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Effects of artichoke on blood pressure: A systematic review and meta-analysis

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ABSTRACT

Purpose: Clinical trials considering the effects of artichoke supplementation on blood pressure have yielded different and contradictory outcomes. Thus, a systematic review and meta-analysis were performed to assess effects of artichoke administration on blood pressure.

Methods: Related studies were detected by searching the Cochrane Library, PubMed, Embase and Scopus databases up to 15 March 2020. Weighted Mean Differences (WMD) were pooled using a random-effects model. Heterogeneity, sensitivity analyses, and publication bias were evaluated using standard methods.

Results: Pooled analysis of eight randomized controlled trials revealed that artichoke supplementation did not have an effect on systolic blood pressure (SBP), (WMD: -0.77 mmHg, 95 % CI: −2.76 to 1.22) or diastolic blood pressure (DBP) (WMD: −0.11 mmHg, 95 % CI: −1.72 to 1.50) when compared to the placebo group. However, subgroup analyses based on health status suggested that artichoke administration among hypertensive patients may significantly reduce SBP (WMD: −3.19 mmHg, 95 % CI: −3.32 to −3.06) and DBP (WMD: −2.33 mmHg, 95 % CI: −2.23 to −2.43), but no such reduction was found in NAFLD patients. Furthermore, our results indicated that artichoke supplementation for 12 weeks led to a significantly decreased DBP (WMD: -2.33 mmHg, 95 % CI: −2.43 to −2.23), but 8 weeks of intervention did not (WMD: 0.80 mmHg, 95 % CI: −1.06 to 2.66).

Conclusion: Artichoke supplementation may potentially lead to SBP and DBP reduction in hypertensive patients. In addition, artichoke supplementation for 12 weeks may significantly improve DBP.

1. Introduction

Fundamentally, high blood pressure (BP) is considered an important leading global cause of a cluster of diseases, namely heart failure, heart attacks, stroke, kidney dysfunction, dementia, and all-cause mortality.[1–3] Epidemiological research has suggested that the prevalence of hypertension has enhanced tremendously around the globe,[4] and it is estimated that more than 1.56 billion people will be suffering from elevated BP by the year 2025.[5] The high prevalence of hypertension and its related diseases incurs a large economic cost, contributing to social and health system burdens globally.[6] Thus, preventing, monitoring, or managing hypertension, especially in the primary stages, can help to reduce the risk of its subsequent disease and treatment burden.[7,8]

Lifestyle changes and medicinal agents are preferred ways to manage

Abbreviations: eNOS, Endothelial nitric oxide synthase; BMI, Body mass index; NO, Nitric oxide; MD, Mean differences; RCTs, Randomized controlled trials; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; NAFLD, Non-alcoholic fatty liver disease; WMD, Weighted mean differences; PRISMA, Preferred reporting items for systematic reviews and meta-analysis; MeSHs, Medical subject headings; CIs, Confidence intervals.

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and treat hypertension among the medical community.[9–11] However, using medicinal agents for long-term care leads to various adverse complications, and adherence to various lifestyle changes leads to issues with compliance and lack of sustained or subsequent improvements in hypertensive status.[11,12] Therefore, introducing potential interventions like herbal agents with antihypertensive characteristics that do not require stringent lifestyle modifications or medicinal agents could be a favorable alternative due to their wide range of biological activities and significantly lower adverse complications.[10] In recent years, several scientific studies have recommended that medicinal plants may effectively manage or treat hypertension [13,14] and other metabolic disorders.[15] Moreover, emerging evidence suggests that herbs rich in bioactive component such as lycopene, pycnogenol, resveratrol, L-citrulline and vitamin C may serve as effective functional foods that can lower BP.[16,17]

Artichoke (Cynara scolymus L.) is a sunflower species belonging to the Asteraceae family.[18] Artichoke contains vitamins, minerals, bioactive phenolic compounds (caffeoylquinic, apigenin, and luteolin), and prebiotics (inulin and fructooligosaccharides); these components have been widely used in the design of several dietary and pharmaceutical agents in the past decade.[18–20] Clinical trials suggest that extracts from artichoke may have healing properties to treat several diseases, such as non-alcoholic fatty liver disease (NAFLD),[21,22] hypocholesteremia,[23] metabolic syndrome,[24,25] and hypertension.[19,26] However, the outcomes of clinical trials have been varied concerning the effects of artichoke on BP. Some of these clinical trials have suggested that artichoke leaf extract may reduce high BP by increasing endothelial nitric oxide synthase (eNOS) gene expression, improving nitric oxide (NO) production in vascular endothelial cells, and/or inhibiting the activity of angiotensin-converting enzyme.[19,22,26] However, other studies conducted in NAFLD,[27] type 2 diabetes,[28] and hypercholesterolemic [23] patients demonstrated that BP did not change after artichoke supplementation.

