Received: 15 October 2021 | Revised: 22 March 2022 | Accepted: 1 April 2022

DOI: 10.1002/ptr.7469

RESEARCH ARTICLE

WILEY

Effect of celery (*Apium graveolens*) seed extract on hypertension: A randomized, triple-blind, placebo-controlled, cross-over, clinical trial

Maryam Shayani Rad[1,2] | Mohsen Moohebati[3] | Seyed Ahmad Mohajeri[1,4]

[1]Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[2]Student Research Committee (SRC), Mashhad University of Medical Sciences, Mashhad, Iran

[3]Cardiovascular Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[4]Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence
Seyed Ahmad Mohajeri, Mashhad University of Medical Sciences, Mashhad, Iran.
Email: mohajeria@mums.ac.ir, seyedahmad_mohajeri@yahoo.com

Funding information
Research of Mashhad University of Medical Sciences, Grant/Award Number: 941237

Abstract

In the present work, the antihypertensive effects of celery seed extract (*Apium graveolens*) with active ingredients, such as 3-n-butylphthalide, were studied as a drug supplement in the treatment of hypertension. This study was a randomized, triple-blind, placebo-controlled, cross-over clinical trial. Fifty-two patients were divided into two groups (celery and placebo) and completed the two-step clinical trial. Four celery seed extract capsules (totally 1.34 g per day) or 4 placebo capsules per day were administered to the patients during a 4-week clinical trial. The blood pressure was assessed using a 24-hr ambulatory blood pressure monitoring method. In celery group, systolic blood pressure changed from 141.2 ± 5.91 to 130.0 ± 4.38 mmHg ($p < .001$) while diastolic blood pressure changed from 92.2 ± 5.74 to 84.2 ± 4.87 mmHg ($p < .001$). Moreover, the mean arterial blood pressure changed from 108.5 ± 5.76 to 99.5 ± 4.66 mmHg ($p < .001$), and pulse pressure decreased from 49.0 ± 6.21 to 45.8 ± 6.01 mmHg ($p < .01$). However, no significant changes were observed in placebo group in terms of the above-mentioned parameters ($p > .05$). Furthermore, no significant side effect was reported in the celery group, compared to the placebo group ($p > .05$). The results were promising and indicated the therapeutic effects of celery seed extract as a supplement in the management of hypertension.

KEYWORDS
ABPM, celery, cross-over clinical trial, drug supplement, herbal medicine, hypertension

1 | INTRODUCTION

Hypertension (HTN) as a "silent killer" is one of the major risk factors for cardiovascular morbidity and mortality and is associated with 54% of episodes of stroke worldwide (Bauer, Briss, Goodman, & Bowman, 2014; Elkind, 2011; Gaciong, Siński, & Lewandowski, 2013; Sliwa, Stewart, & Gersh, 2011). Epidemiological studies have indicated that the prevalence of HTN ranges from 25 to 55% and is destined to increase in the future (Wolf-Maier et al., 2003). Lifestyle modification, particularly dietary habits, such as Mediterranean and Dietary Approaches to Stop Hypertension diets, are effective approaches to prevent HTN or reduce blood pressure (BP) in patients with increased cardiovascular disease risk (Doménech et al., 2014; Saneei, Salehi-Abargouei, Esmaillzadeh, & Azadbakht, 2014). There are a variety of HTN medications, such as alpha and beta-blockers, diuretics, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers (CCBs), vasodilators, and centrally active medications prescribed to lower BP (Khalil & Zeltser, 2020). Most of

Abbreviations: ABPM, 24-hr ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; CCBs, calcium channel blockers; DBP, diastolic blood pressure; FBS, fasting blood sugar; HPLC, high-performance liquid chromatography; HTN, hypertension; MAP, mean arterial blood pressure; MUAC, mid-upper arm circumference; NBP, 3-n-butylphthalide; NC, neck circumference; PP, pulse pressure; SBP, systolic blood pressure; WHR, waist to hip ratio.

the abovementioned medicines have side effects. It should be noted that BP control is still poor, especially in the elderly. Many patients may require two or more medications to control BP. The combination therapy, emphasized by guidelines, is more effective in patients whose BP is not adequately controlled by monotherapy. Moreover, the probability of side effects is greater by increasing the dose of the drug in monotherapy (European Society of Hypertension-European Society of Cardiology Guidelines Committee, 2003; Puig et al., 2007). Therefore, alternative therapies have been considered and several clinical trials have indicated the effectiveness of supplements, such as herbal medicines, on BP (Diao et al., 2013). Hence, recently, many people prefer to use herbal medicine as they believe plant remedies are free from undesirable side effects (George, 2011; Hajian, 2013; Haq, 2004; Kazemipoor, Wan Mohamed Radzi, Cordell, & Yaze, 2012; Rafieian-Kopaei, 2013; Sirtori, Arnoldi, & Cicero, 2015). A large number of herbal medicines have been tested for anti-hypertensive effects (Asgary et al., 2000; Ernst, 2005; Herrera-Arellano, Flores-Romero, Chavez-Soto, & Tortoriello, 2004; Liu et al., 2004). The pharmacological mechanism of these antihypertensive herbs should be evaluated and the effectiveness of herbal medicines must be studied in clinical trials. Some herbal preparations have shown encouraging results (Herrera-Arellano et al., 2004; Kim & Zhou, 2004). For example, the *Luohuo* capsule has quite a promising effect in treating essential HTN of Phlegm-stasis blocking Collateral type, the mechanism might be related to the improvement of hemorheological parameters, increasing blood nitric oxide level and decreasing plasma endothelin and Angiotensin II levels (Kim & Zhou, 2004). Another controlled-randomized clinical trial showed *Hibiscus sabdariffa* extract, standardized on 9.6 mg of total anthocyanins, had antihypertensive effectiveness and tolerability to decrease the systolic BP (SBP) and diastolic BP (DBP) as much as captopril 50 mg/day (Herrera-Arellano et al., 2004). *Apium graveolens*, commonly known as "celery," is from the family of Apiaceae. Different parts of celery have therapeutic effects and can play a role in the control of diabetes, serum lipid, and BP and also the prevention of cardiovascular disease (Madhavi, Kagan, & Rao, 2013; Oktavia & Junaid, 2017; Triyono, Ridha, & Ardianto, 2018). In a cross-over study, the efficacy of celery seed extract with a calcium channel blocking mechanism was compared with lercanidipine (Puig et al., 2007). The therapeutic effects and vasodilation mechanisms of celery seed extract were also studied in our previous animal work. Celery seed extract as an antihypertensive agent did not cause reflex tachycardia (Moghadam, Imenshahidi, & Mohajeri, 2013). Calcium channel blocking properties with a negative chronotropic effect on normotensive and hypertensive rats were also evaluated (Tashakori-Sabzevar, Razavi, et al., 2016). As an active ingredient, 3-n-butylphthalide (NBP), relaxes the artery walls to reduce BP and increase blood flow, probably through its vasodilatory, diuretic, and CCB effects (Madhavi et al., 2013). Moreover, NBP helps control stress hormones which contribute to high BP and reduce bad cholesterol (Diao et al., 2013). Apigenin, as another active ingredient, caused overexpression of ACE2 and inhibits calcium influx through ligand- and voltage-gated calcium channels (Sui et al., 2010; Tashakori-Sabzevar, Razavi, et al., 2016). Other studies have indicated that apigenin functions as a beta-blocker and has a vasodilatory effect on rat aorta by inhibition of calcium release (Chan, Pannangpetch, & Woodman, 2000). Therefore, apigenin has been proved to have a similar effect with CCBs. Luteolin, Linalool, and d-limonene as other active ingredients of celery seed extract were also showed antihypertensive properties (Anjos et al., 2013; Santiago, Jayachitra, Shenbagam, & Nalini, 2010; Su et al., 2015). One of the best methods for the evaluation of the effectiveness of new antihypertensive medications is 24-hr ambulatory BP monitoring (ABPM) which permits the evaluation of different BP variables during the day and night (Fogari et al., 2002). The present study was conducted to report the antihypertensive properties of celery seed extract on hypertensive patients in a randomized, triple-blind, placebo-controlled, cross-over clinical trial using ABPM.

2 | MATERIALS AND METHODS

2.1 | Clinical trial design

The current study is a triple-blind, prospective, placebo-controlled, cross-over, 4-week clinical trial with a 4-week washout period. At the beginning of the clinical trial, the details of the study were explained to the patient. The researchers obtained informed consent before enrolling participants in the clinical trial. 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 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 (ethical code: IR.MUMS.REC.1394.705). This clinical trial was registered at the Iranian Registry of Clinical Trials (IRCT20130418013058N8; www.irct.ir, Registration date: April 22, 2018). The study was carried out between September 21, 2018 and July 20, 2020. The inclusion criteria were age range of 28–68 years old, ability to understand the process of the study, completion of the consent form, SBP more than 120–160 mmHg, or DBP more than 80–100 mmHg. The BP was measured by 24-hr ABPM at the first visit in the clinician's office which could be the first step at the beginning of the study for each patient. The BP was measured every 15 min by ABPM. 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 such as severe hypotension or allergic reaction due to consumption of celery or other antihypertensive medications, alcohol consumption, CCBs consumption, for example, amlodipine, nifedipine, diltiazem, and verapamil. According to the previous in vivo and ex vivo studies in the literature, different ingredients in celery seed extract have calcium channel blocking effects, probably as the main therapeutic mechanism of celery extract (Tashakori-Sabzevar, Razavi, et al., 2016). Thus, using CCB was added to the exclusion criteria to reduce drug-supplement interactions.

2.2 | Data collection

The demographic information, including age, gender, marital status, family disease history, level of education, lifestyle, body mass index (BMI), waist to hip ratio (WHR), neck circumference (NC), and mid-upper arm circumference (MUAC) were measured. For measuring waist circumference in the standing position, a tape measure was placed around the middle of the patient above the hipbones (on the belly button). Afterward, for measuring the hip, the tape was wrapped around the widest part of the hips and buttocks of the patients while they were standing up. It should be mentioned that these tests were performed in the office of a clinician. The BP parameters and the list of medications used by patients at the beginning of the clinical trial were also reported. Blood plasma parameters and daily dietary intake of the participants at the beginning of the clinical trial were also obtained. Blood samples were taken from the forearm veins of patients in the fasting state. Biochemical tests were performed in the laboratory of Ghaem Hospital, Mashhad University of Medical Sciences.

