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Original Article

Safety Assessment of Supplementation with *Cymbopogon citratus* Stapf. (Lemongrass) Extract in Patients with Chronic Kidney Disease Stage 3: A Preliminary 90-Days Prospective Study

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ABSTRACT

Background: Chronic kidney disease is a major public health issue, and due to resource constraints, many can't access dialysis. *C. citratus*, lemongrass is globally prevalent and known to increase urine output without toxicity. **Objective:** To examine the safety of *C. citratus* in patients with CKD stage 3. **Materials and Methods**: The major compound of *C. citratus* was analyzed using high-performance liquid chromatography (HPLC). 64 patients were enrolled and randomly assigned to control or *C. citratus* groups. The control group received a placebo, whereas the *C. citratus* group received 900 mg of *C. citratus* daily for 90 days. All participants were examined BUN, Scr, Cys-C, and eGFR, liver functions, RBC, HCT, Na^+, K^+, Cl^-, and HCO3, and other biochemical parameters. **Results:** HPLC showed *C. citratus* contains of phenolic compounds. Clinically, *C. citratus* group had no notable side effects on T-Bil, AST, ALT and ALP. Also, maintained eGFR, SCys-C, K^+ and Cl level. The level of blood Na^+ was significant increase at day30 ($p < 0.05$). The control group had a significant decrease in eGFR and HCO3 levels ($p < 0.05$) and a significant increase of Cl^- and SCys-C. In addition, no statistical differences had found between groups in eGFR, BUN, Cr, Na^+, K^+, HCO3, PO4, RBC and HCT levels. Throughout the 90 days, no drug allergies or side effects were reported. **Conclusion:** Dietary supplementation with *C. citratus* may have a favorable effect on delaying the course of CKD and is safe to use for patients with CKD stage 3.

Key words: *Cymbopogon citratus* Stapf., Lemongrass, Chronic Kidney Disease, Safety, CKD stage 3.

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INTRODUCTION

In 21st century, chronic kidney disease (CKD) is a progressive disorder which emerged as one of the leading causes of death worldwide. The prevalence of patients with CKD has also been rising, impacting an estimated 800 million people globally in 2022.[1] CKD is more common in older people, as well as in people experiencing diabetes mellitus and hypertension.[2] In addition, CKD represents a significant burden in low-income country due to inadequate resources to manage its effects. Additionally, prior study discovered that the majority of CKD patients may have anemia which is associated with a lower quality of life, a worse prognosis for kidney survival, and a rise in morbidity and mortality.[3] CKD is categorized into 5 stages, defined based on the GFR. Treatment in stages 1 and 2 focuses on slowing CKD progression, managing cardiovascular risks, and controlling blood pressure through dietary therapeutic management. From stage 3 onwards, the management of comorbidities associated with CKD, such as anemia, bone alterations, protein-energy wasting (PEW), and water and electrolyte imbalances, is integrated. In stage 5, patients require either conservative non-dialytic management or renal replacement therapies.[4]

Currently, inflammation is recognizable as a crucial opposed pathway in the progression and development of CKD.[5] Any substance with the ability to reduce inflammation or processes connected to inflammation might be considered a potential therapy method for reducing renal damage. Furthermore, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) were commonly used in CKD pharmacotherapy to manage glomerular hypertension and proteinuria. Unfortunately, the majority of these medications are associated with side effects such as hyperkalemia and hypotension.[6] As a result, in order to avoid the progression of CKD, lower the cost of dialysis and medication therapy, new treatments and ameliorating agents should be investigated.[7]

In recent years, herbal therapies have been recognized as a dietary supplement for the treatment of various diseases, including cancer, diabetes, and CKD.[8-11] In clinical investigations, it has been demonstrated that numerous of herbal remedies have renoprotective effects and improve the outcomes of diseases by activating antioxidant defense mechanisms and reducing proinflammatory signaling pathways.[12-13] For instance, previous study found that curcumin therapy for three months reduced the levels of inflammation-related markers in CKD patients receiving hemodialysis.[14] However, some of herbal medicines have been found to be nephrotoxic when incorrectly utilized. Thus, the proper usage of herbal medicine is necessary to avoid the nephrotoxicity.[15]

Cymbopogon citratus Stapf. (Poaceae), lemongrass, is a widely used herb in tropical countries for more than 2000 years.[16-17] It can be used for a variety

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of therapeutic, dietary, and cosmetic purposes. The phytochemicals in lemongrass include tannins, carotenoids, alkaloids, volatile and nonvolatile terpenoids, and flavonoids.[18] Previous research found that lemongrass is used as an antioxidant and anti-inflammatory, anticarcinogenic, hypoglycemic, and cardioprotective agent in folk medicine.[19] Even though this plant has a wide range of nutritional uses and has been consumed for a while, there lack any comprehensive investigations on its impact on the kidney disease, especially CKD. The information that is currently accessible in the literature is ambiguous and contradictory. Renal toxic effects have been shown in certain investigations, but not in others.[16,20,21] Additional empirical evidence is still necessary to scientifically validate the aforementioned claims and to support its usage or avoidance in patients who are elderly, undergoing dialysis, or taking other drugs with documented harmful renal effects. Therefore, the purpose of this study was to examine the safety of *Cymbopogon citratus* Stapf. aqueous extract in patients with CKD stage 3.

MATERIALS AND METHODS

Plant material (collection, identification and extraction)

The plant was cultivated in Ayutthaya province, Thailand and was collected on April 2021. Its botanical identity was determined and authenticated by a taxonomist, a voucher specimen has been deposited in the herbarium of the Department of Thai Traditional and alternative Medicine, Ministry of Public Health, Thailand, under the register TTM No. 0005470.

The *C. citratus* were cut into small pieces and sun dried for 1 day. Next, the extract was prepared by boiling dried-leave 1 gram in water 10 ml and reflux at 100 °C for 1 hour,[22] then was filtration with filter cloth, then remove the water from the extract with was applied by spray drying technique. *C. citratus* extract powder extract was stored at -20 °C before encapsulated using hard gelatin capsules. Additionally, placebo capsules were manufactured from starch in a factory that meets GMP standards.

Determination contaminated contents of heavy, metal microbial in herbal drugs and phytochemicals compound analysis

According to the Thai Herbal Preparation Pharmacopoeia 2020, the *C. citratus* capsule was analyzed for contents of contaminants, including heavy metals such as lead, mercury, cadmium, and arsenic. Microbiological analyses, which included total plate count, yeast and mold, *Clostridium* spp., *Escherichia coli* and *Salmonella* spp., were conducted at Central Laboratory (Thailand) Co., Ltd., supervised by the Ministry of Agriculture and Cooperatives, Thailand.

