

Original article

Investigating the effect of sweet almond (*Prunus dulcis* (Mill.)) capsule formulation on kidney function in patients with chronic kidney disease: a randomized controlled clinical trial

Seddigheh Meghdadi¹, Amirsaeed Hosseini², Jamshid Yazdani Charati³, Mohammad Kamalinejad⁴, Atefeh Yousefi⁵, Mohammad Yousofpour^{2,6,*}

¹Assistant Professor, Department of Internal Medicine, Faculty of Medicine, North Khorasan University of Medical Sciences, Bojnourd, Iran

²Assistant Professor, Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

³Professor, Department of Biostatistics and Epidemiology, Faculty of Health, Health Sciences Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

⁴Researcher, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁵Assistant Professor, Department of Internal Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

⁶Assistant Professor, Department of Traditional Persian Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

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* Corresponding Author:

Tel: 09111556721

Fax: 01133244893

m.yousefpour@mazums.ac.ir

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Abstract

Objective: Almonds contain healthy fats, antioxidant, and anti-inflammatory compounds that may help protect renal tissues against oxidative damage. Considering these potential nephroprotective properties, this study aimed to evaluate the effect of sweet almond capsules on kidney function in patients with chronic kidney disease (CKD).

Materials and methods: 56 patients with CKD stage 2 and 3 were randomly divided into two groups of almond capsules and placebo. The intervention was carried out for 8 weeks. In this study, glomerular filtration rate (GFR), serum creatinine (Cr), blood urea nitrogen (BUN), 24-hr urine protein, serum albumin, serum uric acid, serum potassium, blood pressure and hemoglobin, C-reactive protein (CRP), lipid profile and fasting blood sugar (FBS) were evaluated before and after the intervention.

Results: After 8 weeks of intervention, we saw an increase in GFR in the almond group compared to the control group, which was statistically significant ($p=0.020$). Also, FBS in the almond group was lower than the control group, and the difference between the two groups was significant ($p=0.037$). In the almond group, by examining the variables before and after the intervention, a significant decrease in creatinine ($p=0.008$) and a significant increase in GFR were observed ($p=0.009$). Also, high density lipoprotein (HDL) ($p=0.049$), and albumin ($p<0.001$) showed a significant increase and total cholesterol showed a significant decrease in the almond group ($p=0.002$).

Conclusion: Findings from this study suggest that almond consumption may have a beneficial effect on kidney function in patients with stage 2 and 3 CKD. This effect may be attributed to the reduction of blood pressure, blood glucose, serum lipids, and inflammation, as well as the protective properties of the flavonoid compounds present in almonds.

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Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by structural and functional changes in the kidney that occurs due to a wide variety of causes (Kalantar-Zadeh *et al.* 2021). The characteristic of this disease is kidney dysfunction and a decrease in glomerular filtration rate (GFR) remaining for three months or more (McManus and Wynter-Minott. 2017). Diabetes and high blood pressure are the main causes of CKD (Webster *et al.* 2017). This disease has five stages based on the reduction of GFR, all of which are associated with increased risk of cardiovascular diseases, reduced quality of life, and premature death. Symptoms of CKD usually do not appear until the final stage of this disease (Hill *et al.* 2016). Mortality rate is high in patients with CKD, and for the patients who are in disease stage 3, the risk of death (usually due to cardiovascular disease) is at least 10 times more than the risk of progression to end-stage kidney disease (ESKD) (Skorecki K *et al.* 2016). When the GFR reaches less than 15 ml/min, it means that the patient has reached the final stage of CKD (Webster *et al.* 2017). At this stage, due to the accumulation of toxins, uremia syndrome occurs and the patient needs kidney replacement treatment, i.e. dialysis or kidney transplant, in order to continue living (Kasper *et al.* 2015). The global incidence of CKD has shown a continuous rise over the past decades. This growing burden is largely attributed to population aging, and the rising prevalence of diabetes and hypertension (Ying *et al.* 2024). The global prevalence of CKD is 13.4% and the number of patients in the final stage of CKD who need kidney replacement treatment is estimated between 4.902 and 7.083 million people (Lv and Zhang. 2019).

Treatment includes reducing the rate of disease progression (drug therapy and diet), dialysis and kidney transplant (Kasper *et al.* 2015). Despite the treatments and efforts to prevent the progression of this disease, the need for kidney replacement treatment is

increasing rapidly so that in most countries, this need exceeds the available capacity to provide services to CKD patients (Eriksen and Ingebretsen. 2006). The prevalence of traditional and complementary medicine use worldwide is considerable. For instance, a systematic review including 14 countries reported that the usage rate of these therapies in the past 12 months ranged from 24 to 71.3% (Lee *et al.* 2022).

