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Original Investigation

Efficacy and Safety of *Abelmoschus manihot* for Primary Glomerular Disease: A Prospective, Multicenter Randomized Controlled Clinical Trial

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Background: *Abelmoschus manihot*, a single medicament of traditional Chinese medicine, has been widely used to treat kidney disease. This is the first randomized controlled clinical trial to assess its efficacy and safety in patients with primary glomerular disease.

Study Design: Prospective, open-label, multicenter, randomized, controlled, clinical trial.

Setting & Participants: From May 2010 to October 2011, a total of 417 patients with biopsy-proven primary glomerular disease from 26 hospitals participated in the study.

Interventions: *A manihot* in the form of a huangkui capsule, 2.5 g, 3 times per day; losartan potassium, 50 mg/d; or combined treatment, a huangkui capsule at 2.5 g 3 times per day, was combined with losartan potassium, 50 mg/d. The duration of intervention was 24 weeks.

Outcomes & Measurements: The primary outcome was change in 24-hour proteinuria from baseline after treatment. Change in estimated glomerular filtration rate (eGFR) from baseline after treatment was a secondary outcome. The 24-hour proteinuria was measured every 4 weeks and eGFR was measured at 0, 4, 12, and 24 weeks.

Results: Mean baseline urine protein excretion was 1,045, 1,084, and 1,073 mg/d in the *A manihot*, losartan, and combined groups, respectively, and mean eGFR was 108, 106, and 106 mL/min/1.73 m^2, respectively. After 24 weeks of treatment, mean changes in proteinuria were protein excretion of −508, −376, and −545 mg/d, respectively ($P = 0.003$ for *A manihot* vs losartan and $P < 0.001$ for the combined treatment

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vs losartan). Mean eGFR did not change significantly. The incidence of adverse reactions was not different among the 3 groups ($P > 0.05$), and there were no severe adverse events in any group.

Limitations: Results cannot be generalized to those with nephrotic syndrome or reduced eGFR.

Conclusions: *A manihot* is a promising therapy for patients with primary kidney disease (chronic kidney disease stages 1-2) with moderate proteinuria.

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INDEX WORDS: Primary glomerular disease; traditional Chinese medicine; *Abelmoschus manihot*; clinical trial; huangkui capsule; proteinuria; estimated glomerular filtration rate (eGFR).

Chronic kidney disease (CKD) is a common disease that affects 11% of the total population.[1] Primary glomerular disease is the most common type of CKD and the leading cause of end-stage kidney disease in China.[2] Effective control of proteinuria may be an important strategy for treating CKD.[3,4] Renin-angiotensin-aldosterone system blockers, glucocorticoids, and immunosuppressants commonly are used for primary glomerular diseases. Immunosuppressive therapies have been used mainly to treat patients with heavy proteinuria and are not entirely suitable for patients with non–nephrotic-range proteinuria. Furthermore, treatment with glucocorticoids and immunosuppressants usually requires a long duration of treatment, which can cause severe adverse effects and increases the potential for rebound.[5,6] Therefore, exploring additional therapeutic strategies for patients with minor- to moderate-range proteinuria is necessary.

Traditional Chinese medicine has shown promising effects on the control of proteinuria, protection of kidney function, and improvements in patients' clinical symptoms.[7,8] *Abelmoschus manihot* is a traditional Chinese medicine that has become increasingly used in a variety of types of CKD, such as immunoglobulin A (IgA) nephropathy (IgAN), membranous nephropathy, and diabetic nephropathy.[9-12] Clinical studies have shown that *A manihot* can reduce proteinuria and protect kidney function.[11,13,14] However, most clinical trials of *A manihot* for the treatment of CKD involved small samples and had a low level of clinical evidence. Previous studies reported that angiotensin II receptor blockers (ARBs) reduce proteinuria and give extra renoprotective effects beyond those from blood pressure control in patients with CKD.[15-17] Losartan is one of the commonly used ARBs and its benefits have been confirmed by several clinical trials in CKD.[18,19] Thus, we chose losartan as the active control drug. We hypothesized that *A manihot* was noninferior to losartan and the combined treatment of losartan and *A manihot* was superior to losartan alone in reducing proteinuria. To test this hypothesis, we conducted a prospective, multicenter, randomized, controlled, clinical trial to evaluate the efficacy and safety of *A manihot* in treating primary glomerular disease.

