



Polyphenols: a route from bioavailability to bioactivity addressing potential health benefits to tackle human chronic diseases

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Abstract

Chronic pathologies or non-communicable diseases (NCDs) include cardiovascular diseases, metabolic syndrome, neurological diseases, respiratory disorders and cancer. They are the leading global cause of human mortality and morbidity. Given their chronic nature, NCDs represent a growing social and economic burden, hence urging the need for ameliorating the existing preventive strategies, and for finding novel tackling therapies. NCDs are highly correlated with unhealthy lifestyle habits (such as high-fat and high-glucose diet, or sedentary life). In general, lifestyle approaches that might improve these habits, including dietary consumption of fresh vegetables, fruits and fibers, may contrast NCD symptoms and prolong life expectancy of affected people. Polyphenols (PPLs) are plant-derived molecules with demonstrated biological activities in humans, which include: radical scavenging and anti-oxidant activities, capability to modulate inflammation, as well as human enzymes, and even to bind nuclear receptors. For these reasons, PPLs are currently tested, both preclinically and clinically, as dietary adjuvants for the prevention and treatment of NCDs. In this review, we describe the human metabolism and bioactivity of PPLs. Also, we report what is currently known about PPLs interaction with gastro-intestinal enzymes and gut microbiota, which allows their biotransformation in many different metabolites with several biological functions. The systemic bioactivity of PPLs and the newly available PPL-delivery nanosystems are also described in detail. Finally, the up-to-date clinical studies assessing both safety and efficacy of dietary PPLs in individuals with different NCDs are hereby reported. Overall, the clinical results support the notion that PPLs from fruits, vegetables, but also from leaves or seeds extracts, are safe and show significant positive results in ameliorating symptoms and improving the whole quality of life of people with NCDs.

Keywords Polyphenols · Bioavailability · Bioaccessibility · Bioactivity · Chronic non-communicable diseases · Gut microbiota · Delivery nanosystems · Personalized medicine

Introduction

Polyphenols (PPLs) are biologically active compounds ubiquitously present in all plants. They are secondary plant metabolites (found in plants roots, leaves, stems, fruits and flowers) which can be produced either during homeostasis or as a stress response mechanism (e.g., to UV light exposure or to pathogen infections) (Durazzo et al. 2019). Overall, PPLs represent the most abundant source of dietary plant metabolites and their daily intake is associated with multiple beneficial effects for human health, in particular for the prevention of chronic diseases (including vascular, neurological and metabolic diseases, as well as cancer) (Costa et al. 2017).

Based on their chemical structure, PPLs can be classified into two main categories: flavonoids and non-flavonoids.

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Flavonoids may contain at least two phenolic aromatic rings and they are divided into six groups: flavonols, flavones, flavanols, flavanones, isoflavones and anthocyanins. While, non-flavonoids are classified in: phenolic acids, stilbenes, lignans, tannins and xanthonones (Dias et al. 2021). PPLs represent an essential component of the human diet being highly present in fruits, nuts, vegetables and also in plant-derived beverages (including wine, tea, coffee). Additionally, PPLs may be purified and often consumed in form of pills or fortified food and drinks (Brglez Mojzer et al. 2016). Figure 1 summarizes the classification of PPLs based on their chemical structure and their main known dietary sources.

Overall, the chemical structure of PPLs largely varies from few hydroxy groups and aromatic rings to highly polymerized compounds with elevated molecular weight (Tsoo 2010). PPLs with polar properties are powerful antioxidants which can scavenge free radicals and chelate free

metal ions in the cell, thereby decreasing lipid peroxidation, as well as other detrimental chain reactions (Rice-Evans et al. 1996). This function may affect the regulation of specific molecular signaling pathways, such as cell survival or cell differentiation (Ricketts and Ferguson 2018). The chemical structure of PPLs can be variously modified through several cellular reactions, such as acylation, glycosylation, sulfation and methylation, which can affect both the stability and the solubility of the resulting adducts, thereby influencing their biological functionality (Pandey and Rizvi 2009). Indeed, dietary PPLs may determine several food properties including flavor, odor and color, being of great importance for food industry, but also for pharmacy and body care sectors (Khan et al. 2019; de Araújo et al. 2021).

Chronic non-communicable diseases (NCDs) include vascular, endocrine and metabolic disorders, neurological, respiratory, gastro-intestinal and immune-related diseases

	Subclass	Main molecule	Dietary sources
Polyphenols	Flavonoids		
	Flavonols	Quercetin	Blueberry, Raspberry, Broccoli, Apple, Tomatoes
	Flavones	Luteolin	Parsley, Celery, Oregano, Green Olives, Hot pepper
	Flavanols	Epicatechin	Green tea, Cocoa, Apple, Red wine, Onion
	Flavanones	Narigenin	Orange, Lemon, Tangerine, Grapefruit
	Isoflavones	Genistein	Soy, Raisins, Lentils, Beans, Peas, Nuts
	Anthocyanins	Cyanidin	Pomegranate, Bilberry, Raspberry, Strawberry, Plum
	Non Flavonoids		
	Phenolic acids	Ferulic acid	Whole grains, Berries, Nuts, Tomatoes, Carrots
	Stilbenes	Resveratrol	Berries, Acai berry, Grape wine, Peanut, Sorghum
	Lignans	Pinoresinol	Pumpkin seeds, Sunflower seeds, Poppy seeds, Wheat
	Tannins	Gallic acid polymers	Coffee beans, Green tea, Red wine, Apricot, Peach
	Xanthonones	Xanthone glycoside	Mangosteen, Gentians, Clusiaceae

Fig. 1 Classification of polyphenols in classes and subclasses. For each subclass the most representative molecule and dietary sources are indicated

and tumors. Such pathologies can be often interconnected between each other, and develop in combination (Christ et al. 2019). According to “The Global Burden of Disease” study from the World Health Organization (WHO), NCDs account for over 70% of the global deaths and it is estimated that one out of four adults might be affected by one or more NCDs during their existence (Vos et al. 2020).

NCDs morbidity experienced a rapid surge during the last century as a result of the novel relationship occurring between the individuals and the environment in which they live in, consequent to the industrial revolution (Prüss-Ustün et al. 2019). In particular, within the developed countries, the exposure to stressing lifestyle is often coupled with bad diet habits (characterized by a higher sugar and fat intake, typical of the so-called Western diet), physical inactivity, sleep disorders, reduced sun exposure and vitamin D deficiency, smoking, drugs and alcohol abuse and, finally, with the elevated environmental pollution (especially within the industrialized areas). Altogether, the listed lifestyle and environmental factors are associated with a significant increased risk of developing NCDs (Frumkin and Haines 2019).

Although the causes behind the insurgence of NCDs are multiple (and usually difficult to dissect), the common feature of all these chronic pathologies is a low-grade, systemic and subclinical inflammatory status, called metaflammation, which worsens with aging (Hotamisligil 2017). The metaflammation might be considered as the subtle response of the organism to non-life-threatening factors. As consequence of the metaflammation, the whole organism responds with the activation of detrimental processes such as: accentuated oxidative stress responses, insurgence of insulin resistance and other dysmetabolism, arthritis, atherosclerosis and neurological diseases (behavioral and/or degenerative) (Deleidi et al. 2015).

To prevent the development of NCDs, the adherence to a healthy diet is pivotal. Epidemiological assessments have shown that a bad or unbalanced diet might increase the risk of NCDs, such as cardiovascular diseases (CVDs) and type 2 diabetes (T2D) (Budreviciute et al. 2020). In particular, a diet rich in fat and energy dense foods, as well as poor in fibers, fatty acids, fruits and vegetables might be associated with the development of NCDs and a lower life expectancy (Bruins et al. 2019). The introduction of anti-oxidants with the diet, such as with the Mediterranean diet, with a higher intake of vitamins, metals and plant metabolites, might be protective against NCDs development (Dominguez et al. 2021).

In this perspective, traditional healthcare approaches are nowadays flanked by more personalized medical viewpoints, where the prevention of NCDs is promoted by the fulfillment of a correct diet and a healthy lifestyle. Plant-derived PPLs are considered the ideal dietary adjuvant. Given their chemical structure, when ingested and assimilated, PPLs are

able to interfere with oxidative stress, to scavenge free radicals, to chelate metal ions or to donate electrons or hydrogen atoms; hence, they might represent the perfect nutraceutical to defeat metaflammation (and associated NCDs), thereby favoring a healthier longevity (Hano and Tungmunthum 2020).

In this review, we explore the current knowledge on the metabolism, bioactivity, mechanism of action and cellular pathways modulated by dietary PPLs, including the role played by intestinal microbial population. Additionally, we will describe current strategies implemented to improve PPL-oral intake and systemic delivery. Finally, as main focus of this review, we will outline the beneficial role of PPLs in the management of chronic diseases, illustrating all the up-to-date clinical knowledge in support of their pivotal preventive and therapeutic potential.

Dietary polyphenols: from intake to actual bioavailability

The human daily estimated intake of dietary PPLs is difficult to quantify and it can range between 0.4 and 1.5 g per individual. Several factors, including geographic area and gender, might affect the actual value (Bo’ et al. 2019). However, the health benefits of dietary PPLs are tightly linked with their bioaccessibility, bioavailability, as well as their bioactivity. Such attributes depend on the original food matrix, the specific food processing (i.e., mechanical and thermal treatments, cooking methods, storage conditions), and the occurring digestive processes (from intake to metabolism, adsorption, and, finally, assimilation). More in general, the final bioefficacy of PPLs is extremely variable depending on their nature and it is not necessarily proportional to their initial concentration in the food matrix and overall bioaccessibility (Di Lorenzo et al. 2021).

PPLs bioaccessibility, meaning the quantity of PPLs released from a complex dietary matrix, is influenced by the presence in food either of positive or negative effectors of absorption, such as fibers or fat. Within the plant cell, PPLs are mostly chemically bound with organic acids, sugars or lipids. Hence, they may accumulate in the endoplasmic reticulum, or within vacuoles, or even be covalently linked with cell wall polysaccharides. Large scientific evidence supports the fact that the nature of food matrix dramatically affects how PPLs are released from the plant cell to oral and gastro-intestinal areas. Moreover, food matrix influences the efficacy by which PPLs are transported across the gut epithelium (Lorenzo et al. 2019).

For example, dietary fibers are known to associate with PPLs, and several studies support that such fibers may act as a control mechanism which delays the gastro-intestinal adsorption of PPLs. While dietary fibers lower the amount of PPLs released in the upper digestive canal, they increase

PPLs release in the lower part (González-Aguilar et al. 2017). The mechanism by which fibers exert this effect is due to both physical trapping of PPLs, and the capability to enhance the viscosity of the gastro-intestinal fluids. The final effect is to delay food mixing with digestive enzymes or bile salts (Palafox-Carlos et al. 2011).

Additionally, dietary fat is shown to exert a dual effect on PPLs bioaccessibility. Fat contained in cocoa may increase the release of PPLs (especially procyanidins) from matrix (Ortega et al. 2009). Fat contained in olive oil (mainly triglyceride esters of oleic acid) may increase the bioaccessibility of olive-PPLs. It allows PPL-rich micelles formation, which can better interact with bile salts (Vitali Čepo et al. 2020). Contrariwise, anthocyanins contained in strawberries may be released slowly if the fruits are eaten with cream. In fact, fat derived from milk may bind anthocyanins and subtract them from the action of digestive enzymes (Mullen et al. 2008).

To avoid possible matrix-related issues, several methods of PPL extraction have been developed. Importantly, extraction approaches may help to recover large quantities of purified PPLs from vegetable and fruit waste, otherwise lost. Depending on the extraction process employed, PPLs may be exposed to direct air oxidation, therefore, losing some of their potential bioefficacy (Brglez Mojzer et al. 2016). For such reason, several encapsulation methods are proposed to preserve the physical–chemical characteristics of PPLs freed from their original food matrix (Polia et al. 2022).

The oral introduction of PPLs determines their potential biotransformation once passing through the multiple regions of the digestive route. In the oral cavity, PPLs react with salivary enzymes, as well as with the oral microbiota. Both human and microbial enzymes, in turn, can solubilize the PPLs lipophilic moieties or, more in general, enhance the anti-oxidant properties of PPLs (Ginsburg et al. 2013). Of note, mastication of certain plant food matrices allows the release of plant-derived enzymes from specific vacuoles within the mouth, such as myrosinase, which can cleave complex dietary PPLs through hydrolysis, hence generating bioactive breakdown products (Oliviero et al. 2018). Vegetables particularly rich in active myrosinase are *Brassicaceae* sprouts (cabbage, kale, broccoli), where the mechanical release through chewing of endogenous plant enzymes (such as myrosinase, but also peroxidase and polyphenol-oxidase) deeply influences the bioavailable PPLs which can be further metabolized and adsorbed through the gastro-intestinal tract (Šamec et al. 2018).

Following the oral cavity, PPLs are then transported with food within stomach, small intestine and large intestine, where they can be variously modified by both human enzymes and gastro-intestinal microbiota. PPLs or their derived metabolites can be then adsorbed in the gut epithelia or, alternatively, the non-adsorbed fraction is finally

excreted with the feces (Scalbert et al. 2002). Despite the lower pH in the stomach, once arrived there, PPLs are only minimally adsorbed or hydrolyzed. The vast majority of PPLs may instead transit towards the small intestine and, hence, the large intestine (Fernández-Ochoa et al. 2022).

Once arrived in the gut, PPLs can be transported through the intestinal barrier inside the enterocytes, either by passive diffusion or by active transport, by means of several different cellular protein transporters (including P-glycoprotein, multidrug resistance proteins, monocarboxylate acid transporter, organic anion polypeptide transporters) (Hussain et al. 2016a). While the direct adsorption within the small intestine is limited to small aglycone-PPLs, other complex PPLs (conjugated with acidic or glucose groups or highly polymerized) are lumenally hydrolyzed either by endogenous gut enzymes or by GM-derived enzymes, especially in the colon tract (Martinez-Gonzalez et al. 2017). In particular, high molecular weight PPLs which are conjugated with glucose groups may be de-glycosylated by human β -glucosidases in the small intestine before being adsorbed as aglycones (Cirilli et al. 2017). While PPLs with lower molecular weight (phenolic acids and isoflavones), can be better adsorbed, other PPLs having a more complex molecular structure (catechins, quercetins, flavanones, galloylated catechins and anthocyanins) cannot be adsorbed as they are. In this case, the enzymatic activity of the GM, as described in detail below, plays a pivotal role in their biotransformation (Scalbert et al. 2002).

Following the intestinal epithelial cells-mediated absorption and further blood transportation to the liver cells, PPLs can be converted by Phase 1 (oxidation, hydrolysis and reduction) and Phase 2 (glucuronidation, methylation and sulfation) metabolic reactions (Saha et al. 2019).

From the liver, once transformed in more polar molecules, PPL metabolites can reach the target tissues through the systemic circulation. From the target tissues, PPL-derived catabolites can be eliminated via kidney and subsequent urinary excretion. From the liver, a fraction of transformed PPLs may be secreted via the biliary route within the intestine, where the GM-mediated biotransformation can take place (van Duynhoven et al. 2011). Additionally, direct GM-mediated biotransformation of not-adsorbed PPLs may drastically affect their absorption through the intestinal barrier and subsequent liver metabolism (Corrêa et al. 2019). Figure 2 summarizes the routes of PPL metabolism in the human gastro-intestinal tract.

