Gualou-Xiebai-Banxia decoction protects against type II diabetes with acute myocardial ischemia by attenuating oxidative stress and apoptosis via PI3K/Akt/eNOS signaling

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[ABSTRACT] Gualou-Xiebai-Banxia decoction has a long history of medical use for treating cardiovascular diseases in China. In this study, we investigated the protective effect and underlying mechanisms GXB in type II diabetes with acute myocardial ischemia (T2DM-AMI) rats. We hypothesized that GXB may display its protective effect on T2DM-AMI by reducing endothelial progenitor cells (EPCs) apoptosis via activating PI3K (phosphatidyl inositol 3-kinase)/Akt (serine/threonine protein kinase B)/eNOS (endothelial nitric oxide synthase) signaling. Rats were challenged with a high-fat diet and intraperitoneal injection of streptozotocin to induce a model of type II diabetes mellitus (T2DM) and coronary ligation to induce acute myocardial infarction (AMI). Changes in metabolites were assessed via enzyme-linked immunoassay and biochemical examination. The number and apoptosis rate of EPCs in peripheral blood were detected by flow cytometry. Target mRNAs and proteins in EPCs were analyzed by RT-PCR and Western blot analysis. The results demonstrated that GXB treatment decreased T2DM-AMI-associated changes in plasma fasting blood glucose, muscular enzymes, and blood lipids, and reduced oxidative stress. Furthermore, EPC apoptosis was increased in T2DM-AMI rats and was associated with decreased mRNA and protein levels of PI3K, Akt, and eNOS compared to the controls. Conversely, T2DM-AMI rats treated with GXB exhibited more circulating EPCs and downregulated levels of cell apoptosis, combined with increased mRNA and protein levels of PI3K, Akt, and eNOS compared to those of untreated T2DM-AMI rats. Our study showed that GXB treatment mitigated EPC apoptosis and promoted PI3K/Akt/eNOS signaling in T2DM-AMI rats.

[KEY WORDS] Gualou-Xiebai-Banxia decoction; Endothelial progenitor cells; Type 2 diabetes; Acute myocardial ischemia; PI3K/Akt/eNOS


Introduction

Ischemic heart disease is a leading cause of death worldwide. Chronic metabolic diseases, such as type II diabetes mellitus (T2DM), induce a 2–4-fold increased probability of developing ischemic heart disease. Thus, there is an urgent need to better understand the mechanisms that link these diseases and to discover and develop treatments to lessen implicated organ injuries [1].

Endothelial progenitor cells (EPCs) are precursors of vascular endothelial cells and can repair damaged blood vessels [2]. EPCs reside in the bone marrow of adult animals, with a portion eventually moving into the circulation (termed CEPCs) to promote the healing of injured blood vessels [3]. Importantly, dysfunctional EPCs may promote the development of cardiovascular diseases (CVDs); meanwhile, EPC numbers have been reported to be reduced in certain CVDs and in conditions of metabolic dysregulation, such as hyperglycemia [4]. However, the mechanism of hyperglycemia and hyperlipidemia reducing EPCs in patients with T2DM and myocardial infarctions remain unclear.

Reactive oxygen species (ROS) generated by oxidative stress plays a key role in the development of diabetes and CVD, and may decrease EPC function in both experimental models and humans [5]. An elevated level of ROS is the major risk factor of vascular endothelial dysfunction and increase of endothelial permeability. Bone marrow-derived circulating EPCs play a critical role in repairing damaged en-
dothelium. Furthermore, there is increasing evidence that the accumulation of ROS is associated with the mobilization of functional defective EPCs, which impairs injury-mediated neovascularization and may result in an increase in ischemic complications [7]. The purpose of our experiment is to study whether GXB treatment can protect EPC from oxidative damage, and improve its function in endothelial repair sites.

