applied sciences

MDPI

Article

Hydroxytyrosol-Rich Olive Extract for Plasma Cholesterol Control

Arrigo F. G. Cicero [1,2,*], Federica Fogacci [1,2], Antonio Di Micoli [1], Maddalena Veronesi [1], Elisa Grandi [1] and Claudio Borghi [1]

[1] Hypertension and Cardiovascular Risk Research Group, Medical and Surgical Sciences Department, University of Bologna, 40100 Bologna, Italy
[2] Italian Nutraceutical Society (SINut), 40100 Bologna, Italy
* Correspondence: arrigo.cicero@unibo.it

Abstract: Emerging research and epidemiological studies established the health benefits of the Mediterranean diet, whose hallmark is the high consumption of olives and olive oil as the primary source of dietary fatty acids and major sources of antioxidants. The aim of this study was to evaluate the effect of daily dietary supplementation with highly standardized polyphenols—mainly hydroxytyrosol—which are derived from olive oil production by-products of an Italian olive variety (Coratina Olive) on the plasma cholesterol of a sample of hypercholesterolemic individuals. This single-arm, non-controlled, non-randomized, prospective pilot clinical study involved a sample of 30 volunteers with polygenic hypercholesterolemia. The study design included a 2-week run-in and a 4-week intervention period. Patients were evaluated for their clinical status and by the execution of a physical examination and laboratory analyses before and after the treatment. The intervention effect was assessed using Levene's test followed by the independent Student's *t* test after the log-transformation of the non-normally distributed continuous variables. Dietary supplementation with highly standardized polyphenols that are derived from Coratina Olive (namely SelectSIEVE® OptiChol) was associated with a significant improvement in systolic blood pressure, pulse pressure, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, non-HDL-C, fasting plasma glucose, and uric acid compared to baseline values. Furthermore, SelectSIEVE® OptiChol was well tolerated by volunteers. We acknowledge that the study has some limitations, namely the small patient sample, the short follow-up, and the lack of randomization and control procedures. However, these results are consistent with previous literature that referred to extracts from different olive varieties. Definitely, our observations lay further foundations for the use of polyphenolic-rich olive extract from Coratina Olive in the prevention and treatment of first-stage metabolic syndrome.

Keywords: olive; Coratina Olive; olive extract; polyphenols; hydroxytyrosol; cholesterol

Citation: Cicero, A.F.G.; Fogacci, F.; Di Micoli, A.; Veronesi, M.; Grandi, E.; Borghi, C. Hydroxytyrosol-Rich Olive Extract for Plasma Cholesterol Control. *Appl. Sci.* **2022**, *12*, 10086. https://doi.org/10.3390/app121910086

Academic Editor: Alessandro Genovese

Received: 12 August 2022
Accepted: 5 October 2022
Published: 7 October 2022

1. Introduction

The Mediterranean diet is typically high in fat and there is evidence about its role in the prevention of cardiovascular disease [1,2], in which the proportions of unsaturated and saturated fatty acids have been shown to play an important role [3,4]. One of the hallmarks of the Mediterranean diet is the high consumption of olives and olive oil as the primary source of dietary fatty acids and major sources of antioxidants [5]. The high nutritional value of these products is due to their richness in monounsaturated fatty acids (MUFA), fiber, vitamin E, and a number of phytochemicals [6]. In effect, olive oil provides an exceptional lipid matrix that is rich in molecules with different bioactive chemical entities [7]. The main phytochemicals that have been identified and quantified in olives and olive oil are phenolic and non-phenolic compounds [8]. Olive phenolic compounds belong to six different classes, including phenolic alcohols (hydroxytyrosol and tyrosol),

flavones (luteolin, luteolin-7-*O*-glucoside, apigenin, and apigenin-7-*O*-glucoside), flavonols (rutin), anthocyanins (cyanidin-3-*O*-glucoside), phenolic acids (5-*O*-caffeoylquinic acid) and a hydroxycinnamic acid derivative (verbascoside), while triterpenic acids (notably maslinic and oleanolic acids) are the main subclass of non-phenolic compounds that have been identified in olives [6].

In 2011, the European Food Safety Authority (EFSA) published a health claim that was related to polyphenols in olive oil and their possible protection of blood lipids against oxidative stress, stating that 5 mg of hydroxytyrosol and its derivatives (e.g., oleuropein complex and tyrosol) should be consumed daily in the context of a balanced diet for the sufficient avoidance of oxidative damage [9,10]. In effect, according to the most recent observations, olive hydroxytyrosol acts as a free-scavenger and metal-chelator [11], and it reduces the levels of low-density lipoprotein cholesterol (LDL-C) oxidation, platelet aggregation, and chronic inflammation, thus counteracting atherosclerosis-related cardiovascular (CV) disease (ASCVD) through the prevention of endothelial dysfunction and macrophages activation [12–14].

In light of this evidence, the aim of this study was to evaluate the effect of daily dietary supplementation with highly standardized polyphenols—mainly hydroxytyrosol—which were derived from the olive oil production by-products of an Italian olive variety (Coratina Olive) on the plasma cholesterol of a sample of hypercholesterolemic individuals.

2. Materials and Methods

2.1. Study Design and Participants

This was designed as a single-arm, non-controlled, non-randomized, prospective pilot clinical study, and it involved a sample of 30 Italian free-living volunteers who were consecutively recruited from the Lipid Clinic of the S. Orsola-Malpighi University Hospital (Bologna, Italy) among patients referring for polygenic hypercholesterolemia.

The participants were required to be aged 20–70 years, with LDL-C > 115 mg/dL and <190 mg/dL, an estimated 10-year ASCVD risk <5% based on the SCORE (Systematic COronary Risk Evaluation) risk charts, and not requiring lipid-lowering treatment according to the relevant International guidelines [15]. The exclusion criteria included having a previous history of ASCVD, diabetes mellitus, uncontrolled hypertension, obesity (defined as body mass index (BMI) > 30 Kg/m^2), TG > 400 mg/dL, a positive test for human immunodeficiency virus (HIV) or viral hepatitis (HBC, HCV, and HEV), uncontrolled thyroid diseases, history of malignancies, using either medications and dietary supplements that altered BP levels or plasma lipids (e.g., anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, statins, ezetimibe, bile acid resins, omega-3 fatty acids, and fibrates), having alcoholism, being pregnant, and breastfeeding.

The enrolled subjects adhered to a low-fat low-sodium Mediterranean diet for two weeks before and for the entire duration of the study. The intervention period lasted 4 weeks. Before and after the dietary supplementation with highly standardized polyphenols, the patients were evaluated for their clinical status and by the execution of laboratory analyses. The study timeline is reported in detail below (Figure 1).