The dual interplay between dietary polyphenols and gut microbiota

As described above, dietary PPLs, once ingested, follow the xenobiotic route (Vrijheid 2014). When not adsorbed in the gut, PPLs are free within the intestinal lumen, where

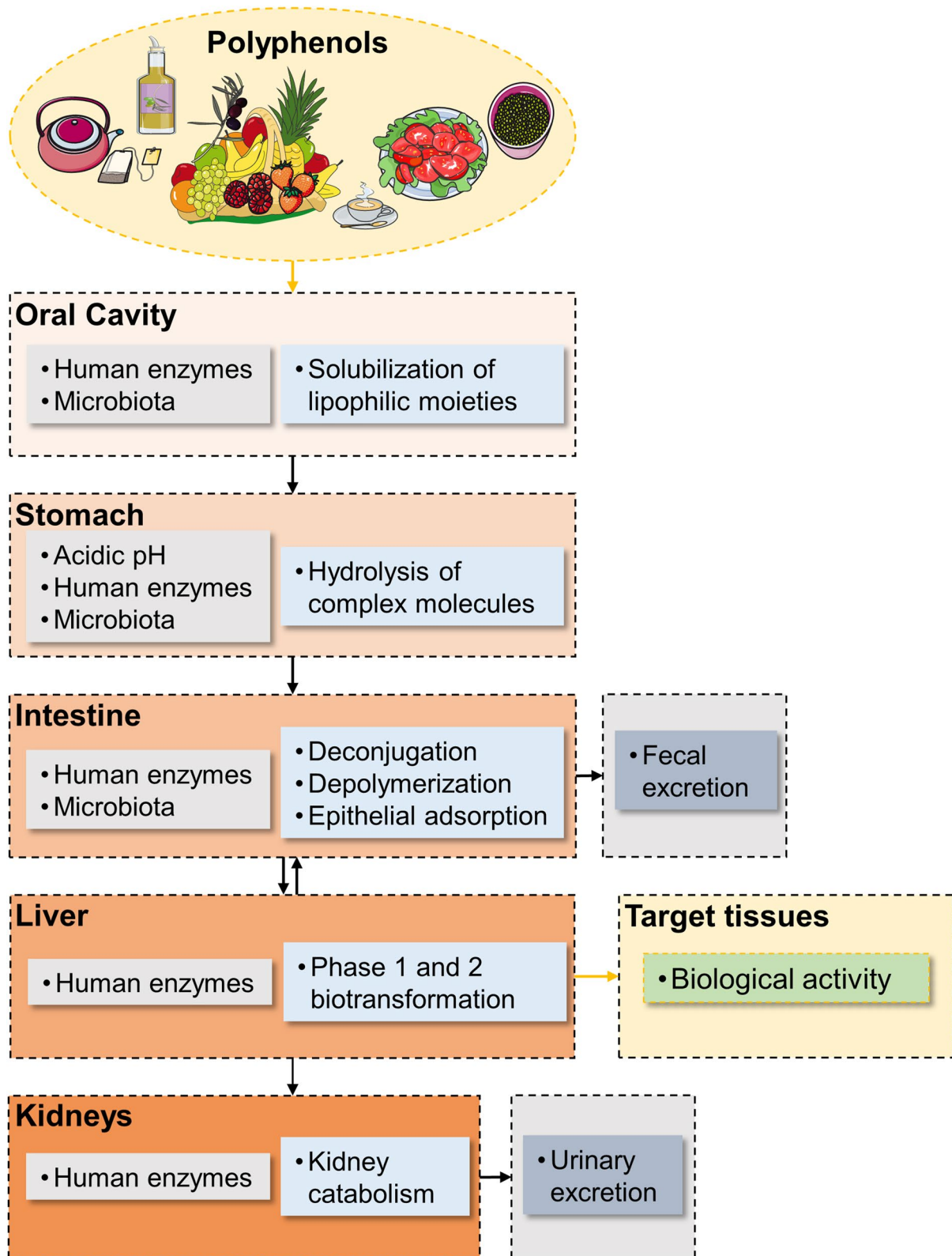


Fig. 2 Oral route of dietary polyphenols. The metabolism of dietary polyphenols starts in the oral cavity and each area of the gastro-intestinal tract is characterized by diverse functions and modifications, which can be mediated by both human and microbial enzymes

they can be directly modified by, and vice-versa modify, the GM, in a two-way relationship. In general, the microbiota is a heterogeneous consortium of microorganisms (including bacteria, archaea, yeasts, eukaryotes, viruses) variously populating all the exposed body surfaces and building with their human host a relationship of mutual advantage (Dai et al. 2017). The most characterized microbiota is the GM, which represents a proper dynamic interface between the encountered ingested substances (including PPLs) and the host physiology (Defois et al. 2018).

GM is composed by a number of microbial species with variable abundance and diversity, depending on the specific gastro-intestinal area. Among bacteria (which are the most characterized portion of the microbiota), *Bacteroidetes* and *Firmicutes* are the main taxa (about 90% of the total GM) (Falony et al. 2016). The GM dynamically changes during the course of a lifetime and it differs between diverse individuals, thereby representing an individual fingerprint. Host-specific genetics, epigenetics and immune system, in association with personal diet, lifestyle and other potential stressors are important shaping factors of the GM composition (Jandhyala 2015). Any external factor passing through the gastro-intestinal route, including food-derived PPLs, may also actively affect the GM milieu (Lin and Zhang 2017).

Overall, GM plays a key role in regulating several functions of the human host, such as food digestion, metabolism, immunomodulation and anti-pathogens barrier activity (Chen et al. 2021). A healthy GM is normally enriched in beneficial taxa, including *Bifidobacteria* or *Lactobacilli* which help to maintain the microbial balance or eubiosis. A healthy eubiotic gut microflora counteracts the proliferation of pathogenic bacteria (e.g., *Enterococci* and *Streptococci*) which can trigger the dysbiosis, with associated mucosal changes, such as gut leakiness and promotion of local intestinal inflammation (Bajinka et al. 2020). This microbial imbalance favors the spread of pathogen infections, as well as the insurgence (or the worsening) of chronic NCDs, including cancer (Vivarelli et al. 2019). Consequently, GM may represent a valuable source of new NCD biomarkers (Fenga 2022; Giambò et al. 2022).

Depending on the specific composition, GM can either trigger or, on the contrary, be protective against NCDs. This dual role is pivotal, for instance, during cancer genesis and development. In particular, *Enterobacteriaceae*, such as *Escherichia*, *Shigella* and *Klebsiella* promote local inflammatory processes (Zeng et al. 2017). Many species actively produce detrimental toxins that can either directly damage cellular epithelial DNA or trigger local secretion of reactive oxygen species (ROS) or, finally, promote uncontrolled cellular proliferation, via cellular WNT and AKT signaling activation (Vivarelli et al. 2019). Additionally, the outer membrane component of Gram-negative bacteria lipopolysaccharide (LPS or endotoxin) can directly activate

immune-mediated response (Paulos et al. 2007). More in general, gut dysbiosis may induce an altered mucosal immune response, with the consequent modulation of specific pro-inflammatory T cell phenotypes (i.e., upregulation of Th17, Th1 and Th2 and downregulation T reg cells) which can favor the development of NCDs (Zheng et al. 2020).

Beneficial effects of the GM are carried out through the fulfillment of many functions. First, commensal GM taxa stimulate mucin secretion and tight junctions' formation, thus reinforcing the gut barrier (Ghosh et al. 2021). Also, other bacteria produce essential micronutrients including linoleic acid (which helps against diabetes development) and vitamins (K and B group) (Rowland et al. 2018). Bacteria belonging to the *Eubacterium*, *Roseburia* and *Faecalibacterium* genera produce hormone-like metabolites in the large intestine, as products of the fermentation of dietary fibers, and known as short chain fatty acids (SCFAs, including butyrate, propionate, acetate), which can be used in the liver as energy source and directly regulate glucose and lipidic metabolism (Blaak et al. 2020).

Overall, GM is actively involved in the metabolism of macro and micronutrients, xenobiotics, secondary bile metabolites and PPLs (Rothschild et al. 2018). Regarding dietary PPLs, especially in the large intestine, GM can directly metabolize poorly adsorbed ones, through the action of a number of bacterial enzymes, such as β -glucosidases, β -glucuronidases, sulfatases, azoreductases, nitroreductases and transferases, thereby mediating PPL-transforming reactions of hydrolysis, reduction, acetylation, methylation or cleavage (including C–C molecular cleavage) (Koppel et al. 2017).

GM acts as a metabolic bioreactor with the effects of obtaining novel low-molecular-weight PPLs metabolites with diverse bioavailability and functionality compared with the original molecules. GM enzymes like tannase, gallate decarboxylase, quercetinase, phenolic acid decarboxylases and esterases increase the local bioavailability of otherwise not absorbable PPLs (Zhao and Jiang 2021). For instance, flavonol glycosides and polymeric flavonols (such as proanthocyanidins) undergo GM transformation in the colon, generating simple phenolic acids, and other small metabolites (Thilakarathna and Rupasinghe 2013). Additionally, hesperidin is catabolized by GM to form dihydroisoferral acid, whereas naringenin is transformed in its acidic form. Ellagic acid is converted by GM enzymes into smaller hydroxy-urolithin. Resveratrol gets also hydroxylated by GM and it can be then easier adsorbed (Corrêa et al. 2019).

Several PPLs such as hydroxy phenylacetic and hydroxy-phenyl propionic acids derived from bacterial transformation of flavonoids, equol and O-desmethylangolensin, isoflavones, urolithins and ellagic acid have been observed to have anti-oxidant effect and a powerful local and systemic anti-inflammatory activity (Tomás-Barberán et al. 2017; Mayo

et al. 2019). GM-derived phenolic acids (deriving from the dihydroxylation of proanthocyanidins) are able to reduce the immune-mediated secretion of pro-inflammatory cytokines (i.e., tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6). Also, the GM-derived PPL catabolite coniferaldehyde is able to inhibit local ROS production and MAPK pro-proliferative intracellular pathway (Hussain et al. 2016b).

A recent review defined PPLs as “duplibiotics”, highlighting this dual beneficial role played by PPLs towards the GM health (Rodríguez-Daza et al. 2021). First, PPLs actively modulate the growth of responder commensal bacteria. Second, PPLs have direct antimicrobial effect against pathogens. A diet rich in PPLs may stimulate the growth of probiotic species such as *Lactobacilli* and *Bifidobacteria*, and other beneficial taxa (e.g., *Akkermansia muciniphila*, *Bacteroides thetaiotaomicron*, *Faecalibacterium prausnitzii*) and, at the same time, it can contrast the proliferation of several pathogens including those belonging to the *Clostridium* genus and those producing detrimental pro-inflammatory LPS (e.g., *Escherichia coli* and other *Enterobacteriaceae*) (Rodríguez-Daza et al. 2021). The molecular mechanisms governing GM modulation by PPLs still need to be clarified, but it might involve either direct or indirect interactions of PPL molecules with specific microbial taxa. For example, resveratrol is bacteriostatic against *Enterococcus faecalis*, *Escherichia coli* and *Salmonella enterica*, but selectively promotes the growth of beneficial *Lactobacilli* and other SCFA-producing taxa (Al Azzaz et al. 2020; Abedini et al. 2021).

The two-way interaction occurring between GM and PPLs actively contributes to the maintenance of gut microbial balance and deeply affects human health, modulating both the immune system and the inflammatory milieu and, hence, protecting against NCDs, including cardiometabolic diseases, neurological diseases and cancer (Mithul Aravind et al. 2021).

Systemic bioactivity of dietary polyphenols

As described above, the bioefficacy of a given dietary PPL partially depends on its potency, as it is additionally affected by several factors including initial concentration in food, bioaccessibility and bioavailability. The specific bioavailability of a given PPL molecule mostly depends on the occurring metabolism. It has been estimated that over 200 enzymes (both human and microbic) are able to interact with dietary PPLs and modify their chemical structure (Bilal Hussain et al. 2019). Consequently, a given PPL can be converted into one or more metabolites, each one with a specific effect at the level of the target tissue(s). An interesting computational study estimated the size of the human protein interactome of dietary PPLs, which includes over 1300 species of PPLs and their metabolites, and about 12,000 unique protein interactions, comprising both the metabolic enzymes and the

putative downstream protein targets (Lacroix et al. 2018). A summary of the main systemic bioactivities mediated by dietary PPLs is reported in Fig. 3.

Recently, it has been discovered that the direct anti-oxidant effect of PPLs, mainly due to their scavenging activity, is coupled with additional effects including anti-inflammatory, anti-lipogenic and anti-tumoral (Fraga et al. 2019). More generally, compared with drugs or xenobiotics, PPLs demonstrate to have a pleiotropic bioactivity across several biological pathways, correlated to many NCDs. For instance, several preclinical studies have shown that PPLs are able to inhibit many human pro-inflammatory enzymes, including cyclooxygenase (COX1 and COX2), phospholipase (PLA2), nitric oxide synthase (NOS1, NOS2 and NOS3) and lipoxygenase (LOX) in several target tissues (including adipose

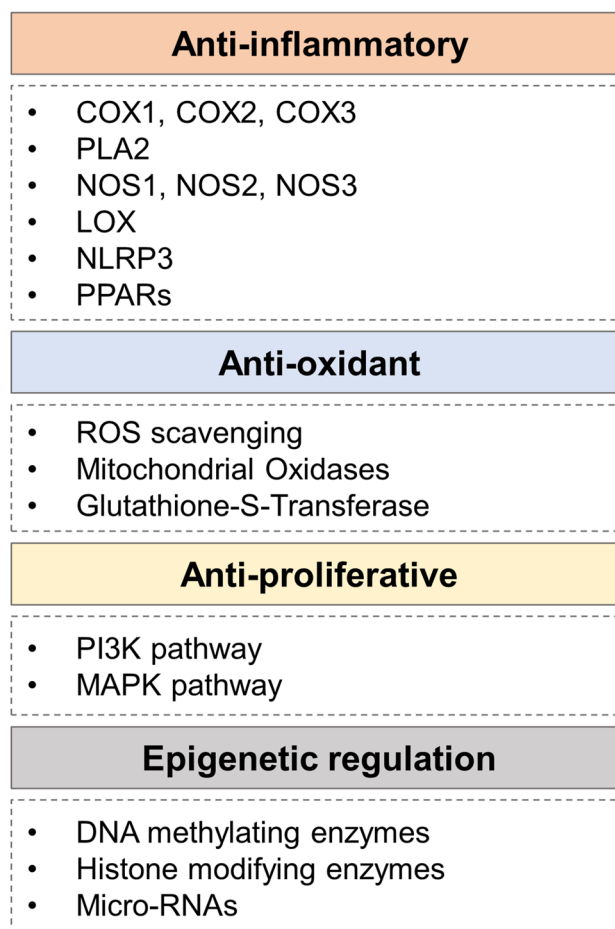


Fig. 3 Systemic bioactivities of dietary polyphenols. The main systemic effects of dietary polyphenols (anti-inflammatory, anti-oxidant, anti-proliferative and epigenetic regulation) according to current literature are reported. These activities are correlated with the property of polyphenols to bind and modulate several enzymes, as well as to scavenge free radicals. COX, Cyclooxygenase; PLA, phospholipase; NOS, nitric oxide synthase; LOX, lipoxygenase, NLRP, nucleotide-binding oligomerization domain; PPARs, peroxisome proliferator-activated receptors; ROX, reactive oxygen species

tissue) and immune cells (Leikert et al. 2002; Hou et al. 2007b, a; da Silva et al. 2009; Ratnasari et al. 2017). The overall observed effects at cellular levels are: reduced secretion of pro-inflammatory cytokines, cellular proliferation and angiogenesis. These biological effects are of particular importance in tumor genesis and development (Owczarek and Lewandowska 2017).