METHODS

Trial Design

This study was a multicenter open-label randomized trial conducted in 26 hospitals across China. The study protocol was designed by members of the executive committee (composed of individuals from the Chinese People's Liberation Army General Hospital, First Affiliated Hospital of Nanjing Medical University, and Second Affiliated Hospital of Dalian Medical University). This study was approved by the Medical Ethics Committee of the Chinese People's Liberation Army General Hospital. Patients were divided into an *A manihot* group, losartan group, and combined treatment group. Approximately 420 patients were to be randomly assigned at a 1:1:1 ratio (140 patients per group). All enrolled patients provided written informed consent. The full trial protocol can be accessed from the Chinese People's Liberation Army General Hospital.

Participants

The process of recruiting participants was based on medical record review. All hospitalized patients having a kidney biopsy from July 2010 to March 2011 and patients with a documented history of primary glomerular disease by kidney biopsy within 1 year were screened. Inclusion criteria were as follows: (1) diagnosis of primary glomerular disease by kidney biopsy within 1 year; (2) aged 18-70 years; (3) blood pressure $\leq$ 130/80 mm Hg; (4) diagnosis of CKD stages 1-2, defined by 2 points: estimated glomerular filtration rate (eGFR) $\geq$ 60 mL/min/1.73 m^2 (calculated with the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation as per the 2002 NKF-KDOQI [National Kidney Foundation–Kidney Disease Outcomes Quality Initiative] CKD guideline[20]) and 24-h proteinuria with protein excretion range of 0.5 ~ 2.0 g; and (5) agreement to participate and signed informed consent. Exclusion criteria were as follows: (1) secondary glomerular diseases; (2) history of *A manihot* and an angiotensin-converting enzyme inhibitor and/or ARB used within 1 month; (3) history of glucocorticoids, immunosuppressants, or a *Tripterygium* drug used for more than 3 months; (4) severe heart, brain, liver, or hematopoietic system disease or other serious illnesses that affect survival; (5) pregnancy or lactation; (6) allergy to *A manihot* or losartan potassium; (7) history of alcohol or drug abuse; and (8) participation in another clinical investigation. Exit criteria were as follows: (1) exacerbations: proteinuria increased one-fold compared with baseline values or protein excretion $\geq$ 3.5 g/24 h, or doubling of serum creatinine level or $\geq$5 mg/dL; (2) serious adverse events: hospitalization (initial or prolonged), disability or permanent damage, life-threatening condition, death, congenital anomaly/birth defect, and other serious events (important medical events)[21]; (3) serious breach of protocol: participants not taking medications according to protocol or taking some drugs that have a significant impact on the primary and secondary outcomes during the 24-week observation period; (4) loss to follow-up or withdrawal from the trial; and (5) pregnancy during the trial.

Data Collection

The clinical investigators filled in the case report forms, and the inspectors reviewed the data. All data were transferred to the data statistical units for data entry and management with the EpiData, version 3.1, database. The database was locked by the principal investigator, sponsor, and data analysts on October 14, 2011. After the data lock, 10% of case report forms were extracted to check the error rate. The error rate of the primary efficacy requirements end point was 0%, and the other error rates of the indicator requirements were $<0.05\%$.

Interventions

Drug Names, Sizes, and Doses

A manihot: huanghui capsule (Jiangsu SuZhong Pharmaceutical Group Co Ltd), 0.5 g × 30 capsules/box. A huangkui capsule is a single plant drug extract of *Flos Abelmoschus manihot*. Content: dry extract (powder), 80%; magnesium stearate, 3%; and calcium hydrogen phosphate, 17%. The medicinal parts are the corolla with stamens and style. The plant is picked in early August to late October (flowering period), undergoes alcohol extraction into ambrette fluid extract, and then is vacuum dried and crushed into a dry extract powder. Pharmaceutical preparation does not involve boiling.

