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The effect of olive leaf use on blood pressure; A systematic review and meta-analysis

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ABSTRACT

Context: Hypertension has been identified as the world's third leading cause of death. Due to their cost-effectiveness and lack of adverse effects compared to antihypertensive medications, medicinal plants have gained popularity in most countries. The olive leaf is one of these plants. As a result, the purpose of the current systematic review and meta-analysis was to determine the effect of olive leaf consumption on systolic and diastolic blood pressure.
Evidence acquisition: The following domestic and international databases were searched in order to retrieve relevant studies: PubMed, Scopus, Web of Science, Embase, Cochrane, ProQuest, and Google Scholar search engine, the ClinicalTrials.gov Protocol Registration and Results System (PRS), the ISRCTN registry administered by BioMed Central, and the World Health Organization's (WHO) International Clinical Trials Registry Platform. The data collected were analyzed using STATA software (version14) at a significance level of $P<0.05$.
Results: Olive leaf consumption had a significant effect on systolic blood pressure [-0.87 (95% CI: -1.09, -0.64)] and diastolic blood pressure [-0.39 (95% CI: -0.57, -0.21)] in five studies with a sample size of 145 people (mean age range of 33.30 ± 5.25 years). Consumption of olive leaves also decreased cholesterol levels [-0.52 (95% CI: -0.81, -0.22)], low-density lipoprotein (LDL-c) levels [-0.35 (95% CI: -0.58, -0.12)], and triglycerides levels [-0.67 (95% CI: -1.19, -0.16)]. Nonetheless, the olive leaf had no statistically significant effect on reducing high-density lipoprotein levels.
Conclusion: We observed that olive leaf consumption significantly reduced the levels of systolic and diastolic blood pressure, cholesterol, triglycerides, and LDL-c.
Registration: The current protocol was also registered on PROSPERO (ID: 221277, Date: 16.04.2022).

Review

Implication for health policy/practice/research/medical education:
Olive leaf consumption had a significant effect on systolic blood pressure [-0.87 (95% CI; -1.09, -0.64)] and diastolic blood pressure [-0.39 (95% CI; -0.57, -0.21)] in five studies with a sample size of 145 people (mean age range of 33.30 ± 5.25 years). Consumption of olive leaves also decreased cholesterol levels [-0.52 (95% CI; -0.81, -0.22)], low-density lipoprotein (LDL-c) levels [-0.35 (95% CI; -0.58, -0.12)], and triglycerides levels [-0.67 (95% CI; -1.19, -0.16)]. Nonetheless, the olive leaf had no statistically significant effect on reducing high-density lipoprotein levels.

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Introduction

Hypertension has long been recognized as one of the most severe diseases in developed countries (1) and a significant health concern in developing countries (2,3). Despite widespread recognition and access to treatment, it is estimated that hypertension will affect approximately 30% of the world's population by 2025, imposing a significant financial burden on public health (4).

Complications of hypertension include brain and retinal artery damage, impaired kidney function, diabetes,

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cardiovascular disease, disability and death (5, 6). Various medications are used to treat hypertension. At standard licensed doses, most antihypertensive medications, such as beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors and thiazide diuretics, have significant adverse effects (7).

Despite the availability of modern medications, traditional medicine has gained popularity in both developing countries and modern nations, particularly in Europe (8). Knowledge of medicinal plants and their traditional use enables the pharmaceutical industry to develop new drugs and use them to prevent and treat various diseases (9).

Olive trees (*Olea europaea* L.), particularly their leaves, have been used to treat wounds, fever, diabetes, gout, atherosclerosis, and hypertension since ancient times (10). Apart from the Mediterranean region, this plant is widely used in the Arabian Peninsula, India, Asia, and other tropical and subtropical regions (11).

