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Preventing effect of astragalus polysaccharide on cardiotoxicity induced by chemotherapy of epirubicin

A pilot study

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Abstract

To assess the clinical effect of astragalus polysaccharide in preventing cardiotoxicity induced by chemotherapy of epirubicin. Two hundred forty-eight patients with breast cancer or malignant lymphoma were randomly divided into the experimental group (EG) (n = 124) and the control group (CG) (n = 124). The EG received chemotherapy regimen containing anthracycline epirubicin and astragalus injection, while CG received only chemotherapy regimen containing anthracycline epirubicin. We detected myocardial function (cardiac troponin I [cTnI], creatine kinase isoenzyme [CK-MB], left ventricular ejection fraction [LVEF], and the ratio of mitral annular diastolic peak velocity to atrial systolic velocity [E/A]) and incidences of cardiotoxicity to assess cardiac function, they were compared at before the first treatment course (T_1), end of the second course (T_2) and 6-month follow-up. We also detected proinflammatory cytokines (IL-6 and TNF-α), reactive oxygen species and antioxidant enzymes, glutathione peroxidase (GPx), and superoxide dismutase (SOD) aimed to discover potential mechanism. There were no statistical significances in differences of LVEF and E/A between 2 groups ($P > .05$) at T_1 and T_2, while levels of LVEF and E/A of EG were significant higher than those of the CG at 6 month follow-up, with statistically significant differences ($P < .05$). At T_1, there were no statistical significances in differences of cTnI and CK-MB between 2 groups ($P > .05$); at T_2 and 6 months follow-up, the cTnI, and CK-MB levels of EG was significantly lower than those of the CG, with statistically significant differences ($P < .05$). The incidence of cardiotoxicity of EG was 15% (17/113), which was significant lower than that of the CG (60%, 66/110), with statistically significant difference ($P < .05$). Moreover, the level of TNF-α, GPx, and SOD did not show significant difference ($P > .05$). The data in this pilot study suggested that astragalus polysaccharide may be an effective therapy for preventing cardiotoxicity induced by chemotherapy of epirubicin. Furthermore, larger, placebocontrolled, perspective studies are needed to assess the efficacy of astragalus injection treatment for preventing cardiotoxicity induced by chemotherapy of epirubicin.

Abbreviations: ATN = anthracyclines, CG = control group, CHF = congestive heart failure, CK-MB = creatine kinase isoenzyme, cTnI = cardiac troponin I, E/A = atrial systolic velocity, EG = experimental group, ELISA = enzyme-linked immunosorbent assay, GPx = glutathione peroxidase, HF = heart failure, LVEF = left ventricular ejection fraction, ROS = reactive oxygen species, SOD = superoxide dismutase, T_1 = the first chemotherapy course, T_2 = the second chemotherapy course.

Keywords: astragalus polysaccharide, cardiotoxicity, epirubicin.

1. Introduction

Anthracyclines (ANT) are among the most effective drugs against cancer, used in a wide spectrum of malignancies, both in adjuvant and metastatic settings.[1] Epirubicin is an anthracycline chemotherapeutic drug widely used in lymphoma, breast cancer, gastric cancer, lung cancer, leukemia, and other patients. However, due to the side effects of bone marrow transplantation and cardiotoxicity, especially the cumulative cardiotoxicity, the clinical application effect is often limited.[2] A Danish nationwide cohort study showed that 2440 patients who received anthracycline-containing chemotherapy treatment developed congestive HF.[3] Epirubicin is highly sensitive to cells in various cycles, especially S phase cells. Its mechanism is to inhibit DNA replication and translation by inserting DNA base pairs and interfering with DNA polymerase.[4,5] Moreover, administration of anthracyclines drugs at high doses has been reported to elicit positive chronotropic and negative inotropic

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The datasets generated during and/or analyzed during the current study are publicly available.

