

Effects of Dill Extract on Blood Lipid Levels (TC, TG, LDL and HDL): A Systematic Review and Meta-Analysis

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ABSTRACT

Background & Objective: In recent years, there has been a growing trend towards the use of herbal medicine in the treatment and prevention of diseases. Blood lipid-lowering drugs have many side effects. On the other hand, various studies have reported the effect of dill (*Anethum graveolens*) on the reduction of blood lipids in different ways. This study aimed to evaluate the effect of dill on reducing the blood lipid levels.

Materials & Methods: In this systematic review, 12 papers that evaluated the effect of dill on blood lipid levels up to the end of 2018 were studied using valid key words such as Lipid Profile, Dill (*Anethum graveolens*), and Hyperlipidemia in Pubmed, Medlib, Scopus, Sciencedirect, Embase, Google Scholar, Magiran, IranMedex, and SID. The results of the studies were combined using the random effects method of meta-analysis. The heterogeneity of studies was investigated using Q statistics and I² Index.

Results: In 12 studies, the weighted mean differences (WMDs) of cholesterol reduction (TC) before and after intervention were estimated to be WMD = -19.22 mg / dl (95% CI: -30.68, -7.77), triglyceride, WMD = -25.47 mg / dl (95% CI: -49.28, -1.66) and low density lipoprotein (LDL), WMD = -14.01 mg / dl (95% CI: -22.14, -5.89) which were statistically significant ($p = 0.001$). Meta-analysis after intervention in the case and placebo groups were (SMD=-2.71, 95% CI:-3.28,-1.06), for TC (SMD=-1.77, 95%CI:-2.71,-0.82) for TG and (SMD=-2.64, 95%CI:-3.88,-1.41)for LDL which indicated statistically significant reduction.

Conclusion: Dill reduces cholesterol, triglyceride and low-density lipoprotein, but does not have a significant effect on high-density lipoprotein levels.

Keywords: Lipid, Meta-analysis, Dill plant, *Anethum graveolens*, Review, Systematic, Hyperlipidemia



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Introduction

Cardiovascular diseases are the primary cause of death in many countries, including Iran. There is a known relationship between serum lipid concentration and atherosclerosis lesions (1). A 25% reduction in cholesterol concentration reduces the incidence of coronary events by about 50% (2). Blood lipids control, especially low-density lipoprotein, can lead to ischemic events reduction. High blood lipids including high total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and triglycerides are known risk factors for heart disease. The risk of death due to cardiovascular disease decreases by increased high-density lipoprotein which is a protective factor (3).

Today, the incidence of hyperlipidemia is increasing due to changes in lifestyle along with the industrialization of societies and changes in dietary habits, and a reduction

in physical activity. Abnormal and chronic increase of cholesterol and triglyceride leads to a lot of problems, including stenosis and occlusion of the vessels in different parts of the body, especially in the heart (4). Currently, various drug groups are used to reduce hyperlipidemia. These drugs can cause gastrointestinal complications such as indigestion, flatulence, constipation, diarrhea and abdominal cramps (5). To our knowledge, there has been no study investigating the complications of dill extract.

In recent years, there has been a trend towards the use of herbal medicine in the treatment and prevention of diseases, with a dramatic increase worldwide, especially in Iran. Dill is one of the plants used in herbal medicine (6). Medicinal plants have played an important role in treating diseases throughout the world for a long time. Currently, there is a lot of interest in restoring the use of

herbal medicines in the form of standard extracts, partly due to numerous side effects and high costs of chemical drugs (7).

Dill is a perennial herb of the Apiaceae family, which is found in most parts of the world (8). Several pharmacological effects have been identified for dill, such as anti-hypertensive (9-11), antiseptic, anticonvulsant, anti-flatulence, anti-vomiting, antispasmodic, pain relief and blood lipid level reduction (12). The extract of this plant has also been shown to be antibacterial (13), antifungal, anticonvulsant, antioxidant, and anti-cancer as well as having, stomach acid secretion and glucose, lipid and cholesterol reduction effects (14). Several studies have examined the effect of dill extract on serum lipid levels (8, 10, 11, 15).

