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

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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 1.34 g 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 also 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.

Keywords Celery capsules · Cross-over clinical trial · Drug supplement · Herbal medicine · Safety evaluation · Hypertensive patients

Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| ABPM         | 24 H Ambulatory blood pressure monitoring |
| ALP          | Alkaline phosphatase |
| BMI          | Body mass index |
| BUN          | Blood urea nitrogen |
| CBC          | Complete blood count |
| DBP          | Diastolic blood pressure |
| FBS          | Fasting blood sugar |
| GCP          | Good clinical practice |
| Hb           | Hemoglobin |
| LDL          | Low-density lipoprotein |
| Lymph        | Lymphocyte number |
| HDL          | High-density lipoprotein |
| MAP          | Mean arterial blood pressure |
| MCHC         | Mean cell hemoglobin concentration |
| MCV          | Mean cell volume |
| NBP          | 3-N-butylphthalide |
| PCV          | Packed cell volume |
| PLT          | Platelet count |
| PP           | Pulse pressure |
| RBC          | Red blood cell count |
| RO           | Reactive oxygen species |
| SBP          | Systolic blood pressure |
| SCr          | Serum creatinine |

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SGOT or AST  Serum glutamic oxaloacetic transaminase
SGPT or ALT  Serum glutamic pyruvic transaminase
TC  Total cholesterol
TG  Triglyceride

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, herbas are safe and have lower unwanted side effects (Cicero et al. 2016; Hajian 2013; Nasri 2013a, b; 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 blood pressure (BP), serum lipid, and diabetes (Madhavi et al. 2013; Triyono and Novianto 2015). 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, hesperidin, linalool, and quercetin (Hedayati et al. 2019; Priezina and Karklina 2014; Tashakori-Sabzevar et al. 2016a, b). 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 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 (Pawona 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. 2010, 2012), neuroprotective effects (Peng et al. 2012), and anti-hyperglycemic (Tashakori-Sabzevar et al. 2016a, b). The most remarkable therapeutic property of celery reported in the studies is 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 the short-term, the 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 h in the darkness at room temperature. Thus, the total amount of applied celery seed in the extraction step was 15,000 g. 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 x 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 a treatment...
effect size of 5 mmHg decrease in systolic blood pressure (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 the 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. The patients received four capsules per day (two capsules every 12 h 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 the trial process was assessed through weekly phone calls and at each visit to the physician.

**Inclusion and 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, 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 biochemistry 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 four steps of the clinical trial (Table 3). BP parameters were taken from the left arm of participants using 24 h 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 h). The laboratory experiments were performed in both groups pre- and post-treatment: hematology 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).

**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 six-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 during 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 between 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 3-n-butylphthalide in the final form of the extract (aqueous-ethanolic 20/80, v/v) extract was 15.68 mg/g. Moreover, the 3-n-butylphthalide amount in each capsule was $5.23 \pm 0.06$ mg. Other ingredients in celery seed extract such as luteolin, d-limonene, phthalides, apigenin, hesperidin, linalool, and quercetin were not measured in the final extract. Thus, the extract and capsules were standardized based on NBP content (Hedayati et al. 2019; Priecina and Karklina 2014; Tashakori-Sabzevar et al. 2016a, b). Figure 1 represents chromatograms of standard methanolic solution of NBP (10 µg/mL) (a), 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, eight patients were excluded due to a change in medication regimen, and a remarkable change in physical activity and discontinuation (Fig. 2). Hence, 51 patients were crossed over and completed the clinical trial.

Data collection

Finally, 51 patients completed the study and 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 the celery and placebo groups were $50.21 \pm 6.66$ and $51.34 \pm 5.91$, respectively. Regarding gender and marital status, 49.09% and 89.09% of the subjects were female and married, respectively. It is also noteworthy that the average educational years for patients in group 1 and group 2 were $12.33 \pm 2.76$ and $12.13 \pm 2.12$, respectively. Lifestyle information showed no significant difference was observed between groups in physical activity (4.76 ± 3.11 versus 4.56 ± 3.23 h 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, the 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 antihypertensive medication regimen of the groups at the start point was not significantly different ($p > 0.05$). Table 3 shows 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 \((p < 0.001)\).

### Effect of celery on blood cells in hypertensive patients

The difference in white blood cell count (WBC), red blood cell count (RBC), Platelet Count (PLT), 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).