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cardiovascular impacts accompanied by acute HF, perturbation of ventricular functions, increased heart rates, and electrocardiogram alterations in various animal species.[6–9]

The mechanism underlying epirubicin-induced cardiotoxicity did not fully understood. However, it is supposed that epirubicin induces cardiotoxicity through an elevation in the generation of reactive oxygen species (ROS) or alteration in the oxidative status of the heart tissue.[10,11] Therefore, impediment of the apoptosis process could be of value in preventing cardiotoxicity induced by chemotherapy of epirubicin.

Astragalus is a perennial herbaceous plant, and it has a history of usage in traditional Chinese medicine as an immunomodulatory substance for curing diarrhea, common cold, anorexia, fatigue, and various cardiovascular disorder.[12,13] The dried root of AM contains numerous bioactive constituents, such as polysaccharides, astragalosides, flavonoids, trace elements, and aminoacids.[14] The main ingredient of astragalus was astragalus polysaccharide. Astragalus polysaccharide has been reported to be responsible for various biological activities, including the antiaging, anti-inflammatory, immunomodulatory, and antitumor et al.[15–18] Previous studies have demonstrated the cardioprotective effects of astragalus and its active constituents against various drugs, chemicals, and xenobiotic-induced cardiopathy, moreover, astragalus polysaccharides could enhances the functions of the cardiovascular system and cures heart diseases such as HF and myocardial hypertrophy.[19,20]

The study aimed to observe the cardiotoxicity of astragalus polysaccharide combined with epirubicin containing regimen and epirubicin containing chemotherapy alone in patients with malignant tumor.

2. Materials and Methods

2.1. Study design

The study was a randomized controlled trial. This study was performed at Shanxi Bethune Hospital from September 2017 and September 2020. Inclusion criteria: (1) 30 years ≦ age ≦ 70 years; (2) the patient was diagnosed as breast cancer and malignant lymphoma by histopathology, and those patients received epirubicin based chemotherapy; (3) the patients had no history of heart disease, the heart function, and the ECG were normal before chemotherapy; (4) Karnofsky score ≧ 70; (5) the expected survival time of the patients was more than 3 months; (6) The cumulative dose of epirubicin does not exceed 900 mg/m^2; (7) the subjects were willing to cooperate and implement the experiment. Exclusion criteria: (1) had a history of mental illness; (2) had a history of congenital heart disease; (3) pregnant and lactating women; (4) had a history of chronic diseases such as hypertension, coronary heart disease, or diabetes. The procedures of this clinical trial are presented Figure 1. The researchers systematically explained the role, purpose, and process of the study to the patients and their families. The patients and their families voluntarily signed the informed consent form to participate in this study. This study was approved and recognized by the ethics committee of our hospital (NO. 20160712).

All subjects were evaluated at baseline using conventional echocardiography. The full echocardiographic protocol was repeated in all patients within 24 hours of the end of the chemotherapy. Cardiotoxicity was defined as reduction in EF of ≥10% to an EF of <55%, without signs or symptoms of heart failure (HF), compared with baseline, after the sixth cycle of treatment.

2.2. Participants and subgroup

Two hundred eighty-seven patients were treated in our Hospital, including 272 patients meeting the inclusion and exclusion criteria. The 248 eligible patients enrolled in this study were randomly allocated into 2 group: the experimental group (EG) (n = 124) or the control group (CG) (n = 124). Because of quit or discontinue, that is, had 113 patients and CG had 110 patients (Fig. 1).

2.3. Interventions

2.3.1. Experimental group. The patients received chemotherapy regimen containing anthracycline epirubicin. Patients with breast cancer were treated with CEF chemotherapy: Phosphoramide 500 mg/m^2 (day 1) + Epirubicin 80 mg/m^2 (day 1) + Fluorouracil 500 mg/m^2 (day 1, 8); Patients with malignant lymphoma were treated with CHOP chemotherapy: cyclophosphamide 600 mg/m^2 (day 1) + Epirubicin 80 mg/m^2 (day 1) + Vinpocetine 2 mg/m^2 (day 1) + Prednisone 100 mg/m^2 (day 1–5). Meanwhile, the patients also received astragalus polysaccharides injection (specification: 500 mg each, Tianjin sanuo Pharmaceutical Co., Ltd), 500 mg astragalus polysaccharides injection was added into 500 mL normal saline, once a day, 2 weeks as a course of treatment, 2 courses of treatment.