Recently, the medicinal properties of olive products have been focused on their phenolic compounds (particularly oleuropein and hydroxytyrosol), which have been shown in animal and laboratory studies to exhibit a broad range of antioxidant, hypoglycemic, antihypertensive, antimicrobial, and antiatherogenic effects (12). Additionally, olive leaves' antihypertensive and cholesterol-lowering properties have been well established (13,14). Thus, the purpose of this systematic review and meta-analysis was to assess the published literature on the effect of olive leaves on systolic and diastolic blood pressure reduction.

Materials and Methods

Study protocol

The present systematic review and meta-analysis examined the effect of olive leaves on systolic and diastolic blood pressure in the global population.

Statistical population

The current study enrolled individuals from diverse communities worldwide who were selected without age, gender, or race restrictions.

Study outcomes

Primary outcome

At least one systolic and diastolic blood pressure measurement was required as the primary outcome in eligible studies.

Secondary outcome

Secondary outcomes included cholesterol, triglyceride, low-density lipoprotein (LDL-c), high-density lipoprotein (HDL-c), and blood glucose levels.

Search strategy

This systematic review searched the electronic databases PubMed, Scopus, Web of Science, Embase, ProQuest, Cochrane, and the Google Scholar search engine without regard for time or language constraints. Articles in languages other than Persian and English were translated to extract their information. The following keywords were used in the literature search: "Hypertension, Blood-pressures, Olive-leaf, Oleuropein, Olea-europaea", as well as their Latin equivalents and MeSH terms (updated until April 29, 2020). Furthermore, the terms mentioned above were searched in combination in English language databases using operators such as AND, OR. The IranDoc information system was queried for dissertations, research reports, and conference or seminar papers to search for unofficial sources.

Additionally, the ClinicalTrials.gov Protocol Registration and Results System (PRS), the ISRCTN registry administered by BioMed Central, and the World Health Organization's International Clinical Trials Registry Platform were searched to identify protocols for unpublished recorded trials. Moreover, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart's list of references for all primary studies was manually searched.

Inclusion and exclusion criteria

Patient/population, intervention, comparison, and outcomes (PICO) elements; the study population consisted of all people who used olive leaves in various forms to lower their blood pressure. "Intervention": olive leaves in various forms (syrup, tablets, or extract), "comparison": the group that did not use olive leaves or received a placebo, and "outcome": blood pressure levels (systolic and diastolic).

Primary studies were included in this systematic review if they were randomized clinical trials with or without blinding or quasi-experimental studies. Olive leaf experiments were conducted on the intervention group, whereas the control group received a placebo or no intervention. At least one systolic or diastolic blood pressure outcomes assessment is required for eligible trials. Additionally, secondary outcomes such as blood glucose and lipid levels should have been mentioned. The following criteria were conducted to exclude individuals; 1) Non-random sample size studies, 2) Case report studies; 3) Failure to report required data; 4) Studies examining the effect of using olive leaves in conjunction with another chemical or herbal medicine; 5) Qualitative studies demonstrating the effect of olive leaves on blood pressure; 6) Studies of low-quality, as defined by the Cochran Institute's clinical quality assessment checklist; 7) Studies examining the effect of olive oil or fruit; and 8) Unavailability of the articles' full text.

Qualitative assessment of studies

Following the identification of preliminary studies, two authors independently evaluated them all using the

Cochrane risk-of-bias tool. This Cochrane risk-of-bias tool checklist is divided into seven distinct domains, each assessing a different dimension or type of significant bias in clinical trials. Moreover, each domain in this checklist assigns trials a risk of bias of 'low,' 'high,' or 'unclear.' After assessing the risk of bias in each study, the discrepancy between the responses in each study was determined; following that, the two evaluators reached consensus on one response.

Data extraction

Two researchers extracted the data independently to minimize reporting bias and data collection errors. The researchers entered the extracted data into a checklist that included the following information: the researcher's name, the year of publication, the title of the research paper, the number of samples, the type of study, the volume of olive leaves consumed, the duration of olive leaf consumption, and the mean and standard deviation of systolic and diastolic blood pressure before and after the intervention (olive leaf). Afterward, the third researcher examined the data extracted by the previous two researchers for inconsistencies. If the necessary data were not included in one of the articles or primary studies, it was obtained via email from the corresponding author.

