

EXPERIMENTAL STUDY

Effects and mechanisms of Bazhen decoction, Siwu decoction, and Sijunzi decoction on 5-fluorouracil-induced anemia in mice

Tian Yunan, Xiang Yuke, Wan Guoran, Wan Dong, Zhu Huifeng, Wang Tao, Yang Xian

Tian Yunan, Xiang Yuke, Wang Tao, Yang Xian, School of Pharmaceutical Sciences & School of Chinese Medicine, Southwest University, Chongqing 400715, China**Wan Guoran**, Tong Liang High School, Chongqing 400715, China**Wan Dong**, Department of Emergency, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China**Supported by** National Training Programs of Innovation for Undergraduates (No. 201310635015)**Correspondence to: Zhu Huifeng and Wan Dong**, Laboratory of Molecular Pharmacology, School of Pharmaceutical Science & School of Chinese Medicine, Southwest University, Chongqing 400715, China. zhfbsci@126.com; wandongcqkdx@126.com.**Telephone:** +86-23-6825-1225; +86-18983707683**Accepted:** February 18, 2016**Abstract****OBJECTIVE:** To investigate the effects of Bazhen decoction (BZD), Siwu decoction (SWD) and Sijunzi decoction (SJZD) in mice with anemia induced by 5-fluorouracil (5-FU) and discussed the possible pharmacological hematopoietic mechanism to provide experimental evidence for the clinical use of the three classical prescriptions in the treatment of anemia.**METHODS:** Anemia was induced by intravenous injection of 5-FU and 80 female Kunming mice were randomly, assigned to oral administration of SWD, SJZD, or BZD daily for 10 days. Peripheral blood cells count and bone marrow cell cycle were monitored to evaluate anti-anemia effects. Serum cytokines, interferon- γ (IFN- γ), interleukin-3 (IL-3), erythropoietin (EPO), granulocyte-macrophage colonystimulating factor (GM-CSF), and tumor necrosis factor- α (TNF- α) were assayed. EPO mRNA expression was assayed in kidney and liver tissue homogenates.**RESULTS:** BZD and SWD significantly increased the number of red blood cells, hemoglobin concentration, and hematocrit, promoted bone marrow cells to enter the cell cycle, proliferate and differentiate, significantly increased IL-3 secretion, and significantly inhibited IFN- γ secretion. BZD stimulated transcription of EPO mRNA in the kidney and liver and enhanced serum EPO expression. A therapeutic effect of SJZD was not observed.**CONCLUSION:** BZD and SWD treatment specifically enhanced hematopoietic function and mediated myelopoiesis by altering serum cytokines levels and accelerating entry of bone marrow cells into the cell cycle. Better curative effects were achieved via nourishing both *Qi* and blood (BZD) than by enriching the blood (SWD) or invigorating *Qi* (SJZD) alone.© 2016 JTCM. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)**Key words:** Anemia; Blood-deficiency; Fluorouracil; Bazhen decoction; Siwu decoction; Sijunzi decoction**INTRODUCTION**In Traditional Chinese Medicine (TCM), blood deficiency is a syndrome with pathological changes such as pale/sallow complexion, brittle nails, dizziness, palpitation, numbness of the hands and feet, scanty and light-colored menses, pale tongue and weak pulse.¹ In

TCM theory, blood deficiency is related to the intricate balance of blood and *Qi*. In TCM, blood is the red fluid circulating through the blood vessels and nourishing the body tissues, a concept that corresponds in part to that of modern Western Medicine.² *Qi* is the invisible basic element or energy that makes up the human body and supports vital activities of the human body.² In brief, insufficient blood generates blood deficiency, subsequently resulting in *Qi* deficiency, which in turn aggravates blood deficiency, ultimately forming a vicious circle.³

In recent decades, many practitioners of TCM have come to regard blood deficiency as similar anemia as defined in modern medicine. According to WHO criteria, anemia is defined as a hemoglobin (Hb) concentration < 13 g/dL in men and < 12 g/dL in women.^{4,6} The pathogenesis of anemia is multifactorial. For example, hematopoietic damage caused by 5-FU can be improved by prescription of blood tonics or drugs.⁷

