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Hematopoietic protective effects of Guiqi crucian carp decoction on chemotherapy-induced leukopenia in rats

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Abstract: **Background**: Chemotherapy-induced leukopenia is a common dose-limiting toxicity that compromises treatment continuity and increases the risk of infection. Current pharmacological interventions are often associated with adverse effects, highlighting the need for safe and effective supportive strategies. Guiqi crucian carp decoction (GQCCD), a traditional dietary therapy derived from the concept of medicine–food homology, has been used to replenish qi and nourish blood; however, its hematopoietic protective effects have not been systematically evaluated. **Objectives**: This study aimed to investigate the hematopoietic and immunoprotective effects of GQCCD in a rat model of chemotherapy-induced leukopenia. **Methods**: A leukopenia model was established in rats using 5-fluorouracil (5-FU). Rats were divided into a blank control group, model group, positive control group (batyl alcohol) and GQCCD-treated group. Peripheral blood parameters, including white blood cell (WBC), neutrophil (NE UT), lymphocyte (LYMPH) and monocyte (MONO) counts, were measured at different time points. Thymus and spleen indices were calculated and histopathological examinations of bone marrow, spleen and thymus were performed. **Results**: 5-FU administration induced significant leukopenia, accompanied by reduced thymus and spleen indices and marked histopathological damage in immune organs and bone marrow. Compared with the model group, GQCCD treatment significantly increased WBC and NEUT counts and MONO percentage ($P < 0.01$), along with significant improvements in thymus and spleen indices ($P < 0.01$). Histopathological analysis revealed substantial restoration of bone marrow and immune organ structures. No statistically significant improvement in LYMPH counts was observed. **Conclusion**: GQCCD effectively alleviated chemotherapy-induced leukopenia in rats by restoring peripheral blood parameters, improving immune organ indices and ameliorating bone marrow and immune organ damage. These findings support the potential of GQCCD as a complementary dietary therapy for managing chemotherapy-related myelosuppression.

Keywords: Angelica sinensis; Astragalus membranaceus; Crucian carp; Leukopenia

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INTRODUCTION

Leukopenia is defined as a condition in which the peripheral blood leukocyte count in adults falls below 4.0 × 10^9/L due to multiple etiological factors (Shi *et al.*, 2020). Chemotherapy-induced leukopenia is a direct result of the impairment of bone marrow hematopoietic function by cytotoxic agents. These hematological alterations not only compromise the continuity and intensity of chemotherapy regimens but also markedly increase the risk of severe infections and mortality. Clinically, commonly used interventions include granulocyte colony-stimulating factor (G-CSF), vitamin B4 and batyl alcohol. However, these treatments are often associated with adverse effects such as fever, bone pain and nausea and their therapeutic efficacy remains inconsistent (Bumbacea *et al.*, 2024). In traditional Chinese medicine (TCM), chemotherapy-induced leukopenia is categorized as a *consumptive disease* or *blood deficiency*, for which therapeutic strategies such as Chinese herbal medicine, acupuncture and moxibustion are widely applied (Yang *et al.*, 2021; Nian *et al.*, 2022). In recent years, traditional Chinese dietary therapy has attracted increasing attention due to its potential efficacy, favorable safety profile, ease of preparation and good palatability. Notably, a previous study from the same research group reported that Qi-tonifying and blood-nourishing dietary formulations exerted protective effects against bone marrow suppression (Ye *et al*., 2022).

Guiqi crucian carp decoction (GQCCD) is a traditional dietary therapy derived from the classical prescription *Danggui Buxue Tang* and guided by the TCM principle of medicine–food homology. It consists of *Angelica sinensis*, *Astragalus membranaceus* and crucian carp and is traditionally prescribed to replenish Qi and nourish blood. Both *Angelica sinensis* and *Astragalus membranaceus* have been extensively reported to support hematopoiesis and improve bone marrow function, while crucian carp provides essential nutrients that may facilitate recovery from chemotherapy-induced injury. Accumulating evidence suggests that dietary therapies incorporating such components can alleviate myelosuppression and improve hematological parameters (Xie *et al.*, 2022). Nevertheless, the hematopoietic protective effects of GQCCD and its specific role in chemotherapy-induced leukopenia have not yet been systematically investigated.

