Zhengyuan capsule alleviates chemotherapy-related fatigue in nude mice with human lung adenocarcinoma A549 xenografts

Jieshan Guan, Lizhu Lin* and Mingzi Ouyang

ABSTRACT

Aim: We aimed to investigate the action mechanism of Zhengyuan capsule (a registered proprietary Chinese medicine) against chemotherapy-related fatigue (CRF).

Methods: BALB/c-nu nude mice model with human lung adenocarcinoma A549 xenografts was constructed by injection of A549 cell suspension. The xenografted mice were randomly divided into model, cisplatin and cisplatin+Zhengyuan groups (n = 20 each). The cisplatin group was given an intraperitoneal injection of 5 mg/kg cisplatin every 3 days for 21 days. The cisplatin+Zhengyuan group was given an intragastric administration of cisplatin and 25 mg/kg Zhengyuan capsule each day for 21 days. Normal control and model groups were administrated with equal amount of saline. Forced swimming assay, tail suspension test, open field test, hepatic glycogen assay, blood analysis, and bone marrow smear was performed.

Results: The cisplatin group developed CRF after receiving chemotherapy. When compared with cisplatin group, the cisplatin+Zhengyuan group exhibited longer exhaustive swimming time ($p<0.001$), shorter immobility time during tail suspension test ($p<0.001$), a longer total movement distance and higher average moving speed during open field test ($p=0.040$ and 0.03, respectively), an increased hepatic glycogen level ($p<0.001$), higher blood cell and bone marrow nucleated cell counts ($p<0.05$ or 0.001), reduced TNF-α and IL-6 levels ($p=0.013$ and $p<0.001$). These results suggested that Zhengyuan capsule alleviated the CRF in the mice.

Conclusion: Zhengyuan capsule decreased the post-chemotherapy serum cytokine secretion, enhanced the hepatic glycogen content, reduced bone marrow suppression, and thereby alleviated CRF in mice.

Keywords: chemotherapy-related fatigue; lung cancer; Zhengyuan capsule; hepatic glycogen; bone marrow suppression; cytokine

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INTRODUCTION

Lung cancer is one of the most common cancers worldwide with an estimated rate of 33.8 per 100,000 in men and 13.5 per 100,000 in women (Ridge, McErlean & Ginsberg 2013). Lung cancer has been the leading cause of cancer-related deaths, accounting for 18.2% of all cancer deaths worldwide (Ferlay et al. 2010). Non-small cell lung cancer is the major type of lung cancer, and adenocarcinoma is the most common subtype of NSCLC, comprising approximately 40% of lung cancer cases (Zappa & Mousa 2016). While surgery remains the primary treatment for resectable stage I, II, and IIIA NSCLCs (Lemjabbar-Alaoui et al. 2015), these patients typically receive post-operative adjuvant chemotherapy for markedly improved survival (Arriagada et al. 2014; Hotta et al. 2004; Winton et al. 2005). For stage IV NSCLC patients, combination cytotoxic chemotherapy is recommended as the first-line therapy by the American Society of Clinical Oncology Clinical Practice Guideline (Masters et al. 2015). Nevertheless, 80-90% of patients undergoing chemotherapy have experienced chemotherapy-related fatigue (CRF) (Huang et al. 2010), which is characterized by persistent and intense tiredness even at several years after the completion of chemotherapy (Huang et al. 2010; Barsevick et al. 2010). CRF has markedly decreased the physical functions of cancer patients, and therefore new strategies or therapeutic drugs are urgently needed to alleviate this side effect of chemotherapy.

Zhengyuan capsule is a proprietary Chinese medicine registered by the Yangtze River Pharmaceutical Group (Taizhou, China) for the prevention and treatment of CRF. Although the drug has been used in clinical settings for CRF, the underlying molecular action mechanism remains unclear. In this study, we constructed a mice model with human lung adenocarcinoma A549 xenografts, evaluated the effect of Zhengyuan capsule against cisplatin-induced CRF, and investigated the potential action mechanism of the drug. Our study shall provide a solid basis for the clinical application of the Zhengyuan capsule.

MATERIALS AND METHODS

Cells, animals and main reagents

Human lung adenocarcinoma cell line A549 were purchased from the Cell Bank of Type Culture Collection of Chinese Academy of Sciences (Shanghai, China), and cultured in RPMI-1640 medium (Gibco, Grand Island, NY, USA) supplented

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with 10% fetal bovine serum (FBS), 100 u/ml penicillin, and 100 μg/ml streptomycine at 37°C, 5% CO_2 in an incubator. Seven-week-old male BALB/c-nu nude mice weighting 18 - 20 g were purchased from Huafukang Biotech. (License number: SCXK (Beijing) 2014-0004, China). All mice were housed in the SPF laboratory under normal 12/12 light/dark cycle in the Guangzhou University of Traditional Chinese Medicine with free access to food and water. This animal study was approved by the Research Ethics Committee at the Guangzhou University of Chinese Medicine and performed in strict accordance with the international and institutional guidelines for the care and use of laboratory animals. Zhengyuan capsules were manufactured by the Yangtze River Pharmaceutical Group (Registration number: Z20148001). Cisplatin was purchased from Nanjing Pharmaceutical Factory Co., Ltd. (Registration number: H20030675).