Persian medicine is one of the oldest medical schools in the world, which has played an important role in the history of medicine (Elgood. 1991). In the sources of Persian medicine, beneath kidney diseases, there is a disease called "*hozal-e- kolye*" which is similar to CKD in some ways. Clinical symptoms of "*hozal-e- kolye*" in Persian medical sources include thinness, urinary symptoms, sexual disorders, vision impairment, musculoskeletal pain, and headache. Eating nuts, especially almonds, which is repeatedly mentioned in various sources of Persian medicine, is one of the important treatments for "*hozal-e- kolye*". Almonds have been mentioned in Persian medicine sources for their powerful effect on kidney recovery (Aghili Khorasani. 2015, Tonkaboni. 2012).

Almonds (*Prunus dulcis* (Mill.)) are rich in essential nutrients, including healthy fats, proteins, dietary fiber, vitamins, minerals, and natural antioxidants such as flavonoids. These components support heart health, help regulate blood sugar levels, reduce cholesterol and blood pressure and decrease inflammation. As a result, almonds are considered a valuable natural food for preventing and managing chronic diseases while promoting overall well-being (Mushtaq *et al.* 2015).

Although an article evaluating the effect of almonds on kidney function has not been published, according to the results of some articles, some plants of the same family as almonds (Rosaceae family) such as apricot, peach and *Rosa laevigata* may help improve kidney function (Zhou *et al.* 2012, Vardi *et al.* 2013, Lee *et al.* 2008).

Effect of sweet almond on chronic kidney disease

In recent years, several studies have shown that flavonoids play an important role in the prevention and management of CKD and kidney fibrosis (Cao et al. 2022). Almonds contain many flavonoids. For example, murine hydrate is one of the flavonoids of almonds that has positive effects on kidney function and oxidative stress (Jonnalagadda et al. 2013). Also, quercetin, which is one of the other flavonoids found in almonds and one of the most important compounds of the flavonoid family, has the greatest antioxidant properties among them and has protective effects on the kidney and liver (Moradi et al. 2015).

Among the other advantages of almonds, we can mention its inexpensiveness compared to the cost of current treatments, its availability, non-toxicity, pleasant taste, its nutritional aspect and better acceptance by patients.

Based on what was said, the aim of this study is to investigate the effect of almond capsules on kidney function in patients with CKD.

Materials and Methods

This study was conducted as a double-blind and randomized clinical trial in comparison with placebo. The studied group was the patients with CKD stage 2 and 3 referring to kidney clinic located in Sari city, Iran. The calculation of GFR and staging of CKD was performed using the Modification of Diet in Renal Disease (MDRD) method. The inclusion criteria for the study included stage 2 and 3 of CKD patients who were between 18 to 75 years old. Exclusion criteria included unstable clinical conditions (recent hospitalization within 4 weeks, uncontrolled hypertension Systolic blood pressure (SBP) > 160 mmHg), cancer, stage 4 and 5 of CKD, heart failure (NYHA Class III or IV), previous diagnosis of primary hyperoxaluria, history of calcium oxalate kidney stones, known allergy to almonds, liver failure, pregnancy, inability to

communicate, or having polycystic kidney disease or acute infectious disease.

The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences (Identifier: IR.MAZUMS.REC.1399.128). This study has been registered in Iranian Registry of Clinical Trials (IRCT) with No. IRCT20200516047465N1.

After providing sufficient explanations about how the study is conducted, informed and written consent was obtained from all patients. Patient profile was collected with demographic information form. Patients were randomly selected among eligible patients and randomly divided into treatment and placebo group. For randomization, a quadruple block randomization method was used.

In order to blind the study, the patient, the physician responsible for evaluating the patients, and the researcher did not know the type of treatment for each group (drug or placebo). For this purpose, after randomizing and dividing the patients into two groups, drug and placebo were separated by code A or B, and the labels were put by a statistical consultant and placed inside the envelope. In this way, the patient, the attending physician, and the researcher were not aware of the type of treatment.

Patients in the intervention group received 2 capsules daily, each containing 350 mg of almond extract and the patients in the placebo group received placebo capsules, which were identical in appearance to the main drug and contained starch.

The dose of almond extract was selected based on the results of a preliminary pilot study conducted prior to the present trial, in which two different daily doses (700 and 1400 mg) were evaluated. Considering safety, tolerability, and the observed biological response, the 700 mg daily dose (350 mg twice daily) was identified as the most appropriate and was therefore used in the current study. In addition, this dose was considered feasible

for long-term administration in patients with renal disease. Moreover, previous studies have reported a daily intake of approximately 10 g of whole almonds to improve lipid profile control, which is roughly equivalent to 700 mg of almond extract, further supporting the rationale for the selected dose in the present study (Jamshed *et al.* 2015).

