Review Article
Is Extra Virgin Olive Oil an Ally for Women’s and Men’s Cardiovascular Health?

Flavia Franconi,1 Ilaria Campesi,1,2 and Annalisa Romani3,4

1Laboratorio Nazionale sulla Farmacologia e Medicina di Genere, Istituto Nazionale Biostrutture Biosistemi, 07100 Sassari, Italy
2Dipartimento di Scienze Biomediche, Università Degli Studi di Sassari, 07100 Sassari, Italy
3Laboratorio PHYTOLAB (Pharmaceutical, Cosmetic, Food Supplement Technology and Analysis), DiSIA Università Degli Studi di Firenze, 50019 Florence, Italy
4Laboratorio di Qualità Delle Merci e Affidabilità di Prodotto, Università Degli Studi di Firenze, 59100 Florence, Italy

Correspondence should be addressed to Ilaria Campesi; icampesi@uniss.it

Received 3 February 2020; Accepted 4 March 2020

Academic Editor: Hangang Yu

Copyright © 2020 Flavia Franconi et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Noncommunicable diseases are long-lasting and slowly progressive and are the leading causes of death and disability. They include cardiovascular diseases (CVD) and diabetes mellitus (DM) that are rising worldwide, with CVD being the leading cause of death in developed countries. Thus, there is a need to find new preventive and therapeutic approaches. Polyphenols seem to have cardioprotective properties; among them, polyphenols and/or minor polar compounds of extra virgin olive oil (EVOO) are attracting special interest. In consideration of numerous sex differences present in CVD and DM, in this narrative review, we applied "gender glasses." Globally, it emerges that olive oil and its derivatives exert some anti-inflammatory and antioxidant effects, modulate glucose metabolism, and ameliorate endothelial dysfunction. However, as in prescription drugs, also in this case there is an important gender bias because the majority of the preclinical studies are performed on male animals, and the sex of donors of cells is not often known; thus a sex/gender bias characterizes preclinical research. There are numerous clinical studies that seem to suggest the benefits of EVOO and its derivatives in CVD; however, these studies have numerous limitations, presenting also a considerable heterogeneity across the interventions. Among limitations, one of the most relevant in the era of personalized medicine, is the non-attention versus women that are few and, also when they are enrolled, sex analysis is lacking. Therefore, in our opinion, it is time to perform more long, extensive and less heterogeneous trials enrolling both women and men.

1. Introduction

The Mediterranean diet (MedDiet) includes high consumption of legumes, cereals, fruits, and vegetables; moderate fish and wine consumption; and low consumption of red meat ([1] and cited literature). The MedDiet also includes the consumption of 25–50 ml/day of extra virgin olive oil (EVOO), which seems to have health benefits [2, 3].

Cardiovascular diseases (CVD) are the main cause of deaths, accounting for >17 million deaths annually [4]. The beneficial effect of MedDiet on CVD is suggested by several randomized clinical trials, although some recent papers stated that the evidence is still uncertain [5, 6]. For example, the Oslo Diet-Heart Study and the Finnish Mental Hospital Study [7–9] tested the effectiveness of low-cholesterol diets, enriched in polyunsaturated fatty acids, showing a decrease in coronary heart diseases (CAD) and blood cholesterol (Chol). Moreover, the Seven Countries Study, enrolling 11,579 middle-aged men from eight nations of seven Mediterranean and non-Mediterranean countries, shows a lower mortality from ischemic heart disease (IHD) in Mediterranean populations compared to those of Northern Europe and America [10]. PREDIMED study proves that EVOO is linked to lower risk of cardiovascular (CV) events [11]. However, a Cochrane Systematic Review proves that elevation in polyunsaturated fatty acids (PUFA) assumption has a small effect, if any, on all-cause mortality or CV deaths although it slightly decreases Chol and probably triglycerides.
Beneficial effects of EVOO are also associated with the presence of minor polar compounds (MPCs) that have antioxidant, anti-inflammatory, anti-aggregating, and antimicrobial activities and regulate serum insulin/glucose response [13–21]. A claim of the European Food Safety Authority (EFSA) declared that “consumption of olive oil polyphenols contributes to the protection of blood lipids from oxidative damage” at a daily dose of 5mg of hydroxytyrosol (HTyr) and its derivatives (e.g., oleuropein complex and tyrosol) [22].

Actually, botanicals are largely used [23, 24], especially by women [25, 26], but rigorous findings regarding their efficacy and safety profiles are still lacking [27]. Besides, the influence of sex on botanicals including EVOO, VOO, OO, and MPCs is also lacking; nevertheless, the individual’s sex and gender is one of the most important modulators of CV health [28–39] and the numerous sex and gender differences at CV level are summarized in Table 1. Previously, we reviewed the sex–gender effect on polyphenols of various origins [25, 26]; here we focus on EVOO and its MPCs because, as already mentioned, EFSA declares their utility in ameliorating low-density lipoproteins (LDL) oxidation and their importance in MedDiet [22].

2. MedDiet and Sex Differences

The Mediterranean Region includes about 20 nations with different ethnic, historical, and cultural backgrounds; religions (Muslims, Orthodox Christians, Catholic Christians, Jews); and economic status [56], and the UNESCO declared that MedDiet is an intangible cultural heritage [57]. Importantly, MedDiet also includes social aspects (social integration) and a peculiar way of life (sleeping and nutrition) that may play a role in reducing age-related diseases [58, 59]. However, the transferability of the benefit of MedDiet outside of Mediterranean Region decreases the importance of social aspects [60, 61]. In particular, it has been found that, in US women who are adherent to MedDiet, the CV risk reduced by about 25% over 12 years, having a reduction in LDL subclasses from smaller to larger LDL, while an opposite trend is observed in women [81]. MedDiet increased telomere length, a marker of biological age, in women [85], although no consensus is found about this effect [86]. Finally, men are less adherent to MedDiet than women [87].

3. EVOO, VOO, OO, and MPC

OO is produced from the fruits of Olea europaea L. evergreen trees, a plant cultivated worldwide, but it is typical cultivation of the Mediterranean area [88]. It mainly contains monounsaturated fats (98-99% of total weight of EVOO), such as oleic acid, followed by a low amount (1-2%) of phenols, phytosterols, tocopherols, and squalene [89]. Importantly, in EVOO only, fatty acids are stabilized by MPCs, with antioxidant activities [90].

EVOO composition and concentration in MPCs are extremely variable either qualitatively or quantitatively (200–600 mg/kg) [91]. MPCs are dependent on the tree cultivar, the climate, growing, and production procedure [92]. The phenolic cluster of EVOO can be subdivided into several subclasses. In particular, EVOO contains saponifiable compounds (triacylglycerol, partial glycerides, esters of fatty acids or free fatty acids, and phosphatides) and unsaponifiable compounds (hydrocarbons (squalene), phytosterols (β-sitosterol, stigmasterol, and campesterol), tocopherols, carotenoids, pigments (chlorophylls), aliphatic and triterpenic alcohols, triterpenic acids (oleanolic acid), volatile compounds, and polyphenols) [93].

In general, secoiridoids are the most representative followed by phenolic alcohols such as Tyr and HTyr, flavonoids, lignans, and phenolic acids [89, 92]. In general, HTyr, Tyr, and conjugated forms of secoiridoids like oleuropein (which are hydrolyzed to HTyr and Tyr in the stomach) are the most representative [94]. HTyr also originates by the hydrolysis of oleuropein during olive ripening or/and during the storage and elaboration of table olives [95]. It can be found in a free form, such as acetate form, or as part of oleacein, verbascoside, and oleuropein [93]. Also ligstroside, oleacein, and oleocanthal are sources of HTyr and Tyr [96].

(TG), leaving practically unaltered high density lipoprotein (HDL) [12].

Importantly, in investigating the rs7903146 polymorphism in the transcription factor 7-like 2 gene, Corella and coworkers [78] proved that in the homozygotes the hypercholesterolemia and hypertriglyceridemia are reduced by MedDiet.

Low adherence to MedDiet and smoking are independent predictors of 10-year CV events in women and in men, respectively [79]. The adherence to the MedDiet, nonsmoking, normal weight, and regular physical activity reduce the mortality in men and in women, but the statistical significance is reached only in women [72, 73, 80]. However, the response to the MedDiet seems to be greater in men than in premenopausal women when cardiometabolic changes are considered [81–84]. MedDiet ameliorates plasma lipid profile and diastolic blood pressure (DBP) without impacting on leptin levels and the leptin-to-adiponectin ratio in both sexes [84]. Only in men, it ameliorates the insulin homeostasis and redistribution of LDL subclasses from smaller to larger LDL, while an opposite trend is observed in women [81]. Finally, MedDiet increased telomere length, a marker of biological age, in women [85], although no consensus is found about this effect [86]. Finally, men are less adherent to MedDiet than women [87].
SOME OF MPCs SUCH AS HTYR, TYP, AND THEIR SECOROIDID DERIVATIVES (OLEOEUROPEIN, OLEOEUROPEIN AGLYCONE, AND ELENOLIC ACID DIALDEHYDES) ARE HYDROPHILIC [97], WHILE OTHER MPCs ARE LIPOPHILIC [89]. LIGNANS BELONG TO THE FAMILY OF PHYTOESTROGEN [98] AND IN GENERAL THE PredOMINANT LIGNAN IS (+)-1-AcETOXYPINORESINOL [98]. THE LEAVES OF THE OLEA EUROPaea L. CONTAIN HIGHER CONCENTRATIONS OF PHENOLS THAN THE OLIVE FRUIT AND DERIVED OILS [99–101]. THE PredOMINANT MPCs IN THE LEAVES ARE VERBASCOSIDE, APIGENIN-7-GLUCOSIDE, LUTEOLIN-7-GLUCOSIDE, HTYR, TYP, AND OLEOEUROPEIN [102]. NOTABLY, A SINGLE MPC MAY POSSESS DISTINCT BIOLOGICAL ACTIVITY [103, 104]. Thus, it is impossible to extrapolate the result of the single EVOO, VOO, and OO to another. For example, Chetoui and Blanquet cultivars (rich in linoleic acid) induce higher total triacylglycerol (TAG) incorporation into THP-1 cells than Buldige and Picual (rich in oleic acid), promoting foam cells formation [104]. Further, extracts of Taggiasca and Seggianese, which have different amounts and composition of MPCs, have a different antioxidant activity being higher in Seggianese extract [103].

Table 1: Examples of sex and gender differences in CVD and risk factors.

| Diseases or risk factors | Sex differences | References |
|-------------------------|-----------------|------------|
| Myocardial infarction   | Women are 10 years older than males and have higher mortality in younger ages and have more atypical symptoms. Women have less anatomical obstructive CAD than men; it is estimated a 20% or greater excess of normal or nonobstructive arteries in women vs men | [40–42] |
| Heart failure           | Lower incidence in women but the prevalence is similar in both sexes, with diastolic heart failure being more common in women. Lower mortality rate in women than in men | [40, 41] |
| Hypertension            | Lower incidence in premenopausal women | [40] |
| Cardiac hypertrophy     | Premenopausal women are better protected than men; men have more cardiac hypertrophy | [40] |
| Ischemia-reperfusion injury | Studies evidenced that females have lower ischemia-reperfusion injury | [40] |
| Diabetes                | Higher increased risk of CVD in women vs men | [40] |
| Endothelial dysfunction | More frequent in women vs men | [44, 45] |
| HDL                     | Higher levels in women vs men; the difference declines with age | [46] |
| TG                      | Higher increased risk of CVD in women vs men. In women, they increase after menopause | [47] |
| Chol                    | Levels rise in menopausal transition period | [47] |
| LDL                     | Levels rise in menopausal transition period | [46] |
| Lp (a)                  | Levels rise in menopausal transition period | [46] |
| Smoking                 | Less women smoke vs men, but smoking has more negative effects on women | [48] |
| Social economic status  | In women, it is inversely associated with increased risk of CAD, stroke, and CVD. In particular, for CHD, it is associated with lower education | [49] |
| Psychological factors   | Women had higher contributions from psychosocial risk factors (45.2% vs 28.8% in men) | [50, 51] |

**Unique for women**

| Gestational diabetes, pre-eclampsia, syndrome of polycystic ovary | Higher increased risk of CVD in women | [48, 52] |
|-------------------------------------------------------------------|-------------------------------------|-----------|
|                                                                   | A large cohort study (1.6 million of women, 15 to 49 years old) shows that ethinylestradiol (20 μg or 30 to 40 μg) is associated with an increased risk of MI. The risk is not significantly varied by progestin | [53] |

**Oral contraceptives**

| OC should not be prescribed for women over the age of 35 years and smokers (American College of Obstetricians and Gynecologists) and should be prescribed with caution in case of CV risk factors such as hypertension, diabetes, and dyslipidemia | [54] |

**Hormone replacement therapy**

| A large cohort study shows that ethinylestradiol is associated with an increased risk of MI that is not significantly changed with progestins | [55] |

4. Pharmacokinetics of MPCs and Influence of Sex

The influence of sex and gender on pharmacokinetics of phenols was recently reviewed [25]. Briefly, in humans, MPCs are well adsorbed (~40%–95%, using HTYR and TYP as proxy) [105, 106]. It is important to recall here that, in humans, there is an endogenous synthesis of HTYR during the metabolism of dopamine with its formation being favored by ethanol [107]. In addition, HTYR is a product of oleuropein hydrolysis that can occur in the stomach. Besides, gut microbiota generates HTYR from oleuropein [108].

In the intestinal tract (both ileum and colon), more than 40% of HTYR is absorbed by bidirectional passive transport [108], which depends on numerous factors such as food matrix or vehicle. The absorption of HTYR and TYP is higher when administered as an OO solution than as aqueous solution [108]. In the gastric and intestinal tract MPCs are hydrolyzed [109], with some exceptions. In particular, oleuropein is degraded by the colon microbiota to HTYR that is then absorbed [109]. HTYR bioavailability seems to be
influenced by sex [110]. The maximum plasmatic concentration of HTyr is reached 5–30 min after administration of EVOO and VOO [108]. HTyr and its derivatives cross the blood brain barriers [111]. Finally, HTyr is incorporated in HDL, which is higher in women than in men [108].

HTyr and Tyr are extensively metabolized by phase I enzymes, such as CYP2D6 and CYP3A4, and by phase II enzymes both at intestinal and hepatic levels [108, 112]. Numerous phase I and II enzymes present numerous sex differences both in animals and in humans [33]. Thus, the metabolism of MPCs can be sex divergent at least in rats [110]. In humans, the biotransformation of HTyr and Tyr mainly occurs through glucuronidation and sulphation, and the main circulating metabolites are both HTyr sulfate and HTyr acetate [108]. HTyr is also metabolized by catechol-O-methyltransferases that are more expressed in men than in women [33] forming 3-hydroxy-4-methoxyphenyl ethanol (homovanillic alcohol) [113]. Globally, HTyr and Tyr have lower bioavailability than their metabolites [107]. Inside the cells, the conjugated forms can be deconjugated and thus HTyr and Tyr metabolites can be formed. Finally, the intestinal microorganisms metabolize HTyr into hydroxylated phenylacetic acid, acetic acid, and benzoic acid [114]. In plasma and urine, 98% of HTyr is recovered as glucuronide form and only 2% is free [115]. Usually, the complete elimination of HTyr and metabolites occurs approximately in 4 and 6 h in rats and humans, respectively [116]. HTyr is mainly excreted by the renal route where it is present both in conjugated and nonconjugated form [108]. Urinary HTyr levels (adjusting for creatinine) are higher in men than in women [107]. In addition, through the biliary route they reach the small intestine where they can be retransformed and absorbed [116]. Despite the enterohepatic recycling, a small amount (about 5%) of total HTyr is excreted by feces [116] and the consumption of MPC-rich OO elevates the free HTyr levels in feces of men [114]. Notably, Tyr, HTyr acetate, 3,4-dihydroxyphenylacetic acid, and homovanillil alcohol administration changes urinary excretion of catecholamines (dopamine, normetanephrine, norepinephrine, and 3-methoxytyramine) in male and female rats, with the excretion being significantly higher in male than in female rats [110].

Oleocanthal constitutes about 10% of the olive’s MPCs (100–300 mg/kg EVOO) [117]. Oleocanthal, as other MPCs, is stable at acid pH and at 37°C and it is biotransformed by phase I and II enzymes, with glucuronidation being the prevalent way [117]. Oleocanthal and other secoiridoids and their metabolites are mainly eliminated by renal route and they are found in human urine 2–6 h after the intake [117].

Little and nonunivocal data are available on sex influence on bioavailability of chlorogenic acids [118] and cited literature) and lignans. After long flaxseed lignan secoisolariciresinol diglycoside exposure, female rats have higher lignan concentrations in heart and thymus than male rats [119]. A strong association between dietary lignan intake and prevalent obesity exists only for boys [120].

Importantly, pharmacokinetic interactions with other botanicals and prescription drugs have been described. For example, bioavailability of HTyr is enhanced when co-administered with the thyme extracts [121].

Considering the role of gut microbiota in sex healthcare paradigm [122, 123] and their ability to expand metabolic activity of the host [124], it important to recall that they could be a modifier of the activity and kinetic of all compounds present in olive and leaves and other matrixes [125]. In turn, OO derivatives may influence the gut microbiome. For example, the dialdehydic form of decarboxymethyl oleuropein aglycone, oleocanthal, HTyr, and Tyr may inhibit the growth of bacteria [126], including the beneficial ones [127]. Sex-gender differences in the microbiota are recently reviewed by Kim et al. [128]. Here, it is important to recall that microbiota modifications may participate in the pathophysiology of CVD [129]. For example, some metabolites of gut microbiota such as short-chain fatty acids and trimethylamine N-oxide may participate in the modulation of blood pressure through G protein receptors [129]. Further gut microbiota may inhibit HDL-coordinated reverse cholesterol transport [129].

Globally, the effects of MPCs on microbiota appear to be compound and sex specific, and in consideration of sex differences that characterize the human microbiota, its effects on MPC fate and activity should be accurately studied.

5. Effect of EVOO, VOO, OO, Leaf Extracts, and MPCs on Endothelial Dysfunction: Influence of Sex

Endothelial function is a barometer of vascular health [130] and it is a predictor and a pathogenic mechanism of atherosclerosis [131], being also related to the prognosis and severity of CVD [50, 132]. Endothelial dysfunction is more precocious than atherosclerotic plaques and it is a more prominent risk factor in women than in men (Table 1). It is related to oxidative stress, inflammation, platelet activity, an alteration of glucose metabolism, and uric acid levels [133–136], and all these processes present sex differences [34, 136–140].

5.1. Effect of EVOO, VOO, OO, Leaf Extracts, and MPCs on Oxidative Stress: Influence of Sex. The influence of sex on oxidative stress is widely reviewed [34, 137]. However, no univocal results are obtained and this could depend on species, tissues, and cells used and on donor age. For example, Brunelli et al. [141] report no differences in the plasma antioxidant barrier, although women present a higher oxidative status than men. Moreover, they suggest that premenopausal and postmenopausal women are similar [141]. By contrast, Vassalle and coworkers [47] report that menopause is a condition that elevates oxidative stress. Further, young men have lower levels of malondialdehyde (MDA) in comparison to fertile women and older men [142]. After correction for body weight (BW), both pre- and postmenopausal women have higher amounts of carboxylated proteins vs men of similar age [142]. Others show that lipid and protein oxidation are increased in peri- and postmenopausal women, whereas superoxide dismutase (SOD) and catalase (CAT) activities are decreased and increased in postmenopause and in perimenopausal women, respectively [143]. Glutathione (GSH) and glutathione
peroxidase (GPx) are lower in women aged 32–39 years than in women aged 20–25 years. Meanwhile, 20–25-year old men have higher GSH and lower glutathione disulfide (GSSG) than women of the same age. The SOD and CAT activities are higher in women aged 32–39 years than in men and women of younger age [144]. Moreover, women with CAD seem to have higher oxidative stress than men [145]. Another study shows that African American women with symptomatic peripheral artery disease produce more ROS than men, while Caucasian men and women do not diverge indicating that ethnicities could play a role in sex and gender differences [146–150]. Others report the opposite trend and others do not find any significant sex difference [151–153].

The antioxidant activity of EVOO, VOO, and MPCs is extensively reviewed [154, 155] (Table 2). It is based on their scavenger, chain breaking, and chelating activities [116]. Moreover, they favor the resistance over oxidation [266]. High dose of oleuropein and HTyr may exert prooxidant activity [267, 268], and this paradoxically could be one of the mechanisms of their antioxidant activity because it can activate the translation of nuclear factor E2-related factor 2 (Nrf2) to the nucleus [269] in a sex-specific manner [270, 271] that leads to modifications of proteins expression and activity such as γ-glutamylcysteine ligase, which is expressed less in female rat livers than in male ones [272]. After trauma and hemorrhage, HTyr elevates liver Nrf2 modulating heme oxygenase-1 (OH-1) especially in rat females (proestrous phase) compared to males [273]. Through Nrf2, MPCs can also activate phase II detoxifying enzymes and mitochondrial biogenesis, two critical pathways in reducing the negative effect of oxidative stress [271]. Oleuropein and HTyr seem to be scavengers of HOCl [274], which starts LDL lipid peroxidation and oxidizes the apolipoprotein (Apo) B-100 [275]. However this is not a univocal result [213]. Finally, in animals and in humans, HTyr may interact with several microRNAs [218, 276] that regulate numerous cellular function including DICER function that is relevant to the redox state [277, 278].

5.2. Effect of EVOO, VOO, OO, Leaf Extracts, and MPCs on Inflammatory Response: Influence of Sex. The effect of sex on inflammatory response has been recently reviewed [138, 139, 279]. Women and men have a different immune system [281] and arachidonic acid (AA) cascade [281]. This last generates numerous compounds with proinflammatory and anti-inflammatory activities. Interestingly, females seem to be protected against endothelial dysfunction induced by systemic inflammation [282]. In particular, COX2 and COX1 female knockout mice have less inflammatory edema and joint destruction than male mice [283]. Consistently, expression of COX2 is more elevated in male than in female cells [284]. More PGF₂α is produced by human male neutrophils vs female ones [284]. In male coronary rat arteries, PGF₂α exerts a major contraction in male arteries than in female ones for the presence of more PG receptors [285]. Also the lipooxygenase (LOX) system presents some sexual dimorphism. 5-LOX and its 5-lipooxygenase-activating protein (FLAP) are downregulated by androgens [286]. Thus, the bigger production of leukotrienes in monocytes and neutrophils of women is not surprising [286]. In human neutrophils and monocytes, the synthesis of lipoxin A₄ (LXA₄), a proresolving molecule [287], is reduced by estradiol [281]. Further, a positive and a negative correlation exist between age and aspirin triggered 15-epi-LXA₄ in women and men, respectively [288]. Resolvins, protectins, and maresins activities may be influenced by sex [289]. For example, D-resolvin is higher in women exudate whereas chemotactant leukotriene B₄ is higher in men [282]. The precursors of oxylipins are higher in the female urine than in male one [290].