Phenolic compounds in the *C. citratus* leaf aqueous extract were further quantitated by high-performance liquid chromatography with diode array detection and a mass spectrometry detector (HPLC-DAD/MS). The phenolic compounds were separated using an Agilent 1100 series HPLC system (Agilent Technologies, Germany). The standard of phenolic compounds and ammonium formate was purchased from Sigma-Aldrich (Germany) and Acetonitrile was purchased from labscan, Ireland. The column used in this study was LiChroCART RP-18e reversed-phase column (150 X 4.6 mm) packed with 5 µm diameter particles (Purospher STAR Merck, USA). The gradient of acetonitrile (solvent A) and 10 mM ammonium formate buffer, pH 4, with formic acid (solvent B) was used as a mobile phase (MP) and the separation of compounds was carried out with a gradient with the condition as follows: 0-5 min (5% B) constant, 5 - 10 min (0 - 20% A), 10 - 20 min (20% A) constant, 20 - 60 min (20 - 40% A). The other conditions were as followed, 1 mL min^{-1} flow rate, 40°C column temperature, a diode array detector recording at 270, 330, 350 and 370 nm and MS detector was scanning mode 100 -700 m/z,[23] mass spectrometry detection was carried out using an Agilent Mass Detector system (Agilent Technologies, USA) for confirming and identifying the components in unresolved chromatographic peaks.

Trial design and patient recruitment

This study was a double-blind placebo-controlled randomized clinical trial carried out between June 2022 and 2023. The trial was approved by the ethics committee under the protocol No. Q004h/64 of Institutional Review Board Royal Thai Army Medical Department and carried out in accordance with the Declaration of Helsinki. The trial was registered at Thai Clinical Trials Registry (TCTR No. 20230720001). Any chronic kidney disease stage 3 patients attending the Nephrology department, Phramongkutklao Hospital in Thailand were assessed for eligibility of enrollment in this study. Inclusion criteria were: male or females had an eGFR between 30-59 ml/min/173m^2, aged between 35-85 years. Exclusion criteria were: diabetes mellitus, malignant disease of all stage, severe congestive heart failure, liver disease and severe chronic systemic infectious. Undergoing with immunosuppressive agents/ corticosteroids agents or received of any investigational drug within one-month preceding screening, systemic lupus erythematosus (SLE), alcohol dependence, pregnancy or lactation period, allergic to lemongrass. All the participants signed the informed consent. Sixty-four patients who met the study criteria were enrolled in the study. Total 64 patients were randomized into two groups: the trial group (n=32) and the controls (n =32); a randomization by block method was used size of four. Clinical investigators, laboratory personnel, and patients were all masked to the treatment assignment. Each patient in the trial group received a safe dose of *C. citratus* (One capsule with each meal containing 450 mg *C. citratus* extract, of which 900 mg, 2 caps/day for 90 day) while the control group received placebo capsules for the same 90-day period. The type and dose of the individualized drugs remained unchanged during the study. All drugs and placebo capsules were exhibited an identical appearance (size 0 gel capsule) similar in size, shape, weight and color.

Safety assessment

The dose range employed was adapted from previous human studies and the dose of the drug examined in this study was the reference Dose (RfD) using probabilistic multiplication from the NOAEL (no-observed-adverse-effect level).[24-25] In this study, a dosage of 900 mg per day was used, with prolonged administration for 90 days. Before the study, all of the patients were receiving a bag including of blood pressure digital machine, pen, blood pressure record and adverse effect questionnaire.

The study patients were requested to record blood pressure (BP), pulse (P) and take notes any symptom changes such as jaundice, gastrointestinal disturbances, nausea and vomiting, headache. There is also avoid excessive physical activity, ingestion of alcohol or any herbs and remain the regular food or water intake, sleep pattern throughout participating in the study. No evidence of adverse/toxic effects was observed day-to-day, as judged by results of the tolerability evaluation. However, during the study, the participants still continued standard treatment with the conventional medicine. All the measurements and clinical evaluations performed by the same person throughout the study (at the start, during, and end). The data collection technique was based on interview and laboratory blood tests. In the study, patients were evaluated during monthly visits to the Nephrology Department for side effects in a pre-post experimental study of each session.

The laboratory test and clinical assessment, including test for liver function, kidney function including of blood urea nitrogen (BUN), serum creatinine (Scr), cystatin C (Cys-C), and estimated glomerular filtration rate (eGFR). Liver function test consist of total bilirubin

(T-Bil), aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP). in addition, red blood cell (RBC), hematocrit (HCT), blood electrolyte with consist of sodium (Na^+), potassium (K^+), chloride (Cl^-), and bicarbonate (HCO3). In terms of other biochemical tests, such as fasting blood sugar (FBS) and blood mineral concentration that consist of calcium (Ca^+), magnesium (Mg), phosphorus (PO_4) and uric acid were also checked of parameters.

However, adverse effects were reported by the patients or observed by the investigation during the follow-up period. Physical examinations were also performed on each participant to check for the presence of jaundice or pallor (evidence of hepatotoxicity or hemolysis) and abnormal skin reactions were reported.[26]

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software, version 15.0 (SPSS Inc). Association between categorical variables was analyzed using the Chi square test. Quantitative data were presented as mean ± standard deviation and compared by independent-samples *t*-test in the between groups. Data variations were performed before and after administration of lemongrass within group by paired-samples t-test and repeated measures ANOVA. All the tests were two-sided, and p values ≤0.05 were considered significant.

RESULTS

Analysis of *Cymbopogon citratus* Stapf. extract

The results of the chemical, physical, and microbial analyses of the *C. citratus* capsule showed that the extract had a loss on drying of ≤ 5.82 %, and a pH (1% in water) was 5.88. HPLC-DAD/MS analysis indicated that each 450 mg capsule contains 0.87 mg of rutin, followed by 0.85 mg of tannic acid. Chromatographic confirmation revealed that the *C. citratus* contained at least six compounds: gallic acid (t_R = 5.59 min), isoquercetin (t_R = 16.11 min), quercetin (t_R = 33.02 min), rutin (t_R = 15.04 min), catechin (t_R = 12.47 min) and tannic acid (t_R = 12.82 min), as shown in figure 2. Furthermore, the *C. citratus* extract capsule was found to be free from various heavy metals and microbial contaminants, as detailed in Table 1. The phytochemical analysis is presented in Table 2.

