Effects of Flaxseed on Blood Lipids in Healthy and Dyslipidemic Subjects: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: To address hyperlipidemia, flaxseed demonstrates a great impact on experimental and clinical trials. Therefore, the effects of flaxseed on lipid profiles of healthy and dyslipidemic subjects were assayed. The literature search was performed based on English reports of randomized control trials (RCTs) up to April 2021 to seek the effect of flaxseed on lipid profiles of healthy and dyslipidemic subjects. A total of 14 RCTs with 1107 participants were evaluated. Based on results, flaxseed significantly improves the lipid profile in dyslipidemic patients comprising total cholesterol (TC), low-density lipoprotein (LDL-C) and triglyceride (TG) in comparison with the control group. Nevertheless, no significant changes were observed in high-density lipoprotein (HDL-C). Although in healthy individual flaxseed significantly increased HDL-C, LDL-C and TG. Subgroup analysis on healthy

Disclosures: There are no conflicts of interest.
Curr Probl Cardiol 2022;47:100931
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2021.100931

subjects showed that flaxseed improved LDL-C on overweight subjects with BMI>25. The evidence suggests that flaxseed significantly improved TC, LDL-C and TG in dyslipidemic subjects and additionally improved the HDL-C on healthy subjects. (Curr Probl Cardiol 2022;47:100931.)

Introduction

Dyslipidemia is one of the major risk factors for atherosclerosis and cardiovascular disease (CVD). The coincidence of dyslipidemia with other metabolic diseases including hypertension, glucose intolerance and obesity can be identified as metabolic syndrome (MS); In this situation, patients demonstrate an increased risk of type II diabetes and CVD.[7,19,62]

Dyslipidemia is a heterogeneous disease characterized by an abnormality in the lipid profile such as triglycerides (TGs), phospholipids, cholesterols, lipoproteins, and other fats.[61,78] Changes in lipid plasma in dyslipidemia are usually associated with an increase in cholesterol, TG, and/or low-density lipoprotein cholesterol (LDL-C), or low levels of high-density lipoprotein cholesterol (HDL-C) which can be also present in combination.[7] Due to the MS epidemic posing an increasing universal public health matter, safe and effective therapies remain a principal challenge. Despite the advancement of the treatment and prevention of dyslipidemia, medications used to treat dyslipidemia are limited to chemical drugs. Although they have some beneficial effects on lipid profiles, they demonstrate some side effects. Statin, the first-line drug treatment, has been associated side effects that the most important of them are myopathy and rhabdomyolysis.[75]

Since people's attention is attracted to the use of herbal medicines as a treatment of their diseases including dyslipidemia, finding the effective interventions, nutritional strategies, and complementary therapies are of important concern.[2,19,52]

Flaxseed or linseed (*Linum usitatissimum*), from the Linaceae family is one of the best anti-atherogenic herbs[2,30,81] that has numerous biological properties including anti-inflammatory, anti-hyperlipidemia, anti-obesity, anti-diabetic, anti-oxidant, anti-microbial, anti-cancer, anti-atherogenic, anti-hypertensive, and anti-arthritic activities.[30] The active component of the flaxseed include α-linoleic acid (ALA), linoleic acid (LA), oleic acid, phenolic compounds, phytoestrogens, lignans, high-quality protein, and

soluble fiber vitamins[2,30,81]; due to its effects and components, it can be used as one of the best lipid-lowering agents.[29]

There are controversial studies on the lipid-lowering effects of flaxseed. Two meta-analyses had been performed in both 2009[55] and 2019[28]; a great variety was observed between the type of diseases and the kind of flaxseed.[12] We tried to minimize the changes and focused on flaxseed and dyslipidemic subjects because dyslipidemia is a multifactorial disease with genetic predispositions or drug-related changes in lipid metabolism.[3] On the other hand, we appraise and compare healthily and dyslipidemic subjects separately, owing to the study that was reported by Schmidt *et al.* It was reported that gene expression profile of normal and dyslipidemia subjects differed substantially after fish oil supplementation. In the dyslipidemic study group more genes were down-regulated while in normolipidemic subjects more genes were up-regulated which was explained by the interrelation between inflammation and dyslipidemia.[14]

Because of low quality and the small number of studies in subjects with dyslipidemia and normolipidemic individuals make it difficult to extrapolate the results, this meta-analysis was performed to further assess the effectiveness of flaxseed on lipid profile in populations with and without dyslipidemia, separately. Moreover, there is clinical evidence reporting the effect of flaxseed on dyslipidemia and healthy human lipid profiles which were missing in the previous meta-analyses.[4,44,56,76] The objective of this meta-analysis was to determine the effect of flaxseed on lipid profile (TC, LDL-C, HDL-C and TGs) of healthy compared with dyslipidemic subjects.

Material and Methods

This meta-analysis has been established according to the preferred reporting items for systematic reviews and meta-analyses statements.

Search Strategy

Five databases (PUBMED, Cochrane Library, Scopus, Web of Science, and Google Scholar) were used to perform literature search for identifying English-language RCTs which investigated the effects of flaxseed on lipid profile with and without dyslipidemic subjects and were published before April 2021. Medical subjects heading (MeSH) and non-MeSH terms were used with the following keywords: lipid OR dyslipidemia OR hyperlipidemia OR hypercholesterolemia OR triglyceride OR cholesterol OR "high density lipoprotein cholesterol" OR "Low Density Lipoprotein Cholesterol" OR "LDL

Cholesterol" AND flax OR linseed OR "*Linum usitatissimum*" OR *linum* and limited to human. Furthermore, a manual search was conducted on the relevant reviews[29,55] and reference lists of included trials for additional eligible studies that may have been missed.