Therefore, the present study aimed to evaluate the hematopoietic protective effects of GQCCD in a 5-

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fluorouracil (5-FU) induced leukopenia rat model, with particular emphasis on peripheral blood parameters and bone marrow histopathology. The findings are expected to provide additional experimental evidence supporting the clinical application of traditional Chinese dietary therapy in the management of chemotherapy-induced leukopenia.

MATERIALS AND METHODS

Animals

Thirty-two male Sprague-Dawley rats, specific pathogen-free grade, 3–4 months old, and weighing 300 – 350g at the start of the experiment, were purchased from Zhejiang Weitong Lihua Laboratory Animal Technology Co., Ltd. (license no. SCXK [Zhe] 2024-0001; animal certificate no. 20240614Aazz0619999530). The rats were housed in the animal facility of Deruikang Biotechnology (Zhejiang) Co., Ltd. (animal use permit no. SYXK [Zhe] 2023-0002). They were maintained at 23 ± 3 °C with 40–70% relative humidity under a 12 h light/dark cycle.

Materials and reagents

(1) GQCCD

Angelica sinensis, *Astragalus membranaceus* and crucian carp were used at a mass ratio of 1:5:50. The ingredient-to-herb ratio was determined with reference to the classical formula *Danggui Buxue Tang* and traditional folk dosages for crucian carp, in which *Angelica sinensis* : *Astragalus membranaceus* = 1:5. The recommended human dosage was 36 g of total herbs/60 kg (normal adult weight)/day (Yang *et al.*, 2025b). The equivalent dose for rats was calculated as 6.3*human dose (Yang *et al.*, 2025b) and the commonly used folk dosage for crucian carp ranged from 250 to 500 g per meal (Tang, 2015). Based on the recommended daily doses for adults (calculated for a 60-kg body weight), the amounts of *Angelica sinensis*, *Astragalus membranaceus* and crucian carp are 6 g/60 kg, 30 g/60 kg and 300 g/60 kg, respectively. Using the standard body surface area conversion factor for rats (6.3), the rat-equivalent crude drug dose was calculated as 6.3 × [(6 + 30) g / 60 kg], resulting in a total dose of 0.378 g per 100 g body weight (i.e., 0.378 g crude drug per 100 g rat body weight). According to commonly accepted gavage volumes for experimental animals, rats were administered 1 mL per 100 g body weight per day. Therefore, the concentration of crude drug in the medicated diet was 0.378 g/mL. Based on the formulation ratio, each milliliter of the medicated preparation contained 0.063 g of *Angelica sinensis*, 0.315 g of *Astragalus membranaceus* and 3.15 g of crucian carp.

For preparation, the scales, viscera and gills of the crucian carp were removed, after which the fish was thoroughly rinsed and set aside. *Angelica sinensis* and *Astragalus membranaceus* were soaked in three times their volume of water for 30 min. Subsequently, all herbal materials and the prepared crucian carp were placed into a clay pot and ten times the volume of water was added. The mixture was brought to a boil over high heat and then gently simmered over low heat for 40 min. When the fish flesh became tender and the decoction turned thick and yellow, the mixture was filtered to obtain the first extract.

Eight times the volume of water was then added to the residue, followed by boiling over high heat and simmering over low heat for an additional 30 min. The resulting decoction was filtered, the upper lipid layer was carefully removed and the filtrate was filtered again. Finally, the combined filtrates were concentrated in a water bath to a final density of 0.378 g/mL. The concentrated extract was aliquoted, refrigerated and stored for subsequent use.

(2) Batyl alcohol

Batyl alcohol (Shanghai Maclin Biochemical Technology Co., Ltd., batch No. C16013588) was prepared as a suspension with a concentration of 0.012 g/mL in physiological saline. After thorough mixing, the suspension was aliquoted and stored at 4 °C. Suspension was shaken vigorously before each use to ensure complete dispersion.

(3) 5-FU

5-FU for injection (Hainan Zhuotai Pharmaceutical Co., Ltd., batch No. 20240309) was used in this study.

Experimental instruments

The main experimental instruments used in this study included the following: a fully automatic blood cell analyzer (TDSF-L-5CBC-5120; Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China); a manual single-channel pipette (Research plus; Eppendorf AG, Hamburg, Germany); a constant-temperature water bath (DK-80; Shanghai Jinghong Instrument Factory, Shanghai, China); an ultra-low temperature freezer (−80 °C; COOL++; AUCMA, Qingdao, China); a tissue dehydrator (JT-12J; Wuhan Junjie Electronics Co., Ltd., Wuhan, China); a tissue embedding machine (JB-L5; Wuhan Junjie Electronics Co., Ltd., Wuhan, China); a rotary microtome (RM2016; Leica Instruments Co., Ltd., Shanghai, China); an upright light microscope (ECLIPSE CI-L; Nikon Corp., Tokyo, Japan); and a panoramic slide scanner (PANNORAMIC MIDI/SCAN 150; 3DHISTECH Ltd., Budapest, Hungary).

