Efficacy of Polyphenols in the Management of Dyslipidemia: A Focus on Clinical Studies

Francis Feldman, Mireille Koudoufio, Yves Desjardins, Schohraya Spahis, Edgard Delvin, and Emile Levy

Abstract: Polyphenols (PLPs), phytochemicals found in a wide range of plant-based foods, have gained extensive attention in view of their antioxidant, anti-inflammatory, immunomodulatory and several additional beneficial activities. The health-promoting effects noted in animal models of various non-communicable diseases explain the growing interest in these molecules. In particular, in vitro and animal studies reported an attenuation of lipid disorders in response to PLPs. However, despite promising preclinical investigations, the effectiveness of PLPs in human dyslipidemia (DLP) is less clear and necessitates revision of available literature. Therefore, the present review analyzes the role of PLPs in managing clinical DLP, notably by dissecting their potential in ameliorating lipid/lipoprotein metabolism and alleviating hyperlipidemia, both postprandially and in long-term interventions. To this end, PubMed was used for article search. The search terms included polyphenols, lipids, triglycerides, cholesterol, LDL-cholesterol and/or HDL-cholesterol. The critical examination of the trials published to date illustrates certain benefits on blood lipids along with co-morbidities in participant’s health status. However, inconsistent results document significant research gaps, potentially owing to study heterogeneity and lack of rigor in establishing PLP bioavailability during supplementation. This underlines the need for further efforts in order to elucidate and support a potential role of PLPs in fighting DLP.

Keywords: polyphenols; dyslipidemia; lipoproteins; nutrition; oxidative stress; inflammation; microbiota; metabolic syndrome; type 2 diabetes

1. Introduction

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in the world. It represents a major concern for global health, and its prevalence as of 2017 is estimated to be around 423 million cases with 18 million deaths [1]. Not surprisingly, its crippling effects on both the healthcare infrastructure and the underlying population are significant, with an appraised annual cost of 600 billion dollars [2,3]. While the causes and risk factors for CVD are complex and multifaceted, lipid disorders such as dyslipidemias (DLP) are clearly associated with its pathological onset and are thus a leading focus of interest for clinicians in primary and secondary prevention. However, DLP management is intricate, and the understanding of the underlying mechanisms is critical for the development of more appropriate innovative therapies.

The Mediterranean diet has garnered considerable attention in the past decades given its beneficial impacts on cardiometabolic and cardiovascular health [4,5]. Indeed, Mediterranean diet intake acts on both healthy individuals and subjects with cardiovascular risk...
factors, resulting in favorable clinical outcomes and more particularly in improvement of lipid disorders. This positive impact may be due to its high polyphenolic content, derived from vegetables, grapes and olive oil. For example, olive oil brings out cardio-protective effects due the presence of a myriad of polyphenolic constituents, including phenolic acids (e.g., caffeic, syringic acids), flavonoids (e.g., apigenin, luteolin), secoiridoids (e.g., oleuropein) and lignin (tyrosol, hydroxytyrosol) [6]. These results have warranted widespread recommendations for the Mediterranean diet with respect to CVD prevention and management [4].

The purpose of this critical review is first to provide a comprehensive summary and update on lipid disorders and PLPs features. In a second step, we will emphasize the major roles of PLPs on both primary and secondary prevention, and discuss the potential mechanisms contributing to their various actions. Third, we will examine the use of PLPs as therapeutic agents while identifying new perspectives for future research.

2. Dyslipidemia

2.1. Definition of Dyslipidemia and Related Biomarkers

DLP is described as abnormal levels of circulating lipids, presenting a high risk for CVD development [7]. Its etiology can be primary (genetic) or secondary [diet, drugs, chronic diseases and metabolic disorders, including obesity, metabolic syndrome (MetS) and type 2 diabetes (T2D)] [8]. To define DLP, clinicians usually rely on rapid fasting lipid profile, which encompasses triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and non-HDL-C. Oftentimes, further evaluation of additional lipoprotein particles is necessary to get an accurate diagnosis, requiring more time and expertise. They include chylomicron (CM), CM remnants, very-low-density lipoprotein (VLDL), small and dense LDL and Lp(a) [9,10]. Apolipoproteins (Apo), the structural components of lipoprotein particles, are also very informative for diagnosis, and in particular Apo(a) (A1 and B-100), the major moieties of HDL and LDL, respectively. DLP, detrimental to human health, is identified by excessive concentration of TG, TC, VLDL, LDL-C, non-HDL-C, Lp(a), CM and CM-remnants, along with decreased levels of HDL-C. Moreover, the inadequate association of lipids (TG, free cholesterol, cholesteryl ester and phospholipids) with Apos (A-I, A-II, A-IV, B-48, B-100, C-II, C-III, E) disrupt the normal composition of the blood lipoproteins, which creates a shift towards an atherogenic lipoprotein phenotype, in essence a hallmark of DLP, and ultimately contributes to atherosclerosis [11].

2.2. Chylomicron Formation and Postprandial Dyslipidemia

One of the major functions of the small intestine is the transport of alimentary fat in the form of CM. Following the digestive phase involving bile acids and pancreatic lipase, the lipolytic products are absorbed by the enterocyte where they undergo lipid esterification along with the synthesis and post translational modification of different Apos, followed by the packaging of lipid and Apo components into lipoprotein particles [12–16]. Three key proteins should be given particular prominence: Apo B-48, microsomal triglyceride transport protein (MTTP) and Sar-1b (a GTPase protein) [17–21]. MTTP shuttles TG, cholesteryl ester and phospholipids to Apo B-48 in the endoplasmic reticulum, allowing packaging of CM particles, which are then exported to the Golgi for maturation under the control of Sar-1b. CMs are targeted to the basolateral site of the enterocyte in order to enter blood via the lymphatic duct. In the systemic circulation, lipoprotein lipase (LPL) hydrolyzes CM-TG in order to provide peripheral tissues with fatty acids (FA)s. Thereafter, CM remnants are mostly incorporated into the liver through Apo E recognition by hepatocyte receptors (Figure 1) [22].
Figure 1. Lipid absorption, excretion and transport by the gut–liver axis. Intestinal lipids contained in diet and in biliary acids (originating from the liver and delivered into intestinal lumen through the bile duct) are absorbed by the small intestine following digestion and uptake by protein transporters: Niemann-Pick-C1-like-1 (NPC1L1), scavenger receptor B-1 (SR-B1) and cluster of differentiation-36 (CD36). In the enterocyte, lipids and apolipoproteins (Apo) are assembled into chylomicrons (CMs), a process requiring the essential proteins Apo B-48, microsomal triglyceride transport protein (MTTP) and Sar1b-GTPase. Subsequently, CM are secreted into the peripheral circulation where their triglyceride (TG) components undergo lipolysis by lipoprotein lipase (LPL) after activation by Apo C-II. The resulting CM remnants are internalized by the liver following recognition by the specific low-density lipoprotein-like receptor protein (LRP). For their part, very-low-density lipoproteins (VLDLs) are assembled in the liver and released into the circulation to release fatty acids for peripheral tissues after hydrolysis by LPL. VLDL remnants or intermediate-density lipoprotein (IDL) can be taken up by liver receptors or be further metabolized into low-density lipoproteins (LDL) for cholesterol delivery in peripheral tissues through interaction with their LDL receptor (LDLR). On their side, high-density lipoproteins (HDL) are derived from the intestine and liver with the involvement of ATP-binding cassette transporter A1 (ABCA1) and Apo A-I. HDL confers atheroprotection via the process of reverse cholesterol transport whereby excess intracellular cholesterol is transported to the liver by HDL particles. Full arrows represent lipoprotein metabolism. Dotted arrows represent lipid movement. Boxed enzymes and receptors in green are associated with reduction of cholesterolemia, whereas red boxes are associated with increase in cholesterolemia. Some images in this figure were obtained and modified from Servier Medical Art (https://smart.servier.com).

Mounting evidence underlines the link between increased intestinal CM production in response to Western diet and atherosclerosis [23,24]. Indeed, raised levels of CM and their remnants correlate to intima media thickness and accelerated atherogenic process in MetS, insulin resistance (IR) and T2D conditions [25–27]. The chylomicronemia syndrome may also result from a deficiency in LPL, Apo CII or its associated proteins, leading to autosomal recessive disorder Type I hyperlipoproteinemia (HLP) [8,28]. Additional factors contributing to DLP from molecular aberrations of LPL and CM-remnant receptors or consequently to polymorphisms of LPL, Apo E, Apo B and MTTP [29–34].

2.3. Intestinal Cholesterol Transporters and Relation to Dyslipidemia

As dietary cholesterol (CHOL) intake contributes to plasma CHOL levels, which are associated with excessive CHOL deposition in the arterial intima, much attention has been paid to intestinal CHOL transporters [35]. The absorption of CHOL by enterocytes is controlled by (i) CHOL uptake at the apical site by Niemann-Pick-C1-like-1 (NPC1L1), scavenger receptor B-1 (SR-B1) and cluster of differentiation-36 (CD36) [36–38]; (ii) CHOL
uptake at the basolateral site by the regulatory system composed of LDL receptor (LDLR) and proprotein convertase subtilisin/kexin type 9 (PCSK9); (iii) CHOL excretion at the apical site by the heterodimer of ATP-binding cassette transporters G5/G8; (iv) CHOL output at the basolateral site by ATP-binding cassette transporter A1 (ABCA1), which transfers cellular CHOL to lipid-poor Apo A-1 for nascent HDL formation; and (v) the trans-intestinal CHOL excretion pathway which significantly enhances neutral sterol excretion in humans (Figure 1). Noteworthy, important intra-enterocyte proteins, including acyl-CoA: cholesterol O-acyltransferase 2 (catalyzing the esterification of CHOL with FA) and hydroxymethylglutaryl-CoA reductase (the rate-limiting enzyme in CHOL biosynthesis) are highly involved in intestinal CHOL absorption [35].

As reviewed above, the small intestine displays absorptive and excretory functions to modulate CHOL fluxes across the intestine, thereby favoring body CHOL homeostasis. Increased CHOL uptake (in response to upregulation of NPC1L1, SR-B1, CD36 and LDLR) or decreased CHOL excretion (due to downregulation of ABCA1, ATP-binding cassette transporter G5/G8 and trans-intestinal CHOL excretion) can influence pathogenesis of hypercholesterolemia, DLP and atherosclerosis [39–43]. Additionally, the transporters mediating intestinal CHOL absorption may act as determinants of Apo B-containing atherogenic lipoproteins [44,45].

2.4. VLDL Metabolism and Relation to Dyslipidemia

Similarly to CM assembly by the enterocyte, VLDL formation in the hepatocyte involves MTTP and Sar1b, while Apo B-100 becomes the major protein component [46]. After entering the bloodstream, VLDL-TG are hydrolyzed by LPL, thus releasing FA. VLDL remnants, or more specifically intermediate-density lipoprotein, can either be recycled back into the liver or undergo further lipolysis to be converted into LDL particles for CHOL delivery to peripheral tissues via LDLR-Apo B-100 interaction (Figure 1).

