Phytotherapy Research

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REVIEW

Efficacy of Olive Leaf Extract in Improving Blood Pressure in Pre-Hypertensive and Hypertensive Individuals: A Systematic Review and Meta-Analysis

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Keywords: blood pressure | *Olea europaea* L. | oleuropein | phytotherapy | pre-hypertension

ABSTRACT

Annually, approximately 10 million deaths are attributed to hypertension, highlighting the critical need for effective treatments beyond conventional medications due to their limitations. Therefore, the aim of this study was to evaluate the impact of *Olea europaea* L. on blood pressure in adults with prehypertension and hypertension. The search, conducted from November/2022-October/2024 was performed on EBSCO, CABI, CNKI, Cochrane Library, DOAJ, PUBMED, SCOPUS, and WEB OF SCIENCE databases using Hypertension AND *Olea europaea* L. Eligible studies included those evaluating the effect of *Olea europaea* L. on systolic/diastolic blood pressure in hypertensive or pre-hypertensive adults. Exclusion criteria were multi-preparation interventions. Data on reference, country, sample, intervention/control details, duration, and differences in systolic and diastolic blood pressure, adverse effects, and medication use were extracted manually. The mean differences, heterogeneity (I^2) and quality of the studies were assessed using Review Manager (version 5.4). From 211 found studies, 3 met the eligibility criteria, considering 248 participants analysed. An antihypertensive effect was observed on systolic and diastolic blood pressure in the pre- vs. post-intervention in the global analysis (systolic −6.03 mmHg, 95% CI: [−11.60, −0.46], $I^2 = 82\%$, $p = 0.03$; diastolic −2.38 mmHg, 95% CI: [−4.96, 0.20], $I^2 = 50\%$, $p = 0.07$) and in the sub-analysis that included the studies with the highest dose (1000 mg/day) (systolic −11.45 mmHg, 95% CI:[−13.99, −8.91], $I^2 = 0\%$, $p \leq 0.001$; diastolic −4.65 mmHg, 95% CI: [−6.56, −2.74], $I^2 = 0\%$, $p \leq 0.001$). Olive leaf extract (1000 mg/day) may reduce systolic and diastolic blood pressure by −11.45 and −4.65 mmHg, respectively. However, limitations include variable trial quality and exclusion of studies not written in English. Additional comprehensive clinical studies are essential to confirm its efficacy and safety.

1 | Introduction

A condition of global concern, arterial hypertension poses significant health risks with far-reaching consequences. Defined by systolic blood pressure (SBP) surpassing 140 mmHg or diastolic blood pressure (DBP) exceeding 90 mmHg, it represents a widespread health challenge (Unger et al. 2020). Furthermore, pre-hypertension, characterized by SBP ranging from 130 to

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BP, blood pressure; CCBs, calcium channel blockers; CVD, cardiovascular disease; DBP, diastolic blood pressure; mmHg, millimeter of mercury; RCTs, randomized controlled trials; SBP, systolic blood pressure.

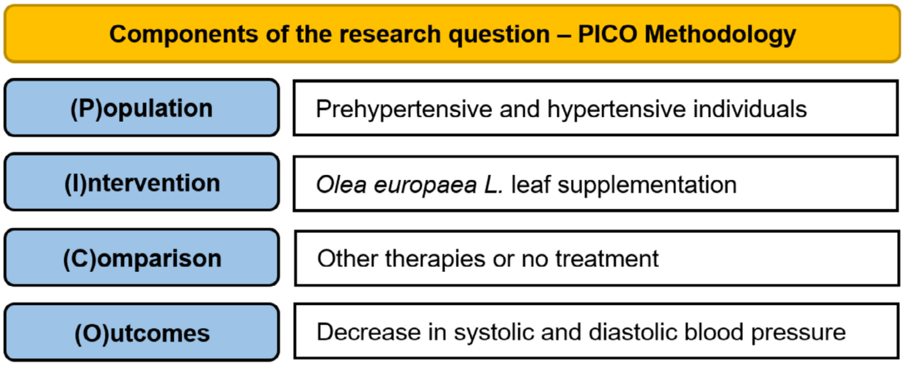

FIGURE 1 | Component of the research question—PICO methodology.

139 mmHg and/or DBP between 85 and 89 mmHg, signals individuals at elevated risk of progressing to full-blown hypertension (Unger et al. 2020).

Hypertension has a profound impact on global health, affecting almost 1.3 billion individuals worldwide and contributing to approximately 10 million deaths annually (World Health Organization 2023; Zhou et al. 2021). Alarmingly, a significant proportion of those affected remain unaware of their condition, while only 21% of diagnosed individuals consistently adhere to treatment regimens (Global Health Observatory (GHO) 2023). When uncontrolled, hypertension significantly increases the risk of cardiovascular morbidity and mortality, including stroke, coronary heart disease, heart failure, atrial fibrillation, peripheral arterial disease, and kidney dysfunction (Liu et al. 2024; Mensah et al. 2023). The World Health Organization estimates that improving the global hypertension control rate to 50% could prevent approximately 76 million deaths between 2023 and 2050 (World Health Organization 2023).

In the realm of treatment, pharmacological interventions play a pivotal role. Initial therapy often includes diuretics, long-acting calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and beta blockers (Joint Committee for Guideline Revision 2019). However, achieving optimal blood pressure control can be challenging, as a substantial proportion of hypertensive patients (~70%) require multiple medications to reach target levels. This not only increases the likelihood of experiencing adverse effects but also escalates treatment costs (Guerrero-García and Rubio-Guerra 2018).

Compounding the issue, a significant subset of hypertensive individuals proves resistant to traditional pharmacotherapy, with approximately 14.7% exhibiting poor response rates (Noubiap et al. 2019; Winner et al. 2024). Consequently, there is a pressing need to explore alternative treatment avenues to effectively manage this chronic condition and mitigate its associated risks (Champaneria et al. 2023). Whether through novel pharmacological agents, lifestyle modifications, or innovative therapeutic approaches, the pursuit of effective hypertension management remains a critical priority in modern healthcare.