Also the nuclear factor-kappa b (NF-κB) pathway, which is crucial for inflammatory response [291], is sex-dependent with its activation being mediated by the adaptor molecule MyD88, which interacts with cytoplasmic estrogen receptor-α [292]. The NF-κB activation is higher in female human umbilical cord vein endothelial cells (HUVEC) than in male ones, under hypoxic conditions [293]. Also the tumor necrosis factor-α (TNF-α) pathway exhibits sex differences. For example, the human female adult cardiac progenitor cells appear to be more responsive to TNF-α when migration and cell cycle progression are considered [294]. Young men have lower levels of TNF-α when compared to fertile women [142]. Also the interleukin systems present some sex differences, with IL-6 being significantly higher in postmenopausal women than in premenopausal women [142], and in young women with CAD either in basal condition or after stress than men [295]. The anti-inflammatory effects of OO and its derivatives are summarized in Tables 2 and 3. In general, female animals and women are less studied and OO with a high content of MPCs is more active in the control inflammation, redox status, and lipid metabolism than OO with low content of MPCs. For example, EVOO with high MPCs reduces peripheral blood mononuclear cells (PBMC) activation of the CD40/CD40 ligand (CD40L) and LDLox and modifies numerous genes [313]. Some MPCs like HTyr exert anti-inflammatory activity with multiple mechanisms attenuating iNOS, COX2, and IL-1β expression and TNF-α and inhibiting the activation of granulocytes and monocytes [116]. Also oleocanthal and Tyr inhibit COX [246, 360].

5.3. Effects of EVOO, VOO, OO, Leaf Extracts, and MPCs on Platelets Function: Influence of Sex. Human platelets are sexually divergent; women have more platelets, longer bleeding time, and more activatable glycoprotein Ilb/Ilia than men whereas platelet spreading and adherence are higher in men than in women [135]. The already described sex differences in AA pathways may induces sex differences in platelet aggregation. Adenosine diphosphate (ADP) and collagen-induced aggregation are higher in women, and women and men respond differently to antiaggregating agents [135, 361]. Both preclinical and clinical studies (Tables 2 and 3) show that EVOO and some of its MPCs (HTyr, oleuropein aglycone, luteolin, and oleocanthal) reduce platelet aggregation [13, 180], interfering either with
Table 2: Some CV effects of EVOO, VOO, OO, leaf extracts, and MPCs.

| Activity | EVOO vs sunflower oil, sunflower oil + oleic acid, MPC-deprived EVOO, sunflower oil enriched with the MPC of EVOO, and sunflower oil + oleic acid + MPC of EVOO | References |
|----------|-------------------------------------------------------------------------------------------------|------------|
| Acetyleprenosiol | Using DPHH test, it exerts antioxidant effects [136] | [136] |
| Caffeic acid | It inhibits 5-LOX and exerts an antioxidant effects in mac rat peritoneal leukocyte triggered by calcium ionophore and PMA [137] | [137] |
| | It decreases IL-1β in human blood cultures (sex not reported) stimulated with LPS [138] | [138] |
| | In healthy men, EVOO reduces urinary excretion of urinary 8-oxo-deoxyguanosine by 13% [139] | [139] |
| | In Apol: deficient mice (14 females and 22 males), the antithromogenic effect of EVOO is reduced by dietary cholesterol [140] | [140] |
| | In Apol: deficient mice (54 females), EVOO from different cultivars reduces atherosclerotic lesions, plaque size, and macrophage recruitment if compared to diets containing palm oil. EVOO also induces a cholesterol-poor, ApoaIV enriched lipoparticles with enhanced arylesterase and antioxidant activities [141] | [141] |
| | In male STZ-diabetic rats, it raises BW and HDL and decreases glyceremia, TG, Chol, being ineffective in healthy rats [142] | [142] |
| | In STZ-diabetic rats (sex not reported), it elevates HDL, and reduces Chol, TG, and LDL [143] | [143] |
| | In human platelets obtained from 3 male and 2 female healthy subjects, it reduces NOX2 activation and H2O2 production [144] | [144] |
| | In vitro, it inhibits α, α-glucosidase, and α-amylase being more active vs α-glucosidase; the richest MPC EVOO is also the most active Suggestive EVOO extract (rich in secoiridoids) is more active in preventing human LDL oxidation than Taggiasca EVOO extract (rich in lignans) (sex not reported) [145] | [145] |
| | In vitro, Spanish EVOO inhibits α-glucosidase, α-amylase, and 5-LOX; LDL and HDL obtained from treated healthy 14 women and 10 men are less oxidizable and are more resistant to lipid peroxidation. Both EVOO and EVOO extract enhance the Chol efflux [146] | [146] |
| | In male hypertensive rats, EVOO + olive + leaf rich in HTPY, 3, 4 dihydroxypropenylglycol, and oleuropein decreases BP, angiotensin II, and endothelin-1 vs low MPC oil. There are no significant differences in plasma Na+, urea, HDL, and LDL [147] | [147] |
| | In an acellular model, HTyr rich extracts have a higher antioxidant and antimutagenic activity than 7yr-rich extract. In HELA cells, the Tyr-rich extract is more effective in increasing GSH whereas ROS levels are not changed by tested EVOO extracts. All extracts upregulate Keap1/Nrf2 pathway [148] | [148] |
| | In male mice, high-fat EVOO diet improves glycemia, insulinaemia, glucose tolerance, insulin sensitivity, and insulin secretion. It reduces β-cell apoptosis and normalizes insulin glucose metabolism vs high fat lard diet EVOO extract inhibits p50 and p65 NF-kB translocation in both stimulated and unstimulated PMA-challenged human monocytes and monocyte-derived macrophages (sex not reported) [149] | [149] |
| | In ECV304 cells (sex not reported), EVOO extract partially prevents the increase of NO/ET-1 levels induced by high glucose/FFA [150] | [150] |
| | In male rats, a bolus of EVOO changes the phospholipid of HDL Serum obtained from 6 healthy males and 6 females treated with EVOO extract rich in oleuropein and ligstroside reduces the VEGF-stimulated increase in NOX, Nox1, and MMP-9 activities, migration, and inflammation. It also regulates VEGF-induced morphological differentiation capacity of HUV EC (sex not reported) into capillary-like structures. In human microvascular endothelial cell line, it reduces the VEGF-induced angiogenesis [151] | [151] |
| | In male rats, subacute administration of both EVOO rich in MPC and native EVOO with low MPCs reduces ADP platelet aggregation, but acutely only MPC-rich extract reduces ADP induced aggregation [152] | [152] |
| | In vitro unfiltered EVOO extract with peptide of low molecular weight inhibits ACE angiotensin converting enzyme in vitro, and in hypertensive male rats, it reduces SRF and DBP [153] | [153] |
| | In Apol: deficient mice (sex not reported), extracts (EVOO vs EVOO + polyphenols green tea) enhance macrophage Chol efflux but only EVOO + polyphenols green tea reduces lipid peroxidation [154] | [154] |
| | In vitro, Galician EVOO with high level of oleuropein and ligstroside derivatives inhibits the α-amylase and α-glucosidase, being more effective in inhibiting α-glucosidase than acarbose [155] | [155] |
| | In all male rats fed with a high-Chol diet, GSH and IL-6 do not vary. EVOO, sunflower oil + MPC of EVOO, and sunflower oil + oleic acid + MPC of EVOO decreases the elevation in MDA and TNF-α levels induced by high-Chol diet [179] | [179] |
| | In healthy men (20 and 30 years), 40 ml of enriched EVOO for one week reduces collagen-stimulated platelet aggregation [180] | [180] |
| | In Apol deficient mice (77 males 63 females), all treatments reduce TG being ineffective versus Chol and vs the number of lesions; however, their dimensions are reduced in females by palm and olive oils [181] | [181] |
| | In male rats, OO reduces and prevents the growth of urinary stones [182] | [182] |
| | In 24 male new Zealand rabbits, it reduces atherosclerosis [183] | [183] |
| | In 40 male new Zealand rabbits, it reduces atherosclerosis [184] | [184] |
| | In human PBMC (sex not reported) and HL60 cells (sex not reported), it inhibits IFN-γ and PMCA induced DNA damage, being HTyr and Tyr, respectively (extract without verbascoside) [185] | [185] |
| | In male rats, single oral administration of the three extracts regulates plasma antioxidant status (DPPH and FRAP) in a time and extract dependent way: In red cells, extracts decrease SOD but increase GPx and CAT [186] | [186] |
In vitro experiments, HTyr and many other phenolic compounds added to standard cell culture media (such as DMEM, MEM, or RPMI) produce H2O2 in the one- to three-digit micromolar range.

In all-trans-diabetic male rats, it lowers glyceremia, TG, Chol, alkaline phosphatases, ALT and AST, augments and lactate transaminases, lipid peroxidation, total and direct bilirubin, creatinine, urea and increases HDL and hepatic renal SOD, CAT, and GPs.

In alloxan-diabetic male rats, it decreases glyceremia, Chol, and oxidative stress.

In STZ-diabetic male rats, it reduces plasma lipid peroxidation, nerve conduction velocity, and thermal nociception and attenuates the decline of sciatic nerve Na+ transport.

In STZ-diabetic male rats, it lowers oxidative, nitrosative, and inflammatory biomarkers and platelet aggregation.

In STZ-diabetic male rats, it reduces retinopathy, lipid peroxidation, nitrosative stress, TBX2, 6-keto-PGF1α, and IL-1β.

In STZ-diabetic male rats, it lowers retinal ganglion cell number, retinal thickness, and cell size.

In STZ-diabetic male rats, it reduces brain lipid peroxidation and inflammation, nitrosative stress, cell death, IL-1β, PGE2.

In STZ-induced diabetic and tretin WR-1339 induced hyperglycemic male mice, it reduces plasma glucose, TG, Chol, lipid peroxidation, TNF-α, CRP and elevates, glucose tolerance, antioxidants, and atherosclerotic index.

It prevents metabolic syndrome and inhibits the hepatic and muscular SREBP-1c/FAS pathway reducing oxidative stress and mitochondrial abnormalities and improving lipid and glucose metabolism in db/db C57BL/6J male mice.

In the brain of diabetic db/db C57BL/6J male mice, it stimulates AMPK, SIRT1, and PPARγ coactivator 1α and reduces oxidative stress.

In LPS-stimulated human monocytic cells (sex not reported), it suppresses NO release and attenuates the transcription and expression of TNF-α, iNOS, and COX2 in a dose-dependent way.

In HUVEC (sex not reported), HTyr and its metabolites suppress TNF-α-induced phosphorylation of NF-κB, ROS production, depletion of GSH, adhesion molecules and downregulate genes encoding antioxidant enzymes. They also reduce the adhesion of human monocytic cells (cell line) to HUVEC. Finally, they reduce carrageenan induced paw edema and TPA-induced ear edema in male mice.

The HTyr pretreatment of HUVEC (sex not reported) suppresses inflammatory angiogenesis induced by PMA and ameliorates mitochondrial function.

In male mice, it ameliorates the impact on body adiposity induced by the obesogenic diet.

In male rats fed with high-fat diet, it reduces AST, ALT, Chol, liver inflammation, and oxidative-stress induced.

It improves glucose tolerance, insulin sensitivity, and intestinal barrier function and increases hepatic PPARα and its downstream-regulated genes.

In male mice fed with diet-induced obesity, it improves glucose homeostasis, insulin signaling markers, chronic inflammation, hepatostasis, and endoplasmic reticulum stress.

In male rats fed with a diet-induced metabolic syndrome, it reduces adiposity and ameliorates impaired glucose, insulin tolerance, and endothelial dysfunction. It also decreases SRB liver fibrillar collagen, and resultant diastolic stiffness and markers of liver damage. Notably, the diet used for induction of metabolic syndrome alters HTyr metabolism.

In endothelial cells obtained from porcine pulmonary arteries (sex not reported), it increases AMPK, CAT activities, forkhead transcription factor, and cytoprotection against TNF-α-induced damage through the suppression of caspase-3 and NF-κB activation. It also promotes wound healing via NF-κB synthesis and stabilization.

In rat aorta VMSC (sex not reported), it exerts a proapoptotic effect through NO production and protein phosphatase 2A activation with subsequent inactivation of Akt.

In rat perilobular leukocytes triggered by calcium ionophore, it inhibits iNOS and exerts antioxidant effects in leukocytes triggered by PMA.

In a female mouse model for accelerated aging, it induces the expression of SIRT1.

In vitro, it inhibits human platelet (sex not reported) aggregation induced by ADP and collagen being more active than other MPCs and TXB2 production induced by collagen and thrombin.

In posol human liver microsomes (sex not reported), it inhibits androstenedione 6β-hydroxylase and reductive TGF-β-HSD activity, whereas it is inactive to oxidative TGF-HSD.

In white adipose of male mice fed with high-fat diet, it reduces the increase in oxidative stress, lipid, and protein oxidation and increases the antioxidant defenses.

In adult male rats, it reduces myocardial infarction area, neurotoxic and apoptosis, the release of LDL and CPK, probably through upregulation of PI3K/AKT pathway.

It is a scavenger of hydroxyl radicals, with peroxynitrite and O2− being inactive vs HOCl and H2O2. It protects LDL against oxidation but is not effective vs the oxidation of LDL isolated from humans by ethanol intake (sex not reported).

It inhibits a glucosidase and α-amylase, being more effective vs α-glucosidase.

In human aortic endothelial cells (sex not reported) stimulated with TNF-α, it significantly reduces the secretion of P-selectin, ICAM-1, VCAM-1, and MCP-1.

In human HUVEC (sex not reported), it reduces the stimulated tube-like differentiation and the stimulated locomotion. MMP-9 secretion induced by PMA, PMA-stimulated COX2 activity and expression. Pretreatment with HTyr before PMA decreases intracellular ROS and nuclear translocation of the p53 NF-κB subunit and NF-κB translocation.

In male rats, HTyr, 3,4-DIPEA-EA and 3,4-DIPEA-EDA reduce the increase in intracortical pumps Ca2+− induced by vasopressin. Further, higher concentration of HTyr exerts an endothelium-independent effect. 3,4-DIPEA-EA and 3,4-DIPEA-EDA exert an endothelium-dependent vasodilatation in aorta increasing the production of NO.

It regulates expression of numerous miRNA in the mice gut (sex not reported) being less effective in other tissues. HTyr administration increases TG.

In male mice, it lowers Chol.

In monocots (sex not reported) stimulated with PMA, it reduces the expression of miRNA and protein of COX2 decreasing PGE2 and PG2 production and increases TNF-α production.

In human neutrophils (sex not reported) stimulated with PMA, or chemotactic peptide FMLP or chemotactic retinoid particles, it does not influence the production of O2− and NOX activity whereas it inhibits the production of H2O2.

In human FBMC (sex not reported) and in human monocytic cell line K562 stimulated with PMA, it reduces the secretion of MMP-9, PGE2, protein production, COX2 protein expression, and COX2 mRNA without modifying COX1. It inhibits both PGE2 and MMP-9 release from human monocyte-derived macrophages. It suppresses NF-κB activation in human mononuclear cells and reduces PKCα and PKCβ1 activation. Notably, it does not affect MMP-9 and COX2 in basal conditions.

In LPS-stimulated human monocytes THP-1 cells (sex not reported), it reduces LPS-stimulated NO and ROS formation in a concentration-dependant way, increases GSH levels, and suppresses the ONOO- activation.

In young male C57BL/6 mice treated with MPC does not modify BW, food intake, and TG but it lowers plasma Chol, leptin. In minir NT-3-LI preadipocytes, it positively modulates the glutathione-driven antioxidant enzymatic machinery reducing GSH/GSSG ratio, through the modulation of genes related to oxidative stress.

In male rats with diet-induced metabolic syndrome, it decreases glucose tolerance, lipids, ALT, AST activity, insulin, weight gain, fat mass, liver steatosis, and ventricular fibrosis.

It prevents COX2, TNF-α, DNA damage, and oxidative stress in Balb/c mice treated with LPS (sex not reported).

It increases the TNF-α mRNA level in LPS-activated human monocytic cells (sex not reported).

In HUVEC (sex not reported), EVOO extracts decrease cell surface expression and mRNA of ICAM-1 and VCAM-1. Olea and HTyr are the main actors for these effects. Homovanillyl alcohol inhibits cell surface expression of adhesion molecules, but the effects on mRNA are small.
HTyr
In male rats fed with high-fat diet, the compounds improve glucose, insulin, leptin levels, lipid peroxidation, and antioxidant status, with HTyr as being the most active. They also reduce the release of inflammatory biomarkers. HTyr-As and HTyr-Et improve adipose tissue distribution and adipokine production, decreasing leptin levels and leptin receptors.

References [227]

HTyr-acetate (HTyr-Ac)
In TNF-α-stimulated HUVEC (sex not reported), it reduces the inflammatory response partly through the TNFR1/2/IKK/NFκB-mediated signaling pathway.

References [229]

HTyr and oleuropein
Both compounds inhibit oxidative burst in human granulocytes and monocytes obtained from healthy individuals (sex not reported) stimulated with PMA. HTyr attenuates the generation of NO and PGE2 in RAW264.7, it reduces NFκB nuclear translocation and mRNA expression.

References [230]

HTyr and HTyr-NO
In vascular ring obtained from male rats, it releases NO while HTyr is ineffective. HTyr NO decreases Chol, TG, lipid peroxidation and increases SOD and NO in the serum of STZ-diabetic male mice. Both HTyr NO and HTyr upregulate SIRT1 expression in the thoracic aorta of male diabetic mice. In HUVEC triggered by hyperglycemia (sex not reported), HTyr NO increases cell viability and reduces oxidative stress through SIRT1

References [231]

HTyr, dihydroxy form of oleic acid linked to HTyr, oleuropein aglycon, oleuropein, Tyr, the dihydroxy form of oleic acid linked to Tyr, caffeic acid, and verbascoside
In human PBM and HLE60 cells (sex not reported), they inhibit H2O2-induced DNA damage

References [185]

Vitamin s mimetic
In male mice fed with a high fat diet, it reduces the triglycerides and elevates the hepatic levels of oleicatropic acid (EPA), docosahexaenoic acid (DHA), resorcinol and attenuates proinflammatory markers.

References [233]

HTyr + eicosapentaenoic acid (EPA)
In STZ-diabetic male rats, the extract augments diabetic abnormalities

References [235]

HTyr + ascorbic acid (EPA)
Both compounds inhibit oxidative burst in human granulocytes and monocytes induced by PMA. HTyr increases cell viability and reduces oxidative stress through SIRT1.

References [236]

Leaf extract
In acellular model, it inhibits DPPH radical generation. In STZ diabetic male rats, the extract causes CAT activity, GSH and lowered lipoperoxidation, Chol, TG, histological pancreas, and hepatic damage

References [237]

HTyr, acetylated form of oleuropein
In male diabetic rats, a high-value is expressed the effects of oleuropein on preventing the cytotoxic effects and only leaf extract preserves Gpx activity

References [238]

HTyr + nicotinate
It inhibits α-glucosidase, and in healthy male mice fed with high-fat diet, it has hypoglycemic, antioxidant, and hypolipidemic activities.

References [239]

HTyr + nicotinate
It inhibits α-glucosidase, and in healthy male mice fed with high-fat diet, it has hypoglycemic, antioxidant, and hypolipidemic activities.

References [240]

HTyr + eicosapentaenoic acid (EPA)
In TNF-α-stimulated HUVEC (sex not reported), it reduces the inflammatory response partly through the TNFR1/2/IKK/NFκB-mediated signaling pathway.

References [241]

HTyr + nicotinate
In male rats, leaf extract containing 28% of HTyr decreases the paw edema induced by carrageenan and IL-1β and TNF-α release. It does not affect the anti-inflammatory cytokine IL-10

References [242]

HTyr + nicotinate
In rat-induced hypercholesterolemic male rats, olive leaf extracts enriched with oleuropein and acetic acid hydrolysates rich in oleuropein aglycone and HTyr decrease Chol, TG, and LDL and elevate HDL and serum antioxidant potential. In livers, hearts, kidneys, and aorta lipid peroxidation decreases while liver CAT and SOD increase

References [243]

Luteolin
In vitro, it inhibits angiotensin converting enzyme

References [244]

Luteolin
It stabilizes atherosclerotic plaque in samples obtained from 20 hypertensive individuals of both sexes

References [245]

Olive water methanol extract
In male rats, when leukocytes are stimulated by PMA (sex not reported), it increases glucose tolerance and oxidative stress but has no effect on obesity.

References [246, 247]

Olive water methanol extract
In in vitro, it inhibits α-glucosidase and α-amylase

References [248, 249]

Olive water methanol extract
In vitro, it inhibits angiotensin converting enzyme

References [250]

Olive water methanol extract
In murine chondrocytic ATDC5 cells and in mouse macrophage J774A.1, it inhibits the LPS-mediated upregulation of NO2 and LPS induced release of cytokines (sex not reported)

References [251]

Olive water methanol extract
In mouse (sex not reported), it reduces the release of O2, PGE2, and the expression of COX2 and inhibits NAPHS-oxidase

References [252]

Oleuropein
In cultured neonatal rat cardiomyocytes (sex not reported), it inhibits NAPH-oxidase and reduces the inflammatory response partly through the α-glucosidase and α-amylase.

References [253]

Oleuropein
In C2C12 cells (sex not reported), it protects against H2O2 induced damage; further it increases glucose consumption and the phosphorylation of PAK2, JAK2, and MAFK and mTOR. It inhibits the insulin sensitivity via insulin-dependent (PI3 kinase/Akt) and insulin independent (AMPK/ACC) pathways.

References [254]

Oleuropein
In bovine VSMC (sex not reported), it inhibits cell proliferation in the G1-S phase by reducing ERK1/2 levels in caco cells (sex not reported), it inhibits malabsorption, human sucrose, glucose transport across Caco-2 monolayers, and uptake of glucose by GLUT2 in Xenopus oocytes; it is a weak inhibitor of human α-amylase

References [255]

Olive water methanol extract
In vitro, it inhibits α-glucosidase and γ-glucosidase and in healthy male rats fed with high-fat diet, it has hypoglycemic, antioxidant, and hypolipidemic activities.

References [256]

Olive water methanol extract
In vivo, it inhibits α-glucosidase and γ-glucosidase

References [257]

Olive water methanol extract
In human monocytes (sex not reported), it reduces the release of O2, PGE2, and the expression of COX2 and inhibits NAPHS-oxidase

References [258]

Olive water methanol extract
In rat and mouse trigeminal ganglia (females and males used in equal ratio) stimulated with serum amyloid A, it reduces the release of IL-6, IL-8, mRNA expression of E-selectin, the phosphorylation of p65 of NFκB, NO production and upregulates COX2 expression, PGE2/B4 synthesis, and NO release

References [259]

Olive water methanol extract
In cultured neonatal rat cardiomyocytes (sex not reported), the diet attenuates hyperglycaemia and impairs glucose tolerance but has no effect on obesity

References [260, 261]
AA pathways [362] or with other mechanisms such as calcium mobilization and attenuating iNOS activity [247, 363]. In hypercholesterolemic patients, MPCs decrease platelet aggregation inhibiting procoagulant factors, such as plasminogen activator inhibitor-1 and factor VII [364]. Small crossover trial proves that oleocanthal is the most active in inhibiting collagen-induced aggregation at least in men [180], probably because it is a nonselective inhibitor of COX. HTyr antiaggregant activity seems to be agonist specific [209]. However, in vivo, it remains difficult to discriminate EVOO associated effects of specific MPCs and phenols. Tables 2 and 3 show that, globally, the majority of the studies are performed on males and even when females are recruited no sex analysis is performed.