Gualou-Xiebai-Banxia decoction [GXB, be consist of Gualou (Trichosanthis Fructus), Xiebai (Allii Macrostemonis Bulbus), and Banxia (Pinelliae Rhizoma Praeparatum)] comes from Jin Gui Yao Lue (Medical Treasures of the Golden Chamber) written by ZHANG Zhong-Jing, a famous medical practitioner of the Eastern Han Dynasty. GXB has been reported to promote “yang energy” and remove obstruction, eliminate phlegm, and soothe chest oppression, and is widely used to treat chest stuffiness and other cardiovascular diseases in China [8-9]. There is also increasing evidence that GXB may be efficacious for coronary heart disease. Experimental studies demonstrated that GXB can significantly ameliorate atherosclerosis and improve ischemia-reperfusion injury, and thus improve myocardial function [10]. However, the underlying mechanism of GXB remains unclear. We have previously shown that GXB can alter oxidative stress in rats after acute myocardial infarction (AMI) [11]. We have also demonstrated that GXB display its protective effect on AMI and T2DM-AMI rats by enhancing the mobilization of EPCs [12-13]. In the present study, we tested the hypothesis that GXB would attenuate T2DM-AMI-associated oxidative stress and EPC apoptosis, and upregulate PI3K/AKT/eNOS signaling.

Materials and Methods

Reagents

An anti-CD34 PE-Cy7-conjugated monoclonal antibody was obtained from Santa Cruz Biotechnology (Shanghai), China. FITC-labeled mouse anti-rat VEGFR-2 polyclonal antibody, mouse anti-rat GAPDH monoclonal antibody, and HRP-labeled goat anti-mouse and goat anti-rabbit polyclonal IgGs were purchased from Abcam (Cambridge, MA, USA; ab184903, ab9484, ab6789, ab6721, respectively). Rabbit anti-rat PI3K-P110α, Akt, eNOS, phospho-PI3K, phospho-Akt, and phospho-eNOS polyclonal antibodies were obtained from Affinity Biosciences (Changzhou, China; AF5112, AF6261, AF0096, AF4369, AF0016, AF3247, respectively). The APC Annexin V-PI apoptosis detection kit was purchased from Bio. Legend (Beijing, China; 640932). A Universal RNA Extraction Kit, PrimeScript RT reagent Kit with gDNA Eraser (Perfect Real Time), and Power SYBR Green Master Mix were obtained from Takara Holdings (Kyoto, Japan; 9767, RR047A, RR820A, respectively). Enzyme-linked immunosorbent assay (ELISA) kits for detecting advanced glycation-end products (AGEs), oxidized low-density lipoprotein (ox-LDL), myeloperoxidase (MPO) levels in the plasma were purchased from Bio-Swamp (Wuhan, China; RA20685, RA20455, RA20325, respectively). ELISA kits for detecting nitrate/nitrite (NOx), thioredoxin (Trx), and xanthine oxidase (XO) plasma levels were purchased from Cayman Chemical (Ann Arbor, MI, USA; 780001), LifeSpan BioSciences (Seattle, WA, USA; LS-F54051), and Biovision (San Francisco, CA, USA; K710-100, respectively). Total cholesterol (TC), total triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), creatine kinase (CK), and creatine kinase isoenzyme (CK-MB) commercial kits were purchased from Nanjing Jiancheng, China (A111, A110, A112, A113, A032, E006, respectively). Enhanced chemiluminescence reagent was purchased from Millipore, USA (WBKLS0500). All other reagents were ultrapure grade.

Traditional Chinese medicinal materials

Gualou, Xiebai, and Banxia were purchased from Shandong University of Traditional Chinese Medicine (SDUTCM) affiliated hospital. The herbal medicines were identified and assessed by the Herbal Identification Staff Room within the School of Pharmaceutical Sciences at Shandong University of TCM.

GXB was prepared as follows. First, 240 g of dry Trichosanthis Fructus, 90 g of dry Allii Macrostemonis Bulbus, and 120 g of dry Pinelliae Rhizoma Praeparatum were placed in a 10 L flask with a round bottom. Then, 4.5 mL of distilled water was added to soak the herb materials for 60 min. Subsequently, the herbal medicine was heated under reflux for 1 h. The decoction, while still hot, was then poured into a beaker. Next, 3.6 mL of preheated distilled water was added to the flask and the herbal materials were heated under reflux for 1 h. To merge with the decoction from the first round of heating, the second decoction was also poured out into the same beaker while hot. Vacuum filtration was carried out on the merged decoction. The filtered liquor was condensed by heating in a water bath until the amount of retained liquid was approximately 225 mL, with the final concentration of the crude herb materials being roughly 2 g·mL⁻¹ (ratio 1 : 2). The decoction was given to rats through gavage for 10 days. Pilot experiments showed that the optimal dose of decoction was 10 mL/kg of bodyweight.