Losartan potassium (Hangzhou MSD Pharmaceutical Co Ltd), 50 mg × 7 capsules/box.

Test Groups

In the *A manihot* group, a huangkui capsule was given orally at 2.5 g 3 times per day after meals. In the losartan group, a losartan potassium tablet was given orally at 50 mg/d in the morning. In the combined treatment group, a huangkui capsule was given orally at 2.5 g 3 times per day after meals, and a losartan potassium tablet was given orally at 50 mg/d in the morning.

Treatment was continued for 24 weeks. Patients with blood pressures > 130/80 mm Hg after treatment were given calcium channel blockers. Appropriate treatment also was given when patients developed hyperlipidemia, infection, or a hypercoagulable state. Glucocorticoids and immunosuppressive agents were prohibited.

Outcomes

The primary outcome was change in 24-hour proteinuria from baseline after treatment. For this measurement, patients were instructed to collect urine over 24 hours (from 7:00 AM to 7:00 AM the next day), noting collection times. A medical flask was used to measure urine output and record the total amount. After stirring, 10 mL of urine was preserved at -40°C. Concentration was measured using the biuret method (Siemens; ADVIA 2400 biochemical analyzer), and 24-hour urinary protein excretion was calculated based on concentration and 24-hour urine volume. Secondary outcome measures included change in eGFR and serum creatinine values from baseline after treatment. Sarcosine oxidase was used to assay serum creatinine (Roche cobas 8000 biochemical analyzer). All urine and blood samples were delivered to a central laboratory within 4 weeks for testing.

Safety

Safety evaluation included patients' general condition, incidence of adverse events, and laboratory assessments (red blood cell count, white blood cell count, platelet count, hemoglobin level, alanine aminotransferase level, aspartate aminotransferase level, triglyceride level, cholesterol level, and low-density lipoprotein level). Adverse events and serious adverse events were defined according to the definitions of "good clinical practice" by the China Food and Drug Administration.[21] Potential adverse events included dizziness, gastrointestinal discomfort, rash, itching, amenorrhea, and cough. Adverse events were recorded every 4 weeks from the baseline visit until the final visit. Serious adverse events were recorded up to 30 days after the final visit.

Follow-up Measurements

Participants were seen every 4 weeks for assessment of clinical condition, blood pressure, adverse events, and treatment adherence. The 24-hour proteinuria was measured every 4 weeks during the 24-week trial, and blood samples were obtained at 0, 4, 12, and 24 weeks for measurement of hemoglobin, red blood cell count, white blood cell count, platelet count, alanine aminotransferase, aspartate aminotransferase, serum urea nitrogen, serum creatinine, serum albumin, and blood lipids.

For measuring blood pressure, patients were seated for at least 5 minutes, relaxed and not moving or speaking before measurements. The arm was supported at the level of the heart and no tight clothing constricted the arm. Measurements were taken twice for each patient by mercury sphygmomanometer, and average values were used for analysis.

Sample Size Determination

Sample size determination was based on the primary outcome and had 2 separate hypotheses. Regarding the multiple testing issue, α level for each test was set to a 2-sided value of 2.5%. We assumed that the expected decline in 24-hour proteinuria in the losartan group was 400 ± 150 (standard deviation) mg. With a 20% dropout rate, to enroll 130 patients per arm would offer 90% power to demonstrate noninferiority of *A manihot* compared to losartan with a 75-mg noninferiority margin (one-half of the estimated standard deviation). The same sample size also had 99.3% power to detect a 100-mg proteinuria difference between the combined treatment versus losartan alone. That means if the assumed change in 24-hour proteinuria in the combined treatment group was >500 mg, the superiority conclusion would be achieved.

Randomization

At the coordinating center, consecutive numbers were assigned to each hospital according to a center-stratified random order generated by SAS Proc Plan (SAS Institute Inc). The hospitals then randomly assigned patients to 1 of the 3 treatment groups.