2.3 | Extraction, capsule preparation, and analysis

The extraction was performed using 80% ethanol (Merck, Germany). The NBP, purchased from Langchem, Inc. (Shanghai, China), was just used for the standardization of the celery seed extract. The celery seed extract was isolated from celery seeds, obtained from Imam Pharmacy, Mashhad, Iran, and the identity was confirmed by the herbarium of the School of Pharmacy (voucher number: 293-0107-18). Briefly, celery seeds were ground and powdered and the dry powder (800 g) was suspended in 2,400 ml ethanol-water (80/20, vol/vol) at room temperature and shaken for 1 hr in the darkness. 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 by 1.5–2.0%. Finally, the dried granules were powdered and filled into the capsules. Placebo capsules were prepared with Avicel® as an inert ingredient. Each patient received four celery seeds extract (a total of 1.34 g extract) or placebo capsules per day. This dose was selected according to our previous in vivo studies on the therapeutic effects of celery seed extracts on HTN (Moghadam et al., 2013; Tashakori-Sabzevar, Razavi, et al., 2016). Chromatographic determination of NBP was carried out using 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. The data analysis was performed in Autochro3000 software. The injection volume and flow rates were 20 μl and 1 ml/min, respectively, while the column temperature was fixed at 30°C. Furthermore, the UV detector was set to 230 nm. A gradient method was applied in which the mobile-phase composition was changed from 20% high-performance liquid chromatography (HPLC)-grade methanol in water to 80% in 20 min. The mobile phase composition was changed during 20 min and then was unchanged from minute 20 to the end of run time. A concentration of 1,000 μg/ml from the capsule content was prepared in HPLC-grade methanol and injected into the HPLC. The concentration of NBP was calculated based on the comparison of the area under the curve and the NBP standard solution.

2.4 | Sample size

Based on previously published works and clinical reports of antihypertensive agents, the minimum valuable effect size was defined as the mean difference of 5 mmHg in SBP with a standard deviation of 5 mmHg in each group, a power of 90%, and a significance level of .05. It should be mentioned that the calculated sample size was 19 patients in each group (Fogari et al., 2002; Puig et al., 2007). In the present study, 52 participants were randomly allocated into two groups (26 in each group). Sigma Plot (version 12.0) (SYSTAT Software, San Jose, CA) was used to calculate the sample size.

2.5 | Intervention

In the first step, 52 patients were randomized into celery and placebo groups. The patients received four capsules per day (two capsules every 12 hr 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 seed extract in the first step received placebo capsules after the cross-over, and those who had received placebo in the first step received celery seed extract capsules in the second step. The participants were not allowed to change their medication regimens or lifestyles during the study. Patient compliance to the medication and trial process was assessed through weekly phone calls and at each visit to the physician. The BP parameters were recorded by ABPM at the beginning and end of the first and second steps of the study at 6:00 p.m. Different ABPM parameters, including SBP, DBP, mean arterial BP (MAP), pulse pressure (PP), and heart rate (HR) were obtained in day-time, night-time, and during 24-hr. Finally, at the end of the study, four series of data were obtained from patients who started with celery capsules: Series 1: at the beginning of step 1 with celery capsule consumption, Series 2: at the end of step 1 with celery capsule consumption, Series 3: After a 4-week washout period and crossed-over, at the beginning of step 2 with placebo capsule consumption, Series 4: at the end of step 2 with placebo capsule consumption. For patients who started with placebo: Series 1: at the beginning of step 1 with placebo capsule consumption, Series 2: at the end of step 1 with placebo capsule

consumption, Series 3: After a 4-week washout period and crossed-over, at the beginning of step 2 with celery capsule consumption, Series 4: at the end of step 2 with celery capsule consumption. The 24-hr ABPM was performed using a portable, noninvasive, fully automated device (CARDIOLINE Walk200b, Trento, Italy) validated against intra-arterial BP measurements. The ABPM recorder was set to take readings at 15-min intervals throughout the 24 hr which started at 6:00 p.m. in the office of the physician. The BP recording was performed four times for each patient, at the beginning and at the end of the first and second steps of the crossover trial.

2.6 | Blinding and randomization

Celery seed extract and placebo capsules were prepared in the same way. 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 group assignments. 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 to their arrival time.

2.7 | Safety

The patients were requested to inform the researcher about any adverse effects or complaints during the trial as soon as their occurrence. Any symptoms or possible side effects were checked and recorded via weekly telephone calls and in each visit to the physician. The physician was responsible for continuing or discontinuing the medications. The adverse effects checklist was completed by independent raters.

2.8 | Statistical analysis

The baseline, demographic, and clinical characteristics of the two groups were compared using the independent *t*-test and Fisher's exact test (χ^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 .05 was considered statistically significant. The analyses were performed using R software (version 4.0.5, R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Amounts of NBP in celery seed extract capsules

The molecular formula and molecular weight of NBP are $C_{12}H_{14}O_2$ and 190.24. NBP is a member of benzofurans. It is a colorless, oily liquid; a warm-spicy herbaceous aroma, and soluble in ethanol. Therapeutic properties of NBP are reported in some studies. NBP helps control stress hormones (Diao et al., 2013; Peng et al., 2012). The hypotensive effect of celery and NBP were studied in some researches (Moghadam et al., 2013; Zhu, Zhang, & Yang, 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, Zufry, Meutia, & Sucipto, 2018). The HPLC analysis showed that the amount of NBP in aqueous-ethanolic (20/80, vol/vol) extract was 15.68 mg/g. Each capsule contained 500 ± 10 mg powder, including dried extract (67%) and excipients (33%). The standard NBP was applied for the standardization of the extract and final capsule powder. According to the collected data, the NBP amount in each capsule was 5.23 ± 0.06 mg. Figure 1 represents chromatograms of standard methanolic

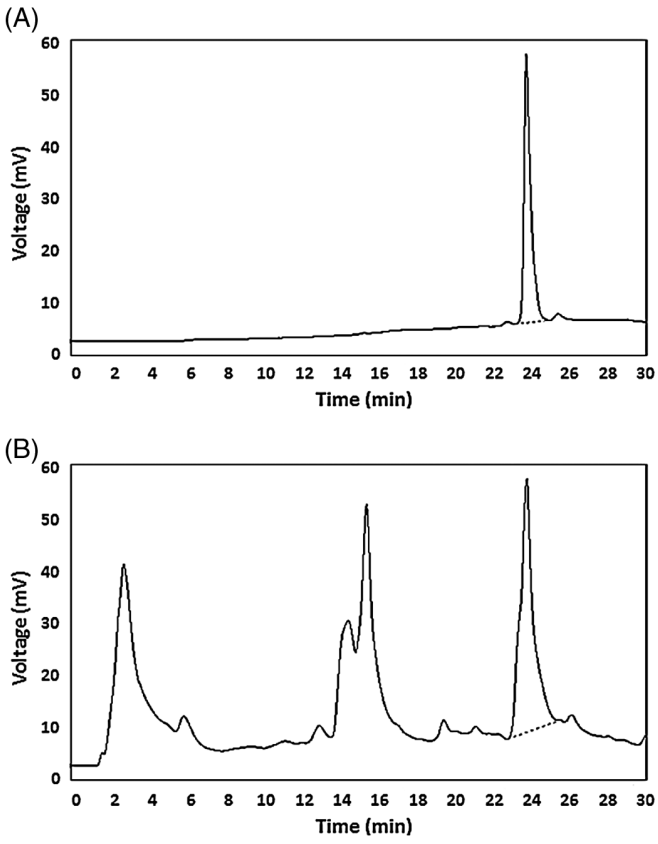

FIGURE 1 Chromatograms of a standard methanolic solution of 3-n-butylphthalide (10 μg/ml) (A), and celery seed extract capsule powder (1,000 μg/ml) (B)

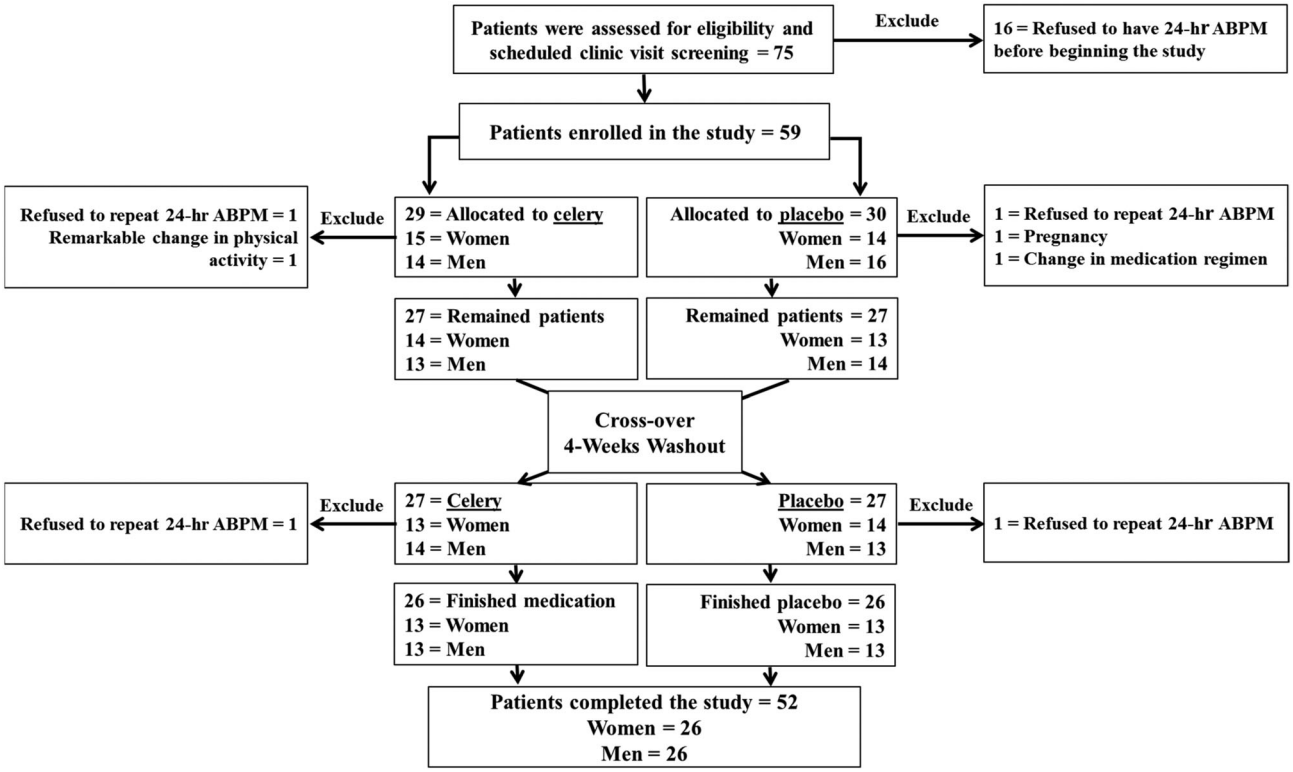

FIGURE 2 Flow chart of patients who participated in the cross-over clinical trial. ABPM, ambulatory blood pressure monitoring

solution of NBP (10 μg/ml) and celery seed extract capsule powder (1,000 μg/ml).

3.2 | Clinical trial design

According to clinical documents, from 3,057 patients; 75 of them met the inclusion criteria and were scheduled for clinic visit screening. Sixteen of the participants refused to have 24-hr ABPM, and finally, 59 patients were 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, 5 patients were excluded due to refusal to repeat 24-hr ABPM, pregnancy, change in medication regimen, and remarkable physical activity (Figure 2). In the second step of the cross-over, two patients were excluded from the study due to refusal to repeat the 24-hr ABPM (Figure 2); hence, 52 patients completed the clinical trial.