Both groups were treated for 8 weeks. The type and dosage of the patients' routine medication did not change as much as possible during the intervention, but in case of any changes, it was recorded. In this study, GFR as the main outcome variable and serum creatinine, blood urea nitrogen (BUN), 24-hr urine protein, serum albumin, serum uric acid, serum potassium, blood pressure, hemoglobin, C-reactive protein (CRP), lipid profile and fasting blood sugar (FBS) as secondary outcome variables were evaluated before and after the intervention.

Biochemical analyses

Fasting venous blood samples were collected from all participants and serum was separated by centrifugation. Biochemical parameters including FBS, Chol, TG, HDL, LDL, BUN, Cr, Alb, K, Hb, Uric acid, CRP and Urine Pr were measured using commercially available kits (Pars Azmoon Co., Tehran, Iran) according to the manufacturer's instructions.

How to make the medicine

Extraction method: The almond kernel was put in water, after moistening its brown skin, it was separated, then almond was dried and powdered. For every 100 g of peeled almond kernel powder, 500 ml of water was added and placed into cool water in the laboratory for 24 hr.

The extract was filtered by filter paper and concentrated and dried by a freeze dryer. Finally, 7 g of dry extract was obtained from every 100 g of almond powder. Then, 500 mg capsule, containing 350 mg of almond extract and 150 mg of starch, were prepared.

Determination of the total phenolic content

In this study, the Folin–Ciocalteu solution was used as a reagent, and gallic acid was utilized as a standard phenolic compound for the measurements. For this purpose, 1 ml of gallic acid solution at various concentrations (20, 40, 60, 80, and 100 µg/ml) was mixed with 5 ml of the Folin–Ciocalteu reagent diluted at a ratio of 1 to 10, and the mixture was incubated at room temperature. After 10 min, 4 ml of sodium carbonate solution (75 mg/ml) was added. The final preparation was then incubated for 30 min at room temperature, protected from light. Then, the absorbance of each gallic acid sample was measured at 765 nm. This experiment was conducted three times for each dilution of gallic acid versus concentration. The same method was performed for the almond product, using 1 ml of almond extract (800 g/ml) instead of gallic acid, and total phenolic content was determined using the gallic acid standard curve.

Statistical analysis

In consideration of the fact that no human studies have previously been conducted to investigate the effectiveness of almonds on CKD, this study was designed as a comparative trial. Initially, a pilot phase was conducted in which 30 participants were randomly allocated into two groups (intervention and placebo) using Random Allocation software, and then entered the study phase. After data collection and analysis of the pilot phase, the final sample size was determined. The mean GFR in the almond extract group was 50.2 ± 8.8 ml/min/1.73m² and 43.5 ± 8.3 ml/min/1.73m² in the placebo group. With a significance level (α) of 0.05 and a power ($1-\beta$) of 80%, a sample size of 25 per group was required. To account for a potential 20% dropout rate, we aimed to recruit 30 participants per group (total n=60). Once the required number of participants was completed, the data were reanalyzed.

After receiving and analyzing the pilot results, the sample size of the study was determined based on GFR, using the following formula and the number of 60 people was determined.

Block randomization with a block size of 4 was performed using Random Allocation Software (version 2.8), and by this method, patients were divided into two groups of 30 people.

$$n_1 = n_2 \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 [\sigma_1^2 + \sigma_2^2]}{(\mu_1 - \mu_2)^2},$$

$$\mu_1 = 40, \mu_2 = 45, \alpha = 0.05, \beta = 0.2, \sigma_1 = \sigma_2 = 8$$

Where σ_1 is the standard deviation in the intervention group, μ_1 is the mean in the intervention group, σ_2 is the standard deviation in the control group, and μ_2 is the mean in the control group.

For statistical analysis, firstly, to describe the data based on the methods of descriptive statistics, including the mean \pm standard deviation, scatter charts, the implementation box of quantitative variables, and frequency tables were used for qualitative data. Baseline characteristics between the two groups were compared using independent t-tests for normally distributed continuous variables (e.g. age), Mann-Whitney u tests for non-normally distributed continuous variables, and Chi-square tests for categorical variables (e.g. gender).