The demographic and clinical characteristics of the patient study

Patients who visited the Nephrology department at Phramongkutklao Hospital in Thailand from June 2022 to 2023 were evaluated for study eligibility. Out of them, sixty-four met the inclusion criteria and were subsequently randomized in a double-blind manner into two distinct groups. 3 patients could not continue due to relocation and an accident, resulting in a total of 61 participants for this research. These were further divided into the trial group with *C. citratus* (n=30) and a control group given a placebo (n=31) as the figure 1. The table 3 presents the baseline demographic clinical characteristics and laboratory in patients with chronic kidney disease stage 3. Notably, there were no significant differences between 2 groups in demographic and clinical baseline, gender, age, body mass index (BMI) which ensure the homogeneity of the group at the before study.

Effect of *Cymbopogon citratus* Stapf. on liver function

Figure 3 shows a comparative analysis of the liver function test parameters, specifically T-Bil, AST, ALT, and ALP, observed at various intervals during the study for both groups. In the placebo group, the T-Bil levels exhibited a significant decrease on day 30 from the baseline (P<0.01), yet no remarkable differences were observed between the two groups. Conversely, on day 60, the ALP levels in the placebo group showed a significant increase from the baseline (P<0.01), and when compared with the *C. citratus* group, the difference was also statistically significant (p=0.05). For the *C. citratus* group, there were no statistical variations in the levels of T-Bil, AST, ALT, and ALP. Additionally, the average value of liver function tests on T-Bil, AST, and ALT did not present any significant different between the two groups. However, it's noteworthy to mention that the liver function levels for both groups remained within the standard range, both at baseline and at the end of study.

Effect of *Cymbopogon citratus* Stapf. on kidney function

Table 4 provides a comparative analysis of kidney function parameters, specifically focusing on blood BUN and SCr levels, measured monthly or every 30 days over a 90-day period for both groups. No significant differences were observed in the BUN levels across the groups. However, both groups displayed a statistically significant increase in the mean SCr level by day 60 and at the end of study. In the *C. citratus* group, the SCr level increased from an initial 1.60±0.33 mg/dL to 1.67±0.33 mg/dL on day 60 and further to 1.66±0.29 mg/dL by day 90 (p=0.01). In contrast, the control group found an increasing from a baseline of 1.60±0.32 mg/dL to 1.70±0.37 mg/dL on day 60, and then to 1.73±0.36 mg/dL at the study's end. Nonetheless, the average SCr levels between the two groups did not differ significantly.

Furthermore, figure 4 represent a comparison of the measured parameters of cystatin C (SCys-C) and estimated glomerular filtration rate (eGFR). The *C. citratus* group exhibited no significant change in eGFR levels, from 40.51±7.25 to 39.37±8.80 ml/min/173m^2, while the control group had a significantly decrease in eGFR from 39.48±6.08 to 36.78±6.35 ml/min/173m^2 (P<0.01). In addition, the mean serum concentrations of SCys-C group did not exhibit significant changes, shifting slightly from 1.46±0.28 to 1.48±0.27 mg/dL by day 90. On the

Table 1: The analysis of heavy metal and microbial contents contaminated in *C. citratus* extract.

Parameters (test method)	Result (limit)
Heavy metals (Analyst, August 1994, Vol.119 1683-1686)	
Lead (Pb)	ND (< 10.0 mg/kg)
Mercury (Hg)	ND (< 0.5 mg/kg)
Cadmium (Cd)	0.019 (< 0.3 mg/kg)
Arsenic (AS)	ND (<5.0 mg/kg)
Microbiology	
Total plate count (INH-USP38/33:2015)	< 10 (< 3000 cfu/g)
Yeast and Mold (FDA BAM *online*, 2001, chapter 18)	< 10 (< 100 cfu/g)
Clostridium spp. (USP38/33:2015)	ND (not detected per 1 gram)
Escherichia coli (INH FDA BAM online, 2020 (chapter 4))	ND (not detected per 1 gram)
Salmonella spp. (INH-ISO 6579-1: 2017(E))	ND (not detected per 10 gram)
Staphylococcus aureus. (USP38/33:2015)	ND (not detected per 1 gram)

ND; Not detected

Table 2: Phytochemical compound detected of *C. citratus* Stapf. Extracts.

Compound	Retention time (min)	Characteristic ions (m/z)	Amount (mg/capsule)
Gallic acid	5.59	188, 209	0.017
Catechin	12.47	185, 329, 503, 649	0.048
Tannic acid	12.82	185, 329, 503, 649	0.85
Rutin	15.04	185, 329, 503, 649	0.87
Isoquercetin	16.11	185, 329, 503, 649	0.26
Hydroquinin	24.56	289, 327, 341	Not detected*
Eroidictyol	30.70	289, 327, 341	Not detected*
Quercetin	33.02	289, 327, 341	0.23
Apigenin	41.07	271, 287, 309, 325	Not detected*
Kaempferol	42.36	271, 287, 309, 325	Not detected*

*Limit of detection: in 450 mg

Table 3: Demographic data of patients according to group allocation (*C. citratus* vs. control).

Characteristic	Group		P -value
	C. citratus (n=30)	Control (n=31)	
Gender (%)			0.42
Male	28.1	37.5	
Female	71.9	69.84	
Age (yr.)	69.28±12.34	69.84±12.34	0.56
High (cm)	63.06±7.85	62.26±8.9	0.08
Weight (Kg)	67.01±13.25	67.07±14.89	0.98
Body mass index (kg/m^2)	25.19±4.15	25.37±4.73	0.87
Systolic blood pressure (mmHg)	135.41±16.22	135.29±14.59	0.97
Diastolic blood pressure (mmHg)	74.41±11.55	78.03±10.34	0.19
eGFR (mL/min/1.73 m^2)	40.51±7.25	39.48±6.08	0.55
Cystatin C (mg/dL)	1.46±0.28	1.59±0.31	0.11
Blood urea nitrogen (mg/dL)	19.74±6.20	20.74±5.79	0.51
Serum creatinine(mg/dL)	1.60±0.33	1.60±0.32	0.99
Total bilirubin (g/dL)	0.60±0.27	0.64±0.20	0.52
Aspartate aminotransferase (g/dL)	27.01±6.67	26.79±5.70	0.88
Alanine transaminase (g/dL)	19.70±11.20	21.72±13.30	0.52
Alkaline phosphatase (U/L)	69.80±20.19	77.74±19.87	0.12
Red blood cell (cell/mm^3)	4.42±0.67	4.53±0.76	0.53
Hematocrit (%)	39.75±4.79	39.44±4.94	0.79
Blood electrolyte (mEq/L)			
Sodium	139.58±2.87	139.81±2.45	0.73
Potassium	4.36±0.45	4.34±0.59	0.93
Chloride	103.67±3.1	104.02±2.64	0.63
Carbon dioxide	26.22±2.56	25.62±2.12	0.31
Fasting blood sugar (mg/dL)	98.08±16.50	100.59±18.45	0.57
Calcium (mg/dL)	9.17±0.43	9.27±0.48	0.46
Magnesium (mg/dL)	2.18±0.15	2.10±0.30	0.18
Phosphorus (mEq/L)	3.15±0.54	3.44±0.52	0.33
uric acid (mg/dL)	7.44±2.39	7.37±1.86	0.99
Alcohol (%)			0.73
Never	15.6	9.4	
Current	75	75	
Ever	9.4	12.5	