Defects or deletion of LDLR or ApoB100 genes result in abnormally low uptake of LDL by various organs, particularly the liver. Consequently, there is a steep accumulation of circulating LDL-C, a condition known as familial hypercholesterolemia (FH), which is associated with aggravated risk of LDL deposition in the vessel wall and atherosclerosis occurrence. Indeed, FH is characterized by an autosomal dominant pattern of inheritance and can result in heterozygosity (2- to 3-fold increase in circulating LDL-C) or more serious homozygotic form (3- to 6-fold LDL-C elevation). Homozygous patients develop atherosclerosis and stenosis (e.g., coronary artery disease, calcifications in the aortic root and ascending aorta, aortic regurgitation, and even death) during the first two decades of life.

Another causative gene in FH encodes PCSK9, which targets LDLR for degradation. Mutations or polymorphisms of PCSK9 are a common cause of FH, where gain-of-function PCSK9 mutations can cause familial autosomal dominant hypercholesterolemia. Moreover, rare mutations in LDLR adapter protein 1, ApoE p.Leu167del, or lysosomal acid lipase genes can mimic FH (Table 1) [8,28,47,48].

| Type | Name | Molecular Defect | Lipoprotein Elevated | Clinical Features | Incidence |
|------|------|------------------|----------------------|-------------------|-----------|
| 1    | Familial Hyperchylomicronemia | LPL, Apo C-II | CM | Juvenile or early adulthood onset; Eruptive xanthomas; Lipemia retinalis; Pancreatitis; Hepatosplenomegaly; Dyspnea; Lymphadenopathy; Neurologic dysfunction | 1:1,000,000 |
Table 1. Cont.

| Type                        | Name                          | Molecular Defect | Lipoprotein Elevated | Clinical Features                                                                 | Incidence                  |
|-----------------------------|-------------------------------|------------------|----------------------|-----------------------------------------------------------------------------------|----------------------------|
| 2a                          | Familial Hypercholesterolemia | a. LDLR           | LDL                  | Onset at all ages; Tendon xanthomas, Arthralgia; Xanthelasmas; Corneal arcus       | a. 1:500                   |
|                             |                               | b. Apo B-100     |                      |                                                                                    | b. <1:1000                 |
|                             |                               | c. PCSK9         |                      |                                                                                    | c. 1:1,000,000             |
| 2b                          | Combined HLP                  | Polygenetic      | LDL, VLDL, IDL, CM-remnants | CVD                                                                              | 1:50–1:200                 |
| 3                           | Dysbetalipoproteinemia        | Apo E            | IDL, CM-remnants     | Palmar xanthomas; CVD                                                              | 1:1000–1:5000              |
| 4                           | Primary or simple hypertriglyceridemia | Unknown           | VLDL              | Eruptive xanthomas; Hepatosplenomegaly; Hyperglycemia; Hyperuricemia;             | 1:50–1:100                 |
|                             |                               |                  |                      | Eruptive xanthomas; Pancreatitis; CVD                                              |                            |
| 5                           | Mixed hypertriglyceridemia    | Unknown           | CM, VLDL            |                                                                                    | Rare                       |

Adapted from [8,28]. CM, chylomicron; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HLP, hyperlipoproteinemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very-low-density lipoprotein.

2.5. Additional Congenital Types of Primary Hyperlipoproteinemia

Apo E constitutes an important component of CM- and VLDL-remnants and is also a ligand for their receptor-mediated hepatic uptake. Apo E deficiency or genetic variants may lead to familial Type III HLP. Apo E2 (substitution of cysteine in the normal Apo E3 variant for arginine at residue 158) interacts poorly with LDLR and LDLR-related protein, thereby DLP and an increased risk for atherosclerosis [28].

Type IV HLP is characterized by fasting hypertriglyceridemia due to a genetic autosomal dominant defect that increases VLDL secretion, raising the risk of abnormal glucose tolerance, athero-eruptive xanthoma, pancreatitis and CVD. Obesity, MetS, T2D, hypopituitarism, contraceptive steroids and glycogen storage disease I are secondary causes that can all trigger the development of Type IV HLP [8].

Lastly, type V HLP, also known as combined/mixed hypertriglyceridemia, is characterized by increased amounts of plasma CM and VLDL and decreased LDL and HDL after overnight fasting. In these conditions, TG levels are considerably elevated and enhance the risk of acute pancreatitis. Some patients exhibit high TC concentrations that can be accounted for increased VLDL [28]. Complete assessment of patients with Type V HLP also involves family sampling to discern the presence of familial Type V. In addition to primary Type V, secondary Type V has been noted and its development involves a multitude of metabolic derangements, including low TG clearance and/or their increased output aggravated by obesity, IR, T2D, alcohol intake, or the use of some hormones [8].

2.6. HDL Metabolism

2.6.1. HDL Synthesis and Functions

The liver and intestine constitute two important sites for the formation of new HDL particles (Figure 1). The crucial step for HDL biogenesis depends essentially on ABCA1. Genetic mutations or overexpression of ABCA1 result in diminished or raised circulating levels of HDL-C, respectively [47–49]. In addition to the contribution of hepatic and intestinal nascent HDL biogenesis, lipolysis of TG-rich lipoproteins (CM and VLDL) by LPL is another important source of HDL production, with mutual exchange of lipids through the action of cholesteryl ester transfer protein (Figure 2) [30,51].
Figure 2. Interaction and lipid exchanges amidst circulating lipoproteins. As very low-density lipoprotein (VLDL) and chylomicron (CM) are secreted by liver and gut, respectively, lipolysis by lipoprotein lipase (LPL) releases fatty acids for peripheral tissues. VLDL- and CM-remnants are captured by the liver following recognition of their apolipoprotein (Apo) E content by low-density lipoprotein-like receptor protein (LRP). A small proportion of intermediate-density lipoprotein (IDL) particles can be directly taken by the liver (via LRP) while circulating IDL-triglyceride (TG)s are degraded by LPL to provide low-density lipoprotein (LDL) particles. The latter are the major carriers of free cholesterol (FC) and cholesteryl ester (CE), which are delivered to peripheral tissues after LDL uptake via LDL receptors (LDLR). Peripheral efflux of FC and phospholipids (PLs) mediated by ATP-binding cassette transporter (ABCA1) towards lipid poor high-density lipoprotein (HDL) represents the first step for reverse cholesterol transport. Esterification of FC in HDLs by lecithin-cholesterol acyltransferase (LCAT) promotes HDL maturation and size. On the other hand, CE can also be exchanged for TG via cholesteryl ester transfer protein (CETP) with TG-rich lipoproteins (e.g., VLDL and CM) or LDL. At this stage, HDLs transfer their CE content to the liver via scavenger receptor B-1 (SR-B1) involvement. The reverse cholesterol transport process ends by the hepatic conversion of cholesterol into bile acids, which represents the only route of cholesterol elimination from the human body. Full arrows indicate lipoprotein metabolism. Dotted arrows indicate lipid movement. Green-boxed enzymes or receptors are associated with HDL metabolism, whereas red-boxed enzymes or receptors are linked with remaining lipoproteins. Some images in this figure were obtained and modified from Servier Medical Art (https://smart.servier.com).

The formation of CHOL-poor nascent HDL particles is achieved via the assembly of Apo A-1 and cellular lipids (mainly CHOL and phospholipids), a reaction catalyzed by ABCA1 [52,53]. The nascent discoidal HDL is progressively filled up in the blood circulation with CHOL transferred from peripheral tissues by ABCA1 and subsequently esterified to cholesteryl ester by lecithin cholesteryl ester transfer protein (LCAT) [54]. Filling with cholesteryl ester turns nascent HDL from a discoidal form into a spherical shape, and into larger HDL₃ and much larger HDL₂ particles. At this stage, HDL-C is removed by hepatic SR-B₁, completing the reverse cholesterol transport process and ultimately ensuring that excess peripheral tissue CHOL is deposited in the liver for bile acids conversion [55–57]. The importance of HDL in protecting against CVD is attributed not only to its role in reverse cholesterol transport but also to its ability to act as an antioxidant, anti-inflammatory, anti-thrombotic, pro-vasodilatory and anti-apoptotic agent (Figure 3) [38,58–61].
2.6.2. HDL-Related Disorders

Deficiency of HDL-C (hypoalphalipoproteinemia) can be a result of genetic defects of ABCA1, LCAT and ApoA1, which leads to Tangier disease, Fish-eye or Familial LCAT deficiency disease, and ApoA1 deficiency or ApoA1 variants [62]. Furthermore, genetic deficiency of cholesteryl ester transfer protein is characterized by markedly elevated levels of HDL-C while being associated with reduced atherosclerosis [63].

2.7. Treatment of Dyslipidemia

Depending on initial risk assessment, management of DLP primarily lies in prevention, and thus mostly consist of a therapeutic lifestyle approach where nutrition plays a key role [10]. However, if therapeutic goals cannot be reached through lifestyle, or in the event of a primary subtype of HLP, drug therapy or extracorporeal treatment is initiated (Table 2). Presently, the available medical arsenal for DLP mainly focuses on reducing LDL-C and non-HDL-C levels, but may act on Apo B, TG and HDL-C as well. Statins are the preferred choice for LDL-C lowering and are routinely prescribed as primary and secondary treatments [9,10]. If therapeutic goals still cannot be reached or if use of statins is contraindicated, secondary options typically include bile acid sequestrants, NPC1L1 inhibitors and PCSK9 antibodies [8–10,64–69].