Statistical analysis

Due to the quantitative nature of the primary outcome, the intervention's effect size was calculated. It was possible to calculate the mean difference (the mean difference between the levels of systolic and diastolic blood pressure before and after the intervention) in the intervention group. The standardized mean difference (SMD), a classical effect size index, indicates the strength of the relationship between the intended intervention and the outcome under study. As standardized mean difference approaches zero, the strength of the relationship would become weaker, while SMD values close to one and even higher are indicative of a stronger relationship.

The computation of SMD is demonstrated in equation 1. If the SMD confidence interval crosses the null line (zero), that relationship is not statistically significant and vice versa.

$$\text{SMD}=\frac{\text{Difference in mean outcome between groups}}{\text{Standard deviation of outcome among participants}}$$

The studies are pooled based on their sample size, mean, and standard deviation. The Q Cochrane test and the I^2 index were conducted to assess study heterogeneity. The fixed-effects model was used for low heterogeneity, whereas the stochastic effects model was employed for high heterogeneity. As a result, the stochastic effects model was applied in this study. Data were analyzed by STATA version 14 software. Moreover, a *P* value of less than 0.05 was deemed statistically significant.

Results

Study selection process

Initially, a search of the literature in the databases mentioned above yielded 951 articles, of which 362 duplicate studies were excluded. After reviewing the abstracts of the remaining 589 articles, 511 were excluded based on the exclusion criteria. Another 73 articles were excluded from the remaining 78 due to insufficient information or the absence of full text. Finally, the five articles underwent qualitative assessment, and all were of good quality. They were then entered into the meta-

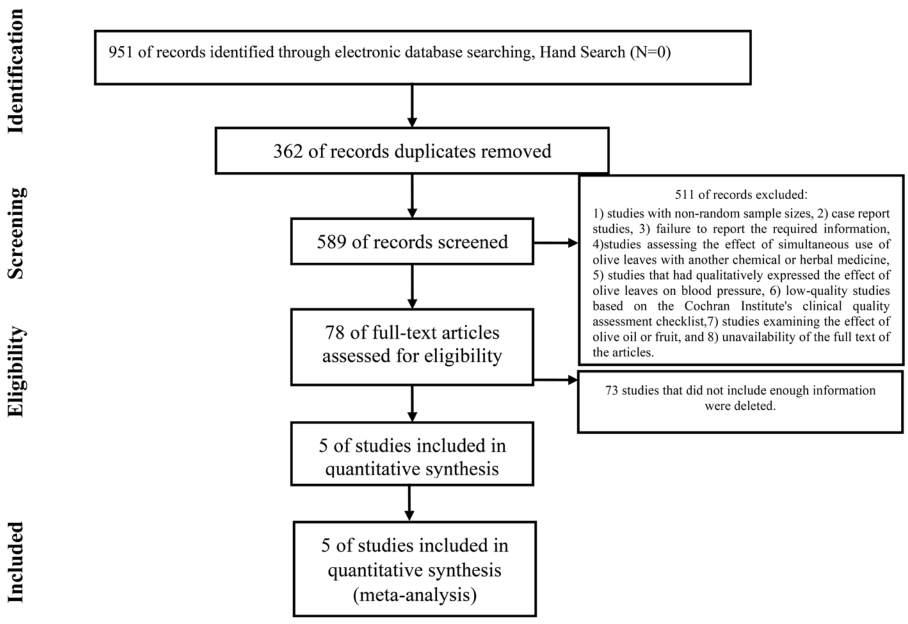

Figure 1. A flowchart of studies into the process of systematic review and meta-analysis.