eGFR; estimated glomerular filtration rate. Data are expressed as mean ± standard deviation (Mean±SD), (%), *Chi-square test, independent sample t test, significant difference ($p \leq 0.05$)

Table 4: Effect of *Cymbopogon citratus* Stapf. on blood urea nitrogen and serum creatinine.

Variable	Group	Time				[a]p-value
		Day0	Day30	Day60	Day90	
BUN (mg/dL)	*C. citratus*	19.74±6.20	21.20±7.86	21.62±7.77	20.75±7.86	0.28
	Control	20.74±5.79	21.63±7.31	23.22±6.47	21.67±6.76	0.16
	[b]***p*-value**	0.51	0.82	0.38	0.62	
SCr (mg/dL)	*C. citratus*	1.60±0.33	1.63±0.35	1.67±0.33	1.66±0.29	0.01*
	Control	1.60±0.32	1.59±0.36	1.70±0.37	1.73±0.36	(P<0.01)*
	[b]***p*-value**	0.99	0.70	0.71	0.41	

BUN; blood urea nitrogen, SCr; serum creatinine. Data are expressed as mean ± standard deviation (Mean±SD), [a]p-value; statistic repeated measures ANOVA and pair sample t test compare with day0, measurement within group, [b]p-value; statistical independent sample t-test measures between groups. *; significant difference *p*-value (p ≤ 0.05)

Table 5: Comparison Mean±SD of blood sugar and mineral concentration level.

Variable	Group	Time		[a]p-value
		Day0	Day90	
FBS (mg/dL)	*C. citratus*	98.08±16.50	103.22±25.17	0.31
	Control	100.59±18.45	103.90±14.48	0.12
	[b]***p*-value**	0.57	0.89	
Ca^{+} (mg/dL)	*C. citratus*	9.19±0.43	9.17±0.45	0.84
	Control	9.27±0.48	9.18±0.42	0.22
	[b]***p*-value**	0.46	0.91	
Mg (mg/dL)	*C. citratus*	2.18±0.15	2.17±0.18	0.54
	Control	2.10±0.30	2.09±0.19	0.87
	[b]***p*-value**	0.18	0.11	
PO_4 (mEq/L)	*C. citratus*	3.15±0.54	3.40±0.56	0.01*
	Control	3.44±0.52	3.35±0.51	032
	[2]***p*-value**	0.33	0.75	
Uric acid mg/dL	*C. citratus*	7.44±2.39	7.31±1.66	0.75
	Control	7.37±1.86	7.36±2.15	0.98
	[2]***p*-value**	0.99	0.92	

FBS; fasting blood sugar, Ca^{+}; calcium, Mg; magnesium, PO_4; phosphorus. Data are expressed as mean ± standard deviation (Mean±SD), [a]p-value; statistic pair t test measurement within group, [b]p-value; statistical independent sample t-test measurement between groups, *; significant difference *p*-value (p ≤ 0.05).

Table 6: Comparison Mean±SD of complete blood count on RBC and HCT.

Variable	Group	Time				[a]p-value
		Day0	Day30	Day60	Day90	
RBC (10^6 cell/mm^3)	*C. citratus*	4.42±0.67	4.07±0.59	4.27±0.72	4.23±0.66	0.31
	Control	4.53±0.76	4.53±0.74	4.33±0.66	4.44±0.76	0.01*
	[b]***p*-value**	0.53	0.17	0.76	0.25	
HCT (%)	*C. citratus*	39.75±4.79	38.91±4.18	38.35±4.66	38.17±4.92	0.01*
	Control	39.44±4.94	39.27±4.99	38.28±4.48	38.49±4.72	0.01*
	[b]***p*-value**	0.79	0.75	0.95	0.79	

RBC; Red Blood Cell, HCT; Hematocrit, Data are expressed as mean ± standard deviation (Mean±SD), [a]p-value; statistic pair t test measurement within group, [b]p-value; statistical independent sample t-test measurement between groups, *; significant difference *p*-value (p ≤ 0.05)

other hand, the placebo group displayed a substantial rise in SCys-C levels, escalating from 1.59±0.31 to 1.74±0.50 mg/dL in the placebo group (*p*=0.05).

Effect of *Cymbopogon citratus* Stapf. on blood electrolyte

Figure 5 presents a comparative analysis of blood electrolyte parameters, measured monthly over a 90-day period between the two groups. There were no significant variations in the electrolyte levels between the groups. Specifically, in the *C. citratus* group, there was a statistically significant decrease in Na^{+} levels from 139.58±2.87 at baseline to 138.79±2.51 mEq/L (P<0.01) at day30 and HCO3 levels dropped from 104.02±2.64 at baseline to 24.76±2.94 on day 60 (p=0.01) and further to 23.21±3.80 by day 90 (P<0.01). However, these variations were not observed in the control group. the control group exhibited a significant increase in Na^{+} and Cl^{-} levels. Specifically, Cl^{-} levels rose from 104.02±2.64 mEq/L at baseline to 105.65±3.40 mEq/L on day 60 (P<0.01) and 105.62±4.24 mEq/L on day 90, with a significant difference noted on day 60 when compared to the *C. citratus* group (p=0.03). Similarly, Na^{+} levels in the control group increased from 139±2.45 mEq/L at baseline to 141.05±3.34 mEq/L by day 90 (p=0.02), yet there was no significant difference between the groups. The average levels of K^{+} and Cl^{-} in the *C. citratus* group remained unchanged from baseline. Throughout the study period, there were no significant differences in the levels of Na^{+}, K^{+}, and HCO3 between the *C. citratus* and control groups. Importantly, both groups-maintained blood electrolyte levels within the clinically accepted range, with no significant side effects observed at either the study's baseline or the end.