Experimental grouping

After a one-week acclimatization period, thirty-two rats were randomly assigned into four groups using a random number table: a blank control group, a model group, a positive control group and a GQCCD group, with eight rats in each group.

Preparation of the bone marrow suppression model

On the day of model induction, rats in the model, positive control and GQCCD groups received a tail vein injection of 5-FU at a dose of 150 mg/kg. Rats in the blank control

group were administered an intraperitoneal injection of an equal volume of 0.9% saline.

Administration method

From day 1 to day 14 after model induction, all rats received treatments once daily via intragastric gavage at a fixed time, with a dosing volume of 1 mL per 100 g of body weight. Rats in the positive control group received a batyl alcohol suspension, whereas those in the GQCCD group were administered Guiqi crucian carp decoction. Under the same conditions, rats in the blank control and model groups received an equivalent volume of normal saline via intragastric gavage. All animals were provided with a standard laboratory diet throughout the experimental period.

Sample collection and detection

(1) Peripheral blood cell count

Peripheral blood samples were collected from the orbital venous plexus of rats one day before model induction, 24 h after model induction and on day 15 after model induction. Routine hematological parameters, including white blood cell (WBC), neutrophil (NEUT), lymphocyte (LYMPH) counts and monocyte percentage (MONO%), were determined using an automated hematology analyzer.

(2) Immune organ index

On day 15 after model induction, rats were weighed and euthanized by cervical dislocation. The thymus and spleen were carefully excised and surrounding mesenteric and adipose tissues were removed. After blotting dry with filter paper, the organs were weighed using a precision electronic balance and the immune organ indices, including the thymus index [Eq. (1)] and spleen index [Eq. (2)], were calculated as follows:

$$\text{Thymus index (g/g)} = \frac{\text{thymus weight (g)}}{\text{body weight (g)}} \quad (1)$$

$$\text{Spleen index (g/g)} = \frac{\text{spleen weight (g)}}{\text{body weight (g)}} \quad (2)$$

(3) Histopathological examination of immune organs

The spleen, thymus and femur were rapidly excised from rats in each group. Fresh tissue samples were fixed in 4% paraformaldehyde for at least 24 h, followed by dehydration, paraffin embedding, sectioning, deparaffinization and staining with hematoxylin and eosin (H&E staining). Bone marrow sections were examined under a light microscope to assess histopathological changes and representative images were captured.

Statistical analysis

All statistical analyses were performed using SPSS version 27.0. Data are presented as the mean ± standard deviation. Comparisons of hematological parameters, thymus index and spleen index among multiple groups were conducted using one-way analysis of variance (ANOVA). When homogeneity of variances was met, the least significant difference (LSD) test was applied for post hoc pairwise comparisons; otherwise, Dunnett's T3 test was used. A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Peripheral blood cell count results after intervention

No significant differences in hematological parameters were observed among the groups one day before model induction ($P > 0.05$). At 24 h after 5-FU administration, total WBC and LYMPH counts were significantly reduced compared with the blank group ($P < 0.05$), whereas NEUT counts did not show a significant decline. This phenomenon is consistent with the time-dependent nature of chemotherapy-induced myelosuppression, in which early peripheral NEUT levels may be transiently maintained by bone marrow reserve pools. Based on these findings, WBC count was used as the primary hematological indicator for validation of leukopenia model establishment. (Fig. 1).

On day 15 after model induction, WBC, NEUT and LYMPH counts, as well as the MONO%, in the model group were significantly lower than those in the blank group ($P < 0.05$). Following the intervention, rats in the positive control group exhibited significantly higher WBC, NEUT and LYMPH counts and MONO% compared with the model group ($P < 0.01$). Compared with the model group, the GQCCD-treated group showed a significant increase in WBC and NEUT counts and MONO% ($P < 0.01$). An increasing trend in LYMPH count was also observed in the GQCCD group; however, the difference did not reach statistical significance ($P > 0.05$) (Table 1).

