Research Progress in Anti-tumor Effects of Traditional Chinese Medicine and Its Extracts

Jingjing LIAO[1△], Hong LEI[1△], Liting LAI[1], Bing QING[2], Wen ZHONG[2*], Yunli TANG[1*]

1. Guangxi University of Chinese Medicine, Nanning 530200, China; 2. Guangxi International Zhuang Medicine Hospital Affiliated to Guangxi University of Chinese Medicine, Nanning 530201, China

Abstract Traditional Chinese medicine and its extracts have received widespread attention due to their significant anti-tumor effects and low adverse reactions. Many traditional Chinese medicine and its extracts have been applied in clinical tumor treatment. In this paper, the research progress in anti-tumor effects of plant-based traditional Chinese medicine and its extracts, animal-based traditional Chinese medicine and its extracts, and traditional Chinese medicine compound is reviewed.

Key words Traditional Chinese medicine, Tumor, Anti-tumor mechanism

1 Introduction

Tumor is a major disease that threatens human health. In February of 2022, the National Cancer Center released China's latest cancer report *Incidence Rate and Mortality of Cancer in China* in 2016 on the *Journal of the National Cancer Center*. The report indicated that there were over 4 million new cases of cancer and over 2 million new deaths from cancer in China in 2016. From this report, it can be seen that the overall incidence of malignant tumors continues to rise nationwide, but it is lower in rural areas than in urban areas. The crude incidence rate of cancer in China shows a significant upward trend. But with the adjustment of population age structure, the standardized mortality rate shows a downward trend[1]. Conventional tumor treatment includes surgery, radiotherapy, and chemotherapy. Although all three treatment methods can improve the survival time of patients, due to the significant toxic side effects of radiotherapy and chemotherapy, patients have received different types of treatment and may have some resistance to chemotherapy. How to develop safe and effective new anticancer drugs is currently an urgent problem to be solved. Traditional Chinese medicine is a precious resource accumulated in China for thousands of years, such as artemisinin antimalarial drugs, and traditional Chinese medicine for COVID-19, which has extensive clinical application value. In recent years, traditional Chinese medicine has been widely used internationally in the treatment of cancer[2]. In this paper, the application and mechanism of traditional Chinese medicine and its extracts in anti-tumor therapy are reviewed.

2 Anti tumor plant-based traditional Chinese medicine and extracts

2.1 Ginsenoside Ginseng is a perennial plant of Panax of Araliaceae, known as the "king of herbs", rich in saponins, polysaccharides, flavonoids and other active substances. Ginsenosides are an important class of bioactive substances that play an important role in anticancer activity among various bioactive substances[4]. In terms of anti-cancer, ginsenoside can block the growth of cancer cells through death receptors, mitochondria, endoplasmic reticulum and other signal pathways, thereby promoting apoptosis of cancer cells, and thus playing an anti-cancer role[5]. Ginsenoside Rg3 has significant anticancer effects, and could activate cancerous cells apoptosis induced by Caspase-3 and Caspace-9, inhibit extracellular regulatory protein kinase (ERK) and Akt signaling pathway, and activate mitochondrial apoptosis pathway[6]. Additionally, Rg3 could inhibit EMT induced by TGF-β1 and make matrix metalloproteinase 2 and p38 mitogen activate and protein kinase and Smad2 deactivate, thereby inhibiting invasion and metastasis of tumors and vascular endothelial growth factor. Ginsenoside Rh2 also has the above functions, and its mechanism of action is more comprehensive and complex[7].

2.2 Artemisinin Artemisinin is an active ingredient extract of annual *Artemisia annua* and is currently the most efficient drug for treating malaria[8]. Artemisinin and its derivatives also have certain antiviral and anti-tumor effects[9]. The research by YAO *et al.*[10] showed that artemisinin derivatives artesunate (ARS) and dihydroartemisinin (DHA) could decline the expression of phosphorylated intracellular signal transduction protein (Smad3) and transforming growth factor β1 (TGF-β1), making that TGF-β signal transduction is inhibited, and cancer related fibroblasts deactivate, which can inhibit tumor growth and metastasis.