Despite the significant effect of the plant in some clinical trials and contradictions in some other studies, no meta-analysis has been carried out so far. This study aimed to determine the general effect of dill on blood lipid levels, which is of great importance for clinical interventions.

Materials and Methods

Databases such as Google Scholar, Pubmed, Embase and Scopus were searched to find relevant resources. This search, in terms of time, included all time periods covered by the relevant databases until the end of 2018. To find scientific articles published in Iranian research journals, the SID databases were examined during the years covered up to the end of December 2018. The list of resources used in all related articles and reports not found in the above electronic search was manually evaluated to allow other possible sources to be added.

Search Method: To maximize the initial search sensitivity, the Pubmed, Medlib, Scopus, Sciencedirect, Embase, and Google Scholar databases were searched with the following keywords and connections:

1. *Anethum graveolens*(Dill) and Lipid Profile
2. *Anethum graveolens*(Dill) and Total Cholesterol (TC), Triglyceride (TG), Low Density Lipoprotein-cholesterol(LDL-cholesterol), High Density Lipoprotein-cholesterol (HDL cholesterol)
3. *Anethum graveolens*(Dill) and Hyperlipidemia and Serum Lipid

The search for articles in persian was done using key words such as blood lipids, cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, and a combination of these in Magiran SID, IranMedex, and the Google Scholar databases. Data extraction was performed via a checklist, including the name of the researcher, the year of the study, the type of study, sample size, location, age of the participants, treatment duration, extract dose and mean blood lipid levels before and after the intervention in the case and control groups.

Data were extracted for all relevant clinical trials eligible for the following:

1. Single-blind, double blind, and case-control clinical trials (before and after intervention)
2. Oral administration of dill in the intervention group
3. Administration of placebo in the control group
4. The statistical population including hyperlipidemia and healthy groups in human and animal models.
5. English and Persian languages

Among the clinical trials with the above criteria, the studies eligible for the following conditions were not included in the meta-analysis:

1. No control group
2. No access to full-text article
3. Lack of average lipid changes

In some studies, two different doses of dill extract were presented. Therefore, the data from these studies were included in the meta-analysis as two separate studies. Two studies did not report the standard deviation of mean changes, but they presented *p*-values of mean comparisons in the case and control groups. Therefore, we calculated the standard deviation and included these studies in the meta-analysis. Evaluation of inclusion and exclusion criteria was made by two people familiar with the method of conducting clinical trials. In cases of disagreement, the issue was discussed with a third person with the same characteristics (in terms of familiarity with research methodology) and a decision was made.

Data analysis

The effect size in this study was considered to be the Mean Difference and Standard Mean Difference (SMD) of variable before and after the intervention. Given that the Standard Mean Difference or SMD had a normal distribution, a random effects model with regard to the heterogeneity of the studies was used to combine the results of studies. To evaluate heterogeneity of studies, I^2 and Q statistics were used. The probability of publication bias was studied using Funnel and Egger's regression asymmetry. Sensitivity analysis was used to evaluate the effect of each study on overall results, and subgroup analysis was done based on the dose and duration of treatment. The data were analyzed using Stata 11 and $p < 0.05$ was considered as a significant level.

Results

Study selection

A list of titles and abstracts of all articles in the above-mentioned databases was prepared by the researcher and examined in order to determine and select relevant topics. After preparing the first list, two project contributors reviewed the list of titles and abstracts of the articles

independently and identified the articles related to the topic. At first, 30 papers were selected and reviewed; 10 were repeated. Of the 20 articles reviewed, 6 were excluded due to a lack of required data in the abstracts of the articles or discordance with the inclusion criteria. Two

studies were excluded because there was no access to full text articles. Controversies were resolved through negotiation; ultimately, 12 randomized controlled clinical trials were selected to enter the meta-analysis stage (Figure 1).

