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Huijuan Tang, Peng Shu, Shenlin Liu, Xu Zhang, and Monica Mattioli-Belmonte

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REVIEW



Traditional Chinese Medicine in Oncotherapy: The Research Status

Q9 Huijuan Tang^{a,b}, Peng Shu^c, Shenlin Liu^c, Xu Zhang^b, and Monica Mattioli-Belmonte^a 

Q1 ^aDepartment of Clinical and Molecular Sciences, Università Politenica delle Marche, Ancona, Italy; ^bFirst College of Clinical Medicine, Nanjing University of Chinese Medicine, Nanjing, China; ^cDepartment of Oncology, Jiangsu Province Hospital of Traditional Chinese Medicine, Nanjing, China

ABSTRACT

In China, traditional Chinese medicine (TCM) plays a vital role in the comprehensive treatment of cancer. As an auxiliary and supplement of major treatment modalities for cancer such as surgery, chemotherapy, and radiotherapy, both clinical observations and biomolecular research have confirmed the therapeutic efficacy of TCM in cancer.

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Introduction

GLOBOCAN announced that in 2018 there were 18.1 million new cancer cases, 9.6 million cancer deaths, and 43.8 million people living with cancer (within 5 years of diagnosis) worldwide. Of this, 48.4% (8.8 million) of new cancer cases, 57.3% (5.5 million) of the cancer deaths, and 39.7% (17.4 million) of the 5-year prevalent cancer cases occurred in Asia (1). China is a developing country with a large population and a high incidence rate of cancer; therefore, cancer remains a major burden for the Chinese population.

Cancer treatment using traditional Chinese medicine (TCM) has a long history in China and is now well integrated into current healthcare systems. The occurrence of the tumor is believed to be caused by the imbalance between the healthy body and the malignant factors: either the body is not enough strong, or the malignant factors are too potent.

In TCM, treatment is based on the differentiation of syndromes. According to syndrome differentiation, TCM mainly emphasizes the treatment of “Yin and Yang balance”: the balance between “strengthening the body resistance to eliminate pathogenic factors,” and “detoxifying and removing blood stasis” (2). Based on the TCM theory, Chinese medicines therefore used for treating cancer are divided into two main categories: “strengthening the body resistance” and “attacking pathogen,” as shown in Figure 1.

Conversely, the development of modern medical research has made it possible for researchers to



explore the mechanism of TCM from a pharmacological perspective. At present, the main recognized mechanisms of TCM in cancer treatment are cytotoxicity, anti-metastasis, anti-angiogenesis, the reversal of multiple drug resistance (MDR), inducing differentiation, regulating immunity, toxicity reducing, and efficacy enhancing (for chemotherapy and radiotherapy) (Figure 2).

Clinical Investigation

In clinical practice, TCM usually uses a combination of several medicines as a formula. Therefore, in most clinical investigations, the prescriptions were compounds rather than single drugs. Tables 1 and 2 summarize some main single Chinese medicines and formulas commonly used in oncotherapy, with relative references.

Chinese Medicine Formulas

The good curative effect of Chinese medicine formulas has been verified in numerous clinical observations. In a multicenter, prospective cohort study (34), *Yiqi Huayu Jiedu Decoction* along with chemotherapy treated 201 cases of gastric cancer patients (stages II and III), compared with 196 patients with chemotherapy alone, found that the group using a combination of TCM and chemotherapy had a 39.1% lower risk of recurrence. Another study showed that *Yangzhengxiaoji Capsule* could improve the syndromes of Chinese medicine and increase the clinical

CONTACT Monica Mattioli-Belmonte  m.mattioli@univpm.it  Department of Clinical and Molecular Sciences, School of Medicine, Via Tronto/10a, 60126 Ancona, Italy.

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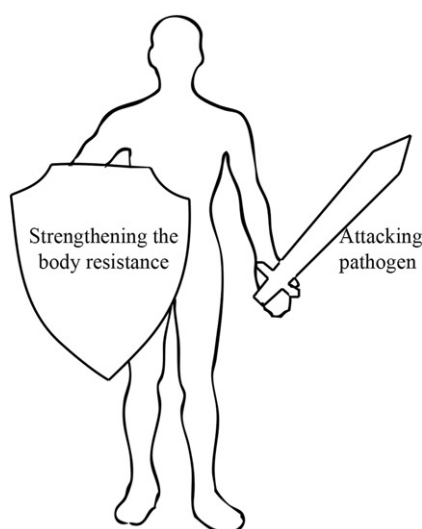


Figure 1. Chinese herbs for oncotherapy classified according to the TCM theory. Chinese medicines are divided into two main categories: “strengthening the body resistance” and “attacking pathogen” based on the TCM theory. Medicines used as “strengthening the body resistance” strengthen the human body, to make it like a shield against disease; others used as “attacking pathogen” act as a weapon to help the body drive away disease.

