Clinical Nutrition xxx (2015) 1–11

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

# Effects of flaxseed supplements on blood pressure: A systematic review and meta-analysis of controlled clinical trial

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ARTICLE INFO

*Article history:*
Received 29 March 2015
Accepted 19 May 2015

*Keywords:*
Flaxseed
*Linum usitatissimum*
Arterial hypertension
Meta-analysis
Systematic review

SUMMARY

*Background & aims:* Many experimental and clinical trials suggested that flaxseed might be a potent antihypertensive, but the evidences concerning the effects of flaxseed supplements on blood pressure (BP) has not been fully conclusive. We aimed to assess the impact of the effects of flaxseed supplements on blood pressure through systematic review of literature and meta-analysis of available randomized controlled trials (RCTs).

*Methods:* The literature search included PUBMED, Cochrane Library, Scopus, and EMBASE up to February 2015 to identify RCTs investigating the effect of flaxseed supplements on plasma blood pressure. Effect size was expressed as weighed mean difference (WMD) and 95% confidence interval (CI).

*Results:* 15 trials (comprising 19 treatment arms) with 1302 participants were included in this meta-analysis. Random-effects meta-analysis suggested significant reductions in both systolic BP (SBP) (WMD: −2.85 mmHg, 95%CI: −5.37 to −0.33, $p = 0.027$) and diastolic BP (DBP) (WMD: −2.39 mmHg, 95%CI: −3.78 to −0.99, $p = 0.001$) following supplementation with flaxseed products. When the studies were stratified according to their duration, there was a greater effect on both SBP and DBP in the subset of trials with ≥12 weeks of duration (WMD: −3.10 mmHg, 95%CI: −6.46 to 0.27, $p = 0.072$ and −2.62 mmHg, 95%CI: −4.39 to −0.86, $p = 0.003$, respectively) *vs* the subset lasting <12 weeks (WMD: −1.60 mmHg, 95%CI: −5.44 to 2.24, $p = 0.413$, and −1.74 mmHg, 95%CI: −4.41 to 0.93, $p = 0.202$, respectively). Another subgroup analysis was performed to assess the impact of flaxseed supplement type on BP. Reduction of SBP was significant with flaxseed powder (WMD: −1.81 mmHg, 95% CI: −2.03 to −1.59, $p < 0.001$) but not oil (WMD: −4.62 mmHg, 95%CI: −11.86 to 2.62, $p = 0.211$) and lignan extract (WMD: 0.28 mmHg, 95% CI: −3.49 to 4.04, $p = 0.885$). However, DBP was significantly reduced with powder and oil preparations (WMD: −1.28 mmHg, 95% CI: −2.44 to −0.11, $p = 0.031$, and −4.10 mmHg, 95%CI: −6.81 to −1.39, $p = 0.003$, respectively), but not with lignan extract (WMD: −1.78 mmHg, 95% CI: −4.28 to 0.72, $p = 0.162$).

*Conclusions:* This meta-analysis of RCTs showed significant reductions in both SBP and DBP following supplementation with various flaxseed products.



## 1. Introduction

Dietary interventions have been recommended as attractive add-on therapies to control blood pressure and decrease the burden of hypertension [1]. Flaxseed (*Linum usitatissimum*), an oilseed crop grown on all continents and highly accessible, has been shown to decrease the risk of cardiovascular disease by

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http://dx.doi.org/10.1016/j.clnu.2015.05.012
0261-5614/

decreasing lipid profile parameters [2], plasma trans fats [3], atherogenicity [4,5], glycemia [2] or pro-inflammatory oxylipins [6]. Furthermore, flaxseed and its components have been associated with blood pressure (BP) reduction in many animal studies and randomized controlled trials [7]. Flaxseed is composed of enterolignan precursors, primarly secoisolariciresinol diglucoside (SDG) [6], total fibers, omega -3 fatty acids and alpha linolenic acid (ALA) [8]. It has been proven that the brown or golden varieties of flaxseed might influence its favorable health effects, by different percent of compounds [9]. Epaminondas et al. found a lower amount of fiber, but a higher amount of soluble carbohydrates in the golden flaxseed than in the brown variety, and no differences regarding the percent of lipids and proteins [10]. Moreover, Sargi et al. detected that golden flaxseed has higher levels of omega -3 and -6, while brown flaxseed has higher antioxidant capacity [11].

