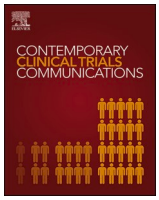
Contemporary Clinical Trials Communications 34 (2023) 101159

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



Effects of Iranian propolis on renal function, prooxidant-antioxidant balance, metabolic status, and quality of life in patients with chronic kidney disease: A study protocol of an ongoing randomized, double-blind, placebo-controlled clinical trial

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ARTICLE INFO

Keywords:
Propolis
Chronic kidney disease
Protocol study
Randomized controlled trial

ABSTRACT

Background: Chronic kidney disease (CKD) is a prevalent and progressive disease that is impacted by hyperglycemia, hypertension (HTN), and oxidative stress (OS). Propolis, a natural resinous mixture produced by honeybees from plant materials, has been shown to possess antioxidant, anti-inflammatory, antihyperglycemic, and antihypertensive properties, along with hepato-renal protective effects. This study aims to evaluate the efficacy of propolis supplementation on patients with CKD.

Methods: This multi-centered, randomized, double-blind, placebo-controlled clinical trial will evaluate the effectiveness of propolis supplementation in 44 eligible patients with CKD. Participants will be randomly allocated to receive either propolis capsule (500 mg, containing 125 mg Iranian alcoholic propolis extract) or placebo, twice daily for three months. The primary outcome is improvement in kidney function parameters of CKD patients, while secondary outcomes include changes in prooxidant-antioxidant balance (PAB), glycemic status, quality of life, and blood pressure (BP). The study will be conducted at Tabriz University of Medical Sciences in Tabriz, Iran.

Discussion: If the results of this study reveal remarkable effectiveness of propolis in improving quality of life and clinical outcomes in patients with CKD, this compound may reach a new milestone as an adjunctive therapy for CKD and it opens a new window for further studies.

Trial registration: Iranian Registry of Clinical Trials, IRCT20191218045798N1. Prospectively registered on 07 June 2020. Updated on 30 August 2021. https://en.irct.ir/trial/48603.

1. Background

Chronic kidney disease (CKD) is a non-communicable progressive disease with high rates of morbidity and mortality, characterized by structural and functional changes in the kidney, primarily caused by diabetes and hypertension (HTN) [1,2]. Based on the present guidelines, CKD is defined by a reduction in renal function, with an estimated glomerular filtration rate (eGFR) below 60 mL/min per 1·73 m^2, or signs of kidney damage such as albuminuria, hematuria, or defects revealed through laboratory analysis or imaging, which persist for more than three months [1]. The severity of CKD varies from renal damage with normal function to renal failure (or end-stage renal disease (ESRD)), which is described as an eGFR below 15 mL/min per 1·73 m^2 [1]. Early CKD is usually asymptomatic until the more advanced stages (i.e., eGFR of less than 30 mL/min per 1·73 m^2) [1]. The global prevalence and burden of CKD is high and increasing, with approximately 10% of the adult population worldwide affected by some form of CKD [3]. Premature death is up to ten times more likely than progression to ESRD in

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https://doi.org/10.1016/j.conctc.2023.101159
Received 22 February 2023; Received in revised form 4 May 2023; Accepted 2 June 2023
Available online 10 June 2023

people with CKD [4]. This greater risk of death is mainly due to cardiovascular disease (CVD) [4]. People with CKD have a significantly lower health-related quality of life compared to the general population, and it decreases in proportion to the lowering rate of GFR [4]. Therefore, early diagnosis and treatment of CKD can be a practical method for attenuating the ESRD, CVD, and total mortality [4,5]. Although non-pharmacological strategies (e.g., dietary and lifestyle modifications) as well as pharmacological treatments can be used to preserve renal function, the development of novel approaches is necessary for slowing down the progression of the disease, preventing complications, and achieving higher longevity and better health-related quality of life, especially in the early-stages [1]. Based on the present evidence, hyperglycemia, HTN, and oxidative stress (OS) are three basic parameters for CKD pathogenesis and progression [1,6].

