7-8] have shown that it exhibits significant antitumor effects against various types of malignant tumors. Based on this, the author used keywords such as "Breviscapine", "Pharmacological effects", "Malignant tumors", "Breviscapin", "Scutellain", "Pharmacology", "Tumor", and searched databases including CNKI (China National Knowledge Infrastructure), Wanfang Data, and PubMed for relevant literature published from May 2000 to August 2022. The aim was to summarize the pharmacological effects and clinical applications of Breviscapine and its derivatives in the treatment of malignant tumors over the past 20 years.

2. The Pharmacological Effects of Erigeron Breviscapus and its Derivatives in the Treatment of Malignant Tumors

In addition to the protective effects on the cardiovascular and nervous systems, the active ingredients of Erigeron brevicapas and its derivatives also play a significant role in the prevention and treatment of cancer through various mechanisms of action. Further research into these active components and their metabolites can provide more possibilities for important clinical applications and also offer potential for the development of new drugs [9].

2.1 Inhibit Tumor Cell Proliferation

The anti-tumor activity of scutellarin has been confirmed in numerous cell experiments, animal studies, and clinical trials [10]. Wei Weitian [11] and others found that scutellarin, an

active component in the flower of the herb Erigeron breviscapus, is important for increasing the apoptosis rate of tumor cells. It significantly inhibits the proliferation of tumor cells. Further research has shown that scutellarin induces apoptosis of A549 cells both in vivo and in vitro. The mechanism may involve scutellarin promoting the expression of Bax and inhibiting the expression of Bcl-2, thereby increasing the ratio of Bax/Bcl-2, activating Caspase-3, and achieving an apoptotic effect. Liu Ting [12] and others found that scutellarin can lower the survival rate of A549 cells by delaying the cell division process, and this effect is dose-dependent. It increases the level of p21 protein, which binds more with PCNA to inhibit DNA synthesis; it also increases the binding of CKI with CDK, inhibiting the activity of CDK, thus affecting the binding of CyclinD1/CDK and preventing A549 cells from quickly transitioning from the G1 phase to the S phase. This reduces the content of Ki-67 protein, blocks the cell cycle of A549 cells, delays the cell division process, and ultimately affects the proliferation of non-small cell lung cancer A549 cells. Some studies indicate [13] that the tumor suppressor gene EGR1 is dysregulated in several human cancers and plays a significant role in the development of tumors. Notably, the expression of EGR1 is closely related to the anti-tumor mechanisms of many natural compounds. By inducing an increase in EGR1 in osteosarcoma cells, scutellarin has been shown to induce apoptosis and inhibit proliferation at the cellular level and in animal models [14]. Research has found [15] that Bre can significantly inhibit the proliferation, invasion, migration, and epithelial-mesenchymal transition (EMT) of prostate cells by blocking the PAQR4-mediated PI3K/Akt pathway.

2.2 Reverse Tumor-induced Immune Suppression, Promote Tumor Cell Apoptosis

Wu Xianchuang [16] and colleagues found that the main component of Erigeron brevicapillatus, erigeron brevicapillatus flavonoids, acts as a TGF-β1 inhibitor and has a reversing effect on tumor-induced immunosuppression in mice. Erigeron brevicapillatus flavonoids enhance the proliferation of mouse spleen cells induced by concanavalin A (ConA) in vitro, inhibit transforming growth factor β1 (TGF-β1) and interleukin 4 (IL-4), and promote the secretion of interferon λ (IFN-λ) and interleukin 2 (IL-2). Erigeron brevicapillatus flavonoids can promote the secretion of immune-enhancing factors in tumor-bearing mice, reduce the secretion of immune-suppressive factors, and restore the immune function of tumor-bearing mice to normal levels.

2.3 Prevent Malignant Tumor Postoperative Metastasis and Recurrence

The growth and metastasis of tumors are associated with the production of vascular endothelial growth factor (VEGF) or VEGF-C in the tumor, as well as the phosphorylation of VEGF receptors (VEGFR)-2 or VEGFR-3 in vascular endothelial cells or lymphatic endothelial cells (LECs), which is related to the formation of blood vessels and lymphatic vessels [17]. Studies have shown [18] that flavonoids in Erigeron brevicapas can reduce the phosphorylation of VEGFR-3 induced by VEGF-C by inhibiting the expression of COX-2 and the production of IL-1β in TAMs, thereby reducing the metastasis and recurrence of malignant tumors after surgery. Research indicates [17] that flavonoids in Erigeron brevicapas have anti-proliferative and anti-migration effects. Yu Lijuan [20] et al. found that erigeron can promote the recovery of immune function by inhibiting the TGF-β1 signaling pathway, thus preventing the recurrence and metastasis after tumor surgery.