As a first line of treatment, nutraceuticals with beneficial cardiometabolic properties such as PLPs are an interesting avenue in primary and secondary prevention of DLP, MetS, IR and atherosclerosis. General lack of undesired effects may make these phytochemicals particularly attractive and thus further warrants interest [70,71].
Table 2. Conventional treatments for dyslipidemia.

| Treatment        | Underlying Mechanism                                                                 | TG  | Lipid Profile Variation (%) | Indication                                                                 | CI Possible Adverse Effects                                                                 | Reference |
|------------------|---------------------------------------------------------------------------------------|-----|----------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------|
| Pharmacological therapies |                                                                                       |     |                            |                                                                            |                                                                                               |           |
| Statins          | HMG-CoA-R inhibitors                                                                   | ↓7–30| ↓15–51                     | ↓18–55                                                                 | ↑5–15                                                                                         | First line treatment                       | [9,10,64–66] |
| Bile acid sequestrants | Cholesterol chelation in gut’s lumen                                                    | ↑0–10| ↓4–16                      | ↓15–30                                                                 | ↑3–5                                                                                         | Adjunct with statins or first line treatment if statins not recommended                      | [9,10,66]  |
| Fibrates         | PPARα agonist (VLDL secretion inhibition, LPL induction)                                | ↓20–50| ↓5–19                      | ↓5–↑20                                                                 | ↑10–20                                                                                       | HyperTG                                       | [9,10,66,67] |
| NPC1L1 inhibitors | Cholesterol absorption inhibitor                                                       | ↓5–11| ↓14–19                     | ↓13–20                                                                 | ↑3–5                                                                                         | Adjunct with statins or first line treatment if statins not recommended                       | [9,10,66,67] |
| PCSK9 inhibitors | Inhibition of LDLR degradation                                                          | ↓50 |                            |                                                                            |                                                                                               | Adjunct with statins or first line treatment if statins intolerance                           | [10,66,71] |
| Mipomersen       | Inhibition of Apo B synthesis                                                           | ↓25 |                            |                                                                            |                                                                                               | In acute pancreatitis                         | [64,65]   |
| Lomitapide       | Inhibition of MTTP in liver and gut                                                    | ↓50 |                            |                                                                            |                                                                                               | HyperTG related to acute pancreatitis         | [64,65]   |
| Niacine          | Increased expression/activity of adipose LPL                                           | ↓20–50| ↓8–23                      | ↓5–25                                                                 | ↑15–35                                                                                       | HyperTG                                       | [9,10,66,67] |

CI: Possible drug-drug interaction (3A4 inhibitors), pre-existent hepatic disease, end-stage kidney failure, heart failure (>class I on NYHA scale), pregnancy and/or breast-feeding. PAE: hepatic toxicity, myopathy, rhabdomyolysis, acute renal failure. PAE: GI symptoms, reduced effectiveness of other medications, increase in TG. PAE: Hepatic steatosis. PAE: GI symptoms, hepatic steatosis.

Reference: [9,10,64–66,67]
| Treatment                      | Underlying Mechanism                     | Lipid Profile Variation (%) | Indication          | CI Possible Adverse Effects | Reference |
|--------------------------------|------------------------------------------|-----------------------------|---------------------|----------------------------|-----------|
| Omega-3 fatty acids           | PPARα agonist                           | ↓19–44                      | ↓5–14               | HyperTG                    | CI: Fish allergy | [9,66,67] |
|                               | Delayed/reduced cholesterol absorption   |                             |                     |                            |           |
| Dietary fibers                |                                          | ↓3–5                        |                     | Primary prevention         | PAE: GI symptoms | [72,73]   |
| Monacolin                     | HMG-CoA-R inhibitor                      | ↓0–20                       |                     | Primary prevention         | PAE: safety issues regarding presence of contaminants | [73]      |
| Phytosterols                  | absorption inhibitor                     | ↓4–9                        | ↓7–10               | Primary prevention         | [66,74,75] |

1 No LDL-C increase if omega-3 supplements contain exclusively eicosapentaenoic acid (no docosahexaenoic acid). CI, contraindication; DLP, dyslipidemia; GI, gastro-intestinal; HDL-C, high-density lipoprotein-cholesterol; HyperTG, hypertriglyceridemia; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; MTTP, microsomal triglyceride transport protein; NPC1L1, Niemann-Pick-C1-like-1; PAE, possible adverse effects; PCSK9, proprotein convertase subtilisin/kexin type 9; PPARα, peroxisome proliferator-activated receptor alpha; TG, triglycerides; VLDL, very low-density lipoprotein.
3. Polyphenols and Metabolic Benefits

3.1. Polyphenol Background

PLPs represent a vast heterogeneous class of phytochemicals. To date, more than 8000 compounds have been identified [70,76]. They are synthesized in plants as abundant secondary metabolites, which act as a powerful innate immunity agent, promoting both protection and survival [77]. Growing evidence underlines beneficial health properties of these natural polyphenolic compounds that work best for both prevention and therapy of multiple diseases (Figure 4). Their basic structure is represented by a benzene ring attached to one or more hydroxyl groups, thus forming the basic molecule upon which are grafted additional units, in association with organic acids and carbohydrates, to produce large polymers. PLPs are most commonly divided into two main families: flavonoids and non-flavonoids. The former is composed of diverse subgroups, including flavones, flavonols, flavan-3-ols, isoflavones, flavanones and anthocyanidins, whereas non-flavonoids regroup phenolic acids, lignans and stilbenes (Figure 5) [74,75,78].

![Figure 4](https://smart.servier.com)

**Figure 4.** Potential health benefits of dietary polyphenols in chronic diseases. CVD, cardiovascular disease; OxS, oxidative stress. Some images in this figure were obtained and modified from Servier Medical Art (https://smart.servier.com).

3.2. Regulation of Oxidative Stress, a Component Affecting Metabolic Syndrome, by Polyphenols

Oxidative stress (OxS) arises when cellular antioxidant defense is exceeded by the overproduction of reactive oxygen species (ROS). The multitude of free radicals like superoxide anions, hydroxyl, peroxyl radicals, alkoxyl radicals and hydrogen peroxides threaten cellular integrity and homeostasis [79]. OxS persistence due to diverse mechanisms (e.g., mitochondrial respiratory chain, uncontrolled arachidonic acid cascade and NADPH oxidase, a membrane-bound enzymatic complex) adversely affects lipids, proteins and DNA nucleic acids, which ultimately leads to disruption of intracellular signaling, loss of physiological function, and cellular death [80,81]. As cell organelles are generally rich in iron, the Fenton’s reaction uses this transition metal to promote ample hydroxyl radical synthesis and biological damage [82]. Fortunately, inter- and intra-cellular antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase) scavenge ROS and succeed in preventing OxS damage [80].
Polyphenols (PLPs), owing to their chemical structure and ROS scavenging properties, have commonly been identified as direct antioxidants. Their properties have been extensively documented over the years, mainly through numerous in vitro studies [83–85]. Nevertheless, a common criticism is that the experimental model too heavily relies on elevated concentrations of unaltered PLPs, which may not accurately reflect in vivo conditions. Indeed, low bioavailability, chemical modification during digestion in the gut lumen (i.e., deglycosylation), post-absorption in the liver (methyl, glucuronide and sulfate conjugation), dubious bioaccessibility, and short biological half-life render such experimental high dosage unrealistic, and even create a rift between in vitro and in vivo experimental conditions by a factor of $10^3$–$10^6$ [75]. Besides, in vitro models cannot account for the complex interaction of PLPs with the gut microbiota and resulting metabolites [75,76,83,84,86–88]. However, specific PLPs have garnered interest owing to their high bioavailability and consequently relatively high plasmatic concentrations. Prime examples, such as resveratrol or combined flavonoids and stilbene from red grapes, have shown clinical evidence of direct amelioration of redox imbalance by either restoring $\alpha$-tocopherol levels or otherwise preventing its degradation by initial ROS first encounter (Figure 6) [85,89].
Figure 6. Antioxidant protection and metabolic actions of polyphenol supplementation. Polyphenols (PLPs) may protect against oxidative stress (OxS) through either direct or indirect antioxidant mechanisms. In the former, PLPs can scavenge and neutralize ROS before the occurrence of oxidative damages to lipids, proteins and DNA. Moreover, PLPs have also the capacity to promote protection by regenerating additional exogenous antioxidants such as tocopherol and ascorbic acid. Solubilization and transport of PLPs by lipoproteins such as chylomicron or high-density lipoprotein/low-density lipoprotein particles may specifically prevent OxS derived from dyslipidemia (DLP) and cardiometabolic complications, notably atherosclerosis. Indirectly, PLPs stimulate endogenous antioxidants, including the regulatory KEAP-ARE-NRF2 pathway, in order to enhance the synthesis of phase 2 cytoprotective enzymes (e.g., γ-glutamylcysteine synthetase, glutathione peroxidase, glutathione reductase, NAD(P)H:quinone oxidoreductase 1, thioredoxin, thioredoxin reductase, catalase and superoxide dismutase). Furthermore, PLPs can stimulate the AMPK/SIRT1/PGC-1α pathway for prevention of mitochondrial dysfunction. AMPK, AMP-activated protein kinase; ARE, Antioxidant response element, KEAP, Kelch-like ECH-associated protein; NR-F2, nuclear factor erythroid-derived 2-like 2; PGC1-α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ROS, reactive oxygen species; SIRT1, sirtuin 1.

Several groups have documented the antioxidant ability of PLPs against OxS-induced damages either in chronic non-communicable diseases such as obesity, MetS, non-alcoholic fatty liver disease, T2D and CVD. A close association has been noted between obesity (the grimmest and most predominant public health threat worldwide) and OxS, which is characterized by NADPH oxidase upregulation and antioxidant enzyme downregulation [90]. High FA and glucose concentrations could account for these abnormalities, which are likely exacerbated by mitochondrial ROS formation [90–92]. PLPs were shown to fight OxS-antioxidant imbalance and avoid free radical injury, operating through direct or indirect antioxidant mechanisms of action (Figure 6). For example, supplementation of epigallocatechin gallate molecules, derived from green tea, not only served as singlet oxygen quenchers and enhanced endogenous antioxidant defenses but also mitigated hepatic lipid peroxidation and protein nitration while attenuating obesity-triggered steatosis through lowering hepatic and adipose tissue lipogenesis [93,94]. Moreover, it appeared in high-fat-induced obese rats that the advantageous impact of green tea PLP on body weight was produced via regulation of obesity-related anorectic genes, and anti-inflammation and antioxidant capacity [95]. For their part, nonflavonoid PLPs (e.g., resveratrol) inhibited oxygen-free radical formation by impeding NADPH oxidase-associated ROS production [96,97], a very important finding since elevated OxS is chiefly implicated in the pathogenesis of hypertension, DLP and CVD [98,99]. Resveratrol-mediated antioxidant upregulation and OxS lessening stimulated endothelial NO, while preventing inflammation and platelet aggregation [100,101]. Noteworthy, kelch-like ECH associated protein 1 and nuclear factor erythroid 2-related factor 2 system was the central cyto-protective mechanism for the decline of OxS elicited by PLPs (Figure 6) [102].
While long-lasting production of ROS induces strong IR, PLP antioxidants reduce ROS levels and exert glucose-lowering effects through amelioration of insulin sensitivity in humans and animal models of T2D [103–107]. In fact, OxS neutralization in various systems such as the muscle, adipose tissue and liver by PLPs contribute to the improvement of metabolic abnormalities [104]. Polyphenolic antioxidants may also serve to temper high blood pressure. For example, resveratrol prevented the development of hypertension and significantly lowered blood pressure in spontaneously hypertensive rats, possibly through the inhibition of Giα overexpression and other upstream signaling molecules [108,109].

DLP occurs very often in metabolic disorders and is associated with elevated OxS [110–113]. Available evidence has shown the susceptibility of lipids and lipoproteins, LDL in particular, to generate ROS [114,115]. Various studies documented high circulating levels of oxidized-LDL in MetS and T2D, as well as in FH [116,117]. Notably, PLPs such as curcumin exhibit hypolipidemic actions via various mechanisms while decreasing lipid peroxidation in lipoproteins. Specifically, PLPs have the potential to reduce circulatory CHOL and lipid peroxides, while increasing HDL-C in both animal models and clinical trial studies [118,119].