Additionally, a number of PPLs have been observed to directly inhibit the NLRP3 inflammasome in endothelial, liver, kidney and pancreatic cells (Han et al. 2012; Wang et al. 2012; Aruna et al. 2014; Tang et al. 2015). The biological effects correlated include the regulation of adipogenesis, thereby conferring resistance against metabolic dysfunctions associated with overweight, diet-induced obesity and liver damage; the latter could be a consequence of caspase-1-mediated pyroptosis, downstream effector of NLRP3 activation (Fan et al. 2020).

Other downstream molecular targets of PPLs are the peroxisome proliferator-activated receptors (PPARs), specific nuclear receptors regulating the expression of genes involved in glucose and lipid metabolism. A high-fat diet impairs PPARs signaling and reduces the expression of genes whose function is to improve lipid and glucose metabolism. Preclinical and clinical evidence showed that the biological effect of dietary PPLs is to positively modulate PPARs expression, thereby reducing dyslipidemia and visceral fat accumulation (Domínguez-Avila et al. 2016).

PPLs contained in green tea can modulate hunger directly by affecting both liver gluconeogenesis, insulin and glucagon-like peptide 1 release in the blood (Huang et al. 2014). Ferulic acid and other PPL metabolites are able to stimulate glucose intracellular uptake (Salau et al. 2022). In general, the biological effects of PPLs in modulating glucose metabolism are linked with their capability to decrease carbohydrates intestinal adsorption, protect the pancreatic cells by glucose-mediated cytotoxicity, suppress glucose release by liver cells (Hanhineva et al. 2010; Parmar et al. 2015).

Given their affinity for lipidic membranes, several PPLs may interact with transmembrane protein receptors and directly regulate downstream intracellular pathways involved in inflammation response, oxidative stress and cell proliferation or migration (Le Sage et al. 2017; Bucciantini et al. 2021). In cancer cells, it has been observed a key role of PPLs in modulating several important pathways such as the PI3K/Akt/mTOR pathway, the Ras/Raf/MAPK pathway, thereby contrasting cell proliferation and metastasization (Cháirez-Ramírez et al. 2021). Moreover, PPLs may inhibit the expression of anti-apoptotic Bcl family factors, pro-inflammatory cytokine TNF- α and NF- κ B pro-proliferating signaling in both tumor and immune cells (Patel et al. 2010). The consequent functional effects are correlated with the induction of apoptosis of transformed cells and, therefore, a general anti-cancer activity (Bulku et al.

2012; Shishodia 2013; Sahebkar et al. 2016; Kunnumakkara et al. 2017; Long et al. 2021). PPLs modulate the expression of cytokines and chemokines involved in angiogenesis and endothelial inflammation, thereby reducing the endothelial stress and decreasing risk for CVDs (Kalfin et al. 2002; Roy et al. 2002). Recently, ourselves and other colleagues comprehensively described the main molecular pathways modulated by dietary PPLs, which are directly associated with cellular inflammatory response and the onset of NCDs (Costa et al. 2017; Jantan et al. 2021).

In addition to the already mentioned Ras/Raf/MAPK, PI3K/Akt/mTOR and NF- κ B pathways, the Wnt/ β -catenin signaling may be a target of dietary PPLs. In this case, the effect mediated by PPLs is controversial. Wnt/ β -catenin dysregulation has been observed in various diseases, such as neurodegenerative diseases, cancer, diabetes and osteoporosis. Curcumin has been shown to inhibit GSK-3 β , hence inducing β -catenin activation in both Parkinson's and Alzheimer's disease. Consequently, the observed biological effect is neuroprotective (Maleki Dana et al. 2021). On the other hand, recent studies showed that both curcumin and resveratrol may inhibit Wnt and, in turn, β -catenin activity, with the consequent block of cell proliferation and induction of apoptosis in many solid tumors, such as CRC (Pashirzad et al. 2021).

Additionally, certain PPLs, such as curcumin and epigallocatechin gallate (EGCG), can also modulate epigenetic pathways. For example curcumin may inhibit histone deacetylases and histone acetyltransferases and suppress DNA methylation (Liu et al. 2005; Chen et al. 2007; Lee et al. 2011). Several PPLs (e.g., curcumin, resveratrol, genistein) can alter the expression of several miRNAs involved in NCDs onset and progression (Dhar et al. 2011; Nwaeburu et al. 2017; Bhardwaj and Mandal 2019). The alteration of cellular epigenetics, including DNA methylation, histone modifications and miRNAs expression is typical in several NCDs, including metabolic diseases, cancer and neurological pathologies. Dietary PPLs may reverse such alterations, and hence reprimarily cellular homeostasis, and in this sense, being proposed as preventive agents to be used against NCDs (Pan et al. 2013).

PPLs are known to be potent anti-oxidants, thanks to their capability of scavenging ROS molecules. Also, PPLs are able to directly bind and modulate the activity of several enzymes involved in ROS generation (i.e., glutathione S-transferase, cellular and mitochondrial oxidases), thereby directly reducing the formation of free oxygen radicals (Pandey and Rizvi 2009). Moreover, it has been demonstrated that certain PPLs may reduce the cellular oxidative stress in a ROS-independent way, by directly targeting mitochondrial processes, including Sirtuins induction (with consequent promotion of mitochondria biogenesis) and respiratory complexes modulation (improving ATP synthesis). The effect is

to contrast mitochondrial damage, which often accompanies NCDs onset or progression (Sandoval-Acuña et al. 2014).

Despite their well-characterized anti-oxidant activity, PPLs occasionally showed a pro-oxidant effect when administered at high doses to cells. Another trigger of pro-oxidant activity of PPLs might be the concurrent presence of high concentration of metals. The cellular effect associated with the increased cellular oxidative status is the induction of DNA damage and, consequently, cell cycle arrest and apoptosis induction (León-González et al. 2015). Hence, this pro-oxidative effect might be of particular importance to contrast cancer-cell growth, although it is difficult to translate the preclinical evidence to clinics (Babich et al. 2011).

Preclinical evidence suggests that PPLs are able to target many cellular pathways involved in NCDs onset and progression. Consequently, PPLs may be potentially proposed as dietary adjuvants for human health preservation. In line with that, over 350 studies currently registered at clinicaltrials.gov, are exploring the preventive/protective effects of PPLs consumption in healthy subjects. Among them, those with results demonstrated that PPLs are safe and may reduce the risk of developing chronic pathologies. Additional 150 studies aim to characterize the role of PPLs in people with occurring NCDs (Marino et al. 2020). The latter studies will be discussed in depth in the dedicated section below.

A main issue with PPLs is that, once ingested, they might be easily degraded within the gastro-intestinal route and they can quickly be oxidized once exposed to ROS, potentially losing their bioactivity before reaching the target tissue. For that reason, the development of novel delivery biosystems may help to improve the final bioavailability and bioactivity of PPLs, helping their actual application in clinics.

Food polyphenols and delivery nanosystems

Dietary PPLs are stable at acidic pH but their stability might be compromised under neutral or basic conditions, as well as with higher temperatures (such as during cooking and other food processing procedures). The potential low solubility, chemical instability under conditions encountered in the gastro-intestinal tract (i.e., differential pH, human and GM enzymes, presence of other nutrients), and the unlikelihood for many PPLs to cross the cellular lipid-bilayer membranes, may explain the frequent low bioavailability of dietary PPLs (Kunnumakkara et al. 2019; Stohs et al. 2020; Truzzi et al. 2021).

Food-derived macromolecules are often used to encapsulate and ameliorate the delivery and biological efficacy of PPLs. Among them, food-grade proteins are widely used to form stable complexes with PPLs, given that food-derived proteins have high biodegradability, non-antigenicity and high nutritional value. Moreover, protein–PPL complexes can be easily obtained (Li et al. 2021). One example is

EGCG thermally co-associated with lactoglobulin, which significantly decreases the gastro-intestinal degradation rate of PPLs (Shpigelman et al. 2012). Also, curcumin–lactoglobulin and resveratrol–lactoglobulin nanocomplexes increase the PPLs permeation rate in vitro (Teng et al. 2014). Another widely used protein for PPLs encapsulation is the milk-derived casein. Encapsulation of curcumin with casein increases the solubility of curcumin and augments its biological anti-cancer efficacy in vitro (Zhao et al. 2021). Additionally, collagen-derived gelatin is widely tested as protein-based PPLs carrier. Both resveratrol and EGCG, when encapsulated with gelatin, show enhanced pro-apoptotic activity towards cancer cells in vitro (Grgić et al. 2020).

Polysaccharides are also studied as effective PPL-encapsulating agents, for example chitosan (chitin-derived polysaccharides). In general, the encapsulation of PPLs with chitosan increases their adhesion to the gastro-intestinal mucosa (Hu and Luo 2016). Also, cellulose is currently tested as PPL polysaccharidic carrier against temperature-mediated degradation of PPLs (Phan et al. 2015). Additionally, encapsulation of PPLs with food-derived lipids may improve, for example resveratrol solubility, stability, and intracellular delivery, with demonstrated higher anti-proliferative activity against skin cancer cells compared to unbound PPLs (Borges et al. 2020).

The incorporation of PPLs with polymer-based nanoparticle delivery systems have been developed extensively to effectively transport PPLs through the blood system toward the target tissues and organs (Wang et al. 2022). Among them, phytosomes may enhance PPLs bioavailability. Phytosomes are phospholipids derived from soy beans meant to emulsify PPLs and facilitate their adsorption through the bilayer cell membrane (Lu et al. 2019). The formation of phytosomes may protect PPLs from gastro-intestinal degradation. Phytosomes have been used as carriers of several PPLs, including catechins, procyanidins, flavonoids, curcumin and naringenin (Semalty et al. 2010). Additionally, PPLs can be loaded and safely transported into other artificial vesicles, namely liposomes, vesicles made of biocompatible natural or synthetic phospholipids (Enaru et al. 2021). Liposomes are able to improve bioavailability of dietary PPLs, demonstrating preclinical beneficial effects in NCDs including cancer and Parkinson's disease (PD) (Marino et al. 2021).

Additional important polymeric nanocarriers for PPLs are the so-called colloidal nanoparticles which can protect the chemical stability of PPLs and favor their delivery within the target tissue, defending the PPLs from potential oxidation or enzymatic degradation during the ingestion route, metabolism and blood transportation (Qin et al. 2021). Colloidal nanoparticles are made of aqueous or alcoholic solutions/suspensions and they have been efficiently used as transporters, for example, of catechin or resveratrol (Dai et al. 2019).

A cutting-edge type of biological carriers for enhancing PPLs bioactivity are the extracellular vesicles (EVs) (Arola-Arnal et al. 2020). EVs are naturally occurring membranous structures, likely produced by any type of cell, and emerging as a novel mechanism of cell-to-cell communication and tissue-compatible drug delivery system (Leggio et al. 2021). Given the phospholipidic bilayer structure, EVs are perfect carriers able to protect from degradation fragile substances, including PPLs, and to convey them as a concentrated pool to the selected target tissue (Kalani and Chaturvedi 2017).

Plant-derived EVs naturally encapsulate PPLs. Such EVs have been isolated and characterized from many plants including lemon fruit, grapefruit, broccoli and ginger. Importantly, such particles are enriched in PPLs (Rome 2019). For example, grapefruit EVs contain naringin and naringenin, while ginger EVs contain shogaols and gingerol (Wang et al. 2014; Man et al. 2021). Grapefruit-derived EVs are resistant to gastric pepsin and intestinal bile. Also, they have been shown to trigger an anti-inflammatory response in mice with colitis (Stanly et al. 2020).

Additionally, EVs derived from mammalian cells can be used as effective PPLs carriers. Several studies demonstrated that PPL-transporting EVs can be generated either by incubating mammalian cells with PPLs or by loading the PPLs directly into the purified EVs (Qi et al. 2021). Several PPLs (including curcumin, genistein and quercetin) have been efficiently loaded into cancer-cell derived EVs upon co-culturing such cells in a PPL-enriched medium (Leggio et al. 2020). Subsequent *in vitro* and *in vivo* characterization demonstrated that PPL-EVs were able to effectively reduce tumor cell growth and local pro-inflammatory cytokine release. Additionally, hydrophobic PPLs have been efficiently loaded into EVs through passive entrapment, as in the case of curcumin, anthocyanidins and celastrol (Aqil et al. 2017). Also in this case, cellular experiments demonstrated that the loading into EVs significantly protected the PPLs from degradation and augmented the cytostatic therapeutic effect exerted by PPLs against cancer cells (Munagala et al. 2017).

Pivotaly, PPL-based nanoparticles are used not only to enhance the biological efficacy of PPLs, but also to increase the bioactivity of the associated nanoparticles. In fact, the molecular structure of PPLs, namely the capability to form hydrogen bonds, ionic interactions, hydrophobic interactions can confer additional stability to the associated nanostructure or nanomaterial (Wang et al. 2020). As described above, PPLs can stably bind natural proteins, sugars, lipids, nucleic acids and synthetic polymers. The resulting PPL-functionalized materials are used to implement gene delivery, to create coating mixtures, hydrogels and other biomaterials (Guo et al. 2021). The applications are very wide, ranging from sun screen formulation to drug delivery to antibacterial delivery to engineered biosurfaces (Esmaili 2016). To

conclude, cutting-edge PPL-based nano-delivery systems are currently used in medicine, nutrition and advanced biotechnology. Importantly, the molecular adducts show gained stability, as well as increased biological activity when compared to PPLs (or nano-scaffolds) alone.

Dietary polyphenols in tackling chronic diseases: clinical evidence

As illustrated above, NCDs are tightly interconnected between each other, sharing the same range of main risk factors, which include unhealthy diet, physical inactivity and tobacco use (Budreviciute et al. 2020). During the latest 20 years research on PPLs increased exponentially, shedding light on both preventive and therapeutic potential of PPLs. Good sources of PPLs are vegetables, fruits, but also leaf and seed extracts, in the form of beverages, solid food or pills. Dietary PPLs (either consumed with food or as plant extracts) represent an ideal adjuvant, easy to assume and free from side toxicity (Costa et al. 2017).

Different approaches are currently employed in the design of clinical trials: long term and short term. Short term or acute administration of PPLs is often utilized to evaluate their efficacy in reducing blood levels of metabolic markers, for example straight after the consumption of a challenging meal or beverage (e.g., high-caloric and/or high-lipidic). Whereas, long-term chronic consumption of PPLs allows to evaluate the associated improvement of several health parameters over long time and with stable health benefits (e.g., reduction of disease risk, decrement of metabolic pathways alterations, improvement of cognitive functions). To follow, we describe all the up-to-date clinical evidence assessing short-term and long-term benefits in patients with one or more NCDs (Fig. 4).

Cancer

Among NCDs, cancer represents the second leading cause of global death (Sung et al. 2021). Dietary PPLs are explored, preclinically and clinically, as a natural food component whose consumption might reduce cancer risk or improve cancer therapy outcomes (Fenga et al. 2016; Briguglio et al. 2020).