The study fully complied with the Ethical Principles for Medical Research Involving Human Subjects of the Declaration of Helsinki and with the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP). The study's protocol was approved by the Local Ethical Committee, and all of the patients signed a written informed consent to participate.

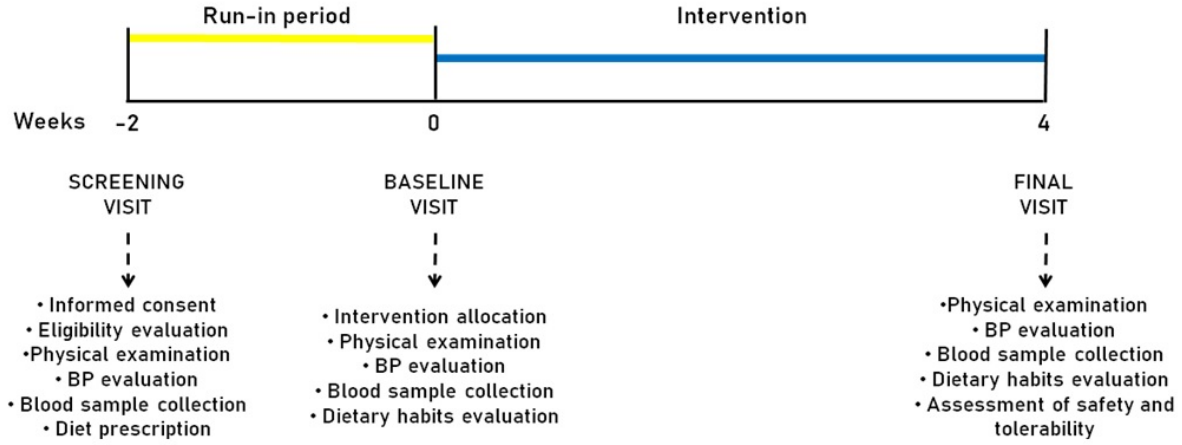

Figure 1. Timeline of the study. BP = Blood pressure.

2.2. Treatment

After a 2-week period of diet standardization, the enrolled subjects were instructed to take a capsule/day of SelectSIEVE® OptiChol containing 100 mg olive-derived extract that was standardized in hydroxytyrosol (Table 1) and acacia gum and maltodextrin as inactive carriers.

Table 1. Analytical specifications of the dietary supplement—namely SelectSIEVE® OptiChol—used in the clinical study.

Active Components Per Capsule (100 mg)
4–9% Hydroxytyrosol 6–15% Other olive polyphenols

The study product was manufactured and packaged by Roelmi HPC (Milan, Italy) in accordance with Quality Management System ISO 9001:2008 and the European Good Manufacturing Practices (GMP), thereby satisfying the requirements in the "Code of Federal Regulation" title 21,volume 2, part 111.

After the run-in, each patient was provided with boxes containing 30 capsules. For the entire duration of the study, the patients were instructed to take a capsule of SelectSIEVE® OptiChol once daily before their breakfast early in the morning. At the end of the study, all of the unused capsules were retrieved for inventory, and the participants' compliance was assessed by counting the number of returned capsules. A pill-count (dispensed pills—remaining pills)/(pills to be consumed between the visits) value of 0.85 to $\leq$1.15 was recorded as appropriate compliance. Underdose (<0.85) and overdose (>1.15) were labeled as non-compliance.

2.3. Assessments

2.3.1. Clinical Data and Anthropometric Measurements

The information that was gathered in the patients' history included the presence of ASCVD, other systemic diseases, and medications. The validated semi-quantitative questionnaires including a Food Frequency Questionnaire (FFQ) were used to assess the demographic variables of smoking and dietary habits and leisure time and physical activities [16].

The quantification and analysis of the energy intake and daily diet composition was performed using the MètaDieta® software (INRAN/IEO 2008 revision/ADI), and the data were handled in compliance with the company procedure IOA87.

Waist circumference (WC) was measured in the minimum perimeter at the end of a normal expiration and with arms being relaxed at the sides. Height and weight were respectively measured to the nearest 0.1 cm and 0.1 Kg with the patients standing erect

with their eyes directed straight and wearing light clothes and having bare feet. BMI was calculated as body weight [Kg], which was divided by the height squared [m^2] (Kg/m^2). Finally, the index of central obesity (ICO) was calculated from the WC-to-height ratio.

2.3.2. Laboratory Parameters Measurements

The biochemical analyses were carried out on venous blood that was withdrawn after an overnight fasting period (~12 h). The plasma was obtained by the addition of disodium ethylenediaminetetraacetate (Na_2EDTA) and blood centrifugation at 3000 RPM for 15 min.

Immediately after the centrifugation, trained personnel performed laboratory analyses according to standardized methods [17]. The following parameters were directly assessed: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), serum uric acid (SUA), creatinine, fasting plasma glucose (FPG), alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyl transferase (gGT).

Non-HDL cholesterol (Non-HDL-C) resulted from the difference between the TC and the HDL-C. The LDL-C was obtained by the use of the Friedewald formula [LDL-C = TC − HDL-C − TG/5]. The glomerular filtration rate (eGFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-epi) equation [18].

2.3.3. Blood Pressure Measurements

The arterial blood pressure (BP) was assessed in accordance with the recommendations of the International Guidelines for the management of arterial hypertension [19]. The resting systolic (SBP) and diastolic BP (DBP) were measured by the use of a validated oscillometric device, while they were in a sitting position and wearing a cuff of the appropriate size which was applied on the right upper arm. To improve the detection accuracy, three BP readings were sequentially obtained at 1 min intervals [20]. The first measurement was performed after 10 to 15 min of rest, and this was discarded. The average between the second and the third readings was recorded as the study variable. Pulse pressure was calculated as the difference between the SBP and the DBP.

2.3.4. Assessment of Safety and Tolerability

The level of safety and tolerability were evaluated through continuous monitoring during the study in order to detect any adverse event (AE) by taking the vital sign measurements, and employing the laboratory findings, clinical safety procedures, and physical examinations [21]. All of the reports of AEs were collected from the time of them giving their informed consent until the end of the study. A 10-point visual analog scale (VAS) was used to measure the patients' acceptability of SelectSIEVE® OptiChol.

2.4. Statistical Analysis

Statistical analysis was performed with intention to treat by means of the Statistical Package for Social Science (SPSS) 25.0, version for Windows.