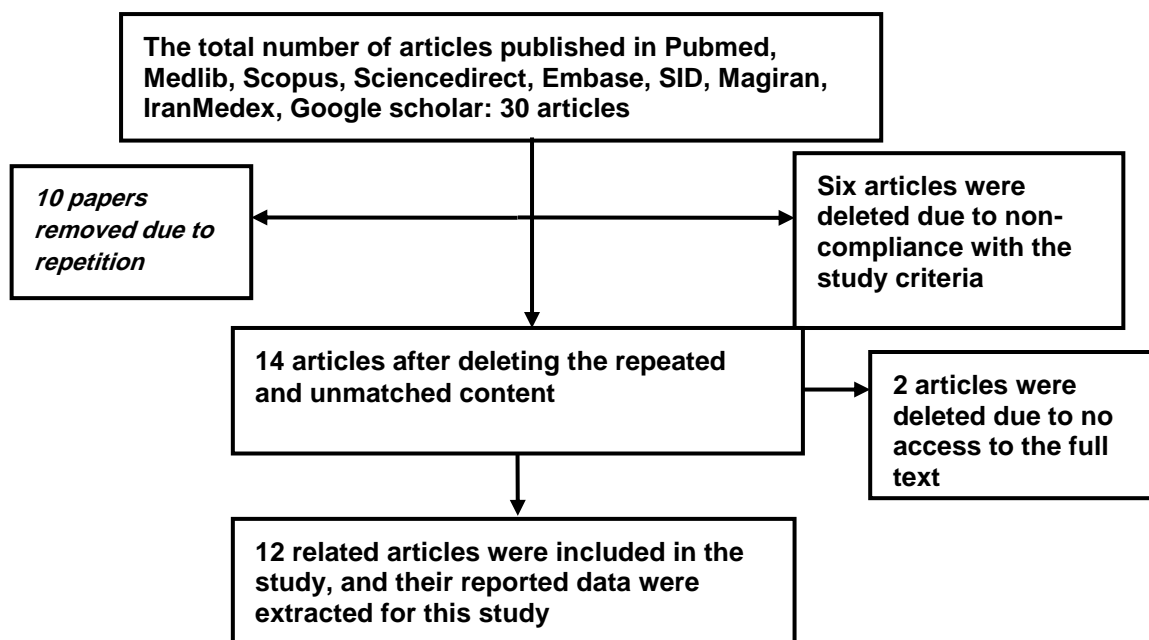


Figure 1. Flowchart of reviewed and searched articles

Of the 30 articles in the database, 12 clinical trials met the meta-analysis criteria. The characteristics of these studies are shown in Table 1.

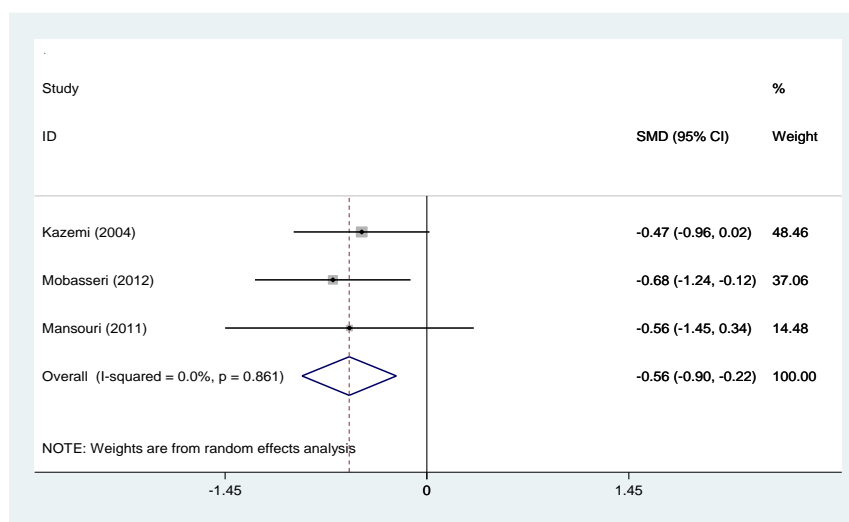
Of the total studies, the overall reduction in cholesterol after administration of dill extract was estimated in 3 studies: statistically insignificant in Kazemi and Mansuri's studies but the reduction was significant in Mobasseri's ($p < 0.05$) (16,18,19). By combining the

results of the three studies and using the random effects model, it was shown that the extract had a significant effect on cholesterol reduction. The standard mean difference (SMD) in cholesterol reduction was $SMD = -0.56$ (95% CI: -0.90, -0.22) (Figure 2(a)). In three studies, using a randomized model with a sample size of 69 people, the dill extract showed an average of 19.22 mg / dl cholesterol reduction (Figure 2(b)).

