Food & Function

ROYAL SOCIETY OF CHEMISTRY

REVIEW

Cite this: *Food Funct.*, 2023, **14**, 675

Effect of flaxseed supplementation on blood pressure: a systematic review, and dose–response meta-analysis of randomized clinical trials†

Lingou Li, ‡[a] Hanzhang Li,‡[b] Yuzhen Gao,[c] Somayeh vafaei,[d] Xingyu Zhang[a] and Mei Yang *[a]

Received 31st August 2022,
Accepted 25th November 2022

DOI: 10.1039/d2fo02566c

rsc.li/food-function

Many clinical trials have revealed that flaxseed supplementation might exert a potent antihypertensive influence, but the findings are inconsistent. In this regard, a meta-analysis was carried out to provide a more accurate estimate of the impact of flaxseed supplementation on blood pressure. We searched international databases including PubMed, Cochrane Library, Web of Science, Scopus, Embase, and Google Scholar till July 2022. A random-effects model was used to calculate weighted mean differences (WMDs). Non-linear dose–response analysis and meta-regression were performed. Meta-analysis of 33 trials (comprising 43 treatment arms) with 2427 participants revealed significant reductions in both systolic (WMD: −3.19 mmHg; 95% CI: −4.15 to −2.24, $p < 0.001$; $I^2 = 92.5\%$, $p < 0.001$) and diastolic blood pressure (WMD = −2.61 mmHg; 95% CI: −3.27, −1.94, $p < 0.001$; $I^2 = 94.1\%$, $p < 0.001$) following flaxseed supplementation. Greater effects on SBP and DBP were found in trials with an intervention duration of >20 weeks, ≥30 g day^{-1} of flaxseed, subjects with BMI 25–30 kg m^{-2}, and in patients with hypertension. Supplementation with various flaxseed products significantly reduced SBP and DBP levels, confirming the hypothesis that flaxseed could be used as an effective supplement for blood pressure management, alongside routine medications.

1. Introduction

High blood pressure (BP) is substantially related to an elevated risk of chronic disorders, such as heart failure, ischemic heart disease, stroke, and kidney disease.[1–3] Often known as hypertension (HTN), [4] high BP is a considerable factor of morbidity which imposes a significant economic burden on society, due to its association with an increased risk of chronic disease.[5] BP management, through altering one's diet and lifestyle, is an effective approach to prevent or alleviate HTN and its health consequences.[6] There is evidence that some special dietary patterns, such as the Mediterranean diet and the DASH diet, can improve BP.[7] Dietary treatments have been proposed as a desirable add-on therapy to regulate BP and mitigate the burden of HTN.[8]

Flaxseed (Linum usitatissimum) is one of the most important and frequently used herbs in the treatment of BP that has recently gained attention.[9,10] This is due to the presence of high-quality protein and soluble fibers,[11] which can alter serum lipid concentrations.[12] Flaxseed is also a good dietary source of phytoestrogen, α-linolenic acid, lignans, and phenolic compounds.[11] Numerous randomized controlled trials (RCTs) and a rencent review have shown that flaxseed and its constituent parts can lower BP.[13–17] Despite growing body of evidence, there is inconsistency amongst trials examining the effects of flaxseed on BP. Two meta-analyses published in 2015 evaluated the anti-hypertensive benefits of flaxseed and flaxseed-derived products on BP.[18,19] However, this association was explored in detail in several articles published since then. Due to the conflicting findings of these studies and the absence of a comprehensive update meta-analysis, we further have investigated the effects of flaxseed and its derivatives on adults' BP. Hence, we conducted the current dose–response systematic review and meta-analysis of RCTs to determine the effects of flaxseed and flaxseed-derived products on BP in normotensive and hypertensive subjects.

[a]*Department of Endocrinology, The First People's Hospital of Chong Qing Liang Jiang New Area, Chongqing, China. E-mail: 3148882@qq.com*
[b]*Hubei University of Chinese Medicine, Hubei, China*
[c]*Department of Clinical Laboratory, Sir Run Run Shaw Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China*
[d]*Department of Obstetrics and Gynecology, University of Chicago, Chicago, IL 60637, USA*

†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2fo02566c

‡These authors equally contributed the study.

2. Methods

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedure for conducting and disseminating systematic reviews and meta-analyses, the current investigation was carried out.[20] Also, we registered our study protocol in PROSPERO (CRD42022352556).

2.1. Search strategy

We conducted a thorough literature search in online databases including PubMed, Cochrane Library, Scopus, Web of Science, Embase, and Google Scholar up to July 2022 to discover related papers on the impact of flaxseed supplementation on BP in adults. In the search strategy, the following Medical Subject Headings (MeSH) and subject terms or keywords were used: (flax* OR flaxseed OR lignan* OR ground flaxseed OR whole flaxseed OR flaxseed oil OR Linum usitatissimum OR linseed*) AND (blood pressure OR hypotension OR anti-hypertensive OR hypertension OR hypotensive) AND (Randomized controlled trial OR Intervention studies OR controlled trial OR intervention OR controlled clinical trial OR randomized OR random OR placebo OR randomized clinical trial OR randomly OR RCT OR assignment OR double blinded). References from all relating peer-reviewed research were consulted and cross-referenced against databases to ensure that no related articles were missed. Duplicates were excluded from consideration and following citations were included in the Endnote screening software.

2.2. Inclusion and exclusion criteria

The inclusion criteria for this study included parallel or crossover clinical trials that investigated the impact of flaxseed preparations on BP, provided baseline and end-of-trial BP values in both intervention and control groups, and had a supplementation period with flaxseed of at least two weeks. Case reports, experimental studies, observational studies, animal experiments, *in vitro* studies, and studies with inadequate data on BP values in the flaxseed and control groups were excluded from the meta-analysis.

2.3. Quality assessment, and certainty assessment

In order to assess the study quality, two independent reviewers used the Cochrane Collaboration modified risk of bias tool. This tool measures bias in seven different areas, such as random sequence generation, performance bias, reporting bias, allocation concealment, detection bias, attrition bias, and other possible sources of bias.[21] As a result, each category of study bias was classified with terms as "low", "high", and "unclear". A corresponding author evaluated and resolved differences in study bias between independent reviewers in each domain. According to the GRADE standards working group, we evaluated the overall certainty of the evidence across studies (gradeworkinggroup.org). According to evaluation standards, there were four categories of evidence quality: high, moderate, low, and very low.[22]

2.4. Study selection and data extraction

Two independent investigators screened every eligible study and extracted data from each of them. Extracted data contained the first author's name, year of publication, study location, sample group size (placebo/control and intervention), participant demographics [(mean ± standard deviation [SD], gender, mean age, and the baseline of body mass index (BMI)], study design, dosage of flaxseed, intervention's duration, mean ± SD of BP (SBP and DBP) changes for both intervention and control groups, and the type of flaxseed supplement and control. To conduct data analysis, values from the dataset were, if possible, converted to the most usual units of an expression.

2.5. Quantitative data synthesis

Mean differences and SD for the intervention and control groups were extracted to calculate the effect size for BP markers. To estimate weighted mean differences (WMDs) with 95% confidence intervals, a random-effects model was utilized (CIs).[23] In studies reporting standard errors (SEs), 95% confidence intervals (CIs), and interquartile ranges (IQRs), means ± SD was converted.[24] All BP units were collated in mmHg. Using Cochran's Q test, the I-square (I^2) statistic was used to examine the degree of between-study heterogeneity. I^2 values greater than 50% or $p < 0.1$ was considered to indicate high heterogeneity between studies. To identify potential sources of heterogeneity, we performed a subgroup analysis in conformity with the baseline BMI, study duration, intervention dosage, health condition, mean age, type of flaxseed product, study quality, control intervention type, gender, and sample size. In order to estimate the effect of the single studies on the overall effect size, a sensitivity analysis was conducted. To investigate the effects of small studies, Begg's adjusted rank correlation and Egger's regression asymmetry test were also applied.[25,26] An assessment of publication bias was carried out using funnel plots. As a result of publication bias, we used the "trim and fill" method in order to impute potentially missing studies in cases of publication bias detection. Non-linear dose–response and meta-regression was performed to investigate the association between overall effect size and sample size, flaxseed dosage ($g\ day^{-1}$), and the intervention's duration (week). It was statistically analyzed using STATA software, version 16 (Stata Corp, College Station, TX). A *P*-values of <0.05 were regarded as statistically meaningful for each analysis.

3. Results

3.1. Study selection

Initially searched, 1912 studies were found; however, 625 of them were eliminated due to duplication. Additional 1247 studies were discarded since of irrelevant titles and abstracts (n = 934), animal studies (n = 185), and review studies (n = 128). In the end, 40 relevant studies were left to be reviewed in full-text. Seven studies were omitted due to a lack of BP marker

reporting or a inappropriate design. Finally, 33 trials were included in this meta-analysis (Fig. 1).

3.2. Characteristics of the studies

A summary of the characteristics of the included studies is provided in Table 1. Totally, 2427 subjects were included (case = 1220; control = 1207), and the dates of publications were between 1999 and 2021. Among the 33 studies, 28 were parallel studies,[10,13–16,27–49] and five were crossover[50–54] studies. The intervention duration ranged from 3 to 48 weeks and the sample size varied from 14 to 189 individuals. BMI at baseline ranged from 23 to 32 kg m^{-2}. Studies were conducted in the following countries: Canada,[39,40,42,47,49,50,52] Iran,[14,15,28,29,32–38] China,[10,30,43,53] India,[13,45,46] Brazil,[27,31] Australia,[44] Finland,[54] Denmark,[51] USA,[41] Netherlands,[48] and Cuba.[16]

Whole flaxseed, ground flaxseed, roasted flaxseed, defatted Flaxseed (doses from 10 to 100 g),[15,16,27–33,36–38,42,43,45,46,52] flaxseed oil (doses from 1 to 30 g),[10,13,14,32,34,35,39,41,44,48,54] and flaxseed lignan supplements (doses from 0.36 to 0.6 g)[40,47,49–51,53] were used in studies.