Several clinical studies have been conducted in cancer patients. The most significant results were observed for prostate cancer (PC) patients. In particular, the three randomized studies described below assessed the adjuvant role of green tea extract, enriched in catechins (particularly EGCG), in decreasing PC, as well as inflammatory biomarkers in newly diagnosed patients scheduled for prostatectomy (Guo et al. 2017). A randomized pilot study (NCT01912820) evaluated if chronic consumption of quercetin with green tea extract

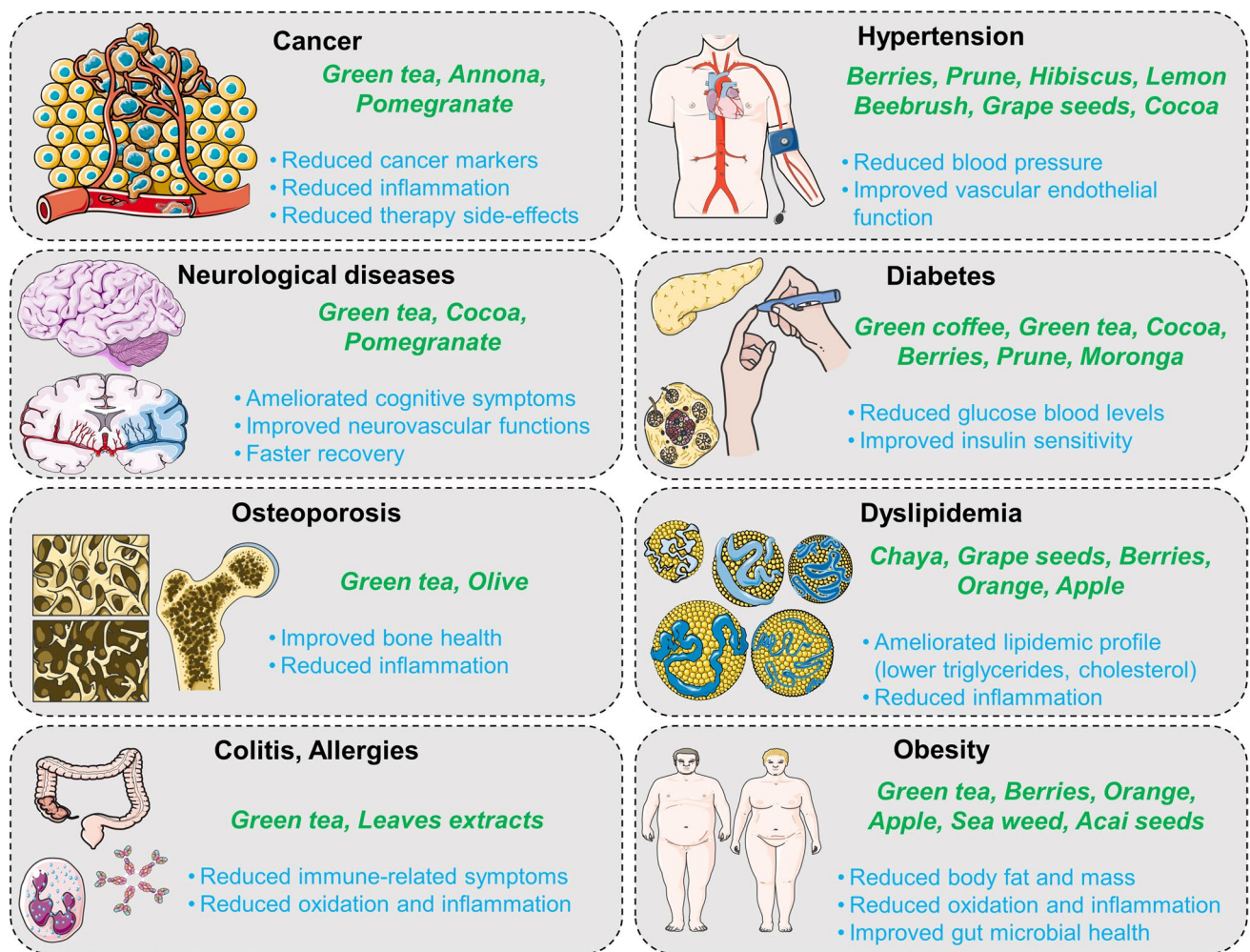


Fig. 4 Clinical role of dietary polyphenols in chronic diseases. The schematic summarizes for each chronic pathology the main food sources of polyphenols (green) and the observed functional effects from clinical trials (bullet points, blue) according to the clinical studies reviewed

enhanced the bioavailability of PPLs from green tea and reduced methylation activity in PC tissues. Green tea extract was administered daily (or not, in control group) in combination with quercetin, for 4 weeks before prostatectomy. Patients enrolled were 33 in total. Quercetin increased glucuronidation of EGCG (from green tea) measured in urine, although no significant effects on methylation profile was detected in prostate tissue biopsies analyzed (Henning et al. 2020).

Ninety-three men diagnosed with PC were enrolled in a randomized phase II clinical study (NCT00685516) aiming to evaluate the anti-cancer properties of green tea and black tea versus water used as control beverage. Green tea is known to be enriched in PPLs compared with black tea. The enrolled patients drank 6 cups of tea or water daily before prostatectomy (roughly 20 days). The study demonstrated that tumor markers of cancer development and progression in tumor tissues were reduced in the group of males

consuming green tea compared with the other two groups. Additionally, green tea produced a systemic anti-oxidant effect (demonstrated by the reduced urinary 8-hydroxydeoxyguanosine oxidation biomarker) and a small but not significant decrease of serum prostate serum antigen (PSA) (Henning et al. 2015).

Another clinical study (NCT00676780) assessed the effects of administering green tea extract enriched in EGCG (Polyphenon E) to 26 men diagnosed with PC and scheduled for total prostatectomy. The administration was programmed daily, from the day of diagnosis till the day of surgery. Serum samples were collected at the start and at the end of the intervention. From serum analyses, levels of several biomarkers were evaluated and the results showed a change of their levels over time following the PPL-extract administration. In particular, it was observed a decrease in blood levels of specific tumor markers (i.e., HGF, VEGF, PSA, IGF-I, IGFBP-3 and IGF-I/IGFBP-3

ratio) with no concurrent elevation of liver enzymes. This suggests that the intervention might be useful to prevent or treat PC, although different doses and long-term effect still need to be further evaluated in future (McLarty et al. 2009). In addition to these published clinical findings, few more studies are currently enrolling PC patients to assess the preventive value of PPLs contained, respectively, in walnuts and pomegranate (Table 1).

Green tea extract was also studied as a potential curative ointment to treat skin basal cell cancer, although the results were not significant. In particular, a clinical placebo-controlled study (NCT02029352) characterized the effect of topic administration of 10% ointment containing green tea PPLs leaves extract (with more than 85% of catechins) in 42 patients diagnosed with superficial skin basal cell carcinoma. The study was based on preclinical observations demonstrating the anti-proliferative properties of catechins. The results evidenced no significant difference in histological tumor clearance between the catechins and placebo groups, therefore, the complete tumor clearances observed probably reflected a biopsy-induced immune response (Kessels et al. 2017).

For breast cancer (BC) patients, few clinical studies explored the potential beneficial role of PPLs consumption as preventive and adjuvant treatment measurement. For this type of cancer, the results were less striking, given that, although well tolerated, PPLs did not improve BC patients' diagnosis or prognosis. 40 newly diagnosed BC patients were included in trial NCT03482401. Subjects were randomized to receive (or not, in controls) a mixture of 37 different PPLs. They assumed three capsules daily, from biopsy-confirmed diagnosis to surgery (average of 6 days of treatment). Capsules contained extracts from: pomegranate, orange, lemon, olive, cocoa, grapeseed, plus resveratrol, theobromine and caffeine. The study was aimed to assess the metabolic profiling of dietary PPLs in plasma, urine and breast tissue (both malignant and matching normal). A number of PPL metabolites were identified in all specimens and interestingly some of them were present in a significant concentration within mammary tumor tissues (i.e., urolithin-A-3-O-glucuronide, resveratrol-3-O-sulfate, dihydroresveratrol-3-O-glucuronide). Further tested in BC cells, the Phase 2 conjugated metabolites did not exert any anti-proliferative activity in vitro, although long-term in vivo chemoprevention cannot be excluded (Ávila-Gálvez et al. 2019) (Table 2).

A randomized, controlled, double-blind clinical trial (NCT02195960) enrolled 193 BC patients scheduled for radiotherapy to assess the improvement of skin damage following radiotherapy upon anthocyanin-rich extract of corn cob or placebo daily administration, from 1 week before the radiotherapy till the end of the treatment. Although anthocyanin supplementation was well tolerated, it did not

prevent radiotherapy-induced local skin toxicity (Bracone et al. 2021).

Three clinical studies explored the use of several dietary sources of PPLs in colorectal cancer (CRC) patients, with promising results as anti-inflammatory sources, although future larger studies would be needed to corroborate their preventive role. A placebo-controlled trial (NCT01360320) assessed the recurrence of intestinal adenomas following 3 years from polypectomy in 600 individuals with polyps. The individuals were randomized to receive for the entire 3 years after the operation, either EGCG from green tea extract or placebo every day. The study showed that the daily intake of EGCG was well tolerated and showed a trend towards a preventive effect on colon adenoma in the large bowel though not statistically significant (Fizazi et al. 2019).

Another clinical study (NCT01916239) assessed the effects of daily administration of pomegranate extract (rich in ellagitannins and ellagic acid), versus placebo, to 35 patients with CRC. The patients were divided in two arms to assume two different doses of the extract, or the placebo. The composition of the extract, rich in punicalagin and ellagic acid in different ratios, was previously established (Nuñez-Sánchez et al. 2014). The supplements were assumed daily, from the initial colonoscopy until the programmed surgery. The colon tissue gene expression was analyzed to assess changes due to extract intake. The expression of CD44, CTNBN1, CDKN1A, EGFR and TYMs was modulated in cancer tissues after oral intake of PPLs, without changes in the urolithin metabolites profile (Nuñez-Sánchez et al. 2017).

An additional randomized double-blind placebo-controlled study (NCT02439580) was conducted in a group of 20 CRC patients who had undergone primary tumor resection, to assess the anti-inflammatory value of *Annona muricata L* extract (rich of catechin, quercetin, procyanidins and tannins) versus placebo administration. The two randomized groups received either annona or placebo daily for 8 weeks. The results obtained demonstrated that the annona-treated group activated an anti-inflammatory response with an increase of IL-10 serum production in comparison to TNF- α and interferon (IFN)- γ pro-inflammatory cytokines, highlighting the potential chemo-protective properties of annona in CRC patients (Surono Suryati et al. 2017). Overall, the clinical observations reported highlight a potential cancer preventive and therapeutic protective role of consuming dietary PPLs, especially in PC and CRC patients, although larger cohort studies in patients with wider range of tumors are strongly needed.

Cardiovascular diseases

CVDs, mainly ischemic heart disease and stroke, represent the leading cause of global mortality, taking an estimated

Table 1 Clinical studies registered at clinicaltrials.gov, yet without published results concerning the use of polyphenols in individuals with chronic pathologies

NCT number	Polyphenol source	Group of diseases	Specific condition	Enrollment	Status
NCT00719030	Pomegranate pills	Cancer	Prostate cancer	25	c
NCT03824652	Walnuts	Cancer	Prostate cancer	50	o
NCT01585519	Apple extract	Cardiovascular	Cardiovascular diseases	50	c
NCT04760093	Extra virgin olive oil	Cardiovascular	Cardiovascular diseases	90	o
NCT05220059	Polyphenol extract	Cardiovascular	Cardiovascular diseases	20	o
NCT03824041	Aronia berries	Cardiovascular	Endothelial dysfunction	24	o
NCT03370991	Blueberries	Cardiovascular	Hypertension	58	o
NCT00654862	Cocoa	Cardiovascular	Hypertension	48	c
NCT03620266	Bilberries	Cardiovascular	Myocardial infarction	900	o
NCT03524742	Avocado	Cardiovascular	Stroke	200	o
NCT04763291	Vegetable and berry blend	Cardiovascular, metabolism	Cardiovascular diseases, overweight, obesity	112	o
NCT05062954	Cranberry extract	Metabolism	Abdominal obesity	60	o
NCT04383639	Cocoa and carob	Metabolism	Diabetes	20	o
NCT00639665	Cocoa	Metabolism	Diabetes	228	c
NCT03722199	Flavanoids	Metabolism	Diabetes	43	c
NCT04764786	Extra virgin olive oil	Metabolism	Diabetes	22	c
NCT02291250	Berries	Metabolism	Diabetes	16	o
NCT04419948	Oleocanthal-rich olive oil	Metabolism	Diabetes	15	o
NCT04864860	Sea weed (Ecklonia Cava Extract)	Metabolism	Diabetes	30	o
NCT04004182	Bilberry and apple extracts	Metabolism	Glucose metabolism disorders	24	o
NCT05221346	Oleactiv	Metabolism	Hypercholesterolemia	26	o
NCT04914416	OxyneGS	Metabolism	Hyperglycemia	10	o
NCT03034291	Cocoa	Metabolism	Insulin resistance	92	c
NCT03990181	Meal matrix (Polyphenol-rich supplement)	Metabolism	Iron metabolism disorders	14	c
NCT04194567	Finger millet	Metabolism	Iron metabolism disorders	22	c
NCT03266055	Blueberries	Metabolism	Metabolic syndrome	59	o
NCT03620617	Raspberries	Metabolism	Metabolic syndrome	59	o
NCT03825276	Mango	Metabolism	Metabolic syndrome	35	o
NCT04011618	Ellagic acid	Metabolism	Metabolic syndrome	32	o
NCT04053569	Grape	Metabolism	Metabolic syndrome	40	o
NCT05158673	Cocoa	Metabolism	Metabolic syndrome	30	o
NCT03800277	Cranberry and agaves extract	Metabolism	Metabolic syndrome	80	o
NCT04731987	Orange juice and hesperidin	Metabolism	Metabolic syndrome	42	o
NCT04874961	Olive	Metabolism	Metabolic syndrome	75	o
NCT05282316	Extra virgin olive oil	Metabolism	Metabolic syndrome	90	o
NCT03101436	Extra virgin olive oil and red wine	Metabolism	Obesity	20	c
NCT03203915	Chardonnay grape marc powder	Metabolism	Obesity	31	c
NCT04970589	Mango	Metabolism	Obesity	100	c
NCT03994029	Polyphenol-rich supplement	Metabolism	Obesity	60	o
NCT04347304	Dark chocolate	Metabolism	Obesity	74	o
NCT04974450	Trigona honey	Metabolism	Obesity	40	o
NCT02633150	Red grapes	Metabolism	Obesity, insulin resistance	23	c
NCT04476160	Cinnamon	Metabolism	Obesity, insulin resistance	100	o
NCT01729949	Fruit polyphenols	Metabolism	Overweight	34	c
NCT04130321	Camu camu	Metabolism	Overweight, metabolic syndrome	35	o
NCT03754504	Cranberry powder	Metabolism	Overweight, metabolic syndrome	24	c
NCT04117802	Maple syrup	Metabolism	Overweight, metabolic syndrome	47	c

Table 1 (continued)