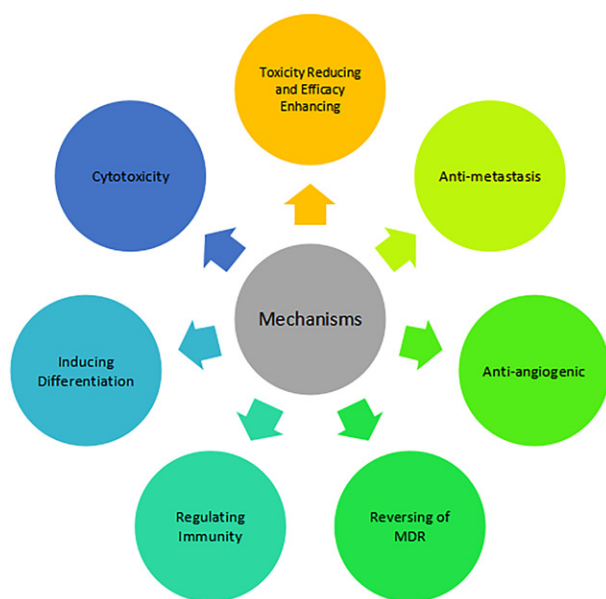


Figure 2. The main mechanisms of Chinese herbs for oncotherapy.

efficacy of patients with advanced digestive tract malignancies (35). There remains a wealth of evidence for the role of Chinese medicine formulas in western biomedicine and TCM.

Strengthening the Body Resistance

The good curative effect of “strengthening the body resistance” medicines, when used as an auxiliary for chemotherapy, has been found in modern medicine to

be mainly related to reducing toxicity, increasing efficiency, and regulating immunity. The contribution of TCM in alleviating adverse reactions is unquestionable; *Yiguan Decoction* and *Xiangsha Liujunzi Decoction* combined with western medicine can relieve vomiting, anorexia, and fatigue adverse reactions caused by chemotherapy (36).

Regarding TCM effects on regulating immunity, routine chemoradiotherapy combined with *Yiqi Yangyin Decoction* can effectively reduce tumor load and optimize the antitumor immune function in patients with advanced non-small-cell lung cancer (37). Another clinical study found that docetaxel–cisplatin (DC) chemotherapy combined with *Yiqi Guben Decoction* in the treatment of advanced non-small-cell lung cancer could effectively reduce the serum tumor marker levels, the inflammatory stress, and improve immune function (38).

In view of the outstanding performance of TCM in this area, some of the effective compounds have even been approved for mass production as adjuvant drugs for chemoradiotherapy, such as *Shenqi Fuzheng Injection* (39).

Attacking Pathogen

The most representative example of “attacking pathogen” medicine against the tumor is the remarkable efficacy of arsenic in the treatment of leukemia. Other representative TCM patent prescriptions of “attacking pathogen” in clinical observation, such as *Aidi Injection*, not only improve the efficacy of cisplatin regime but also have the function of reducing adverse events and preventing the overexpression of P-glycoprotein (P-gp) induced by chemotherapy of cisplatin regimen (40). Recent studies suggest that treating advanced gastric cancer with *sodium cantharidinate* could improve the quality of life and decrease bone marrow suppression and gastrointestinal side effects (41). *Xiaoai ping Injection* as a retention enema in the treatment of colorectal cancer (CRC) can significantly improve the clinical efficacy and relieve clinical symptoms of patients (42).

Mechanism of Action

Cytotoxicity

Many Chinese herbs used in TCM, like *Oldenlandia diffusa*, *Scutellaria baicalensis*, *Solanum lyratum*, *Paris polyphylla*, contain cytotoxic components. Their components mainly inhibit cell proliferation and induce apoptosis. For example, after spongioblastoma

Table 1. Single Chinese medicines commonly used in formulas for oncotherapy.

