

Journal Pre-proof

A GRADE-assessed systematic review and meta-analysis of randomized controlled trials evaluating the effects of olive leaf or olive pomace supplementation on cardiometabolic and anthropometric health markers.

Fatemeh Mansouri, Mahnaz Mardani, Chiara Rucci, Laura Bordoni, Rosita Gabbianelli

PII: S0939-4753(26)00283-8

DOI: <https://doi.org/10.1016/j.numecd.2026.104821>

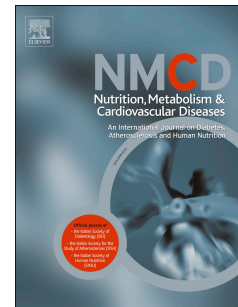
Reference: NUMECD 104821

To appear in: *Nutrition, Metabolism and Cardiovascular Diseases*

Received Date: 16 March 2026

Revised Date: 18 May 2026

Accepted Date: 1 June 2026



Please cite this article as: Mansouri F, Mardani M, Rucci C, Bordoni L, Gabbianelli R, A GRADE-assessed systematic review and meta-analysis of randomized controlled trials evaluating the effects of olive leaf or olive pomace supplementation on cardiometabolic and anthropometric health markers., *Nutrition, Metabolism and Cardiovascular Diseases*, <https://doi.org/10.1016/j.numecd.2026.104821>.

This is a PDF of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability. This version will undergo additional copyediting, typesetting and review before it is published in its final form. As such, this version is no longer the Accepted Manuscript, but it is not yet the definitive Version of Record; we are providing this early version to give early visibility of the article. Please note that Elsevier's sharing policy for the Published Journal Article applies to this version, see: <https://www.elsevier.com/about/policies-and-standards/sharing#4-published-journal-article>. Please also note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2026 Published by Elsevier B.V. on behalf of The Italian Diabetes Society, the Italian Society for the Study of Atherosclerosis, the Italian Society of Human Nutrition and the Department of Clinical Medicine and Surgery, Federico II University.

A GRADE-assessed systematic review and meta-analysis of randomized controlled trials evaluating the effects of olive leaf or olive pomace supplementation on cardiometabolic and anthropometric health markers.

Fatemeh Mansouri ^{1,2, #}, Mahnaz Mardani ^{3,4, #}, Chiara Rucci ^{1,2}, Laura Bordoni ^{2, *}, Rosita Gabbianelli ^{2, *}

¹ School of Advanced Studies, University of Camerino, Camerino, Italy

² Unit of Molecular Biology and Nutrigenomics, School of Pharmacy and Health Products,
University of Camerino, Camerino, Italy

³ School of Public Health and Nutrition, Lorestan University of Medical Sciences, Khorramabad, Iran

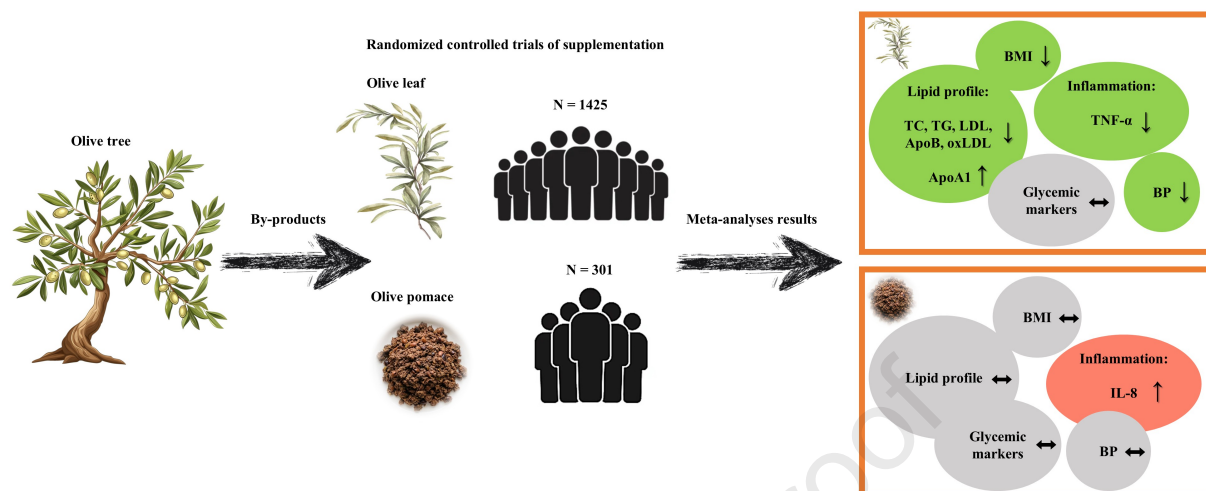
⁴ Nutritional Health Research Center, Health and Nutrition Department, Lorestan University of Medical Sciences, Khorramabad, Iran

* Corresponding authors:

Laura Bordoni
Assistant Professor
Unit of Molecular Biology and Nutrigenomics,
School of Pharmacy, University of Camerino,
62032 Camerino (MC). Italy
laura.bordoni@unicam.it
ORCID: orcid.org/0000-0001-6968-1164

Rosita Gabbianelli
Full Professor
Unit of Molecular Biology and Nutrigenomics,
School of Pharmacy, University of Camerino,
62032 Camerino (MC). Italy
rosita.gabbianelli@unicam.it
ORCID: <https://orcid.org/0000-0003-0037-7740>

Co-first authors: Fatemeh Mansouri and Mahnaz Mardani.



A GRADE-assessed systematic review and meta-analysis of randomized controlled trials evaluating the effects of olive leaf or olive pomace supplementation on cardiometabolic and anthropometric health markers.

Fatemeh Mansouri ^{1,2, #}, Mahnaz Mardani ^{3,4, #}, Chiara Rucci ^{1,2}, Laura Bordoni ^{2, *}, Rosita Gabbianelli ^{2, *}

¹ School of Advanced Studies, University of Camerino, Camerino, Italy

² Unit of Molecular Biology and Nutrigenomics, School of Pharmacy and Health Products,
University of Camerino, Camerino, Italy

³ School of Public Health and Nutrition, Lorestan University of Medical Sciences, Khorramabad, Iran

⁴ Nutritional Health Research Center, Health and Nutrition Department, Lorestan University of Medical
Sciences, Khorramabad, Iran

* Corresponding authors:

Laura Bordoni

Assistant Professor

Unit of Molecular Biology and Nutrigenomics,

School of Pharmacy, University of Camerino,

62032 Camerino (MC). Italy

laura.bordoni@unicam.it

ORCID: orcid.org/0000-0001-6968-1164

Rosita Gabbianelli

Full Professor

Unit of Molecular Biology and Nutrigenomics,

School of Pharmacy, University of Camerino,

62032 Camerino (MC). Italy

rosita.gabbianelli@unicam.it

ORCID: <https://orcid.org/0000-0003-0037-7740>

Co-first authors: Fatemeh Mansouri and Mahnaz Mardani.

Abstract

Aims: Cardiometabolic diseases (CMDs) are major contributors to global morbidity and mortality, and dietary bioactives such as polyphenols may modulate key risk factors. Olive by-products, particularly olive leaves (OL) and olive pomace (OP), are rich in phenolic compounds with antioxidant, anti-inflammatory, and cardiometabolic effects demonstrated across in vitro, preclinical, and clinical studies.

Data synthesis: This GRADE-assessed systematic review and meta-analysis included 30 randomized controlled trials ($n = 1,726$) evaluating OL or OP supplementation on 21 standardized biomarkers, encompassing inflammatory markers, lipid profile, glycemic control, insulin sensitivity, anthropometric measures, and blood pressure. Meta-analyses were conducted using random-effects models, with effect sizes calculated as mean differences (or standardized mean differences for oxLDL). Between-study heterogeneity was assessed with I^2 statistics, and sensitivity and subgroup analyses explored potential sources of variability. Publication bias was evaluated using Begg's test and funnel plots where appropriate. OL supplementation significantly improved lipid parameters (total cholesterol, triglycerides, LDL-C, ApoB, oxLDL) and increased ApoA1, while reducing TNF- α , systolic and diastolic blood pressure, body weight, and BMI. No significant effects were observed on glycemic markers. OP supplementation showed no consistent cardiometabolic benefits and was associated with an increase in IL-8. Certainty of evidence ranged from very low to high, with several outcomes downgraded due to imprecision, heterogeneity, or limited study numbers.

Conclusion: These findings support the targeted use of OL as an adjunctive strategy for cardiometabolic risk management. Evidence for OP supplementation remains limited, underscoring the need for well-powered, high-quality RCTs to clarify its clinical effects.

Keywords

Olive leaf/ Olive pomace/ Cardiometabolic health/ Polyphenols/ Systematic review/ meta-analysis

Introduction

Cardiometabolic diseases (CMDs) remain leading causes of global morbidity and mortality [1–3]. These disorders share overlapping pathophysiological features, including chronic low-grade inflammation [4–6], oxidative stress [7], dyslipidemia, impaired glucose metabolism, and increased adiposity [8,9]. Such alterations are reflected in changes in diverse biomarkers, including inflammatory markers (e.g., C-reactive protein [CRP], interleukins), lipid fractions, fasting glucose, insulin resistance indices, and anthropometric measures. Among the foundational determinants of cardiometabolic health, diet and nutritional supplementation play pivotal roles [10]. Specifically, dietary patterns rich in plant-derived foods and bioactive compounds, including Mediterranean and other predominantly plant-based dietary patterns, are consistently associated with reduced CMD risk and improved metabolic profiles [11–15].

Polyphenols, a heterogeneous class of plant secondary metabolites abundant in fruits, vegetables, and herbs, are recognized for their antioxidant, anti-inflammatory, and cardioprotective properties [16–18]. Diets rich in polyphenols, such as the Mediterranean diet [11], have been linked to lower cardiovascular disease incidence, improved lipid profiles, enhanced glycemic control, reduced inflammatory markers, and favorable effects on body composition [11,19]. Consequently, growing attention has been directed toward polyphenol-rich diets and supplementation as adjunctive strategies for improving cardiometabolic biomarkers in both clinical and at-risk populations.

In parallel, the concept of sustainable diets—which promote human health while minimizing environmental impact—has gained prominence in public health nutrition research. Sustainable diets emphasize whole food consumption, reduction of food waste, and valorization of agricultural by-products as strategies to enhance nutritional outcomes and environmental stewardship [20–23]. Valorizing food waste not only mitigates environmental burden but also offers opportunities to recover bioactive compounds for functional food and nutraceutical applications [24].

The olive tree (*Olea europaea* L.), a cornerstone of Mediterranean agriculture and diet, produces olive oil—a staple associated with cardiometabolic benefits [11,25]. Olive cultivation, however, generates substantial by-products, primarily olive leaves (OL) and olive pomace (OP, the solid residue of oil extraction). These by-products are rich in phenolic compounds, including oleuropein, hydroxytyrosol, and flavonoids, which exhibit potent antioxidant and anti-inflammatory activities across in vitro and preclinical studies [26–28].

Olive leaves have traditionally been utilized and increasingly investigated in vitro and in vivo [29–34], as well as in clinical studies [34–58], for their potential to improve blood pressure, lipid metabolism, glucose homeostasis, inflammatory status, and anthropometric measures [29–58]. Olive pomace, historically regarded as waste, similarly contains residual phenolics and dietary fibers with demonstrated bioactivity in vitro and in vivo [59–65], as well as in clinical trials [66–70], including modulation of oxidative stress, metabolic pathways, and cardiovascular health parameters [59–70]. Despite growing evidence supporting the benefits of these by-products, findings remain heterogeneous, and study quality varies. While most studies suggest favorable effects—particularly for olive leaves [29–34,37–42,44,47–51,53–58]—some trials report no significant improvements in certain biomarkers [35,36,43,45,46,52]. Moreover, few randomized controlled trials (RCTs) have evaluated olive pomace supplementation in humans [66–70], limiting definitive conclusions regarding its clinical efficacy.

Several systematic reviews [71] and meta-analyses have assessed olive leaf supplementation [72–76]. For instance, Frumuzachi et al. reported that OL extract and hydroxytyrosol supplementation may improve cardiometabolic outcomes as well as bone, joint, and cognitive health [71]. Razmpoosh et al. found that OL extract supplementation benefited blood pressure and lipid profiles, particularly in hypertensive

adults, though evidence quality for glycemic, hepatic, renal, and inflammatory markers was low-to-very low, highlighting the need for higher-quality RCTs [72]. Similarly, Alvares et al. noted that low-dose OL extract did not significantly affect fasting glycemia [73], while other meta-analyses reported reductions in systolic and diastolic blood pressure, cholesterol, triglycerides, and LDL-C [76], or selective improvements in blood pressure and inflammatory markers in prehypertensive and hypertensive populations [74,75]. To date, no systematic review or meta-analysis of RCTs has comprehensively evaluated the effects of olive pomace supplementation on cardiometabolic outcomes or assessed these interventions across a broad range of standardized biomarkers using evidence grading frameworks.

Current study evaluated the effects of OL or OP supplementation on key cardiometabolic biomarkers—including inflammatory markers, lipid profile, glycemic control, insulin sensitivity, anthropometric, and clinical parameters—through a Grading of Recommendations Assessment, Development, and Evaluation (GRADE)-assessed systematic review and meta-analysis of RCTs. Unlike previous studies, this analysis integrates a broader spectrum of 21 markers, offering an updated and more rigorous synthesis of the clinical evidence. By systematically grading and consolidating available data, this work aims to clarify the impact of olive by-products on cardiometabolic health and inform future research, clinical practice, and sustainable utilization of olive industry by-products. Importantly, the valorization of OL and OP also aligns with circular economy principles, as their use as bioactive-rich ingredients represents an upcycling strategy that contributes to waste reduction and adds value to the olive oil production chain.

2. Methods

2.1. Search strategy

A comprehensive systematic search was conducted between June 15 and August 11, 2025, across PubMed, EMBASE, MEDLINE, Scopus, Web of Science, and Cochrane CENTRAL to identify RCTs. In addition, a manual search of related literature was performed, including screening reference lists, bibliographies, and databases of relevant articles, to capture studies potentially missed by automated searches. Two independent reviewers performed the search to minimize selection bias. Searches were conducted without restrictions on language or publication date, and all retrieved records were imported into EndNote 21.2 [77] for citation management, duplicate removal, and streamlined workflow. To ensure inclusion of recently published studies, automated keyword alerts were maintained throughout the review process, and the database search was updated between November 10 and December 15, 2025.

The search strategy incorporated an exhaustive set of keywords and MeSH terms covering olive by-products and anthropometric markers, and all keywords were carefully adapted to the indexing and search syntax of each database. The full search strategies used to identify relevant studies across all databases are provided in Supplementary Table 1.

This systematic review and meta-analysis were conducted in strict accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [78], and the study protocol was prospectively registered in PROSPERO (CRD42024543845).

2.2. Inclusion and exclusion criteria

RCTs investigating the effects of olive by-products—specifically OL or OP—or foods containing these ingredients—on anthropometric and cardiovascular health markers in humans were considered for inclusion. Eligible populations comprised healthy adults and individuals with cardiometabolic risk factors, including overweight or obesity, hypertension, dyslipidemia, type 2 diabetes, and metabolic syndrome, as these groups are directly relevant to the outcomes of interest.

Trials were excluded if participants had active COVID-19 infection, cancer, or were undergoing chemotherapy, since disease- and treatment-related factors could independently influence cardiometabolic and anthropometric outcomes, introducing potential confounding [79]. Studies were excluded if the intervention involved olive oil or whole olive fruit (including extracts or powders). Trials were also excluded when the comparator was an active pharmaceutical agent rather than a placebo, usual diet, or non-drug control, or if the intervention duration was shorter than one week. Additionally, studies were excluded if participants consumed products from animals fed with olive by-products.

Interventions consisting of OL or OP alone, or dietary supplements in which these by-products were among the primary active ingredients, were considered eligible. Studies were excluded if the control group received olive leaf or pomace, or if final results were not publicly available and data could not be obtained from the authors. These criteria ensured that included trials directly assessed the effects of olive by-products on anthropometric, cardiovascular, inflammatory, metabolic, and lipid outcomes, without confounding from other treatments or diseases.

2.3. Article Screening and Selection

Two reviewers (F.M. and C.R.) independently screened all retrieved records and assessed each report for eligibility. In cases of disagreement regarding study selection, a third reviewer (M.M.) was consulted to reach a consensus.

2.4. Data extraction

A standardized data extraction form developed in Microsoft Excel was used to systematically collect and organize relevant data from the included studies. Data extraction was performed independently by two reviewers, and any discrepancies were resolved through discussion or, when necessary, by consultation with a third reviewer.

The following information was extracted from each eligible study: first author's surname, country of origin, year of publication, study design (parallel [34,36–44,46–54,56–58,66,67] or crossover [35,45,55,68–70]), study duration, sample size, sex distribution, mean age with corresponding standard deviation (SD) [34–41,43–53,55–58,66–69] or standard error (SE) [42,70], details of the dietary intervention and control conditions, participants' health status, smoking and alcohol consumption, and medication use. Additionally, mean values with SD [34,37–41,43–54,56–58,66–69], SE [35,36,42,70], 95% confidence intervals (CIs)[55] or medians and interquartile ranges [53,66] for all relevant outcome measures were extracted for both the intervention and control groups at baseline and post-intervention. When required data were missing or unclear, the corresponding authors were contacted to obtain additional information.