Eligibility Criteria

Inclusion criteria were: (1) RCTs-control study designs; (2) studies that supported sufficient TC, and/or LDL-C, and/or HDL-C, and/or TG data at baseline and follow-up in both flaxseed supplementation and control groups; (3) studies that subjects consumed flaxseed for >1 week; (4) the studies administrated flaxseed in the form of whole flaxseed, ground flaxseed, flaxseed oil and dietary fiber (5) studies that evaluated the effect of flaxseed on dyslipidemia and healthy subjects.

Exclusion criteria were: (1) studies that carried out in animals or in vitro; (2) studies on other disease (like MS, diabetes, CVD, and prostate cancer) or on postmenstrual women; (3) studies that reported dose of one ingredient of flaxseed like secoisolariciresinol (SDG) or ALA or lignans; (4) studies that evaluated the effects of flaxseed alongside other supplements (like other oils or vitamins); (5) studies that conducted flaxseed product (like muffin or bread); (6) studies with insufficient information for meta-analysis and (8) grey literature such as conference papers and dissertations.

According to this criterion, a total of 14 citations were identified. Disagreements regarding the selection of articles were resolved by discussion until a consensus was reached among the reviewers.

Data Extraction

All citations from databases searches were exported to the reference manager software Endnote, version X9, and duplicates removed. Then two reviewers (M.M and S.A) selected studies independently without being blinded to authors, institutions, journal name, as well as trial results. The data extraction performed for articles that reported results on chart. If there was an absence in data reporting, the corresponding author was contacted via email to obtain to required data. The following data were collected with a standardized data collection form: (1) first author's last name; (2) year of publication; (3) study location; (4) study design; (5) sample size; (6) type and dose of flaxseed; (7) trial duration; (8) age, gender, body mass index (BMI) and health status of participants; (9) type of diet (10) mean and standard deviation (SD) of outcome measures at baseline, post-trial follow-up and/or changes in outcome measures from

baseline to the end of the study. If a study reported multiple follow-ups through the study duration, then each duration was evaluated as a separate study.

Data Synthesis and Statistical Analysis

At first, in each study, information about the mean before and after the intervention along with its standard deviation was extracted in both experimental and control groups. We calculated mean changes (before and after) and standard deviation (SD) for all outcomes (LDL-C, HDL-C, TC and TG) in each group, to assessing the overall effect sizes, SMD (95% CI). If heterogeneity between studies was significant (I2 > 50 or *P*-value <0.01), a random model (Der Simonian and Laird) was used, otherwise a fixed effect model (inverse variance) was applied.[17,31] Subgroup analysis was performed based on some influential factors[67] to examine the root of heterogeneity between the studies. Publication bias was assessed using the Egger's regression test and the 'trim and fill' method was used if any publication bias was significant.[17,21] All statistical analyses were performed in Stata version 14.

Results

Study Selection

In the initial search, 1,462 studies were yielded from PubMed (397), Scopus (614), Web of Science (264), Cochrane library (179), bibliographies, and experts (8). After removing duplicates (n = 482), 980 articles remained; of that, 177 were excluded after the screening of title: a review (n = 70) and in vitro or animal studies (n = 107). 753 studies were removed after careful evaluation of the 803 remained abstracts based on PICOS criteria: (1) unrelated title (n = 526), (2) other supplements (n = 94), other disease (n = 97), other outputs (n = 24) and other reasons (no access to article or conference abstract) (n = 12). The review follows diagram is showed in Figure 1.

Subsequently, 50 potentially relevant articles were retrieved for full-text assessment and detailed examination. 36 full-text articles were excluded due to following reasons: The study was on children[50] (n = 1), control problem[49,60] (n = 2), no data in blood lipid[46,82] (n = 2), combining intervention along with flaxseed[22,26,45,48,68,77,83] (n = 7), SD problem[8] (n = 1), dose of ingredient of flaxseed reported[15,18,25,86] (n = 4), inadequate results[11,47,53] (n = 3), flaxseed product[1,9,10,12,16,34,42,84] (n = 8), another language[23] (n = 1), and different design[69,79] (n = 2), cross over study design[24,32,38,41,73] (n = 5). Finally, a total of 14 eligible RCTs met all inclusion criteria.