Name	Classified	Study type	Disease	Anticancer activity	Ref.
<i>Astragalus mongholicus</i>	Strengthening the body resistance	Mechanism research	Multiple	Cytotoxicity, antimetastasis, anti-angiogenesis, regulating immunity	(3–7)
<i>Panax ginseng</i>	Strengthening the body resistance	Mechanism research	Multiple	Cytotoxicity, antimetastasis, anti-angiogenesis, regulating immunity, toxicity reducing and efficacy enhancing	(8–11)
<i>Curcuma longa</i>	Attacking pathogen	Mechanism research	Multiple	Cytotoxicity, antimetastasis, anti-angiogenesis	(12–15)
<i>Scolopendra subspinipes</i>	Attacking pathogen	Mechanism research	Multiple	Cytotoxicity, anti-angiogenesis	(16–18)
<i>Agrimonia eupatoria</i>	Strengthening the body resistance and attacking pathogen	Mechanism research	Multiple	Cytotoxicity, regulating immunity	(19, 20)
<i>Solanum nigrum</i>	Attacking pathogen	Mechanism research	Colorectal cancer	Cytotoxicity, antimetastasis, regulating immunity	(21, 22)

Table 2. Chinese medicine formulas commonly used for oncotherapy.

Name	Components	Classified	Study Type	Disease	Anticancer activity	Ref.
Dahuang Zhechong pill	<i>Rheum palmatum</i> , <i>Scutellaria baicalensis</i> , <i>Glycyrrhiza uralensis</i> , the seed of <i>Prunus persica</i> , the seed of <i>Amygdalus communis</i> , <i>Rehmannia glutinosa</i> , <i>Paeonia lactiflora</i> , <i>Toxicodendron vernicifluum</i> , <i>Tabanus mandarinus</i> , <i>Hirudo medicinalis</i> , <i>Eupolyphaga sinensis</i> , <i>Holotrichia diomphalia</i>	Attacking pathogen	Clinical Investigation and mechanism research	Multiple	Cytotoxicity, anti-angiogenesis, regulating immunity, reversal of MDR, toxicity reducing and efficacy enhancing	(23–28)
Da Huangqi Decoction	<i>Astragalus mongholicus</i> , <i>Panax ginseng</i> , <i>Cinnamomum cassia</i>	Strengthening the body resistance	Clinical Investigation and mechanism research	Lung cancer	Antimetastasis	(29, 30)
Jianpi Liqi Decoction	<i>Codonopsis pilosula</i> , <i>Atractylodes macrocephala</i> , <i>Wolfiporia cocos</i> , <i>Akebia trifoliata</i> , <i>Oldenlandia diffusa</i>	Strengthening the body resistance and attacking pathogen	Clinical Investigation	Liver cancer	Benefiting the survival of patients	(31)
Jianpizaoshi Myogenic Decoction	<i>Astragalus mongholicus</i> , the seed of <i>Coix lacryma-jobi</i> , <i>Dioscorea opposita</i> , <i>Psoralea corylifolia</i> , <i>Scutellaria baicalensis</i> , <i>Phellodendron amurense</i> , <i>Bletilla striata</i> , <i>Sophora flavescens</i> , <i>Lithospermum erythrorhizon</i>	Strengthening the body resistance and attacking pathogen	Clinical Investigation	Enteritis caused by radiotherapy	Toxicity reducing for radiotherapy	(32)
Qiyu Sanlong Decoction	<i>Astragalus mongholicus</i> , <i>Polygonatum odoratum</i> , <i>Scolopendra subspinipes</i> , <i>Pheretima</i> , <i>Solanum nigrum</i> , <i>Oldenlandia diffusa</i> , the seed of <i>Coix lacryma-jobi</i> , <i>Euphorbia helioscopia</i> , <i>Curcuma longa</i> , <i>Fritillaria cirrhosa</i>	Strengthening the body resistance and attacking pathogen	Mechanism research	Lung cancer	Cytotoxicity	(33)

U87MG cells transformation induced by *paclitaxel* (from *Taxus chinensis*), the spindle appeared, the number of centrosomes changed, and the nuclear crumbled (43). *Tripterine* (from *Tripterygium wilfordii*) can activate DR-5/p53/Bax/caspase-9/caspase-3 and DR-5/FADD/caspase-8/lysosomal/cathepsin B/caspase-3 signaling pathway to inhibit osteosarcoma MG63 cells (44). *Saikosaponin-d* (from *Bupleurum chinense*) can inhibit the proliferation of HeLa cell though blocking of the cell cycle at the G1 phase and induce apoptosis (45).