Construction of A549 lung cancer xenograft model and drug treatment

Twenty randomly selected mice were used as normal control group (NC). The remaining 60 mice were subjected to injection of A549 cells. Briefly, A549 cells at exponential phase were collected and prepared into cell suspension at the density of 5×10^7 cells/mL. Each mouse was given a subcutaneous injection of 0.2 mL of A549 cell suspension at the right armpit. Tumor volume was measured with a digital electric caliper and calculated as width^2 × length/2. The treatment started when the xenograft tumor reached 50~100 mm^3 at 7 days after the inoculation. The mice were randomly divided into model, cisplatin and cisplatin plus Zhengyuan groups (n = 20 each). Staring from day 7 after inoculation, the cisplatin group was given an intraperitoneal injection of 5 mg/kg body weight cisplatin every 3 days for 21 days. In addition to the cisplatin treatment, the cisplatin plus Zhengyuan group was given an intragastric administration of 25 mg/kg body weight Zhengyuan capsule at 9 AM each day for 21 consecutive days. Normal control and model groups were administrated with equal amount of saline.

Forced swimming assay

The swimming test was performed both before the treatment and on the 18th day of the treatment. Briefly, 10 mice were randomly selected from each group. Each mouse was tied with a lead pendent (7% of body weight) by the tail and forced to swim in a glass cylinder (diameter: 190 mm, height: 290 mm) filled with warm water of 25 ± 1°C. The total swimming time was recorded as soon as mice failed to rise to the surface of water for breath within a 10-s period. The total swimming time was considered the time until fatigue. The mice were dried with towel immediately after the test and subjected to tail suspension test on the next day (Day 19).

Tail suspension test

On Day 19, the tail suspension test was performed as previously described (Yi et al. 2009). Briefly, the 10 mice in each group was suspended in the tail suspension system (Flyde Biotech., Guangzhou, China) by the tail using adhesive tape (2 cm from the end), with the head 5 cm from the bottom of the apparatus. The immobility time was recorded as the duration of absence of movement over 6 min. The mice were subjected to open field test on the next day (Day 20).

Open field test

On Day 20, the open field test was performed as previously described (Yonezaki et al. 2015). Briefly, the 10 mice in each group was removed from the cage and gently placed in the center of a clean open field test system (50 x 50 x 40 cm, Flyde Biotech.) in the dark. The distance moved in the center area (20 x 20 cm) or the arena over a 5-min period were recorded using a computer-operated behavior analysis system for small animals (Chucai Electronic, Shanghai, China). The mean speed was calculated. After each test, the test apparatus was cleaned by 75% ethanol.

Blood analysis

On Day 21, the 10 mice without any swimming and behavorial experiments were removed from the cage at 1 h after the completion of treatment. Blood samples were collected from the orbital plexus and immediately transferred into K2-EDTA tubes. Red blood cell (RBC), white blood cell (WBC), hemoglobin (HGB), and platelet (PLT) count was measured using an Mindray BC 6800 automated hematology analyzer (Mindray Biotech., Shenzhen, China). The level of IL-6 and TNF-α was determined using cytokine antibody microarray (Luminex, Austin, TX, USA) following the manual of the kit. The detection was made through a Luminex 200 Function flow dot matrix instrument and analyzed by FLEXMAP 3DTM.

Hepatic glycogen assay

At 1 h after the completion of treatment, mice were sacrificed by overdose with 10% chloral hydrate (4 ml/kg). Liver was removed and rinsed with saline. Liver tissue (100 mg) was accurately weighed and subjected to glycogen assay using a hepatic glycogen assay kit according to the manufacture's instructions.

Determination of bone marrow nucleated cell count

Immediately after sacrifice, the muscle and tissue around the left femur of each mouse were removed. Both ends of the femur were cut, and the bone marrow cavity was repeatedly rinsed with 2 mL of PBS using a sterilized syringe to collect all bone marrows. Bone marrow cells were fully dispersed and 10 μL of cell suspension was put on the cell count plate. The bone marrow nucleated cell count was measured using a cell counter (Bio-Rad, Hercules, CA, USA).

Bone marrow smear

The bone marrow was collected from the right femur of 5 randomly selected mice in each group, smeared on the slide with EDTA anticoagulant, and stained using a Wright-Giemsa staining kit (Baso Biotech., Zhuhai, China) according to the manufacture's instructions.

Statistical analysis

All statistical analysis was performed using SPSS software 17.0 (IBM SPSS, Chicago, IL. USA). Data was expressed as mean ± standard deviation. Differences among groups were compared by one-way ANOVA followed by post-hoc LSD tests. p values smaller than 0.05 was considered statistically significant.