Phytotherapy is an area of medicine that uses plants to treat diseases or as health-promoting agents (Falzon and Balabanova 2017). Studies indicate that some plants have antihypertensive properties (Ajebli and Eddouks 2020; Jänicke et al. 2003; Verma et al. 2021). The olive (*Olea europaea* L.) leaf has been used to treat hypertension, atherosclerosis, and diabetes since ancient times (Jänicke et al. 2003; de Oliveira et al. 2024). Recent research has confirmed that the concentration of phenolic compounds varies widely between leaves, fruits, and extra virgin olive oil, highlighting that leaves are the main source of phenols, justifying their use in nutraceutical and therapeutic applications, such as in the management of cardiovascular and metabolic conditions (López-Salas et al. 2024; de Oliveira et al. 2024). The phenolic compounds present in the olive leaf are part of the Mediterranean diet, notably through olive oil. Adherence to this diet has been associated with the prevention of cardiovascular disease (CVD) (García-Gavilán et al. 2023; Martínez-González et al. 2022). However, this herbal medicine is not the most widely used for the treatment of hypertension and, consequently, is not the most studied in relation to other medicinal species (Ajebli and Eddouks 2020; Jänicke et al. 2003; Verma et al. 2021).

For this reason, the aim of this systematic review and meta-analysis was to gather and synthesize data from experimental trials that explored this phytotherapeutic intervention in order to analyse its impact on blood pressure (BP) in pre-hypertensive and hypertensive adults.

2 | Methods

This systematic review adhered to the PRISMA guidelines (Page et al. 2020) and aimed to address the research question formulated according to the PICO criteria (Huang et al. 2006) (Figure 1): Is olive leaf supplementation effective in reducing blood pressure among individuals with pre-hypertension and hypertension compared to alternative treatments or no treatment?

Population: Individuals with pre-hypertension or hypertension, aged at least 18 years, with no restrictions on sex or ethnicity.

Intervention: Use of phytotherapy with *Olea europaea* L., in any dosage, pharmaceutical form, or administration time.

Comparator: Antihypertensive drugs, dietary adjustments, lifestyle, placebo, or no treatment.

Outcome: Changes in systolic and/or diastolic blood pressure.

Eligible for inclusion in this review were intervention studies involving human subjects diagnosed with pre-hypertension or hypertension who underwent phytotherapy with olive leaf. Studies involving normotensive individuals were excluded, as no significant blood pressure-lowering effect was observed in this population (Ismail et al. 2021; Razmpoosh et al. 2022; Stevens et al. 2021).

The protocol for this systematic review was not formally registered. The lack of registration was due to the limited timeframe for the study and the exploratory nature of the research.

2.1 | Search Strategy

The bibliographic search encompassed electronic databases such as EBSCO, CABI, CNKI, Cochrane Library, DOAJ, PUBMED, SCOPUS, WEB OF SCIENCE. The search terms used were "Hypertension AND *Olea europaea* L.". This search was conducted between November 2022 and October 2024, without any time constraints for article inclusion. The data from the retrieved studies was compiled in a Microsoft Excel database (2019). Duplicate studies were eliminated, and each title and abstract were meticulously reviewed against the predefined eligibility criteria, this process was carried out by two researchers (RL and JAS), reaching a consensus in all cases, and a third researcher (VFL) checked and confirmed the information extracted from the articles. Articles failing to meet these criteria were excluded from further consideration.

2.2 | Study Selection

2.2.1 | Participants

We included experimental studies, written in English, conducted on individuals with pre-hypertension and/or hypertension, evaluating the impact of *Olea europaea* L. leaf supplementation on blood pressure. There were no restrictions based on sex or ethnicity, and the minimum age parameter set was 18 years, with no maximum limits intentionally set.

2.2.2 | Intervention

The focus of this study is on *Olea europaea* L. leaf herbal medicine, regardless of dosage, pharmaceutical form, administration time, or whether it is administered alongside conventional drugs or alone. Experimental studies involving animals, in vivo or in vitro, as well as studies in which the intervention involved other medicinal plants (multi-preparations) were excluded.

2.2.3 | Control Group

The intervention was compared with control groups who received antihypertensive drug therapy, the same herbal medication but in varying doses, dietary modifications, adoption of healthy lifestyle practices, or a combination of these interventions, with or without placebo.

2.2.4 | Result Measurement

We included studies that measured the effect of the intervention on systolic and/or diastolic blood pressure.

2.3 | Extraction of Results

The data extracted included the bibliographic reference of the article, the country where the study was conducted, the study design, sample characteristics (degree of hypertension, sample size, distribution by sex in intervention and control groups), details of the intervention and control groups (including doses, pharmaceutical forms, type of extract and chemical composition), treatment duration, wash-out period, average blood pressure values before and after treatment, and between groups when applicable. Additionally, any reported adverse effects and the use of antihypertensive medication were recorded when available.

2.4 | Statistical Analysis

Statistical analyses were carried out using Review Manage 5.4 (The Cochrane Collaboration 2020). Mean differences between groups were calculated using the Inverse Variance statistical method with 95% confidence intervals; heterogeneity was assessed using the I^2 statistic ($I^2 \geq 50\%$ indicating significant heterogeneity) and the random effect model was used to determine the effect.

2.5 | Quality Assessment

The systematic quality of the included studies was assessed using the Review Manage 5.4 (The Cochrane Collaboration 2020).