Results of our systematic literature search indicated that no previously published reviews have endeavored to evaluate the efficacy of artichoke administration on BP control. Furthermore, clinical trials have shown differing results regarding the effects of artichoke administration on BP, but the outcomes from these clinical trials might not be sufficient to make a clear conclusion. Thus, the present systematic review and meta-analysis of clinical trials was performed to evaluate the effects of artichoke administration on BP.

2. Methods

2.1. Literature search and selection

This study was performed based on Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[29] A systematic literature search was conducted by searching the Cochrane Library, Scopus, PubMed and Embase databases up to 15 March 2020. Medical subject headings (MeSHs), abstracts, and keywords were searched without language and date limitations. The systematic search was performed with the search terms delineated in **Supplementary** Table 1. Electronic searches were completed, and reference lists and citations were reviewed for additional relevant resources. The research process was conducted by two investigators (SM and AH) separately and in duplicate. Any nonconformity was resolved via discussion with the third author (MHF).

2.2. Eligibility criteria

Two authors detected eligible studies independently by reading headlines and abstracts, and full-text articles were searched if preliminary searches indicated relevance. All human randomized controlled trials (RCTs) with either parallel or cross-over designs which demonstrated the effects of artichoke administration on BP were selected. The following articles were removed: (1) RCTs with intervention durations less than 2 weeks and (2) clinical trials without any comparative placebo group. Disagreements regarding the study selection process were resolved by face to face discussion.

2.3. Data extraction

The following data were extracted from the full-text studies of selected articles using a pre-designed abstraction form general features of studies, which are reported in Table 1. When the outcomes were reported at multiple time points throughout a study, only the final results were included in the analysis. When relevant data were not reported, corresponding authors were contacted via e-mail to solicit help. Data extraction was carried out separately by two investigators (SM and MHF) to decrease possible error risk. If nonconformity presented, it was resolved by consensus.

2.4. Quality assessment of studies

The Cochrane Collaboration tool was used for quality evaluation of studies.[30] The tool includes a judgment about the risk of bias and a description of the support for that judgment through a series of items covering different domains of bias. Two authors (SM and AH) separately assessed the quality of the included articles via the Cochrane Collaboration tool.[30] The process of quality evaluation was reported previously.[31,32]

2.5. Meta-analysis of data

To analyze the effect size for BP, the mean change and its standard deviation for both the intervention and control groups (as a comparison group) were extracted. A random effects model was used to calculate weighted mean differences (WMDs) with 95 % confidence intervals (CIs). Between-study heterogeneity was tested by Cochran's Q test and quantified by I^2 statistic. A subgroup analysis according to the trial duration (8 or 12 weeks), artichoke dose intervention ($\leq$1000 or $>$1000 mg/d), weight status (normal weight and overweight or obese), and health status (hypertensive patients and NAFLD patients) was performed to identify possible origination of heterogeneity. Between subgroup heterogeneity was evaluated by a fixed-effect model. Sensitivity analysis was carried out by omitting each study one by one and recalculating the pooled effects. Begg's rank correlation test and Egger's regression asymmetry test were conducted for identifying potential publication bias. Statistical analysis was performed using STATA, version 11.2 (Stata Corp, College Station, TX). Statistical significance was defined as P values <0.05.