2.4 Improve Microcirculatory Disorders and Hypercoagulability State

Zhao Juan [21] and others found through experimental studies that the flavonoids in breviscapine have the effect of dilating blood vessels, causing peripheral vascular resistance to decrease, thereby increasing arterial blood flow. Guo Lin [22] and others found through experiments that although the application of breviscapine cannot reduce vascular dilation and capillary hyperplasia, it promotes the generation of benign blood vessels by affecting and maintaining vascular integrity and spatial structure, increases blood supply, thereby increasing oxygen supply, reducing hypoxic cells, thereby enhancing the efficacy of chemotherapy drugs, achieving an anti-tumor effect.

2.5 Targeted Inhibition of Cancer Growth

Studies have shown [23] that scutellarin can target and inhibit the growth of lung cancer cells by directly suppressing the PBK/TOPK gene in them. Other studies have indicated [13] that scutellarin can regulate the P13K/Akt pathway by reducing RQP4, thereby exerting anti-prostate cancer effects.

2.6 Disrupt the Inflammatory Microenvironment

Although the mechanism is not yet fully understood, the malignant transformation of chronic inflammation is a common pattern in the occurrence and development of most cancers [24]. Studies have shown [25] that the tumor inflammatory microenvironment plays a major role in the migration, invasion, and metastasis of tumors, which is composed of neutrophils, lymphocytes, macrophages, and their secreted cytokines, chemokines, and growth factors, etc. Li Zhaofei [26] and Bai Rujun [27] et al. found through research that scutellarin can increase the levels of wnt, FzD1, AX1N1, β-catenin, VGRF to reduce the expression of GSK-3β, control the stability of blood vessels, thereby protecting the damaged rat vascular endothelial cells, to achieve the destruction of the inflammatory microenvironment and thus inhibit the growth of tumor cells, and it shows a significant dose-effect relationship. Li Yinghua [28] et al. found through research that scutellarin can effectively reduce the expression of inflammatory cytokines, reduce oxidative stress and pro-apoptotic protein expression, inhibit the activation of NF-κB signal transduction and microglia in I/R injured tissues, thereby reducing inflammatory responses. The mechanism may be to destroy the tumor growth microenvironment by alleviating inflammatory responses.

2.7 Inducing Senescence in Tumor Cells and Anti-tumor

Cellular senescence is considered a potential mechanism for tumor suppression. Studies have shown [29] that senescent cells activate the proliferative mechanisms of various organs,

collectively combating cellular senescence, which allows cancer cells within the body the opportunity to develop into tumors. In addition to inhibiting the vitality, metastasis, regulating autophagy and apoptosis, and blocking the cell cycle of cancer cells, active components of traditional Chinese medicine (TCM) and natural medicines can also exert anti-tumor effects by promoting cellular senescence. Therefore, selectively clearing senescent cells is of significant importance in preventing the occurrence and development of tumors. Zhang Yan [30] and others have shown through research that scutellarin does not indiscriminately promote apoptosis in all cells, but has a stronger effect on T cells and B cells. Dou Jie [31] and others have shown that active components of TCM or natural medicines can induce senescence in tumor cells and selectively clear aged cells. Scutellarein and scutellarin are active components of scutellaria, both of which have extensive anti-tumor activities. In addition, both can induce cell cycle arrest, inhibit the formation and migration of cancer cell colonies. Scutellarein and scutellarin respectively mediate apoptosis and senescence in colon cancer cells, which are mechanisms for inhibiting apoptosis in colon cancer cells. It was also found that the induction of tumor cell senescence by scutellarin is due to its inhibition of the expression of telomerase reverse transcriptase in tumor cells, and the MAPK ERK and p38 signaling pathways are involved in the regulation of colon cancer cell apoptosis and senescence mediated by scutellarein and scutellarin. Furthermore, in vivo studies on a humanized mouse xenograft model of human colon cancer cells have further demonstrated that scutellarein and scutellarin can induce apoptosis and senescence in tumor cells, thereby inhibiting the occurrence and growth of colon cancer in vivo. This proves that scutellarein and scutellarin have a powerful anti-cancer effect against human colon cancer.