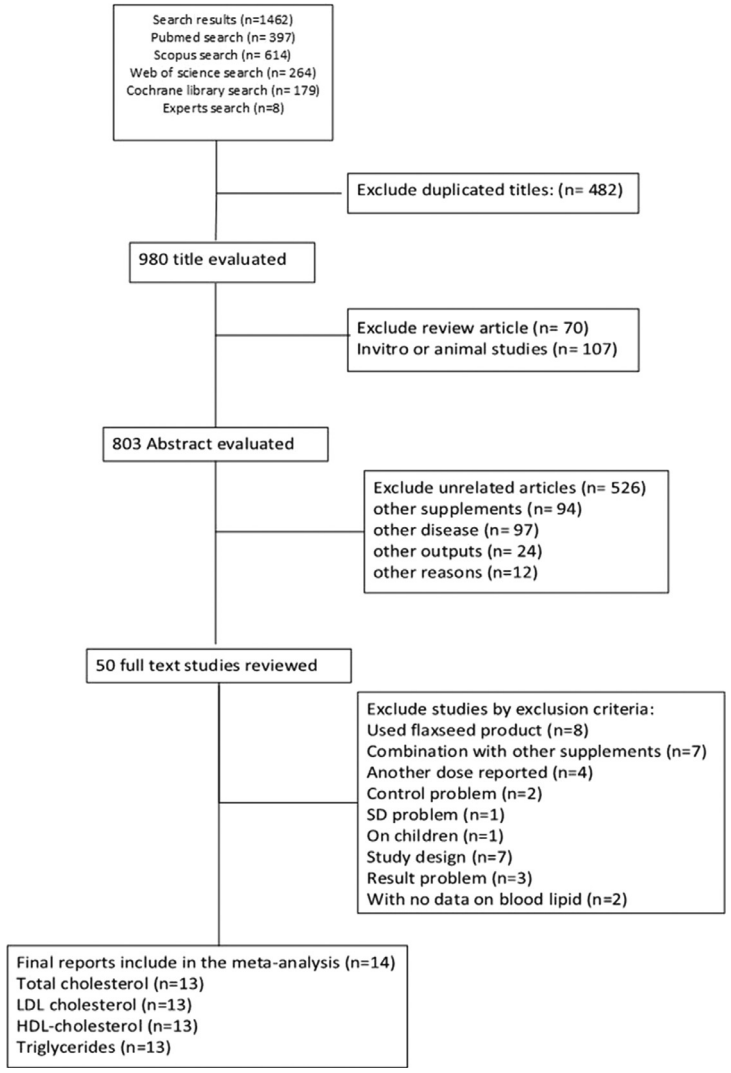

FIG 1. Review flow diagram according to the quality of reporting of meta-analyses (QUOROM) statement.

Characteristics of Studies

The characteristics of the included studies are detailed in Table 1. Overall, 1107 participants were randomly assigned and completed the study that divided to two groups of dyslipidemia[20,35,39,51,56,58,64,70,76,80] and healthy subjects.[3,4,36,43] These studies were published between 2003 and 2018 and conducted in Brazil,[3,4] Iran,[39,80] India,[35,70] Greece,[58,64]

TABLE 1. Characteristics of eligible studies.

Author, country, year, and reference	Design	Population	Male	Age	Duration	Outcome	Patient features	BMI	Type of diet	intervention	Placebo	dose	Case/control
		n	%	y	wk							g/day	n/n
Avelino, Brazil, 2015[3]	RCT	110	20.8	≥60	12	TC, TG, LDL, HDL	healthy	28.6	LF	LO	PB	3	57/53
Avelino, Brazil, 2015[3]	RCT	110	14	≥60	12	TC, TG, LDL, HDL	healthy	28.6	HF	LO	PB	3	57/53
Barroso, Brazil, 2015	RCT	60	14.3	≥60	4, 8	TC, LDL, HDL	healthy	Obese	Usual	GBLF	nothing	30	20/21
Dittrich, Germany, 2015[20]	RCT	59	34.7	56 ± 12	10	TC, TG, LDL, HDL	HT	28.1	Usual	LO	SFO	20	15/46
Katare, India, 2013[35]	RCT	75	44/56	40-50/ 50-60	12	TC, TG, LDL, HDL	HC	28.48	Usual	RF	nothing	30	25/25
Kaul, Canada, 2008[37]	RCT	86	Both	34.7	6, 12	TC, TG, LDL, HDL	Healthy	24.28	Usual + E	FO	SAO	2	22/22
Khalatbari, Iran, 2013[39]	RCT	30	67	54	8	TC, TG, LDL, HDL	HD/HT	25.5	Usual	GF	nothing	40	15/15
Kristensen, Denmark, 2013[44]	RCT	34	100	18-40	1	TG	Healthy	25.4	Usual	WF	MJ	2.4	18/18

(*continued on next page*)

TABLE 1. (*continued*)

Author, country, year, and reference	Design	Population	Male	Age	Duration	Outcome	Patient features	BMI	Type of diet	intervention	Placebo	dose	Case/ control
		n	%	y	wk							g/day	n/n
Kristensen, Denmark, 2013[44]	RCT	34	100	18-40	1	TG	healthy	25.4	Usual	LMJ FDF	MJ	2.4	18/18
Kristensen, Denmark, 2013[44]	RCT	34	100	18-40	1	TG	healthy	25.4	Usual	HMJ FDF	MJ	3.4	18/18
Mandasescu, 2005[51]	RCT	40	NR	NR	8.5	TC, TG, LDL, HDL	HC	30	LF	GF	nothing	20	20/10
Parameshwari, 2012[56]	RCT	40	Both	40-50	4	TC, TG, LDL, HDL	HC	NR	Usual + E	RF	nothing	15	20/20
Paschos, Greece, 2007[58]	RCT	35	100	38-71	12	TC, TG, LDL, HDL	DLP	28	Usual	FO	SFO	15	18/17
Rallidis, Greece, 2003[65]	RCT	90	100	50.4	12	TC, TG, LDL, HDL	DLP	28.42	Usual	LO	SAO	15	60/30
Saxena, India, 2014[70]	RCT	50	NR	40-60	12	TC, TG, LDL, HDL	HC	28.48	Usual	RF	nothing	30	25/25

(*continued on next page*)

TABLE 1. (*continued*)

Author, country, year, and reference	Design	Population	Male	Age	Duration	Outcome	Patient features	BMI	Type of diet	intervention	Placebo	dose	Case/ control
		n	%	y	wk							g/day	n/n
Skoczyńska, Poland, 2018[76]	RCT	150	37.5	49.9(M)-53.2(F)	4	TC, TG, LDL, HDL	MHC/ HBP	25.4(F)-30.8(M)	LF	CPLO	nothing	15	40/51
Skoczyńska, Poland, 2018[76]	RCT	150	27.2	49.9(M)-53.2(F)	4	TC, TG, LDL, HDL	MHC/ LBP	27.3(F)-27.5(M)	LF	CPLO	nothing	15	59/51
Torkan, Iran, 2015[80]	RCT	70	34.3	25-50	6	TC, TG, LDL, HDL	HC	27.28	LF	Raw F	nothing	30	35/35