3 | Results

3.1 | Study Selection

Out of 211 studies initially identified, 90 duplicates were eliminated, leaving 121 articles for manual selection by the authors. Of these, 113 were excluded for not meeting the eligibility criteria. After reviewing the full text of the remaining 8 studies, 2 essays were excluded because it was not written in English (Saberi et al. 2008; Yaghoobzadeh et al. 2019), 2 with multi-preparation interventions (Elkafrawy et al. 2020; Wong et al. 2014) and 1 without pressure parameters (SBP/DBP) (Javadi et al. 2019). Ultimately, 3 articles were deemed suitable for inclusion in this review. The detailed process of study selection is depicted in Figure 2 for better visualization.

3.2 | Characteristics of the Studies

A total of 3 studies analysing the effects of *Olea europaea* L. on BP were included (Table 1), published between 2008 and 2017, carried out in the following countries: Indonesia (Susalit et al. 2011), New Zealand (Lockyer et al. 2017) and the third study

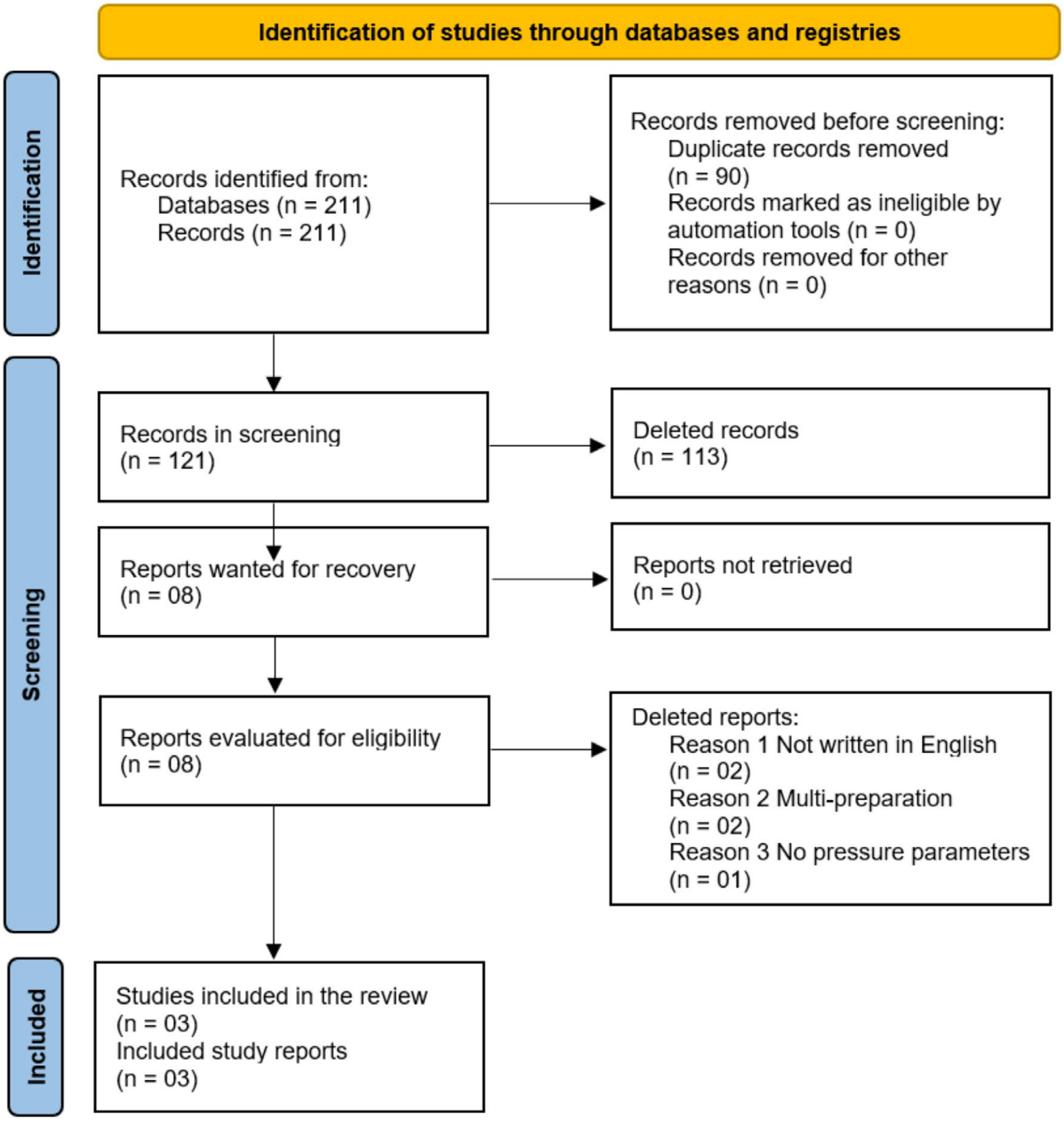

FIGURE 2 | PRISMA 2020 diagram and study selection.

did not provide clear information on the location (Perrinjaquet-Moccetti et al. 2008). All study designs were RCTs, with double blinding (Lockyer et al. 2017; Susalit et al. 2011) and one open study (Perrinjaquet-Moccetti et al. 2008). Overall, the analysis involved a total of 248 participants, with sample sizes ranging from 40 to 148. The age range was between 33 and 51 years, covering both sexes, with the exception of one investigation which included only male participants (Lockyer et al. 2017). Two studies investigated pre-hypertensive individuals (Lockyer et al. 2017; Perrinjaquet-Moccetti et al. 2008), while another focused exclusively on hypertensive individuals (Susalit et al. 2011).

The dosages and galenic forms used in the interventions varied considerably, 1000 mg daily in capsules, 500 and 1000 mg daily in pill, and 20 mL daily in oil, with total intake after treatment being 56 g; 28–56 g and 840 mL, respectively. Two studies used the 80% m/m ethanol extraction method (Perrinjaquet-Moccetti et al. 2008; Susalit et al. 2011), while the third study did not reveal any information about the extraction procedure used (Lockyer et al. 2017) and the Oleuropein value ranged from 19.9% to 20.8% m/m (Perrinjaquet-Moccetti et al. 2008; Susalit et al. 2011) and 6.81 mg/mL (Lockyer et al. 2017). Only one study compared the intervention to placebo (Lockyer et al. 2017); the others compared to other treatments.