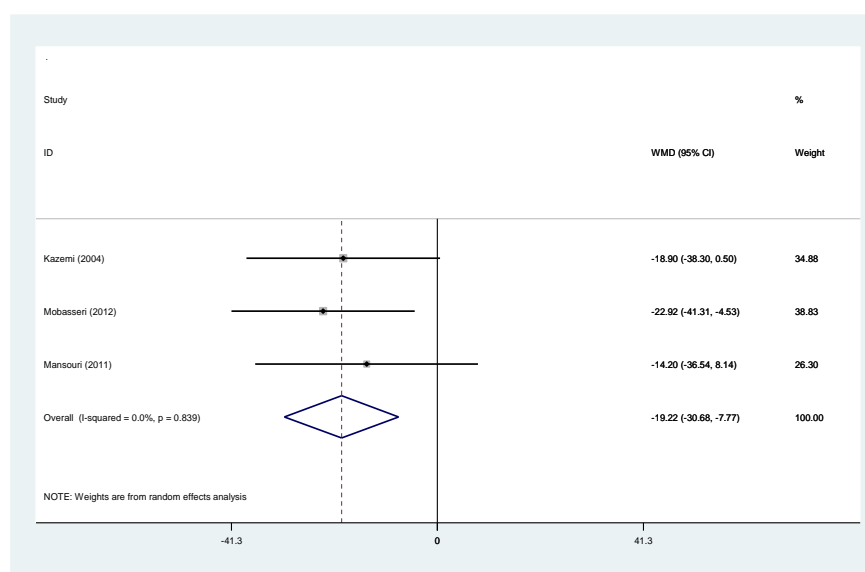
Table 1. Characteristic of studies included in the review

Study	Number of participants (placebo/case)	Subject	Design	Country	Intervention Periods Weeks
Kazemi(16) 2004	65 (32/33)	Human	RCT double blind	Iran	4
Yazdanpanah(17) 1999	46 (24/22)	Human	RCT double blind	Iran	4
Kojuri(15) 2005	100 (50/50)	Human	RCT double blind	Iran	6
Mobasseri(18) 2012	52 (26/26)	Human	RCT blind	Iran	12
Mansouri(19) 2011	20 (10/10)	Human	RCT double blind	Iran	12
Rafati(20) 2004	16 (8/8)	Rat	Case- control	Iran	3

Study	Number of participants (placebo/case)	Subject	Design	Country	Intervention Periods Weeks
Setorki(12) 2010	16 (8/8)	Rat	Case- control	Iran	3
Rezapor(21) 2011	12 (6/6)	Rat	Case- control	Iran	3
Yousofvand(22) 2014	12 (6/6)	Rat	Case- control	Iran	4
Yousofvand(22) 2014	12 (6/6)	Rat	Case- control	Iran	4
Askari(23) 2015	24 (12/12)	Rat	Case- control	Iran	6
Madani(24) 2005	10 (5/5)	Rat	Case- control	Iran	3



(a)