CPLO, cold pressed Linseed oil; DLP, dyslipidemia; E, exercise; FDF, flaxseed dietary fiber; FO, flaxseed oil; GBLF, Ground brown linseed flour; GF, ground flaxseed; HBP, higher blood pressure; HC, hypercholesterolemia; HD, hemodialysis; HF, high fat diet; HMJ, high mucilage; HT, hypertriglyceridemia; LBP, lower blood; LF, low fat diet pressure; LIG, lignans; LMJ, low mucilage; LO, linseed oil; MHC, mild hypercholesterolemia; NR, not reported; PB, placebo; RCT, randomized control clinical trial; RF, roasted flaxseed; SAO, safflower oil; SFO, sunflower oil.

Germany[20] and Poland.[76] The follow-up period ranged from 1 to 12 weeks. The daily supplementation dose of flaxseed varied between 2-30 g/d in the healthy group and 15-40 g/d in dyslipidemia group. The sample size of RCTs ranged from 34-150. Of these 14 trials, most of them were conducted on both sexes,[3,4,20,35,37,40,56,76,80] 3 were conducted on men only,[44,59,65] and 2 trials did not mention the sex of participants.[51,71] The study design of these experimental studies were RCTs.

The intervention in dyslipidemic subjects were two groups of flaxseed oil,[20,58,64,76] and other form of flaxseed included: roasted flaxseed,[35,56,70] ground flaxseed[39,51] or raw flaxseed.[80] In healthy subjects, flaxseed oil,[3, 37] ground brown flaxseed,[4] whole flaxseed and flaxseed dietary fiber[42] were used. In dyslipidemic subjects, the control group didn't receive any treatment[20,35,39,51,56,70,76,80] with the exception of two articles, one of which used sunflower oil[20,58] while the other used safflower oil.[65] However, in healthy subjects, the intervention in control groups was safflower oil,[37] mucilage,[44] placebo[3] or nothing.[4] In the dyslipidemic group, the majority of the participants received a typical diet[20,35,39,56,58,65,70] and just three trials received a low-fat diet[51,76,80]; in the healthy group, two trials received low fat diet,[3,44] one trial received high fat diet,[3] one trial received usual diet[4] and one trial received a typical diet along with exercise.[37]

Baseline lipid profile of participants in the dyslipidemic group were TG>150 mg/dl, cholesterol>200 mg/dl, LDL-C>130 mg/dl,[35,58,65,70] mild hypercholesterolemia,[76] hyperlipidemia with TC>240 mg/dl or TC (250-275) mg/dl, TG (150-300) mg/dl, LDL-C (125-200) mg/dl,[51, 56, 80] moderate hypertriglyceridemia TG>1.5 mmol/L[20] and hemodialysis patients with TG>200 mg/dl or HDL-C<40 mg/dl.[39]

Quality Assessment

The study quality was assessed by using revman5 software. Domains of bias risk in this software were (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data; (6) selective reporting; (7) other bias. We considered the methodological domains of individual studies as low, high, or unclear risk of bias. Of the 14 studies performed on healthy individuals and dyslipidemia, only three studies had performance bias (were not blinded), and in general, all studies were out of bias. This table was designed according to Review Manager 5.3.

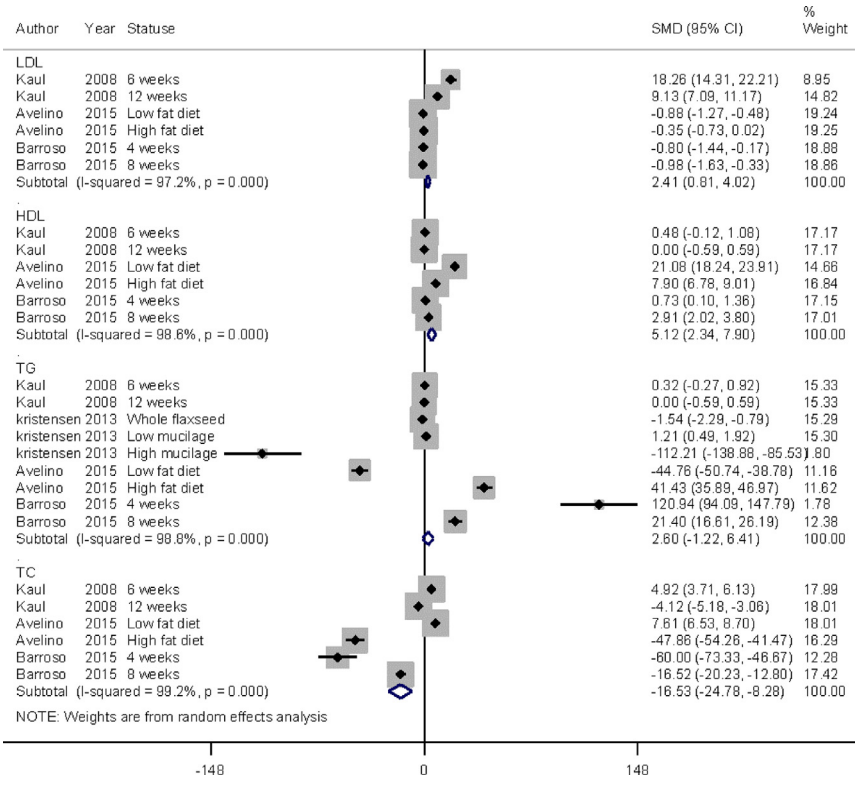

FIG 2. Results of flaxseed on lipid profile in healthy subjects.

