The Renal Protective Potential Effect of Infusion of Anti-urolithiasis Formula in Urolithiasis Patients: A Randomized Clinical Study

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Abstract: Kidney stones and related urological procedures can lead to chronic kidney disease (CKD). The constituent plants of an anti-urolithiasis formula developed by B2P2TOOT have a potential renoprotective effect, thus preventing CKD progression. This randomized open-label clinical study with end-blinded observation was aimed to evaluate the possible renoprotective effect of anti-urolithiasis formula infusions in urolithiasis patients. Two hundred volunteer subjects were randomly allocated into two groups: anti-urolithiasis herbal formula (AHF) and commercial polyextract lithotripsy (CPL). Urine tests were performed, and the estimated glomerular filtration rate (eGFR) was calculated using a CKD-EPI equation at baseline (day 0) and after the intervention (day 56). The analysis was done within each group and between both groups using paired sample T-test and independent T-tests. An increase in the eGFR of subjects in the AHF group was found, although it was not statistically significant (p=0.35). The mean of the eGFR of subjects in the CPL group after the intervention was lower, also statistically insignificant (p=0.56). Nevertheless, there were significant differences in the eGFR after intervention between both groups (p=0.044, 95% CI 0.16–12.4). Our findings suggest that AHF has a slight potential effect on renal function preservation in urolithiasis patients.

1 INTRODUCTION

Urolithiasis has become a worldwide health burden. Its incidence rates are 10% for men and 5% for women (D'Costa *et al*., 2016). The high recurrence rate of urolithiasis results in health financing issues and considerable morbidity (Lee *et al*., 2015). Also, several studies have revealed that the formation of stones in the urinary tract has a strong correlation with adverse renal outcomes. However, the mechanism underlying kidney stones and diminished kidney function is likely multifactorial (Alexander *et al*., 2012; Coe *et al*., 2010). Urolithiasis plays a significant role in influencing the risk of adverse renal outcomes and prior history of recurrent symptomatic episodes. Accordingly, it might produce an increased risk of end-stage renal disease (ESRD). For example, the progressive calcification of calcium kidney stones at the tubular basement membrane and the ducts of Bellini causes renal damage through progressive scarring, leading to ESRD (Coe *et al*., 2010; Evan, 2010).

Urolithiasis management has recently played an essential role in preventing several future health complications—one of the standard procedures in the management of nephrolithiasis is extracorporeal shock wave lithotripsy (ESWL). ESWL had been regularly utilized in the management of urolithiasis. Nevertheless, it might significantly contribute to the increased risk of recurring stones and result in greater difficulty when comminuting stones with ESWL (Evan, 2010). Moreover, it can result in several complications, leading to kidney function loss (Shekar Kumaran and Patki, 2011). This hypothesis

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has suggested a decrease in renal function by vasoconstriction, and its persistent stone fragments may induce acute renal injury (Agawane *et al*., 2019; Khan *et al*., 2011; Nizami *et al*., 2012; Srisubat *et al*., 2014). By contrast, another study found no correlation between ESWL and CKD development (D'Costa *et al*., 2016; E. *et al*., 2008). The retrospective study revealed that urological procedures could significantly increase the risk of developing elevated serum creatinin but were not significant in progressing CKD itself (D'Costa *et al*., 2016). There is no appropriate drug for the treatment of urolithiasis despite technological advances in the field of medicine. However, it is worthwhile to explore the potential benefits of medicinal plants, which may affect anti-urolithiasis and restore renal impairments.

