Safety Evaluation and Biochemical Efficacy of Celery Seed Extract (Apium Graveolens) Capsules in Hypertensive Patients: A Randomized, Triple-blind, Placebo-Controlled, Cross-Over, Clinical Trial

Maryam Shayani Rad
Mashhad University of Medical Sciences
Mohsen Moohebati
Mashhad University of Medical Sciences
Shahab MohammadEbrahimi
Mashhad University of Medical Sciences
Vahideh Sadat Motamedshariaty
Mashhad University of Medical Sciences
Seyed Ahmad Mohajeri (mohajeria@mums.ac.ir)
Mashhad University of Medical Sciences https://orcid.org/0000-0002-7907-9625

Research Article

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Abstract

The present study was conducted to evaluate the safety of celery seed extract (*Apium graveolens*), as a medicinal herb with active ingredients such as 3-n-butylphthalide (NBP), in hypertensive patients. This study was a randomized, triple-blind, placebo-controlled, cross-over clinical trial. Hypertensive patients (51 participants) received 4 celery seed capsules (a total of 1.34g extract per day) or 4 placebo capsules per day for 4-weeks as a supplement to their usual medication regimen. The results indicated that the celery seed capsule not only was safe for hypertensive patients but caused a reduction in BP, FBS, and lipid profile values. Also, it had beneficial effects on kidney and liver functions. No significant change was observed in blood cells and serum electrolytes ($P > 0.05$). The mean reduction in BUN and SCr were 3.43 and 0.075 mg/dL, and in SGPT and SGOT were 4.08 and 3.03 U/L, respectively ($P < 0.05$). FBS reduced from 108.53 to 97.96 mg/dL after 4-weeks of celery administration ($P < 0.01$). The decrease in TC, TG, LDL, and increase in HDL were 16.37, 16.22, 11.84, and 2.52 mg/dL, respectively ($P < 0.001$). According to the promising results of this clinical trial, celery seed extract can be considered a safe supplement for hypertensive patients. The study is limited by the small sample size; therefore, larger randomized trials are required.

Introduction

Herbal therapy is an important part of medicine due to its safety and low side effects (Stout et al., 2003). Nowadays, many people prefer to use medicinal herbs. In their opinion, herbals are safe and have lower unwanted side effects (Cicero et al., 2016; Hajian, 2013; Nasri, 2013, 2013; Rafieian-Kopaei, 2013; Sirtori et al., 2015). *Apium graveolens*, generally known as “celery” has many health benefits and is a pharmaceutical herb used as a food supplement (Jung et al., 2011). Organs of celery, such as seeds, stems, leaves, roots, and stalks, contain ingredients with antibacterial, anti-inflammatory, antioxidant, antifungal, antitumor, and insecticidal properties (Sellami et al., 2012). Celery can play a role in the control of BP, serum lipid, and diabetes (Madhavi et al., 2013; Triyono and Novianto, 2017). Compared to other parts of the plant, celery seeds have more effective ingredients (Moghadam et al., 2013; Popović et al., 2006). The celery seeds contain various active ingredients, including luteolin, d-limonene, phthalides, apigenin, hesperitin, rosmarinic acid, linalool, and quercetrin (Hedayati et al., 2019; Priecina and Karklina, 2014; Tashakori-Sabzevar, Razavi, et al., 2016). The pharmacological mechanisms of these active ingredients are discovered and reported in previous studies (Anjos et al., 2013; Dianat et al., 2015; Su et al., 2015; Triyono et al., 2018). Celery contains a group of phytochemicals called phthalides, e.g. 3-n-butylphthalide (NBP), which are from the most active components in celery seed. NBP helps control stress hormones which contribute to high BP and reduces bad cholesterol (Diao et al., 2013; Peng et al., 2012). No significant toxicologically sub-chronic effects of oral celery were investigated in rats (Powanda and Rainsford, 2011). One of the therapeutic properties of celery seed is the hepatoprotective effect which is reported in some works. (Niaz, 2013), cognitive strengthening (Peng et al., 2012; Peng et al., 2010), neuroprotective effects (Peng et al., 2012) and anti-hyperglycemic (Tashakori-Sabzevar, Ramezani, et al., 2016). The most remarkable therapeutic property of celery reported in the studies is blood pressure

(BP) reduction (Dimo et al., 2003; Fogari et al., 2002; Shivashri et al., 2013). There is not enough information on the safety evaluation of celery seed in humans for assurance as a medication. This clinical trial study was conducted to evaluate, for short-term, safety of celery seed extract in hypertensive patients in a randomized, triple-blind, placebo-controlled, cross-over clinical trial. The biochemical and mineral parameters were assessed four times during the study for each patient. The results were promising and indicated the safety of celery seed extract as a drug supplement in the management of hypertension.

Materials And Methods

Extraction, capsule preparation, and analysis

The celery seed extraction was performed using 80% ethanol (Merck, Germany). The NBP purchased from Langchem, Inc. (Shanghai, China) was used for the standardization of the celery extract. The celery seeds were purchased from Imam Pharmacy (Mashhad, Iran). Herbarium of the School of Pharmacy certified their identity (voucher number: 293-0107-18). Briefly, the extraction process was done as follows. An amount of 800 g celery seeds were powdered, suspended in 2400 mL ethanol-water (80/20, v/v), and shaken for 1 hour in the darkness at room temperature. After filtration, the remaining suspended wet powder was collected and the abovementioned step was repeated two more times to complete the extraction process. Finally, the collected liquid was filtered again by a Buchner filtration set to create a cleaner extract with higher quality. The extract was sprayed onto the mixture of AEROSIL® (colloidal silicon dioxide) and maltodextrin in a fluid bed processor at the bed temperature of 35 ± 5°C. In the next step, the wet granules were dried in the fluid bed processor instrument to decrease the moisture. Finally, the dried granules were powdered and filled into the capsules. Each patient received four celery seeds (1.34 g extract per day) or placebo capsules per day. An Acme 9000 system (Young Lin, South Korea) consisting of an SP930D solvent delivery module, SDV50A solvent mixing vacuum degasser, column oven CTS30, UV730 dual-wavelength UV/VIS detector, and ODSA C18 (4.6 mm×150 mm, 5-µm) column was applied to the chromatographic determination of NBP. The data analysis was carried out in Autochro-3000. The column temperature, flow rate, injection volume, and UV detector were 50°C, 1 mL/min, 20 µL, and 230 nm, respectively. Moreover, the gradient method was used in which the mobile-phase composition was 20% HPLC-grade methanol in water and changed to 80% during 20 min. A concentration of 100 µg/mL from the capsule content was prepared in HPLC-grade methanol and injected into the HPLC. The concentration of NBP was measured based on the comparison of the area under the curve with the NBP standard solution.

Sample Size

The final volume of the study was calculated by Sigma Plot (version 12.0) (SYSTAT Software, USA) with a statistical power of 90% a significance level of 0.05, and treatment effect size of 5 mmHg decrease in SBP, a minimum sample size of 25 patients for each arm was calculated.

Study Design

The current study is a triple-blind, placebo-controlled, cross-over, 4-week clinical trial with a 4-week washout period. Details and procedures of the study were completely explained to patients through an interview, consent was obtained before the start of study treatment. This clinical trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements. Moreover, the study is in compliance with the regulations of Iran and approved by an independent ethics committee of Mashhad University of Medical Sciences, Mashhad, Iran (ethics committee reference number and approval date: IR.MUMS.REC.1394.705, 2016-02-27). This clinical trial was registered at the Iranian Registry of Clinical Trials (www.irct.ir, IRCT registration number and date: IRCT20130418013058N8, 2018-04-22). In the first step, 51 hypertensive patients were allocated into celery and placebo groups (Fig. 1). The patients received four capsules per day (2 capsules every 12 hours before meal) for 4-weeks as a supplement to their usual medication regimen. After a 4-week washout period, in the second step, the patients were crossed over into another medication group. Therefore, the patients who had received celery extract in the first step received placebo capsules after the cross-over, and those who had received placebo in the first step received celery extract capsules in the second step. The participants were not allowed to change their medication regimens or lifestyles during the study. Patient compliance with medication and trial process was assessed through weekly phone calls and at each visit to the physician.