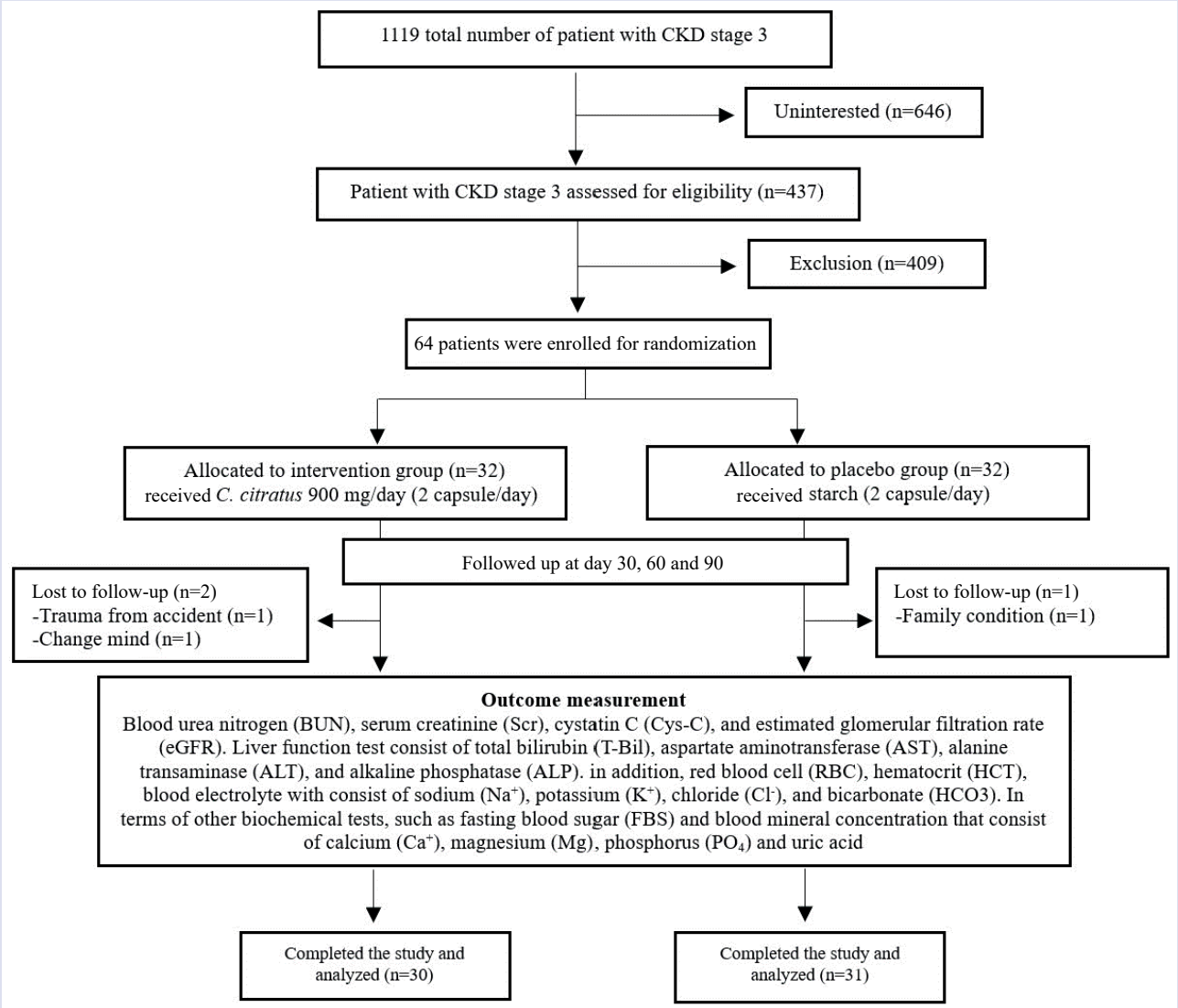

Figure 1: Trial study flow diagram of the patients, enrollment, allocation and analysis.

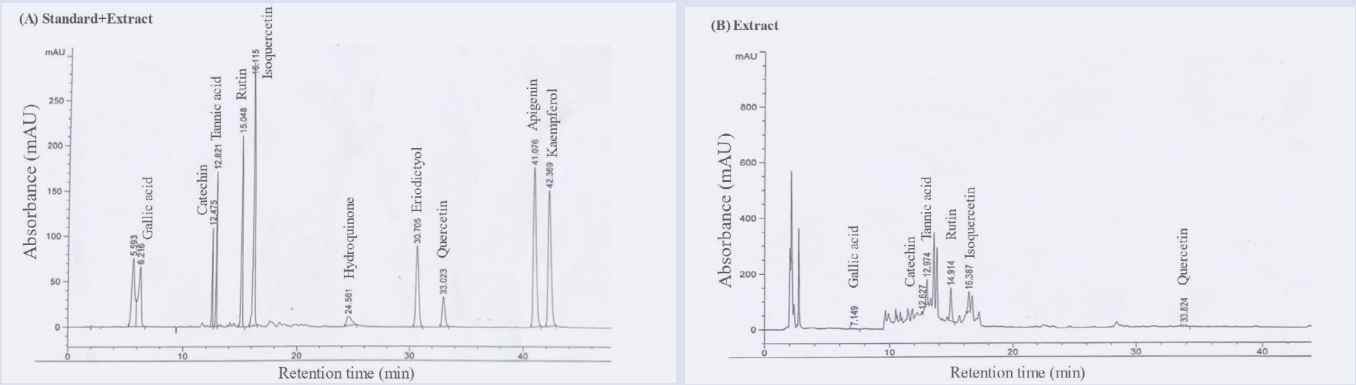

Figure 2: HPLC-DAD/MS chromatographic of phenolic substances mixture (A), representative sample of *Cymbopogon citratus* Stapf. leaf aqueous extracts (B).