5.4. Effect of EVOO, VOO, OO, Leaf Extracts, and MPCs on Glucose Metabolism: Influence of Sex. Their effects are summarized in Tables 2 and 3. Briefly, the antidiabetic actions may reside in the inhibition of α-amylase and α-glucosidase [166, 167, 214, 365], which might lead to less effective absorption of glucose [366]. Some authors suggest that HTyr is a better inhibitor of α-amylase than of α-glucosidase [214]. Also oleuropein inhibits these enzymes [214]. Beyond the inhibition of these enzymes, other mechanisms have been proposed for the antidiabetic activity including antioxidant and anti-inflammatory action (see above) and activation of AMP-activated protein kinase and of incretin release [197, 205–207, 341]. In particular, the antidiabetic activity of HTyr and oleuropein is recently reviewed [367, 368]. Again it emerges that the antidiabetic activity has been mainly studied in males; nevertheless, it clearly shows that DM presents numerous sex differences [39], including the relative risk for CVD associated with hyperglycaemia that is higher in women than in men (Table 1).

5.5. Effects of EVOO, VOO, OO, Leaf Extracts, and MPCs on Uric Acid: Influence of Sex. It is related to CV events both in women and in men [140, 369, 370], but it is a higher risk in women [371]. However, these are not univocal data because others sustain that this association is present only in women [372–374], who have lower plasma levels that men [375]. Leaf extracts of olive tree and HTyr inhibit xanthine oxidase reducing uric acid synthesis [376]. In male rats, HTyr also regulates transcription of some renal transporters that favor uric acid excretion [377].

6. Clinical Studies

Results of clinical studies are summarized in Table 3. The beneficial aspects of regular use of OO on CVD has been suggested by numerous authors [2, 154, 306, 310, 378–380], through the biological activities discussed above and summarized in Table 2. However, clinical studies have common limitations: (a) despite the numerosity of studies, the size of samples is very small and they do not take into account the high interindividual variability; (b) they are relatively limited or of questionable quality; (c) with some exceptions they are very short in duration; (d) they are mainly performed on Mediterranean populations; (e) they have heterogeneous designs, with variation in control diets and in the type of oil used. Therefore, to overcome these limitations we focus on meta-analyses.

Schwingshackl and Hoffmann [381] reported that the use of OO is associated with a 20–40% lower risk of stroke and CHD. Another meta-analysis of case-control, prospective cohort studies and randomized controlled trials proves a negative relationship between OO consumption and stroke (and stroke and CHD combined), but the association is not significant for CHD [348]. A successive meta-analysis proves that high EVOO MPCs ameliorate surrogate end points such as lipid peroxidation, oxLDL, Chol, and HDL [382]. In addition, the subgroup analysis indicates an improvement in inflammatory biomarkers and in BP [382]. After pooling oil interventions, PCR and IL-6 are lowered compared to baseline [380]. Others show that the regular dietary intake of OO reduces CRP, IL-6, and TNF-α [383]. The comparison of the effect of different types of OO (refined, mixed, low and high MPC EVOO) shows no significant effects on Chol, HDL, TG, or DBP [3]. However, in secondary analyses, EVOO may reduce oxLDL vs refined OO in a dose-dependent manner. Finally, one meta-analysis that includes 1089 participants shows that OO increases HDL reducing LDL and TG, while ApoA1 and ApoB are not significantly changed [384].

Table 2: Continued.

| EVOO, VOO, OO, leaf extracts, and MPCs | Activity | References |
|--------------------------------------|----------|------------|
| In RAW 26/4 macrophages (sex not reported), triggered by oxLDL-stimulated Tyr reverts H2O2 generation and the AA release and PGE2 production | [262] |
| In human monocytes (sex not reported) stimulated with PMA, it reduces the production of O2− and the expression of mRNA and protein of COX2, dose-dependently decreasing PGE2 production | [220] |
| In RAW 26/4 macrophages (sex not reported), it reduces the activation of iNOS and COX2 gene expression, NF-κB, interferon regulatory factor-1 (IRF-1), and activation of transcription-1α (STAT-1α) induced by gliadin + IFN-γ | [263] |
| In male rat peritoneal leukocytes triggered by calcium ionophore, it inhibits 5-LOX and exerts antioxidant effects when leukocytes are stimulated by PMA | [157] |
| In human PBMC (sex not reported) and HL60 cells, it inhibits H2O2-induced DNA damage | [185] |
| In PBMC obtained by healthy men and women, it inhibits the increase of IL-1β, MIF, and RANTES induced by endotoxins | [220] |
| In TNF-α-treated HUVEC (sex not reported), Tyr and Tyr-SUL prevent ROS generation and GSH decrease and downregulate Gp91, GCL, and HO-1 genes. Tyr-SUL and Tyr-GLU prevent the phosphorylation of NF-κB signaling proteins. Tyr-GLU and Tyr-SUL prevent the increase of genes and proteins expression and sequestration of adhesion molecules. In vivo, Tyr and Tyr-SUL, in a dose-dependent manner, ameliorate plantar and ear edemas in male mice | [264] |
| In anoxic EA.hy926 human endothelial cell line (sex not reported), both Tyr and oleuropein attenuate anoxia-induced expression of AMPK-9 and MMP-2. Tyr is more efficient than oleuropein in reducing TNF-α. The olive pomace ameliorates all the above parameters and induces time-dependent phosphorylation of p38 MAPK and ERK1/2, and inhibits anoxia-induced NF-κB activation. | [265] |
| Verbascoside | In PBMC (sex not reported) and HL60 cells, it inhibits H2O2-induced DNA damage | [185] |
| Tyr, Tyr glucuronate (Tyr-GLU), and sulfate (Tyr-SUL) | | |
Table 3: Clinical studies on the effect of EVOO, VOO, OO, leaf extracts, and MPCs.

| Compounds                        | Individuals                          | Design                        | Main data                                                                                      | References |
|----------------------------------|--------------------------------------|-------------------------------|-------------------------------------------------------------------------------------------------|------------|
| High MPC EVOO vs moderate and low MPC EVOO | 200 healthy men                      | Multicenter RC crossover design | The negative association between the oleic/linoleic acid ratio and biomarkers of oxidative stress and improvement of LDL fatty acid profile | [296]      |
| EVOO vs saturated fat diet       | 18 healthy postmenopausal women       | Prospective, longitudinal, study | EVOO decreases the risk to develop the metabolic syndrome and CAD                               | [297]      |
| EVOO vs soya oil                 | 41 adult women with excess body fat   | Double-blinded RC vs placebo  | EVOO increases fat loss and reduces DBP and some biochemical parameters After EVOO-based breakfast, numerous inflammatory genes involved in factor NF-κB, AP-1, MAPK, and AA pathways are repressed in PBMC High MPC VOO-based breakfast attenuates plasma LPS, TLR4, and SOCS3 proteins, activation of NF-κB and the IL-6 vs low and intermediate oil. In PBMC, postprandial expression of IL-1B, IL-6, and CXCL1 is reduced especially by high MPC VOO Acute high MPC EVOO transiently improves glycaemia and insulin sensitivity. It directly modifies the miRNA of PBMC. Acute EVOO poor in MPC is less effective EVOO has postprandial anti-inflammatory effects Both atorvastatin and EVOO reduce plasma lipids and increase HDL with a higher activity of atorvastatin After EVOO meal, glucose, TG, ApoB-48, and DPP4 activity decrease, whereas insulin and GLP-1 increase vs meal without EVOO. Chol and HDL do not change after EVOO meal vs meal without EVOO No changes in BW, BMI, central adiposity, fasting blood glucose, SBP, and DBP for all diets. Butter increases LDL; coconut increases HDL EVOO decreases SBP and increases anti-CD3/anti-CD28 stimulated T cell proliferation vs VOO | [298] [299] [300] [278] [301] [302] [303] [304] [305] |
| High MPC VOO vs intermediate and low VOO | 19 men and 30 women with metabolic syndrome | RC, crossover design |                                                                         |            |
| High MPC EVOO vs low MPC EVOO    | 6 healthy men and 6 healthy women; 6 men and 6 women with metabolic syndrome | Paired study                   |                                                                         | [278]      |
| EVOO vs ROO                      | 14 healthy and 14 hypertriacylglycerolemia men | Blind RC crossover design      |                                                                         | [301]      |
| EVOO                             | 26 male and 34 female DM2 patients    | RC trial                      |                                                                         | [302]      |
| EVOO                             | 17 males and 13 females with impaired fasting glucose | Blind RC crossover design      |                                                                         | [303]      |
| EVOO vs coconut oil vs unsalted butter | Healthy women (67%) and men (33%) | RC trial                      |                                                                         | [304]      |
| EVOO vs VOO                      | 41 males and females (overweight or obese) | Single-blinded RC              |                                                                         | [305]      |
| Compounds | Individuals | Design | Main data | References |
|-----------|-------------|--------|-----------|------------|
| VOO rich in MPC vs ROO | 11 women at stage 1 of essential hypertension or 13 with normal-high BP | Double-blind RC crossover design | VOO rich in MPC decreases SBP, DBP, CRP, LDL, ADMA and increases nitrites/nitrates and hyperemic area after ischemia The VOO, walnut, and almond diets reduce LDL; They reduce LDL, Chol, and LDL/HDL ratio. Other lipid fractions, oxidation, and inflammatory biomarkers do not change | [306] |
| Diet enriched with VOO, walnuts, or almonds | 9 female and 9 male hypercholesterolemic patients | RC crossover design | The intake of OO rich in OA reduces the risk of developing DM in individuals with impaired fasting glucose and impaired glucose tolerance | [307] |
| OO rich in MPC vs OO + EGCG | Patients with endothelial dysfunction, OO rich in MPC (13 men and 15 women) OO + EGCG (10 men and 14 women) | Double-blinded RC | They reduce endothelial dysfunction, but only OO reduces inflammatory biomarkers, white blood cells, monocytes, and lymphocytes | [308] |
| OO enriched with oleanolic acid (OA) vs OO | 176 individuals of both sexes with impaired fasting glucose and impaired glucose tolerance | Multicenter double-blind RC trial | The intake of OO rich in OA reduces the risk of developing DM in individuals with impaired fasting glucose and impaired glucose tolerance | [309] |
| MedDiet + EVOO vs MedDiet + nut vs control | 7447 old participants of PREIDMED (43% men and 57% women) at risk for CVD | Observational study in primary prevention | Long intake of MedDiet + EVOO and MedDiet + nut reduces primary CV events High PMC EVOO reduces SBP vs basal values and low PMC VOO. It maintains DBP values compared to low PMC VOO. Further, it reduces ACE and NR1H2 gene expressions vs basal and IL-8RA vs low PMC MPC In plasma, MedDiet + EVOO reduces oxidative and inflammatory status. In PBMC, it reduces oxidative stress, the gene expression of INF-γ, Rho GTPase-activating protein 15, IL-7 receptor, adrenergic β2 receptor and polymerase (DNA-directed) κ. These effects with the exception of polymerase (DNA-directed) κ are more elevated when EVOO rich in polyphenols was added | [11] |
| High MPC EVOO vs moderate and low MPC VOO | 18 healthy men | Double-blind RC, crossover design | Long intake of MedDiet + EVOO and MedDiet + nut reduces primary CV events High PMC EVOO reduces SBP vs basal values and low PMC VOO. It maintains DBP values compared to low PMC VOO. Further, it reduces ACE and NR1H2 gene expressions vs basal and IL-8RA vs low PMC MPC In plasma, MedDiet + EVOO reduces oxidative and inflammatory status. In PBMC, it reduces oxidative stress, the gene expression of INF-γ, Rho GTPase-activating protein 15, IL-7 receptor, adrenergic β2 receptor and polymerase (DNA-directed) κ. These effects with the exception of polymerase (DNA-directed) κ are more elevated when EVOO rich in polyphenols was added | [310] |
| MeDiet + EVOO vs MeDiet + washed EVOO vs habitual diet | 26 healthy men and 64 healthy women | RC crossover design | No effect on fasting plasma lipids, oxLDL, and LPO Only EVOO rich in MPCs lowers oxLDL being ineffective vs plasma lipids | [311] |
| High MPC EVOO vs low MPC EVOO | 46 healthy subjects (14 men and 32 women) | RC crossover design | No effect on fasting plasma lipids, oxLDL, and LPO Only EVOO rich in MPCs lowers oxLDL being ineffective vs plasma lipids | [106] |
| EVOO vs refined OO | 24 men | RC crossover design | No effect on fasting plasma lipids, oxLDL, and LPO Only EVOO rich in MPCs lowers oxLDL being ineffective vs plasma lipids | [312] |
| Compounds | Individuals | Design | Main data | References |
|-----------|-------------|--------|-----------|------------|
| High MPC VOO vs moderate and low MPC VOO | 18 healthy men | RC crossover design | High MPC VOO reduces oxLDL, MPC-1, CD40L, IL-23A, IL-7R, IL-8RA, ADRB2, and OLR1 genes, whereas IFNG, IL-7R, IL-23A, CD40L, MCP-1, and IL-8RA decrease with low MPC VOO | [313] |
| High MPC VOO + triterpenes (OVOO) vs OVOO + higher MPC and triterpenes (FOO) vs low MPC and triterpenes (VOO) | 27 healthy men and 26 healthy women | Double-blind RC, crossover design | Urinary 8-hydroxy-2′-deoxyguanosine, plasma IL-8, and TNF-α decrease more after FOO vs OVOO After OVOO, HDL increases only in females. Chol increases after FOO and TG after VOO and OVOO. SBP decreases after the VOO and increases after the FOO. DBP and pulse pressure do not vary as well as LDL, sICAM-1, and sVCAM-1. Plasma ET-1 decreases after the VOO, OVOO, and FOO | [314] |
| High MPC VOO + triterpenes (OVOO) vs OVOO + higher amounts of MPC and triterpenes (FOO) vs low MPC and triterpenes (VOO) | 27 healthy men and 26 healthy women | Double-blind RC, crossover design | Urinary HTyr sulfate and thymol sulfate increase after FVOO or after FVOOT, respectively. FVOO and FVOOT do not change blood lipids and microbial populations but elevates the coprostanone vs FVOOT | [315] |
| VOO, VOO + MPC (FVOO), VOO + MPC + Thyme phenols (FVOOT) | Hypercholesterolemic men and women | Double-blind RC, crossover design | FVOO decreases ischemic reactive hyperemia, oxLDL, postprandial glycaemia, TG, PAI-1, and CRP vs VOO | [316] |
| VOO vs VOO + MPC (FVOO) vs VOO + MPC + Thyme phenols (FVOOT) | Hypercholesterolemic volunteers: 5 women and 7 men | Double-blind RC, crossover design | FVOO decreases ischemic reactive hyperemia, oxLDL, postprandial glycaemia, TG, PAI-1, and CRP vs VOO | [317] |
| VOO vs VOO + MPC (FVOO) | Hypercholesterolemic volunteers: 19 men and 14 women | Double-blind, RC crossover design | FVOO and FVOOT change the lipoprotein subclasses profile and decrease insulin resistance index. BP and BMI do not change | [318] |
| VOO vs VOO + MPC (FVOO) Prehypertensive or stage 1 hypertension participants (7 men and 6 women) | Double-blind RC crossover design | FVOO decreases ischemic reactive hyperemia, oxLDL, postprandial glycaemia, TG, PAI-1, and CRP vs VOO | [319] |
Table 3: Continued.

| Compounds                                                                 | Individuals                                      | Design                      | Main data                                                                                                                                                                                                                           | References |
|---------------------------------------------------------------------------|--------------------------------------------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| VOO vs VOO + MPC and VOO + Thyme                                           | 8 men and 14 women hypercholesterolemic subjects | Double-blind, RC crossover | In PBMC, the intake of enriched VOO and VOO + thyme increases the expression of proteins involved in Chol efflux and nuclear receptor-related genes                                                                                                         | [320]      |
| VOO vs VOO + MPC (FVOO) and VOO + Thyme (FVOOT)                           | Hypercholesterolic subjects: 19 men and 14 women | Double-blind, RC crossover | The 2 enriched oils elevate antioxidants in HDL, whereas α-tocopherol is elevated only after FVOOT Their consumption of each oil affects the HDL proteome in a cardioprotective mode Only VOO decreases SBP and DBP, serum asymmetric dimethylarginine, oxLDL, and CRP. It increases the plasma nitrites/nitrates ratio and hyperemic area after ischemia After the high MPC breakfast, FVIIa increases less and PAI-1 activity decreases more than after the low MPC breakfast Both OO improve the urinary proteomic CAD score but not chronic kidney disease or DM proteomic biomarkers. No differences are measured between the two OO In white blood cells, high MPC OO increases gene expression of ATP binding cassette transporter-A1, scavenger receptor class B type 1, PPARα, PPARγ, PPAR δ, and CD36 vs moderate MPC OO | [321] [322] [306] [169] |
| VOO vs VOO + MPC vs VOO + MPC + Thyme phenols                             | 19 hypercholesterolic men and 14 women           | Double-blind RC crossover   |                                                                                                                                                                                                                                      | [322]      |
| Diets with VOO and refined OO vs sunflower or corn oil during washout period | 24 young women with high-normal BP or stage 1 essential hypertension | Double-blind RC crossover   |                                                                                                                                                                                                                                      | [306]      |
| High MPC OO enriched breakfast vs low MPC OO breakfast                    | 5 hypercholesterolic men and 16 women            | RC design sequential crossover |                                                                                                                                                                                                                                      | [169]      |
| OO rich in MPC vs refined OO                                               | 69 healthy participants of both sexes             | Double-blind RC parallel design |                                                                                                                                                                                                                                      | [99]       |
| OO with high vs OO with moderate MPC                                       | pre/hypertensive patients 17 men and 6 women     | RC crossover design         |                                                                                                                                                                                                                                      | [323]      |
| High MPC OO vs moderate MPC and low MPC OO                                | 30 healthy subjects of unknown sex               | Double-blind RC vs placebo- crossover design | The consumption of oil rich in MPCs increases MPCs in LDL-C and decreases oxLDL All OO promote postprandial increase in F2-isoprostanes whereas the LDL oxidation is inversely linked with MPCs HDL and Chol increase and decrease linearly with the MPC amounts, respectively. OxLDL and MPC amount are inversely related. TG decrease is not influenced by MPC amount | [324] [325] |
| High MPC OO vs moderate and low MPC OO                                     | 12 healthy male subjects                         | Double-blind RC, crossover design |                                                                                                                                                                                                                                      | [325]      |
| High MPC OO vs moderate and low MPC OO                                     | 200 healthy men                                  | RC crossover design         |                                                                                                                                                                                                                                      | [325]      |
| Compounds                  | Individuals                                      | Design                       | Main data                                                                                                                                  | References |
|----------------------------|--------------------------------------------------|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------|
| High MPC OO vs low MPC OO  | 10 menopausal healthy women                       | RC design crossover          | MPC-rich OO diet reduces DNA damage vs low MPC OO whereas plasma antioxidant capacity does not diverge                                      | [326]      |
| High MPC OO vs moderate and low MPC OO | 12 male healthy subjects                           | Double-blind, RC crossover design | Short-term consumption of MPC-rich OO decreases plasma oxLDL, urinary 8-oxo-dg and increases plasma HDL and GPx vs moderate and low MPC OO | [327]      |
| High MPC OO                 | Patients with polymorphism in NOS3 Glu298Asp (rs1799983) of eNOS (22 men, 35 women) | RC sequential crossover design | Single administration seems to reduce the deleterious effect of the T allele carrier’s condition MPC-rich OO is more effective in protecting LDL oxidation and in raising HDL than OO with lower quantities of MPCS MPC-rich OO lowers plasma TXB₂ and elevates plasma antioxidant capacity vs low MPC OO. Urinary F2-isoprostanes and plasma lipids do not diverge between the two groups High MPC OO protects against postprandial endothelial dysfunction and decreases lipid peroxide and F2-isoprostanes vs low MPC OO. | [328]      |
| High MPC OO vs low MPC OO   | 30 healthy men from a religious center             | RC, crossover design         | Enriched OO decreases IL-6 and CRP being ineffective on soluble sICAM-sVCAM-1 and lipid profile Enriched OO decreases TXB₂ and LTB₄ and increases plasma antioxidant capacity MPC-rich OO decreases oxLDL and LPO and increases GPx. Postprandial lipid and lipoprotein concentrations are not greatly affected versus rapeseed and OO diets have the same effect on LDL oxidation OO may attenuate the acute procoagulant effects of fatty meals | [331]      |
| High MPC OO vs low MPC OO   | 22 mildly dyslipidemic subjects                   | RC crossover design          | It increases in GLP-1 and GIP                                                                                                              | [332]      |
| High MPC OO vs low MPC OO enriched breakfast | 21 hypercholesterolemic subjects (5 men and 16 postmenopausal women) | RC crossover design | Enriched OO decreases IL-6 and CRP being ineffective on soluble sICAM-sVCAM-1 and lipid profile Enriched OO decreases TXB₂ and LTB₄ and increases plasma antioxidant capacity MPC-rich OO decreases oxLDL and LPO and increases GPx. Postprandial lipid and lipoprotein concentrations are not greatly affected versus rapeseed and OO diets have the same effect on LDL oxidation OO may attenuate the acute procoagulant effects of fatty meals | [333]      |
| High MPC OO vs low phenolic OO | 28 individuals with CHD (sex not reported)        | Double-blind RC placebo-controlled, crossover design | Enriched OO decreases IL-6 and CRP being ineffective on soluble sICAM-sVCAM-1 and lipid profile Enriched OO decreases TXB₂ and LTB₄ and increases plasma antioxidant capacity MPC-rich OO decreases oxLDL and LPO and increases GPx. Postprandial lipid and lipoprotein concentrations are not greatly affected versus rapeseed and OO diets have the same effect on LDL oxidation OO may attenuate the acute procoagulant effects of fatty meals | [334]      |
| High MPC OO vs low MPC OO vs corn oil | 12 healthy men                                    | The study has a Latin square design | It increases in GLP-1 and GIP                                                                                                              | [335]      |
| High MPC OO vs low MPC OO   | 40 men with stable CID                            | RC crossover design          | Enriched OO decreases IL-6 and CRP being ineffective on soluble sICAM-sVCAM-1 and lipid profile Enriched OO decreases TXB₂ and LTB₄ and increases plasma antioxidant capacity MPC-rich OO decreases oxLDL and LPO and increases GPx. Postprandial lipid and lipoprotein concentrations are not greatly affected versus rapeseed and OO diets have the same effect on LDL oxidation OO may attenuate the acute procoagulant effects of fatty meals | [336]      |
| OO vs sunflower-seed vs and rapeseed | 18 healthy men                                    | Double-blind RC crossover design | Enriched OO decreases IL-6 and CRP being ineffective on soluble sICAM-sVCAM-1 and lipid profile Enriched OO decreases TXB₂ and LTB₄ and increases plasma antioxidant capacity MPC-rich OO decreases oxLDL and LPO and increases GPx. Postprandial lipid and lipoprotein concentrations are not greatly affected versus rapeseed and OO diets have the same effect on LDL oxidation OO may attenuate the acute procoagulant effects of fatty meals | [337]      |
| OO                         | 18 healthy men                                    | RC crossover design          | It increases in GLP-1 and GIP                                                                                                              | [338]      |
| OO                         | 8 men and 5 women with type DM2                   | Single-blinded RC crossover design | It increases in GLP-1 and GIP                                                                                                              | [339]      |
| Compounds | Individuals | Design | Main data | References |
|-----------|-------------|--------|-----------|------------|
| OO (unrefined) | 23 hypertensive patients of both sexes | Double-blind RC crossover design | Resting SBP and DBP are significantly lower at the end of the MUFA diet vs the PUFA diet. The cold pressor test and isometric exercise are similar. Daily drug dosage is significantly reduced during the MUFA vs PUFA diet | [337] |
| High MPC OO vs low MPC OO | Healthy smokers: 11 men and 14 women | Single-blind RC crossover design | Plasma antioxidant capacity and oxLDL do not differ significantly between the rich and low MPC OO. HPCOO decreases ApoB-100 and small LDL particles vs baseline and LPCOO. LPCOO increases previous parameters. HPCOO increases the lag time of LDL oxidation, which is not affected by LPCOO. LPL gene expression is not significantly changed by both OO. HPCOO increases HDL cholesterol efflux capacity vs the LPCOO and incorporation of MPC and their metabolites in HDL and HDL2. HPCOO intake decreases HDL3 and the HDL core becomes TG-poor, and HDL fluidity increased. | [18] |
| High MPC OO (HPCOO); low MPC VOO (LPCOO), refined OO | 25 healthy men | RC parallel, crossover, design | | [338] |
| High MPC OO (HPCOO); VOO low MPC OO (LPCOO); refined OO | 47 healthy men | RC crossover design | | [339] |
| HTyr | Healthy subjects (12 men and 16 women) | Double-blinded, RC crossover design | Regular intake of HTyr improves the antioxidant defense and decreases nitrate and MDA | [340] |
| HTyr | 21 healthy volunteers (sex not reported) | Double-blinded, RC crossover design | In PBMC, it induces miR-193a-5p, which leads to the generation of anti-inflammatory molecules. No effect on postprandial glucose derived from bread, but in solution it attenuates postprandial blood glucose after 25 g sucrose, but has no effect after 50 g of sucrose or glucose. Its intake lowers glycaemia, DPP-4 activity, soluble NADPH oxidase-derived peptide activity, 8-iso-PGF2α, platelet p47phox phosphorylation and elevates insulin and GLP-1. | [218] |
| Oleuropein | 24 healthy participants (sex not reported) | Double-blind RC Latin square design | | [254] |
| Oleuropein | Healthy 10 men and 10 women | Double-blind RC crossover study | | [341] |
| Low-fat diet vs high in saturated fat (butter) vs high in monounsaturated fat (EVOO) diets | 8 women and 5 men with type 1 DM | RCT crossover design | The addition of EVOO attenuates the early postprandial glucose response | [342] |
### Table 3: Continued.