The anti-hypertensive action of dietary fiber was demonstrated in some meta-analyses [12], but the exactly effects on blood pressure are still inconclusive [13,14]. Therefore, we systematically review all the published trials on flaxseed supplementation and assess its overall efficacy on BP reduction.

## 2. Methods

### 2.1. Search strategy

This systematic review and meta-analysis was performed according to the guiding principles of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [15]. The following search terms in titles and abstracts were used to retrieve relevant articles from SCOPUS (http://www.scopus.com) and Medline (http://www.ncbi.nlm.nih.gov/pubmed) databases: ("randomized controlled trial" OR randomized) and ("blood pressure" OR hypertension OR anti-hypertensive OR hypotension OR hypotensive) and (flaxseed OR *L. usitatissimum*). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human subjects. The literature was searched until February 12, 2015.

### 2.2. Study selection

To include studies to the meta-analysis, the following criteria were considered: (i) clinical trials with a case–control or cross-over design, (ii) investigation of the effect of flaxseed preparations on blood pressure, (iii) Providing baseline and end-trial blood pressure values in both flaxseed and control groups, and (iv) having a supplementation (with flaxseed) period of at least two weeks. Non-clinical studies, uncontrolled trials, and trials with insufficient data on blood pressure values in flaxseed and control groups were excluded from the meta-analysis.

### 2.3. Data extraction

Eligible studies that met the inclusion criteria were reviewed and the following information were extracted: 1) first author's name; 2) year of publication; 3) location of the study; 4) number of participants in the flaxseed and control groups; 5) dose and duration of supplementation with flaxseed products; 6) age, gender and body mass index (BMI) of participants; 7) plasma (or serum) concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides and glucose; and 8) systolic and diastolic blood pressure (SBP and DBP).

### 2.4. Quality assessment

Assessment of risk of bias in the studies included in the analysis was performed systematically using the Cochrane quality assessment tool for RCTs [16]. Cochrane tool has 7 criteria for quality assessment: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The risk of bias in each study was judged to be low, high or unclear.

### 2.5. Quantitative data synthesis

Meta-analysis was performed using the Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ). Net changes in SBP and DBP between flaxseed and control group were calculated by subtracting the values at end of follow-up from those at baseline. For cross-over trials, each treatment arm was treated as an individual RCT, and net changes were calculated as difference between the values after treatment and control intervention. All BP units were collated in mmHg. In order to calculate the standard deviations (SDs) for the net changes, the following formula was used: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient ($R$) = 0.5. If the outcome measures were reported in median and inter-quartile range, mean and SD values were estimated as described by Hozo et al. [17]. To convert interquartile range into Min–Max range, the following equations were used: $A$ = median + 2 × ($Q_3$ − median) and $B$ = median − 2 × (median − $Q_1$), where $A$, $B$, $Q_1$ and $Q_3$ are upper and lower ends of the range, upper and lower ends of the interquartile range, respectively. For studies that reported standard error of the mean (SEM), standard deviation (SD) was estimated using the following formula: SD = SEM × sqrt ($n$), where $n$ is the number of subjects. For studies with multiple measurements that reported data at different time points, only to the values of the longest duration of treatment were used. In order to avoid double-counting of values in trials comparing multiple treatment arms versus a common control group, the number of subjects in the control group was divided by the number of treatment arms. When no SD was provided for BP values in a study, the missing value was imputed by the pooled SD of other studies. Meta-analysis was performed using a random-effects model (DerSimonian–Laird method) and the generic inverse variance method. The choice of random-effects model was to compensate for the inter-study heterogeneities in terms of demographic characteristics of populations being studied and also differences in study designs. Heterogeneity was quantitatively assessed using $I^2$ index. The summary statistic of effect size was weighted mean difference (WMD) and 95% confidence interval (CI). Sensitivity analysis was performed using a leave-one-out method, i.e. iteratively removing one study each time and repeating the analysis [18,19].

### 2.6. Meta-regression

The impact of supplementation duration and flaxseed dose as potential moderators of effect size was explored using meta-regression. An unrestricted maximum likelihood method under a random-effects model was applied to detect the association between calculated WMD and above-mentioned moderators.

### 2.7. Publication bias

Assessment of publication bias was performed using visual inspection of Begg's funnel plot asymmetry. Quantitative

Please cite this article in press as: Ursoniu S, et al., Effects of flaxseed supplements on blood pressure: A systematic review and meta-analysis of controlled clinical trial, Clinical Nutrition (2015), http://dx.doi.org/10.1016/j.clnu.2015.05.012