3. Clinical Application of Erigeron Brevicapas in the Treatment of Malignant Tumors

3.1 Improve Hypercoagulability, Reduce Thrombosis Formation

Research indicates [32] that malignant tumor patients experience a hypercoagulable state due to elevated platelet levels. This condition not only leads to arterial and venous thrombosis but also serves as a risk factor for tumor proliferation and metastasis. The incidence of venous thrombosis in patients with malignant tumors is five times higher than in the general population and is the second leading cause of death among these patients [33]. The hypercoagulable state in malignant tumor patients generally refers to the procoagulant effects produced by the interaction between tumor cells themselves or between tumor cells and other blood cells, as well as pathological blood coagulability increases caused by various antitumor treatments. Thrombosis is prone to formation under hypercoagulable conditions, increasing the mortality risk of patients with arterial and venous thrombosis [34]. Studies have pointed out [35] that patients with venous thromboembolism (VTE) accompanied by malignant tumors have a significantly increased probability of severe bleeding and death. Wang Yuhui [36] et al. selected 60 patients with chronic renal insufficiency and randomly divided them into a treatment group and a control group. The treatment group received intravenous injections of Erigeron brevicapas after general treatment, while the control group only received general treatment. Neither group was given other lipid-lowering, anticoagulant, or platelet aggregation inhibiting drugs. After 14 days of treatment, both groups of patients were tested for blood lipids and blood coagulation. The results showed that the TG, LDL, and FIB indicators in the treatment group were lower than those in the control group, suggesting that Erigeron brevicapas not only improves microcirculation but also has a certain lipid-lowering effect. Ren Minshan [37] et al. selected 56 patients with advanced malignant tumors and administered Erigeron brevicapas injection to all patients who met the criteria. After 7 to 10 days of treatment, the platelet count (PLT) and fibrinogen (FIB) levels in 49 patients returned to normal, while 7 did not recover, with an effective rate of 87.5%. This suggests that Erigeron brevicapas injection has effects such as dilating blood vessels, inhibiting platelet and red blood cell aggregation, promoting fibrinolysis activity, reducing fibrinogen, scavenging oxygen free radicals, combating lipid peroxidation, and ischemia-reperfusion injury, thereby effectively inhibiting thrombosis formation and reducing blood viscosity, improving microcirculation. Traditional medicine believes that the formation of tumors is due to emotional factors, diet, six exogenous pathogenic factors, and dysfunction of the zang-fu organs, but "stasis" is the main cause of its formation. Whether it is phlegm congestion, qi stagnation, heat toxicity, dampness accumulation, or the spread of toxic pathogens through the channels or organs due to weakness of the zang-fu organs, it ultimately leads to tumor formation due to blood stasis [38]. Therefore, the method of promoting blood circulation and removing blood stasis is a major therapeutic principle in the treatment of tumors in traditional medicine.

3.2 Alleviate Postoperative Brain Tumor Damage

Gliomas are the most common type of intracranial malignant tumor, originating from neuroepithelial tissue, and account for 40% to 50% of all intracranial tumors clinically. The most direct and effective method of treating gliomas is extensive surgical resection. However, the brain damage caused by surgery can negatively affect the recovery of cognitive functions post-operation. Wu Youyang et al. randomly divided 84 patients scheduled for elective glioma resection into a control group and an observation group. Both groups received standard postoperative treatment, but the observation group was additionally given an intravenous infusion of 30mL of Erigeron brevicapas injection in 0.9% saline before anesthesia induction. The serum levels of neuron-specific enolase (NSE) and S100β protein (S100β) in the observation group were significantly lower than those in the control group. After anesthesia, the observation group had significantly shorter orientation recovery time and eye-opening time compared to the control group (all $P < 0.05$), and the OAAS scores of the observation group were significantly higher than those of the control group after extubation, before leaving the room, and 1 hour after extubation. Clinical observation found that propofol combined with remifentanil target-controlled infusion and Erigeron brevicapas injection could reduce vascular permeability, alleviate cerebral edema, reduce brain injury, and improve the quality of awakening. Xu Xiaomei et al. found that, on the basis of comprehensive treatment, the combined use of breviscapine could reduce vascular

resistance, increase cerebral blood flow, enhance the permeability of the blood-brain barrier, and achieve improved microcirculation and vasodilation to relieve cerebral vasospasm after brain tumor surgery and reduce postoperative injury. This has a positive effect on improving patient treatment satisfaction and the quality of life.