2.3.2. Control group. The patients received only chemotherapy regimen traditional treatment. Patients with breast cancer were treated with CEF chemotherapy: phosphoramide 500 mg/m^2 (day 1) + epirubicin 80 mg/m^2 (day 1) + fluorouracil 500 mg/m^2 (day 1, 8); patients with malignant lymphoma were treated with CHOP chemotherapy: cyclophosphamide 600 mg/m^2 (day 1) + epirubicin 80 mg/m^2 (day 1) + vinpocetine 2 mg/m^2 (day 1) + prednisone 100 mg/m^2 (day 1–5).

2.3. Primary outcome measure

The primary outcome measure was myocardial function: the serum levels of cardiac troponin I (cTnI) and creatine kinase isoenzyme (CK-MB). Echocardiography was performed before the first chemotherapy course (T_1), at the end of the second chemotherapy course (T_2) and 6 months follow-up. Left ventricular ejection fraction (LVEF) and the ratio of mitral annular diastolic peak velocity to atrial systolic velocity (E/A) were measured before the first chemotherapy course (T_1), at the end of the second chemotherapy course (T_2) and 6 months follow-up. Meanwhile, blood samples were collected for the assessment of circulating levels of proinflammatory cytokines (IL-6 and TNF-α), ROS and antioxidant enzymes, glutathione peroxidase (GPx) and superoxide dismutase (SOD). Fasting venous blood (3 mL) was obtained from patients the next morning after admission and on the morning of physical examination for participants in the CG. Serum was obtained after centrifugation of the samples at 2000 r/min for 5 minutes. ROS, IL-6, GPx, SOD, and TNF-α were detected by enzyme-linked immunosorbent assay (ELISA) using the Multiskan Ascent automatic enzyme labeling instrument and ROS, IL-6, GPx, SOD, and TNF-α reagents provided by Genzyme company. The assay procedures were performed in accordance with the kit instructions.

2.4. Criteria for cardiotoxicity

Grade I: the patient had abnormal cardiac signs but no clinical symptoms; grade II: the patient had transient cardiac insufficiency, but no clinical treatment was needed; grade III: the patient has obvious cardiac insufficiency, which needs treatment, and the treatment effect is obvious; grade IV: the patient had obvious cardiac insufficiency and needed treatment, but the treatment was ineffective.

2.5. Statistical analysis

All data were analyzed by SPSS 22.0. Among them (n, %) refers to the calculated data. The comparison of relevant data between groups and within groups was performed by chi square test, and the measurement data was applied (± s). The comparison between groups was conducted by t test, $P < .05$ was the difference with statistical significance.

