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Review Article

The Effect of Argan Oil on Surrogate Markers in Cardiovascular Diseases: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Argan oil is a natural vegetable oil recently received much attention because of ingredients such as tocopherols, particularly in its γ-isoform, polyphenols, and phytosterols which are rich sources of antioxidants with therapeutic effects on cardiovascular diseases, diabetes, obesity, hypercholesterolemia, hypertension, hepatic disease, cancer, acne, sebum, and aging. One half tablespoon per day was shown to be effective to prevent metabolic diseases.

Methods: The current systematic review and meta-analysis evaluated the effect of argan oil on cardiovascular health. PubMed, Scopus, EMBASE, and Web of Science databases were searched from their beginning to August 2019. All clinical trials studied the effect of argan oil on the systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), vitamin E, apolipoprotein A (Apo A) and apolipoprotein B (Apo B) levels for at least two weeks were included. Five studies underwent meta-analysis techniques using random-effects models.

Results: Collective outcomes showed that argan oil increased the vitamin E level (SMD: 2.98, 95%CI: -0.51, 6.48, p=0.09) non-significantly compared with control group. Argan oil could significantly raise the Apo A level (SMD: 0.74, 95%CI: 0.39, 1.10, p<0.001), and decrease the Apo B level significantly (SMD: -0.58, 95%CI: -0.93, -0.23, p=0.001).

Conclusion: Our study showed that consumption of argan oil increased Apo-A and vitamin E levels and decreased Apo-B, but further clinical studies on a larger number of patients are needed to explain and confirm the biological and clinical effects of argan oil.

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Introduction

Cardiovascular disease (CVD) remains the major global cause of mortality (1). One of the main risk factor of CVD is dyslipidemia which is associated with elevated plasma level of triglycerides, low-density lipoprotein (LDL) cholesterol and apolipoprotein B (Apo-B) levels, and lower level of plasma high-density lipoprotein (HDL) cholesterol (1). The therapeutic and

preventing effects of some diets on the cardiovascular disease and related risk factors like dyslipidemia have been indicated by many researchers (2). Among food component, dietary fat has a fundamental role in preventing cardiovascular diseases (2). Saturated fatty acids by increase in low-density lipoprotein cholesterol levels are associated with elevated risk of coronary artery diseases, whereas unsaturated fatty acids link to lower the risk (2, 3).

Argan oil is a natural vegetable oil extracted from the fruits of Argan tree (*Argania spinose L.*) by cold pression (2, 4-6) and is widely used for cosmetic (moisturizers, shampoos, and other processed cosmetics), pharmacological and nutritional values (2, 5). It is reported that this oil supply around 25% of dietary fats in the southwestern Moroccan in the form of breakfast, on toast, and for cooking (1, 4, 6). It has been consumed as a daily diet and traditional medication for its beneficial effects in numbers of diseases such as acne, eczema, wrinkles, dry skin, joint pain, psoriasis, and skin inflammation (1, 5).

Argan oil consists of 20% saturated fatty acids (SFA), 45% monounsaturated fatty acid (MUFA), 35% ω-6 polyunsaturated fatty acid (PUFA), and 0.1-0.3% ω-3 PUFA. Alpha linolenic/linoleic acid ratio is 0.003 (1, 2, 6). This oil is recently received much attention due to its special ingredients, such as tocopherols particularly in its γ-isoform, polyphenols, and phytosterols (4, 7). It is also rich in caffeic acid, vanillic acid, ferulic acid, resorcinol and catechin (8, 9). Recent studies have identified coenzyme Q10 (CoQ10) and melatonin in argan oil (10). This ingredients make argan oil as a rich source of antioxidants which can insert therapeutic effects on several diseases, such as cardiovascular diseases, diabetes, obesity, hypercholesterolemia, hypertension, hepatic disease, cancer, acne, sebum, and aging (8, 9).