2.5. Quality assessment and risk of bias

The study quality was assessed using version 2 of the Cochrane risk of bias tool for RCTs (RoB2.0) [80]. The following methodological domains were considered: Risk of bias arising from the randomization process, Risk of bias arising from period and carryover effects (crossover RCTs), Risk of bias due to deviations from the intended interventions, risk of bias due to missing outcome data, Risk of bias in measurement of the outcome, Risk of bias in selection of the reported result. Each item was scored as a low, some concerns or high regarding risk of bias. Two authors (F.M. and M.M.) independently assessed the studies. The final evaluations were determined through agreement between authors.

2.6. Statistical analysis

Meta-analyses were conducted for 21 outcomes across four categories: (1) inflammatory biomarkers (IL-6, IL-8, TNF- α , CRP, adiponectin); (2) lipid profile markers (TC, TG, HDL, LDL, ApoA1, ApoB, oxLDL); (3) glycemic control/insulin sensitivity markers (FPG, FPI, HOMAIR); and (4) anthropometric/clinical parameters (BMI, weight, WC, HC, SBP, DBP). Separate meta-analyses were performed for each outcome following supplementation with foods containing OL or OP when at least two independent RCTs were available [80]. This meta-analysis was conducted using the dplyr, meta, and metafor packages in RStudio (version 2023.12.1+402[81]). For 20 of the outcomes, effect sizes were reported as mean difference (MD). For oxLDL, standardized mean difference (SMD) was used because the data across studies were reported in different units, making it infeasible to convert them to a common unit for MD calculation. Data were collected as mean (SD) of change before and after the intervention for both the experimental and control groups. When mean changes were not reported, they were calculated by subtracting the baseline mean from the post-intervention mean. The SD for these calculated means was determined following the method described in the Cochrane guidelines [82]. Data in the RCTs were reported as mean with SD [34,37–41,43–54,56–58,66–69], mean with SE [35,36,42,70], mean with 95% CI [55] or median with interquartile range [53,66]. When SDs were unavailable, they were derived from 95% CIs or SE [82], and when only the median with interquartile range was reported, both the mean and SD were calculated according to the method specified in the Cochrane guideline [82].

To account for heterogeneity in study methodologies, random-effects models with the restricted maximum likelihood (REML) estimator were used to calculate pooled effect sizes. The REML approach was selected because it provides unbiased estimates of variance components, particularly in models incorporating random effects. Study weights were assigned using inverse-variance weighting, so that each study's contribution to the pooled estimate was inversely proportional to the variance of its effect size, thereby giving greater influence to studies with more precise (lower variance) estimates [82]. Thirteen studies [36,40,41,44,46,48,51,53,54,57,66,69,70] were included multiple times in the meta-analysis for certain outcomes due to variations in the intervention and control groups, as well as the evaluation of outcomes at multiple time points. Crossover trials [35,45,55,68–70] were incorporated into the meta-analysis alongside parallel trials by comparing outcomes from the intervention periods with those from the control periods. While this approach may introduce a unit-of-analysis error, it is considered a conservative method [82]. Additionally, sensitivity analyses were conducted on the crossover trials using paired analyses with different correlation coefficients (0.25, 0.5, and 0.75) to assess the potential underweighting of these studies.

Sensitivity and subgroup analyses were performed to explore potential sources of heterogeneity. Sensitivity analyses included a leave-one-out approach, in which each study was sequentially excluded to evaluate its impact on the overall pooled effect, applied when at least five RCTs were available for a given outcome [82]. Additional sensitivity analyses were conducted by excluding studies with a high risk of bias, where appropriate. Subgroup analyses were performed based on study duration (<8 vs. $\geq$ 8 weeks), study design (parallel vs. crossover), participants' health status (healthy vs. unhealthy), intervention characteristics (olive leaves or olive pomace alone vs. combined with other bioactive compounds), participants' use of medications (yes vs. no), mean age (<60 vs. $\geq$ 60 years), sex (male only, female only, or both), and geographical location (Europe, North and South America, Asia, Oceania/Australasia), when applicable. Between-study heterogeneity was evaluated using the I^2 statistic and categorized according to Cochrane guidelines: low (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%) [82]. Given the exploratory nature of assessing multiple outcomes ($n = 21$), no formal adjustment for multiple comparisons was applied; therefore, the possibility of type I error inflation should be considered when interpreting statistically significant findings.

To assess potential publication bias in the meta-analysis, Begg's test, a rank-based method that evaluates the correlation between effect estimates and their variances, was used when applicable. Begg's test was chosen over Egger's test because some outcomes were based on small datasets; it is more robust for smaller samples and does not rely on the linear regression assumptions required by Egger's test [82–85]. Nevertheless, results should be interpreted with caution due to the limited number of studies and the resulting low statistical power [82–84]. For outcomes with at least 10 independent studies, funnel plots were also generated [82]. For outcomes with only two or three RCTs, publication bias tests were not performed because they are considered unreliable [82]. A significance threshold of $P < 0.05$ was applied throughout the study.

2.7. Certainty Assessment

The overall certainty of evidence across studies was assessed following the guidelines of the GRADE working group [86,87](<https://www.gradeworkinggroup.org/>). Based on this evaluation, the quality of evidence was classified into four levels: high, moderate, low, and very low [88].

3. Results

3.1. Study selection

Figure 1 illustrates the PRISMA flow diagram [78], outlining the systematic search and study selection process. A total of 604 records were initially identified through database searches. After removing duplicate records, 349 studies remained for title and abstract screening. Of these, 284 were excluded due to irrelevance to the research topic or because the study design was not a RCT.

Full-text assessments were conducted for the remaining 65 articles, resulting in the exclusion of 35 studies that did not meet the predefined eligibility criteria. Additionally, seven records were identified through manual searches, of which two were retrieved for full-text review; however, none met the inclusion criteria. In total, 30 RCTs [34–58,66–70] met the eligibility criteria and were included in this systematic review and meta-analysis.

3.2. Study characteristics

Table 1 provides a comprehensive overview of the specific characteristics of the trials included in this study. The 30 studies included in this systematic review and meta-analysis were conducted across 13 countries, with the highest representation in Spain [38,39,53,69,70](16.7%) and Iran [42,47,49,50,58](16.7%), followed by Greece [52,57,66](10.0%), Italy [54,67,68](10.0%), and the Netherlands [36,43,48](10.0%). Other countries included New Zealand [45,55](6.7%), Israel [34,40](6.7%), Australia [35,46] (6.7%), and Japan [56], Poland [51], Switzerland [44], the United Kingdom [41], and France [37](each 3.3%). The studies were published between 2008 and 2025. Six studies employed a crossover design [35,45,55,68–70] while the remaining studies used a parallel design[34,36–44,46–54,56–58,66,67]. Regarding blinding, 24 studies were double-blind [34–43,45–49,51–53,55,56,58,66–68], three were partially blinded [50,69,70], and three were not blinded [44,54,57]. The duration of the included trials ranged from 4 to 48 weeks; however, one study did not report information regarding trial duration [42]. Five RCTs evaluated the effects of foods or supplements containing OP [66–70], whereas the remaining 25 RCTs investigated OL [34–58].

Regarding the evaluated outcomes, IL-6 [38,45,47,51,53,66,68–70] and CRP [38,45,51,53,54,66,67,69,70] were each assessed in 9 RCTs, IL-8 in 5 RCTs [45,47,68–70], TNF- α in 6 RCTs [38,45,47,68–70], and adiponectin in 4 RCTs [45,49,66,70]. For lipid profile markers, TC [35–39,41,43–45,48,49,51–55,57,58,66–70] and TG [35–39,41,43,45,48,49,51–58,66–70] were each

evaluated in 23 RCTs, HDL and LDL in 24 RCTs [35–39,41,43–45,48,49,51–58,66–70], ApoA1 and ApoB in 5 RCTs [39,53,67,69,70], and oxLDL in 8 RCTs [36,38,39,45,54,55,67,70]. In terms of glycemic control and insulin sensitivity, FPG was assessed in 17 RCTs [35–37,41,43,45,47,49,50,52–54,56,66–68,70], FPI in 16 RCTs [34–37,41,43,45,47,49,50,52,54,66–68,70], and HOMAIR in 11 RCTs [35,37,41,45–47,49,52,54,68,70]. Regarding anthropometric and clinical parameters, BMI was evaluated in 14 RCTs [35–41,45,49,54,57,66,67,70], body weight in 11 RCTs [36–40,45,49,54,56,67,70], WC in 7 RCTs [37,41,49,54,56,67,70], HC in 4 RCTs [37,54,67,70], and SBP and DBP in 15 RCTs [35–38,41–45,55,58,66,67,69,70]. Detailed information regarding the distribution of RCTs evaluating olive pomace and olive leaf interventions is presented in Table 1.

3.3. Participant characteristics

The analysis included 25 studies [34–58] comprising a total of 1,425 participants that examined the effects of foods or supplements containing OL, and 5 RCTs [66–70] involving 301 participants that evaluated the effects of OP on the outcomes of interest. Among the included studies, three enrolled exclusively male participants [43,45,55], while four enrolled exclusively female participants [48–51]. The mean age of randomly assigned participants ranged from 30 ± 2 [70] to 64.7 ± 3.46 [50] years; however, one study did not report participants' age [54]. Sample sizes varied across studies, ranging from 19 [68] to 148 participants [54].

In five RCTs [44,56,67–69], participants were within the normal BMI range, whereas in the remaining studies, some or all participants were classified as overweight or obese [34–43,45–55,57,66,70]. One study did not report BMI information [58]. Participants across the included studies exhibited a range of health conditions. Some had cardiometabolic risk factors, including dyslipidemia (mild or primary hypercholesterolemia, elevated cholesterol) [36,39,53,57,67], impaired glucose metabolism or prediabetes [37,52,54] and type 2 diabetes mellitus [34,46]. Others presented with blood pressure–related conditions, including pre-hypertension, mild-to-moderate hypertension, essential hypertension, or untreated borderline blood pressure [35,41,42,44,45,47,58]. Additional conditions included osteopenia [51] and participants with stable cardiometabolic conditions under medication [40]. The remaining participants were healthy adults with no reported chronic conditions [38,43,48–50,55,56,66,68–70] (Table 1).

3.4. Quality assessment and risk of bias

The methodological quality and risk of bias of the eligible trials were assessed using the Cochrane Risk of Bias tool (RoB 2) [80]. The results are summarized in Table 2 and Supplementary Table 2. Seventeen RCTs were judged to be at low risk of bias [34–38,41–43,45,46,48–50,53,68–70], twelve RCTs were assessed as having some concerns [39,40,47,51,52,54–58,66,67], and one study was rated as high risk of bias [44]. Overall, the risk of bias among the included studies ranged from low to high. Detailed assessments and the specific reasons for judgments are presented in Table 2 and Supplementary Table 2.

3.5. Meta-analyses results

3.5.1 Effect of OL or OP supplementation on inflammatory biomarkers

The meta-analysis results for the effects of OL and OP on five inflammatory markers (IL-6, IL-8, TNF- α , CRP, Adiponectin) are presented in Table 3, with forest plots shown in Supplementary Figure 1. Based on three studies (216 observations; 141 intervention and 135 control subjects), TNF- α levels significantly decreased following OL supplementation (MD = -0.43 ; 95% CI -0.68 to -0.18 ; $P = 0.0006$), with substantial between-study heterogeneity ($I^2 = 70.2\%$; 95% CI 0.0% to 91.3%; $P = 0.035$). The meta-analysis of three studies (151 observations; 151 intervention and 151 control subjects) indicated that IL-8

levels significantly increased after OP supplementation (MD = 1.7; 95% CI 0.24 to 3.16; $P = 0.02$), with no between-study heterogeneity ($I^2 = 0.0\%$; 95% CI 0.0% to 79.2%; $P = 0.85$), indicating a statistically significant increase in IL-8 following OP supplementation. No significant changes were observed for the other biomarkers after either supplementation (Table 3, Supplementary Figure 1). For TNF- α , heterogeneity remained unresolved.

3.5.2 Effect of OL or OP supplementation on lipid profile markers

The meta-analysis results for the effects of OL and OP on lipid profile markers (TC, TG, HDL, LDL, ApoA1, ApoB, oxLDL) are summarized in Table 4, with forest plots in Supplementary Figure 2. OL supplementation significantly decreased TC (eighteen studies, 1103 observations; 665 intervention and 605 control subjects; MD = -9.72; 95% CI -13.73 to -5.72; $P < 0.0001$) with substantial heterogeneity ($I^2 = 62.5\%$; 95% CI 42.8% to 75.5%; $P < 0.0001$), TG (eighteen studies, 1122 observations; 675 intervention and 589 control subjects; MD = -5.97; 95% CI -9.11 to -2.83; $P = 0.0002$) with no heterogeneity ($I^2 = 0.0\%$; 95% CI 0.0% to 43.9%; $P = 0.8$), LDL (nineteen studies, 1142 observations; 680 intervention and 599 control subjects; MD = -8.44; 95% CI -12.92 to -3.96; $P = 0.0002$) with substantial heterogeneity ($I^2 = 67.1\%$; 95% CI 50.9% to 78%; $P < 0.0001$), ApoB (two studies, 63 observations; 34 intervention and 29 control subjects; MD = -11.43; 95% CI -14.81 to -8.05; $P < 0.0001$) with low heterogeneity ($I^2 = 33.4\%$; 95% CI 0.0% to 78.0%; $P = 0.2$), and oxLDL (six studies, 449 observations; 283 intervention and 271 control subjects; MD = -0.34; 95% CI -0.57 to -0.11; $P = 0.0034$) with substantial heterogeneity ($I^2 = 60.7\%$; 95% CI 14.6% to 81.9%; $P = 0.01$). ApoA1 increased significantly (two studies, 63 observations; 34 intervention and 29 control subjects; MD = 5.98; 95% CI 0.9 to 11.06; $P = 0.02$) with no heterogeneity ($I^2 = 0.0\%$; 95% CI 0.0% to 89.6%; $P = 0.8$), indicating potential improvement in lipid profile. OP supplementation did not significantly affect any of these markers (Table 4, Supplementary Figure 2).

Subgroup analysis revealed that for TC and LDL, studies using OL extract alone (without other bioactives) showed reduced heterogeneity while maintaining a significant effect. Subgroup analysis by trial duration resolved heterogeneity for LDL, with the reducing effect remaining significant (Supplementary Table 3). For oxLDL, removing individual trials solved heterogeneity, indicating strong influence of each study.

3.5.3 Effect of OL or OP supplementation on glycemic control / insulin sensitivity biomarkers

The effects on glycemic control and insulin sensitivity markers (FPG, FPI, HOMAIR) are presented in Table 5, with forest plots in Supplementary Figure 3. Neither OL nor OP supplementation produced significant changes in these markers (Table 5, Supplementary Figure 3).

3.5.4 Effect of OL or OP supplementation on clinical / anthropometric parameters

The meta-analysis results for six clinical/anthropometric parameters (SBP, DBP, BMI, body weight, WC, HC) are presented in Table 6, with forest plots shown in Supplementary Figure 4. OL supplementation significantly decreased SBP (eleven studies, 581 observations; 408 intervention and 375 control subjects; MD = -3.72; 95% CI -5.94 to -1.51; $P = 0.001$) with substantial heterogeneity ($I^2 = 57.4\%$; 95% CI 24.3% to 76%; $P = 0.003$), DBP (MD = -1.52; 95% CI -2.64 to -0.4; $P = 0.008$) with low heterogeneity ($I^2 = 12\%$; 95% CI 0.0% to 49.9%; $P = 0.32$), BMI (eleven studies, 721 observations; 450 intervention and 353 control subjects; MD = -0.26; 95% CI -0.5 to -0.02; $P = 0.035$) with substantial heterogeneity ($I^2 = 54.4\%$; 95% CI 21.0% to 73.6%; $P = 0.004$), and body weight (nine studies, 593 observations; 347 intervention and 306 control subjects; MD = -0.71; 95% CI -1.21 to -0.21; $P = 0.0055$) with substantial heterogeneity ($I^2 = 54\%$; 95% CI 13.9% to 75.4%; $P = 0.01$). Olive leaf supplementation did not

significantly affect the remaining markers, and OP showed no significant effects on any parameter (Table 6, Supplementary Figure 4).

Subgroup analyses indicated that for SBP, heterogeneity among studies conducted in healthy participants was resolved while the reducing effect remained significant. For BMI, studies with trial duration <8 weeks, healthy participants, no medication use, and conducted in Europe showed reduced heterogeneity; however, the effect became non-significant. For body weight, in studies including healthy participants not taking medication, heterogeneity was resolved and the reducing effect remained significant (Supplementary Table 3).

3.6. Subgroup and sensitivity analysis

Subgroup analyses were conducted based on study duration, study design, participants' health status, intervention characteristics, medication use, mean age, sex, and geographical location, where applicable. The results are presented in Supplementary Table 3 and supplementary Table 4.

To determine whether the outcomes may have been underestimated in crossover trials, paired analyses of crossover RCTs were conducted using correlation coefficients of 0.25, 0.5, and 0.75 (Supplementary Table 5 and Supplementary Table 6). The inclusion of correlation coefficients suggested that the overall results for CRP levels after OL supplementation may differ from the primary analyses and reach statistical significance (Supplementary Table 5). In contrast, incorporating correlation coefficients for OP supplementation did not reveal any significant differences (Supplementary Table 6).