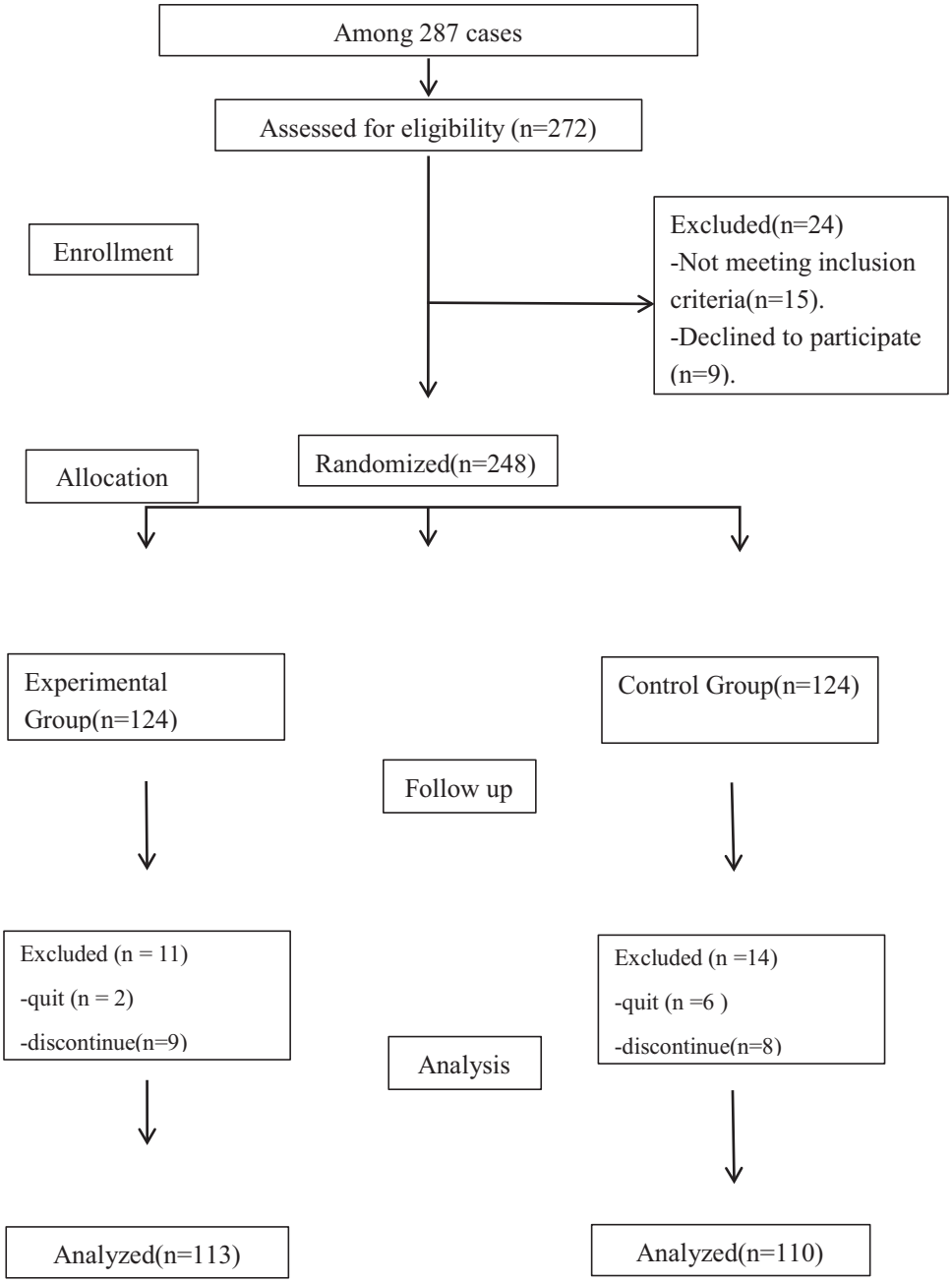

Figure 1. Flow chart showing recruitment through the study.

3. Result

3.1. Participant recruitment

Figure 1 showed the recruitment of participants in our study. We recruited 287 patients in our Hospital, including 272 patients meeting the inclusion and exclusion criteria. The 248 eligible patients enrolled in this study were randomly allocated into 2 groups: the EG (n = 124) or the CG (n = 124). The number of follow-up patients were 223. Eleven participants were quit or discontinue in EG and 14 in CG.

3.2. Clinical characteristics

Table 1 shown characteristics of the participants. The research included 223 patients after follow-up, involved 113 patients in EG, a mean age (57 ± 4.6) years old, while in CG, a mean age (58 ± 4.37) years old. The BMI in EG was 17.15 ± 2.03 kg/m^2, and in CG was 18.25 ± 1.87 kg/m^2, there was no statistical significance between 2 group (P = .09, >.05). The tumor type of breast cancer in EG was 65 (57.5%), and malignant lymphoma in EG was 48 (42.5%), while the tumor type of breast cancer in CG was 59 (53.6%), and malignant lymphoma in CG was 51 (46.4%), there was no statistical difference between 2 group (P = .72, >.05).

