

# Effectiveness and safety of XiaoBai granule and Losartan Potassium for the reduction of albuminuria in patients with Chronic Glomerulonephritis (CKD stage 1-2) a multicenter, randomized, double-blind, controlled clinical trial

**Meijie Yuan**

Shanghai University of Traditional Chinese Medicine

**Yi Wang**

Shanghai University of Traditional Chinese Medicine

**Xiaolu Qu**

Shanghai University of Traditional Chinese Medicine

**Qinghua Zhou**

Shanghai University of Traditional Chinese Medicine

**Xiuhua Mi**

Shanghai University of Traditional Chinese Medicine

**Xuezhong Gong**

Shanghai University of Traditional Chinese Medicine

**Guoxin Wang**

Shanghai University of Traditional Chinese Medicine

**Yanying Shen**

Shanghai University of Traditional Chinese Medicine

**Yimei Hu**

Shanghai University of Traditional Chinese Medicine

**Chaoyang Ye**

Shanghai University of Traditional Chinese Medicine

**Chen Wang**

chenwang42@163.com

Shanghai University of Traditional Chinese Medicine

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## Research Article

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# Abstract

**OBJECTIVE:** To evaluate the effectiveness and safety of XiaoBai granule and losartan potassium (LP) in patients with CGN (CKD stage 1-2).

**METHODS:** Totally 160 patients who underwent CGN (CKD stage 1-2) between June, 2020 and July, 2022 in 9 hospitals in Shanghai were assigned (1:1) to treatment group (XBG + LP) and control group (XBG placebo + LP) for 6 months. The primary outcome was the change in 24-hour urinary total protein quantity (24hUTP) over 6 months. The secondary outcomes were composite of Traditional Chinese Medicine (TCM) symptom scores, renal function, and renal tubular injury signature. Meanwhile, the safety of the study was evaluated.

**RESULTS:** Altogether 74 patients in control group and 78 patients in treatment group were included in the final analysis. Compared to the control group, the treatment group had a significant decrease in 24hUTP, improved renal function and TCM symptom scores over the 6 months with statistically significant differences ( $p \leq 0.001$ ). Besides, the 24hUTP was positively correlated with urine N-acetyl- $\beta$ -D-amino glucoside (NAG) and urine retinol-binding protein (RBP) ( $p \leq 0.001$ ). During the study, no side effects were observed in either group.

**CONCLUSION:** The combination of XBG with LP was found to be safe and more effective in improving albuminuria and protecting renal function than LP alone. Traditional Chinese medicine can enhance the effectiveness of Western medicine in the treatment of CGN.

## 1. INTRODUCTION

Chronic glomerulonephritis (CGN) is currently a public health problem requiring urgent global attention. The latest cross-sectional study of a nationally representative sample of Chinese adults showed that the prevalence of CKD was 8.2%; of these, 73.3% was at CKD stage 1–2<sup>1</sup>, and albuminuria prevalence was 6.7%<sup>2</sup>. In recent years, with the aging of the population and the increasing prevalence of diabetes and hypertension, the prevalence of CGN has been increasing significantly<sup>3</sup>. Due to the insidious onset and mild symptoms of CGN, it is easy to be neglected and will eventually progress to end-stage renal disease (ESRD) if early intervention is not timely<sup>4</sup>. And among the various causes of ESRD<sup>5</sup>, CGN accounted for 57.4% and ranked first<sup>1</sup>. Uncertainty about the prognosis and potential progression of CGN places a huge financial and psychological burden on patients.

Albuminuria is one of the main symptoms of CGN, which directly affects the prognosis of CGN. The glomerular filtration barrier consists of three layers, breaking down any renal filtration barrier can lead to the loss of albumin (Alb) from renal capillaries to urine. The permeability of the renal filter is modulated through compression of the capillary wall; morphological alterations of the glomerular filtration barrier lead to reduced compressive forces that counteract filtration pressure, resulting in capillary dilatation, and ultimately albuminuria<sup>6</sup>. Albuminuria is an independent worsening factor of progressive hyperalgesia, and is linearly associated with renal outcome<sup>7</sup>. The mainstay of medical management to prevent CGN is angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blockade (ARB), which prevent and delay the progressive deterioration of renal function, while its toxic side effects should not be underestimated<sup>8,9</sup>.

TCM has a recorded history of over 2000 years that may be used in the treatment of CKD<sup>10</sup>. The limitations of managing CGN drive many patients to seek Chinese herbal medicine (CHM). Although evidence for the renoprotective benefits of CHMs has been gradually accumulating<sup>11,12</sup>, there are few high-quality studies in CGN (CKD stage 1–2). The Xiao Bai granule (XBG) is a herbal prescription developed for the treatment of CGN (CKD stage 1–2) in the 2000s in the Department of Nephrology of Shuguang Hospital, Shanghai University of Traditional Chinese Medicine<sup>13</sup>. In the past 50 years, our group has focused on the basic and clinical research of CGN, including animal<sup>14,15</sup> and clinical experiments. A previous study by our group showed an association between XBG use and the preservation of CGN by reducing albuminuria<sup>16</sup>. In addition, XBG combined with hydroxychloroquine sulfate has a synergistic effect in reducing urinary protein excretion in patients with IgA Nephropathy (IgAN)<sup>17</sup>.