### 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 \((p > 0.05)\) (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.

### 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 TC, TG, LDL, and promotion in 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 3  Values for daily nutrition intake in all 51 hypertensive patients during treatment with celery and placebo and their cross-over condition

|                     | 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  |
| **Weight (g)**      |                  |                |         |
| Celery              | 3598.51 ± 215.01 | 3626.04 ± 238.34 | 0.5826  |
| Placebo             | 3612.48 ± 222.77 | 3607.29 ± 231.92 | 0.5913  |
| **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  |
| **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  |
| **Carbohydrate (g)** |              |                |         |
| Celery              | 219.53 ± 13.76  | 221.18 ± 15.18 | 0.6036  |
| Placebo             | 222.82 ± 14.22  | 220.50 ± 13.01 | 0.5936  |
| **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  |
| **Protein (g)**     |                  |                |         |
| Celery              | 68.78 ± 4.87    | 69.01 ± 5.01   | 0.8942  |
| Placebo             | 69.74 ± 4.91    | 70.88 ± 5.08   | 0.8503  |
| **Starch (g)**      |                  |                |         |
| Celery              | 110.92 ± 7.18   | 112.17 ± 7.72  | 0.6620  |
| Placebo             | 112.11 ± 7.55   | 111.59 ± 7.38  | 0.6937  |
| **Total sugars (g)** |              |                |         |
| Celery              | 108.50 ± 7.94   | 109.14 ± 8.02  | 0.7585  |
| Placebo             | 109.70 ± 8.07   | 110.22 ± 7.88  | 0.7573  |
| **Fat (g)**         |                  |                |         |
| Celery              | 84.75 ± 5.14    | 85.30 ± 5.67   | 0.8145  |
| Placebo             | 85.99 ± 5.33    | 86.25 ± 5.52   | 0.7942  |
| **Cholesterol (mg)** |              |                |         |
| Celery              | 260.09 ± 16.69  | 261.59 ± 17.12 | 0.6740  |
| Placebo             | 262.12 ± 16.78  | 263.65 ± 16.84 | 0.7027  |
| **Calcium (mg)**    |                  |                |         |
| Celery              | 749.41 ± 45.27  | 752.72 ± 49.67 | 0.5647  |
| Placebo             | 750.99 ± 47.55  | 751.89 ± 48.07 | 0.5982  |

Table 3 (continued)

|                     | Before mean ± SD | After mean ± SD | p value |
|---------------------|------------------|----------------|---------|
| **Copper (µg)**     |                  |                |         |
| Celery              | 1512.49 ± 99.55  | 1528.70 ± 101.13 | 0.2665  |
| Placebo             | 1531.93 ± 103.61 | 1521.56 ± 98.69 | 0.4927  |
| **Iodine (µg)**     |                  |                |         |
| Celery              | 102.68 ± 5.89    | 103.48 ± 6.36  | 0.6301  |
| Placebo             | 104.27 ± 6.12    | 103.29 ± 6.29  | 0.6839  |
| **Iron (mg)**       |                  |                |         |
| Celery              | 8.55 ± 0.49      | 8.51 ± 0.56    | 0.7160  |
| Placebo             | 8.61 ± 0.53      | 8.60 ± 0.51    | 0.9375  |
| **Magnesium (mg)**  |                  |                |         |
| Celery              | 350.77 ± 20.98   | 347.69 ± 23.5  | 0.7275  |
| Placebo             | 356.20 ± 22.22   | 352.87 ± 21.87 | 0.6737  |
| **Manganese (mg)**  |                  |                |         |
| Celery              | 2.45 ± 0.14      | 2.49 ± 0.16    | 0.3185  |
| Placebo             | 2.48 ± 0.15      | 2.46 ± 0.14    | 0.3788  |
| **Phosphorus (mg)** |                  |                |         |
| Celery              | 1151.53 ± 69.48  | 1146.12 ± 77.11 | 0.8976  |
| Placebo             | 1159.37 ± 74.77  | 1152.43 ± 71.83 | 0.9584  |
| **Selenium (µg)**   |                  |                |         |
| Celery              | 39.46 ± 2.27     | 40.19 ± 2.64   | 0.7132  |
| Placebo             | 40.07 ± 2.55     | 39.69 ± 2.38   | 0.7736  |
| **Zinc (mg)**       |                  |                |         |
| Celery              | 7.55 ± 0.48      | 7.58 ± 0.51    | 0.6983  |
| Placebo             | 7.63 ± 0.42      | 7.59 ± 0.40    | 0.7349  |
| **Potassium (g)**   |                  |                |         |
| Celery              | 3.19 ± 0.18      | 3.22 ± 0.21    | 0.8204  |
| Placebo             | 3.23 ± 0.20      | 3.20 ± 0.16    | 0.8026  |
| **Sodium (g)**      |                  |                |         |
| Celery              | 1.37 ± 0.07      | 1.39 ± 0.09    | 0.8033  |
| Placebo             | 1.39 ± 0.08      | 1.37 ± 0.08    | 0.8737  |
| **Chloride (mg)**   |                  |                |         |
| Celery              | 2.38 ± 0.13      | 2.36 ± 0.16    | 0.7305  |
| Placebo             | 2.40 ± 0.15      | 2.39 ± 0.14    | 0.7573  |
| **Retinol (µg)**    |                  |                |         |
| Celery              | 253.52 ± 14.58   | 257.89 ± 16.15 | 0.8619  |
| Placebo             | 254.44 ± 15.33   | 255.04 ± 14.91 | 0.7942  |
| **Carotene (µg)**   |                  |                |         |
| Celery              | 1432.42 ± 88.82  | 1428.35 ± 94.61 | 0.7451  |
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.