Preparation of high-fat emulsion

A high-fat emulsion (HFE) was prepared as reported previously [12]. Cholesterol (80 g), sodium deoxycholate (16 g), and methylthiouracil (8 g) were added sequentially to melted lard (160 g) in a 2 L beaker and were thoroughly mixed. Tween-80 (160 mL) was added to the mixture. Propylene glycol (160 mL) and distilled water (240 mL) were added to another 500 mL beaker and were mixed at 60 °C in an electric oven. Subsequently, the two components were mixed to prepare a HFE, which was then stored at 4 °C. Pilot experiments showed that, for the establishment of a hyperlipidemia model in rats, the optimal dose of HFE was 10 mL/kg bodyweight.

Animals

Animal studies were conducted in accordance with the
 standards and guidelines established by the Guide for the Care and Use of Laboratory Animals formulated by the National Institutes of Health (China), and were approved by the Institutional Committee for Animal Care and Use of Shandong University of Traditional Chinese Medicine (No: DWSY200710227). All efforts were made to minimize animal distress and the number of animals used. Experiments were conducted on male Wistar rats (220–250 g, SPF) obtained from the Lunan Animal Experimental Center (SCXK (LU) 20130001, Shandong Province, China), and were housed under 23–25 °C, 35%–65% room humidity, and a 12-h light/dark cycle (lights on at 06:00), with access to food and water provided ad libitum. Animals were habituated to laboratory conditions for at least one week before testing. The health and general behavior of each rat was assessed daily.

**Rat model of T2DM-AMI**

As we reported previously [13], we used the method of HFE intragastric + intraperitoneal injection of small dose streptozotocin (STZ) to construct the T2DM rats, and selected successful rats to perform coronary artery ligation. The model of T2DM-AMI was established via three stages, details of the experimental groups are presented in Fig. 1.

**Hyperlipidemia**

To induce hyperlipidemia, rats were gavaged daily with HFE (10 mL·kg\(^{-1}\)) for three weeks. On the 14th and the 21st days following HFE administrations, rats were anaesthetized, venous blood was collected from the inner canthus, and the plasma contents of TC, TG, HDL-C, and LDL-C were measured via commercial kits. Rats with TC ≥ 3.0 mmol·L\(^{-1}\), TG ≥ 2.5 mmol·L\(^{-1}\), LDL ≥ 1.50 mmol·L\(^{-1}\), and HDL ≤ 0.50 mmol·L\(^{-1}\) were defined as hyperlipidemic.

**T2DM**

After the successful establishment of hyperlipidemia, that is, the 22nd day, rats were given STZ for 3 days at 40 mg·kg\(^{-1}\) via intraperitoneal injection, and then rats were fasted for 18 h on the 25th day to measure fasting blood glucose (FBG) levels. During oral-glucose tolerance testing (OGTT), rats were given glucose water (2 g·kg\(^{-1}\)), and 2 h later post-prandial blood glucose (PBG) was measured. Rats with a FBG > 10 mmol·L\(^{-1}\) or a PBG > 16.7 mmol·L\(^{-1}\) were classified as diabetic.

**T2DM-AMI**

AMI was induced as described previously [12]. Diabetic rats were anaesthetized with an intraperitoneal injection of 10% chloral hydrate (0.3 mL/100 g) and were then placed on an operating table. A tracheotomy was performed and an intubation cannula was connected to a volume-controlled ventilator. The chest was opened between the left third and fourth inter-costal spaces. Heart rhythms were monitored via electrocardiograms. The left anterior descending artery (LAD) was ligated by a 6-0 silk suture at 1 mm below the tip of the left atrial appendage. Successful ligation was verified by echocardiography and by a color change of the heart and ST segment elevation.