The current situation of CGN in China mainly relies on empirical data, and few randomized controlled trials (RCTs) have been conducted. Previous studies indicated that XBG could be effective in improving albuminuria. With the aim of finding a novel treatment project for CGN (CKD stage 1–2) to increase the clinical curative effect, reduce the presumed side effects, and improve the clinical benefit for patients, we attempt to design this trial to evaluate the efficacy and safety of XBG in renal progression.

## 2. METHODS

### 2.1. Study objectives

This study was a multicenter, randomized, double-blind, controlled clinical trial. The study has been done at 9 hospitals from June 6, 2020, to July 14, 2022. The primary objective of the present study was to assess the efficacy and safety of XBG combined with LP in CGN (CKD stage 1-2) so as to enhance the therapeutic effect of reducing albuminuria and provide a reliable evidence-based rationale for applying TCM in treating CGN (CKD stage 1-2). This study has been registered on the Chinese Clinical Trial Registry (Registration number: ChiCTR2000033666) and was approved by the Medical Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine (No. 2019-703-58-01). Signed informed consent was obtained from all patients. All procedures were conducted in accordance with the Good Clinical Practice and the Declaration of Helsinki. The trial registration information is publicly available on the Chinese Clinical Trial Registry website (<https://www.chictr.org.cn/>).

### 2.2. Participants

This study recruited 160 patients at nine hospitals in Shanghai: 30 patients (15 in the treatment group and 15 in the control group) each in Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai

University of Traditional Chinese Medicine, and Shanghai Municipal Hospital of Traditional Chinese Medicine. 16 patients (8 in the treatment group and 8 in the control group) each in Punan Branch of Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai Baoshan Integrated traditional Chinese and Western Medicine Hospital, and Shanghai Pudong New Area People's Hospital. 6 patients (3 in the treatment group and 3 in the control group) each in Shanghai Xuhui District Changqiao Street Community Health Service Center, Yingbo Community Health Service Center in Pudong New Area, and Shanghai Pudong New Area Tangqiao Community Health Service Center. The patients were mainly from the nephrology outpatient and inpatient departments. The patients were diagnosed with CGN (CKD stage 1-2) and with TCM patterns of spleen and kidney deficiency, damp-heat, and blood stasis. To be enrolled in the trial, potential participants must meet the inclusion and exclusion criteria listed below.

### 2.3.Diagnostic criteria for CGN

CGN is associated with immune-mediated inflammatory chronic diseases<sup>19</sup>. Patients with abnormal urinalysis (proteinuria, hematuria), with or without oedema and a history of hypertension for more than three months should be considered, regardless of the presence or absence of renal impairment. After excluding secondary or hereditary CGN, they can be clinically diagnosed with CGN. For patients with CGN, the estimated glomerular filtration rate (eGFR) should be  $\geq 60$  ml/min/1.73 m<sup>2</sup>.

### 2.4.Diagnostic criteria for TCM pattern syndrome differentiation

According to the Guidelines for Clinical Research of Chinese Medicine (New Drug)<sup>20</sup>, a patient must have at least two of the primary symptoms and more than two of the secondary symptoms listed below that can be diagnosed with spleen and kidney deficiency, damp heat, and blood stasis.

Evidence of Spleen and Kidney Qi Deficiency: (1) Primary signs and symptoms: lack of energy and laziness, fatigue, edema of the face or limbs, back and knee soreness, anorexia; (2) Secondary symptoms: abdominal fullness and distension, diarrhea; (3) Tongue and pulse: the tongue is light red with a thin white coating, bordered by teeth marks, and the pulse is thready.

Damp Heat pattern: (1) primary signs and symptoms: swelling of the face or limbs, nausea or vomiting, scanty dark urine, faint and sticky mouth, and sore throat; (2) secondary symptoms: bitter mouth or thirst without desire to drink, dullness and stuffiness; (3) tongue and pulse: yellowish tongue coating and moist or slippery pulse.

Blood Stasis Pattern: (1) primary signs and symptoms: darkish, the pain in the lumbar spine is fixed, or the pain is pinprick-like in nature; (2) secondary symptoms: the skin is dry and rough, difficult to touch, visible as fish scale manifestations, or numbness of the extremities; (3) tongue and pulse: purple tongue or petechiae, tortuous veins under the tongue, astringent or unsmooth pulse.