Adverse effects were reported in two articles (Lockyer et al. 2017; Susalit et al. 2011), namely: acne, mild stomach pain, cough, dizziness, headaches, fatigue, myalgia, and muscle cramps.

The methods used to measure SBP and DBP results were the digital sphygmomanometer (Perrinjaquet-Moccetti et al. 2008) and the 24-h ambulatory blood pressure monitoring (ABPM) (Lockyer et al. 2017); one study did not clarify the method used to measure BP (Susalit et al. 2011).

TABLE 1 | Summary of results *Olea europaea* L.

Reference	Country	Study design	Participants	Sample (% male)	Age	Dose of OLE/day	Galenical form	Type of extract	Chemical composition	Comparison	Duration	Wash-out	Parameters		Results: Mean ± SD IGpre (mmHg)	Results: Mean ± SD IGpost (mmHg)	Results: IGpost − IGpre (mmHg)	Results: Mean ± SD IGpost − CGpost (mmHg)		Adverse effects	Others (Measuring device/Use of antihyper tensive drugs)
(Perrinjaquet-Moccetti et al. 2008)	Not clear	RCT Not blind Parallel Co-twin study	♂♀Prehypertensive monozygotic twins (SBP > 120 mmHg or DBP > 80 mmHg)	n = 40 (30%) IG1 and CG2: n = 20 (30%) IG2: 10 (30%) CG1: 10 (30%)	IG1 and CG2: $\bar{x}$ 36 yo IG2: $\bar{x}$ 33 yo CG1: $\bar{x}$ 38 yo	IG1: 500 mg IG2: 1000 mg	Pill	Ethanol 80% m/m	20.8% m/m oleuropein 30%–40% m/m polyphenols, verbascoside and luteolin-7-glucoside	CG1: No treatment CG2: Olive Leaf Extract 500 mg	8 W	—	SBP	IG1	135 ± 8	130 ± 11	−5	IG1 vs. CG1	No significant differences between groups	Not found	Digital sphygmoma nometer/ No antihyper tensive treatment
														IG2	137 ± 10	126 ± 9	**−11****	IG2 vs. CG2	No significant differences between groups		
													DBP	IG1	76 ± 6	77 ± 7	−1	IG1 vs. CG1	No significant differences between groups		
														IG2	80 ± 10	76 ± 6	−4	IG2 vs. CG2	No significant differences between groups		
(Lockyer et al. 2017)	New Zealand	RCT D. Blind crossover	♂Prehypertensive (SBP between 120–140 mmHg and DBP 81–90 mmHg)	n = 60 (100%)	$\bar{x}$ 45 yo	20 mL	Oil	Not reported	6.81 mg/mL oleuropein, 0.32 mg/mL hydroxytyrosol, 0.73 mg/mL oleoside, 0.17 mg/mL luteolin-7-O-glucoside, 0.12 mg/mL tyrosol, 0.09 mg/mL verbascoside, 0.07 mg/mL apigenin-7-O-glucoside, 0.02 mg/mL rutin, 0.01 mg/mL Vanillic acid, Vanillin, Luteolin	Placebo	6 W	4 W	SBP		134.75 ± 11.67	133.27 ± 9.45	−1.48	**Different***		Acne (2%) Mild stomach pain (7%)	ABPM (24-h) / No antihypertensive treatment
													DBP		80.35 ± 8.65	80.03 ± 8.09	−0.32	**Different***			

(Continues)

TABLE 1 | (Continued)

Reference	Country	Study design	Participants	Sample (% male)	Age	Dose of OLE/day	Galenical form	Type of extract	Chemical composition	Comparison	Duration	Wash-out	Parameters	Results: Mean ± SD IGpre (mmHg)	IGpost (mmHg)	IGpost − IGpre (mmHg)	Mean ± SD IGpost − CGpost (mmHg)	Adverse effects	Others (Measuring device/Use of antihypertensive drugs)
(Susalit et al. 2011)	Indonesia	RCT D. Blind Parallel	♂♀Hypertensive patients (SBP between 140 and 159 mmHg and DBP <90 mmHg or between 90 and 99 mmHg)	$n=148$ IG: $n=72$ (17%) CG: $n=76$ (13%)	IG: $\bar{x}$ 51 yo CG: $\bar{x}$ 50 yo	1000 mg	Capsules	Ethanol 80% m/m	19.9% m/m oleuropein	CG: Captopril 25 or 50 mg	8 W	—	S B P	145.0 ± 5.0	133.5 ± 10.4	**−11.5*****	No significant differences between groups	Cough (5%) Vertigo (6%) Muscle discomfort, headache, fatigue, malaise, myalgia and muscle cramps (<5%)	Not clear/No antihypertensive treatment
													D B P	91.3 ± 5.1	86.6 ± 6.9	**−4.8*****	No significant differences between groups		

Note: Age and results expressed as average. *$p<0.05$, **$p<0.01$, and ***$p<0.001$ represent significant difference. Values in bold denote statistical significance.
Abbreviations: ANOVA, analysis of variance; CG, control group; D., double; DBP, diastolic blood pressure; IG, intervention group; mmHg, millimeter of mercury; OLE, Olive Leaf Extract; RCTs, randomized controlled trials; S., simple; SBP, systolic blood pressure; SD, Standard deviation; T., triple; W, week; YO, years old.

None of the randomized clinical trials included participants taking conventional antihypertensive drugs.

In addition to administering the herbal medicine, participants were instructed to avoid using creams enriched with plant sterols/stanols and any product containing olives, such as olives, olive oil, olive margarine, and tapenade, throughout the study (Lockyer et al. 2017). Another study provided participants with dietary guidelines to maintain low saturated and total fat intake, reduce cholesterol intake, and limit sodium intake to less than 2.4 g per day (Susalit et al. 2011). Only the control group in one study received healthy lifestyle advice for lowering BP (Perrinjaquet-Moccetti et al. 2008).