**Flow-cytometric analysis of CEPCs**

EPCs express cluster of differentiation 34 (CD34) and endothelial markers, such as vascular endothelial growth factor receptor 2 (VEGFR-2) [14-15]. In the present study, CEPCs were defined as CD34\(^{-}\)/VEGFR-2\(^{-}\) cells. APC-conjugated Annexin V and a PI assay kit were used to characterize the level of apoptotic CD34\(^{-}\}/VEGFR2\(^{-}\) cells. This assay discriminates between intact (FITC/PI\(^{-}\)), early apoptotic (FITC\(^{-}\)/PI\(^{-}\)), and late apoptotic (FITC\(^{-}\)/PI\(^{-}\)) cells.

To assess cell-surface markers, fresh blood samples anti-coagulated by EDTA-2Na were incubated with PE-Cy7-conjugated anti-CD34 antibody and FITC-conjugated anti-VEGFR-2 antibody. Hemolysin dissolved in distilled water at a final concentration of 10% (V/V) was applied to the blood samples for 10 min. Samples were centrifuged (300 g, 8 min, 4 °C) and subsequently washed with phosphate-buffered saline (PBS). Finally, cells were resuspended in binding buffer and incubated with APC-conjugated anti-Annexin V and PI.

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**Fig. 1** Experimental procedures. Thirty-six male rats were participated in the experiment, and after removing model-failed rats (those that did not meet criteria for T2DM-AMI), the number of rats in the Ctrl, T2DM-AMI and GXB group were 9, 8 and 9 respectively. On the 4th day after coronary artery ligation, rats in each group were sacrificed to be phlebotomized from their celiac artery after being anesthetized by chloral hydrate respectively. FCM, ELSIA, RT-PCR and Western blots analysis were performed respectively, i.g., gavage administration; NS, normal saline; Ctrl, T2DM-AMI, and GXB represents the control, T2DM-AMI model, and GXB groups respectively.
10 min before analysis via flow cytometry. Four-color cytometry analysis of the above samples was performed on a Jass cytometer (Becton Dickinson). Appropriate gate analysis was used for the detection of CEPCs while excluding events from different origins, such as from non-hematopoietic circulating cells and non-specific stained events. For each sample, data were collected from 50 000 cells and results were analyzed with BD FACS software.

In pilot studies, CEPCs were noted to peak on the fourth day after coronary ligation, providing a rationale for the timing of blood sampling in our rat model.

**Enzyme-linked immunosorbent assays**

ELISAs were used to measure the plasma levels of CK, CK-MB, AGEs, ox-LDL, XO, MPO, NOx, and Trx in rats, according to the manufacturer’s instructions. Blood samples were centrifuged for 15 min at 3000 r·min⁻¹. Supernatants were stored at 4 °C for later batch testing.

**Enrichment of CEPCs**

Heparinized blood (5 mL) was used to isolate and quantify circulating EPCs. Mononuclear cells (MNCs) were isolated using Ficoll-Paque density-gradient centrifugation (400 g, 10 min, 20 °C) and were then washed twice with PBS, counted, and resuspended in PBS. Cells were then incubated with PE-conjugated anti-CD34 antibody and PE-conjugated anti-VEGFR-2 antibody, centrifuged (500 g, 5 min, 4 °C), washed with PBS, suspended in binding buffer, incubated with Anti-PE MicroBeads, washed with PBS, suspended in binding buffer, incubated with magnetic beads. Western blotting

Total protein was extracted using a total protein extraction kit and concentrations were determined by a BCA protein assay kit. Total RNA was extracted from CEPCs using the Universal RNA Extraction Kit according to the manufacturer’s instructions and were reversed transcribed to cDNA with the PrimeScript RT reagent Kit with gDNA Eraser (Perfect Real Time). Quantitative PCR was performed in duplicates on the CFX96 Real-Time PCR System using Power SYBR Green Master Mix and gene-specific primers (Table 1). Based on gene sequences published in the GenBank database, primers were designed with Primer 5.0 design software and synthesized by the Shanghai Gene Pharma Co., Ltd. (Shanghai, China). The mRNA levels were normalized by Gadph expression within the same sample and results are reported as fold changes to those of Ctrl rats (2⁻ΔΔCt method).

**Statistical analysis**

Continuous variables are presented as the mean ± standard error of the mean (SEM). For categorical variables, statistical significance was determined by one-way analysis of variance (ANOVA) and post-hoc Bonferroni tests via SPSS Statistics version 19.0 (IBM, USA). A P value of less than 0.05 was considered statistically significant.