All patients met the following inclusion criteria: (1) adult subjects with a diagnosis of CGN(CKD stage 1-2) as described above and with a TCM diagnosis of the spleen and kidney deficiency, damp heat or blood stasis pattern; (2) aged 18–65 years; (3)  $eGFR \geq 60$  ml/min/1.73 m<sup>2</sup>; (4)  $0.5g/24h \leq 24hUTP \leq 2.5g/24h$ ; (5) effective control of hypertension(BP:130-100/80-60mmHg); (6) blood potassium at normal levels; (7) signed informed consent form.

Patients were excluded according to the following criteria: (1) unable or unwilling to participate in the study; (2) applied hormones and immunosuppressants within the last 3 months; (3) non-primary kidney disease; (4) pregnant and lactating women; (5) probable, highly likely, or definite allergy to any of the ingredients in the test drug; (6) participating in or having participated in other clinical trials within 3 months.

Participants will be withdrawn from the study if: (1) they violate any of the key criteria for inclusion or exclusion; (2) they refuse to continue to participate or withdraw their consent; (3) they undergo a serious adverse event (SAE); (4) the principal investigator or co-investigators judge that they need to be withdrawn from the study.

### 2.5.Randomization and blinding

A total of 160 patients were consecutively enrolled between June 2020 and July 2022. Potential trial participants fulfilling the inclusion criteria were recruited consecutively. The included patients were randomly assigned to two groups at a ratio of 1:1 (using SAS software 9.4, SAS Institute, Cary, NC, USA) by the Clinical Research Centre for Design Measurement and Evaluation from Shanghai University of Chinese Medicine. Randomization was blinded and stratified by site. The randomization number table, drug coding, and emergency envelopes were made into random cards, put in small sealed Envelopes, and given an identification number. The schedules will be sent to Tianjiang Pharmaceuticals Co., Ltd. For drug packaging and preparation of the code break envelopes.

### 2.6.XBG, Placebos, and LP

For the TCM treatment, XBG, manufactured by Tianjiang Pharmaceuticals Co, Ltd., (Jiangyin, Zhejiang, China) consisted of Huangqi (*Astragalus*) 30g, Lianxu (*Nelumbinis Stamen*) 15g, Yiyigen (*the root of Coix Lacryma-jobi*) 30g, Shiwei (*Pyrrosia lingua*) 15g, Zelan (*Herba Lycopi*) 15g, Guijianyu (*Ramulus Euonymi*) 15g, Qingfengteng (*Caulis sinomenii*) 9g, and Canjianke (Silk Cocoon) 9g. The XBG herbs were extracted with hot water, concentrated, spray-dried, made into granules, and packed in sealed opaque sachets, and controlled rigorously according to good manufacturing practice (GMP) standards. The XBG placebo was produced by the same manufacturer as the original using a concentrate of Colyx Tea (leaf of Broadleaf Holly), caramel pigments, gardenia yellow pigment, sunset yellow pigment, saccharose, and dextrin. The XBG placebo was similar in color, smell, taste, appearance, and packaging with the XBG. Qualities of XBG and placebo granules, such as appearance, determination of water, size of granule, solubility, hygroscopicity, heavy metals, toxic elements, pesticide residues, and microbial limit, were controlled rigorously according to the 2010 Chinese pharmacopeia and Chinese Medicine Council of Hong Kong.

In China, ARB, especially LP, is used more frequently than ACEI due to the side effects such as cough and was selected for the control group<sup>18</sup>. LP was purchased from Hangzhou Merck Sharp & Dohme Pharmaceutical Company Limited (Hangzhou, China, Batch number: J20190006, 100mg/tablet).

2.7.Intervention

After enrollment and prior to randomization, the participants who were taking ACEi and/or ARB before enrollment were administered alternative antihypertensive agents during a 3 week run-in period according to the protocol. All the patients included in this trial need to be treated by LP (100 mg, once daily for 6 months). Eligible participants will be randomized to treatment group and control group, patients in treatment group will be treated with optimal medical therapy and XBG (11.8 g, twice per day for 6 months), and patients in the control group will be treated with optimal medical therapy and placebo (11.8 g, twice per day for 6 months). Both XBG and placebo are prepared by Tianjiang Pharmaceuticals Co, Ltd., and the appearance, color and smell of placebo are basically consistent with XBG. There were no dose adjustments. All participants received conventional CKD management according to guidelines. Any ACEI, ARB, or CHM (except the drug used in this research) was prohibited during the trial.

2.8.Quality control

A clinical training session was conducted before the clinical trial commenced. The session focused on important technical aspects of the implementation plan, which included the randomization method, guidelines for administering XBG and LP of the case report form, and meticulous clinical data entry. During the implementation of the study, one specific quality control personnel visited each sub-center weekly to conduct onsite supervision and resolve any problems to ensure the authenticity, accuracy, and completeness of research data records and reports.