NCT number	Polyphenol source	Group of diseases	Specific condition	Enrollment	Status
NCT04321590	Green coffee beans	Metabolism	Overweight, obesity	60	c
NCT04100200	Berries	Metabolism	Overweight, obesity	88	o
NCT04149288	Olive oil	Metabolism	Overweight, obesity	44	o
NCT05255367	Berries and pomegranate juice, dark chocolate and green tea	Metabolism	Overweight, obesity	22	o
NCT03628937	Decaffeinated green tea	Metabolism	Pediatric obesity	80	o
NCT04654689	Liposomed polyphenols	Neurological	Amyotrophic lateral sclerosis	60	o
NCT02700685	Pycnogenol (French maritime pine bark extract)	Neurological	Attention deficit hyperactivity disorder	88	c
NCT05343611	Chocolate	Neurological	Dementia	75	o
NCT01183767	Sunphenon tea extract	Neurological	Duchenne muscular dystrophy	33	c
NCT02502253	Grape seed and resveratrol	Neurological	Mild cognitive impairment, Alzheimer's disease	48	o
NCT05234203	Polyphenol-rich supplement	Immune system	Immunity disorders	50	o
NCT04824976	Blueberries	Gastrointestinal	Gastrointestinal disorders	55	o
NCT05016024	Colifen (polyphenol-rich supplement)	Gastrointestinal	Irritable bowel syndrome	66	o
NCT04869852	Mango	Aging	Photoaging	70	o
NCT04554901	Cocoa	Blood	Platelet dysfunction	25	o
NCT03260803	Oligopin (low molar mass procyanidins)	Bones	Osteopenia	43	c
NCT02822378	Dried plums	Bones	Osteoporosis	322	o
NCT04919876	Fruit and vegetable supplement	Energy	Mitochondrial functions	60	o
NCT02369549	Curcumin	Kidney	Chronic kidney disease	518	c
NCT03819517	Resveratrol	Lung	Chronic obstructive pulmonary disease	48	o
NCT03989271	Quercetin	Lung	Chronic obstructive pulmonary disease	15	o

O, open; C, closed

17.9 million lives each year. According to the WHO, they also are a major contributor to disability representing a heavy socio-economic burden (Roth et al. 2020). For such reasons, it is strongly necessary the implementation of innovative evidence-based preventive and treatment approaches, as well as the development of new supporting strategies, including consistent surveillance and monitoring within the entire population (Townsend et al. 2022). Several preclinical, as well as epidemiological studies suggest that a diet rich in PPLs may reduce the incidence of CVDs, including coronary heart disease and myocardial infarction. This effect seems to be linked with several properties of dietary PPLs, mainly by improving cellular endothelial function and by inhibiting circulating platelet aggregation (Alotaibi et al. 2021). For that reason, an increasing number of clinical trials are presently evaluating the potential preventive and therapeutic properties of dietary PPL consumption in subjects with elevated cardiovascular risk, such as those with blood pressure issues or peripheral circulatory diseases (Table 1), and many of them showed already encouraging results, as detailed below.

A clinical randomized controlled study (NCT01319786) enrolled subjects with high blood pressure to study the effects of high-PPL diet, with the daily consumption of 6 portions of fruits and vegetables plus a portion of red berries and a portion of dark chocolate, rich in PPLs (see (Martini et al. 2018) for a composition analysis), for 8 weeks. The results showed that the increased intake of PPL-rich foods for 8 weeks resulted in a significant improvement in endothelium-dependent vasodilation in hypertensive participants, thus suggesting that a well-tolerated PPL-rich diet could have a positive effect on microvascular functionality and CVD risk (Noad et al. 2016).

A 12-week double-blinded randomized controlled intervention trial (NCT01568983) analyzed the effect of PPL-enriched fruit juice (formulation called Opti juice, containing grape, cherry, bilberry and aronia) in lowering the blood pressure in subjects affected by pre-hypertension or hypertension (systolic blood pressure higher than 130 mmHg). It was observed that in the PPL-enriched juice group there was a reduction in stress-sensitive blood pressure compared with the placebo group, meaning that PPLs might contribute to

Table 2 Features and outcomes of the clinical studies with published results concerning the use of polyphenols in individuals with chronic pathologies

NCT number	Conditions	Enrolled	Intervention time	Dietary supplement	Polyphenols	Daily dose	Outcomes reached
NCT01912820	PC	33	4 W	GTE	EGCG, quercetin	2 cps of GTE (830 mg of polyphenols), 1 cp of quercetin (800 mg)	None
NCT00685516	PC	93	3 W	GT beverage	EGCG	6 cups	All
NCT00676780	PC	26	3 W	GTE (<i>Polyphenon E</i>)	EGCG	4 cps (200 mg EGCG each)	All
NCT02029352	BCC	42	6 W	GT ointment (<i>Veregen</i>)	EGCG	10% ointment	None
NCT03482401	BC	40	1 W	Fruit extract CP (<i>Phenolics</i>)	Several	3 cps (474 mg of extract each)	None
NCT02195960	BC	193	6 W	Corn extract	Anthocyanins	3 stick packs	None
NCT01360320	CRC	600	3 Y	GTE (<i>Camellia Sinensis</i>)	EGCG	2 cps (150 mg of EGCG each)	All
NCT01916239	CRC	35	2 W	Pomegranate extract	Punicalagin, ellagic acid	1 cp (900 mg of polyphenols each)	All
NCT02439580	CRC	20	8 W	<i>Annona muricata L</i> extract	Catechin, quercetin, procyanidins, tannins	2 cps (300 mg of EtOH soluble fraction each)	All
NCT01319786	HYP	92	8 W	Red berries, dark chocolate	Several	6 portions (berries), 50 g (dark chocolate)	All
NCT01568983	HYP	130	12 W	Grape, cherry, bilberry, aronia juice (<i>Opri juice</i>)	Several	500 ml	All
NCT00421499	HYP	44	18 W	Dark chocolate	Several	6.3 g (30 mg of polyphenols)	All
NCT03507023	HYP	84	6 W	Lenon verben, hibiscus flower extracts (<i>Metabolaid</i>)	Proprietary formula	2 cps (250 mg of extract each)	All
NCT02063477	HYP	24	6 W	French maritime pine bark extract (<i>Oligopin</i>)	Procyanidins	2 cps (250 mg of extract each)	All
NCT02234648	HYP	15	Ac Ad	Montmorency tart cherry	Anthocyanins, flavonoids	60 ml	All
NCT02616822	ED	24	Ac Ad	n.a	Trans-resveratrol	300 mg	All
NCT00539916	HYP	25	4 W	Blonde orange juice	Hesperetin	600 ml	All
NCT01690676	HYP	60	4 W	Apple extract	Epicatechin, flavan-3-ol	100 mg	Partial
NCT00869193	HYP	70	8 W	Grape seed extract (<i>MegaNatural BP</i>)	Tannins, procyanidins	1 cp (300 mg of extract)	Partial
NCT02130141	HYP	22	8 W	Dark chocolate	Several	50 g	None
NCT00099476	HYP	20	2 W	Cocoa	Flavanol	300 ml (900 mg of polyphenols)	None
NCT01947712	PAD	20	Ac Ad	Dark chocolate	Several	40 g	All
NCT02246660	PAD	66	6 M	n.a	Resveratrol	125 mg or 500 mg	None
NCT01154478	MetS	78	8 W	High-PPL diet	Several	360 mg or 2900 mg	All
NCT01400724	MetS	80	6 M	Supplement formula (cocoa, myo-inositol, soy), isoflavones	Several	Cocoa-polyphenols 30 mg, isoflavones 80 mg	All
NCT03076463	MetS	49	6 W	Dried grape pomace (<i>Grapom</i>)	Anthocyanins	8 g dissolved in water	All
NCT01414647	MetS	27	8 W	Berries	Flavonoids, phenolic acids, lignans, phenolic polymers	300 g of strawberry, raspberry, cloudberry or 400 g of bilberry	All
NCT03265184	MetS	43	8 W	Green coffee extract	Chlorogenic acid	400 mg	None
NCT02764957	MetS	43	8 W	Green coffee extract	Chlorogenic acid	400 mg	All

Table 2 (continued)

NCT number	Conditions	Enrolled	Intervention time	Dietary supplement	Polyphenols	Daily dose	Outcomes reached
NCT03592511	MetS	27	4 W	Wine grape pomace flour burger	Several	41 mg gallic acid, 1.5 mg cyanidin 3-glucoside	All
NCT03619941	MetS	12	1 W	Montmorency tart cherry juice	Anthocyanins, flavonoids	30 ml	All
NCT01886989	T2D	25	Ac Ad	Cocoa beverage	Flavanol	2 cups (960 mg of polyphenols)	All
NCT01245270	T2D	8	Ac Ad	Bilberry extract (<i>Mirtoselect</i>)	Anthocyanins	470 mg of extract	All
NCT01923597	D Neph	50	12 W	GTE	EGCG	4 cps (200 mg of polyphenols each)	All
NCT01766570	D	41	6 W	Strawberry and cranberry extract	Phenolic acids, flavonoids	333 mg of extract	All
NCT01754662	T2D	84	8 W	Soy, cocoa, isoflavones	Several	2 bars (16 mg isoflavones and 400 mg cocoa-polyphenols each)	All
NCT04734132	D	72	12 W	<i>Moringa oleifera</i> leaves	Astragalin, chlorogenic acid, kaempferitrin, luteolin, quercetin	6 cps (400 mg dry leaf powder each)	All
NCT04110392	DYSL	30	6 W	Chaya leaf extract	Amentoflavone, EGCG, hesperidin, lignin, quercetin	40 g of Chaya leaves	All
NCT00713167	DYSL	52	8 W	Grape seed extract (<i>Vitagrpe</i>)	Tannins, procyanidins	2 cps (100 mg of extract each)	All
NCT02612090	DYSL	34	4 W	Freeze-dried strawberry powder	Phenolic acids, flavonoids	Beverage with 50 g of powder	Partial
NCT01988389	DYSL	40	8 W	Apples	Catechins	2 fruits	All
NCT01290250	OV, OB	100	12 W	Orange juice, flavanone	Several	299 mg or 745 mg of polyphenols	All
NCT01568827	OV, OB	10	Ac Ad	Lyophilized black raspberries	Anthocyanins, ellagitannins	45 g of black raspberry powder	All
NCT03523403	OV, OB	26	Ac Ad	Gala apples	Phenolic acids	3 fruits	All
NCT03423719	OV, OB	72	16 W	GT, guarana, grape seeds, grapefruit extracts (<i>Fitt-ins</i>)	Naringin, hesperidin, catechins	2 cps (450 mg of extract each)	All
NCT02295878	OV, OB	80	8 W	Sea weed extract	Bromophenols, flavonoids, phenolic terpenoids	1 cps (400 mg of extract)	All
NCT01302639	OV, OB	18	Ac Ad	n.a	EGCG, resveratrol	282 mg (EGCG), 200 mg (Resveratrol)	All
NCT02479035	OV, OB	21	Ac Ad	Red raspberries frozen	Anthocyanins	125 g (1 cup) or 250 g (2 cups) of fruit	All
NCT01518764	OV, OB	29	8 W	Red wine extract (<i>Provinols</i>)	Quercetin, anthocyanins, procyanidins, ellagic acid, catechins	600 mg of extract	None
NCT02710461	OV, OB	20	Ac Ad	Grape and pomegranate pomace	Anthocyanins, gallic acid	10 g of dietary supplement	None
NCT00668928	OV, OB	20	Ac Ad	Cocoa, GT	Flavanols	30 mg, 180 mg, or 400 mg of flavanols	None
NCT03741218	OV, OB	25	Ac Ad	Freeze-dried grape	Anthocyanins, flavonols, flavanols, stilbenes	300 g of fresh grapes equivalent	None
NCT02292329	OV, OV, CVD	23	Ac Ad	Acai fruit smoothie	Quercetin, orientin, cyanidins, anthocyanidins	150 g of acai fruit	All
NCT00692731	OV, OV, CVD	240	12 W	GT	Catechins	500 ml (625 mg of catechins)	All

Table 2 (continued)

NCT number	Conditions	Enrolled	Intervention time	Dietary supplement	Polyphenols	Daily dose	Outcomes reached
NCT01674231	OV, OV, CVD	20	Ac Ad, 4 W	Freeze-dried grape powder	Anthocyanidins, catechins, epicatechins, quercetin	60 g pf fruit (296 mg of polyphenols)	Partial
NCT01364961	OV, OV, CVD	45	4 W	n.a	Resveratrol	2 cps (75 mg of resveratrol each)	None
NCT02228291	OV, OV, CVD	68	6 W	n.a	Hesperidin	450 mg	None
NCT02743195	OV, OB, GM	51	4 W	Blueberry, blackcurrant, black rice extracts	Anthocyanins	1 sachet of powder (215 mg of anthocyanins)	All
NCT01293175	OV, OB, GM	80	8 W	Whole-grain wheat	Ferulic acid	80 g of wheat	All
NCT02061098	OV, OB, GM	49	3 W	Pomegranate extract	Ellagitannins, ellagic acid	1 or 4 cps (160 mg of polyphenols each)	All
NCT00461942	PD	32	6 M	GTE	EGCG, ECG	400, 800 or 1200 mg	All
NCT03740295	MS	51	4 M	n.a	EGCG	600 mg of EGCG	All
NCT02442804	Stroke	16	1 W	Pomegranate extract (<i>POMx</i>)	Tannins, flavonoids	1 g of supplement	All
NCT00825695	CVD	60	4 W	Cocoa (<i>Cocoaipro</i>)	Flavanol	2 servings of supplement	All
NCT01855971	FXS	27	12 W	n.a	EGCG	10 mg/kg	All
NCT00625391	OP	171	6 M	GTE	EGCG	500 mg	All
NCT00789425	OP	69	12 M	Olive extract	Caffeic acid, ferulic acid, cinnamic acid, tyrosol, oleuropein	1 cps (250 mg of polyphenols)	All
NCT00718094	UC	19	2 M	GTE (<i>Polyphenon E</i>)	EGCG	400 mg or 800 mg	All
NCT03902392	Allergy	25	3 M	Red-grape extract (<i>Natturox</i>)	Proprietary formula	1 cps (280 mg of proanthocyanidins)	All
NCT04872868	Allergy	27	3 M	Iron-catechin complexes (<i>Holo-BLG</i>)	Proprietary formula	2 tablets	All
NCT04477382	Allergy	38	3 M	Iron-catechin complexes (<i>Holo-BLG</i>)	Proprietary formula	2 tablets	All

PC, prostate cancer; BCC, basal cell carcinoma, BC, breast cancer; CRC, colorectal cancer; HYP, hypertension; ED, endothelial dysfunction; PAD, peripheral arterial disease; MetS, metabolic syndrome; DYSL, dyslipidemia; OV, overweight; OB, obesity; CVD, cardiovascular disease; PD, Parkinson's disease; MS, multiple sclerosis; FXS, fragile-X syndrome; OP, osteoporosis; UC, ulcerative colitis; GT, green tea; GTE, green tea extract; PPL, polyphenol; EGCG, epigallocatechin gallate; cps, capsules; W, weeks; M, months; Y, years

postpone the regular use of anti-hypertensive drugs (Tjelle et al. 2015).

A randomized and controlled study (NCT00421499) enrolled 44 individuals with upper range pre-hypertension or stage 1 hypertension. The aim was to assess the effect of dietary consumption of dark chocolate rich in PPLs versus white chocolate with no PPLs, daily for 18 weeks. The trial demonstrated that the administration of dark chocolate significantly reduced blood pressure and improved the formation of nitric oxide (NO) with vasodilative effects. Hence, the introduction of small quantities of dark chocolate rich in PPLs may be beneficial in individuals with blood pressure issues (Taubert et al. 2007).