RESULTS

Zhengyuan capsule prolonged the exhaustive swimming time in nude mice

The exhaustive swimming time of each group was compared (Table 1). Before the intervention, there was no significant difference in the total exhaustive swimming time among all 4 groups (F=0.600, p=0.619). On day 18, significant differences in exhaustive swimming time was observed among the groups (F=73.002, p<0.001). The exhaustive swimming time in model, cisplatin and cisplatin+Zhengyuan groups on day 18 was significantly shorter compared to the respective pre-treatment swimming time (p<0.001). Post-hoc analyses showed that the swimming time in model group was significantly shorter than that in normal control group (p<0.001, Figure 1). Model and cisplatin groups had similar swimming time (p=0.671). The swimming time in cisplatin+Zhengyuan group was significantly increased compared with both model and cisplatin groups (both p<0.001), suggesting that

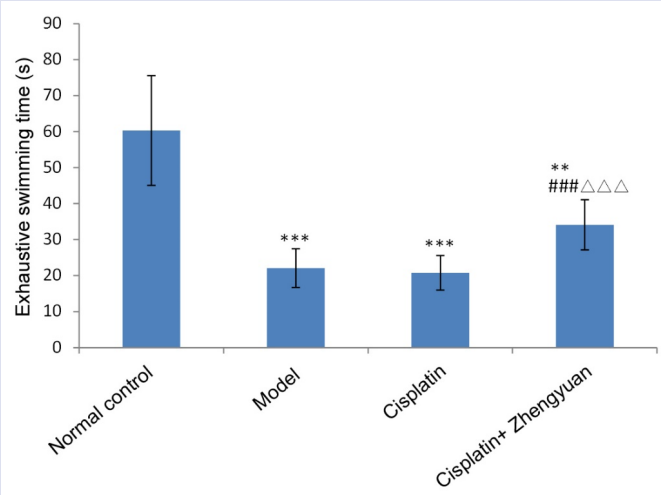

Figure 1: Zhengyuan capsule prolonges the exhaustive swimming time in nude mice. On day 18 since the start of treatment, 10 randomly selected mice in each group were subjected to forced swimming assay. The exhaustive swimming time in each group was compared. Data were expressed as mean ± standard deviation. **, p < 0.01, ***, p < 0.001 compared with normal control group; ###, p < 0.001 compared with model group; and △△△, p < 0.001 compared with cisplatin group.

Zhengyuan capsule had effectively improved exhaustive swimming time in nude mice.

Zhengyuan capsule improved the activities of nude mice

The activities of nude mice were assessed by tail suspension test and open field test. The suspension tail time in normal control, model, cisplatin and cisplatin+ Zhengyuan groups were 67.89 ± 20.06, 89.78 ± 19.13, 77.90 ± 23.11, and 51.60 ± 23.77 s, respectively (F=5.295, p=0.004). The total movement distance of the four groups were 2508.46 ± 392.13, 2003.82 ± 551.78, 1466.31 ± 308.41, and 1937.67 ± 435.07 mm, respectively (F=8.812, p<0.001). The average moving speed of the four groups were 8.36 ± 1.31, 6.68 ± 1.84, 4.89 ± 1.03, and 6.46 ± 1.45 mm/s, respectively (F=8.791, p<0.001). Further post-hoc analyses showed that the time of immobility in model group was significantly longer than that in normal control group during tail suspension test (p=0.040, Figure 2A). There was no significant difference in the time of immobility between model and cisplatin groups (p=0.242). The time of immobility in cisplatin+Zhengyuan group was significantly shorter compared with both model and cisplatin groups (p=0.011 and 0.001, respectively). As shown in Figure 2B, the total movement distance in model group was significantly decreased compared with normal control group (p=0.018). The total movement distance in cisplatin group was significantly shorter than that in model group (p=0.012). The cisplatin+Zhengyuan group exhibited a total movement distance that was significantly longer cisplatin group (p=0.040), but comaprable to model group (p=0.740). Similar pattern was observed in the change of the average moving speed among these groups (Figure 2C).

Zhengyuan capsule increased the hepatic glycogen level in nude mice

The levels of hepatic glycogen in normal control, model, cisplatin and cisplatin+Zhengyuan groups were 8.97 ± 2.14, 7.49 ± 3.52, 4.67 ± 1.56, and 11.82 ± 1.92 mg/g, respectively, with significant difference (F=10.788, p<0.001). As shown in Figure 3, the hepatic glycogen level in cisplatin group was significantly lower compared with both normal control and model groups (p=0.038 and 0.012, respectively). The hepatic glycogen level in cisplatin+Zhengyuan group was significantly increased compared with both model and cisplatin groups (both p<0.001).

Zhengyuan capsule enhanced peripheral blood cell count

The peripheral blood cell counts and hemoglobin (HGB) level of all groups were listed in Table 2. There was significant difference in the count of white blood cells (WBCs), red blood cells (RBCs), and platelet (PLT), as well as HGB level among normal control, model, cisplatin and cisplatin+Zhengyuan groups (all p<0.05 or 0.001). As shown in Figure 4A-C, cisplatin group had significantly lower WBC and RBC counts, and HGB level compared with normal control and model groups (all p<0.001). Although the WBC and RBC counts, and HGB level in cisplatin plus Zhengyuan group was slightly lower than that in normal control and model groups, Zhengyuan treatment had significantly increased the WBC and RBC counts, and HGB level in cisplatin plus Zhengyuan group when compared with cisplatin group (p<0.01 or 0.001). Normal control, model and cisplatin groups had similar PLT counts (all p>0.05, Figure 4D), whereas cisplatin plus Zhengyuan group had significant higher PLT count compared with the other three groups (p=0.002, 0.005 and 0.016, respectively).