| Compounds | Individuals | Design | Main data | References |
|-----------|-------------|--------|-----------|------------|
| Lunch + EVOO | 17 men and 13 women patients with impaired fasting glucose | RCT crossover design | Lunch + EVOO reduces glucose, TG, apoB-48, and DPP4 activity and increases insulin and GLP1. Chol and HDL do not change. | [303] |
| Lunch + EVOO | 12 healthy men and 13 healthy women | RC crossover design | Lunch + EVOO decreases postprandial glucose and LDL. Lunch + EVOO ameliorates postprandial oxidative stress and endothelial dysfunction being lunch + corn oil ineffective. | [343] |
| Lunch + EVOO vs lunch + corn oil | Healthy subjects (12 men and 13 women) | RCT crossover design | | [344] |
| Lunch + EVOO | 30 patients with impaired fasting glucose | RC crossover design | Lunch+EVOO attenuates the increase of oxidative stress and in LPS MedDiet + EVOO decreases urinary 8-oxo-7,8-dihydro-2′-deoxyguanosine and prostanoids. | [345] |
| Lunch + EVOO | Subgroup of the PREDIMED study, 110 women with metabolic syndrome | Multicenter, controlled parallel group | MedDiet + EVOO and MedDiet + nuts reduce the incidence of major CV events by approximately 30% vs the control diet. | [346] |
| MedDiet + EVOO vs MedDiet + nuts vs MedDiet with advice to use low fat | 7477 individuals (57% women) at high CV risk | Randomized multicenter PREDIMED study testing the MedDiet in primary CV prevention | MedDiet + EVOO reduces the risk of atrial fibrillation. | [347] |
| MedDiet + EVOO vs MedDiet + nuts vs MedDiet with advice to use low fat | 2292 (1343 women) patients with high CV risk 2210 (1200 women) 2203 (1323 women) | Post hoc analysis of the PREDIMED study | MedDiet + EVOO decreases the BW and changes fat distribution. | [348] |
| MedDiet + EVOO vs MedDiet + nuts vs MedDiet with advice to use low fat | 351 men and women with DM2 or CV risk ≥3 | A subgroup of PREDIMED study | The MedDiet + EVOO reduces DM2 risk among persons with high CV risk MedDiet + EVOO may delay the introduction of glucose-lowering medications MedDiet especially if supplemented with EVOO changes the transcriptomic response of genes related to CV risk. | [349] |
| MedDiet + EVOO vs MedDiet + nuts vs MedDiet with advice to use low fat | Men and women (3541 patients) at high CV risk | PREDIMED study | Both diets decrease IL-6, IL-8, MCP-1, and MIP-1β. MedDiet + EVOO decreases IL-1β, IL-5, IL-7, IL-12p70, IL-18, TNF-α, IFNγ, GCSF, GM-CSF, ENA78, E-selectin, and sVCAM-1 vs the MedDiet + nuts group. | [350] |
| MedDiet + EVOO vs MedDiet + nuts, low-fat diet | 3230 men and women with DM2 | PREDIMED study | | [351] |
| MedDiet + EVOO vs MedDiet + nuts, low-fat diet | Old men and women | PREDIMED study | | [352] |
| MedDiet + EVOO vs MedDiet + nuts, low-fat diet | Old men and women | PREDIMED study | | [353] |
Another crucial risk factor for CVD is hypertension [385], a condition that presents numerous sex differences [386]. After 4 years of follow-up, results of interventional and randomized PREDIMED study show no significant variations in systolic blood pressure (SBP), whereas DBP is decreased in EVOO and EVOO + nuts MedDiet [387]. The 1-year trial that examines 235 subjects (56.5% women) proves that MedDiet supplemented with either EVOO or mixed nuts reduces SBP and DBP [388]. A meta-analysis, which includes primary and secondary prevention trials proves that high MPC OO slightly reduces SBP and oxLDL compared to low MPC OO, leaving Chol, TG, MDA, and DBP unchanged [389]. A very small decrease in blood pressure is observed in MedDiet + EVOO or nut vs low-fat control group [390]. Finally, the meta-analysis of RTC of PREDIMED shows that the MedDiet lowers SBP by 3.02 mm Hg and DBP by 1.99 mm Hg [391]. Importantly, a systemic review that includes primary prevention proves the importance of pharmaceutical form because only liquid oil but not capsule with oil significantly reduces DBP [392].

OO impacts on glucose metabolism, two meta-analyses, which include cohort and interventional studies in prevention and care of DM2 [380, 393], prove that there is a 16% risk reduction in people that consume more OO with high

### Table 3: Continued.

| Compounds | Individuals | Design | Main data | References |
|-----------|-------------|--------|-----------|------------|
| MedDiet + EVOO vs MedDiet + nuts, low-fat diet | 160 (74 men and 86 women) with high CV risk | PREDIMED study subgroup | Both diets reduce CRP, IL-6, TNF-α, and MCP-1. After 3 years, both reduce CD49d and CD40 expressions in T lymphocytes and monocytes and increase HDL but decrease Chol, LDL, TG, and BP. At 5 y, low-fat diet increases glucose and glycated hemoglobin EVOO but not corn oil counteracts the upregulation of NOX2 protecting from postprandial oxidative stress. | [354] |
| MedDiet vs MedDiet + EVOO MedDiet + corn oil | 12 men and 13 women | RC crossover design | MedDiet rich in OO improves endothelial function in patients with prediabetes and DM vs low-fat diet. It reduces plasma TC, LDL, TAG, HDL, Chol/HDL ratio, IL-8. It does not affect oxLDL, CRP, adiponectin, ICAM-1, VCAM-1, P-selectin, E-selectin, IL-6, IL-10, IL-1β, TNF-α, fasting glucose, insulin, fructosamine or calculated HOMA-IR or QUICKI indices, nitrites. It reduces SBP and DBP. | [344] |
| MedDiet rich in OO | 805 patients (sex not reported) with CHD, who had their last coronary event more than 6 months before enrolment, stratified in diabetes and prediabetes | Prospective, randomized, single-blind, controlled trial (CORDIOPREV) | MedDiet rich in OO improves endothelial function in patients with prediabetes and DM vs low-fat diet. It reduces plasma TC, LDL, TAG, HDL, Chol/HDL ratio, IL-8. It does not affect oxLDL, CRP, adiponectin, ICAM-1, VCAM-1, P-selectin, E-selectin, IL-6, IL-10, IL-1β, TNF-α, fasting glucose, insulin, fructosamine or calculated HOMA-IR or QUICKI indices, nitrites. It reduces SBP and DBP. | [335] |
| Leaf extract | 60 prehypertensive men | Double-blind, RC crossover design | Leaf extract 9 male and 9 female healthy volunteers | Double-blind, RC crossover design | Leaf extract reduces plasma TC, LDL, TAG, HDL, Chol/HDL ratio, IL-8. It does not affect oxLDL, CRP, adiponectin, ICAM-1, VCAM-1, P-selectin, E-selectin, IL-6, IL-10, IL-1β, TNF-α, fasting glucose, insulin, fructosamine or calculated HOMA-IR or QUICKI indices, nitrites. It reduces SBP and DBP. | [356] |
| Leaf extract | 9 male and 9 female healthy volunteers | Double-blind, RC crossover design | Leaf extract 46 participants (sex not reported) | Double-blinded RC, placebo-controlled trial | Leaf extract 46 participants (sex not reported) | Double-blinded RC, placebo-controlled trial | Leaf extract reduces plasma TC, LDL, TAG, HDL, Chol/HDL ratio, IL-8. It does not affect oxLDL, CRP, adiponectin, ICAM-1, VCAM-1, P-selectin, E-selectin, IL-6, IL-10, IL-1β, TNF-α, fasting glucose, insulin, fructosamine or calculated HOMA-IR or QUICKI indices, nitrites. It reduces SBP and DBP. | [358] |
| Leaf extract | 152 patients with stage-1 hypertension (85.4% and 87.6% women in OO and captopril groups, respectively) | Double-blind RC | Leaf extract 152 patients with stage-1 hypertension (85.4% and 87.6% women in OO and captopril groups, respectively) | Double-blind RC | Leaf extract and captopril reduce SBP and DBP in a similar manner. Only leaf extract reduces TG. | [359] |
amount of MPCs vs those who consume OO with small amounts of MPCs. In patients with DM2, OO supplementation reduces HbA1c, fasting plasma glucose and inflammatory biomarkers, compared to controls [380]. In addition, MedDiet and MedDiet+EVOO+nuts reduce metabolic syndrome and insulin resistance in the postpartum [394, 395].

Indeed, a systemic review and meta-analysis, which includes RC trials that examine lipid profile, inflammation, and oxidative stress biomarkers in individuals that consume low MPC OO and high MPC OO, observed the improvement in MDA, oxLDL, Chol, and HDL. The subgroup analyses and individual studies measure additional improvements in inflammatory markers and blood pressure. Nevertheless, the authors conclude that there is a need for longer-term studies in non-Mediterranean populations because most studies were rated as having low-to-moderate risk of bias [382]. A recent meta-analysis, including RC trials for more than 3 weeks and examining at least two of the following OO: refined OO, mixed OO, low MPC EVOO, and high MPC EVOO, suggests that it is not possible to reach any clear conclusion for the beneficial effects [3]. Moreover, in line with what was observed with prescription drugs [39], a gender gap exists because the majority of clinical studies are performed mainly on males, and if they include females, results are not stratified for sex. This leads to low scientific value of the results in consideration of the numerous sex differences observed in CVD, DM, and hypertension (Table 1).

7. Conclusions

To have a clear conclusion, it is important to harmonize study design. For example, it will be important to declare whether the goal is the use of OO as a supplement or as a part of dietary pattern. If it is given as a supplement, it is important to consider the pharmaceutical form (liquid, capsule, and excipients) because this could modify both the pharmacokinetics and pharmacodynamics. Furthermore, considering the prevention and therapy of non-communicable diseases such as CVD and DM, there is a need for long-term studies that consider also a sufficient number of extra-Mediterranean people and low-risk populations (most of the trials are conducted on high-risk populations and this could result in underestimation of possible benefits on low-risk populations [396]).

Considering the great sex differences observed in CVD (Table 1) and in DM [32, 39, 397] and the possible sex-divergent effects of MPCs [25, 26, 398, 399], it is necessary to enroll males and females in studies, to overcome the sex and gender gap that pervades all the research in the field of the OO, VO0, EVOO, leaf extracts, and MPCs. In the era of personalized medicine, it is mandatory to consider the sex and gender aspects to answer a multiplicity of questions regarding the effects of diet and specific diet components on health and to relieve consumer uncertainty and promote health, comprehensive cross-demographic studies using the latest technologies, which include foodomics, integrated omics approaches, personomics, and appropriate study design.

Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| ACC          | Acetyl-CoA carboxylase |
| ACE          | Angiotensin converting enzyme |
| PI3 kinase   | Phosphatidylinositol 3-kinase/Akt |
| ADAMTS       | A disintegrin and metalloproteinase with thrombospondin motifs (aggrecanase) |
| AMPK         | AMP-activated protein kinase |
| AP-1         | Activator protein-1 |
| AR           | Androgen receptor |
| ALT          | Alanine aminotransferase |
| AST          | Aspartate aminotransferase |
| Chol         | Cholesterol |
| COX          | Cyclo-oxygenase |
| CRP          | C reactive protein |
| CVD          | Cardiovascular disease |
| DPP4         | Dipeptidyl-peptidase-4 |
| DPHH         | 1,1-Diphenyl-2-picrylhydrazyl radical |
| ERK          | Extracellular regulated mitogen-activated protein kinase |
| EDHF         | Endothelium-derived hyperpolarization factor |
| EFSAs        | The European Food Safety Authority |
| eNOS         | Endothelial nitric oxide synthase |
| ET           | Endothelin |
| ET-1         | Endothelin receptor-1 |
| EGFR         | Epidermal growth factor receptor |
| EET          | Epoxyeicosatrienoic acid |
| ERK, PI3K/Akt/FOXO3a | Phosphoinositide 3-kinase/Akt/Forkhead box O3 |
| FAS          | Fatty acid synthase |
| FPPS         | Farnesyl diphosphate synthase |
| GCL          | Glutamate-cysteine ligase |
| GIP          | Glucose-dependent insulinotropic polypeptide |
| GLP-1        | Glucagon-like peptide-1 |
| GM-CSF       | Granulocyte-macrophage-colony-stimulating factor |
| GPx-1        | Glutathione peroxidase 1 |
| 17-beta-HSD  | 17-beta-hydroxysteroid dehydrogenase |
| HEL60        | Promyelocytic leukemia cells |
| HMEC-1       | Human microvascular endothelial cell line |
| HIF-1α       | Hypoxia-inducible factor-1 |
| ICAM         | Intercellular adhesion molecule-1 |
| iNOS         | Inducible nitric oxide synthase |
| IL           | Interleukin |
| JNK          | c-Jun N-terminal kinase |
| LPS          | Lipopolysaccharide |
| LPL          | Lipoprotein lipase |
| LTB4         | Leukotriene B4 |
| IRF-1        | Interferon regulatory factor-1 |
| MDA          | Malondialdehyde |
| MIF          | Macrophage migration inhibitory factor |
| MMP          | Matrix metalloproteinases |
| MAPK         | Mitogen-activated protein kinases |
| MCP-1        | Monocyte chemoattractant protein |
| MIP-1α       | Macrophage inflammatory protein-1α |
MPC: Minor polar compound
MPO: Myeloperoxidase
EGFR: Epidermal growth factor receptor
miRNAs: Micro-ribonucleic acids
NADPH oxidase: Nicotinamide adenine dinucleotide phosphate oxidase
NEP: Neutral endopeptidase
NO: Nitrogen oxide
NF-κB: Nuclear factor-kappa B
Nrf2: Nuclear factor E2-related factor 2
oxLDL: Oxidized low-density lipoprotein
OH-1: Heme oxygenase-1
PAI-1: Plasminogen activator inhibitor-1
PI3: Phosphatidylinositol 3-kinase/Akt
PMAS: Phosphatidylserine
PHL-2: Prostacyclin
PPAR: Peroxisome proliferator activated receptor
coactivator-1α: PPARγ coactivator 1α
ROS: Reactive oxygen species
mTOR: Mammalian target of rapamycin
TXA2: Thromboxane A2
TXB2: Thromboxane B2
TRPA1: Transient receptor potential channel subtype A1
SIRT: Sirtuin
SREBP-1c: Sterol regulatory element binding protein 1c
STZ: Streptomyein
TG: Triacylglycerol
VCAM-1: Vascular cell adhesion molecule-1
VEGF: Vascular endothelial growth factor
VSMC: Vascular smooth muscle cells
Akt: Protein kinase B
CBS: Cystathionine β-synthase
CD: Cluster of differentiation
CSE: Cystathionine γ-lyase
EGFR: Epidermal growth factor receptor
FMO3: Flavin containing monoxygenase 3
p-Akt: Phosphorylated Akt
p-ERK: Phosphorylated Akt

Conflicts of Interest
The authors confirm that there are no conflicts of interest.

Acknowledgments
This work was supported by EXTRANUTRAOILS, MIPAF Project, 2019, and BIOSINOILS Project, PEI-AGRI, GO2017, Tuscany Region, Italy.

References
[1] G. Grosso, S. Marventano, J. Yang et al., "A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: are individual components equal?" Critical Reviews in Food Science and Nutrition, vol. 57, no. 15, pp. 3218–3232, 2017.
[2] G. Buckland and C. A. Gonzalez, "The role of olive oil in disease prevention: a focus on the recent epidemiological evidence from cohort studies and dietary intervention trials," British Journal of Nutrition, vol. 113, no. S2, pp. S94–S101, 2015.
[3] L. Schwingshackl, M. Krause, C. Schmucker, G. Hoffmann, G. Rücker, and J. J. Meinshausen, "Impact of different types of olive oil on cardiovascular risk factors: a systematic review and network meta-analysis," Nutrition, Metabolism and Cardiovascular Diseases, vol. 29, no. 10, pp. 1030–1039, 2019.
[4] World Health Organisation, Cardiovascular Diseases (CVDs). Fact Sheet, World Health Organisation, Geneva, Switzerland, 2017, http://www.who.int/mediacentre/factsheets/fs317/en/.
[5] M. Dinu, G. Pagliai, A. Casini, and F. Soﬁ, "Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials," European Journal of Clinical Nutrition, vol. 72, no. 1, pp. 30–43, 2018.
[6] K. Rees, A. Takeda, N. Martin et al., "Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease," The Cochrane Database of Systematic Reviews, vol. 3, no. 3, Article ID CD009825, 2019.
[7] P. Leren, "The Oslo diet-heart study," Circulation, vol. 42, no. 5, pp. 935–942, 1970.
[8] O. Turpeinen, J. Marttunen, J. Miettinen, R. Elosuo, and E. Paavilainen, "Dietary prevention of coronary heart disease: the Finnish mental hospital study," International Journal of Epidemiology, vol. 8, no. 2, pp. 99–118, 1979.
[9] M. L. Burr, J. F. Gilbert, R. M. Holliday et al., "Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART)," The Lancet, vol. 334, no. 8666, pp. 757–761, 1989.
[10] A. Keys, A. M. M. Karvonen et al., "The diet and 15-year death rate in the seven countries study," American Journal of Epidemiology, vol. 124, no. 6, pp. 903–915, 1986.
[11] R. Estruch, E. Ros, J. Salas-Salvado et al., "Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts," New England Journal of Medicine, vol. 378, no. 25, pp. 2441-2442, 2018.
[12] A. S. Abdelhamid, N. Martin, C. Bridges et al., "Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease," The Cochrane Database of Systematic Reviews, vol. 11, no. 11, Article ID CD012345, 2018.
[13] S. Cicerale, L. Lucas, and R. Keast, "Biological activities of phenolic compounds present in virgin olive oil," International Journal of Molecular Sciences, vol. 11, no. 2, pp. 458–479, 2010.
[14] T. Weinbrenner, M. Fito, M. Farre Argalló et al., "Bioavailability of phenolic compounds from olive oil and oxidative/antioxidant status at postprandial state in healthy humans," Drugs under Experimental and Clinical Research, vol. 30, no. 5-6, pp. 207–212, 2004.
[15] I. Marrugat, M.-I. Covas, M. Fitó et al., "Effects of differing phenolic content in dietary olive oils on lipids and LDL
oxidation,” *European Journal of Nutrition*, vol. 43, no. 3, pp. 140–147, 2004.

[16] F. Visioli and E. Bernardini, “Extra virgin olive oil’s polyphenols: biological activities,” *Current Pharmaceutical Design*, vol. 17, no. 8, pp. 786–804, 2011.

[17] W. H. F. Sutherland, S. A. de Jong, R. J. Walker et al., “Effect of meals rich in heated olive and safflower oils on oxidation of postprandial serum in healthy men,” *Atherosclerosis*, vol. 160, no. 1, pp. 195–203, 2002.

[18] J. Moschandreas, M. Vissers, S. Wiseman, K. van Putte, and A. Kafatos, “Extra virgin olive oil phenols and markers of oxidation in Greek smokers: a randomized cross-over study,” *European Journal of Clinical Nutrition*, vol. 56, no. 10, pp. 1024–1029, 2002.

[19] M.-I. Covas, K. de la Torre, M. Farré-Albaladejo et al., “Postprandial LDL phenolic content and LDL oxidation are modulated by olive oil phenolic compounds in humans,” *Free Radical Biology and Medicine*, vol. 40, no. 4, pp. 608–616, 2006.

[20] C. Thomsen, H. Storm, J. J. Holst, and K. Hermansen, “Differential effects of saturated and monounsaturated fats on postprandial lipemia and glucagon-like peptide 1 responses in patients with type 2 diabetes,” *The American Journal of Clinical Nutrition*, vol. 77, no. 3, pp. 605–611, 2003.

[21] N. Mekki, M. Charbonnier, P. Borel et al., “Butter differs from olive oil and sunflower oil in its effects on postprandial lipemia and triacylglycerol-rich lipoproteins after single mixed meals in healthy young men,” *The Journal of Nutrition*, vol. 132, no. 12, pp. 3642–3649, 2002.

[22] 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 3468), “can help to maintain a normal function of gastrointestinal tract” (3779), and “contributes to body defences against external agents” (ID 3467) pursuant to Article 13(1) of Regulation (EC) No 1924/2006,” *EFSA Journal*, vol. 9, no. 4, p. 2033, 2011.

[23] P. M. Barnes, B. Bloom, and R. L. Nahin, “Complementary and alternative medicine use among adults and children: United States, 2007,” *National Health Statistics Reports*, vol. 10, no. 12, pp. 1–23, 2008.

[24] R. A. Matulka, *Dietary Supplements in the U.S. and Abroad: Similarities and Differences*, Burdock Group, Orlando, FL, USA, 2016.

