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Review Article

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Flaxseed Lowers Blood Pressure in Hypertensive Subjects: A Meta-Analysis of Randomized Controlled Trials

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

This systematic review and meta-analysis study aimed to evaluate the effectiveness of flaxseed supplementation on blood pressure (BP) in patients with hypertension based on the data from randomized clinical trials (RCTs). Three databases (PubMed [MEDLINE], Scopus, and ISI Web of Science) were searched from inception up to August 10, 2024. Relevant studies meeting our eligibility criteria were obtained. A random-effects model was used to estimate pooled weighted mean differences (WMDs) with 95% confidence intervals (CIs). The methodological quality of individual studies was assessed using the Cochrane Collaboration risk of bias tool. A total of 5 studies were included and analyzed using STATA software version 12. The results show that there is a significant decrease in systolic BP (WMD, −8.64 mmHg; 95% CI, −15.41 to −1.87; $p \leq 0.001$) and diastolic BP (WMD, −4.87 mmHg; 95% CI, −8.37 to −1.37; $p = 0.006$) of patients with hypertension as compared to control groups. This study supported that flaxseed supplementation had favorable effects on BP control in hypertensive patients. It may be a promising adjuvant therapy for patients with hypertension.

Keywords: Flaxseed; Hypertension; Blood pressure; Systematic review; Meta-analysis

INTRODUCTION

According to the American Heart Association reports, hypertension is a known risk factor for cardiovascular diseases (CVDs), which are the leading cause of death globally [1]. In addition, hypertension is linked to an increased risk of other non-communicable diseases such as chronic kidney disease and neurodegeneration. Based on reports, 25% of adults worldwide suffer from high blood pressure (BP), and this percentage is expected to increase to 29% by 2025 [2]. Generally, several types of drugs, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and thiazide diuretics, are recommended as first-line antihypertensive medications [3]. However, these drugs often have side effects and may lead to patient complaints [4]. Diet management is the cornerstone of managing hypertension and related complications. First, they may reduce the burden on healthcare systems with limited resources where access to and affordability of medication is often restricted. Second, individuals may be more

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Conceptualization: Fazeli Moghadam E, Shekarchizadeh-Esfahani P. Formal analysis: Shekarchizadeh-Esfahani P. Investigation: Fazeli Moghadam E, Khaghani L, Shekarchizadeh-Esfahani P. Methodology: Fazeli Moghadam E, Khaghani L, Shekarchizadeh-Esfahani P. Supervision: Shekarchizadeh-Esfahani P. Writing - original draft: Fazeli Moghadam E, Khaghani L, Shekarchizadeh-Esfahani P. Writing - review & editing: Fazeli Moghadam E, Khaghani L, Shekarchizadeh-Esfahani P.

willing to consume bioactive foods or nutritional supplements instead of antihypertensive medications due to the lower risk of side effects [5,6]. Dietary interventions such as reducing sodium intake, increasing consumption of fruits and vegetables, increasing consumption of dairy products, and decreasing saturated fat intake have been considered the primary treatment for high BP [7-9]. Exercise is also globally recommended as a first-line approach for treating hypertension [10]. Despite the positive impact of lifestyle changes on BP and the effectiveness of antihypertensive medications, control rates for hypertension are still not optimal [11]. For a long time, traditional remedies, particularly herbal medicine, have been embraced by societies for controlling BP [12]. As a result, researchers have increasingly focused on investigating this issue in recent years [13]. One herbal product with various health effects is flaxseed.

Flaxseed, scientifically named *Linum usitatissimum*, is a functional food and a member of the family Linaceae [14]. It has been used for centuries for various purposes such as drying oil in painting, varnishing, and for medical conditions including abdominal pain, urinary tract infections, respiratory disorders, constipation, and skin inflammation [15]. The seeds and compounds within them are known for their health benefits in reducing risks associated with heart disease, cancer, stroke, diabetes, and metabolic syndrome [16]. This is mainly due to the high content of α-linolenic acid (ALA), phytoestrogen, phenolic compounds, dietary fiber, and lignans found in flaxseed [17,18]. The beneficial effects of flaxseed include improving anthropometric indices [19], lipid and blood sugar levels [20,21], reducing inflammation [22], improving liver enzymes [23], and increasing the body's antioxidant power [24], as demonstrated in meta-analyses. In recent years, randomized controlled trials (RCTs) have shown inconsistent results regarding the effect of flaxseed on BP. Some studies have indicated a positive impact on BP, while others have not found significant effects [25-29].

Due to the inconsistent findings and the lack of a comprehensive meta-analysis specifically focusing on patients with hypertension, we aimed to gather all existing RCTs to evaluate the effectiveness of flaxseed supplementation on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with hypertension.

MATERIALS AND METHODS

The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [30] and the Population, Intervention, Comparison, Outcome, and Setting (PICOS) criteria. The primary outcomes were SBP and DBP. There were no additional secondary outcomes.