Antimetastasis

Even when the effects of chemotherapy and radiation are significant, many patients will lose their lives due to

recurrence and metastasis. Research has found that *geranyl lignin* (from the *Citrus limon*) through matrix metalloproteinase (MMP) pathway could inhibit the expression of MMP-2 and MMP-9 protein levels and reduce the hydrolysis of the extracellular matrix, and the extracellular matrix has powerful resistance to invasion and metastasis in liver cancer (46). FAM46C plays a critical role in migration and invasion of hepatocellular carcinoma cells via TGF- β /Smad signaling. *Norcantharidin* (a *cantharidin* derivative, from *Lytta vesicatoria*) could antimetastatic by upregulating FAM46C expression and regulating TGF- β /Smads signaling pathway that prevents the expression of EMT-related transcription factors (47). *Berberine* (from *Coptis chinensis*) can significantly inhibit the extracorporeal and internal

migration of HCT-116 cells in CRC by regulating the Ras-ERK signaling pathway (48).

Anti-angiogenic

There are currently many adverse reactions and contraindications of using anti-angiogenesis drugs in western medicine. More and more, clinicians are considering alternative TCM medicine options. *Curcumin* (from *Curcuma longa*) has been found to inhibit vascular shape by regulating the vascular endothelial growth factor (VEGF)-VEGFR2 signaling pathway to improve the hematopoietic defect induced by VEGF (49). *Scutellaria baicalensis*, capable of inhibiting gastric cancer cells Y705 phosphorylation loci of STAT3 activation, indirectly plays an inhibitory role of the VEGF expression and can directly prevent the angiogenesis induced by VEGF (50).

Reversing MDR

At present, there is no optimal solution to the multi-drug resistance (MDR). *Evodiamine* (from *Tetradium rutilcarpum*) can inhibit the proliferation of oxaliplatin resistance colon cancer cells, promote apoptosis, inhibit the phosphorylation of NF- κ B, and then reverse the drug resistance (51). *Resveratrol* (from *Polygonum cuspidatum*) can reverse the drug resistance of CRC cells by inhibiting EMT, activating NF-kappa B, and enhancing colon cells sensitivity to 5-fluorouracil (52).

Inducing Differentiation

There is sparse research on TCM mechanism of induction of cell differentiation. For example, *shikonin* (from *Lithospermum erythrorhizon*) and *glycyrrhizin* (from *Glycyrrhiza uralensis*) seem capable of inducing leukemia HL-60 cell differentiation (53, 54). In the case of *glycyrrhizin*, NADPH oxidase plays an important role in this process (54).

Regulating Immunity

Regulating immunity is a crucial aspect of TCM in the treatment of cancer. *Soybean sterol B* (from *Glycine max*) can significantly inhibit the growth and metastasis of subcutaneous tumors in a mouse model of osteosarcoma (LM8 tumor mice) and induce the immune response of mice against tumor (55). Polysaccharide extracted from *Astragalus mongholicus* and *Codonopsis pilosula* can effectively enhance the

dendritic cell-based vaccine 4T1 preventing breast cancer metastasis in mice; enhance the expression of CD40, CD80, and CD86 markers; and effectively modulate the specific cellular function of dendritic cells (56).

Reducing Toxicity and Enhancing the Efficacy

Adverse reactions of radiotherapy and chemotherapy seriously affect the quality of life of oncologic subjects. TCM can reduce toxicity and enhance the efficacy of chemotherapy and radiotherapy (57). After observing 191 patients with advanced lung cancer treated with platinum-containing chemotherapy regimen along with or without *Shengbai* oral solution (composed of *Epimedium brevicornu*, *Psoralea corylifolia*, processed *Aconitum carmichaelii*, *Lycium barbarum*, *Astragalus mongholicus*, *Millettia dielsiana*, *Rubia cordifolia*, *Angelica sinensis*, *Phragmites australis*, *Ophiopogon japonicus*, and *Glycyrrhiza uralensis*), it has been shown that the latter could decrease bone marrow suppression caused by chemotherapy in these patients and reduce the amount of G-CSF used in these subjects (58). However, at present, there is little research on the molecular mechanism underpinning TCM capability to reduce the toxicity of chemoradiotherapy and enhance the efficacy.

Forecast

More progress needs to be made in the study of the antitumor activity of TCM. The development of evidence-based medicine has improved knowledge of this matter. But the collection of clinical data is still not perfect, and the epidemiological survey is not developed in China, especially in the field of TCM; therefore, the research of the role of TCM in oncotherapy lacks large clinical database. At the same time, as new research directions are being explored, TCM will continue to contribute to oncotherapy developments.