3.3. Risk of bias, and grade assessment

The results of the Cochrane criteria to assess the risk of bias of the included studies were depicted in Table 2. Using the GRADE approach, both outcomes were rated moderate for evidence quality. The level of evidence was downgraded because of serious limitations for imprecision (Table 3).

3.4. Effect of flaxseed supplementation on SBP

The overall estimate from the random-effect model carried out on 33 studies with 43 arms, including 1220 cases and 1207 controls, revealed that flaxseed had a significant effect on SBP (WMD: −3.19 mmHg; 95% CI: −4.15 to −2.24, $p < 0.001$) (Fig. 2). Between-study heterogeneity was found to be quite high ($I^2 = 92.5\%$, $p < 0.001$). Therefore, sub-group analysis was conducted based on different variables and it was revealed that the potential sources of between-study heterogeneity were sample size, health condition, duration, age, dose, study quality, control intervention type, and baseline BMI (Table 4). Performing subgroup analysis showed that the effect of flaxseed supplementation on SBP in studies with a treatment

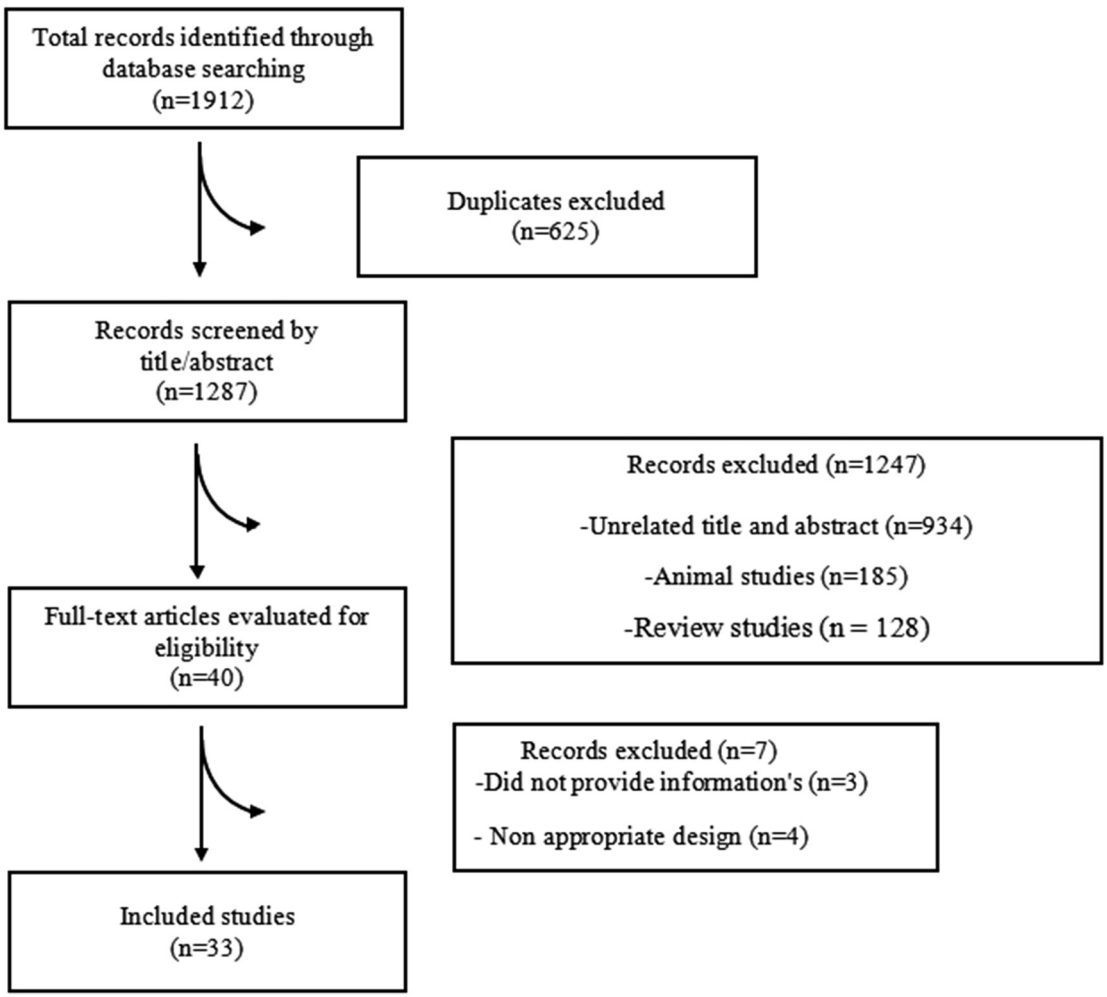

Fig. 1 Flow diagram of study selection.

Table 1 Study characteristics of included studies

Author, year, country	Design	Participants, *n*	Health condition	Age, year	Intervention		Duration (week)
					Treatment group	Control group	
Jenkins, 1999, Canada[52]	RA/crossover	M: 56 Int: 28, Con: 28	Hyperlipidemia	57	50 g d^{-1} flaxseed	Placebo: wheat bran	3
Dodin, 2005, Canada[42]	RA/DB/parallel	F: 179 Int: 85, Con: 94	Healthy post menopause	Int: 54, Con: 55.4	40 g d^{-1} flaxseed	Placebo: wheat germ	48
Hallund, 2006, Denmark[51]	RA/DB/crossover	F: 22 Int: 11, Con: 11	Post menopause	61	0.5 g d^{-1} lignan complex isolated from flaxseed	Placebo: placebo muffin	6
Schwab, 2006, Finland[54]	RA/DB/crossover	M/F: 14 Int: 7, Con: 7	Healthy	45	30 g d^{-1} flaxseed oil	Placebo: Hempseed oil	4
Pan, 2007, China[53]	RA/DB/crossover	M/F: 68 Int: 34, Con: 34	T2DM	Int: 63.4, Con: 63	0.36 g d^{-1} isolated flaxseed lignan	Placebo: rice flour	12
Barcelo, 2008, Canada[39]	RA/parallel	M/F: 21 Int: 12, Con: 9	Firefighters	Int: 36.6, Con: 40.8	1.2 g d^{-1} flaxseed oil	Placebo: sunflower oil	12
		M/F: 19 Int: 10, Con: 9		Int: 41.2, Con: 40.8	2.4 g d^{-1} flaxseed oil		
		M/F: 19 Int: 10, Con: 9		Int: 43.7, Con: 40.8	3.6 g d^{-1} flaxseed oil		
Cornish, 2009, Canada[40]	RA/DB/parallel	M: 92 Int: 48, Con: 44	Healthy older adults	Int: 61, Con: 62.5	0.543 g d^{-1} flaxseed lignan	Placebo: maltodextrin	24
Barden, 2009, Australia[44]	RA/parallel	M: 36 Int: 18, Con: 18	Healthy	Int: 51, Con: 51	9 g d^{-1} flaxseed oil	Placebo: olive oil	4
Wu, 2010, China[43]	RA/parallel	M/F: 189 Int: 94, Con: 95	Metabolic syndrome	Int: 48.5, Con: 48.6	30 g d^{-1} flaxseed	Placebo: lifestyle counseling	12
Dewell, 2011, USA[41]	RA/parallel	M/F: 40 Int: 20, Con: 20	Metabolic syndrome	Int: 50, Con: 48	2.2 g d^{-1} flaxseed oil	Placebo: soybean oil	8
		M/F: 40 Int: 20, Con: 20		Int: 50, Con: 48	6.6 g d^{-1} flaxseed oil		
Barre, 2012, Canada[50]	RA/DB/crossover	M/F: 16	T2DM	66.2	0.6 g d^{-1} flaxseed lignan complex	Placebo: placebo	12
Rodriguez-Leyva, 2013, Cuba[61]	RA/DB/parallel	M/F: 86 Int: 45, Con: 41	Hypertensive Patients	Int: 67.4, Con: 65.3	30 g d^{-1} milled flaxseed	Placebo: wheat	24
Katare, 2013, India[45]	RA/parallel	M/F: 50 Int: 25, Con: 25	Dyslipidemia	52	30 g d^{-1} roasted flaxseed chutney powder	Placebo: control	12
Saxena, 2014, India[46]	RA/parallel	M/F: 50 Int: 25, Con: 25	Dyslipidemia	40–60	30 g d^{-1} roasted flaxseed powder	Placebo: control	12
Cassani, 2015, Brazil[27]	RA/parallel	M/F: 27 Int: 14, Con: 13	Cardiovascular risk factors	Int: 40, Con: 33	60 g d^{-1} flaxseed powder	Placebo: raw rice powder	6
Machado, 2015, Brazil[31]	RA/parallel	M/F: 41 Int: 20, Con: 21	overweight adolescents	13.7	28 g d^{-1} brown flaxseed	Placebo: wheat bran	11
		M/F: 41 Int: 20, Con: 21			28 g d^{-1} golden flaxseed		
Javidi, 2016, Iran[15]	RA/parallel	M/F: 59 Int: 30, Con: 29	Prediabetic individuals	Int: 52.93, Con: 50.55	20 g d^{-1} flaxseed powder	Placebo: control	12
		M/F: 62 Int: 33, Con: 29		Int: 52.15, Con: 50.55	40 g d^{-1} flaxseed powder		
Yari, 2016, Iran[37]	RA/parallel	M/F: 44 Int: 22, Con: 22	Metabolic syndrome	Int: 45.82, Con: 45.2	30 g d^{-1} brown milled flaxseed	Placebo: lifestyle advice	12
Di, 2017, Canada[47]	RA/DB/parallel	M/F: 13 Int: 7, Con: 6	Older healthy adults	Int: 67.9, Con: 68.1	0.6 g d^{-1} flaxseed lignan complex	Placebo: whey protein	24
		M/F: 19 Int: 12, Con: 7		Int: 67.9, Con: 68.1	0.6 g d^{-1} flaxseed lignan complex	Whey protein	