3. Results

3.1. Selection and identification of studies

Out of the original 538 studies that were detected via a systematic search, 135 were removed due to being duplicate records, and 427 were eliminate because, based on our eligibility criteria, they were unrelated to the current study (Fig. 1). After evaluating the full text of the remaining 21 studies, 11 articles did not meet the inclusion criteria. Overall, eight eligible clinical trials with eight intervention arms were selected for our analysis.[19,21–24,26–28] Two articles were excluded from quantitative assessment [33,34] because they used the same study population as another study.[24]

3.2. Characteristics of studies

The main features of the detected articles in this study are mentioned in Table 1. Generally, fifteen effect sizes were obtained from eight RCTs which were conducted on a total of 512 individuals (275 participants in

Table 1
Main characteristics of included studies.

First author (publication year)	Country	Sample size (Intervention/ Control)	Target Population	Mean Age (Intervention/ Control)	Mean BMI (Intervention/ Control)	RCT design (Blinding)	Duration (Weeks)	Form and dose of intervention	Comparison	Results
Roghani-Dehkordi et al (2009)	Iran	107 (74/33)	Hypertensive Patients	43.8 ± 1.4/43.7 ± 1.3	24.1 ± 0.7/ 24.8 ± 0.6	Parallel (None)	12	Artichoke leaf juice 100 mg/day	Placebo (NR)	Use of artichoke juice concentrate may have a BP-lowering effect in mild hypertension
Talebi Pour et al (2015)	Iran	60 (30/30)	Patients with NAFLD	38 ± 8/35 ± 7	27 ± 4/27 ± 3	Parallel (None)	8	Artichoke powder - 1000 mg/day	Placebo (Metformin)	Artichoke powder supplementation significantly decreases SBP and DBP compared to metformin
Rangboo et al (2016)	Iran	60 (30/30)	Patients with Nonalcoholic Steatohepatitis	47.27 ± 8.12 / 49.83 ± 12.79	NR	Parallel (Double)	8	Artichoke leaf extract - 2700 mg/day	Placebo (NR)	Artichoke leaf extract supplementation did not change SBP and DBP in comparison to placebo
Panahi et al (2018)	Iran	90 (49/41)	Patients with NAFLD	45.2 ± 11.8 /47.1 ± 10.5	29.4 ± 4.1 / 28.9 ± 3.5	Parallel (Double)	8	Artichoke leaf extract - 600 mg/day	Placebo (NR)	Artichoke leaf extract supplementation significantly changed SBP compared to placebo
Ebrahimi-Mameghani et al (2018)	Iran	68 (33/35)	Patients with MetS	38.7 ± 7.6 /39.1 ± 6.2	35.3 ± 4.3/ 33.3 ± 4.0	Parallel (Double)	12	Artichoke leaf extract - 1800 mg/day	Placebo (NR)	Artichoke leaf extract supplementation did not change SBP and DBP in comparison to placebo
Cicero et al (2018)	Italy	40 (20/20)	Hypercholesterolemic Patients	53.8 ± 2.5/ 52.4 ± 2.7	24.3 ± 1.8/ 23.7 ± 2.1	Parallel (Double)	8	Dry Extract of Artichoke and Berberis - 500 mg/day	Placebo (NR)	Artichoke leaf extract supplementation did not change SBP and DBP in comparison to placebo use
Ahn et al (2018)	Korea	47 (22/25)	Type 2 diabetics	54.4 ± 1.31/ 56.0 ± 1.28	23.8 ± 0.63/ 24.6 ± 0.50	Parallel (Double)	12	Artichoke and fermented soybean powder mixture (19.45 g/d each)	Placebo (NR)	Artichoke and fermented soybean powder supplementation did not change SBP and DBP in comparison to placebo
Ardalani et al (2020)	Iran	40 (20/20)	Hypertensive Patients	58.33 ± 6.66/ 56.21 ± 8.25	28.50 ± 1.41/ 29.05 ± 1.88	Parallel (Double)	8	Artichoke leaf powder - 500 mg/day	Placebo (NR)	Artichoke leaf powder supplementation significantly changed DBP compared to placebo

BP: Blood pressure, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, NR: not reported, MetS: metabolic syndrome, NAFLD: Non-alcoholic fatty liver disease.