Statistical Methods

Categorical variables are presented as count with percentage and compared by χ^2 test or Fisher exact test. Continuous variables are presented as mean ± standard deviation and compared by analysis of variance, and then the pairwise comparison was carried out. An analysis of covariance model was used for the comparison of changes in 24-hour proteinuria, with 95% confidence intervals estimated from mean differences ± 1.96 standard error. Statistical analyses were performed using SAS, version 9.1.3. Data analysis followed the principles of intention-to-treat analysis. The full analysis set was defined as all randomly assigned patients with both a baseline and postbaseline assessment.

RESULTS

Participant Flow

In total, 417 patients were enrolled; 3 of them were excluded because they did not meet the inclusion criteria after medical record verification. Thus, 414 patients were randomly assigned to the study groups. Nine patients were randomly assigned but withdrew consent before initiating treatment, leaving 405 who received the study drugs. One patient was lost to

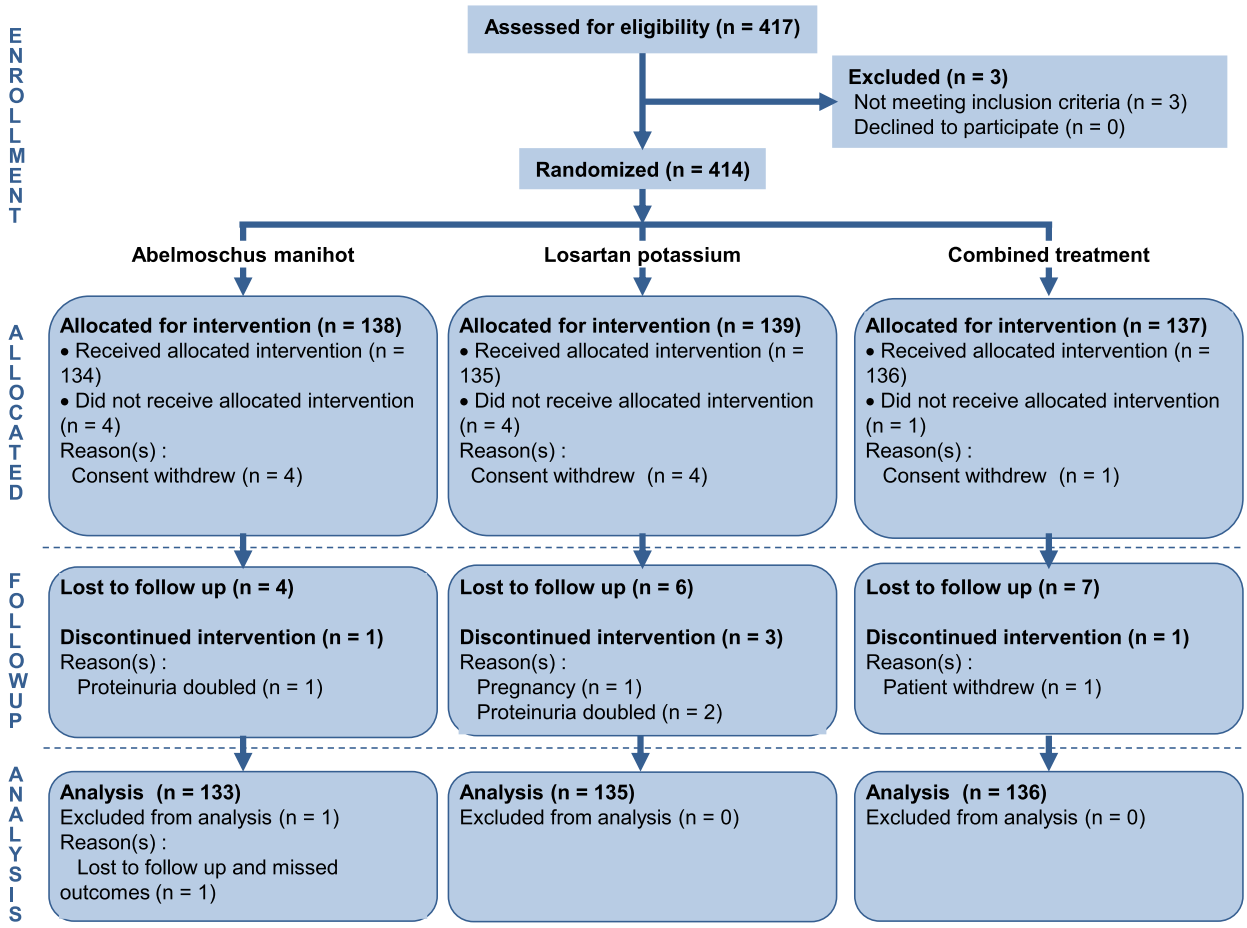

Figure 1. Randomization and flow of patients.