3.3. Comparison of cTnI and CK-MB at different time periods between 2 groups

As shown in Table 2, Figures 2 and 3, there was no significant difference in cTnI and CK-MB levels between the 2 groups (P > .05) before the first chemotherapy course (T_1). The levels of cTnI and CK-MB in the EG were significantly lower than those in the CG (P < .05) at the end of the second chemotherapy course (T_2) and 6 months follow-up.

Table 1

Clinical characteristics of chemotherapy patients in EG and in CG.

	EG (n = 113)	CG (n = 110)	t/X²	*P*
Age (yrs)	57 ± 4.6	58 ± 4.37	0.45	.54
Sex				
Male (n%)	52 (46%)	47 (42.7%)	2.68	.68
Female (n%)	61 (54%)	63 (52.3%)		
BMI (kg/m²)	17.15 ± 2.03	18.25 ± 1.87	6.39	.09
Tumor type				
Breast cancer	65 (57.5%)	59 (53.6%)	6.96	.72
Malignant lymphoma	48 (42.5%)	51 (46.4%)		

Significant difference as $P < .05$.

CG = control group, EG = experimental group.

Table 2

Comparison of cTnI and CK-MB at different time periods between 2 groups.

	EG group (n = 113)	CG group (n = 110)	t	*P*
cTnI (μg/L)				
T_1	0.088 ± 0.02	0.089 ± 0.010	5.892	.089
T_2	0.101 ± 0.03	0.112 ± 0.012	4.967	.042
6 mo follow-up	0.125 ± 0.014	0.212 ± 0.053	8.135	.001
CK-MB(μg/L)				
T_1	13.231 ± 2.331	12.391 ± 4.360	7.539	.327
T_2	13.661 ± 2.152	17.365 ± 4.123	9.324	.013
6 mo follow-up	16.322 ± 3.120	21.232 ± 4.685	11.273	.00001

Significant difference as $P < .05$.

CG = control group, CK-MB = creatine kinase isoenzyme, cTnI = cardiac troponin I, EG = experimental group, T_1 = before the first chemotherapy course, T_2 = at the end of the second chemotherapy course.

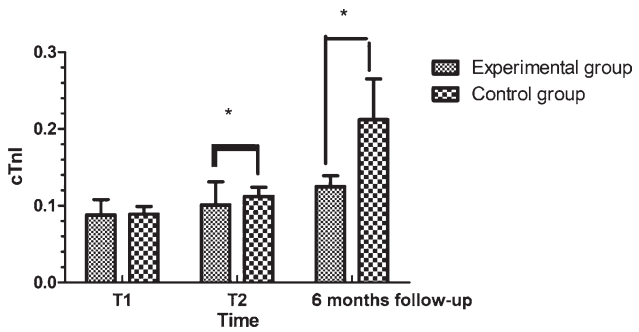

Figure 2. Comparison of cTnI at different time periods between 2 groups. **P* < .05. cTnI = cardiac troponin I.

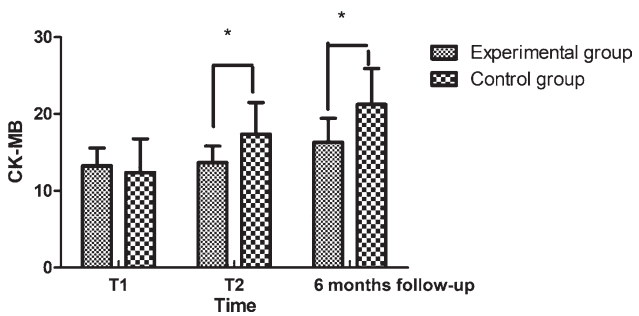

Figure 3. Comparison of CK-MB at different time periods between 2 groups. **P* < .05. CK-MB = creatine kinase isoenzyme.

Table 3

Comparison of LVEF and E/A at different time periods between 2 groups.