Sensitivity analyses using the leave-one-out method were further performed to identify studies that may have inflated the effect sizes. For CRP and oxLDL following OL supplementation, heterogeneity was resolved after sequential removal of individual trials, indicating that each study had a strong influence on overall heterogeneity. For all other outcomes, leave-one-out analyses did not eliminate heterogeneity; similarly, excluding studies with a high risk of bias had no impact on heterogeneity (data not shown).

3.7 Publication bias

The results of Begg's tests and the corresponding funnel plots for the 10 markers following OL supplementation are presented in Supplementary Figure 5. Visual inspection of the funnel plots suggested slight asymmetry, with a few studies falling outside the funnel boundaries. However, Begg's rank correlation tests did not indicate statistically significant publication bias for any of the markers (all $p > 0.05$). For HOMAIR, WC, oxLDL, CRP, and IL-6 following OL supplementation, only Begg's test was conducted, and no significant publication bias was detected.

For IL-6, CRP, TC, TG, HDL, LDL, FPG, FPI, SBP, DBP, and BMI following OP supplementation, funnel plots were not feasible due to the limited number of included RCTs; only Begg's test was performed. Among these, CRP showed a significant result (Begg's $\tau = 0.6482$, $p = 0.0186$), suggesting potential publication bias.

For IL-8, TNF- α , adiponectin, ApoA1, ApoB, and HC (after OL and OP supplementation), as well as oxLDL, HOMA-IR, and body weight (only after OP supplementation), publication bias was not assessed due to the small number of RCTs and the unreliability of statistical tests under these conditions.

3.8. Certainty Assessment Results

The certainty of the evidence was evaluated using the GRADE approach (Table 7). The quality of evidence was downgraded for several markers due to serious imprecision, with the exception of TC, TG, HDL, LDL, oxLDL, SBP, DBP, BMI, and weight under OL supplementation. Inconsistency resulted in

downgrading for all inflammatory markers, as well as for TC, oxLDL, and WC under OL supplementation.

Additionally, Risk of bias led to downgrading only for SBP and DBP under OL supplementation. Publication bias resulted in downgrading for CRP under OP supplementation, and for Apo A1, Apo B, and weight under OL supplementation. Overall, the certainty of the evidence ranged from very low to high, as summarized in Table 7.

4. Discussion

In this GRADE-assessed systematic review and meta-analysis of 30 RCTs ($n = 1,726$ adult participants), the effects of olive by-products—OL or OP—on 21 cardiometabolic, inflammatory, glycemic, lipid, anthropometric, and clinical markers were evaluated. Findings demonstrate that OL extract supplementation significantly improved several lipid parameters (TC, TG, LDL, ApoB, oxLDL), increased ApoA1, reduced TNF- α , and lowered SBP, DBP, BMI, and body weight. In contrast, OL did not significantly affect glycemic indices (FPG, FPI, HOMAIR) or most inflammatory markers. Notably, OP supplementation showed no beneficial effects across cardiometabolic outcomes and was associated with a significant increase in IL-8; however, this finding should be interpreted cautiously given the very limited number of contributing RCTs and the resulting imprecision of the estimate, and may not necessarily reflect a consistent pro-inflammatory response.

Subgroup analyses by baseline health status suggested that the blood pressure-lowering effects of OL supplementation were more pronounced in participants with pre-existing cardiometabolic risk conditions than in healthy individuals. No clear subgroup differences were observed for the remaining outcomes. However, given the limited number of studies in several strata and the resulting low statistical power, these findings should be interpreted as exploratory.

The certainty of evidence varied across outcomes. High-certainty evidence was limited to triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and body mass index (BMI) under OL supplementation. Moderate-certainty evidence was observed for most lipid profile outcomes (including total cholesterol, TG, HDL-C, LDL-C, oxLDL, and ApoA1 under OP), glycemic control markers (FPG, FPI, and HOMA-IR), and several clinical parameters (SBP, DBP, BMI, weight, waist circumference, and hip circumference under OP). Inflammatory markers generally showed lower certainty, with moderate certainty for IL-6, TNF- α , CRP, and adiponectin under OP, but low to very low certainty for IL-6, TNF- α , CRP, adiponectin, and IL-8 under OL supplementation. Very low-certainty evidence was observed for IL-8, ApoA1, and ApoB under OL supplementation, reflecting substantial imprecision and inconsistency, while ApoB under OP and weight and waist circumference under OL supplementation were also supported by low-certainty evidence.

Importantly, beyond statistical significance, the magnitude of the observed effects should be interpreted in a clinical context. The reductions in systolic blood pressure (-3.72 mmHg) and diastolic blood pressure (-1.52 mmHg) associated with OL supplementation, although modest at the individual level, may be epidemiologically relevant at the population level, as small reductions in blood pressure have been associated with meaningful reductions in cardiovascular risk; for example, a 2-5 mmHg reduction in systolic blood pressure has been associated with an approximately 10% lower risk of major cardiovascular events, while earlier population-based estimates suggested that even small reductions in blood pressure could reduce coronary heart disease and stroke risk [89–91].

Similarly, the observed reductions in LDL-C (-8.44 mg/dL) and total cholesterol (-9.72 mg/dL) are consistent with modest lipid-lowering effects expected from dietary or nutraceutical interventions rather than pharmacological therapy [92–94]. When compared with established dietary interventions, these effects appear broadly comparable to those reported for plant sterols and stanols, which typically reduce LDL-C by approximately 8–10% at intakes of about 2 g/day [95–97], and are lower than the lipid-lowering magnitude observed with red yeast rice preparations containing monacolin K, which can reduce LDL-C by approximately 15–25% [92,98]. Therefore, OL supplementation should be considered a supportive adjunctive strategy within a broader cardiometabolic risk reduction approach rather than a stand-alone therapeutic alternative.

These health benefits of OL have been reported in numerous clinical studies, including lipid-lowering effects [39,45,51,55], reductions in systolic and diastolic blood pressure [37,38,42,45], and body weight management [40,49]. However, the effects on glycemic control and inflammatory biomarkers remain inconsistent. While some clinical trials have demonstrated beneficial effects on glucose metabolism or inflammatory status [34,37,47,54,55] others have reported no significant changes [35,46,52], and in some cases, even pro-inflammatory responses, such as increased IL-6 levels, have been observed [55].

Regarding OP, clinical evidence evaluating its effects on inflammatory markers, lipid profile, glycemic parameters, blood pressure, and anthropometric outcomes remains limited, as only a few RCTs have been conducted [66–70]. Moreover, the available findings are inconsistent, even within different participant subgroups of the same study. For example, glucose levels increased following OP oil consumption and decreased after sunflower oil intake in normocholesterolemic subjects, whereas hypercholesterolemic individuals showed different or inconsistent responses [70]. These discrepancies highlight the need for larger, well-designed RCTs to clarify the metabolic and clinical effects of OP.

Overall, clinical studies investigating olive by-products have reported heterogeneous outcomes, likely influenced by differences in participant characteristics, health status, study design, intervention diversities such as dosage and formulation.

The present findings are largely consistent with previously published systematic reviews and meta-analyses evaluating OL extract supplementation. Razmpoosh et al. [72] reported significant reductions in triglycerides and systolic blood pressure, with subgroup improvements in LDL-C and TC, particularly among hypertensive individuals. Similarly, Álvares et al. [73] demonstrated favorable effects of OL extract on lipid profile and blood pressure, while glycemic outcomes were reported to be inconsistent—an observation aligned with the absence of significant pooled effects on FPG, fasting insulin, and HOMAIR in the current synthesis.

Evidence derived from hypertensive and prehypertensive populations further corroborates these findings. Ismail et al. [74] and Lachovicz et al. [75] documented clinically meaningful reductions in systolic blood pressure, particularly at higher doses (e.g., 1000 mg/day). Likewise, Fatahian et al. [76] reported significant reductions in SBP, DBP, total cholesterol, LDL-C, and triglycerides. The magnitude of blood pressure and lipid reductions observed across these analyses closely parallels the pooled estimates identified here, suggesting consistency of effect across different populations and study designs.

With respect to inflammatory markers, Ismail et al. [74] described reductions in IL-6, IL-8, and TNF- α following OL extract supplementation. A reduction in TNF- α was similarly observed in the present analysis, although broader inflammatory outcomes did not demonstrate consistent improvements across

markers. Furthermore, the systematic review by Frumuzachi et al. [71], focusing on oleuropein and hydroxytyrosol supplementation, reported heterogeneous yet generally favorable effects on body weight, lipid metabolism, and glucose regulation. These findings mirror the overall cardiometabolic profile observed in this synthesis, characterized by more robust lipid and blood pressure effects compared with glycemic outcomes.

Consistent with prior pooled analyses [72,73], no robust improvements in glycemic indices were detected. Although individual trials have suggested enhanced insulin sensitivity in specific subgroups, aggregated evidence indicates that glycemic benefits are less consistent than lipid-lowering and antihypertensive effects.

The results of the present study reinforce these conclusions while expanding the evidence base through the inclusion of additional recent RCTs and the application of the GRADE framework to evaluate the certainty of evidence. Furthermore, this analysis incorporated outcomes not previously assessed in earlier systematic reviews and meta-analyses providing a more comprehensive evaluation of the cardiometabolic effects of OL supplementation. For example, improvements in Apo B and oxLDL (newly found in this study) strengthen the cardioprotective profile of OL extract, as ApoB-containing lipoproteins and oxidized LDL are considered more robust predictors of atherogenic risk than LDL-C alone [99,100]. Reductions in oxLDL are particularly relevant, given its central role in endothelial dysfunction and plaque formation [101].

Importantly, to the best of current knowledge, no previous systematic review has comprehensively synthesized RCTs assessing OP supplementation across such a wide range of cardiometabolic markers using the GRADE framework. The lack of significant cardiometabolic effects associated with OP thus provides novel evidence and highlights the biological and compositional differences between olive-derived by-products.

The cardiometabolic benefits of olive by-products, OL, are biologically plausible and supported by mechanistic evidence. OL is notably rich in oleuropein, hydroxytyrosol, and other phenolic secoiridoids [26–28,102]. These compounds exert potent antioxidant effects through both direct scavenging of reactive oxygen species and activation of endogenous antioxidant defense pathways. Specifically, they promote nuclear translocation and activation of nuclear factor erythroid-2-related factor 2 (Nrf2), resulting in upregulation of phase II detoxifying and antioxidant enzymes, including glutathione-related enzymes, heme oxygenase-1, and NAD(P)H quinone oxidoreductase 1 [103–107].

Reduced oxidative stress may underlie the observed decreases in oxidized LDL and improvements in lipid profiles, as well as some of the anti-inflammatory effects associated with OL. Olive polyphenols have been shown to limit lipid peroxidation, enhance anti-inflammatory capacity, and improve lipid metabolism [108–110]. Furthermore, OL exerts anti-inflammatory effects by inhibiting NF- κ B activation and suppressing pro-inflammatory cytokine production [111].

Regarding hypotensive effects, polyphenols such as oleuropein can lower blood pressure through inhibition of angiotensin-converting enzyme (ACE), reducing angiotensin II levels and vascular resistance [112]. Additionally, these compounds enhance endothelial function by increasing nitric oxide bioavailability, promoting vasodilation, and improving arterial compliance [113,114]. Their antioxidant activity further protects endothelial cells from oxidative stress, contributing to blood pressure regulation [103–107].

Modest reductions in body weight and BMI may reflect secondary metabolic effects, potentially mediated by improved lipid metabolism. Oleuropein and hydroxytyrosol have also been shown to modulate adipokine secretion and enhance mitochondrial efficiency, thereby influencing adipogenesis and key energy metabolism pathways [115,116].

Although some clinical studies have reported hypoglycemic effects of OL, for example via inhibition of starch digestion in diabetic patients [34] current study did not detect significant effects on glycemic markers. This may be attributable to the limited number of RCTs and the predominance of normoglycemic participants, which likely reduced the capacity to observe measurable improvements.

Considering OP effects, while it contains residual phenolics and dietary fiber, industrial processing—particularly high-temperature oil extraction—may degrade sensitive polyphenols or reduce their bioaccessibility, limiting biological efficacy [117–120]. Moreover, the small number of OP trials substantially reduces statistical power, increases imprecision, and limits the reliability of pooled estimates. Consequently, these findings should be interpreted cautiously, and additional high-quality RCTs are needed to clarify the potential effects of OP supplementation.

As strengths, this review provides a comprehensive synthesis of both OL and OP supplementation, evaluating 21 standardized cardiometabolic and anthropometric markers. A rigorous methodology was applied, including the use of the GRADE framework, which enhances transparency and strengthens the reliability of evidence assessment.

Limitations include the small number of RCTs evaluating OP supplementation for all outcomes and OL for certain biomarkers, leading to imprecision that may affect pooled estimates and limiting the assessment of publication bias due to low statistical power. The imbalance between OL and OP trials further restricts direct comparability. Twelve included RCTs were rated as “some concerns” and one as high risk of bias, potentially influencing effect estimates. Substantial heterogeneity persisted for certain outcomes, which was partially addressed through subgroup and sensitivity analyses. Several outcomes were downgraded in GRADE due to imprecision and inconsistency. In addition, the heterogeneity of the included interventions and doses did not allow for a meaningful dose–response analysis. In several RCTs, dose information was incompletely reported or expressed as total product rather than standardized olive-derived bioactive content, and in some multi-ingredient formulations the specific contribution of olive products could not be isolated. Moreover, due to the limited number of studies available for several outcomes, dose–response modelling was not statistically feasible in the present meta-analysis.

Furthermore, variability in the standardization and characterization of bioactive compounds, such as oleuropein, hydroxytyrosol, due to differences in extraction methods, processing conditions, formulation type, and reporting practices limited the feasibility of performing subgroup analyses based on supplement standardization, such as high-oleuropein extracts versus general phenolic extracts. This variability should be considered when interpreting the clinical applicability of the findings, particularly because inconsistent reporting of individual phenolic compounds prevents precise recommendations regarding specific bioactive doses.

Future research should focus on well-powered, longer-duration RCTs using standardized OP preparations, direct head-to-head comparisons between OL and OP, standardized and transparent reporting of olive-derived bioactive composition and extraction methods, dose-response investigations, assessment of bioavailability and mechanistic biomarkers, and studies in well-characterized high-risk populations. Trials conducted with rigorous methodology and minimal risk of bias are essential to strengthen certainty of evidence and clarify clinical applicability.

In conclusion, this GRADE-assessed systematic review and meta-analysis of RCTs indicates that OL supplementation improves cardiometabolic outcomes, particularly lipid profile, blood pressure, and select inflammatory markers. Evidence for OP supplementation remains limited and inconclusive, underscoring the need for well-designed trials to clarify its potential benefits. Although findings support the targeted use of OL as an adjunctive strategy in cardiometabolic risk management, they should be interpreted with caution due to variability in the certainty of evidence across outcomes, which was often limited by imprecision and inconsistency.

Statement of Potential Conflict of Interest

No potential conflict of interest was reported by the authors.

Funding/Support

This work was supported by the doctoral grant AGRIBIOSERV_PNC_MISURA B4, University of Camerino.

Acknowledgements

None.

Data Availability Statement:

The data supporting the findings of this study are available from Fatemeh Mansouri upon request. Email address: fatemeh.mansouri@unicam.it.

Author contributions

F. Mansouri: conceptualization, investigation, methodology, search, data extraction, formal analysis, visualization, validation, risk of bias analysis, writing – original draft, editing, data curation. M. Mardani: writing – original draft, search, methodology, risk of bias analysis. C. Rucci: search. L. Bordoni: conceptualization, supervision of the work, and manuscript revision. R. Gabbianelli: supervision of the work, manuscript revision, and funds acquisition.

Figures legend

Figure 1. Flow diagram of literature search and study selection process.