Table 1 *(Contd.)*

Author, year, country	Design	Participants, *n*	Health condition	Age, year	Intervention		Duration (week)
					Treatment group	Control group	
Alcorn, 2017, Canada[49]	RA/parallel	M/F: 32 Int: 19, Con: 13	Older healthy adults	Int: 67.9, Con: 68.1	0.6 g d^{-1} flaxseed lignan	Placebo: whey powder	24
Akrami, 2017, Iran	RA/parallel	M/F: 52 Int: 26, Con: 26	Metabolic syndrome	Int: 48.3, Con: 48.8	25 ml d^{-1} flaxseed oil	Placebo: Sunflower oil	7
Haghighatsiar, 2019, Iran[28]	RA/DB/ parallel	M/F: 80 Int: 40, Con: 40	Dyslipidemic and hypertensive patients	Int: 44, Con: 42.7	36 g d^{-1} flaxseed sachet	Placebo: placebo sachet	8
Hasaniani, 2019, Iran[29]	RA/DB/ parallel	M/F: 57 Int: 29, Con: 28	T2DM	Int: 54.18, Con: 52.59	30 g d^{-1} flaxseed	Placebo: plain yogurt	8
Morshedzadeh, 2019, Iran[32]	RA/parallel	M/F: 50 Int: 25, Con: 25 M/F: 50 Int: 25, Con: 25	Ulcerative colitis	Int: 29.92, Con: 32.52 Int: 32.20, Con: 32.52	30 g d^{-1} grounded flaxseed 10 g d^{-1} flaxseed oil	Placebo: medical advice and routine medications	12
Saleh-Ghadimi, 2019, Iran[35]	RA/DB/ parallel	M/F: 40 Int: 21, Con: 19	Coronary artery disease	Int: 55.67, Con: 54.8	5 g d^{-1} flaxseed oil	Placebo: milk	10
Pieters, 2019, Netherlands[48]	RA/DB/ parallel	M/F: 59 Int: 29, Con: 30	Overweight and obese adults	60	1 g d^{-1} refined cold-pressed flaxseed oil	Placebo: sunflower oil	12
Yang, 2019, China	RA/DB/ parallel	M/F: 74 Int: 36, Con: 38	Hypertensive patients	Int: 56.52, Con: 58.24	2.5 g d^{-1} flaxseed oil	Placebo: corn oil	12
Kuang, 2020, China[30]	RA/DB/ parallel	M/F: 51 Int: 27, Con: 24	Overweight and obese adults	Int: 22.74, Con: 21.79	100 g d^{-1} flaxseed meal	Placebo: control biscuits	8
Rezaei, 2020, Iran[34]	RA/DB/ parallel	M/F: 68 Int: 34, Con: 34	NAFLD	Int: 45.5, Con: 40.8	20 g d^{-1} flaxseed oil	Placebo: sunflower oil	12
Yari, 2020, Iran	RA/parallel	M/F: 47 Int: 25, Con: 22 M/F: 44 Int: 22, Con: 22	Metabolic syndrome	Int: 44.64, Con: 46.41 Int: 45.27, Con: 45.82	30 g d^{-1} whole flaxseed powder 30 g d^{-1} flaxseed + 1 g d^{-1} hesperidin	Placebo: lifestyle intervention program, hesperidin	12
Morshedzadeh, 2021, Iran[33]	RA/parallel	M/F: 64 Int: 32, Con: 32	Ulcerative colitis	Int: 30.35, Con: 32.10	30 g d^{-1} ground flaxseed powder	Placebo: control	12
Toulabi, 2021, Iran	RA/TB/ parallel	M/F: 76 Int: 36, Con: 40 M/F: 76 Int: 36, Con: 40	Hypertensive patients	35–70	10 g d^{-1} flaxseed 30 g d^{-1} flaxseed	Placebo: wheat flour	12
Bhardwaj, 2021, India	RA/DB/ parallel	M/F: 102 Int: 50, Con: 52 M/F: 102 Int: 50, Con: 52	Coronary artery disease	Int: 62.44, Con: 53.33 Int: 62.44, Con: 53.33	30 g d^{-1} blended flaxseed oil 30 g d^{-1} blended flaxseed oil	Placebo: sunflower oil Sunflower oil	24

Table 2 Results of risk of bias assessment for randomized clinical trials included in the current meta-analysis on the effects of flaxseed supplementation on blood pressure[a]

Author, year, country	Random Sequence Generation	Allocation concealment	Reporting bias	Other sources of bias	Performance bias	Detection bias	Attrition bias
Jenkins, 1999, Canada[52]	L	U	L	H	U	U	L
Dodin, 2005, Canada[42]	L	L	L	H	L	L	L
Hallund, 2006, Denmark[51]	L	U	L	H	L	L	H
Schwab, 2006, Finland[54]	L	U	L	H	L	L	L
Pan, 2007, China[53]	L	L	L	H	L	L	L
Barcelo, 2008, Canada[39]	L	L	L	H	U	U	H
Cornish, 2009, Canada[40]	L	L	L	H	L	L	L
Barden, 2009, Australia[44]	L	L	L	L	U	U	H
Wu, 2010, China[43]	L	L	L	L	U	U	L
Dewell, 2011, USA[41]	L	U	L	H	U	U	H
Barre, 2012, Canada[50]	L	H	L	L	L	L	L
Rodriguez-Leyva, 2013, Cuba[61]	L	L	L	H	L	L	L
Katare, 2013, India[45]	U	U	L	H	U	U	H
Saxena, 2014, India[46]	L	L	L	H	U	U	H
Cassani, 2015, Brazil[27]	L	L	L	H	H	H	L
Machado, 2015, Brazil[31]	L	H	L	L	H	H	L
Javidi, 2016, Iran[15]	L	L	L	H	U	U	L
Yari, 2016, Iran[37]	L	U	L	L	U	U	L
Di, 2017, Canada[47]	L	H	L	L	L	L	H
Alcorn, 2017, Canada[49]	L	L	L	H	L	H	L
Akrami, 2017, Iran	L	L	L	H	U	U	U
Haghighatsiar, 2019, Iran[28]	L	L	L	L	L	L	L
Hasaniani, 2019, Iran[29]	L	H	L	H	L	L	L
Morshedzadeh, 2019, Iran[32]	L	L	L	L	U	U	L
Saleh-Ghadimi, 2019, Iran[35]	L	L	L	L	L	L	L
Pieters, 2019, Netherlands[48]	L	L	L	H	L	L	L
Yang, 2019, China	L	L	L	L	L	L	L
Kuang, 2020, China[30]	L	L	L	H	L	L	L
Rezaei, 2020, Iran[34]	L	L	L	H	L	L	L
Yari, 2020, Iran	L	U	L	L	U	U	L
Morshedzadeh, 2021, Iran[33]	L	L	L	L	U	U	L
Toulabi, 2021, Iran	L	L	L	L	L	L	L
Bhardwaj, 2021, India	L	L	L	H	L	L	H

[a] Each study was assessed for risk of bias using the Cochrane Risk of Bias Assessment tool (ref. 21). Domains of assessment were included random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias and other sources of bias. Each domain was scored as "high risk" if it contained methodological flaws that may have affected the results, "low risk" if the flaw was deemed inconsequential, and "unclear risk" if information was insufficient to determine. If a study got "low risk" for all domains, it considered as a high quality study with totally low risk of bias.

dosage of >30 g day^{-1}, intervention duration of >20 weeks, and subjects with HTN and non-alcoholic fatty liver disease (NAFLD) were more robust than the entire sample (Table 4). According to sensitivity analysis, the pooled estimate of the effect of flaxseed supplementation on SBP was unaffected by the removal of any particular study. Egger's but not Begg's tests revealed a significant small-study effect (p = 0.015 and 0.391, respectively). A trim and fill analysis was carried out using seven imputed studies after a visual assessment of the funnel plot (Fig. S1†) revealed an unequal distribution of trials (WMD: −3.81 mmHg; 95% CI: −4.75 to −2.87, p < 0.05) (Fig. S2†).

3.5. Effect of flaxseed supplementation on DBP

The results of our analysis of 32 RCTs with 41 arms including 1201 cases and 1193 controls indicated that flaxseed supplementation substantially reduced DBP (WMD = −2.61 mmHg; 95% CI: −3.27, −1.94, p < 0.001; I^2 = 94.1%,

Table 3 GRADE approach summary of findings and quality of evidence assessment

Outcome measure	Summary of findings: No of patients (trials)	Summary of findings: WMD (95% CI)	Quality of evidence assessment (GRADE): Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	Quality of evidence[f]
Blood pressure								
SBP (mmHg)	2427 (43)	−3.19 (−4.15, −2.24)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate
DBP (mmHg)	2394 (41)	−2.61 (−3.27, −1.94)	Not serious	Not serious	Not serious	Serious	Not serious	Moderate

SBP = systolic blood pressure; DBP = diastolic blood pressure. [a] Risk of bias based on the Cochrane risk of bias tool. This tool assesses selection bias, performance bias, detection bias, attrition bias, and reporting bias. Only one study had clear selection bias, performance bias, and detection bias. Four of 14 studies had attrition bias. [b] Downgraded if there was a substantial unexplained heterogeneity ($I^2 > 50\%$, $P < 0.10$) that was unexplained by meta-regression or subgroup analyses. [c] Downgraded if there were factors present relating to the participants, interventions, or outcomes that limited the generalizability of the results. [d] optimal information size was not met, or the 95% CI include the null value lower and upper bounds of the 95% CI were <0.95 and >1.05, respectively. [e] Downgraded if there was an evidence of publication bias using funnel plot. [f] Since all included studies were randomized clinical trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded based on prespecified criteria. Quality was graded as high, moderate, low, very low.

$p < 0.001$) (Fig. 3). A high amount of heterogeneity was detected ($I^2 = 94.1\%$, $p < 0.001$) that was lowered by subgrouping based on sample size, health condition, study quality, control intervention type, type of flaxseed product, and mean age (Table 4). Subgroup analysis indicated that flaxseed supplementation with a dosage of >30 g day^{-1} on overweight or obese patients with HTN contributes to a greater effect in lowering DBP (Table 4). As a result of the sensitivity analysis, it was found that removing a single study had no effect on the effect size. Egger's unlike Begg's test found a substantial small-study effect ($p = 0.003$ and $p = 0.999$). Moreover, publication bias was evident from visual inspection of the funnel plot (Fig. S3†). Consequently, we conducted trim and fill analysis with three imputed studies that led to no alterations in the significance of the results (WMD = −2.73 mmHg; 95% CI: −3.39, −2.07, $p < 0.05$) (Fig. S4†).