3.3 | Data collection

In total, 52 patients completed the study and were included in the final analysis. No statistically significant difference was observed between the two groups in terms of demographic information ($p > .05$). According to the demographic information summarized in Table 1, the mean ages of the participants in the celery and placebo groups were 51.88 ± 7.89 and 49.15 ± 6.88, respectively. Moreover, the minimum and maximum ages were 29 and 63 years old, respectively. Regarding gender and marital status, 50 and 90% of the subjects were female and married, respectively. 69% of the participants in the celery group (18 patients) and 81% of the participants in the placebo group (21 patients) had a history of cardiovascular disease or HTN in their families. It is also noteworthy that only 6% of the patients were illiterate. Lifestyle data showed that 73% of patients had physical activity for about 4.58 hr per day. The mean sleep duration per 24-hr was 7.33 hr; however, most of the patients complained about the low quality of their sleep during the night. It should be mentioned that 65% of the women in this study were in reproductive years and 35% of them were in menopause. According to the obesity classification provided by World Health Organization, it can be said that the BMI of only 25% of the participants was within the normal range. Furthermore, the BMI of 35, 33, and 6% of them were within the overweight, obesity of class I, and obesity of class II categories, respectively. According to Table 1, no significant difference was observed between the two groups in terms of the above-mentioned parameters ($p > .05$). Table 2 shows that the mean SBP, DBP, and HR of the groups at the start point were not significantly different ($p > .05$). Moreover, no significant difference was observed between the two groups of treatment in terms of medications used by patients at the beginning of the clinical trial ($p > .05$). Table 3 shows that at the start of the study, the two groups were the same in terms of serum biochemical parameters, particularly fasting blood sugar (FBS) and lipid profile ($p > .05$). Dietary habits (energy and macronutrient intake that is, carbohydrate, protein, and fat) were also the same at the beginning of the clinical trial.

TABLE 1 Baseline characteristics of patients[a]

	Group 1: Celery ($n = 26$)	Group 2: Placebo ($n = 26$)	*p*-Value
Age			
Mean (years)	51.88 ± 7.89	49.15 ± 6.88	.1897
	Min: 36	Min: 29	
	Max: 63	Max: 61	
Sex			
Female (*n*)	13	13	1.0000
Male (*n*)	13	13	
Marital status			
Married (*n*)	23	24	.6381
Single (*n*)	3	2	
Female period status			
Menopause (*n*)	8	9	.6802
In reproductive years (*n*)	5	4	.7139
Family disease history			
History of cardiovascular disease in family (*n*)	19	18	.7595
History of hypertension in family (*n*)	21	19	.5104
Level of education			
Illiterate (*n*)	2	1	.6825
Primary school (*n*)	5	6	
High school diploma (*n*)	10	8	
Bachelor of science (*n*)	7	5	
Master of science (*n*)	1	2	
PhD (*n*)	1	4	
Lifestyle			
Have physical activity (*n*)	20	18	.5318
Physical activity (hr/24-hr)	4.5 ± 3.02	4.65 ± 3.65	.8724
Sleep (hr/24-hr)	7.13 ± 1.05	7.52 ± 1.97	.3786
Use salt with food (*n*)	12	11	.7801
BMI			
Female (kg/m^2)	28.55 ± 4.08	28.94 ± 4.12	.7331
Male (kg/m^2)	29.16 ± 3.01	29.65 ± 3.74	.6052
Underweight (*n*)	1	1	.9547
Normal weight (*n*)	6	7	
Overweight (*n*)	8	10	
Obesity class I (*n*)	9	8	
Obesity class II (*n*)	2	1	
WHR			
Female	0.89 ± 0.04	0.91 ± 0.06	.1644
Male	0.95 ± 0.05	0.97 ± 0.07	.2420
NC (cm)	38.73 ± 2.67	39.68 ± 2.96	.2301
MUAC (cm)	32.88 ± 3.32	33.15 ± 2.85	.7544

Note: Data are mean ± SD.

Abbreviations: BMI, body mass index; MUAC, mid-upper arm circumference; NC, neck circumference; WHR, waist-to-hip ratio.

[a]Fisher's exact test (χ^2) was applied for categorical variables and independent *t*-test was applied for and continuous variables.

TABLE 2 Blood pressure parameters and antihypertensive, antidiabetic, and antihyperlipidemic medications used by patients at the beginning of the clinical trial[a]

	Group 1: Celery ($n = 26$)	Group 2: Placebo ($n = 26$)	p-Value
SBP (mmHg)	141.3 ± 5.97	140.04 ± 6.27	.4615
DBP (mmHg)	92.29 ± 5.87	91.82 ± 6.07	.7777
HR (bpm)	73.66 ± 8.14	72.75 ± 9.32	.7093
High blood pressure medication			
Losartan (*n*: %)	10:38.5%	9:34.6%	.7734
Valsartan (*n*: %)	2:7.7%	3:11.5%	.6381
Captopril (*n*: %)	4:15.4%	5:19.2%	.7139
Hydrochlorothiazide (*n*: %)	3:11.5%	2:7.7%	.6381
Bisoprolol (*n*: %)	2:7.7%	3:11.5%	.6381
Metoprolol (*n*: %)	3:11.5%	2:7.7%	.6381
No medication (*n*: %)	2:7.7%	2:7.7%	1.0000
High blood lipid medication			
Atorvastatin (*n*: %)	5:19.2%	4:15.4%	.7139
Lovastatin (*n*: %)	4:15.4%	3:11.5%	.6874
Gemfibrozil (*n*: %)	2:7.7%	3:11.5%	.6381
Diabetes medication			
Metformin (*n*: %)	6:23.1%	5:19.2%	.7209
Glibenclamide (*n*: %)	4:15.4%	5:19.2%	.7139

Note: Data are mean ± SD.
[a]Independent *t*-test was applied for continuous variables and Fisher's exact test (χ^2) was applied for categorical variables.
Abbreviations: DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

TABLE 3 Fasting blood sugar (FBS), lipid profile, and daily dietary intake of the participants at the beginning of the clinical trial[a]

	Group 1: Celery ($n = 26$)	Group 2: Placebo ($n = 26$)	p-Value
Blood plasma parameters			
FBS (mg/dl)	108.47 ± 13.87	108.72 ± 14.34	.8744
TC (mg/dl)	191.57 ± 6.06	191.43 ± 6.08	.7058
TG (mg/dl)	181.33 ± 15.35	181.13 ± 14.74	.8499
LDL (mg/dl)	116.69 ± 4.10	116.95 ± 3.90	.5957
HDL (mg/dl)	42.32 ± 1.57	42.48 ± 1.66	.7210
Daily dietary intake			
Energy (kcal)	1891.34 ± 101.56	1907.84 ± 110.21	.5771
Carbohydrate (g)	218.77 ± 14.45	221.86 ± 15.76	.4647
Protein (g)	68.81 ± 4.73	70.02 ± 5.12	.3803
Fat (g)	84.01 ± 5.89	85.19 ± 6.51	.4963
Fiber (g)	19.88 ± 1.26	20.07 ± 1.31	.5964

Note: Data are mean ± SD.
[a]Independent *t*-test was applied.
Abbreviations: FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

3.4 | Clinical trial results

Results for 24-hr, day-time, and night-time SBP, DBP, and HR obtained by ABPM 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: 141.3 ± 5.97 and DBP: 92.29 ± 5.87 mmHg) and placebo (SBP: 140.04 ± 6.27 and DBP: 91.82 ± 6.07 mmHg) groups at the beginning of this study (*t*-test, unpaired, $p > .05$). Figure 3 shows that the BP parameters (in 24-hr, day-time, and night-time) did not change during the placebo treatment ($p > .05$), while the abovementioned parameters significantly decreased during celery seed extract treatment ($p < .001$). The mean reduction in day-time SBP and night-time SBP were 12.12 and 10.16 mmHg, respectively, during celery therapy ($p < .001$), while the

TABLE 4 Values for 24 hr, day-time, and night-time systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate during treatment with celery and placebo and their cross-over condition[a]

	Start: Week 0	End: Week 4	*p*-Value		Start: Week 8	End: Week 12	*p*-Value
SBP (mmHg)							
24 hr SBP				4-week washout			
Group 1: Celery-washout-placebo	141.30 ± 5.97	130.07 ± 4.65	1.11E-09		142.37 ± 6.31	142.12 ± 6.18	.8858
Group 2: Placebo-washout-celery	140.04 ± 6.27	139.8 ± 6.01	.8885		141.10 ± 6.06	129.99 ± 4.19	1.06E-09
p-Value	.4615	4.23E-08			.4626	1.59E-10	
Day-time SBP							
Group 1: Celery-washout-placebo	145.20 ± 6.16	133.07 ± 5.02	4.66E-10		145.57 ± 5.92	144.53 ± 5.44	.5126
Group 2: Placebo-washout-celery	144.23 ± 5.96	143.69 ± 6.83	.7626		144.98 ± 6.10	132.88 ± 4.78	2.79E-10
p-Value	.5665	7.62E-08			.7249	9.11E-11	
Night-time SBP							
Group 1: Celery-washout-placebo	127.30 ± 5.45	117.07 ± 4.34	1.39E-09		127.57 ± 5.18	126.93 ± 5.05	.6539
Group 2: Placebo-washout-celery	127.44 ± 5.88	126.3 ± 5.91	.4889		127.23 ± 5.25	117.14 ± 4.67	2.03E-09
p-Value	.9294	6.88E-08			.8151	2.45E-09	
DBP (mmHg)							
24 hr DBP				4-week washout			
Group 1: Celery-washout-placebo	92.29 ± 5.87	84.26 ± 4.88	2.27E-06		92.83 ± 6.04	92.61 ± 6.17	.8971
Group 2: Placebo-washout-celery	91.82 ± 6.07	91.62 ± 5.95	.9003		92.10 ± 5.74	84.12 ± 4.95	2.17E-06
p-Value	.7777	1.22E-05			.6570	1.61E-06	
Day-time DBP							
Group 1: Celery-washout-placebo	95.19 ± 5.66	86.27 ± 4.97	2.02E-07		95.73 ± 4.88	95.68 ± 4.56	.9697
Group 2: Placebo-washout-celery	94.74 ± 5.41	94.53 ± 5.17	.8868		94.87 ± 5.14	86.01 ± 4.43	2.26E-08
p-Value	.7707	3.46E-07			.5389	4.00E-10	
Night-time DBP							
Group 1: Celery-washout-placebo	82.29 ± 5.86	75.26 ± 4.33	1.15E-05		81.93 ± 4.81	82.18 ± 4.23	.8431
Group 2: Placebo-washout-celery	81.65 ± 4.66	81.28 ± 4.78	.7786		82.22 ± 5.39	75.24 ± 4.09	3.54E-06
p-Value	.6649	1.73E-05			.8387	2.09E-07	
MAP (mmHg)							
24 hr MAP				4-week washout			
Group 1: Celery-washout-placebo	108.63 ± 5.89	99.53 ± 4.77	1.64E-07		109.34 ± 6.09	109.11 ± 6.14	.8927
Group 2: Placebo-washout-celery	107.23 ± 6.07	107.01 ± 5.94	0.8954		108.43 ± 5.73	99.41 ± 4.62	1.06E-07
p-Value	.4027	7.96E-06			.5814	6.15E-08	