Abbreviations

ACE : Angiotensin-converting enzyme
ApoA1 : Apolipoprotein A1
ApoB : Apolipoprotein B
BMI : Body mass index
CI : Confidence interval
CRP : C-reactive protein
DBP : Diastolic blood pressure
FPG : Fasting plasma glucose
FPI : Fasting plasma insulin
HC : Hip circumference
HDL-C : High-density lipoprotein cholesterol
HOMAIR : Homeostatic model assessment of insulin resistance
IL-6 : Interleukin-6
IL-8 : Interleukin-8

611 LDL-C : Low-density lipoprotein cholesterol
612 NF- κ B : Nuclear factor kappa B
613 NO : Nitric oxide
614 Nrf2 : Nuclear factor erythroid 2-related factor 2
615 oxLDL : Oxidized low-density lipoprotein
616 RCT : Randomized controlled trial
617 SBP : Systolic blood pressure
618 SD : Standard deviation
619 SE : Standard error
620 TC : Total cholesterol
621 TG : Triglycerides
622 TNF- α : Tumor necrosis factor-alpha
623 WC : Waist circumference

624

625

626

627

628

629

630

631

632

633

634

635

636

637

638

639

640

641

642

643

644

References

1. Kones R, Rumana U. Cardiometabolic diseases of civilization: history and maturation of an evolving global threat. An update and call to action. *Ann Med*. 2017 Apr 3;49(3):260–74. doi:10.1080/07853890.2016.1271957
2. Ferreira SRG, Chiavegatto Filho ADP, Lebrão ML, Duarte YA de O, Laurenti R. Doenças cardiometabólicas. *Revista Brasileira de Epidemiologia*. 2018;21(suppl 2). doi:10.1590/1980-549720180008.supl.2
3. Rao GH. Cardiometabolic Diseases: A Global Perspective. *J Cardiol Cardiovasc Ther*. 2018 Sep 25;12(2). doi:10.19080/JOCCT.2018.12.555834
4. Onat A, Hergenç G. Low-grade inflammation, and dysfunction of high-density lipoprotein and its apolipoproteins as a major driver of cardiometabolic risk. *Metabolism*. 2011 Apr;60(4):499–512. doi:10.1016/j.metabol.2010.04.018
5. Hamjane N, Benyahya F, Nourouti NG, Mechita MB, Barakat A. Cardiovascular diseases and metabolic abnormalities associated with obesity: What is the role of inflammatory responses? A systematic review. *Microvasc Res*. 2020 Sep;131:104023. doi:10.1016/j.mvr.2020.104023
6. Manabe I. Chronic Inflammation Links Cardiovascular, Metabolic and Renal Diseases. *Circulation Journal*. 2011;75(12):2739–48. doi:10.1253/circj.CJ-11-1184
7. Madamanchi NR, Runge MS. Redox signaling in cardiovascular health and disease. *Free Radic Biol Med*. 2013 Aug;61:473–501. doi:10.1016/j.freeradbiomed.2013.04.001
8. Grundy SM. Metabolic Syndrome: A Multiplex Cardiovascular Risk Factor. *J Clin Endocrinol Metab*. 2007 Feb 1;92(2):399–404. doi:10.1210/jc.2006-0513
9. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and Management of the Metabolic Syndrome. *Circulation*. 2005 Oct 25;112(17):2735–52. doi:10.1161/CIRCULATIONAHA.105.169404
10. Karagiannidi A, Kanellopoulou A, Panagiotakos D. Dietary Patterns and Cardiovascular Disease: A systematic review of 29 prospective studies with 1,249,644 participants, published in the last 20 years. *Journal of Atherosclerosis Prevention and Treatment*. 2022 Jan 3;13(1):7–16. doi:10.53590/japt.02.1029
11. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventós RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí J V., Martínez JA, Fitó M, Gea A, Hernán MA, Martínez-González MA. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *New England Journal of Medicine*. 2018 Jun 21;378(25). doi:10.1056/NEJMoa1800389
12. van Kalker CA, Adam TC, Blaak EE. Gut Microbiome-Associated Effects of Plant-Based Diets on Glucose Homeostasis, Body Composition, and Cognitive Function: A Scoping Review. *Advances in Nutrition*. 2026 Apr;17(4):100610. doi:10.1016/j.advnut.2026.100610

- 682 13. Murciano A, Malavolti M, Fairweather-Tait S, Paduano S, Vinceti M, Filippini T. Plant-based diets
683 and risk of type 2 diabetes: systematic review and dose–response meta-analysis. *British Journal of*
684 *Nutrition*. 2025 Aug 28;134(4):277–96. doi:10.1017/S0007114525104157
- 685 14. Bell L, Gibbs J, Cappuccio FP. The effect of plant-based dietary patterns on C-reactive protein: A
686 systematic review and meta-analysis of randomised controlled trials. *Nutrition, Metabolism and*
687 *Cardiovascular Diseases*. 2026 Feb;104631. doi:10.1016/j.numecd.2026.104631
- 688 15. Conceição AR, Cruz MA, Hermsdorff HHM, Pimenta AM, Bressan J. Healthy plant-based and
689 healthy Brazilian dietary patterns are associated with a lower incidence of metabolic syndrome
690 (CUME Study). *Nutrition, Metabolism and Cardiovascular Diseases*. 2026 Feb;104633.
691 doi:10.1016/j.numecd.2026.104633
- 692 16. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and
693 bioavailability. *Am J Clin Nutr*. 2004 May;79(5):727–47. doi:10.1093/ajcn/79.5.727
- 694 17. Del Rio D, Rodriguez-Mateos A, Spencer JPE, Tognolini M, Borges G, Crozier A. Dietary
695 (Poly)phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects
696 Against Chronic Diseases. *Antioxid Redox Signal*. 2013 May 10;18(14):1818–92.
697 doi:10.1089/ars.2012.4581
- 698 18. Iqbal I, Wilairatana P, Saqib F, Nasir B, Wahid M, Latif MF, Iqbal A, Naz R, Mubarak MS. Plant
699 Polyphenols and Their Potential Benefits on Cardiovascular Health: A Review. *Molecules*. 2023
700 Sep 1;28(17):6403. doi:10.3390/molecules28176403
- 701 19. Babio N, Bulló M, Salas-Salvadó J. Mediterranean diet and metabolic syndrome: the evidence.
702 *Public Health Nutr*. 2009 Sep 1;12(9A):1607–17. doi:10.1017/S1368980009990449
- 703 20. Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, Garnett T, Tilman D,
704 DeClerck F, Wood A, Jonell M, Clark M, Gordon LJ, Fanzo J, Hawkes C, Zurayk R, Rivera JA,
705 De Vries W, Majele Sibanda L, Afshin A, Chaudhary A, Herrero M, Agustina R, Branca F, Lartey
706 A, Fan S, Crona B, Fox E, Bignet V, Troell M, Lindahl T, Singh S, Cornell SE, Srinath Reddy K,
707 Narain S, Nishtar S, Murray CJL. Food in the Anthropocene: the EAT–Lancet Commission on
708 healthy diets from sustainable food systems. *The Lancet*. 2019 Feb;393(10170):447–92.
709 doi:10.1016/S0140-6736(18)31788-4
- 710 21. Mármol I, Quero J, Ibarz R, Ferreira-Santos P, Teixeira JA, Rocha CMR, Pérez-Fernández M,
711 García-Juiz S, Osada J, Martín-Belloso O, Rodríguez-Yoldi MJ. Valorization of agro-food by-
712 products and their potential therapeutic applications. *Food and Bioprocess Processing*. 2021
713 Jul;128:247–58. doi:10.1016/j.fbp.2021.06.003
- 714 22. Socas-Rodríguez B, Álvarez-Rivera G, Valdés A, Ibáñez E, Cifuentes A. Food by-products and
715 food wastes: are they safe enough for their valorization? *Trends Food Sci Technol*. 2021
716 Aug;114:133–47. doi:10.1016/j.tifs.2021.05.002
- 717 23. Zambela A, Dias MC, Guilherme R, Lorenzo P. Valorization of Agri-Food Waste to Promote
718 Sustainable Strategies in Agriculture and Improve Crop Quality with Emphasis on Legume Crop
719 Residues. *Agronomy*. 2025 Sep 23;15(10):2254. doi:10.3390/agronomy15102254
- 720 24. Liu Z, de Souza TSP, Holland B, Dunshea F, Barrow C, Suleria HAR. Valorization of Food Waste
721 to Produce Value-Added Products Based on Its Bioactive Compounds. *Processes*. 2023 Mar
722 10;11(3):840. doi:10.3390/pr11030840

25. Covas MI, Nyyssönen K, Poulsen HE, Kaikkonen J, Zunft HJF, Kiesewetter H, Gaddi A, de la Torre R, Mursu J, Bäumler H, Nascetti S, Salonen JT, Fitó M, Virtanen J, Marrugat J. The Effect of Polyphenols in Olive Oil on Heart Disease Risk Factors. *Ann Intern Med*. 2006 Sep 5;145(5):333–41. doi:10.7326/0003-4819-145-5-200609050-00006
26. Sun Q, Huang M, Zeng J, Ma M, Li J, Le T. Beyond waste to bioactive potential: advances in olive by-product valorization and resource recovery. *Food Chem*. 2025 Dec;496:146727. doi:10.1016/j.foodchem.2025.146727
27. Bubulac L, Bogdan-Andreescu CF, Voica DV, Cristea BM, Chiş MS, Slăvescu DA. From Olive Oil to Pomace: Sustainable Valorization Pathways Linking Food Processing and Human Health. *Applied Sciences*. 2025 Oct 4;15(19):10717. doi:10.3390/app151910717
28. Greco M, Fuertes-Rabanal M, Frey C, Grosso C Del, Coculo D, Moretti P, Saldarelli P, Agresti S, Caliendo R, Mélida H, Lionetti V. Phenolic compounds-enriched extract recovered from two-phase olive pomace serves as plant immunostimulants and broad-spectrum antimicrobials against phytopathogens including *Xylella fastidiosa*. *Plant Stress*. 2024 Dec;14:100655. doi:10.1016/j.stress.2024.100655
29. Mansour HMM, Zeitoun AA, Abd-Rabou HS, El Enshasy HA, Dailin DJ, Zeitoun MAA, El-Sohaimy SA. Antioxidant and Anti-Diabetic Properties of Olive (*Olea europaea*) Leaf Extracts: In Vitro and In Vivo Evaluation. *Antioxidants*. 2023 Jun 14;12(6):1275. doi:10.3390/antiox12061275
30. Ghanema IIA, Sadek KM. Olive Leaves Extract Restored the antioxidant Perturbations in Red Blood Cells Hemolysate in Streptozotocin Induced Diabetic Rats. *World Academy of Science, Engineering and Technology, International Journal of Biological, Biomolecular, Agricultural, Food and Biotechnological Engineering [Internet]*. 2012;6:124–30. Available from: <https://api.semanticscholar.org/CorpusID:55776795>
31. Kaeidi A, Esmaeili-Mahani S, Sheibani V, Abbasnejad M, Rasoulzadeh B, Hajializadeh Z, Afrazi S. Olive (*Olea europaea* L.) leaf extract attenuates early diabetic neuropathic pain through prevention of high glucose-induced apoptosis: In vitro and in vivo studies. *J Ethnopharmacol*. 2011 Jun;136(1):188–96. doi:10.1016/j.jep.2011.04.038
32. Eidi A, Eidi M, Darzi R. Antidiabetic effect of *Olea europaea* L. in normal and diabetic rats. *Phytotherapy Research*. 2009 Mar 9;23(3):347–50. doi:10.1002/ptr.2629
33. Liu YN, Jung JH, Park H, Kim H. Olive leaf extract suppresses messenger RNA expression of proinflammatory cytokines and enhances insulin receptor substrate 1 expression in the rats with streptozotocin and high-fat diet-induced diabetes. 2014 May;34(5):450–7. doi:10.1016/j.nutres.2014.04.007
34. Wainstein J, Ganz T, Boaz M, Bar Dayan Y, Dolev E, Kerem Z, Madar Z. Olive Leaf Extract as a Hypoglycemic Agent in Both Human Diabetic Subjects and in Rats. *J Med Food*. 2012 Jul;15(7):605–10. doi:10.1089/jmf.2011.0243
35. Wong R, Garg M, Wood L, Howe P. Antihypertensive Potential of Combined Extracts of Olive Leaf, Green Coffee Bean and Beetroot: A Randomized, Double-Blind, Placebo-Controlled Crossover Trial. *Nutrients*. 2014 Nov 5;6(11):4881–94. doi:10.3390/nu6114881

36. Stevens Y, Winkens B, Jonkers D, Masclee A. The effect of olive leaf extract on cardiovascular health markers: a randomized placebo-controlled clinical trial. *Eur J Nutr.* 2021 Jun 9;60(4):2111–20. doi:10.1007/s00394-020-02397-9
37. Sirvent P, Chavanelle V, Otero YF, Bargetto M, Le Joubioux F, Boisseau N, Maugard T, Cazaubiel M, Pereira B, Guigas B, Hadjadj S, Peltier SL, Marette A, Bard J. <scp>TOTUM</scp> -63, a plant-based polyphenol-rich extract, improves glycaemic control in subjects with prediabetes or early stage newly-diagnosed type 2 diabetes in a randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab.* 2022 Dec;24(12):2331–40. doi:10.1111/dom.14817
38. Sánchez Macarro M, Martínez Rodríguez JP, Bernal Morell E, Pérez-Piñero S, Victoria-Montesinos D, García-Muñoz AM, Cánovas García F, Castillo Sánchez J, López-Román FJ. Effect of a Combination of Citrus Flavones and Flavanones and Olive Polyphenols for the Reduction of Cardiovascular Disease Risk: An Exploratory Randomized, Double-Blind, Placebo-Controlled Study in Healthy Subjects. *Nutrients.* 2020 May 19;12(5):1475. doi:10.3390/nu12051475
39. Victoria-Montesinos D, Abellán Ruiz MS, Luque Rubia AJ, Guillén Martínez D, Pérez-Piñero S, Sánchez Macarro M, García-Muñoz AM, Cánovas García F, Castillo Sánchez J, López-Román FJ. Effectiveness of Consumption of a Combination of Citrus Fruit Flavonoids and Olive Leaf Polyphenols to Reduce Oxidation of Low-Density Lipoprotein in Treatment-Naïve Cardiovascular Risk Subjects: A Randomized Double-Blind Controlled Study. *Antioxidants.* 2021 Apr 11;10(4):589. doi:10.3390/antiox10040589
40. Said O, Khalil K, Fulder S, Marie Y, Kassis E, Saad B. A Double Blinded-Randomized Clinical Study with “Weighlevel”, a Combination of Four Medicinal Plants Used in Traditional Greco-Arab and Islamic Medicine. *The Open Complementary Medicine Journal.* 2010.
41. Saibandith B, Tolfrey K, Spencer J, Rowland I, Commane D. The synergistic anti-hypertensive effects of consuming olive leaf extract alongside increasing physical activity. *Proceedings of the Nutrition Society.* 2016 Nov 24;75(OCE3):E210. doi:10.1017/S0029665116002251
42. Saberi M, Kazemisaleh D, Bolurian V. Effect of Olive Leaf on Mild to Moderate Hypertension Resistant to Normal Treatments. *jmpir [Internet].* 2008 Aug 1;7(27):52–9. Available from: <http://jmp.ir/article-1-434-en.html>
43. Pinckaers PJ, Petrick HL, Horstman AM, Moreno-Asso A, De Marchi U, Hendriks FK, Kuin LM, Fuchs CJ, Grathwohl D, Verdijk LB, Zorenc AH, Senden JM, Migliavacca E, Metairon S, Poquet L, Morin-Rivron D, Karagounis LG, Holloway GP, Feige JN, van Loon LJ. Oleuropein Supplementation Increases Resting Skeletal Muscle Fractional Pyruvate Dehydrogenase Activity but Does Not Influence Whole-Body Metabolism: A Randomized, Double-Blind, and Placebo-Controlled Trial in Healthy, Older Males. *J Nutr.* 2025 May;155(5):1373–86. doi:10.1016/j.tjnut.2025.02.015
44. Perrinjaquet-Moccetti T, Busjahn A, Schmidlin C, Schmidt A, Bradl B, Aydogan C. Food supplementation with an olive (*Olea europaea* L.) leaf extract reduces blood pressure in borderline hypertensive monozygotic twins. *Phytotherapy Research.* 2008 Sep 27;22(9):1239–42. doi:10.1002/ptr.2455
45. Lockyer S, Rowland I, Spencer JPE, Yaqoob P, Stonehouse W. Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: a randomised controlled trial. *Eur J Nutr.* 2017 Jun 7;56(4):1421–32. doi:10.1007/s00394-016-1188-y

46. Leach MJ, Breakspear I. Efficacy and safety of olive leaf extract (*Olea europaea* L.) for glycaemic control in adults with type 2 diabetes mellitus (ESOLED): A pilot randomised controlled trial. *Complement Ther Clin Pract*. 2025 May;59:101949. doi:10.1016/j.ctcp.2025.101949
47. Javadi H, Yaghoobzad H, Esfahani Z, Reza Memar M, Mehdi Mirh S. Effects of Olive Leaf Extract on Metabolic Response, Liver and Kidney Functions and Inflammatory Biomarkers in Hypertensive Patients. *Pakistan Journal of Biological Sciences*. 2019 Jun 15;22(7):342–8. doi:10.3923/pjbs.2019.342.348
48. Imperatrice M, Lasfar A, van Kalkeren CAJ, Troost F. Olive Leaf Extract Supplementation Improves Postmenopausal Symptoms: A Randomized, Double-Blind, Placebo-Controlled Parallel Study on Postmenopausal Women. *Nutrients*. 2024 Nov 14;16(22):3879. doi:10.3390/nu16223879
49. Haidari F, Shayesteh F, Mohammad-shahi M, Jalali MT, Ahmadi-Angali K. Olive Leaf Extract Supplementation Combined with Calorie-Restricted Diet on Reducing Body Weight and Fat Mass in Obese Women: Result of a Randomized Control Trial. *Clin Nutr Res*. 2021;10(4):314. doi:10.7762/cnr.2021.10.4.314
50. Hamed Ghiyami S, Mahmoodi R, Pourrazi H, Moradi H. The effect of 8 weeks of HICT training with olive leaf extract on insulin resistance and serum ghrelin level in obese elderly women [Internet]. doi:10.22049/jahssp.2024.29964.1681
51. Filip R, Possemiers S, Heyerick A, Pinheiro I, Raszewski G, Davicco MJ, Coxam V. Twelve-month consumption of a polyphenol extract from olive (*Olea europaea*) in a double blind, randomized trial increases serum total osteocalcin levels and improves serum lipid profiles in postmenopausal women with osteopenia. *J Nutr Health Aging*. 2015 Jan;19(1):77–86. doi:10.1007/s12603-014-0480-x
52. Florentin M, Liberopoulos E, Elisaf MS, Tsimihodimos V. No effect of fenugreek, bergamot and olive leaf extract on glucose homeostasis in patients with prediabetes: a randomized double-blind placebo-controlled study. *Archives of Medical Science – Atherosclerotic Diseases*. 2019 Jul 18;4(1):162–6. doi:10.5114/amsad.2019.86756
53. Domenech M, Casas R, Ruiz-León AM, Sobrino J, Ros E, Estruch R. Effects of a Novel Nutraceutical Combination (Aquilea Cholesterol®) on the Lipid Profile and Inflammatory Biomarkers: A Randomized Control Trial. *Nutrients*. 2019 Apr 26;11(5):949. doi:10.3390/nu11050949
54. Derosa G, D'Angelo A, Maffioli P. *Olea Europaea* Effects on Glyco-Metabolic Parameters and on Glycemic Status in Patients with Impaired Fasting Glucose. *Journal of Food and Nutrition Research*. 2022 Oct 26;10(10):674–80. doi:10.12691/jfnr-10-10-5
55. de Bock M, Derraik JGB, Brennan CM, Biggs JB, Morgan PE, Hodgkinson SC, Hofman PL, Cutfield WS. Olive (*Olea europaea* L.) Leaf Polyphenols Improve Insulin Sensitivity in Middle-Aged Overweight Men: A Randomized, Placebo-Controlled, Crossover Trial. *PLoS One*. 2013 Mar 13;8(3):e57622. doi:10.1371/journal.pone.0057622
56. Araki R, Fujie K, Nakata Y, Suzuki H, Matsui K, Uematsu K, Shibasaki H, Ando T, Ueyama Y, Isoda H, Hashimoto K. An Exploratory Study of the Effects of Continuous Intake of Olive Leaf Tea on Physique and Glucose and Lipid Metabolism. *Nippon Eiyo Shokuryo Gakkaishi*. 2018;71(3):121–31. doi:10.4327/jsnfs.71.121