Polyherbal treatment can be considered an alternative approach to treating urolithiasis. The investigation of phytotherapy for urolithiasis has been reported in an ethnopharmacology study, in vitro, and in vivo models (Ahmed *et al*., 2016; Akanae *et al*., 2010; Nisa and Astana, 2018; Patankar *et al*., 2020; Yadav, RD., Jain, SK., Alok, Shashi., Mahor, Alok., Bharti, JP., Jaiswal *et al*., 2011). The diuretic activity of *Orthosiphon stamineus* is different when combined with hydrochlorothiazide and furosemide (Adam *et al*., 2009). It takes a longer time to produce effects than synthetic diuretics but, notably, does not include any side effects (Tiwari *et al*., 2017). Meanwhile, *Phyllanthus niruri* can inhibit lithiasis' growth in rats (Morán *et al*., 2013). The administration of *Phyllanthus niruri* can decrease mRNA p65NF-κB and mRNA IL-6 levels in the kidneys of diabetic rats (Giribabu *et al*., 2017). Jonnel B.P. et al. revealed that an increase in *Imperata cylindraca* extract concentration is related to decreased serum creatinine and blood urea nitrogen (BUN) levels. Thus, several medicinal plants appear to have distinct mechanisms for urolithiasis that generate synergetic effects to facilitate stones' passage.

The constituent plants of the anti-urolithiasis formula developed by the Medicinal Plant and Traditional Medicine Research and Development Center (B2P2TOOT-in Bahasa) have a potential renoprotective effect, which suggests they can serve as an alternative method of preventing CKD progression. This method's safety and efficacy have been proven in clinical trials (Nisa and Astana, 2019). Several compositions of the AHF had been reported to have a potential renoprotective effect in a single-use form. This study aims to evaluate the possible renoprotective effect of an anti-urolithiasis herbal formula in urolithiasis patients.

2 MATERIALS AND METHODS

The study was conducted by the Traditional Plant and Traditional Medicine Research and Development Center at the Ministry of Health Indonesian and involved191 urolithiasis patients. The design of the study was a purposive randomized open-label study design, with end-blinded observation. We involved 70 physicians, who all have Saintifikasi Jamu (SJ) certifications as investigators. The ethics committee approved the study protocol of the National Institute of Research and Development (LB.02.01/5.2/KE 063/2016) on March 13th, 2017. The principal investigator was qualified in traditional and allopathic medicine and clinical trials, in accordance with Good Clinical Practices (GCP).

Volunteer patients who fulfilled the inclusion criteria participated in this study. Before participating in the study, each subject was requested to read and sign an informed consent form. The inclusion criteria were: an age of 17-60 years old, a history of urolithiasis, the presence of a stone<2 cm in diameter, serum creatinine levels of<2 g/dl, and liver and kidney function within a normal range. Patients with complications from severe diseases and those requiring surgical intervention were excluded from the study. Eligible subjects were randomized by computer software into two groups: the AHF and the CPL group.

In the AHF group, each subject was given an herbal formula, which consisted of a dried simplisia of 10 g of S. *arvensis*, 6 g of *O. stamineus*, 4 g of *Strobilanthes crispus*, 5 g of *Imperata cylindrica*, 5 g of *C. xanthorrhiza*, 4 g of *Curcuma domestica*, and 3 g of *P. niruri*. Each subject was requested to prepare an infusion from the formula. The AHFwas prepared by boiling 1 L of water, adding the simplisia into the boiling water, and letting the mixture boil for 15 minutes. Subjects were instructed to drink the filtered water twice a day for 56 days, after breakfast and dinner. Meanwhile, in the CPL group, subjects consumed CPL, which consisted of an extract of 18 mg of *O. stamineus*, 6 mg of *S. crispa,* 24 mg of *S. arvensis L*., 2.4 mg of *P. niruri*, and 100 mg of *Plantago major*. They took one capsule of CPL four times daily, also for 56 days.

Demographic data such as age, sex, BMI, history of stone recurrence, and stone size were recorded at day 0 of the study. Urine tests (routine and microscopic), including tests of urine turbidity, pH, specific gravity, LE, Nitrit, RBC, and albuminuria, were performed on days 0, 28, and 56 to observe the fluctuation of urine quality. The kidney's biochemical parameters (creatinine and BUN) were measured on