The Kolmogorov–Smirnov test was used to test the normality distribution of the recorded data. The non-normally distributed variables were log-transformed before further statistical testing was conducted. The intervention effect was assessed using Levene's test which was followed by the independent Student's *t* test. All of the data were expressed as means and standard deviations (SDs). A 2-tailed $p < 0.05$ was considered as statistically significant for all of the tests.

3. Results

3.1. Efficacy Analysis

A total of 36 volunteers was screened, and 30 subjects (Men: 16; Women: 14) were enrolled and successfully completed the study according to its design (Figure 2).

No patient was found to be noncompliant with the study protocol (Figure 2). No statistically significant changes were recorded in dietary habits during the study, with no changes in the total energy and the macronutrient intake occurring (Table 2).

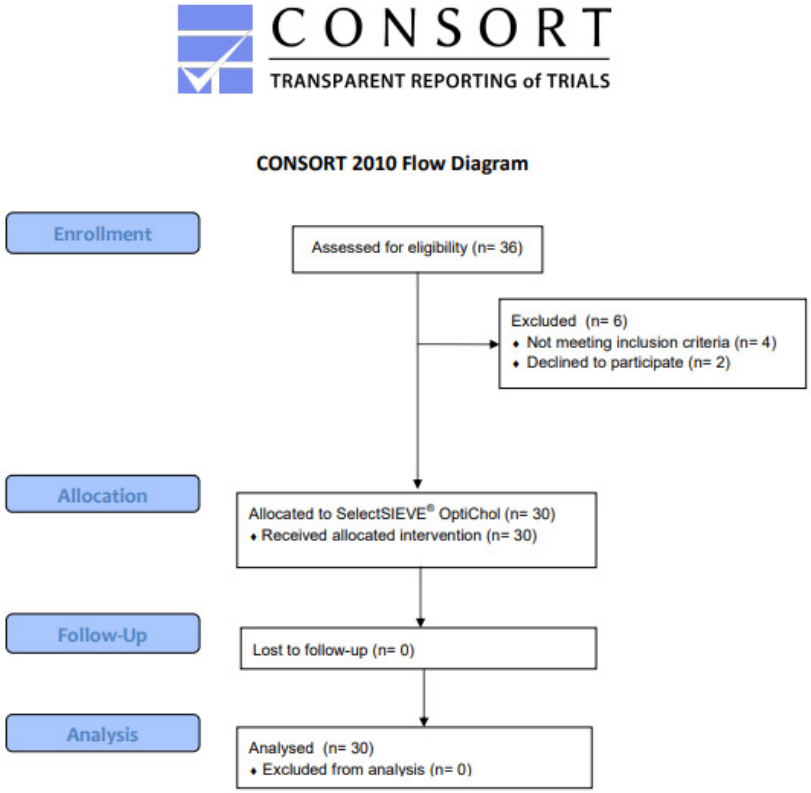

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

Table 2. Diet composition (g/day) at enrollment and at the end of the intervention. Values are reported as mean ± SD.

Parameters	Baseline	Week 4	*p*-Value
Total energy (Kcal/day)	1627 ± 121	1630 ± 105	n.s.
Carbohydrates (% of total energy)	55.2 ± 2.7	54.8 ± 3.1	n.s.
Proteins (% of total energy)	17.8 ± 2.1	18.1 ± 1.9	n.s.
Animal protein (% of total energy)	11.1 ± 0.7	10.9 ± 0.7	n.s.
Vegetal protein (% of total energy)	6.7 ± 0.4	7.2 ± 0.2	n.s.
Total fats (% of total energy)	26.9 ± 2.4	27.1 ± 1.8	n.s.
Saturated fatty acids (% of total energy)	8.9 ± 0.5	9.1 ± 0.2	n.s.
MUFA (% of total energy)	13.3 ± 1.4	12.9 ± 1.5	n.s.
PUFA (% of total energy)	4.7 ± 0.8	5.1 ± 0.9	n.s.
Total dietary fibers (g/day)	15.7 ± 1.8	15.9 ± 1.3	n.s.
Cholesterol (mg/day)	193.1 ± 12.7	192.8 ± 11.9	n.s.

MUFA = Monounsaturated fatty acids; N = Number of individuals; n.s. = not significant; PUFA = Polyunsaturated fatty acids.

At the end of the study, the dietary supplementation with SelectSIEVE® OptiChol was associated with a significant improvement in SBP, PP, FPG, TC, HDL-C, LDL-C, non-HDL-C, and SUA when they were compared to the baseline values (Table 3).

3.2. Safety Analysis

All of the participants completed the study according to its design (dropout rate = 0%). No treatment-emergent adverse events were reported, nor did any laboratory abnormality occurred. The volunteers' acceptability of SelectSIEVE® OptiChol was good.

Table 3. Anthropometric, hemodynamic, and blood chemistry parameters from the baseline to the end of the clinical trial.

Parameters	SelectSIEVE® OptiChol (N. 30)			
	Pre-Run-in	Baseline	Week 4	
	Mean ± SD	Mean ± SD	Mean ± SD	*p*-Value versus Baseline
Age (years)	53 ± 5			
WC (cm)	89.8 ± 5.3	88.9 ± 5.1	87.7 ± 5.5	n.s.
ICO	0.56 ± 0.08	0.54 ± 0.07	0.53 ± 0.08	n.s.
BMI (Kg/m^2)	24.8 ± 2.2	24.6 ± 2.2	24.3 ± 2.3	n.s.
SBP (mmHg)	134 ± 5	133 ± 5	130 ± 2	<0.05
DBP (mmHg)	87 ± 2	86 ± 3	86 ± 2	n.s.
PP (mmHg)	47 ± 2	47 ± 2	44 ± 2	<0.05
HR (bpm)	74 ± 4	74 ± 4	75 ± 5	n.s.
FPG (mg/dL)	88 ± 3	90 ± 3	85 ± 2	<0.05
TC (mg/dL)	248 ± 13	238 ± 12	225 ± 7	<0.05
HDL-C (mg/dL)	44 ± 3	44 ± 3	48 ± 2	<0.05
LDL-C (mg/dL)	161 ± 8	155 ± 8	145 ± 5	<0.05
Non HDL-C (mg/dL)	204 ± 11	198 ± 11	177 ± 8	<0.05
TG (mg/dL)	216 ± 19	197 ± 16	186 ± 18	n.s.
AST (mg/dL)	23 ± 3	25 ± 4	24 ± 3	n.s.
ALT (mg/dL)	22 ± 3	22 ± 3	23 ± 4	n.s.
gGT (mg/dL)	32 ± 2	33 ± 2	30 ± 5	n.s.
SUA (mg/dL)	8.5 ± 1.8	8.6 ± 1.5	7.7 ± 1.1	<0.05
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	n.s.
eGFR (ml/min)	88 ± 4	89 ± 4	87 ± 5	n.s.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BMI = Body mass index; DBP = Diastolic blood pressure; eGFR = Estimated glomerular filtration rate; FPG = Fasting plasma glucose; gGT = Gamma-glutamyl transferase; HDL-C = High-density lipoprotein cholesterol; HR = Heart rate; ICO = Index of central obesity; LDL-C = Low-density lipoprotein cholesterol; N = Number of individuals; n.s. = Not significant; PP = Pulse pressure; SD = Standard deviation; SUA = Serum uric acid; SBP = Systolic blood pressure; TG = Triglycerides; WC = Waist circumference.