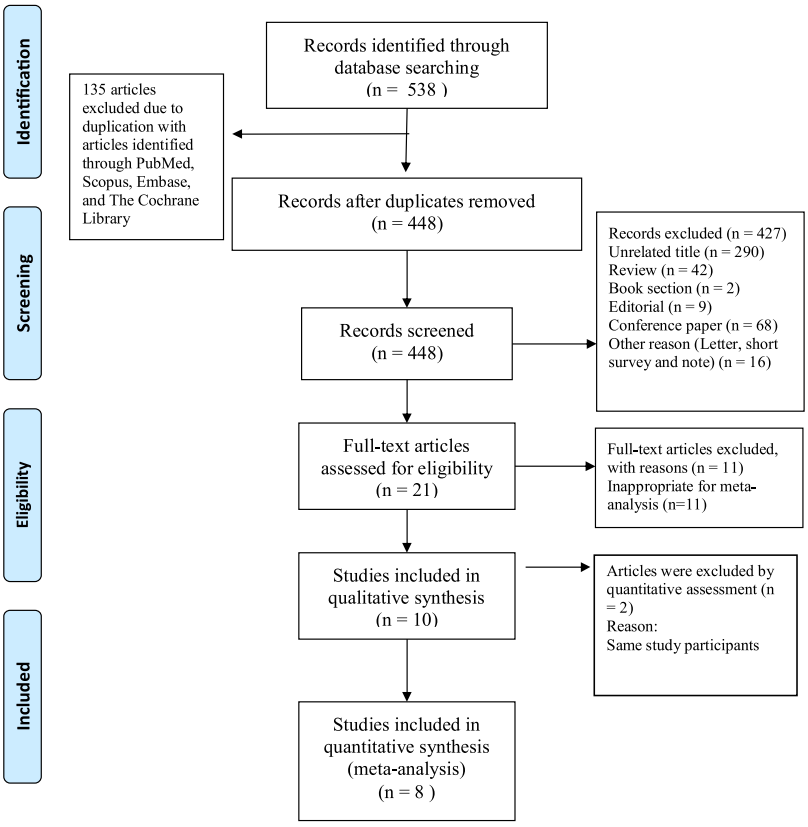

Fig. 1. PRISMA flowchart describing the study's systematic literature search and study selection.

the artichoke intervention group and 237 individuals in the control group). The mean age of subjects among included articles was from 35 to 58 years. These RCTs were carried out in NAFLD patients,[21,22] nonalcoholic steatohepatitis patients,[27] hypertensive patients,[19,26] type 2 diabetics,[28] hypercholesterolemic patients,[23] and metabolic syndrome participants.[24] All included studies used a parallel study design. These RCTs were published between 2009 and 2020. The studies were carried out in Iran,[19,21,22,24,26,27,34] Italy,[23] and Korea.[28] The dose of artichoke ranged from 100 mg/day to 19.45 g/day. The length of study duration varied from 8 to 12 weeks. Based on Cochrane scores, seven studies were categorized as high-quality studies (score ≥ 3),[19,21,23,24,27,28,34], and two were categorized as low-quality studies (score < 3[22,26] (Table 2).

3.3. Meta-analysis of data

3.3.1. Effects of artichoke on systolic blood pressure

Pooling nine RCTs (nine treatment arms) together did not show any significant change in systolic blood pressure (SBP) (WMD: -0.77 mmHg, 95 % CI: -2.76 to 1.22) compared to the control group (Fig. 2). High heterogeneity was found among the studies ($I^2 = 97.8$ %, $P < 0.001$). We found weight and health status were a source of heterogeneity. Subgroup analyses according to health status suggested that artichoke administration among hypertensive patients significantly decreased SBP (WMD: -3.19 mmHg, 95 % CI: −3.32 to −3.06), but not among NAFLD patients (WMD: −0.14 mmHg, 95 % CI: −3.53 to 3.24). Other subgroup analyses did not show a significant effect of artichoke administration on SBP (Table 3).

3.3.2. Effects of artichoke on diastolic blood pressure

In the same nine studies, artichoke administration did not produce a significant effect on diastolic blood pressure (DBP) (WMD: -0.11 mmHg, 95 % CI: −1.72 to 1.50) compared to the control group (Fig. 3). High heterogeneity was found among the studies ($I^2 = 97.8$ %, $P < 0.001$). Subgroup analyses indicated that weight and health status as well as trial duration were sources of heterogeneity. Our results indicated artichoke supplementation for 12 weeks led to significantly decreased

Table 2
Quality assessment.