3.3 | Statistical Analysis

The analysis of the effects of olive leaf extract consumption on hypertension, pre- and post-intervention, included the three studies selected according to the initial eligibility criteria. However, for the study carried out on monozygotic twins, it was split into three, since two daily doses of 500 mg were analysed for two different groups of the herbal medicine and one daily dose of 1000 mg for another group. The total population was 162 participants, whose average systolic blood pressure before and after the intervention was −6.03 mmHg, 95% CI: [−11.60, −0.46] (Figure 3) and diastolic blood pressure −2.38 mmHg, 95% CI: [−4.96, 0.20] (Figure 4). The effect of olive leaf extract consumption was statistically different in reducing SBP ($z=2.12$; $p=0.03$) and DBP ($z=1.81$; $p=0.07$) (Figures 3 and 4, respectively). Heterogeneity was reported as "high" for systolic $I^2=82\%$ ($chi^2=22.82$, $df=4$; $p<0.001$) and "moderate" for diastolic $I^2=50\%$ ($chi^2=7.95$, $df=4$; $p=0.09$).

With the effect of the herbal medicine determined, and evidence of high heterogeneity, the subgroup analysis, which separated according to the dose administered, ≤ 500 or 1000 g, showed an I^2 considered "low" for SBP of 1000/≤ 500 mg = 0% ($chi^2=0.01$, $df=1$; $p=0.91$) (Figure 5)/0% ($chi^2=0.65$, $df=2$; $p=0.72$) (Figure 6) and for DBP 1000/≤ 500 mg = 0% ($chi^2=0.03$, $df=1$; $p=0.85$) (Figure 7)/0% ($chi^2=0.92$, $df=2$; $p=0.63$) (Figure 8). Efficacy was maintained for the highest dose, SBP ($z=8.84$; $p<0.001$) and DBP ($z=4.77$; $p<0.001$) (Figures 5 and 7), while no statistical difference was observed for the lowest dose, SBP ($z=1.14$; $p=0.25$) and DBP ($z=0.39$; $p=0.69$) (Figures 6 and 8).

For the analysis of the intervention and control groups, we excluded the studies that compared olive leaf extract with itself and with the drug captopril, since the clinical heterogeneity of the studies could be high, so we compared it with placebo and untreated groups. The total population analysed was 70 participants, for the intervention and control group, whose average systolic blood pressure was −1.49 mmHg, 95% CI: [−4.86, 1.88] (Figure 9) and diastolic blood pressure −1.40 mmHg, 95% CI: [−4.12, 1.33] (Figure 10). The effect of olive leaf extract consumption was not statistically different in reducing SBP ($z=0.87$; $p=0.39$) and DBP ($z=1.00$; $p=0.32$) (Figures 9 and 10, respectively). Heterogeneity was reported as "low" in the analysis for systolic $I^2=0\%$ ($chi^2=0.58$, $df=1$; $p=0.45$) and diastolic $I^2=0\%$ ($chi^2=0.33$, $df=1$; $p=0.57$).

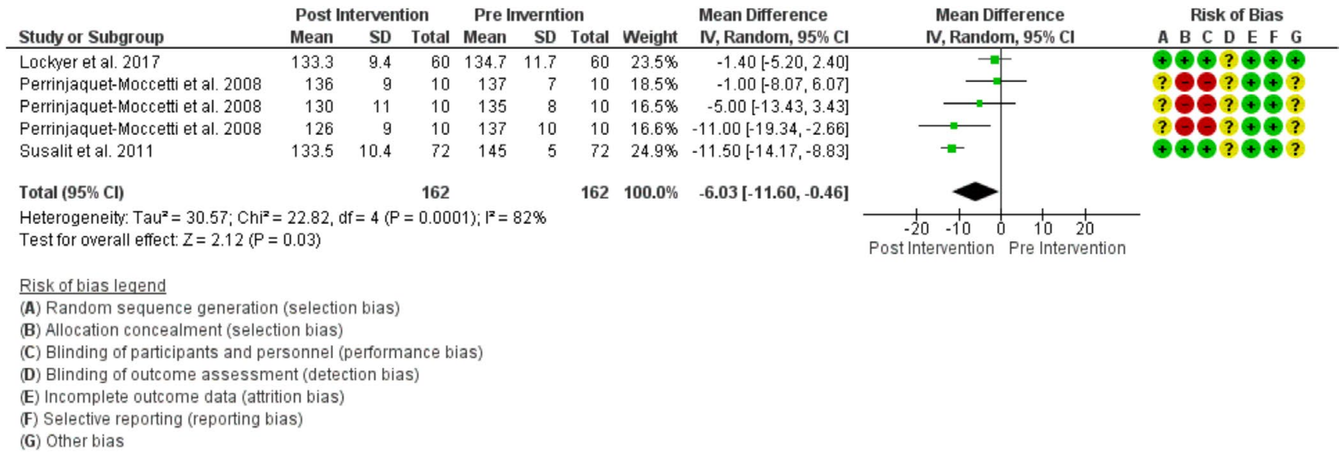

FIGURE 3 | Mean pre and post intervention (SBP) and risk of bias.