follow-up and missed the first assessment of the primary outcome measure. The number of participants included in the full analysis set was 404. A total of 383 (92.5%) patients completed 24 weeks of study drugs and assessments. Three (0.7%) patients were dismissed from the study early because of treatment failure (doubling of proteinuria). Twenty-six (6.2%) patients were lost to follow-up (Fig 1).

Baseline Data

Age, sex, history, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), 24-hour proteinuria, serum creatinine level, eGFR, and pathologic classifications of the 3 groups were comparable before treatment ($P > 0.05$; Table 1).

Outcome Evaluation

Primary Outcome Measure: 24-Hour Proteinuria

After 12 weeks of treatment, mean reductions from baseline in 24-hour proteinuria in the *A manihot*, losartan, and combined treatment groups were 283, 258, and 290 mg and rates of decline were 23%, 21%, and 28%, respectively. The 24-hour proteinuria level in all 3 groups decreased significantly ($P < 0.001$). Changes in proteinuria level among the 3 groups were not significantly different after 12 weeks of treatment ($P > 0.05$). After 24 weeks of treatment, mean reductions from baseline in 24-hour proteinuria in the *A manihot*, losartan, and combined treatment groups were 508, 376, and 545 mg and rates of decline were 47%, 33%, and 51%, respectively. The 24-hour proteinuria level in all 3 groups decreased significantly ($P < 0.001$). Declines in proteinuria levels in the *A manihot* and combined treatment groups were higher than that in the losartan group ($P < 0.05$). Declines in proteinuria levels between the *A manihot* and combined treatment groups were not significantly different ($P > 0.05$). Results are shown in Table 2.

Secondary Outcome Measures

Estimated GFR. After 24 weeks of treatment, mean increase from baseline in eGFR in the *A manihot* group was 1 mL/min/1.73 m^2. Mean reductions from baseline in eGFRs were 3 and 1 mL/min/1.73 m^2 in the losartan and combined treatment groups, respectively. The 3 groups did not show significant changes in eGFRs

Table 1. Baseline Participant Characteristics by Treatment Group

	A manihot (n = 133)	Losartan (n = 135)	Combined Treatment (n = 136)	*P*
Age (y)	37.3 ± 12.5	38.1 ± 12.7	37.1 ± 11.1	0.9
Sex				0.6
Male	67 (50.4)	72 (53.3)	64 (47.1)	
Female	66 (50.0)	63 (46.7)	72 (52.9)	
Pathologic classification				0.5
IgAN	60 (45.1)	76 (56.3)	72 (52.9)	
Non-IgAN mesangial proliferative GN	35 (26.3)	28 (20.7)	34 (25.0)	
FSGS	18 (13.5)	16 (11.9)	10 (7.4)	
Minimal-change nephropathy	9 (6.8)	6 (4.44)	10 (7.4)	
Membranous nephropathy	10 (7.5)	8 (5.9)	7 (5.2)	
Mesangial proliferative GN	1 (0.8)	0 (0.0)	0 (0.0)	
Other	0 (0.0)	1 (0.7)	3 (2.2)	
SBP (mm Hg)	120.2 ± 8.6	120.7 ± 8.2	121.0 ± 7.8	0.7
DBP (mm Hg)	74.0 ± 6.0	74.9 ± 5.6	74.7 ± 5.6	0.4
24-h proteinuria (mg)	1,045 ± 420	1,084 ± 453	1,073 ± 439	0.9
Serum creatinine (mg/dL)	0.80 ± 0.22	0.82 ± 0.21	0.81 ± 0.23	0.4
eGFR (mL/min/1.73 m^2)	108 ± 24	106 ± 23	106 ± 24	0.8

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation. Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations and definitions: *A manihot, Abelmoschus manihot*; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; other, pathologic manifestation was glomerular ischemia associated with tubulointerstitial damage; SBP, systolic blood pressure.

after treatment ($P > 0.05$). Differences among the 3 groups were not significant ($P > 0.05$; Table 3).