Inclusion & exclusion criteria

The inclusion criteria were age range of 20–70 years old, ability to understand the process of the study, completion of the consent form, systolic blood pressure (SBP) between 120 and 160 mmHg, or diastolic blood pressure (DBP) between 80 and 100 mmHg. On the other hand, the exclusion criteria were pregnancy or breastfeeding, liver or kidney failure, aortic stenosis, infectious and inflammatory diseases, fever, any intolerable side effects, allergic symptoms, and alcohol consumption.

Data collection

The demographic information, including age, gender, marital status, education, physical activity, and body mass index (BMI) are summarized in Table 1. The blood biochemical parameters, BP parameters, and BP medications of the participants at the beginning of the clinical trial are summarized in Table 2. Daily dietary intake in detail was recorded in 4 steps of the clinical trial (Table 3). BP parameters were taken from the left arm of participants using 24-hour ambulatory blood pressure monitoring (ABPM) device at the end of each step. Biochemical tests were carried out in Ghaem Hospital, Mashhad University of Medical Sciences, Iran. Blood samples (5 ml) were taken from the forearm veins of patients in the fasting state (14-hours). The laboratory experiments were performed in both groups pre- and post-treatment: Hematologic tests performed included complete blood count with differentiation (CBC diff), plasma lipids; total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG), liver function tests; serum glutamic oxaloacetic transaminase (SGOT or AST), serum glutamic pyruvic transaminase (SGPT or ALT) and alkaline phosphatase (ALP), blood urea nitrogen (BUN) and serum creatinine (SCr), electrolytes; sodium (Na), potassium (K), calcium (Ca) and phosphorus (P).

Table 1
Baseline characteristics of patients. Data are mean ± SD.

	Group 1: Celery (n = 25)	Group 2: Placebo (n = 26)	p-value
Mean age (years) [a]	50.21 ± 6.66	51.34 ± 5.91	0.5628
Gender [b]			0.4896
Female (%)	48.15%	50.00%	
Male (%)	51.85%	50.00%	
Marital status [b]			0.6839
Married (%)	88.89%	89.29%	
Single (%)	11.11%	10.71%	
Education (years) [a]	12.33 ± 2.76	12.13 ± 2.12	0.876
Physical activity (hours/24-hours) [a]	4.76 ± 3.11	4.56 ± 3.23	0.798
BMI [c, a]			
Female (kg/m^2)	27.43 ± 3.87	27.89 ± 3.99	0.8012
Male (kg/m^2)	28.21 ± 3.66	28.77 ± 3.56	0.7659

[a] Independent t-test were applied continuous variables.

[b] Fisher's exact test (χ^2) were applied for categorical variables.

[c] BMI: Body Mass Index

Table 2
FBS, lipid profile, blood pressure parameters and blood pressure medications of the participants at the beginning of the clinical trial. Data are mean ± SD [a].

	Group 1: Celery (n = 25)	Group 2: Placebo (n = 26)	p-value
FBS [b] (mg/dL)	108.62 ± 14.33	108.41 ± 14.02	0.8953
TC [c] (mg/dL)	191.86 ± 6.01	190.85 ± 5.93	0.7446
TG [d] (mg/dL)	181.70 ± 15.81	180.71 ± 14.29	0.8137
LDL [e] (mg/dL)	117.13 ± 4.19	116.91 ± 3.92	0.6835
HDL [f] (mg/dL)	42.25 ± 1.49	42.41 ± 1.55	0.7060
SBP [g] (mm Hg)	142.06 ± 5.11	140.54 ± 5.77	0.8264
DBP [h] (mm Hg)	92.05 ± 5.52	91.99 ± 5.73	0.7539
Blood pressure medications			
ARB [i] (%)	7.41%	7.14%	0.9263
ACE [j] (%)	18.52%	17.86%	0.8353
Diuretic (%)	37.04%	39.29%	0.8102
Beta blocker (%)	14.81%	14.29%	0.9022
No medication (%)	22.22%	21.43%	0.8529

[a] Independent t-test were applied.

[b] FBS: Fasting Blood Sugar

[c] TC: Total Cholesterol

[d] TG: Triglyceride

[e] LDL: Low-Density Lipoprotein

[f] HDL: High-Density Lipoprotein

[g] SBP: Systolic Blood Pressure

[h] DBP: Diastolic Blood Pressure

[i] ACE: Active Inhibitor of Angiotensin-Converting Enzyme

[j] ARB: Angiotensin Receptor Blocker

Table 3
Values for daily nutrition intake in all 51 hypertensive patients during treatment with celery and placebo and their cross-over condition. Data are mean ± SD [a].

		Before Mean ± SD	After Mean ± SD	p-value
Energy (kcal)	Celery	1894.67 ± 119.67	1905.49 ± 125.24	0.5855
	Placebo	1909.63 ± 129.01	1919.30 ± 111.55	0.5196
	p-value	0.5902	0.5931	
Weight (g)	Celery	3598.51 ± 215.01	3626.04 ± 238.34	0.5826
	Placebo	3612.48 ± 222.77	3607.29 ± 231.92	0.5913
	p-value	0.5338	0.6137	
Total Nitrogen (g)	Celery	10.90 ± 0.69	11.09 ± 0.72	0.8886
	Placebo	10.96 ± 0.55	11.04 ± 0.59	0.8109
	p-value	0.7883	0.8091	
Total Water (L)	Celery	3.19 ± 0.18	3.21 ± 0.21	0.5992
	Placebo	3.23 ± 0.19	3.20 ± 0.22	0.9584
	p-value	0.9537	0.8175	
Carbohydrate (g)	Celery	219.53 ± 13.76	221.18 ± 15.18	0.6036
	Placebo	222.82 ± 14.22	220.50 ± 13.01	0.5936
	p-value	0.6126	0.6090	
Dietary Fiber (g)	Celery	19.91 ± 1.28	20.11 ± 1.37	0.7623
	Placebo	20.07 ± 1.31	19.99 ± 1.35	0.8149
	p-value	0.7864	0.8088	
Protein (g)	Celery	68.78 ± 4.87	69.01 ± 5.01	0.8942
	Placebo	69.74 ± 4.91	70.88 ± 5.08	0.8503
	p-value	0.8230	0.8133	
Starch (g)	Celery	110.92 ± 7.18	112.17 ± 7.72	0.6620
	Placebo	112.11 ± 7.55	111.59 ± 7.38	0.6937
	p-value	0.5819	0.6392	
Total Sugars (g)	Celery	108.50 ± 7.94	109.14 ± 8.02	0.7585

[a] Independent t-test were applied.

		Before Mean ± SD	After Mean ± SD	p-value
	Placebo	109.70 ± 8.07	110.22 ± 7.88	0.7573
	p-value	0.8067	0.7843	
Fat (g)	Celery	84.75 ± 5.14	85.30 ± 5.67	0.8145
	Placebo	85.99 ± 5.33	86.25 ± 5.52	0.7942
	p-value	0.8592	0.8262	
Cholesterol (mg)	Celery	260.09 ± 16.69	261.59 ± 17.12	0.6740
	Placebo	262.12 ± 16.78	263.65 ± 16.84	0.7027
	p-value	0.6303	0.7326	
Calcium (mg)	Celery	749.41 ± 45.27	752.72 ± 49.67	0.5647
	Placebo	750.99 ± 47.55	751.89 ± 48.07	0.5982
	p-value	0.5834	0.5223	
Copper (µg)	Celery	1512.49 ± 99.55	1528.70 ± 101.13	0.2665
	Placebo	1531.93 ± 103.61	1521.56 ± 98.69	0.4927
	p-value	0.3394	0.4154	
Iodine (µg)	Celery	102.68 ± 5.89	103.48 ± 6.36	0.6301
	Placebo	104.27 ± 6.12	103.29 ± 6.29	0.6839
	p-value	0.7238	0.6929	
Iron (mg)	Celery	8.55 ± 0.49	8.51 ± 0.56	0.7160
	Placebo	8.61 ± 0.53	8.60 ± 0.51	0.9375
	p-value	0.7951	0.7514	
Magnesium (mg)	Celery	350.77 ± 20.98	347.69 ± 23.5	0.7275
	Placebo	356.20 ± 22.22	352.87 ± 21.87	0.6737
	p-value	0.5838	0.5937	
Manganese (mg)	Celery	2.45 ± 0.14	2.49 ± 0.16	0.3185
	Placebo	2.48 ± 0.15	2.46 ± 0.14	0.3788
	p-value	0.3183	0.3491	

[a] Independent t-test were applied.