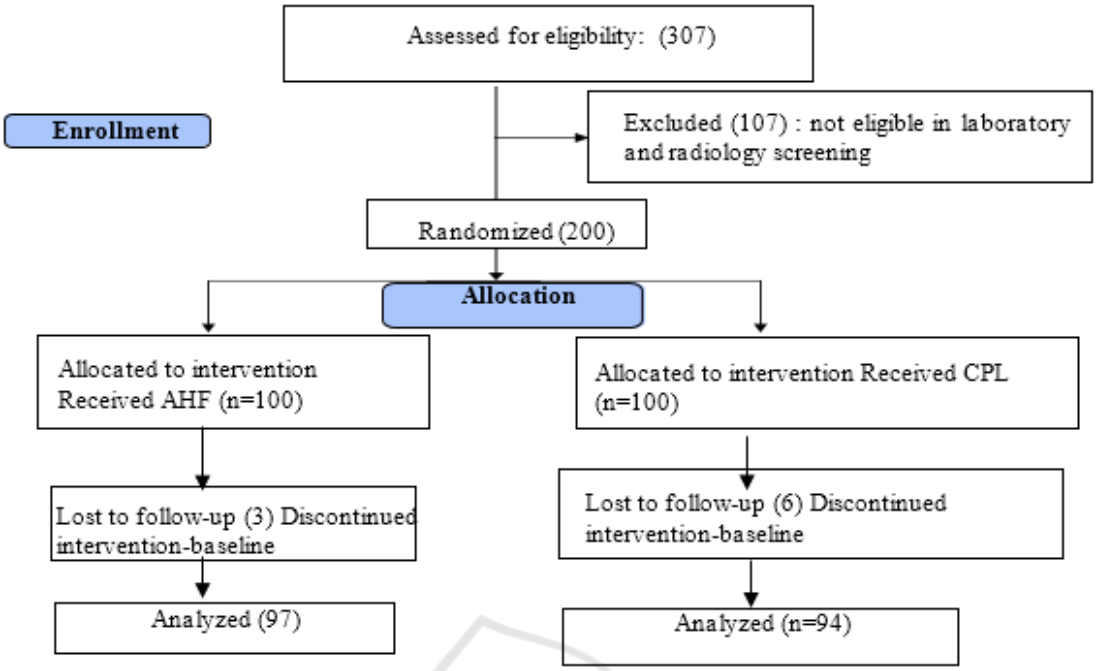

Figure 1: Enrollment, randomization, allocation, follow-up, and analysis

day 0 and day 56, followed by a calculation of the estimated glomerular filtration rate (eGFR) using a CKD-EPI equation.

The data were analyzed statistically using a GraphPad Prism program for statistical analysis version 8.0. Descriptive data were calculated and presented in Table 1. To determine differences before and after treatment, we performed a paired T-test. An independent T-test was also conducted to determine the differences between the two groups. Alternatively, the Wilcoxon test and Mann–Whitney U-test were used when there was an abnormal data distribution in the Kolmogorov–Smirnov test results.

3 RESULTS

Based on Figure 1, the total number of patients recruited in this studywas191 patients. As many as97 and 94 subjects were analyzed in the AHF and CPL group, respectively. Each group had subjects who could not continue the intervention because of a failure to follow up. The baseline characteristics of patients are summarized in Table 1.

Table 1: Demographic data of patients.

Parameters	AHF (N=97)	CPL (N=94)
Mean age	45-55 yr	45-55 yr
Male:female	1.9:1	1.7:1
BMI (Overweight:normoweight)	1.18:1	1.38:1
History of recurrent urolithiasis	1 yr (34%)	1 yr (33%)
Average size of stone	10.82±8.19	8.07±5.19

Comparing male and female participants between the two groups were 1.9:1 and 1.7:1 in the AHF and CPL group, respectively. Each group also had a similar BMI ratio between overweight and normoweight participants. The majority of patients were in the range of 45-55 years old. About 30% of patients had a history of stone recurrence within one year before the study started. The mean of the size of the stone was similar between the two groups. Figure 2A shows information about the mean of the eGFR for pre-treatment(day 0) and post-treatment(day 56). There was no significant difference in the eGFR between the two groups on day 0. However, after 56 days of treatment, there were significant differences in the eGFR between the AHF group and the CPL group ($p=0.044$, 95% CI 0.16 – 12.4).