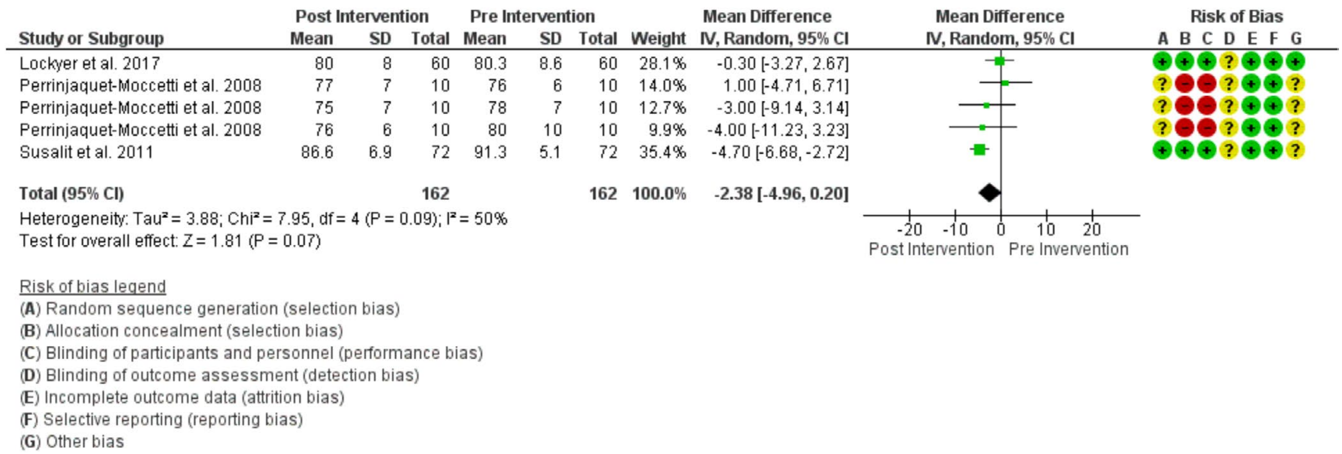

FIGURE 4 | Mean pre and post intervention (DBP) and risk of bias.

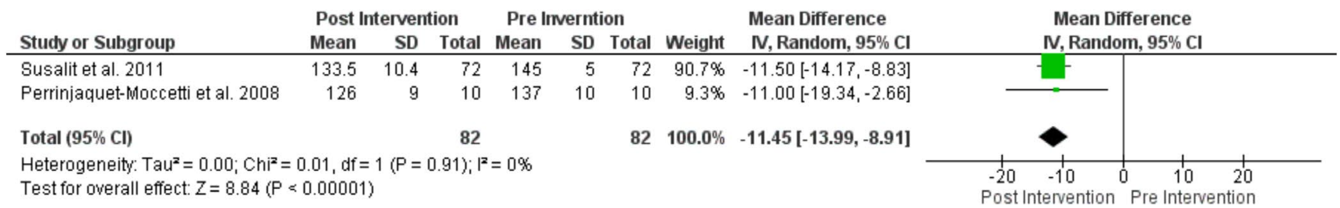

FIGURE 5 | Sub-group analysis mean pre- and post-intervention SBP (1000 mg).

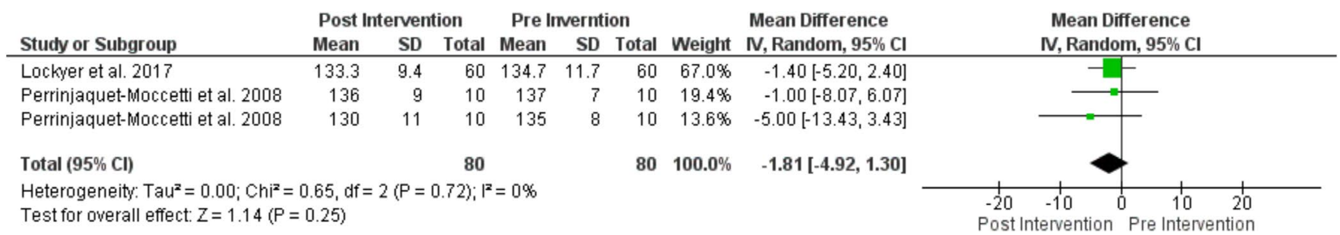

FIGURE 6 | Sub-group analysis mean pre- and post-intervention SBP (≤ 500 mg).

Study or Subgroup	Post Intervention Mean	SD	Total	Pre Intervention Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Susalit et al. 2011	86.6	6.9	72	91.3	5.1	72	93.0%	-4.70 [-6.68, -2.72]
Perrinjaquet-Moccetti et al. 2008	76	6	10	80	10	10	7.0%	-4.00 [-11.23, 3.23]
Total (95% CI)			**82**			**82**	**100.0%**	**-4.65 [-6.56, -2.74]**

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 4.77 (P < 0.00001)

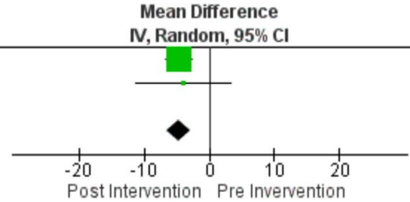

FIGURE 7 | Sub-group analysis mean pre- and post-intervention DBP (1000 mg).

Study or Subgroup	Post Intervention Mean	SD	Total	Pre Intervention Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lockyer et al. 2017	80	8	60	80.3	8.6	60	66.4%	-0.30 [-3.27, 2.67]
Perrinjaquet-Moccetti et al. 2008	77	7	10	76	6	10	18.0%	1.00 [-4.71, 6.71]
Perrinjaquet-Moccetti et al. 2008	75	7	10	78	7	10	15.6%	-3.00 [-9.14, 3.14]
Total (95% CI)			**80**			**80**	**100.0%**	**-0.49 [-2.91, 1.94]**

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)

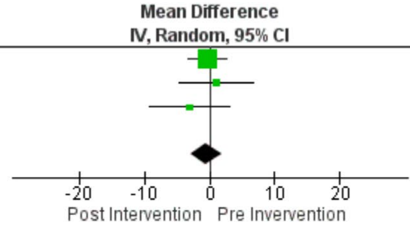

FIGURE 8 | Sub-group analysis mean pre- and post-intervention DBP (≤ 500 mg).