Serum creatinine level. After 24 weeks of treatment, mean reduction from baseline in serum creatinine level in the *A manihot* group was 0.005 mg/dL. Mean increases from baseline in serum creatinine levels were 0.03 and 0.01 mg/dL in the losartan and combined treatment groups, respectively. The 3 groups did not show significant changes in serum creatinine levels after treatment ($P > 0.05$). Differences among the 3 groups were not significant ($P > 0.05$; Table 3).

Blood Pressure

After 24 weeks of treatment, SBPs were 119.5 ± 8.5, 118.8 ± 8.8, and 118.5 ± 8.6 mm Hg in the *A manihot*, losartan, and combined treatment groups, respectively. DBPs were 72.9 ± 5.8, 72.7 ± 5.4, and 73.4 ± 5.3 mm Hg, respectively. Eighteen patients were given calcium channel blockers for blood pressures ≥ 130/80 during the treatment period (*A manihot* group, 9; losartan group, 3, and combined treatment group, 6).

SBPs and DBPs in the losartan and combined treatment groups were significantly lower after treatment (SBP: $P = 0.004$ and $P < 0.001$; DBP: $P < 0.001$ and $P = 0.02$, respectively). SBPs and DBPs in the *A manihot* group were not significantly different after treatment ($P > 0.05$). Change in SBP showed a significant difference between the *A manihot* and combined treatment groups ($P = 0.02$). The other SBPs and DBPs among the groups were not statistically significant ($P > 0.05$).

Safety Evaluation

Adverse events occurred in 9 patients (14 cases) in the *A manihot* group, for an incidence of 6.7%; in 10 patients (11 cases) in the losartan group, for an incidence of 7.4%; and in 11 patients (15 cases) in the combined treatment group, for an incidence of 8.1%. There were no severe adverse events in any of the 3 groups. Rates of adverse events were not significantly different among the 3 groups ($P > 0.05$; Table 4).

Subgroup Analysis

The most common pathologic diagnosis in this study was IgAN (51.5%). Therefore, subgroup analysis restricted to patients with IgAN was performed and results were not different from those in the overall group (Tables S1 and S2, available as online supplementary material).

DISCUSSION

Traditional Chinese medicine is the most distinctive and widely used therapy for CKD in China and other Asian countries. The efficacy of Chinese medicine has been confirmed in some randomized controlled studies in recent years.[7] In our study, patients with primary glomerular disease, non–nephrotic-range proteinuria, normal kidney function, and well-controlled blood pressure who were given *A manihot* had significant reductions in proteinuria and

Table 2. Change From Baseline in 24-Hour Proteinuria Over 24-Week Follow-up Period

	A manihot (n = 133)	Losartan (n = 135)	Combined Treatment (n = 136)	*A manihot* vs Losartan	Combined Treatment vs *A manihot*	Combined Treatment vs Losartan
0 wk	1,045 ± 420	1,084 ± 453	1,073 ± 439	$P = 0.9$	$P = 0.9$	$P = 0.9$
12 wk	762 ± 533	825 ± 706	783 ± 658	$P = 0.7$	$P = 0.7$	$P = 0.5$
Δ 24-h proteinuria	−283 ± 553	−258 ± 701	−290 ± 542	−25 (−177 to 128) $P = 0.9$	−7 (−124 to 139) $P = 0.8$	−32 (−118 to 181) $P = 0.8$
Comparison within group	$P < 0.001$	$P < 0.001$	$P < 0.001$			
24 wk	537 ± 409	708 ± 588	529 ± 509	$P = 0.02$	$P = 0.4$	$P < 0.001$
Δ 24-h proteinuria	−508 ± 457	−376 ± 577	−545 ± 500	−132 (−257 to −7) $P = 0.003$	−36 (−151 to 79) $P = 0.3$	−169 (−298 to −39) $P < 0.001$
Comparison within group	$P < 0.001$	$P < 0.001$	$P < 0.001$			

Note: The 24-hour proteinuria (mg) and changes in 24-hour proteinuria from baseline (mg) in 3 groups are given as mean ± standard deviation. Differences of change in proteinuria between groups are given as mean (95% confidence interval).