4. Conclusion

Erigeron brevicapas, as a traditional Chinese medicine, has the advantages of low toxicity and side effects, and low cost. In the treatment of malignant tumors, it has pharmacological effects such as increasing the apoptosis rate of malignant tumor cells, reducing the proliferation rate of malignant tumor cells, reversing the immune suppression induced by malignant tumors, preventing postoperative metastasis and recurrence of malignant tumors, promoting the generation of benign blood vessels, inducing tumor cell senescence, and enhancing the effect of chemotherapy when used in combination with other drugs. Clinically, it is mostly used in the form of injections to improve the hypercoagulable state caused by malignant tumors, reducing postoperative damage and complications of malignant tumors. At present, most of the research on the treatment of malignant tumors with Erigeron brevicapas is still at the level of animal or cell experiments in vitro, lacking high-quality clinical therapeutic evidence, and there is a problem with a small number of cases. With the increasing incidence of malignant tumors in our country, and at the same time, under the existing treatment methods, the treatment is expensive, the side effects are obvious, and the treatment effect is not satisfactory, finding a safe and effective treatment method and continuously optimizing the existing treatment methods have become the key to current tumor prevention and treatment. Therefore, it is of great significance to carry out large-sample, randomized controlled clinical studies on the treatment of malignant tumors with Erigeron brevicapas in the future. The inhibitory effect of Erigeron brevicapas and its derivatives on tumors is obvious [43], and they have a certain degree of selectivity for tumor cells and the advantage of "multi-target, multi-pathway". At present, due to the low oral solubility of erigeronol, limited membrane permeability, and the problem of low bioavailability caused by the first exclusion in the gastrointestinal tract, it has not been widely used in clinical practice. In recent years, researchers have tried to use nanoparticles, liposomal nanocomposites, phospholipid complexes, and other formulations to improve the oral bioavailability of erigeronol [44]. Therefore, the research on Erigeron brevicapas and its derivatives in the clinical treatment of malignant tumors, as well as the improvement of the processing technology of Erigeron brevicapas, will promote its application in tumor treatment and enrich the choices of clinical treatment for malignant tumors.

References

[1] Sung H; Ferlay J; Siegel RL; Laversanne M; Soerjomataram I; Jemal A; Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.

[2] Cao Maomao; Chen Wanqing (N.Interpretation on the global cancer statistics of GLOBOCAN 2020[J]. Chinese Journal of the Frontiers of Medical Science (Electronic Version), 2021, 13(3):63-69.

[3] ZHANG Binglei, ZHANG Zhiming, SONG Zhongyang, et al. Discussion on TCM prevention and treatment of malignant tumor based on the idea of "Removing bad accumulation by strengthening healthy energy" [J]. Clinical Journal of Chinese Medicine, 2022, 14(18): 130-132+143.

[4] SHARMA; NEELESH; SAMARAKOON; KALPA W.; GYAWALI; RAJENDRA, et al. Evaluation of the Antioxidant, Anti-Inflammatory, and Anticancer Activities of Euphorbia hirta Ethanolic Extract[J]. Molecules, 2014, 19(9):14567-14581.

[5] GE Wen-xiu; LUO Yun; XIE Xue-heng; SUN Gui-bo; YU Miao; SUN Xiao-bo. Research Progress on Pharmacological Mechanisms of Scutellarin[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2020, 26(22):193-200.

[6] Shi Senlin; Xu Lianying; et al. Study on physicochemical properties and influence factors on stability of breviscapine [J]. China Journal of Chinese Materia Medica, 2009, 34(7):843-847.

[7] Liu Y, Wen PH, Zhang XX, et al. Breviscapine ameliorates CCl4 induced liver inj ury in mice through inhibiting inflammatory apoptotic response and ROS generation[J]. Int J Mol Med, 2018, 42(2):755-768.

[8] Wang Q, Wang Q, Wang SF, et al. Oral Chinese herbal medicine as maintenance treatment after chemotherapy for advanced non-smal-l cell lung cancer: A systematic review and Meta-analysis [J]. Current Oncology, 20 1 7, 24 (4):2 6 9-2 7 6.

[9] Fan Hua, Lin Peng, Kang Qiang, et al. Metabolism and Pharmacological Mechanisms of Active Ingredients in Erigeron breviscapus [J]. Current drug metabolism, 2021, 22(1):24-39.

[10] EGHBALIFERIZ, SAMIRA, TALEGHANI, AKRAM, TAYARANI-NAJARAN, ZAHRA. Scutellaria: Debates on the anticancer property[J]. Biomedicine & pharmacotherapy =: Biomedecine & pharmacotherapie, 2018, 1051299-1310.