	EG group (n = 113)	CG group (n = 110)	t	*P*
LVEF				
T_1	65.33 ± 8.12	65.26 ± 7.15	2.167	.49
T_2	63.86 ± 7.54	64.02 ± 8.36	7.842	.046
6 mo follow-up	62.36 ± 9.25	58.12 ± 8.27	9.326	.0002
E/A				
T_1	1.21 ± 0.21	1.21 ± 0.11	4.239	.792
T_2	1.20 ± 0.14	1.91 ± 0.33	7.924	.033
6 mo follow-up	1.16 ± 0.25	1.12 ± 0.31	14.273	.037

Significant difference as $P < .05$.

CG = control group, E/A = trial systolic velocity, EG = experimental group, LVEF = Left ventricular ejection fraction, T_1 = before the first chemotherapy course, T_2 = at the end of the second chemotherapy course.

3.4. Comparison of LVEF and E/A at different time periods between 2 groups

There was no significant difference in LVEF and E/A between the 2 groups before the first chemotherapy course (T_1) and at the end of the second chemotherapy course (T_2); while LVEF and E/A levels in the EG were significantly higher than those in the CG ($P < .05$) at 6 months follow-up (Table 3).

3.5. Comparison of incidences of cardiotoxicity between 2 groups

Number of grade I cardiotoxicity in EG was 9 (8%), grade II was 6 (5.3%), grade III was 2 (1.8%), and none happened grade IV cardiotoxicity in EG. Meanwhile, number of grade I cardiotoxicity in CG was 23 (20.9%), grade II was 15 (13.6%), grade III was 18 (16.4%), and grade IV was 10 (9.1%). There was obviously significant difference between the 2 groups ($P < .05$) (Table 4).

3.6. Comparison of inflammation and oxidative stress markers at different time periods between 2 groups

As shown in Table 5, the level of TNF-α, GPx, and SOD did not show significant difference in any of the 2 groups throughout the study ($P > .05$) (Table 5). The ROS show significant difference between 2 groups at 6 months follow-up ($P < .05$) (Fig. 4), and the level of IL-6 also had significant difference between 2 groups the end of the second chemotherapy course (T_2) and 6 months follow-up ($P < .05$) (Fig. 5).

4. Discussion

Epirubicin is one of the anthracycline anticancer drugs, which was widely used in blood and solid tumors because of its wide antitumor spectrum and strong anticancer effect. However, its clinical application is severely limited by nausea, vomiting, bone marrow suppression, especially various cardiac toxicity. At present, the mechanism of cardiotoxicity induced by epirubicin is unclear, which may be related to the dosage and course of treatment. Long term use of epirubicin may cause lipid peroxidation, resulting in the dysfunction of Ca^{2+}—ATP pump conversion.[21] A study research indicated that epirubicin-induced myocardial dysfunction detected early by serial tissue Doppler echocardiography has been correlated with oxidative stress markers with an unchanged LVEF during epirubicin chemotherapy.[22]

Cardiac troponin I (cTnI) and cardiac creatine isoenzyme (CK-MB) are special markers of myocardial cell injury. They have high specificity and sensitivity in the diagnosis of myocardial failed. They can accurately reflect the cardiotoxicity caused

Table 4

Comparison of incidences of cardiotoxicity between 2 groups.

	EG group (n = 113)	CG group (n = 110)	t	*P*
Incidences of cardiotoxicity				
I	9 (8%)	23 (20.9%)	19.673	.00001
II	6 (5.3%)	15 (13.6%)		
III	2 (1.8%)	18 (16.4%)		
IV	0	10 (9.1%)		

Significant difference as $P < .05$.

I: the patient had abnormal cardiac signs but no clinical symptoms; II: the patient had transient cardiac insufficiency, but no clinical treatment was needed; III: the patient has obvious cardiac insufficiency, which needs treatment, and the treatment effect is obvious; IV: the patient had obvious cardiac insufficiency and needed treatment, but the treatment was ineffective.

EG = experimental group, CG = control group.

Table 5

Comparison of inflammation and oxidative stress markers at different time periods between 2 groups.