[25] I. Campesi, A. Romani, and F. Franconi, “The sex–gender effects in the road to tailored botanicals,” *Nutrients*, vol. 11, no. 7, 2019.

[26] I. Campesi, M. Marino, M. Cipolletti, A. Romani, and F. Franconi, “Put gender glasses on the effects of phenolic compounds on cardiovascular function and diseases,” *European Journal of Nutrition*, vol. 57, no. 8, pp. 2677–2691, 2018.

[27] B. M. Dietz, A. Hajirihamkhan, T. L. Dunlap, and J. L. Bolton, “Botanicals and their bioactive phytochemicals for women’s health,” *Pharmacological Reviews*, vol. 68, no. 4, pp. 1026–1073, 2016.

[28] L. Mosca, S. M. Grundy, D. Judelson et al., “AHA/ACC scientific statement: consensus panel statement. Guide to preventive cardiology for women,” *American Heart Association/American College of Cardiology*, *Journal of the American College of Cardiology*, vol. 33, no. 6, pp. 1751–1755, 1999.

[29] H. M. den Ruijter, S. Hattjema, F. W. Asselbergs, and G. Pasterkamp, “Sex matters to the heart: a special issue dedicated to the impact of sex related differences of cardiovascular diseases,” *Atherosclerosis*, vol. 241, no. 1, pp. 205–207, 2015.

[30] R. E. Harvey, K. E. Coffman, and V. M. Miller, “Women-specific factors to consider in risk, diagnosis and treatment of cardiovascular disease,” *Women’s Health*, vol. 11, no. 2, pp. 239–257, 2015.

[31] R. Ventura-Clapier, E. Dworatzek, U. Seeland et al., “Sex in basic research: concepts in the cardiovascular field,” *Cardiovascular Research*, vol. 113, no. 7, pp. 711–724, 2017.

[32] V. Regitz-Zagrosek, S. Oertelt-Prigione, E. Prescott et al., “Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes,” *European Heart Journal*, vol. 37, no. 1, pp. 24–34, 2016.

[33] F. Franconi, C. Carru, I. Spoletini et al., “A GENs-based approach to cardiovascular pharmacology: impact on metabolism, pharmacokinetics and pharmacodynamics,” *Therapeutic Delivery*, vol. 2, no. 11, pp. 1437–1453, 2011.

[34] F. Franconi, G. Rosano, S. Basili, A. Montella, and I. Campesi, “Human cells involved in atherosclerosis have a sex,” *International Journal of Cardiology*, vol. 228, pp. 983–1001, 2017.

[35] A. P. Arnold, L. A. Cassis, M. Eghbali, K. Reue, and K. Sandberg, “Sex hormones and sex chromosomes cause sex differences in the development of cardiovascular diseases,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 37, no. 5, pp. 746–756, 2017.

[36] R. Addis, I. Campesi, M. Fois et al., “Human umbilical endothelial cells (HUVECs) have a sex: characterisation of the phenotype of male and female cells,” *Biol Sex Differ*, vol. 5, no. 1, p. 18, 2014.

[37] I. Campesi, S. Occhiioni, G. Capobianco et al., “Sex-specific pharmacological modulation of autophagic process in human umbilical artery smooth muscle cells,” *Pharmacological Research*, vol. 113, no. Pt A, pp. 166–174, 2016.

[38] I. Campesi, G. Capobianco, S. Desole, S. Occhioni, A. Montella, and F. Franconi, “Estrogenic compounds have divergent effects on human endothelial progenitor cell migration according to sex of the donor,” *Journal of Vascular Research*, vol. 52, no. 4, pp. 273–278, 2015.

[39] I. Campesi, F. Franconi, G. Seghieri, and M. Meloni, “Sex–gender-related therapeutic approaches for cardiovascular complications associated with diabetes,” *Pharmacological Research*, vol. 119, pp. 195–207, 2017.

[40] M. C. Kander, Y. Gui, and Z. Liu, “Gender difference in oxidative stress: a new look at the mechanisms for cardiovascular diseases,” *Journal of Cellular and Molecular Medicine*, vol. 21, no. 5, pp. 1024–1032, 2017.

[41] A. E. Staniewicz, M. M. Wenner, and N. S. Stachenfeld, “Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan,” *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 315, no. 6, pp. H1569–H1588, 2018.

[42] R. D. Anderson and C. J. Pepine, “Gender differences in the treatment for acute myocardial infarction,” *Circulation*, vol. 115, no. 7, pp. 823–826, 2007.

[43] J. Wu, F. Dai, C. Li, and Y. Zou, “Gender differences in cardiac hypertrophy,” *Journal of Cardiovascular Translational Research*, vol. 13, no. 1, pp. 73–84, 2019.
[44] K. Thygesen, J. S. Alpert, A. S. Jaffe et al., “Third universal definition of myocardial infarction,” *Circulation*, vol. 126, no. 16, pp. 2020–2035, 2012.

[45] N. Johnston, B. Jönelid, C. Chrisisterson et al., “Effect of gender on patients with ST-elevation and non-ST-elevation myocardial infarction without obstructive coronary artery disease;,” *The American Journal of Cardiology*, vol. 115, no. 12, pp. 1661–1666, 2015.

[46] G. M. Rosano, S. Maffeì, M. G. Andreassi et al., “Hormone replacement therapy and cardioprotection: a new dawn? A statement of the study group on cardiovascular disease in women of the Italian society of cardiology on hormone replacement therapy in postmenopausal women,” *Journal of Cardiovascular Medicine*, vol. 10, no. 1, pp. 85–92, 2009.

[47] C. Vassalle, A. Mercuri, and S. Maffeì, “On oxidative status and cardiovascular risk in women: keeping pink at heart,” *World Journal of Cardiology*, vol. 1, no. 1, pp. 26–30, 2009.

[48] M. Woodward, “Cardiovascular disease and the female disadvantage,” *International Journal of Environmental Research and Public Health*, vol. 16, no. 7, p. 1165, 2019.

[49] K. Backholer, S. A. E. Peters, S. H. Bots, A. Peeters, K. A. Peters, and S. H. van der Schouw, “Sex differences in the relationship between socioeconomic status and cardiovascular disease: a systematic review and meta-analysis,” *Journal of Epidemiology and Community Health*, vol. 71, no. 6, pp. 550–557, 2017.

[50] S. Yusuf, S. Hawken, S. Öunpuu et al., “Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study,” *The Lancet*, vol. 364, no. 9438, pp. 937–952, 2004.

[51] A. J. Shah, N. Ghasemzadeh, E. Zaragoza-Macias et al., “Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events,” *Journal of the American Heart Association*, vol. 3, no. 3, Article ID e000741, 2014.

[52] L. Mosca, E. J. Benjamin, K. Berra et al., “Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update,” *Circulation*, vol. 123, no. 11, pp. 1243–1262, 2011.

[53] O. Lidegaard, E. Lokkegaard, A. Jensen, C. W. Skovlund, and N. Keiding, “Thrombotic stroke and myocardial infarction with hormonal contraception,” *New England Journal of Medicine*, vol. 366, no. 24, pp. 2257–2266, 2012.

[54] C. L. Shufelt and C. N. Bairey Merz, “Contraceptive hormone use and cardiovascular disease,” *Journal of the American College of Cardiology*, vol. 53, no. 3, pp. 221–231, 2009.

[55] J. E. Rossouw, G. L. Anderson, R. L. Prentice et al., “Risks and benefits of estrogen plus progesterin in healthy postmenopausal women: principal results from the women’s health initiative randomized controlled trial,” *JAMA*, vol. 288, no. 288, pp. 321–333, 2002.

[56] L. Serra-Majem, B. Román-Viñas, A. Sanchez-Villegas, M. Guasch-Ferré, D. Corella, and C. La Vecchia, “Benefits of the Mediterranean diet: epidemiological and molecular aspects,” *Molecular Aspects of Medicine*, vol. 67, pp. 1–55, 2019.

[57] United Nations Educational SaCo, *The Mediterranean Diet/ Intangible Heritage*, UNESCO, Paris, France, 2010, http://www.unesco.org/archives/multimedia/document-1680-Eng-2.

[58] G. Grosso, S. Marventano, M. D’Urso, A. Mistretta, and F. Galvano, “The Mediterranean healthy eating, ageing, and lifestyle (MEAL) study: rationale and study design,” *International Journal of Food Sciences and Nutrition*, vol. 68, no. 5, pp. 577–586, 2017.

[59] A. Diolintzi, D. B. Panagiotakos, and L. S. Sidossis, “From Mediterranean diet to Mediterranean lifestyle: a narrative review,” *Public Health Nutrition*, vol. 22, no. 14, pp. 2703–2713, 2019.

[60] H. Gardener, C. B. Wright, Y. Gu et al., “Mediterranean-style diet and risk of ischemic stroke, myocardial infarction, and vascular death: the Northern Manhattan Study,” *The American Journal of Clinical Nutrition*, vol. 94, no. 6, pp. 1458–1464, 2011.

[61] D. Steffer, S. Malysutina, R. Kubinova et al., “Mediterranean diet score and total and cardiovascular mortality in Eastern Europe: the HAPIEE study,” *European Journal of Nutrition*, vol. 56, no. 1, pp. 421–429, 2017.

[62] S. Ahmad, M. V. Mookhey, O. V. Demler et al., “Assessment of risk factors and biomarkers associated with risk of cardiovascular disease among women consuming a Mediterranean diet,” *JAMA Network Open*, vol. 1, no. 8, Article ID e185708, 2018.

[63] World Health Organization, *Health Statistics 2010*, World Health Organization, Geneva, Switzerland, 2010.

[64] C.-M. Kastorini, H. J. Milionis, K. Esposito, D. Giugliano, J. A. Goudevenos, and D. B. Panagiotakos, “The effect of mediterranean diet on metabolic syndrome and its components,” *Journal of the American College of Cardiology*, vol. 57, no. 11, pp. 1299–1313, 2011.

[65] M. A. Martinez-Gonzalez and M. Bes-Rastrollo, “Dietary patterns, Mediterranean diet, and cardiovascular disease,” *Current Opinion in Lipidology*, vol. 25, no. 1, pp. 20–26, 2014.

[66] D. Sleiman, M. R. Al-Badri, and S. T. Azar, “Effect of mediterranean diet in diabetes control and cardiovascular risk modification: a systematic review,” *Front Public Health*, vol. 3, p. 69, 2015.

[67] I. Castro-Quezada, B. Román-Viñas, and L. Serra-Majem, “The Mediterranean diet and nutritional adequacy: a review,” *Nutrients*, vol. 6, no. 1, pp. 231–248, 2014.

[68] R. J. Widmer, A. J. Flammer, L. O. Lerman, and A. Lerman, “The Mediterranean diet, its components, and cardiovascular disease,” *The American Journal of Medicine*, vol. 128, no. 3, pp. 229–238, 2013.

[69] D. Romaguera, T. Norat, A.-C. Vergnaud et al., “Mediterranean dietary patterns and prospective weight change in participants of the EPIC-PANACEA project,” *The American Journal of Clinical Nutrition*, vol. 92, no. 4, pp. 912–921, 2010.

[70] M. A. Martinez-Gonzalez, A. Gea, and M. Ruiz-Canela, “The Mediterranean diet and cardiovascular health,” *Circulation Research*, vol. 124, no. 5, pp. 779–798, 2019.

[71] F. Sofi, C. Macchi, R. Abbate, G. F. Gensini, and A. Casini, “Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score,” *Public Health Nutrition*, vol. 17, no. 12, pp. 2769–2782, 2014.

[72] F. R. P´erez-L´opez, P. Chedraui, J. Haya, and J. L. Cuadros, “Effects of the Mediterranean diet on longevity and age-related morbidity,” *Maturitas*, vol. 64, no. 2, pp. 67–79, 2009.

[73] P. A. van den Brandt, “The impact of a Mediterranean diet on metabolic syndrome and its components,” *The American Journal of Clinical Nutrition*, vol. 92, no. 4, pp. 912–921, 2010.

[74] World Health Organization, *Geneva, Switzerland, 2010.*
The Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses,” *BMJ Open*, vol. 5, no. 8, Article ID e008222, 2015.

K. Esposito, M. I. Maiorino, M. Ciottola et al., “Effects of a Mediterranean-style diet on the need for antihypertensive drug therapy in patients with newly diagnosed type 2 diabetes,” *Annals of Internal Medicine*, vol. 151, no. 5, pp. 306–314, 2009.

K. Esposito, M. I. Maiorino, M. Petrizzo, G. Bellastella, and D. Giugliano, “The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial,” *Diabetes Care*, vol. 37, no. 7, pp. 1824–1830, 2014.

D. Corella, P. Carrasco, J. V. Sorli et al., “Mediterranean diet reduces the adverse effect of the TCF7L2 rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population,” *Diabetes Care*, vol. 36, no. 11, pp. 3803–3811, 2013.

M. Kouvari, D. B. Panagiotakos, C. Chrysohoou et al., “Gender-specific, lifestyle-related factors and 10-year cardiovascular disease risk; the ATTICA and GREECS cohort studies,” *Current Vascular Pharmacology*, vol. 17, no. 4, pp. 401–410, 2019.

S. Soltani, A. Jayedi, S. Shah-Bidar, N. Becerra-Tomás, and J. Salas-Salvadó, “Adherence to the Mediterranean diet in relation to all-cause mortality: a systematic review and dose-response meta-analysis of prospective cohort studies,” *Advances in Nutrition*, vol. 10, no. 6, pp. 1029–1039, 2019.

A. Bédard, L. Corneau, B. Lamarche, S. Dodin, and S. Lemieux, “Sex differences in the impact of the Mediterranean diet on LDL particle size distribution and oxidation,” *Nutrients*, vol. 7, no. 5, pp. 3705–3723, 2015.

A. Bédard, B. Lamarche, L. Corneau, S. Dodin, and S. Lemieux, “Sex differences in the impact of the Mediterranean diet on systemic inflammation,” *Nutrition Journal*, vol. 14, no. 1, p. 46, 2015.

A. Bédard, M. Riverin, S. Dodin, L. Corneau, and S. Lemieux, “Sex differences in the impact of the Mediterranean diet on cardiovascular risk profile,” *British Journal of Nutrition*, vol. 108, no. 8, pp. 1428–1434, 2012.

A. Bédard, A. Tchernof, B. Lamarche, L. Corneau, S. Dodin, and S. Lemieux, “Effects of the traditional Mediterranean diet on adiponectin and leptin concentrations in men and premenopausal women: do sex differences exist?”, *European Journal of Clinical Nutrition*, vol. 68, no. 5, pp. 561–566, 2014.

M. Crous-Bou, T. T. Fung, J. Prescott et al., “Mediterranean diet and telomere length in nurses’ health study: population based cohort study,” *BMJ*, vol. 349, no. dec02 5, p. g6674, 2014.

S. Davinelli, A. Trichopoulou, G. Corbi, I. De Vivo, and G. Scapagnini, “The potential nutrigenoprotective role of Mediterranean diet and its functional components on telomere length dynamics,” *Aging Research Reviews*, vol. 49, pp. 1–10, 2019.

L. Barrea, G. Annunziata, G. Muscogiuri et al., “Trimethylamine N-oxide, Mediterranean diet, and nutrition in healthy, normal-weight adults: also a matter of sex?” *Nutrition*, vol. 62, pp. 7–17, 2018.

C. L. Huang and B. E. Sumpio, “Olive oil, the Mediterranean diet, and cardiovascular health,” *Journal of the American College of Surgeons*, vol. 207, no. 3, pp. 407–416, 2008.

A. Romani, F. Ieri, S. Urciuoli et al., “Health effects of phenolic compounds found in extra-virgin olive oil, by-products, and leaf of Olea europaea L,” *Nutrients*, vol. 11, no. 8, 2019.

D. E. Boskou, “Olive oil,” in *Mediterranean Diets*, A. P. Simopoulos and F. Visioli, Eds., pp. 56–77, Karger Publishers, Basel, Switzerland, 2000.

S. Cicerale, L. Lucas, and R. Keast, “Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil,” *Current Opinion in Biotechnology*, vol. 23, no. 2, pp. 129–135, 2012.

S. Cicerale, X. A. Conlan, A. J. Sinclair, and R. S. Keast, “Chemistry and health of olive oil phenolics,” *Critical Reviews in Food Science and Nutrition*, vol. 49, no. 49, pp. 218–236, 2009.

D. Boskou, G. Blekas, and M. Tsimitoud, “History and characteristics of the olive tree,” in *Olive Oil Chemistry and Technology*, D. Boskou, Ed., American Oil Chemists’ Society Press, Champaign, IL, USA, 1996.

G. Corona, X. Tzonis, M. Assunta Dessì et al., “The fate of olive oil polyphenols in the gastrointestinal tract: implications of gastric and colonic microflora-dependent bio-transformation,” *Free Radical Research*, vol. 40, no. 6, pp. 647–658, 2006.

S. Charoenprasert and A. Mitchell, “Factors influencing phenolic compounds in table olives (Olea europaea),” *Journal of Agricultural and Food Chemistry*, vol. 60, no. 29, pp. 7081–7095, 2012.

M. Brenes, A. García, P. García, and A. Garrido, “Acid hydrolysis of secoiridoid aglycons during storage of virgin olive oil,” *Journal of Agricultural and Food Chemistry*, vol. 49, no. 11, pp. 5609–5614, 2001.

M. Brenes, A. García, P. García, J. J. Rios, and A. Garrido, “Phenolic compounds in Spanish olive oils,” *Journal of Agricultural and Food Chemistry*, vol. 47, no. 9, pp. 3535–3540, 1999.

L. Cecchi, M. Innocenti, F. Melani, M. Migliorini, L. Conte, and N. Mulinacci, “New isobaric lignans from refined olive oils as quality markers for virgin olive oils,” *Food Chemistry*, vol. 219, pp. 148–157, 2017.

S. Silva, M. R. Bronze, M. E. Figueira et al., “Impact of a 6-wk olive oil supplementation in healthy adults on urinary proteomic biomarkers of coronary artery disease, chronic kidney disease, and diabetes (types 1 and 2): a randomized, parallel, controlled, double-blind study,” *The American Journal of Clinical Nutrition*, vol. 101, no. 1, pp. 44–54, 2015.

A. M. Kountouri, A. Mylona, A. C. Kalia, and N. K. Andrikopoulos, “Bioavailability of the phenolic compounds of the fruits (drupes) of Olea europaea (olives): impact on plasma antioxidant status in humans,” *Phytotherapy Research*, vol. 14, no. 10, pp. 659–667, 2007.

R. W. Owen, W. Mier, A. Giacosa, W. E. Hull, B. Spiegelhalder, and H. Bartsch, “Phenolic compounds and squalene in olive oils: the concentration and antioxidant potential of total phenols, simple phenols, secoiridoids, lignansand squalene,” *Food and Chemical Toxicology*, vol. 38, no. 8, pp. 647–659, 2000.

M. Servilli and G. Montedoro, “Contribution of phenolic compounds to virgin olive oil quality,” *European Journal of Lipid Science and Technology*, vol. 104, no. 9–10, pp. 602–613, 2002.

F. Franceschi, R. Coini, S. Carta et al., “Antioxidant effect of two virgin olive oils depends on the concentration and composition of minor polar compounds,” *Journal of Agricultural and Food Chemistry*, vol. 54, no. 8, pp. 3121–3125, 2006.
[104] S. De Santis, M. Cariello, E. Piccinin, C. Sabha, and A. Moschetta, “Extra virgin olive oil: lesson from nutrigenomics,” *Nutrients*, vol. 11, no. 9, 2019.

[105] F. Visioli, D. Caruso, C. Galli, S. Viappiani, G. Galli, and A. Sala, “Olive oils rich in natural catecholic phenols decrease isoprostane excretion in humans,” *Biochemical and Biophysical Research Communications*, vol. 278, no. 3, pp. 797–799, 2000.

[106] M. Vissers, P. Zock, S. Wiseman, S. Meyboom, and M. Katan, “Effect of phenol-rich extra virgin olive oil on markers of oxidation in healthy volunteers,” *European Journal of Clinical Nutrition*, vol. 55, no. 5, pp. 334–341, 2001.

[107] J. Rodríguez-Morató, A. Boronat, A. Kotronoulas et al., “Metabolic disposition and biological significance of simple phenols of dietary origin: hydroxytyrosol and tyrosol,” *Drug Metabolism Reviews*, vol. 48, no. 2, pp. 218–236, 2016.

[108] R. M. de Pablos, A. M. Espinosa-Oliva, R. Hormedo-Ortega, M. Cano, and S. Argüelles, “Hydroxytyrosol protects from aging process via AMPK and autophagy; a review of its effects on cancer, metabolic syndrome, osteoporosis, immune-mediated and neurodegenerative diseases,” *Pharmacological Research*, vol. 143, pp. 58–72, 2019.

[109] G. Corona, J. P. Spencer, and M. A. Dessi, “Extra virgin olive oil phenolics: absorption, metabolism, and biological activities in the GI tract,” *Toxicol Ind Health*, vol. 25, no. 4–5, pp. 285–293, 2009.

[110] R. Domínguez-Perles, D. Auñón, F. Ferreres, and A. Gil-Izquierdo, “Gender differences in plasma and urine metabolites from Sprague-Dawley rats after oral administration of normal and high doses of hydroxytyrosol, hydroxytyrosol acetate, and DOPAC,” *European Journal of Nutrition*, vol. 56, no. 1, pp. 215–224, 2017.

[111] M. Robles-Almazán, M. Pulido-Moran, J. Moreno-Fernández et al., “Hydroxytyrosol: bioavailability, toxicity, and clinical applications,” *Food Research International*, vol. 105, pp. 654–667, 2018.

[112] J. Rodríguez-Morató, P. Robledo, J.-A. Tanner et al., “CYP2D6 and CYP2A6 biotransform dietary tyrosol into hydroxytyrosol,” *Food Chemistry*, vol. 217, pp. 716–725, 2017.

[113] R. De la Torre, D. Corella, O. Castañer et al., “Protective effect of homovanillyl alcohol on cardiovascular disease and total mortality: virgin olive oil, wine, and catechol-methylol,” *The American Journal of Clinical Nutrition*, vol. 105, no. 105, pp. 1297–1304, 2017.

[114] J. I. Moséle, S. Martín-Peláez, A. Maciá et al., “Faeical microbial metabolism of olive oil phenolic compounds: in vitro and in vivo approaches,” *Molecular Nutrition & Food Research*, vol. 58, no. 9, pp. 1809–1819, 2014.

[115] E. Miro-Casas, M.-I. Covas, M. Farre et al., “Hydroxytyrosol disposition in humans,” *Clinical Chemistry*, vol. 49, no. 6, pp. 945–952, 2003.

[116] A. Karkovic Markovic, J. Toric, M. Barbaric, and C. Jakobusic Bral, “Hydroxytyrosol, tyrosol and derivatives and their potential effects on human health,” *Molecules*, vol. 24, no. 10, p. 2001, 2019.

[117] K. L. Pang and K. Y. Chin, “The biological activities of oleocanthal from a molecular perspective,” *Nutrients*, vol. 10, no. 5, 2018.

[118] L. Marin, E. M. Miguelez, C. J. Villar, and F. Lombo, “Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties,” *BioMed Research International*, vol. 2015, Article ID 905215, 18 pages, 2015.