		Before Mean ± SD	After Mean ± SD	p-value
Phosphorus (mg)	Celery	1151.53 ± 69.48	1146.12 ± 77.11	0.8976
	Placebo	1159.37 ± 74.77	1152.43 ± 71.83	0.9584
	p-value	0.9537	0.8175	
Selenium (µg)	Celery	39.46 ± 2.27	40.19 ± 2.64	0.7132
	Placebo	40.07 ± 2.55	39.69 ± 2.38	0.7736
	p-value	0.7947	0.7351	
Zinc (mg)	Celery	7.55 ± 0.48	7.58 ± 0.51	0.6983
	Placebo	7.63 ± 0.42	7.59 ± 0.40	0.7349
	p-value	0.6482	0.7495	
Potassium (g)	Celery	3.19 ± 0.18	3.22 ± 0.21	0.8204
	Placebo	3.23 ± 0.20	3.20 ± 0.16	0.8026
	p-value	0.7523	0.7939	
Sodium (g)	Celery	1.37 ± 0.07	1.39 ± 0.09	0.8033
	Placebo	1.39 ± 0.08	1.378 ± 0.08	0.8737
	p-value	0.7819	0.8392	
Chloride (mg)	Celery	2.38 ± 0.13	2.36 ± 0.16	0.7305
	Placebo	2.40 ± 0.15	2.39 ± 0.14	0.7573
	p-value	0.7767	0.6843	
Retinol (µg)	Celery	253.52 ± 14.58	257.89 ± 16.15	0.8619
	Placebo	254.44 ± 15.33	255.04 ± 14.91	0.7942
	p-value	0.8592	0.8262	
Carotene (µg)	Celery	1432.42 ± 88.82	1428.35 ± 94.61	0.7451
	Placebo	1429.39 ± 91.97	1425.92 ± 92.56	0.8027
	p-value	0.8303	0.7726	
Vitamin C (mg)	Celery	117.66 ± 6.94	115.41 ± 7.84	0.6565
	Placebo	119.48 ± 8.02	118.36 ± 7.13	0.7382

[a] Independent t-test were applied.

		Before Mean ± SD	After Mean ± SD	p-value
	p-value	0.6834	0.5902	
Vitamin D (µg)	Celery	10.22 ± 0.58	10.28 ± 0.67	0.4148
	Placebo	10.27 ± 0.63	10.23 ± 0.60	0.5927
	p-value	0.6394	0.7154	
Vitamin E (mg)	Celery	11.96 ± 0.77	12.12 ± 0.81	0.4289
	Placebo	12.14 ± 0.85	12.03 ± 0.79	0.4839
	p-value	0.4024	0.5929	
Thiamin (mg)	Celery	1.41 ± 0.08	1.43 ± 0.10	0.7887
	Placebo	1.43 ± 0.11	1.41 ± 0.09	0.8375
	p-value	0.7951	0.8114	
Riboflavin (mg)	Celery	1.40 ± 0.08	1.41 ± 0.09	0.8601
	Placebo	1.42 ± 0.09	1.40 ± 0.08	0.8737
	p-value	0.7838	0.9537	
Niacin (mg)	Celery	16.51 ± 1.05	16.63 ± 1.11	0.6102
	Placebo	16.60 ± 1.10	16.65 ± 1.07	0.7012
	p-value	0.7183	0.8491	
VitB6 (mg)	Celery	1.79 ± 0.10	1.81 ± 0.12	0.7085
	Placebo	1.82 ± 0.11	1.80 ± 0.10	0.8584
	p-value	0.7537	0.8175	
Folate (µg)	Celery	277.41 ± 16.68	282.40 ± 18.56	0.5901
	Placebo	281.70 ± 18.02	279.07 ± 17.72	0.6646
	p-value	0.6478	0.6951	
Vitamin B12 (µg)	Celery	3.00 ± 0.17	2.98 ± 0.19	0.8684
	Placebo	3.02 ± 0.18	3.01 ± 0.17	0.8349
	p-value	0.7482	0.7495	
Pantothenate (mg)	Celery	6.48 ± 0.33	6.45 ± 0.42	0.8889

[a] Independent t-test were applied.

		Before Mean ± SD	After Mean ± SD	p-value
	Placebo	6.46 ± 0.40	6.43 ± 0.38	0.8026
	p-value	0.9023	0.8693	
Biotin (µg)	Celery	31.32 ± 1.83	31.41 ± 2.08	0.8329
	Placebo	31.40 ± 2.00	31.30 ± 1.91	0.7937
	p-value	0.7819	0.8192	

[a] Independent t-test were applied.

Blinding and Randomization

Celery and placebo capsules were prepared similarly. They had identical shapes, colors, sizes, textures, and odors. The capsules were packed in the same containers with random code numbers. Hence, the participants, researcher, physician, and data analyzer were all blinded to the treatment and placebo groups essence. The coding of capsule containers and randomization were performed using 6-digit numbers obtained from the “random number table”. The first column of the random number table was assigned to the celery-washout-placebo group and the second one to the placebo-washout-celery group. The codes were written on a piece of paper and put into an opaque envelope. The envelopes were sealed and placed sequentially in a box and kept by the researcher and physician. The envelopes and their codes were assigned sequentially to eligible participants in order of their arrival time.

Safety

The researcher asked the patients to inform her of any side effects or complaints during the trial as soon as their incident. Any possible side effects and symptoms were recorded via weekly telephone calls and in each visit to the physician. Continuing or discontinuing the medications was the physician's responsibility. The side effects checklist was completed by an independent person.

Statistical analysis

The baseline, demographic, and clinical characteristics of the two groups were compared using the independent t-test and Fisher's exact test ($\chi 2$). Paired t-test was used for the comparison of changes before and after treatment within each study group. Independent t-tests were used to compare the mean differences of the celery and placebo groups. All p-values were two-sided, without adjustment of multiple comparisons, and a p-value of less than 0.05 was considered statistically significant. The analyses were performed using R software (version 4.0.5, R Foundation for Statistical Computing).

Results

Standardization of Celery Seed Extract and capsules

The standard NBP was applied for the standardization of the extract and final capsule powder. The HPLC analysis revealed that the amount of NBP in aqueous-ethanolic (20/80, v/v) extract was 15.68 mg/g. According to the collected data, the NBP amount in each capsule was 5.23 ± 0.06 mg. Figure 1 represents chromatograms of standard methanolic solution of NBP (10 µg/mL) and celery seed capsule powder (1000 µg/mL).

Clinical Trial Design

According to clinical documents, from 3057 patients; 59 of them met the inclusion criteria, were scheduled for clinic visit screening, and enrolled in the study. Participants were randomly allocated into the celery (n = 29) and placebo (n = 30) groups. In the first step of the cross-over trial, 8 patients were excluded due to a change in medication regimen, and a remarkable change in physical activity and discontinuing (Fig. 2). Hence, 51 patients were crossed over and completed the clinical trial.