2.9.Outcome Measurement

2.9.1.Primary efficacy outcome

The primary efficacy outcome was 24hUTP. Patients were examined 24hUTP at baseline and thereafter every 2 months from baseline to month 6. The change rate of 24hUTP $\Delta R = \frac{24hUTP \text{ after treatment} - 24hUTP \text{ before treatment}}{24hUTP \text{ before treatment}} \times 100\%$ .

2.9.2.Secondary efficacy outcomes

The secondary efficacy outcomes were renal function and renal tubular injury signature urine protein, including serum creatinine (Scr), blood urea nitrogen (BUN), eGFR, NAG and RBP at baseline and thereafter every 2 months from baseline to month 6. What's more, TCM symptom scores were scored.

2.9.3.Safety indicators

Meanwhile, serum potassium (K<sup>+</sup>), alanine aminotransferase (ALT), aspartate transaminase (AST), Alb, red blood cell (RBC), total cholesterol (TC), triglyceride (TG), stool routine, and electrocardiogram will be examined at each time point for safe monitoring throughout the trial.

2.10.Sample size

The sample size was calculated by SAS (version 9.4) and based on the effective rate of treatment. To determine the sample size, we reviewed the results of preliminary clinical research on XBG and set the P2=92.90%. Referring to previous studies on ARB drugs, P1 was set at 72.90%. Power was set at 0.9, assuming an attrition rate of 10% and a target of 160 patients. Participants were randomly assigned to each group on a scale of 1:1 to 80.

2.11.Statistical Analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) statistical analysis software was used for statistical analysis. Regarding demographic and pathological types at baseline, quantitative variables were reported as mean±standard deviation (SD), and qualitative variables as frequencies and percentages. Variations in each group at each point were analyzed by one-way ANOVA test. The non-normally distributed measurement data were expressed using the median (interquartile spacing), and all were tested using non-parametric tests. The Mann-Whitney U test was used to compare groups before and after treatment for grade data. A P value less than 0.05 was considered statistically significant.

3. RESULTS

A total of 160 patients in 9 hospitals agreed to participate and were randomized to either the treatment group (n = 80) or the control group (n = 80) .152 patients completed final follow-up, 78 patients in the treatment group, 74 patients in the control group. During the trial, 7 patients withdrew for various reasons and the treatment of a patient was discontinued because of pregnancy (Figure 1).

3.1.Baseline characteristics of clinical and functional status

Baseline demographic data and clinical characteristics were summarized in Table1. 51.3% of the patients were men. The mean age was 45.3±12.4 years, and the average duration of illness was 5.3±4.1 years. The most common pathological type was IgA nephropathy. Patient demographics and pathological types were similar between the two groups.

Table1 Baseline demographic data and clinical characteristics

| Characteristics                       | Total        | Control group | Treatment group | p-Value |
|---------------------------------------|--------------|---------------|-----------------|---------|
|                                       | <b>n=152</b> | <b>n=74</b>   | <b>n=78</b>     |         |
| Male sex, n(%)                        | 78 (51.3%)   | 40 (54.1%)    | 38 (48.7%)      | 0.511   |
| Age (years) (mean±SD)                 | 45.3±12.4    | 45.2±12.4     | 45.5±12.6       | 0.762   |
| Duration of illness (years) (mean±SD) | 5.3±4.1      | 5.7±4.1       | 5.0±4.1         | 0.332   |
| Pathological type, n(%)               |              |               |                 | 0.363   |
| IgAN                                  | 56(36.9)     | 30(40.5)      | 26(33.3)        |         |
| MCGN                                  | 46(30.3)     | 22(29.7)      | 24(30.8)        |         |
| FSGS                                  | 14(9.2)      | 6(8.1)        | 8(10.3)         |         |
| Other types                           | 6(3.9)       | 2(2.7)        | 4(5.1)          |         |
| None                                  | 30(19.7)     | 14(19.0)      | 16(20.5)        |         |

Notes: IgAN: IgA nephropathy; MCGN: mesangiocapillary glomerulonephritis; FSGS: Focal segmental glomerulosclerosis; P value: comparison between the treatment group and the control group.  $P < 0.05$  indicates a significant difference.

### 3.2. Clinical outcomes

#### 3.2.1. Primary efficacy outcome

The results of 24hUTP during treatment are demonstrated in Table 3. Prior to treatment, there was no significant difference between groups at 24hUTP ( $p = 0.05$ ). 24hUTP in the treatment group decreased gradually with the prolongation of treatment time; there were statistical differences between each time point and month 2 ( $p = 0.001$ ). The 24hUTP of the control group increased gradually with the prolongation of treatment time, and there were statistical differences between each time point and 0 week ( $p = 0.001$ ) (Table 2). The treatment group had a larger 24hUTP $\Delta$ R than the control group; the decrease of 24hUTP in the treatment group was more rapidly than that in the control group, and there were statistical differences between the two groups ( $p = 0.001$ ).