4. Discussion

In vitro and in vivo studies have previously found that hydroxytyrosol from *Olea europaea* extract exerts a number of potential clinical benefits with putative anti-atherosclerotic and anti-ischemic properties [22]. The mechanisms underlying the vascular protective effect of hydroxytyrosol consist in the prevention of LDL-C oxidation, in the reversion of angiogenesis through the inhibition of the activity of matrix metalloproteinase-2 (MMP-2) and 9 (MMP-9), in the reduction of inflammatory damage and eicosanoid formation, and in the expression of the vascular cell adhesion molecule1 (VCAM-1) and the intercellular adhesion molecule 1 (ICAM-1) [14,23]. Moreover, a significant reduction in E-selectin, P-selectin, ICAM-1, and VCAM-1 secretions were found in the human aortic endothelial cells that were treated with physiological concentrations of hydroxytyrosol and co-incubated with tumor necrosis factor alpha (TNF-α) [24]. Finally, hydroxytyrosol exerts antithrombotic properties by decreasing the platelet aggregation and the expression of the cell adhesion molecules, and by reducing the synthesis of thromboxane B2 and leukotriene B4 and their capacity to reduce cyclic adenosine (cAMP) and guanosine (cGMP) monophosphate platelet phosphodiesterase [8].

In humans, a dietary supplementation with polyphenolic-rich olive extract exerts antioxidant properties, thereby resulting in a number of cardioprotective effects whose extents are heterogeneous across the published studies and are largely dependent on the differences in the phenolic tested doses and the treatment duration [25]. Starting from these observations, a recently released systematic review and meta-analysis of the controlled clinical trials has aimed to assess whether the effects on the single components of metabolic syndrome (MetS)—including obesity, glucose intolerance, dyslipidemia, and

high BP—were related to hydroxytyrosol or oleic acid contents or their combination inolive oil [26]. By summarizing the available evidence, this pooled analysis did not show any significant effects of the hydroxytyrosol consumption on the MetS components, while the polyphenolic-rich olive oil was as good as a standard care for MetS management. These findings are definitely conclusive in determining that the supplementation with a phenolic-rich olive extract (also known as "virgin olive oil") is an effective tool for the prevention and treatment of MetS, unlike the isolated polyphenolic fractions. Of course, there is no doubt that Mediterranean dietary patterns that are rich in olive oil exert per se different protective action against CV aging. As a matter of fact, in the Seguimiento University of Navarra (SUN) project, the hazard ratio for CVD for olive oil consumption ≥30 g/day (versus <10 g/day) was 0.57 (95% Confidence Interval (CI): 0.34, 0.96) in a follow-up that was conducted over 10.8 years [27]. Moreover, in the European Prospective Investigation into Cancer and Nutrition (EPIC, Spain) that had a follow-up of 22.8 years, the hazard ratios for stroke according to the amount of olive oil consumption were 0.84 (0.70, 1.02), 0.80 (0.66, 0.96), 0.89 (0.74, 1.07) for 0 to <10, 10 to <20, 20 to <30, and ≥30 g/day of olive oil, respectively [27]. However, it is necessary to specify that not all of the commercially available olive oils have the same polyphenols content. Furthermore, olive oil intake is hardly predictable because it is a seasoning, not a food, and its antioxidant effect is variably impaired by the exposition of it at cooking temperature. It should also be taken into account that olive oil is a source of lipids, so the recommended daily amount of olive oil in weight-management programs should be less than that which is recommended for the maintenance of CV health in normal-weight individuals [28]. Last but not least, not everyone likes the taste of olive oil and, of consequence, not everyone is able to adhere to a Mediterranean dietary pattern on the long-term. For all of these reasons, an olive-derived extract that is standardized in hydroxytyrosol to be consumed on top of Mediterranean diet could be of particular interest, taking into consideration that olive oil's supposed beneficial effects on the vascular and metabolic parameters depend only on its polyphenolic fraction and not MUFA.

According to our observations, 100 mg olive-derived extracts that are standardized in hydroxytyrosol are able to yield a broad-spectrum of activity with significant improvement in SBP, PP, FPG, TC, HDL-C, LDL-C, non-HDL-C, and SUA after one month of its dietary supplementation. Previously, evidence from clinical trials had been mostly limited to highly selected demographic groups such as elderly people who were either free-living or living in protective residences [29,30]. A randomized, double-blind, placebo-controlled, clinical study had already showed that one-year consumption of a polyphenol extract from *Olea europaea* improved the lipid profile of postmenopausal women (pre-post treatment changes: TC = −26.2 mg/dL in the active group, $p = 0.01$ versus placebo; LDL-C = −34.7 mg/dL in the active group, $p = 0.02$ versus placebo; TG = −4.15 mg/dL in the active group, $p = 0.01$ versus placebo) [29]. Another randomized, double-blind, clinical study involving institutionalized individuals that were aged 65–96 years had already revealed that a nutritional intervention testing a 6-week daily dietary supplementation with virgin oil improved the antioxidant status in the elderly by reducing the serum lipid levels, the serum total antioxidant capacity (TAC), and the superoxide dismutase (SOD) and glutathione peroxidase (GH-PX) activity, and by increasing the catalase (CAT) in the erythrocytes [30]. Most recently, the lipid-lowering effect of dietary supplementation with phenolic-rich olive extract has been investigated as it is associated with red yeast rice. In this context, a nutraceutical compound containing red yeast rice and olive fruit extract that is highly concentrated in hydroxytyrosol (5 mg hydroxytyrosol equivalent) has been found to be effective in reducing the serum lipid levels and also well tolerated by hypercholesterolemic patients with a history of statin-associated muscle symptoms (SAMS) [31]. Another randomized, double-blind, placebo-controlled, clinical study has showed that a food supplement combining red yeast rice and olive fruit extract (for a daily intake of 10.82 mg of monacolins and 9.32 mg of hydroxytyrosol) was able to exert beneficial effects in patients with MetS even in the short term by lowering the LDL-C by 24% (+1% in the placebo group) and also improving the TC