To compare the results before and after intervention, paired t statistical tests and in the case of an intervention effect, covariance analysis was used; if there was no primary intervention effect before the intervention, independent t or Mann-Whitney tests were used, and in the case of intervention, the methods based on generalized linear regression were used for analysis. To do this, SPSS statistical software was used at a significance level of 0.05.

Results

Almonds are a rich source of flavonoids and other essential nutrients with potent antioxidant, anti-inflammatory, and protective properties. The standardized aqueous extract of almond contains 2.25 % total phenols per 100 g, as shown in Table 1.

Table 1. Determination of total phenolic content in the almond product using the Folin- Ciocalteu method and gallic acid standard curve.

Herbal product	Concentration	Total phenolic/ Gallic acid ($\mu\text{g/ml}$)	Total phenol
Almond product	800 $\mu\text{g/ml}$	18.04	2.25%

This study was conducted as a double-blind randomized clinical trial from January 2021 to December 2021. Eighty nine patients with CKD were examined, 24 patients did not meet the inclusion criteria. The remaining 65 patients were randomly divided into two groups: intervention (n=32) and control (n=33). Four people from the intervention group (2 people due to unwillingness to continue cooperation, 1 person due to digestive problem, and 1 person hospitalized due to Covid-19) and 5 people from the control group (3 people due to unwillingness to continue cooperation, and 2 people due to digestive problem) were excluded from the study. Finally, the data of 28 patients in each group were analyzed (Figure 1).

In the intervention group, there were 19 males and 9 females, while the control group consisted of 9 males and 19 females. As shown, there was a significant difference in the gender structure between the intervention and control groups (p=0.008); therefore, we controlled its effect in covariance analysis and we observed no significant effect, Analysis of covariance (ANCOVA) was used to control for the effect of pre-intervention values, namely GFR and creatinine. The patients of the two groups did not have significant differences in other demographic characteristics (Table 2).

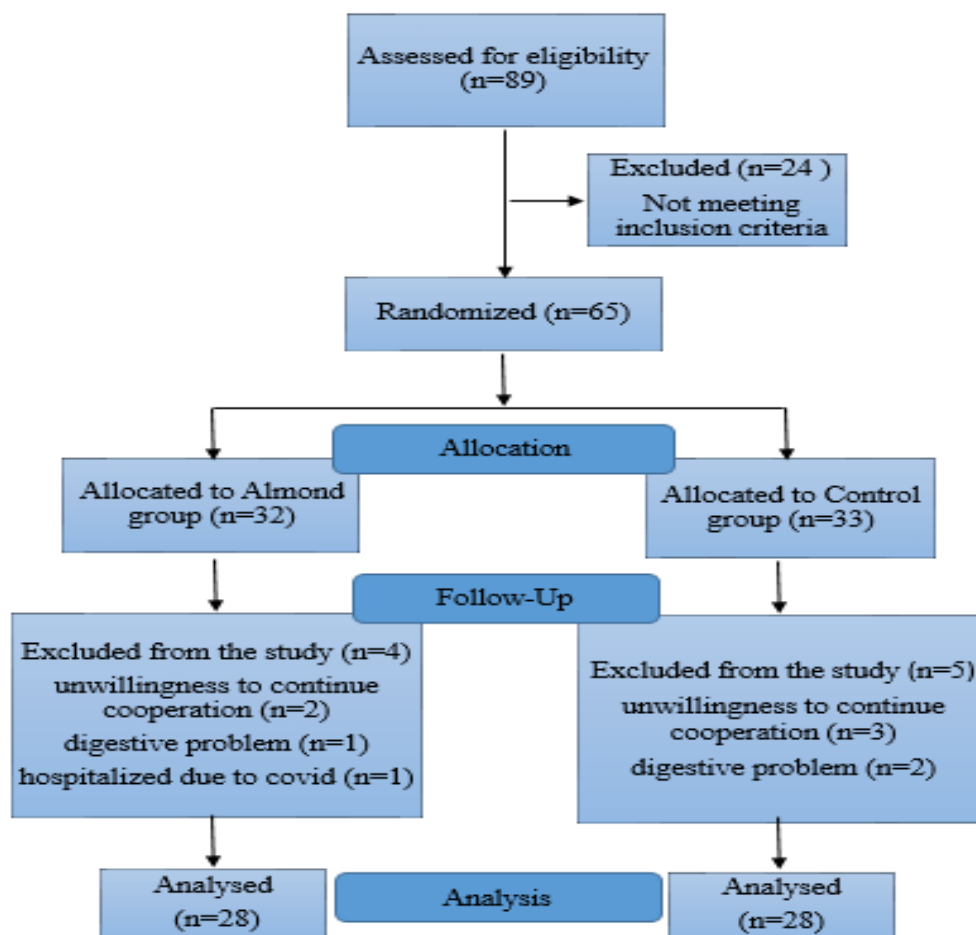


Figure 1. Flowchart of the study

Table 2. Demographic and laboratory characteristics of patients in the baseline phase