3.3. Regulation of Inflammation in Cardiometabolic Disorders by Polyphenols

As is the case for OxS, inflammatory processes are highly necessary for immunosurveillance and host defense since they respond to infectious agents, clear out necrotic cells and debris, and heal injuries and tissue damage [120]. However, if harmful triggers are persistent, inflammation can turn against healthy tissues, which become damaged and are even destroyed, thereby resulting in metabolic disorders and atherosclerosis [121]. Sustained low-grade inflammation predisposes to MetS components in view of raised levels of inflammatory cytokines, along with reduced concentrations of anti-inflammatory adiponectin [122]. This chronic inflammatory state could affect vascular and endothelial functions via nitric oxide lowering and ROS elevation [123]. Noteworthy, interactive relationship between OxS and inflammation constitutes the driving force for the severity of cardiometabolic complications and CVD [124]. Their interplay activates immune cell responses; recruits leukocytes, chemokines and adhesion molecules; and triggers vascular dysfunction via the activation of NADPH oxidase, xanthine oxidase and mitochondrial ROS overproduction. Collectively, these events contribute to both vascular and functional abnormalities, notably atherosclerosis progression and thrombus formation [125,126]. Furthermore, the simultaneous rise in inflammatory and oxidative status induces pathogenic mechanisms, favoring atherogenic lipoprotein production, oxLDL formation, atherogenic Apo B-containing lipoprotein retention in sub-endothelium, and HDL dysfunction [127–129].

On the other hand, down-regulation of pro-inflammatory cell signaling modulators, such as the nuclear factor-κB, the activated protein-1 and the mitogen activated protein kinases along with upregulation of nuclear factor-κB cytoplasmic inhibitor IκB, have been proposed as potential mechanisms of action of PLPs [130]. Further, PLPs may operate through inhibition of the arachidonic cascade and derivative eicosanoids [130,131]. Eicosanoids serve a modulating drive to the physiological inflammatory response, and consequently several anti-inflammatory drugs operate by limiting and/or inhibiting their production [132]. PLPs may block cellular release of arachidonic acid and/or inhibit the enzymes implicated in the cyclooxygenase pathway [130,131].

3.4. Polyphenols Counteract Cardiometabolic Complications by Regulating the Gut Microbiota

The gut microbiota has emerged in recent years as a novel and key player for metabolic diseases. Indeed, dysbiosis is associated with impaired gut integrity, local and systemic inflammation, OxS, reduced satiety, increased adiposity and ectopic lipid deposition [133]. On the other hand, healthy diets can favorably alter the composition of intestinal bacteria, which in turn promotes energy balance and body weight control, thereby reducing the risk of developing cardiometabolic complications [134]. In such cases, bacteria increase the production of short-chain FAs, such as acetate, propionate and butyrate, acting as
signaling molecules and resulting in “energy harvest”. For example, butyrate provides a desirable energy source for colonocytes in the gut, improves mucus function via increased mucin production, strengthens gut barrier defense integrity via the promotion of tight junction proteins and stimulates gastrointestinal peptide secretion for improved insulin secretion and satiety [135–137]. Further, commensal bacterial colonization in the gut could either limit the invasion of nefarious species or halt their spread, therefore limiting the local production of pathogenic metabolites such as LPS and gut immunity overstimulation leading to metabolic endotoxemia and inflammation [138,139].

The polymeric fraction of PLP, indigestible and unabsorbable in the proximal intestine, interacts with colonic microflora, thereby increasing production of beneficial metabolites such as short-chain FAs and stimulating their advantageous effects (Figure 7). Animal models challenged with PLPs exhibit a high production of beneficial bacterial population such as Akkermansia municiphilia sp. with a significant amelioration of inflammatory markers, gut permeability and insulin sensitivity [135,140–142]. Further, safeguard of a metabolically healthy gut–liver axis via microbiota reconfiguration may present an interesting avenue in the lipid-lowering potential of PLPs.

Figure 7. Protection against inflammation and microbiota dysbiosis by polyphenols. Polyphenols (PLP) included in diet may be composed of a wide range of molecules, from monomers to polymers. While the smaller mono-/di- and trimers can be directly absorbed in the proximal intestine, polymers need to continue their transit to undergo catabolism by microbiota in the colon. Commensal bacteria and their metabolites promote a wide variety of beneficial metabolic outcomes for local epithelial cells. Advantageous actions include improvement of gut integrity and production of both mucus and of gastrointestinal peptides. In addition, control over microbiota dysbiosis aderts the formation of nefarious metabolites such as bacterial lipopolysaccharide (LPS), thereby enhancing anti-inflammatory protection, and limiting further environmental stressors such as oxidative stress and lipid metabolism dysregulation. GLP-1, glucagon-like peptide 1; PYY, peptide YY; SCFA, short-chain fatty acids. Some images in this figure were obtained and modified from Servier Medical Art (https://smart.servier.com).
4. Methods

The available literature regarding polyphenol challenge on lipid profile in humans has been searched and analyzed. Electronic database Medline (PUBMED) was used for article research. The following keywords were employed: “polyphenols”, “lipids”, “triglycerides”, “cholesterol”, “LDL-C” and/or “HDL-C”. In order to be considered eligible, clinical trials had to comprise at least one parameter of this lipid profile, challenged by PLP intake and with the indication of lipid levels at baseline and following intervention. No discrimination was made regarding publication date, number or sex of participants enrolled. We excluded trials focusing on other pathologies. We also rejected meta-analyses, reviews and animal studies. Thus, 49 published clinical trials corresponding to our selection criteria were retained and thoroughly analyzed.

5. Polyphenol Supplementation in Humans—Intervention Trials

Recently, interest in dietary PLPs for human health has led to a great deal of research, especially in the cardiometabolic field. The following sections of this review particularly cover in vivo clinical studies, with a special focus on the potential of PLP to treat various types of human DLP.

5.1. Chronic Intake Interventions

Trials lasting more than a single time point (2 weeks to a whole year) were considered as a chronic intake/supplementation of PLP. The clinical status of the anthropometric and biochemical markers of participants enrolled, in essence their cardiometabolic state and overall level of risk, may severely impact their responsiveness to treatment and therefore account for the extensive amount of variability in clinical trials [136]. Further, since DLP is a pathology not only associated with the MetS, but which serves as a defining risk factor for diagnosis as well, the qualitative and quantitative assessment of other risk factors at play (namely abdominal obesity, systolic high blood pressure and IR) could thereby better reflect the initial metabolic state of participants enrolled. This could in turn potentially provide a better indication for the preventive use of PLP supplementation.

5.1.1. Impact of Polyphenols on Healthy Participants

The hypothesis of the first set of studies was that the chronic consumption of PLP-rich nutrients would maintain or improve the lipid profile of healthy participants while ensuring safety and lack of side effects. In total, 15 clinical trials are summarized in Table 3. Subjects were between the ages of 26 and 42, with a mean age of 34. The most relevant lipid findings in response to PLP indicate a decrease in TG in 8/12, TC in 7/12 and LDL-C in 8/11 along with an increase in HDL-C in 6/10 studies. The other clinical trials showed opposite trends. Although side effects have not been reported by the different groups, the results do not provide a clear picture of the favorable effect of PLPs on lipid and lipoprotein parameters in healthy individuals. The inconsistency may stem from the study design, huge PLPs concentration (45.3–3589 mg/day), intake duration (14–168 days), and matrix (Table 3). Importantly, food matrix represents one of the major limiting factor affecting PLP bioavailability and subsequent gastrointestinal absorption [84]. Further studies are certainly warranted to investigate the preventive actions of PLP in healthy individuals. Above all, efforts are needed in order to distinguish the specific effects of PLPs versus those of the many pro-health components (e.g., vitamins, fibers, functional food products, and minerals) present in fruits, vegetables and plants. This is a central aspect for understanding the ultimate contribution of PLPs, which will provide a cost-effective and safe alternative for the prevention of lipid disorders.
| Polyphenols                                                                 | Dietary Source (Main PLP) | Dosage (mg/Day) | Matrix                  | Intake Repartition | Length S.D. (Days) | n (Female) | Age (Years) | D.-O. (%) | TG     | TC     | LDL-C     | HDL-C     | Reference |
|---------------------------------------------------------------------------|---------------------------|-----------------|-------------------------|--------------------|--------------------|------------|-------------|------------|--------|--------|-----------|-----------|-----------|
| Red grape (anthocyanidins, quercetin, myricetin)                          | Diet (drink)              | 640             | Bid                     | 14 P               | 15 (7)             | 34.4 ± 3.3 | 10          | ↑19%       | ↓6% *  | ↓13% *  | ↑16% *    |           | [89]      |
| Potato                                                                    | Diet (whole food)         | 288             | Die                     | 14 CO              | 14 (8)             | 33.5 ± 2.9 | 0           | ↓11% *     | ↑9%    | ↑11%    | NV        |           | [137]     |
| Shampion apple (quercetin, epicatechin) + pectin                         | Diet (apple pomace)       | 75              | Die                     | 28 CO              | 23 (14)            | 36.2 ± 3.7 | 32          | ↓11%       | ↓5% *  | ↓10%    | NV        |           | [143]     |
| Shampion apple (Procyanidin, epicatechin) + pectin                        | Diet (whole apple)        | 239             | Die                     | 28 CO              | 23 (14)            | 36.2 ± 3.7 | 32          | ↓7% *      | ↓7% *  | ↓8% *   | ↓6%       |           | [143]     |
| Shampion apple (Procyanidin, chlorogenic acid)                           | Diet (cloudy apple juice) | 145             | Die                     | 28 CO              | 23 (14)            | 36.2 ± 3.7 | 32          | ↑1%        | ↓3% *  | ↓4% *   | NV        |           | [143]     |
| Shampion apple (Procyanidin, chlorogenic acid)                           | Diet (clear apple juice)  | 108             | Die                     | 28 CO              | 23 (14)            | 36.2 ± 3.7 | 32          | ↑4%        | ↑2%    | ↑6%     | ↓1%       |           | [143]     |
| Yerba mate tea (green or roasted)                                         | Diet (drink)              | 3589            | Tid                     | 40 P               | 15 (14)            | 42.0 ± 3.2 | 11          | ↓3% *      | ↓7% *  | ↑2%     | ↑2%       |           | [144]     |
| Yerba mate tea (green or roasted)                                         | Diet (drink)              | 3589            | Tid                     | 20 P               | 15 (14)            | 42.0 ± 3.2 | 11          | ↑13%       | ↓2%    | ↓9%     | ↑4%       |           | [144]     |
| Olive leaf extract (oleuropein)                                           | Liquid supplement          | 167             | Bid                     | 42 CO              | 60 (0)             | 45.3 ± 1.6 | 2           | ↓12% *     | ↓6% *  | ↓6% *   | ↓4%       |           | [145]     |
| Chocolate (flavanol, epicatechin) + fibers                                | Diet (drink)              | 45.3            | Bid                     | 28 CO              | 24 (13)            | 27.0 ± 4.8 | 12          | ↓2%        | ↑4%    | ↑1%     | ↑16% *    |           | [146]     |
| Resveratrol                                                                | Capsule                   | 150             | Die                     | 30 CO              | 15 (12)            | 38.2 ± 2.1 | 18          | ↓1%        | ↑2%    | ↑2%     | ↑1%       |           | [85]      |
### Table 3. Cont.