Meta-Analysis Results

Effect Of Flaxseed on Lipid Profile in Healthy Subjects. Six studies examined the effect of flaxseed on TC, LDL-C and HDL-C in healthy people and nine studies on TG. The result of combination of studies showed that consuming flaxseed in healthy people significantly reduced TC (SMD: -16.53; 95%CI (-24.78, -8.28); $P < 0.001$), and significantly increased HDL-C (SMD: 5.12; 95%CI (2.34, 7.90); $P = 0.006$) and LDL-C (SMD: 5.11; 95%CI (2.48, 7.74); $P = 0.003$). The use of flaxseed did not have a significant effect on TG (SMD: 2.60; 95%CI (-1.22, 6.41); $P = 0.182$) which was shown in Figure 2.

Subgroup Analysis (Healthy Subjects). Subgroup analysis was performed on some influential factors including: dose and form of flaxseed consumption, duration of studies and BMI. As shown in Table 2,

TABLE 2. Summary results of flaxseed on healthy subjects.

	NO. of studies	MD (95%CI)	I^2 (%)	*P*-value for test (ES = 0)	*P*-value for publication bias	
TC	6	-16.53 (-24.78, -8.28)	97.2	<**0.001**	0.092	
Low dose	4	-8.71 (-17.44, 0.03)	99.4	0.051		
High dose	2	-37.67 (-80.37, 4.83)	97.2	0.082		
BMI >25	4	-28.65 (-54.67, -2.62)	99.4	**0.031**		
BMI <25	2	0.39 (-8.47, 9.26)	99.2	0.931		
Duration >8 wk	3	-13.96 (-27.08, -0.85)	99.6	**0.04**		
Duration <8 wk	3	-22.49 (-44.60, -0.39)	99	**0.05**		
flaxseed Oil	4	-8.71 (-17.44, 0.03)	99.4	0.051		
Other	2	-37.67 (-80.37, 4.83)	97.4	0.082		
HDL	6	5.12 (2.34, 7.90)	98.6	**0.006**	0.001	5.12 (2.34, 7.90)
Low dose	4	7.07 (2.41, 11.73)	99.1	**0.003**		
High dose	2	1.80 (-0.34, 3.93)	93.5	0.099		
>25	4	7.92 (2.95, 12.88)	98.9	**0.002**		
<25	2	0.24 (-0.23, 0.71)	20.2	0.323		
>8 wk	3	9.53 (0.88, 18.18)	99.4	**0.031**		
<8 wk	3	1.33 (0.03, 2.64)	90.6	**0.046**		
Oil	4	7.07 (2.41, 11.73)	99.1	**0.003**		
Other	2	1.80 (-0.34, 3.93)	93.5	0.099		
LDL	6	2.41 (0.81, 4.02)	97.2	**0.003**	0.023	1.85 (0.28, 3.42)
Low dose	4	5.11 (2.48,7.74)	98.3	<**0.001**		
High dose	2	-0.89 (-1.34, -0.43)	0	<**0.001**		
>25	4	-0.71(-1.01, -0.40)	37.7	<**0.001**		
<25	2	13.53 (4.59, 22.47)	93.8	**0.003**		
>8 wk	3	2.06 (-0.07, 4.18)	97.7	**0.06**		
<8 wk	3	4.07 (0.46, 7.68)	97.8	**0.03**		
Oil	4	5.11 (2.48, 7.74)	98.3	<**0.001**		
Other	4	-0.89 (-1.34, -0.43)	0	<**0.001**		
TG	9	2.60 (-1.22, 6.41)	98.8	0.182	0.720	

subgroup analysis on TC index showed that consumption of flaxseed had a significant reduction in people with a BMI more than 25 ($P = 0.031$), but it did not have a significant effect on people with a BMI less than 25 ($P = 0.931$). Also, analysis on duration of the studies in both subgroups, above 8 weeks and below 8 weeks showed a significant effect of flaxseed on lowering cholesterol. ($P < 0.05$). In the case of HDL-C, the results of the analysis in the subgroup receiving a low dose of flaxseed as well as studies that had a BMI > 25 and studies that used the flaxseed in the oil form showed a significant increase in HDL-C levels after flaxseed consumption ($P \leq 0.05$). There was no difference in duration of studies between the two subgroups ($\leq$ 8 weeks and > 8 weeks), and both had a significant effect on the increase in HDL-C. Regarding LDL-C, the results of the analysis in the subgroup receiving a high dose of flaxseed as well as studies that had a BMI > 25 and studies that used the flaxseed in other form (non-oily) showed a significant decrease on LDL-C levels after flaxseed consumption ($P \leq 0.05$). Also, there was no difference in the duration of studies between the two subgroups ($\leq$ 8 weeks and > 8 weeks), and both had a significant effect on the increase in HDL-C. But in the other subgroups, a significant effect was obtained from increasing LDL-C after flaxseed consumption.

Effect Of Flaxseed on Lipid Profile in Dyslipidemic Subjects. Among the selected studies on dyslipidemic patients, 11 studies reported the effect of flaxseed on cholesterol, HDL-C, and TGs and 10 studies only showed the effect on LDL-C. The results of a combination studies in dyslipidemic patients showed that consumption of flaxseed significantly reduced TC (SMD: -1.41; 95%CI (-2.30, -0.79); $P < 0.001$), LDL-C (SMD: -0.69; 95%CI (-1.13, -0.25); $P = 0.002$) and TG (SMD: -1.47; 95%CI (-2.21, -0.72); $P < 0.001$). However, in the case of HDL-C, no significant change was observed in patients after consuming flaxseed (SMD: 0.32; 95%CI (-0.07, 0.70); $P = 0.111$) which was shown in Figure 3.