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Authors' Contributions

Conceptualization, Monica Mattioli-Belmonte and Huijuan Tang; Writing—Original Draft Preparation, Huijuan Tang; Writing—Review & Editing, Monica Mattioli-Belmonte; Supervision, Monica Mattioli-Belmonte.

Disclosure Statement

The authors declare no conflict of interest.

ORCID

Monica Mattioli-Belmonte  <http://orcid.org/0000-0002-2087-2776>

References

1. Globocan: Data visualization tools for exploring the global cancer burden in 2018, 2018. Available at http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed July 2019.
2. Ji Q, Luo Y-q, Wang W-h, Liu X, Li Q, et al.: Research advances in traditional Chinese medicine syndromes in cancer patients. *J Integr Med* **14**, 12–21, 2016.
3. Zheng X, Wang S, Chen D, and Yang X: Swainsonine induces apoptosis of rat cardiomyocytes via mitochondria-mediated pathway. *Cell Mol Biol (Noisy-le-Grand)* **64**, 136–141, 2018.
4. Zhang J, Liu L, Wang J, Ren B, Zhang L, and Li W: Formononetin, an isoflavone from *Astragalus membranaceus* inhibits proliferation and metastasis of ovarian cancer cells. *J Ethnopharmacol* **221**, 91–99, 2018. doi:10.1016/j.jep.2018.04.014.
5. Zhang C, Cai T, and Zeng X: Astragaloside IV reverses MNNG-induced precancerous lesions of gastric carcinoma in rats: regulation on glycolysis through miRNA-34a/LDHA pathway. *Phytother Res* **1–9**, 2018. doi:10.1002/ptr.6070.
6. Liu A-j, Yu J, Ji H-y, Zhang H-c, Zhang Y, et al.: Extraction of a novel cold-water-soluble polysaccharide from *Astragalus membranaceus* and its antitumor and immunological activities. *Molecules* **23**, 62, 2017. doi:10.3390/molecules23010062.
7. Luo S, Yin G, and Tang DC: Effects of Astragaloside IV and curcumin on angiogenesis of tumor in situ transplantation in nude mice with human liver cancer. *Chinese J Cancer Prevention Treatment* **23**, 12–13, 2016. doi:10.16073/j.cnki.cjcp.2016.s1.006. (in Chinese)
8. Wang Y, Xu H, Lu Z, Yu X, Lv C, et al.: Pseudo-Ginsenoside Rh2 induces A549 cells apoptosis via the Ras/Raf/ERK/p53 pathway. *Exp Ther Med* **15**, 4916–4924, 2018. doi:10.3892/etm.2018.6067.
9. Fang H, Yang S, Luo Y, Zhang C, Rao Y, et al.: Notoginsenoside R1 inhibits vascular smooth muscle cell proliferation, migration and neointimal hyperplasia through PI3K/Akt signaling. *Sci Rep* **8**, 2018. doi:10.1038/s41598-018-25874-y.
10. Liu TG, Duo LN, and Duan P: Ginsenoside. Rg3 sensitizes colorectal cancer to radiotherapy through downregulation of proliferative and angiogenic biomarkers. *Evid-Based Complementary Altern Med* **2018**, 1580427, 2018. doi:10.1155/2018/1580427.
11. Jiang Z, Yang Y, Yang Y, Zhang Y, Yue Z, et al.: Ginsenoside Rg3 attenuates cisplatin resistance in lung cancer by downregulating PD-L1 and resuming immune. *Biomed Pharmacother* **96**, 378–383, 2017. doi:10.1016/j.biopha.2017.09.129.
12. Lee Y-H, Song N-Y, Suh J, Kim D-H, Kim W, et al.: Curcumin suppresses oncogenicity of human colon cancer cells by covalently modifying the cysteine 67 residue of SIRT1. *Cancer Letters* **431**, 219–229, 2018. doi:10.1016/j.canlet.2018.05.036.
13. Wang J, Wu J, Li X, Liu H, Qin J, et al.: Identification and validation nucleolin as a target of curcumin in nasopharyngeal carcinoma cells. *J Proteomics* **182**, 1–11, 2018. doi:10.1016/j.jprot.2018.04.025.
14. Zang WH, Tang DC, Yin G, et al.: Inhibition effects of compatibility of Astragali Radix and Curcumae Rhizoma and combination with cisplatin on orthotopic tumor in nude mice bearing human hepatocellular carcinoma. *Chinese J Exp Traditional Med Formulae* **05**, 131–136, 2018. (in Chinese)
15. Lai YN, Yan YW, and Xu PP: Pharmacological mechanism of Curcumae Rhizoma based on system pharmacology. *Chinese J Exp Traditional Med Formulae* **14**, 177–182, 2017. http://en.cnki.com.cn/Article_en/CJFDTotat-ZSFX201714029.htm. (in Chinese)
16. Yan W, Lu J, Li G, Wei H, Ren W-H, et al.: Amidated Scolopin-2 inhibits proliferation and induces apoptosis of Hela cells in vitro and in vivo. *Biotechnol Appl Biochem* **65**, 672–679, 2018. doi:10.1002/bab.1661.
17. Lee JH, Kim I-W, Kim S-H, Kim M-A, Yun E-Y, et al.: Anticancer activity of the antimicrobial peptide scolopendrasin VII derived from the centipede, *Scolopendra subspinipes mutilans*. *J Microbiol Biotechnol* **25**, 1275–1280, 2015. doi:10.4014/jmb.1503.03091.
18. Ma W, Zhang D, Zheng L, Zhan Y, Zhang Y, et al.: Potential roles of Centipede Scolopendra extracts as a strategy against EGFR-dependent cancers. *Am J Transl Res* **7**, 39–52, 2015.
19. Huang W, Deng H, Jin S, Ma X, Zha K, et al.: The isolation, structural characterization and anti-osteosarcoma activity of a water soluble polysaccharide from *Agrimonia pilosa*. *Carbohydr Polym* **187**, 19–25, 2018. doi:10.1016/j.carbpol.2018.01.047.
20. Zhu K, Zhang C, Wang J, and Xiu-quan XU: Extraction of total polysaccharides from *Agrimonia pilosa* and evaluation of its inhibitory activity on human glioblastoma U251 cells in vitro. *Chinese J Exp Traditional Med Formulae* **12**, 188–191, 2012. doi:10.3969/j.issn.1005-9903.2012.12.053. (in Chinese)
21. Akshatha GM, Raval SK, Arpitha GM, Raval SH, Ghodasara DJ, et al.: Immunohistochemical, histopathological study and chemoprotective effect of *Solanum nigrum* in N-nitrosodiethylamine-induced hepatocellular carcinoma in Wistar rats. *Vet World* **11**, 402–409, 2018. doi:10.14202/vetworld.2018.402-409.
22. Zhuang Y-w, Wu C-e, Zhou J-y, Chen X, Wu J, et al.: Solasodine inhibits human colorectal cancer cells through suppression of the AKT/glycogen synthase kinase-3 β / β -catenin pathway. *Cancer Sci* **108**, 2248–2264, 2017. doi:10.1111/cas.13354.
23. Wu L, Cao KX, Ni ZH, Li WD, Chen ZP, et al.: Effects of Dahuang zhechong pill on doxorubicin-resistant SMMC-7721 xenografts in mice. *J Ethnopharmacol* **222**, 71–78, 2018. doi:10.1016/j.jep.2018.03.039.