3.6. Meta-regression

Meta-regression was conducted to investigate the potential association between a reduction in SBP, and DBP, dosage (g day^{-1}), sample size, and duration (weeks) of flaxseed supplementation. Meta-regression analysis revealed no linear association between dosage, sample size, duration, and SBP and DBP changes (Fig. S5 and S6†).

3.7. Non-linear dose-responses between dosage of flaxseed supplementation and BP

Dose–response analysis indicated a trend to a significant impact of flaxseed dosage on SBP ($P_{\text{non-linear}} = 0.04$). Also, the most substantial reduction was at dosage ≥30 g day^{-1} (Fig. 4). Furthermore, flaxseed supplementation did not significantly alter DBP level based on dose ($P_{\text{non-linear}} = 0.15$) (Fig. 5).

4. Discussion

The current updated meta-analysis on 33 article showed that flaxseed supplementation has decreasing effects on SBP and DBP. Subgroup analysis revealed that ≥50-year subjects in both genders with HTN, NAFLD, and overweight BMI (25–30 kg m^{-2}) were more benefited from flaxseed supplementation. Moreover, duration more than 20-week of flaxseed supplementation in the higher dosages (>30 g day^{-1}) led to more beneficial effects on SBP and DBP. Also, more significant reduction of SBP and DBP was observed with lignan extract and whole flaxseed, respectively. Dose–response analysis revealed that the effects of flaxseed on SBP was in a non-linear dose-dependent manner.

A systematic review and meta-analysis by Ursoniu *et al.*[18] in 2015 reported that flaxseed supplementation resulted in a significant decrease in BP. Similar results were driven from a meta-analysis by Khalesi *et al.*,[19] which included 14 trials, and the results of their subgroup analysis were consistent with ours. However, their investigations did not include dose–response analysis. In addition, their results were not reported based on the mean age, BMI, health condition, and control intervention type. Most importantly, they did not evaluate the evidence according to the GRADE approach. Hence, the quality of their results cannot be trusted. Moreover, their protocol was not registered in databases for systematic reviews such as PROSPERO or Cochrane database.

Aging is considered as a risk factor of BP. HTN in people over 50 years of age is related to various types of cardiovascular diseases, stroke, heart attack, kidney and liver failure.[55,56] Our results demonstrated that supplementing with flaxseed had a substantially greater impact in people over 50 than those under 50 years, due to increased oxidative stress and vascular damage in elders.[57] Therefore, supplements that have antioxidant properties may show better effects old.[58,59] Sub group analysis for sex revealed flaxseed supplementation had no more desirable effects in woman than men. Even so, some evidence showed the antagonistic effect of flaxseed phytoestrogen on estrogen receptors, and estrogen can increase BP by increasing the secretion of angiotensinogen.[60,61] However, there were discordances between the effects that estradiol had on angiotensin II and BP.[62] Thus, it seems hormonal fluctuations in women, especially during menarche, and the phytoestrogenic properties of flaxseed lignans have not been

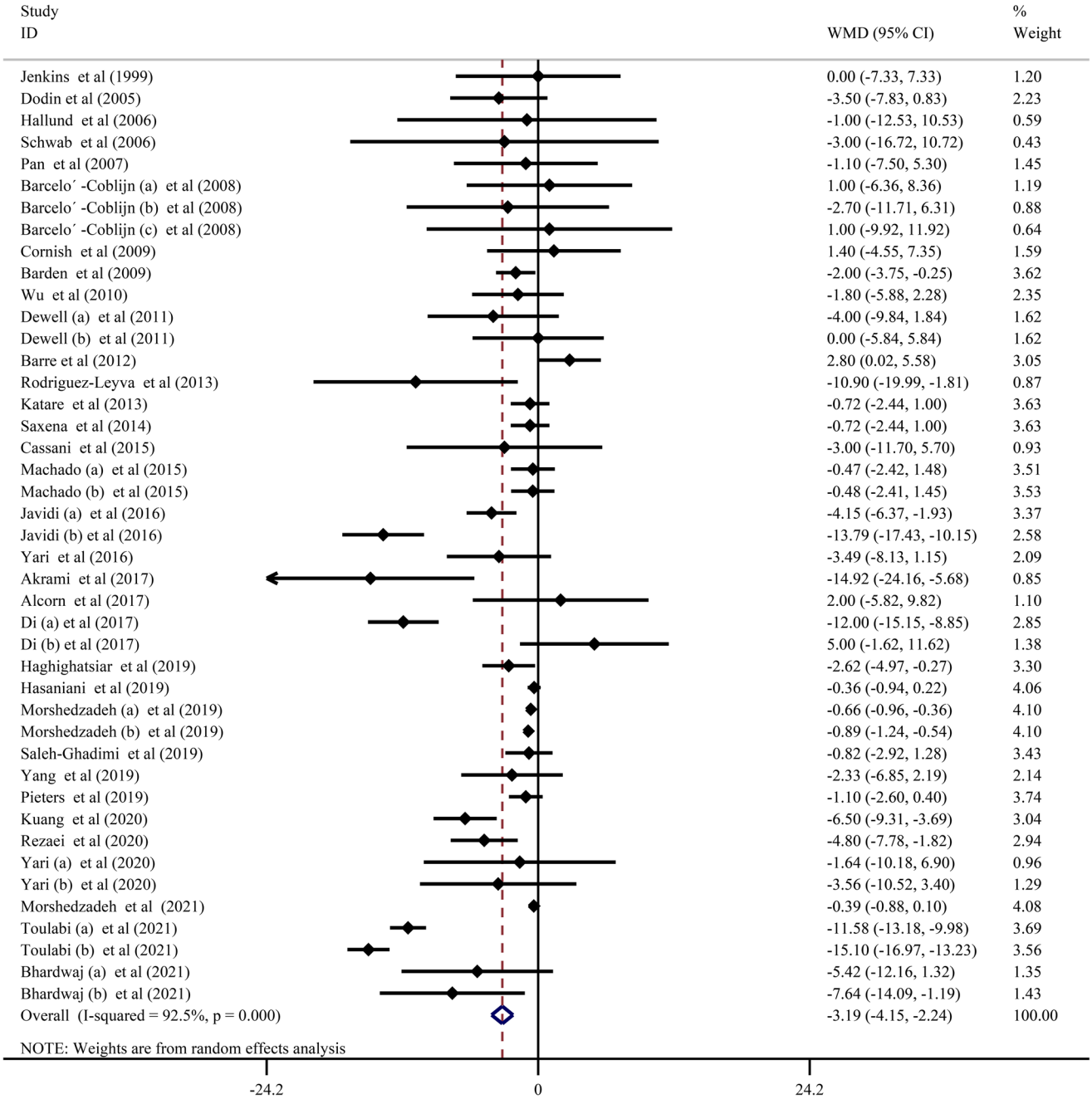

Fig. 2 Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of flaxseed supplementation on SBP levels.

affected.[63] The effects of flaxseed on different genders need to be further demonstrated.

Sources of high heterogeneity were determined by performing subgroup analysis, with sample size, duration, age, dose, health condition, study quality, and control intervention type being possible sources. Therefore, the detected heterogeneity was related to clinical and methodological issues, not statistical problems resulting in high reliability of the results. This means that these subgroups had a different true effect. Subgroup analysis also revealed that in the interventions period of >20 weeks, the-lowering effect of flaxseed was the most significant. In long-term interventions, the anti-inflammatory and antioxidant effects of flaxseed supplementation are more visible,[64] the subgroup analysis of dosage showed that high doses (more than 30 g day^{-1}) had more favorable effect than low doses. Flaxseed (oil or lignan or whole seed) in the long term and in high doses leads to better reconstruction of the vessel endothelium, water and electrolyte regulation.[65–67] Besides, flaxseed indirectly reduces BP *via* modulating hyperlipidemia, hyperglycemia, weight loss, intestinal microbiota and *etc.*[68–70] Subgroup analysis about intervention type revealed that lignan extract was more effective on

Table 4 Subgroup analyses for the effects of flaxseed supplementation on blood pressure