Search strategy

A comprehensive literature search was conducted by 2 investigators from the earliest available date until August 10, 2024, in the three databases: PubMed (MEDLINE), Scopus, and ISI Web of Science. We searched using the following MeSH and free words: ("flax" OR "flaxseed" OR "ground flaxseed" OR "whole flaxseed" OR "flaxseed oil" OR "lignan" OR "*Linum usitatissimum*" OR "linseed)") AND ("hypertension" OR "hypertensive" OR "blood pressure") AND ("Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment"). This meta-analysis exclusively included articles in English. The wild-card term "*" was used to increase the sensitivity of the search strategy. In addition, a manual search was conducted for potentially relevant papers and the reference lists of relevant papers were analyzed to identify further pertinent studies. A search for gray literature was also carried out to identify unpublished studies that could potentially be included in the review. Additionally, we reached out to specialized authors in this field via email to request introductions to relevant studies. **Supplementary Table 1** displays the standardized search strategy used for the databases.

Study selection

Two investigators blinded to each other's results screened the titles and abstracts for duplicate studies and eligibility. Subsequently, the same authors screened full-text articles, and disagreements were resolved by discussion until a consensus was reached. Articles were included if they met all of the following inclusion criteria (PICOS): 1) Population: the participants must be hypertensive adults aged over 18 years; 2) Intervention: the trials must have investigated the use of flaxseed as an intervention for at least 1 week; 3) Comparison: the use of placebo or a comparison group is required; 4) Outcome: the outcomes reported must include SBP or DBP; 5) Setting: the study must be an RCT with either a parallel or crossover design. Animal tests, reviews, or experimental studies were not included. Studies that assessed the effects of flaxseed in combination with other herbs or ingredients as a mixture were not included unless that compound was also prescribed in the control group.

Data extraction and quality assessment

The data extraction and quality assessment were conducted independently by two authors. Any discrepancies were resolved through face-to-face discussion. The authors extracted data regarding the key characteristics of the articles, including the first author's last name, publication year, location of the study, study design, gender, mean age and body mass index (BMI) of participants, total sample size, study duration, dose and type of flaxseed supplementation, and the type of control groups. When data were reported at multiple measurements, only the outcomes at the end of the intervention were included in the analysis. If these characteristics were not reported in available publications, we contacted the corresponding author to obtain the necessary data.

The methodological quality of the selected studies was assessed according to the revised Cochrane risk-of-bias tool for randomized trials [31]. The methodological quality was evaluated with regard to the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other biases. Using this tool, each study was assigned a 'high,' 'unclear,' or 'low' score for each of the mentioned items.

Statistical analysis

The meta-analysis used STATA software version 12 (STATA Corp, College Station, TX, USA). Continuous variables were presented as weight mean difference (WMD) and 95% confidence intervals (CIs). A random effects meta-analysis was performed due to expected heterogeneity. Following formula was used for estimating standard deviation (SD) of mean difference: $(\text{SD Pre-intervention})^2 + \{(\text{SD Pre-intervention})^2 - (2R \times \text{SD Pre-intervention} \times \text{Post-intervention})\}$; assuming a correlation coefficient (R) = 0.5. If the required data were not reported in available publications, we contacted the corresponding author to obtain it. The I-squared (I^2) index was used to measure heterogeneity, with values of 0%–30% indicating low heterogeneity, more than 30%–60% indicating moderate heterogeneity, and more than 60% indicating high heterogeneity [32]. Subgroup analyses were carried out to assess the impact of different factors on the results and also find the source of heterogeneity.

Sensitivity analysis was conducted using the one-study removal method. Additionally, publication bias was evaluated using Egger's regression asymmetry test, with statistical significance set at $p < 0.05$ unless otherwise specified.

RESULTS

Selection of studies

The database search found 387 publications, and we obtained one additional article by manually searching the references of the included RCTs. After excluding 121 duplicate records, we were left with 266 articles for screening. Upon screening the titles and abstracts, 246 articles were further excluded. The full texts of the remaining 20 potentially relevant studies were assessed according to the inclusion and exclusion criteria. Finally, we included five RCTs [25-29] in this systematic review and meta-analysis. The PRISMA flow diagram of the study process is presented in **Figure 1**.

Study characteristics

The main characteristics of the included studies are shown in **Table 1**. The publication dates of the eligible studies ranged between 2013 and 2024. In total, 388 hypertensive patients were enrolled in selected articles. These studies were carried out in Iran, China, Canada, and Nepal. All studies adopted a parallel design and were performed in both genders. The mean age of the participants ranged from 43 to 66 years old. The follow-up period ranged from 8 to 24 weeks. The daily recommended dosage of flaxseed varied between 500 mg/day and 36 g/day in these studies. The details of quality assessment in individual studies are provided in **Table 2**.

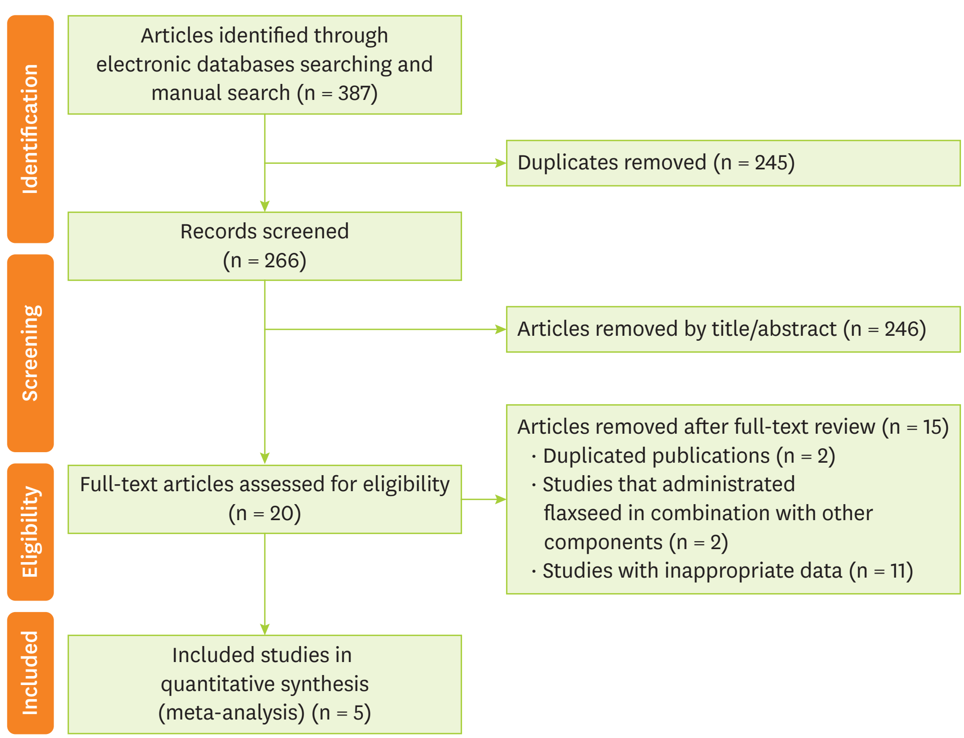

Figure 1. Flow chart of the process of the study selection.

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Table 1. Baseline characteristics of included studies

First author (publication year)	Region	Sample size	RCT design	Gender	Mean age (yr)	Course (wk)	Intervention (name and daily dose)	Control
Rodriguez-Leyva (2013) [26]	Canada	86	Parallel	Both	66	24	30 g/day milled flaxseed	Placebo
Haghighatsiar (2019) [25]	Iran	80	Parallel	Both	43	8	36 g/day flaxseed sachet	Placebo
Yang (2019) [29]	China	74	Parallel	Both	57	12	2.5 g/day flaxseed oil	Corn oil
Toulabi (2021) [27]	Iran	76	Parallel	Both	52	12	10 g/day flaxseed	Placebo
Verma (2024) [28]	Nepal	72	Parallel	Both	55	13	Amlodipine 5 mg + Flaxseed capsule 500 mg	Amlodipine 5 mg + Placebo

RCT, randomized controlled trial.

Table 2. Quality assessment of included studies based on Cochrane guidelines

First author (publication year)	Random Sequence Generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Rodriguez-Leyva (2013) [26]	Low	Low	Low	High	Low	Unclear	Unclear
Haghighatsiar (2019) [25]	Low	Low	Low	Low	Low	Unclear	Unclear
Yang (2019) [29]	Low	Low	Low	Low	Low	Low	Unclear
Toulabi (2021) [27]	Low	Low	Low	Low	Low	Low	Low
Verma (2024) [28]	Low	Low	Low	High	Low	Unclear	Unclear

Meta-analysis findings

The effects of flaxseed supplementation on SBP

The combination of findings from 5 studies [25-29] showed a significant reduction in SBP levels after flaxseed supplementation (WMD, −8.64 mmHg; 95% CI, −15.41 to −1.87; $p \leq 0.001$). However, there was significant heterogeneity between the studies ($I^2 = 95.0\%$; $p < 0.001$) (**Figure 2**). A subgroup analysis suggested that the duration of the studies and the mean age of the participants could be potential sources of this heterogeneity. In addition, the reduction effect of flaxseed on SBP remained significant in all subgroups except for the trials with a duration of ≤ 12 weeks (WMD, −6.78 mmHg; 95% CI, −16.26 to 2.70; $p = 0.16$) (**Figures 3** and **4**).

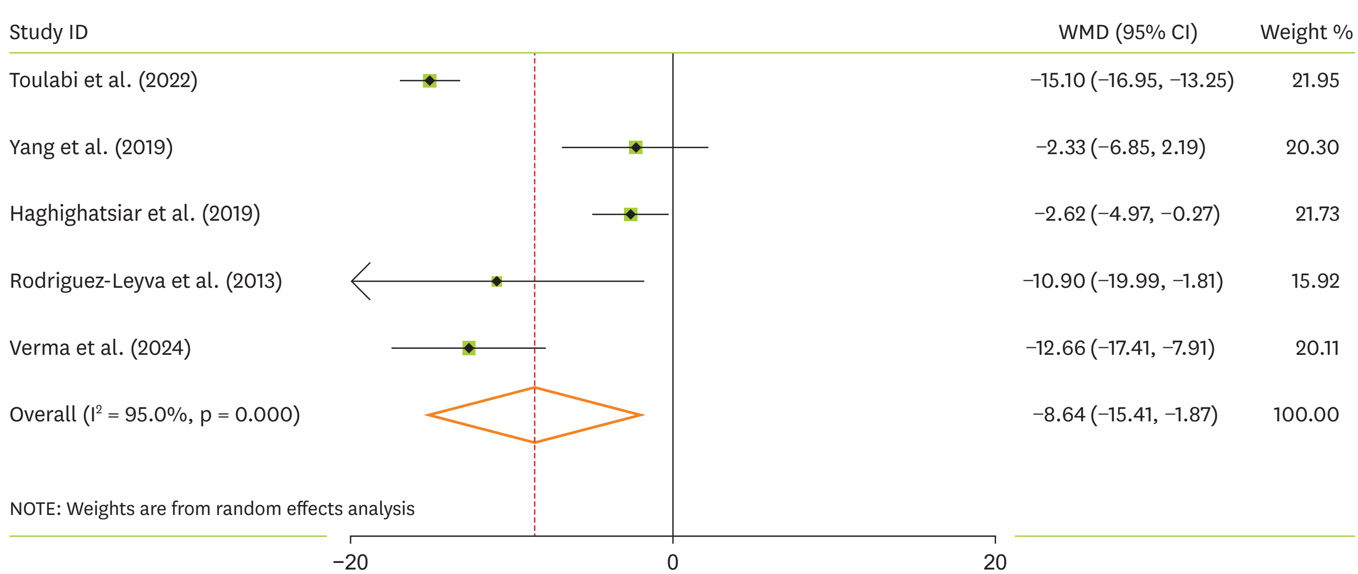

Figure 2. Forest plot of the effect flaxseed supplementation on systolic blood pressure.
WMD, weighted mean difference; CI, confidence interval.

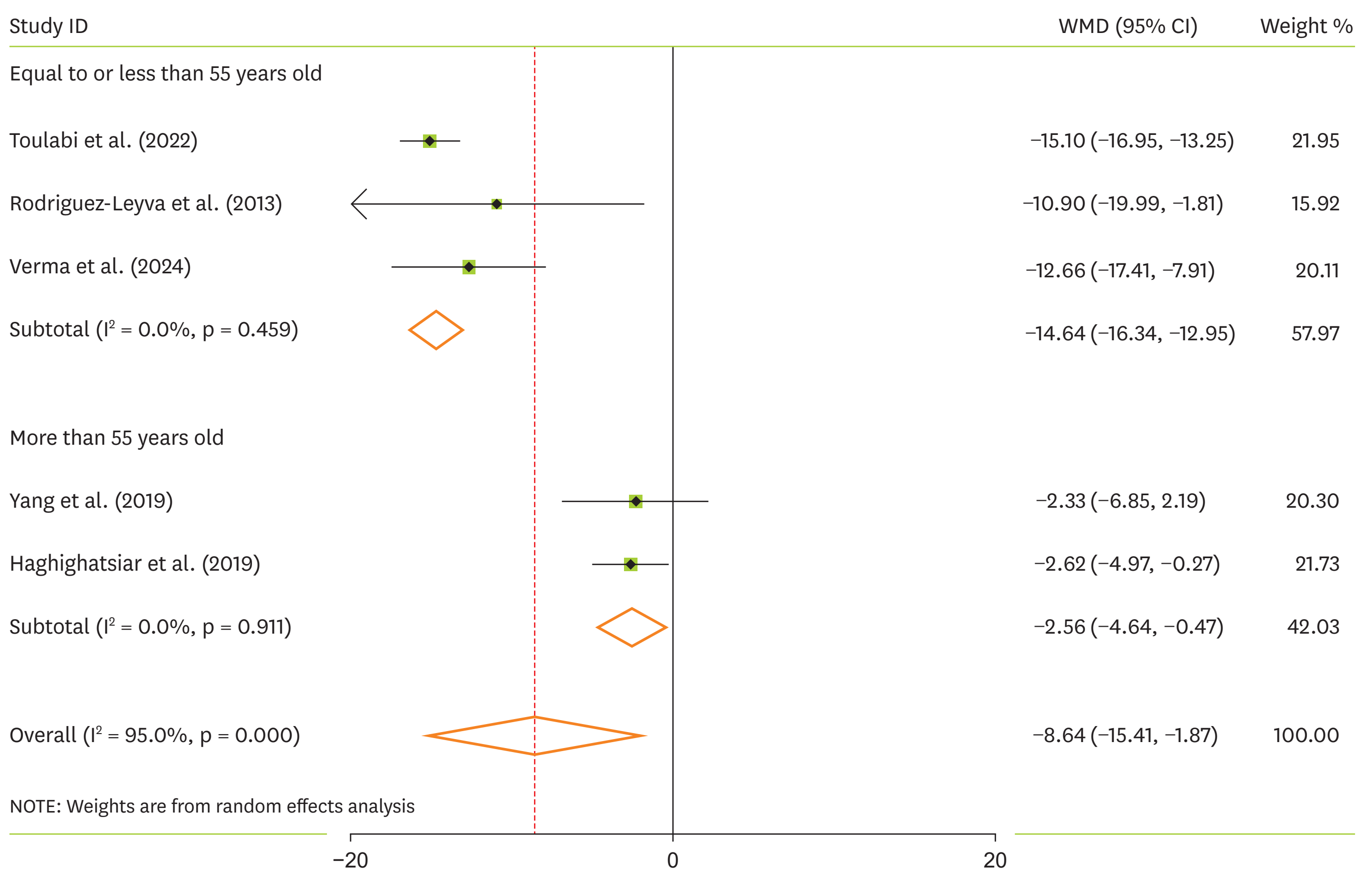

Figure 3. Forest plot showing the impact of flaxseed supplementation on systolic blood pressure based on participants' mean age.
WMD, weighted mean difference; CI, confidence interval.

The effects of flaxseed supplementation on DBP

After analyzing the results of 5 studies [25-29], a significant reduction in DBP levels was observed following flaxseed supplementation (WMD, −4.87 mmHg; 95% CI, −8.37 to −1.37; $p = 0.006$). However, there was significant heterogeneity between the studies ($I^2 = 83.9\%$; $p < 0.001$) (**Figure 5**). A subgroup analysis suggested that only the mean age of the participants could be a potential source of this heterogeneity. Additionally, this decrease was significant only in the subgroup of studies with a duration of more than 12 weeks (WMD, −7.15 mmHg; 95% CI, −10.66 to −3.64; $p < 0.001$) and participants with an age of 55 years or less (WMD, −7.56 mmHg; 95% CI, −9.55 to −5.76; $p < 0.001$) (**Figures 6** and **7**).

Sensitivity analysis and publication bias

The results following the systematic removal of each study did not significantly change the overall effects of flaxseed supplementation on DBP. However, findings from sensitivity analysis showed that the exclusion of the Verma et al.'s study [28], significantly changes the results of the study on SBP (WMD, −7.63 mmHg; 95% CI, −15.80 to 0.53; $p = 0.06$). Egger's regression asymmetry test was conducted to assess publication bias. There was no evidence of publication bias for studies examining the effect of flaxseed supplementation on SBP ($p = 0.68$) and DBP ($p = 0.59$).

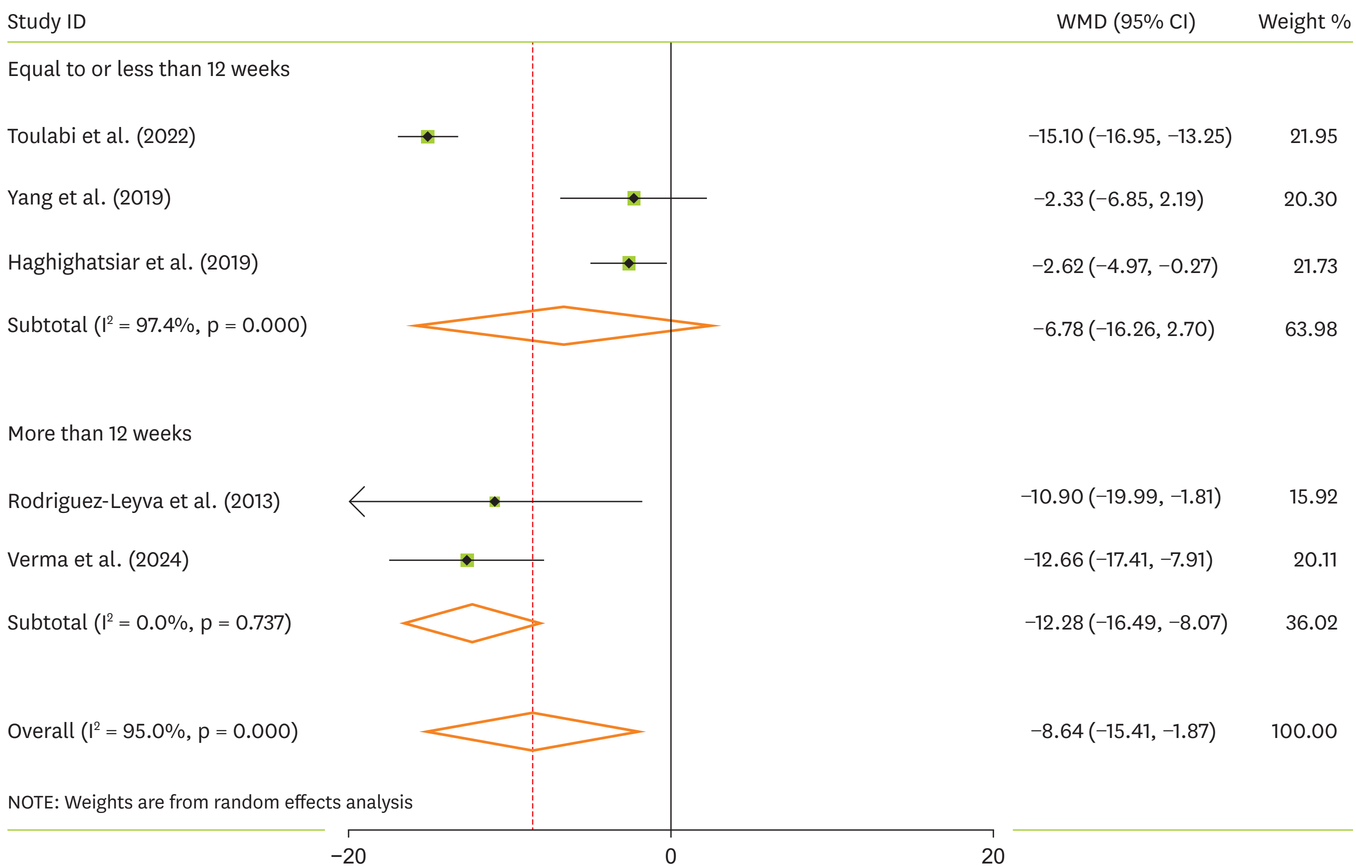

Figure 4. Forest plot showing the impact of flaxseed supplementation on systolic blood pressure across different duration subgroups.
WMD, weighted mean difference; CI, confidence interval.

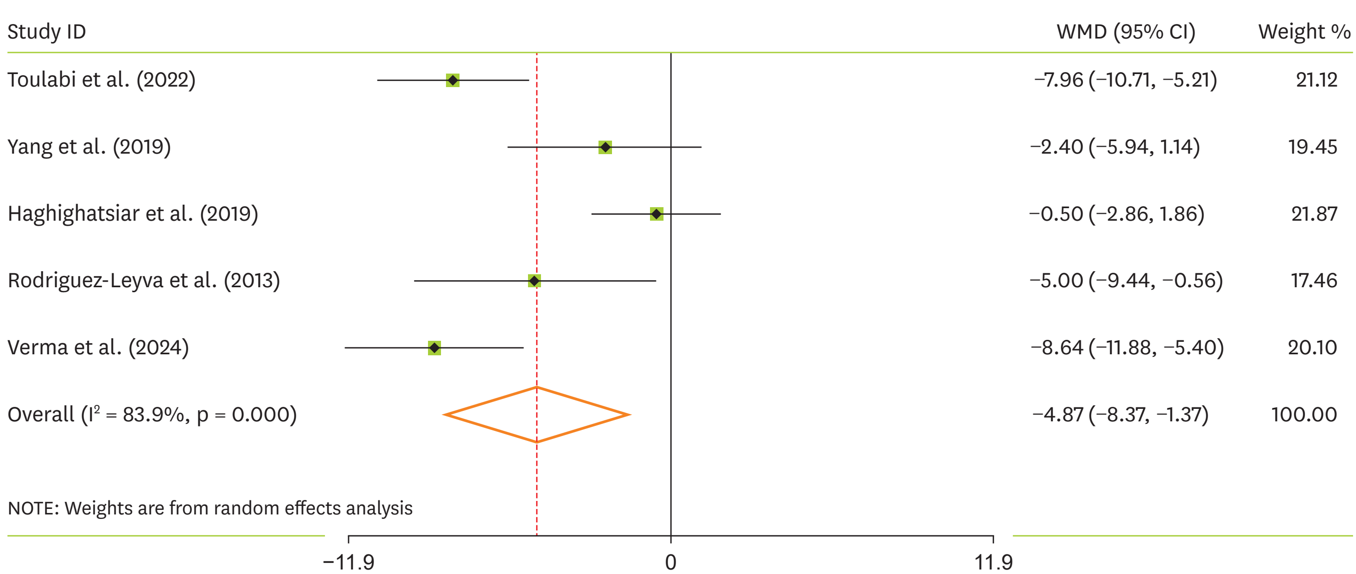

Figure 5. Forest plot of the effect flaxseed supplementation on diastolic blood pressure.
WMD, weighted mean difference; CI, confidence interval.

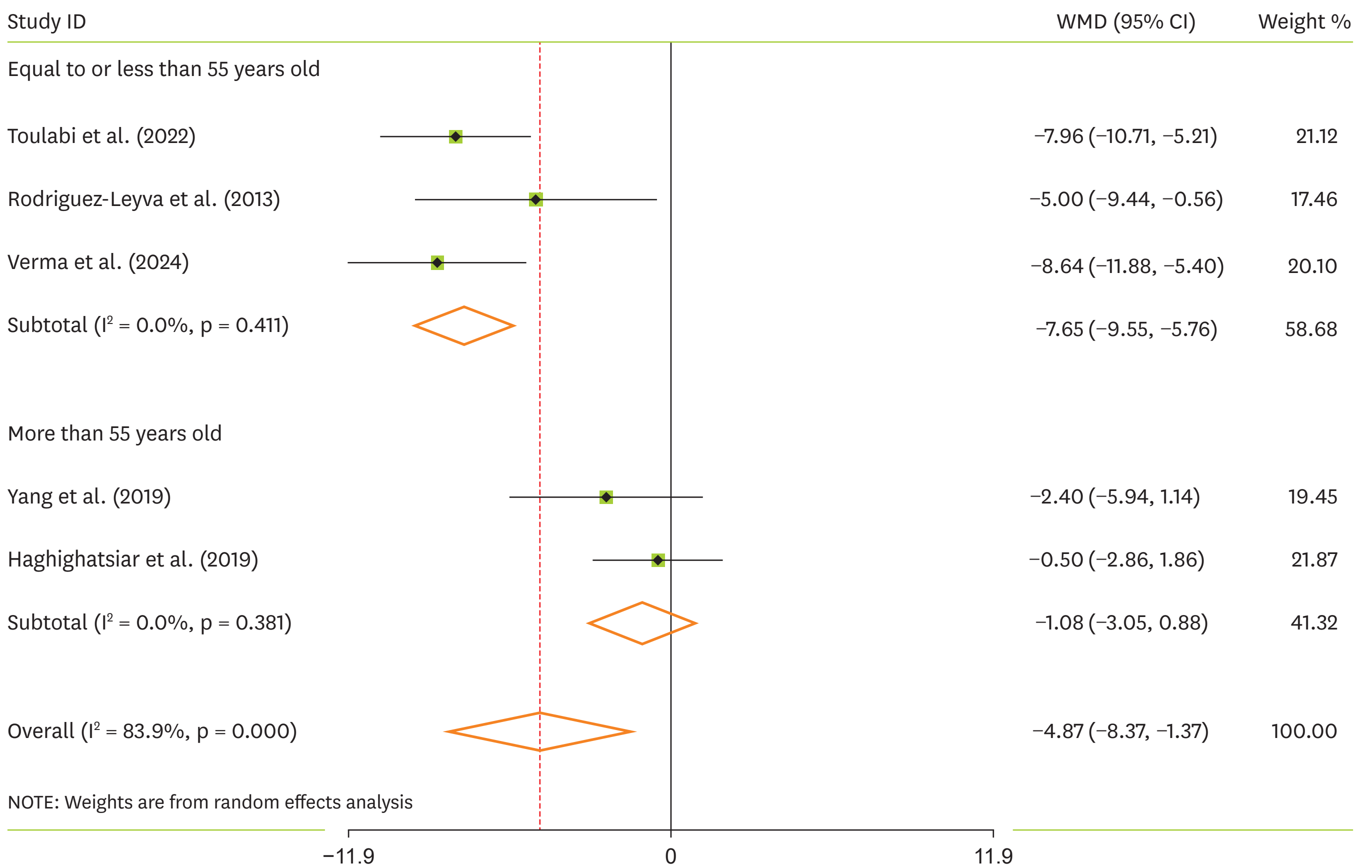

Figure 6. Forest plot showing the impact of flaxseed supplementation on diastolic blood pressure based on participants' mean age.
WMD, weighted mean difference; CI, confidence interval.

DISCUSSION

This meta-analysis aimed to investigate the effects of flaxseed supplementation on SBP and DBP. We included a total of 5 RCTs that examined the impacts of various types of flaxseed supplementation on BP in patients with hypertension. Our findings demonstrated that flaxseed supplementation significantly improved both SBP and DBP in patients with hypertension. Although the subgroup analysis indicated that participant age was the primary source of heterogeneity, the results should be interpreted cautiously due to the high heterogeneity between studies. Sensitivity analysis revealed that the removal of any study did not affect the overall estimates. No evidence of publication bias was observed.

In general, our study and previous meta-analyses [33-36] in the same field have confirmed the SBP-reducing effect of flaxseed. Additionally, we found that flaxseed has a significant inhibitory effect on DBP, which is consistent with three previous systematic reviews [33,35,36]. However, the results from one meta-analysis [34] contradicted ours, as they showed no significant change in DBP after flaxseed supplementation. There may be two reasons for the inconsistent results. One reason is that the number of included studies differs. The other reason is that different types of diseases were included in previous studies. In previous studies, both healthy and unhealthy individuals were analyzed together. Since the disease can significantly affect BP, there was a need for a study focusing solely on

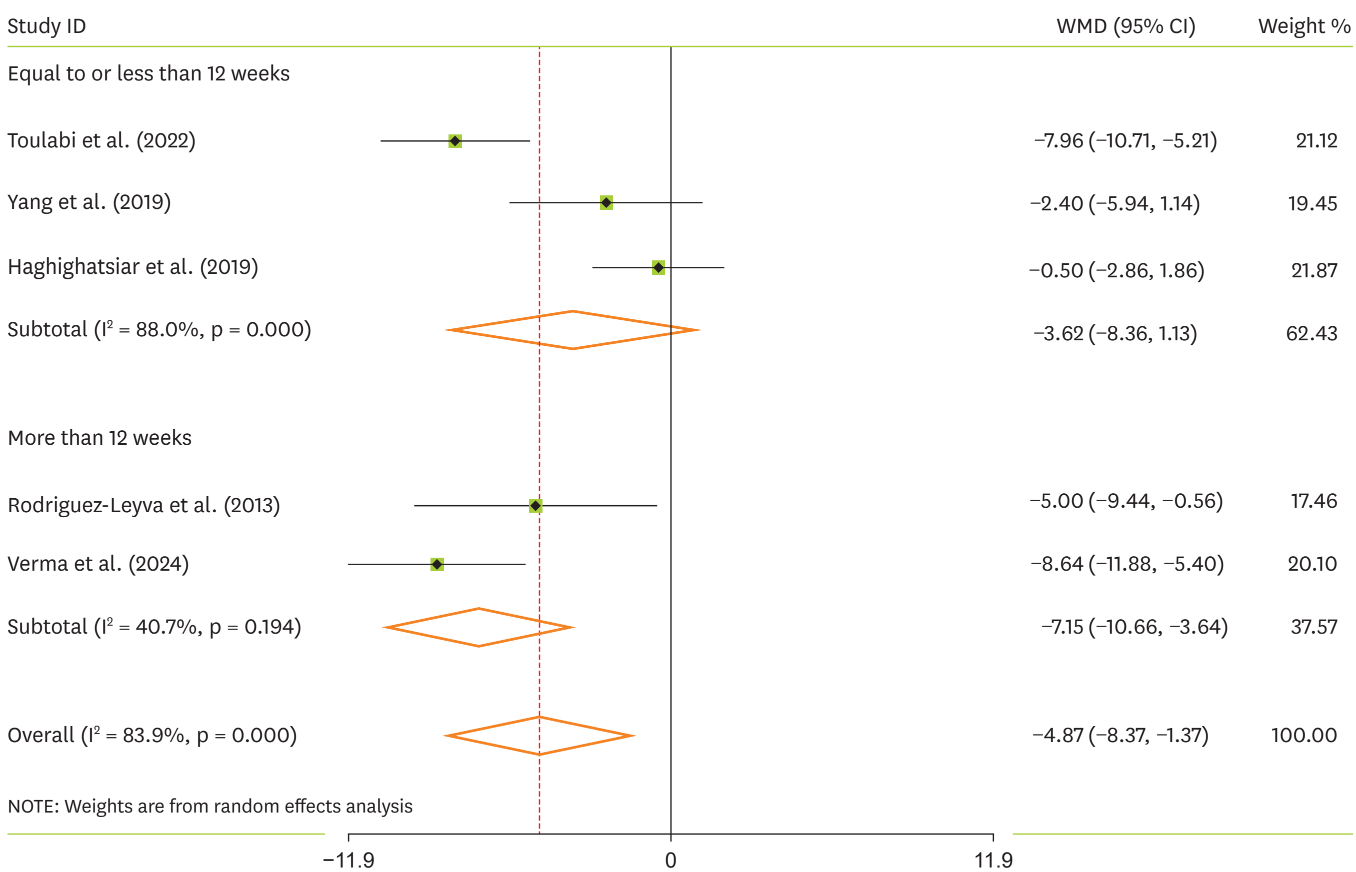

Figure 7. Forest plot showing the impact of flaxseed supplementation on diastolic blood pressure across different duration subgroups.
WMD, weighted mean difference; CI, confidence interval.

hypertensive patients. Additionally, due to the publication of new clinical trials in this area, an update on this issue was necessary.

The precise mechanisms by which flaxseed supplementation affects BP are not fully understood. However, several mechanisms have been proposed. Flaxseed may increase the release of nitric oxide in the body, causing blood vessels to dilate and thereby lowering BP [37]. Additionally, the abundance of compounds with antioxidant properties in flaxseed can improve BP by reducing inflammation and neutralizing free radicals in the body [33,36]. Furthermore, the soluble fibers in flaxseed can regulate blood sugar and lipid levels, as well as reduce anthropometric indices, thereby contributing to improved BP [19,20,21,33,36]. Flaxseed also contains other beneficial compounds such as phytosterols and unsaturated fats that may lead to improvements in BP [33].

A dietary supplement is an affordable, safe, and healthy addition to medical treatment. It can help decrease the number of medications patients need by providing essential vitamins and nutrients. These supplements can serve as complementary therapies for various conditions, particularly hypertension. Furthermore, dietary supplements may reduce drug side effects and enhance patient compliance [38-40]. One notable example is flaxseed, a traditional herbal remedy that has gained significant attention for its potential to improve BP management [41]. The results of this study indicate that consuming flaxseeds can help reduce both systolic and diastolic BP, making it a beneficial option for patients

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with hypertension. Incorporating flaxseeds into one's diet may improve BP control and subsequently lower the risk of heart disease and other conditions associated with high BP.

Regarding the safety of flaxseed supplementation, most of the trials included in the current meta-analysis did not report any significant side effects after treatment with flaxseed, especially in the long term. However, it is important to note that chronic consumption of flaxseed can lead to the following side effects: diarrhea, allergic reactions, and skin irritation [34,42]. Further research is needed before long-term flaxseed administration, especially in conjunction with drugs used in patients with hypertension, can be considered safe.

To our knowledge, our study is the first to conduct a meta-analysis examining the effects of flaxseed supplements on the BP of patients with hypertension, which is our main strength. However, there are some limitations to our study. Firstly, the number of included studies was limited, and those studies used small sample sizes. Additionally, a weakness of our work was the inclusion of different types of flaxseed supplements. We did not register the protocol of the current study on the PROSPERO registry system. This lack of registration might introduce bias to this review. Lastly, confounding factors and their influence were not reported and analyzed in the majority of trials, which precluded their analysis in our study. We suggest that future research should consider the influence of confounding factors such as physical activity and smoking status.

CONCLUSION

In summary, evidence from RCTs suggests that supplementing with flaxseed may help lower both SBP and DBP. However, before recommending flaxseed supplementation for preventing hypertension or as an additional treatment for high BP, further trials with larger sample sizes, longer durations, various flaxseed dosages, and high quality are needed in the future.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Search terms

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