[119] N. M. Saarinen and L. U. Thompson, “Prolonged administration of secoisolariciresinol diglycoside increases lignan excretion and alters lignan tissue distribution in adult male and female rats,” *British Journal of Nutrition*, vol. 104, no. 6, pp. 833–841, 2010.

[120] J. L. Péchalvo, B. Moreno-Franco, L. Ribas-Barba, and L. Serra-Majem, “Determinants of dietary lignan intake in a representative sample of young Spaniards: association with lower obesity prevalence among boys but not girls,” *European Journal of Clinical Nutrition*, vol. 66, no. 7, pp. 795–798, 2012.

[121] L. Rubió, A. Maciá, A. Castell-Auvi et al., “Effect of the co-occurring olive oil and thyme extracts on the phenolic bioaccessibility and bioavailability assessed by in vitro digestion and cell models,” *Food Chemistry*, vol. 149, pp. 277–284, 2014.

[122] D. L. Bohlick, L. K. Snowberg, P. E. Hirsch et al., “Individual diet has sex-dependent effects on vertebrate gut microbiota,” *Nat Commun*, vol. 5, p. 4500, 2014.

[123] M. Elderman, P. de Vos, and M. Faas, “Role of microbiota in sexually dimorphic immunity,” *Frontiers in Immunology*, vol. 9, p. 1018, 2018.

[124] R. N. Carmody and P. J. Turnbaugh, “Host-microbial interactions in the metabolism of therapeutic and diet-derived xenobiotics,” *Journal of Clinical Investigation*, vol. 124, no. 10, pp. 4173–4181, 2014.

[125] G. Clarke, K. V. Sandhu, B. T. Griffin, T. G. Dinan, J. F. Cryan, and N. P. Hyland, “Gut reactions: breaking down xenobiotic-microbiome interactions,” *Pharmacological Reviews*, vol. 71, no. 2, pp. 198–224, 2019.

[126] E. Tripoli, M. Giammanco, G. Tabacchi, D. Di Majo, S. Giammanco, and M. La Guardia, “The phenolic compounds of olive oil: structure, biological activity and beneficial effects on human health,” *Nutrition Research Reviews*, vol. 18, no. 1, pp. 98–112, 2005.

[127] E. Medina, A. de Castro, C. Romero, and M. Brenes, “Comparison of the concentrations of phenolic compounds in olive oils and other plant oils: correlation with antimicrobial activity,” *Journal of Agricultural and Food Chemistry*, vol. 54, no. 14, pp. 4954–4961, 2006.

[128] Y. S. Kim, T. Unno, B. Y. Kim, and M. S. Park, “Sex differences in gut microbiota,” *The World Journal of Men’s Health*, vol. 38, no. 1, pp. 48–60, 2019.

[129] A. C. Razavi, K. S. Potts, T. N. Kelly, and L. A. Bazzano, “Sex, gut microbiome, and cardiovascular disease risk,” *Biology of Sex Differences*, vol. 10, no. 1, p. 29, 2019.

[130] A. Kruger-Genge, A. Blocki, R. P. Franke, and F. Jung, “Vascular endothelial cell biology: an update,” *International Journal of Molecular Sciences*, vol. 20, no. 18, p. 4411, 2019.

[131] M. W. Roos and G. O. Sperber, “A diffusion model of cerebrovascular microcirculation,” *Experimental Neurology*, vol. 147, no. 1, pp. 142–150, 1997.

[132] J. P. J. Halcox, A. E. Donald, E. Ellins et al., “Endothelial function predicts progression of carotid intima-media thickness,” *Circulation*, vol. 119, no. 7, pp. 1005–1012, 2009.

[133] A. D. Hingorani, J. Cross, R. K. Kharbanda et al., “Acute systemic inflammation impairs endothelium-dependent dilatation in humans,” *Circulation*, vol. 102, no. 9, pp. 994–999, 2000.

[134] M. El Assar, J. Angulo, and L. Rodríguez-Mañas, “Oxidative stress and vascular inflammation in aging,” *Free Radical Biology and Medicine*, vol. 65, pp. 380–401, 2013.

[135] G. Patti, R. De Caterina, R. Abbate et al., “Platelet function and long-term antiplatelet therapy in women: is there a
gender-specificity? A “state-of-the-art” paper,” European Heart Journal, vol. 35, no. 33, pp. 2213–2223, 2014.

[136] Y. Shi and P. M. Vanhoutte, “Macro- and microvascular endothelial dysfunction in diabetes,” Journal of Diabetes, vol. 9, no. 5, pp. 434–449, 2017.

[137] W. Malorni, I. Campesi, E. Straface, S. Vella, and F. Fracconi, “Redox features of the cell: a gender perspective,” Antioxidants & Redox Signaling, vol. 9, no. 11, pp. 1779–1802, 2007.

[138] S. L. Klein and K. L. Flanagan, “Sex differences in immune responses,” Nature Reviews Immunology, vol. 16, no. 10, pp. 626–638, 2016.

[139] D. Fairweather, “Sex differences in inflammation during atherosclerosis,” Clinical Medicine Insights: Cardiology, vol. 8, no. Suppl 3, pp. 49–59, 2014.

[140] A. H. Wu, J. D. Gladden, M. Ahmed, A. Ahmed, and D. Fairweather, “Sex differences in oxidative stress status with coronary artery disease,” International Journal of Cardiology, vol. 213, pp. 4–7, 2016.

[141] E. Brunelli, F. Domanico, D. Russa, and D. Pellegrino, “Sex differences in oxidative stress biomarkers,” Current Drug Targets, vol. 15, no. 8, pp. 811–815, 2014.

[142] I. Campesi, S. Occhioni, G. Tonolo et al., “Ageing/menopausal status in healthy women and ageing in healthy men differently affect cardiometabolic parameters,” International Journal of Medical Sciences, vol. 13, no. 2, pp. 124–132, 2016.

[143] O. Taleb-Belkadi, H. Chaib, L. Zemour, A. Fatah, B. Chafi, I. Campesi, S. Occhioni, G. Tonolo et al., “Ageing/menopausal status in peri- and postmenopausal women,” Gynecological Endocrinology, vol. 32, no. 12, pp. 982–985, 2016.

[144] K. Kowalska and H. Milnerowicz, “The influence of age and gender on the pro/antioxidant status in young healthy people,” Annals of Clinical and Laboratory Science, vol. 46, no. 46, p. 480, 2016.

[145] C. Vassalle, R. Sciarrotto, S. Bianchi, D. Battaglia, A. Mercuri, and S. Maffei, “Sex-related differences in association of oxidative stress status with coronary artery disease,” Fertility and Sterility, vol. 97, no. 2, pp. 414–419, 2012.

[146] A. W. Gardner, D. E. Parker, P. S. Montgomery et al., “Gender and racial differences in endothelial oxidative stress and inflammation in patients with symptomatic peripheral artery disease,” Journal of Vascular Surgery, vol. 61, no. 5, pp. 1249–1257, 2015.

[147] G. Block, M. Dietrich, E. P. Norkus et al., “Factors associated with oxidative stress in human populations,” American Journal of Epidemiology, vol. 156, no. 3, pp. 274–285, 2002.

[148] C. Coudray, A. M. Roussel, F. Mainard, J. Arnaud, and A. Favier, “Lipid peroxidation level and antioxidant micronutrient status in a pre-aging population; correlation with chronic disease prevalence in a French epidemiological study (Nantes, France),” Journal of the American College of Nutrition, vol. 16, no. 6, pp. 584–591, 1997.

[149] H. Hirose, H. Kawabe, N. Komiya, and I. Saito, “Relations between serum reactive oxygen metabolites (ROMs) and various inflammatory and metabolic parameters in a Japanese population,” Journal of Atherosclerosis and Thrombosis, vol. 16, no. 2, pp. 77–82, 2009.

[150] T. Fukui, K. Yamauchi, M. Maruyama, T. Yasuda, M. Kohno, and Y. Abe, “Significance of measuring oxidative stress in lifestyle-related diseases from the viewpoint of correlation between d-ROMs and BAP in Japanese subjects,” Hypertension Research, vol. 34, no. 9, pp. 1041–1045, 2011.

[151] T. Ide, H. Tsutsumi, N. Ohashi et al., “Greater oxidative stress in healthy young men compared with premenopausal women,” Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 22, no. 3, pp. 438–442, 2002.
peroxide-mediated NADPH-oxidase 2 activation,” *Nutrition*, vol. 55-56, pp. 36–40, 2018.

[166] M. R. Loizzo, G. D. Lecce, E. Boselli, F. Menichini, and N. G. Frega, “Inhibitory activity of phenolic compounds from extra virgin olive oils on the enzymes involved in diabetes, obesity and hypertension,” *Journal of Food Biochemistry*, vol. 35, no. 2, pp. 381–399, 2011.

[167] M. Figueiredo-González, P. Reboredo-Rodríguez, C. González-Barreiro, A. Carrascos-Pancharo, B. Cancho-Grande, and J. Simal-Gándara, “The involvement of phe-nolic-rich extracts from Galician autochthonous extra-virgin olive oils against the α-glucosidase and α-amylase inhibition,” *Food Research International*, vol. 116, pp. 447–454, 2019.

[168] H. Berrougui, S. Ikhlief, and A. Khalil, “Extra virgin olive oil polyphenols promote cholesterol efflux and improve HDL functionality,” *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, Article ID 208062, 9 pages, 2015.

[169] A. Vazquez, E. Sanchez-Rodriguez, F. Vargas et al., “Cardioprotective effect of a virgin olive oil enriched with bio-active compounds in spontaneously hypertensive rats,” *Nutrients*, vol. 11, no. 8, 2019.

[170] P. Kouka, G. Tsakiri, D. Tzortzi et al., “The polyphenolic composition of extracts derived from different Greek extra virgin olive oils is correlated with their antioxidant potency,” *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 1870965, 13 pages, 2019.

[171] E. Jurado-Ruiz, L. Alvarez-Amor, L. M. Varela et al., “Extra virgin olive oil diet intervention improves insulin resistance and islet performance in diet-induced diabetes in mice,” *Scientific Reports*, vol. 9, no. 1, p. 11311, 2019.

[172] S. Brunelleschi, C. Bardelli, A. Amoruso et al., “Minor polar compounds extra-virgin olive oil extract (MPC-OOE) inhibits NF-κB translocation in human monocyte/macrophages,” *Pharmacological Research*, vol. 66, no. 6, pp. 542–549, 2007.

[173] C. E. Storniolo, J. Roselló-Catafau, X. Pintó, M. T. Mitjavila, and J. J. Moreno, “Polyphenol fraction of extra virgin olive oil protects against endothelial dysfunction induced by high glucose and free fatty acids through modulation of nitric oxide and endothelin-1,” *Redox Biology*, vol. 2, pp. 971–977, 2014.

[174] R. Martinez-Beamonte, M. A. Navarro, S. Acin et al., “Postprandial changes in high density lipoproteins in rats subjected to gavage administration of virgin olive oil,” *PloS One*, vol. 8, no. 1, Article ID e55231, 2013.

[175] N. Calabriso, M. Massaro, E. Scoditti et al., “Extra virgin olive oil rich in polyphenols modulates VEGF-induced angiogenic responses by preventing NADPH oxidase activity and expression,” *The Journal of Nutritional Biochemistry*, vol. 28, pp. 19–29, 2016.

[176] R. Priora, D. Summa, S. Frosali et al., “Administration of minor polar compound-enriched extra virgin olive oil decreases platelet aggregation and the plasma concentration of reduced homocysteine in rats,” *The Journal of Nutrition*, vol. 138, no. 1, pp. 36–41, 2008.

[177] J. M. Alcaide-Hidalgo, M. Margalef, F. I. Bravo, B. Muguerza, and E. Lopez-Villacorta, “Virgin olive oil (unfiltered) extract contains peptides and possesses ACE inhibitory and anti-hypertensive activity,” *Clinical Nutrition*, vol. 39, 2019.

[178] M. Rosenblat, N. Volkova, R. Coleman, Y. Almagor, and M. Aviram, “Antithrombogenicity of extra virgin olive oil and its enrichment with green tea polyphenols in the atherosclerotic apolipoprotein-E-deficient mice: enhanced macrophage cholesterol efflux,” *The Journal of Nutritional Biochemistry*, vol. 19, no. 8, pp. 514–523, 2008.

[179] A. I. Katsarou, A. C. Caliora, A. Chiou et al., “Amelioration of oxidative and inflammatory status in hearts of cholesterol-fed rats supplemented with oils or oil-products with extra virgin olive oil components,” *European Journal of Nutrition*, vol. 55, no. 3, pp. 1283–1296, 2016.

[180] K. Arawal, E. Melliou, X. Li et al., “Oleocanthal-rich extra virgin olive oil demonstrates acute anti-platelet effects in healthy men in a randomized trial,” *Journal of Functional Foods*, vol. 36, pp. 84–93, 2017.

[181] L. Calleja, M. A. Paris, A. Paul et al., “Low-cholesterol and high-fat diets reduce atherosclerotic lesion development in ApoE-knockout mice,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 19, no. 10, pp. 2368–2375, 1999.

[182] J. P. De La Cruz, M. A. Villalobos, J. A. Carmona, M. Marín-Romero, J. M. Smith-Agreda, and F. S. de la Cuesta, “Antithrombotic potential of olive oil administration in rabbits with elevated cholesterol,” *Thrombosis Research*, vol. 100, no. 4, pp. 305–315, 2000.

[183] M. Alenzi, S. Rahman, and B. A. Tantry, “Antiangiogenic effect of olive oil “in a mouse model of ethylene glycol-induced urolithiasis,” *Investigative and Clinical Urology*, vol. 58, no. 3, pp. 210–216, 2017.

[184] O. Bayindir, D. Özmén, I. Mutaf et al., “Comparison of the effects of dietary saturated, mono-, and n-6 polyunsaturated fatty acids on blood lipid profile, oxidant stress, protein synthesis and aortic histology in rabbits,” *Annals of Nutrition and Metabolism*, vol. 46, no. 5, pp. 222–228, 2002.

[185] R. Fabiani, P. Rosignoli, A. De Bartolomeo et al., “Oxidative DNA damage is prevented by extracts of olive oil, hydroxytyrosol, and other olive phenolic compounds in human blood mononuclear cells and HL60 cells,” *The Journal of Nutrition*, vol. 138, no. 8, pp. 1411–1416, 2008.

[186] L. Rubíó, A. Serra, C.-Y. O. Chen et al., “Effect of the co-occurring components from olive oil and thyme extracts on the antioxidant status and its bioavailability in an acute ingestion in rats,” *Food & Function*, vol. 5, no. 4, pp. 740–747, 2014.

[187] S. Schaffer and B. Halliwell, “Comment on hydroxytyrosol induces proliferation and cytoprotection against oxidative injury in vascular endothelial cells: role of Nrf2 activation and HO-1 induction,” *Journal of Agricultural and Food Chemistry*, vol. 59, no. 19, pp. 10770–10771, 2011.

[188] L. H. Long, A. Hoi, and B. Halliwell, “Instability of, and generation of hydrogen peroxide by, phenolic compounds in cell culture media,” *Archives of Biochemistry and Biophysics*, vol. 501, no. 1, pp. 162–169, 2010.

[189] K. Hamden, N. Allouche, M. Damak, and A. Elfeki, “Hypoglycemic and antioxidant effects of phenolic extracts and purified hydroxytyrosol from olive mill waste in vitro and in rats,” *Chemico-Biological Interactions*, vol. 180, no. 3, pp. 421–432, 2009.

[190] H. Jemai, A. El Feki, and S. Sayadi, “Anti-diabetic and anti-oxidant effects of hydroxytyrosol and oleuropein from olive leaves in alloxan-diabetic rats,” *Journal of Agricultural and Food Chemistry*, vol. 57, no. 19, pp. 8798–8804, 2009.

[191] G. Ristagno, F. Fumagalli, C. Porretta-Serapiglia et al., “Hydroxytyrosol attenuates peripheral neuropathy in streptozotocin-induced diabetes in rats,” *Journal of Agricultural and Food Chemistry*, vol. 501, no. 1, pp. 514–523, 2008.
biomarkers in experimental diabetes mellitus,” *The Journal of Nutritional Biochemistry*, vol. 37, pp. 94–100, 2016.

[193] J. A. González-Correja, M. D. Rodríguez-Pérez, L. Márquez-Estrada et al., “Neuroprotective effect of hydroxytyrosol in experimental diabetic retinopathy: relationship with cardiovascular biomarkers,” *Journal of Agricultural and Food Chemistry*, vol. 66, no. 3, pp. 637–644, 2018.

[194] J. J. Reyes, B. Villanueva, J. A. López-Villodres et al., “Neuroprotective effect of hydroxytyrosol in experimental diabetes mellitus,” *Journal of Agricultural and Food Chemistry*, vol. 65, no. 22, pp. 4378–4383, 2017.

[195] Y. Xie, Y. Xu, Z. Chen et al., “A new multifunctional hydroxytyrosol-fenofibrate with anti-diabetic, anti-hyperlipidemic, antioxidant and anti-inflammatory action,” *Biomedicine & Pharmacotherapy*, vol. 95, pp. 1749–1758, 2017.

[196] K. Cao, J. Xu, X. Zou et al., “Hydroxytyrosol prevents diet-induced metabolic syndrome and attenuates mitochondrial abnormalities in obese mice,” *Free Radical Biology and Medicine*, vol. 67, pp. 396–407, 2014.

[197] A. Zheng, H. Li, J. Xu et al., “Hydroxytyrosol improves mitochondrial function and reduces oxidative stress in the brain of db/db mice: role of AMP-activated protein kinase activation,” *British Journal of Nutrition*, vol. 113, no. 11, pp. 1667–1676, 2015.

[198] X. Zhang, J. Cao, and L. Zhong, “Hydroxytyrosol inhibits pro-inflammatory cytokines, iNOS, and COX-2 expression in human monocyctic cells,” *Naunyn-Schmiedeberg’s Archives of Pharmacology*, vol. 379, no. 6, pp. 581–586, 2009.

[199] S. Lopez, S. Montserrat-de la Paz, R. Lucas et al., “Effect of metabolites of hydroxytyrosol on protection against oxidative stress and inflammation in human endothelial cells,” *Journal of Functional Foods*, vol. 29, pp. 238–247, 2017.

[200] N. Calabrissio, A. Gnoni, E. Stanca et al., “Hydroxytyrosol ameliorates endothelial function under inflammatory conditions by preventing mitochondrial dysfunction,” *Oxidative Medicine and Cellular Longevity*, vol. 2018, Article ID 9086947, 14 pages, 2018.

[201] A. Voigt, J. Ribot, A. G. Sabater, A. Palou, M. L. Bonet, and S. Klaus, “Identification of Mest/Peg1 gene expression as a predictive biomarker of adipose tissue expansion sensitive to dietary anti-obesity interventions,” *Genes & Nutrition*, vol. 10, no. 5, p. 27, 2015.

[202] C. Pirozzi, A. Lama, R. Simeoli et al., “Hydroxytyrosol prevents metabolic impairment reducing hepatic inflammation and restoring duodenal integrity in a rat model of NAFLD,” *The Journal of Nutritional Biochemistry*, vol. 30, pp. 108–115, 2016.

[203] N. Wang, Y. Liu, Y. Ma, and D. Wen, “Hydroxytyrosol ameliorates insulin resistance by modulating endoplasmic reticulum stress and prevents hepatic steatosis in diet-induced obesity mice,” *The Journal of Nutritional Biochemistry*, vol. 57, pp. 180–188, 2018.

[204] H. Poudyal, N. Lemonakis, P. Efentakis et al., “Hydroxytyrosol ameliorates metabolic, cardiovascular and liver changes in a rat model of diet-induced metabolic syndrome: pharmacological and metabolism-based investigation,” *Pharmacological Research*, vol. 117, pp. 32–45, 2017.

[205] H. Zrelli, M. Matsuoka, S. Kitazaki, M. Zarrouk, and H. Miyazaki, “Hydroxytyrosol reduces intracellular reactive oxygen species levels in vascular endothelial cells by upregulating catalase expression through the AMPK-FOXO3a pathway,” *European Journal of Pharmacology*, vol. 660, no. 2-3, pp. 275–282, 2011.

[206] H. Zrelli, C. W. Wu, N. Zhghonda, H. Shimizu, and H. Miyazaki, “Combined treatment of hydroxytyrosol with carbon monoxide-releasing molecule-2 prevents TNF alpha-induced vascular endothelial cell dysfunction through NO production with subsequent NF kappaB inactivation,” *BioMed Research International*, vol. 2013, Article ID 912431, 10 pages, 2013.

[207] H. Zrelli, M. Kusunoki, and H. Miyazaki, “Role of hydroxytyrosol-dependent regulation of HO-1 expression in promoting wound healing of vascular endothelial cells via Nrf2 de novo synthesis and stabilization,” *Phytotherapy Research*, vol. 29, no. 7, pp. 1011–1018, 2015.

[208] B. Bayram, B. Ozcelik, S. Grimm et al., “A diet rich in olive oil phenolics reduces oxidative stress in the heart of SAMP8 mice by induction of Nrf2-dependent gene expression,” *Rejuvenation Research*, vol. 15, no. 1, pp. 71–81, 2012.

[209] A. Petroni, M. Blasevich, M. Salami, N. Papini, G. F. Montedoro, and C. Galli, “Inhibition of platelet aggregation and eicosanoid production by phenolic components of olive oil,” *Thrombosis Research*, vol. 78, no. 2, pp. 151–160, 1995.

[210] J. Stupans, G. Stretch, and P. Hayball, “Olive oil phenols inhibit human hepatic microsomal activity,” *The Journal of Nutrition*, vol. 130, no. 9, pp. 2367–2370, 2000.

[211] P. Ilesca, R. Valenzuela, A. Espinosa et al., “Hydroxytyrosol supplementation ameliorates the metabolic disturbances in white adipose tissue from mice fed a high-fat diet through recovery of transcription factors Nrf2, SREBP-1c, PPAR-γ and NF-κB,” *Biomedicine & Pharmacotherapy*, vol. 109, pp. 2472–2481, 2019.

[212] Y. H. Pei, J. Chen, L. Xie et al., “Hydroxytyrosol protects against myocardial ischemia/reperfusion injury through a PI3K/Akt-dependent mechanism,” *Mediators of Inflammation*, vol. 2016, Article ID 1232103, 9 pages, 2016.

[213] S. J. Rietjens, A. Bast, and G. R. M. M. Haenen, “New insights into controversies on the antioxidant potential of the olive oil antioxidant hydroxytyrosol,” *Journal of Agricultural and Food Chemistry*, vol. 55, no. 18, pp. 7609–7614, 2007.

[214] F. Hadrich, Z. Bouallagui, H. Junkyu, H. Isoda, and S. Sayadi, “The α-glucosidase and α-amylase enzyme inhibitory of hydroxytyrosol and oleuropein,” *Journal of Oleo Science*, vol. 64, no. 8, pp. 835–843, 2015.

[215] Ú. Catalán, M.-C. López de las Hazas, L. Rubió et al., “Protective effect of hydroxytyrosol and its predominant plasmatic human metabolites against endothelial dysfunction in human aortic endothelial cells,” *Molecular Nutrition & Food Research*, vol. 59, no. 12, pp. 2523–2536, 2015.