	EG group (n = 113)	CG group (n = 110)	t	*P*
TNF-α				
T_1	23.21 ± 9.4	24.11 ± 7.15	1.958	.26
T_2	25.73 ± 10.16	25.57 ± 9.36	5.243	.84
6 mo follow-up	27.12 ± 8.9	28.21 ± 7.17	4.516	.09
GPx				
T_1	7425 ± 2187	7386 ± 3042	2.139	.31
T_2	7137 ± 2933	6998 ± 1553	9.514	.07
6 mo follow-up	6482 ± 2132	6423 ± 3018	3.973	.89
SOD				
T_1	125.2 ± 42.7	130.2 ± 9.3	16.634	.19
T_2	141.2 ± 41.1	139.8 ± 20.9	3.246	.48
6 mo follow-up	154.8 ± 38.8	155.9 ± 40.3	7.673	.32

Significant difference as $P < .05$.

CG = control group, EG = experimental group, GPx = glutathione peroxidase, SOD = superoxide dismutase, T_1 = before the first chemotherapy course, T_2 = at the end of the second chemotherapy course.

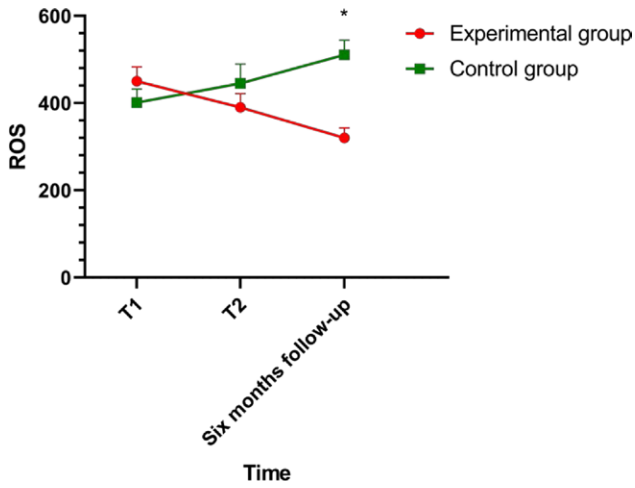

Figure 4. Comparison of ROS at different time periods between 2 groups. ROS = reactive oxygen species.

by anthracyclines of epirubicin. During chemotherapy, the levels of cTnI and CK-MB in blood are significantly correlated with the cumulative dose of anthracyclines.[23] The results of the present study indicate, in the CG (epirubicin chemotherapy), the level of cTnI and CK-MB were raised compared with before chemotherapy (T_1), moreover, echocardiography showed that

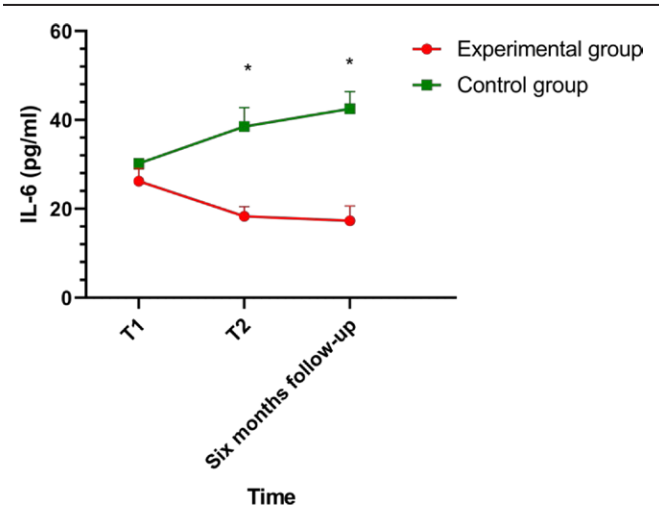

Figure 5. Comparison of IL-6 at different time periods between 2 groups.

LVEF and E/A ratio decreased significantly compared with T_1, that result showed that epirubicin caused severe myocardial injury.