Zhengyuan capsule stimulated bone marrow hematopoiesis

Bone marrow smear was performed to evaluate the bone marrow hematopoiesis in different groups. As shown in Figure 5, normal control group exhibited active bone marrow hematopoiesis with a large amount of hematopoietic islands. Normal proportion of erythroid cells, granular cells and megakaryocytes was observed. In model group, much less hematopoietic islands were observed, indicating a reduced bone marrow hematopoiesis. The model group also had a relatively lower proportion of erythroid cells, but a higher proportion of granular cells and lymphocytes. In cisplatin group, bone marrow hematopoiesis was severely reduced with very few hematopoietic islands. A large amount of granular cells and lymphocytes were observed. In contrast, cisplatin plus Zhengyuan group exhibited more active bone marrow hematopoiesis, and higher numbers of hematopoietic islands and erythroid cells compared with cisplatin group. The count of bone

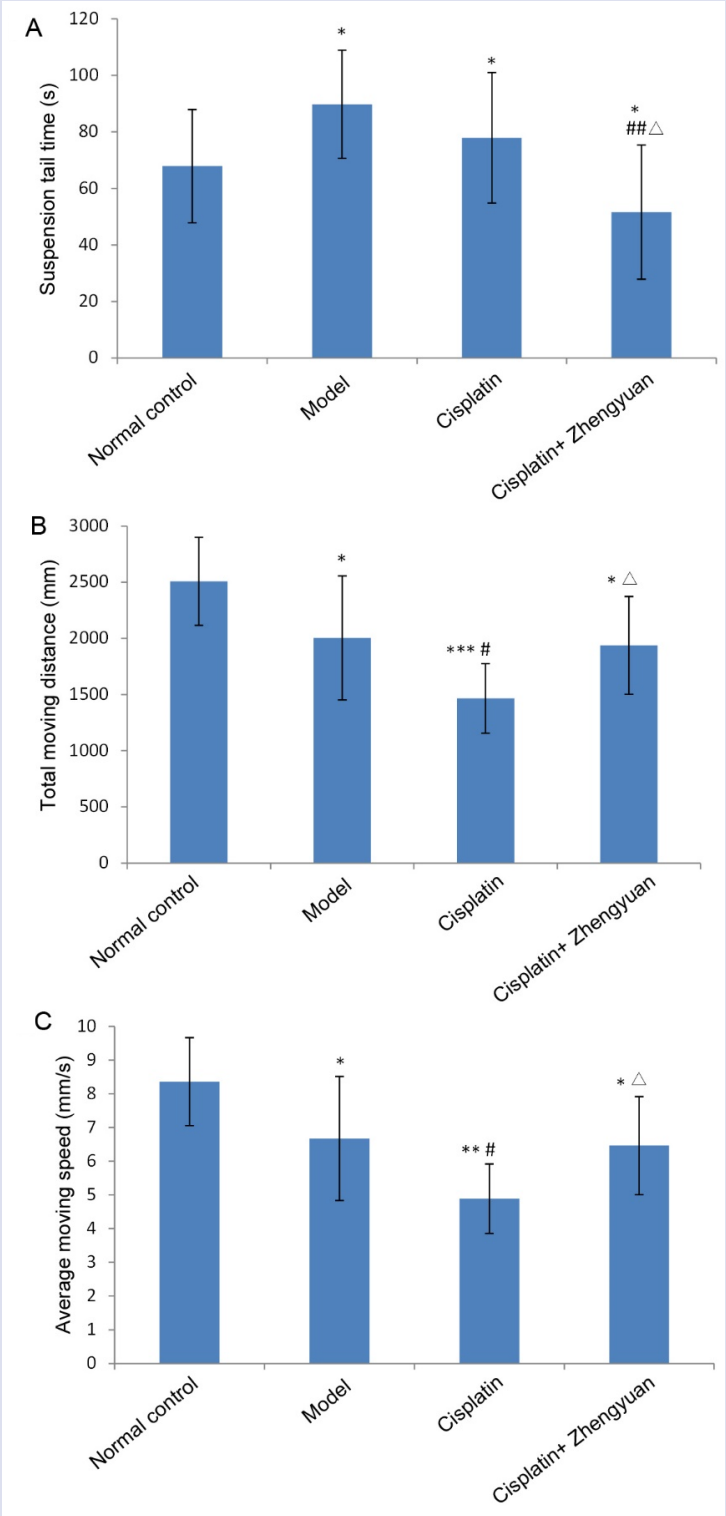

Figure 2: Zhengyuan capsule improves the activities of nude mice. On day 19, the tail suspension test was performed (n=10 each) and the immobility time (A) was recorded as the duration of absence of movement over 6 min. On day 20, the open field test was performed (n = 10), and the moving distance (B) and average moving speed (C) was compared. Data were expressed as mean ± standard deviation. *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$ compared with normal control group; ##, $p < 0.01$ compared with model group; and △, $p < 0.05$ compared with cisplatin group.