(−17% versus +2% in the control group), apolipoprotein B (−15% versus +6%, $p < 0.001$), TG (−9% versus + 16%, $p = 0.02$), oxidized LDL (−20% versus +5% in the control group. $p < 0.001$), SBP (mean difference versus placebo = −0.3 mmHg, $p = 0.001$), and DBP (mean difference versus placebo = −0.4 mmHg, $p = 0.05$) after only 6 weeks of dietary supplementation taking place [32]. In effect, the preclinical evidence suggests that olive polyphenols are able to partially inhibit the activity of 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase and acetyl-Coenzyme A cholesterol acyltransferase (ACAT), thus resulting in a decreased cholesterol biosynthesis [33]. Moreover, olive polyphenols might have effect on the bile flow and secondarily promote lipid fecal excretion by increasing the biliary cholesterol and the bile acid concentrations [34]. Previous evidence has shown that diet is one of the most important contributors to the balance of both the gut microbiota and bile acid homeostasis [35]. In particular, population studies that demonstrate a higher consumption of fruits and vegetables with a high content in polyphenols are associated with the enhancement of the growth of the probiotic bacteria that actively interact with the bile acid metabolising activity [36]. In addition, to date, a number of polyphenols have been reported to exert bile acid sequestering activity [37,38]. As intervention studies have showed that the pharmaceutical sequestering agents decrease the circulating LDL-C, reduce obesity, improve insulin sensitivity, and induce thermogenesis [39], it is likely that polyphenols too—as bile acid sequestering agents of a natural origin—have potential for the treatment of the metabolic disease.

In addition to the LDL-C lowering effect, SelectSIEVE® OptiChol increases the plasma levels of HDL-C. It is well known that the increase of TC and particularly of LDL-C is positively associated with the risk of ASCVD, while higher values of HDL-C are inversely correlated with the risk of ASCVD [40,41]. A large meta-analysis of four prospective studies (namely the Lipid Research Clinics Prevalence Mortality Follow-Up Study, the Multiple Risk Factor Intervention Trial (MRFIT), the Framingham Heart Study, and the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)) showed that every 1 mg/dL increase in the HDL-C was associated with a significant coronary heart disease (CHD) risk reduction by3% in women and 2% in men [42]. For this reason, the favorable change in the HDL-C after the supplementation with SelectSIEVE® OptiChol is clinically relevant and deserves consideration. In effect, a systematic review on this topic has recently provided evidence that polyphenol-rich olive oil favors the enhancement of the HDL-C through the promotion of the HDL cholesterol efflux capacity, which is HDL-C main antiatherogenic function [43]. Based on the published evidence, olive polyphenols increase the HDL size and improve the HDL oxidative status and composition (i.e., promote a greater HDL stability, which is reflected as a TG-poor core) [44]. In this regard, a randomized crossover clinical trial involving 200 healthy male volunteers has recently showed that a 15-week dietary supplementation with olive oil with high phenolic content is able to exert further benefits on the HDL-C serum levels and the oxidative damage compared to refined olive oil, and it has definitely provided additional evidence to recommend the use of virgin olive oil as a source of bioactive compounds that are able to promote the optimization of some CV risk factors, including the increase in the HDL-C [45].

As expected [26], following the dietary supplementation with SelectSIEVE® OptiChol, also FPG and SUA mildly but significantly improved. This is particularly interesting and lays further conceptual foundations for the use of this extract in the prevention and treatment of first-stage MetS, considering that high SUA levels predict the incidence of MetS in populations [46]. In the past, a number of studies focused on the importance of the insulin resistance for hyperuricemia, bringing as link a fructose intake excess [47–49]. To date, several polyphenols have been tested as SUA-lowering agents and have been recognized for their ability to reduce the SUA levels through the inhibition of xanthine oxidase and renal urate transporters [50–52].

Finally, the observed effect on BP following the dietary supplementation with SelectSIEVE® OptiChol also needs to be discussed. Previously, dietary supplementation with a phenolic-rich olive leaf extract had been already showed to significantly reduce in patients with

pre-hypertension either 24-h and daytime SBP and DBP, with an extent being potentially associated to a 9–14% risk reduction in developing CHD and a 20–22.5% risk reduction in stroke and heart attack, based on published literature [53,54]. However, according to our current observations, the effects on SBP and PP can be also detectable in non-hypertensive patients and after their dietary supplementation with olive fruit extract that usually contains fewer bioactive compounds than olive leaf extract does [55]. Certainly, it must also be noted that the positive effects that were observed in our study were obtained after the dietary supplementation with an extract that was derived from olives and that it is, of consequence, ecofriendly.

Of course, we acknowledge that our study has some limitations, namely, the small patient sample and the short study duration. Moreover, the absence of randomization and control procedures cannot preclude the positive role of potential confounding variables. However, despite the preliminary nature of the study findings, our observations are relevant and consistent with the previous literature, and certainly deserve to be further investigated in placebo-controlled clinical trials.

From a toxicological point of view, the tested extract has not to be considered as a novel food. As a matter of fact, it has been derived from a well-known food source with a very-well characterized method of extraction and standardization, and it contains polyphenols with non-dramatic concentrations. [56]. Moreover, the single components that are included in the extract are the same as those that are found in olives and olive oil, whose safety has been largely shown in the everyday use byentire population and by a number of preclinical trials [57]. Of course, longer term clinical trials on larger population samples wouldbe able to confirm the high tolerability and safety of the extract.

5. Conclusions

In conclusion, according to the findings of this non-randomized, prospective pilot clinical study, the tested dietary supplement (namely SelectSIEVE® OptiChol) containing 100 mg olive-derived extracts that were standardized in hydroxytyrosol is well tolerated and able to improve a number of metabolic parameters (i.e., BP, FPG, SUA, and plasma lipids) in the individuals with polygenic hypercholesterolemia. Even though we acknowledge the limitations of the present study, of course these results are particularly interesting and consistent with the previous literaturethat, however, referred to extracts from different olive varieties. Our observations lay further foundations for the use of polyphenolic-rich olive extract from Coratina Olive in the prevention and treatment of first-stage MetS.