Table 1. Characteristics of articles entered into the meta-analysis process

First author	Year of publication	Type of study	Country	Sample size	Age (y)	Duration (wk)	Daily consumption (mg)	Consumption instruction	Control group
Lockyer (15)	2017	Randomized controlled trial	New Zealand	30	45.3	6	142	Consume the extract in liquid form	No consumption
Cabrera-Vique (16)	2015	Preliminary clinical study	Spain	10		4	1600	Consumption of the extract in the form of capsules	No consumption
De Bock (17)	2013	Randomized, placebo-controlled, crossover trial	New Zealand	23	46.4	12	60	Consumption of the extract in the form of capsules	Placebo
Susalit (18)	2011	Randomized, double-blind, active-controlled clinical study	Indonesia	72	51.5	1	500	Tab EFLA®943	Captopril
Susalit (18)	2011	Randomized, double-blind, active-controlled clinical study	Indonesia	72	51.5	2	500	Tab EFLA®943	Captopril
Susalit (18)	2011	Randomized, double-blind, active-controlled clinical study	Indonesia	72	51.5	3	500	Tab EFLA®943	Captopril
Susalit (18)	2011	Randomized, double-blind, active-controlled clinical study	Indonesia	72	51.5	4	500	Tab EFLA®943	Captopril
Susalit (18)	2011	Randomized, double-blind, active-controlled clinical study	Indonesia	72	51.5	5	500	Tab EFLA®943	Captopril
Susalit (18)	2011	Randomized, double-blind, active-controlled clinical study	Indonesia	72	51.5	6	500	Tab EFLA®943	Captopril
Susalit (18)	2011	Randomized, double-blind, active-controlled clinical study	Indonesia	72	51.5	7	500	Tab EFLA®943	Captopril
Susalit (18)	2011	Randomized, double-blind, active-controlled clinical study	Indonesia	72	51.5	8	500	Tab EFLA®943	Captopril
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	35.7	1	500	Tab EFLA®943	No consumption
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	35.7	2	500	Tab EFLA®943	No consumption
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	35.7	4	500	Tab EFLA®943	No consumption
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	35.7	6	500	Tab EFLA®943	No consumption
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	35.7	8	500	Tab EFLA®943	No consumption
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	33.3	1	1000	Tab EFLA®943	500 mg of olive leaf extract
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	33.3	2	1000	Tab EFLA®943	500 mg of olive leaf extract
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	33.3	4	1000	Tab EFLA®943	500 mg of olive leaf extract
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	33.3	6	1000	Tab EFLA®943	500 mg of olive leaf extract
Perrinjaquet-Moccetti (19)	2008	Controlled, parallel-group, co-twin study	Switzerland	10	33.3	8	1000	Tab EFLA®943	500 mg of olive leaf extract

analysis process (Figure 1).

Table 1 summarizes the characteristics of the studies that qualified for the systematic review and meta-analysis stage.

As illustrated in Figures 2 and 3, five studies comprised a sample size of 145 cases (mean age range of 33.30 ± 55.25). These five studies were conducted in 21 stages between 2008 and 2017 in Spain, Indonesia, New Zealand, and Switzerland. The studies cited above used varying doses of olive leaves to lower blood pressure (doses of 60, 142, 500, 1000, and 1600 mg). The effect of olive leaf consumption on systolic and diastolic blood pressure levels was (-0.87 [95% CI: -1.09, -0.64]) and -0.39 (95% CI: -0.57, -0.21), respectively, and both relationships were statistically significant.