Data Collection

Finally, 51 patients completed the study and were participated in the final analysis. No statistically significant difference was observed between the two groups in baseline information ($P > 0.05$). According to the information summarized in Table 1, the mean ages of the patients in celery and placebo groups were 50.21 ± 6.66 and 51.34 ± 5.91, respectively. Regarding gender and marital status, 49.09% and 89.09% of the subjects were female and married, respectively. It is also noteworthy that average educational years for patients in group 1 and group 2 were 12.33 ± 2.76 and 12.13 ± 2.12, respectively. Lifestyle information showed no significant difference was observed between groups in physical activity (4.76 ± 3.11 versus 4.56 ± 3.23 hours per day). The average BMI values of all participants were 27.66 and 28.49 for females and males, respectively. Table 2 shows that at the start of the study, two groups were the same in serum biochemical parameters, particularly fasting blood sugar (FBS) and lipid profile ($P > 0.05$). also, this table shows that the mean SBP and DBP and anti-hypertensive medication regimen of the groups at the start point was not significantly different ($P > 0.05$). Table 3 showed no significant difference between the two groups and within each group in daily nutrition intake during the study ($P > 0.05$).

Clinical Trial Results

Effect of celery on blood pressure parameters in hypertensive patients

Results for SBP, DBP, MAP, and PP obtained during treatment with celery and placebo and their cross-over condition are summarized in Table 4. There was no statistically significant difference between the celery (SBP: 142.06 ± 5.11 and DBP: 92.05 ± 5.52 mmHg) and placebo (SBP: 140.54 ± 5.77 and DBP: 91.99 ± 5.73 mmHg) groups at the beginning of this study (t-test, unpaired, $P > 0.05$). This table shows that all BP parameters did not change during the placebo treatment ($P > 0.05$), while the abovementioned parameters

significantly decreased after celery treatment ($P < 0.001$). The mean reduction in SBP and DBP were 11.08 and 6.54 mmHg, respectively, during celery therapy ($P < 0.001$).

Table 4
Values for blood pressure parameters during treatment with celery and placebo and their cross-over condition. Data are mean ± SD [a].

	Start: week 0	End: week 4	p-value	4-weeks washout	Start: week 8	End: week 12	p-value
SBP [b] (mmHg)							
Group 1: Celery-Washout-Placebo	142.06 ± 5.11	131.07 ± 5.53	7.71E-08		141.74 ± 5.53	142.11 ± 5.90	0.7264
Group 2: Placebo-Washout-Celery	140.54 ± 5.77	141.81 ± 5.39	0.7254		142.04 ± 5.62	130.78 ± 5.74	7.76E-08
p-value	0.8264	6.66E-08			0.8264	5.54E-08	
DBP [c] (mmHg)							
Group 1: Celery-Washout-Placebo	92.05 ± 5.52	85.74 ± 5.52	7.70E-06		92.36 ± 5.33	92.43 ± 5.84	0.7235
Group 2: Placebo-Washout-Celery	91.99 ± 5.73	91.98 ± 5.17	0.7352		92.22 ± 5.92	85.53 ± 5.06	7.10E-06
p-value	0.7539	5.60E-06			0.7264	5.30E-06	
MAP [d] (mmHg)							
Group 1: Celery-Washout-Placebo	107.99 ± 6.02	100.09 ± 5.88	7.40E-06		108.22 ± 6.75	107.89 ± 6.34	0.8264
Group 2: Placebo-Washout-Celery	107.83 ± 6.11	107.64 ± 6.23	0.8254		107.88 ± 6.34	100.04 ± 5.63	6.30E-06
p-value	0.7494	7.10E-06			0.7398	6.81E-06	
PP [e] (mmHg)							
Group 1: Celery-Washout-Placebo	49.33 ± 3.89	46.03 ± 3.08	0.0007		49.31 ± 3.82	49.10 ± 3.75	0.9872

[b] SBP: Systolic Blood Pressure

[c] DBP: Diastolic Blood Pressure

[d] MAP: Mean Arterial Pressure

[e] PP: Pulse Pressure

Group 2: Placebo-Washout-Celery	49.29 ± 3.79	49.33 ± 3.82	0.9536		49.26 ± 3.76	45.99 ± 3.02	0.0006
p-value	0.9374	0.0008			0.9648	0.0007	
[b] SBP: Systolic Blood Pressure							
[c] DBP: Diastolic Blood Pressure							
[d] MAP: Mean Arterial Pressure							
[e] PP: Pulse Pressure							

Effect of celery on blood cells in hypertensive patients

The difference in WBC, RBC, platelet, and their indices treatment were compared between the groups after 4-weeks. There were no significant differences between placebo and treatment groups and within each group pre- and post-intervention ($P > 0.05$) (Table 5).

Table 5
Values for hematological indices in hypertensive patients during treatment with celery and placebo and their cross-over condition. Data are mean ± SD [a].

	Start: week 0	End: week 4	p-value	4-weeks washout	Start: week 8	End: week 12	p-value
WBC [b] (x1000/µl)							
Group 1: Celery-Washout-Placebo	6.25 ± 0.11	6.31 ± 0.13	0.8325		6.31 ± 0.12	6.30 ± 0.11	0.7138
Group 2: Placebo-Washout-Celery	6.31 ± 0.14	6.28 ± 0.10	0.7781		6.26 ± 0.09	6.29 ± 0.15	0.8375
p-value	0.7951	0.7514			0.7019	0.9846	
RBC [c] (x1000000/µl)							
Group 1: Celery-Washout-Placebo	4.46 ± 0.10	4.58 ± 0.11	0.5194		4.52 ± 0.12	4.49 ± 0.11	0.6649
Group 2: Placebo-Washout-Celery	4.51 ± 0.11	4.55 ± 0.12	0.6214		4.48 ± 0.10	4.57 ± 0.13	0.9737
p-value	0.5838	0.6937			0.8183	0.7464	
Hb [d] (g/dl)							
Group 1: Celery-Washout-Placebo	14.06 ± 0.79	14.12 ± 0.88	0.7896		14.12 ± 0.73	14.09 ± 0.84	0.8675
Group 2: Placebo-Washout-Celery	14.09 ± 0.81	14.10 ± 0.85	0.9464		14.07 ± 0.87	14.11 ± 0.78	0.8118
p-value	0.8183	0.8491			0.7237	0.9037	
Hct [e] (%)							
Group 1: Celery-Washout-Placebo	41.31 ± 1.18	41.38 ± 1.21	0.8311		41.34 ± 1.22	41.31 ± 1.19	0.8769
Group 2: Placebo-Washout-Celery	41.33 ± 1.19	41.32 ± 1.17	0.9488		41.35 ± 1.20	41.36 ± 1.21	0.9584
p-value	0.9537	0.8175			0.9731	0.9147	
MCV [f] (fl)							
Group 1: Celery-Washout-Placebo	87.01 ± 2.32	86.75 ± 2.76	0.5476		86.51 ± 2.64	86.65 ± 2.51	0.5283
Group 2: Placebo-Washout-Celery	86.91 ± 2.45	86.44 ± 2.57	0.6484		86.71 ± 2.39	87.02 ± 2.48	0.8364