TCM researchers develop animal models of blood deficiency by methods including radiation exposure, chemical agents, and immune modulation.⁸ Recent studies of blood deficiency syndrome have utilized a mouse model in which anemia is induced by 5-fluorouracil (5-FU).^{7,9} 5-FU is an antineoplastic, cell-cycle specific drug that is widely used to treat a variety of tumors including colorectal, breast and liver carcinomas. Following administration, 5-FU is converted to fluorouracil deoxynucleotide, which binds thymidine synthase, leading to disruption of RNA, DNA, and protein biosynthesis. However, 5-FU usually suppresses the bone marrow, and causes adverse gastrointestinal reactions because nucleic acid metabolism in tumors is similar to that in normal tissues.^{10,11} 5-FU administration at a dose of 150 mg/kg is known to result in long-term lesions of erythropoiesis and erythropoietin (EPO) production in which mature erythroid cells (reticulocytes, erythrocytes) and erythropoietic precursors (erythroid colony-forming units, erythroid burst-forming units) in the bone marrow were severely reduced.¹²

TCM is an excellent example of alternative and complementary medicine with a long history, unique theory system, and a variety of herbal remedies.¹³ In TCM, enriching blood and balancing *Qi* and blood are the basic therapies for blood deficiency. Siwu decoction (SWD), Sijunzi decoction (SJZD), and Bazhen decoction (BZD), have been used in TCM clinical practice to treat blood deficiency, *Qi* deficiency and blood- and-*Qi* deficiency, respectively. It is reported that BZD promotes the proliferation of bone marrow cells of anemic mice, and that addition of BZD to the media in cultures of spleen cells, macrophages, lung and skeletal muscle resulted in strong stimulation of hematopoietic cells.¹⁴ Previous studies of SWD have shown that it affected the expression of apoptosis proteins, proliferation and differentiation of hematopoietic progenitor stem cells,¹⁵ ameliorated bone marrow damage after radiation.¹⁶ It has been proposed as an effective, nontoxic, orally administered agent for cancer chemoprevention via activation of the nuclear factor-erythroid 2-related factor-2 (Nrf2) pathway.¹⁷ Combined chemotherapy with SJZD plus low-dose mitomycin C significantly inhibited tumor growth in mice with bladder carcinoma, while attenuating toxicity attenuation and increasing efficacy.¹⁸ A comparison of the radioprotection conferred by SWD and SJZD found that SJZD and its ingredients were not as effective as SWD.¹⁹ The three decoctions are closely linked by TCM pharmacology, but comparative studies of the three formulae have not been conducted.

The aim of this study was to compare the anti-anemia effects of BZD, SWD and SJZD in mice with 5-FU-induced anemia and to investigate the hematopoietic mechanisms of these three TCM preparations. It is hoped that this preliminary laboratory data will support the scientific rationale for further clinical applications, reflect the modern *Qi* and blood concept in Chinese medicine.

Table 2 Effects of the three decoctions on hematologic parameters determined on day 15 ($\bar{x} \pm s$)

Group	RBC ($\times 10^{12}/L$)	HGB (g/L)	WBC ($\times 10^9/L$)	HCT (%)	RC (%)
Normal	8.597 \pm 0.324 ^a	131.833 \pm 5.981 ^a	6.698 \pm 1.014 ^a	44.667 \pm 1.954 ^a	0.673 \pm 0.055 ^a
Model	5.438 \pm 0.244 ^b	83.5 \pm 9.731 ^b	2.91 \pm 0.438 ^b	28.683 \pm 3.544 ^b	0.093 \pm 0.029 ^b
BZD	6.986 \pm 0.728 ^a	106.333 \pm 8.981 ^a	4.03 \pm 0.560 ^a	35.333 \pm 3.075 ^c	0.277 \pm 0.042 ^a
SWD	6.897 \pm 0.623 ^a	109.6 \pm 8.620 ^a	3.9 \pm 0.328 ^c	33.6 \pm 4.665 ^d	0.148 \pm 0.034 ^c
SJZD	6.02 \pm 0.422 ^b	90.857 \pm 7.081 ^b	3.6 \pm 0.556 ^d	28.083 \pm 2.803 ^b	0.126 \pm 0.035 ^b

Notes: mice in the SWD, SJZD and BZD groups were given the decoctions by intragastric administration at a daily dose of 0.2 mL/10 g body weight for 10 days. Mice in the Normal and Model groups were given an equal volume of normal saline. Mice were sacrificed on day 15 and femur was aseptically removed for cell cycle analysis. After administrated with three decoctions for 10 days (0.2 mL/10 g body weight), about 100 μ L of retro-orbital sinus blood was collected using EDTA-coated capillary tubes. RBC, HGB, WBC, HCT and RC were measured. BZD: Bazhen decoction; SWD: Siwu decoction; SJZD: Sijunzi decoction; RBC: red blood cell; HGB: hemoglobin; WBC: white blood cell; HCT: hematocrit; RC: reticulocyte. ^a $P < 0.001$, ^c $P < 0.01$, ^d $P < 0.05$ vs Model group; ^b $P < 0.001$ vs Normal group.

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