Received: May 6, 2023 Accepted: September 15, 2023

Supported by Innovation and Entrepreneurship Training Program Project of College Student in 2021 (202110600016); Key R&D Projects of Guangxi Science and Technology Department (GUIKE AB21196057); Guangxi Traditional Chinese Medicine Multidisciplinary Cross Innovation Team Project (GZKJ2309); National Administration of Traditional Chinese Medicine "12th Five-Year Plan" Key Discipline of Traditional Chinese Medicine Ethnology (Zhuang Pharmacy); the "High-level Talent Cultivation and Innovation Team" Project of Guangxi University of Chinese Medicine (2022A008).

△ These authors contributed equally to this work.

* Corresponding author. E-mail: 214998680@qq.com

2.3 Resveratrol Resveratrol is a natural polyphenol plant antitoxin, which exists in peanuts, grapes and their seeds, *Reynoutria japonica*, and is rich in content. It has many pharmacological effects, such as antioxidant, anti-inflammatory, anti-cancer, anti neuropathy, immune regulation, *etc*[11-12]. The research by YUAN *et al.*[13] showed that resveratrol can significantly inhibit the expression of N-cadherin, phosphorylated AKT1, phosphorylated glycogen synthase kinase-3β and Snail protein in colorectal cancer cells. It can also regulate Akt/GSK-3 β/Snail signaling pathway, thereby reversing epithelial mesenchymal transition in tumor tissue and inhibiting tumor invasion and metastasis.

2.4 *Sculellaria barbata* *S. barbata* is perennial herb of Labiatae, and it has the functions of clearing heat and detoxifying, promoting blood circulation and resolving blood stasis, reducing swelling and diuresis, and various pharmacological effects such as anti-tumor, immune regulation, anti-inflammatory, antiviral, *etc.* Its main chemical components include flavonoids, diterpenoids, polysaccharides, volatile oils, organic acids, and trace elements[14-15]. The study found that almost all the chemical components of *S. barbata* have different degrees of anti-tumor effects[16]. *S. barbata* flavonoids could decline the levels of CD163, CD206 and IL-10, block Toll like receptor 4/myeloid differentiation factor (MyD88)-NF-κB signal pathway, and affect polarization of macrophage M1 to M2 in the tumor microenvironment of endometrial carcinoma[17]. The research by Zhang Haifang *et al.*[18] showed that the volatile oil contained in *S. barbata* has a significant inhibitory effect on the proliferation of human lymphoma cell U937 and human gastric adenocarcinoma cell AGS.

2.5 Herba Hedyotidis Herba Hedyotidis is from dry whole grass of *Olden-landia diffusa* (Wilid.) Roxb., which belongs to *Hedyotis*, Rubiaceae Juss. This plant is unique in China, mainly distributed in Guangxi, Fujian, and surrounding areas. It has a bitter and light taste, a cold nature, and belongs to the stomach, large intestine, and small intestine meridians. It has the functions of clearing heat and detoxifying, reducing swelling, and promoting diuresis and dehumidification. Additionally, it has various pharmacological activities such as anti-tumor, neuroprotection, anti-inflammatory and antibacterial, antioxidant and anti-aging, and enhancing immunity[19-20]. Herba Hedyotidis is a common medicinal herb in the compound treatment of anti-tumor, and has been widely used in various anti-tumor treatments such as digestive system tumors, reproductive system tumors, respiratory system tumors, and myeloma[19-20]. As a traditional Chinese medicine, Herba Hedyotidis is used in many classic prescriptions for cancer treatment in clinic.

2.6 Berberine Berberine is the main bioactive component of *Coptis chinensis*, and its functions include antibacterial, anti-inflammatory, antioxidant, anti diabetes, improving cardiovascular disease, anti-tumor, *etc*[21-22]. Due to the fact that the growth of tumor cells relies on a large amount of lipids, increased lipid metabolism represents malignant tumors. In colon cancer cells DLD1 and Caco-1, LIU *et al.*[23] found that berberine can down regulate the expression of binding protein of cholesterol regulatory element and SREBP cleavage activating protein, and then regulate the expression of downstream fatty acid synthase, including fatty acid synthase, ATP citrate lyase, acetyl-CoA carboxylase, inhibit the lipid synthesis of tumor cells, and make Wnt/ β-catenin pathway inactivated. The cell cycle is blocked in G_0/G_1 phase, and the proliferation of colon cancer cells is inhibited.