57. Angelopoulos N, Paparodis RD, Androulakis I, Boniakos A, Argyrakopoulou G, Livadas S. Low Dose Monacolin K Combined with Coenzyme Q10, Grape Seed, and Olive Leaf Extracts Lowers LDL Cholesterol in Patients with Mild Dyslipidemia: A Multicenter, Randomized Controlled Trial. *Nutrients*. 2023 Jun 9;15(12):2682. doi:10.3390/nu15122682
58. Yaghoobzadeh H, Mehravar S, Javadi H, Memarzadeh MR, Mirhashemi SM. Determining Cardiometabolic and Antioxidant Effects of Olive Leaf Extract in Patients with Essential Hypertension. *The Journal of Qazvin University of Medical Sciences*. 2019 Dec 30;372–81. doi:10.32598/JQUMS.23.5.372
59. Herrero-Encinas J, Blanch M, Pastor JJ, Mereu A, Ipharraguerre IR, Menoyo D. Effects of a bioactive olive pomace extract from *Olea europaea* on growth performance, gut function, and intestinal microbiota in broiler chickens. *Poult Sci*. 2020 Jan;99(1):2–10. doi:10.3382/ps/pez467
60. Munekata P, Nieto G, Pateiro M, Lorenzo J. Phenolic Compounds Obtained from *Olea europaea* By-Products and Their Use to Improve the Quality and Shelf Life of Meat and Meat Products—A Review. *Antioxidants*. 2020 Oct 29;9(11):1061. doi:10.3390/antiox9111061
61. Di Leo EG, Stranieri C, Zoccatelli G, Bellumori M, Zonfrillo B, Cominacini L, Fratta Pasini AM. Olive Pomace Extract Acts as a New Potent Ferroptosis Inhibitor in Human Cells. *Molecules*. 2025 Jul 24;30(15):3095. doi:10.3390/molecules30153095
62. Alimenti C, Lianza M, Antognoni F, Giusti L, Bistoni O, Liotta L, Angeloni C, Lupidi G, Beghelli D. Characterization and Biological Activities of In Vitro Digested Olive Pomace Polyphenols Evaluated on Ex Vivo Human Immune Blood Cells. *Molecules*. 2023 Feb 24;28(5):2122. doi:10.3390/molecules28052122
63. Schmidt L, Vargas BK, Monteiro CS, Pappis L, Mello R de O, Machado AK, Emanuelli T, Ayub MAZ, Moreira JCF, Augusti PR. Bioavailable Phenolic Compounds from Olive Pomace Present Anti-Neuroinflammatory Potential on Microglia Cells. *Foods*. 2023 Nov 7;12(22):4048. doi:10.3390/foods12224048
64. Vergani L, Vecchione G, Baldini F, Voci A, Ferrari PF, Aliakbarian B, Casazza AA, Perego P. Antioxidant and hepatoprotective potentials of phenolic compounds from olive pomace. *Chem Eng Trans*. 2016 Apr 1;49:475–80. doi:10.3303/CET1649080
65. Quero J, Ballesteros LF, Ferreira-Santos P, Velderrain-Rodriguez GR, Rocha CMR, Pereira RN, Teixeira JA, Martin-Belloso O, Osada J, Rodríguez-Yoldi MJ. Unveiling the Antioxidant Therapeutic Functionality of Sustainable Olive Pomace Active Ingredients. *Antioxidants*. 2022 Apr 24;11(5):828. doi:10.3390/antiox11050828
66. Antonopoulou S, Detopoulou M, Fragopoulou E, Nomikos T, Mikellidi A, Yannakoulia M, Kyriacou A, Mitsou E, Panagiotakos D, Anastasiou C. Consumption of yogurt enriched with polar lipids from olive oil by-products reduces platelet sensitivity against platelet activating factor and inflammatory indices: A randomized, double-blind clinical trial. *Human Nutrition & Metabolism*. 2022 Jun;28:200145. doi:10.1016/j.hnm.2022.200145
67. Conterno L, Martinelli F, Tamburini M, Fava F, Mancini A, Sordo M, Pindo M, Martens S, Masuero D, Vrhovsek U, Dal Lago C, Ferrario G, Morandini M, Tuohy K. Measuring the impact of olive pomace enriched biscuits on the gut microbiota and its metabolic activity in mildly

- hypercholesterolaemic subjects. *Eur J Nutr.* 2019 Feb 9;58(1):63–81. doi:10.1007/s00394-017-1572-2
68. Dinu M, Pagliai G, Scavone F, Bellumori M, Cecchi L, Nediani C, Maggini N, Sofi F, Giovannelli L, Mulinacci N. Effects of an Olive By-Product Called Pâté on Cardiovascular Risk Factors. *J Am Coll Nutr.* 2021;40(7):617–23. doi:10.1080/07315724.2020.1813060 PubMed PMID: 32976051.
69. González-Rámila S, Sarriá B, Seguido MA, García-Cordero J, Mateos R, Bravo L. Olive pomace oil can improve blood lipid profile: a randomized, blind, crossover, controlled clinical trial in healthy and at-risk volunteers. *Eur J Nutr.* 2023 Sep 24;62:589–603. doi:10.1007/s00394-022-03001-y
70. González-Rámila S, Sarriá B, Seguido MÁ, García-Cordero J, Bravo-Clemente L, Mateos R. Effect of Olive Pomace Oil on Cardiovascular Health and Associated Pathologies. *Nutrients.* 2022 Sep 22;14(19):3927. doi:10.3390/nu14193927
71. Frumuzachi O, Gavrilas LI, Vodnar DC, Rohn S, Mocan A. Systemic Health Effects of Oleuropein and Hydroxytyrosol Supplementation: A Systematic Review of Randomized Controlled Trials. *Antioxidants.* 2024 Aug 27;13(9):1040. doi:10.3390/antiox13091040
72. Razmpoosh E, Abdollahi S, Mousavirad M, Clark CCT, Soltani S. The effects of olive leaf extract on cardiovascular risk factors in the general adult population: a systematic review and meta-analysis of randomized controlled trials. *Diabetol Metab Syndr.* 2022 Oct 21;14(1):151. doi:10.1186/s13098-022-00920-y
73. Álvares AA, Garcêz A, Silva LT, Averbuch N, Garavaglia J. Olive leaf extract effect on cardiometabolic risk factors: a systematic review and meta-analysis of randomized clinical trials. *Nutr Rev.* 2024 Dec 1;82(12):1710–25. doi:10.1093/nutrit/nuad164
74. Ismail MA, Norhayati MN, Mohamad N. Olive leaf extract effect on cardiometabolic profile among adults with prehypertension and hypertension: a systematic review and meta-analysis. *PeerJ.* 2021 Apr 7;9:e11173. doi:10.7717/peerj.11173
75. Lachovicz R, Ferro-Lebres V, Almeida-de-Souza J, Pereira JA. Efficacy of Olive Leaf Extract in Improving Blood Pressure in Pre-Hypertensive and Hypertensive Individuals: A Systematic Review and Meta-Analysis. *Phytotherapy Research.* 2025 Jun 5;39(6):2863–74. doi:10.1002/ptr.8509
76. Fatahian A, Yousefi SS, Azadbakht M, Moosazadeh M, Fakhri M. The effect of olive leaf use on blood pressure; A systematic review and meta-analysis. *J Renal Inj Prev.* 2022 Jun 9. doi:10.34172/jrip.2022.31933
77. EndNote [Internet]. Clarivate Analytics; 2022. Available from: https://support.clarivate.com/Endnote/s/article/Download-EndNote?language=en_US
78. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 2009 Jul 21;6(7):e1000097. doi:10.1371/journal.pmed.1000097
79. Parashar Y, Awwad A, Bagchi S, Claggett B, Siddiqui SA, Ogheneochuko AW, Ballantyne CM, deFilippi C. A Meta-Analysis and Systematic Review of Cardiac Troponin I vs T in Community

- 924 Dwelling Adults: Is Specificity at Risk? *Clin Chem*. 2025 Jun 3;71(6):664–76.
925 doi:10.1093/clinchem/hvaf023
- 926 80. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY,
927 Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR,
928 Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart
929 LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias
930 in randomised trials. *BMJ*. 2019 Aug 28;44898. doi:10.1136/bmj.l4898
- 931 81. RStudio Version 2023.12.1+402 [Internet]. 2024. Available from:
932 <https://dailies.rstudio.com/version/2023.12.1+402/>
- 933 82. Higgins JPT TJJCMLTPMWV (editors). *Cochrane Handbook for Systematic Reviews of*
934 *Interventions* version 6.4 (updated August 2023). Available from
935 www.training.cochrane.org/handbook. Cochrane; 2023.
- 936 83. Sterne JAC, Gavaghan D, Egger M. Publication and related bias in meta-analysis. *J Clin*
937 *Epidemiol*. 2000 Nov;53(11):1119–29. doi:10.1016/S0895-4356(00)00242-0
- 938 84. Thornton A. Publication bias in meta-analysis its causes and consequences. *J Clin Epidemiol*. 2000
939 Feb;53(2):207–16. doi:10.1016/S0895-4356(99)00161-4
- 940 85. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple,
941 graphical test. *Bmj*. 1997;315(7109):629–34.
- 942 86. Schünemann H BJGGOA editors. *GRADE handbook for grading quality of evidence and strength*
943 *of recommendations*. Updated October 2013. <https://guidelinedevelopment.org/handbook>. The
944 GRADE Working Group; 2013.
- 945 87. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P,
946 Debeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1.
947 Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011
948 Apr;64(4):383–94. doi:10.1016/j.jclinepi.2010.04.026 PubMed PMID: 21195583.
- 949 88. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ.
950 GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.
951 *BMJ*. 2008 Apr 26;336(7650):924–6. doi:10.1136/bmj.39489.470347.AD
- 952 89. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A,
953 Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a
954 systematic review and meta-analysis. *The Lancet*. 2016 Mar;387(10022):957–67.
955 doi:10.1016/S0140-6736(15)01225-8
- 956 90. Cook NR. Implications of Small Reductions in Diastolic Blood Pressure for Primary Prevention.
957 *Arch Intern Med*. 1995 Apr 10;155(7):701. doi:10.1001/archinte.1995.00430070053006
- 958 91. Rahimi K, Bidel Z, Nazarzadeh M, Copland E, Canoy D, Ramakrishnan R, Pinho-Gomes AC,
959 Woodward M, Adler A, Agodoa L, Algra A, Asselbergs FW, Beckett NS, Berge E, Black H,
960 Brouwers FPJ, Brown M, Bulpitt CJ, Byington RP, Cushman WC, Cutler J, Devereaux RB, Dwyer
961 J, Estacio R, Fagard R, Fox K, Fukui T, Gupta AK, Holman RR, Imai Y, Ishii M, Julius S, Kanno
962 Y, Kjeldsen SE, Kostis J, Kuramoto K, Lanke J, Lewis E, Lewis JB, Lievre M, Lindholm LH,
963 Lueders S, MacMahon S, Mancia G, Matsuzaki M, Mehlum MH, Nissen S, Ogawa H, Ogihara T,

- Ohkubo T, Palmer CR, Patel A, Pfeffer MA, Pitt B, Poulter NR, Rakugi H, Reboldi G, Reid C, Remuzzi G, Ruggerenti P, Saruta T, Schrader J, Schrier R, Sever P, Sleight P, Staessen JA, Suzuki H, Thijs L, Ueshima K, Umemoto S, van Gilst WH, Verdecchia P, Wachtell K, Whelton P, Wing L, Yui Y, Yusuf S, Zanchetti A, Zhang ZY, Anderson C, Baigent C, Brenner BM, Collins R, de Zeeuw D, Lubsen J, Malacco E, Neal B, Perkovic V, Rodgers A, Rothwell P, Salimi-Khorshidi G, Sundström J, Turnbull F, Viberti G, Wang J, Chalmers J, Teo KK, Pepine CJ, Davis BR. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *The Lancet*. 2021 May;397(10285):1625–36. doi:10.1016/S0140-6736(21)00590-0
92. Cicero AFG, Fogacci F, Banach M. Red Yeast Rice for Hypercholesterolemia. *Methodist Debaque Cardiovasc J*. 2019 Jul 1;15(3):192. doi:10.14797/mdcj-15-3-192
93. Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, Fras Z, Katsiki N, Langlois M, Latkovskis G, Panagiotakos DB, Paragh G, Mikhailidis DP, Mitchenko O, Paulweber B, Pella D, Pitsavos C, Reiner Ž, Ray KK, Rizzo M, Sahebkar A, Serban MC, Sperling LS, Toth PP, Vinereanu D, Vrablík M, Wong ND, Banach M. Lipid lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Archives of Medical Science*. 2017;5:965–1005. doi:10.5114/aoms.2017.69326
94. Trautwein EA, Koppenol WP, de Jong A, Hiemstra H, Vermeer MA, Noakes M, Luscombe-Marsh ND. Plant sterols lower LDL-cholesterol and triglycerides in dyslipidemic individuals with or at risk of developing type 2 diabetes; a randomized, double-blind, placebo-controlled study. *Nutr Diabetes*. 2018 May 25;8(1):30. doi:10.1038/s41387-018-0039-8
95. Ras RT, Geleijnse JM, Trautwein EA. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. *British Journal of Nutrition*. 2014 Jul 28;112(2):214–9. doi:10.1017/S0007114514000750
96. Demonty I, Ras RT, van der Knaap HCM, Duchateau GSMJE, Meijer L, Zock PL, Geleijnse JM, Trautwein EA. Continuous Dose-Response Relationship of the LDL-Cholesterol-Lowering Effect of Phytosterol Intake. *J Nutr*. 2009 Feb;139(2):271–84. doi:10.3945/jn.108.095125
97. Gylling H, Plat J, Turley S, Ginsberg HN, Ellegård L, Jessup W, Jones PJ, Lütjohann D, Maerz W, Masana L, Silbernagel G, Staels B, Borén J, Catapano AL, De Backer G, Deanfield J, Descamps OS, Kovanen PT, Riccardi G, Tokgözoğlu L, Chapman MJ. Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. *Atherosclerosis*. 2014 Feb;232(2):346–60. doi:10.1016/j.atherosclerosis.2013.11.043
98. Galimberti F, Casula M, Olmastroni E. Apolipoprotein B compared with low-density lipoprotein cholesterol in the atherosclerotic cardiovascular diseases risk assessment. *Pharmacol Res*. 2023 Sep;195:106873. doi:10.1016/j.phrs.2023.106873
99. Fonseca L, Paredes S, Ramos H, Oliveira JC, Palma I. Apolipoprotein B and non-high-density lipoprotein cholesterol reveal a high atherogenicity in individuals with type 2 diabetes and controlled low-density lipoprotein-cholesterol. *Lipids Health Dis*. 2020 Dec 6;19(1):127. doi:10.1186/s12944-020-01292-w
100. Pirillo A, Norata GD, Catapano AL. LOX-1, OxLDL, and Atherosclerosis. *Mediators Inflamm*. 2013;2013:1–12. doi:10.1155/2013/152786