Author Contributions: Conceptualization, A.F.G.C.; methodology, A.F.G.C. and F.F.; software, A.F.G.C.; formal analysis, A.F.G.C.; investigation, A.F.G.C., F.F., A.D.M., M.V. and E.G.; data curation, F.F., A.D.M., M.V. and E.G.; writing—original draft preparation, A.F.G.C. and F.F.; writing—review and editing, A.D.M., M.V., E.G. and C.B.; supervision, C.B.; project administration, A.F.G.C.; funding acquisition, A.F.G.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Local Institutional Review Board.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data supporting study's findings are available from the Corresponding Author with the permission of the University of Bologna.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ros, E.; Martínez-González, M.A.; Estruch, R.; Salas-Salvadó, J.; Fitó, M.; Martínez, J.A.; Corella, D. Mediterranean diet and cardiovascular health: Teachings of the PREDIMED study. *Adv. Nutr.* **2014**, *5*, 330S–336S. [CrossRef] [PubMed]
2. Sofi, F.; Abbate, R.; Gensini, G.F.; Casini, A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: An updated systematic review and meta-analysis. *Am. J. Clin. Nutr.* **2010**, *92*, 1189–1196. [CrossRef] [PubMed]

3. Beulen, Y.; Martínez-González, M.A.; van de Rest, O.; Salas-Salvadó, J.; Sorlí, J.V.; Gómez-Gracia, E.; Fiol, M.; Estruch, R.; Santos-Lozano, J.M.; Schröder, H.; et al. Quality of Dietary Fat Intake and Body Weight and Obesity in a Mediterranean Population: Secondary Analyses within the PREDIMED Trial. *Nutrients* **2018**, *10*, 2011. [CrossRef] [PubMed]
4. Guasch-Ferré, M.; Babio, N.; Martínez-González, M.A.; Corella, D.; Ros, E.; Martín-Peláez, S.; Estruch, R.; Arós, F.; Gómez-Gracia, E.; Fiol, M.; et al. Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease. *Am. J. Clin. Nutr.* **2015**, *102*, 1563–1573. [PubMed]
5. Nan, J.N.; Ververis, K.; Bollu, S.; Rodd, A.L.; Swarup, O.; Karagiannis, T.C. Biological effects of the olive polyphenol, hydroxytyrosol: An extra view from genome-wide transcriptome analysis. *Hell. J. Nucl. Med.* **2014**, *17*, 62–69. [PubMed]
6. Uylaşer, V.; Yildiz, G. The historical development and nutritional importance of olive and olive oil constituted an important part of the Mediterranean diet. *Crit. Rev. Food Sci. Nutr.* **2014**, *54*, 1092–1101. [CrossRef] [PubMed]
7. Claro-Cala, C.M.; Jiménez-Altayó, F.; Zagmutt, S.; Rodriguez-Rodriguez, R. Molecular Mechanisms Underlying the Effects of Olive Oil Triterpenic Acids in Obesity and Related Diseases. *Nutrients* **2022**, *14*, 1606. [CrossRef] [PubMed]
8. Rocha, J.; Borges, N.; Pinho, O. Table olives and health: A review. *J. Nutr. Sci.* **2020**, *9*, e57. [CrossRef] [PubMed]
9. Rizwan, S.; Benincasa, C.; Mehmood, K.; Anjum, S.; Mehmood, Z.; Alizai, G.H.; Azam, M.; Perri, E.; Sajjad, A. Fatty Acids and Phenolic Profiles of Extravirgin Olive Oils from Selected Italian Cultivars Introduced in Southwestern Province of Pakistan. *J.Oleo. Sci.* **2019**, *68*, 33–43. [CrossRef] [PubMed]
10. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on the substantiation of health claims related to polyphenols in olive and protection of LDL particles from oxidative damage (Id 1333, 1638, 1639, 1696, 2865), maintenance of normal blood HDL cholesterol concentrations (Id 1639), maintenance of normal blood pressure (Id 3781), "anti-inflammatory properties" (id 1882), "contributes to the upper respiratory tract health" (Id 3467) pursuant to article 13(1) of regulation (ec) no 1924/2006. *EFSA J.* **2011**, *9*, 2033.
11. Visioli, F.; Poli, A.; Gall, C. Antioxidant and other biological activities of phenols from olives and olive oil. *Med. Res. Rev.* **2002**, *22*, 65–75. [CrossRef] [PubMed]
12. KarkovićMarković, A.; Torić, J.; Barbarić, M.; JakobušićBrala, C. Hydroxytyrosol, Tyrosol and Derivatives and Their Potential Effects on Human Health. *Molecules* **2019**, *24*, 2001. [CrossRef] [PubMed]
13. Tejada, S.; Pinya, S.; Del Mar Bibiloni, M.; Tur, J.A.; Pons, A.; Sureda, A. Cardioprotective Effects of the Polyphenol Hydroxytyrosol from Olive Oil. *Curr. Drug Targets* **2017**, *18*, 1477–1486. [CrossRef] [PubMed]
14. Vilaplana-Pérez, C.; Auñón, D.; García-Flores, L.A.; Gil-Izquierdo, A. Hydroxytyrosol and potential uses in cardiovascular diseases, cancer, and AIDS. *Front. Nutr.* **2014**, *1*, 18. [CrossRef] [PubMed]
15. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis* **2019**, *290*, 140–205. [CrossRef]
16. Cicero, A.F.G.; Fogacci, F.; Bove, M.; Giovannini, M.; Borghi, C. Impact of a short-term synbiotic supplementation on metabolic syndrome and systemic inflammation in elderly patients: A randomized placebo-controlled clinical trial. *Eur. J. Nutr.* **2021**, *60*, 655–663. [CrossRef]
17. Cicero, A.F.G.; Fogacci, F.; Rosticci, M.; Parini, A.; Giovannini, M.; Veronesi, M.; D'Addato, S.; Borghi, C. Effect of a short-term dietary supplementation with phytosterols, red yeast rice or both on lipid pattern in moderately hypercholesterolemic subjects: A three-arm, double-blind, randomized clinical trial. *Nutr. Metab.* **2017**, *14*, 61. [CrossRef]
18. Levey, A.S.; Stevens, L.A.; Schmid, C.H.; Zhang, Y.L.; Castro, A.F., III; Feldman, H.I.; Kusek, J.W.; Eggers, P.; Van Lente, F.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration); et al. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* **2009**, *150*, 604–612. [CrossRef]
19. Williams, B.; Mancia, G.; Spiering, W.; AgabitiRosei, E.; Azizi, M.; Burnier, M.; Clement, D.; Coca, A.; De Simone, G.; Dominiczak, A.; et al. Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J. Hypertens.* **2018**, *36*, 2284–2309. [CrossRef]
20. Cicero, A.F.G.; Fogacci, F.; Veronesi, M.; Grandi, E.; Dinelli, G.; Hrelia, S.; Borghi, C. Short-Term Hemodynamic Effects of Modern Wheat Products Substitution in Diet with Ancient Wheat Products: A Cross-Over, Randomized Clinical Trial. *Nutrients* **2018**, *10*, 1666. [CrossRef]
21. Cicero, A.F.G.; Fogacci, F.; Veronesi, M.; Strocchi, E.; Grandi, E.; Rizzoli, E.; Poli, A.; Marangoni, F.; Borghi, C. A randomized Placebo-Controlled Clinical Trial to Evaluate the Medium-Term Effects of Oat Fibers on Human Health: The Beta-Glucan Effects on Lipid Profile, Glycemia and inTestinal Health (BELT) Study. *Nutrients* **2020**, *12*, 686. [CrossRef] [PubMed]
22. Efentakis, P.; Iliodromitis, E.K.; Mikros, E.; Papachristodoulou, A.; Dagres, N.; Skaltsounis, A.L.; Andreadou, I. Effects of the olive tree leaf constituents on myocardial oxidative damage and atherosclerosis. *Planta Med.* **2015**, *81*, 648–654. [CrossRef] [PubMed]
23. Granados-Principal, S.; Quiles, J.L.; Ramirez-Tortosa, C.L.; Sanchez-Rovira, P.; Ramirez-Tortosa, M.C. Hydroxytyrosol: From laboratory investigations to future clinical trials. *Nutr. Rev.* **2010**, *68*, 191–206. [CrossRef] [PubMed]
24. Catalán, Ú.; López de Las Hazas, M.C.; Rubió, L.; Fernández-Castillejo, S.; Pedret, A.; de la Torre, R.; Motilva, M.J.; Solà, R. Protective effect of hydroxytyrosol and its predominant plasmatic human metabolites against endothelial dysfunction in human aortic endothelial cells. *Mol. Nutr. Food Res.* **2015**, *59*, 2523–2536. [CrossRef]