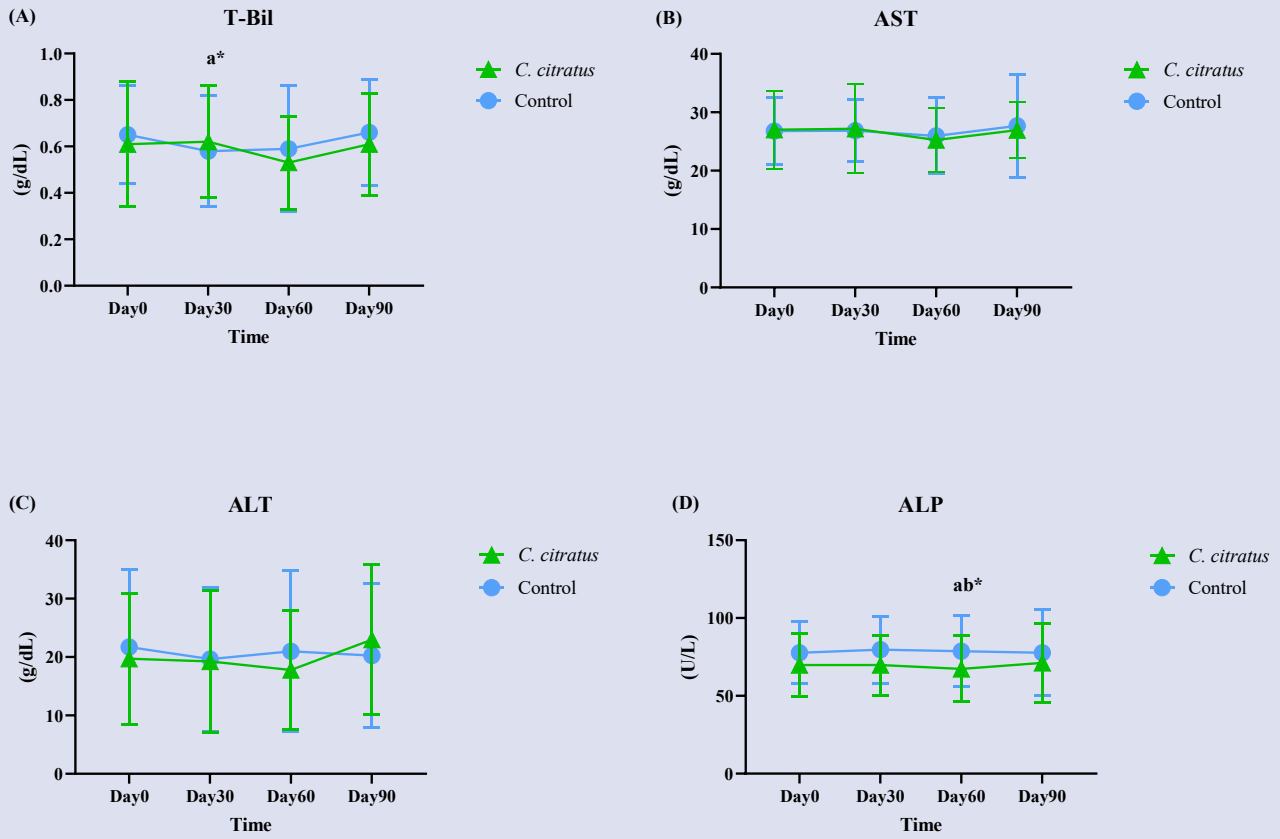

Figure 3: Effect of lemongrass on liver function, T-Bil; Total bilirubin (A), AST; Alanine aminotransferase (B), ALT; Aspartate aminotransferase (C), ALP; Alkaline phosphatase (D).
a; p-value statistic significantly with repeated measures ANOVA and pair sample t test compare with baseline/day0 measures within group,
b; p-value statistical significantly with independent sample t-test measures between groups.
*; significant difference *p*-value ($p \leq 0.05$)

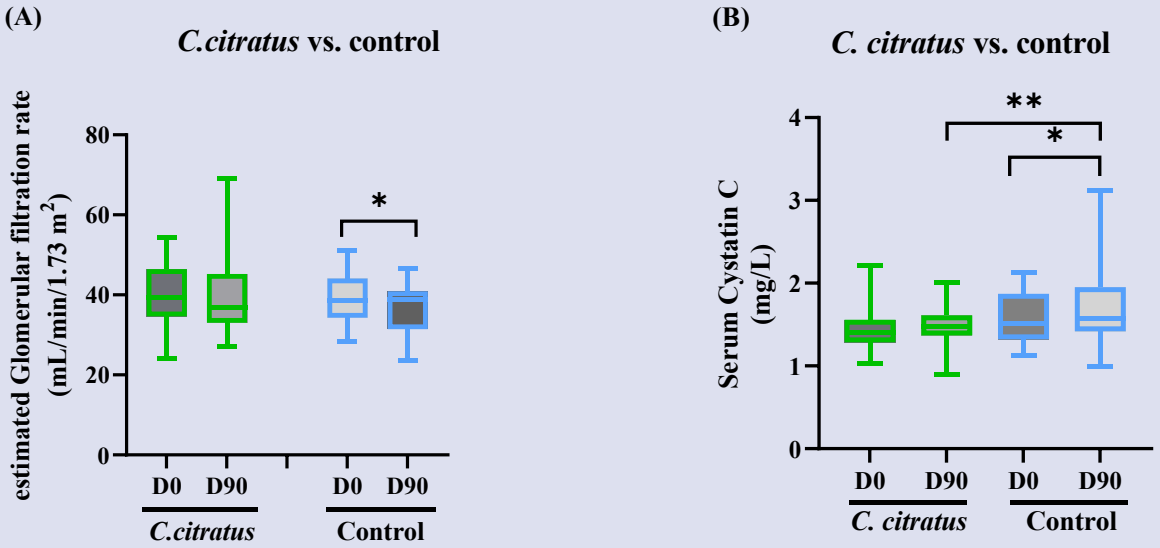

Figure 4: Effect of lemongrass on serum cystatin C in *Cymbopogon citratus* Stapf.
(A) Mean estimated glomerular filtration rate between the C. citratus group and the control group.
(B) Mean of serum cystatin C between the C. citratus group and the control group.
**p*-value; statistical pair sample t test
***p*-value; statistical independent sample t test
ns; non-significant, significant difference ($p \leq 0.05$).