101. Mir-Cerdà A, Granados M, Saurina J, Sentellas S. Olive tree leaves as a great source of phenolic compounds: Comprehensive profiling of NaDES extracts. *Food Chem.* 2024 Oct;456:140042. doi:10.1016/j.foodchem.2024.140042
102. Martín MA, Ramos S, Granado-Serrano AB, Rodríguez-Ramiro I, Trujillo M, Bravo L, Goya L. Hydroxytyrosol induces antioxidant/detoxificant enzymes and Nrf2 translocation *via* extracellular regulated kinases and phosphatidylinositol-3-kinase/protein kinase B pathways in HepG2 cells. *Mol Nutr Food Res.* 2010 Jul;54(7):956–66. doi:10.1002/mnfr.200900159
103. Simos Y V, Zerikiotis S, Lekkas P, Zachariou C, Halabalaki M, Ververidis F, Trantas EA, Tsamis K, Peschos D, Angelidis C, Vezyraki P. Hydroxytyrosol produced by engineered *Escherichia coli* strains activates Nrf2/HO-1 pathway: An *in vitro* and *in vivo* study. *Exp Biol Med.* 2023 Sep 10;248(18):1598–612. doi:10.1177/15353702231187647
104. Zhu L, Liu Z, Feng Z, Hao J, Shen W, Li X, Sun L, Sharman E, Wang Y, Wertz K, Weber P, Shi X, Liu J. Hydroxytyrosol protects against oxidative damage by simultaneous activation of mitochondrial biogenesis and phase II detoxifying enzyme systems in retinal pigment epithelial cells. *J Nutr Biochem.* 2010 Nov;21(11):1089–98. doi:10.1016/j.jnutbio.2009.09.006
105. Zorić N, Kopjar N, Rodriguez JV, Tomić S, Kosalec I. Protective effects of olive oil phenolics oleuropein and hydroxytyrosol against hydrogen peroxide-induced DNA damage in human peripheral lymphocytes. *Acta Pharmaceutica.* 2021 Mar 1;71(1):131–41. doi:10.2478/acph-2021-0003
106. Zrelli H, Matsuoka M, Kitazaki S, Araki M, Kusunoki M, Zarrouk M, Miyazaki H. Hydroxytyrosol Induces Proliferation and Cytoprotection against Oxidative Injury in Vascular Endothelial Cells: Role of Nrf2 Activation and HO-1 Induction. *J Agric Food Chem.* 2011 May 11;59(9):4473–82. doi:10.1021/jf104151d
107. Moratilla-Rivera I, Pérez-Jiménez J, Ramos S, Portillo MP, Martín MÁ, Mateos R. Hydroxytyrosol supplementation improves antioxidant and anti-inflammatory status in individuals with overweight and prediabetes: A randomized, double-blind, placebo-controlled parallel trial. *Clinical Nutrition.* 2025 Sep;52:17–26. doi:10.1016/j.clnu.2025.07.006
108. Hernáez Á, Remaley AT, Farràs M, Fernández-Castillejo S, Subirana I, Schröder H, Fernández-Mampel M, Muñoz-Aguayo D, Sampson M, Solà R, Farré M, de la Torre R, López-Sabater MC, Nyssönen K, Zunft HJF, Covas MI, Fitó M. Olive Oil Polyphenols Decrease LDL Concentrations and LDL Atherogenicity in Men in a Randomized Controlled Trial. *J Nutr.* 2015 Aug;145(8):1692–7. doi:10.3945/jn.115.211557
109. Czlapka-Matyasik M, Wadolowska L, Gut P, Gramza-Michałowska A. Changes in Oxidative Stress, Inflammatory Markers, and Lipid Profile After a 6-Week High-Antioxidant-Capacity Dietary Intervention in CVD Patients. *Nutrients.* 2025 Feb 26;17(5):806. doi:10.3390/nu17050806
110. Somma F, Romano B, Maresca DC, Maisto M, Tenore G, Ianaro A, Ercolano G. Olive leaf extract (OLE) reduces mast cell-mediated allergic inflammation. *Biomedicine & Pharmacotherapy.* 2025 Jan;182:117784. doi:10.1016/j.biopha.2024.117784
111. Rubio-Senent F, Bermúdez-Oria A, Fernández-Prior Á, Lama-Muñoz A, Rodríguez-Gutiérrez G, Fernández-Bolaños J. Olive-derived bioactive combinations: synergistic angiotensin-I-converting

- enzyme (*ACE*) inhibition and distinct mechanisms of triterpenic acids and phenolics. *J Sci Food Agric*. 2025 Dec 9. doi:10.1002/jsfa.70372
112. Vijakumaran U, Shanmugam J, Heng JW, Azman SS, Yazid MD, Haizum Abdullah NA, Sulaiman N. Effects of Hydroxytyrosol in Endothelial Functioning: A Comprehensive Review. *Molecules*. 2023 Feb 16;28(4):1861. doi:10.3390/molecules28041861
113. Visioli F, Bellosta S, Galli C. Oleuropein, the bitter principle of olives, enhances nitric oxide production by mouse macrophages. *Life Sci*. 1998 Jan;62(6):541–6. doi:10.1016/S0024-3205(97)01150-8
114. Hadrich F, Garcia M, Maalej A, Moldes M, Isoda H, Feve B, Sayadi S. Oleuropein activated AMPK and induced insulin sensitivity in C2C12 muscle cells. *Life Sci*. 2016 Apr;151:167–73. doi:10.1016/j.lfs.2016.02.027
115. Shen Y, Song SJ, Keum N, Park T. Olive Leaf Extract Attenuates Obesity in High-Fat Diet-Fed Mice by Modulating the Expression of Molecules Involved in Adipogenesis and Thermogenesis. *Evidence-Based Complementary and Alternative Medicine*. 2014 Jan 28;2014(1). doi:10.1155/2014/971890
116. Dermesonlouoglou E, Limnaios A, Bouskou I, Ntzimani A, Tsevdou M, Taoukis P. Design, Production and Quality Assessment of Antioxidant-Enriched Olive Paste Dips Using Agro-Food By-Products. *Molecules*. 2025 Sep 1;30(17). doi:10.3390/molecules30173459 PubMed PMID: 40941987.
117. García A, Ruiz-Méndez MV, Romero C, Brenes M. Effect of refining on the phenolic composition of crude olive oils. *J Am Oil Chem Soc*. 2006 Feb;83(2):159–64. doi:10.1007/s11746-006-1189-8
118. Madureira J, Melgar B, Santos-Buelga C, Margaça FMA, Ferreira ICFR, Barros L, Cabo Verde S. Phenolic Compounds from Irradiated Olive Wastes: Optimization of the Heat-Assisted Extraction Using Response Surface Methodology. *Chemosensors*. 2021 Aug 19;9(8):231. doi:10.3390/chemosensors9080231
119. Rodríguez-Pérez M, García-Béjar B, Burgos-Ramos E, Silva P. Valorization of Olive Oil and Wine Industry Byproducts: Challenges and Opportunities in Sustainable Food Applications. *Foods*. 2025 Jul 15;14(14):2475. doi:10.3390/foods14142475

Table 1. Characteristics of the included studies in the systematic review and meta-analysis evaluating the effects of OL or OP extracts on cardiometabolic and anthropometric health markers

First author, year	Country	N ^a	Study design	Duration (week)	Intervention groups	Sex	Age (year)	Outcomes included in SR and MA	Note about participants
Angelopoulos, 2023 [57]	Greece	Group A: 39 Group B: 31 Group C (control): 27	P	8	Group A: LM + high-dose monacolin ^b K (10 mg/d) Group B: LM + low-dose monacolin K (3 mg/d) Group C: LM only	13m/84f	Group A: 56.89 ± 9 Group B: 55.83 ± 9.25 Group C: 57.42 ± 12.3	BMI (kg/m ²), HDL, LDL, TC, TG (mg/dL)	Healthy, mild hypercholesterolemia; no statins; smoking not reported; controlled alcohol BMI (kg/m ²): 25.39 ± 3.23 (A), 24.76 ± 3.53 (B), 27.1 ± 3.31 (C).
Antonopoulou, 2022 [66]	Greece	Group A: 30 Group B: 28 Group C: 30	P	8	Group A (control): no intervention Group B: 150 g/d of plain yogurt daily Group C: 150 g/d of yogurt enriched with OOPLE daily	45m/43f	Group A: 49.4 ± 8.8 Group B: 48.8 ± 8.9 Group C: 46.8 ± 8.3	BMI (kg/m ²), HDL, LDL, TC, Triacylglycerols, Glucose, CRP (mg/dL), Insulin (μU/mL), SBP and DBP (mmHg), Adiponectin, (μg/mL), IL-6 (pg/mL)	Healthy overweight; no medications; some smokers; alcohol not reported. BMI (kg/m ²) = 27.7 ± 6.4 (A), 28.6 ± 3.8 (B), 27.5 ± 3.9 (C)
Araki, 2018 [56]	Japan	Intervention: 20 Control: 19	P	12	Intervention: 1000 mL/d of OL tea (~424 mg/d oleuropein + ~6.4 mg/d hydroxytyrosol), control: 1000 mL/d of green tea	8m/31f	Intervention: 53.4 ± 7.7, Control: 55.2 ± 7.9	Body weight (kg), WC (cm), HDL, LDL, TG, FPG (mg/dL)	Healthy; no medications; smoking and alcohol not reported. BMI (kg/m ²) = 21.6 ± 3.3 (intervention), 22.5 ± 2.7 (control)
Conterno, 2019 [67]	Italy	Intervention: 34 Control: 28	P	8	Intervention: 90 g/d of OP-enriched bakery product Control: 90 g/d of matched bakery product with negligible polyphenol content	30m/32f	The female group = 48 ± 8.5, the male group = 49 ± 9.6	SBP and DBP (mmHg), WC, HC (cm), weight (kg), BMI (kg/m ²), TC, HDL, LDL, TG, Apo A1, Apo B, FPG (mg/dL), plasma insulin (mU/mL), CRP (mg/L), OxLDL (U/L)	Healthy, elevated cholesterol; no lipid medications; non-smokers; moderate alcohol. BMI (kg/m ²) = 24 ± 3.4 (intervention), 24 ± 3 (control)
de Bock, 2013 [55]	New Zealand	45	C	12	Intervention: OL extract capsules (51.1 mg/d oleuropein + 9.7 mg/d hydroxytyrosol), control: placebo capsules	45m	46.5 ± 5.5	SBP and DBP (mmHg), TC, TG, LDL, HDL (mmol/L), Ox-LDL (mU/mL)	Overweight; stable antihypertensive/lipid medications allowed; non-smokers; alcohol not reported. BMI (kg/m ²) = 28 ± 2
Derosa, 2022 [54]	Italy	Intervention: 74 Control: 74	P	12	Intervention: hypocaloric diet + 70 mL/d of Olife [®] (OL and marigold extract), control: hypocaloric diet.	71m/77f	NI	TC, TG, LDL, HDL, FPG (mg/dL), OxLDL (mg/mL), FPI (μU/mL), HOMA index, weight (kg), BMI (kg/m ²), WC (cm), HC (cm), Hs-CRP (mg/L)	Impaired fasting glucose; no medications; smoking and alcohol not reported. BMI (kg/m ²) = 27.3 ± 1.5 (intervention), 27.2 ± 1.4 (control)
Dinu, 2020 [68]	Italy	19	C	8	Intervention: Pate (OP paste) tablets (3.2 g/d), control: placebo	6m/13f	38.1 ± 6.4	TC, TG, LDL, HDL, Glucose (mg/dL), Insulin (mU/L), HOMA1r, TNF-α, IL-6, IL-8 (pg/mL)	Healthy; no medications; smoking and alcohol not reported. BMI (kg/m ²) = 24.1 ± 2.4
Domenech, 2019 [53]	Spain	Intervention: 20 Control: 20	P	12	Intervention: 1 stick/d of Nutraceutical (phytosterols, monacolin K, 5 mg/d of OL extract, and vitamin E), control: placebo	13m/27f	Intervention: 59.3 ± 9.5, control: 63.5 ± 12.3	TC, TG, LDL, HDL, Glucose (mmol/L), Apo A1, Apo B, hs-CRP (mg/dL), IL-6 (pg/mL)	Primary hypercholesterolemia; drug-free; smoking and alcohol not reported. BMI (kg/m ²) = 26.9 ± 3.8

									(intervention), 27.3 ± 4.4 (control)
Filip, 2015 [51]	Poland	after 6 months by end of study: t:27, c:21	P	48	Intervention: 250 mg/d of OL extract plus 1 g/d of calcium, control: placebo plus 1 g calcium	48f	Intervention: 59.72 ± 4.39, control: 59.35 ± 5.55	TC, TG, LDL, HDL (mg/dL), hs-CRP (mg/L), IL-6 (pg/mL)	Healthy postmenopausal women (osteopenia); no medications; smoking and alcohol not reported. BMI (kg/m ²) = t:25.90 ± 4.25 (9ntervention), 27.52 ± 4 (control)
Florentin, 2019 [52]	Greece	Intervention: 50 Control: 50	P	24	Intervention: active agent containing fenugreek, OL polyphenols and bergamot extract, control: Placebo	49m/51f	57 ± 7	TC, TG, LDL, HDL, FPG (mg/dl), FPI (μU/ml), HOMA IR index	Prediabetes; some medications; some smokers; alcohol not reported. BMI (kg/m ²) = 29 ± 3 (intervention), 30.4 ± 5.8 (control)
Ghiyami, 2024 [50]	Iran	Intervention: 10 Control: 10 °	P	8	Intervention: OL extract capsules (125 mg/d), control: placebo capsules	20f	Intervention: 64.4 ± 3.43, control: 64.7 ± 3.46	FPG (mg/dl), Insulin (μUI/mL)	Obese elderly women; no medications; non-smokers; no alcohol. BMI (kg/m ²) = 31.69 ± 1.1 (intervention), 32.65 ± 1.21 (control)
González-Rámila, 2022 [70]	Spain	Normocholesterolemic participants: 31 Hypercholesterolemic participants: 37	C	4	Intervention: 45 g/d of OP oil, control: 45 g/d of high-oleic acid sunflower oil	27m/41f	Normocholesterolemic participants: 30 ± 2 Hypercholesterolemic participants: 41 ± 2	TC, TG, LDL, HDL, Apo A1, Apo B, Glucose, CRP (mg/dL), Insulin (μUI/mL), HOMAIR, Weight (kg), BMI (kg/m ²), WC (cm), HC (cm), IL-6, IL-8, TNF-α (pg/mL), Adiponectin(ng/mL)	Healthy / hypercholesterolemia risk; medications, smoking, and alcohol not reported. BMI (kg/m ²) = 23 ± 2 (Normocholesterolemic), 26 ± 1 (Hypercholesterolemic)
González-Rámila, 2023 [69]	Spain	Normocholesterolemic participants: 34 Hypercholesterolemic participants: 30	C	4	Intervention: 45 g/d of OP oil, control: 45 g/d of high-oleic acid sunflower oil	30m/34f	Normocholesterolemic participants: 35 ± 7 Hypercholesterolemic participants: 44 ± 5.2	SBP and DBP (mmHg), TC, TG, LDL, HDL, Apo A1, Apo B, CRP (mg/dL), IL-6, IL-8, TNF-α (pg/mL)	Healthy / hypercholesterolemia risk; medications, smoking, and alcohol not reported. BMI (kg/m ²) = 24 ± 1.7 (Normocholesterolemic and Hypercholesterolemic),
Haidari, 2021 [49]	Iran	Intervention: 35 Control: 35	P	8	Intervention: hypocaloric diet + 250 mg/d of OL extract, control: hypocaloric diet + Placebo	70f	Intervention: 35.7 ± 9.1, Control: 34.9 ± 10.6	TC, TG, LDL, HDL, FBS (mg/dL), Insulin (μUI/mL), HOMAIR, Weight (kg), BMI (kg/m ²), WC (cm), Adiponectin(ng/mL)	Obese premenopausal women; no medications; smoking and alcohol not reported. BMI (kg/m ²) = 34.97 ± 3.4 (intervention), 34.7 ± 3.1 (control)
Imperatrice, 2024 [48]	The Netherlands	Intervention: 29 Control: 31	P	12	Intervention: OL extract capsule (~100 mg oleuropein/d), control: placebo capsule	60f	Intervention: 58.4 ± 6.2, Control: 59.8 ± 5.4	TC, TG, LDL, HDL (mmol/L)	Healthy postmenopausal women; no medications; non-smokers; no alcohol abuse. BMI (kg/m ²) = 24.9 ± 2.1 (intervention), 25.9 ± 3.4 (control)
Javadi, 2019 [47]	Iran	Intervention: 30 Control: 30	P	12	Intervention: OL extract tablets (500 mg/d), control: placebo tablets	27m/33f	Intervention: 53.8 ± 8, Control: 55.6 ± 8.8	FBS (mg/dL), Insulin (μUI/mL), HOMA IR, IL-6, IL-8, TNF-α (ng/mL)	Hypertension; stable medications; smoking and alcohol not reported. BMI (kg/m ²) = 28.3 ± 4.3 (intervention), 27.5 ± 4.5 (control)