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lockyer et al. 2017	133	9	60	134	11	60	87.8%	-1.00 [-4.60, 2.60]
Perrinjaquet-Moccetti et al. 2008	130	11	10	135	11	10	12.2%	-5.00 [-14.64, 4.64]
Total (95% CI)			**70**			**70**	**100.0%**	**-1.49 [-4.86, 1.88]**

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.39)

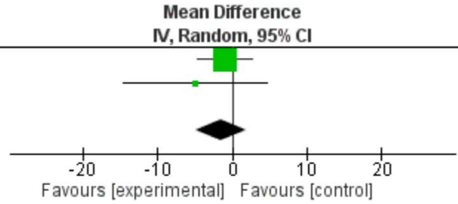

FIGURE 9 | Mean post intervention and control (SBP).

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lockyer et al. 2017	80	8	60	81	9	60	80.2%	-1.00 [-4.05, 2.05]
Perrinjaquet-Moccetti et al. 2008	77	7	10	80	7	10	19.8%	-3.00 [-9.14, 3.14]
Total (95% CI)			**70**			**70**	**100.0%**	**-1.40 [-4.12, 1.33]**

Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

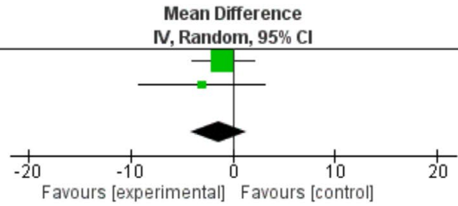

FIGURE 10 | Mean post intervention and control (DBP).

3.4 | The Methodological Quality of the Included Trials

The studies included in this meta-analysis presented a low (Lockyer et al. 2017), moderate (Susalit et al. 2011) and high (Perrinjaquet-Moccetti et al. 2008) risk of bias (Figures 3 and 5). This last study was an open design which did not clearly present the randomization applied and, in particular, the intervention administered to the groups and administrators was not blinded. The categorization of risk of bias was based on the categories "blinding" of both participants and evaluator and allocation (Figure 11). Publication bias was not assessed because the number of studies was less than 10 (Dalton et al. 2016).

4 | Discussion

The aim of this systematic review was to gather and synthesize data from experimental trials that analysed the impact of the medicinal plant *Olea europaea* L. leaf on blood pressure in pre-hypertensive and hypertensive adults. It was possible to observe a hypotensive effect in the herbal medicines studied, which ranged from −11.60 to −0.46 mmHg for SBP and −4.96 to 0.20 mmHg for DBP. The hypotensive effect was also found when the intervention group was compared to placebo. These findings emphasize the use of herbal medicines, since each decrease of 10 mmHg in SBP and 5–6 mmHg in DBP substantially reduces the risk of CVD (Fuchs and Whelton 2020). To our knowledge, this systematic review is the first to carry out a meta-analysis of information covering only the herbal medicine *Olea europaea* L. for the treatment of hypertensive and pre-hypertensive patients. Previous studies have carried out this analysis in the general population (Razmpoosh et al. 2022), and others have included studies that analysed olive leaf extract together with other active compounds in the same group (Ismail et al. 2021).

The bioactive compounds present in *Olea europaea* L. leaf (oleuropein, oleacein, tyrosol, and hydroxytyrosol) may be responsible for the actions that bring benefits in terms of hypertension

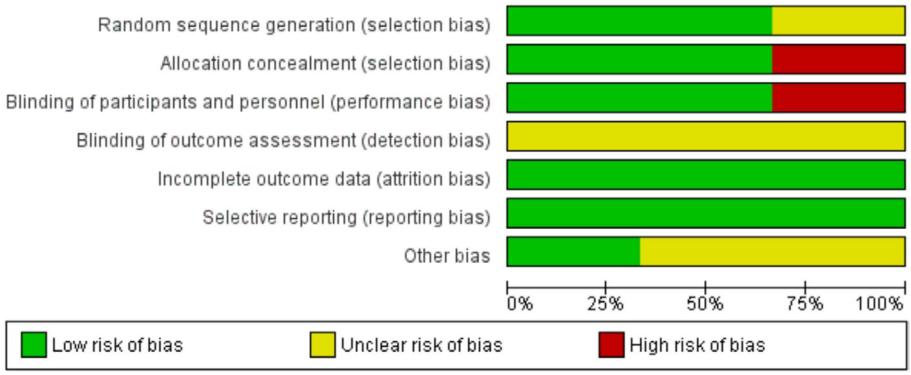

FIGURE 11 | Risk of bias graph.

control and cardiovascular protection. A review focused on studies exploring the molecular mechanisms underlying the cardioprotective properties of different olive oils, in vitro in rodent models and in human clinical trials, concluded that hydroxytyrosol and oleuropein have been identified as the main bioactive compounds responsible for antioxidant, anti-inflammatory, anti-platelet aggregation, and anti-atherogenic activities (Dabravolski et al. 2024). The ability of the compound tyrosol to eliminate oxygen radical species has also been clearly demonstrated (in vitro) (Cuffaro et al. 2023). With regard to olive leaf extract, the active constituents oleuropein and oleacein reduced the vascular stiffness index in humans and attenuated it after a meal (Lockyer et al. 2015), may be associated with angiotensin inhibition and appear to be responsible for the antihypertensive effect (in vivo) (Asghari et al. 2022; Hansen et al. 1996), as well as the reduction in the production of inflammatory cytokines (IL-6 and IL-8) and tumor necrosis factor alpha (TNF-α) both in hypertensive patients and in ex vivo (IL-8) studies (Javadi et al. 2019; Lockyer et al. 2015).