TABLE 4 (Continued)

	Start: Week 0	End: Week 4	*p*-Value		Start: Week 8	End: Week 12	*p*-Value
Day-time MAP							
Group 1: Celery-washout-placebo	111.86 ± 5.92	101.87 ± 4.78	2.19E-08		112.34 ± 5.87	111.96 ± 4.83	.7999
Group 2: Placebo-washout-celery	111.24 ± 5.54	110.92 ± 5.82	.8399		111.57 ± 5.37	101.63 ± 4.61	3.78E-09
p-Value	.6983	9.06E-08			.6238	2.51E-10	
Night-time MAP							
Group 1: Celery-washout-placebo	97.30 ± 5.67	89.20 ± 4.45	6.73E-07		97.14 ± 5.12	97.09 ± 4.48	.9703
Group 2: Placebo-washout-celery	96.91 ± 5.18	96.29 ± 5.14	.6667		97.22 ± 5.09	89.21 ± 4.37	1.73E-07
p-Value	.7968	2.58E-06			.9552	4.86E-08	
PP (mmHg)							
24 hr PP				4-week washout			
Group 1: Celery-washout-placebo	49.01 ± 3.89	45.81 ± 3.08	.0009		49.22 ± 3.82	49.19 ± 3.75	.9769
Group 2: Placebo-washout-celery	49.10 ± 3.79	49.18 ± 3.82	.9387		49.12 ± 3.76	45.87 ± 3.02	.0009
p-Value	.9317	.0008			.9231	.0007	
Day-time PP							
Group 1: Celery-washout-placebo	51.01 ± 3.82	46.90 ± 3.14	7.41E-05		50.84 ± 3.73	50.95 ± 3.66	.9133
Group 2: Placebo-washout-celery	50.79 ± 3.73	50.96 ± 3.77	.8684		51.05 ± 3.65	46.87 ± 3.18	4.14E-05
p-Value	.8313	7.84E-05			.8352	6.06E-05	
Night-time PP							
Group 1: Celery-washout-placebo	44.98 ± 3.34	41.96 ± 3.02	.0010		45.04 ± 3.40	44.93 ± 3.37	.9054
Group 2: Placebo-washout-celery	45.07 ± 3.39	45.02 ± 3.43	.9572		44.95 ± 3.32	41.90 ± 3.06	.0010
p-Value	.9221	.0010			.9220	.0010	

Note: Data are mean ± SD.

Abbreviations: DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

[a]Paired *t*-test was applied for variables in each group and Independent *t*-test was applied for variables between two groups.

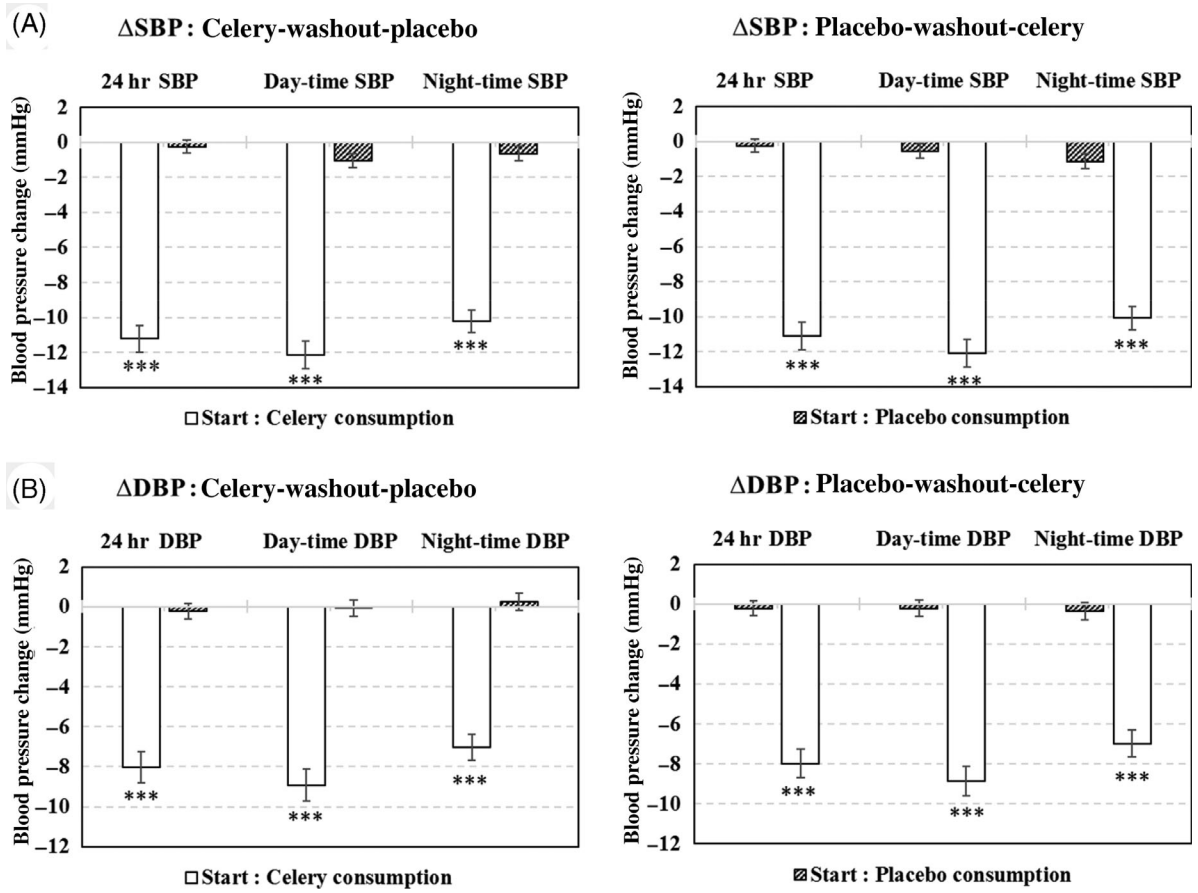

FIGURE 3 Blood pressure changes in 24 hr, day-time, and night-time (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) after 4 weeks of treatment follow celery-washout-placebo and placebo-washout-celery procedure. Paired *t*-test was applied for variables. Data are mean ± *SEM*, ***$p < .001$ versus placebo

changes in the aforementioned values were 0.79 and 0.89 mmHg during placebo therapy ($p > .05$). The mean reduction in day-time DBP and night-time DBP were 8.89 and 7.005 mmHg ($p < .001$), respectively, during celery therapy, while the changes in DBP values were 0.13 and 0.06 mmHg during placebo therapy ($p > .05$). Figure 4 shows the mean of 24-hr SBP, DBP, and MAP values measured with 15 min intervals before and after treatment in all patients. According to these data, celery seed extract maintains its antihypertensive effect during day and night, while placebo does not affect BP. Table 5 reported the effects of celery seed extract and placebo on BP changes measured by ABPM in all 52 patients in both treatment groups (celery and placebo). These data show significant changes in the BP of the celery group ($p < .001$) as the mean values of SBP, DBP, MAP, and PP decreased. Accordingly, SBP decreased from 141.20 to 130.03 mmHg, DBP decreased from 92.19 to 84.19 mmHg, MAP decreased from 108.53 to 99.47 mmHg, and PP decreased from 49.01 to 45.84 mmHg. These data had no difference in the placebo treatment group ($p > .05$). The maximum, minimum, and average values of BP parameters are also represented in this table. Table 6 shows that parameters, such as age, BMI, WHR, MUAC, and NC, did not influence SBP reduction ($p > .05$). Table 7 represents the mean SBP reduction in different intervals and the percentage of the remaining male and female population after 4 weeks of celery therapy. Figure 5 illustrates the mean reduction in SBP according to the SBP start point. Celery seed extract has a stronger effect in lowering BP in patients with higher initial SBP. Based on Table 8, celery had no effect on the mean, maximum, and minimum HR measured by 24-hr ABPM ($p > .05$). Table 9 shows that FBS, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) did not change after the placebo consumption ($p > .05$). FBS was reduced from 108.47 to 97.97 mg/dl after 4-week of celery administration ($p < .01$). TC, TG, and LDL significantly decreased after celery treatment from 191.57, 181.33, 116.69 mg/dl to 175.35, 165.11, 104.67 mg/dl, respectively ($p < .001$). HDL parameter was also improved during celery therapy from 42.32 to 44.85 mg/dl ($p < .001$). Data shows that serum glutamic-pyruvic transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), and alkaline phosphatase (ALP) did not change during the placebo treatment ($p > .05$). SGPT and SGOT were significantly reduced from 29.11 and 22.54 to 25.01 and 19.48 U/L, during celery therapy, respectively ($p < .05$). There were no significant differences in ALP values between the treatment and placebo groups and within each group pre-and post-intervention ($p > .05$). Furthermore, significant changes were observed in kidney functions; blood urea nitrogen and serum creatinine, after celery consumption,