Study	Random Sequence Generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Roghani-Dehkordi et al (2009)	+	?	–	–	+	?	–
Talebi Pour et al (2015)	+	+	–	–	?	?	–
Rangboo et al (2016)	+	+	+	–	–	+	?
Panahi et al (2018)	+	+	+	–	–	+	?
Ebrahimi-Mameghani et al (2018)	+	+	+	+	–	?	–
Cicero et al (2018)	+	–	+	+	?	+	–
Ahn et al (2018)	+	+	+	+	+	–	+
Ardalani et al (2020)	+	+	+	+	+	?	–

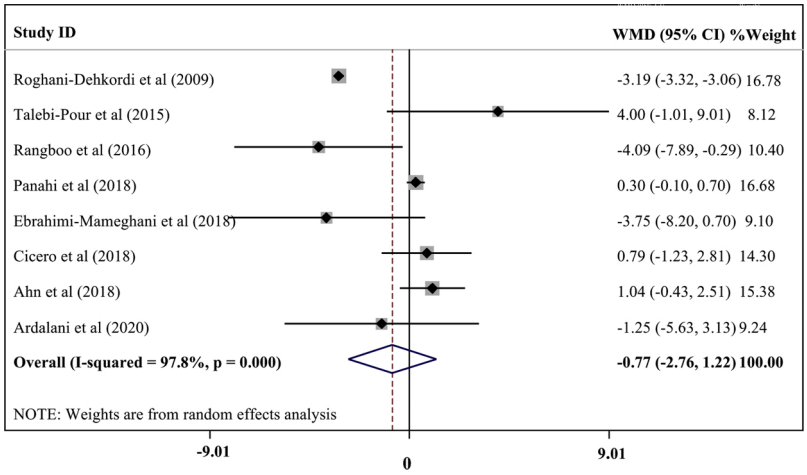

Fig. 2. Forest plot of the comparison of the effects of artichoke supplementation versus placebo on systolic blood pressure.

Table 3
Subgroup analyses of artichoke supplementation on blood pressure.

	NO	WMD (95 %CI)	P heterogeneity	I^2
Subgroup analyses of artichoke supplementation versus placebo on systolic blood pressure				
Trial duration (weeks)				
8	6	−0.75 (−2.93, 1.43)	<0.001	98.1 %
12	3	−1.76 (−5.16, 1.63)	<0.001	93.7 %
Artichoke Dose (mg)				
≤1000	4	−0.86 (−3.47, 1.76)	<0.001	98.9 %
>1000	4	−0.68 (−4.05, 2.68)	0.01	73.6 %
Weight status				
Normal weight	3	0.08 (−3.76, 3.91)	<0.001	94.9 %
Overweight or obese	4	0.12 (−0.9, 1.13)	0.27	22.4 %
Health Status				
Hypertensive Patients	**3**	**−3.19 (−3.32, −3.06)**	**0.66**	**0.0 %**
NAFLD Patients	3	−0.14 (−3.53, 3.24)	0.02	72.3 %
Subgroup analyses of artichoke supplementation versus placebo on diastolic blood pressure				
Trial duration (weeks)				
8	6	0.80 (-1.06, 2.66)	<0.001	82.7 %
12	**3**	**−2.33 (−2.43, −2.23)**	**0.54**	**0.0 %**
Artichoke Dose (mg)				
≤1000	4	−0.73 (−2.66, 1.2)	<0.001	98.7 %
>1000	4	1.88 (−4.47, 6.63)	<0.001	92.1 %
Weight status				
Normal weight	3	2.22 (−6.92, 11.66)	<0.001	97.5 %
Overweight or obese	4	0.07 (−0.56, 0.69)	0.31	15.1 %
Health Status				
Hypertensive Patients	**3**	**−2.33 (−2.23, −2.43)**	**0.45**	**0.0 %**
NAFLD Patients	3	1.73 (−2.18, 5.64)	<0.001	91.1 %

Abbreviations: CI, confidence interval; WMD, weighted mean differences; NAFLD, Non-alcoholic fatty liver disease.