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. Safety and efficacy are two important factors in dose translation from animal models to human clinical trials. In our previous work, daily doses of 100 to 300 mg/kg of celery seed extract were evaluated in the animal model (Moghadam et al. 2013). According to the dose translation formula from animal to human, 1.147 g/day to 3.442 g/day could be used in the clinical trial. In the present study, celery seed extract was administered as a supplement to other antihypertensive medications. Thus, to reduce possible side effects and drug–supplement interactions, a daily dose of 1.34 g/day which is near to minimum effective calculated dose was selected for the clinical trial. Based on previously published works, the selected dose was safe for human studies. Other limitations in dose selection were the size of prepared capsules and the frequency of daily administered dose of the supplement. 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 (Iles 2021; Niaz 2013; Tashkori-Sabzevar et al. 2016a, b; 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

| Table 3 (continued) | Before mean ± SD | After mean ± SD | \( p \) value |
|---------------------|-----------------|----------------|-------------|
| 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      |
| \( p \) 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      |
| 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         |             |

Data are mean ± SD

\(^a\) Independent \( t \)-test were applied
A 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 (1.34 g extract per day for 4 weeks) decreased BP parameters; SBP, DBP, MAP, and PP ($p < 0.001$). 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). The data showed that administration of 300 mg/kg of extract of the celery seed caused a 23-mmHg reduction in BP. They concluded that celery seed extract had antihypertensive properties, which appear to be attributable to the actions of its active hydrophobic constituents such as NBP, and other active ingredients and can be considered an antihypertensive agent in the chronic treatment of elevated BP. The therapeutic effects and vasodilatation mechanisms of celery seed extract were reported in the animal work (Moghadam et al. 2013). Calcium channel blocking properties with a negative chronotropic effect on normotensive and hypertensive rats were also evaluated (Tashakori-Sabzevar et al. 2016a, b). Our previous in vivo and ex vivo studies and review of the literature revealed that celery seed extract regulates BP through different mechanisms, such as calcium channel blocking, beta-receptor blocking, and diuretic activity (Tashakori-Sabzevar et al. 2016a, b). The combination of several mechanisms is expected to have a synergistic effect on lowering BP due to the chemical content of several active ingredients of celery seed extract. 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, PLT, and their indices in comparison with placebo treatment ($p > 0.05$). All blood cell 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, packed cell volume (PCV), and hemoglobin (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 was also observed in mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), and lymphocyte number (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.