	NO	WMD[a] (95% CI)	*P*-Within[b]	I^2 [c] (%)	*P*-Heterogeneity[d]
Flaxseed supplementation on SBP					
Overall	43	−3.19 (−4.15, −2.24)	<0.001	92.5	<0.001
Age (year)					
<50	20	−0.77 (−0.97, −0.57)	<0.001	54.9	0.002
≥50	20	−1.16 (−1.61, −0.72)	<0.001	85.5	<0.001
NR	3	−8.95 (−9.94, −7.95)	<0.001	98.6	<0.001
Gender					
Women	2	−3.19 (−7.24, 0.86)	0.123	0	0.691
Men	2	−2.04 (−3.76, −0.32)	0.020	0	0.825
Both	39	−1.09 (−1.28, −0.91)	<0.001	93.2	<0.001
Intervention duration (week)					
≤10	12	−0.90 (−1.40, −0.40)	<0.001	66.2	<0.001
10–20	23	−1.09 (−1.29, −0.90)	<0.001	95.3	<0.001
>20	8	−5.88 (−7.77, −3.99)	<0.001	81.2	<0.001
Dosage of flaxseed (g day^{-1})					
≤10	16	−1.00 (−1.32, −0.67)	<0.001	75.8	<0.001
10–30	23	−1.06 (−1.28, −0.84)	<0.001	94.9	<0.001
>30	6	−5.48 (−6.94, −4.02)	<0.001	83.1	<0.001
Intervention type					
Lignans	7	−2.12 (−3.86, −0.37)	0.017	89.4	<0.001
Whole flaxseed	21	−1.12 (−1.34, −0.90)	<0.001	95.8	<0.001
Flaxseed oil	15	−1.04 (−1.37, −0.72)	<0.001	42.5	0.041
Study design					
RCT	38	−1.13 (−1.31, −0.94)	<0.001	93.3	<0.001
Cross over	5	1.68 (−0.64, 4.01)	0.156	0	0.698
Study population					
Diabetic	5	−0.76 (−1.30, −0.23)	0.005	94	<0.001
Metabolic syndrome	8	−3.11 (−5.22, −1.00)	0.004	12.6	0.332
Menopausal	2	−3.19 (−7.24, 0.86)	0.123	0	0.691
Overweight and obese	4	−1.42 (−2.37, −0.47)	0.004	79.4	0.002
Healthy	9	−3.15 (−4.52, −1.79)	<0.001	81.6	<0.001
Heart diseases	3	−1.79 (−3.71, 0.12)	0.011	60.7	0.079
Hyperlipidemia	4	−1.10 (−2.17, −0.03)	0.044	0	0.558
Hypertension	4	−12.32 (−13.48, −11.15)	<0.001	89.3	<0.001
Ulcerative colitis	3	−0.69 (−0.90, −0.48)	<0.001	25.9	0.259
NAFLD	1	−4.80 (−7.78, −1.82)	0.002	—	—
Control intervention type					
Placebo	7	−0.76 (−1.19, −0.33)	<0.001	91.3	<0.001
whey protein	3	−7.60 (−10.27, −4.93)	<0.001	92.6	<0.001
Wheat (barn, and germ)	7	−7.28 (−8.16, −6.40)	<0.001	96.9	<0.001
Rice	2	−1.77 (−6.92, 3.39)	0.502	0	0.730
Sunflower oil	8	−2.32 (−3.55, −1.08)	<0.001	58.6	0.018
Lifestyle Modification	3	−2.44 (−5.32, 0.45)	0.098	0	0.850
Medical advice	2	−0.76 (−0.99, −0.53)	<0.001	0	0.333
Corn oil	1	−2.33 (−6.85, 2.19)	0.312	—	—
Soybean oil	2	−2.00 (−6.13, 2.13)	0.342	0	0.342
hempseed oil	1	−3.00 (−16.72, 10.72)	0.668	—	—
Olive oil	1	−2.00 (−3.75, −0.25)	0.025	—	—
Others	6	−0.62 (−1.16, −0.08)	0.024	73.3	0.002
Sample size					
≤50	23	−0.81 (−1.02, −0.59)	<0.001	66.5	<0.001
>50	20	−1.80 (−2.13, −1.47)	<0.001	96.0	<0.001
BMI					
≤25	10	−0.70 (−0.90, −0.49)	<0.001	2.8	0.413
25–30	22	−2.66 (−3.07, −2.26)	<0.001	95.4	<0.001
>30	5	−1.07 (−2.45, 0.31)	0.128	72.8	0.005
NR	6	−3.84 (−7.34, −0.34)	<0.001	56.0	0.045
Study quality					
Low	21	−0.94 (−1.33, −0.54)	<0.001	74.1	<0.001
High	22	−1.16 (−1.36, −0.95)	<0.001	95.7	<0.001
Flaxseed supplementation on DBP					
Overall	41	−2.61 (−3.27, −1.94)	<0.001	94.1	<0.001
Age (year)					
<50	20	−0.52 (−0.64, −0.40)	<0.001	86.6	<0.001
≥50	18	−1.23 (−1.53, −0.93)	<0.001	89.4	<0.001
NR	3	−4.70 (−5.29, −4.11)	<0.001	98.9	<0.001
Gender					
Women	2	−2.39 (−5.17, 0.38)	0.091	0	0.704

Table 4 *(Contd.)*

	NO	WMD[a] (95% CI)	*P*-Within[b]	I^2 [c] (%)	*P*-Heterogeneity[d]
Men	2	−1.93 (−3.11, −0.76)	<0.001	0	0.463
Both	37	−0.75 (−0.86, −0.64)	<0.001	94.7	<0.001
Intervention duration (week)					
≤10	12	−1.20 (−1.56, −0.84)	<0.001	86.9	<0.001
10–20	23	−0.71 (−0.82, −0.59)	<0.001	95.7	<0.001
>20	6	−1.82 (−2.87, −0.76)	<0.001	93.2	<0.001
Dosage of flaxseed (g day^{-1})					
≤10	16	−0.74 (−0.90, −0.58)	<0.001	96	<0.001
10–30	19	−0.60 (−0.76, −0.45)	<0.001	88.6	<0.001
>30	6	−4.71 (−5.43, −3.98)	<0.001	83.7	<0.001
Intervention type					
Lignans	5	0.11 (−0.98, 1.19)	0.845	61.5	0.034
Whole flaxseed	21	−0.97 (−1.13, −0.82)	<0.001	96.4	<0.001
Flaxseed oil	15	−0.54 (−0.71, −0.38)	<0.001	85.2	<0.001
Study design					
RCT	36	−0.76 (−0.87, −0.65)	<0.001	94.9	<0.001
Cross over	5	−1.02 (−2.65, 0.61)	0.220	0	1.000
Study population					
Diabetic	5	−0.98 (−1.37, −0.58)	<0.001	94.9	<0.001
Metabolic syndrome	8	−1.40 (−2.49, −0.30)	0.013	8.4	0.365
Menopausal	2	−2.39 (−5.17, 0.38)	0.091	0	0.704
Overweight and obese	4	−3.95 (−4.64, −3.26)	<0.001	89.9	<0.001
Healthy	4	0.88 (−1.72, −0.03)	0.043	66.1	0.007
Hyperlipidemia	4	−0.86 (−1.41, −0.32)	0.002	0	0.991
Ulcerative colitis	3	−0.41 (−0.53, −0.28)	<0.001	38.5	0.196
Hypertension	4	−8.49 (−9.31, −7.68)	<0.001	80.8	<0.001
Heart diseases	3	−4.08 (−5.31, −2.84)	<0.001	94.6	<0.001
NAFLD	1	−2.10 (−3.73, −0.47)	0.012	—	—
Control intervention type					
Placebo	7	−0.79 (−1.10, −0.47)	<0.001	92.9	<0.001
Wheat (barn, and germ)	7	−7.45 (−8.15, −6.75)	<0.001	87.7	<0.001
Rice	2	−0.89 (−3.88, 2.11)	0.562	0	0.614
Lifestyle modification	3	−1.50 (−2.83, −0.17)	0.027	0	0.728
Sunflower oil	8	−2.83 (−3.65, −2.01)	<0.001	85.1	<0.001
Olive oil	1	−2.00 (−3.19, −0.81)	<0.001	—	—
Medical advice	2	−0.44 (−0.57, −0.31)	<0.001	0	0.411
Soybean oil	2	1.00 (−2.33, 4.33)	0.556	0	1.000
Corn oil	1	−2.40 (−5.94, 1.14)	0.184	—	—
Hempseed oil	1	0.00 (−9.53, 9.53)	1.000	—	—
Whey powder	1	1.00 (−0.31, 2.31)	0.134	—	—
Others	6	−1.15 (−1.55, −0.76)	<0.001	93.8	<0.001
Sample size					
≤50	21	−0.52 (−0.64, −0.39)	<0.001	71.5	<0.001
>50	20	−1.78 (−2.03, −1.53)	<0.001	96.4	<0.001
BMI					
≤25	11	−0.46 (−0.58, −0.34)	<0.001	91	<0.001
25–30	19	−2.02 (−2.28, −1.75)	<0.001	95.9	<0.001
>30	5	−1.97 (−2.82, −1.12)	<0.001	0	0.861
NR	6	−2.95 (−4.76, −1.15)	<0.001	0	0.480
Study quality					
Low	21	−1.08 (−1.37, −0.79)	<0.001	85.1	<0.001
High	20	−0.71 (−0.83, −0.59)	<0.001	96.5	<0.001

[a] Obtained from the Random-effects model. [b] Refers to the mean (95% CI). [c] Inconsistency, percentage of variation across studies due to heterogeneity. [d] Obtained from the *Q*-test. Abbreviation: WMD; weighted mean differences, CI: confidence interval, NR: not reported, NAFLD; non-alcoholic fatty liver disease.

SBP, when compared to whole seed or flaxseed oil. This result was contrary to the results of the two previously-mentioned meta-analyses, which showed that the effects of whole flaxseed are stronger than other types of intervention. This could be due to the number of studies included in the analysis or the fact that lignan was more effective as one of the most active compounds in flaxseed. Studies have shown that lignan is an anti-hypertensive phytoestrogen that acts as an angiotensin-converting enzyme (ACE) inhibitor.[71,72]

Subgroup analysis based on the study population suggested that the greatest effect of flaxseed on SBP was observed in people with HTN, NAFLD and healthy people. Regarding DBP, greatest effects were observed in subjects with HTN, heart disease, overweight and obesity, respectively. Subgroup analysis also revealed that flaxseed supplement had the greatest effect in reducing BP (SBP and DBP) in BMI 25–30 kg m^{-2}.

Subgroup of control intervention type showed whey protein, wheat bran or germ and sunflower oil had significant effect on