DBP (WMD: -2.33 mmHg, 95 % CI: −2.43 to −2.23), but not when supplementation only lasted 8 weeks (WMD: 0.80 mmHg, 95 % CI: −1.06 to 2.66). Furthermore, subgroup analyses according to health status revealed that artichoke supplementation reduced DBP in hypertensive patients (WMD: −2.33 mmHg, 95 % CI: −2.23 to −2.43) but not NAFLD patients (WMD: 1.73 mmHg, 95 % CI: −2.18 to 5.64). Other subgroup analyses did not show differing effects of artichoke administration on DBP (Table 3).

3.3.3. Publication bias and sensitivity analysis

The sensitivity analysis indicated that evaluated effect sizes were not changed after omitting each effect size. Moreover, the outcome of Begg's test suggested no publication bias for SBP (P = 0.621) or DBP (P = 0.652). Similarly, Egger's test revealed no publication bias for SBP (P = 0.229) or DBP (P = 0.213).

4. Discussion

To the best of our knowledge, this meta-analysis with systematic review is the first to determine whether current evidence suggests a role for artichoke to reduce BP. In this study, we have compiled the evidence from eight RCTs, including 512 subjects, for meta-analysis. While artichoke supplementation is not supported for a global reduction in BP, our study suggests that artichoke supplementation may lower SBP and DBP among hypertensive patients, but to reduce DBP, the duration may need to be at least 12 weeks.

While previous reviews have not considered the efficacy of artichoke on BP, the role of artichoke in the improvement of lipid profiles has been previously reviewed,[35] where researchers concluded that artichoke can improve lipid profiles, thereby improving the cardiovascular risk profile. Here, we suggest for the first time, upon meta-analysis, that artichoke may also have an anti-hypertensive effect on BP among hypertensives, or those who are most in need of a reduction in BP. Therefore, the available literature indicates that artichoke supplementation may improve cardiovascular health, and because of the role of hypertension in various diseases,[2,3,36] may also reduce risk of multiple diseases.

Several components found within artichokes could give potential mechanistic insight into the anti-hypertensive effects observed in the study. First, artichokes are very rich in antioxidant content.[37] Some of the antioxidants found in artichokes include at least 27 different phenolic compounds,[38] which consist of: mono- and di-caffeoylquinic acid (cynarin and chlorogenic acid), luteolins, cynaroside and caffeic acid, among others.[27] Since oxidative stress has been hypothesized as a major regulator in the pathogenesis of hypertension, reducing oxidative stress may confer a subsequent reduction in BP.[39] Artichoke extracts [40,41] have distinct protective properties that aid against oxidative stress through reductions in intracellular reactive oxygen species (ROS) production and the reduction of oxidized low density lipoprotein (ox-LDL) in human cells.

Additionally, luteolin and cymaroside have been shown to increase eNOS promoter activity as well as eNOS mRNA expression, which resulted in a subsequent increase in NO production.[42] NO deficiency contributes to increased BP,[43] so an increase in NO could help remedy these effects. Thus, the polyphenols and antioxidants found in artichokes may regulate BP through their free radical scavenging abilities or their capacity to influence NO production.

Additionally, another potent mechanism of artichoke administration that could contribute to the BP lowering effects could be the endothelial

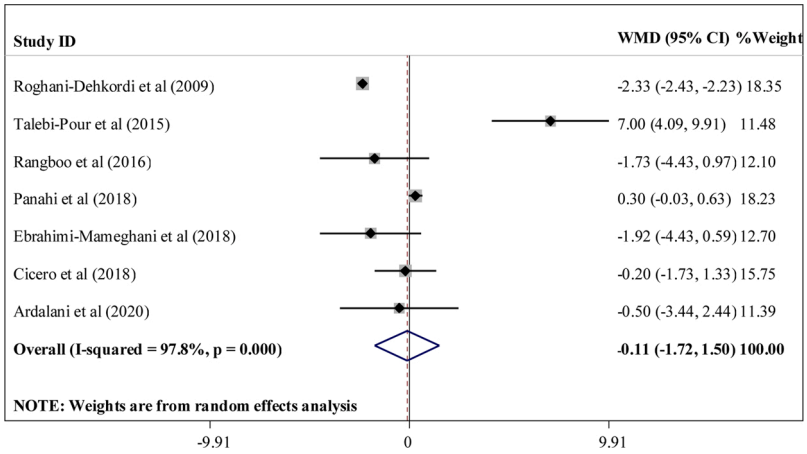

Fig. 3. Forest plot of the comparison of the effects of artichoke supplementation versus placebo on diastolic blood pressure.