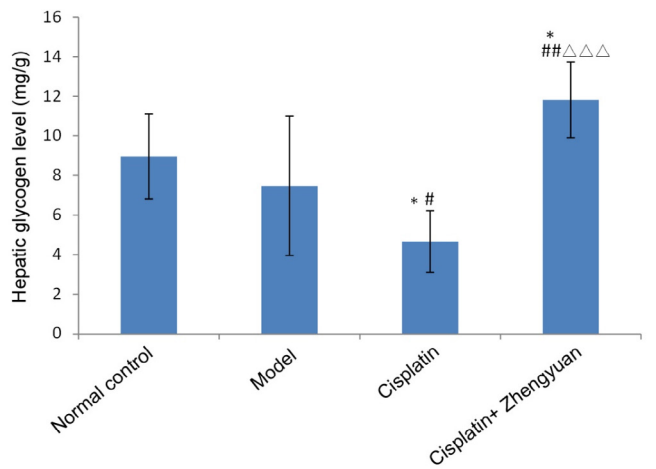

Figure 3: Zhengyuan capsule increases the hepatic glycogen level in nude mice. Glycogen assay was performed (n=10 each) on day 21. Data were expressed as mean ± standard deviation. *, $p < 0.05$, compared with normal control group; ##, $p < 0.01$ compared with model group; and △△△, $p < 0.001$ compared with cisplatin group.

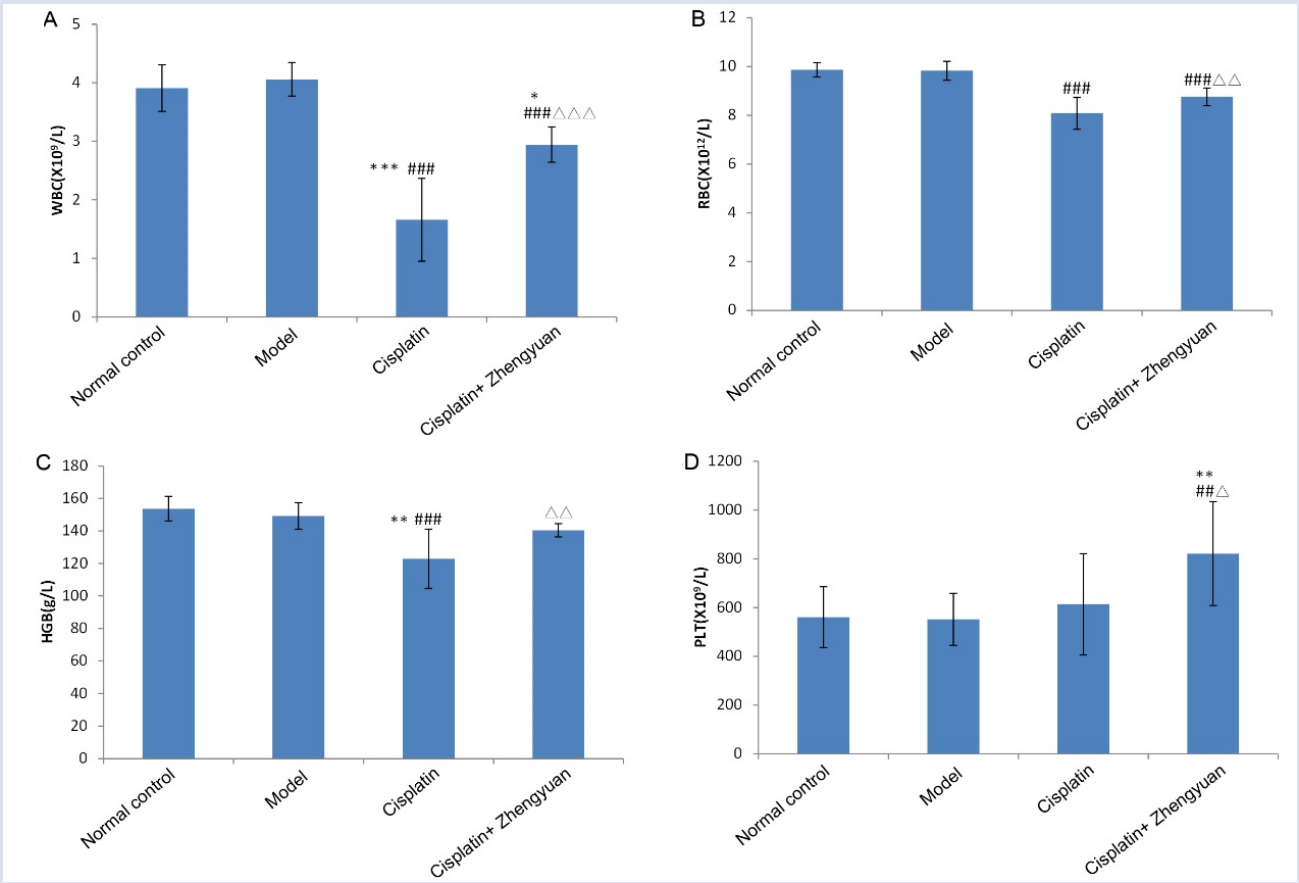

Figure 4: Zhengyuan capsule enhances peripheral blood cell count. Blood test was performed (n=10 each) on day 21 to measure WBC (white blood cell, 4A), RBC (red blood cell, 4B), HGB level (hemoglobin, 4C), and PLT (platelet, 4D). *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$ compared with normal control group; ##, $p < 0.01$, ###, $p < 0.001$ compared with model group; and △, $p < 0.05$, △△, $p < 0.01$, △△△, $p < 0.001$ compared with cisplatin group.

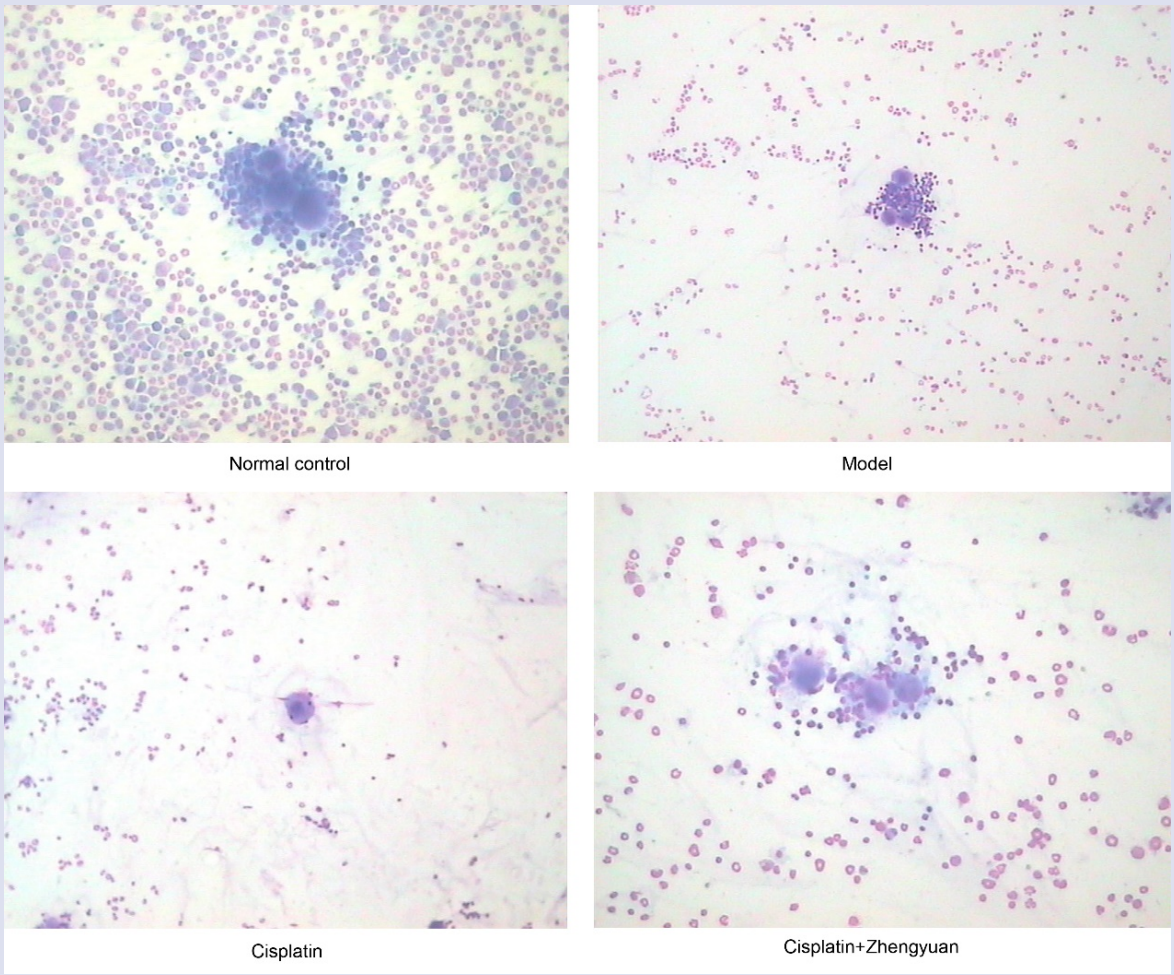

Figure 5: Zhengyuan capsule stimulates bone marrow hematopoiesis. Bone marrow smear was performed on day 21 (n = 6 each). Normal control group exhibited active bone marrow hematopoiesis with a large amount of hematopoietic islands. In model group, much less hematopoietic islands were observed, indicating a reduced bone marrow hematopoiesis. In cisplatin group, bone marrow hematopoiesis was severely reduced with very few hematopoietic islands. Cisplatin +Zhengyuan group exhibited more active bone marrow hematopoiesis, and higher numbers of hematopoietic islands and erythroid cells compared with cisplatin group.

marrow nucleated cells (BMNCs) in normal control, model, cisplatin and cisplatin+ Zhengyuan groups were 1.64 ± 0.38, 1.35 ± 0.38, 0.77 ± 0.24, and 1.37 ± 0.26 x10^7/femur, respectively (F=10.405, p<0.001). The BMNC count in cisplatin group was significantly reduced compared with normal control and model groups (p=0.004 and 0.001, respectively Figure 6). Zhengyuan intervention had significantly increased the number of BMNCs in cisplatin+Zhengyuan group when compared with cisplatin group (p=0.001).

Zhengyuan capsule reduced the peripheral cytokine production in nude mice

The TNF-α levels in normal control, model, cisplatin and cisplatin plus Zhengyuan groups were 10.11 ± 3.50, 19.58 ± 4.79, 14.59 ± 3.62, and 7.86 ± 5.21 pg/ml, respecitvely. The IL-6 levels were 14.67 ± 6.88, 67.25 ± 7.87, 45.66 ± 7.57, and 8.49 ± 3.47, respectively. Significant difference in both TNF-α and IL-6 levels was observed among the four groups (F=9.507, p<0.001; F=110.260, p<0.001). As shown in Figure 7A, the TNF-α level in model group was significantly higher than that in normal control group (p<0.001). The TNF-α level in cisplatin group was comaprable to that in model group (p>0.05), but was significantly higher than that in normal control group (p=0.005). The TNF-α level in cisplatin plus Zhengyuan group was significantly lower compared with model and cisplatin groups (p<0.001 and p=0.013). Similialy, the IL-6 level in model group was significantly higher comapred with normal control group (p<0.001, Figure 7B). The IL-6 level in cisplatin group was significantly lower than that in model group (p<0.001), but was obviously higher compared with normal control group (p<0.001). The IL-6 level in cisplatin plus Zhengyuan group was significantly reduced compared with model and cisplatin groups (both p<0.001), and was similar to that in normal control group (p>0.05).

DISCUSSION

Chemotherapy is one of the main treatment methods for lung cancer, but CRF markedly affects the quality of life in patients, and may even impair the treatment effect of chemotherapy. We herein evaluated the therapeutic effect and action mechanism of Zhengyuan capsule against CRF in nude mice with lung cancer xenograft.

CRF typically includes physical fatigue and psychological fatigue (Groenvold et al. 2007). Physical fatigue is mainly manifested as decreased activities, and is commonly assessed by weight-bearing swimming test in animal models (Oh et al. 2013; Liu et al. 2013) In this study, we found that the exhaustive swimming time in cisplatin group was significantly shorter compared with normal control group, whereas the swimming time in cisplatin plus Zhengyuan group was

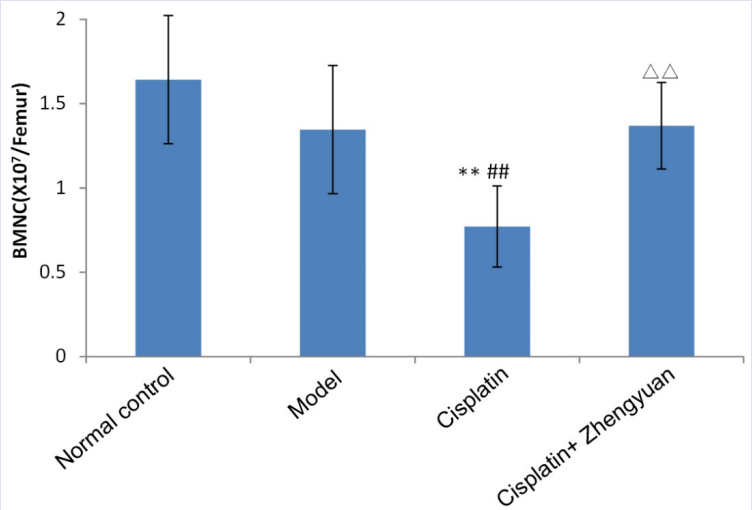

Figure 6: Zhengyuan capsule increases bone marrow nucleated cell (BMNC) count. The number of bone marrow nucleated cell was counted on day 21 (n = 10 each). **, $p < 0.01$, compared with normal control group; ##, $p < 0.01$ compared with model group; and △△, $p < 0.01$, compared with cisplatin group.

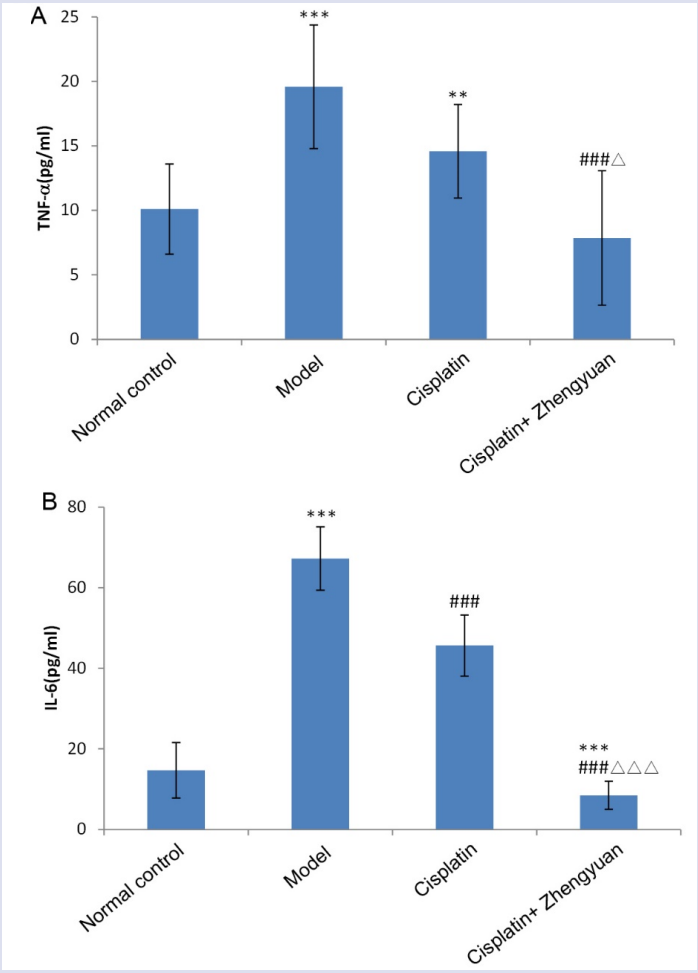

Figure 7: Zhengyuan capsule reduces the peripheral cytokine production in nude mice. On day 21, the peripheral level of TNF-α (A) and IL-6 (B) was determined. **, $p < 0.01$, ***, $p < 0.001$ compared with normal control group; ###, $p < 0.001$ compared with model group; and △, $p < 0.05$, △△△, $p < 0.001$ compared with cisplatin group.

significantly increased compared with cisplatin group, suggesting that Zhengyuan capsule had alleviated the physical fatigue developed after receiving the chemotherapy. Psychological fatigue is frequently evaluated by behavioral experiments such as tail suspension test and open field test (Walz et al. 2004). In this study, we performed both tests and found that cisplatin group had slightly longer suspension tail time, and significantly shorter total movement distance and lower average moving speed in the open field when compared with model group, indicating the development of CRF. The cisplatin plus Zhengyuan group exhibited significantly shorter suspension tail time, longer total movement distance and higher average moving speed, which suggested that Zhengyuan had exerted a therapeutic effect against the chemotherapy-induced psychological fatigue.

Glycogen is an important source of energy for muscle activity. During activities, muscle glycogen depletion triggers the release of glycogen by the liver, and fatigue occurs when glycogen levels are significantly depleted in active muscles and the liver. Therefore, hepatic glycogen level is a sensitive marker for the extent of fatigue (Narkhede et al. 2016). In this study, cisplatin group had significantly lower hepatic glycogen level than that in model group, whereas the hepatic glycogen level in cisplatin plus Zhengyuan group was significantly increased compared with both model and cisplatin groups. These results suggested that the therapeutic effect of Zhengyuan capsule was associated with the hepatic glycogen level.

BMNCs refer to the immature cells in the bone marrow including white blood cells, megakaryocytes and erythroid cells. The total number of BMNCs is a direct indicator of bone marrow hematopoiesis. Our study showed that the BMNC count in cisplatin group was significantly lower than that in model group, whereas Zhengyuan capsule had markedly increased the BMNC count in cisplatin plus Zhengyuan group. Consistently, the bone marrow smear also demonstrated that Zhengyuan capsule stimulated the hematopoiesis of bone marrow. Peripheral blood cell counts can indirectly reflect the hematopoietic function of bone marrow, and thus can be used to evaluate the effect of a drug on bone marrow hematopoiesis. In this study, we found that cisplatin plus Zhengyuan group had significantly higher count of WBC, RBC and PLT, and higher level of HGB when compared with cisplatin group, indicating a stimulatory effect of Zhengyuan capsule on bone marrow hematopoiesis after chemotherapy.

TNF-α and IL-6 are the most common and important proinflammatory cytokines. There are abundant amount of TNF-α and IL-6 in tumor microenvironment, which stimulates the growth, metastasis and immune escape of tumors (Balkwill 2009; Peddareddigari, Wang & Dubois 2010; York et al. 2011). Studies have suggested an association between peripheral immune system dysfunction and persistent fatigue. In the immune-to-brain signaling pathway, peripheral pro-inflammatory cytokines such as TNF-α and IL-6 transmit signals to the brain, leading to pathological behavior, including fatigue, sleep disturbances, depression, etc. (Bower 2017; Bower & Lamkin 2012). Moreover, elevated serum IL-6 level is often detected in patients with CRF (Bower & Lamkin 2012). Therefore, the development of proinflammatory cytokines inhibitors has recently become a research hotspot in the treatment of CRF. In a clinical trial, the incidence of CRF was obviously lower in advanced cancer patients who had underwent docetaxel chemotherapy followed by treatment with TNF-α receptor blockers when compared with control group without TNF-α receptor blockers (Steptoe, Hamer & Chida 2007). In addition, both TNF-α and IL-6 are negative hematopoietic regulators. While TNF-α can cause anemia by inhibiting the synthesis of erythropoietin (Monk et al. 2006), IL-6 induces the synthesis of hepeidin by the liver, which causes iron metabolism disorder, inhibits the production of RBCs, and ultimately leads to anemia (Bayliss et al. 2011). In the current study, increased levels of TNF-α and IL-6 were detected in both model and cisplatin groups compared with normal control group, which is consistent with numerous studies (Balkwill 2009; Peddareddigari, Wang & Dubois 2010; York et al. 2011). The TNF-α and IL-6 level in cisplatin plus Zhengyuan group was significantly reduced compared with cisplatin group, indicating that the therapeutic effect of Zhengyuan capsule against CRF might be mediated through the inhibition of TNF-α and IL-6 level in the tumor.

CONCLUSION

In this study, we showed that Zhengyuan capsule reduced the post-chemotherapy bone marrow suppression, decreased serum TNF-α and IL-6 levels, and thereby alleviated CRF in nude mice. Additionally, we found that Zhengyuan capsule enhanced the hepatic glycogen content, which might also be associated with its anti-CRF effect. Our results shed light into the mechanism of the therapeutic effect of Zhengyuan capsule against CRF, and provided a solid basis for its clinical application in the treatment of the condition.

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