p-value	0.7947	0.7351		0.8364	0.6485	
MCH [g] (pg)						
Group 1: Celery-Washout-Placebo	29.96 ± 0.88	30.21 ± 0.81	0.6839	29.77 ± 0.79	29.88 ± 0.84	0.8445
Group 2: Placebo-Washout-Celery	30.06 ± 0.83	29.87 ± 0.85	0.7565	29.76 ± 0.84	30.11 ± 0.87	0.7349
p-value	0.6482	0.7495		0.6396	0.7492	
MCHC [h] (g/dl)						
Group 1: Celery-Washout-Placebo	33.85 ± 1.06	33.90 ± 1.11	0.4989	33.88 ± 1.10	33.92 ± 1.08	0.5193
Group 2: Placebo-Washout-Celery	33.91 ± 1.09	33.87 ± 1.05	0.5484	33.95 ± 1.08	33.90 ± 1.11	0.7026
p-value	0.6230	0.5293		0.7359	0.7240	
PLT [i] (x1000/µl)						
Group 1: Celery-Washout-Placebo	247.97 ± 3.87	248.68 ± 3.91	0.5774	248.02 ± 3.90	247.34 ± 3.97	0.7028
Group 2: Placebo-Washout-Celery	248.11 ± 3.88	249.36 ± 3.90	0.7292	249.19 ± 3.88	248.71 ± 3.89	0.6937
p-value	0.5819	0.6392		0.7880	0.8165	
RDW-CV [j] (%)						
Group 1: Celery-Washout-Placebo	13.42 ± 1.01	13.48 ± 1.03	0.7217	13.51 ± 1.03	13.47 ± 1.02	0.8135
Group 2: Placebo-Washout-Celery	13.49 ± 1.02	13.43 ± 1.01	0.8764	13.46 ± 1.02	13.44 ± 1.01	0.7573
p-value	0.8367	0.7843		0.8385	0.7351	
PDW [k] (fl)						
Group 1: Celery-Washout-Placebo	15.89 ± 1.11	15.93 ± 1.09	0.8117	15.93 ± 1.09	15.98 ± 1.08	0.8037
Group 2: Placebo-Washout-Celery	15.92 ± 1.10	15.97 ± 1.11	0.7239	15.90 ± 1.10	15.93 ± 1.11	0.7942
p-value	0.8592	0.8262		0.8461	0.9262	
MPV [l] (fl)						
Group 1: Celery-Washout-Placebo	10.51 ± 0.77	10.55 ± 0.76	0.7564	10.54 ± 0.78	10.56 ± 0.76	0.8363

Group 2: Placebo-Washout-Celery	10.58 ± 0.75	10.57 ± 0.78	0.8937		10.57 ± 0.75	10.52 ± 0.77	0.8027
p-value	0.6303	0.7726			0.8639	0.7393	
PMN [m] (%)							
Group 1: Celery-Washout-Placebo	60.71 ± 1.09	61.04 ± 1.13	0.4015		60.38 ± 1.12	61.04 ± 1.10	0.5293
Group 2: Placebo-Washout-Celery	61.14 ± 1.12	60.89 ± 1.11	0.5938		61.13 ± 1.09	60.78 ± 1.11	0.4982
p-value	0.4834	0.5023			0.4539	0.5204	
Lymph [n] (x1000/µl)							
Group 1: Celery-Washout-Placebo	32.55 ± 0.91	33.02 ± 0.86	0.5926		32.91 ± 0.87	32.58 ± 0.91	0.8264
Group 2: Placebo-Washout-Celery	33.02 ± 0.89	32.87 ± 0.87	0.7284		33.19 ± 0.90	32.81 ± 0.86	0.7927
p-value	0.6394	0.7154			0.7037	0.6339	
Mix							
Group 1: Celery-Washout-Placebo	4.56 ± 0.13	4.60 ± 0.12	0.7931		4.54 ± 0.14	4.59 ± 0.12	0.7463
Group 2: Placebo-Washout-Celery	4.59 ± 0.14	4.52 ± 0.14	0.7139		4.58 ± 0.13	4.51 ± 0.13	0.6839
p-value	0.7238	0.6929			0.7259	0.6374	

[a] Paired t-test were applied for variables in each group and independent t-test between two groups.

[b] WBC: White Blood Cell count

[c] RBC: Red Blood Cell count

[d] Hb: Hemoglobin

[e] Hct: Hematocrit

[f] MCV: Mean Cell Volume

[g] MCH: Mean Cell Hemoglobin

[h] MCHC: Mean Cell Hemoglobin Concentration

[i] PLT: Platelet Count

[j] RDW-CV: Red Cell Distribution Width- Coefficient of Variation

[k] PDW: Platelets Distribution Width

[l] MPV: Mean Platelet Volume

[m] PMN: Polymorphonuclear Leukocytes

[n] Lymph: Lymphocyte Number

Effect of celery seed on kidney function tests and serum electrolytes in hypertensive patients

The difference between the two groups was compared in kidney function tests; BUN and SCr and some important serum electrolytes; Na, K, Ca, and P after 4-weeks of treatment. There were no significant differences between the treatment and placebo groups and within each group pre- and post-intervention in Na, K, Ca, and P values ($P > 0.05$) (Table 6). Furthermore, significant changes were observed in BUN and SCr after celery consumption ($P < 0.05$). The mean reduction in BUN and SCr were 3.43 and 0.08 mg/dL, respectively.

Table 6
Values for biochemistry function of kidney and serum electrolytes during treatment with celery and placebo and their cross-over condition. Data are mean ± SD [a].

	Start: week 0	End: week 4	p-value	4-weeks washout	Start: week 8	End: week 12	p-value
BUN [b] (mg/dL)							
Group 1: Celery-Washout-Placebo	28.91 ± 1.34	25.67 ± 0.89	0.0220		28.67 ± 1.22	28.88 ± 1.45	0.5746
Group 2: Placebo-Washout-Celery	29.13 ± 1.33	29.01 ± 1.21	0.7351		29.08 ± 1.29	25.41 ± 0.94	0.0310
p-value	0.5551	0.0340			0.3596	0.0472	
SCr [c] (mg/dL)							
Group 1: Celery-Washout-Placebo	1.16 ± 0.14	1.09 ± 0.09	0.0294		1.17 ± 0.15	1.16 ± 0.15	0.8110
Group 2: Placebo-Washout-Celery	1.15 ± 0.11	1.17 ± 0.12	0.5339		1.15 ± 0.14	1.08 ± 0.11	0.0331
p-value	0.7073	0.0266			0.6214	0.0229	
Na [d] (mEq/L)							
Group 1: Celery-Washout-Placebo	138.10 ± 0.91	139.11 ± 1.04	0.6463		138.75 ± 0.98	138.10 ± 0.89	0.7877
Group 2: Placebo-Washout-Celery	137.17 ± 0.89	138.01 ± 1.01	0.6945		138.13 ± 0.93	139.51 ± 0.92	0.6139
p-value	0.6811	0.7427			0.7863	0.8486	
K [e] (mEq/L)							
Group 1: Celery-Washout-Placebo	3.89 ± 0.05	4.02 ± 0.07	0.7461		3.85 ± 0.06	3.91 ± 0.06	0.8441
Group 2: Placebo-Washout-Celery	3.82 ± 0.06	3.88 ± 0.06	0.8729		3.88 ± 0.06	4.01 ± 0.06	0.7167
p-value	0.8357	0.7636			0.8917	0.8173	
Ca [f] (mg/dL)							
Group 1: Celery-Washout-Placebo	9.15 ± 0.08	9.46 ± 0.11	0.0878		9.16 ± 0.09	9.16 ± 0.08	0.2124
Group 2: Placebo-Washout-Celery	9.16 ± 0.09	9.15 ± 0.09	0.1645		9.17 ± 0.08	9.49 ± 0.12	0.0847
p-value	0.1254	0.0827			0.1831	0.0819	

P [g] (mg/dL)						
Group 1: Celery-Washout-Placebo	3.75 ± 0.08	3.72 ± 0.06	0.6334	3.74 ± 0.08	3.73 ± 0.07	0.7388
Group 2: Placebo-Washout-Celery	3.71 ± 0.09	3.74 ± 0.07	0.5496	3.72 ± 0.07	3.75 ± 0.06	0.5869
p-value	0.5724	0.5923		0.7523	0.6956	

[a] Paired t-test were applied for variables in each group and independent t-test between two groups.

[b] BUN: Blood Urea Nitrogen

[c] SCr: Serum Creatinine

[d] Na: Sodium

[e] K: Potassium

[f] Ca: Calcium

[g] P: Phosphorus

Effect of celery seed on liver function tests in hypertensive patients

Liver functions; SGOT, SGPT, and ALP after 4-weeks treatment were compared between the groups. There were no significant differences in ALP values between the treatment and placebo groups and within each group pre- and post-intervention ($P > 0.05$) (Table 7). Data shows SGOT and SGPT did not change during the placebo treatment ($P > 0.05$), while both of them significantly decreased after celery treatment ($P < 0.05$). The mean reduction for SGOT and SGPT were 4.08 and 3.03 U/L, respectively.