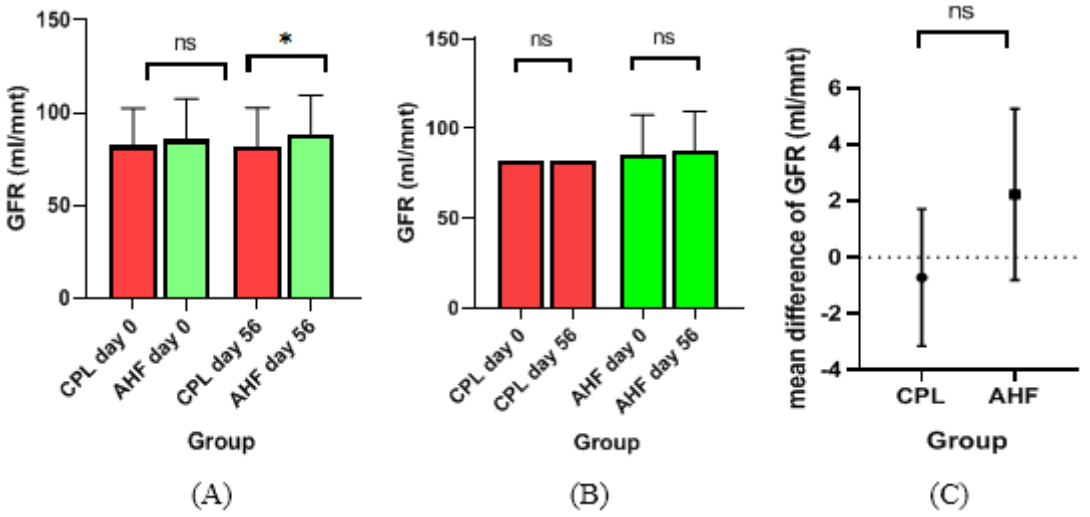

Figure 2: (A) Mean of eGFRfor pre- and post-treatment between the two groups.(B)Mean difference between AHF and CPL groups. (C)Mean of eGFR before and after treatment in each group.

An increase in subjects' eGFR was found in the AHF group on day 56 compared with day 0 (2.24 mL/min per 1.73 m2). However, this was not statistically significant (p=0.35). In the CPL group, the average eGFR of subjects on day 56 was lower than on day 0, though this was also not statistically significant (p=0.56) (Figure 2B). We calculated the difference in theeGFR value between day 0 and day 56 in each group, as represented in figure 2C. The difference in the eGFR in the AHF group showed a positive value, while in the CPL group, it showed a negative one.

However, the independent T-test analysis showed no significant differences. Table 2 shows the urine test parameters of subjects. These results demonstrate that both groups' urine turbidity had lower scores at the end of treatment than in the middle or baseline. There was a statistically significant difference during treatment compared to the baseline.

Furthermore, the CPL group's urine turbidity had substantial differences in the middle of treatment compared to the baseline. From the table, we can also see that there is no change in any other urine test parameter (pH, specific gravity, LE, Nitrite, RBC, or albuminuria).

4 DISCUSSION

This study was conducted to the potential renoprotective effect of an anti-urolithiasis herbal formula in urolithiasis patients. The eGFR Anti-urolithiasis Herbal Formula's group has a significant

Table 2: Effect of treatment on urine test parameters.

Parameters	AHF			CPL		
	day 0	day 28	day 56	day 0	day 28	day 56
Urine turbidity	1.95 ± 0.08	1.80 ± 0.08[a]	1.62±0.0 [a]p<0.05 [b]p<0.05	1.88 ± 0.08	1.73 ± 0.07 [a]p<0.05	1.68±0.07 [b]p<0.05
Urine pH	5.90 ± 0.09	6.74 ± 0.76	6.47 ± 0.57	5.97±0.096	6.02 ± 0.09	6.01 ± 0,09
Specific gravity	1.014±0.001	1.016±0.002	1.013±0.001	1.000±0.02	1.015±0.02	1.014±0.02
LE	82.55±16.41	74.64±15.85	72.73±15.90	92.02±17.95	91.76±18.06	87.04±18.09
Nitrite	0.04±0.02	0.03±0.02	0.04 ±0.02	0.08 ±0.03	0.05 ± 0.02	0.03 ± 0.02
No.of RBC's perHPF	59.10± 9.65	51.01±8.96	53.19±9.42	48.39±8.55	36.83±7.49	36.94±7.66
Albuminuria	20.57 ±3.75	16.94±3.71	17.89±4.05	16.40±2.52	14.84±2.50	12.83±2.20