| Dietary Source (Main PLP) | Dosage (mg/Day) | Matrix | Intake Repartition | Length (Days) | n (Female) | Age (Years) | D.-O. (%)  | TG | TC | LDL-C | HDL-C | Reference |
|---------------------------|-----------------|--------|--------------------|---------------|------------|-------------|------------|----|----|-------|-------|-----------|
| Resveratrol (+300mg Orlistat die) | 300 | Capsule | Tid | 168 P | 24 (21) | 40.9 ± 1.6 | 48 | ↓7% | N/A | N/A | N/A | [147] |
| Resveratrol               | 300 | Capsule | Tid | 168 P | 15 (12) | 33.7 ± 2.0 | 48 | ↑10% | N/A | N/A | N/A | [147] |
| Resveratrol               | 500 | Capsule | Die  | 30 CO  | 49 (42) | 35.9 ± 1.6 | 0  | ↓0.4% * | NV  | N/A | N/A | [148] |
| Coffee (hydroxycinnamic acids, methylxanthines) | 510.6 | Diet (drink) | Tid  | 56 CO | 25 (15) | 26.2 ± 1.4 | 4  | NV  | N/A | N/A | ↑4% | [149] |

1 Change as percentage of baseline. Up and down arrows indicate lipid/lipoprotein increase and decrease, respectively, following PLP challenge. * indicates significant variation (p < 0.05).
2 As specified by the authors in the case of a non-purified extracts.
3 Values represent mean ± standard error of the mean. Bid, twice a day; CO, cross-over intervention; Die, daily; D.-O., drop-out rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NV, no variation; P, parallel intervention; PLP, polyphenol; S.D., Study design; TC, total cholesterol; TG, triglycerides; Tid, thrice a day.
5.1.2. Impact of Polyphenols on Dyslipidemia

As there presently lacks any studies examining PLP challenge on any primary subtypes of DLP, the following sections address clinical interventions including participants presenting any subtype of secondary DLP. To this end, it was important to consider the baseline lipid profile, which had one of the following criteria: hypertriglyceridemia (>1.7 mM), hypercholesterolemia (>5.2 mM), elevated LDL-C (>3.4 mM) and/or low levels of HDL-C (<1 mM for men/1.3 mM for women) [10,150]. We then analyzed whether study participants with high CVD risk were more likely to benefit from PLP challenge. Importantly, studies were further separated based on the number of co-morbidities accompanying DLP, which ranges from one to three (Tables 4–6), and by including the CVD risk based on the Framingham risk score. The latter was chosen since it takes into account the age, the levels of TC and HDL-C, systolic blood pressure and presence of T2D.

Impact of Polyphenols on Patients with a Single Dyslipidemia Component

In the 15 of clinical trial studies listed with a single component of DLP (Table 4), an improvement is noted in TG (n = 10), TC (n = 8) and HDL-C (n = 11) in response to PLP treatment in the majority of clinical trials. However, mixed results were observed in LDL-C.

The variability of the findings may be due to the divergences in the study design involving PLP type, the matrix (as method of delivery) and dosage (0.05–2148 mg/d), as well as trial length (15–56 days), number of patients (20–184) and gender (number of women limited to 0–21).

Impact of Polyphenols on Patients with Two Dyslipidemia Components

Intriguingly, only 8 studies are available in this DLP category involving two morbidities (Table 5). Despite the limited number, it is possible to observe an improvement in TG (6/8), TC (5/8), LDL-C (5/8) and HDL-C (6/8). We can observe a great variability in the dose of PLPs (40–1500 mg/day), number of patients (n = 8–43), age of subjects (42–62 years), duration of the trial (14–77 days), matrix and gender.

Impact of Polyphenols on Patients with Three Dyslipidemia Components

The majority of trials in this category of patients showed an improvement of TG (8/10), TC (8/10, LDL-C (8/10) and HDL-C (6/9) in response to PLPs (Table 6). Noteworthy, in this category of DLP with three morbidity factors, two studies using resveratrol yielded poor results. Findings of a few studies were controversial as revealed in a meta-analysis conducted by Zhang et al. who found that resveratrol supplementation significantly increased total- and LDL-C concentrations [151]. Nevertheless, we expected hypocholesterolemic effects of resveratrol given positive findings in mice, including CHOL lowering and atherosclerosis protection via enhanced activity of peroxisome proliferator-activated receptor α [152], improvement of the endothelial activity [153], suppression of platelet aggregation [154], and reduction of blood pressure [155].
Table 4. Clinical studies evaluating lipid/lipoprotein status of dyslipidemia participants with a single morbidity in response to polyphenol supplementation.

| Dietary Source (Main PLPs) | Dosage (mg/Day) | Protocol Matrix | Intake Repartition Length S.D. (Days) | n (Female) | Age (Years) | D.-O. (%) | ↑LDL-C | ↑TG ↓HDL-C | Obesity IR | ↑SBP | FRS (%) | TG | TC | LDL-C | HDL-C | Reference |
|---------------------------|----------------|----------------|--------------------------------------|------------|-------------|-----------|--------|-----------|-----------|------|---------|-----|-----|-------|-------|-----------|
| Coffee (hydroxycinnamic acids, methylxanthines) | 510.6 | Diet (drink) Tid | 56 CO | 27 (17) | 33.7 ± 1.8 | 4 | ✓ | | | 0.4 | ↓20% * | N/A | N/A | ↓1% | [149] |
| Virgin olive oil (lignans) | 2.9 | Diet | Die | 21 CO | 33 (14) | 55.2 ± 1.8 | 15 | ✓ | | | 9.5 | ↓6% | ↓5% | ↑1% | NV | [156] |
| Enriched virgin olive oil (hydroxytyrosol derivatives, lignans, flavonoids) | 12.1 | Diet | Die | 21 CO | 33 (14) | 55.2 ± 1.8 | 15 | ✓ | | | 9.5 | ↑3% | ↓4% | NV | ↑2% | [156] |
| Enriched virgin olive oil (hydroxytyrosol derivatives, lignans) | 12.6 | Diet | Die | 21 CO | 33 (14) | 55.2 ± 1.8 | 15 | ✓ | | | 9.5 | ↑3% | ↓4% | ↓8% * | ↓1% | [156] |
| Olive oil (not specified) | 0.05 | Diet | Die | 21 CO | 182 (0) | 33.3 ± 0.8 | 8 | ✓ | | | 1.9 | ↓6% | NV | ↑1% | ↑2% * | [157] |
| Olive Oil (not specified) | 3.6 | Diet | Die | 21 CO | 184 (0) | 33.3 ± 0.8 | 8 | ✓ | | | 1.9 | ↓4% | NV | ↑1% | ↑3% * | [157] |
| Olive Oil (not specified) | 8.1 | Diet | Die | 21 CO | 183 (0) | 33.3 ± 0.8 | 8 | ✓ | | | 1.9 | ↓5% | NV | ↑2% | ↑4% * | [157] |
| Pine Bark (flavonoids) | 150 | Capsule | Die | 42 CO | 25 (15) | 30.0 ± 1.5 | 0 | ✓ | | | 1.7 | ↑2% | ↓2% | ↓7% * | ↑11% * | [158] |
| Dietary Source (Main PLPs) 2 | Dosage (mg/Day) | Matrix | Protocol | n (Female) | Age 3 (Years) | D.-O. (%) | nLDL-C | ↑TG ↓HDL-C | Obesity IR | ↑SBP FRS (%) | TG | TC | LDL-C | HDL-C | Reference |
|----------------------------|----------------|--------|----------|------------|--------------|-----------|--------|-----------|------------|--------------|-----|-----|-------|-------|-----------|
| Cocoa (epicatechin, catechin, procyanidin) | 282 | Diet (drink) | Bid 28 P | 37 (21) | 49.9 ± 1.3 | 0 | ✓ | 5.5 | ↓7% | ↓3% | ↓5% * | ↑9% * | [159] |
| Cocoa (epicatechin, catechin, procyanidin) | 211 | Diet (drink) | Bid 28 P | 32 (18) | 49.9 ± 1.3 | 0 | ✓ | 5.4 | ↓2% | ↓3% | ↓4% * | ↑7% * | [159] |
| Cocoa (epicatechin, catechin, procyanidin) Chocolate (flavanol, epicatechin) + fibers | 141 | Diet (drink) | Bid 28 P | 31 (18) | 49.9 ± 1.3 | 0 | ✓ | 5.5 | NV | ↓3% | ↓3% * | ↑5% * | [159] |
| Chocolate (flavanol, epicatechin) + fibers | 45.3 | Diet (drink) | Bid 28 CO | 20 (11) | 30.0 ± 6.2 | 12 | ✓ | 2.0 | ↑1% | ↑2% | NV | ↑12% * | [146] |
| Dark chocolate (not specified) | 2148 | Diet | Die 15 CO | 92 (34) | 45.0 ± 1.1 | 40 | ✓ | 5.9 | ↓8% | ↑2% | ↑14% | ↑5% * | [160] |
| Dark chocolate (not specified) | 1000 | Diet | Die 42 P | 15 (15) | 57.6 ± 1.3 | 0 | ✓ | 6.3 | ↓2% | ↓1% | NV | ↓5% | [86] |
| Mate Tea (chlorogenic acid) | 107 | Diet (drink) | Die 15 CO | 92 (34) | 45.0 ± 1.1 | 40 | ✓ | 5.9 | ↓3% | ↑1% | ↑3% | ↑1% * | [160] |

1 Change as percentage of baseline. Up and down arrows indicate lipid/lipoprotein increase and decrease, respectively, following PLP challenge. * indicates significant variation (p < 0.05). 2 As specified by the authors in the case of a non-purified extracts. 3 Values represent mean ± standard error of the mean. Bid, twice a day; CO, cross-over intervention; Die, daily; D.-O., drop-out rate; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NV, no variation; P, parallel intervention; PLP, polyphenol; SBP, systolic blood pressure; S.D., Study design; TC, total cholesterol; TG, triglycerides; Tid, thrice a day.
Table 5. Clinical studies evaluating lipid/lipoprotein status of dyslipidemia participants with two morbidities in response to polyphenol supplementation.