protection due to modulation of inflammatory factors.[40,41,44,45] Miláčková et al.[40] suggested that artichoke leaf extract reduced the expression of the inflammatory enzymes associated with Cyclo-oxygenase 2 (COX-2) and matrix metalloproteinase 2 (MMP-2), likely by inhibiting the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in human cells. Majeed et al.[45] also demonstrated that artichoke extract administration led to a significant reduction in serum concentration of interleukin-6 (IL-6) and Complement C3a that was present with acute inflammation in Wistar rats. Hence, the beneficial effects of artichoke on inflammation and oxidative stress,[40,45]which are risk factors for cardiovascular disease and hypertension,[46,47]could suggest the use of artichoke to improve cardiovascular function.

Furthermore, artichokes are rich in prebiotics, namely inulin and fructooligosaccharides. Prebiotics are non-digestible and pass through the acidic portion of the upper gastrointestinal tract as substrates to the lower gastrointestinal tract. The anti-hypertensive properties of artichoke may also be connected to the anti-cholesterolemic effects which include decreased plasma concentrations of total cholesterol, LDL, and triglycerides.[48] The insoluble prebiotics reaching the lower gastrointestinal tract may inhibit cholesterol and bile absorption through enhancing the viscosity of chime in the small intestine.[49] As prebiotics bind bile acids and reduce solubilized cholesterol, cholesterol is reduced.[49] This can contribute to an overall reduction in large artery stiffening, thereby lowering BP.[49] However, the mild lipid-lowering effects of various nutraceuticals [50,51] may not be potent enough to produce this kind of effect on BP. Another potential mechanism by which prebiotics may exert their effects on BP is through the attenuation of insulin resistance, as prebiotics have been shown to decrease post-prandial insulin secretion and improve glucose response.[52] Insulin resistance is associated with reduced endothelium-dependent vasodilation, which plays a role in BP.[53] Furthermore, prebiotics have been shown to increase calcium absorption in the gastrointestinal tract with a concomitant, associated reduction in BP.[54] Therefore, prebiotics may stimulate anti-hypertensive effects through exerting anti-hypercholesterolemic effects, attenuating insulin resistance, or increasing calcium absorption.

The goal of this present review was to determine whether artichokes and artichoke supplementation are effective in reducing BP. While we have speculated on the mechanisms that lead to reductions in BP based on current evidence, the precise mechanisms were not the focus of this review and are currently unknown. Mechanistic insight, particularly in humans, needs to be directly studied to elucidate the processes by which artichoke supplementation reduces BP among hypercholesterolemic patients. In addition, the degree of SBP and DBP reduction is mild and only observed among hypertensive patients. Due to the current definition of hypertension and recommended targets for blood pressure, it is unlikely that artichoke supplementation would normalize SBP and DBP. Thus, the need for pharmacological therapies would likely remain in most patients.

5. Strengths and limitations

The current study is the first meta-analysis to evaluate the efficacy of artichoke on BP. We conducted a comprehensive search based on the PRISMA guidelines. Most of the assessed articles in the peresent study were of high quality. We used conservative statistical approaches and included sensitivity and subgroup analyses to detect any impact of trial duration, artichoke dose intervention, weight status, and health status on the overall effect estimates. However, there are some limitation in the present meta-analysis that should be discussed. At first, significant heterogeneity was observed in the meta-analysis. However, subgroup analyses were conducted to detect the potential origination of heterogeneity. Secondly, the results of the current study are supported by several previous studies. Thus, care has been taken to reduce potential limitations, but results should be interpreted with some caution.

6. Conclusion

In conclusion, artichokes reduce SBP and DBP in our meta-analysis. However, these effects may be contained to hypertensive patients, and DBP may only be reduced when the supplementation period is at least 12 weeks in duration. Similar effects were not seen in NAFLD patients. Further work is needed to understand the mechanisms that result in this reduction in BP, but the antioxidants, polyphenols, and prebiotics found in artichokes are likely contributors based on current evidence.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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None.

Appendix A. Supplementary data

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