According to animal models, the probable neuroprotective effect, as well as healing effects in second-degree burns of argan oil have also been shown (5, 10). Some studies have found that one-two tablespoon per day of argan oil seems to be an effective dose to prevent metabolic diseases (10, 11). Although several systematic review and meta-analysis have been performed in this area, but there is no thorough study regarding the effect of argan oil on blood pressure, BMI, vitamin E, apolipoprotein A (Apo-A) and Apo B levels to be investigated. The aim of this study was to assess the effect of argan oil on blood pressure (BP), body mass index (BMI), vitamin E, Apo A and Apo B levels.

Materials and Methods

Search Strategy and Article Selection

The present study was done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide (12). The PubMed, Web of sciences (ISI), Embase and Scopus (Elsevier) databases (until August 18, 2019) were searched. The following terms were used in every possible combination: ""argan oil"," "argan," "argania spinosa kernel oil," "argania spinosa", "apolipoproteins A", "apolipoproteins B" and "Vitamin E". Inclusion criteria were the reports that (i) were the clinical trials (parallel or crossover design), (ii) were written in the English language, (iii) were performed on human subjects, and (iv) subjects ingested argan oil for at least 2 weeks. A screening form was used to select eligible articles. Studies were screened by two reviewers (MGH, MT). Furthermore, the reference lists of all included articles were evaluated for additional potentially qualified studies.

Data Extraction

Data from eligible studies were extracted by two reviewers and cross-checked for consistency (MGH, MT). Any discrepancies were resolved via consensus-based discussions between the reviewers. Data of each study were extracted, including demographic (number of patients, mean age, sex), BMI, treatment duration, type and dose of argan, systolic blood pressure (SBP), diastolic blood pressure (DBP), vitamin E, Apo A and Apo B in both the intervention and placebo groups at baseline and at the end of study. For the continuous outcomes, we extracted the mean, and standard deviation.

Quality Assessment

We used the Cochrane tool to assess the methodological quality of included articles, included the following items: random description, allocation concealment, blinding, incomplete data outcome and protocol registration (Table 1).

Statistical Analysis

Stata software version 13 (Stata Corp LP, College Station, TX, USA) was used for statistical analysis of data. We evaluated the effect of argan on the changes in the following outcomes: (i) BMI (kg/m^2), (ii) SBP (mmHg), (iii) DBP (mmHg), (iv) vitamin E (micmol/L), (v) Apo A (micromol/L) and (vi) Apo B (micromol/L). The standardized mean difference (SMD) and 95% confidence interval (CI) were applied to explain their effect. The mean and standard deviation (SD) of the mentioned outcomes levels were extracted before and after argan consumption.

The mean change was computed as follows: (amount at end of the follow-up in the treatment group – amount at baseline in the treatment group) –

Table 1: Quality assessment of the studies according to Cochrane tool.

Author, Year	Random assignments	Allocation concealment	Blinding	Incomplete data outcome	Protocol registration	Total	Quality
Essouiri *et al*., 2017	Unclear	Unclear	0	1	Unclear	1	Low
Batta *et al*., 2016	Unclear	Unclear	0	1	Unclear	1	Low
Sour *et al*., 2012	Unclear	Unclear	0	1	Unclear	1	Low
OuldMohamedou *et al*., 2011	Unclear	Unclear	0	1	Unclear	1	Low
Eljaoudi *et al*., 2015	Unclear	Unclear	0	1	Unclear	1	Low

(amount at end of the follow-up in the control group – amount at baseline in the control group). If SD of the mean difference was not reported, it was computed as follows: SD=square root [(SD pre-treatment)^2 + (SD post-treatment)^2 – (2 R-SD pre-treatment-SD post-treatment)], assuming a correlation coefficient of 0.5, as a conservative estimate for R which ranged between 0 and 1 (13). In case that median or range or 95% CIs was reported, mean and SD values were estimated using Hozo *et al*.'s procedure (14). Plot digitizer software was used to extract the data when the outcome variable was demonstrated only in the graphic form.