Leach, 2025 [46]	Australia	Intervention: 16 Control: 15	P	24	Intervention: OL extract capsules (1466.68 mg/d), control: placebo capsules	22m/8f/1 other	Intervention: 63.4 ± 10.3, Control: 63.2 ± 7	HOMAIR	Type 2 diabetes; oral medications; mostly non-smokers; mixed alcohol intake. BMI (kg/m ²) = 27.2 ± 7.2 (intervention), 27.7 ± 3.8 (control)
Lockyer, 2017 [45]	New Zealand	60	C	6	Intervention: liquid OL extract (136.2 mg/d of oleuropein and 6.4 mg/d of Hydroxytyrosol), control: placebo	60m	45.3 ± 12.7	SBP and DBP (mmHg), TC, TAG, HDL, LDL, Glucose (mmol/L), oxLDL (U/L), Insulin (mU/L), HOMAIR, IL-6, IL-8, TNF-α (pg/mL), Adiponectin, CRP (μg/mL)	Pre-hypertensive; no medications; non-smokers; moderate alcohol. BMI (kg/m ²) = 27.0 ± 3.4
Perrinjaquet-Moccetti, 2008 [44]	Switzerland	Intervention: 10 Control: 10 ^d	P	8	Intervention: 500 mg/d of OL extract, control: advice on a favorable lifestyle	6m/14f	Intervention: 35.7 ± 14.8, Control: 38.1 ± 14.7	SBP and DBP (mmHg), TC, HDL, LDL (mmol/L)	Borderline hypertension; no medications; smoking and alcohol not reported. BMI (kg/m ²) = 23 ± 4 (intervention), 23 ± 3 (control)
Pinckaers, 2025 [43]	The Netherlands	Intervention: 20 Control: 20	P	5 + 1 day (36 days)	Intervention: 250 mg/d of OL extract, control: placebo	40m	Intervention: 60 ± 6, Control: 60 ± 4	SBP and DBP (mmHg), TC, TAG, HDL, LDL, Glucose (mmol/L), Insulin (pmol/L)	Healthy; no medications; smoking and alcohol not reported. BMI (kg/m ²) = 24.7 ± 2.3 (intervention), 26 ± 2.4 (control)
Saberi, 2008 [42]	Iran	Intervention: 32 Control: 32	P	NI	Intervention: 1000 mg/d of OL powder, control: placebo	31m/33f	Intervention: 52.25 ± 15.3, Control: 53.54 ± 17.9	SBP and DBP (mmHg)	Resistant hypertension; antihypertensive medications; smoking and alcohol not reported. BMI (kg/m ²) = Normal range
Saibandith, 2016 [41]	United Kingdom	Intervention: 16 Control: 15 ^e	P	12	Intervention: olea europea leaf extract (132 mg/d of oleuropein), control: placebo	14m/17f	Intervention: 46.4 ± 14.6, Control: 49.6 ± 13.4	SBP and DBP (mmHg), TC, TG, HDL, LDL, FPG (mmol/L), insulin (mU/L), HOMAIR, BMI (kg/m ²), WC (cm)	Overweight, pre-hypertensive; no medications; non-smokers; no alcohol misuse. BMI (kg/m ²) = 26.1 ± 8.2 (intervention), 28.8 ± 5.2 (control).
Said, 2010 [40]	Israel	Intervention: 16 Control: 13	P	12	Intervention: capsule made of OL (150 mg/d), Alchemilla vulgaris, Mentha longifolia L extract and Cuminum cyminum seeds, control: placebo	14m/15f	Intervention: 33.44 ± 7.43, Control: 37.5 ± 9.9	BMI (kg/m ²), weight (kg)	Overweight/obese; stable medications; non-smokers; no alcohol misuse. BMI (kg/m ²) = 31.03 ± 2 (intervention), 31.7 ± 2.8 (control).
Sánchez Macarro, 2020 [38]	Spain	Intervention: 51 Control: 45	P	8	Intervention: 1000 mg/d of Citroven (OL, immature grapefruit, and bitter orange extract), control: Placebo.	53m/43f	Intervention: 47.3 ± 11.2, Control: 51.3 ± 10.8	SBP and DBP (mmHg), TC, TG, HDL, LDL (mg/dL), CRP (mg/L), IL-6, TNF-α, oxLDL (pg/mL), BMI (kg/m ²), weight (kg)	Healthy; no medications; non-smokers; no alcohol abuse. BMI (kg/m ²) = 27.2 ± 4.2 (intervention), 26.5 ± 3.9 (control)
Sirvent, 2022 [37]	France	Intervention: 38 Control: 13	P	24	Intervention: ~ 5 g/d of TOTUM-63 (blend of OL, Chrysanthellum, artichoke, bilberry, black pepper extract). control: Placebo.	16m/35f	Intervention: 57.4 ± 9.3, Control: 56.2 ± 12.9	SBP and DBP (mmHg), TC, TG, HDL, LDL, FPG (mmol/L), FPI (mU/L), HOMAIR, BMI (kg/m ²), weight (kg), WC, HC (cm)	Prediabetes/mild T2D; medications NR; some smokers; limited alcohol. BMI (kg/m ²) = 30.6 ± 5 (intervention), 33.3 ± 6.1 (control)
Stevens, 2021 [36]	The Netherlands	Intervention: 39	P	8	Intervention: 500 mg/d of OL extract with	35m/42f	Intervention: 56 ± 11,	SBP and DBP (mmHg), TC, TG, HDL, LDL,	Healthy, elevated cholesterol; no medications; non-smokers;

		Control: 38			maltodextrin, control: Placebo		Control: 57 ± 9	Glucose (mmol/L), OxLDL (U/L), insulin (pmol/L), BMI (kg/m ²), weight (kg)	no alcohol abuse. BMI (kg/m ²) = 28.5 ± 2.6 (intervention), 29.6 ± 2.8 (control)
Victoria-Montesinos, 2021 [39]	Spain	Intervention: 14 Control: 9	P	12	Intervention: 1000 mg/d of Citrolive (OL and Bitter orange extract), control: placebo	16m/7f	Intervention: 42.7 ± 9.7, Control: 40.6 ± 9.4	TC, TG, HDL, LDL, Apo A1, Apo B (mg/dL), oxLDL (U/L), BMI (kg/m ²), weight (kg)	Overweight, mild hypercholesterolemia; medications and smoking not reported; no alcohol abuse. BMI (kg/m ²) = 26.4 ± 4.5 (intervention), 28.9 ± 4.6 (control)
Wainstein, 2012 [34]	Israel	Intervention: 41 Control: 38	P	14	Intervention: 500 mg/d of OL extract, control: placebo	51m/28f	61 ± 8	FPI (IU)	Stable T2D; oral medications; smoking not reported; no alcohol abuse. BMI (kg/m ²): mixed (<25 and >25).
Wong, 2014 [35]	Australia	37	C	12	Intervention: active tablets (1000 mg/d of OL, 200 mg/d of green coffee bean extract, and 300 mg/d of beetroot powder), control: placebo	20m/17f	58.5 ± 10.7	SBP and DBP (mmHg), TC, TG, HDL, LDL, Glucose, insulin (mmol/L), HOMA IR, BMI (kg/m ²)	Elevated blood pressure; no antihypertensive medications; non-smokers; alcohol not reported. BMI (kg/m ²) = 27.2 ± 3.7
Yaghoobzadeh, 2019 [58]	Iran	Intervention: 30 Control: 30	P	12	Intervention: 500 mg/d of OL extract, control: placebo	30m/30f	Intervention: 52.9 ± 10.3, Control: 57.9 ± 10.8	SBP and DBP (mmHg), TC, TG, HDL, LDL (mg/dL)	Essential hypertension; other details not reported

1084 Abbreviations: SR and MA; systematic review and meta-analysis, OL; olive leaf, OP; olive pomace, LM; lifestyle
 1085 modification, LDL; low-density lipoprotein, HDL; high-density lipoprotein, TC; total cholesterol, TG; triglycerides,
 1086 BMI; body mass index, OOPLE; polar lipid extract of olive pomace, SBP; systolic blood pressure, DBP; diastolic
 1087 blood pressure, CRP; C-reactive protein, IL-6; interleukin-6, FPG; fasting plasma glucose, WC; waist
 1088 circumference, HC; hip circumference, oxLDL; oxidized low-density lipoprotein, Apo A1; apolipoprotein A1, Apo
 1089 B; apolipoprotein B, FPI; fasting plasma insulin, HOMA-IR; homeostatic model assessment of insulin resistance,
 1090 IL-8; interleukin-8, TNF- α ; tumor necrosis factor-alpha, FBS; fasting blood sugar, TAG; triacylglycerols.

1091 ^a Number of participants who finished the study and analyses.

1092 ^b A dietary supplement containing red yeast rice-derived monacolin K combined with coenzyme Q10, grape seed
 1093 extract, and OL extract.

1094 ^c This study has 4 parallel experimental groups (Placebo, intervention, exercise, and exercise plus intervention) but
 1095 we only consider two of them (placebo and intervention).

1096 ^d This study has two experiments (experiment 1: control and 500 mg of EFLA and experiment 2: 500 mg of EFLA
 1097 and 1000 mg of EFLA), we only considered experiment 1.

1098 ^e This study has 4 parallel experimental groups (Placebo, intervention, increased physical activity (PA), and PA plus
 1099 intervention) but we only consider two of them (placebo and intervention).

1100

1101

1102

1103

1104

1105

1106

Table 2. Summary of risk of bias assessments for each RCT included in the meta-analysis evaluating the effects of OL or OP extracts on 21 cardiometabolic and anthropometric health markers (RoB 2.0 domains).

Study references	Randomization process	Period and carryover effects (crossover design)	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Quality Score	Reasons for concern
Angelopoulos et al, 2023 [57]	Low	-	Some concerns	Low	Some concerns	Some concerns	Some concerns	Open-label design with potential deviations from intended interventions, outcome assessor blinding not reported, multiple eligible outcomes and analyses with no pre-specified analysis plan.
Antonopoulou et al, 2022 [66]	Some concerns	-	Low	Low	Low	Some concerns	Some concerns	Allocation concealment and potential selective reporting raise concerns, but the trial is otherwise well-conducted, double-blind, with minimal missing data and objective outcome measures.
Araki et al, 2018 [56]	Some concerns	-	Low	Low	Low	Some concerns	Some concerns	Randomization concealment not reported, some multiple outcomes/time points without pre-specified analysis plan.
Conterno et al, 2019 [67]	Low	-	Low	Low	Low	Some concerns	Some concerns	Lack of a publicly available pre-specified statistical analysis plan and multiple reported outcomes, creating potential for selective reporting.
de Bock et al, 2013 [55]	Low	Low	Low	Low	Low	Some concerns	Some concerns	Due to potential selective reporting in the context of multiple outcomes and analyses.
Derosa et al, 2022 [54]	Some concerns	-	Some concerns	Low	Low	Some concerns	Some concerns	Due to open-label design and unclear allocation concealment.
Dinu et al, 2020 [68]	Low	Low	Low	Low	Low	Low	Low	No concerns
Domenech et al, 2019 [53]	Low	-	Low	Low	Low	Low	Low	No concerns
Filip et al, 2015 [51]	Low	-	Low	Some concerns	Low	Low	Some concerns	Missing data may not have been fully addressed, potentially biasing the results.
Florentin et al, 2019 [52]	Low	-	Low	Some concerns	Low	Some concerns	Some concerns	Missing outcome data are unclear.
Ghiyami et al, 2024 [50]	Low	-	Low	Low	Low	Low	Low	No concerns

González-Rámila et al, 2022 [70]	Low	Low	Low	Low	Low	Low	Low	No concerns
González-Rámila et al, 2023 [69]	Low	Low	Low	Low	Low	Low	Low	No concerns
Haidari et al, 2021 [49]	Low	-	Low	Low	Low	Low	Low	No concerns
Imperatrice et al, 2024 [48]	Low	-	Low	Low	Low	Low	Low	No concerns
Javadi et al, 2019 [47]	Low	-	Low	Low	Low	Some concerns	Some concerns	Multiple outcomes measured without a fully pre-specified analysis plan, which could allow selective reporting.
Leach et al, 2025 [46]	Low	-	Low	Low	Low	Low	Low	No concerns
Lockyer et al, 2017 [45]	Low	Low	Low	Low	Low	Low	Low	No concerns
Perrinjaquet-Moccetti et al, 2008 [44]	Some concerns	-	High	Low	Some concerns	Some concerns	High	Open-label design with no blinding, no placebo control, unclear allocation concealment, and no pre-registered protocol.
Pinckaers et al, 2025 [43]	Low	-	Low	Low	Low	Low	Low	No concerns
Saberi et al, 2008 [42]	Low	-	Low	Low	Low	Low	Low	No concerns
Saibandith et al, 2016 [41]	Low	-	Low	Low	Low	Low	Low	No concerns
Said et al, 2010 [40]	Low	-	Some concerns	Some concerns	Low	Some concerns	Some concerns	Limited reporting on allocation concealment and analysis of only completers
Sánchez Macarro et al, 2020 [38]	Low	-	Low	Low	Low	Low	Low	No concerns
Sirvent et al, 2022 [37]	Low	-	Low	Low	Low	Low	Low	No concerns
Stevens et al, 2021 [36]	Low	-	Low	Low	Low	Low	Low	No concerns
Victoria-Montesinos et al, 2021 [39]	Low		Some concerns	Some concerns	Low	Low	Some concerns	per-protocol analysis, which may introduce bias from excluding non-completers, along with some concerns related to incomplete outcome data.
Wainstein et al, 2012 [34]	Low	-	Low	Low	Low	Low	Low	No concerns
Wong et al, 2014 [35]	Low	Low	Low	Low	Low	Low	Low	No concerns
Yaghoobzadeh et al, 2019 [58]	Some concerns	-	Some concerns	Low	Low	Some concerns	Some concerns	Insufficient information regarding allocation concealment and analysis approach.

1110

1111

1112

1113

Table 3. Results of the pooled meta-analysis of RCTs the effects of OL or OP extracts on Inflammatory markers.

Marker	Intervention	Number of RCTs	Number of participants		Effect estimate (MD) [95% CI], P	I ² [95% CI], P
			Intervention	Control		
IL-6	Olive leaves	5	188	176	-0.2 [-0.7; 0.3], 0.425	84.7% [65.9%; 93.1%], < 0.0001
	Olive Pomace	4	181	209	-0.04 [-0.17; 0.1], 0.59	0.0% [0.0%; 64.8%], 0.7
IL-8	Olive leaves	2	90	90	-3.43 [-10.54; 3.67], 0.34	72.4% [0.0%; 93.8%], 0.057
	Olive Pomace	3	151	151	1.7 [0.24; 3.16], 0.02	0.0% [0.0%; 79.2%], 0.85
TNF- α	Olive leaves	3	141	135	-0.43 [-0.68; -0.18], 0.0006	70.2% [0.0%; 91.3%], 0.035
	Olive Pomace	3	151	151	0.53 [-0.9; 1.96], 0.47	0.0% [0.0%; 79.2%], 0.9
CRP	Olive leaves	5	232	220	-0.01 [-0.04; 0.02], 0.59	66.9% [21%; 86.1%], 0.01
	Olive Pomace	4	196	218	0.0 [-0.03; 0.04], 0.83	0.0% [0.0%; 64.8%], 0.9
Adiponectin	Olive leaves	2	95	95	0.07 [-0.18; 0.32], 0.57	45.7%. 0.17
	Olive Pomace	2	98	126	0.01 [-0.02; 0.04], 0.46	10.9% [0.0%; 77.4%], 0.3

Abbreviations: OL; olive leaf, OP; olive pomace, MD; mean difference, CI; confidence interval, CRP; C-reactive protein, IL-6; interleukin-6, IL-8; interleukin-8, TNF- α ; tumor necrosis factor-alpha.

Table 4. Results of the pooled meta-analysis of RCTs the effects of OL or OP extracts on Lipid profile markers.

Marker	Intervention	Number of RCTs	Number of participants		Effect estimate (MD or SMD) ^a [95% CI], P	I ² [95% CI], P
			Intervention	Control		
TC	Olive leaves	18	665	605	-9.72 [-13.73; -5.72], < 0.0001	62.5% [42.8%; 75.5%], < 0.0001
	Olive Pomace	5	215	237	-2.63 [-7.61; 2.36], 0.3	0.0% [0.0%; 62.4%], 0.98
TG	Olive leaves	18	675	589	-5.97 [-9.11; -2.83], 0.0002	0.0% [0.0%; 43.9%], 0.8
	Olive Pomace	5	215	237	-1.76 [-9.57; 6.04], 0.66	0.0% [0.0%; 62.4%], 0.9
HDL	Olive leaves	19	680	599	0.25 [-0.69; 1.19], 0.6	20.9% [0.0%; 50.9%], 0.16
	Olive Pomace	5	215	237	1.02 [-1.1; 3.13], 0.34	0.0% [0.0%; 62.4%], 0.99
LDL	Olive leaves	19	680	599	-8.44 [-12.92; -3.96], 0.0002	67.1% [50.9%; 78%], < 0.0001
	Olive Pomace	5	215	237	-3.26 [-7.79; 1.27], 0.16	0.0% [0.0%; 62.4%], 0.9
ApoA1	Olive leaves	2	34	29	5.98 [0.9; 11.06], 0.02	0.0% [0.0%; 89.6%], 0.8
	Olive Pomace	3	166	160	0.56 [-3.11; 4.23], 0.76	37% [0.0%; 76.5%], 0.17
ApoB	Olive leaves	2	34	29	-11.43 [-14.81; -8.05], < 0.0001	33.4% [0.0%; 78.0%], 0.2
	Olive Pomace	3	166	160	-1.83 [-4.12; 0.46], 0.11	0.0% [0.0%; 79.2%], 0.67
oxLDL	Olive leaves	6	283	271	-0.34 [-0.57; -0.11], 0.0034	60.7% [14.6%; 81.9%], 0.01
	Olive Pomace	2	102	96	-0.11 [-0.39; 0.17], 0.43	0.0% [0.0%; 89.6%], 0.65

Abbreviations: OL; olive leaf, OP; olive pomace, MD; mean difference, SMD; standardized mean difference, CI; confidence interval, LDL; low-density lipoprotein, HDL; high-density lipoprotein, TC; total cholesterol, TG; triglycerides, oxLDL; oxidized low-density lipoprotein, Apo A1; apolipoprotein A1, Apo B; apolipoprotein B.

^a The effect estimate for oxLDL was expressed as standardized mean difference (SMD), whereas for the other markers it was expressed as mean difference (MD).