A clinical randomized trial (NCT03507023) assessed the anti-hypertensive power of a registered dietary supplement, Metabolaid, composed of a combination of lemon verbena (*Lippia citriodora*) and hibiscus flower (*Hibiscus sabdariffa*) extracts, containing high concentrations of PPLs (proprietary formula). The study enrolled 84 individuals with stage 1 hypertension (non-medicated) and randomized to receive daily either the PPLs or a placebo for 6 weeks. The authors found that daily administration of plant-derived PPL-extract improved diastolic blood pressure and reduced the body fat content, therefore, this treatment may be useful to decrease the cardiovascular risk in pre-hypertensive subjects (Boix-Castejón et al. 2021).

A randomized double-blind, placebo-controlled, crossover study (NCT02063477) enrolled 24 stage-1-hypertensive subjects and assessed the effect of 6-week daily administration of either Oligopin (a French maritime pine bark extract rich in low-molecular-weight procyanidins) or placebo. The results showed that Oligopin increased high density lipoprotein (HDL) cholesterol and apolipoprotein A-1 and reduced the ratio of apolipoprotein B-100/A-1. It also reduced systolic blood pressure and decreased oxidized low density lipoprotein (LDL), thereby representing an effective intervention to ameliorate cardiovascular parameters in hypertensive subjects (Valls et al. 2016).

Another placebo-controlled, blinded, crossover, randomized study (NCT02234648) assessed the acute effect of Montmorency tart cherry (*Prunus cerasus*) rich in PPLs (including anthocyanins such as cyanidin-glycosylrutinoside, and flavonoids such as quercetin-rutinoside) in improving cardiovascular function in 15 early hypertensive male subjects. Individuals received one single dose of either cherry concentrated juice or placebo and after a washout of 14 days the systolic blood pressure was measured showing that PPLs intake acutely reduces systolic blood pressure in men with early hypertension (Keane et al. 2016).

A randomized, crossover, double-blind, placebo-controlled trial (NCT02616822) evaluated the acute effect of trans-resveratrol administration in 24 men and women with hypertension. It was administered a single dose of the PPL

or the placebo and then, after 1 week washout, the administrations were crossed over and the measurements were done 1 h before and 1.5 h after the treatment. The study showed that supplementation of trans-resveratrol promoted an improvement in endothelial function, especially in women and those with higher LDL cholesterol, demonstrating that such PPL dietary intervention may help to ameliorate central hemodynamic parameters in individuals with hypertension (Marques et al. 2018).

A randomized and placebo-controlled study (NCT00539916) assessed the effect of administering blonde orange juice, rich in hesperetin, versus placebo to 25 males presenting at least two cardiovascular risk factors (i.e., age over 50 years, high LDL cholesterol and high blood pressure). The administration will be of one glass three times per day for 4 weeks with a subsequent 5-week washout. The results confirmed that blond orange juice daily consumption has positive effects on the cardiovascular system, by reducing endothelial dysfunction, and decreasing ROS blood release (Constans et al. 2015).

Additionally, a placebo-controlled crossover study (NCT01690676), conducted in 60 male and female subjects with borderline hypertension or mild unmedicated hypertension, aimed to assess the effects of apple-PPLs extract, enriched in epicatechin and flavan-3-ol, on endothelium-dependent brachial artery flow-mediated vasodilation compared with a placebo treatment. The study was characterized by 4-week daily consumption of either PPLs or placebo, 4-week washout, and other 4-week crossover. The results confirmed an acute improving effect of the flow-mediated vasodilation, but a lack of long-lasting differences between treated and control groups (Saarenhovi et al. 2017).

A placebo-controlled, randomized parallel-group trial (NCT00869193) assessed the effect of daily intake for 8 weeks of grape seed extract (a mixture of tannins and procyanidins) pills versus placebo in reducing the daytime blood pressure in 70 subjects (males and postmenopausal women) with stage 1 hypertension. The study found only a smaller but not significant blood pressure lowering effect in individuals consuming grape seeds suggesting that novel studies using higher doses of the treatment for more prolonged time are further needed (Ras et al. 2013).

A randomized, controlled, crossover trial (NCT02130141) involving 22 adults with mild hypertension was aimed to assess the effect of dark chocolate versus placebo in ameliorating cardiovascular functions. The consumption was daily for 8 weeks. The study showed that dark chocolate administration, despite being safe, had no effects on blood pressure or other cardiovascular risk factors (Koli et al. 2015).

A randomized, placebo-controlled, double-blind, crossover trial (NCT00099476) assessed in 20 individuals with essential hypertension the potential cardiovascular benefits of a flavanol-rich cocoa drink administered twice per day

for 2 weeks followed by a 1-week washout before the group crossover. Although in cocoa-treated group was observed an increased insulin-stimulated change in brachial artery diameter compared with placebo, this was not sufficient to reduce blood pressure in subjects with essential hypertension (Muniyappa et al. 2008).

A randomized study determined the effects of dark chocolate enriched with PPLs versus milk chocolate acute administration in patients with peripheral arterial disease, a condition linked with substantial increase of the risk of developing CVDs (NCT01947712). This study demonstrated that dark chocolate but not milk chocolate intake significantly increased maximal walking distance and time, and serum levels of nitrite/nitrate ratio. It also decreased serum isoprostanes and soluble NOX2-derived peptide. This effect was mediated by the PPL vasodilating and anti-oxidant activity, ultimately leading to enhanced NO generation, which might represent a novel approach to treat vasodilation in patients with peripheral arterial disease (Loffredo et al. 2014).

Another randomized placebo-controlled study (NCT02246660) was performed in 66 elderly patients with peripheral arterial disease and associated with walking and mobility problems. Patients were randomly allocated to receive low and high doses of resveratrol or placebo, daily, for 6 months. The study found no consistent evidence that resveratrol improved walking performance in elderly patients with peripheral arterial disease (McDermott et al. 2017).

The vast majority of the clinical results evidenced that the consumption of PPLs from vegetables, fruits, plants (in form of fruit or vegetable or as PPL-extract) was beneficial in subjects with hypertension or peripheral vascular disfunctions, in particular by ameliorating endothelial function, increasing NO local production, and, consequently, lowering central and peripheral blood pressure (Fig. 4). Only for cocoa and dark chocolate consumption, the clinical outcomes observed were contrasting, as half of the studies demonstrated substantial cardiovascular improvements, whereas the other half only non-significant trends.

Metabolic syndrome

The above-described hypertension is considered one among the disorders typical of the so-called metabolic syndrome, which overall rises the risk of developing NCDs including CVDs, cancer and neurological conditions (Swarup et al. 2022). According to the WHO, metabolic syndrome may be characterized by the occurrence, often in concurrence, of obesity, insulin resistance, hypertension and hyperlipidemia. Especially in urban areas, the increase in consumption of high-calories, high-fat and low-fiber diet, together with the rise of sedentary lifestyle choices may favor the development of this pathology, leading to an imbalance between calories

intake and energy consumption (which may be aggravated by the individual genetic and epigenetic background), finally leading to the occurrence of chronic diseases such as diabetes, CVDs, cancer and other NCDs, even among the youngest people (Saklayen 2018).

Mechanistically, gaining extra weight induces a buildup of the adipose tissue, especially in the upper body, which, in turn, may lead to altered glucose and lipidic metabolism, increased production of pro-inflammatory cytokines (e.g., leptin, adiponectin, plasminogen activator inhibitor, TNF- α), mitochondrial dysfunction, altered cellular energetics and rise of insulin resistance (Bhatti et al. 2017; Zaha et al. 2020). As a consequence, insulin resistance, increased oxidative imbalance and pro-inflammatory milieu may induce dyslipidemia, endothelial vascular inflammation and damage, hypertension, atherosclerosis and other cardiovascular issues (Lee and Olefsky 2021). Moreover, additional organs may be also injured, and it is common the appearance of liver (fatty liver) and kidney damage (renal failure) (Lonardo et al. 2015).

Dietary PPLs are investigated as a natural approach to tackle NCDs, especially metabolic syndrome and the pre-clinical and clinical findings strongly support the adjuvant role of PPLs associated to a healthy diet and to improved exercise as key measurements to prevent or reduce health issues correlated with metabolic syndrome (Chiva-Blanch and Badimon 2017). Many are the clinical trials currently ongoing aimed to dissect the role of dietary PPLs in metabolic syndrome management (Table 1). And a number of them, described in detail below, showed already supporting results.

A clinical study (NCT01154478) enrolled 80 individuals with high waist circumference and at least a marker of metabolic syndrome. The enrolled subjects were randomized in different intervention groups and followed an 8-week diet supplemented either with PPLs or PPLs and omega-3 fatty acids or omega-3 fatty acids alone, or, finally, without supplement (control group). The study assessed the lipidemic profile changes upon treatment. Interestingly, groups receiving PPLs (alone or in combination with omega-3 fatty acids) showed positive effects on blood lipid concentrations, especially the reduction of VLDL1 lipid with modifications in lipid composition of lipoproteins, hence lowering the overall cardiovascular risk (Della Pepa et al. 2020).

A randomized controlled study (NCT01400724) explored the effect of the chronic administration for 6 months of a new supplement formula, combining cocoa PPLs, myo-inositol and soy isoflavones. The study enrolled 80 postmenopausal women with metabolic syndrome and randomized them to receive either the formula or the placebo. After 6 months the supplement enriched in PPLs demonstrated to improve most of the blood biomarkers linked to metabolic syndrome, including glucose and triglycerides reduction and

bone-specific alkaline phosphatase increase (D'Anna et al. 2014).

A clinical study (NCT03076463) enrolled 49 patients with at least two altered markers of metabolic syndrome. The subjects were randomly assigned to receive either dried grape pomace (rich in anthocyanins) or placebo for 6 weeks. Endpoint samples were analyzed after a 4-weeks washout timeframe. The first observation was that grape pomace supplementation significantly improved fasting blood insulin levels (Martínez-Maqueda et al. 2018). Second, such treatment was associated with a tendency of decrease in the proportion of *Lactobacilli*, and an increase in the proportion of *Bacteroides* in non-responder subjects (Ramos-Romero et al. 2020). Finally, in the plasma of PPL-responders in terms of fasting insulin rate, it was detected an increase of miRNAs associated with insulin resistance and diabetes (miR-30c and miR-222) (Léniz et al. 2021).

A clinical randomized and controlled study (NCT01414647) examined the effect of a diet abundant in berries, enriched in phenolic compounds (including flavonoids, phenolic acids, lignans and complex phenolic polymers), on glucose and lipid metabolisms as well as on inflammation in subjects with metabolic syndrome. Individuals were divided in two groups, one following a berry-rich diet (15 individuals) and the other one a control diet (12 individuals). The dietary intervention lasted 8 weeks followed by a wash up time of 4 weeks. The results showed that berries consumption decreased inflammatory markers in human peripheral blood mononuclear cells (PBMCs) thereby reducing low-grade inflammation in subjects with metabolic syndrome (Kolehmainen et al. 2012). Moreover, berry-derived ellagitannins changed the GM profile in particular within the subgroup of urolithin producers. Hence GM composition may influence PPLs from biological effects (Puupponen-Pimiä et al. 2013).

In another randomized controlled study (NCT03265184), which enrolled 43 individuals with metabolic syndrome, the anti-inflammatory effects of medium-term administration of green coffee extract (rich in chlorogenic acid) versus placebo were evaluated. Upon daily intervention for 8 weeks, it was not found any significant difference in the serum expression of oxidative stress, systemic or vascular inflammation between groups (Nikpayam et al. 2018). Additionally, in the same study but different registration number (NCT02764957) it was studied the effect of green coffee extract administration on cardiovascular risk factors. And the results in this case showed an ameliorating effect on some of the metabolic syndrome components (including high systolic blood pressure, high fasting blood glucose, insulin resistance and abdominal obesity) suggesting that green coffee extract consumption could ameliorate altered glucose metabolism and cardiovascular issues in individuals with metabolic syndrome (Roshan et al. 2018).

An interventional randomized and controlled clinical trial (NCT03592511) assessed the effect of dietary use of wine grape pomace flour, rich in PPLs, on glucose metabolism, inflammation and oxidative stress of 27 male individuals with metabolic syndrome. The subjects consumed 1 hamburger daily for 1 month containing wine grape pomace flour (or not in the control group). Interestingly, after the intervention men consuming the PPL-rich burger showed an improved fasting glucose and insulin sensitivity, plasma anti-oxidant levels and oxidative damage markers, making this PPL-rich flour a dietary supplement to manage chronic diseases (Urquiaga et al. 2018).

A randomized, single-blind, placebo-controlled, crossover trial (NCT03619941) included 12 participants with metabolic syndrome, and assessed the effect of daily consumption of Montmorency tart cherry juice, rich in anthocyanins and flavonoids, or placebo, for 7 days in preventing further cardiometabolic dysregulation. The results showed that Montmorency tart cherry juice significantly lowered systolic and diastolic blood pressure, improved fasting glucose, total cholesterol and total cholesterol to HDL ratio, and also lowered resting respiratory exchange ratio compared to control group (Desai et al. 2021).

All the studies conducted in subjects with metabolic syndrome showed promising results demonstrating that the chronic consumption of PPLs from raw fruit, juice and fruit extract (grape, grape seeds, berries), but also from green coffee extract, improved lipidemic and glucose profile, fasting blood insulin, decreased blood pressure and reduced inflammation and oxidative stress, therefore, counteracting detrimental health issues of metabolic syndrome. Several other studies (Table 1) are currently registered at clinicaltrials.gov and novel results are yet to come.

Diabetes

Both preclinical and clinical evidence support that dietary PPLs (from fruit, berries, leaves extracts) may influence blood glucose thereby helping management of diabetes and prevention of diabetes-linked complications. PPLs decrease blood glucose levels and improve insulin metabolism and individual sensitivity. Mechanistically, it has been observed that PPLs actively contrast glucose intestinal cellular absorption, as well as modulate insulin and glucose metabolism (Aryaeian et al. 2017). Novel clinical studies evidenced the benefits of dietary PPLs consumption, either acute or over longer periods (of weeks or months), in diabetic subjects, with positive effects also on cardiovascular functions, lipid metabolism and inflammation, hence reducing the onset of correlated metabolic syndrome and significantly reducing CVD risk.

A clinical study (NCT01886989) characterized the health effects of flavanol-rich cocoa acute supplementation

associated with high-fat meal breakfast challenge. Upon intervention, modulation of glucose and lipids blood levels, and surrogate markers of atherosclerosis were measured in 25 T2D voluntary patients. Although HDL cholesterol and insulin remained higher throughout the postprandial period, serum IL-18 was decreased and HDL total levels increased. Meaning that PPL-rich cocoa may alleviate postprandial dyslipidemia and inflammation following a high-fat dietary challenge in adults with T2D, thus preventing cardiovascular risk in susceptible populations (Basu et al. 2015; Davis et al. 2020).

A clinical study (NCT01245270) assessed the effect of acute administration of bilberry (*Vaccinium myrtillus L*) extract (rich in anthocyanins) versus placebo in ameliorating glucose metabolism in 8 T2D untreated patients, controlling their diabetes exclusively through diet and lifestyle. The administration was a single acute oral capsule (bilberry extract or placebo) followed by a polysaccharide drink. The study demonstrated that the ingestion of concentrated bilberry extract significantly decreased glucose and insulin levels compared with the placebo, reducing postprandial glycaemia and insulin, probably by decrementing the rates of carbohydrate digestion and/or absorption (Hoggard et al. 2013).