Propolis is a natural resinous mixture produced by honeybees by mixing exudate collected from plants with salivary enzymes and beeswax, and it contains multiple polyphenolic compounds, mostly flavonoids and phenolic acids [7–9]. Human and animal studies showed beneficial effects of propolis on various chronic diseases like diabetes mellitus (DM), HTN and liver and renal dysfunction due to its antioxidant, anti-inflammatory, antihyperglycemic, antihypertensive, and hepato-renal protective effects [9]. Considering the mutual interaction between OS, HTN, and hyperglycemia in CKD, it seems that propolis supplementation would contribute to improve the treatment outcomes of CKD patients. To the best of our knowledge, there is no clinical trial investigating the effects of propolis on kidney function, prooxidant-antioxidant balance (PAB), metabolic status, and quality of life in patients with CKD.

1.1. Objectives

The current clinical trial aims to assess the following:

1) To determine the effect of Iranian propolis supplementation on proteinuria, 24-h urine volume, and serum creatinine in patients with CKD.
2) To evaluate the effect of Iranian propolis supplementation on PAB in patients with CKD.
3) To identify the effect of Iranian propolis supplementation on glycemic status (Homeostatic model assessment for insulin resistance (HOMA-IR), fasting blood sugar (FBS), hemoglobin A1C (HbA1C), and insulin levels) in patients with CKD.
4) To ascertain the effect of Iranian propolis supplementation on quality of life in patients with CKD.
5) To determine the effect of Iranian propolis supplementation on blood pressure (BP) in patients with CKD.

2. Methods

2.1. Trial design

The current study is a prospective, multi-centered, randomized, double-blind, placebo-controlled, parallel-arm phase III clinical trial evaluating the effectiveness of propolis supplementation for three months in subjects with CKD. Randomization is at a 1:1 ratio for the two arms of the trial. The study has been registered with the Iranian Registry of Clinical Trials (IRCT) under ID number IRCT20191218045798N1. The study protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist (Additional file 1), and any protocol amendments will be reported to the Medical Ethics Committee of Tabriz University of Medical Sciences for approval and will be documented in the IRCT.

2.2. Study setting

The projected randomized clinical trial (RCT) will take place at Salamat Specialized Community Clinic and Asad Abadi Academic Hospital in Tabriz, Iran.

2.3. Eligibility criteria

Subjects who meet the following criteria may recruit in this project: the ability and willingness to participate in the study, having stage 2 or 3 CKD according to eGFR of 30–89 ml/min per 1.73 m^2, aged between 20 and 80 years, and body mass index (BMI) of 18.5–35 kg/ m^2. Patients with kidney transplant, pregnant women or nursing mothers, professional athletes, smokers, opium or alcohol users, people with allergies to bee products, those with an inflammatory or infectious diseases, malignancy, asthma, or severe liver disease, patients who are being treated by psychotherapy, steroids or other immune system suppressors, and subjects who take herbal supplements during the three months before participating in the study, will be excluded. All volunteers will be given written informed consent before allocation to study arms, with all the information needed including risks and benefits, confidentiality of the data, contact information of the principal investigator for asking the questions, and other necessary details. Participants will be free to withdraw from the study project for any reasons including: sensitivity to propolis compound, become pregnant, have any changes in their medication, have poor compliance with the study protocol (less than 80%), and develop an acute illness such as acute kidney injury (AKI) or start dialysis.

2.4. Study interventions

Participants in the intervention group will receive a propolis capsule twice a day, one capsule before breakfast and one capsule before dinner, for three months. Capsules will be provided in containers of 60 (one month's supply) and will be stored in a dry, cool location during the study. Each propolis capsule contains 125 mg of Iranian alcoholic propolis extract, 187.5 mg of bee pollen, and 187.5 mg of oat, including 36 mg total amount of phenolic compounds. The propolis sample is collected from honey bee colonies located in Isfahan, Iran. The comparator is an identical placebo capsule. Patients in the control group will receive a placebo capsule (containing 125 mg wheat starch, 187.5 mg bee pollen, and 187.5 mg oat) twice a day, before breakfast and dinner, for three months. The dosage of propolis was obtained from studies that had used similar amounts without observing side effects [10,11]. Propolis and placebo capsules are similar in appearance, odor, taste, weight, and packaging and are produced by the Asal Shahdineh Golha Co., Isfahan, Iran. This intervention will not interfere with the standard treatment of patients with CKD. Subjects in both groups, along with supplementation, will receive a renal-specific diet and be encouraged to increase their physical activity.