24. Zhou L: Dahuang zhechong pill combined with gemcitabine and oxaliplatin treatment of primary liver cancer clinical observation. *J New Chinese Med* **02**, 161–163, 2014. (in Chinese)
25. Xie MQ, Zhao XF, and Liu XD: Effects of Dahuang Zhechong pill on liver fibrosis caused by interventional therapy of liver cancer. *Guangxi J Traditional Chinese Med* **02**, 46–47, 2014. (in Chinese)
26. Wu L, Zhao J, Cai H, Wang J, Chen Z, et al.: Dahuang Zhechong pill combined with doxorubicin induces cell death through regulating energy metabolism in human hepatocellular carcinoma cells. *Evid-Based Complementary Altern Med* **2017**, 1, 2017. doi:10.1155/2017/6279576.
27. Tong HL: Clinical observation of Dahuang Zhechong pill combined with chemotherapy for advanced gastric cancer. *Henan Med Res* **07**, 1289–1290, 2016. doi:10.3969/j.issn.1004-437X.2016.07.099. (in Chinese)
28. Zhao RB, Cao HH, Zhang RQ, et al.: The influence of Dahuang Zhechong Bolus on Lewis lung cancer mice. *J Shanxi College Traditional Chinese Med* **03**, 13–16, 2016. (in Chinese)
29. Xiong SQ, Li YL, Luo QY, et al.: Effects and mechanisms of Da Huangqi Decoction inhibit Lewis carcinoma lung metastasis induced by chemotherapeutics. *J Chengdu Univ of TCM* **41**, 16–19, 2018. doi:10.13593/j.cnki.51-1501/r.2018.01.016. (in Chinese)
30. Xiong SQ, Luo QY, Li YL, et al.: Clinical research on Da Huangqi Decoction combined with chemotherapy inhibiting new metastasis for advanced non-small lung carcinoma. *J Chengdu Univ TCM* **41**, 46–49, 2018. doi:10.13593/j.cnki.51-1501/r.2018.01.046. (in Chinese)
31. Chen XL, Xu LT, Wang P, et al.: Survival analysis of Jianpi Liqi Decoction comprehensive therapy on primary liver cancer. *China J Traditional Chinese Med Pharm* **33**, 2018–2022, 2018. (in Chinese)
32. Qian C, Zhang XC, He ZF, et al.: Analysis of efficacy of Jianpizaoshi Myogenic Decoction retention enema in the treatment of radiation enteritis. *China Continuing Med Educ* **10**, 120–121, 2018. doi:10.3969/j.issn.1674-9308.2018.13.064. (in Chinese)
33. Tong JB, Zhang XX, Wang XH, et al.: Qiyusanlong decoction suppresses lung cancer in mice via Wnt/ β -catenin pathway. *Mol Med Rep* **4**, 5320–5327, 2018. doi:10.3892/mmr.2018.8478.
34. Shu P, Liu SL, and Wang RP: A clinical study of 201 cases of gastric cancer recurrence and metastasis of Yiqi Huayu Jiedu decoction. *Jiangsu J Traditional Chinese Med* **04**, 23–24, 2014. (in Chinese)
35. Xu JX, Li LM, Xu HY, et al.: The effect of Yangzhengxiaoji capsule on the quality of life (QOL) and TCM syndromes in advanced digestive tract malignancies. *Chinese Arch Traditional Chinese Med* **03**, 535–537, 2018. doi:10.13193/j.issn.1673-7717.2018.03.005. (in Chinese)
36. Zhou L, Zhu XZ, Xia JH, et al.: Clinical study on Yiqi Yangyin recipe in treating the adverse effects after the chemotherapy in the tumor patients. *Clin J Traditional Chinese Med* **07**, 1072–1075, 2017. doi:10.16448/j.cjtc.2017.0359. (in Chinese)