A randomized, double-blind, placebo-controlled trial (NCT01923597) assessed the effect of administering either green tea extract pills (containing high doses of EGCG) or placebo daily for 12 weeks to 50 people with diabetic nephropathy. The individuals enrolled in the study were all diagnosed with diabetes and hypertension and they had to take renin-angiotensin inhibitors. The study demonstrated that the group treated with PPLs derived from green tea had reduced albuminuria. Also, in vitro assessment of albumin permeability showed a reduction in podocyte apoptosis when these cells were exposed in vitro to plasma from individuals treated with green tea pills (Borges et al. 2016).

A randomized clinical trial (NCT01766570) assessed the benefits of strawberry and cranberry (rich in phenolic acids and flavonoids) in 41 insulin-resistant overweight or obese human subjects. From the study it was observed that a daily 6-week uptake of PPLs from strawberries and cranberries significantly improves insulin sensitivity and prevents an increase in compensatory insulin secretion whereas plasma lipid levels, pro-inflammatory cytokines release in blood and anti-oxidant capacity was not affected (Paquette et al. 2017).

An additional parallel, double-blind, placebo-controlled study (NCT01754662) assessed the effect of daily administration for 8 weeks of soy protein with or without isoflavones, and with or without cocoa in 84 patients with metformin-treated T2D. It was found that only soy proteins and isoflavones but not cocoa had intrinsic activity on glycemic control and improved both insulin resistance and LDL compared to controls (Konya et al. 2019).

A double-blind, randomized, placebo-controlled, parallel-group clinical trial (NCT04734132) assessed the capability of leaf extract from *Moringa oleifera*, rich in astragaloside, chlorogenic acid, kaempferitrin, luteolin and quercetin (Zhang et al. 2020), to ameliorate glucose metabolisms when consumed by prediabetic subjects. The study was conducted by administering Moringa extract or placebo, daily for 12 weeks. As a result, the study demonstrated that prediabetic patients receiving Moringa treatment showed favorable changes in glycaemia markers compared to placebo, meaning that Moringa extract may be used as natural antihyperglycemic agent (Gómez-Martínez et al. 2021).

Dyslipidemia

Among the features of metabolic syndrome there is the frequent occurrence of dyslipidemia, characterized by the unbalance of circulating lipids such as cholesterol, LDL cholesterol, triglycerides and HDL which might expose to increased CVD risk (Kopin and Lowenstein 2017). It has been observed that the consumption of dietary PPLs may correct such unbalance, in particular thanks to their ROS scavenging properties (Feldman et al. 2021). The clinical studies below evidenced the beneficial role of PPLs (from seeds, leaves and fruits) in ameliorating the lipidemic profile, and improving endothelial functions in subjects with dyslipidemia.

A clinical study (NCT04110392) assessed the metabolic effects of Chaya leaf extract, enriched amentoflavone, EGCG, hesperidin, lignin and quercetin (Temesgen et al. 2022). Chronic consumption of such extract in 30 individuals with dyslipidemia was studied. The individuals consumed one portion of Chaya beverage daily, over a 6-week period. The results showed that consumption of Chaya had hypotriglyceridemic and anti-oxidant effects in subjects with dyslipidemia. In fact, it was measured an increase in plasma of both anti-oxidant activity and polyphenol concentration, as well as a reduction in the oxidative stress marker malondialdehyde and an increase in the anti-oxidant catalase enzyme expression in PBMCs (Guevara-Cruz et al. 2021).

Fifty-two mild hyperlipidemic individuals were enrolled in a randomized double-blind placebo-controlled crossover clinical trial (NCT00713167). The aim was to investigate the effect of grape seed extract (with tannins and procyanidins) versus placebo on lipidemic profile and atherosclerosis after 8 weeks administration, 8-week washout and other 8 weeks of crossover treatment. The study demonstrated that PPLs from grape seeds reduced total cholesterol, LDL cholesterol and oxidized LDL particles, with consequent beneficial effects on lipid profile, consequently decreasing the risk of atherosclerosis and cardiovascular disorders-in mild hyperlipidemic individuals (Razavi et al. 2013).

A randomized, controlled, double-blinded, crossover trial (NCT02612090) assessed the metabolic and cardiovascular effect of strawberry PPL-rich juice (such as phenolic acids and flavonoids) versus placebo, in 34 adults with moderate hypercholesterolemia. The participant drank twice a day the treatment or control beverage for 4 weeks followed by a 4-week washout before the crossover. Although the treatment did not change metabolic lipidic parameters, it was observed a significant improvement of flow-mediated dilation and attenuated systolic blood pressure, supporting the inclusion of strawberries as healthy diet measurement in adults with moderate hypercholesterolemia (Huang et al. 2021).

A randomized, controlled, crossover, intervention study (NCT01988389) determined the efficacy of catechin-rich whole apple consumption in ameliorating vascular function parameters in 40 mildly hypercholesterolemic individuals (17 men and 23 women). The assessment was done after either whole apple or apple juice administration (in control group) daily, for 8 weeks and a 4-week washout window. It was observed that, compared with control, PPL-rich whole apples, consumed 2 per day, lowered blood LDL cholesterol and triacylglycerol. Additionally, the response to endothelium-dependent microvascular vasodilation was greater after entire fruit consumption. Altogether, the results have proven that PPLs from apples had beneficial hypocholesterolemic and vascular effects in mildly hypercholesterolemic individuals (Koutsos et al. 2020).

Subjects suffering of dyslipidemia are more prone to develop atherosclerosis and CVD-related chronic pathologies. The clinical observations hereby reported evidenced that either acute dietary PPLs administration (before a meal challenge) or a chronic consumption (in the form of fruits, fruit juices or plant extracts) significantly ameliorated lipidemic profile, reduced blood oxidative stress markers, ameliorated vasodilating endothelial functions and reduced blood pressure, thereby representing a natural remedy to improve dyslipidemia and prevent metabolic syndrome in subjects with altered blood lipidic profile (Fig. 4). Additional ongoing clinical studies with yet no results are reported in Table 1.

Obesity

Weight gain and chronic buildup of adipose tissue might lead to overweight and finally to obesity, which is a condition characterized by chronic metaflammation and correlated with all the devastating effects of the metabolic syndrome (James et al. 2001). It has been showed that PPLs may contrast obesity at different levels, including by inhibiting adipocytes differentiation, by regulating the activity of relevant enzymes involved in lipid assimilation and metabolism, and also through the suppression of appetite and the stimulation

of energy consumption (Singh et al. 2020). Hence, PPLs may represent a natural dietary intervention to reduce body weight and contrast the development of detrimental obesity. Several clinical studies are currently ongoing (Table 1), while many other already had results, which are illustrated below. Overall, while the majority of the studies confirmed that dietary intake of PPLs, either chronic or acute, has positive effects on improving food energy expenditure and metabolic health, few of them could not find any significant change, especially for what concerns insulin sensitivity modulation.

A randomized clinical trial (NCT01290250) assessed the effects on anti-oxidant defense system, DNA damage and lipid peroxidation of daily administration of orange juice supplemented with different concentrations of flavanone. The study was conducted on 100 obese individuals for 12 weeks with a subsequent 7-week washout period. The group treated with higher flavanone orange juice showed an enhanced erythrocyte superoxide dismutase activity and both groups treated with higher and lower levels of flavanone in orange juice showed a decrease in body mass index, waist circumference and leptin when compared with placebo-treated controls. Hence, flavanols in orange juice showed a protective effect against NCD risk factors (Rangel-Huerta et al. 2015).

Additionally, a 14-day randomized crossover trial (NCT01568827) demonstrated that the daily administration of lyophilized black raspberries, rich in anthocyanins and ellagitannins, prior to a challenge meal (high-fat and high-calories) attenuated circulation pro-inflammatory markers in 10 obese and overweight male subjects (Sardo et al. 2016).

A randomized, crossover trial (NCT03523403) was conducted with 26 overweight or obese individuals to assess the effect of acute consumption of 3 Gala apples (rich in several phenolic acids) following a high-fat meal to mitigate meal-induced postprandial inflammation. PBMCs isolated from blood of treated subjects were stimulated with LPS. PBMCs from apple-treated subjects showed increased total anti-oxidant capacity, suggesting that Gala apple consumption may be an effective dietary strategy to reduce postprandial inflammation in subjects with higher risk of CVDs such as those with metabolic syndrome (Liddle et al. 2021).

In a randomized, double-blind, placebo-controlled study (NCT03423719) 72 overweight or obese voluntaries assumed daily for 16 weeks the PPL-based supplement Fiitns (rich in naringin, hesperidin, catechins from green tea, guarana, grape seeds grapefruit and black carrot extracts) or placebo. After 16 weeks, the health-related quality of life was assessed through a questionnaire and the body fat mass was measured and compared with baseline values. It was observed that the health-related quality of life upon 16-week consumption of the supplement, associated with both caffeine and vitamin B3, significantly improved mental and

physical subjective feelings and this was associated with a decrease in body fat mass and the significantly increased engagement in physical activity. Hence, chronic administration of PPLs had positive effects on quality of life and improved metabolic health by exerting both anti-oxidative and anti-inflammatory effects (Romain et al. 2021).

A randomized, double-blind, placebo-controlled, crossover design study enrolled 80 obese and overweight subjects to test the metabolic effects of chronic sea weed PPL-extract administration on metabolic profile (NCT02295878). Sea weed extract (rich in bromophenols, flavonoids and phenolic terpenoids) or placebo was consumed daily for 8 weeks. Fasting blood and urine samples were collected from each volunteer at 4 time-points, including the baseline and the end of the study. The results showed that subjects consuming sea weed derived PPLs had a mild reduction of lymphocyte DNA damage. The study also characterized the bioavailability and metabolism of such PPLs, identifying the phlorotannin metabolites as potential biomarkers of sea weed consumption (Baldrick et al. 2018).

In an interventional study (NCT01302639), 18 overweight men and women (9 and 9) were given for 3 days, daily, either EGCG and resveratrol alone or in combination with soy isoflavones. It was demonstrated that combined EGCG and resveratrol supplementation for 3 days significantly increased fasting and postprandial energy expenditure after a challenge meal, which was accompanied by improved metabolic flexibility in men but not in women. Whereas the addition of soy isoflavones partially reversed the observed effects (maybe due to their higher lipolytic potential). Altogether, the results showed that dietary EGCG, when combined with resveratrol may improve metabolic health and body weight in overweight individuals (Most et al. 2014).

A randomized study (NCT02479035) assessed the acute effect of administering anthocyanins-rich frozen red raspberries in association with a challenge breakfast meal (high lipids and moderate glucose). The study was conducted in 21 pre-obese individuals which were randomized in three groups to receive breakfast meal either with no, medium dose or high dose of frozen raspberries. Upon analysis of glycemic and insulin levels, the results confirmed that red raspberries (each dosage compared with control) significantly aided post-meal glycemic control in individuals with pre-obesity, thereby reducing glycemic burden with less insulin metabolism, which may be related to an improved tissue insulin sensitivity (Xiao et al. 2019).

Contrariwise, an 8-week clinical study (NCT01518764) enrolling 29 obese individuals (divided in two groups, treated and placebo) assessed the effect of daily intake of PPLs from red wine (i.e., quercetin, anthocyanins, procyanidins, ellagic acid, catechins from a commercial supplement, Provinols) on insulin resistance. The study showed that such supplementation did not improve insulin sensitivity, thereby

disproving that PPLs from red wine would ameliorate insulin resistance in human obesity (Woerdeman et al. 2018). Also, a controlled acute clinical study (NCT02710461) was performed to evaluate the acute effect of a single dose of grape and pomegranate pomace (rich in anthocyanins and gallic acid) in 20 subjects with abdominal obesity. The dietary supplement did not ameliorate either glucose or insulin blood levels after a challenge high-glucose beverage. No improvement in anti-oxidant capacity was also observed neither in plasma nor in urine. A non-significant tendency towards improved insulin sensitivity was observed in PPL-treated subjects when the PPLs were consumed 10 h before oral glucose administration. Hence, a single dose of grape/pomegranate PPLs is not able to clearly improve glucose metabolism and, alternatively, chronic intake must be evaluated in the future (Pérez-Ramírez et al. 2020).

A clinical study (NCT00668928) assessed the levels of circulating trimethylamine N-oxide (deriving from GM-mediated transformation of choline and carnitine to release trimethylamine, then converted in the liver into trimethylamine N-oxide) which is a marker of CDVs, upon short-term flavanol consumption in 20 obese subjects. The results did not show any decrease of circulating trimethylamine N-oxide in subjects treated with flavanols compared to controls. This study suggested that alternative chronic administration should be evaluated (Angiletta et al. 2018). Moreover, a randomized and placebo-controlled study (NCT03741218) assessed the acute effect of freeze-dried grape (rich in anthocyanins, flavonols, flavanols, stilbenes) administered after two successive meals in 25 subjects with obesity. Blood test was collected through a time-course. Results showed that acute grape supplementation at nutritional doses did not lead to an improvement in postprandial metabolism of glucose and chronic supplementation might be studied instead (García-Díez et al. 2021). To conclude, while the majority of the results showed that consumption (especially chronic) of dietary PPLs may help to restore glucose and insulin metabolism in obese and overweight subjects, few studies (especially upon acute administration of dietary PPLs in concurrence with a challenge meal or beverage) failed to show such amelioration.

Other interventional studies conducted on obese or overweight subjects had as primary outcome the assessment of cardiovascular health. For what concerns the effects of dietary PPLs on vascular functions in obese or overweight individuals, although the majority of the trials recorded positive effects on cardiovascular system, not all of them reported significant beneficial effects towards endothelial cellular health. An acute randomized study (NCT02292329) conducted in 23 overweight male subjects demonstrated that the acute administration of açai (*Euterpe oleracea*) fruit puree (rich in quercetin, orientin, cyanidins, anthocyanidins) with a high-fat breakfast meal challenge, was associated with

significant improvements in vascular function, which may lower the risk of a cardiovascular events (Alqurashi et al. 2016).

A double-blind parallel multicenter trial (NCT00692731) enrolled 240 subjects with visceral fat-type obesity. The study assessed the effect of daily consumption of green tea catechins for 12 weeks, after a 2-week diet run-in period. The groups were divided in high-catechins and low-catechins receivers. The study revealed significant decrease in body weight, body mass index, body fat ratio, body fat mass, waist circumference, hip circumference, visceral fat area and subcutaneous fat area in the high-catechins group. Also, greater decrease in systolic blood pressure and LDL cholesterol decrease were observed in such group, overall suggesting that the ingestion of green tea beverage contributed to a decrease in obesity and CVD risks (Nagao et al. 2007).

A randomized study (NCT01674231) assessed the effect of consuming freeze-dried whole grape powder (rich in anthocyanidins, catechins, epicatechins, quercetin) versus placebo in 20 obese subjects. The effects of PPLs in regulating metabolism and cardiovascular parameters were assessed both acutely (upon administration followed by a high-fat and high-glucose meal), as well as chronically following 4-week daily administration. The results obtained showed that while the acute administration upon meal challenge determined the decrease of the vasoconstrictor endothelin-1 concentration and the increased nuclear factor erythroid 2 gene expression in peripheral blood cells (related to oxidative stress defense), the chronic administration did not result in clinically significant changes in endothelial function markers or inflammatory markers (Bardagjy et al. 2018).

In a randomized crossover study (NCT01364961), 45 subjects with overweight or slight obesity were subjected to daily administration of either resveratrol or placebo for 4 weeks (with a 4-week washout period). The aim was to assess the effects of resveratrol on cardiovascular functions and inflammation. The results showed that daily intake of trans-resveratrol for 4 weeks did not change plasma biomarkers of endothelial function or inflammation in the fasting state or postprandial phase (van der Made et al. 2015).