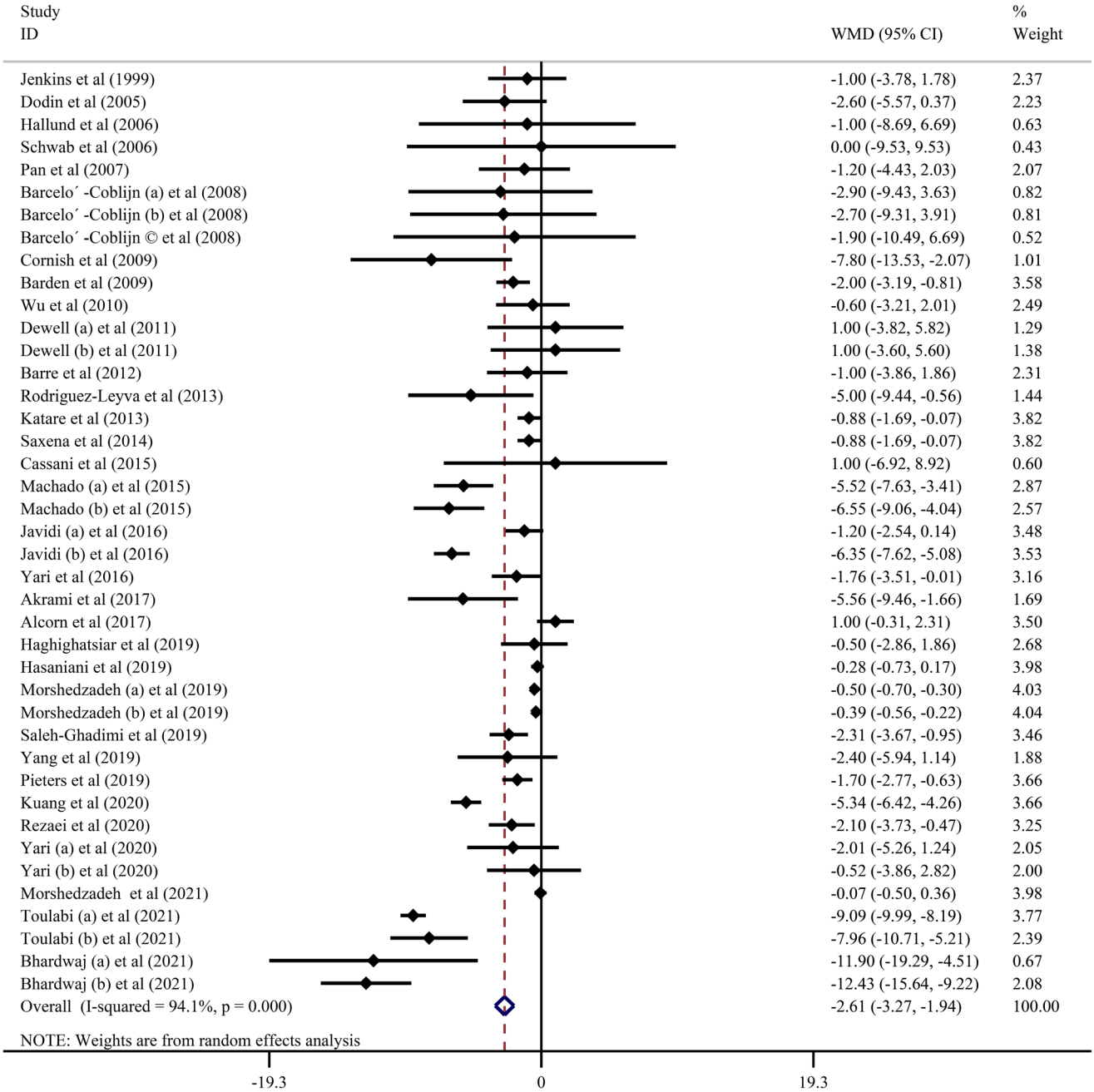

Fig. 3 Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of flaxseed supplementation on DBP levels.

BP. This can be attributed to active peptides in whey protein which results in BP improvement *via* enhancing vascular endothelial function.[73,74] Wheat bran, as a source of fiber, especially hemicellulose and some minerals such as magnesium and chromium, is effective in controlling BP.[75]

The exact mechanism of action of flaxseed on BP is yet not known. Flaxseed can affect BP *via* several ways: lignan compounds that inhibit ACE.[71,76] Alpha-Linolenic acid (ALA) is another important component of flaxseed that can affect BP. ALA is a PUFA from which some BP-reducing compounds such as lipoxins, prostaglandins and prostacyclins are derived.[77,78] Also, ALA react with nitric oxide (NO) to yield their respective nitro alkene derivatives that induce vascular relaxation.[79,80] Besides, ALA reduces the inflammation of blood vessels by inhibiting the activity of soluble epoxide hydrolase, thus improves the elasticity of arterials.[81] Another compound found in flaxseed that leads to BP reduction is a protein hydrolysate and a rich in arginine fraction isolated by potassium chloride (KCI-F1) rich.[82] In general, the synergistic effect of strong antioxidants such as lignans or different bioactive substances such as secoisolariciresinol glucoside (SDG), ALA or KCl-F1 in flaxseed can moderate BP.

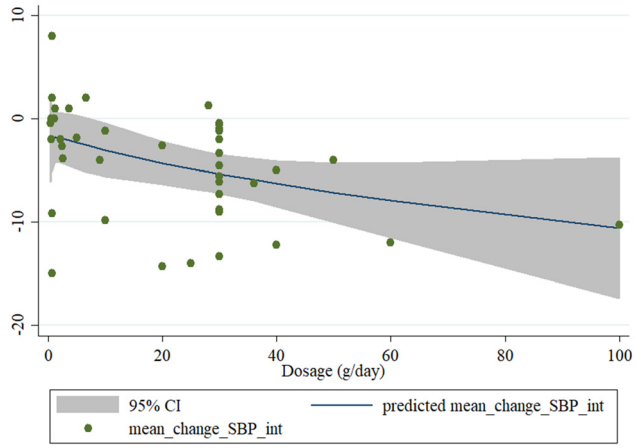

Fig. 4 Non-linear dose–response relations between dose of flaxseed supplementation (g day^{-1}) and absolute mean differences in SBP.

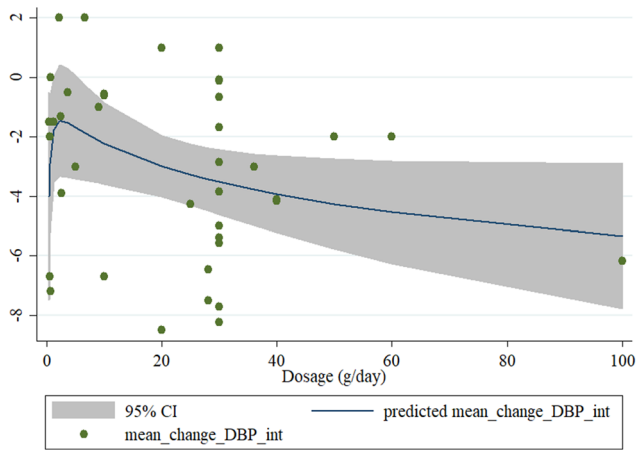

Fig. 5 Non-linear dose–response relations between dose of flaxseed supplementation (g day^{-1}) and absolute mean differences in DBP.

Most of the included studies had small numbers of participants and were heterogeneous concerning patient characteristics and study design, which may have impacted the findings. Further, different varieties of flaxseed were used in the included studies, and it was not possible to separate the effects from them were current study limitations. The strengths of the study include subgroup analysis for age, sex, disease, *etc.* Also, we registered our study protocol in PROSPERO. Considering the subgroup analysis for the dose and duration of the intervention, therapists can safely determine the safe dose and duration of administration.

5. Conclusion

Our findings with appropriate quality of evidence showed that flaxseed supplementation in a dose-dependent manner have improving effects on BP. Overweight or obese individuals in both genders receiving the higher dosages (>30 g day^{-1}) with moderate durations >20 weeks are benefited more from flaxseed supplementation. Therefore, flaxseed supplementation may be administered as an anti-hypertensive component alongside routine treatment, especially in ≥50-year patients with HTN and NAFLD.

Author contributions

LL, HL, XZ and MY designed the study; LL, YG, and SV performed the study; LL and YG analyzed the data and drafted the manuscript; YG and LL participated amending the manuscript. All authors approved the final version of the manuscript. This work was supported by The First batch of key Disciplines On Public Health in Chongqing.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1 G. C. Oh and H.-J. Cho, Blood pressure and heart failure, *Clin. Hypertens.*, 2020, **26**, 1–8.
2 F. D. Fuchs and P. K. Whelton, High blood pressure and cardiovascular disease, *Hypertension*, 2020, **75**, 285–292.
3 D. Malta, K. S. Petersen, C. Johnson, K. Trieu, S. Rae, K. Jefferson, J. A. Santos, M. M. Wong, T. S. Raj and J. Webster, High sodium intake increases blood pressure and risk of kidney disease. From the Science of Salt: A regularly updated systematic review of salt and health outcomes (August 2016 to March 2017), *J. Clin. Hypertens.*, 2018, **20**, 1654–1665.
4 W. H. Organization and I. S. o. H. W. Group, 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension, *J. Hypertens.*, 2003, **21**, 1983–1992.
5 E. A. F. Nilson, A. B. Metlzer, M.-E. Labonté and P. C. Jaime, Modelling the effect of compliance with WHO salt recommendations on cardiovascular disease mortality and costs in Brazil, *PLoS One*, 2020, **15**, e0235514.
6 R. M. Carey, P. K. Whelton and A. A. H. G. W. Committee, Prevention, detection, evaluation, and management of high blood pressure in adults: synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline, *Ann. Intern. Med.*, 2018, **168**, 351–358.
7 L. Strilchuk, R. I. Cincione, F. Fogacci and A. F. Cicero, Dietary interventions in blood pressure lowering: current evidence in 2020, *Kardiol. Pol.*, 2020, **78**, 659–666.
8 L. A. Bazzano, T. Green, T. N. Harrison and K. Reynolds, Dietary approaches to prevent hypertension, *Curr. Hypertens. Rep.*, 2013, **15**, 694–702.
9 V. Musazadeh, J. Jafarzadeh, M. Keramati, M. Zarezadeh, M. Ahmadi, Z. Farrokhian and A. Ostadrahimi, Flaxseed Oil

Supplementation Augments Antioxidant Capacity and Alleviates Oxidative Stress: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, *Evidence-Based Complementary Altern. Med.*, 2021, **2021**, 4438613.

10 B. Yang, L. Shi, A.-m. Wang, M.-q. Shi, Z.-h. Li, F. Zhao, X.-j. Guo and D. Li, Lowering effects of n-3 fatty acid supplements on blood pressure by reducing plasma angiotensin II in inner mongolia hypertensive patients: a double-blind randomized controlled trial, *J. Agric. Food Chem.*, 2018, **67**, 184–192.

11 S. Wu, X. Wang, W. Qi and Q. Guo, Bioactive protein/peptides of flaxseed: A review, *Trends Food Sci. Technol.*, 2019, **92**, 184–193.

12 A. Hadi, M. Askarpour, S. Salamat, E. Ghaedi, M. E. Symonds and M. Miraghajani, Effect of flaxseed supplementation on lipid profile: An updated systematic review and dose-response meta-analysis of sixty-two randomized controlled trials, *Pharmacol. Res.*, 2020, **152**, 104622.

13 K. Bhardwaj, N. Verma, R. Trivedi and S. Bhardwaj, Effect of essential fatty acid blend on circadian variations of ambulatory blood pressure in patients with essential hypertension and coronary artery disease risk markers, *J. Hum. Hypertens.*, 2022, **36**, 289–298.