| Dietary Source (Main PLPs) | Dosage (mg/Day) | Protocol | Intake Repartition | Length (Days) | n | D.-O. (%) | Age (Years) | Variation of Lipid Profile | Reference |
|---------------------------|-----------------|----------|--------------------|---------------|---|-----------|-------------|-----------------------------|-----------|
| Carob (not specified)     | 40              | Capsule  | Bid                | 30 P          | 43 (22) | 42.9 ± 9.5 | 9           | ▲ LDL-C ▲ TG ▼ HDL-C       | ▼ SBP     | 6.6 ▼ 23% * ▼ 18% *       | ▼ 23% * | ▼ 6% * [161] |
| Red grape                 | 640             | Juice    | Bid                | 14 P          | 26 (13) | 62.0 ± 0.4 | 10          | ▲ LDL-C ▲ TG ▼ HDL-C       | ▼ SBP     | 12.8 ▼ 8% ▼ 11% * ▼ 18% * | ▼ 13% * | [89] |
| Red wine (not specified)  | 1000            | Diet     | Die                | 42 P          | 14 (14) | 58.4 ± 1.3 | 0           | ▲ LDL-C ▲ TG ▼ HDL-C       | ▼ SBP     | 7.3 ▼ 17% NV ▼ 8% *       | ▼ 17% * | [86] |
| Catechins, theaflavins    | 224.4           | Capsule  | Die                | 77 P          | 31 (11) | 50.1 ± 0.5 | 0           | ▲ LDL-C ▲ TG ▼ HDL-C       | ▼ SBP     | 7.0 ▼ 13% ▼ 1% * ▼ 2% *  | ▼ 3% *  | [162] |
| Theaflavins               | 77.5            | Capsule  | Die                | 77 P          | 34 (12) | 47.5 ± 1.0 | 0           | ▲ LDL-C ▲ TG ▼ HDL-C       | ▼ SBP     | 7.0 ▼ 7% ▼ 3% * ▼ 7% *  | ▼ 2% *  | [162] |
| Resveratrol               | 1500            | Capsule  | Bid                | 14 CO         | 8 (0)    | 45.8 ± 3.1 | 0           | ▲ LDL-C ▲ TG ▼ HDL-C       | ▼ SBP     | 6.7 ▼ 20% N/A N/A N/A     | N/A      | [163] |
| Resveratrol               | 150             | Capsule  | Bid                | 30 CO         | 18 (11) | 50.4 ± 2.0 | 18          | ▲ LDL-C ▲ TG ▼ HDL-C       | ▼ SBP     | 5.4 ▼ 8% ▼ 4% ▼ 1% ▼ 3%  | ▼ 3%     | [85] |
| Cranberry (proanthocyanins, anthocyans) | 346             | Diet     | Bid                | 56 P          | 29 (15) | 76.6 ± 1.6 | 12          | ▲ LDL-C ▲ TG ▼ HDL-C       | ▼ SBP     | 4.7 ▼ 8% NV ▼ 1% ▼ 3%  | ▼ 3%     | [164] |

1 Change as percentage of baseline. Up and down arrows indicate lipid/lipoprotein increase and decrease, respectively, following PLP challenge. * indicates significant variation (p < 0.05). 2 As specified by the authors in the case of a non-purified extracts. 3 Values represent mean ± standard error of the mean. Bid, twice a day; CO, cross-over intervention; Die, daily; D.-O., drop-out rate; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NV, no variation; ▲, parallel intervention; PLP, polyphenol; SBP, systolic blood pressure; S.D., Study design; TC, total cholesterol; TG, triglycerides.
Table 6. Clinical studies evaluating lipid/lipoprotein status of dyslipidemia participants with three morbidities in response to polyphenol supplementation.

| Dietary Source (Main PLPs) ² | Dosage (mg/Day) | Matrix | Intake Repartition | Length S.D. (Days) | n (Female) | Age ³ (Years) | D.-O. (%) | ↑LDL-C | ↑TG | ↓HDL-C | Obesity IR | ↑SBP FRS (%) | TG | TC | LDL-C | HDL-C | Reference |
|-----------------------------|-----------------|--------|-------------------|--------------------|-----------|--------------|----------|--------|-----|--------|------------|---------------|----|----|-------|-------|-----------|
| Bergamot PLP (neoeriocitrin, naringin, neohesperidin) (+ statin) | 1000 Capsule Die 30 P ¹5 (N/A) | N/A | 0 | ✓ ✓ ✓ | >20 | ↓36% * | ↓38% * | ↓53% * | ↑37% * | [165] |
| Bergamot PLP (neoeriocitrin, naringin, neohesperidin) | 1000 Capsule Die 30 P ¹5 (N/A) | N/A | 0 | ✓ ✓ ✓ | >20 | ↓31% * | ↓31% * | ↓41% * | ↑18% * | [165] |
| Amla (Indian gooseberry) (not specified) | 350 Capsule Bid 84 P ¹49 (27) | 40.7 ± 1.6 | 0 | ✓ ✓ ✓ | 5.5 | ↓34% * | ↓24% * | ↓20% * | ↓10% * | [166] |
| Chokeberry (anthocyanidins) | 772 Diet (drink) Die 28 P ¹23 (11) | 47.5 ± 1.5 | 0 | ✓ ✓ ✓ | ✓ ⁶ | 6.7 | ↓19% * | ↓4% | ↓7% | ↓1% | [167] |
| Yerba mate tea (green or roasted) (chlorogenic acid, 4,5-dicaffeolquinic acid, gallocatechin) | 3589 Diet (drink) Tid 20 P ¹57 (34) | 45.8 ± 1.6 | 12 | ✓ ✓ ✓ | 3.9 | ↓3% | ↓3% | ↓8% * | ↑4% * | [144] |
| Yerba mate tea (green or roasted) (chlorogenic acid, 4,5-dicaffeolquinic acid, gallocatechin) | 3589 Diet (drink) Tid 40 P ¹57 (34) | 45.8 ± 1.6 | 12 | ✓ ✓ ✓ | 3.9 | ↓3% | ↓5% * | ↓9% * | ↑3% | [144] |
Table 6. Cont.

| Dietary Source (Main PLPs) ² | Dosage (mg/Day) | Matrix | Intake Repartition | Length S.D. (Days) | n (Female) | Age ³ (Years) | D.-O. (%) | ↑LDL-C | ↑TG | ↓HDL-C | Obesity IR | ↑SBP | FRS (%) | TG | TC | LDL-C | HDL-C | Reference |
|-------------------------------|-----------------|--------|-------------------|------------------|------------|---------------|------------|--------|-----|--------|------------|------|---------|----|----|------|------|-----------|
| Whole red grape (not specified) + 2.7 g of fibers | 63 | Diet | 5x/day | 56 P | 22 (18) | 50.5 ± 1.5 | 0 | √ | √ | √ | 9.5 | ↓1% | ↓9% * | ↓15% * | ↓6% | [168] |
| Whole white grape (not specified) + 5.3 g of fibers | 58 | Diet | 5x/day | 56 P | 24 (18) | 50.6 ± 1.3 | 0 | √ | √ | √ | 7.1 | ↓4% | ↓8% * | ↓10% * | ↓7% | [168] |
| Resveratrol | 500 | Capsule | Bid | 30 P | 24 (12) | 58.5 ± 3.4 | 0 | √ | | | | 12.8 | ↑2% | ↑5% * | ↑15% * | ↓2% | [169] |
| Resveratrol | 3000 | Capsule | Bid | 56 P | 10 (0) | 48.8 ± 1.7 | 0 | √ | | | | 18.4 | ↑31% | ↑12% | ↑19% | NV | [170] |

¹ Change as percentage of baseline. Up and down arrows indicate lipid/lipoprotein increase and decrease, respectively, following PLP challenge. * indicates significant variation. ² As specified by the authors in the case of a non-purified extracts. ³ Values represent mean ± standard error of the mean. Bid, twice a day; CO, cross-over intervention; Die, daily; D.-O., drop-out rate; FRS, Framingham risk score; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NV, no variation; P, parallel intervention; PLP, polyphenol; SBP, systolic blood pressure; S.D., Study design; TC, total cholesterol; TG, triglycerides; Tid, thrice a day.
5.1.3. Impact of Polyphenols on Metabolic Syndrome and Type 2 Diabetes

As the MetS is viewed as one of the most challenging health problems of our century, numerous scientists and clinicians are actively seeking effective drugs to reduce severity-associated co-morbidities, including T2D and CVD. Currently, the treatment of the MetS is based on multiple pharmacological agents directed against each of its components. Although lifestyle modification remains an interesting approach, many groups attempt to uncover novel effective nutraceuticals to alleviate its severity and development of cardiometabolic complications. Dietary PLPs have often been proposed as a powerful tool to fight the pathophysiological complexity related to both T2D and CVD. The goal in this following section is to determine whether PLPs may tackle T2D and CVD according to available clinical evidence.

Surprisingly, only 14 clinical trials have been conducted on the modulation of the lipid profile associated-MetS patients as a function of dietary PLPs. As noted in Table 7. About two thirds of these trials showed an improvement in TG, TC and LDL-C in response to PLPs supplementation, whereas a negative effect was observed on HDL-C. The large variability of the data could not recapitulate the results obtained in in vitro and preclinical investigations [171–176]. The discrepancy is likely due to the variation in the dose of PLPs (150–3000 mg/d), length of the studies (21–56 days), number of participants (10–68), female-male ratios (0–1) and food matrix. Therefore, future research is needed before supporting a potential role of PLPs in reducing lipid concentrations. The same holds true for HDL-C in view of its PLP-promoting increase reported by the work of various groups. Ultimately, PLP effectiveness demonstration in ameliorating DLP would be helpful towards integrating them in MetS treatment.