In a country-level analysis, olive leaf consumption's lowest and highest effects on systolic blood pressure levels were found in Spain and New Zealand, respectively, both of which were statistically significant. Olive leaves had a statistically significant effect on lowering systolic blood pressure in people who consumed them for one to eight weeks. However, the effect of olive leaf consumption on

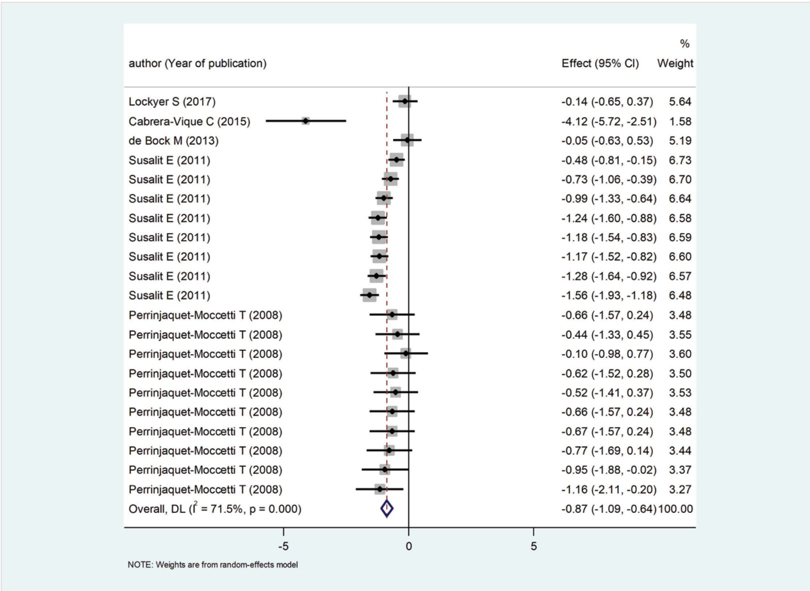

Figure 2. The standard effect size of olive leaf consumption on the lowering of systolic blood pressure based on the author's name, the year of study, and 95% CI.

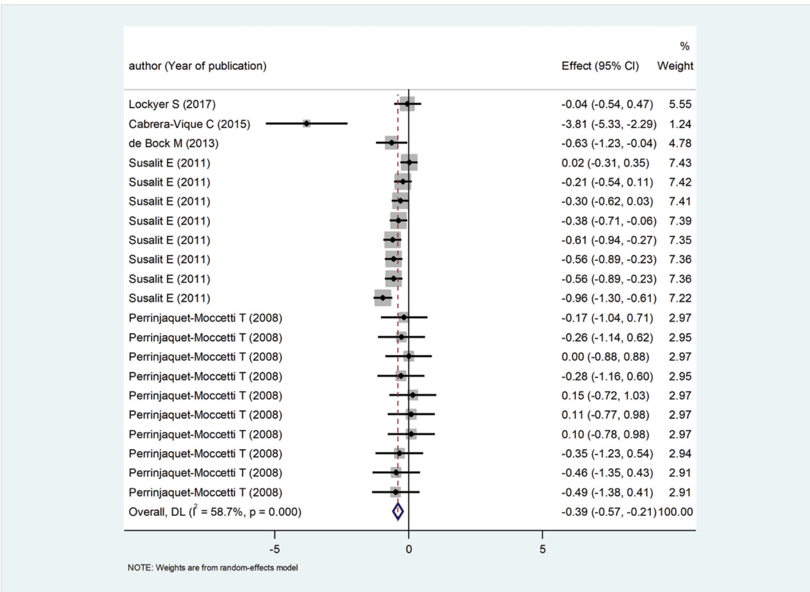

Figure 3. The standard effect size of olive leaf consumption on the reduction of diastolic blood pressure based on the author's name, the year of study, and its 95% CI.

systolic blood pressure reduction was not statistically significant in the group that consumed olive leaves for 12 weeks. The effect of olive leaf consumption on reducing systolic blood pressure levels was statistically significant in those who consumed 60, 500, 1000, and 1600 mg of olive leaves. Nonetheless, the effect of olive leaf consumption on systolic blood pressure reduction was not statistically significant in the group that consumed 142 mg of olive leaf (Table 2). In assessing this association across countries, we observed that the relationship between olive

Table 2. The effect of olive leaf consumption on primary and secondary outcome levels