25. Romani, A.; Ieri, F.; Urciuoli, S.; Noce, A.; Marrone, G.; Nediani, C.; Bernini, R. Health Effects of Phenolic Compounds Found in Extra-Virgin Olive Oil, By-Products, and Leaf of *Olea europaea* L. *Nutrients* **2019**, *11*, 1776. [CrossRef]
26. Pastor, R.; Bouzas, C.; Tur, J.A. Beneficial effects of dietary supplementation with olive oil, oleic acid, or hydroxytyrosol in metabolic syndrome: Systematic review and meta-analysis. *Free Radic. Biol. Med.* **2021**, *172*, 372–385. [CrossRef]
27. Hooper, L.; Abdelhamid, A.S.; Jimoh, O.F.; Bunn, D.; Skeaff, C.M. Effects of total fat intake on body fatness in adults. *Cochr. Database Syst. Rev.* **2020**, *6*, CD013636. [CrossRef]
28. Donat-Vargas, C.; Sandoval-Insausti, H.; Peñalvo, J.L.; Moreno Iribas, M.C.; Amiano, P.; Bes-Rastrollo, M.; Molina-Montes, E.; Moreno-Franco, B.; Agudo, A.; Mayo, C.L.; et al. Olive oil consumption is associated with a lower risk of cardiovascular disease and stroke. *Clin. Nutr.* **2022**, *41*, 122–130. [CrossRef]
29. Filip, R.; Possemiers, S.; Heyerick, A.; Pinheiro, I.; Raszewski, G.; Davicco, M.J.; 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**, *19*, 77–86. [CrossRef]
30. Oliveras-López, M.J.; Molina, J.J.; Mir, M.V.; Rey, E.F.; Martín, F.; de la Serrana, H.L. Extra virgin olive oil (EVOO) consumption and antioxidant status in healthy institutionalized elderly humans. *Arch. Gerontol. Geriatr.* **2013**, *57*, 234–242. [CrossRef]
31. TshongoMuhindo, C.; Ahn, S.A.; Rousseau, M.F.; Dierckxsens, Y.; Hermans, M.P. Efficacy and safety of a combination of red yeast rice and olive extract in hypercholesterolemic patients with and without statin-associated myalgia. *Complement. Ther. Med.* **2017**, *35*, 140–144. [CrossRef] [PubMed]
32. Verhoeven, V.; Van der Auwera, A.; Van Gaal, L.; Remmen, R.; Apers, S.; Stalpaert, M.; Wens, J.; Hermans, N. Can red yeast rice and olive extract improve lipid profile and cardiovascular risk in metabolic syndrome? A double blind, placebo controlled randomized trial. *BMC Complement. Altern. Med.* **2015**, *15*, 52. [CrossRef]
33. Lee, J.S.; Choi, M.S.; Jeon, S.M.; Jeong, T.S.; Park, Y.B.; Lee, M.K.; Bok, S.H. Lipid-lowering and antioxidative activities of 3,4-di(OH)-cinnamate and 3,4-di(OH)-hydrocinnamate in cholesterol-fed rats. *Clin. Chim. Acta* **2001**, *314*, 221–229. [CrossRef]
34. Krzeminski, R.; Gorinstein, S.; Leontowicz, H.; Leontowicz, M.; Gralak, M.; Czerwinski, J.; Lojek, A.; Cíz, M.; Martin-Belloso, O.; Gligelmo-Miguel, N.; et al. Effect of different olive oils on bile excretion in rats fed cholesterol-containing and cholesterol-free diets. *J. Agric. Food Chem.* **2003**, *51*, 5774–5779. [CrossRef] [PubMed]
35. Pushpass, R.G.; Alzoufairi, S.; Jackson, K.G.; Lovegrove, J.A. Circulating bile acids as a link between the gut microbiota and cardiovascular health: Impact of prebiotics, probiotics and polyphenol-rich foods. *Nutr. Res. Rev.* **2021**, 1–20. [CrossRef] [PubMed]
36. Koutsos, A.; Tuohy, K.M.; Lovegrove, J.A. Apples and cardiovascular health–is the gut microbiota a core consideration? *Nutrients* **2015**, *7*, 3959–3998. [CrossRef] [PubMed]
37. Hylemon, P.B.; Zhou, H.; Pandak, W.M.; Ren, S.; Gil, G.; Dent, P. Bile acids as regulatory molecules. *J. Lipid Res.* **2009**, *50*, 1509–1520. [CrossRef] [PubMed]
38. Li, T.; Chiang, J.Y. Bile acids as metabolic regulators. *Curr. Opin. Gastroenterol.* **2015**, *31*, 159–165. [CrossRef] [PubMed]
39. Watanabe, M.; Morimoto, K.; Houten, S.M.; Kaneko-Iwasaki, N.; Sugizaki, T.; Horai, Y.; Mataki, C.; Sato, H.; Murahashi, K.; Arita, E.; et al. Bile acid binding resin improves metabolic control through the induction of energy expenditure. *PLoS ONE* **2012**, *7*, e38286. [CrossRef] [PubMed]
40. Allard-Ratick, M.P.; Kindya, B.R.; Khambhati, J.; Engels, M.C.; Sandesara, P.B.; Rosenson, R.S.; Sperling, L.S. HDL: Fact, fiction, or function? HDL cholesterol and cardiovascular risk. *Eur. J. Prev. Cardiol.* **2021**, *28*, 166–173. [CrossRef] [PubMed]
41. Fogacci, F.; Borghi, C.; Cicero, A.F.G. New evidences on the association between high-density lipoprotein cholesterol and cardiovascular risk: A never ending research story. *Eur. J. Prev. Cardiol.* **2022**, *29*, 842–843. [CrossRef] [PubMed]
42. Gordon, D.J.; Probstfield, J.L.; Garrison, R.J.; Neaton, J.D.; Castelli, W.P.; Knoke, J.D.; Jacobs, D.R., Jr.; Bangdiwala, S.; Tyroler, H.A. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* **1989**, *79*, 8–15. [CrossRef]
43. Rondanelli, M.; Giacosa, A.; Morazzoni, P.; Guido, D.; Grassi, M.; Morandi, G.; Bologna, C.; Riva, A.; Allegrini, P.; Perna, S. MediterrAsian Diet Products That Could Raise HDL-Cholesterol: A Systematic Review. *Biomed. Res. Int.* **2016**, *2016*, 2025687. [CrossRef] [PubMed]
44. Hernáez, Á.; Fernández-Castillejo, S.; Farràs, M.; Catalán, Ú.; Subirana, I.; Montes, R.; Solà, R.; Muñoz-Aguayo, D.; Gelabert-Gorgues, A.; Díaz-Gil, Ó.; et al. Olive oil polyphenols enhance high-density lipoprotein function in humans: A randomized controlled trial. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 2115–2119. [CrossRef]
45. Covas, M.I.; Nyyssönen, K.; Poulsen, H.E.; Kaikkonen, J.; Zunft, H.J.; Kiesewetter, H.; Gaddi, A.; de la Torre, R.; Mursu, J.; EUROLIVE Study Group; et al. The effect of polyphenols in olive oil on heart disease risk factors: A randomized trial. *Ann. Intern. Med.* **2006**, *145*, 333–341. [CrossRef]
46. Cicero, A.F.G.; Fogacci, F.; Giovannini, M.; Grandi, E.; Rosticci, M.; D'Addato, S.; Borghi, C. Serum uric acid predicts incident metabolic syndrome in the elderly in an analysis of the Brisighella Heart Study. *Sci. Rep.* **2018**, *8*, 11529. [CrossRef]
47. Facchini, F.; Chen, Y.D.; Hollenbeck, C.B.; Reaven, G.M. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *J. Am. Med. Assoc.* **1991**, *266*, 3008–3011. [CrossRef]
48. Vuorinen-Markkola, H.; Yki-Järvinen, H. Hyperuricemia and insulin resistance. *J. Clin. Endocrinol. Metab.* **1994**, *78*, 25–29. [PubMed]
49. Zhu, Y.; Hu, Y.; Huang, T.; Zhang, Y.; Li, Z.; Luo, C.; Luo, Y.; Yuan, H.; Hisatome, I.; Yamamoto, T.; et al. High uric acid directly inhibits insulin signalling and induces insulin resistance. *Biochem. Biophys. Res. Commun.* **2014**, *447*, 707–714. [CrossRef]