Table 7
Values for liver function during treatment with celery and placebo and their cross-over condition. Data are mean ± SD [a].

	Start: week 0	End: week 4	p-value	4-weeks washout	Start: week 8	End: week 12	p-value
SGPT [b] (U/L)							
Group 1: Celery-Washout-Placebo	29.22 ± 1.98	25.06 ± 1.68	0.0474		29.11 ± 1.83	28.97 ± 1.82	0.5877
Group 2: Placebo-Washout-Celery	28.94 ± 1.81	29.17 ± 1.77	0.7785		28.99 ± 1.79	24.96 ± 1.63	0.0487
p-value	0.4173	0.0434			0.6366	0.0424	
SGOT [c] (U/L)							
Group 1: Celery-Washout-Placebo	22.69 ± 1.71	19.55 ± 1.41	0.0465		22.55 ± 1.62	22.41 ± 1.67	0.7686
Group 2: Placebo-Washout-Celery	22.43 ± 1.67	22.55 ± 1.59	0.5491		22.38 ± 1.48	19.41 ± 1.31	0.0480
p-value	0.3372	0.0456			0.3445	0.0436	
ALP [d] (U/L)							
Group 1: Celery-Washout-Placebo	189.84 ± 14.25	187.75 ± 13.97	0.0923		189.87 ± 14.13	189.90 ± 14.20	0.9792
Group 2: Placebo-Washout-Celery	190.14 ± 14.31	190.01 ± 14.22	0.9664		190.03 ± 14.18	187.90 ± 13.88	0.0951
p-value	0.7972	0.0945			0.8881	0.0927	

[a] Paired t-test were applied for variables in each group and independent t-test between two groups.

[b] SGPT: Serum Glutamic-Pyruvic Transaminase

[c] SGOT: Serum Glutamic-Oxaloacetic Transaminase

[d] ALP: Alkaline Phosphatase

Effect of celery on fasting blood sugar and serum lipid profile in hypertensive patients

The difference in FBS and serum lipid profile TC, TG, LDL, HDL, LDL: HDL ratio, and TC: HDL ratio, after 4-weeks of treatment were compared between the groups. There was no statistically significant difference between the celery and placebo groups at the beginning of this study (t-test, unpaired, $P > 0.05$). Table 8 shows that FBS significantly decreased after celery treatment ($P < 0.01$) while, it did not change after the

placebo consumption ($P > 0.05$). FBS reduced from 108.53 to 97.96 mg/dL after 4-weeks of celery administration ($P < 0.001$). The mean reduction in FBS was 10.48 mg/dL. The serum lipid profile parameters did not change during the placebo treatment ($P > 0.05$), while the abovementioned parameters significantly decreased after celery treatment ($P < 0.001$). The mean reduction in cholesterol, triglyceride, LDL, and HDL were 16.37, 16.22, 11.84, and 2.52 mg/dL, respectively, during celery therapy ($P < 0.001$). Moreover, the ratio of LDL: HDL and TC: HDL were significantly decreased after treatment with celery ($P < 0.01$).

Table 8
Values for fasting blood sugar and serum lipid profile during treatment with celery and placebo and their cross-over condition. Data are mean ± SD [a].

	Start: week 0	End: week 4	p-value		Start: week 8	End: week 12	p-value
FBS [b] (mg/dL)				**4-weeks washout**			
Group 1: Celery-Washout-Placebo	108.62 ± 14.33	98.13 ± 13.91	0.0086		109.02 ± 14.65	108.29 ± 14.9	0.9743
Group 2: Placebo-Washout-Celery	108.41 ± 14.02	108.55 ± 14.77	0.9413		108.31 ± 13.41	97.79 ± 12.41	0.0042
p-value	0.8953	0.0081			0.8534	0.0045	
TC [c] (mg/dL)				**4-weeks washout**			
Group 1: Celery-Washout-Placebo	191.86 ± 6.01	175.71 ± 5.46	0.0001		192.01 ± 6.22	191.98 ± 6.34	0.9863
Group 2: Placebo-Washout-Celery	190.85 ± 5.93	191.75 ± 6.03	0.9045		191.27 ± 6.11	174.98 ± 5.77	0.0002
p-value	0.7446	0.0007			0.6670	0.0008	
TG [d] (mg/dL)							
Group 1: Celery-Washout-Placebo	181.70 ± 15.81	165.51 ± 13.77	0.0007		181.55 ± 15.18	181.01 ± 14.72	0.8969
Group 2: Placebo-Washout-Celery	180.71 ± 14.29	181.65 ± 14.66	0.9329		180.95 ± 14.88	164.71 ± 13.65	0.0005
p-value	0.8137	0.0005			0.8861	0.0003	
LDL [e] (mg/dL)							
Group 1: Celery-Washout-Placebo	117.13 ± 4.19	104.97 ± 3.45	0.0005		116.98 ± 3.88	116.55 ± 3.64	0.6820

[a] Paired t-test were applied for variables in each group and independent t-test between two groups.

[b] FBS: Fasting Blood Sugar

[c] TC: Total Cholesterol

[d] TG: Triglyceride

[e] LDL: Low-Density Lipoprotein

[f] HDL: High-Density Lipoprotein

	Start: week 0	End: week 4	p-value		Start: week 8	End: week 12	p-value
Group 2: Placebo-Washout-Celery	116.91 ± 3.92	116.11 ± 3.92	0.8548		116.25 ± 4.01	104.37 ± 3.33	0.0003
p-value	0.6835	0.0008			0.5078	0.0007	
HDL [f] (mg/dL)							
Group 1: Celery-Washout-Placebo	42.25 ± 1.49	44.78 ± 1.18	0.0006		42.55 ± 1.76	42.33 ± 1.18	0.5992
Group 2: Placebo-Washout-Celery	42.41 ± 1.55	42.33 ± 1.32	0.8420		42.39 ± 1.64	44.91 ± 1.09	0.0007
p-value	0.7060	0.0005			0.7359	0.0009	
LDL:HDL ratio				**4-weeks washout**			
Group 1: Celery-Washout-Placebo	2.77	2.34	0.0021		2.75	2.75	0.9999
Group 2: Placebo-Washout-Celery	2.76	2.74	0.8064		2.74	2.32	0.0022
p-value	0.8831	0.0023			0.8902	0.0021	
TC:HDL ratio							
Group 1: Celery-Washout-Placebo	4.54	3.92	0.0039		4.51	4.54	0.7528
Group 2: Placebo-Washout-Celery	4.51	4.53	0.8938		4.52	4.08	0.0052
p-value	0.7943	0.0041			0.9378	0.0057	

[a] Paired t-test were applied for variables in each group and independent t-test between two groups.

[b] FBS: Fasting Blood Sugar

[c] TC: Total Cholesterol

[d] TG: Triglyceride

[e] LDL: Low-Density Lipoprotein

[f] HDL: High-Density Lipoprotein

Side effects

According to the data reported in Table 9, no major negative effects were reported during the trial in the celery group compared to the placebo group ($P > 0.05$). Celery also had some positive side effects,

reported by the patients during celery treatment, such as improved sleep quality, a sense of relaxation and freshness during the day, better breathing, and less dizziness, which were significant in comparison with the placebo group ($P < 0.05$). Moreover, no patient was withdrawn from the clinical trial due to adverse events.

Table 9
The side effects checklist during celery and placebo consumption [a].

	Group 1: Celery (n = 51)	Group 2: Placebo (n = 51)	p-value
Positive side effect			
Better breathing	5	1	0.0069
Lowering dizziness	7	1	0.0037
Improve sleep quality	9	1	0.0007
Feeling more relax	8	1	0.0010
Feeling fresh during day	5	0	0.0041
Negative side effect			
Stomach reflux	2	1	0.6648
Skin irritation	1	0	0.3947
swelling	1	0	0.3947
nausea	1	1	1
[a] Fisher's exact test ($\chi 2$) between two groups was applied.			