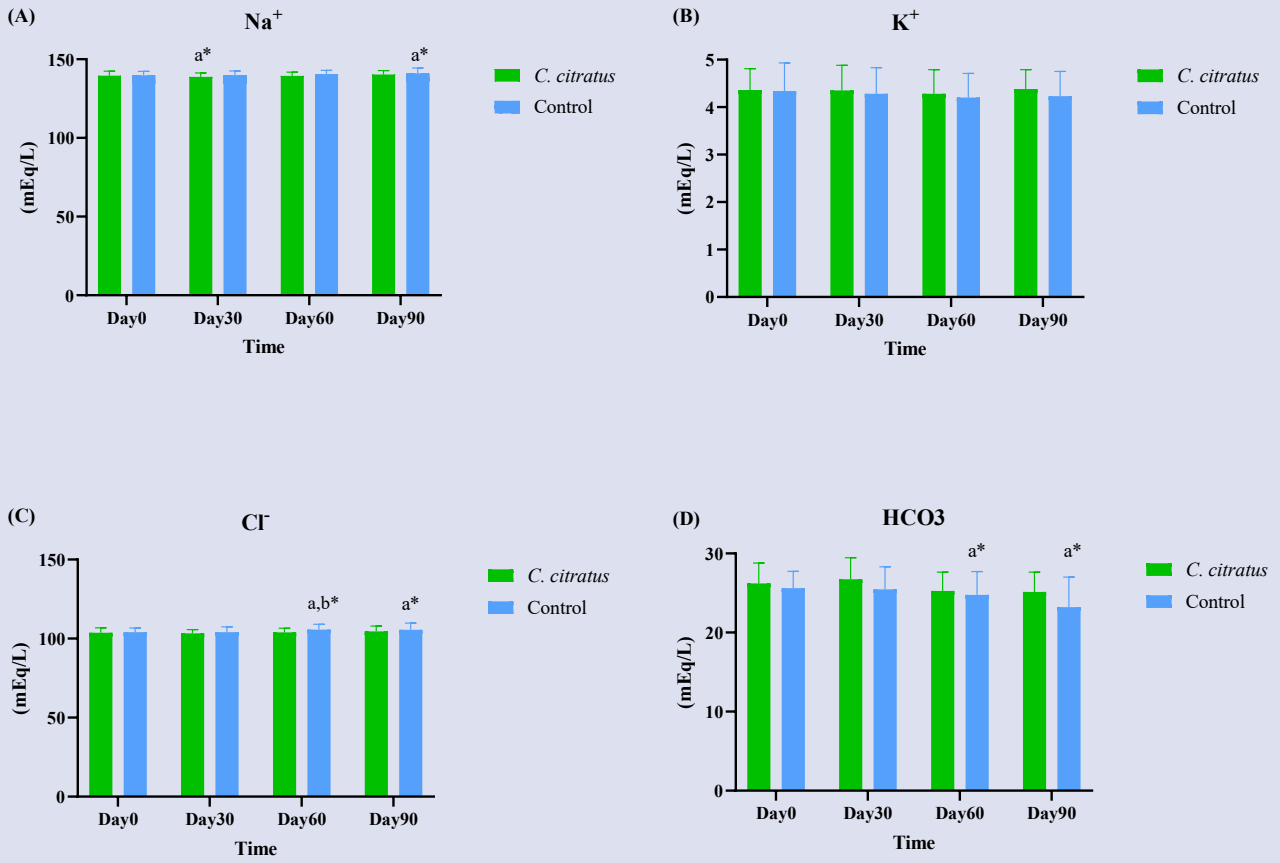

Figure 5: Comparison Mean±SD of blood electrolyte, Na^+; sodium (A), K^+; potassium (B), Cl^-; chloride (C), HCO3; bicarbonate (D).
a; p-value statistic significantly with repeated measures ANOVA and pair sample t test compare with baseline/day0 measures within group,
b; p-value statistical significantly with independent sample t-test measures between groups.
*; significant difference *p*-value ($p \leq 0.05$)

Effect of *Cymbopogon citratus* Stapf. on blood sugar and mineral concentration level

Table 5 presents a comparison of the measured of FBS and mineral parameters, which included Ca^+, Mg, PO_4 and uric acid, observed pre and post the experimental study between the two groups. There were no significant variations found in FBS or minerals. Specifically, in the C. citratus group, there was a statistically significant increase in PO_4 levels, with no associated clinical symptoms. The mean of PO_4 level increased from 3.15±0.54 mEq/L at baseline (day0) to 3.40±0.56 mEq/L (p=0.01) and there was no difference between two groups.

Effect of *Cymbopogon citratus* Stapf. on red blood cell and hematocrit

Table 6 presents a comparison of RBC and HCT, components of a complete blood count (CBC), Measurements were taken every 30 days for a duration of 90 days to assess the safety of consuming lemongrass extract. The data revealed a statistically significant decrease in HCT levels in both groups post-intervention compared to baseline values (p=0.01). The mean HCT value for the *C. citratus* group was 38.49±4.72 (%), while it was 38.49±4.72 (%) for the control group (p=0.01). Additionally, a significant reduction in RBC count was observed specifically in the control group (p=0.01).

DISCUSSION

Chronic kidney disease (CKD) was a major public health issue worldwide. The incidence of CKD tended to rise.[1] Consequently, it necessitated the investigation of novel methods to postpone the start of dialysis or attenuate the progression of CKD.

In traditional medicine, the benefits of lemongrass in treating various ailments are recognized. Lemongrass is used for several reason to treat the patient such as fever reduction, as a diuretic, and for relieving bloating. In many countries, it is used as a spice and an ingredient in food.[27]

Our present study utilized an aqueous extraction of lemongrass. This method, which involves boiling, aligns with traditional consumption methods where dried lemongrass leaves are boiled for medicinal purposes or brewed as tea for treating various diseases. This study advances the practice of herbal tea or infusion by converting it into capsule form, making the administration of the medicine more convenient. Upon analysis of the lemongrass extract, with a concentration of 450 mg per capsule, the most abundant compound was Rutin, followed by Tannic acid. These findings are consistent with previous studies. Furthermore, the lemongrass extract exhibited antioxidant and anti-inflammatory properties from a phytochemical perspective,[22] lemongrass extract may be beneficial when used in conjunction with the slow progression of CKD disease.

To the best of our knowledge, no research had so far reported the effectiveness or safety of lemongrass in CKD patients. Thus, this was the first study that examine the safety impact of the dietary supplementation with *C. citratus* (lemongrass). Although previous studies indicated that lemongrass compounds are non-toxic to the liver and kidneys in healthy volunteers.[26] But in patients with CKD stage 3 need close clinical and laboratory monitoring. The results of our study,

which tracked symptoms in CKD stage 3 patients. According to the findings, lemongrass had no clinically significant side effects on liver or renal function and adverse drug reaction.