Although the number of clinical trials (n = 7) remains limited in investigating diabetic DLP in response to supplementation of PLPs, findings are more meaningful in T2D (Table 8) compared to MetS (Table 7). The majority of studies described their reducing effect on TG (13–42%), TC (2–12%) and LDL-C (1–15%), as well as their increasing effect on HDL-C (1–11%). Only resveratrol failed to alleviate diabetic DLP [177]. Diversity in length of supplementation (56–183 days) and delivery through capsules could account for the differences noted in PLPs effects. Long-term studies involving a large cohort of subjects together with careful diet control are needed in order to confirm the potential effect of PLPs on MetS and T2D in humans, without, of course, leaving aside genetic differences between populations.
### Table 7. Clinical studies evaluating lipid/lipoprotein status of participants with metabolic syndrome in response to polyphenol supplementation.

| Dietary Source (Main PLPs) 3 | Dosage (mg/Day) | Matrix | Intake Repartition | Length (Days) | n (Female) | Age 4 (Years) | D.-O. (%) | ↑LDL-C | ↑TG ↓HDL-C | Obesity IR | ↑SBP | FRS (%) | TG | TC | LDL-C | HDL-C | Reference |
|------------------------------|----------------|--------|--------------------|---------------|------------|---------------|------------|--------|------------|------------|------|---------|-----|-----|-------|-------|-----------|
| Eckonia cava (not specified) | 144            | Diet   | Bid 84 P           | 32 (21)       | 0          | 40.2 ± 10.1  | 0          | √      | √          | √          |      | 3.8     | ▼8% | ▼9% | ▼14% | ▼13% | [178]    |
| Eckonia cava (not specified) | 72             | Diet   | Bid 84 P           | 33 (22)       | 0          | 40.6 ± 9.3   | 0          | √      | √          | √          |      | 3.8     | ▼3% | ▼7% | ▼10% | ▼9%  | [178]    |
| Grape (flavanols, anthocyanidins) | 195          | Diet   | Bid 28 CO          | 20 (8)        | 0          | 53.5 ± 1.4   | 0          | √      | √          | √          |      | 9.6     | ▼22% | ▼4% | NV    | ▼1%  | [179]    |
| PLP (various)                 | 2776          | Diet   | Tid 56 P           | 20 (11)       | 9          | 53.0 ± 1.2   | 9          | √      | √          | √          |      | 7.7     | ▼15% | ▼5% | ▼6%  | ▼6%  | [180]    |
| PLP (various) + omega-3 Cranberry (proanthocyanidins, anthocyanidins) | 2667          | Diet   | Tid 56 P           | 19 (11)       | 9          | 55.0 ± 1.2   | 9          | √      | √          | √          |      | 5.4     | ▼12% | ▼1% | ▼5%  | ▼8%  | [180]    |
| Cranberry and strawberries (phenolic acids, proanthocyanidins) | 458           | Diet   | Bid 56 P           | 15 (15)       | 3          | 52.0 ± 1.1   | 3          | √      | √          | √          |      | 8.6     | ▼4% | ▼3% | ▼4%  | ▼3%  | [181]    |
| Red wine (catechin, epicatechin, gallic acid) | 333           | Liquid supplement | Die 42 P | 20 (11) | 9 | 57.0 ± 1.0 | 9 | √ | √ | √ | √ | 9.1 | ▼10% | ▼2% | NV | ▼1% | [182] |
| Dealcoholized wine (catechin, epicatechin, gallic acid) | 798           | Diet   | Die 28 CO          | 67 (0)        | 8          | 60.0 ± 1.0   | 8          | √      | √          | √          |      | >30     | ▼2% | ▼1% | ▼4%  | ▼7%  | [183]    |
| Pomegranate (not specified)   | 733           | Diet   | Die 28 CO          | 67 (0)        | 8          | 60.0 ± 1.0   | 8          | √      | √          | √          |      | >30     | ▼2% | ▼4% | ▼2%  | NV    | [183]    |
| Pomegranate (not specified)   | 119.1         | Diet   | die 365 P          | 66 (29)       | 34         | 65.9 ± 1.4   | 34         | √      | √          | √          |      | 24.5    | ▼9% | ▼1% | ▼6%  | ▼11% | [184]    |
Table 7. Cont.

| Dietary Source (Main PLPs) | Dosage (mg/Day) | Matrix | Intake Repartition | Length (Days) | n (Female) | Age (Years) | D.-O. (%) | ↑LDL-C | ↑TG ↓HDL-C | Obesity IR | ↑SBP | FRS (%) | TC | LDL-C | HDL-C | Reference |
|---------------------------|----------------|--------|--------------------|---------------|------------|-------------|-----------|--------|------------|------------|------|---------|----|-------|-------|-----------|
| Onion (quercetin)         | 162            | Capsule| Tid                | 21 CO         | 68 (34)    | 47.4 ± 1.5 | 3         | √      | √          |            |      | 9.3     | 1% | 1%    | 1%   | 2% | [185] |
| Quercetin                 | 150            | Capsule| Tid                | 56 CO         | 19 (0)     | 59.5 ± 1.4 | 0         | √      | √          |            |      | 13.3    | 31%| 5%    | 3%   | 2% | [186] |
| Quercetin                 | 150            | Capsule| Tid                | 56 CO         | 30 (0)     | 59.4 ± 0.9 | 0         | √      | √          |            |      | 15.6    | 4% | 2%    | 2%   | 1% | [186] |
| Resveratrol              | 150            | Capsule| Die               | 30 CO         | 11 (0)     | 52.5 ± 2.1 | 0         | √      | √          |            |      | 11.2    | 13%| N/A   | N/A  | N/A | [187] |

1 Baseline characteristics of participants include 3 or more of the following parameters in order to be associated with the metabolic syndrome: abdominal obesity (BMI > 30 kg/m² and/or WC > 102 cm (male)/88 cm (female)), hypertension (SBP > 130 mmHg), insulin resistance presenting as elevated fasting blood glucose (>5.5 mM), hyperTG (>1.7 mM) and low HDL-c (<1 mM (male)/1.3 mM (female)). 2 Change as a percentage from baseline. Up and down arrows indicate lipid/lipoprotein increase and decrease, respectively, following PLP challenge. * indicates significant variation (p < 0.05). 3 As specified by the authors in the case of a non-purified extracts. 4 Values represent mean ± standard error of the mean. Bid, twice a day; BMI, body mass index; CO, cross-over intervention; Die, daily; D.-O., drop-out rate; FRS, Framingham risk score; HDL-C, high-density lipoprotein-cholesterol; IR, insulin resistance; LDL-C, low-density lipoprotein-cholesterol; N/A, not available; NV, no variation; P, parallel intervention; PLP, polyphenol; SBP, Systolic blood pressure; S.D., study design TC, total cholesterol; TG, triglycerides; Tid, thrice a day.
Table 8. Clinical studies evaluating lipid/lipoprotein status of participants with type 2 diabetes\(^1\) in response to polyphenol supplementation.

| Dietary Source (Main PLP)\(^3\) | Dosage (mg/Day) | Matrix | Intake Repartition | Length (Days) | n (Female) | Age \(^4\) (Years) | D.-O. (%) | TG | TC | LDL-C | HDL-C | Reference |
|-------------------------------|----------------|--------|-------------------|---------------|------------|-------------------|-----------|----|----|-------|-------|----------|
| Black soybean (proanthocyanidin, isoflavone) (+120 mg fenofibrate) (+70 mg fibers) | 538 | Capsule | Die | 56 \(^\text{P}\) | 7 (3) | 57.4 ± 4.3 | N/A | ↓42% * | ↓6% | ↓15% * | ↑11% | [188] |
| Black soybean (proanthocyanidin, isoflavone) (+70 mg fibers) | 538 | Capsule | Die | 56 \(^\text{P}\) | 18 (6) | 56.7 ± 2.7 | N/A | ↓13% | ↑2% | ↓1% | ↑2% | [188] |
| Chlorogenic acid | 1200 | Capsule | Tid | 84 \(^\text{P}\) | 14 (14) | 43.0 ± 1.7 | 13 | ↓19% * | ↓4% * | ↓17% * | ↑6% | [189] |
| Curcuminoid | 70 | Capsule | Die | 56 \(^\text{P}\) | 37 (20) | 46.4 ± 1.7 | 7 | ↓13% * | ↓12% * | ↓11% | ↑5% | [190] |
| Grapefruit, green tea, black carrot and guarana seed extract (no information provided) | 370 | Capsule | Bid | 84 \(^\text{P}\) | 8 (4) | 40.7 ± 0.7 | 0 | ↓14% * | ↓9% * | ↓10% * | ↑9% * | [191] |
| Resveratrol | 40 | Capsule | Die | 183 \(^\text{P}\) | 59 (25) | 64.9 ± 1.1 | 7 | ↑1% | ↑5% | ↑7% | ↑1% | [177] |
| Resveratrol | 500 | Capsule | Die | 183 \(^\text{P}\) | 62 (23) | 65.0 ± 0.9 | 7 | ↑21% * | ↑6% * | ↑6% | NV | [177] |

\(^1\) As specified in inclusion criteria of study population or subgroup. \(^2\) Change as a percentage of the baseline. Up and down arrows indicate lipid/lipoprotein increase and decrease, respectively, following PLP challenge. * indicates significant variation (\(p<0.05\)). \(^3\) As specified by the authors in the case of a non-purified extracts. \(^4\) Values represent mean ± standard error of the mean. Bid, twice a day; Die, daily; D.-O., drop-out rate; CO, cross-over intervention; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; N/A, not available; NV, no variation; \(^\text{P}\), parallel intervention; PLP, polyphenol; S.D., study design; TC, total cholesterol; TG, triglycerides; Tid, thrice a day.
5.2. Postprandial Interventions

As we postulated that chronic intake of PLPs over an extended period of time could ameliorate lipidemia, we similarly investigated their postprandial potential through acute intake studies. The studies summarized in Table 9 comprised a high-fat challenge, alternatively referred to as an oral lipid tolerance test. This was administered to participants either following a period of chronic intake of PLPs (14–56 days) or alternatively at a single time point with no prior chronic intake. Reduction of TG is the most frequent beneficial outcome reported (↓5–39%) although improvements in TC, LDL-C and HDL-C were noted. Absence or negative variation of lipidemia was reported in 6 studies. These were all acute postprandial challenges without prior chronic intake and were made of either healthy [192–194] or DLP participants [195,196]. High-fat meal composition (both in terms of energy density and fat) and intervention length, following ingestion, adds even greater heterogeneity to these trials. This issue originates from the fact that there is no standardized universally accepted oral lipid tolerance test. Indeed, challenges can differ based on fat content (5–140 g), macronutrient composition and time of measurement following ingestion (2–10 h) [197–199]. As a reference, an expert panel in 2011 recommended for the sake of standardization and repeatability that an oral lipid tolerance test should consist of an 8-hour fast followed by a high-fat meal comprising 75 g of fat with a single measurement of TG after 4 hours [200].

In all trials, the composition of the high-fat meal displayed moderate amounts of lipids (ranging from 25 to 60 g) with sparse information on fat saturation and additional macronutrients. Interestingly, nearly half of the included studies were closely part of a chronic supplementation protocol, which provides more beneficial effects towards lowering of postprandial TG and OxS. However, it should be noted that participants had either baseline DLP, MetS or T2D background, whereas the remaining trials (with no adjunct chronic intake) generally aimed at investigating healthy participants. Nevertheless, the composition of supplemented PLPs was not reported. However, in some cases, when composition was rigorously described, PLP metabolites such as quercetin dehydrate and resveratrol were found to significantly prevent the rise of postprandial TG or Apo B-48/100 production rates [163,186].

Postprandial trials also tend to address OxS, inflammation, glucose intolerance and IR. In their study, Farràs et al. [192] reported that PLPs from olive oil increased the gene expression of circulating white blood cell biomarkers in association with DLP, OxS and inflammation.