37. Qiao ZA: Effects of Yiqi Yangyin prescription combined with radiotherapy on the tumor load and anti-tumor immune response in patients with advanced lung cancer. *J Hainan Med Univ* **01**, 75–78, 2018. doi:10.13210/j.cnki.jhmu.20171227.002. (in Chinese)
38. Duan M, Jia CF, and Duan X: Effects of Yiqi Gu Ben Decoction combined with DC chemotherapy on serum tumor markers, inflammatory factors and immune function in patients with locally advanced non-small cell lung cancer. *J Hainan Med Univ* **01**, 79–82, 2018. doi:10.13210/j.cnki.jhmu.20171127.007. (in Chinese)
39. Song M, Xi SS, Liu JP, et al.: Effects of Shenqi Fuzheng injection on immune function and toxic reactions in chemotherapy patients after rectum carcinoma resection. *Guiding J Traditional Chinese Med Pharm* **02**, 46–48, 2015. doi:10.13862/j.cnki.cn43-1446/r.2015.02.017. (in Chinese)
40. Ma JJ and Liu HP: Efficacy of Aidi injection on over-expression of P-glycoprotein induced by vinorelbine and cisplatin regimen in patients with non-small cell lung cancer. *Chin J Integr Med* **07**, 504–509, 2017. doi:10.1007/s11655-016-2511-4.
41. Meng H, Sun X, Nian JY, et al.: Sodium cantharidate combined with chemotherapy in advanced gastric cancer: a meta-analysis. *World Chinese Med* **10**, 2496–2500, 2017. doi:10.3969/j.issn.1673-7202.2017.10.055. (in Chinese)
42. Liu F, Hu WS, Ye XW, et al.: Clinical efficacy of Xiaoaiping injection as retention enema in the treatment of colorectal cancer. *Chinese J Gen Practice* **11**, 1831–1835, 2014. (in Chinese)
43. Pacioni S, D'Alessandris QG, Giannetti S, Morgante L, De Pascalis I, et al.: Mesenchymal stromal cells loaded with paclitaxel induce cytotoxic damage in glioblastoma brain xenografts. *Stem Cell Res Ther* **6**, 194, 2015. doi:10.1186/s13287-015-0185-z.
44. Zhao XW, Zhang Q, and Chen L: Triptolide induces the cell apoptosis of osteosarcoma cells through the TRAIL pathway. *Oncol Rep* **36**, 1499–1505, 2016. doi:10.3892/or.2016.4957.
45. Liu ZH, Wang G, and Shen JF: Mechanism of saikosaponin-d inhibiting cervical cell Hela. *Chinese Arch Traditional Chinese Med* **12**, 2931–2934, 2016. doi:10.13193/j.issn.1673-7717.2016.12.031. (in Chinese)
46. Liu JIE, Wen X, Liu BIN, Zhang Q, Zhang J, et al.: Diosmetin inhibits the metastasis of hepatocellular carcinoma cells by downregulating the expression levels of MMP-2 and MMP-9. *Mol Med Rep* **13**, 2401–2408, 2016. doi:10.3892/mmr.2016.4872.
47. Wan X-Y, Zhai X-F, Jiang Y-P, Han T, Zhang Q-Y, et al.: Antimetastatic effects of norcantharidin on hepatocellular carcinoma cells by up-regulating FAM46C expression. *Am J Transl Res* **9**, 155–166, 2017.
48. Huang T, Xiao Y, Yi L, et al.: Coptisine from *Rhizoma Coptidis* suppresses HCT-116 cells-related tumor growth in vitro and in vivo. *Sci Rep* **2**, 38524–38532, 2017. doi:10.1038/srep38524.
49. Fu Z, Chen X, Guan S, Yan Y, Lin H, et al.: Curcumin inhibits angiogenesis and improves defective hematopoiesis induced by tumor-derived VEGF in tumor model through modulating VEGF-VEGFR2