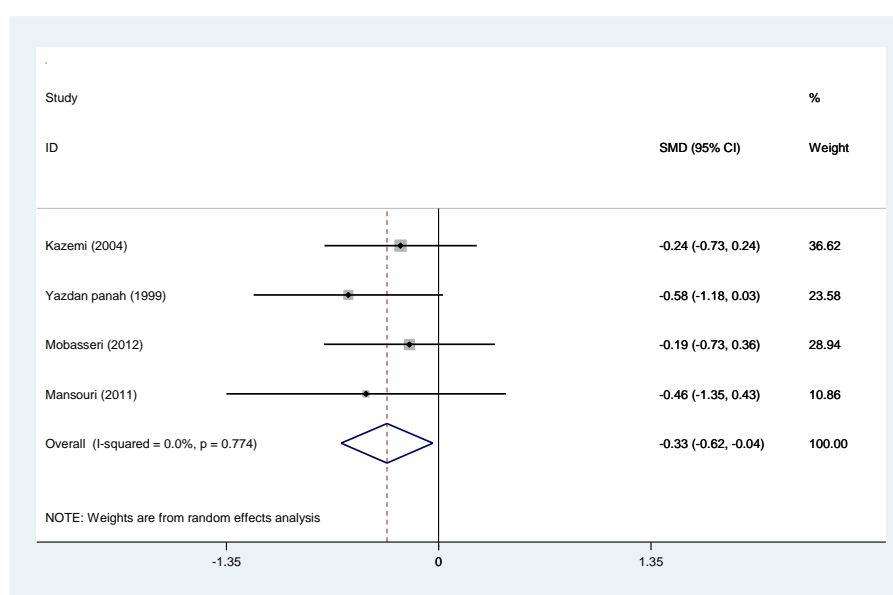
(b)

Figure2. Standard mean difference (SMD) (a) Weighted mean difference (WMD) (b) of total cholesterol (TC) reduction before and after intervention in the case group. Squares show point estimate of TC and lines show 95% CI TC in each study. The diamond shows pooled estimate of studies.

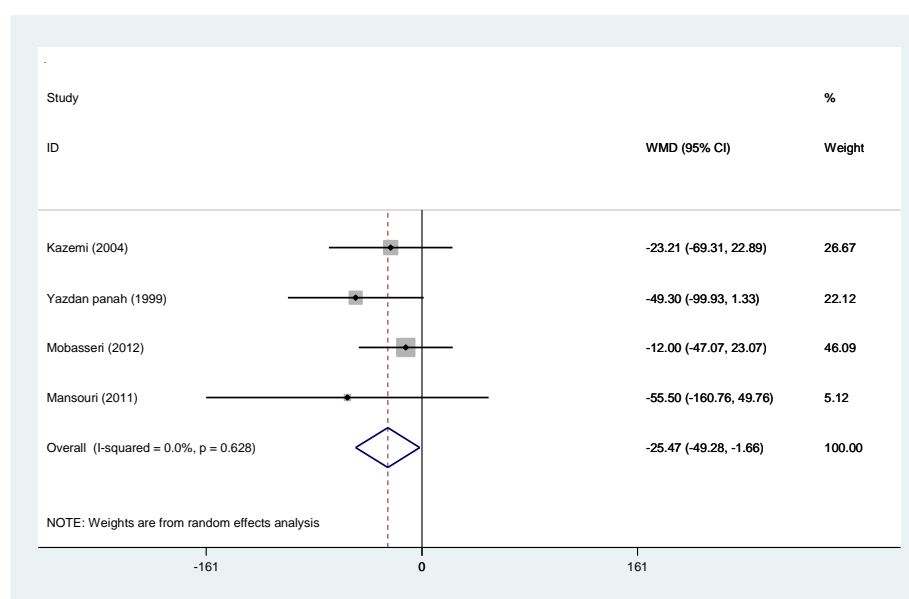
Triglycerides were decreased in Kazemi, Yazdanpanah, Mansouri and Mobasseri's studies, but they were not statistically significant in all studies (16-19). By combining the results of the four studies and using the random effect model, it was shown that dill extract had a significant effect on the triglyceride reduction. The standard mean difference of triglyceride reduction was estimated to be (0.95% CI: -0.62, -0.04) SMD = -0.33 (Figure 3(a)). In the four studies examined, using a randomized model with a sample size of 91 subjects in the case group, it was shown that dill extract reduced blood glucose levels by an average of 25.47 mg / dl (Figure 3(b)).