Subgroups			SMD	Low	High	*P* value	I^2 (%)
SBP	Total	SBP level	-0.87	-1.09	-0.64	<0.0001	71.5
		New Zealand	-0.10	-0.48	-0.28	0.812	0
		Spain	-4.12	-5.72	-2.51	-	-
		Indonesia	-1.07	-1.31	-0.83	0.001	72.9
		Switzerland	-0.64	-0.93	-0.36	0.950	0
	Age (y)	30-39	-0.64	-0.93	-0.36	0.950	0
		40-49	-0.10	-0.48	-0.28	0.812	0
		50-59	-1.07	-1.31	-0.83	0.001	72.9
	Duration of use (wk)	1	-0.52	-0.81	-0.22	0.882	0
		2	-0.69	-0.99	-0.39	0.840	0
		3	-0.99	-1.33	-0.64	-	-
		4	-1.35	-2.40	-0.30	<0.0001	84.6
		5	-1.18	-1.54	-0.83	-	-
		6	-0.72	-1.31	-0.14	0.012	72.6
		7	-1.28	-1.64	-0.92	-	-
		8	-1.18	-1.81	-0.55	0.098	56.9
		12	-0.50	-1.38	0.38	0.026	79.9
	Dosage (mg)	60	-0.05	-0.62	-0.53	-	-
		142	-0.14	-0.65	0.37	-	-
		500	-0.95	-1.15	-0.75	0.001	62.3
		1000	-0.83	-1.24	-0.42	0.940	0
		1600	-4.12	-5.72	-2.51	-	-
DBP	Total	DBP level	-0.39	-0.57	-0.21	<0.0001	58.7
		New Zealand	-0.32	-0.90	-0.27	0.134	55.4
		Spain	-3.81	-5.33	-2.29	-	-
		Indonesia	-0.44	-0.65	-0.24	0.004	66.5
		Switzerland	-0.16	-0.44	0.12	0.979	0
	Age (y)	30-39	-0.16	-0.44	0.12	0.979	0
		40-49	-0.32	-0.90	0.27	0.134	55.4
		50-59	-0.44	-0.65	-0.24	0.004	66.5
	Duration of use (wk)	1	0.01	-0.28	0.30	0.903	0
		2	-0.18	-0.47	0.11	0.794	0
		3	-0.30	-0.62	0.03	-	-
		4	-0.91	-1.94	0.12	<0.0001	84.9
		5	-0.61	-0.94	-0.27	-	-
		6	-0.40	-0.65	-0.14	0.399	0
		7	-0.56	-0.89	-0.23	-	-
		8	-0.52	-1.20	0.16	0.055	65.5
		12	-0.52	-0.91	-0.14	0.628	0
	Dosage (mg)	60	-0.63	-1.23	-0.04	-	-
		142	-0.04	-0.54	-0.47	-	-
		500	-0.39	-0.56	-0.22	0.020	50
		1000	-0.21	-0.61	0.18	0.782	0
		1600	-3.81	-5.33	-2.29	-	-
Cholesterol (mg/dL)			-0.52	-0.81	-0.22	0.036	51.4
HDL-c (mg/dL)			-0.07	-0.24	0.11	0.993	0
LDL-c (mg/dL)			-0.35	-0.58	-0.12	0.204	27
TG (mg/dL)			-0.67	-1.19	-0.16	<0.0001	81.6

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride.

leaf consumption and diastolic blood pressure was not statistically significant in Switzerland.

Moreover, olive leaf consumption did not affect systolic blood pressure in the group that consumed 1000 mg. Secondary outcomes showed that olive leaf consumption had a statistically significant impact on lowering cholesterol (SMD=-0.52), LDL-c (SMD=-0.35), and TG (triglyceride) (SMD=-0.67). Nonetheless, different doses of olive leaves did not affect their HDL-c levels (Table 2).