Discussion

Findings and previous studies

The current study aims to evaluate the safety of celery seed extract capsules, as a drug supplement, in hypertensive patients, in a randomized, triple-blind, placebo-controlled, cross-over clinical trial. The results of the present study showed that celery seed extract capsules (1.34 g per day for 4-weeks) not only are safe for hypertensive patients but also could improve some clinical, biochemical, and hematological parameters. The variations were in normal ranges which could be important clinically. The hypotensive effect of celery and NBP were studied in some research (Moghadam et al., 2013; Zhu et al., 2015). Also, some studies have reported hypolipidemic and hypoglycemic properties of celery and NBP in animal models and clinical trials (Illes, 2021; Niaz, 2013; Tashakori-Sabzevar, Ramezani, et al., 2016; Yusni et al., 2018). Based on Tables 1 and 2, the two groups had no significant difference at the beginning of the clinical trial in terms of demographic characteristics, FBS, lipid profile, and BP parameters ($P > 0.05$).

Furthermore, no significant differences were seen in terms of dietary intake within and between the groups during the study ($P > 0.05$). The cross-over study was applied to minimize the underlying and confounding factors which can affect the results in the clinical trial. In this study, celery seed extract capsules (1.34g extract per day for 4-weeks) decreased BP parameters; SBP, DBP, MAP, and PP ($P < 0.001$). The mean reduction in SBP and DBP were 11.08 and 6.54 mmHg, respectively, during celery therapy ($P < 0.001$). In a study by Moghadam *et al.*, the chronic effect of celery seed extract on hypertension was demonstrated in hypertensive and normotensive male rats. It has been reported that celery seed extract reduced BP, which is ascribed to its vasodilatory and diuretic effects (Moghadam et al., 2013). Moreover, a significant reduction in BP, due to NBP administration, was observed in the chronic kidney disease model against hypertensive nephropathy using spontaneously hypertensive rats (Zhu et al., 2015). In another study, the hypotensive effects of NBP were reported *in vivo* model which significantly decreased BP (Tsi and Tan, 1997). In the present clinical study, celery capsules had no significant effect on blood cells including WBC, RBC, platelet, and their indices in comparison with placebo treatment ($P > 0.05$). All blood cells factors were in the normal range clinically. The results of another study by Masar *et al.* on male rats indicated a significant increase in RBC, PCV, and Hb concentration in the celery groups ($P > 0.05$), while the results of WBC count showed non-significant differences ($P < 0.05$) compared to control group (Al-Kurdy, 2016). Khuon *et al.* reported that the oral administration of aqueous extract of celery (200 mg/kg for 2 weeks) significantly increased WBC, RBC and Hb ($P < 0.01$) in rats subjected to the hematotoxicity induced by carbon tetrachloride. No significant increase or decrease were also observed in MCV, MCHC and Lymph ($P > 0.05$) (Khuon, 2012). In another work, alcoholic extract of celery leaves (10 mg/kg) in birds caused a significant increase in RBC, Hb, and PCV with no significant change in WBC (Al–Gnami, 2014). This increase may be attributed to the release of erythropoietin from the kidneys, which stimulates hematopoiesis (Al–Gnami, 2014). Moreover, celery seed could improve kidney function by decreasing BUN and SCr in hypertensive patients ($P < 0.05$). The mean reduction in BUN and SCr were 3.43 and 0.08 mg/dL, respectively. These changes are in the normal range clinically. Some important serum electrolytes including Na, K, Ca, and P were not affected during celery seed extract consumption ($P > 0.05$). Celery extract contains flavonoids with inhibitory effect on oxidative stress in different tissues such as the kidney. Flavonoids increase antioxidant activity and synthesis of glutathione s-transferase. They also trap ROS by donating hydrogen atoms to free radicals and thereby produce non-reactive free radicals. This effect can improve kidney function (Kang et al., 2016). In a study, oral administration of ethanolic extract of celery at a dose of 1000 mg/kg protected kidney harm in the kidney ischemia/ reperfusion injury rat model (Afifah et al., 2019). The protective effect of celery extract may be due to the content of phthalide and apiin glycosides as anti-inflammatory compounds (Mencherini et al., 2007; Zhu et al., 2017). Regarding the effect on liver function, in the present work, SGOT and SGPT significantly reduced during 4-weeks celery treatment ($P < 0.05$) while ALP had no change after celery administration ($P > 0.05$). The mean reduction for SGOT and SGPT were 4.08 and 3.03 U/L which are in the normal range clinically. Celery stimulates the healthy and normal functioning of the liver (Kolarovic et al., 2010). Celery root and leaf juices enhance antioxidative capacity i.e. decrease glutathione content and the antioxidative capacity in liver homogenate (Kolarovic et al., 2009). Celery seed is effective in liver injuries, caused by a single dose of paracetamol, in rats. Celery has

the protective effect against thioacetamide medications (Hamza and Amin, 2007). In another study in Wistar rats, celery seed had an inhibitive effect on liver carcinoma (Singh and Handa, 1995). Another study showed a reduction in the release of AST and ALT enzymes into the blood and the ingredients of celery stabilize liver cell membranes (Taher et al., 2007). In another study biochemical analysis of serum liver enzymes and blood, lipids showed that celery reduces ALT, AST, and ALP (Abd El-Mageed, 2011). In the present study, celery therapy could significantly reduce FBS after 4-weeks of administration in hypertensive patients ($P < 0.01$). The mean reduction in FBS was 10.48 mg/dL. In a 12 days study by Yusni *et al.* celery capsules (250 mg, three times per day) effectively decreased the glucose levels of blood (Yusni et al., 2018). In addition, it has been achieved that celery seed extract reduced serum glucose levels and induction of insulin release from pancreatic islets (Niaz, 2013). In another experiment, it was reported that celery seed extract decreased glucose levels in rats. Compared to the negative control group, the concentrations of alanine aminotransferase and aspartate aminotransferase were decreased in the diabetic animals (Tashakori-Sabzevar, Ramezani, et al., 2016). Another research showed that hepatic glucose-6-phosphatase and serum glucose levels decreased in the alloxan-induced diabetic mice model. Also, in comparison with the control group, concentrations of serum insulin were increased significantly (Panda and Kar, 2007). Furthermore, NBP demonstrated the neuroprotective property by increasing vascular endothelial growth factor expression and inhibiting caspase-3-mediated apoptosis (Zhang et al., 2010). In our clinical research, celery seed extract capsules were found to have antihyperlipidemic properties and have the potential for decreasing serum lipid profile in hypertensive patients ($P < 0.001$). Celery treatment reduced TC, TG, LDL, and increased HDL as 16.37, 16.22, 11.84, and 2.52 mg/dL, respectively. Moreover, the ratio of LDL: HDL and TC: HDL were significantly decreased after treatment with celery ($P < 0.01$). In the 8-weeks study, rats were fed a high-fat diet to induce hyperlipidemia. Celery has a significant effect on reducing TC, TG and LDL concentrations (Tsi et al., 1995). In other studies, celery caused a reduction in serum levels of LDL, LDL:HDL ratio, TC and TG (Cheng et al., 2010; Iyer and Patil, 2011; Kooti, Ghasemiboroon, et al., 2014; Kooti, Mansori, et al., 2014). In a 12-week study, celery seed extract reduced the liver lipids and serum lipid profile (Ahmed and Sayedda, 2012). Moreover, aqueous and ethanolic extracts of celery seeds showed hypolipidemic bioactivity, and decreasing in LDL concentration in hamsters (Lin et al., 2011).

Limitations of The Study

Current work is one of the first cohesive clinical studies for the safety evaluation of celery seed extract capsules as a drug supplement in hypertensive patients. The small size of each group and the short time of each step were the limitations of the study. Moreover, some confounding factors including ethnicity or genetic diversity were not evaluated in this work.