Of the three studies included, only one investigated this herbal medicine in its oil pharmaceutical form (Lockyer et al. 2017), revealing neutral values for blood pressure parameters. However, it is important to note that the oil form showed superior bioavailability compared to capsules and tablets (de Bock et al. 2013). However, this study provided a daily dose of oleuropein of 136.2 mg, while another study in this meta-analysis administered 100 mg daily of oleuropein in capsules, obtaining the same results (Perrinjaquet-Moccetti et al. 2008). Nonetheless, when the daily dose was increased to 200 mg, statistically significant differences were observed (Perrinjaquet-Moccetti et al. 2008; Susalit et al. 2011), which can be confirmed by the analysis conducted in this article (Figures 5 and 7) and the results of previous articles (Ismail et al. 2021; Razmpoosh et al. 2022). In addition, it is important to note that this was the only study that assessed participants' BP using 24-h ABPM, which could provide more accurate results (Lockyer et al. 2015). Using 24-h ABPM is the most accurate method for analysing BP, compared to isolated measurements made using sphygmomanometers (Green et al. 2021). This method is able to-can differentiate hypertension from the white coat, which is individuals who have elevated BP in the doctor's office and normal daytime BP measured by ABPM (Kario et al. 2019; Unger et al. 2020).

Another factor that can be considered in studies of oleuropein's daily dose of ~100 mg is its pre-hypertensive population (Lockyer et al. 2017; Perrinjaquet-Moccetti et al. 2008). Evidence has shown that herbal medicines may have no effect on participants with BP values close to normotensive levels, so it may be safe for these groups to include these herbal medicines in their diet and not develop hypotension (Ismail et al. 2021; Razmpoosh et al. 2022).

As for the comparisons, the lack of association between the herbal medicine and the control and untreated groups can be attributed to the small number of studies and the high heterogeneity between them and in relation to the comparison with Captopril, similar reductions to the intervention were observed, that is, the reduction in BP caused by the herbal medicine was almost similar to that caused by the drug Captopril. The study carried out with monozygotic twins found effectiveness in reducing BP for the average of the pre- and post-intervention groups in relation to the highest dose; however, when comparing pairs of twins, there was no statistically significant reduction for the intervention groups vs. control (Perrinjaquet-Moccetti et al. 2008). This last analysis allowed greater control of environmental factors and the detection of effects at a sensitive level.

Regarding adverse effects, no serious symptoms were identified in general. However, only an exhaustive analysis of all available clinical data, including randomized clinical trials, case reports, post-marketing surveillance studies, and spontaneous reports through systematic reviews, can provide reliable information on the safety of herbal medicines (Izzo et al. 2016).

Due to the lack of strict regulation in the nutraceutical sector, the manufacturer's obligation to demonstrate the efficacy, safety, and quality of products is less enforced compared to the pharmaceutical sector. As a result, many products available on the market may be ineffective, which reinforces the need for critical and rigorous evaluations. In this context, it stands out that systematic reviews and meta-analyses are at the top of the clinical evidence documentation, offering a solid and reliable basis for making informed health decisions (Williamson et al. 2020).

The results found in this systematic review provide evidence to support the use of *Olea europaea* L. leaf extract in the treatment of blood pressure, particularly in hypertensive individuals. Despite the small number of studies included, the meta-analysis carried out contributes to a preliminary understanding of the efficacy of *Olea europaea* L. leaf offering a basis for future research. It should be noted that the variations in formulations, dosages, and populations studied indicate the need for standardized protocols in future research, exploring long-term effects and employing robust methodologies, such as 24-h ABPM, to confirm these results.

4.1 | Limitations

Our meta-analysis recorded the efficacy of the herbal medicine on blood pressure, but some parameters must be taken into account, such as the low number of studies carried out and the often poor quality and notable variation between studies included.

Regarding the study with the highest risk of bias assessment (Perrinjaquet-Moccetti et al. 2008), true randomization was not clearly mentioned, there was no blinding of participants as to treatment allocation and assignment, and treatment administrators were aware of the different treatments and allocations, making the placebo effect and observer bias possible. In another article (Susalit et al. 2011), selection bias was an increased risk for internal validity, as there was no similarity at baseline between participants. The quality of outcome measurement has not been reported for BP assessment, nor has the exclusivity and training of the assessors. The feasibility of 24-h ABPM has already been mentioned in this review, but only 1 article used this method (Lockyer et al. 2017). Blinding of outcome assessors was not reported in 2 studies, increasing the risk of measurement bias in the results (Perrinjaquet-Moccetti et al. 2008; Susalit et al. 2011). None of the studies included in this review reported information on the blinding or lack of blinding of outcome assessors, which may introduce an increased risk of measurement bias.

In carrying out this review, we faced some limitations, such as the exclusion of articles published in languages other than English, despite our fluency in Portuguese, Spanish, Italian, French, and English. This choice aims to ensure the accuracy and feasibility of the work, since most of the literature is available in English. In addition, we identified only three potential studies that evaluated the use of the herbal medicine *Olea Europaea* L. leaf in the treatment of blood pressure in pre-hypertensive and hypertensive individuals. Although the trials included have some methodological limitations, the meta-analysis carried out contributes to a preliminary understanding of the efficacy of the herbal medicine, offering a basis for future research. As such, research into this herbal medicine is still limited, and more studies need to be conducted to strengthen the available evidence.

5 | Conclusion

The use of olive leaf extract at a dose of 1000 mg/day demonstrated an average reduction in high blood pressure levels of −11.45 mmHg in systolic pressure and −4.65 mmHg in diastolic pressure. However, these data must be analysed with caution due to the varying quality of studies and differences between treatments. There is a clear need to conduct more comprehensive human clinical studies to accurately assess the efficacy and safety of olive leaf extract on blood pressure.

Author Contributions

Rebeca Lachovicz: data curation, formal analysis, investigation, methodology, writing – original draft. **Vera Ferro-Lebres:** funding acquisition, project administration, writing – review and editing. **Juliana Almeida-de-Souza:** conceptualization, supervision, writing – review and editing. **José Alberto Pereira:** funding acquisition, project administration.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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