Cochran's Q-test was used to assess the heterogeneity (with significance set at $p<0.1$) and for computing the percentage of heterogeneity (I^2 value ≥50% indicating significant heterogeneity), the I^2 test and a random effect model were used. The leave-one-out method (i.e. removing a single trial each time and repeating the analysis) was used for sensitivity analysis to determine the effect of each study on the overall effect size (15). The meta-analysis was done using STATA software version 13 (Stata Corp LP, College Station, TX, USA). The probability value (p value)<0.05 was considered as statistically significant.

Results

Flow and Characteristics of Included Studies

A total of 146 reports were firstly identified; after eliminating the duplicates (n=70), 76 articles remained. Of the 76 articles, 67 were excluded because they were either not human clinical trial or unrelated to our current meta-analysis according to the inclusion criteria, after an accurate review of the titles and abstracts. Thus 9 potentially pertinent articles were chosen for full text assessment and detailed examination. Furthermore, 4 articles were excluded for one or more of the following reasons: the studies that did not have usable data (n=2) and those with no access to the full text of the article (n=2). After ultimate evaluation, 5 eligible studies satisfied the inclusion criteria and were qualified for the final meta-analysis.

Features of Included Studies

The flowchart of the selection process in the meta-analysis was demonstrated in Figure 1. The Features of the eligible studies were shown in Table 2. Data were assembled from 5 eligible studies with 158 subjects in control group and 159 in intervention group. The number of participants in these trials ranged from 20 (16) to 43 (17). The included studies were published between 2005 and 2017 and all were conducted in Morocco (5 studies) (17-20), except a study which was conducted in Algeria (16). The participants' mean age alternated from 23.4 to 57.73 years. All studies were performed on both sexes. The treatment duration differed from 3 (17) to 8 (20) weeks. The participants in two trials were hemodialysis patients, in four studies were healthy adults, and in one study, the diabetic with dyslipidemia, an osteoarthritis and one postmenopausal patients.

Meta-analysis Results

Figures 2 A-F show forest plots summarizing the meta-analysis of studies on BMI, SBP, DBP, vitamin E, Apo A and Apo B. Data for BMI were available from three studies representing 96 participants. Collective outcomes indicated that however; argan oil increased the BMI, it was not significant (SMD: 0.047, 95%CI: -0.23, 0.33, p=0.74), (Figure 2A). A total of 2 studies included 59 patients' supplied data regarding the SBP. Figure 2B indicates the pooled outcomes combining the SMD for the impact of argan oil on SBP in the study population, revealing that the increase in SBP level was not significant after consuming argan oil when compared with control group (SMD: 0.11, 95%CI: -0.24, 0.48, p=0.52).

The results of DPB were reported by 2 studies including 59 subjects. Overall, after consuming argan oil in comparison with control group, the decrease in the DBP level was not significant (SMD: -0.21, 95%CI: -0.58, 0.14, p=0.24), (Figure 2C). The findings for vitamin E were reported from 2 studies representing 57 participants. However, collective results from the random-effect model displayed that consuming argan oil increased the vitamin E level, that was not statistically significant (SMD:

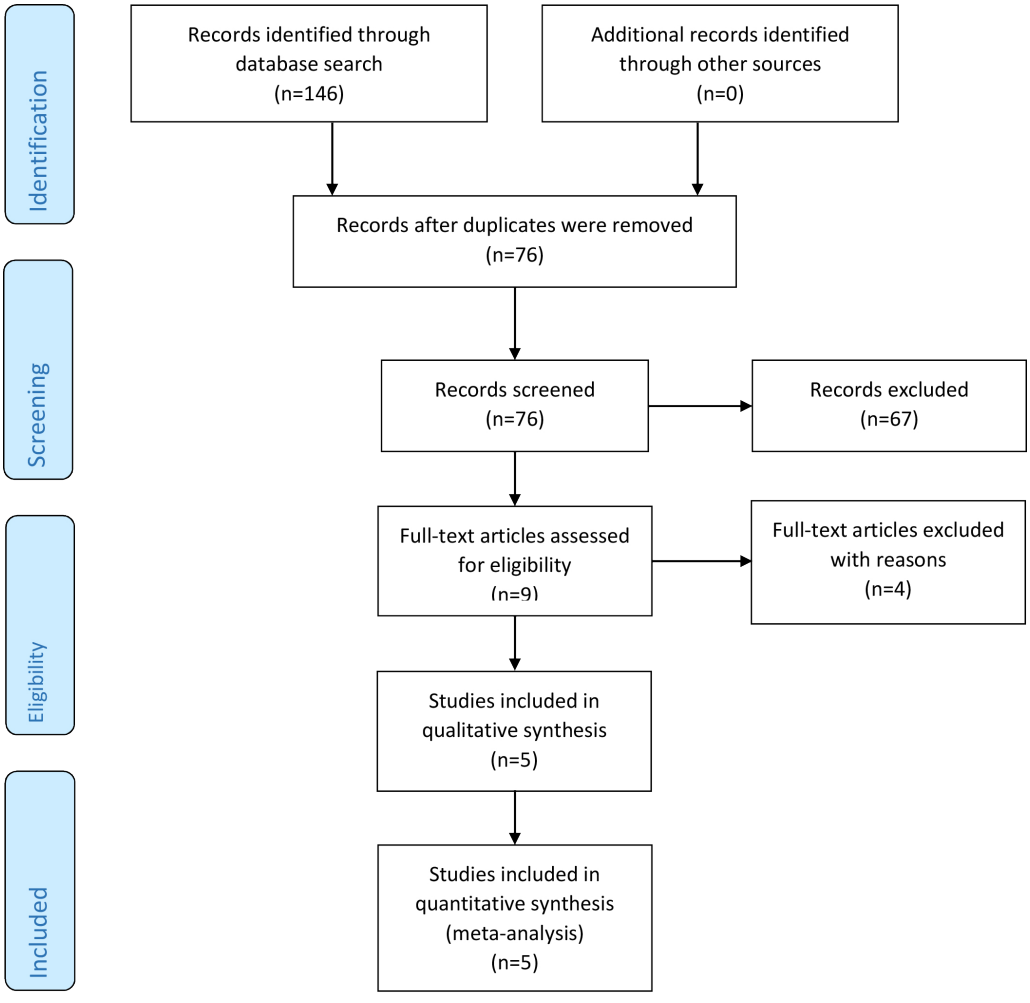

Figure 1: Flow diagram.

Table 2: Characteristic of studies that evaluated the effect of argan oil on the serum level of branched-chain amino acids.

Author, Year	Country	Sex	Age (Year)	Study Population	Duration (week)	Participants (control group, intervention group)	Dose of argan oil (mL/d)	Outcome
Essouiri *et al*., 2017	Morocco	Both	57.73	Osteoarthritis population	8	34, 38	30	BMI, SBP, DBP
Batta *et al*., 2016	Morocco	Both	48.95	Hemodialysis patients	5	24, 21	30	BMI, SBP, DBP, Apo A, Apo B
Sour *et al*., 2012	Algeria	Both	37.9	Healthy adult	4	20, 20	15	Vitamin E
OuldMohamedou *et al*., 2011	Morocco	Both	52.9	Diabetic patients with dyslipidemia	3	43, 43	25	Apo A, Apo B
Eljaoudi *et al*., 2015	Morocco	Both	50.7	Hemodialysis patients	4	37, 37	30	BMI, vitamin E

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Apo A: Apolipoprotein A, Apo B: Apolipoprotein B.

2.98, 95%CI: -0.51, 6.48, p=0.09), with significant heterogeneity (I^2=96.3%, p<0.001) (Figure 2D).