2.5. Adherence to the intervention

Compliance with the physical activity program, renal-specific diet, and propolis or placebo supplement will be assessed at each phone call (twice a month) and will be rechecked by interviewing the patients and counting the returned capsules during each study visit (monthly). To enhance adherence, patients will receive adherence counseling in these sessions. Those who miss more than twenty percent of the supplementation dosage will be excluded from the study at the end of the trial. Compliance will be measured by the following formula:

Compliance rate: (Capsules taken/ Capsules prescribed) × 100

2.6. Safety evaluation

Propolis and most of its chemical constituents are harmless and well-

tolerated if used in moderation, and it is generally recognized as safe (GRAS) [12,13]. There have been no reported side effects after 250 mg/day propolis consumption. It is estimated that ingestion of approximately 1.4 mg propolis/kg/day or 70 mg propolis/day is potentially safe for the organism; however, doses above 15 g/day may cause adverse effects [14]. The median lethal dose (LD50) of propolis extract while given to mice is higher than 7.34 g/kg, which assures human therapeutic dosage safety [14]. However, Tabriz University of Medical Sciences is responsible for monitoring any adverse events and reporting them to the Medical Ethics Committee of Tabriz University of Medical Sciences for decision making. If the stated adverse events are related to the investigational product, the trial will be discontinued, and patients will be referred to a study physician for immediate treatment in which can be provided free of charge to the participants; and they will be followed until satisfactory consequence.

2.7. Outcomes

The primary outcome of this RCT is the change in the kidney function parameters of CKD patients from baseline to the 12 weeks of the intervention. The secondary outcomes are the change in PAB, glycemic status, quality of life, and BP of CKD patients from the study commencement to the end of the intervention period.

Patients will be asked to obtain informed consent at the beginning of the study. Next, a questionnaire covering demographic information, past medical history, family history, drug history, and medication will be filled.

2.7.1. Instruments

2.7.1.1. Dietary intake. Dietary intake will be assessed by a 24-h dietary recall and 3-day food record (two weekdays and one weekend day) questionnaires at the trial's onset, middle, and end. In addition, a validated 7-item appetite questionnaire will be filled for each patient at these time points.

2.7.1.2. KDQOL-SF. Validated Kidney Disease and Quality of Life-Short Form (*KDQOL-SF*) version 1.3 will be used to assess the CKD patients' quality of life at 0 and 12 weeks.

2.7.1.3. Anthropometrics. The anthropometric variables, including weight, height, and BMI, will be assessed by validated tools at 0 and 12 weeks. Weight will be considered with light clothes and without shoes, to the nearest 100 g using a digital Seca scale (Seca 22089, Hamburg, Germany). Height will be measured by a portable stadiometer (Seca, Hamburg, Germany), in the standing position and without shoes, with an accuracy of 0.5 cm. Then, BMI will be estimated by dividing weight in kilograms by height in meters squared.

2.7.1.4. Blood pressure. Blood pressure will be measured by a mercury sphygmomanometer (ALPK2, Japan) at the end of each visit.