Demographic characteristics	Control group Mean (\pm Std deviation)	Almond group Mean (\pm Std deviation)	p-value
Age (year)	62.17 (\pm 9.56)	60.71 (\pm 9.61)	0.57
Male	9 (32.1%)	19 (67.9%)	0.008
Weight (kg)	79.1 (\pm 11.9)	81.39 (\pm 10.93)	0.45
Marital status			
married	22 (78.6%)	24 (85.7%)	0.15
DM	18 (64.3%)	21 (75%)	0.38
Underlying Disease			
HTN	24 (85.7%)	23 (82.1%)	0.71
HLP	22 (78.6%)	17 (60.7%)	0.14
Blood pressure			
Systolic (mmHg)	127.5 (\pm 18.97)	133.21 (\pm 23.14)	0.31
Diastolic	79.46 (\pm 7.73)	80.35 (\pm 11.13)	0.73
Laboratory characteristics			
Cr (mg/dl)	1.44 (\pm 0.23)	1.53 (\pm 0.22)	0.12
GFR (ml/min/1.73 m ²)	44.46 (\pm 8.38)	46.1 (\pm 8.83)	0.47
BUN (mg/dl)	22.93 (\pm 5.83)	22.15 (\pm 6.64)	0.64

DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipidemia; Cr: Creatinine; GFR: Glomerular filtration rate; BUN: Blood urea nitrogen

Effect of sweet almond on chronic kidney disease

As can be seen in Table 3, GFR after the intervention in the almond group was higher than the control group and this difference was statistically significant ($p=0.020$). In addition, FBS in the intervention group was lower than the control group, and this difference was statistically significant ($p=0.037$).

By comparing the variables before and after the intervention in each group, it can be seen that the creatinine in the drug group

decreased significantly after the intervention ($p=0.008$) and the GFR increased significantly ($p=0.009$), but in the control group there was no significant difference in these variables. In addition, a significant increase in serum albumin ($p<0.001$) and HDL ($p=0.049$), and a significant decrease in cholesterol ($p=0.002$), were seen in the drug group (Table 3).

Table 3. Comparison between biochemical factors in almond and control group before and after the intervention

Variables		Control group Mean (\pm Std deviation)	Almond group Mean (\pm Std deviation)	p-value
Cr (mg/dl)	Before	1.44 (\pm 0.23)	1.53 (\pm 0.22)	0.12
	After	1.46 (\pm 0.25)	1.42 (\pm 0.25)	0.59
	p-value	0.50	0.008	
GFR (ml/min/1.73 m ²)	Before	44.46 (\pm 8.38)	46.1 (\pm 8.83)	0.47
	After	44.14 (\pm 10.04)	51 (\pm 11.36)	0.02
	p-value	0.79	0.009	
BUN (mg/dl)	Before	22.93 (\pm 5.83)	22.15 (\pm 6.64)	0.64
	After	22.48 (\pm 5.18)	20.55 (\pm 5.58)	0.18
	p-value	0.71	0.18	
Urine Pr (mg/24h)	Before	571.28 (\pm 576.41)	645 (\pm 1070.59)	0.82
	After	662.35 (\pm 636.44)	768/84 (\pm 890)	0.72
	p-value	0.35	0.494	
Alb (gr/dl)	Before	4.16 (\pm 0.48)	4 (\pm 0.34)	0.15
	After	4.35 (\pm 0.27)	4.47 (\pm 0.39)	0.21
	p-value	0.074	< 0.001	
K (mEq/L)	Before	4.69 (\pm 0.54)	4.64 (\pm 0.7)	0.79
	After	4.9 (\pm 0.63)	4.82 (\pm 0.67)	0.67
	p-value	0.019	0.08	
Hb (mg/dl)	Before	12.06 (\pm 1.54)	12.48 (\pm 1.6)	0.31
	After	12.36 (\pm 1.72)	12.73 (\pm 1.84)	0.44
	p-value	0.034	0.18	
Uric acid (mg/dl)	Before	5.59 (\pm 1.3)	5.9 (\pm 1.73)	0.46
	After	6 (\pm 1.49)	5.85 (\pm 1.59)	0.71
	p-value	0.008	0.78	
TG (mg/dl)	Before	176.78 (\pm 55.83)	174.25 (\pm 70.96)	0.88
	After	173.57 (\pm 91.99)	168.39 (\pm 66.44)	0.81
	p-value	0.83	0.51	
Chol (mg/dl)	Before	154.6 (\pm 48.44)	144.28 (\pm 35.22)	0.36
	After	151.57 (\pm 45.62)	130.78 (\pm 32.01)	0.054
	p-value	0.54	0.002	
LDL (mg/dl)	Before	80.07 (\pm 32.69)	76.53 (\pm 24.56)	0.65
	After	78.14 (\pm 30.07)	73.67 (\pm 21.76)	0.52
	p-value	0.64	0.26	
HDL (mg/dl)	Before	44.71 (\pm 12.83)	40.32 (\pm 8.81)	0.14
	After	46.35 (\pm 14.49)	43.42 (\pm 9.47)	0.37
	p-value	0.26	0.049	
FBS (mg/dl)	Before	122.32 (\pm 36.43)	114.28 (\pm 27.62)	0.356
	After	130.35 (\pm 45.07)	110.35 (\pm 20.32)	0.037
	p-value	0.078	0.27	
SBP (mmHg)	Before	127.5 (\pm 18.97)	133.21 (\pm 23.14)	0.31
	After	128.57 (\pm 19.14)	129.28 (\pm 18.89)	0.89
	p-value	0.43	0.054	
DBP (mmHg)	Before	79.46 (\pm 7.73)	80.35 (\pm 11.13)	0.73
	After	79.64 (\pm 6.92)	79.28 (\pm 8.13)	0.86
	p-value	0.81	0.40	
CRP positive	Before	3 (10.7%)	1 (3.6%)	0.61
	After	2 (7.1%)	0	0.49