Collective outcomes indicated that however, argan oil could significantly increase the Apo A level (SMD: 0.74, 95% CI: 0.39, 1.10, p<0.001), (Figure 2E), the reduction in Apo B level was statistically significant (SMD: -0.58, 95%CI: -0.93, -0.23, p=0.001) (Figure 2F). It can be explained that the heterogeneity among various studies for BMI, SBP, DBP, Apo A and Apo B levels was not statistically significant.

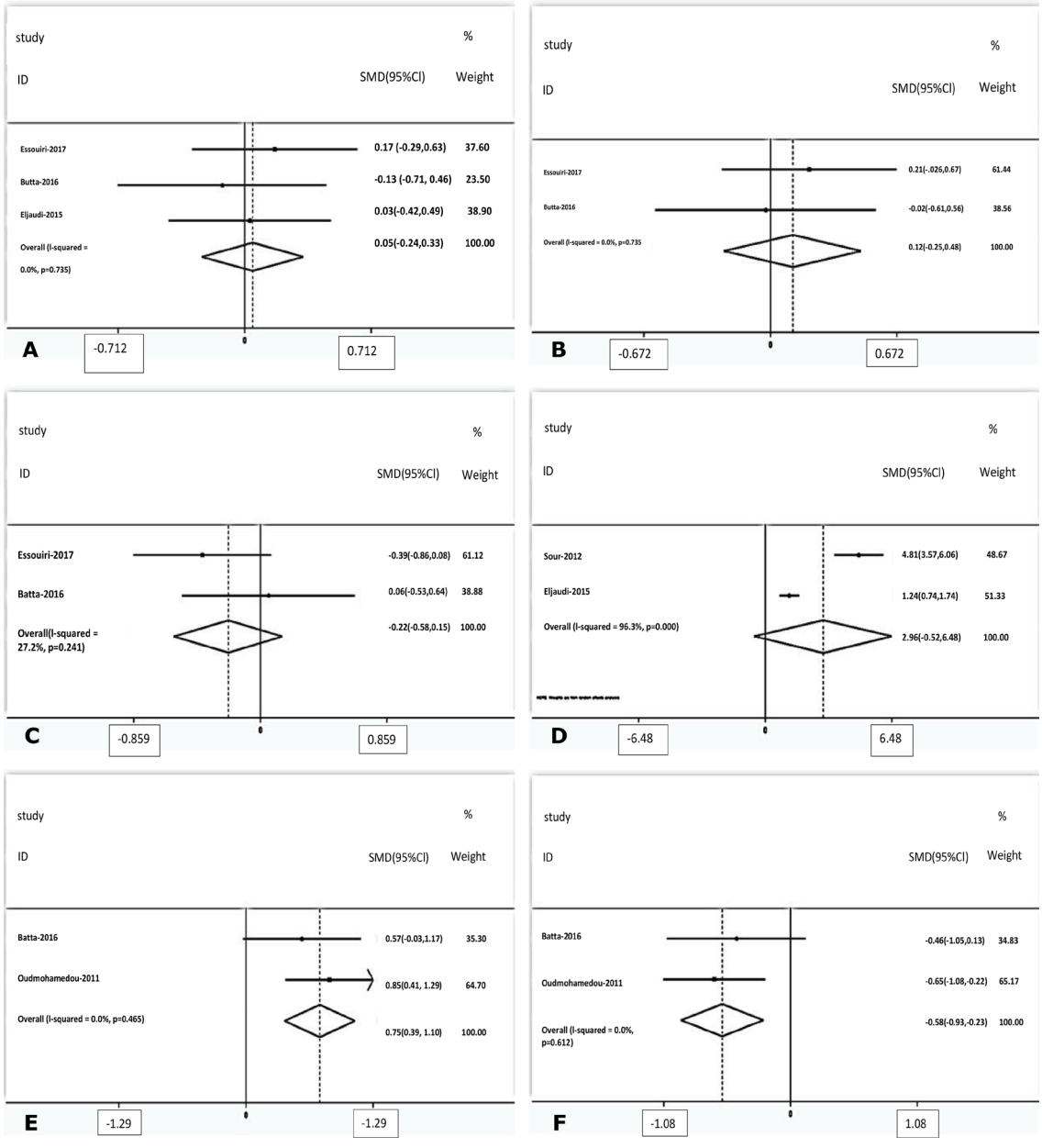

Figure 2: A: Forest plot displaying standard mean difference and 95% confidence interval for the impact of argan oil on body mass index. **B:** Forest plot displaying standard mean difference and 95% confidence interval for the impact of argan oil on systolic blood pressure. **C:** Forest plot demonstrating standard mean difference and 95% confidence interval for the impact of argan oil on diastolic blood pressure. **D:** Forest plot illustrating standard mean difference and 95% confidence interval for the impact of argan oil on vitamin E levels. **E:** Forest plot showing standard mean difference and 95% confidence interval for the impact of argan oil on Apo A levels. **F:** Forest plot depicting standard mean difference and 95% confidence interval for the impact of argan oil on Apo B levels.

Sensitivity Analysis

According to the sensitivity analysis, the results of the current study were not affected by any individual study.

Discussion

Results of this meta-analysis showed that consumption of argan oil could significantly raise the Apo A level, but Apo B level significantly reduced. However, the serum vitamin E level in comparison with the control group did not change significantly. Argan oil is well-known for its valuable medicinal properties and has been used as a natural medicine for centuries (21). Argan oil can insert protective impact on cardiovascular diseases due to high amounts of antioxidants, especially polyphenols, tocopherols and sterols (22), and its fat composition consists 45% MUFA and 35% PUFA (2, 21).

Several mechanism has been shown for the therapeutic effects of argan oil throughout these elements and compounds, including scavenging of reactive oxygen species (ROS), peroxy radicals in particular, which fracture the reaction of

peroxidation chain, chelating free Cu^{2+} to form redox-inactive complexes and therefore, diminishing metal-catalyzed oxidation of LDL, and inhibiting the binding of Cu^{2+} to apolipoproteins and subsequently inhibiting the modification of amino acid-apo-B protein residue (22).