#### 3.2.2. Secondary efficacy outcomes

Table 3 displays the changes in Scr, BUN, eGFR, NAG, and RBP over 6 months. Scr in the treatment group decreased gradually, and eGFR ascended significantly with the prolongation of treatment time (Table 2). There were statistical differences between each time point and 0 month ( $p = 0.05$ ). Changes in Scr and eGFR in the control group were limited and unstable after treatment. The effect of the treatment group on decreasing Scr and improving eGFR was better than that of the control group ( $p = 0.05$ ). The BUN of the two groups decreased compared to before; there was no significant comparison between them ( $p = 0.05$ ).

NAG and RBP decreased gradually in the treatment group and deteriorated gradually in the control group with the prolongation of treatment time. There were statistical differences between each time point and 0 week ( $p = 0.001$ ) (Table 2). The decline of 24hUTP was positively correlated with NAG and RBP (Table 4).

As for the composite of TCM symptom scores, symptoms such as lack of energy and laziness, back and knee soreness, anorexia, scanty dark urine, bitter mouth or thirst without desire to drink, the skin is tricky to touch, and visible as fish scale manifestations were significantly improved in the treatment group, and the treatment group was significantly lower than the control group ( $p = 0.001$ ) (Table 3).

Table 2 Changes in 24hUPro, Scr, BUN and eGFR over 6 months

|                                   | Control group n=74 |                 |                  |         | Treatment group n=78 |                  |                 |         |
|-----------------------------------|--------------------|-----------------|------------------|---------|----------------------|------------------|-----------------|---------|
|                                   | 2months            | 4months         | 6months          | p-Value | 2months              | 4months          | 6months         | p-Value |
| 24hUPro g/24h                     | 1.71±1.20          | 1.73±1.24       | 1.94±1.35        | <0.001  | 1.04±0.55            | 0.77±0.46        | 0.54±0.37       | <0.001  |
| 24hUTP ΔR 100%                    | 0.50±0.32          | 0.51±0.34       | 0.57±0.72        | <0.001  | -1.20±0.45           | -0.88±0.23       | -0.63±0.19      | <0.001  |
| Scr (μmol/L)                      | 75.89±21.16        | 79.45±16.65     | 82.35±22.64      | <0.001  | 75.67±15.46          | 72.14±4.93       | 68.62±14.84     | <0.001  |
| BUN (mmol/L)                      | 6.40±0.25          | 6.53±0.22       | 6.34±0.34        | 0.12    | 6.34±0.26            | 6.30±0.21        | 6.28±0.23       | 0.15    |
| eGFR<br>mL/min/1.73m <sup>2</sup> | 88.30±16.72        | 88.7±14.71      | 84.20±15.54      | <0.001  | 86.38±16.89          | 90.85±13.98      | 93.69±15.90     | <0.001  |
| NAG (U/L)                         | 39.83              | 30.78           | 27.51            | <0.001  | 40.20                | 27.33            | 14.22           | <0.001  |
|                                   | (35.8<br>41.30)    | (28.7<br>22.40) | (23.20<br>31.20) |         | (37.60<br>44.20)     | (24.23<br>14.20) | (13.50<br>6.50) |         |
| RBP (U/L)                         | 1.31               | 0.92            | 0.81             | <0.001  | 1.31                 | 0.30             | 0.29            | <0.001  |
|                                   | (1.31<br>1.32)     | (0.90<br>0.94)  | (0.80<br>0.804)  |         | (1.21<br>1.32)       | (0.29<br>0.31)   | (0.29<br>0.30)  |         |

Notes: 24hUTP: 24-hour urinary total protein quantity; The change rate of 24hUTPΔR=24hUTP before treatment24hUTP after treatment24hUTP before treatment×100%; Scr: serum creatinine; BUN: blood urea nitrogen; eGFR: the estimated glomerular filtration rate; Notes: NAG: N-acetyl-β-D-amino glucoside ; RBP: retinol-binding protein; r: relevant index; P value: comparison between the treatment group and the control group. P < 0.05 indicates a significant difference.

Table3 Comparison of the disappearance rates of the TCM symptoms in the two groups