[216] E. Scoditti, N. Calabrissio, M. Massaro et al., “Mediterranean diet polyphenols reduce inflammatory angiogenesis through MMP-9 and COX-2 inhibition in human vascular endothelial cells: a potentially protective mechanism in atherosclerotic vascular disease and cancer,” *Archives of Biochemistry and Biophysics*, vol. 527, no. 2, pp. 81–89, 2012.

[217] M. Segade, R. Bermejo, A. Silva, F. Paiva-Martins, J. Gil-Longo, and M. Campos-Toimil, “Involvement of endothelin in the vasorelaxant effects of 3,4-DHPEA-EA and 3,4-DHPEA-EDA, two major functional bioactives in olive oil,” *Journal of Functional Foods*, vol. 23, pp. 637–646, 2016.

[218] J. Tomé-Carneiro, M. C. Crespo, E. Iglesias-Gutierrez et al., “Hydroxytyrosol supplementation modulates the expression of miRNAs in rodents and in humans,” *The Journal of Nutritional Biochemistry*, vol. 34, pp. 146–155, 2016.
[219] S. Acín, M. A. Navarro, J. M. Arbonés-Mainar et al., “Hydroxytyrosol administration enhances atherosclerotic lesion development in apo E deficient mice,” *The Journal of Biochemistry*, vol. 140, no. 3, pp. 383–391, 2006.

[220] F. Rosignoli, R. Fuccelli, R. Fabiani, M. Servili, and G. Morozi, “Effect of olive oil phenols on the production of inflammatory mediators in freshly isolated human monocytes,” *The Journal of Nutritional Biochemistry*, vol. 24, no. 8, pp. 1513–1519, 2013.

[221] E. Scoditti, A. Nestola, M. Massaro et al., “Hydroxytyrosol suppresses MMP-9 and COX-2 activity and expression in activated human monocytes via PKCα and PKCβ1 inhibition,” *Atherosclerosis*, vol. 232, no. 1, pp. 17–24, 2014.

[222] X. Zhang, J. Cao, L. Jiang, and L. Zhong, “Suppressive effects of hydroxytyrosol on oxidative stress and nuclear factorκB activation in THP-1 cells,” *Biological & Pharmaceutical Bulletin*, vol. 32, no. 4, pp. 578–582, 2009.

[223] E. Giordano, A. D´avalos, and F. Visioli, “Chronic hydroxytyrosol feeding modulates glutathione-mediated oxido-reduction pathways in adipose tissue: a nutrigenomic study,” *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 24, no. 10, pp. 1144–1150, 2014.

[224] R. Fuccelli, R. Fabiani, and P. Rosignoli, “Hydroxytyrosol exerts anti-inflammatory and anti-oxidant activities in a mouse model of systemic inflammation,” *Molecules*, vol. 23, no. 12, 2018.

[225] R. Fuccelli, R. Fabiani, M. V. Sepporta, and P. Rosignoli, “The hydroxytyrosol-dependent increase of TNF-α in LPS-activated human monocytes is mediated by PGE2 and adenylyl cyclase activation,” *Toxicology in Vitro*, vol. 29, no. 5, pp. 933–937, 2015.

[226] M. Dell’Aghi, R. Fagnani, N. Mitro et al., “Minor components of olive oil modulate proatherogenic adhesion molecules involved in endothelial activation,” *Journal of Agricultural and Food Chemistry*, vol. 54, no. 9, pp. 3259–3264, 2006.

[227] M. Tabernero, B. Sarrià, C. Largo et al., “Comparative evaluation of the metabolic effects of hydroxytyrosol and its lipophilic derivatives (hydroxytyrosyl acetate and ethyl hydroxytyrosyl ether) in hypercholesterolemic rats,” *Food Funct.*, vol. 5, no. 7, pp. 1556–1563, 2014.

[228] G. Serra, M. Deiana, J. P. E. Spencer, and G. Corona, “Olive oil phenolics prevent oxysterol-induced proinflammatory cytokine secretion and reactive oxygen species production in human peripheral blood mononuclear cells, through modulation of p38 and JNK pathways,” *Molecular Nutrition & Food Research*, vol. 61, no. 12, Article ID 1700283, 2017.

[229] F. Yao, G. Yang, Y. Xian et al., “The protective effect of hydroxytyrosol acetate against inflammation of vascular endothelial cells partly through the SIRT6-mediated p53 and JNK pathways,” *Food Funct.*, vol. 10, no. 9, pp. 5789–5803, 2019.

[230] E. Bigagli, L. Cinci, S. Paccosi, A. Parenti, M. D’Ambrosio, and C. Luceri, “Nutritionally relevant concentrations of resveratrol and hydroxytyrosol mitigate oxidative burst of human granulocytes and monocytes and the production of pro-inflammatory mediators in LPS-stimulated RAW 264.7 macrophages,” *International Immunopharmacology*, vol. 43, pp. 147–155, 2017.

[231] W. Wang, C. Shang, W. Zhang et al., “Hydroxytyrosol NO regulates oxidative stress and NO production through SIRT1 in diabetic mice and vascular endothelial cells,” *Phytomedicine*, vol. 52, pp. 206–215, 2019.

[232] Y.-D. Xie, Z.-Z. Chen, N. Li et al., “Hydroxytyrosol nicotinate, a new multifunctional hypolipidemic and hypoglycemic agent,” *Biomedicine & Pharmacotherapy*, vol. 99, pp. 715–724, 2018.

[233] F. Echeverria, R. Valenzuela, A. Espinosa et al., “Reduction of high-fat diet-induced liver proinflammatory state by eicosapentaenoic acid plus hydroxytyrosol supplementation: involvement of resolvins and D1-like,” *The Journal of Nutritional Biochemistry*, vol. 63, pp. 35–43, 2018.

[234] A. Cumaoglu, L. Rackova, M. Stefk, M. Kartal, P. Macchler, and C. Karasu, “Effects of olive leaf polyphenols against H2O2 toxicity in insulin secreting beta-cells,” *Acta Biochim. Pol.*, vol. 58, no. 1, pp. 45–50, 2011.

[235] A. M. Al-Attar and F. A. Alsalmi, “Effect of Olea europaea leaves extract on streptozotocin induced diabetes in male albino rats,” *Saudi Journal of Biological Sciences*, vol. 26, no. 1, pp. 118–128, 2019.

[236] M. A. Temiz and A. Temur, “The effect of olive leaf extract on digestive enzyme inhibition and insulin production in streptozotocin-induced diabetic rats,” *Ankara Üniversitesi Veteriner Fakültesi Dergisi*, vol. 66, pp. 163–169, 2019.

[237] D. Bencheikh, S. Khenouf, A. Bouaziz et al., “Antioxidant and anti-diabetic activities of the methanolic extract of Olea europaea L. leaves in streptozotocin induced diabetic rats,” *International Journal of Pharmacy and Pharmaceutical Research*, vol. 8, pp. 1347–1357, 2016.

[238] A. A. Khabat, “Effect of aqueous olive leaves extract on the pancreatic islets in rats,” *Rafidain Journal of Science*, vol. 25, pp. 1–9, 2014.

[239] A. Scheffler, H. W. Rauwald, B. Kampa, U. Mann, F. W. Mohr, and S. Dhein, “Olea europaea leaf extract exerts L-type Ca2+ channel antagonistic effects,” *Journal of Ethnopharmacology*, vol. 120, no. 2, pp. 233–240, 2008.

[240] H. Poudyal, F. Campbell, and L. Brown, “Olive leaf extract attenuates cardiac, hepatic, and metabolic changes in high carbohydrate-, high fat-fed rats,” *The Journal of Nutrition*, vol. 140, no. 5, pp. 946–953, 2010.

[241] B. Burja, T. Kuret, T. Janko et al., “Olive leaf extract attenuates inflammatory activation and DNA damage in human arterial endothelial cells,” *Frontiers in Cardiovascular Medicine*, vol. 6, p. 56, 2019.

[242] D. Gong, C. Geng, L. Jiang, J. Cao, H. Yoshimura, and L. Zhong, “Effects of hydroxytyrosol-20 on carrageenan-induced acute inflammation and hyperalgesia in rats,” *Phytomedicine Research*, vol. 23, no. 5, pp. 646–650, 2009.

[243] H. Jemai, M. Bouaziz, I. Fki, A. El Feki, and S. Sayadi, “Hypolipidemic and antioxidant activities of oleuropein and its hydrolysis derivative-rich extracts from Chemlali olive leaves,” *Chemico-Biological Interactions*, vol. 176, no. 2-3, pp. 88–98, 2008.

[244] K. Hansen, A. Adersen, S. B. Christensen, S. R. Jensen, U. Nyman, and U. W. Smitt, “Isolation of an angiotensin converting enzyme (ACE) inhibitor from Olea europaea and Olea lancea,” *Phytomedicine*, vol. 2, no. 4, pp. 319–325, 1996.

[245] A. Filippek, M. E. Czerwińska, A. K. Kiss, J. A. Polański, and M. Naruszewicz, “Oleacein may inhibit destabilization of carotid plaques from hypertensive patients. Impact on high mobility group protein-1,” *Phytomedicine*, vol. 32, pp. 68–73, 2017.

[246] G. K. Beauchamp, R. S. J. Keast, D. Morel et al., “Ibuprofen-like activity in extra-virgin olive oil,” *Nature*, vol. 437, no. 7055, pp. 45–46, 2005.

[247] K. Vougogiannopoulou, C. Lemus, M. Halabalaki et al., “One-step semisynthesis of oleacein and the determination as a 5-lipoxygenase inhibitor,” *Journal of Natural Products*, vol. 77, no. 3, pp. 441–445, 2014.
[248] F. Viana, "TRPA1 channels: molecular sentinels of cellular stress and tissue damage," *The Journal of Physiology*, vol. 594, no. 15, pp. 4151–4169, 2016.

[249] C. Peyrot des Gachons, K. Uchida, B. Bryant et al., "Unusual pungency from extra-virgin olive oil is attributable to restricted spatial expression of the receptor of oleocanthal," *Journal of Neuroscience*, vol. 31, no. 3, pp. 999–1009, 2011.

[250] M. Mete, I. Aydemir, U. U. Unsal et al., "Neuroprotective effects of Oleocanthal, a compound in virgin olive oil, in a rat model of traumatic brain injury," *Turkish Neurosurgery*, vol. 28, no. 6, pp. 858–865, 2018.

[251] A. Iacono, R. Gómez, J. Sperry et al., "Effect of oleocanthal and its derivatives on inflammatory response induced by lipopolysaccharide in a murine chondrocyte cell line," *Arthritis & Rheumatism*, vol. 62, no. 6, pp. 1675–1682, 2010.

[252] F. Hadrich, M. García, A. Maalej et al., "Oleuropein activated AMPK and induced insulin sensitivity in C2C12 muscle cells," *Life Sciences*, vol. 151, pp. 167–173, 2016.

[253] R. Abe, J. Beckett, R. Abe et al., "Olive oil polyphenol oleuropein inhibits smooth muscle cell proliferation," *European Journal of Vascular and Endovascular Surgery*, vol. 41, no. 6, pp. 814–820, 2011.

[254] A. Kerimi, H. Nyambe-Silawwe, A. Pyner et al., "Nutritional implications of olives and sugar: attenuation of post-prandial glucose spikes in healthy volunteers by inhibition of sucrose hydrolysis and glucose transport by oleuropein," *European Journal of Nutrition*, vol. 58, no. 3, pp. 1315–1330, 2019.

[255] R. Turner, N. Etienne, M. Garcia Alonso et al., "Antioxidant and anti-atherogenic activities of olive oil phenolics," *International Journal for Vitamin and Nutrition Research*, vol. 75, no. 1, pp. 61–70, 2005.

[256] I. Stupans, M. Murray, A. Kirlich, K. L. Tuck, and P. J. Hayball, "Inactivation of cytochrome P450 by the food-derived complex phenol oleuropein," *Food and Chemical Toxicology*, vol. 39, no. 11, pp. 1119–1124, 2001.

[257] F. Visioli, G. Bellomo, and C. Galli, "Free radical-scavenging properties of olive oil polyphenols," *Biochemical and Biophysical Research Communications*, vol. 247, no. 1, pp. 60–64, 1998.

[258] R. de la Puerta, M. E. M. Dominguez, V. Ruiz-Gutierrez, J. A. Flavill, and J. R. S. Houl, "Effects of virgin olive oil phenolics on scavenging of reactive nitrogen species and upon nitrergic neurotransmission," *Life Sciences*, vol. 10, no. 12, pp. 1213–1222, 2001.

[259] K. Murotomi, A. Umeno, M. Yasunaga et al., "Oleuropein-rich diet attenuates hyperglycemia and impaired glucose tolerance in type 2 diabetes model mouse," *Journal of Agricultural and Food Chemistry*, vol. 63, no. 30, pp. 6715–6722, 2015.

[260] A. H. Gilani, A. U. Khan, A. J. Shah, J. Connor, and Q. I. Zainellu, "Blood pressure lowering effect of oleic is mediated through calcium channel blockade," *International Journal of Food Sciences and Nutrition*, vol. 56, no. 56, pp. 613–620, 2005.

[261] J. J. Moreno, "Effect of olive oil minor components on oxidative stress and arachidonic acid mobilization and metabolism by macrophages RAW 264.7," *Free Radical Biology and Medicine*, vol. 35, no. 9, pp. 1073–1081, 2003.

[262] M. Vivancos and J. J. Moreno, "Effect of resveratrol, tyrosol and β-sitosterol on oxidised low-density lipoprotein-stimulated oxidative stress, arachidonic acid release and prostaglandin E2 synthesis by RAW 264.7 macrophages," *British Journal of Nutrition*, vol. 99, no. 6, pp. 1199–1207, 2008.

[263] D. De Stefano, M. C. Maiuri, V. Simeon et al., "Lycopene, quercetin and tyrosol prevent macrophage activation induced by gliadin and IFN-gamma," *European Journal of Pharmacology*, vol. 566, no. 1–3, pp. 192–199, 2007.

[264] E. J. G. Muriana, S. Montserrat-de la Paz, R. Lucas et al., "Tyrosol and its metabolites as antioxidative and anti-inflammatory molecules in human endothelial cells," *Food & Function*, vol. 8, no. 8, pp. 2905–2914, 2017.

[265] D. Palmieri, B. Aliakbarian, A. A. Casaza et al., "Effects of polyphenol extract from olive pomace on anoxia-induced endothelial dysfunction," *Microvascular Research*, vol. 83, no. 3, pp. 281–289, 2012.

[266] M. Servili, S. Esposto, R. Fabiani et al., "Phenolic compounds in olive oil: antioxidant, health and organoleptic activities according to their chemical structure," *Inflammopharmacology*, vol. 17, no. 2, pp. 76–84, 2009.

[267] R. Fabiani, R. Fuccelli, F. Pieravanti, A. De Bartolomeo, and G. Morozzi, "Production of hydrogen peroxide is responsible for the induction of apoptosis by hydroxytyrosol on HL60 cells," *Molecular Nutrition & Food Research*, vol. 53, no. 7, pp. 887–896, 2009.

[268] C. Luo, Y. Li, H. Wang et al., "Hydroxytyrosol promotes superoxide production and defects in autophagy leading to anti-proliferation and apoptosis on human prostate cancer cells," *Current Cancer Drug Targets*, vol. 13, no. 6, pp. 625–639, 2013.

[269] B. Halliwell, "Cell culture, oxidative stress, and antioxidants: avoiding pitfalls," *Biomedical Journal*, vol. 37, no. 3, pp. 99–105, 2014.

[270] G. G. Pellegrini, M. G. Gregor, K. McAndrews et al., "Nrf2 regulates mass accrual and the antioxidant endogenous response in bone differently depending on the sex and age," *PLoS One*, vol. 12, no. 2, Article ID e0171161, 2017.

[271] L. Zhu, Z. Liu, Z. Feng et al., "Hydroxytyrosol protects against oxidative damage by simultaneous activation of mitochondrial biogenesis and phase II detoxifying enzyme systems in retinal pigment epithelial cells," *The Journal of Nutritional Biochemistry*, vol. 21, no. 11, pp. 1089–1098, 2010.

[272] I. Campesi, A. Galistu, C. Carru, F. Franconi, M. Fois, and A. Zinellu, "Glutamyl cycle in the rat liver appears to be sex- and gender-specific," *Experimental and Toxicologic Pathology*, vol. 65, no. 5, pp. 585–589, 2013.

[273] B. Toth, Y. Yokoyama, J. F. Kuebler et al., "Sex differences in hepatic heme oxygenase expression and activity following trauma and hemorrhagic shock," *Archives of Surgery*, vol. 138, no. 12, pp. 1375–1382, 2003.

[274] F. Visioli, S. Bellosta, and C. Galli, "Oleuropein, the bitter principle of olives, enhances nitric oxide production by mouse macrophages," *Life Sciences*, vol. 62, no. 6, pp. 541–546, 1998.

[275] A. C. Carr, T. Tijerina, and B. Frei, "Vitamin C protects against and reverses specific hypochlorous acid- and chloramine-dependent modifications of low-density lipoprotein," *Biochemical Journal*, vol. 346, no. 2, pp. 491–499, 2000.

[276] S. Rigacci and M. Stefani, "Nutraceutical properties of olive oil: anti-inflammatory and anti-oxidant activity," *Molecular Medicine*, vol. 23, no. 23, pp. 7885–7889, 2019.

[277] S. D’Amore, M. Vacca, M. Cariello et al., "Genes and miRNA expression signatures in peripheral blood mononuclear cells".
in healthy subjects and patients with metabolic syndrome after acute intake of extra virgin olive oil,” *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids*, vol. 1861, no. 11, pp. 1671–1680, 2016.

[279] Y. Momiyama, H. Adachi, D. Fairweather, N. Ishizaka, and E. Saita, “Inflammation, atherosclerosis and coronary artery disease,” *Clinical Medicine Insights: Cardiology*, vol. 8, no. Suppl 3, pp. 67–70, 2016.

[280] A. Bhatia, H. K. Sekhon, and G. Kaur, “Sex hormones and immune dimorph,” *Scientific World Journal*, vol. 2014, 2014.

[281] S. Pace, L. Sautebin, and O. Werz, “Sex-biased eicosanoid biology: impact for sex differences in inflammation and consequences for pharmacotherapy,” *Biochemical Pharmacology*, vol. 145, pp. 1–11, 2017.

[282] K. S. Rathod, V. Kapil, S. Velmurugan et al., “Accelerated resolution of inflammation underlies sex differences in inflammatory responses in humans,” *The Journal of Clinical Investigation*, vol. 127, no. 127, pp. 169–182, 2017.

[283] N. L. Chillingworth, S. G. Morham, and L. F. Donaldson, “Sex differences in inflammation and inflammatory pain in cyclooxygenase-deficient mice,” *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, vol. 291, no. 2, pp. R327–R334, 2006.

[284] S. Pace, A. Rossi, V. Krauth et al., “Sex differences in prostaglandin biosynthesis in neutrophils during acute inflammation,” *Scientific Reports*, vol. 7, no. 1, p. 3759, 2017.

[285] A. A. Ahmad, M. D. Randall, and R. E. Roberts, “Sex differences in the role of phospholipase A2-dependent arachidonic acid pathway in the perivascular adipose tissue function in pigs,” *The Journal of Physiology*, vol. 395, no. 21, pp. 6623–6634, 2017.

[286] S. Pace, C. Pergola, F. Dehm et al., “Androgen-mediated sex bias impairs efficiency of leukotiene biosynthesis inhibitors in males,” *Journal of Clinical Investigation*, vol. 127, no. 8, pp. 3167–3176, 2017.

[287] J. Z. Haegstström, “Leukotriene biosynthetic enzymes as therapeutic targets,” *Journal of Clinical Investigation*, vol. 128, no. 7, pp. 2680–2690, 2018.

[288] N. Chiang, S. Hurwitz, P. M. Ridker, and C. N. Serhan, “Aspirin has a gender-dependent impact on antiinflammatory 15-epi-lipoxin A4 formation,” *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 26, no. 2, pp. e14–e17, 2006.

[289] X. Luo, Y. Gu, X. Tao, C. N. Serhan, and R. R. Ji, “Resolvin D5 inhibits neuropathic and inflammatory pain in male but not female mice: distinct actions of D-series resolvins in chemotherapy-induced peripheral neuropathy,” *Frontiers in Pharmacology*, vol. 10, p. 745, 2019.

[290] N. Suzuki, T. Hishinuma, T. Saga et al., “Determination of urinary 12(S)-hydroxyecosatetraenoic acid by liquid chromatography-tandem mass spectrometry with column-switching technique: sex difference in healthy volunteers and patients with diabetes mellitus,” *Journal of Chromatography B*, vol. 783, no. 2, pp. 383–389, 2003.

[291] K. Lingappan, “NF-xB in oxidative stress,” *Current Opinion in Toxicology*, vol. 7, pp. 81–86, 2018.

[292] R. El Sabeh, M. Bonnet, K. Le Corf et al., “A gender-dependent molecular switch of inflammation via MyD88/estrogen receptor-alpha interaction,” *bioRxiv*, vol. 39, Article ID 255778, 2018.

[293] Y. Zhang and K. Lingappan, “Differential sex-specific effects of oxygen toxicity in human umbilical vein endothelial cells,” *Biochemical and Biophysical Research Communications*, vol. 486, no. 2, pp. 431–437, 2017.

[294] E. Straface, L. Gambardella, F. Pagano et al., “Sex differences of human cardiac progenitor cells in the biological response to TNF-alpha treatment,” *Stem Cells International*, vol. 2017, Article ID 4790563, 9 pages, 2017.

[295] S. Sullivan, M. Hammadah, K. Wilmot et al., “Young women with coronary artery disease exhibit higher concentrations of interleukin-6 at baseline and in response to mental stress,” *Journal of the American Heart Association*, vol. 7, no. 23, Article ID e010329, 2018.

[296] A. F. G. Cicero, S. Nascetti, M. C. López-Sabater et al., “Changes in LDL fatty acid composition as a response to olive oil treatment are inversely related to lipid oxidative damage: the EUROLIVE study,” *Journal of the American College of Nutrition*, vol. 27, no. 2, pp. 314–320, 2008.

[297] H. E. Anderson-Vasquez, P. Perez-Martinez, P. Ortega Fernandez, and C. Wanden-Berghe, “Impact of the consumption of a rich diet in butter and it replacement for a rich diet in extra virgin olive oil on anthropometric, metabolic and lipid profile in postmenopausal women,” *Nutricion Hospitalaria*, vol. 31, no. 6, pp. 2561–2570, 2015.

[298] F. Galvão Cândido, F. Xavier Valente, L. E. da Silva, O. Gonçalves Leão Coelho, M. D. C. Gouveia Peluzio, and R. d. C. Gonçalves Alfenas, “Consumption of extra virgin olive oil improves body composition and blood pressure in women with excess body fat: a randomized, double-blinded, placebo-controlled clinical trial,” *European Journal of Nutrition*, vol. 57, no. 7, pp. 2445–2455, 2018.

[299] A. Camargo, J. Ruano, J. M. Fernandez et al., “Gene expression changes in mononuclear cells in patients with metabolic syndrome after acute intake of phenol-rich virgin olive oil,” *JRC Genomics*, vol. 11, no. 1, p. 253, 2010.