14 A. Akrami, F. Nikaein, S. Babajafari, S. Faghih and H. Yarmohammadi, Comparison of the effects of flaxseed oil and sunflower seed oil consumption on serum glucose, lipid profile, blood pressure, and lipid peroxidation in patients with metabolic syndrome, *J. Clin. Lipidol.*, 2018, **12**, 70–77.

15 A. Javidi, H. Mozaffari-Khosravi, A. Nadjarzadeh, A. Dehghani and M. H. Eftekhari, The effect of flaxseed powder on insulin resistance indices and blood pressure in prediabetic individuals: A randomized controlled clinical trial, *J. Res. Med. Sci.*, 2016, **21**, 70.

16 D. Rodriguez-Leyva, W. Weighell, A. L. Edel, R. LaVallee, E. Dibrov, R. Pinneker, T. G. Maddaford, B. Ramjiawan, M. Aliani and R. Guzman, Potent antihypertensive action of dietary flaxseed in hypertensive patients, *Hypertension*, 2013, **62**, 1081–1089.

17 T. Mahmudiono, S. A. Jasim, Y. S. Karim, D. O. Bokov, W. K. Abdelbasset, K. S. Akhmedov, G. Yasin, L. Thangavelu, Y. F. Mustafa and S. Shoukat, 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, *Phytother. Res.*, 2022, **36**(10), 3766–3773.

18 S. Ursoniu, A. Sahebkar, F. Andrica, C. Serban and M. Banach, Lipid and B. P. M.-a. Collaboration, Effects of flaxseed supplements on blood pressure: A systematic review and meta-analysis of controlled clinical trial, *Clin. Nutr.*, 2016, **35**, 615–625.

19 S. Khalesi, C. Irwin and M. Schubert, Flaxseed consumption may reduce blood pressure: a systematic review and meta-analysis of controlled trials, *J. Nutr*, 2015, **145**, 758–765.

20 D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman and P. G. The, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, *PLoS Med.*, 2009, **6**, e1000097.

21 J. P. T. Higgins, D. G. Altman, P. C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savović, K. F. Schulz, L. Weeks and J. A. C. Sterne, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, *Br. Med. J.*, 2011, **343**, d5928.

22 G. H. Guyatt, A. D. Oxman, G. E. Vist, R. Kunz, Y. Falck-Ytter, P. Alonso-Coello and H. J. Schünemann, GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, *Br. Med. J.*, 2008, **336**, 924–926.

23 R. DerSimonian and N. Laird, Meta-analysis in clinical trials, *Controlled Clin. Trials*, 1986, **7**, 177–188.

24 S. P. Hozo, B. Djulbegovic and I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample, *BMC Med. Res. Methodol.*, 2005, **5**, 1–10.

25 C. B. Begg and M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, *Biometrics*, 1994, 1088–1101.

26 M. Egger, G. D. Smith, M. Schneider and C. Minder, Bias in meta-analysis detected by a simple, graphical test, *Br. Med. J.*, 1997, **315**, 629–634.

27 R. S. L. Cassani, P. G. Fassini, J. H. Silvah, C. M. M. Lima and J. S. Marchini, Impact of weight loss diet associated with flaxseed on inflammatory markers in men with cardiovascular risk factors: a clinical study, *Nutr. J.*, 2015, **14**, 1–8.

28 N. Haghighatsiar, G. Askari, S. Saraf-Bank, A. Feizi and H. Keshmiri, Effect of flaxseed powder on cardiovascular risk factor in dyslipidemic and hypertensive patients, *Int. J. Prev. Med.*, 2019, **10**(10), 218.

29 N. Hasaniani, M. Rahimlou, A. R. Ahmadi, A. M. Khalifani and M. Alizadeh, The effect of flaxseed enriched yogurt on the glycemic status and cardiovascular risk factors in patients with type 2 diabetes mellitus: randomized, open-labeled, controlled study, *Clin. Nutr. Res.*, 2019, **8**, 284–295.

30 X. Kuang, Y. Kong, X. Hu, K. Li, X. Guo, C. Liu, L. Han and D. Li, Defatted flaxseed flour improves weight loss and lipid profile in overweight and obese adults: A randomized controlled trial, *Food Funct.*, 2020, **11**, 8237–8247.

31 A. M. Machado, H. de Paula, L. D. Cardoso and N. M. Costa, Effects of brown and golden flaxseed on the lipid profile, glycemia, inflammatory biomarkers, blood pressure and body composition in overweight adolescents, *Nutrition*, 2015, **31**, 90–96.

32 N. Morshedzadeh, S. Shahrokh, H. A. Aghdaei, M. A. Pourhoseingholi, V. Chaleshi, A. Hekmatdoost, S. Karimi, M. R. Zali and P. Mirmiran, Effects of flaxseed and flaxseed oil supplement on serum levels of inflammatory markers, metabolic parameters and severity of disease in patients with ulcerative colitis, *Complement. Ther. Med.*, 2019, **46**, 36–43.

33 N. Morshedzadeh, M. Rahimlou, S. Shahrokh, S. Karimi, P. Mirmiran and M. R. Zali, The effects of flaxseed sup-

plementation on metabolic syndrome parameters, insulin resistance and inflammation in ulcerative colitis patients: An open–labeled randomized controlled trial, *Phytother. Res.*, 2021, **35**, 3781–3791.
34 S. Rezaei, M. R. Sasani, M. Akhlaghi and A. Kohanmoo, Flaxseed oil in the context of a weight loss programme ameliorates fatty liver grade in patients with non-alcoholic fatty liver disease: a randomised double-blind controlled trial, *Br. J. Nutr.*, 2020, **123**, 994–1002.
35 S. Saleh-Ghadimi, S. Kheirouri, A. Golmohammadi, J. Moludi, H. Jafari-Vayghan and M. Alizadeh, Effect of flaxseed oil supplementation on anthropometric and metabolic indices in patients with coronary artery disease: a double-blinded randomized controlled trial, *J. Cardiovasc. Thorac. Res.*, 2019, **11**, 152.
36 T. Toulabi, M. Yarahmadi, F. Goudarzi, F. Ebrahimzadeh, A. Momenizadeh and S. Yarahmadi, Effects of flaxseed on blood pressure, body mass index, and total cholesterol in hypertensive patients: A randomized clinical trial, *Explore*, 2022, **18**, 438–445.
37 Z. Yari, M. Rahimlou, H. Poustchi and A. Hekmatdoost, Flaxseed supplementation in metabolic syndrome management: a pilot randomized, open–labeled, controlled study, *Phytother. Res.*, 2016, **30**, 1339–1344.
38 Z. Yari, M. Cheraghpour and A. Hekmatdoost, Flaxseed and/or hesperidin supplementation in metabolic syndrome: An open-labeled randomized controlled trial, *Eur. J. Nutr.*, 2021, **60**, 287–298.
39 G. Barceló-Coblijn, E. J. Murphy, R. Othman, M. H. Moghadasian, T. Kashour and J. K. Friel, Flaxseed oil and fish-oil capsule consumption alters human red blood cell n–3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n–3 fatty acid, *Am. J. Clin. Nutr.*, 2008, **88**, 801–809.
40 S. M. Cornish, P. D. Chilibeck, L. Paus-Jennsen, H. J. Biem, T. Khozani, V. Senanayake, H. Vatanparast, J. P. Little, S. J. Whiting and P. Pahwa, A randomized controlled trial of the effects of flaxseed lignan complex on metabolic syndrome composite score and bone mineral in older adults, *Appl. Physiol., Nutr., Metab.*, 2009, **34**, 89–98.
41 A. Dewell, F. F. Marvasti, W. S. Harris, P. Tsao and C. D. Gardner, Low-and high-dose plant and marine (n-3) fatty acids do not affect plasma inflammatory markers in adults with metabolic syndrome, *J. Nutr.*, 2011, **141**, 2166–2171.
42 S. Dodin, A. Lemay, H. Jacques, F. Légaré, J.-C. Forest and B. Masse, The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: a randomized, double-blind, wheat germ placebo-controlled clinical trial, *J. Clin. Endocrinol. Metab.*, 2005, **90**, 1390–1397.
43 H. Wu, A. Pan, Z. Yu, Q. Qi, L. Lu, G. Zhang, D. Yu, G. Zong, Y. Zhou and X. Chen, Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome, *J. Nutr.*, 2010, **140**, 1937–1942.
44 A. E. Barden, K. D. Croft, T. Durand, A. Guy, M. J. Mueller and T. A. Mori, Flaxseed oil supplementation increases plasma F1-phytoprostanes in healthy men, *J. Nutr.*, 2009, **139**, 1890–1895.
45 C. Katare and S. Saxena, Amelioration of selected cardiac risk factors through supplementation of diet with flaxseed and soya bean, *Int. J. Nutr., Pharmacol., Neurol. Dis.*, 2013, **3**, 352.
46 S. Saxena and C. Katare, Evaluation of flaxseed formulation as a potential therapeutic agent in mitigation of dyslipidemia, *Biomed. J.*, 2014, **37**(6), 386–390.
47 Y. Di, J. Jones, K. Mansell, S. Whiting, S. Fowler, L. Thorpe, J. Billinsky, N. Viveky, P. C. Cheng and A. Almousa, Influence of flaxseed lignan supplementation to older adults on biochemical and functional outcome measures of inflammation, *J. Am. Coll. Nutr.*, 2017, **36**, 646–653.
48 D. J. Pieters, P. L. Zock, D. Fuchs and R. P. Mensink, Effect of α-linolenic acid on 24-h ambulatory blood pressure in untreated high-normal and stage I hypertensive subjects, *Br. J. Nutr.*, 2019, **121**, 155–163.
49 J. Alcorn, S. Whiting, N. Viveky, Y. Di, K. Mansell, S. Fowler, L. Thorpe, A. Almousa, P. C. Cheng and J. Jones, Protocol for a 24-week randomized controlled study of once-daily oral dose of flax lignan to healthy older adults, *JMIR Res. Protocols*, 2017, **6**, e6817.
50 D. Barre, K. Mizier-Barre, E. Stelmach, J. Hobson, O. Griscti, A. Rudiuk and D. Muthuthevar, Flaxseed lignan complex administration in older human type 2 diabetics manages central obesity and prothrombosis—an invitation to further investigation into polypharmacy reduction, *J. Nutr. Metab.*, 2012, **2012**, 585170.
51 J. Hallund, I. Tetens, S. Bügel, T. Tholstrup, M. Ferrari, T. Teerlink, A. Kjaer and N. Wiinberg, Daily consumption for six weeks of a lignan complex isolated from flaxseed does not affect endothelial function in healthy postmenopausal women, *J. Nutr.*, 2006, **136**, 2314–2318.
52 D. J. Jenkins, C. W. Kendall, E. Vidgen, S. Agarwal, A. V. Rao, R. S. Rosenberg, E. P. Diamandis, R. Novokmet, C. C. Mehling and T. Perera, Health aspects of partially defatted flaxseed, including effects on serum lipids, oxidative measures, and ex vivo androgen and progestin activity: a controlled crossover trial, *Am. J. Clin. Nutr.*, 1999, **69**, 395–402.
53 A. Pan, J. Sun, Y. Chen, X. Ye, H. Li, Z. Yu, Y. Wang, W. Gu, X. Zhang and X. Chen, Effects of a flaxseed-derived lignan supplement in type 2 diabetic patients: a randomized, double-blind, cross-over trial, *PLoS One*, 2007, **2**, e1148.
54 U. S. Schwab, J. C. Callaway, A. T. Erkkilä, J. Gynther, M. I. Uusitupa and T. Järvinen, Effects of hempseed and flaxseed oils on the profile of serum lipids, serum total and lipoprotein lipid concentrations and haemostatic factors, *Eur. J. Nutr.*, 2006, **45**, 470–477.
55 E. O. Gosmanova, M. K. Mikkelsen, M. Z. Molnar, J. L. Lu, L. T. Yessayan, K. Kalantar-Zadeh and C. P. Kovesdy, Association of systolic blood pressure variability with mor-