Mean±SEM, Statistical analysis performed using independent T-test
[a] As compared to day0
[b] As compared to day 28

difference in day 56 after treatment compared to the CPL group. However, other parameters have not a significant difference in both groups. Furthermore, after urolithiasis formation, the hindrance of urine flow can cause a decrease in the Glomerular Filtration Rate (GFR). Therefore, waste material, especially BUN (Blood Urea Nitrogen), creatinine, and uric acid, can be collected in the blood(Kaleeswaran *et al*., 2019). This study showed that the AHF and CPL had diuretic activity, preventing the elevation of these parameters. Following a previously published report, the improvement of the eGFR in the AHF group compared to the CPL group was correlated to decreased urinary stones size (Nisa and Astana, 2019).

Orthosiphon stamineus and *Phyllanthus niruri* L are indigenous medicines widely used in Indonesia(Nisa and Astana, 2018). Meanwhile, previous studies reported that the content of rosmarinic acid in *Orthosiphon stamineus* had nephroprotective effects in diabetic nephropathy. It may have conserved glomerular number loss(Almatar *et al*., 2014; Tavafi *et al*., 2011). However, this complex mechanism remains unclear, and the antioxidant properties of *Orthosiphon stamineus* may play a significant role in this process. The activation of s cellular oxidation process was associated with urolithiasis and chronic calculus pyelonephritis(Boonla, 2018; Ceban *et al*., 2016). The potential anti-urolithiasis activity of *Phyllantus niruri* plays an essential role in the early stages of stone formation. *Phyllanthus niruri*can makes stones smoother and more fragile, facilitating the dissolution of calculi (Lee *et al*., 2016).

On the other hand, most of the AHF's constituents' main activity is as a diuretic agent. In terms of diuretic action, various phytoconstituents may interact with a synergistic effect, leading to enhanced renal output. The AHF treatment was revealed to increase the GFR by dual effects of controlling the growth of stones and may also have a nephroprotective effect. The renoprotective strategies of the AHF are based on several mechanisms and are exceedingly complex. Meanwhile, the antioxidant and anti-inflammatory effects of AHF may contribute to the preservative effects of microcirculation.

The present study results show the proportion of subjects who had a history of recurrence, the rate of which was 33%. Meanwhile, the ordinary recurrence rate of kidney stone disease within one year is only 10%(Patankar *et al*., 2020). Indeed, the high recurrency of urolithiasis disease was closely correlated with side effects, leading to renal function loss progression. Various degrees of renal insufficiency is associated with urolithiasis as well. This phenomenon suggests that a combination of frequent stone episode recurrence, urinary tract reinfection, and frequent urological interventions may initiate renal insufficiency. Many studies have found that urine parameters could serve as predictive factors for estimating renal function. One of the key biomarkers of renal damage is albuminuria. Several studies have reported that this decreases the risk of renal damage and urine albumin levels(Abebe *et al*., 2019). Albuminuria is a dysfunctional endothelial marker in the renal region, brain, and heart (Mardiana *et al*., 2012). Thus, anti-albuminuria was a target for the renoprotective agent. Remuzi and Bertani suggested that albuminuria was a severity marker for renal injury, indicating that an increase in leak plasma protein is associated with an increase in kidney damage severity (De Zeeuw *et al*., 2004). Several theories attempt to explain how urolithiasis can induce renal progression. Several mechanisms underlying nephrolithiasis can lead to CKD development through scarring and the deterioration of renal function. This phenomenon may also cause direct damage to post-calcifications and crystallization of the tubular lumen, resulting from recurrent stone obstruction (D'Costa *et al*., 2016).

The limitation of this study is the parameters of renal function, which used an estimated calculation. It still needs further research for real renal function parameters.

5 CONCLUSIONS

Our findings suggest that AHF has a slight potential effect on renal function preservation in urolithiasis patients.

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