**Results**

**GXB treatment decreases T2DM-AMI-induced changes in muscular enzymes**

Changes in CK and CK-MB are sensitive indexes of myocardial damage. CK and CK-MB levels were determined in T2DM-AMI rats with or without GXB treatment. Compared with those of the control group, the plasma levels of CK and CK-MB were higher in T2DM-AMI rats. However, GXB treatment in T2DM-AMI rats was associated with a significant attenuation of the elevated enzyme levels compared to those in untreated T2DM-AMI rats (Fig. 2).

**GXB treatment decreases T2DM-AMI-induced changes in plasma FBG and AGEs**

Both FBG and AGEs are elevated in Diabetes Mellitus. Many changes observed in type 2 diabetes and complication are correlated with the increased FBG and AGEs. Consistent with a protective effect, T2DM-AMI rats treated with GXB showed less elevation in plasma levels of FBG and AGEs compared with those of control and untreated T2DM-AMI rats (Figs. 3A, 3B).

**GXB treatment suppresses T2DM-AMI-associated elevation in blood lipids and ox-LDL**

The severity of coronary artery disease correlates with levels of blood lipids. Compared with those of the control group, T2DM-AMI rat blood TC, TG, LDL, and ox-LDL levels were all significantly higher, whereas HDL levels were lower. Conversely, in T2DM-AMI rats treated with GXB, lip-

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**Table 1** **The primer sequences used in qRT-PCR**

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<thead>
<tr>
<th>Gene</th>
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FP, Forward primer; RP, Reverse primer
Diabetes mellitus is an independent risk factor for CVD and promotes severe myocardial ischemia [19], and diabetic patients with coronary artery disease have increased mortality [20]. EPCs are precursors of vascular endothelial cells and are mobilized from bone marrow to repair injured blood vessels [21-23]. T2DM, hypertension and hypercholesterolemia are linked to reduced EPC function [24]. Furthermore, EPCs have been found to be decreased in some individuals concurrent with endothelial dysfunction [25]. EPCs exhibit impaired proliferation, adhesion, and incorporation into vascular structures under hyperglycemic states [24]. Our present results suggest that multiple factors—including hyperglycemia, hyperlipidemia, and cardiac ischemia—negatively impact EPC mobilization and angiogenic potential. However, defining a dominant or synergistic effect of these processes will require further study.

Nitric oxide (NO) is an important angiogenic and anti-inflammatory biogas produced by healthy endothelial cells to support vascular homeostasis and blood flow. However, ischemia and metabolic/lipid imbalance, all drivers of pathological reactive oxygen species (ROS), limit the pleiotropic effects of NO [28]. Our present results revealed that in rats with both metabolic/lipid imbalance and cardiac ischemia,
CEPCs were fewer in number and were functionally depressed. Based on this finding, it would be interesting to consider if such dysfunctionality in CEPCs would be retained after the correction of metabolic/ischemic processes.

Oxidative stress is associated with higher levels of ROS, such as superoxide anions and hydrogen peroxide, and negatively alters protein structures and cellular homeostasis \[20-27\]. Hyperglycemia, ischemia, and ischemia-reperfusion are associated with ROS elevation \[28\]. In turn, ROS can chemically ablate NO and decrease its beneficial downstream signaling. Certain enzymes, such as NADPH oxidase, XO, and MPO, are sources of pathological ROS \[29\]. Consistent with this pattern, we found alterations in plasma levels of enzymatic ROS sources and alterations in canonical NO pathway targets \(\text{e.g., Akt/eNOS}\) in rats exposed to metabolic and ischemic challenge. T2DM-AMI was associated with increased, whereas GXB treatment was associated with decreased, changes in ROS enzymes. Akt/eNOS plays a pivotal role in protecting EPCs from apoptosis and in improving EPC function \[21,30\]. It remains unknown if our present findings were correlative changes or were proximate causes of CPEC dysfunction.