Thymus and spleen index results

Following the intervention, thymus and spleen indices in the model group were significantly reduced compared with those in the blank control group ($P < 0.01$). In contrast, both the positive control group and the GQCCD-treated group showed significantly higher thymus and spleen indices than the model group ($P < 0.01$). (Fig. 2).

Histopathological findings of immune organs

In the blank control group, the splenic architecture was preserved, with intact white pulp, no evidence of degeneration or necrosis in the lymphoid sheaths and clearly defined splenic trabeculae. In contrast, the model group exhibited marked disruption of splenic structure, characterized by atrophy of the lymphoid sheaths within the white pulp, expansion of the red pulp and a pronounced reduction in lymphocyte numbers. In the positive control group, degenerative necrosis of lymphoid nodules in the white pulp and nuclear fragmentation were observed.

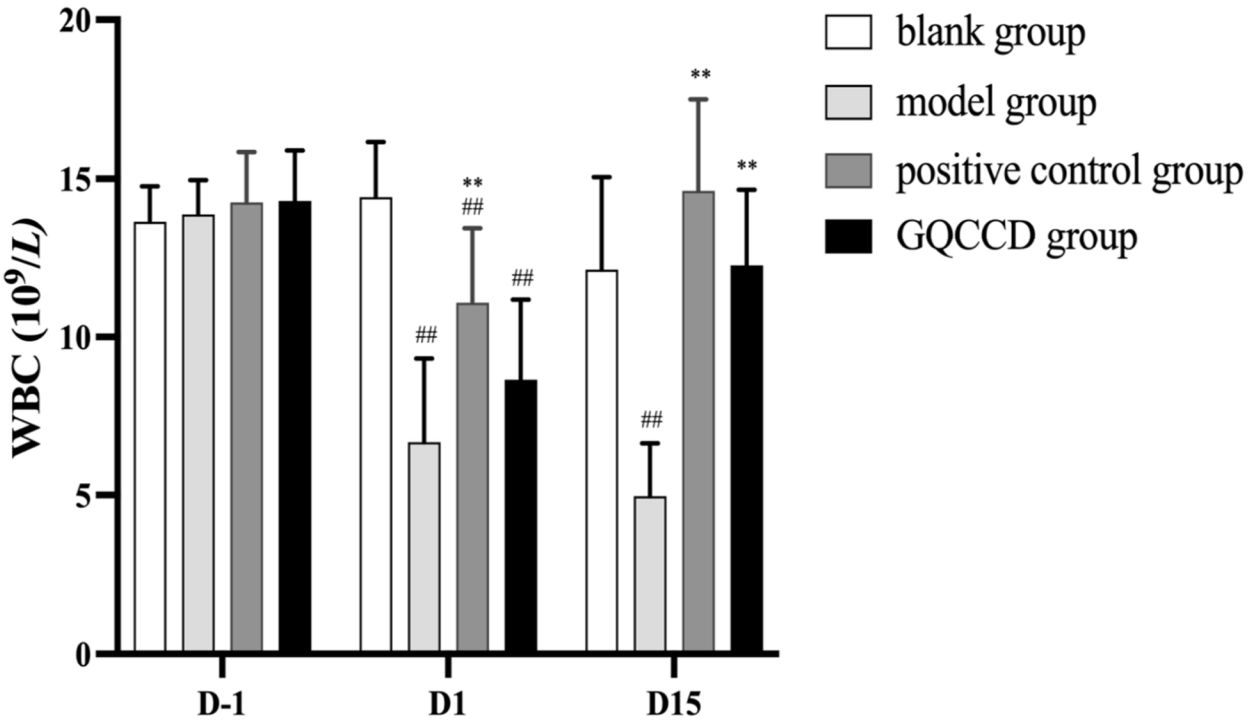

Fig. 1: Changes in total WBC counts at baseline, 24 hours after 5-FU administration, and day 15 after modeling.
Note: WBC was selected as the primary hematological indicator for validation of chemotherapy-induced leukopenia due to early dynamic fluctuations observed in leukocyte subsets. D-1 denotes 24 hours before modeling; D1 denotes 24 hours after modeling; D15 denotes 15 days after modeling. Compared with the blank group, # denotes P<0.05, ## denotes P<0.01; compared with the model group, * denotes P<0.05, ** denotes P<0.01.