tality, coronary heart disease, stroke, and renal disease, *J. Am. Coll. Cardiol.*, 2016, **68**, 1375–1386.

56 R.-E. W. Kavey, V. Allada, S. R. Daniels, L. L. Hayman, B. W. McCrindle, J. W. Newburger, R. S. Parekh and J. Steinberger, Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association expert panel on population and prevention science; the councils on cardiovascular disease in the young, epidemiology and prevention, nutrition, physical activity and metabolism, high blood pressure research, cardiovascular nursing, and the kidney in heart disease; and the interdisciplinary working group on quality of care and outcomes research: endorsed by the American Academy of Pediatrics, *Circulation*, 2006, **114**, 2710–2738.

57 M. El Assar, J. Angulo and L. Rodríguez-Mañas, Oxidative stress and vascular inflammation in aging, *Free Radicals Biol. Med.*, 2013, **65**, 380–401.

58 J. R. Jackson, M. J. Ryan, Y. Hao and S. E. Alway, Mediation of endogenous antioxidant enzymes and apoptotic signaling by resveratrol following muscle disuse in the gastrocnemius muscles of young and old rats, *Am. J. Physiol.: Regul., Integr. Comp. Physiol.*, 2010, **299**, R1572–R1581.

59 H. Kara, A. Orem, E. Yulug, F. B. Yucesan, G. Kerimoglu, S. O. Yaman, A. Bodur, S. Turedi and C. Alasalvar, Hazelnut consumption improves testicular antioxidant function and semen quality in young and old male rats, *Food Chem.*, 2019, **294**, 1–8.

60 T. Oseni, R. Patel, J. Pyle and V. C. Jordan, Selective estrogen receptor modulators and phytoestrogens, *Planta Med.*, 2008, **74**, 1656–1665.

61 J. A. Cohen, S. H. Lindsey, N. T. Pirro, K. B. Brosnihan, P. E. Gallagher and M. C. Chappell, Influence of estrogen depletion and salt loading on renal angiotensinogen expression in the mRen (2). Lewis strain, *Am. J. Physiol.: Renal, Fluid Electrolyte Physiol.y*, 2010, **299**, F35–F42.

62 X. Xu, J.-C. Xiao, L.-F. Luo, S. Wang, J.-P. Zhang, J.-J. Huang, M.-L. Liu, C.-G. Liu, K.-Q. Xu, Y.-J. Li and H.-P. Song, Effects of ovariectomy and 17β-estradiol treatment on the renin–angiotensin system, blood pressure, and endothelial ultrastructure, *Int. J. Cardiol.*, 2008, **130**, 196–204.

63 D. A. Nowak, D. C. Snyder, A. J. Brown and W. Demark-Wahnefried, The Effect of Flaxseed Supplementation on Hormonal Levels Associated with Polycystic Ovarian Syndrome: A Case Study, *Curr. Top. Nutraceutical Res.*, 2007, **5**, 177–181.

64 A. R. Zheng, C. K. Wei, Z. J. Ni, K. Thakur, J. G. Zhang and Z. J. Wei, Gut modulatory effects of flaxseed derived Maillard reaction products in Sprague-Dawley rats during sub-chronic toxicity, *Food Chem. Toxicol.*, 2022, **165**, 113115.

65 S. P. B. Caligiuri, A. L. Edel, M. Aliani and G. N. Pierce, Flaxseed for Hypertension: Implications for Blood Pressure Regulation, *Curr. Hypertens. Rep.*, 2014, **16**, 499.

66 C. M. Dupasquier, A.-M. Weber, B. P. Ander, P. Rampersad, S. Steigerwald, J. T. Wigle, R. W. Mitchell, E. A. Kroeger, J. S. Gilchrist and M. M. Moghadasian, Effects of dietary flaxseed on vascular contractile function and atherosclerosis during prolonged hypercholesterolemia in rabbits, *Am. J. Physiol.: Heart Circ. Physiol.*, 2006, **291**, H2987–H2996.

67 C. C. Udenigwe, Y.-S. Lin, W.-C. Hou and R. E. Aluko, Kinetics of the inhibition of renin and angiotensin I-converting enzyme by flaxseed protein hydrolysate fractions, *J. Funct. Foods*, 2009, **1**, 199–207.

68 C. Yang, M. Wan, D. Xu, D. Pan, H. Xia, L. Yang and G. Sun, Flaxseed powder attenuates non-alcoholic steatohepatitis via modulation of gut microbiota and bile acid metabolism through gut–liver axis, *Int. J. Mol. Sci.*, 2021, **22**, 10858.

69 U. Afzal, M. S. Butt, F. Ashfaq, A. Bilal and H. A. R. Suleria, Bioassessment of flaxseed powder and extract against hyperglycemia and hypercholesterolemia using Sprague Dawley rats, *Clin. Phytosci.*, 2020, **6**, 1–13.

70 F. E. Mohamed, A. K. Taha and O. A. Khalid, Influence of defatted flaxseed diet on insulin sensitivity, vascular permeability and lipid profile in a rat model of type 2 diabetes mellitus, *J. Med. Plants Res.*, 2012, **6**, 2188–2193.

71 K. Prasad, Secoisolariciresinol diglucoside (SDG) isolated from flaxseed, an alternative to ACE inhibitors in the treatment of hypertension, *Int. J. Angiol.*, 2013, **22**, 235–238.

72 D. Desmawati and D. Sulastri, Phytoestrogens and their health effect, *Maced. J. Med. Sci.*, 2019, **7**, 495.

73 T. G. Tavares and F. X. Malcata, Whey proteins as source of bioactive peptides against hypertension, *Bioact. Food Pept. Health Dis.*, 2013, **75**, 77–159.

74 A. A. Fekete, C. Giromini, Y. Chatzidiakou, D. I. Givens and J. A. Lovegrove, Whey protein lowers blood pressure and improves endothelial function and lipid biomarkers in adults with prehypertension and mild hypertension: results from the chronic Whey2Go randomized controlled trial, *Am. J. Clin. Nutr.*, 2016, **104**, 1534–1544.

75 M. A. E. Elmadbouly, Impact of Wheat Bran Supplementation on Body Weight, Blood Pressure, Blood Glucose and Blood Lipids Among Obese Diabetic Women in Holy Makkah, *Vedic Res. Int. Biol. Med. Chem.*, 2015, **3**, 5–9.

76 S. H. Sawant and S. L. Bodhankar, Flax lignan concentrate attenuate hypertension and abnormal left ventricular contractility via modulation of endogenous biomarkers in two-kidney-one-clip (2K1C) hypertensive rats, *Rev. Bras. Farmacogn.*, 2016, **26**, 601–610.

77 U. N. Das, Lipoxins, resolvins, protectins, maresins, and nitrolipids: connecting lipids, inflammation, and cardiovascular disease risk, *Curr. Cardiovasc. Risk Rep.*, 2010, **4**, 24–31.

78 A. Wiktorowska-Owczarek, M. Berezinska and J. Z. Nowak, PUFAs: structures, metabolism and functions, *Adv. Clin. Exp. Med.*, 2015, **24**, 931–941.

79 U. N. Das, Essential fatty acids and their metabolites could function as endogenous HMG-CoA reductase and ACE enzyme inhibitors, anti-arrhythmic, anti-hypertensive, anti-atherosclerotic, anti-inflammatory, cytoprotective, and cardioprotective molecules, *Lipids Health Dis.*, 2008, **7**, 1–18.

80 U. N. Das, Essential fatty acids: biochemistry, physiology and pathology, *Biotechnol. J.*, 2006, **1**, 420–439.
81 S. P. Caligiuri, A. L. Edel, M. Aliani and G. N. Pierce, Flaxseed for hypertension: implications for blood pressure regulation, *Curr. Hypertens. Rep.*, 2014, **16**, 1–13.
82 A. E.-D. A. Bekhit, A. Shavandi, T. Jodjaja, J. Birch, S. Teh, I. A. M. Ahmed, F. Y. Al-Juhaimi, P. Saeedi and A. A. Bekhit, Flaxseed: Composition, detoxification, utilization, and opportunities, *Biocatal. Agric. Biotechnol.*, 2018, **13**, 129–152.