3 Anti tumor animal-based traditional Chinese medicine and extracts

3.1 Cinobufotalin Cinobufotalin is water soluble extract of the skin from *Bufo gargarizans* or *Bufo melanostictus* schneider through water alcohol method, and its components include toad dienolactones, alkaloids, peptides, toad cyclic amides, amino acids, *etc*[24]. Huachansu is a modern Chinese medicine injection developed based on the traditional Chinese medicine Bufonis Venenum, and belongs to the national protected variety of traditional Chinese medicine. It has the effects of clearing heat and detoxification, reducing swelling and relieving pain, dispelling blood stasis and dispersing nodules, and can be used to treat various malignant tumors, chronic hepatitis B and other diseases clinically[25]. Clinically, cinobufotalin has a very good anti-cancer effect. It can be used alone or in combination with chemotherapy and radiotherapy. It can effectively inhibit the growth and metastasis of tumors, and improve the symptoms related to cancer[26-27], especially for primary liver cancer, gastric cancer, pancreatic cancer, non-small cell lung cancer and other diseases. Cinobufotalin has a wide spectrum of anticancer, with less toxic side effects compared to chemotherapy drugs, and could enhance human immune function. Especially in clinical practice, cinobufotalin can significantly alleviate various tumor related pain, pain caused by tumors such as gastrointestinal tumors, lung cancer, and bone metastasis, and its total effective rate can reach 50% -97%. It greatly improves the quality of life of patients with advanced tumors[28], and demonstrates its unique advantages in clinical practice.

3.2 Scorpion Scorpion is dry body of *Buthus mar-tensii* Karsch from Buthidae, and traditional Chinese medicine for treating spasms and convulsions, as well as for treating rheumatic and stubborn arthralgia, various sores and swollen toxins[29]. Scorpion venom is the most studied anti-tumor component of scorpion at present, and its anti-tumor effect is mainly reflected in inhibiting proliferation, inducing apoptosis, inhibiting tumor invasion and metastasis, inhibiting angiogenesis, regulating ion channel, *etc*[29]. The metabolomics research by Cai Yuqing *et al.*[30] displayed that scorpion Cl^- channel toxin BmK CT can affect the transcription and expression of pyruvate kinase isozyme in glioma U251 cells, inhibit the consumption of glucose and the synthesis of intracellular ATP, significantly reduce the aerobic glycolysis of tumor cells, and inhibit proliferation activity. Chen Qianqi *et al.*[31] analyzed combination of Fuzheng Huayu Decoction with scorpion and chemotherapy for the treatment of gastric cancer. The results displayed that after treatment in the experimental group,

the levels of CD_3^+ and CD_4^+ were significantly higher than those in the control group. Therefore, they believed that Fuzheng Huayu Decoction can enhance the patient's immune system. Professor Xu Zhengshun reported on a case of significant efficacy in the treatment of giant liver cancer using Xiezhi Jueyin Decoction[32].

4 TCM compound

Reasonable combination and use of traditional Chinese medicine can improve drug efficacy and reduce adverse reactions. The anti-tumor mechanism of polypill has not been fully explained due to its various and complex components. The research by LU *et al.*[33] found that the mechanism of Gegen Qinlian Decoction enhancing anti-tumor activity is to regulate the metabolic pathway of glycerophospholipid and sphingolipid, enhance the effect of programmed death receptor in colorectal cancer, down regulate PD-1 and increase IL-2 and IFN-γ expression, and make T cell function restore and promote infiltration of CD_8^+ T cells in tumor tissue. After using Fuzheng Powder binder and erlotinib in NSCLC patients, the side effects of chemotherapy and tumor markers were reduced, suggesting its application value in the treatment of NSCLC[34]. Wang Qingjie *et al.*[35] developed an anti-tumor polypill containing 27 Chinese herbs, which has achieved certain results in the treatment of colorectal cancer. Through research on the oral toxic side effects of this drug, it has been proven that the drug is non-toxic and safe in clinical practice for colorectal cancer.