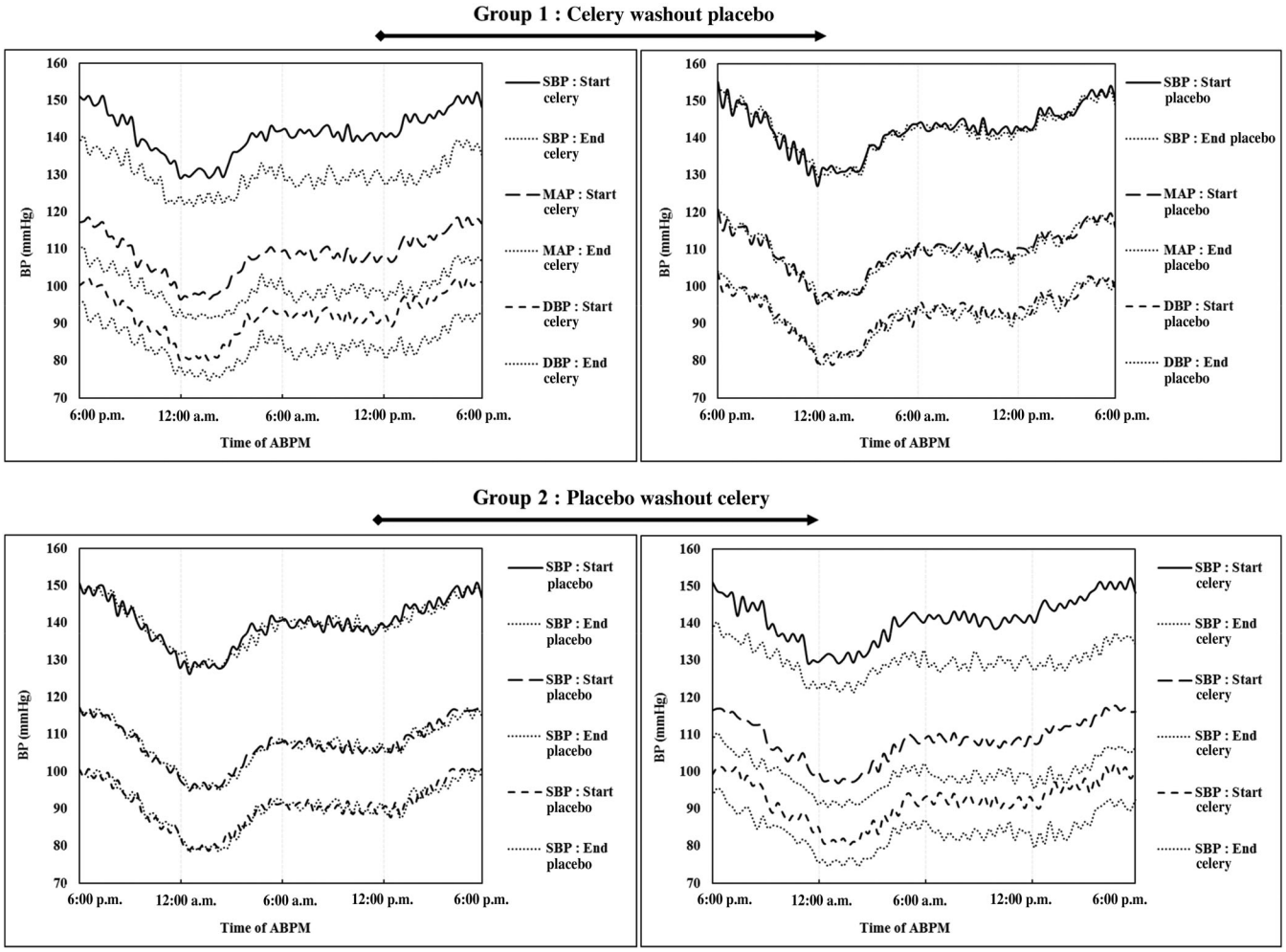

FIGURE 4 Twenty-four hr profile of systolic blood pressure (SBP), diastolic blood pressure (DBP), and arterial blood pressure (MAP) of 52 patients before and after treatment with celery and placebo in group 1: celery-washout-placebo and group 2: placebo-washout-celery. ABPM, ambulatory blood pressure monitoring; BP, blood pressure

TABLE 5 Average, minimum, and maximum blood pressure values measured by ambulatory blood pressure monitoring for all 52 patients during celery or placebo therapy

Overall blood pressure change (mmHg)	Baseline			After 4 weeks		
	Max	Average	Min	Max	Average	Min
Celery consumption						
SBP	150.25 ± 6.23	**141.20 ± 6.11**	131.98 ± 6.01	139.04 ± 4.61	**130.03 ± 4.52*****	120.71 ± 4.48
DBP	101.25 ± 6.02	**92.19 ± 5.91**	83.05 ± 5.84	93.22 ± 5.03	**84.19 ± 4.93*****	75.09 ± 4.86
MAP	117.75 ± 6.12	**108.53 ± 6.06**	99.32 ± 5.91	108.53 ± 4.80	**99.47 ± 4.72*****	90.18 ± 4.66
PP	55.58 ± 3.89	**49.01 ± 3.81**	42.47 ± 3.76	52.41 ± 3.11	**45.84 ± 3.05****	39.35 ± 2.96
Placebo consumption						
SBP	150.37 ± 6.26	**141.21 ± 6.13**	131.86 ± 6.04	150.13 ± 6.08	**140.96 ± 5.97**	131.63 ± 5.89
DBP	100.93 ± 5.95	**91.83 ± 5.87**	82.69 ± 5.79	100.72 ± 5.91	**91.62 ± 5.83**	82.41 ± 5.78
MAP	117.36 ± 6.09	**108.29 ± 5.98**	98.98 ± 5.90	117.09 ± 6.07	**108.06 ± 5.92**	98.74 ± 5.86
PP	55.97 ± 4.02	**49.38 ± 3.92**	43.01 ± 3.84	55.88 ± 3.98	**49.35 ± 3.89**	42.98 ± 3.78

Note: Data are mean ± SD.

Abbreviations: DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

** ($p < 0.01$) and *** ($p < 0.001$) represent significant difference in comparison with baseline.

TABLE 6 Systolic blood pressure (SBP) reduction after 4 weeks treatment with celery capsules for all 52 patients according to gender, age, body mass index (BMI), waist-to-hip ratio (WHR), neck circumference (NC), and mid-upper arm circumference (MUAC) at the start point

SBP reduction interval (mmHg)	Gender (*n*: %)	Age (years)	BMI	WHR	NC (cm)	MUAC (cm)
0–5	F (3:5.77%)	50.33 ± 6.50	29.47 ± 3.30	0.91 ± 0.02	40.33 ± 2.05	33.33 ± 2.47
	M (2:3.85%)	40.50 ± 7.50	32.56 ± 4.14	0.95 ± 0.03	45.50 ± 2.50	35.00 ± 3.06
5–10	F (6:11.54%)	53.00 ± 6.30	28.88 ± 3.72	0.96 ± 0.07	37.83 ± 2.34	32.50 ± 3.15
	M (15:28.85%)	51.73 ± 7.96	27.83 ± 3.29	0.93 ± 0.06	40.93 ± 2.26	33.07 ± 2.46
10–15	F (3:5.77%)	45.00 ± 7.48	30.20 ± 3.97	0.90 ± 0.04	39.00 ± 2.74	31.00 ± 2.16
	M (3:5.77%)	53.33 ± 6.94	28.98 ± 4.22	0.92 ± 0.04	43.00 ± 2.01	32.50 ± 2.50
15–20	F (6:11.54%)	51.75 ± 7.42	29.68 ± 3.69	0.96 ± 0.03	38.00 ± 2.58	35.25 ± 3.34
	M (6:11.54%)	47.00 ± 6.08	29.75 ± 4.27	0.97 ± 0.06	44.17 ± 2.03	34.17 ± 3.52
20–25	F (5:9.62%)	50.50 ± 7.23	25.71 ± 3.78	0.86 ± 0.03	36.33 ± 2.25	31.33 ± 2.25
	M (0:0%)	—	—	—	—	—
25–30	F (1:1.92%)	60.00 ± 0.00	21.13 ± 0.00	0.84 ± 0.00	33.00 ± 0.00	29.00 ± 0.00
	M (0:0%)	—	—	—	—	—
30–35	F (2:3.85%)	50.50 ± 3.50	29.75 ± 3.18	0.91 ± 0.03	37.50 ± 2.50	33.00 ± 3.02
	M (0:0%)	—	—	—	—	—

Note: Data are mean ± SD.
Abbreviations: F, female; M, male.

TABLE 7 Systolic blood pressure (SBP) reduction after 4 weeks treatment with celery capsules for all 52 patients according to SBP start point

SBP reduction (mmHg)	Gender (*n*: %)	SBP at start point	SBP reduction average (mmHg)
0–5	F (3:5.77%)	139.54 ± 7.43	1.79 ± 0.60
	M (2:3.85%)	140.94 ± 5.00	0.2 ± 0.11
5–10	F (6:11.54%)	138.04 ± 6.18	7.48 ± 1.48
	M (15:28.85%)	134.69 ± 7.70	7.59 ± 1.21
10–15	F (3:5.77%)	151.66 ± 5.22	13.12 ± 1.28
	M (3:5.77%)	146.17 ± 6.15	13.62 ± 0.95
15–20	F (6:11.54%)	138.29 ± 5.94	16.92 ± 2.30
	M (6:11.54%)	147.88 ± 7.08	16.46 ± 1.69
20–25	F (5:9.62%)	142.35 ± 5.89	21.08 ± 1.22
	M (0:0%)	—	—
25–30	F (1:1.92%)	146.44 ± 0.00	25.46 ± 0.00
	M (0:0%)	—	—
30–35	F (2:3.85%)	157.05 ± 2.34	33.33 ± 3.28
	M (0:0%)	—	—

Note: Data are mean ± SD.
Abbreviations: F, female; M, male.

were decreased from 28.99 and 1.16 to 25.54 and 1.09, respectively ($p < .05$). All these changes are in the normal range clinically. According to the data reported in Table 10, celery did not have a significant negative side effect, compared to the placebo group ($p > .05$). Celery also had some positive side effects, reported by the patients during celery treatment, such as reduction in chest pain, better breathing, less dizziness, improved sleep quality, and sense of relaxation and freshness during the day, which were all significant in comparison with the placebo group ($p < .05$). Decreased appetite and increased urination were also reported in the celery seed extract group which could be a positive effect in patients with obesity and HTN. No patient was withdrawn from the clinical trial due to adverse events.

4 | DISCUSSION

4.1 | Findings

This study aimed to evaluate the antihypertensive effects of celery seed extract, as a drug supplement, in a cross-over placebo-controlled clinical trial. This cross-over study was applied to minimize the

underlying and confounding factors which can affect BP results in this clinical trial. Combining celery with antihypertensive drugs can affect the pharmacodynamics and pharmacokinetics of the latter drugs. For example, Siska, Munim, Bahtiar, and Suyatna (2018) were reported celery extract can alter the pharmacokinetics of captopril when given in combination. The combination might be beneficial for the treatment of HTN, as celery causes an increase in the plasma level of captopril, which can enhance its efficacy. In a study by Deng, Pu, Wang, and Yu (2016), celery extract inhibited the levels of mouse CYP2A5 and human CYP2A6 activity via different mechanisms. Thus, celery can reduce the metabolism of other drugs and increase their blood concentration. Some of the complications of HTN are metabolic syndrome, memory disorder, and dementia of the central nerves, and stroke. Celery and its ingredients have therapeutic effects on abovementioned disorders. For example, it has been effective in Alzheimer (Peng et al., 2012), cerebral ischemia (Chong & Feng, 1999), strokes (Sheng et al., 2015), metabolic syndrome (Hedayati, Bemani, Mohammadinejad, & Mohajeri, 2019), obesity (Sowbhagya, 2014), prevention of cardiovascular disease (Khalid et al., 2016), vasorelaxant and relaxation of aortic rings (Jorge et al., 2013; Tang, Guo, Zhang, Li, & Su, 2007), bradycardic effect and vasodilatory features (Tashakori-Sabzevar, Ramezani, et al., 2016), beneficial effects in menstrual discomfort (Fazal & Singla, 2012), and liver diseases (Wang et al., 2012). According to the previously published works, a 4-week wash-out period was selected to remove the effect of therapeutic agents on SBP and DBP before the cross-over step (Baber, Templeman, Morton, Kelly, & West, 1999; Levin et al., 2019; Young et al., 2012). The ABPM device was performed to remove the white-coat effect and observer bias. This method provides assessment under normal living conditions during day and night with greater reproducibility (Puig et al., 2007). The 24-hr BP measurement is more predictive for the incidence of cardiovascular-related events than office-measured SBP and DBP (Staessen et al., 1999). As the results of the current clinical study SBP, DBP, PP, and MAP reduction values after administration of celery seed extract were 11.17, 8.005, 3.225, and