Discussion

Olive leaf consumption significantly reduced systolic and diastolic blood pressure, cholesterol, triglycerides, and LDL-c levels. Nonetheless, the reduction in HDL-c was not statistically significant. Zamora-Zamora et al conducted a systematic review and meta-analysis on the effect of olive oil on blood pressure reduction. This study found that while olive oil did not significantly change systolic blood pressure, it significantly reduced diastolic blood pressure (20).

A meta-analysis of 355 patients concluded that olive oil consumption did not affect diastolic blood pressure, total cholesterol, HDL-c, LDL-c, or triglycerides (21). According to another meta-analysis conducted by Nissensohn et al, employing a sample size of 7000 sizes. They observed that extra virgin olive oil had a beneficial effect on both systolic and diastolic blood pressure [-1.44 (-2.88, 0.01)] and diastolic blood pressure [-0.70 (-1.34, -0.07)] (22).

Filip et al demonstrated in a similar study that olive leaf extract consumption reduces both systolic and diastolic blood pressure in people with hypertension. Additionally, they reported improved lipid profiles in individuals with normal or hypercholesterolemia (23). These results align with current research findings that olive leaf consumption significantly reduces cholesterol, triglyceride, and LDL-c levels. In contrast to the current meta-findings, an analysis conducted by De Bock et al concluded that using olive leaf extract did not affect blood pressure or plasma lipids in overweight men (17).

Various reviews in diverse populations have indicated the efficacy of herbal medicines in treating hypertension, several of which will be discussed in the present study. Nonetheless, this meta-analysis is the first to look at the effect of olive leaf consumption on blood pressure reduction. Tahraoui et al reviewed the available medicinal plants to treat diabetes and hypertension. According to the study, 64 medicinal plants were used to treat these two diseases, with 45, 36, and 18 plants used to treat diabetes, hypertension, or both, respectively (24).

Moreover, in another ethnobotanical study conducted by Hassaïne et al on medicinal plants used to treat hypertension in a region of Northwestern Algeria, traditional therapies were found to be highly effective. This study enrolled 242 hypertensive patients and utilized eleven different types of pharmaceutical plants (25).

Limitations of the study

There was a paucity of data on other countries due to a lack of conducted research and a scarcity of published articles. As a result, gender-specific analyses comparing the effects of olive leaf consumption on blood pressure in men and women were impossible. Without a consistent distribution of studies across countries, it was impossible to assess the obtained result accurately.

Conclusion

Olive leaf consumption had a significant effect on systolic blood pressure [-0.87 (95% CI: -1.09, -0.64)] and diastolic blood pressure [-0.39 (95% CI: -0.57, -0.21)] in five studies with a total sample size of 145 people. The results imply that consumption of olive leaves significantly lowers both systolic and diastolic blood pressure. Additionally, olive leaves have a twice-as-effective effect on lowering systolic blood pressure than diastolic blood pressure. Furthermore, olive leaf consumption decreased cholesterol levels [-0.52 (95% CI: -0.81, -0.22)], LDL-c levels [-0.35 (95% CI: -0.58, -0.12)], and TG levels [-0.67 (95% CI: -1.19, -0.16)].

According to the lipid profile, olive leaf consumption had the most significant effect on triglyceride, cholesterol, and LDL-c levels, respectively. Nonetheless, olive leaf consumption had no statistically significant effect on HDL-c levels. Given the effect of olive leaf consumption on blood pressure and lipid profile reduction in study participants and the small number of studies included in the review, it is recommended that additional research be conducted in this field.

Authors' contribution

Conceptualization: AF and MF. Methodology: MF and MM. Formal Analysis: MF and MM. Investigation: SSY and MA. Resources: SSY and MA. Data Curation: SSY, AF and MA. Writing—Original Draft Preparation: All authors. Writing—Review and Editing: All authors. Supervision: MF and AF. Funding Acquisition: MF.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The institutional ethical committee of Mazandaran University of Medical Sciences approved all study protocols (Ethical code# IR.MAZUMS.REC.1399.7844). The current protocol was also registered on PROSPERO (ID: 221277, Date: 16.04.2022). Additionally, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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