50. Wu, D.; Chen, R.; Zhang, W.; Lai, X.; Sun, L.; Li, Q.; Zhang, Z.; Cao, J.; Wen, S.; Lai, Z.; et al. Tea and its components reduce the production of uric acid by inhibiting xanthine oxidase. *Food Nutr. Res.* **2022**, *66*, 8239. [CrossRef] [PubMed]
51. Cicero, A.F.G.; Caliceti, C.; Fogacci, F.; Giovannini, M.; Calabria, D.; Colletti, A.; Veronesi, M.; Roda, A.; Borghi, C. Effect of apple polyphenols on vascular oxidative stress and endothelium function: A translational study. *Mol. Nutr. Food Res.* **2017**, *61*, 1700373. [CrossRef] [PubMed]
52. Olechno, E.; Puścion-Jakubik, A.; Zujko, M.E. Chokeberry (A. melanocarpa (Michx.) Elliott)-A Natural Product for Metabolic Disorders? *Nutrients* **2022**, *14*, 2688. [CrossRef] [PubMed]
53. Lockyer, S.; Rowland, I.; Spencer, J.P.E.; 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**, *56*, 1421–1432. [CrossRef]
54. Cook, N.R.; Cohen, J.; Hebert, P.R.; Taylor, J.O.; Hennekens, C.H. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch. Intern. Med.* **1995**, *155*, 701–709. [CrossRef]
55. Nocella, C.; Cammisotto, V.; Fianchini, L.; D'Amico, A.; Novo, M.; Castellani, V.; Stefanini, L.; Violi, F.; Carnevale, R. Extra Virgin Olive Oil and Cardiovascular Diseases: Benefits for Human Health. *Endocr. Metab. Immune Disord. Drug Targets* **2018**, *18*, 4–13. [CrossRef] [PubMed]
56. Konstantinidou, V.; Garcia-Santamarina, S. Moving forward the Effects of Gene-Diet Interactions on Human Health. *Nutrients* **2022**, *14*, 3782. [CrossRef]
57. Del Saz-Lara, A.; López de Las Hazas, M.C.; Visioli, F.; Dávalos, A. Nutri-epigenetic Effects of Phenolic Compounds from Extra Virgin Olive Oil: A Systematic Review. *Adv. Nutr.* **2022**, *13*, 2039–2060. [CrossRef] [PubMed]