- signaling pathway. *Oncotarget* **6**, 19469–19482, 2015. doi:10.18632/oncotarget.3625.
50. Xiao W, Wu K, Yin M, Han S, Ding Y, et al.: Wogonin inhibits tumor-derived regulatory molecules by suppressing STAT3 signaling to promote tumor immunity. *J Immunother* **38**, 167–184, 2015. doi:10.1097/CJI.0000000000000080.
 51. Sui H, Zhou L-H, Zhang Y-L, Huang J-P, Liu X, et al.: Evodiamine suppresses ABCG2 mediated drug resistance by inhibiting p50/NF- κ B pathway in colorectal cancer. *J Cell Biochem* **117**, 1471–1481, 2016. doi:10.1002/jcb.25451.
 52. Buhrmann C, Shayan P, Kraehe P, Popper B, Goel A, et al.: Resveratrol induces chemosensitization to 5-fluorouracil through up-regulation of intercellular junctions, epithelial-to-mesenchymal transition and apoptosis in colorectal cancer. *Biochem Pharmacol* **98**, 51–68, 2015. doi:10.1016/j.bcp.2015.08.105.
 53. Zhang B, Chen N, Chen H, Wang Z, Zheng Q, et al.: The critical role of redox homeostasis in shikonin induced HL-60 cell differentiation via unique modulation of the Nrf2/ARE pathway. *Oxid Med Cell Longev* **2012**, 1, 2012. doi:10.1155/2012/781516.
 54. Chen H, Zhang B, Yao Y, Chen N, Chen X, et al.: NADPH oxidase-derived reactive oxygen species are involved in the HL-60 cell monocytic differentiation induced by isoliquiritigenin. *Molecules* **17**, 13424–13438, 2012. doi:10.3390/molecules171113424.
 55. Fujiwara Y, Shiraishi D, Yoshitomi M, Ikeda T, Mizuta H, et al.: Soyasapogenols contained in soybeans suppress tumour progression by regulating macrophage differentiation into the protumoural phenotype. *J Funct Foods* **19**, 594–605, 2015. doi:10.1016/j.jff.2015.09.055.
 56. Chang WT, Lai TH, Chyan YJ, Yin SY, Chen YH, et al.: Specific medicinal plant polysaccharides effectively enhance the potency of a DC-based vaccine against mouse mammary tumor metastasis. *PLoS One* **10**, e0122374, 2015. doi:10.1371/journal.pone.0122374.
 57. Li J and Liu XB: Advances in medicine of toxicity and synergistic effects in cancer treatment. *J Pharm Res* **04**, 229–231, 2015. (in Chinese)
 58. Zhou CH, Chen G, Zeng L, et al.: Clinical observation of Shengbai oral solution on prevention of neutropenia induced by chemotherapy for lung cancers. *Chinese J Surg Integ Traditional Western Med* **02**, 131–134, 2018. doi:10.3969/j.issn.1007-6948.2018.02.001. (in Chinese)