5 Conclusions

With the development of social economy, the incidence rate of tumors has been increasing year by year in recent years. At present, surgery, radiotherapy, chemotherapy, *etc.* are still the main treatment methods for cancer in clinical practice. However, the efficacy of traditional Chinese medicine has been recognized by both clinical practice and patients. With in-depth research on its mechanisms, the role of traditional Chinese medicine in cancer treatment is gradually becoming known. The therapeutic effects of traditional Chinese medicine on different biological levels of tumor tissue are not independent, but interrelated and interactive. It is precisely these interrelated effects that enable them to exert different therapeutic effects on tumor cells. Although traditional Chinese medicine has the advantages of high efficacy and no side effects in treatment, it is currently not feasible to independently apply traditional Chinese medicine to the treatment of cancer in clinical practice. Moreover, based on the research level of traditional Chinese medicine at home and abroad, it is indeed unable to achieve the effect of independently treating tumors.

References

[1] The National Cancer Center issuing the latest national cancer statistics [J]. Shanghai Nursing, 2022, 22(4): 72. (in Chinese).

[2] WU JX. Clinical application and safety analysis of commonly used anti-tumor traditional Chinese medicine[J]. Nei Mongol Journal of Traditional Chinese Medicine, 2017, 36(3): 105 – 106. (in Chinese).

[3] LI PY, FENG H, LIU JP, *et al.* Research and development of novel drugs based on Panax ginseng: Comprehensive technology development program of ginsenoside [J]. Chinese Traditional and Herbal Drugs, 2021, 52(17): 5350 – 5357. (in Chinese).

[4] GAO J, LU SW. Research progress in chemical constituents and pharmacological action of Renshen (Ginseng)[J]. Guiding Journal of Traditional Chinese Medicine and Pharmacy, 2021, 27(1): 127 – 130, 137. (in Chinese).

[5] LI JW, BO L, JIN D, *et al.* Research progress on anti-tumor mechanisms of ginsenoside and their metabolites[J]. Chinese Archives of Traditional Chinese Medicine, 2021, 39(11): 121 – 124. (in Chinese).

[6] SUN MY, YE Y, XIAO L, *et al.* Anticancer effects of ginsenoside Rg3 (review)[J]. International Journal of Molecular Medicine, 2017, 39(3): 507 – 518.

[7] LI X, CHU SF, LIN M Y, *et al.* Anticancer property of ginsenoside Rh2 from ginseng[J]. European Journal of Medicinal Chemistry, 2020(203): 112627.

[8] MA N, ZHANG Z, LIAO F, *et al.* The birth of artemisinin[J]. Pharmacology and Therapeutics, 2020(216): 107658.

[9] LI HB, QIN DP, GE W, *et al.* Research progress on chemical components and pharmacological effects of *Artemisia annua*[J]. Chinese Traditional and Herbal Drugs, 2019, 50(14): 3461 – 3470. (in Chinese).

[10] YAO Y, GUO Q, CAO Y, *et al.* Artemisinin derivatives inactivate cancer-associated fibroblasts through suppressing TGF-β signaling in breast cancer[J]. Journal of Experimental and Clinical Cancer Research, 2018, 37(1): 282.

[11] GALINIAK S, AEBISHER D, BARTUSIK-AEBISHER D. Health benefits of resveratrol administration[J]. Acta Biochimica Polonica, 2019, 66(1): 13 – 21.

[12] MALAGUARNERA L. Influence of resveratrol on the immune response [J]. Nutrients, 2019, 11(5): 946.

[13] YUAN L, ZHOU M, HUANG D, *et al.* Resveratrol inhibits the invasion and metastasis of colon cancer through reversal of epithelial mes- enchymal transition via the Akt/GSK3 β/Snail signaling pathway[J]. Molecular Medicine Reports, 2019, 20(3): 2783 – 2795.

[14] SONG TX, HE MS, LU JL, *et al.* Research progress on chemical components and anti-tumor effects of *Scutellaria barbata*[J]. Journal of Liaoning University of Traditional Chinese Medicine, 2020, 22(10): 126 – 133. (in Chinese).

[15] WANG ML. Preliminary study on the chemical constituents and antitumor mechanism of *Scutellaria barbata*[D]. Nanjing: Nanjing University of Chinese Medicine, 2020. (in Chinese).