| TCM syndromes                                                     | Group     | Total number | Symptom disappear number | Symptom exist number | Symptom disappear rate(%) | Symptom exist rate(%) | p-Value |
|-------------------------------------------------------------------|-----------|--------------|--------------------------|----------------------|---------------------------|-----------------------|---------|
| lack of energy and laziness                                       | Control   | 73           | 12                       | 61                   | 16.4                      | 83.6                  | 0.0     |
|                                                                   | Treatment | 67           | 31                       | 36                   | 46.3                      | 53.7                  |         |
| back and knee soreness                                            | Control   | 72           | 15                       | 57                   | 20.8                      | 79.2                  | 0.0     |
|                                                                   | Treatment | 73           | 32                       | 41                   | 43.8                      | 56.2                  |         |
| anorexia                                                          | Control   | 58           | 18                       | 40                   | 31.0                      | 69.0                  | 0.0     |
|                                                                   | Treatment | 64           | 25                       | 39                   | 39.1                      | 60.9                  |         |
| scanty dark urine                                                 | Control   | 71           | 20                       | 51                   | 28.2                      | 71.8                  | 0.0     |
|                                                                   | Treatment | 54           | 21                       | 33                   | 38.9                      | 61.1                  |         |
| bitter mouth or thirst without desire to drink                    | Control   | 64           | 20                       | 44                   | 31.3                      | 68.8                  | 0.0     |
|                                                                   | Treatment | 54           | 17                       | 37                   | 31.5                      | 68.5                  |         |
| the skin is tricky to touch, visible as fish scale manifestations | Control   | 63           | 12                       | 51                   | 19.1                      | 81.0                  | 0.0     |
|                                                                   | Treatment | 65           | 21                       | 44                   | 32.3                      | 67.7                  |         |

Notes: TCM: Traditional Chinese Medicine; P value: comparison between the treatment group and the control group. P < 0.05 indicates a significant difference

Table4 The decline of 24hUTP was positively correlated with that of NAG and RBP of control and treatment group over 6 months

|                  | NAG  |         | RBP  |         |
|------------------|------|---------|------|---------|
|                  | r    | p-Value | r    | p-Value |
| 24hUTP (2months) | 0.81 | 0.001   | 0.73 | 0.001   |
| 24hUTP (4months) | 0.83 | 0.001   | 0.83 | 0.001   |
| 24hUTP (6months) | 0.85 | 0.001   | 0.86 | 0.001   |

Notes: NAG: N-acetyl-β-D-amino glucoside ; RBP: retinol-binding protein; r: relevant index;

### 3.2.3.Safety indicators

Throughout the study, no side effects were observed.

## 4. DISCUSSION

We conducted a multicenter, randomized, double-blind, controlled clinical trial across 9 hospitals to evaluate the efficacy and safety of XBG combined with LP for the treatment of albuminuria in patients with CGN (CKD stage 1–2). We also aimed to systematically validate the role of the combined use of Chinese and Western Medicine in individuals with CGN. The results showed that the combination of XBG with LP was more effective than LP alone, as indicated by a significantly lower 24hUTP at the end of the treatment course. Importantly, there was no significant difference in the rate of adverse events between the two groups. These findings suggest that combining XBG with LP is more effective than using LP alone for improving albuminuria. However, a minimum of 2 months of treatment is required to achieve these benefits. Previous studies and our study have demonstrated that the combination of Chinese and Western medicines significantly increases the disappearance rates of the TCM symptoms. The disappearance of the TCM symptoms was greater with the combination treatment than with Western medicine alone, which indicated that the combination treatment was more effective. For example, in Li's study<sup>21</sup>, after the application of TCM, the value of urine red blood cells decreased significantly, which also had a great impact on the urine protein of patients. In a meta-analysis<sup>22</sup> identified 72 clinical investigations involving 5,895 participants. Compared to a RAS blocker alone, Huangkui capsule combined with a RAS blocker was more effective in reducing 24hUTP, urinary albumin excretion rate (UAER), and Scr levels. However, it is important to note that by comparing renal function in both groups during the trial, the combination of XBG with LP significantly reduced Scr and improved eGFR. It can be seen that XBG combined with LP can improve renal function and delay CKD progression. Furthermore, the combination of XBG with LP reduced NAG and RBP expression, and 24hUTP was positively correlated with them. We can infer that combining XBG with LP might improve renal tubular injury more than LP alone.

Our study primarily focused on the effectiveness and safety of combining Chinese and Western Medicine for reducing patients' albuminuria and improving renal function. However, further research is necessary to determine whether this combination therapy significantly enhances the degree of decline and efficiency in proteinuric patients with CGN. Over the past few years, some research has shown that CHMs have potential benefits for the prevention and treatment of albuminuria<sup>23–25</sup>. Tripterygium wilfordii/tripterygium glycosides combined with ARB/ACEI significantly improved 24hUTP, urinary UAER, Scr, and albumin more than did ARB/ARB alone. There was no significant difference in the BUN between the treatment group and the control group. Moreover, the efficacy of the combination treatment for CGN was better than that of Western Medicine, which is consistent with our findings. Some minor side effects such as abnormal liver function tests were observed in the combined treatment group, with the risk of adverse reactions increased by 8%<sup>26,27</sup>. In contrast, no significant adverse events, toxicities, or side effects occurred in the clinical trial.

The ACEI, or ARB, of conventional CGN strategies is administered to achieve optimal BP control and proteinuria reduction, with factors possibly associated with delayed CKD progression<sup>28,29</sup>. ACEI and ARB are thought to produce renoprotection by reducing intra-glutinous pressure, which also results in an early decline in kidney function. However, these effects may be harmful to patients with CGN. There are some limitations and risks of ACEI or ARB, such as hyperkalaemia and acute kidney injury<sup>30,31</sup>. This study attempted to determine whether there was a safe, more effective alternative for patients with CGN (CKD stage 1–2) using XBG. This study presented a novel approach to integrating TCM with Western pharmacotherapy in treating CGN.