Subgroup Analysis (Dislipidemic Subjects). For these studies, subgroup analysis was performed on two influential factors including form of flaxseed consumption and duration of studies. The results of the subgroup analysis showed that LDL-C, TC and TG, in all subgroups, a significant effect of flaxseed consumption on the reduction of these three variables was shown, and no difference was observed between the subgroup results. However, regarding HDL-C which was not significant in general, subgroups on duration < 8 weeks and

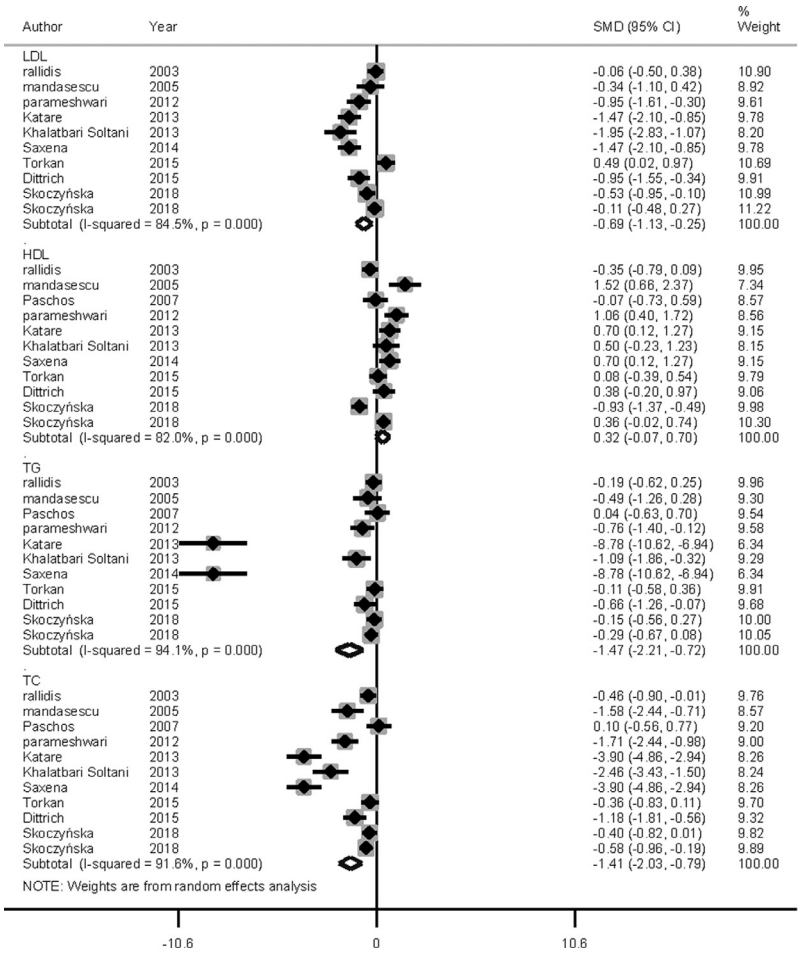

FIG 3. Results of flaxseed on lipid profile in dyslipidemia subjects.

in other forms of flaxseed consumption (non-oily) significantly increased the HDL-C consumption. In contrast, in subgroups above 8-week period and oily flaxseed consumption, flaxseed consumption significantly reduced HDL-C levels in dyslipidemia individuals. The summary of the results is shown in Table 3.

Publication Bias. *Publication Bias (Healthy Subjects).* The results of the publication bias test on TC and TG variables were not significant, although, it showed significant variations for LDL-C and HDL-C. The pooled estimate was obtained after using the trim and fill method for

TABLE 3. Summary results of investigating the effects flaxseed on dyslipidemia patients.

Variables and subgroup	NO. of studies	MD (95%CI)	I^2 (%)	P-value for test (ES = 0)	P-value for publication bias	Trim and fill result
TC	11	-1.41 (-2.30, -0.79)	91.6	<**0.001**	0.002	-1.41 (-2.30, -0.79)
>8 wk	5	-1.82 (-3.23, -0.41)	95.4	**0.011**	-	-
≤8 wk	6	-1.07 (-1.62, -0.51)	82.4	<**0.001**	-	-
Oil	5	-0.51 (-0.82, -0.19)	51.5	**0.001**	-	-
Other	6	-2.29 (-3.51, -1.06)	93.2	<**0.001**	-	-
HDL	11	0.32 (-0.07, 0.70)	82	0.111	0.06	-
>8 wk	5	0.26 (-4.68, -0.18)	68.7	0.258	-	-
≤8 wk	6	0.38 (-0.27, 1.03)	88.3	0.248	-	-
Oil	5	-0.13 (-0.65, 0.39)	82.5	0.624	-	-
Other	6	0.69 (0.31, 1.08)	55.8	<**0.001**	-	
LDL	10	-0.69 (-1.13, -0.25)	84.5	**0.002**	0.025	-0.69 (-1.13, -0.25)
>8 wk	4	-0.97 (-1.70, -0.23)	85.1	**0.01**	-	-
≤8 wk	6	-0.50 (-1.04, -0.05)	83.5	0.075	-	-
Oil	4	-0.37 (-0.72, -0.01)	60.7	**0.046**	-	-
Other	6	-0.93 (-1.73, -0.13)	88.9	**0.023**	-	-
TG	11	-1.47 (-2.21, -0.72)	94.1	<**0.001**	0.014	-1.47 (-2.21, -0.72)
>8 wk	5	-1.72 (-3.27, -0.18)	96.2	**0.029**	-	-
≤8 wk	6	-1 (-1.69, -0.31)	88.8	**0.004**	-	-
Oil	5	-0.63 (-1.37, 0.11)	90.3	0.094	-	-
Other	6	-1.95 (-3.27, -0.62)	94.7	**0.004**	-	-

LDL-C 1.85 (0.28, 3.42) and for HDL-C 5.12 (2.34, 7.90). The results remained significant.