[16] LI N, WANG P, SUN TF, *et al.* Research progress on chemical constituents, pharmacological action and quality control of *Scutellaria barbata* [J]. China Journal of Chinese Materia Medica, 2020, 45(21): 5117 – 5128. (in Chinese).

[17] LIAO YX. Function and mechanism of tumor immune by bidirectional regulation of flavonoids from *Scutellaria barbata*[D]. Yangzhou: Yangzhou University, 2014. (in Chinese).

[18] ZHANG HF, XU HX. Chemical composition analysis and in vitro anti-tumor effect of supercritical CO_2 extract from *Scutellaria barbata*[J]. Shandong Medical Journal, 2010, 50(47): 47 – 48. (in Chinese).

[19] LI ZM, ZHANG JY, LI F, *et al.* Research progress on chemical components and pharmacological action of *Hedyotis diffusa* in treating cancer [J]. Information on Traditional Chinese Medicine, 2021, 38(2): 74 – 79. (in Chinese).

[20] JI BY, FAN CQ, PEI LX, *et al.* Advance on the chemical and pharmacological effects studies of *Hedyotis diffusa*[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2014, 20(19): 235 – 240. (in Chinese).

[21] SINGH S, PATHAK N, FATIMA E, *et al.* Plant isoquinoline alkaloids: Advances in the chemistry and biology of berberine[J]. European Journal of Medicinal Chemistry, 2021(226): 113839.

[22] HU CY, MO ZX. Research progress on pharmacological effects and mechanisms of berberine[J]. Chinese Journal of Experimental Traditional Medical Formulae, 2017, 23(20): 213 - 219. (in Chinese).
[23] LIU Y, HUA W, LI Y, *et al.* Berberine suppresses colon cancer cell proliferation by inhibiting the SCAP/SREBP-1 signaling pathway-mediated lipogenesis [J]. Biochemical Pharmacology, 2020, 174 (C): 113776.
[24] WU HL, CHEN JB, XU K, *et al.* Research progress on the anti-tumor effect and mechanism of cinobufotalin[J]. The Chinese Journal of Clinical Pharmacology, 2021, 37(2): 192 - 196. (in Chinese).
[25] WANG TT, XU GX. Advancement on study of pharmacological action and clinical application of cinobufotalin[J]. International Journal of Ophthalmology, 2009, 9(7): 1330 - 1333. (in Chinese).
[26] TANG W, HU KW. Progress in clinical application on anti-tumor of cinobufacini[J]. Guiding Journal of Traditional Chinese Medicine and Pharmacy, 2017, 23(12): 41 - 44. (in Chinese).
[27] WANG ZJ, JIANG SL. Research progress in the mechanism of antineoplastic action of Huachansu[J]. World Journal of Integrated Traditional and Western Medicine, 2020, 15(2): 385 - 387, 392. (in Chinese).
[28] MIAO YD, QUAN WX. Clinical observation on the treatment of cancer pain patients with Huachansu capsules[J]. Chinese Traditional Patent Medicine, 2018, 40(9): 2107 - 2110. (in Chinese).
[29] REN XR, ZHANG EX, WU HJ. Research progress of anti-cancer Chinese traditional medicine Quanxie (Scorpio)[J]. Chinese Archives of Traditional Chinese Medicine, 2021, 39(11): 90 - 93. (in Chinese).
[30] CAI YQ, DU J, BO T, *et al.* BmK CT inhibits the proliferation of glioma cells by down-regulating PKM2-mediated aerobic glycolysis[J]. Chinese Journal of Biochemistry and Molecular Biology, 2019, 35(1): 42 - 50. (in Chinese).
[31] CHEN QQ, PAN SY, ZHAO Y. Analysis of clinical effect of Fuzheng Huayu Decoction combined with chemotherapy on gastric cancer patients [J]. World Chinese Medicine, 2016, 11(8): 1477 - 1479. (in Chinese).
[32] XU ZS. Treating a case of giant liver cancer with family inherited formula[J]. Electronic Journal of Clinical Medical Literature, 2019, 6(15): 166. (in Chinese).
[33] LYU J, JIA Y, LI J, *et al.* Gegen Qinlian Decoction enhances the effect of PD-1 blockade in colorectal cancer with microsatellite stability by remodelling the gut microbiota and the tumour microenvironment[J]. Cell Death and Disease, 2019, 10(6): 1 - 15.
[34] SUN XF, ZHOU F, WU T. Study on the clinical effect of Fuzheng San combined with erlotinib in patients with advanced non-small cell lung cancer and its influence on tumor markers[J]. World Journal of Integrated Traditional and Western Medicine, 2021, 16(1): 104 - 107. (in Chinese).
[35] WANG QJ, LIU ZM, YANG WX, *et al.* Study on the acute toxicity and effect of an anti-tumor traditional Chinese medicine compound formulations on the blood physiological and biochemical indexes of mice[J]. Journal of Yunnan Agricultural University (Natural Science), 2019, 34(3): 420 - 424. (in Chinese).