Abbreviation: *A manihot, Abelmoschus manihot*.

preservation of kidney function. Interestingly, *A manihot* showed a better therapeutic effect on reducing proteinuria than losartan (50 mg/d) after 24 weeks of treatment. In addition, the combination of *A manihot* and losartan showed better efficacy than losartan monotherapy.

Angiotensin-converting enzyme inhibitors and ARBs are used commonly to treat proteinuria, and the range of reduction is reportedly 30%-50% in adults.[22,23] Thus, we used losartan as the positive control. Flowers of *A manihot* (Linn) Medicus (family Malvaceae) have been used as a traditional treatment of chronic glomerulonephritis in China for centuries. Many (>20) pharmacologically active compounds have been isolated from *A manihot*, including flavonoids, organic acids, tannins, and long-chain hydrocarbons.[24] The major biologically active components are flavonoids (eg, isoquercitrin, hyperoside, hibifolin, quercetin-3′-O-glucoside, quercetin, and gossypetin).[25] Metabolic profiles of these active components are critical for understanding the safety and efficacy of *A manihot*. This herb can ameliorate proteinuria and hematuria and improve kidney function in patients with CKD, including diabetic

Table 3. Change From Baseline in Serum Creatinine and eGFR Over 24-Week Follow-up Period

	A manihot (n = 133)	Losartan (n = 135)	Combined Treatment (n = 136)	*A manihot* vs Losartan	Combined Treatment vs *A manihot*	Combined Treatment vs Losartan
Comparison of Scr						
0 wk	0.80 ± 0.22	0.82 ± 0.21	0.81 ± 0.23	$P = 0.4$	$P = 0.6$	$P = 0.8$
12 wk	0.81 ± 0.22	0.83 ± 0.22	0.85 ± 0.25	$P = 0.4$	$P = 0.07$	$P = 0.3$
24 wk	0.80 ± 0.20	0.85 ± 0.22	0.82 ± 0.24	$P = 0.05$	$P = 0.3$	$P = 0.4$
ΔScr	−0.005 ± 0.19	+0.03 ± 0.18	+0.01 ± 0.17	−0.03 (−6.94 to 1.21); $P = 0.2$	0.02 (−2.37 to 5.47); $P = 0.4$	−0.02 (−5.15 to 2.53); $P = 0.5$
Comparison within group	$P = 0.7$	$P = 0.1$	$P = 0.4$			
Comparison of eGFR						
0 wk	108 ± 24	106 ± 23	106 ± 24	0.5	0.4	0.9
12 wk	108 ± 23	105 ± 23	105 ± 23	0.2	0.2	0.9
24 wk	109 ± 22	104 ± 25	105 ± 23	0.07	0.1	0.7
ΔeGFR	+1 ± 20	−3 ± 19	−1 ± 18	1.6 (−1 to 9); $P = 0.1$	−1.2 (−8 to 2); $P = 0.2$	0.02 (−6 to 3); $P = 0.9$
Comparison within group	$P = 0.5$	$P = 0.1$	$P = 0.07$			

Note: Serum creatinine and eGFR values are given as mean ± standard deviation and expressed as mg/dL and mL/min/1.73 m^2, respectively. Differences of change in serum creatinine and eGFR between groups are given as mean (95% confidence interval).

Abbreviations: *A manihot, Abelmoschus manihot*; eGFR, estimated glomerular filtration rate; Scr, serum creatinine.