Dietary fatty acids have been shown to improve blood pressure and vascular function. (23). Virgin argan oil (VAO) is identified to have a high concentration of oleic acid and linoleic acid (18). Increasing the amount of linoleic acid in the diet can reduce SBP (23). Study on spontaneously hypertensive rats (SHR) showed that diets enriched with linoleic or g-linolenic acid can reduce the trend of increasing blood pressure (23). Linoleic acid (C18:2n-6) is known as essential fatty acids involved in the biosynthesis of arachidonic acid (C20:4n-6), which is a precursor of prostaglandin E1 (PGE1), prostacyclin (PGI2) and PGI3 and thromboxane (TXA2) that are known for their platelet anti-aggregator and vasodilator activities. In addition, linoleic acid reduces blood pressure by inhibiting PUFA on angiotensin converting enzyme (ACE), which is known as a strong vasoactive factor (22).

Furthermore, the high content of tocopherols contributes to reducing blood pressure. In this regard, One study demonstrated that the dose of alpha-tocopherols administered in the argan oil to rats (3·8 mg/kg/day) was comparable to the preventive dose of high blood pressure in SHR (23). This meta-analysis showed that the SBP and the DBP levels did not change significantly after consuming argan oil compared with control group. Studies have shown inconsistent results on the effect of organ oil on blood pressure improvement. One study conducted by Derouiche *et al*. illustrated no significant changes in blood pressure levels after using argan or olive oil for 3 weeks (24).

Insignificant impact of argan oil on blood pressure has been proved by other studies, as well (16, 18). However, another study demonstrated slight but significant modification in blood pressure (2.5 % decrease in SBP and 8.2% decrease in DBP) during the 8 weeks after consuming argan oil (20). The study has been done by Berrada *et al*., also showed the reduction in SBP and DBP (25). In an animal study, long-term consumption of argan oil, prevented high blood pressure and caused a significant change in mean blood pressure, without changing the heart rate (23). One study revealed that argan oil could improve blood pressure, hyperglycemia and insulin resistance via its antioxidant content in five-week glucose-fed rats (7).