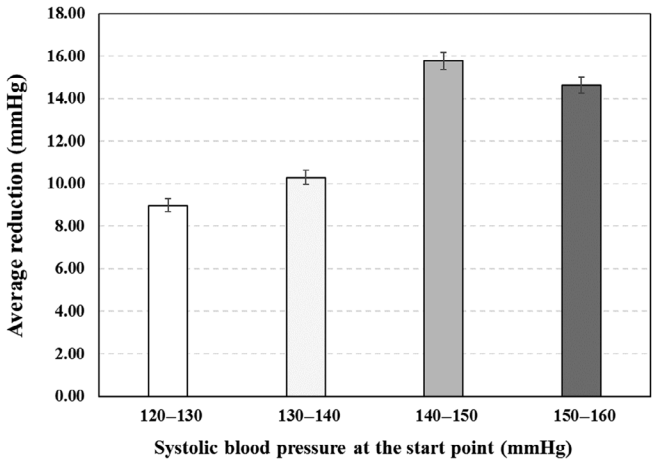

FIGURE 5 Mean reduction in systolic blood pressure (SBP) after 4 weeks treatment with celery capsules for all 52 patients according to the SBP start point. Data are mean ± *SEM*

TABLE 8 Values for mean, maximum and minimum heart rate during treatment with celery and placebo and their cross-over condition[a]

	Start: Week 0	End: Week 4	*p*-Value		Start: Week 8	End: Week 12	*p*-Value
Mean HR in 24 hr (bpm)				4-week washout			
Group 1: Celery-washout-placebo	73.66 ± 8.14	72.35 ± 7.93	.5593		74.68 ± 7.93	74.9 ± 9.24	.9270
Group 2: Placebo-washout-celery	72.75 ± 9.32	72.18 ± 8.88	.8223		73.95 ± 8.48	72.81 ± 8.08	.6219
p-Value	.7093	.9423			.7499	.3895	
Max HR in 24 hr (bpm)							
Group 1: Celery-washout-placebo	97.62 ± 9.19	96.92 ± 12.79	.8217		106.24 ± 13.82	105.81 ± 15.76	.9171
Group 2: Placebo-washout-celery	97.28 ± 19.48	97.74 ± 12.89	.9205		96.75 ± 13.4	95.15 ± 11.31	.6438
p-Value	.9363	.8188			.01521	.0074	
Min HR in 24 hr (bpm)							
Group 1: Celery-washout-placebo	57.12 ± 7.37	57.73 ± 6.05	.7457		57.98 ± 7.51	57.27 ± 7.02	0.7262
Group 2: Placebo-washout-celery	58.85 ± 8.91	58.35 ± 8.69	.8385		58.06 ± 7.04	58.84 ± 6.3	0.6756
p-Value	.4492	.7667			0.9685	0.4001	

Note: Data are mean ± SD.

Abbreviations: HR, heart rate.

[a]Paired *t*-test was applied for variables in each group and Independent *t*-test was applied for variables between two groups.

TABLE 9 Values for fasting blood sugar, serum lipid profile, liver, and kidney function parameters during treatment with celery and placebo[a]

	Baseline ($n = 52$)	End of treatment ($n = 52$)	*p*-Value
FBS (mg/dl)			
Celery	108.47 ± 13.87	97.96 ± 13.16	.0064
Placebo	108.72 ± 14.34	108.42 ± 14.84	.9578
p-Value	.8744	.0063	
TC (mg/dl)			
Celery	191.57 ± 6.06	175.35 ± 5.62	.0002
Placebo	191.43 ± 6.08	191.87 ± 6.19	.9454
p-Value	.7058	.0007	
TG (mg/dl)			
Celery	181.33 ± 15.35	165.11 ± 13.71	.0006
Placebo	181.13 ± 14.74	181.33 ± 14.69	.9149
p-Value	.8499	.0004	
LDL (mg/dl)			
Celery	116.69 ± 4.10	104.67 ± 3.39	.0004
Placebo	116.95 ± 3.90	116.33 ± 3.78	.7684
p-Value	.5957	.0008	
HDL (mg/dl)			
Celery	42.32 ± 1.57	44.85 ± 1.14	.0007
Placebo	42.48 ± 1.66	42.33 ± 1.25	.7206
p-Value	.7210	.0007	
SGPT (U/L)			
Celery	29.11 ± 1.89	25.01 ± 1.66	.0481
Placebo	29.03 ± 1.82	29.07 ± 1.80	.6831
p-Value	.5270	.0429	
SGOT (U/L)			
Celery	22.54 ± 1.60	19.48 ± 1.36	.0473
Placebo	22.49 ± 1.65	22.48 ± 1.63	.6589
p-Value	.3409	.0446	
ALP (U/L)			
Celery	189.94 ± 14.22	187.83 ± 13.93	.0937
Placebo	190.01 ± 14.23	189.96 ± 14.21	.9728
p-Value	.8427	.0936	
BUN (mg/dl)			
Celery	28.99 ± 1.32	25.54 ± 0.92	.0265
Placebo	28.90 ± 1.28	28.95 ± 1.33	.6549
p-Value	.4574	.0406	
SCr (mg/dl)			
Celery	1.16 ± 0.14	1.09 ± 0.10	.0313
Placebo	1.16 ± 0.13	1.17 ± 0.14	.6725
p-Value	.6644	.0248	

Note: Data are mean ± SD.

[a]Paired *t*-test was applied for variables.

Abbreviations: ALP, alkaline phosphatase; BUN, blood urea nitrogen; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCr, serum creatinine; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; TC, total cholesterol; TG, triglyceride.

9.06 mmHg, which indicated 7.91, 8.68, 6.57, and 8.35% changes, respectively. Analysis of previous randomized trials revealed that, a 5 mmHg reduction of SBP reduced the risk of major cardiovascular events by about 10%, irrespective of previous diagnoses of cardiovascular disease, and even at normal or high-normal BP values (Adler et al., 2021). Since the reduction in SBP over a 4-week period in this

TABLE 10 The side effects checklist during celery and placebo consumption[a]

	Group 1: Celery ($n = 52$)	Group 2: Placebo ($n = 52$)	p-Value
Positive side effect			
Reduction in chest pain	4	0	.0414
Better breathing	4	0	.0414
Lowering dizziness	7	1	.0272
Improve sleep quality	10	0	.0009
Feeling more relax	7	1	.0273
Feeling fresh during the day	4	0	.0414
Decreased appetite	6	0	.0116
Increased urination	6	0	.0116
Negative side effect			
Stomach reflux	2	1	.5580
Headache	1	2	.5580
Flushing	1	2	.5580
Dizziness	0	1	.3150
Skin irritation	1	0	.3150
Swelling	1	0	.3150
Nausea	1	1	1.0000
Abdominal pain	1	1	1.0000
Constipation	0	1	.3150
Fatigue	0	1	.3150
Fast heartbeat	1	1	1.0000

[a]Fisher's exact test (χ^2) was applied between two groups.

study was 11.20 ± 6.11 mmHg, it can be concluded that it has a remarkable effect on the CVD prevention. Generally, a higher therapeutic response in BP reduction was observed in women, compared to men. Also, SBP reduction was significantly higher in patients with higher SBP at the baseline (between 140 and 160 mmHg). Moreover, SBP and DBP were decreased in the day-time more than the night-time. On average, SBP reduction was not affect by higher or lower obesity. In details, the most reduction in SBP (more than 20 mmHg) happened in women who comprised 15.38% of all patients. The mean SBP reduction in the beforementioned patients was 24.69 ± 3.52 mmHg. In total, 34.62% of the patients showed 10–20 mmHg SBP reduction with a mean value of 15.58 ± 2.37 mmHg. There was no difference between male and female participants in this regard. The SBP reduction between 5 and 10 mmHg was more prevalent in men (28.85%), compared to women (11.54%). In addition, only 9.62% of the patients showed less than 5 mmHg reduction in SBP. In other words, more than 90% of all patients showed more than 5 mmHg SBP reduction which is the primary outcome of this study. Besides, SBP reduction was significantly higher in patients with SBP between 140 and 160 mmHg at the baseline. The BP is also characterized by its pulsatile component which is estimated by PP and steady that is estimated by MAP components (Safar, 1989). The pulsatile component, which is estimated by PP and represents BP variation, is affected by left ventricular ejection fraction, large-artery stiffness, early pulse wave reduction, and HR (Franklin et al., 1997). The steady component, estimated by MAP, is a function of left ventricular contractility, HR, vascular resistance, and elasticity averaged over time (Benetos, Laurent, Asmar, & Lacolley, 1997). In addition, celery seed extract therapy had no significant effect on HR during the study. Therefore, it can be concluded that the antihypertensive effects of celery seed extract may be due to its vasodilatory effect while its possible inhibitory effects on heart muscles prevent reflex tachycardia. Anthropometric measures, such as WHR and NC were used as biomarkers of central adiposity and cardiovascular risk (Elsayed et al., 2008; Famodu et al., 2018). Besides, MUAC, a fat-free mass indicator, and muscle atrophy measure could be applied as an alternative to BMI.

4.2 | Previous studies

Results of our previous animal study indicated that celery seed extract has calcium channel blocking properties with a negative chronotropic effect on normotensive and hypertensive rats (Tashakori-Sabzevar, Razavi, et al., 2016). Moreover, in another animal study performed by Moghadam et al. (2013), 100 and 200 mg/kg celery seed extract as an antihypertensive agent did not cause reflex tachycardia. In the present study, the lack of changes in HR despite the hypotensive effect may be due to its inhibitory effect on cardiac calcium channels. Some researchers have reported the effect of celery as a food supplement on BP reduction. In their research, the daily consumption dose was between 2 and 15 g/day in the form of decoction or steeped bag. The SBP reduction in the abovementioned studies was between 5 and

17.05 mmHg (Gharooni & Sarkarati, 2000; Madhavi et al., 2013; Oktavia & Junaid, 2017; Puig et al., 2007; Triyono et al., 2018). In a randomized clinical trial conducted by Triyono et al. (2018), consumption of decoction and steeped forms of an herbal mixture, including 25% celery powder, significantly decreased BP ($p < .05$). In a study performed by Gharooni and Sarkarati (2000), one-week consumption of celery seeds powder (using teabag containing 2 g powder twice a day) significantly decreased SBP from 171.35 to 154.30 mmHg and DBP from 94.3 to 89.6 mmHg ($p < .05$). In another work, 60 patients received 20 g of the herbal mixture, including celery, three times a day for 8 weeks. The SBP values in decoction and steeped bag groups decreased from 151.91 to 141.83 mmHg and 155.92 to 138.83 mmHg, respectively. Obviously, a part of this BP reduction was due to the effect of celery active ingredients (Triyono & Novianto, 2017). Findings of a study performed by Oktavia & Junaid, 2017 indicated that administration of celery decoction significantly decreased SBP from 172.27 to 141.82 mmHg and DBP from 106.36 to 90.45 mmHg after 2 days ($p < .05$) (Oktavia & Junaid, 2017). In a pilot study carried out by Madhavi et al. (2013) on the BP measured in the office of the physician, celery capsule (containing 75 mg celery seed extract, twice per day) supplying 85% NBP caused 8.9 and 8.5 mmHg reduction in SBP and DBP after 6 weeks, compared to the baseline ($p < .05$), respectively. The BP measurements in all the above-mentioned studies were performed in the office of the physician and ABPM was not used as a reliable, accurate, and precise 24-hr BP assessment method. The present research was the first cross-over clinical trial to report the effects of celery seed extract capsules, as a drug supplement, on different BP parameters using the ABPM apparatus. A review of the clinical studies with baseline SBP similar to the current work revealed that administration of synthetic antihypertensive medications showed 6–17.9 and 3.4–9.2 mmHg reduction in SBP and DBP, respectively. In a 4-week study conducted by Fogari et al., daily consumption of valsartan 80 mg, losartan 50 mg, and telmisartan 40 mg caused about 10.5, 8.2, and 7.5 mmHg SBP reduction, respectively; whereas the DBP reductions were 9.2, 7.5, and 7.5 mmHg (Fogari et al., 2002). In another cross-over study using ABPM, consumption of lercanidipine 10 mg and enalapril 20 mg led to 8.2 and 12.9 mmHg SBP reduction, respectively, and also 3.9 and 6.0 mmHg DBP reduction, respectively, after 4 weeks (Puig et al., 2007). Lercanidipine is a CCB and its efficacy is comparable with celery seed extract with a calcium channel blocking mechanism. In the current work, as a natural drug supplement, administration of celery seed extract caused 11.2 and 8 mmHg SBP and DBP reduction after a 4-week clinical trial.