2.7.1.5. Biochemical assessment. At the start and end of the study, 10 mL of blood will be obtained from each patient after 12 h of overnight fasting. The samples will be collected into the EDTA tubes (for HbA1C analysis) and tubes without anticoagulant (for centrifugation to obtain the serum). The serum will be used to determine the FBS (enzymatic-colorimetric, Mancompany), insulin (enzyme-linked immunosorbent assay (ELISA), Monobind), and creatinine (Jaffe, Parsazmun). The remaining serum samples will be stored at −20 °C up to the end of the intervention to measure PAB (ELISA, Merck KGaA). Hemoglobin A1C (corrected-enzymatic, Biorexfars) will be measured from whole blood samples. 24-hour urine will be taken at the baseline and the end of the study to measure volume and protein (Photometric, Parsazmun). All biochemical tests except PAB will be conducted immediately after sampling. Homeostatic model assessment for insulin resistance will be calculated as fasting glucose (mmol/L) × fasting serum insulin (μIU/mL)/22.

Researchers blinded to the treatment assignment will assess anthropometric variables, BP, and biological specimens and will interview patients to fill the questionnaires; however, regarding the 3-day food record questionnaire, patients will be instructed on how to complete it by themselves. The timeline of the study and protocol flow chart are provided in Figs. 1 and 2, respectively.

TIMEPOINT; week	STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						Close-out
	$-t_1 = -2$ to -1	0	$t_1 = 2$	$t_2 = 4$	$t_3 = 6$	$t_4 = 8$	$t_5 = 10$	$t_6 = 12$	t_7 = first day
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Randomization		X							
Allocation		X							
INTERVENTIONS:									
Propolis supplementation			←	—	—	—	→		
Placebo supplementation			←	—	—	—	→		
Renal-specific diet			←	—	—	—	→		
Compliance			X	X	X	X	X	X	
Adverse events			X	X	X	X	X	X	
ASSESSMENTS:									
Demographic		X							X
Anthropometrics measurements		X							X
24-h dietary recall		X			X				X
3-day food record		X			X				X
Appetite questionnaire		X			X				X
KDQOL-SF		X							X
Blood pressure		X		X		X			X
Blood collection		X							X
Urine collection		X							X

	STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT; week	*-t_1=-2 to -1*	*0*	*t_1=2*	*t_2=4*	*t_3=6*	*t_4=8*	*t_5=10*	*t_6=12*	*t_7= first day*
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Randomization		X							
Allocation		X							
INTERVENTIONS:									
Propolis supplementation			←	—	—	—	—	→	
Placebo supplementation			←	—	—	—	—	→	
Renal-specific diet			←	—	—	—	—	→	
Compliance			X	X	X	X	X	X	
Adverse events			X	X	X	X	X	X	
ASSESSMENTS:									
Demographic		X							X
Anthropometrics measurements		X							X
24-hour dietary recall		X			X				X
3-day food record		X			X				X
Appetite questionnaire		X			X				X
KDQOL-SF		X							X
Blood pressure		X		X		X			X
Blood collection		X							X
Urine collection		X							X

Fig. 1. Schedule of enrollment, interventions, and assessments for study period based on SPIRIT guidelines. Abbreviation: KDQOL-SF: Kidney Disease and Quality of Life-Short Form; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

2.8. Sample size calculation

In this clinical trial, the sample size was calculated based on eGFR from a study on propolis supplementation in CKD patients conducted by Silveira M.A.D. et al. [10]. As a result, 17 patients in each group were computed using PASS version 15 software and considering 95% confidence interval and 80% power. To compensate for drop-out during follow-up, we raised the final sample size by 30% to 22 patients in each group.

2.9. Study participants and recruitment

The research team will identify potential patients at each study center (Salamat Specialized Community Clinic and Asad Abadi Academic Hospital of Tabriz, Iran). A team member will then contact these patients by phone to provide additional information and evaluate their eligibility. Patients who meet the eligibility criteria and express interest will be enrolled in the study.

2.10. Assignment of interventions: allocation

2.10.1. Sequence generation

In this RCT, stratified block randomization will be used to balance age and diabetes between propolis and placebo groups. Four strata will be developed considering age and diabetes as follows:

- Stratum 1: patients in the age of 20–60 years with DM
- Stratum 2: patients in the age of 20–60 years without DM
- Stratum 3: patients in the age of 60–80 years with DM
- Stratum 4: patients in the age of 60–80 years without DM

Within each stratum indicated above, eligible patients who provided written informed consent will be randomly allocated in a ratio of 1:1 to either propolis or placebo group with a block size of 2. A block size of 2 creates 22 different blocks to assign patients to the study groups. The sequence of the blocks for each stratum will be provided using a table of random numbers.

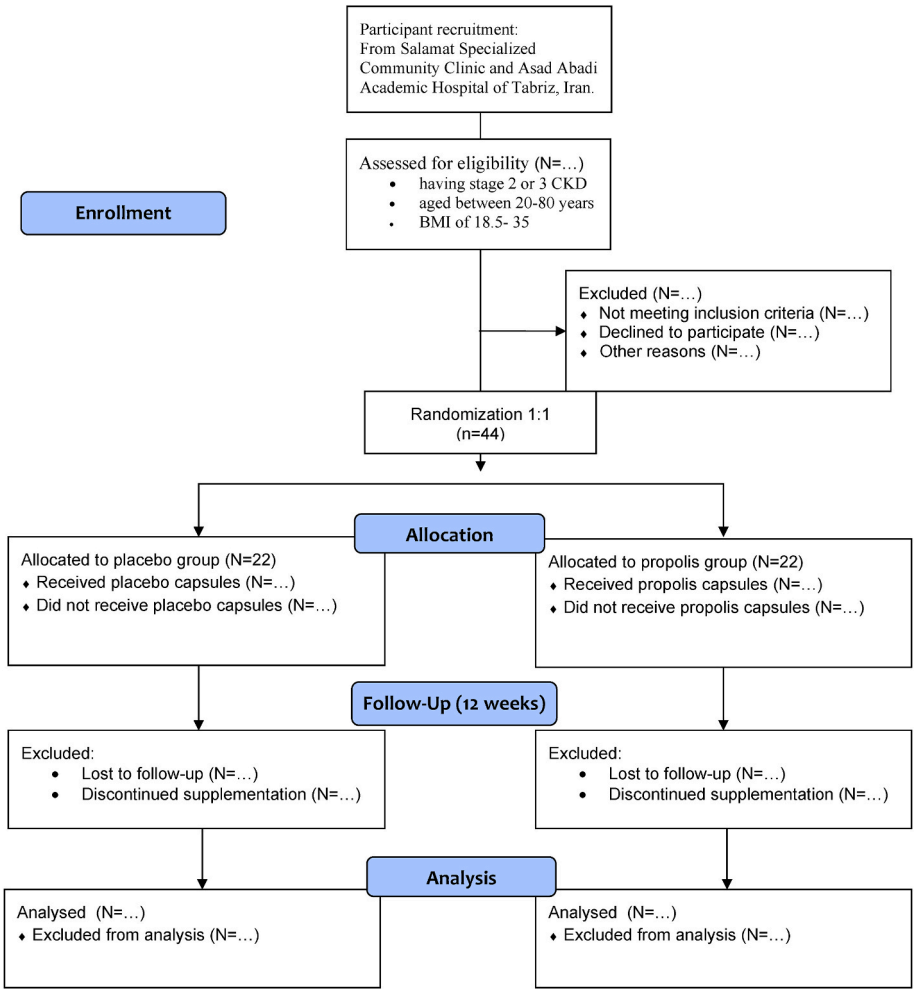

Fig. 2. Study flow chart of enrolment, allocation, intervention, and assessment. Abbreviations: CKD, chronic kidney disease; BMI, body mass index.

2.10.2. Concealment mechanism

The company producing the supplements will provide placebo capsules that are similar in weight and appearance to propolis capsules. These capsules will be held in identical drug containers in terms of shape, color, odor, size, and weight. The company will label the containers with two different codes based on whether they contain propolis or placebo. An independent statistician who is not involved in the recruitment, intervention, assessment, or statistical analysis of the trial will be informed by the company of the intervention codes. This person will then generate an allocation sequence and provide drug containers inside sequentially numbered, opaque, sealed envelopes. Researchers who are unaware of the allocation sequence will assign patients to each group, ensuring concealed allocation and complete blinding.