Cr: Creatinine; GFR: Glomerular filtration rate; BUN: Blood urea nitrogen; Urine Pr: Urine protein; Alb: Albumin; K: Potassium; Hb: Hemoglobin; TG: Triglyceride; Chol: Cholesterol; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FBS: Fasting blood sugar; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CRP: C-reactive protein

To determine the changes in GFR after the intervention (GFR2) in the intervention group compared to the control group, analysis of covariance was performed adjusting for baseline GFR (GFR1), as shown in Table 4. Based on this, the intervention group had an average increase of 8.43 units (with a 95% confidence interval) in GFR2 compared to the control group, which is statistically significant ($p=0.011$).

To determine the changes in Cr after the intervention (Cr2) in the intervention group compared to the control group, analysis of covariance was performed with adjusting for baseline creatinine (Cr1), as shown in Table 4. Based on this, the intervention group had an average decrease of 0.21 units (with a 95% confidence interval) in Cr2

compared to the control group after adjusting for baseline Cr (Cr1), which is statistically significant ($p=0.007$).

To determine the changes in BUN after the intervention (BUN2) in the intervention group compared to the control group, analysis of covariance was performed adjusting for baseline BUN (BUN1), as shown in Table 4. Based on this, the intervention group had an average decrease of 3.582 units (with a 95% confidence interval) in BUN2 compared to the control group after adjusting for baseline BUN (BUN1), but this decrease is not statistically significant ($p=0.078$).

The observed side effects in this study, which were mostly mild digestive discomfort, were reported by one participant in the intervention group and two participants in the placebo group.

Table 4. Analysis of covariance (ANCOVA) adjusting for baseline GFR (GFR1), Cr (Cr1), and BUN (BUN1)

Parameter	B (Regression coefficient)	Std. Error	p- value	95% Confidence Interval		Partial Eta Squared
				Lower Bound	Upper Bound	
baseline GFR (GFR1)	0.851	0.144	< 0.001	0.563	1.139	0.408
Intervention group	8.438	3.179	0.011	2.057	14.819	0.121
baseline Cr (Cr1)	0.796	0.115	< 0.001	0.565	1.027	0.485
Intervention group	-0.21	0.075	0.007	-0.36	-0.06	0.135
baseline BUN (BUN1)	0.386	0.109	0.001	0.168	0.604	0.198
Intervention group	-3.582	1.995	0.078	-7.587	0.423	0.059

Discussion

CKD is one of the important diseases with many complications that greatly affect people's quality of life. Today, due to people's lifestyle and the prevalence of diabetes and blood pressure, the incidence of this disease is increasing.

This study was conducted in order to determine the effect of sweet almond extract on kidney function of patients with CKD.