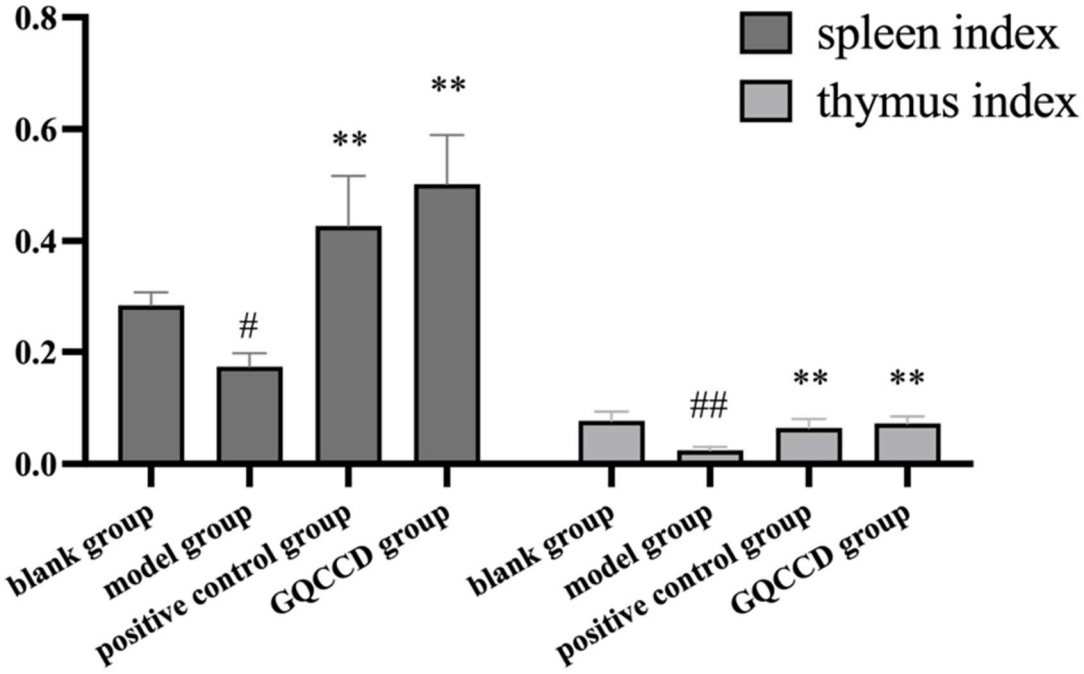

Fig. 2: Comparison of immune organ index in rats.
Note: Compared with the blank group, # denotes P<0.05, ## denotes P<0.01; compared with the model group, * denotes P<0.05, ** denotes P<0.01.

Table 1: Peripheral blood cell counts of rats in each group 15 days after modeling.

Group	WBC (10^9/L)	NEUT (10^9/L)	LYMPH (10^9/L)	MONO (%)
Blank	12.11±2.94	2.68±0.86	7.58±2.18	13.1±4.1
Model	4.96±1.70$^{\#\#}$	0.38±0.28$^{\#\#}$	4.42±1.55$^{\#\#}$	2.5±1.4$^{\#\#}$
Positive control	14.63±2.88$^{\#**}$	3.68±1.74**	8.03±1.49**	18.6±2.6$^{\#\#**}$
GQCCD	12.25±2.40**	3.60±1.35**	6.13±1.93	15.5±6.0**

Note: Compared with the blank group, $^{\#}$ denotes $P<0.05$, $^{\#\#}$ denotes $P<0.01$; compared with the model group, * denotes $P<0.05$, ** denotes $P<0.01$.