2.10.3. Assignment of interventions: blinding

All patients, physicians, and researchers (enrolling, assessing, and analyzing) will be kept blinded to the allocated intervention until the final analysis, except for the independent statistician. The blind codes will be revealed when the statistical analysis is completed.

2.10.4. Procedure for unblinding if needed

An independent statistician, who was not involved in the study, has access to sealed envelopes for each patient. This allows for the disclosure of group allocation if required, particularly in cases where there is evidence of adverse effects.

2.10.5. Data management

Case record forms (CRFs) will be constructed for all participants, with each patient assigned a unique trial number for use on all CRFs. Data will be double-entered by two independent researchers using statistical package for the social sciences (SPSS) version 25 software, with procedures in place to ensure reliability, accuracy, and consistency of records. All the data will be archived and backed up daily and patient health records and information obtained during the trial will be kept strictly confidential. The Medical Ethics Committee of Tabriz University of Medical Sciences will review personal data to ensure the trial is conducted correctly. At the end of the study, we will publish and report the research results for use by other researchers and interested parties without revealing the names or identifying information of participants.

2.11. Statistical methods

2.11.1. Statistical methods for primary and secondary outcomes

Data analysis will be performed using SPSS software (Version 25, SPSS Inc., and Chicago, IL, USA), with a *P*value < 0.05 considered statistically significant. Qualitative variables will be reported as frequency and percentage, while quantitative variables will be reported as mean and standard deviation. The Kolmogorov-Smirnov test will determine the distribution of quantitative data. Demographic and baseline variables between groups will be compared using a chi-square test for qualitative data and an independent sample *t*-test for quantitative data. Within-group comparisons will be performed using the Paired-samples *t*-test and between-group comparisons after the intervention by

modulating the baseline values and potential confounding factors will be analyzed using analysis of covariance (ANCOVA) test. If the data distribution is not normal, appropriate transformation and/or nonparametric equivalent tests will be used. We will use both per-protocol and intention-to-treat analysis to assess the efficacy of this trial. Missing data will be analyzed by suitable multiple imputation methods. The stratification criteria for randomization will be taken into account in the subgroup analyses.

2.11.2. Oversight and monitoring

This clinical study will not include a data monitoring external committee. Nonetheless, an internal committee consisting of the principal investigators and the chief researcher who supervise the trial's correct development will monitor the trial preliminary data regarding safety. The data monitoring committee (DMC) will continuously analyze preliminary data looking for effectiveness and safety. In case of any adverse events, this committee will report them to the Medical Ethics Committee of Tabriz University of Medical Sciences for decision making. The DMC will meet either face-to-face or by teleconference twice a month. This committee is independent of the sponsor and competing interests.

2.11.3. Dissemination plans

After completing this study, the results will be disseminated regardless of the significance or direction of effect to relevant patients and audiences of interest, presented at clinical and scientific conferences, published in journals, and shared with physicians and health workers. Furthermore, the trial website will be updated at the appropriate time to guarantee results are easily accessible.