Conclusion

As the most remarkable therapeutic property of celery is BP reduction, it was important to figure out the safety evaluation of celery in humans as herbal medicine. In this study, celery seed capsules (1.34g extract per day) were given to patients as drug supplements in a randomized, triple-blind, placebo-

controlled, cross-over clinical trial. The results indicated that the celery seed capsule not only is safe for hypertensive patients but also caused a reduction in BP values, improved kidney and liver function, FBS, and lipid profile, which are statistically and clinically significant and were in normal ranges. However, no significant change was observed in blood cells and serum electrolytes. According to the promising results of this clinical trial, celery seed extract can be considered a safe supplement for hypertensive patients.

Abbreviations

ALP Alkaline Phosphatase

BMI Body Mass Index

BUN Blood Urea Nitrogen

CBC Complete Blood Count

DBP Diastolic Blood Pressure

GCP Good Clinical Practice

SBP Systolic Blood Pressure

LDL Low-Density Lipoprotein

HDL High-Density Lipoprotein

MAP Mean Arterial Blood Pressure

PP Pulse Pressure

TC Total Cholesterol

TG Triglyceride

SCr Serum Creatinine

SGOT Serum Glutamic Oxaloacetic Transaminase

SGPT Serum Glutamic Pyruvic Transaminase

Declarations

Conflict of interest: We declare there is no conflict of interest related to this study and there was no financial support that influence its outcome.

Ethics approval: The study is in compliance with the regulations of Iran and approved by an independent ethics committee of Mashhad University of Medical Sciences, Mashhad, Iran (ethics committee reference number and approval date: IR.MUMS.REC.1394.705, 2016-02-27).

Consent to participate: Details and procedures of the study were completely explained to patients through an interview, consent to participate was obtained before the start of study treatment.

Consent for publicationI give my consent for the publication of identifiable details, which can include details within the text to be published in the EPMA Journal.

Availability of data and material: The data that support the findings of this study are available on request from the corresponding author.

Code availability: Not applicable

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Author contributions

Maryam Shayani Rad: Conceptualization; Data curation; Data analysis; Investigation; Methodology; Software; Validation; Visualization; Writing - original draft; Writing - review & editing; Writing - review & editing.

Mohsen Moohebati: Conceptualization; Data curation; Project administration; Validation; Visualization.

Shahab MohammadEbrahimi: Statistical analysis

Vahideh Sadat Motamedshariaty: HPLC analysis

Seyed Ahmad Mohajeri: Idea design, Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Supervision; Resources; Validation; Writing - review & editing.

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Figures

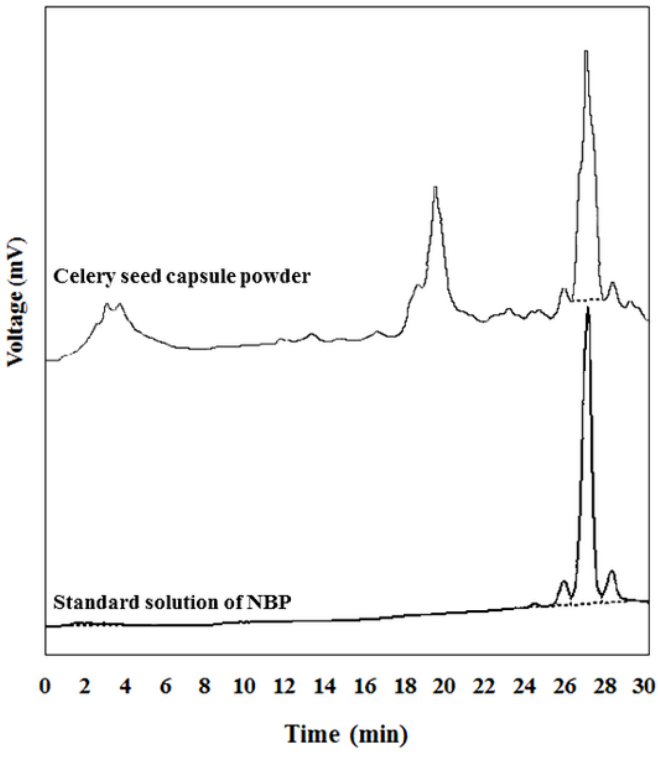

Figure 1

Chromatograms of a standard methanolic solution of NBP (10 mg/mL) (a), and celery seed capsule powder (1000 mg/mL)

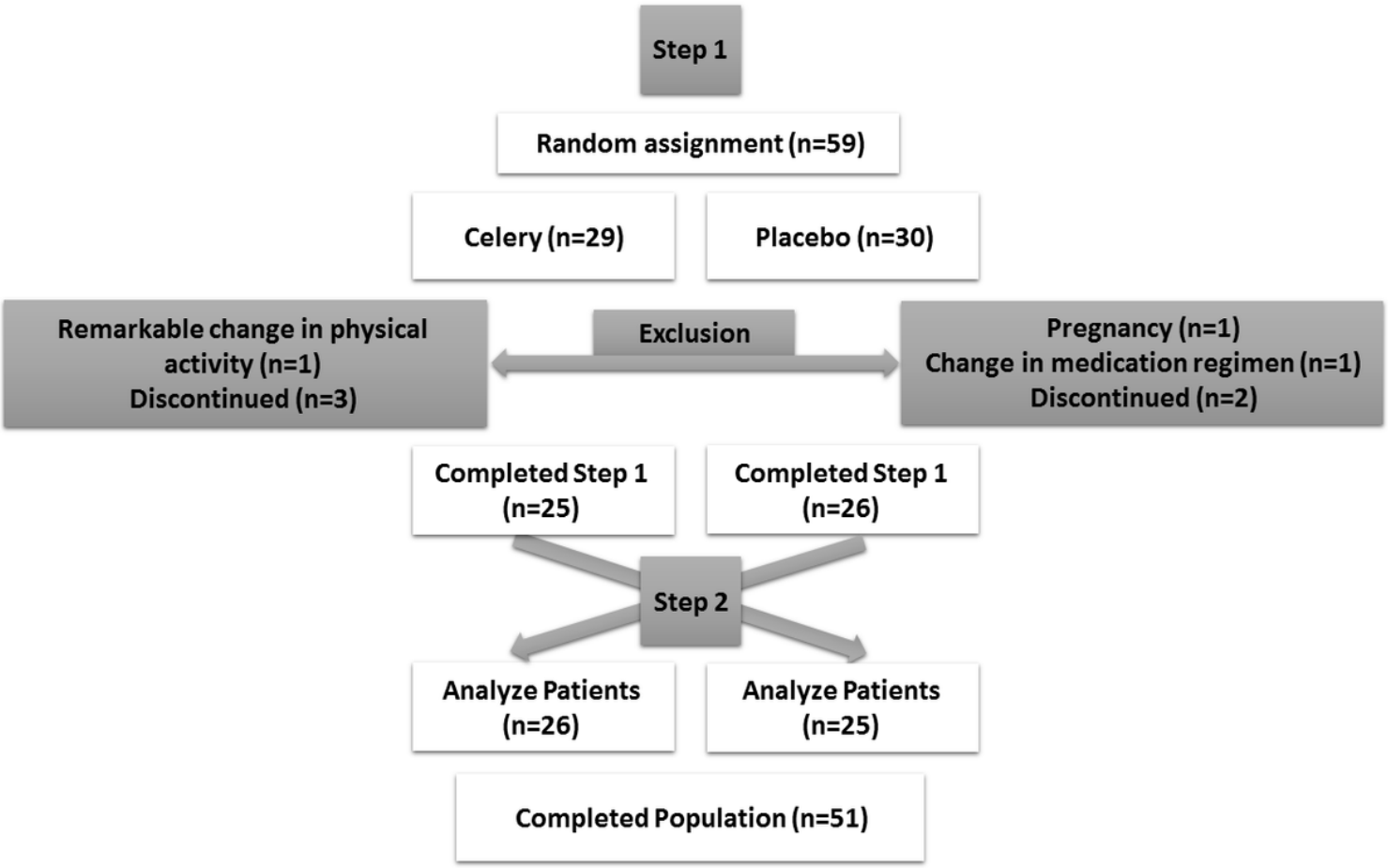

Figure 2

Flow chart of patients who participated in the cross-over clinical trial