[11] WEI Weitian;CHEN Sheng;WANG Liang;ZENG Jian. Breviscapine induced the apoptosis of non-small cell lung cancer A549 cells[J]. Chinese Journal of Clinical Pharmacology and Therapeutics, 2020, 25(6):618-624.

[12] LIU Ting; LI Yang; SHI Zhihong. Effects of breviscapine on proliferation and apoptosis of non-small cell lung cancer A549 cells[J]. Shaanxi Journal of Traditional Chinese Medicine, 2021, 42(10):1363-1366.

[13] Tongtong LI, Manru LIU, Dongsheng PEI. Friend or foe, the role of EGR-1 in cancer[J]. Medical oncology., 2020, 37(1):7.

[14] Han J, Wang P, Xia X, Zhang L, Zhang H, Huang Y, Li X, Zhao W, Zhang L. EGR1 promoted anticancer effects of Scutellarin via regulating LINC00857/miR-150-5p/c-Myc in osteosarcoma. [J] Cell Mol Med. 2021 Sep;25(17):8479-8489.

[15] Ye J, Gao M, Guo X, Zhang H, Jiang F. Breviscapine suppresses the growth and metastasis of prostate cancer through regulating PAQR4-mediated PI3K/Akt pathway. Biomed Pharmacother. 2020 Jul;127:110223.

[16] Wu Xianchuang. Research on the Anti-fibrotic and Anti-tumor Effects of Scutellarin[D]. Henan: Henan University, 2010.