4.3 | Active ingredients and possible mechanisms

Organs of celery, such as seeds, stems, leaves, roots, and stalks, contain phthalides with antitumor, antiinflammatory, and insecticidal properties (Sellami et al., 2012). The celery seed extract contains different active ingredients, including apigenin, luteolin, linalool, d-limonene, and phthalides (Hedayati et al., 2019; Tashakori-Sabzevar, Ramezani, et al., 2016; Tashakori-Sabzevar, Razavi, et al., 2016). Apigenin causes overexpression of ACE2 and inhibits calcium influx through ligand- and voltage-gated calcium channels (Sui et al., 2010; Tashakori-Sabzevar, Razavi, et al., 2016). Other studies have indicated that apigenin functions as a beta-blocker and has a vasodilatory effect on rat aorta by inhibition of calcium release (Chan et al., 2000). Therefore, apigenin has been proved to have a similar effect with CCBs. Luteolin inhibits the proliferation and migration of Ang II-induced vascular smooth muscle cells, and thereby decreases hypertensive vascular remodeling. As an antioxidant, luteolin regulates the mitogen-activated protein kinase signaling pathway and the production of reactive oxygen species (Su et al., 2015). Linalool is a CCB and shows antihypertensive properties through its direct effect on smooth muscles (Anjos et al., 2013). Furthermore, d-limonene has antihyperlipidemic and antioxidant activities that reduce pathological changes and restore the physiological functions of vascular systems (Santiago et al., 2010). The NBP, as a phthalide, is reported to have an antihypertensive effect, probably through its vasodilatory, diuretic, and CCB effects (Madhavi et al., 2013). Results of another study indicated that celery seed extract has diuretic and vasodilatory effects, similar to CCBs (Hedayati et al., 2019). 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. 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. Compared to other mechanisms, the calcium channel blocking property of celery seed extract was more reported in different studies. The dihydropyridine CCBs, such as nifedipine, cause a reflex tachycardia which may worsen arrhythmia and angina. In comparison with dihydropyridines, celery seed extract had no reflex tachycardia which may be due to the blockage of beta receptors or the calcium channels located in the muscle cells of the heart.

4.4 | Limitations of the study

Current work is one of the first cohesive clinical studies for the antihypertensive effect of celery seeds extract on hypertensive patients. The small size of each group, self-report assessments of side effects, exclusion of patients from the study, and 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.

5 | CONCLUSIONS

In this study, four celery seed extract capsules containing a total of 1.34 g extract were given to patients as drug supplements in a randomized, triple-blind, placebo-controlled, cross-over clinical trial. The ABPM device was used to obtain accurate and realistic results. The results indicated that celery seed extract capsules caused 11 and 8 mmHg reduction in SBP and DBP values, respectively, which is

statistically and clinically significant; however, no significant change was observed in HR. The results of safety and biochemical parameters showed that the celery seed extract capsule not only is safe for hypertensive patients but also improves FBS, lipid profile, liver, and kidney functions, which are statistically and clinically significant and were in normal ranges. According to the results of this clinical trial, celery seed extract can be considered a supplement for the management of HTN.

AUTHOR CONTRIBUTIONS

Maryam Shayani Rad: Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; visualization; writing—original draft; writing—review and editing. **Mohsen Moohebati**: Conceptualization; data curation; project administration; validation; visualization. **Seyed Ahmad Mohajeri**: Conceptualization; data curation; funding acquisition; methodology; project administration; supervision; resources; validation; writing—review and editing.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Vice Chancellor for Research of Mashhad University of Medical Sciences for financial support. This article is a part of the results of the Ph.D. dissertation, grant number 941237 registered in the Mashhad University of Medical Sciences, Mashhad, Iran. They would also like to gratefully thank Dr. Shahab MohammadEbrahimi, Dr. Vahideh Sadat Motamedshariaty, and Mr. Seyed Sadegh Assaran for their participation in data analysis, assistance in HPLC data processing, and blood sampling from patients in Ghaem Hospital, respectively.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest in this work.

DATA AVAILABILITY STATEMENT

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

ORCID

Seyed Ahmad Mohajeri https://orcid.org/0000-0002-7907-9625

REFERENCES

Adler, A., Agodoa, L., Algra, A., Asselbergs, F. W., Beckett, N. S., Berge, E., … Bulpitt, C. J. (2021). Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: An individual participant-level data meta-analysis. *The Lancet*, *397*(10285), 1625–1636.

Anjos, P. J., Lima, A. O., Cunha, P. S., De Sousa, D. P., Onofre, A. S., Ribeiro, T. P., … Santos, M. R. (2013). Cardiovascular effects induced by linalool in normotensive and hypertensive rats. *Zeitschrift für Naturforschung. Section C*, *68*(5–6), 181–190.

Asgary, S., Naderi, G., Sarrafzadegan, N., Mohammadifard, N., Mostafavi, S., & Vakili, R. (2000). Antihypertensive and antihyperlipidemic effects of Achillea wilhelmsii. *Drugs under Experimental and Clinical Research*, *26*(3), 89–94.

Baber, R., Templeman, C., Morton, T., Kelly, G., & West, L. (1999). Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. *Climacteric*, *2*(2), 85–92.

Bauer, U. E., Briss, P. A., Goodman, R. A., & Bowman, B. A. (2014). Prevention of chronic disease in the 21st century: Elimination of the leading preventable causes of premature death and disability in the USA. *The Lancet*, *384*(9937), 45–52.

Benetos, A., Laurent, S., Asmar, R. G., & Lacolley, P. (1997). Large artery stiffness in hypertension. *Journal of Hypertension*, *15*(2), S89–S97.

Chan, E. C., Pannangpetch, P., & Woodman, O. L. (2000). Relaxation to flavones and flavonols in rat isolated thoracic aorta: Mechanism of action and structure-activity relationships. *Journal of Cardiovascular Pharmacology*, *35*(2), 326–333.

Chong, Z.-Z., & Feng, Y.-P. (1999). dl-3-n-butylphthalide attenuates reperfusion-induced blood-brain barrier damage after focal cerebral ischemia in rats. *Acta Pharmacologica Sinica*, *20*(8), 696–700.

European Society of Hypertension-European Society of Cardiology Guidelines Committee. (2003). 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *Journal of Hypertension*, *21*(6), 1011–1053.

Deng, X., Pu, Q., Wang, E., & Yu, C. (2016). Celery extract inhibits mouse CYP2A5 and human CYP2A6 activities via different mechanisms. *Oncology Letters*, *12*(6), 5309–5314.

Diao, X., Deng, P., Xie, C., Li, X., Zhong, D., Zhang, Y., & Chen, X. (2013). Metabolism and pharmacokinetics of 3-n-butylphthalide (NBP) in humans: The role of cytochrome P450s and alcohol dehydrogenase in biotransformation. *Drug Metabolism and Disposition*, *41*(2), 430–444.

Doménech, M., Roman, P., Lapetra, J., Garcia de la Corte, F. J., Sala-Vila, A., de la Torre, R., … Lamuela-Raventós, R.-M. (2014). Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: One-year randomized, clinical trial. *Hypertension*, *64*(1), 69–76.

Elkind, M. S. (2011). Epidemiology and risk factors. *CONTINUUM: Lifelong Learning in Neurology*, *17*(6), 1213–1232.

Elsayed, E. F., Tighiouart, H., Weiner, D. E., Griffith, J., Salem, D., Levey, A. S., & Sarnak, M. J. (2008). Waist-to-hip ratio and body mass index as risk factors for cardiovascular events in CKD. *American Journal of Kidney Diseases*, *52*(1), 49–57.

Ernst, E. (2005). Complementary/alternative medicine for hypertension: A mini-review. *Wiener Medizinische Wochenschrift*, *155*(17), 386–391.

Famodu, O. A., Barr, M. L., Colby, S. E., Zhou, W., Holásková, I., Leary, M. P., … Olfert, M. D. (2018). Neck circumference positively relates to cardiovascular risk factors in college students. *International Journal of Environmental Research and Public Health*, *15*(7), 1480.

Fazal, S. S., & Singla, R. K. (2012). Review on the pharmacognostical & pharmacological characterization of *Apium graveolens* Linn. *Indo Global Journal of Pharmaceutical Sciences*, *2*(1), 36–42.

Fogari, R., Mugellini, A., Zoppi, A., Derosa, G., Rinaldi, A., Fogari, E., … Preti, P. (2002). Efficacy of losartan, valsartan, and telmisartan in patients with mild to moderate hypertension: A double-blind, placebo-controlled, crossover study using ambulatory blood pressure monitoring. *Current Therapeutic Research*, *63*(1), 1–14.

Franklin, S. S., Gustin, W., IV, Wong, N. D., Larson, M. G., Weber, M. A., Kannel, W. B., & Levy, D. (1997). Hemodynamic patterns of age-related changes in blood pressure: The Framingham heart study. *Circulation*, *96*(1), 308–315.

Gaciong, Z., Siński, M., & Lewandowski, J. (2013). Blood pressure control and primary prevention of stroke: Summary of the recent clinical trial data and meta-analyses. *Current Hypertension Reports*, *15*(6), 559–574.

George, P. (2011). Concerns regarding the safety and toxicity of medicinal plants–An overview. *Journal of Applied Pharmaceutical Science*, *1*(6), 40–44.

Gharooni, M., & Sarkarati, A. (2000). Application of Apium graveolens in treatment of hypertension. *Tehran University Medical Journal*, *58*(3), 67–69.