About the compatible composition of XBG, as the sovereign medicine in XBG, Astragalus strengthens the spleen and stomach to protect Central Asia, making up for the loss of essence and preventing a recurrence of albuminuria. It also stops bleeding by strengthening the kidney, tightening essence, and reducing protein loss. As the ministers of medicine, The combination of Nelumbinis Stamen and Astragalus achieves Yishen astringent, the work of "plug flow" to reduce protein loss; Herba Lycopi is good at activating blood circulation and promoting urination with no yin damage. It encourages the effectiveness of Astragalus, the sovereign medicine, by activating yang and draining water, and achieves the function of "promoting blood circulation and dispelling wind pathogens". Ramulus Euonymi specializes in breaking blood and expelling blood stasis to circulate meridians. The root of Coix Lacryma-jobi and Pyrrosia lingua can clear heat, excrete water, dispel wind-damp, circulate meridians, promote urination, and break the dampness of the blood. Both medicines guide damp-heat down and out, reinforcing and storing essence. Caulis sinomenii has the effect of benefiting Qi, circulating meridians, dispelling wind, clearing heat, and resolving dampness. Silk Cocoon is also adjuvant, which collectively causes dampness and heat to go down, making dampness and heat independent, eliminating dampness and fixing fine. The whole formula is guided by traditional Chinese medicine theory, which helps to cure the root of the problem by reinforcing healthy qi, and clearing heat and dampness, invigorating blood circulation, and removing blood stasis to treat the symptom. Simultaneous treatment of symptoms and roots replenishes qi, resolves dampness, clears heat, and circulates meridians.

Regarding the potential mechanism of TCM in treating CGN, it is thought that the components of XBG work synergistically to exhibit reduce albuminuria and protect renal function effects. Firstly, Astragalus, Nelumbinis Stamen, and the root of Coix Lacryma-jobi can all attenuate albuminuria and protect renal function by inhibiting inflammation and excessive autophagy<sup>32–35</sup>. The main component Astragaloside II in Astragalus ameliorate podocyte injury and mitochondrial dysfunction<sup>32</sup>. The biological activity of Nelumbinis Stamen from its characteristic chemical constituents flavonoids, which showed good activities of anti-inflammatory and anti-thrombosis<sup>33</sup>. Caulis sinomenii exerts its immunomodulatory effect through the NF- $\kappa$ B signalling pathway and inhibits IL-6 and TNF- $\alpha$ <sup>34</sup>. It can exert an anti-inflammatory effect, thus reducing albumin and albuminuria, inflammation of renal tissue, and kidney injury from mesangial proliferative nephritis<sup>35</sup>. Secondly, both the root of Coix Lacryma-jobi and Pyrrosia lingua can reduce albuminuria and protect kidney by the effect of antioxidant stress<sup>36,37</sup>. Polysaccharide in the root of Coix Lacryma-jobi has anti-oxidation, anti-inflammatory effects and immune regulation, and a certain intake can effectively prevent and inhibit the occurrence of CKD<sup>36</sup>. Pyrrosia lingua may attenuate renal injuries caused by oxidative stress and prevent kidney diseases such as nephrolithiasis<sup>37</sup>. Thirdly, Herba Lycopi, Ramulus Euonymi, and Silk Cocoon can all lighten glomerulosclerosis and renal interstitial fibrosis, and then then play a role in improving albuminuria and protecting the kidney<sup>38–41</sup>. The water-extraction of Herba Lycopi significantly lowered urine albumin through inhibition of TGF- $\beta$ 1 mRNA and protein expression, and regulation of the Smad3, Smad7, Smurf1, Smurf2 mRNA and protein expression, as well as elevated 26S proteasome activity to play control effect<sup>38</sup>. The effect of Ramulus Euonymi in reducing urinary red blood cell count, 24hUTP, and improving renal function in rats with glomerulosclerosis is more prominent, and it is also an important Chinese medicine for the prevention and treatment of IgA nephrotic glomerulosclerosis<sup>39</sup>. The sericin of Silk Cocoon can inhibit activation of TGF-beta1/Smad3 signal pathway in kidney of DN rats, lighten

glomerulosclerosis and renal interstitial fibrosis, so has protective and preventive effects on kidney injury<sup>40</sup> It may be through the inhibition of TNF- $\alpha$ -P38 MAP kinase signaling pathway to exert antifibrotic and anti-inflammatory activities to exert renoprotective effects<sup>41</sup>.