In this study, it was observed that almond consumption had a positive effect on kidney function, leading to a reduction in Cr levels and an increase in GFR. Although a search across various databases revealed no studies specifically examining

the effects of almonds on kidney function, numerous investigations have focused on the bioactive compounds found in almonds, including flavonoids, whose protective effects on the kidneys have been well established. According to these studies, flavonoids play a key role in the prevention and management of CKD and renal fibrosis. These compounds possess antidiabetic, antihypertensive, antioxidant, and anti-inflammatory properties, and by inhibiting harmful pathways such as oxidative stress and inflammation, they can prevent or slow the progression of kidney dysfunction and improve renal performance (Cao *et al.* 2022).

Almonds are rich in flavonoids such as quercetin, isorhamnetine, protocatechuic acid, and morin hydrate (Milbury et al. 2006, Jonnalagadda et al. 2013). Studies have shown that quercetin exerts protective effects against diabetic nephropathy and methotrexate-induced nephrotoxicity (Gomes et al. 2015, Moradi et al. 2015). Morin hydrate also reduces gentamicin-induced nephrotoxicity and cisplatin-induced renal injury by alleviating oxidative stress (Jonnalagadda et al. 2013, KV et al. 2016). In addition, isorhamnetine has been reported to have protective effects against acute kidney injury (Gong et al. 2020). Furthermore, protocatechuic acid improves kidney function by reducing oxidative stress, tissue necrosis, and blood levels of urea and Cr (Kakkar and Bais. 2014).

Therefore, the activities attributed to flavonoids provide a plausible mechanism for kidney protection. Our study findings indicated that consumption of almond extract led to a decrease in Cr levels and an increase in GFR, which is likely due to the synergistic effects of the flavonoids it contains on renal oxidative and inflammatory pathways. These results are consistent with previous studies and suggest that the flavonoid compounds in almonds may act as a natural protective agent in maintaining and improving kidney function (Jonnalagadda et al. 2013, Kakkar and Bais. 2014, Gomes et al. 2015, Moradi et al. 2015, KV et al. 2016, Gong et al. 2020).

In this study, it was observed that the consumption of almond products significantly reduced total cholesterol and blood glucose levels while increasing HDL levels. Our findings are consistent with previous studies that highlight the modulatory role of almonds on metabolic indicators. For example, a study reported that daily consumption of 10 g of almonds led to an increase in HDL cholesterol and improvement in other indicators of lipid

metabolism disorders in patients with coronary artery disease (Jamshed et al. 2015). Similarly, another study showed that consuming almonds or almond oil significantly reduced triglycerides, total cholesterol, and LDL while increasing HDL (Hyson et al. 2002). Supporting these findings, another study reported that almond consumption significantly decreased total cholesterol, serum triglycerides, and LDL, while markedly increasing HDL (Parsaeian et al. 2008). Another study indicated that adding almonds to the diet could improve lipid and blood glucose profile control (Li et al. 2011).

From the perspective of blood glucose control, Hou et al. reported that almond consumption in patients with type 2 diabetes resulted in a significant reduction in FBS and HbA1c, although no significant effect was observed on lipid profile or interleukin-6 levels (Hou et al. 2018). Additionally, Abazarfard et al. showed that almond consumption was associated with significant reductions in total cholesterol, triglycerides, FBS, and diastolic blood pressure (Abazarfard et al. 2014).

Liu et al. examined a novel aspect and found that consuming 56 g of almonds before meals led to reductions in body fat and visceral fat, while consuming them as a snack reduced total cholesterol and LDL without affecting HDL. This finding suggests that the timing of almond consumption may influence body composition and blood lipid levels (Liu et al. 2017).

At the same time, some evidence has reported more limited effects. For example, Phung et al. showed that although almond consumption may reduce total cholesterol, it does not have a significant effect on LDL, HDL, or triglycerides (Phung et al. 2009). Coates et al. also noted a significant reduction in triglycerides and systolic blood pressure following almond consumption (Coates et al. 2020). Tahir et al. found that almond consumption in individuals with normal weight led to a significant decrease

in total cholesterol, LDL, and VLDL, whereas in overweight and obese individuals, only total cholesterol was reduced, suggesting that the beneficial effects of almonds on lipid profile are more pronounced in individuals with normal weight (Tahir *et al.* 2019). Furthermore, Zibaenezhad *et al.* reported that almond oil consumption in patients with hyperlipidemia significantly reduced total cholesterol and LDL, without having a notable effect on triglycerides or HDL (Zibaenezhad *et al.* 2019).

It is important to note that dyslipidemia itself can be a major risk factor in the progression of kidney damage. As Agarwal and Curley pointed out, since the 1980s, the concept of “lipid nephrotoxicity” has been introduced to describe the damaging effects of lipids on kidney function (Agarwal and Curley, 2005). Based on this, it can be hypothesized that almonds, through improving the serum lipid profile, may also play a protective role in slowing the progression of CKD.