[17] Li Zhonghai; Wang Jingze. Vascular Endothelial Growth Factor-C and Tumour Metastasis[J]. Chemistry of Life, 2003, 23(4):300-302.
[18] KIMURA, Y., SUMIYOSHI, M.. Anti-tumor and anti-metastatic actions of wogonin isolated from Scutellaria baicalensis roots through anti-lymphangiogenesis [J]. Phytomedicine: international journal of phytotherapy and phytopharmacology, 2013, 20(3/4):328-336.
[19] LI, JIANKUN, WANG, HAIRONG, SHI, XIAOWEI, et al. Anti-proliferative and anti-migratory effects of Scutellaria strigillosa Hemsley extracts against vascular smooth muscle cells[J]. Journal of Ethnopharmacology: An Interdisciplinary Journal Devoted to Bioscientific Research on Indigenous Drugs, 2019, 235155-163.
[20] Yu Lijuan; Lin Haihong; Du Gangjun;et al. Preventive effect of breviscapine on metastasis and recurrence of breast cancer after the tumor removal in mice[J]. Journal of Henan University: Medical Science, 2009, 28(3): 182-184.
[21] Zhao Juan. Observation on the Efficacy of Hyperbaric Oxygen Liquid and Erigeron brevicapas Injection in the Treatment of Acute Cerebral Infarction[J]. Chinese Journal of Practical Nervous Diseases, 2006, 9(5):83-83.
[22] He Lin; He Furong. The Difference and Similar Regard of Tumor's Antiagiogenic Therapy between East-west Medicines[J]. Medicine & Philosophy(B), 2009, 30(10):72-74.
[23] Diao X, Yang D, Chen Y, Liu W. Baicalin suppresses lung cancer growth by targeting PDZ-binding kinase/T-LAK cell-originated protein kinase. Biosci Rep. 2019 Apr 9;39(4):BSR20181692.
[24] LIU Wenbin; CAO Guangwen. Cancer evolution-development: novel theory based on studies of inflammation-cancer transformation[J]. Chinese Journal of Cancer Biotherapy, 2017, 24(2):103-111.
[25] Shen Zhengjie; Cheng Haibo; Shen Weixing; Wu Mianhua. Correlation between tumor inflammatory microenvironment and “cancerous toxin” pathogenesis [J]. Journal of Beijing University of Traditional Chinese Medicine, 2015, 38(1):14-17.
[26] Li zhaofei. Research on the Protective Effect and Mechanism of Scutellarin on Vascular Endothelial Cell Injury[D]. Guangxi University of Chinese Medicine, 2016.
[27] BAI Rujun, LIU Jun, ZHOU Youli. Effects of Breviscapine on Wnt/β-catenin Signaling Pathway and Inflammatory Mediators in Rats with Vascular Endothelial Cell Injury[J/OL]. World Chinese Medicine1-13[2022-11-23]. http://kns.cnki.net/kcms/detail/11.5529.R.20221030.1720.004.html
[28] Li Y, Li S, Li D. Breviscapine Alleviates Cognitive Impairments Induced by Transient Cerebral Ischemia/Reperfusion through Its Anti-Inflammatory and Anti-Oxidant Properties in a Rat Model. ACS Chem Neurosci. 2020 Dec 16;11(24):4489-4498.
[29] Liu Yiman, Yang Shenshen, Wang Kailong, Lu Jia, Bao Xiaomei, Wang Rui, Qiu Yuling, Wang Tao, Yu Haiyang. Cellular senescence and cancer: Focusing on traditional Chinese medicine and natural products. [J]. Cell proliferation, 2020, 53(10).
[30] Zhang Yan. Research on the Anti-inflammatory and Immunoregulatory Effects of Baicalin and Baicalein[D]. Shanghai: Second Military Medical University, 2012.
[31] Dou J, Wang Z, Ma L, Peng B, Mao K, Li C, Su M, Zhou C, Peng G. Baicalein and baicalin inhibit colon cancer using two distinct fashions of apoptosis and senescence. Oncotarget. 2018 Jan 8;9(28):20089-20102.
[32] Elalamy I, Verdy E, Gerotziafas G, et a1. Pathogenesis ofvenous thromboemloolic disease in cancer[J]. Pathol Biol, 2008, 56(4): 184.
[33] Fernandes CJ, Morinaga LTK, Alves JL Jr, Castro MA, Calderaro D, Jardim CVP, Souza R. Cancer-associated thrombosis: the when, how and why. Eur Respir Rev. 2019 Mar 27;28(151):180119.
[34] LI Xiao-xiao; MA Yun-fei; LI Guang-da; WANG Xiao-min; ZHANG Yi. Pathogenesis of hypercoagulable state in patients with malignant tumor and its treatment by TCM and western medicine[J].World Journal of Integrated Traditional and Western Medicine, 2019, 14(11):1619-1623.
[35] Gussoni G, Frasson S, La Regina M, et al. Three 一month mortality rate and clinical predictors in patients with venousthromboembolism and cancer. Findings from the RIETE registry[J]. Thromb Res, 2013, 131(1):24-30.
[36] Wang Yuhui; Tong Mengli. Clinical observation of chronic renal with blood clotting and blood-lipid abnormality treated with Herba Erigerontis [J]. Acta Chinese Medicine and Pharmacology, 2003, 31(3):4-5.
[37] Ren Minshan; Huang Shanshan; Guo Wenxiu. Effects and mechanisms of erigeron injection in improving the hypercoagulable state of malignant tumors[J]. Journal of Clinical Medicine in Practice, 2013, 17(14):62-64.
[38] Wu Jiping; Li Shihui. Treatment of 39 cases of gastrointestinal tumors with blood-activating and stasis-removing method combined with chemotherapy. [J]. Shaanxi Journal of Traditional Chinese Medicine, 1999, (2):52.
[39] QUINN T. OSTROM, LUC BAUCHET, FAITH G. DAVIS, et al. The epidemiology of glioma in adults: a 'state of the science' review[J]. Neuro-oncology, 2014, 16(7):896-913.
[40] Zhangrui; Jin Hua; Lv Zhonghua, et al. Advances in Glioma Surgery and Adjunctive Techniques[J]. Journal of Modern Oncology, 2014, 22(4):937-941.
[41] Wu Youran; Zhou Chunli; Wang Yong. The effect of propofol combined with remifentanil target-controlled infusion and breviscapine injection on cerebral protection and emergence quality in patients undergoing brain glioma resection surgery. [J]. Modern Journal of Integrated Traditional Chinese and Western Medicine, 2018, 27(29):3290-3293.
[42] Xu Xiaomei. Study on the Effect of Scutellarin in Treating Cerebral Vasospasm after Brain Tumor Surgery[J]. Integrated Chinese-Western Medicine Journal of Cardiovascular Diseases, 2016, 4(21):127.
[43] TONG HAN, YAN WANG, MINGYING WANG, et al. Synthesis of scutellarein derivatives with antiproliferative activity and selectivity through the intrinsic pathway[J]. European Journal of Medicinal Chemistry: Chimie Therapeutique, 2018, 158493-158501.

[44] Wang JN, Tan JY, Luo JH, et al., 2017. Enhancement of scutellarin oral delivery efficacy by vitamin B12-modified amphiphilic chitosan derivatives to treat type II diabetes induced-retinopathy. J Nanobiotechnol, 15: 18.