Table 5. Results of the pooled meta-analysis of RCTs the effects of OL or OP extracts on glycemic control / insulin sensitivity markers.

Marker	Intervention	Number of RCTs	Number of participants		Effect estimate (MD) [95% CI], P	I ² [95% CI], P
			Intervention	Control		
FPG	Olive leaves	13	449	421	-1.08 [-2.23; 0.07], 0.06	23% [0.0%; 57.7%], 0.2
	Olive Pomace	4	151	173	-0.33 [-2.19; 1.53], 0.7	17.9% [0.0%; 60.8%], 0.3
FPI	Olive leaves	12	450	420	-0.51 [-1.23; 0.21], 0.16	44.4% [0.0%; 69.7%], 0.03
	Olive Pomace	4	151	173	-0.22 [-1.12; 0.69], 0.6	0.0% [0.0%; 67.6%], 0.8
HOMA-IR	Olive leaves	9	356	329	0.01 [-0.07; 0.09], 0.74	0.0% [0.0%; 58.3%], 0.7
	Olive Pomace	2	87	87	-0.01 [-0.37; 0.35], 0.9	37.9% [0.0%; 80.5%], 0.2

Abbreviations: OL; olive leaf, OP; olive pomace, MD; mean difference, CI; confidence interval, FPG; fasting plasma glucose, FPI; fasting plasma insulin, HOMA-IR; homeostatic model assessment of insulin resistance.

Table 6. Results of the pooled meta-analysis of RCTs the effects of OL or OP extracts on clinical / anthropometric parameters.

Marker	Intervention	Number of RCTs	Number of participants		Effect estimate (MD) [95% CI], P	I ² [95% CI], P
			Intervention	Control		
SBP	Olive leaves	11	408	375	-3.72 [-5.94; -1.51], 0.001	57.4% [24.3%; 76%], 0.003
	Olive Pomace	4	196	218	1.79 [-0.7; 4.28], 0.16	0.0% [0.0%; 64.8%], 0.99
DBP	Olive leaves	11	408	375	-1.52 [-2.64; -0.4], 0.008	12.0% [0.0%; 49.9%], 0.32
	Olive Pomace	4	196	218	0.25 [-1.38; 1.88], 0.76	0.0% [0.0%; 64.8%], 0.56
BMI	Olive leaves	11	450	353	-0.26 [-0.5; -0.02], 0.035	54.4% [21.0%; 73.6%], 0.004
	Olive Pomace	3	132	154	-0.03 [-0.63; 0.56], 0.9	0.0% [0.0%; 70.8%], 0.99
Weight	Olive leaves	9	347	306	-0.71 [-1.21; -0.21], 0.0055	54.0% [13.9%; 75.4%], 0.01
	Olive Pomace	2	102	96	0.29 [-2.51; 3.1], 0.8	0.0% [0.0%; 89.6%], 0.9
WC	Olive leaves	5	183	156	-0.5 [-2.29; 1.29], 0.6	75.3% [47.7%; 88.3%], 0.005
	Olive Pomace	2	102	96	-0.01 [-2.62; 2.59], 0.99	0.0% [0.0%; 89.6%], 0.8
HC	Olive leaves	2	112	87	-0.2 [-1.08; 0.67], 0.6	0.0% [0.0%; 89.6%], 0.86
	Olive Pomace	2	102	96	0.22 [-1.42; 1.86], 0.8	0.0% [0.0%; 89.6%], 0.9

Abbreviations: OL; olive leaf, OP; olive pomace, MD; mean difference, CI; confidence interval, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, WC; waist circumference, HC; hip circumference.

Table 7. GRADE profile of RCTs evaluating the effects of OL or OP extracts on 21 cardiometabolic and anthropometric health markers.

Biomarkers	Outcome	Intervention	Number of studies	Sample size (intervention/control) ^a	Effect size (95% CI) ^b	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence ^c
Inflammatory markers	IL-6	Olive leaves	5	304 (188/176)	-0.2 (-0.7; 0.3)	No serious limitations	Serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{def} Low
		Olive Pomace	4	239 (181/209)	-0.04 (-0.17; 0.1)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
	IL-8	Olive leaves	2	120 (90/90)	-3.43 (-10.54; 3.67)	No serious limitations	Very serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{def} Very Low
		Olive Pomace	3	151 (151/151)	1.7 (0.24; 3.16)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
	TNF-α	Olive leaves	3	216 (141/135)	-0.43 (-0.68; -0.18)	No serious limitations	Serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{def} Low
		Olive Pomace	3	151 (151/151)	0.53 (-0.9; 1.96)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
	CRP	Olive leaves	5	392 (232/220)	-0.01 (-0.04; 0.02)	No serious limitations	Serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{def} Low
		Olive Pomace	4	282 (196/218)	0.0 (-0.03; 0.04)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	Very serious limitations	⊕⊕⊕⊕ ^{efg} Very Low
	Adiponectin	Olive leaves	2	130 (95/95)	0.07 (-0.18; 0.32)	No serious limitations	Serious limitations	No serious limitations	Very serious limitations	No serious limitations	⊕⊕⊕⊕ ^{def} Very Low
		Olive Pomace	2	156 (98/126)	0.01 (-0.02; 0.04)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
Lipid profile markers	TC	Olive leaves	18	1103 (665/605)	-9.72 (-13.73; -5.72)	No serious limitations	Serious limitations	No serious limitations	No serious limitations	No serious limitations	⊕⊕⊕⊕ ^d Moderate
		Olive Pomace	5	301 (215/237)	-2.63 (-7.61; 2.36)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
	TG	Olive leaves	18	1122 (675/589)	-5.97 (-9.11; -2.83)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	⊕⊕⊕⊕ ^d High
		Olive Pomace	5	301 (215/237)	-1.76 (-9.57; 6.04)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
	HDL	Olive leaves	19	1142 (680/599)	0.25 (-0.69; 1.19)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	⊕⊕⊕⊕ ^d High
		Olive Pomace	5	301 (215/237)	1.02 (-1.1; 3.13)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
	LDL-C	Olive leaves	19	1142 (680/599)	-8.44 (-12.92; -3.96)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	⊕⊕⊕⊕ ^d High
		Olive Pomace	5	301 (215/237)	-3.26 (-7.79; 1.27)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
	Ox-LDL	Olive leaves	6	449 (283/271)	-0.34 (-0.57; -0.11)	No serious limitations	Serious limitations	No serious limitations	No serious limitations	No serious limitations	⊕⊕⊕⊕ ^d Moderate

		Olive Pomace	2	130 (102/96)	-0.11 (-0.39; 0.17)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	ApoA1	Olive leaves	2	63 (34/29)	5.98 (0.9; 11.06)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations	Serious limitations	 ^{efg} Very Low
		Olive Pomace	3	194 (166/160)	0.56 (-3.11; 4.23)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	ApoB	Olive leaves	2	63 (34/29)	-11.43 (-14.81; -8.05)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations	Serious limitations	 ^{efg} Very Low
		Olive Pomace	3	194 (166/160)	-1.83 (-4.12; 0.46)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	Serious limitations	 ^{ef} Low
Glycemic control / insulin sensitivity markers	FPG	Olive leaves	13	773 (449/421)	-1.08 (-2.23; 0.07)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
		Olive Pomace	4	237 (151/173)	-0.33 (-2.19; 1.53)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	FPI	Olive leaves	12	773 (450/420)	-0.51 (-1.23; 0.21)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
		Olive Pomace	4	237 (151/173)	-0.22 (-1.12; 0.69)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	HOMA-IR	Olive leaves	9	588 (356/329)	0.01 (-0.07; 0.09)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
		Olive Pomace	2	87 (87/87)	-0.01 (-0.37; 0.35)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations	No serious limitations	 ^{ef} Low
Clinical / anthropometric parameters	SBP	Olive leaves	11	581 (408/375)	-3.72 (-5.94; -1.51)	Serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	 ^h Moderate
		Olive Pomace	4	282 (196/218)	1.79 (-0.7; 4.28)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	DBP	Olive leaves	11	581 (408/375)	-1.52 (-2.64; -0.4)	Serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	 ^h Moderate
		Olive Pomace	4	282 (196/218)	0.25 (-1.38; 1.88)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	BMI	Olive leaves	11	721 (450/353)	-0.26 (-0.5; -0.02)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	 ^h High
		Olive Pomace	3	218 (132/154)	-0.03 (-0.63; 0.56)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	Weight	Olive leaves	9	593 (347/306)	-0.71 (-1.21; -0.21)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Very serious limitations	 ^g Low
		Olive Pomace	2	130 (102/96)	0.29 (-2.51; 3.1)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	WC	Olive leaves	5	339 (183/156)	-0.5 (-2.29; 1.29)	No serious limitations	Serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{def} Low
		Olive Pomace	2	130 (102/96)	-0.01 (-2.62; 2.59)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate
	HC	Olive leaves	2	199 (112/87)	-0.2 (-1.08; 0.67)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	 ^{ef} Moderate

		Olive Pomace	2	130 (102/96)	0.22 (-1.42; 1.86)	No serious limitations	No serious limitations	No serious limitations	Serious limitations	No serious limitations	⊕⊕⊕⊕ ^{ef} Moderate
--	--	--------------	---	--------------	--------------------	------------------------	------------------------	------------------------	---------------------	------------------------	--------------------------------

Abbreviations: GRADE; Grading of Recommendations Assessment, Development, and Evaluation, OL; Olive Leaf, OP; Olive Pomace, CI; Confidence Interval, IL-6; Interleukin-6, IL-8; Interleukin-8, TNF- α ; Tumor Necrosis Factor- α , CRP; C-Reactive Protein, TC; Total Cholesterol, TG; Triglycerides, HDL; High-Density Lipoprotein Cholesterol, LDL; Low-Density Lipoprotein Cholesterol, ox-LDL; Oxidized Low-Density Lipoprotein, Apo A1; Apolipoprotein A1, Apo B; Apolipoprotein B, FPG; Fasting Plasma Glucose, FPI; Fasting Plasma Insulin, HOMA-IR; Homeostatic Model Assessment of Insulin Resistance, SBP; Systolic Blood Pressure, DBP; Diastolic Blood Pressure, BMI; Body Mass Index, WC; Waist Circumference, HC; Hip Circumference.

^a Numbers in parentheses represent participants contributing data to each arm; crossover trial participants contributed to both intervention and control groups.

^b The effect estimate for ox-LDL was expressed as standardized mean difference (SMD), whereas for the other markers it was expressed as mean difference (MD).

^c ⊕⊕⊕⊕ (high quality): there is a strong belief that the true effect lies close to estimated effect; ⊕⊕⊕○ (moderate quality): there is a reasonable degree of certainty that the actual effect is near the estimated effect while, there exists a chance of significant difference; ⊕⊕○○ (low quality): the confidence in the estimated effect is restricted and there is a possibility of substantial disparity between the actual and estimated effects; ⊕○○○ (very low quality): there is a minimal confidence in the estimated effect and The actual effect is probable to vary from the estimated one considerably.

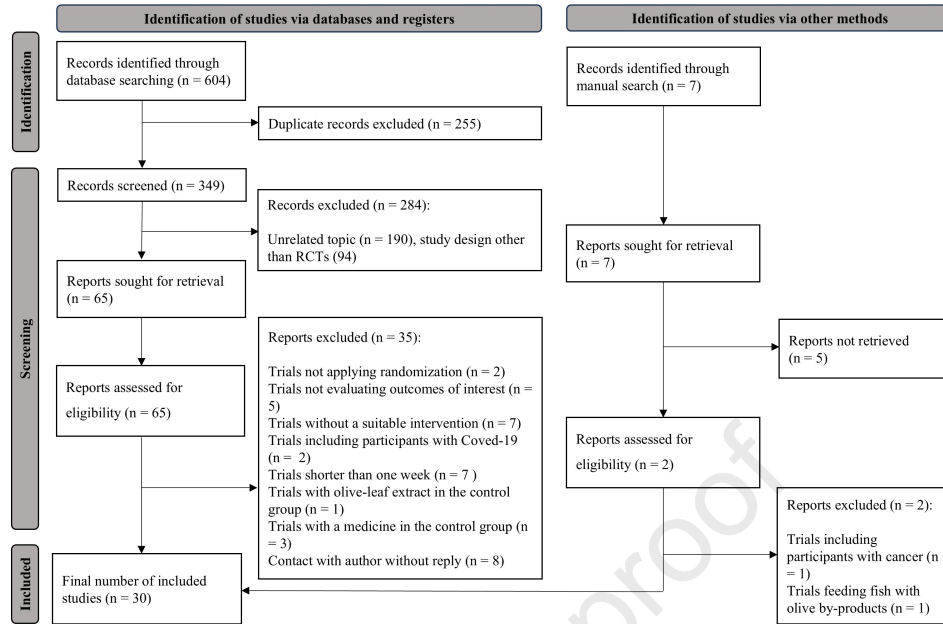
^d Heterogeneity was moderate to substantial (I^2) and remained largely unexplained (inconsistency)

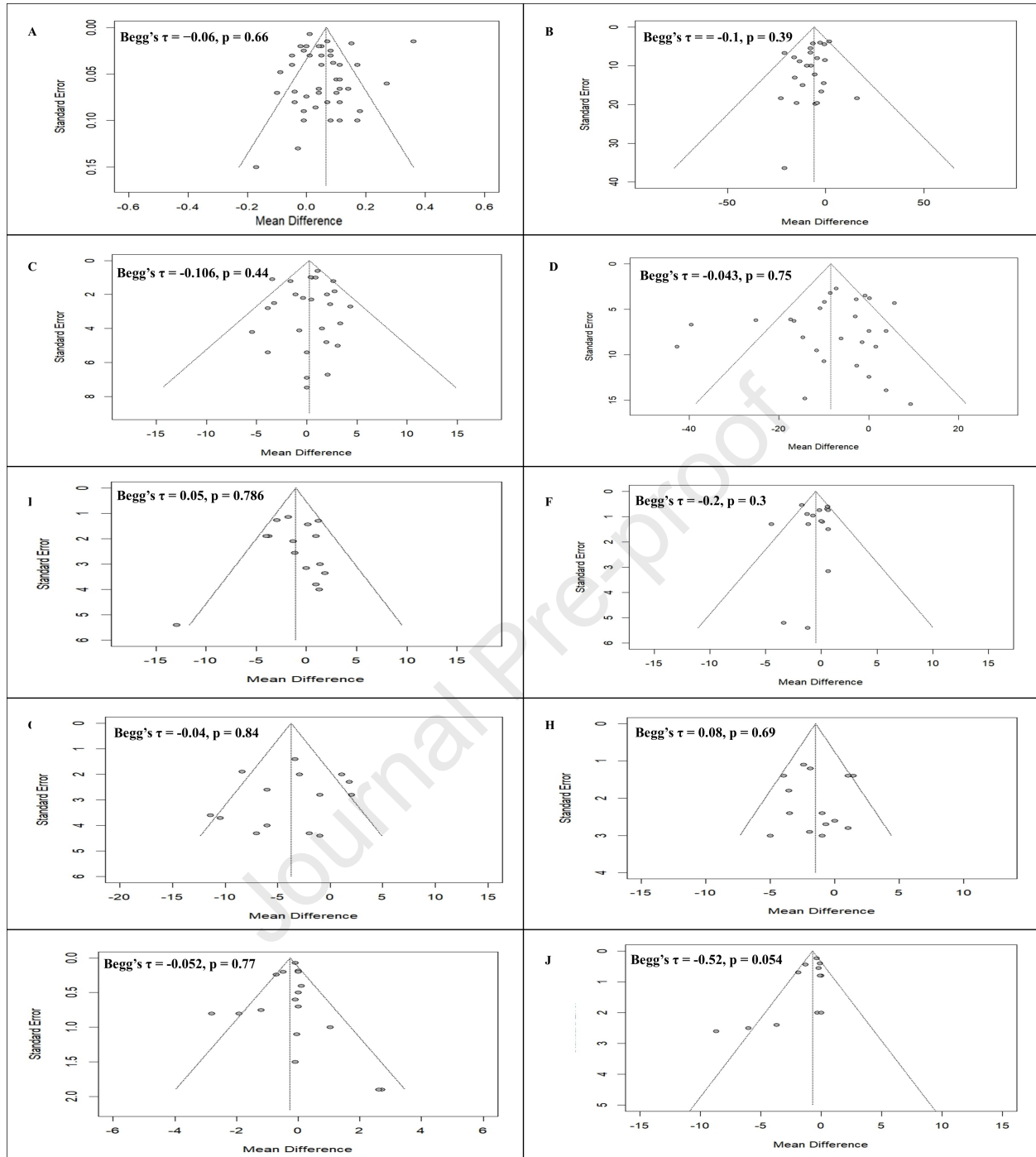
^e Wide CI crossing the line of no effect and clinical decision thresholds, leading to uncertainty in the estimate (imprecision).

^f The total number of participants was limited, falling below the commonly accepted threshold of 400 for adequate precision. (imprecision)

^g Evidence suggests the presence of publication bias, contributing to uncertainty in the estimate. (publication bias)

^h One RCT judged at high risk of bias contributed multiple time-point outcomes to the meta-analysis, increasing its influence on the pooled estimate.





Highlights

- Olive leaf supplementation improved lipid profile markers: TC, TG, LDL, ApoB, oxLDL, ApoA1
- Olive leaf supplementation had no significant effects on glycemic control markers
- Olive pomace supplementation showed no cardiometabolic or anthropometric benefits

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: