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by Trias Mahmudiono

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REVIEW

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The effect of flaxseed oil consumtion on blood pressure among patients with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized clinical trials

Trias Mahmudiono[1] | Saade Abdalkareem Jasim[2] | Yasir Salam Karim[3,4] | Dmitry Olegovich Bokov[5,6] | Walid Kamal Abdelbasset[7,8] | Kholmurod S. Akhmedov[9] | Ghulam Yasin[10] | Lakshmi Thangavelu[11] | Yasser Fakri Mustafa[12] | Shehla Shoukat[13] | Mazin A.A. Najm[14] | Mohammad Amraei[15]

[1]Department of Nutrition, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia

[2]Al-maarif University College, Medical Laboratory Techniques Department, Al-anbar-Ramadi, Iraq

[3]Department of Pharmacy, Al-Manara College for Medical Sciences, Maysan, Iraq

[4]Department of Pharmacy, Al-Nisour University College, Baghdad, Iraq

[5]Institute of Pharmacy, Sechenov First Moscow State Medical University, Moscow, Russian Federation

[6]Laboratory of Food Chemistry, Federal Research Center of Nutrition, Biotechnology and Food Safety, Moscow, Russian Federation

[7]Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia

[8]Department of Physical Therapy, Kasr Al-Aini Hospital, Cairo University, Giza, Egypt

[9]Professor, Doctor of Medical Sciences, Head of the Department of Internal Diseases No.3, Tashkent Medical Academy, Tashkent, Uzbekistan

[10]Department of Botany, Bahauddin Zakariya University, Multan, Pakistan

[11]Center for Transdisciplinary Research, Department of Pharmacology, Saveetha Dental College, Saveetha Institute of Medical and Technical Science, Saveetha University, Chennai, India

[12]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq

[13]Plant Genomics and Biotechnology, National Institute for Genomics and Advanced Biotechnology, National Agricultural research centre, Islamabad, Pakistan

[14]Pharmaceutical Chemistry Department, College of Pharmacy, Al-Ayen University, Thi-Qar, Iraq

[15]Kuhdasht Health Center, Lorestan University of Medical Sciences, Khorramabad, Iran

Correspondence
Mohammad Amraei, Kuhdasht Health Center, Lorestan University of Medical Sciences, Khorramabad, Iran.
Email: amraie.mohammd69@gmail.com

Abstract

We systematically reviewed randomized clinical trials (RCTs) to elucidate the overall effects of flaxseed oil consumption on blood pressure (BP) in patients with metabolic syndrome and related disorders. PubMed, Scopus, Cochrane Library, and ISI Web of Science databases were systematically searched until March 31, 2020, to find RCTs that examined the effect of flaxseed oil consumption on BP. Weighed mean difference (WMD) was pooled using a random-effects model. Standard methods were used for the assessment of heterogeneity, sensitivity analysis, and publication bias. Meta-analysis of five trials (6 arms) showed significant reductions in systolic (WMD: −3.86 mmHg, 95% CI: −7.59 to −0.13, $p = .04$) BP (SBP) after flaxseed oil consumption. However, the overall effect illustrated no significant change in diastolic (WMD:

−1.71 mmHg, 95% CI: −3.67 to 0.26, $p = .09$) BP (DBP) in the intervention group compared with the control group. Our findings revealed that flaxseed oil consumption has favorable effects on SBP in patients with metabolic syndrome and related disorders. However, further investigations are needed to provide more reliable evidence.

KEYWORDS
blood pressure, flaxseed, hypertension, meta-analysis, systematic review

1 | INTRODUCTION

Hypertension (HTN) is a major risk factor for multiple serious complications such as cardiovascular diseases (CVDs), renal failure, and premature death, which is becoming a worldwide health problem for human beings (Burnier & Egan, 2019; Suhat et al., 2022). The incidence of HT was significantly increased in most countries (37.3% in developed countries and 22.9% in developing countries) owing to rapid urbanization (Guan, Dai, & Wang, 2020). One in four adults worldwide suffers from high blood pressure (BP), and it is estimated that more than 1.5 billion people will have hypertension by 2025 (Council et al., 2013). Different classes of antihypertensive drugs are available; however, good BP control is obtained in less than one-third of patients (Sahebkar, 2014; Saugel & Sessler, 2021). There are still some problems in BP management such as poor medication compliance, medication side effects, and high medication costs (Bumier, Polychronopoulou, & Wuerzner, 2020; Goswami, Sarkar, Bhattacharjee, & Sengupta, 2021; Nies, 1975; Waeber, Burnier, & Brunner, 1999). In recent years, there has been a growing interest and demand for the use of medicinal plants for managing BP reducing the burden of HTN (Ahmad et al., 2018). Previous studies have demonstrated medicinal plants such as ginger (Hasani et al., 2019), garlic (Wang, Yang, Qin, & Yang, 2015), cinnamon (Hadi et al., 2020), and black seed (Sahebkar, 2014) can significantly lower BP. One of the most important herbal medicines which has been widely used is flaxseed.

Flaxseed or linseed (*Linum usitatissimum*), an oilseed crop grown on all continents, was recently acknowledged as a functional food(Basch et al., 2007; Didarkhah, Vatandoost, & Dirandeh, 2020; Hajiahmadi, Hosseinzadeh, & Hosseinzadeh, 2021). Flaxseed gained much attention because of its components (high amounts of α-linolenic acid [ALA], soluble fiber, lignan, and mucilage) and the potential effect on the prevention of CVDs (Masjedi, Pour, Shokoohinia, & Asgary, 2021; Sahebkar, Katsiki, Ward, & Reiner, 2021). Flaxseed oil has different effects, including anti-inflammatory (Oomah, 2001), anti-chemotactic (Monk et al., 2016), antioxidant (Barthet, Klensporf-Pawlik, & Przybylski, 2014), anti-atherosclerotic (Zanwar, Hegde, & Bodhankar, 2014), and anti-microbial (Mohammed & Hameed, 2018). In addition, flaxseed supplementation produces various potentially protective effects against chronic diseases, such as obesity (Mohammadi-Sartang et al., 2017), dyslipidemia (Hadi et al., 2020), diabetes (Mohammadi-Sartang, Sohrabi, Barati-Boldaji, Raeisi-Dehkordi, & Mazloom, 2018), and metabolic syndrome (Tamtaji et al., 2020). Some trials claimed flaxseed could improve BP in adults (Dodin et al., 2005; Rodriguez-Leyva et al., 2013), whereas others did not (Billinsky et al., 2013; Dewell, Marvasti, Harris, Tsao, & Gardner, 2011). Therefore, in clinical settings, the effects of flaxseed on BP are controversial.

Previous meta-analyzes have shown that flaxseed supplementation can significantly reduce systolic BP (SBP) and diastolic BP (DBP) in adults (Khalesi, Irwin, & Schubert, 2015; Ursoniu et al., 2016). In term of characteristics of participants, previous meta-analyzes have included healthy and unhealthy subjects in their analysis. Healthy status may differently influence the effect of flaxseed oil on BP response. Therefore, it is better to measure the effects of flaxseed separately in these people.

We, therefore, aimed to examine and explore the effect of flaxseed oil on BP in patients with metabolic syndrome and related disorders by performing a systematic review and meta-analysis of all published RCTs.

2 | METHODS

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.1 | Search strategy

Two investigators independently performed a systematic search of the literature across the PubMed, Scopus, Cochrane Library, and ISI Web of Science databases from inception till March 31, 2020, using the following keywords interposed with appropriate Boolean operators: ("flax" OR "linseed" OR "flaxseed oil" OR "lignan" OR "Linum usitatissimum") AND ("blood pressure" OR "systolic blood pressure" OR "diastolic blood pressure" OR "hypertension"). We further restricted the search to English articles. Additionally, the reference lists of selected studies and relevant reviews were also checked to ensure a complete collection. Discrepancies were resolved through discussion between reviewers until consensus was reached.

2.2 | Study selection

After the removal of duplicates, a two-stage screening process consisting of a title and abstract scan and a full-text review was used to

ensure the accurate identification of eligible articles. Human studies were included if they met the following criteria, including: (a) population: adults (age ≥ 18 years); (b) intervention: oral supplementation with flaxseed oil compared to control group; (c) outcome: reporting enough data about intended outcomes (SBP and DBP) at baseline and the end of the study in each group; (d) study design: RCTs with parallel design lasting at least for 2 weeks. The exclusion criteria included: (a) non-randomized, non-control, or crossover investigations; (b) RCTs on flaxseed in combination with other herbs or ingredients as a mixture; (c) investigations with healthy participants and (d) studies with a lack of sufficient data required for meta-analysis. Study selection was independently conducted by two reviewers and disagreement was resolved by consensus.

2.3 | Data extraction

Data were extracted independently by two authors and entered into a pre-defined table. Collected data included: the first author's name, year of publication, country, intervention sample size, characteristics of the subjects (sex, health status, mean age, and mean body mass index [BMI]), duration of supplementation, and details of the intervention and control groups. Any disagreements were resolved by discussion with a third reviewer. For any missing information, corresponding authors were contacted by email.

2.4 | Quality assessment

A systematic assessment of bias in the included study was performed using the Cochrane criteria (Higgins et al., 2011) which included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other biases. We rated each domain of the trials as low risk, unclear, or high risk. Two authors independently conducted the quality assessment. The third author was consulted in case of any disagreement in the appraisal score.

2.5 | Statistical analyses

The statistical analysis was undertaken by using the STATA software (StataCorp, College Station, Texas, USA). Differences were expressed as weighted mean differences (WMD) with a 95% confidence interval (CI). To calculate WMDs, means and mean change scores and their standard deviations (SDs) were employed. If only SD for the baseline and final values were provided, SD for the net changes was assigned based on the Follmann method (Follmann, Elliott, Suh, & Cutler, 1992). When the information was reported as standard error (SE), SD was calculated by multiplying SE by the square root of the sample size. Because selected trials were carried out in different settings, the random-effects model was employed to calculate the overall effect from effect sizes. Statistical heterogeneity among articles was assessed using I^2 statistics. Values of 25%, 50%, and 75% were used for the I^2 analysis and corresponded to low, moderate, and high heterogeneity, respectively (Higgins et al., 2019). To identify potential sources of heterogeneity, a predefined subgroup analysis was conducted based on trial duration, and participant's health status. To investigate whether the results of the meta-analysis were dependent on a particular trial or group of trials, we recomputed the meta-analysis statistic after omitting one study at a time (sensitivity analysis). Given that the effect size of each outcome was less than 10, we were not able to create funnel plots, and the existence of publication bias was inspected only through Egger's regression model. $p < .05$ were considered statistically significant.

3 | RESULTS

3.1 | Study selection

Of the 1894 articles identified in the electronic databases, 478 were excluded for being duplicated studies, and 1,399 were excluded for not meeting the eligibility criteria. Ultimately, five studies (6 arms) (Akrami, Nikaein, Babajafari, Faghih, & Yarmohammadi, 2018; Dewell et al., 2011; Kestin, Clifton, Belling, & Nestel, 1990; Paschos et al., 2007; Yang et al., 2018) were included in the meta-analysis. The study selection procedure is outlined in Figure 1.

3.2 | Study characteristics

The details of the included studies are shown in Table 1. A total of five studies (Akrami et al., 2018, Dewell et al., 2011, Kestin et al., 1990, Paschos et al., 2007, Yang et al., 2018) were included in the systematic review and meta-analysis. The number of participants in these trials ranged from 11 to 42. The included trials were published between 1990 and 2018 and were performed in Iran, the USA, China, Australia, and Greece. Duration of flaxseed oil intake was ranged from six to 12 weeks. The mean age of participants ranged from 49 to 56 years old. Patients' BMI ranged from 26 to 30 Kg/m^2. Two studies were performed on metabolic syndrome patients, two on subjects with hypercholesterolemia, and one on hypertensive patients. Table 2 reflected the quality of included studies with the risk of bias based on the Cochrane Handbook.

3.3 | Meta-analysis

3.3.1 | Effects of flaxseed oil on systolic blood pressure

The overall effect of flaxseed oil consumption on SBP was presented in Figure 2. The results of the random-effects analysis on five included trials (6 arms) showed that flaxseed oil consumption significantly

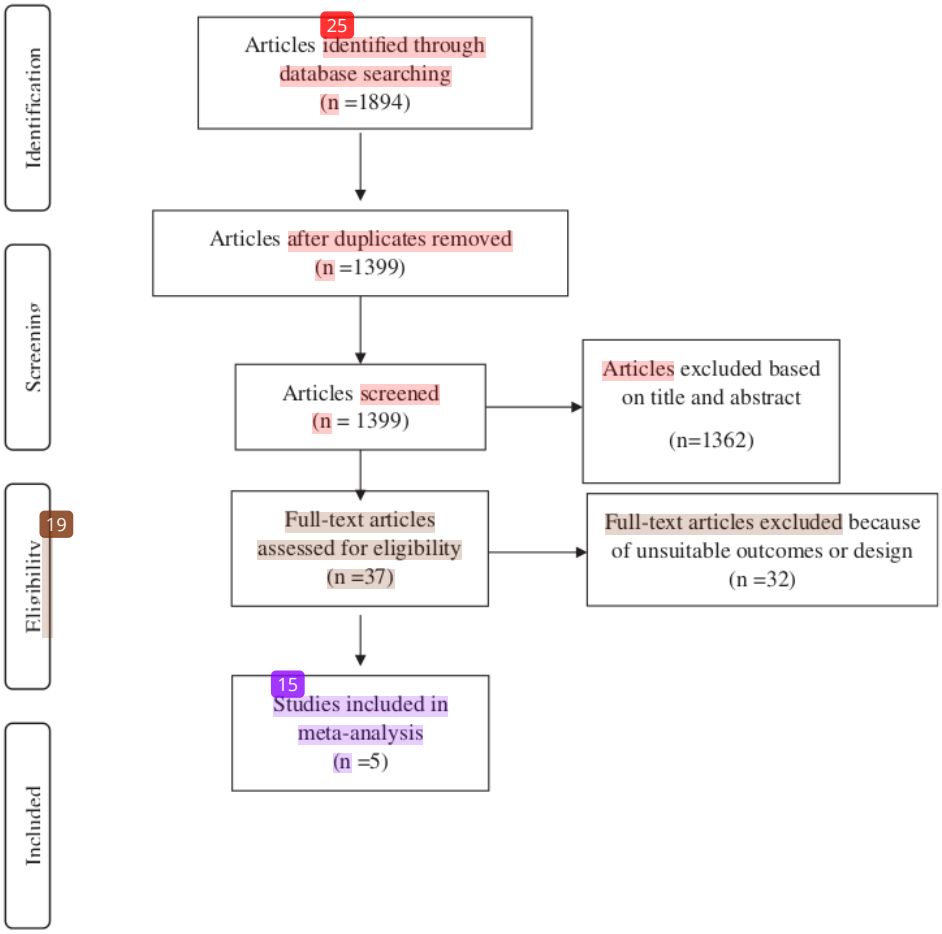

FIGURE 1 Flow diagram of the included and excluded studies

TABLE 1 Characteristics of included studies in the comparison of flaxseed versus control

First author (publication year)	Country	Participant's health status	Interventions sample size	Mean age	Mean BMI (kg/m2)	Sex	Intervention of experimental group	Intervention of control group	Duration (weeks)
Akrami et al. (2018)	Iran	Metabolic syndrome	26	49	29	Both	Flaxseed oil/ 25 mL	Sunflower oil	7
Dewell et al. (2011)[a]	USA	Metabolic syndrome	20	50	30	Both	Flaxseed oil/ 6.6 g	Soybean oil	8
Dewell et al. (2011)[b]	USA	Metabolic syndrome	20	51	30	Both	Flaxseed oil/ 2.2 g	Soybean oil	8
Kestin et al. (1990)	Australia	Hypercholesterolemia	11	50	26	Male	Flaxseed oil/ 9.2 g	Safflower oil	6
Paschos et al. (2007)	Greece	Hypercholesterolemia	18	49	28	Male	Flaxseed oil/ 8.1 g	Safflower oil	12
Yang et al. (2018)	China	Hypertensive patients	42	56	26	Both	Flaxseed oil/ 4 g	Corn oil	12

Abbreviation: BMI, Body mass index.
[a]high dose
[b]low dose.

TABLE 2 Risk of bias assessment for included randomized controlled clinical trials

First author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Akrami et al. (2018)	L	L	U	U	L	L	U
Dewell et al. (2011)	U	U	U	U	L	L	U
Kestin et al. (1990)	U	U	L	L	L	L	U
Paschos et al. (2007)	U	U	L	U	L	L	U
Yang et al. (2018)	L	L	L	L	L	L	U

Abbreviations: H, High risk; L: Low risk; U, Unclear.

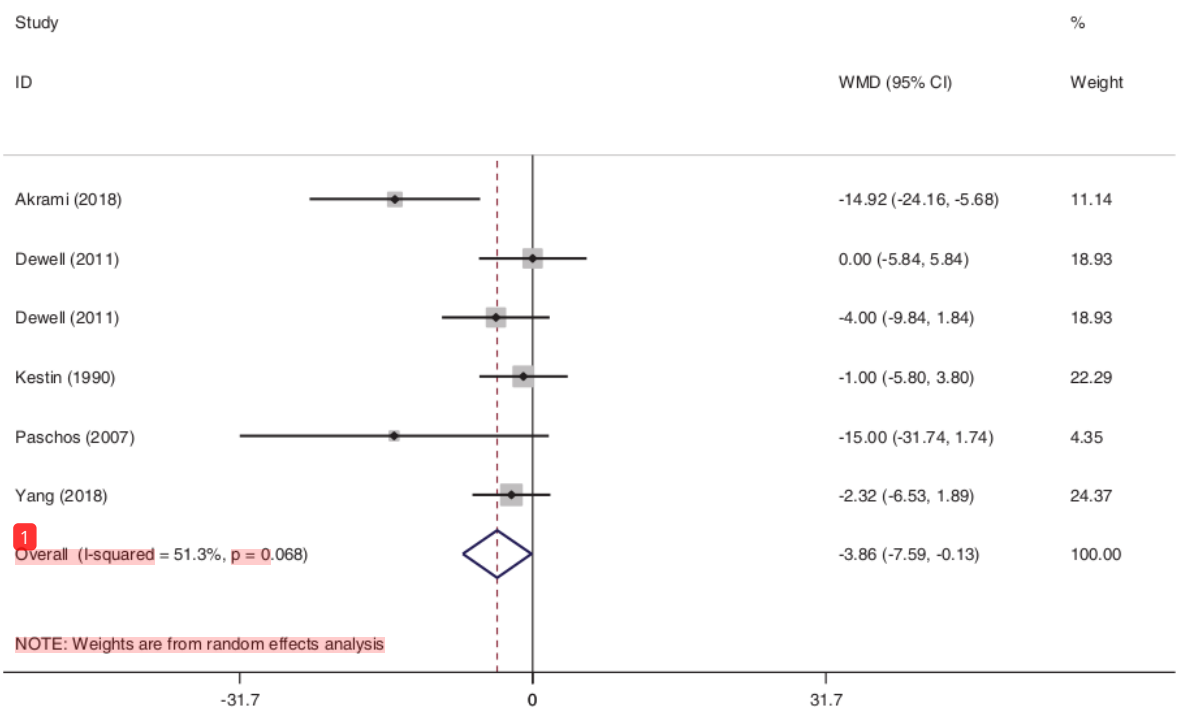

FIGURE 2 Forest plot of the effect of flaxseed oil consumption on systolic blood pressure

reduced SBP (WMD: −3.86 mmHg, 95% CI: −7.59 to −0.13, $p = .04$). The heterogeneity between studies was moderate ($I^2 = 51.3\%$, $p = .06$), and could not be eliminated by different subgroup analyses. Also, after classifying the studies based on the health status of the participants and the duration of the intervention, the results were not significant in all subgroups (Supplementary Figures S1 and S2).

3.3.2 | Effects of flaxseed oil on diastolic blood pressure

A total of five studies (6 arms) investigated the effect of flaxseed oil on DBP (Figure 3). We observed that consumption of flaxseed oil could not significantly change DBP compared with the control group (WMD: −1.71 mmHg, 95% CI: −3.67 to 0.26, $p = .09$) with a non-significant between-study heterogeneity ($I^2 = 36.4\%$, $p = .16$). Despite classifying the studies based on the duration of the intervention and the health status of the participants, the results remained insignificant in all subgroups (Supplementary Figures S3 and S4).

3.3.3 | Sensitivity analysis and publication bias

To explore each study's impact on the overall effect size, we omitted each trial from the analysis step by step. After removing the study by Akrami et al. (WMD: −2.12 mmHg, 95% CI: −4.61 to 0.35), Dewell et al. (low dose) (WMD: −4.15 mmHg, 95% CI: −8.84 to 0.53), Paschos et al. (WMD: −3.28 mmHg, 95% CI: −6.90 to 0.33) and Yang et al. (WMD:

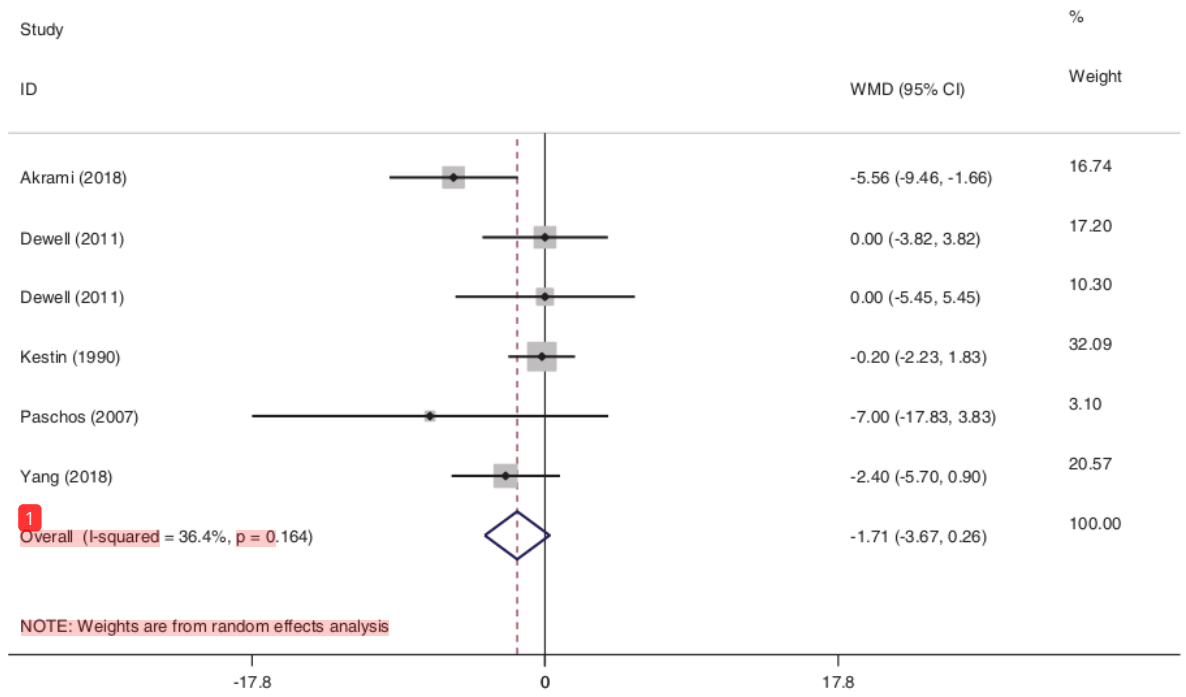

FIGURE 3 Forest plot of the effect of flaxseed oil consumption on diastolic blood pressure

−4.80 mmHg, 95% CI: −9.89 to 0.27), the overall results of SBP were significantly changed. In addition, eliminating the study by Kestin et al. significantly changed the overall result of DBP (WMD: −2.41 mmHg, 95% CI: −4.77 to −0.05). Furthermore, the results of Egger's regression test indicated no publication bias for SBP ($p = .06$) or DBP ($p = .31$).

4 | DISCUSSION

There are several meta-analysis studies that have investigated the effect of flaxseed administration on BP. However, to our knowledge, the present meta-analysis is the first meta-analysis focus on the patients with metabolic syndrome and related disorders. This systematic review and meta-analysis of five clinical trials assessed available evidence about the blood pressure-lowering effect of flaxseed oil in patients with metabolic syndrome and related disorders. The pooled results revealed a significant effect of flaxseed oil in lowering SBP when compared with control. However, we failed to find any significant effect of flaxseed oil consumption on DBP. Results of subgroup analysis regarding DBP revealed that subgroup analysis based on intervention duration, participant's health status could not change their results. The lack of significant benefit of flaxseed oil in subgroup analysis was likely due to limited power, with only 2–3 studies for each subgroup. Indeed, the power of a meta-analysis strongly depends on number of included studies.

Although the amount of SBP reduction found in the current study is modest, a slight reduction of BP may be important in reducing cardiovascular risk (McInnes, 2005). It has been suggested that SBP is more important than DBP as the CVD risk factor for persons aged over 50 years (Ishii, 2000). It would be useful to perform stratified analysis by hypertension status, but the small number of trials conducted in hypertensive subjects precluded such analysis.

Although the precise mechanisms were not fully understood, the BP-lowering effect of flaxseed oil involves angiotensin converting enzyme inhibition (by the secoisolariciresionol diglucoside) (Prasad, 2013), nitric oxide production (Caligiuri, Edel, Aliani, & Pierce, 2014), and antioxidation and anti-inflammatory activities (Caligiuri et al., 2014; Sahebkar et al., 2021). In addition, flaxseed oil can lower BP due to its dietary fiber, especially soluble fiber, by regulating blood lipids, reducing insulin resistance, and improving the intestinal microbial flora (Anderson et al., 2009; Klosterbuer, Roughead, & Slavin, 2011). Additionally, dietary fiber appears to improve anthropometric indices, and weight loss can play a role in lowering BP (Jovanovski et al., 2021; Kang, 2021).

Consumption of flaxseed oil has been reported to be safe and well-tolerated in previous investigations, but large doses can cause diarrhea and loose stools. Allergic reactions are also possible. People with coagulation problems, pregnant women, breastfeeding mothers, and children should also be careful in consuming flaxseed oil (Cardoso Carraro, Dantas, Espeschit, Martino, & Ribeiro, 2012; O'keefe, Kapur, Rex, & Watson, 2010; Sahebkar et al., 2021).

A number of certain limitations of our findings should also be acknowledged. Firstly, the results of the current systematic review and meta-analysis were based on relatively small number of studies

and must be interpreted with caution. Secondly, heterogeneity still existed in the trials concerning SBP, which makes our interpretation of the results more complex. Third, the included studies had a short duration, with the majority shorter than 2 months. Therefore, the effect of flaxseed oil supplementation on BP as well as its safety in long term is uncertain. Forth, confounding factors and their influence were nor reported and analyzed in the majority of trials, precluding their analysis in our study. Finally, although formal statistical test did not detect evidence of this bias in our meta-analysis, the power of these tests was limited due to the small number of studies.

5 | CONCLUSION

Our findings revealed that flaxseed oil consumption has favorable effects on SBP in patients with metabolic syndrome and related disorders. However, due to limited availability of studies with hypertensive cases and relatively small sample sizes, well-designed RCTs with adequate sample sizes aimed at hypertensive populations are recommended. In addition, the investigators should balance the confounding impact of dietary variety between the intervention and control group and conduct the safety assessment in their studies.

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ORCID

Dmitry Olegovich Bokov https://orcid.org/0000-0003-2968-2466
Ghulam Yasin https://orcid.org/0000-0002-4923-871X
Yasser Fakri Mustafa https://orcid.org/0000-0002-0926-7428
Mohammad Amraei https://orcid.org/0000-0001-6750-6987

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