5.3. Matrix and Methods of Delivery

Regarding optimal polyphenolic challenge, there is an extreme heterogeneity in study design and there appears to be a lack of consensus regarding their most favorable administration in human interventions. Indeed, there is a notable absence of studies comparing the preferable matrix for supplementation (i.e., whole food, liquid supplement or purified capsule), dosage or repartition throughout the day (e.g., die, bid, tid, with or without meal, etc.).

Since evidence suggests that the hypolipidemic actions of PLPs may initially come into play in the gut either through nutritional or bile acid chelation, and inhibition of pancreatic lipase, thereby limiting lipid absorption, polyphenolic supplementation should ideally be done in clinical trials during meal intakes for optimal effect such as in the case of other nutritional binders [204]. Nevertheless, this precaution is rarely addressed in clinical trials centered on DLP, where instructions are instead focused on patient adherence rather than on the cum cibum (cc) potential of PLPs. Consequently, polyphenolic intake is usually once to twice a day and is less commonly extended to thrice a day. The only circumstance under which PLPs are systematically administered with food intake is in the case where their source derives from the entire diet regimen. These are the studies that systematically present the greatest benefits on lipid/lipoprotein status.
Table 9. Clinical studies evaluating the effect of polyphenols on postprandial dyslipidemia.

| Dietary Source                  | Polyphenol                  | Length of Chronic Intake (Days; If Available) | Composition of High-Fat Meal | Length of Challenge (Hours) | Participants N (Female); Baseline Characteristics | Reported Effects                                                                 | Reference |
|--------------------------------|-----------------------------|-----------------------------------------------|------------------------------|-----------------------------|----------------------------------------------------|----------------------------------------------------------------------------------|-----------|
| Quercetin dihydrates           | 150 Capsule                 | 56                                            | N/A                         | 60                          | 8                                                 | ↓11% * of AUC 0–4 h—TG vs placebo; No effect overall on other lipid parameters, glucose and insulin levels. ↓11% * AUC 0–4 h—TG vs placebo; No effect overall on other lipid parameters, glucose and insulin levels. | [186]     |
| Quercetin dihydrates           | 150 Capsule                 | 56                                            | N/A                         | 60                          | 8                                                 | 30 (0) MetS, ApoE3/E4 heterozygotes                                                                                       | [186]     |
| Tea, coffee, chocolate, fruits, olive oil | 2903 Diet                  | 21                                            | 1000                        | N/A                         | 6                                                 | 20 (11) MetS                                                                                                                   | [180]     |
| Resveratrol                    | 1500 Capsule                | 14                                            | N/A                         | 49%                         | 10                                                | 8 (0) DLP                                                                                                                    | [163]     |
Table 9. Cont.

| Dietary Source       | Dosage (mg) | Matrix          | Length of Chronic Intake (Days; if Available) | Composition of High-Fat Meal | Length of Challenge (Hours) | Participants N (Female); Baseline Characteristics | Reported Effects | Reference |
|----------------------|-------------|-----------------|-----------------------------------------------|------------------------------|-----------------------------|---------------------------------------------------|------------------|-----------|
| Strawberry           | 338         | Liquid supplement| 42                                            | 960                          | 31                          | 6                                                 | ↓5% * TG, ↓4% * TC, ↓3% * HDL-C, ↓48% oxLDL vs placebo. | [201]          |
| Strawberry           | 338         | Liquid supplement| 0                                             | 960                          | 31                          | 6                                                 | ↓3% * TG; ↑11% * LDL-C; ↓1% * HDL-C; ↓115% * oxLDL vs placebo; No effect on TC. ↑2% * HDL-C; ↑overall insulin levels vs placebo; | [201]          |
| Cocoa                | 960         | Liquid supplement| 0                                             | 766                          | 50                          | 6                                                 | No effect on TC, ↑overall insulin levels and glucose levels. No effect on TG, Apo B-48 and insulin levels vs placebo. | [202]          |
| Red wine (no alcohol)| 880         | Liquid supplement| 0                                             | N/A                          | 25                          | 7                                                 | ↑15% * TG; ↓9% * oxLDL; ↓7% * glucose vs baseline; no other effect on lipid, OxS or inflammation parameters. | [196]          |
| Olive oil            | 8           | Diet            | 0                                             | N/A                          | 27                          | 5                                                 | 13 (6) Healthy                                            | [192]          |
Table 9. Cont.

| Dietary Source | Dosage (mg) | Matrix | Length of Chronic Intake (Days; if Available) | Composition of High-Fat Meal | Length of Challenge (Hours) | Participants N (Female); Baseline Characteristics | Reported Effects | Reference |
|----------------|-------------|--------|-----------------------------------------------|-----------------------------|----------------------------|-----------------------------------------------|-----------------|----------|
| Olive oil      | 26          | Diet   | 0                                             | N/A                        | 27 5                       | 13 (6) Healthy                                | ↑24% * TG; ↓7% * oxLDL; ↓6% * glucose vs baseline; no other effect on lipid, OxS or inflammation parameters. | [192]     |
| Pomegranate    | 652–948     | Liquid supplement | 0                          | N/A                        | 50 2                       | 19 (0) Healthy                                | No effect overall on lipid parameters. | [195]     |
| Red wine       | 561         | Diet   | 0                                             | N/A                        | 26 3                       | 12 (6) Healthy                                | ↑15% * TG, lipid hydroperoxides *, oxyCHOLs *, 7-ketoCHOL * and 7-β-hydroxyCHOL * vs placebo. No effect overall on TG, glucose, insulin and OxS levels. | [203]     |
| Strawberry     | 196         | Powder | 0                                             | N/A                        | 50 4                       | 30 (13) DLP                                   | No effect overall on TG, glucose, insulin and OxS levels. | [193]     |
| Coffee         | 600         | Liquid supplement | 0                          | N/A                        | 30 6                       | 13 (0) Healthy                                | No effect overall on TG, TC, glucose, insulin, OxS and inflammation levels. | [194]     |

1 If not available, this implies that the reported trial did not include chronic intake. * Indicates significant variation (p < 0.05). AUC, area under the curve; DLP, dyslipidemia; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MetS, metabolic syndrome; N/A, not available; oxLDL, oxidized low-density lipoprotein; OxS, oxidative stress; PLP, polyphenol; TC, total cholesterol; TG, triglycerides; TRL, triglyceride-rich lipoprotein; VLDL-TC, very low-density lipoprotein total cholesterol; VLDL-TG, very low-density lipoprotein triglycerides.
5.4. Dosage

A recurring and puzzling problem in clinical trials is that high polyphenolic doses (e.g., >500 mg/day) are not necessarily associated with a better outcome on lipid profile [177,178,185,188]. A recent review on polyphenolic consumption showed that populations with either a 1170 or 2632 mg/day intake reduced atherosclerosis risk and T2D-related events, respectively [205]. However, mounting evidence points that flavonoids and their subclasses could have a decreasing linear dose-response effect on lipidemia, most notably between the 100–400 mg/day intake [206]. As these conclusions are drawn from prospective studies with whole foods instead of isolated supplements in randomized controlled trials, caution is warranted as the suggested hypolipidemic effects cannot be exclusively attributed to PLPs.

Nevertheless, this suggests that aside from dosage, there may be other factors at play which could mitigate polyphenolic intervention, such as qualitative composition, bioavailability and method of delivery. This complexity is reflected by the lack of solid advice regarding daily intake. As opposed to other nutraceuticals, there presently lacks any form of official recommendation for PLPs in terms of blood lipid management [73]. Our showings demonstrate that no single intake of any given PLP convincingly ameliorates blood lipids. Rather, a combination of PLP, reflective of a more natural, unprocessed intake of foods, appears to be the most important criteria. This highlights the importance for future studies to properly assess not only composition of supplements used, by the bioavailability of PLP as well. For now, the closest official nutritional recommendation available stems from the European Food Safety Authority, which in 2012 certified PLPs from olives and olive-derived products as safe-warranting normal HDL-C blood levels and limiting LDL oxidation [207]. In a similar panel, the European Food Safety Authority also concluded that flavanols from cocoa origin were beneficial to endothelium-dependent vasodilatation and recommended a 200 mg/day intake in order to achieve desirable effects [208]. Concomitantly, the USDA considers anthocyanidins as the most potent antioxidants amongst flavonoids to prevent LDL oxidation, without, however, specifying a particular dose or intake recommendations [79,209].

6. Conclusions and Future Perspectives

Evidence-based knowledge has been stated herein regarding the effectiveness and indications of PLP-based phytochemicals. Surprisingly, there is currently a research gap relating to the challenge of PLP on primary DLPs in humans. Regarding DLP as a secondary, cardiometabolic complication, lipid-lowering activity of PLPs has been reported in various clinical studies, which we thoroughly and critically examined and analyzed in order to determine whether PLPs have the potential to treat or ameliorate lipid metabolism. Generally, the majority of clinical investigations showed an advantage in treating hypertriglyceridemia and hypercholesterolemia, whether in healthy participants or subjects with one, two and three disturbed lipid/lipoprotein components, or in MetS, T2D and postprandial DLP in response to PLP intake. Despite these promising findings, the review clearly exhibited an invariable or opposite trend as was the case for resveratrol. In these instances, the low study power and sample size may explain the conflicting data. Additionally, the inconsistency may stem from the PLP type, vast concentration range and intake duration, as well as the whole study design. More particularly, matrix represents a great challenge for PLP studies since the presence of non-polyphenolic constituents in fruits and vegetables may interfere with the pharmacological responses to PLP phytocomplex. The future of collection evidence as to the efficacy of PLPs in preventing or curtailing dyslipidemic risk factors entails the achievement of rigorously clinical trials with a well-defined design, stringent enrollment criteria, optimum dose and well-characterized PLPs formulations along with specific alimentary regimen, anticipated endpoints and extended follow-ups. Only then can we reach the goals of clinical PLP use in DLP without potentially being biased by a number of factors.
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Abbreviations

Apo Apolipoprotein
ABCA1 ATP-binding cassette transporter A1
CVD Cardiovascular disease
CHOL Cholesterol
CM Chylomicron
CD-36 Cluster of Differentiation-36
DLP Dyslipidemia
FH Familial hypercholesterolemia
FA Fatty acid
HDL-C High-density lipoprotein cholesterol
HLP Hyperlipoproteinemia
IR Insulin resistance
LCAT lecithin cholesteryl ester transfer protein
LDL-C Low-density lipoprotein cholesterol
LDLR LDL receptor
LPL Lipoprotein lipase
MetS Metabolic syndrome
MTTP Microsomal triglyceride transport protein
NPC1L1 Niemann-Pick-C1-like-1
OxS Oxidative stress
PLP Polyphenol
PCSK9 Proprotein convertase subtilisin/kexin type 9
ROS Reactive oxygen species
SR-B1 Scavenger receptor B-1
TC Total cholesterol
TG Triglycerides
T2D Type 2 diabetes
VLDL Very-low-density lipoprotein

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