In the study of Kazemi, Mansouri and Mobasseri, low density lipoprotein (LDL) was decreased using dill

extract. LDL reduction was statistically significant in Kazemi and Mobasseri's studies ($p < 0.05$) (16,18,19). However, in Mansouri's study, LDL reduction was not statistically significant. By combining the results of the three studies using the random effects model, dill had a significant effect on LDL reduction. The standard mean difference in LDL reduction, was estimated to be SMD = -0.60 (0.95% CI: -0.94, -0.25) (Figure 4(a)) (19). In three studies, using a randomized model with a sample size of 69 subjects in the case group, it was shown that the dill extract reduced LDL by an average of 14.01 mg / dl, (Figure 4(b)). The Weighted mean difference in LDL reduction before and after the intervention was WMD = -14.01 mg / dl (95% CI: -22.14, -5.89), which was statistically significant ($p < 0.05$).



(a)



(b)

Figure 3. Standardized mean difference (SMD) (a) and Weighted mean difference (WMD) (b) of triglyceride reduction before and after intervention in the case group. Squares show point estimate of TG and lines show 95% CI TG in each study. The diamond shows pooled estimate of studies.

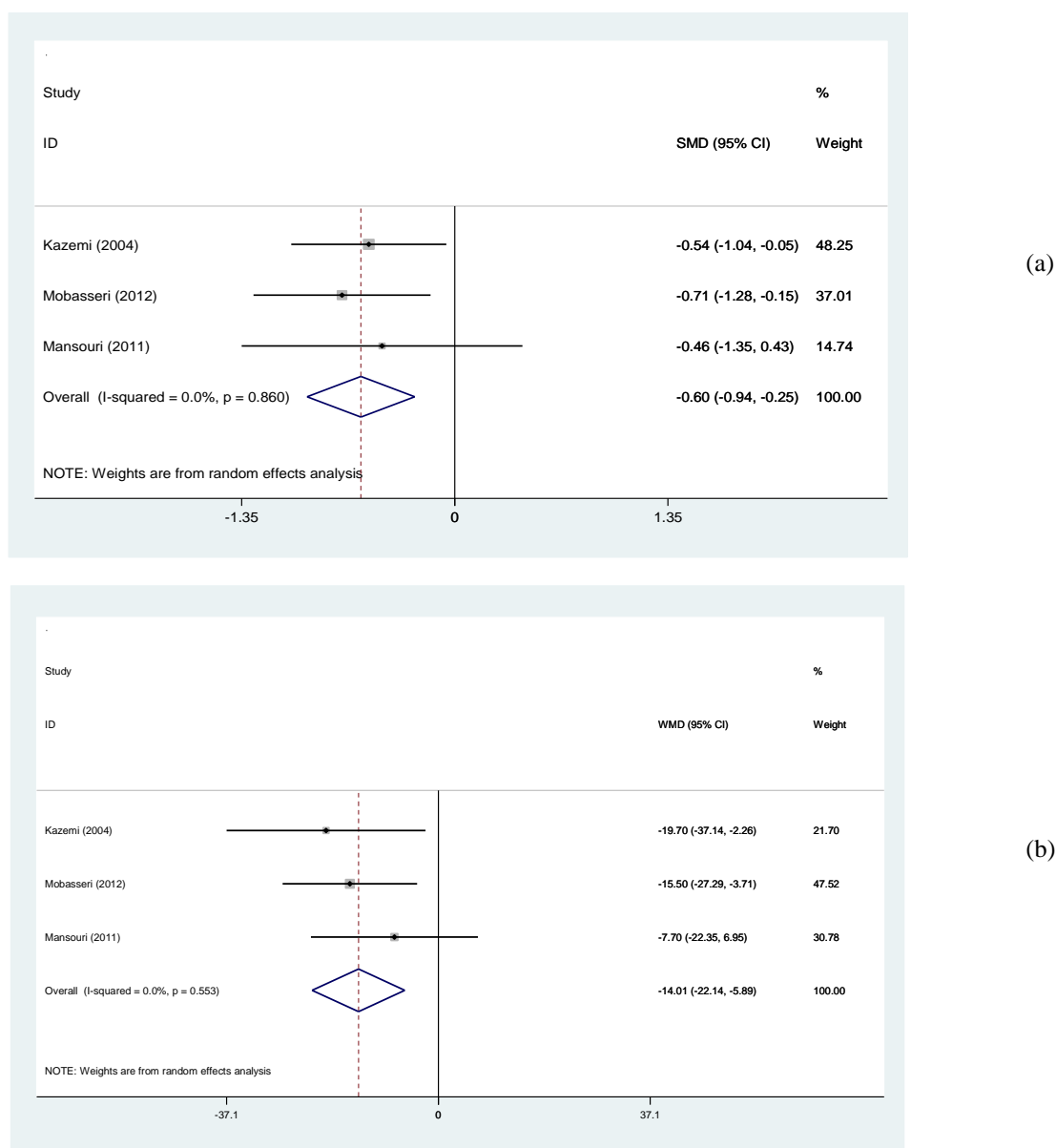


Figure 4. Standard mean difference (SMD) (a) and Weighted mean difference (WMD) (b) of LDL reduction before and after intervention in the case group. Squares show point estimate of LDL and lines show 95% CI LDL in each study. The diamond shows pooled estimate of studies.

There were also other trials in relation to the effect of dill extract on lipid levels in the body, in which another drug group (such as lovastatin) was used instead of placebo in the compared group. The results of these studies were not included in the meta-analysis (25). Begg's Test showed that the effect of publication bias was not significant ($p = .855$), that is, it seems that both studies that were positive or studies that were negative had a chance to be published and included in this study.

Discussion

In a systematic review, a number of articles were identified during the search. After reviewing the titles of the articles, article abstracts and various aspects examined in the study were entered into a checklist.

After a final evaluation, the researcher obtained 12 articles and their full text. Systematic review and meta-analysis of the findings obtained from clinical trials indicated effectiveness of dill in reducing lipid levels in the body. Our results showed that dill reduced cholesterol, triglycerides, and low-density lipoprotein (LDL), which was statistically significant; however, there was no significant effect on high-density lipoprotein (HDL).