Publication Bias (Dyslipidemic Subjects). The results of the publication bias except for LDL-C ($P = 0.006$), were not significant for other variables. The pooled estimate after the trim and elephant method on LDL-C was -3.26 (-4.58, -1.94).

Discussion

Dyslipidemia is in correlation with a raised risk for CVD, atherosclerosis, diabetes and MS which has led to the death of millions of people world-wide.[14,66,74,85] Therefore, strategies to improve therapeutic treatment have been developed to modify lipid profiles and prevent MS and coronary heart disease, comprising a range of dietary herbal supplements.[10] Among dietary herbal supplements with advantageous impacts on human health, flaxseed have gained growing attention[5] due to its ability to modify lipid profiles.[63] Recent studies showed that whole flaxseed and lignan supplements can reduce total and LDL cholesterol.[28] These changes varied substantially depending on the treatment form of flaxseed, sex, initial lipid profile and underlying disease. Thus, in this study we focused on dyslipidemia and healthy subjects received flaxseed pure.

According to the results, flaxseed supplements lead to remarkable improvement in lipid profile of dyslipidemic subjects and healthy subjects specifically with BMI > 25. In dyslipidemic subjects of the experimental group, LDL-C (-0.69 mg/dl), TC (-1.41 mg/dl), and TG (-1.47 mg/dl) levels significantly decreased compared to controls. However, the HDL-C was not changed significantly (0.32, $P = 0.06$). In the healthy, experimental group, a significant reduction in TC (-16.53 mg/dl) and elevation in HDL-C (5.12 mg/dl) and LDL-C (2.41 mg/dl) were observed compared to controls. The effect on TG was insignificant (2.6, $P = 0.720$). The difference in results of the dyslipidemic and normolipidemic subjects is due to the expression of lipid metabolism-related genes modulated by inflammation mediators associated with dyslipidemia. These regulatory pathways result in induction of lipolysis and reduction in lipogenesis.[72] In the present meta-analysis, although TC decreased in both group but LDL-C, HDL-C and TG had different results in dyslipidemic and healthy individuals. One of the important parameters that separated dyslipidemic subjects from healthy individuals is obesity. All of the dyslipidemic subjects had a BMI > 25. In addition, subgroup analysis in healthy group indicated that lipid profile significantly improved in subjects who were overweight. Dyslipidemia in obesity is

commonly manifested as high plasma TG, low HDL-C and normal LDL-C with majority of small dense LDL-C particles. Low plasma HDL-C levels in obesity can occur in the presence or absence of hypertriglyceridemia. The TG-lowering effect of omega-3 fatty acid (that flaxseed is a rich source) consumption is well recognized. Sometimes, omega-3 fatty acid−related decrease in plasma TG level is associated with a modest reduction in HDL-C possibly through increasing the fractional catabolic rate of medium sized HDL-C particles.[54]

In subgroup analysis the variation was substantially connected with dosage form of flaxseed (flaxseed oil/ defatted flaxseed) and BMI (> 25 or < 25). According to the findings in subgroup analysis, lipid profile significantly improved in overweight subjects (BMI > 25). In addition, defatted flaxseed had a better effect on lipid profile, more so than oil of flaxseed. Flaxseed can be considered as a potential nutraceutical as well as functional food that has potential health benefits comprising reduction of hyperlipidemia, and insulin resistance and reduced risk or severity of hypertension, cardiovascular diseases, diabetes, cancer, arthritis, osteoporosis, autoimmune and neurological disorders.[27,80]

The anti-dyslipidemic activity of flaxseed is associated with the bioactive components.[27,29] Omega-6 and omega-3 polyunsaturated FAs are essential FAs that must be a part of the daily diet due to the lack of endogenous enzymes for omega-3 desaturation. One of the main omega-6 FAs is linoleic acid (LA) and omega-3 FAs is alpha linolenic acid (ALA). LA is metabolized to arachidonic acid while ALA is metabolized to eicosapentaenoic acid (EPA) (20:5ω3) and docosahexaenoic acid (DHA).[70] LA is widely distributed in nature and presents in the chloroplasts of green leafy vegetables and in the seeds of flax, grape, chia, perilla and walnuts.[70] EPA and DHA are presented in fish oil. Regrettably, fish oil consumption is limited due to concerns regarding its taste, smell, allergies, and potential toxins such as methylmercury, dioxins, and polychlorinated biphenyls.[57]

Flaxseed oil is one of the richest sources of ALA which helps to reduce concentrations of TC and LDL-C and increases expression of hepatic LDL-C receptors thereby increase catabolism of cholesterol. In addition, flaxseed oil significantly increases omega-3 content in the plasma or membrane of erythrocytes and decreases the omega-6 to omega-3 ratio. Epidemiological studies have shown that replacing ALA instead of saturated FAs reduces blood lipids.[80] ALA, is an essential fatty acid that promotes cholesterol efflux from macrophages through inhibition of stearoyl-coA desaturase-1 activity, which is an important protective mechanism for decreasing circulating cholesterol.[29]