GXB is a traditional Chinese medicine employed as a prophylactic and treatment of AMI, coronary heart disease, and hyperlipidemia. Our previous studies have conducted a pharmacodynamic study on GXB in the early stage \[31\]. We set the high dose (10 mL·kg\(^{-1}\)) group, the medium dose (5 mL·kg\(^{-1}\)) group and the low dose (2.5 mL·kg\(^{-1}\)) group of GXB, and Danshen injection was set as the positive drug. The indexes such as blood lipid, blood glucose, myocardial enzyme and myocardial infarction area were detected to compare the protective effect of GXB on T2DM-AMI rats, and the optimal concentration of GXB was determined to be 10 mL/kg bodyweight. On this basis, the level of CEPCs in the peripheral blood of T2DM-AMI rats after 7 d of coronary ligation was detected continuously after GXB(1 mL/100 g) intervention, and the dynamic change curve of 7 d was drawn to clarify the mobilization effect of GXB on EPCs \[31\]. The study showed that, the 1 mL/100 g administration dose of GXB can significantly promote the mobilization of CEPCs in the peripheral blood of T2DM-AMI rats, and the number of CEPCs in T2DM-AMI and GXB both peaked on the 4\(^{th}\) day after coronary ligation. Expanding upon these findings, the dose of GXB in this study was set as 10 mL/kg bodyweight, and we selected the 4\(^{th}\) day after coronary ligation to study the effect of GXB on the apoptotic rate of CEPCs in peripheral blood of T2DM-AMI rats. Our present study revealed that GXB treatment had several beneficial effects on CEPCs, including increased circulating cell numbers, upregulation of NO pathway genes, and reductions in apoptosis. Furthermore, it would be useful for future studies to determine if GXB effects are enhanced further via glycemic control and a low-fat diet in our rat model of T2DM-AMI, since single-agent treatments are rarely effective in the clinical setting of chronic CV and metabolic disease.

The present study had some limitations. First, cardiovascular disease and metabolic diseases are common in women, but the included rats were all male and relatively young. Second, since our present study did not include knockout or knock-in experiments, we do not know whether there are any specific gene changes that are sufficient or necessary to ac-
count for the beneficial effects mediated by GXB. In further mechanistic studies, the genetic knock-out and the transgenic animals will be used to verify this hypothesis, and to identify the mechanism underlying the beneficial effect of GXB.

Fig. 6 GXB limited CEPCs apoptosis in T2DM-AMI rats. FACS analysis of blood samples from rats effectively discriminates CEPCs. The mononuclear cells (MNCs) in blood were positively identified as CEPCs by immunofluorescent staining for both CD34 and VEGFR2. APC-conjugated Annexin V and PI assay kits were used to identify the number of apoptotic cells among the above CD34+/VEGFR2+ cells. (A) The parent-child relationship of cells in the P3, P4-Q2 (CD34+/VEGFR2+), and P5-Q2 (Annexin V+/PI+) gates. Cells in the P3, P4-Q2, and P5-Q2 gate represent MNCs, CEPCs, and apoptotic EPCs respectively. (B1) Fluorescence-intensity scatter plots of MNCs in rats from the Ctrl, T2DM-AMI, and GXB group, respectively. Cells in P4-Q2 represent EPCs. (B2) EPC counts per milliliter of blood in each group. Compared with T2DM-AMI group, CEPC numbers were increased in GXB group. (C1) Fluorescence-intensity scatter plots of EPCs in rats from the Ctrl, T2DM-AMI, and GXB groups. Cells in P5-Q2 represent apoptotic EPCs. (C2) The apoptotic rate of EPCs in each group. Apoptotic CEPCs were reduced in T2DM-AMI rats following GXB treatment. Ctrl, T2DM-AMI and GXB represent the control, T2DM-AMI model, and GXB group respectively. Data were shown as mean ± SD (n = 8). *P < 0.05, **P < 0.01 vs model group.
Conclusion

T2DM-AMI-associated CEPCs apoptosis were attenuated by the traditional Chinese medicine, GXB. We also found that the efficacy of GXB in T2DM-AMI rats was associated with improved NO pathway activation and less pathological ROS. Moreover, further studies are warranted to elucidate the in vivo implications of GXB treatment in terms of ameliorating metabolic and ischemic diseases.

References


[10] Chen M, Li M, Ou L, et al. Effectiveness and safety of Chinese herbal medicine formula Gualou Xiebai Banxia (GLXBBX) de-