Given that the accuracy of the conclusions in meta-analysis studies based on the mean and standard deviation of the studies before and after the intervention was higher compared with the time when the p -values were combined, it seems that dill has no significant effect on HDL, but its effect on cholesterol, triglycerides and LDL is statistically significant. Based

on the mean and standard deviation of the studies, none of the variables was significant in the placebo group. Similarly, by combining *p*-value results of the studies in placebo group, it was shown that only cholesterol and triglycerides were statistically significant.

The results of the Hajj Hashemi and the Abbasi studies showed that the extract of aerial part of dill decreased triglycerides and low density lipoprotein in male rats (8). Madani et al., reported that the aerial part of dill extract had a significant effect on decreasing the concentration of low density lipoproteins and triglycerides in diabetic animals (24).

The exact mechanism for reduction of blood lipids by dill extract is unknown, but some researchers have reported that the reduction effect of the aerial part of dill extract may be related to the flavonoid composition of quercetin (26). Based on the results of this study, quercetin in dill significantly reduces glucose, cholesterol and low density lipoprotein (26-28). Blood lipid

reduction after dill use was reported differently in various studies. Given the effect of the dose and duration of the use, this may probably be the main reason for the difference in blood lipid levels in different studies.

Limitation

There were some limitations in this article including the access to full text of some articles. Incomplete reported information in some studies, and variations in quality of articles. The main limitation of this meta-analysis, like any other overview, is that the participants in the study and the results in the various studies are not completely similar.

Conclusion

Dill reduces cholesterol, triglyceride, and low-density lipoprotein, but does not have a significant effect on high-density lipoprotein levels. With regard to the results of this study, it is recommended that dill be used in the treatment of hyperlipidemia because of lower side effects and low price, however, because complications are not investigated, the recommendation needs more evaluations and studies.

Acknowledgments

None.

Conflict of Interest

There is no conflict of interest.

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