### Table 4 Values for blood pressure parameters during treatment with celery and placebo and their cross-over condition

| SBPb (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 |
| DBPc (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 |
| MAPd (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 |
| PP (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 |

Data are mean ± SD$^a$

$^a$SBP Systolic Blood Pressure

$^b$DBP Diastolic Blood Pressure

$^c$MAP Mean Arterial Pressure

$^d$PP Pulse Pressure
Table 5  Values for hematological indices in hypertensive patients during treatment with celery and placebo and their cross-over condition

|                      | Start: week 0 | End: week 4  | p value | Start: week 8 | End: week 12 | p value |
|----------------------|---------------|--------------|---------|---------------|--------------|---------|
| **WBCb (×1000/μl)** |               |              |         | 4 weeks       |              |         |
| 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**            |               |              |         | 4 weeks       |              |         |
|                       | 0.7951        | 0.7514       |         | 0.7019        | 0.9846       |         |
| **RBCc (×1,000,000/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       |         |
| **Hbd (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**            |               |              |         |               |              |         |
|                       | 0.5813        | 0.8491       |         | 0.7237        | 0.9037       |         |
| **Hcte (%)**           |               |              |         |               |              |         |
| 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       |         |
| **MCVf (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       |         |
| **MCHg (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       |         |
| **MCHCh (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       |         |
| **PLTi (×1000/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-CVf (%)**        |               |              |         |               |              |         |
| 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  |
Safety evaluation and biochemical efficacy of celery seed extract (Apium Graveolens) capsules…

…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 ($p < 0.05$). 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 an 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 reactive oxygen species (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-week celery treatment ($p < 0.05$) while ALP had no change after celery administration ($p > 0.05$). 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 a 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).

### Table 6

|                | Start: week 0 | End: week 4 | $p$ value | Start: week 8 | End: week 12 | $p$ value |
|----------------|--------------|-------------|-----------|--------------|-------------|-----------|
| **BUN** (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 |
| $p$ value | 0.5551 | 0.0340 | | 0.3596 | 0.0472 | |
| 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 |
| **SCr** (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 |
| $p$ value | 0.7073 | 0.0266 | | 0.6214 | 0.0229 | |
| 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 |
| **Na** (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 |
| $p$ value | 0.6811 | 0.7427 | | 0.7863 | 0.8486 | |
| 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 |
| **K** (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 |
| $p$ value | 0.8357 | 0.7636 | | 0.8917 | 0.8173 | |
| 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 |
| **Ca** (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 |
| $p$ value | 0.1254 | 0.0827 | | 0.1831 | 0.0819 | |
| 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** (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 |
| $p$ value | 0.5724 | 0.5923 | | 0.7523 | 0.6956 | |
| 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 |

Data are mean ± SD$^a$

$^a$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 Phosphorous
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 reduced 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 et al. 2016a, b). 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 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 \( (p < 0.001) \). Reduction in TC, TG, LDL, and in the ratio of LDL: HDL and TC: HDL and promotion in HDL were significant during celery therapy. In the 8 week 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 et al. 2014a, b). In a 12-week study, celery seed extract reduced the liver lipids and serum lipid profile (Ahmed and Sayemma 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 (1.34 g 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.

### Table 7

|                | Start: week 0 | End: week 4 | \( p \) value | Start: week 8 | End: week 12 | \( p \) value |
|----------------|---------------|-------------|---------------|---------------|--------------|---------------|
| SGPT\(^a\) (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        |
| p value | 0.4173        | 0.0434      |               |               |              |               |
| 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 | 0.6366        | 0.0424      |               |               |              |               |
| SGOT\(^b\) (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        |
| p value | 0.3372        | 0.0456      |               |               |              |               |
| 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 | 0.3445        | 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        |
| p value | 0.7972        | 0.0945      |               |               |              |               |
| 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 | 0.8881        | 0.0927      |               |               |              |               |

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\(^a\)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
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.

Table 8 Values for fasting blood sugar and serum lipid profile during treatment with celery and placebo and their cross-over condition

|                  | 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 | 115.55 ± 3.64 | 0.6820 |
| 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 |

Data are mean ± SD\(^a\)

\(^a\)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
Table 9 The side effects checklist during celery and placebo consumption

| Positive side effect | Group 1: celery (n=51) | Group 2: placebo (n=51) | p value |
|----------------------|------------------------|------------------------|---------|
| 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 (χ^2) between two groups was applied

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Author contributions MSR: conceptualization; data curation; data analysis; investigation; methodology; software; validation; visualization; writing—original draft; writing—review and editing. MM: conceptualization; data curation; project administration; validation; visualization. SME: statistical analysis. VSM: HPLC analysis. SAM: conceptualization; data curation; funding acquisition; methodology; project administration; supervision; resources; validation; writing—review and editing.

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

Code availability Not applicable.

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 publication Consent for publication gives my consent for the publication of identifiable details, which can include details within the text to be published in Inflammopharmacology.

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