3. Discussion

Despite implementing various health strategies, the burden of CKD highlights the need for new approaches to improve the effectiveness of existing treatments or supplement them [1]. Propolis, a natural substance produced by bees, has gained attention for research due to its diverse chemical composition, including over 300 different compounds such as polyphenols, terpenoids, steroids, amino acids, and sugars [7]. Numerous scientific articles have been published regarding propolis' bioactivity and health benefits [8]. Clinical trials and animal studies have shown that propolis is generally safe and well-tolerated when used in moderation [12]. As mentioned earlier, there is a tight relationship between OS, hyperglycemia, and HTN in the pathogenesis and progression of CKD [1,6]. A large number of in vitro, animal, and clinical studies have supported the potential antioxidant capacity of propolis [7,15,16]. Based on existing evidence, propolis can also improve glucose metabolism through several mechanisms such as stimulating insulin production and increasing peripheral sensitivity to it [17], suppressing α-glycosidase and intestinal sucrase activity [18,19], triggering glucose uptake and the translocation of insulin-sensitive glucose transporter (GLUT) 4 in peripheral tissues like skeletal muscle cells [20], down-regulating the expression of gluconeogenic genes in hepatocytes, especially the glucose-6-phosphatase gene [21], and improving glucose utilization by the liver [22]. Furthermore, experimental studies have demonstrated that propolis has BP-lowering properties due to its diuretic effects, angiotensin-converting enzyme inhibitor-like effects, acetylcholine-induced vasodilation, and nitric oxide pathway [23–27]. Propolis vasorelaxant effects also result from an inhibitory action on calcium transposition through the vascular smooth muscle cell membrane [27]. Considering CKD pathophysiology and unique properties of propolis, we hypothesize that propolis might improve the health outcomes of CKD patients, including kidney function parameters, PAB, glycemic status, quality of life, and BP. However, experimental studies and clinical trials targeting propolis efficacy on CKD are rare, and their results are usually controversial [10,26]. Therefore, further clinical trials are needed to clarify the effectiveness of propolis on treatment outcomes, health status and quality of life in CKD patients. If the hypothesis of propolis effectiveness in the management of CKD is confirmed, it could be introduced as a novel, safe, and inexpensive therapy in this group of patients for further clinical studies in the future. This trial will also have potential limitations. First, there may be a lack of biomarkers for monitoring propolis intake compliance. However, we will measure compliance with treatments by counting the returned capsules during each study visit. Second, the results of this study may not be generalizable to other populations due to only recruiting stage 2 or 3 CKD patients with a BMI between 18.5 and 35 kg/ m^2. However, this limitation will be partially offset by the double-blind and placebo-controlled study design, stratified block randomization, adjusting the results for potential confounders, and inclusion of patients with CKD of different etiologies.

Trial status

This is version 01, 30/8/2021 of the protocol. Recruitment began on 1 January 2021 and is expected to be completed by March 2023 (now, it is performing).

Ethics approval and consent to participate

The current trial was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences, which is conducted according to the latest version of the declaration of Helsinki (approval number: IR.TBZMED.REC.1399.177). Besides, it is registered in the IRCT (registration number: IRCT20191218045798N1) and is available at https://en.irct.ir/trial/48603. Written, informed consent to participate will be obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

The final trial dataset will be available from the corresponding author on reasonable request.

Funding

This study was funded and supported by Tabriz University of Medical Sciences. The Tabriz University of Medical Sciences, Tabriz, Iran, and Asal Shahdineh Golha Co., Isfahan, Iran, have no role in designing the study and collecting, analyzing, and interpreting data or in writing the manuscript.

Authors' contributions

Study design and development of the proposal: PA, MA, ZG, AO, and MRA. Study management: PA, MA, ZG, AO, and MRA. Study conduct and data collection: PA and MA. PA and MA drafted the protocol manuscript, and ZG, MRA, and AO revised the paper critically. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are grateful to the Tabriz University of Medical Sciences for the financial support. We thank Asal Shahdineh Golha Co., Isfahan, Iran, for

manufacturing and providing propolis and placebo capsules with discount. Special thanks to all staff and patients who are participating in this trial.

Abbreviations

CKD	Chronic kidney disease
HTN	hypertension
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
CVD	cardiovascular disease
OS	oxidative stress
DM	diabetes mellitus
PAB	prooxidant-antioxidant balance
HOMA-IR	Homeostatic model assessment for insulin resistance
FBS	fasting blood sugar
HbA1C	hemoglobin A1C
BP	blood pressure
IRCT	Iranian Registry of Clinical Trials
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
RCT	randomized clinical trial
BMI	body mass index
AKI	acute kidney injury
GRAS	generally recognized as safe
KDQOL-SF	Kidney Disease and Quality of Life-Short Form
ELISA	enzyme-linked immunosorbent assay
CRFs	case record forms
SPSS	statistical package for the social sciences
ANCOVA	analysis of covariance
DMC	data monitoring committee
GLUT 4	insulin-sensitive glucose transporter 4

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101159.

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