Hajian, S. (2013). Renoprotective effects of green tea. *Journal of Nephropharmacology*, *2*(2), 21–22.

Haq, I. (2004). Safety of medicinal plants. *Pakistan Journal of Medical Research*, *43*(4), 203–210.

Hedayati, N., Bemani, N. M., Mohammadinejad, A., & Mohajeri, S. A. (2019). Beneficial effects of celery (*Apium graveolens*) on metabolic syndrome: A review of the existing evidences. *Phytotherapy Research*, *33*(12), 3040–3053.

Herrera-Arellano, A., Flores-Romero, S., Chavez-Soto, M., & Tortoriello, J. (2004). Effectiveness and tolerability of a standardized extract from *Hibiscus sabdariffa* in patients with mild to moderate hypertension: A controlled and randomized clinical trial. *Phytomedicine*, *11*(5), 375–382.

Illes, J. D. (2021). Blood pressure change after celery juice ingestion in a hypertensive elderly male. *Journal of Chiropractic Medicine*, *20*, 90–94.

Jorge, V.-G., Ángel, J.-R. L., Adrián, T.-S., Francisco, A.-C., Anuar, S.-G., Samuel, E.-S., … Emmanuel, H.-N. (2013). Vasorelaxant activity of extracts obtained from *Apium graveolens*: Possible source for vasorelaxant molecules isolation with potential antihypertensive effect. *Asian Pacific Journal of Tropical Biomedicine*, *3*(10), 776–779.

Kazemipoor, M., Wan Mohamed Radzi, C., Cordell, G. A., & Yaze, I. (2012). Safety, efficacy and metabolism of traditional medicinal plants in the management of obesity: A review. *International Journal of Chemical Engineering and Applications*, *3*(4), 288–292.

Khalid, Z., Osuagwu, F. C., Shah, B., Roy, N., Dillon, J. E., & Bradley, R. (2016). Celery root extract as an inducer of mania induction in a patient on venlafaxine and St John's Wort. *Postgraduate Medicine*, *128*(7), 682–683.

Khalil, H., & Zeltser, R. (2020). *Antihypertensive medications*. Treasure Island (FL): StatPearls Publishing.

Kim, R., & Zhou, W. (2004). Clinical study on effect of Luohuo capsule in treating essential hypertension of phlegm-stasis blocking collateral type. *Chinese Journal of Integrated Traditional and Western Medicine*, *24*(7), 610–612.

Levin, J., Maaß, S., Schuberth, M., Giese, A., Oertel, W. H., Poewe, W., … Südmeyer, M. (2019). Safety and efficacy of epigallocatechin gallate in multiple system atrophy (PROMESA): A randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*, *18*(8), 724–735.

Liu, X., Wei, J., Tan, F., Zhou, S., Würthwein, G., & Rohdewald, P. (2004). Pycnogenol®, French maritime pine bark extract, improves endothelial function of hypertensive patients. *Life Sciences*, *74*(7), 855–862.

Madhavi, D., Kagan, D., & Rao, V. (2013). A pilot study to evaluate the antihypertensive effect of a celery extract in mild to moderate hypertensive patients. *Age*, *57*(10), 1–3.

Moghadam, M. H., Imenshahidi, M., & Mohajeri, S. A. (2013). Antihypertensive effect of celery seed on rat blood pressure in chronic administration. *Journal of Medicinal Food*, *16*(6), 558–563.

Niaz, K. (2013). Antihyperglycemic/hypoglycemic effect of celery seeds (ajwain/ajmod) in streptozotocin induced diabetic rats. *Journal of Rawalpindi Medical College*, *17*(1), 134–137.

Oktavia, I. E., & Junaid, J. (2017). Pengaruh Pemberian Air Rebusan Seledri (*Apium graveolens*) terhadap Penurunan Tekanan Darah Sistolik dan Diastolik Penderita Hipertensi di Wilayah Kerja Puskesmas Puuwatu Kota Kendari Tahun 2016. *Jurnal Ilmiah Mahasiswa Kesehatan Masyarakat*, *2*(6), 1–12.

Peng, Y., Hu, Y., Xu, S., Li, P., Li, J., Lu, L., … Wang, X. (2012). L-3-n-butylphthalide reduces tau phosphorylation and improves cognitive deficits in AβPP/PS1-Alzheimer's transgenic mice. *Journal of Alzheimer's Disease*, *29*(2), 379–391.

Puig, J., Calvo, C., Luurila, O., Luurila, H., Sulosaari, S., Strandberg, A., & Ghezzi, C. (2007). Lercanidipine, enalapril and their combination in the treatment of elderly hypertensive patients: Placebo-controlled, randomized, crossover study with four ABPM. *Journal of Human Hypertension*, *21*(12), 917–924.

Rafieian-Kopaei, M. (2013). Medicinal plants for renal injury prevention. *Journal of Renal Injury Prevention*, *2*(2), 63–65.

Safar, M. E. (1989). Pulse pressure in essential hypertension: Clinical and therapeutical implications. *Journal of Hypertension*, *7*(10), 769–776.

Saneei, P., Salehi-Abargouei, A., Esmaillzadeh, A., & Azadbakht, L. (2014). Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: A systematic review and meta-analysis on randomized controlled trials. *Nutrition, Metabolism, and Cardiovascular Diseases*, *24*(12), 1253–1261.

Santiago, J. V. A., Jayachitra, J., Shenbagam, M., & Nalini, N. (2010). d-limonene attenuates blood pressure and improves the lipid and antioxidant status in high fat diet and L-NAME treated rats. *Journal of Pharmaceutical Sciences and Research*, *2*(11), 752.

Sellami, I. H., Bettaieb, I., Bourgou, S., Dahmani, R., Limam, F., & Marzouk, B. (2012). Essential oil and aroma composition of leaves, stalks and roots of celery (*Apium graveolens* var. dulce) from Tunisia. *Journal of Essential Oil Research*, *24*(6), 513–521.

Sheng, X., Hua, K., Yang, C., Wang, X., Ji, H., Xu, J., … Zhang, Y. (2015). Novel hybrids of 3-n-butylphthalide and edaravone: Design, synthesis and evaluations as potential anti-ischemic stroke agents. *Bioorganic & Medicinal Chemistry Letters*, *25*(17), 3535–3540.

Sirtori, C. R., Arnoldi, A., & Cicero, A. F. (2015). Nutraceuticals for blood pressure control. *Annals of Medicine*, *47*(6), 447–456.

Siska, S., Munim, A., Bahtiar, A., & Suyatna, F. D. (2018). Effect of *Apium graveolens* extract administration on the pharmacokinetics of captopril in the plasma of rats. *Scientia Pharmaceutica*, *86*(1), 6.

Sliwa, K., Stewart, S., & Gersh, B. J. (2011). Hypertension: A global perspective. *Circulation*, *123*(24), 2892–2896.

Sowbhagya, H. (2014). Chemistry, technology, and nutraceutical functions of celery (*Apium graveolens* L.): An overview. *Critical Reviews in Food Science and Nutrition*, *54*(3), 389–398.

Staessen, J. A., Thijs, L., Fagard, R., O'Brien, E. T., Clement, D., De Leeuw, P. W., … Parati, G. (1999). Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA*, *282*(6), 539–546.

Su, J., Xu, H.-T., Yu, J.-J., Gao, J.-L., Lei, J., Yin, Q.-S., … Mi, W.-J. (2015). Luteolin ameliorates hypertensive vascular remodeling through inhibiting the proliferation and migration of vascular smooth muscle cells. *Evidence-based Complementary and Alternative Medicine*, *2015*, 1–14.

Sui, H., Yu, Q., Zhi, Y., Geng, G., Liu, H., & Xu, H. (2010). Effects of apigenin on the expression of angiotensin-converting enzyme 2 in kidney in spontaneously hypertensive rats. *Journal of Hygiene Research*, *39*(6), 693–696, 700.

Tang, F.-F., Guo, J.-X., Zhang, J., Li, J., & Su, M. (2007). Study on hypotensive and vasodilatory effects of celery juice. *Food Science*, *28*(1), 322–325.

Tashakori-Sabzevar, F., Ramezani, M., Hosseinzadeh, H., Parizadeh, S. M. R., Movassaghi, A. R., Ghorbani, A., & Mohajeri, S. A. (2016). Protective and hypoglycemic effects of celery seed on streptozotocin-induced diabetic rats: Experimental and histopathological evaluation. *Acta Diabetologica*, *53*(4), 609–619.

Tashakori-Sabzevar, F., Razavi, B. M., Imenshahidi, M., Daneshmandi, M., Fatehi, H., Sarkarizi, Y. E., & Mohajeri, S. A. (2016). Evaluation of mechanism for antihypertensive and vasorelaxant effects of hexanic and hydroalcoholic extracts of celery seed in normotensive and hypertensive rats. *Revista Brasileira de Farmacognosia*, *26*(5), 619–626.

Triyono, A., & Novianto, F. (2017). Studi Klinik Efek Seduhan Formula Jamu Hipertensi Terhadap Fungsi Ginjal. *Jurnal Ilmu Farmasi dan Farmasi Klinik*, *14*, 62–65.

Triyono, A., Ridha, P., & Ardianto, D. (2018). Clinical trial the efficacy of boiled hypertension herbs compared with steeped hypertension herbs. *Jurnal Ilmu Kefarmasian Indonesia*, *16*(1), 78–85.

Wang, W.-B., Li, J., Liu, Y.-L., Li, Y., Gao, S.-Y., Ma, H.-X., & Song, C.-M. (2012). Effects of celery seed powder on blood lipid and liver function in high fat-diet rats. *Journal of Jilin Medical College*, *3*, 9.

Wolf-Maier, K., Cooper, R. S., Banegas, J. R., Giampaoli, S., Hense, H.-W., Joffres, M., … Rodríguez-Artalejo, F. (2003). Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA*, *289*(18), 2363–2369.

Young, J. M., Florkowski, C. M., Molyneux, S. L., McEwan, R. G., Frampton, C. M., Nicholls, M. G., … George, P. M. (2012). A randomized, double-blind, placebo-controlled crossover study of coenzyme Q10 therapy in hypertensive patients with the metabolic syndrome. *American Journal of Hypertension*, *25*(2), 261–270.

Yusni, Y., Zufry, H., Meutia, F., & Sucipto, K. W. (2018). The effects of celery leaf (*Apium graveolens* L.) treatment on blood glucose and insulin levels in elderly pre-diabetics. *Saudi Medical Journal*, *39*(2), 154–160.

Zhu, J., Zhang, Y., & Yang, C. (2015). Protective effect of 3-n-butylphthalide against hypertensive nephropathy in spontaneously hypertensive rats. *Molecular Medicine Reports*, *11*(2), 1448–1454.

How to cite this article: Shayani Rad, M., Moohebati, M., & Mohajeri, S. A. (2022). Effect of celery (*Apium graveolens*) seed extract on hypertension: A randomized, triple-blind, placebo-controlled, cross-over, clinical trial. *Phytotherapy Research*, 1–19. https://doi.org/10.1002/ptr.7469