Astragalus injection plays an important role in scavenging oxygen free radicals, improving myocardial function, enhancing immune function, antitumor, and reducing side effects of drugs. In our research, astragalus injection could prevent myocardial injury induced by epirubicin. The level of cTnI and CK-MB were decreased in treatment with astragalus injection compared with the CG at T_2 and 6 months follow-up ($P < .05$), and LVEF and E/A ratio increased significantly compared with the CG at T_2 and 6 months follow-up ($P < .05$). Moreover, the result of ROS and IL-6 were improved in the EG compared with the CG ($P < .05$). ROS is defined as oxidative stress, and significant increases in generation of ROS (a collective name for hydrogen peroxide, superoxide, and hydroxyl radicals) in cardiomyocytes, as well as serum concentrations, have been reported in epirubicin-induced cardiotoxicity.[24,25] ROS are excessively generated from a likely mitochondrial source, then hasten lipid peroxidation and DNA damage, and consequently initiate cell apoptosis or necrosis.[26] Astragalus polysaccharides administration has been reported to significantly increase the activity of antioxidant enzymes and decrease the lipid peroxides in the serum and liver of mice.[27] It can markedly improve the activity of T-AOC and SOD in the plasma of weaned lambs,[28] significantly enhance superoxide dismutase, catalase, and glutathione peroxidase, and demonstrate antihydroxyl radical activity in aging mice liver.[28] Furthermore, astragalus polysaccharides could provide a cardioprotective effect by decreasing the formation of lipid peroxides.[29] Zahran et al[30] stated that AP supplementation in the diet of *Oreochromis niloticus* up-regulated the activity of both superoxide dismutase and glutathione peroxidase. The reason maybe that astragalus polysaccharide could improve energy metabolism and reduce myocardial injury by eliminating free radicals, increasing catalase activity, decreasing lipid peroxidase content, and increasing ATP content. However, astragalus polysaccharides administration in the present study did not significantly improve the activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD), the reason, we deduced that astragalus polysaccharides may be produce antioxidant activity by other ways, such as via the endoplasmic reticulum stress pathway,[31] macrophage activation[32] or relieve oxidative damage to mtDNA.[27]

Up to now, the use of traditional antioxidants such as vitamin C, vitamin E, coenzyme Q10, and acetylcysteine, or cardioprotective drugs such as angiotensin-converting enzyme inhibitor

and angiotensin receptor blocker have shown little cardioprotective effects against epirubicin-induced cardiotoxicity both in vivo and in vitro.[33–35] Thus far, only dexrazoxane has been shown to exert cardioprotective effects.[36,37] However, multiple studies have reported various side effects associated with dexrazoxane, including an increased risk of secondary malignancy and compromising antitumor effects of chemotherapy, which has limited its clinical use.[38–40] Astragalus polysaccharide has been used for years in traditional Chinese medicine to treat cardiovascular diseases including coronary heart disease and HF. Astragalus polysaccharide has been shown to improve heart function and ameliorate cardiovascular symptoms, such as palpitations, shortness of breath, and chest pain.[41,42] In addition, astragalus polysaccharide extracts have stronger antioxidant effects compared with conventional antioxidants. Particularly, astragalus polysaccharide could reduce ROS formation and lipid peroxidation, which showed in our research. Hence, astragalus polysaccharide-mediated reduction of oxidative stress may be the main mechanism by which astragalus polysaccharide contributes to the prevention of epirubicin-induced cardiotoxicity.

One clear weakness of our current study is the small single center study. Particularly, the difficulties in enrolling patients were related to limits on the strict entry criteria. On the other hand, although our results are promising, the explanation is limited by the self-control designed study. These interpretations prompted the need for a larger, placebocontrolled, perspective study to investigate its potential mechanism in vivo and in vitro.

Our pilot study demonstrated that astragalus polysaccharide can provide a protective effect against epirubicin-induced cardiotoxicity in patients with breast cancer or malignant lymphoma, and the protective effects provided by astragalus polysaccharide may be explained by its reduction of oxidative stress. Moreover, further research are needed to investigate its potential mechanism.

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