[300] A. Camargo, O. A. Rangel-Zuñiga, C. Haro et al., “Olive oil phenolic compounds decrease the postprandial inflammatory response by reducing postprandial plasma lipopolysaccharide levels,” *Food Chemistry*, vol. 162, pp. 161–171, 2014.

[301] Y. M. Pacheco, S. Lopez, B. Bermudez, R. Abia, and F. J. G. Muriana, “Extra-virgin vs. refined olive oil on postprandial hemostatic markers in healthy subjects,” *Journal of Thrombosis and Haemostasis*, vol. 4, no. 6, pp. 1421–1422, 2006.

[302] T. M. Khan, S. Iqbal, and M. A. Rashid, “Comparison of lipid lowering effect of extra virgin olive oil and atorvastatin in dyslipidaemia in type 2 diabetes mellitus,” *JACC*, vol. 29, no. 1, pp. 83–86, 2017.

[303] R. Carnevale, L. Loffredo, M. Del Ben et al., “Extra virgin olive oil improves post-prandial glycemic and lipid profile in patients with impaired fasting glucose,” *Clinical Nutrition*, vol. 36, no. 3, pp. 782–787, 2017.

[304] K. T. Khaw, S. J. Sharp, L. Finikarides et al., “Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in healthy men and women,” *BMJ Open*, vol. 8, no. 3, Article ID e020167, 2018.

[305] M. Rozati, J. Barnett, D. Wu et al., “Cardio-metabolic and immunological impacts of extra virgin olive oil consumption in overweight and obese older adults: a randomised controlled trial,” *Nutrition & Metabolism*, vol. 12, no. 1, p. 28, 2015.

[306] R. Moreno-Luna, R. Munoz-Hernandez, M. L. Miranda et al., “Olive oil polyphenols decrease blood pressure and improve endothelial function in young women with mild
hypertension,” *American Journal of Hypertension*, vol. 25, no. 12, pp. 1299–1304, 2012.

[307] N. R. T. Damasceno, A. Pérez-Heras, M. Serra et al., “Crossover study of diets enriched with virgin olive oil, walnuts or almonds. Effects on lipids and other cardiovascular risk markers,” *Nutrition, Metabolism and Cardiovascular Diseases*, vol. 21, no. Suppl 1, pp. S14–S20, 2011.

[308] R. J. Widmer, M. A. Freund, A. J. Flammer et al., “Beneficial effects of polyphenol-rich olive oil in patients with early atherosclerosis,” *European Journal of Nutrition*, vol. 52, no. 3, pp. 1223–1231, 2013.

[309] J. M. Santos-Lozano, M. Rada, J. Lapetra et al., “Prevention of type 2 diabetes in prediabetic patients by using functional olive oil enriched in oleic acid: the PREDIABOLE study, a randomized controlled trial,” *Diabetes, Obesity and Metabolism*, vol. 21, no. 11, pp. 2526–2534, 2019.

[310] S. Martin-Peláez, O. Castaña, V. Konstantinidou et al., “Effect of olive oil phenolic compounds on the expression of blood pressure-related genes in healthy individuals,” *European Journal of Nutrition*, vol. 56, no. 2, pp. 663–670, 2017.

[311] V. Konstantinidou, M. I. Covas, D. Muñoz-Aguayo et al., “In vivo nutrigenomic effects of virgin olive oil polyphenols within the frame of the Mediterranean diet: a randomized controlled trial,” *The FASEB Journal*, vol. 24, no. 7, pp. 2546–2557, 2010.

[312] M. C. Ramírez-Tortosa, G. Urbano, M. López-Jurado et al., “Extra-virgin olive oil increases the resistance of LDL to oxidation more than refined olive oil in free-living men with peripheral vascular disease,” *The Journal of Nutrition*, vol. 129, no. 12, pp. 2177–2183, 1999.

[313] O. Castaña, M.-I. Covas, O. Khymenets et al., “Protection of LDL from oxidation by olive polyphenols is associated with a downregulation of CD40-ligand expression and its downstream products in vivo in humans,” *The American Journal of Clinical Nutrition*, vol. 95, no. 5, pp. 1238–1244, 2012.

[314] E. Sánchez-Rodríguez, S. Biel-Glessen, J. R. Fernández-Navarro et al., “Effects of virgin olive oils differing in their bioactive compound contents on biomarkers of oxidative stress and inflammation in healthy adults: a randomized double-blind controlled trial,” *Nutrients*, vol. 11, no. 3, 2019.

[315] E. Sánchez-Rodríguez, E. Lima-Cabello, S. Biel-Glessen et al., “Effects of virgin olive oils differing in their bioactive compound contents on metabolic syndrome and endothelial functional risk biomarkers in healthy adults: a randomized double-blind controlled trial,” *Nutrients*, vol. 10, no. 5, 2018.

[316] S. Fernandez-Castillejo, A. I. García-Heredia, R. Sola et al., “Phenol-enriched olive oils modify paraoxonase-related variables: a randomized, crossover, controlled trial,” *Molecular Nutrition & Food Research*, vol. 61, no. 10, 2017.

[317] S. Martin-Peláez, J. I. Mosele, N. Pizarro et al., “Effect of virgin olive oil and thyme phenolic compounds on blood lipid profile: implications of human gut microbiota,” *European Journal of Nutrition*, vol. 56, no. 1, pp. 119–131, 2017.

[318] S. Fernández-Castillejo, R.-M. Valls, O. Castaña et al., “Polyphenol rich olive oils improve lipoprotein particle atherogenic ratios and subclasses profile: a randomized, crossover, controlled trial,” *Molecular Nutrition & Food Research*, vol. 60, no. 7, pp. 1544–1554, 2016.

[319] R.-M. Valls, M. Farrás, M. Suárez et al., “Effects of functional olive oil enriched with its own phenolic compounds on endothelial function in hypertensive patients. A randomised controlled trial,” *Food Chemistry*, vol. 167, pp. 30–35, 2015.
N. S. Nielsen, A. Pedersen, B. Sandström, P. Marckmann, and C.-E. Hoy, "Different effects of diets rich in olive oil, rapeseed oil and sunflower-seed oil on postprandial lipid and lipoprotein concentrations and on lipoprotein oxidation susceptibility," British Journal of Nutrition, vol. 87, no. 5, pp. 489–499, 2002.

L. F. Larsen, J. Jespersen, and P. Marckmann, "Are olive oil diets antithrombotic? Diets enriched with olive, rapeseed, or sunflower oil affect postprandial factor VII differently," The American Journal of Clinical Nutrition, vol. 70, no. 6, pp. 976–982, 1999.

M. J. Mandoe, K. B. Hansen, J. A. Windelev et al., "Comparing olive oil and C4-dietary oil, a prodrug for the GPR119 agonist, 2-oleoyl glycerol, less energy intake of the latter is needed to stimulate incretin hormone secretion in overweight subjects with type 2 diabetes," Nutrition & Diabetes, vol. 8, no. 8, p. 2, 2018.

L. A. Ferrara, A. S. Raimondi, L. d’Episcopo, L. Guida, A. Dello Russo, and T. Marotta, "Olive oil and reduced need for antihypertensive medications," Archives of Internal Medicine, vol. 160, no. 6, pp. 837–842, 2000.

A. Hernández, A. T. Remaley, M. Farrás et al., "Olive oil polyphenols decrease LDL concentrations and LDL atherogenicity in men in a randomized controlled trial," The Journal of Nutrition, vol. 145, no. 8, pp. 1692–1697, 2015.

A. Hernández, S. Fernández-Castillejo, M. Farrás et al., "Olive oil polyphenols enhance high-density lipoprotein function in humans," Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 34, no. 9, pp. 2115–2119, 2014.

C. Colica, L. Di Renzo, D. Trombetta et al., "Antioxidant effects of a hydroxytyrosol-based pharmaceutical formulation on body composition, metabolic state, and gene expression: a randomized double-blinded, placebo-controlled crossover trial," Oxidative Medicine and Cellular Longevity, vol. 2017, Article ID 2473495, 14 pages, 2017.

R. Carnevale, R. Silvestri, L. Loffredo et al., "Oleuropein, a component of extra virgin olive oil, lowers postprandial glycaemia in healthy subjects," British Journal of Clinical Pharmacology, vol. 84, no. 7, pp. 1566–1574, 2018.

L. Bozzetto, A. Alderisio, M. Giorgini et al., "Extra virgin olive oil reduces glycemic response to a high-glycemic index meal in patients with type 1 diabetes: a randomized controlled trial," Diabetes Care, vol. 39, no. 4, pp. 518–524, 2016.

F. Violi, L. Loffredo, P. Pignatelli et al., "Extra virgin olive oil use is associated with improved post-prandial blood glucose and LDL cholesterol in healthy subjects," Nutrition & Diabetes, vol. 5, no. 7, p. e172, 2015.

R. Carnevale, P. Pignatelli, C. Nocella et al., "Extra virgin olive oil blunts post-prandial oxidative stress via NOX2 down-regulation," Atherosclerosis, vol. 235, no. 2, pp. 649–658, 2014.

R. Carnevale, D. Pastori, C. Nocella et al., "Gut-derived lipopolysaccharides increase post-prandial oxidative stress via NOX2 activation in patients with impaired fasting glucose tolerance: effect of extra-virgin olive oil," European Journal of Nutrition, vol. 58, no. 2, pp. 843–851, 2019.

M. T. Mitjavila, M. Fandos, J. Salas-Salvadó et al., "The Mediterranean diet improves the systemic lipid and DNA oxidative damage in metabolic syndrome individuals. A randomized, controlled, trial," Clinical Nutrition, vol. 32, no. 2, pp. 172–178, 2013.

M. Guasch-Ferré, J. Salas-Salvadó, E. Ros et al., "The PREDIMED trial, Mediterranean diet and health outcomes: how strong is the evidence?" Nutrition, Metabolism and Cardiovascular Diseases, vol. 27, no. 7, pp. 624–632, 2017.

M. Á. Martínez-González, E. Toledo, F. Arós et al., "Extravirgin olive oil consumption reduces risk of atrial fibrillation," Circulation, vol. 130, no. 1, pp. 18–26, 2014.

J. Álvarez-Pérez, A. Sánchez-Villegas, E. M. Díaz-Benítez et al., "Influence of a Mediterranean dietary pattern on body fat distribution: results of the PREDIMED-canarias intervention randomized trial," Journal of the American College of Nutrition, vol. 35, no. 6, pp. 568–580, 2016.

J. Salas-Salvadó, M. Bulló, R. Estruch et al., "Prevention of diabetes with Mediterranean diets," Annals of Internal Medicine, vol. 160, no. 1, pp. 1–10, 2014.

F. J. Basterra-Gortari, M. Ruiz-Canela, M. A. Martínez-González et al., "Effects of a Mediterranean eating plan on the need for glucose-lowering medications in participants with type 2 diabetes: a subgroup analysis of the PREDIMED trial," Diabetes Care, vol. 42, no. 8, pp. 1390–1397, 2019.

O. Castañer, D. Corella, M. I. Covas et al., "In vivo transcriptomic profile after a Mediterranean diet in high-cardiovascular risk patients: a randomized controlled trial," The American Journal of Clinical Nutrition, vol. 98, no. 98, pp. 845–853, 2013.

R. Casas, M. Urpi-Sارد, E. Sacanella et al., "Anti-inflammatory effects of the Mediterranean diet in the early and late stages of atheroma plaque development," Mediators of Inflammation, vol. 2017, Article ID 3674390, 12 pages, 2017.

R. Casas, E. Sacanella, M. Urpi-Sارد et al., "Long-term immunomodulatory effects of a Mediterranean diet in adults at high risk of cardiovascular disease in the PREVencion con Dita MEDiterránea (PREDIMED) randomized controlled trial," The Journal of Nutrition, vol. 146, no. 9, pp. 1684–1693, 2016.

J. D. Torres-Pena, A. Garcia-Rios, N. Delgado-Casado et al., "Mediterranean diet improves endothelial function in patients with diabetes and prediabetes: a report from the CORDIOPREV study," Atherosclerosis, vol. 269, pp. 50–56, 2018.

S. Lockyer, I. Rowland, J. P. E. Spencer, P. Yaqoob, and W. Stonehouse, "Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: a randomised controlled trial," European Journal of Nutrition, vol. 56, no. 4, pp. 1421–1432, 2017.

S. Lockyer, G. Corona, P. Yaqoob, J. P. E. Spencer, and I. Rowland, "Secoiridoids delivered as olive leaf extract induce acute improvements in human vascular function and reduction of an inflammatory cytokine: a randomised, double-blind, placebo-controlled, cross-over trial," British Journal of Nutrition, vol. 114, no. 1, pp. 75–83, 2015.

M. de Bock, J. G. Derckx, C. M. Brennan et al., "Olive (Olea europaea L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial," PLoS One, vol. 8, no. 3, Article ID e57622, 2013.

E. Susali, N. Agus, I. Effendi et al., "Olive (Olea europaea) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril," Phytotherapy Research, vol. 18, no. 4, pp. 251–258, 2011.

T. C. Yadav, N. Kumar, U. Raj et al., "Exploration of interaction mechanism of tyrosol as a potent anti-inflammatory agent," Journal of Biomolecular Structure and Dynamics, vol. 38, no. 2, pp. 382–397, 2019.

S. Basili, V. Raparelli, M. Proietti, G. Tanzilli, and F. Franconi, "Impact of sex and gender on the efficacy of antiplatelet therapy: the female perspective," Journal of Atherosclerosis and Thrombosis, vol. 22, no. 2, pp. 109–125, 2015.
32 Cardiovascular Therapeutics

[362] M. I. Covas, M. Fito, and R. de la Torre, “Minor bioactive olive oil components and health: key data for their role in providing health benefits in humans,” in Olive and Oil Bioactive Constituents, D. E. Boskou, Ed., p. 31, AOCS Press, Urbana, IL, USA, 2015.

[363] P. Reboredo-Rodríguez, A. Varela-Lopez, T. Y. Forbes-Hernandez et al., “Phenolic compounds isolated from olive oil as nutraceutical tools for the prevention and management of cancer and cardiovascular diseases,” International Journal of Molecular Sciences, vol. 19, no. 8, p. 2305, 2018.

[364] J. Ruano, J. López-Miranda, R. de la Torre et al., “Intake of phenol-rich virgin olive oil improves the postprandial prothrombotic profile in hypercholesterolemic patients,” The American Journal of Clinical Nutrition, vol. 86, no. 2, pp. 341–346, 2007.

[365] M. Figueiredo-González, P. Reboredo-Rodriguez, C. González-Barreiro et al., “Evaluation of the neuro-protective and anti-diabetic potential of phenol-rich extracts from virgin olive oils by in vitro assays,” Food Research International, vol. 106, pp. 558–567, 2018.

[366] G. Oboh, A. O. Ademiluyi, A. J. Akinyemi, T. Henle, J. A. Saliu, and U. Schwarzenbolz, “Inhibitory effect of polyphenol-rich extracts of jute leaf (Corchorus olitorius) on key enzyme linked to type 2 diabetes (α-amylase and α-glucosidase) and hypertension (angiotensin I converting) in vitro,” Journal of Functional Foods, vol. 4, no. 2, pp. 450–458, 2012.

[367] F. Vlavcheski, M. Young, and E. Tsiani, “Anti-diabetic effects of hydroxytyrosol: in vitro and in vivo evidence,” Antioxidants (Basel), vol. 8, no. 6, 2019.

[368] G. Annunziata, M. Maisto, C. Schisano et al., “Oleuropein as a novel anti-diabetic nutraceutical. An overview,” Archives of Diabetes & Obesity, vol. 1, no. 3, 2018.

[369] J. Fang and M. H. Alderman, “Serum uric acid and cardiovascular mortality,” JAMA, vol. 283, no. 18, pp. 2404–2410, 2000.

[370] I. Holme, A. H. Aastveit, N. Hammar, I. Jungner, and G. Walldius, “Uric acid and risk of myocardial infarction, stroke and congestive heart failure in 417 734 men and women in the Apolipoprotein MOrtality RISK study (AMORIS),” Journal of Internal Medicine, vol. 266, no. 6, pp. 558–570, 2009.

[371] K. R. Tuttle, R. A. Short, and R. J. Johnson, “Sex differences in uric acid and risk factors for coronary artery disease,” The American Journal of Cardiology, vol. 87, no. 12, pp. 1411–1414, 2001.

[372] A. Højsgen, M. H. Alderman, S. E. Kjeldsen et al., “The impact of serum uric acid on cardiovascular outcomes in the LIFE study,” Kidney International, vol. 65, no. 65, pp. 1041–1049, 2004.

[373] A. Strasak, E. Ruttman, L. Brant et al., “Serum uric acid and risk of cardiovascular mortality: a prospective long-term study of 83 683 Austrian men,” Clinical Chemistry, vol. 54, no. 2, pp. 273–284, 2008.

[374] A. M. Strasak, C. C. Kelleher, L. J. Brant et al., “Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: a prospective 21-year follow-up study,” International Journal of Cardiology, vol. 125, no. 2, pp. 232–239, 2008.

[375] B. F. Culleton, M. G. Larson, W. B. Kannel, and D. Levy, “Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study,” Annals of Internal Medicine, vol. 131, no. 1, pp. 7–13, 1999.

[376] J. Flemmig, K. Kuchta, J. Arnhold, and H. W. Rauwald, “Olea europaea leaf (Ph.Eur.): extract as well as several of its isolated phenolics inhibit the gout-related enzyme xanthine oxidase,” Phytomedicine, vol. 18, no. 7, pp. 561–566, 2011.

[377] Y. Wan, Y.-X. Liang, B. Zou, G.-M. Fu, and M.-Y. Xie, “The possible mechanism of hydroxytyrosol on reducing uric acid levels,” Journal of Functional Foods, vol. 42, pp. 319–326, 2018.

[378] D. Mozaffarian, “Dietary and policy priorities for cardiovascular disease, diabetes, and obesity,” Circulation, vol. 133, no. 2, pp. 187–225, 2016.

[379] M. A. Martín, S. Ramos, A. B. Granado-Serrano et al., “Hydroxytyrosol induces antioxidant/detoxificant enzymes and Nrf2 translocation via extracellular regulated kinases and phosphatidylinositol-3-kinase/protein kinase B pathways in HepG2 cells,” Molecular Nutrition & Food Research, vol. 54, no. 7, pp. 956–966, 2010.

[380] L. Schwinghackl, M. Christoph, and G. Hoffmann, Effects of olive oil on markers of inflammation and endothelial function: A systematic review and meta-analysis,” Nutrients, vol. 7, no. 9, pp. 7651–7675, 2015.

[381] L. Schwinghackl and G. Hoffmann, “Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies,” International Journal of Cancer, vol. 135, no. 8, pp. 1884–1897, 2014.

[382] E. S. George, S. Marshall, H. L. Mayr et al., “The effect of high-polyphenol extra virgin olive oil on cardiovascular risk factors: a systematic review and meta-analysis,” Critical Reviews in Food Science and Nutrition, vol. 59, no. 17, pp. 2772–2795, 2019.

[383] I. Fernandes, M. Fialho, R. Santos et al., “Is olive oil good for you? A systematic review and meta-analysis on anti-inflammatory benefits from regular dietary intake,” Nutrition, vol. 69, Article ID 110559, 2020.

[384] S. Ghobadi, Z. Hassanzadeh-Rostami, F. Mohammadian et al., “Comparison of blood lipid-lowering effects of olive oil and other plant oils: a systematic review and meta-analysis of 27 randomized placebo-controlled clinical trials,” Critical Reviews in Food Science and Nutrition, vol. 59, no. 13, pp. 2110–2124, 2019.

[385] World Health Organisation, Global Status Report on Non-communicable Diseases 2014, WHO, Geneva, Switzerland, 2014.

[386] C. Cadeddu, F. Franconi, L. Cassisa et al., “Arterial hyper-tension in the female world,” Journal of Cardiovascular Medicine, vol. 17, no. 4, pp. 229–236, 2016.

[387] E. Toledo, F. B. Hu, R. Estruch et al., “Effect of the Medi terranean diet on blood pressure in the PREDIMED trial: results from a randomized controlled trial,” BMC Medicine, vol. 11, no. 1, p. 207, 2013.

[388] M. Doménech, P. Roman, J. Lapetra et al., “Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids,” Hypertension, vol. 64, no. 1, pp. 69–76, 2014.

[389] C. D. Hohmann, H. Cramer, A. Michalsen et al., “Effects of high phenolic olive oil on cardiovascular risk factors: a systematic review and meta-analysis,” Phytomedicine, vol. 22, no. 6, pp. 631–640, 2015.

[390] M. Nissensohn, B. Román-Viñas, A. Sánchez-Villegas, S. Piscopo, and L. Serra-Majem, “The effect of the Mediterranean diet on hypertension: a systematic review and meta-analysis,” Journal of Nutrition Education and Behavior, vol. 48, no. 1, pp. 42–53, 2016.
[391] R. N. Ndanuko, L. C. Tapsell, K. E. Charlton, E. P. Neale, and M. J. Batterham, "Dietary patterns and blood pressure in adults: a systematic review and meta-analysis of randomized controlled trials," Advances in Nutrition, vol. 7, no. 1, pp. 76–89, 2016.

[392] F. Zamora-Zamora, J. M. Martínez-Galiano, J. J. Gaforio, and M. Delgado-Rodríguez, "Effects of olive oil on blood pressure: a systematic review and meta-analysis," Grasas Aceites, vol. 69, no. 4, p. e272, 2018.

[393] L. Schwingshackl, A.-M. Lampousi, M. P. Portillo, D. Romaguera, G. Hoffmann, and H. Boeing, "Olive oil in the prevention and management of type 2 diabetes mellitus: a systematic review and meta-analysis of cohort studies and intervention trials," Nutrition & Diabetes, vol. 7, no. 4, p. e262, 2017.

[394] C. Assaf-Balut, N. García de la Torre, A. Duran et al., "An early, universal mediterranean diet-based intervention in pregnancy reduces cardiovascular risk factors in the "fourth trimester”" Journal of Clinical Medicine, vol. 8, no. 9, p. 1499, 2019.

[395] C. Assaf-Balut, N. García de la Torre, A. Duran et al., "A mediterranean diet with an enhanced consumption of extra virgin olive oil and pistachios improves pregnancy outcomes in women without gestational diabetes mellitus: a sub-analysis of the st. carlos gestational diabetes mellitus prevention study," Annals of Nutrition and Metabolism, vol. 74, no. 1, pp. 69–79, 2019.

[396] B. M. Egan, D. T. Lackland, and D. W. Jones, "Pre-hypertension: an opportunity for a new public health paradigm," Cardiology Clinics, vol. 28, no. 4, pp. 561–569, 2010.

[397] F. Franconi, V. Raparelli, and V. Regitz-Zagrosek, "Sex and gender landscape in pharmacology," Pharmacological Research, vol. 123, pp. 93–94, 2017.

[398] S. Eilat-Adar and U. Goldbourt, "Nutritional recommendations for preventing coronary heart disease in women: evidence concerning whole foods and supplements," Nutrition, Metabolism and Cardiovascular Diseases, vol. 20, no. 6, pp. 459–466, 2010.

[399] M. Marino, R. Masella, P. Bulzomi, I. Campesi, W. Malorni, and F. Franconi, "Nutrition and human health from a sex-gender perspective," Molecular Aspects of Medicine, vol. 32, no. 1, pp. 1–70, 2011.