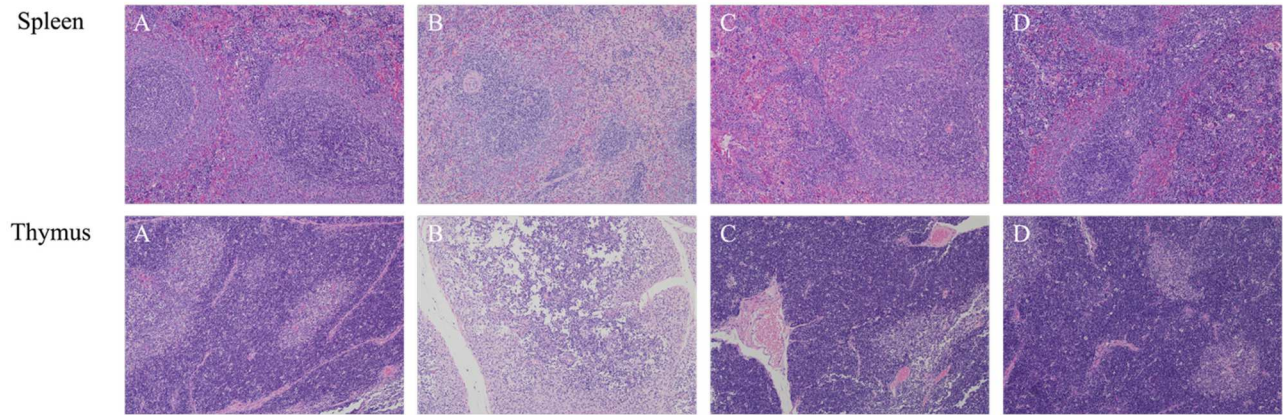

Fig. 3: Comparison of histopathological examination results of spleen and thymus tissues in each group of rats (H&E staining, ×100). Upper row: spleen; lower row: thymus. (A) Blank group; (B) Model group; (C) Positive control group; (D) GQCCD group.

In addition, immune-inflammatory reactions were present in the red pulp, accompanied by prominent proliferation of multinucleated giant cells. In the GQCCD-treated group, the white pulp showed partial structural disorganization, while immune-inflammatory reactions were observed in the red pulp, along with prominent proliferation of lymphocytes and multinucleated giant cells (Figs. 3 A-D, upper row).

In the blank control group, the thymic architecture appeared normal, with clearly demarcated lobules. The thymic cortex contained abundant and evenly distributed T lymphocytes, with no necrotic foci and the medullary structure remained intact. In the model group, the thymus exhibited severe structural damage, including lobular disintegration and necrosis. The corticomedullary boundary was indistinct, accompanied by a marked reduction in lymphocytes and evident proliferation of stromal fibroblasts. In the positive control group, mild structural abnormalities were observed in the thymus. By contrast, the GQCCD-treated group displayed an overall thymic architecture comparable to that of the blank control group, with abundant and evenly distributed T lymphocytes in the cortex (Figs. 3 A-D, lower row).

Histopathological findings of the bone marrow

Under light microscopy, bone marrow tissue in the blank control group exhibited a normal overall architecture. The reticular fiber framework was intact, with no evidence of necrosis or structural disorganization. Both erythroid and myeloid lineages were abundant, with occasional adipocytes observed and no apparent proliferation of megakaryocytes. In the model group, the bone marrow architecture was severely disrupted. The reticular fiber framework showed extensive necrosis and collapse and large amounts of necrotic fibrinoid material were present within the marrow cavity. Hematopoietic cellularity was markedly reduced, and the marrow space was occupied by numerous erythrocytes. In the positive control group, the bone marrow structure appeared largely restored, with an intact reticular framework and no obvious signs of necrosis or disorganization. No significant proliferation of megakaryocytes was observed. In the GQCCD group, the bone marrow architecture was also largely preserved. The reticular fiber framework remained intact, with no necrotic or disordered structures evident. Both erythroid and myeloid cells were abundant, adipocytes were markedly reduced or absent and localized proliferation of megakaryocytes was observed (Figs. 4 A-D).

DISCUSSION

Chemotherapy-induced leukopenia represents a major dose-limiting toxicity of cytotoxic agents and is primarily caused by suppression of bone marrow hematopoietic function. In the present study, administration of GQCCD significantly increased total WBC and NEUT counts, as well as the MONO%, in a 5-FU induced leukopenia rat model.

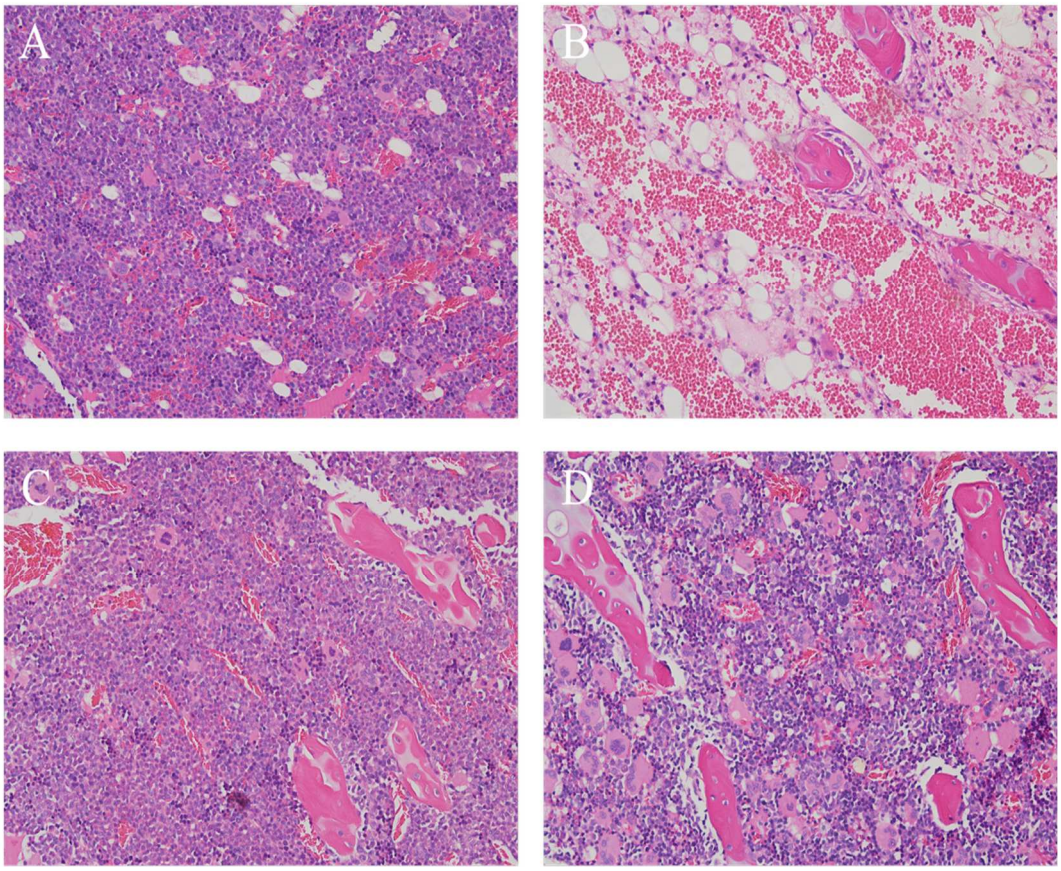

Fig. 4: Comparison of histopathological examination results of bone marrow tissues in each group of rats (H&E staining, ×200). (A) Blank group; (B) Model group; (C) Positive control group; (D) GQCCD group.

These hematological improvements were accompanied by marked restoration of bone marrow histopathological features. Collectively, these findings suggest that GQCCD exerts a hematopoietic-supportive effect and mitigates chemotherapy-induced myelosuppression.

The hematopoietic protective effects of GQCCD may be attributed to the synergistic actions of its components. Angelica sinensis, a traditional blood-tonifying herb, has been shown to support hematopoietic activity by promoting the proliferation and differentiation of hematopoietic stem cells and bone marrow mesenchymal stem cells, enhancing the secretion of hematopoietic growth factors and improving the bone marrow microenvironment through angiogenesis (Mu *et al.*, 2017; Shen *et al.*, 2024). *Astragalus membranaceus* is traditionally used to strengthen Qi and promote hematopoiesis. Pharmacological studies have demonstrated that its active constituents can stimulate hematopoietic stem cell proliferation and delay cellular senescence (Bao *et al.*, 2021;Zhang *et al.*, 2013). Notably, the combination of *Angelica sinensis* and *Astragalus membranaceus* synergistically improves myelosuppression, enhances hematopoietic recovery and immune function (Li *et al.*, 2025; Yang *et al.*, 2025a; Huang *et al.*, 2024). Crucian carp, a widely consumed freshwater fish in Chinese aquaculture, is traditionally regarded as having spleen- and stomach-tonifying properties in TCM (Wang *et al.*, 2024). Clinical studies conducted in China have reported that dietary therapies incorporating crucian carp can increase leukocyte, erythrocyte and hemoglobin levels in patients with chemotherapy-induced myelosuppression (Guang, 2013). In addition to its nutritional value, crucian carp is a source of bioactive peptides with documented anti-inflammatory, antioxidative and immunomodulatory activities. Experimental evidence suggests that crucian carp–derived components can attenuate systemic and neuroinflammatory responses and enhance physiological resilience, supporting their potential role as a functional food for maintaining immune homeostasis and facilitating recovery under pathological or stress-related conditions (Chataigner *et al.*, 2021; Han *et al.*, 2025). Collectively, the combination of *Angelica sinensis*, *Astragalus membranaceus* and crucian carp in GQCCD thus embodies the TCM concept of *medicine-food homology* and may underlie the observed improvements in hematopoietic function in the present study. In the present study, GQCCD significantly increased total WBC and neutrophil counts, as well as MONO%, whereas lymphocyte counts showed only a modest, statistically nonsignificant increase. This differential response may reflect lineage-specific vulnerability and recovery kinetics after chemotherapy.