According to the results in the *C. citratus* group, lemongrass had the ability to alter the electrolyte level in the blood by 0.5-0.8%. However, the level of each parameter was similarly in accordance with normal criteria for CKD stage 3,[28] and it did not differ from the control group. Evidence from the literature, which was consistent with our findings, also supported the idea that the level of blood electrolyte composition might change in the *C. citratus* group. When healthy volunteers were given once-daily infusions made from 8 g of lemongrass leaf powder, their electrolyte composition considerably increased by day 30.[20]

Furthermore, we discovered that the levels of creatinine in both groups considerably rose; however, the level of creatinine in the *C. citratus* group at day 90 was 1.69±0.30 mg/dL, whereas the level in the control group was 1.73±0.36 mg/dL.

Our study showed that the Scys-C level decreased significantly in patients with CKD stage 3 who received *C. citratus* extract as compared to placebo. More importantly, *C. citratus* group had no effect on eGFR whereas the control group had a significant decrease in eGFR. To support our study, previous research discovered that oral administration of lemongrass significantly restored Cr level near to the normal ranges in rats with adenine-induced chronic renal disease. This research suggested that the antioxidant and anti-inflammatory properties of lemongrass may be responsible for this impact.[17] SCys-C as a marker of glomerular filtration, where an increase in levels indicates the occurrence of acute kidney injury[29] and is associated with inflammation.[30] the lemongrass might have a beneficial effect in delaying the progression of CKD. However, the further research should be investigated on the optimal dose, duration and in-dept mechanism of action for anti-inflammation.

Anemia was one of the most common CKD complications. It was frequently coming with a higher risk of mortality and was linked to poor prognosis for chronic renal disease. [31-33] As a result, new treatment should focus on enhancing renal function and increasing red blood cell production. In the current investigation, *C. citratus* group had no effect on red blood cells, whereas the control group had significantly lower levels of red blood cells. Additionally, patients in the *C. citratus* group appear to benefit more from regulating the level of HCO3 and Cl^- than those in the control group. Although there are statistically significant differences, there were no changes in clinical manifestations.

CONCLUSION

To the best of our knowledge, lemongrass was generally safe when given for up 90 days in CKD patients. In addition, lemongrass had beneficial effect on regulating bicarbonate and red blood cell in CKD patients. Lemongrass may have a minor effect on creatinine levels, but these remain within the normal range in CKD stage 3 patients. The findings of the current study may have practical implications for clinicians and consumers regarding dosage adjustments, consumption duration, or even contraindications, particularly in CKD patients. Additionally, these findings should be shared with patients in areas where lemongrass is commonly used, especially those taking medications such as diuretics, aminoglycoside antibiotics, and angiotensin-converting enzyme inhibitors, which have a negative impact on renal function. Future multicenter randomized trials with larger sample sizes and extended treatment durations are needed to further validate the long-term efficacy and safety of incorporating lemongrass into the treatment regimen for CKD stage 3 patients.

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CONFLICTS OF INTEREST

There is no competing interest among the authors.

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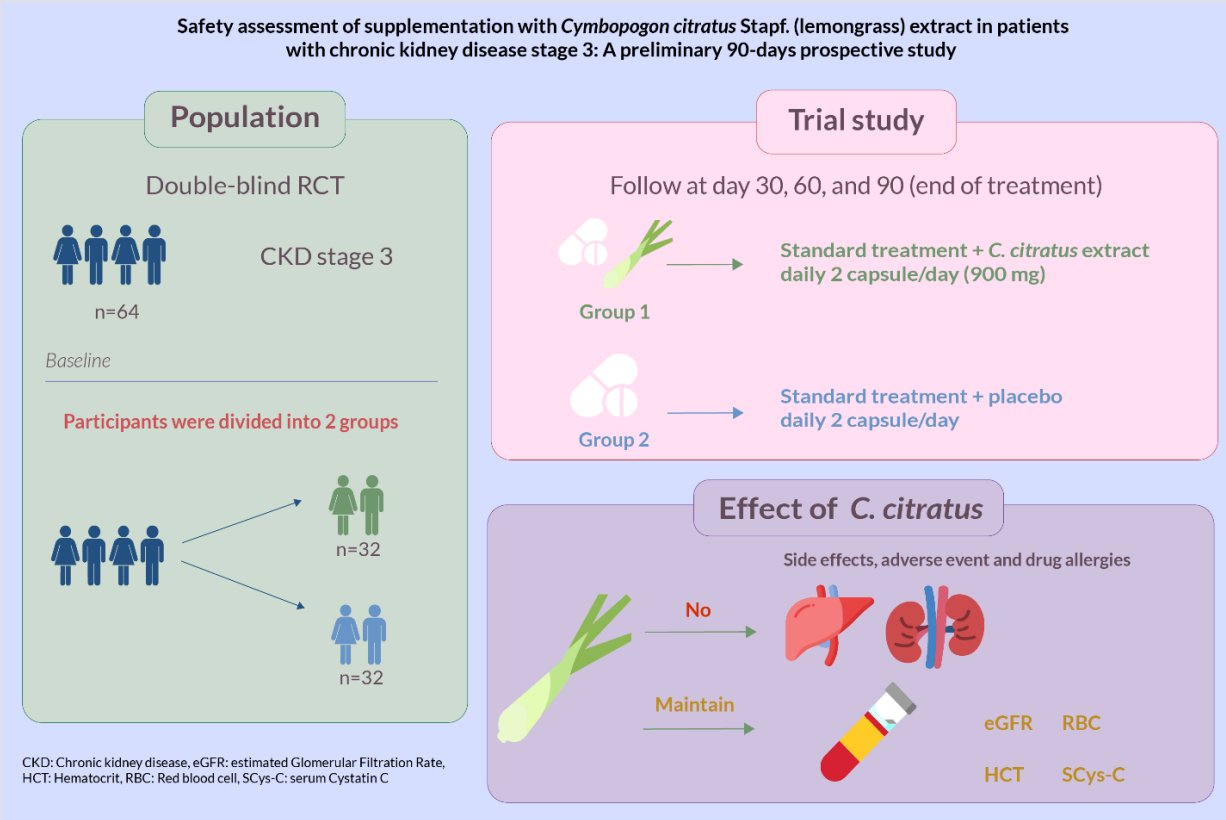
GRAPHICAL ABSTRACT



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