Inevitably, however, there are some limitations to the trial. The first one is although this was a multicenter study, the sample size was not large enough and confirmation of efficacy is still up for debate; most patients in this study came from Shanghai, so the scope of samples needed to expand to guarantee the universality of the result. Second, In this study, there was no direct efficacy comparison between XBG and LP. Thirdly, the duration of the study; longer follow-up is required to evaluate the long-term effects.

In conclusion, the combination of XBG with LP was found to be safe and more effective in improving albuminuria than LP alone. Traditional Chinese medicine can enhance the effectiveness of Western medicine in the treatment of CGN.

## Declarations

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## Author Contribution

Meijie Yuan: Responsible for study design, clinical data collection and collation, statistical analysis, and drafting the manuscript; Yi Wang, Xiaolu Qu, Qinghua Zhou, Xiuhua Mi, Xuezhong Gong, Guoxin Wang, Yanying Shen, Yimei Hu: Participated in clinical recruitment, data entry, and follow-up; Chaoyang Ye: Responsible for methodological guidance and data verification; Chen Wang: Corresponding author, responsible for project conception, quality control, manuscript revision, and finalization.

## Data Availability

The raw data, statistical methods, and supporting materials of this study are available from the corresponding author upon reasonable request.

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## Figures

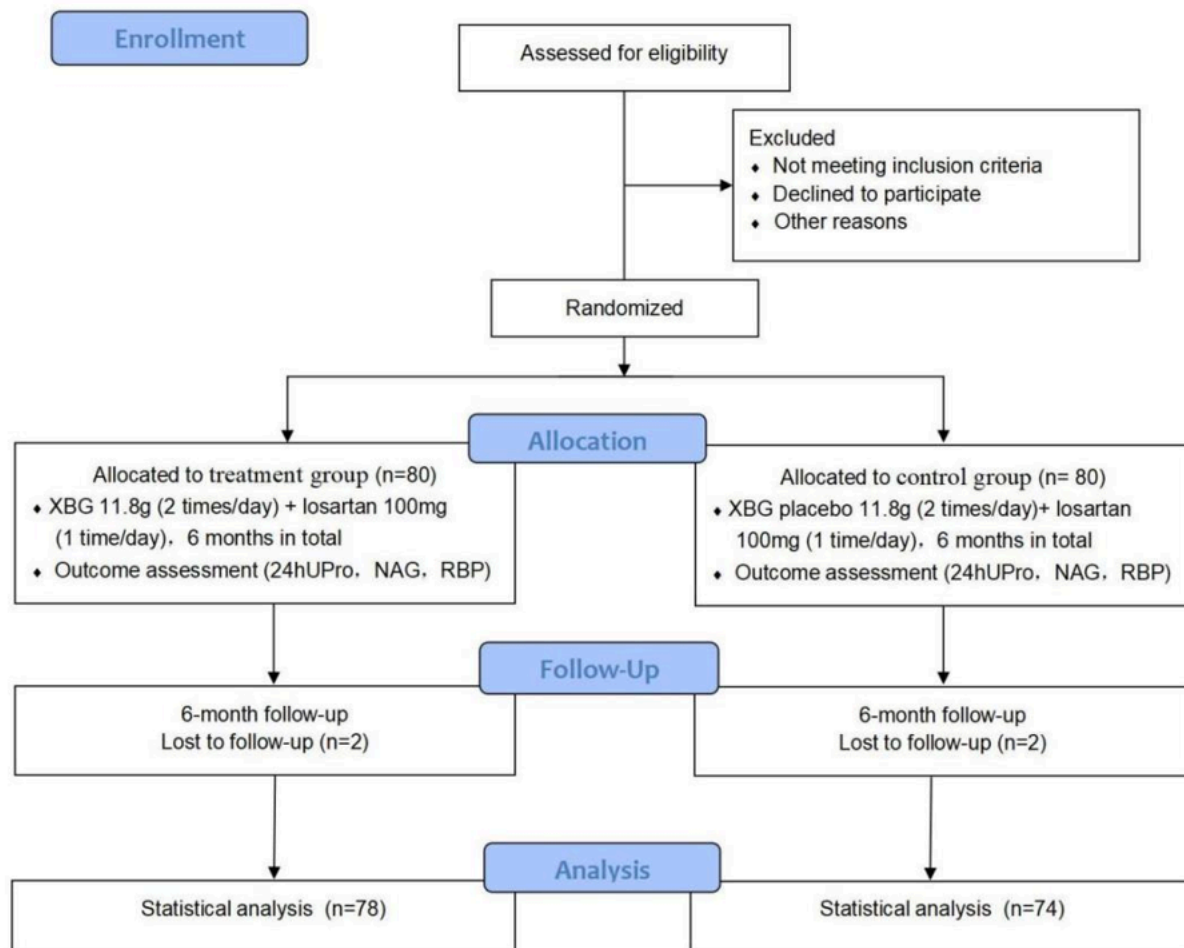


Figure 1

The participant flowchart of the trial