In addition, flaxseed contains one of the richest source of lignans. Lignans are diphenolic compounds containing a 2, 3-dibenzylbutane structure which possesses cholesterol lowering properties. Lignans act as both antioxidants and phytoestrogens.[27] Flax lignans are considered to be more active and bioavailable when metabolized by gut bacteria which can convert them to the enterolignans enterodiol and enterolactone.[29] The most important lignan in flaxseed is SDG which is metabolized in the intestine and converted in to phytoestrogens. In addition, lignans inhibits PEPCK gene expression which has a role in producing an inhibitor enzyme for gluconeogenesis in the liver.[80]

One of the other aspects of the flaxseed is its high fiber content. Soluble fibers in flaxseed contain gums, and mucilage and its main insoluble fiber include cellulose and lignin[27, 80] that will protect against dyslipidemia by promoting satiety, reduce caloric intake, and food transit time, by stimulating bile acid excretion, and reducing its reabsorption through increased fecal excretion of cholesterol. Fiber also influences multiple metabolic pathways, including fatty acid synthesis, lipolysis, and cholesterol synthesis through the formation of short-chain FAs that inhibit hepatic cholesterol synthesis.[29] Furthermore, 2.3%-3.3% of the flaxseed contains phytic acid[27] which has demonstrated antioxidant, anticancer, hypocholesterolemic, and hypolipidemic effects[27]; based on the Ibrahim *et al.* study, the high polyphenol content of flaxseed exhibited anti-atherogenic, anti-angiogenic, anti-inflammatory, and hypo-lipidemic characteristics.[33] Flaxseed also decreased the risk of atherosclerosis via increasing leptin levels through consuming a diet full of omega-3 and ALA.[3]

Omega-6 and omega-3 FAs often have important opposing role in physiological systems, so keeping their balance in the diet is important.[7,37] Omega-6 FAs increase cellular TG content by increasing membrane permeability, while omega-3 FAs reduce fat deposition in adipose tissues by suppressing lipogenic enzymes and increasing β-oxidation.[7] Omega-3 FAs induce favorable changes in other lipoproteins, including a reduction in non− HDL-C, VLDL, and residue like particle cholesterol. Omega-3 FAs containing DHA also shift small dense LDL-C to large LDL-C and modestly improve HDL-C. Omega-3 FAs are considered to provide cardio protection via additional mechanisms beyond TG lowering, and also may help to combat the paradoxical effects of statins such as increases in proprotein convertase subtilisin/kexin type 9 and arachidonic acid levels.[8] Omega-3 FAs may lead to an increase in LDL-C. However, it decreases the amount of small, dense LDL-C and is not accompanied by an increase in apolipoprotein B, lead to a shift in LDL-C particle size instead of a true increase in LDL-C.[6] On the other hand,

recently published results of the veterans affairs HDL-C intervention trail (VA-HIT) clearly showed that pharmacotherapy aimed at increasing plasma HDL-C levels reduces the risk of Coronary Heart Disease, even in the absence of any change in plasma LDL-C levels.[13]

A recently meta-analysis in 2019 included 62 studies[29] and assessed the effects of flaxseed or flaxseed derived products on the lipid profiles of adults with any health status and indicated a reduction in circulating TC, LDL-C, and TG after flaxseed supplementation. However, change in lipid profiles may depend on the intake form of flaxseed, BMI, time duration, dosage, sex, initial lipid profile, and age.[80] In that meta-analysis, control subjects received supplementation with different components include ALA (canola oil = 10%, olive oil = 3.5-21%, soybean oil = 2-13%) or other oils with different components (maltodextrin, manioc flour, mineral oil, cassava powder, hempseed oil) that cover or change the positive effect of flaxseed. In addition, health status and biochemical pathway in some disease (MS, T2DM, and prostate cancer) play a critical role in lipid profile that could change the results.

For human consumption four forms of flaxseed are available: ground flaxseed, whole flaxseed, flaxseed oil, and partially defatted flaxseed meal. The composition of whole flaxseed (22.8 g ALA, 82-2600 mg lignan) and ground flaxseed (23.1 g ALA, 82-2600 mg lignan) are similar while flaxseed oil (57 g ALA) and partially defatted flaxseed meal (6 g ALA, 2500 mg lignan) are different.[57] Based on evidence, other forms of flaxseed such as whole flaxseed, ground flaxseed and dietary flaxseed had a better effect than flaxseed oil on lipid profile; this is probably due to the lipid lowering effect of lignans, fiber, phytic acid and polyphenols which are all absent in flaxseed oil but present in other forms of flaxseed.

Conclusion

Flaxseed supplementation (dosage: 2-40 g/d) in dyslipidemic subjects and healthy subjects with a BMI $>$ 25 has a beneficial effect on lipid profile.

Author Contributions

The authors contribution was as follows: M.M and P.M.: conducted the systematic search, screening and data extraction. M.M: prepared the primary manuscript, P.M, Y.SH and S.A: finalized the manuscript, and; P. M, M.M Y.SH and S.A. proofread the manuscript for native English writing; all authors read and approved the final manuscript. Sedigheh Asgary, Conceptualization; Motahareh Sadat Masjedi, Data curation; Sedigheh

Asgary, Formal analysis; Sedigheh Asgary, Investigation; Sedigheh Asgary, Methodology; Sedigheh Asgary, Supervision; Sedigheh Asgary and Pardis Mohammadi Pour, Validation; Motahareh Sadat Masjedi and Pardis Mohammadi Pour, Roles/Writing - original draft; Pardis Mohammadi Pour and Yalda Shokoohinia, Writing - review & editing.

Ethical Consideration

We assert that this meta-analysis complied with ethical standards. Ethical issues may include double publications, plagiarism, data fabrication, misconduct, falsification and redundancy have been observed and addressed by the authors.

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