Lymphocytes are highly sensitive to cytotoxic therapy and may remain depleted or recover more slowly after treatment, which may partly explain the lack of a statistically significant increase during the observation window in the present study (Verma *et al.,* 2016; Dixon-Douglas *et al.,* 2024).

In addition, the pharmacological positive control demonstrated greater efficacy than GQCCD, which was expected given its established therapeutic potency. By contrast, GQCCD, as a dietary therapy, is designed to provide supportive and adjunctive benefits rather than rapid pharmacological correction. These findings suggest that GQCCD may serve as a complementary intervention to support hematopoietic recovery, rather than as a substitute for conventional treatments. The dose of GQCCD used in the present study was selected based on traditional human consumption practices combined with standard body surface area–based dose conversion for rodents. This approach was intended to reflect a clinically relevant dietary exposure rather than to achieve a maximal pharmacological effect.

Consistent with the hematological findings, GQCCD significantly ameliorated chemotherapy-induced pathological damage in immune organs, including the spleen and thymus, as well as in bone marrow. The spleen functions as the largest peripheral immune organ (Lewis et al., 2019), whereas the thymus is essential for T-lymphocyte differentiation and maturation (Thapa and Farber, 2019). Restoration of spleen and thymus indices observed in the GQCCD-treated group corroborated improvements in peripheral blood parameters, suggesting enhanced integrity of immune organs and overall immune regulation. Furthermore, histopathological improvements in these tissues provided direct morphological evidence supporting the protective effects of GQCCD on both hematopoietic and immune systems.

CONCLUSION

In summary, GQCCD effectively alleviated chemotherapy-induced leukopenia in rats. GQCCD treatment restored peripheral hematological parameters, including total leukocyte, neutrophil and monocyte levels and markedly ameliorated histopathological damage in the spleen, thymus and bone marrow. These findings indicate that GQCCD exerts hematopoietic and immunoprotective effects, potentially through supporting hematopoietic stem cell activity and improving the bone marrow microenvironment. Overall, this study provides experimental evidence supporting the traditional Chinese medicine concept of *medicine–food homology* and highlights GQCCD as a promising complementary dietary strategy for managing chemotherapy-induced myelosuppression. Several limitations of the present study should be acknowledged. First, a single-dose regimen and a fixed observation window were employed, which may have limited the assessment of dose–response relationships and long-term efficacy. Second, the chemical composition of GQCCD was not characterized in this study, which restricts the identification of specific bioactive constituents responsible for the observed hematopoietic effects. In addition, although no apparent treatment-related toxicity, such as abnormal behavior, body weight loss, or increased mortality, was observed during the intervention period, the safety and tolerability of GQCCD were not systematically evaluated, representing another limitation of the present study. Furthermore, the specific molecular targets and signaling pathways underlying the hematopoietic effects of GQCCD were not investigated. Future studies should incorporate extended intervention periods, multiple dosing regimens, comprehensive safety assessments and mechanistic analyses, including omics-based approaches (e.g., transcriptomics and metabolomics) and pathway validation involving key hematopoietic signaling cascades to further elucidate the therapeutic potential and mechanisms of GQCCD.

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None.

Authors' contributions
Ye Hui: Contributed to the experimental design, data collection and analysis and drafting of the manuscript; Wang Hangsai and Cao Lingli: participated in the data analysis and drafting of the manuscript; Panhuiying: Responsible for research supervision, manuscript revision and final approval. All authors have read and approved the final manuscript.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was approved by the Institutional Animal Care and Use Committee (IACUC) of Deruikang Biotechnology (Zhejiang) Co., Ltd. (Approval No. DRK2024061601). This study was performed in adherence with the ARRIVE guidelines. See supplementary file for the ARRIVE checklist.

Conflict of interest
The authors declare no conflict of interest.

Supplementary data
https://pjps.pk/uploads/2026/08/SUP1787209511.pdf

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