Overall, a review of the available evidence indicates that almond consumption—whether as raw nuts or in various processed forms—can play a significant role in promoting metabolic health by improving lipid profiles, lowering blood glucose levels, and potentially exerting protective effects on kidney function. The findings of the present study are consistent with this perspective and may serve as a basis for future research on the protective effects of almonds on renal function.

One of the main factors contributing to the onset and progression of CKD is high blood pressure. In our study, both systolic and diastolic blood pressure decreased in the almond-consuming group after the intervention, although these reductions were not statistically significant. The reduction in systolic blood pressure was greater than that in diastolic blood pressure. Previous studies have also examined the effect of almond consumption on blood pressure, but their results have been

inconsistent. For example, a systematic review reported that almond intake can reduce systolic blood pressure but has no significant effect on diastolic blood pressure (Li *et al.* 2020). Conversely, another systematic review found that almond consumption may reduce diastolic blood pressure without affecting systolic blood pressure (Eslampour *et al.* 2020). Additionally, Coates *et al.* reported that almond consumption can lower systolic blood pressure (Coates *et al.* 2020).

Considering this evidence, the results of our study are partially consistent with previous findings, particularly regarding the reduction in systolic blood pressure, although the decrease observed in our study did not reach statistical significance due to the limited sample size. This suggests that almonds may have a positive effect on blood pressure, but their impact on diastolic blood pressure still requires further investigation.

Another important factor in the progression of CKD is oxidative stress and inflammation. In our study, the number of participants with positive CRP decreased after the intervention, although this reduction was not statistically significant between the two groups. These findings are somewhat consistent with previous studies; clinical research has shown that almond consumption can reduce certain inflammatory markers, such as CRP and E-selectin (Rajaram *et al.* 2010). Additionally, studies in smokers have indicated that almonds may have protective effects against oxidative stress and DNA damage (Jia *et al.* 2006). Therefore, the relative reduction in CRP observed in our study supports the potential impact of almonds on inflammatory markers, although the effect in our study was modest and did not reach statistical significance.

As previously noted, a search of the databases revealed that no direct study has yet been published on the effects of almonds on kidney function. However, there is evidence of renal effects from other members of the almond family (Rosaceae).

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For example, *Prunus armeniaca* has been shown to help prevent increases in urea and Cr and to reduce methotrexate-induced oxidative stress (Vardi et al. 2013). Similarly, *Prunus persica* extract demonstrated protective effects against cisplatin-induced acute nephrotoxicity and hepatotoxicity (Lee et al. 2008), and the fruit of *Rosa laevigata* Michx has potential benefits in the treatment of diabetic nephropathy (Zhou et al. 2012). These findings, together with our results, suggest that almonds and other members of their family may have significant protective effects on kidney function.

The limitations of this study include the small sample size and the 8-week duration. Assessing the long-term effects of almond extract requires studies with longer follow-up periods and larger sample sizes. Furthermore, the use of almond extract instead of whole almonds may lead to differences in its effects, which warrants further investigation. Finally, considering the characteristics of the studied population, the results should be interpreted with caution when generalizing to larger populations.

The findings of this study indicate that almond consumption may have a positive impact on kidney function in patients with stage 2 and 3 CKD. This potential benefit appears to be multifactorial, likely resulting from almonds ability to help regulate blood pressure and blood glucose levels, improve lipid profiles, and reduce systemic inflammation. Additionally, the high content of flavonoid compounds in almonds may exert protective effects on renal tissues through their antioxidant and anti-inflammatory properties. However, considering the limitations of this study, the results should be interpreted with caution, and larger, longer-term studies are necessary to confirm these findings.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Ethical Considerations

The study was conducted in accordance with ethical principles for medical research involving human subjects. Written informed consent was obtained from all participants, and confidentiality of participants' information was maintained throughout the study.

Code of Ethics

The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences with the ethics code: IR.MAZUMS.REC.1399.128.

Authors' Contributions

Seddigheh Meghdadi, Amirsaeed Hosseini, Jamshid Yazdani Charati, and Mohammad Yousofpour conceived and designed the study. Seddigheh Meghdadi and Atefeh Yousefi collected the data. Jamshid Yazdani Charati performed the data analysis. Mohammad Kamalinejad contributed to the pharmaceutical aspects of the study. Seddigheh Meghdadi, Amirsaeed Hosseini, and Mohammad Yousofpour drafted the manuscript. All authors critically reviewed and revised the manuscript and approved the final version.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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