(From page 93)

only affected by physical diseases, but more importantly, it is related to the various social consequences of these diseases on the psychological impact of urban elderly people.

At present, the trend of population aging in China is constantly increasing. The society should really identify and solve the physical and mental problems of the elderly from the perspective of superiority theory and promote "active aging". We have found that in addition to physical diseases themselves, the prevalence of depression among urban elderly people is closely related to the long-term unmet psychological needs of the elderly, such as autonomy and relationship needs, due to physical diseases and life events. From the perspective of the new biological-psychological-social medical model, LLD is the result of the interaction of many factors such as biology, psychology, and social environment. The results of this study indicated that some physical diseases and life events may affect the onset process of LLD in cities. Hawkins' stress hypothesis theory[9] suggests that individuals with depression or a tendency towards depression tend to experience higher levels of life stress (such as life events that rely on personality traits and interpersonal relationships) compared with those without such "fragility", and the reverse relationship between physical illness and depression has also been confirmed by other studies. Therefore, it is necessary to consider the possibility of a bidirectional relationship between life events and physical diseases, and depression. Considering that this study is a cross-sectional study and cannot indicate the causal relationship between physical diseases and life events, and depression, further exploration of prospective research is needed, emphasizing the timely assessment after the occurrence of life events among urban elderly people and the early screening of physical diseases and depression.

References

[1] ZHANG B, CHEN R, MA Y, *et al.* Meta analysis of the effects of psychological nursing intervention on elderly depression patients in China [J]. Chinese Journal of Gerontology, 2016, 36(3): 680 - 683. (in Chinese).
[2] DICKEN C, ANTHONY K, JASON L, *et al.* Association between life events and change in depressive symptoms in Hong Kong Chinese elderly [J]. Journal of Affective Disorders, 2012(136): 963 - 970.
[3] KEN-ICHI I, ZHAO C, NAOMI N, *et al.* Reprint of "iPSCs, aging and age-related diseases"[J]. New Biotechnology, 2015, 32(1): 169 - 179.
[4] JRM C. A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT [J]. Psychology Medicine, 1986(16): 89 - 99.
[5] MUNIRE HUSAIYIN. Analysis of predisposing factors and clinical performance for depression in elderly patients[J]. China Journal of Health Psychology, 2015, 23(5): 654 - 657. (in Chinese).
[6] LIU J, LI SR, ZHANG WX, *et al.* Preliminary testing of the computer diagnosis system for the community brief version of Geriatric Mental State Schedule in China[J]. Chinese Mental Health Journal, 2001, 15(4): 220 - 222. (in Chinese).
[7] HAGHGOO HA, PAZUKI ES, HOSSEINI AS, *et al.* Depression, activities of daily living and quality of life in patients with stroke[J]. Journal of the Neurological Sciences, 2013, 328(1 - 2): 87 - 91.
[8] HORNSTEN C, MOLANDER L, GUSTAFSON Y. The prevalence of stroke and the association between stroke and depression among a very old population[J]. Archives of Gerontology and Geriatrics, 2012, 55(3): 555 - 559.
[9] HAWKINS MAW, CALLAHAN CM, STUMPTE, *et al.* Depressive symptom clusters as predictors of incident coronary artery disease: A 15-year prospective study[J]. Psychosomatic Medicine, 2014, 76(1): 38 - 42.