Several studies demonstrated considerable elevation in plasma vitamin E level after argan oil consumption (19, 21). Our meta-analysis denoted to insignificant increase in the vitamin E level following consuming argan oil. The surge of plasma vitamin E level may be due to richness of tocopherols in argan oil (636 mg/kg) (22, 24). Argan oil is about twice as rich in tocopherol as olive oil (23). In a previous study, improvement in antioxidant status, such as plasma vitamin E, has been observed after consuming argan oil (20), due to the high content of tocopherols, carotenoids and polyphenols in the argan oil (16, 18). Moreover, it was demonstrated that these compounds can prevent oxidation of LDLc and HDLc, so it can insert antiatherogenic effects (2, 18).

The principal tocopherol in virgin argan oil is gamma-tocopherol, however, plasma alpha-tocopherol levels are increased after argan oil consumption. The result can be related to transformation of gamma-tocopherol to alpha-tocopherol due to the close similarity between their chemical structures. To confirm this theory, several studies have shown that gamma-tocopherol supplementation can increase gamma and alpha levels concurrently (19, 21, 22). Our findings showed however, argan oil can increased the Apo A level significantly, while the Apo B level showed a significant decrease. It has been documented in diabetic patients that after argan oil consumption, there was a significant decrease in the Apo B/Apo A-1 ratio (17).

In another study, a significant growth in HDL-cholesterol and Apo A-l levels were shown in argan and olive groups, although , LDL-cholesterol and apo-B reduced significantly only in olive oil group (22). It has been shown that Apo B/Apo A-1 proportion was a better predictor for cardiovascular risk when compared to cholesterol indicators (26). The balance between atherogenic particles, rich in Apo B, and the antiatherogenic ones, rich in Apo A-1, has been represented by Apo B/Apo A-1 ratio, and as previously was mentioned, it is a better parameter for prediction of cardiovascular diseases. Furthermore, apolipoprotein concentration is less affected by biological variables when compared to lipid measurements (27).

It has been well documented that Apo A level, like HDL level, are reversely associated with the risk of cardiovascular diseases. Argan oil is supposed to have antiatherogenic and preventive effects on cardiovascular diseases, because Apo A-1 significantly increases after argan oil consumption (17). Also, phenolic and tocopherols compounds of argan oil dramatically contribute to the antiatherogenic effects (28). Phenolic compounds have been offered to protect against atherosclerosis, hyperlipidemia and hypercholesterolemia (29).

Their beneficial effects may be through inducing of apoptosis in 3T3-L1 adipocytes (29).

Therefore, as shown in this study, argan oil can have beneficial effects in the prevention and control of cardiovascular diseases by increasing the ratio of Apo A-1/Apo B. In current meta-analysis, it was shown that BMI remained unchanged after argan oil interventional diets when compared with the baseline. In order to investigate the effect of argan oil consumption on anthropometric parameters, one study presented no significant changes for all anthropometric parameters such as body weight (BW) after 3 weeks' intervention with argan oil (24). Another study likewise indicated similar effects (25).

There are some limitations to this study, including small number of total and included studies that limit the ability to perform sub-group and meta-regression analysis that can affect the findings. In addition, all included studies in this meta-analysis were of low quality according to the results of the quality assessment analysis. Therefore, more clinical trials with stronger study designs are recommended.

Conclusion

Our study showed that consumption of argan oil increased Apo A and vitamin E levels and decreased Apo B levels, so argan oil may have antiatherogenic and preventive effects for cardiovascular diseases. Further clinical studies on a larger number of patients with high quality assessments are needed to confirm the biological and clinical effects of argan oil.

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Conflict of Interest

None declared.

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