Table 4. Summary of Adverse Events by Treatment Group

	Total	*A manihot*	Losartan	Combined Treatment
Dizziness	1	0	0	1
Nausea	1	1	0	0
Diarrhea	1	0	0	1
Tonsillitis	2	0	0	2
Upper respiratory tract infection	13	4	5	4
Gingivitis	1	0	0	1
Pregnancy during treatment	1	0	1	0
Schizophrenia	1	1	0	0
Elevated white blood cell or neutrophil count	2	0	1	1
Anemia	1	0	1	0
Thrombocytopenia	1	0	0	1
Elevated cholesterol or triglycerides	11	5	2	4
Liver injury	4	3	1	0
Total	40	14	11	15

Abbreviation: *A manihot, Abelmoschus manihot*.

nephropathy, IgAN, membranous nephropathy, and Henoch-Schönlein purpura nephritis.[13,26-29] A modern pharmacology study found that the above-mentioned effects of *A manihot* might be associated with inhibition of immune reactions and inflammatory injury, amelioration of kidney interstitial fibrosis, anticoagulant effects, and protection of kidney tubular epithelial cells.[10,30,31] However, no randomized controlled trials have been conducted to evaluate the efficacy and safety of *A manihot*.

Our data show that after 12 weeks of treatment, *A manihot* significantly reduced proteinuria to the same extent as losartan, and the efficacy of the combination of the 2 drugs was not superior to monotherapy. After 24 weeks of treatment, proteinuria with *A manihot* decreased by 49%, and the effect was superior to that of losartan; the 2-drug combination therapy was superior to losartan monotherapy. Previous studies have suggested that high ARB doses could delay the progression of kidney disease in hypertensive and/or diabetic patients.[32,33] Nevertheless, according to Shen et al,[34] "in daily practice of nephrology, quite a number of nondiabetic patients with CKD who are normotensive do not tolerate even moderate dosages of ARBs because of adverse effects such as systemic hypotension, especially for Chinese patients."[34(p1,041)] This study was based on losartan at 50 mg/d as a positive control, and one of the inclusion criteria was effective control of hypertension (blood pressure $\leq$ 130/80 mm Hg); thus, we did not change the losartan dosage. After 24 weeks' treatment, blood pressures in the *A manihot* and losartan groups were not statistically different and only 9 patients in *A manihot* group and 3 patients in the losartan group required calcium channel blockers.

In terms of kidney function, our results showed that although not statistically significant, serum creatinine levels in the *A manihot* group nominally decreased while eGFRs nominally increased. Changes in kidney function in the losartan and combined treatment groups showed the opposite trends, but comparisons among the 3 groups indicated no significant differences. Other research has demonstrated that *A manihot* can significantly reduce serum creatinine level and protect kidney function in patients with decreased kidney function.[35,36] No study has confirmed that *A manihot* affects kidney function in patients with normal serum creatinine levels and eGFRs. The change in serum creatinine level and eGFR in the losartan group was related to the pharmacologic effects of renin-angiotensin-aldosterone system blockers on the hemodynamic origin.[37]

A manihot and losartan generally were well tolerated. There were no severe adverse events or decreases in kidney function in the *A manihot* group. The overall incidence of adverse events was low and generally similar among treatment groups. Overall, *A manihot* was well tolerated with minimal adverse events. Since the huangkui capsule acquired national approval from the China Food and Drug Administration in 1999, there have been no reports of severe adverse events. The most common adverse event is mild to moderate gastrointestinal discomfort.[38]

This trial has some limitations. The first limitation is that the patients enrolled in this study had mild kidney disease and those with nephrotic syndrome were excluded. In addition, this study did not include patients with secondary glomerular diseases. Other studies have shown that *A manihot* has good efficacy in patients with nephrotic syndrome and diabetic nephropathy.[14,39-41] The short follow-up time is an additional limitation.

In conclusion, *A manihot* can reduce proteinuria levels of patients with CKD stages 1-2 with primary glomerular disease and has better efficacy than losartan (50 mg/d). In addition, *A manihot* can maintain stable kidney function. Despite the need for long-term studies, results of this study provide initial evidence for the efficacy and safety of *A manihot* in the treatment of early CKD with low to moderate proteinuria.

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SUPPLEMENTARY MATERIAL

Table S1: Baseline characteristics of IgAN patients.

Table S2: Change from baseline in proteinuria, Scr, and eGFR during follow-up in IgAN patients.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.01.431) is available at www.ajkd.org

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