A randomized, double-blind, placebo-controlled study (NCT02228291) assessed the effect of administering hesperidin 2S (citrus flavonoid) or placebo to 68 overweight individuals. Following 6-week daily administration it was not observed any improvement of basal or postprandial endothelial dilation, although there was a tendency towards a reduction of adhesion molecules and a decrease in systolic blood pressure (Salden et al. 2016).

Importantly, a number of clinical studies conducted on obese or overweight subjects had among the primary outcomes the assessment of GM changes upon dietary PPLs consumption, finding that PPLs positively affected gut microbial health. In fact, a clinical 8-week study

(NCT02743195) in 51 males and females with uncomplicated obesity assessed the effect on fecal GM composition upon daily supplementation with a blend of anthocyanins and prebiotics. The results were very encouraging: treated individuals showed a significant increase in the beneficial *Bacteroidetes* taxa. These changes were also associated in an overall amelioration of bowel symptoms including gas, bloating and abdominal pain (Hester et al. 2018).

A placebo-controlled randomized trial (NCT01293175) assessed the bioavailability and effect on fecal microbiota of a daily consumption for 8 weeks of whole-grain containing high values of ferulic acid. The study enrolled 80 overweight and obese subjects that were randomized to consume precise portions of either refined wheat or whole-grain wheat. The results showed that whole-grain consumption significantly increased the blood levels and excreted levels of ferulic acid. This metabolic increase positively influenced the microbial balance in the intestine, by favoring the increase of beneficial *Bacteroidetes* and *Firmicutes* and reduction of detrimental *Clostridium* (Vitaglione et al. 2015).

A double-blind, crossover, dose–response, randomized, placebo-controlled trial (NCT02061098) was conducted to assess the effects of ellagitannin-rich pomegranate extract on lipid metabolism in 49 overweight subjects. The extract (low or high dose) or the placebo were consumed daily for 3 weeks, followed by a 3-week washout and 3-week crossover. The results showed that only a certain category of individuals with a specific urolithin metabolic-type (urolithins are bioactive GM metabolites of ellagic acid) had a significant reduction of lipid serum markers, independently of the dose of pomegranate extract consumed. Hence, the GM profile might explain the controversial effects of such extract in improving the metabolic lipidic profile of selected overweight subjects (González-Sarrías et al. 2017). Additionally, it was also observed that the GM of responders was able to produce four unknown urolithins, which might be used for further stratification of the subjects truly benefitting from extract administration (García-Villalba et al. 2019).

To conclude, 68% of the studies conducted on pre-obese or obese subjects showed that consumption of dietary PPLs from fruit, berries and leaves extract improved the fasting of glucose and ameliorated the insulin metabolism. It was also observed an improvement of body mass weight, a decrease in body fat, an amelioration of inflammatory profile in blood cells, following PPL usage. Moreover, few studies, having as primary endpoint GM alterations, evidenced an increase in beneficial taxa and a decrease in detrimental ones, which might be also associated with a different PPLs metabolism, in particular regarding urolithins from ellagic acid (Fig. 4). However, a smaller percentage of studies found only tendencies or no benefits in administering dietary PPLs in obese individuals (despite their proven safety), therefore, new larger cohort studies are needed, to assess the effect

of different doses or different formulations which could improve final PPL bioavailability (including nanovesicle-mediated delivery).

Neurological diseases

Dietary PPLs are also able to ameliorate chronic neurological conditions, in cases of chronic neurodegenerative diseases or brain damage upon stroke or cardiovascular illnesses (Bhullar and Rupasinghe 2013; Ayaz et al. 2019). The molecular mechanism seems to be linked with their anti-oxidative stress and the capability to chelate oxidative species and preserve the health of the nervous system (Faria et al. 2010). For these reasons, dietary PPLs are currently investigated in clinics to assess their potential as molecules able to alleviate neurological symptoms or even slow-down the neurodegenerative process or to heal neuronal injuries (Polverino de Laureto et al. 2020).

A placebo-controlled study (NCT00461942) assessed the beneficial effects of daily administration of green tea-derived PPLs (in particular EGCG and ECG) to untreated early PD patients. PD is the second most common neurodegenerative disease, characterized by the progressive loss of dopaminergic neurons in the central nervous system, and accompanied by the gradual occurrence of motor and non-motor debilitating symptoms (Deus et al. 2022). Preliminary results in 32 early PD patients showed that upon 6 months administration, PPLs from green tea were well tolerated and provided a mild symptomatic benefit, as measured by the Unified Parkinson Disease Rating Scale, which is the rating tool used to measure the development of PD and the amelioration upon treatment (Chan et al. 2009).

A placebo-controlled clinical study (NCT03740295) enrolled 51 patients with different grades of multiple sclerosis, a neurological disease characterized by neuroinflammation, to study the effect of daily administering EGCG in association with coconut oil (rich in β -hydroxybutyrate). The study assessed several neurological and inflammatory parameters after 4 months intervention. First results showed that in PPL-treated subjects it was observed a significant decrease in serum IL-6 levels and a significant increase in muscle percentage (de la Rubia Ortí et al. 2021a). Also, following the intervention, butyrylcholinesterase (whose levels are positively correlated with disease onset) increased in blood. This increase was associated with augmentation of: paraoxonase 1 blood level, body fat percentage and triglycerides. Overall, the results demonstrated that chronic consumption of EGCG, in association with coconut oil, significantly decreased both lipolytic activity and inflammation status in treated patients (de la Rubia Ortí et al. 2021b).

A small placebo-control double-blind clinical study (NCT02442804) assessed the effects of dietary supplementation with a pomegranate extract with anti-oxidant properties

(POMx supplement, rich in several PPLs including tannins and flavonoids) in enhancing cognitive functions in 16 patients with stroke (8 PPL-treated and 8 placebo-treated). The supplementation was twice a day for 1 week, starting from 2 weeks after the stroke. The study showed that pomegranate-treated subjects had more neuropsychological and functional improvement and spent less time in the hospital than placebo controls, thus positively enhancing cognitive and functional recovery after stroke (Bellone et al. 2019).

A parallel-arm, double-blind clinical trial (NCT00825695) assessed the effect of 30 days daily consumption of flavanol-rich cocoa supplement (Cocoapro) in 60 elderly subjects with vascular risk factors. The study demonstrated that there was a strong correlation between neurovascular coupling and cognitive function, and both can be ameliorated by daily cocoa supplement consumption. Better neurovascular coupling was also associated with greater white matter structural integrity in subjects eligible for MRI (Sorond et al. 2013).

Also, in case of genetic-linked mental disability, dietary PPLs were investigated as a potential natural defense against oxidative stress. A double-blind placebo-controlled phase I clinical trial (NCT01855971) enrolled 27 subjects affected by fragile-X syndrome. The study wanted to assess whether the daily administration of EGCG combined with cognitive training for 3 months (compared to the control group receiving cognitive training alone) ameliorated core cognitive and behavioral features. The results showed that patients receiving EGCG combined with cognitive training, significantly improved cognition (visual episodic memory) and functional competence compared with control group, demonstrating the beneficial potential of EGCG in individuals affected by fragile-X syndrome (de la Torre et al. 2020).

Although few, the published studies showed that chronic administration of dietary PPLs (from green tea leaves, pomegranate and other fruit extracts) positively affects cognitive parameters, thereby helping recovering or ameliorating symptoms, hence they can be suggested as beneficial adjuvants in chronic conditions characterized by neurological impairment (Fig. 4). Also in this case, future results coming from more ongoing studies (Table 1) and possible enrollment of larger cohorts of patients may help to improve our knowledge about the potential preventive and therapeutic value of PPLs in neurological conditions.

Other chronic conditions

Other chronic conditions have been also considered to assess the benefits of dietary PPLs. According to WHO, osteoporosis is a disease caused by low bone mass and bone tissue degradation leading to increased bone fragility and fracture risk (Sozen et al. 2017). Postmenopausal estrogen deficiency may trigger such detrimental process (Cheng et al. 2022). A

number of studies demonstrated that the excessive generation of ROS may induce osteoblast dysfunction and osteoclast activation, together with stimulated expression of genes with pro-inflammatory role (e.g., the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) which in turn activates the downstream expression of several pro-inflammatory cytokines) (Callaway and Jiang 2015). Thanks to their anti-inflammatory properties, PPLs ameliorate bone structure thereby representing a potential remedy to prevent and treat postmenopausal osteoporosis (Niwanon et al. 2022).

As listed below, novel clinical studies have positively showed that chronic consumption of dietary PPLs increases anti-oxidative blood biomarker levels and the bone-promoter hormone osteocalcin. A 6-month randomized and placebo-controlled clinical trial was conducted in 171 postmenopausal women with osteopenia (NCT00625391). The subjects were subdivided in four arms of treatment: either PPLs from green tea consumed daily for the length of the study, alone or in combination with tai chi practice (60 min three times per week), plus placebo-control and tai chi only control groups. Blood and urine samples were collected at the baseline, 1-, 3- and 6-months during intervention. In a first study it was demonstrated that there was a significant time- and dose-dependent mitigation of the oxidative damage biomarker 8-hydroxydeoxyguanosine in all the intervention groups compared to the control (Qian et al. 2012). Moreover, bone-specific alkaline phosphatase and tartrate-resistant acid phosphatase markers of calcium metabolism, and muscle strength were significantly improved with green tea PPLs consumption with or without tai chi practice, suggesting beneficial effects of chronic consumption of PPLs and tai chi practicing to ameliorate the health in women with osteopenia (Shen et al. 2012).

Another study (NCT00789425) conducted in 69 women with osteopenia randomly allocated in two groups one receiving a standardized olive extract rich in PPLs (i.e., caffeic acid, ferulic acid, cinnamic acid, tyrosol, oleuropein) and calcium versus the control group receiving only calcium (Ciriminna et al. 2016). The administration was daily for 12 months. After 12 months, women with osteopenia treated with PPLs showed a significant increase of the pro-osteoblastic marker osteocalcin compared to untreated control, thus suggesting that olive-PPLs affect serum osteocalcin levels and may stabilize lumbar spine bone mineral density. Moreover, the improved blood lipid profiles suggest additional health benefits (Filip et al. 2015).

Other clinical studies assessed the beneficial effects of dietary PPLs in chronic diseases triggered by inflammation and immune system overactivation (allergies), as well as hereditary chronic metabolic diseases. In particular, 19 patients with ulcerative colitis were enrolled in a randomized placebo-controlled study (NCT00718094) to evaluate the

beneficial effects of 2 months daily treatment either with EGCG from green tea extract or placebo. The study showed that patients treated with PPLs had a 53% remission rate compared to 0% in the control group, demonstrating that this treatment might be an option for patients with ulcerative colitis (Dryden et al. 2013).

PBMCs isolated from 25 patients (NCT03902392) with Ni-dependent contact dermatitis were evaluated in terms of cytokine release and NO production by blood-isolated white cells in the presence or absence of red grape-derived PPLs in culture. The results showed that PPLs were able to reduce the increased release of IFN- γ and IL-4, while maintaining the equilibrium between IL-10 and IL-17 secretion (Magrone et al. 2017a). A subsequent experiment, always isolating PBMCs from 25 patients with ACD and treating them with red-grape PPLs, restored the unbalanced production of IL-17 (Magrone et al. 2017b). Finally, a dietary supplement based on red-grape extract, Naturox (proprietary composition, rich in proanthocyanidins) was administered orally to the ACD patients, daily, for 3 months. Upon treatment, serum levels of IFN- γ , IL-4, IL-17, pentraxin 3 and NO decreased, while IL-10 levels increased compared to basal, confirming the anti-oxidant, anti-inflammatory and anti-allergic effects of PPLs also in patients with Ni allergies (Magrone et al. 2021).

A clinical study enrolled 32 subjects suffering of house dust mite allergic rhino-conjunctivitis and measured the effectiveness of a daily dietary supplement containing beta-lactoglobulin, iron, retinoic acid, zinc and iron-catechin complexes (NCT04872868; NCT04477382). The administration lasted 12 weeks and changes in allergy parameters were measured. The dietary supplement significantly improved allergic parameters compared to the baseline, after 3 months and also the effects were retained in the following 8 months after treatment (Bergmann et al. 2021, 2022).

In conclusion, also in other chronic conditions, including osteoporosis, ulcerative colitis and allergies, dietary chronic consumption of PPLs from green tea leaves or other sources may ameliorate symptoms and improve the overall quality of life of affected subjects. More studies are currently enrolling individuals with intestinal, immune, lung or kidney chronic disorders to study the adjuvant effects of introducing PPLs with diet and beverages (Table 1).

Conclusions

Currently, NCDs represent the major cause of death worldwide. Given their chronic nature and the prolongation of life expectancy they are a growing socio-economic burden for the healthcare systems, the governments and the affected population (Forouzanfar et al. 2016). Nowadays, personalized medical approaches are becoming pivotal to prevent

and treat chronic pathologies. In particular, to manage such conditions, it is advised to choose healthier lifestyle habits, including following a diet rich in fresh fruits, vegetables, fibers and low in fat and elaborated carbohydrates, such as the Mediterranean diet (Drapkina and Ivanova 2021). Thanks to their health promoting ability, plant-derived PPLs might represent natural biomolecules which can be easily assumed with food, drinks, extracts or dietary supplements to ameliorate the overall quality of life, to prevent the development of NCDs or to improve the survival of individuals affected by one or more NCDs (Hano and Tungmunthum 2020).

Dietary PPLs, once ingested, follow the metabolic route of xenobiotics, including their dual interaction with the GM, which, together with the gastro-intestinal enzymes, may determine the overall formation of a plethora of PPL-derived metabolites with a number of different bioactivities. In general, PPLs, given their heterogeneous molecular moieties, are able to chelate ions, therefore, exerting an anti-oxidant effect. Also, many PPLs can trespass cellular membranes, and hence, they may interact with lipids, proteins and other molecules within the cell. Consequently, PPLs are powerful anti-oxidant, anti-inflammatory and anti-proliferative

molecules. Medical research is currently assessing also how to improve systemic bioavailability and bioactivity of PPLs, for example by encapsulating them in vesicles or by binding them with biological molecules (i.e., proteins, carbohydrates, lipids, nucleic acids) (Pedrioli et al. 2021).

Can PPLs be used against human chronic diseases? Yes, PPLs can be employed to effectively prevent or ameliorate the outcome of several human NCDs. In the latest 20 years, the number of clinical studies designed to assess both safety and efficacy of PPL-based interventions in subjects with NCDs has grown exponentially, and more than 150 clinical trials are presently registered at clinicaltrials.gov. About half of them (71 studies) got already results (Table 2). As described in this review, the vast majority of the published studies (75%) have proven that the acute or chronic consumption of dietary PPLs is able to ameliorate NCD symptomatology or to prevent the worsening of chronic conditions, thus improving the health of affected subjects (Fig. 5). Hence, when consumed regularly (and coupled with a healthier lifestyle and diet), PPLs may effectively delay the use of standard drug therapies for a given NCD, and they can slow-down the worsening of such

Fig. 5 Outcomes of the clinical studies with percentages. Although all the reviewed studies demonstrated that polyphenols were safe when administered to individuals with chronic pathologies, not all of them equally reached primary and secondary interventional outcomes. The percentage of the studies reaching totally, partially or not reaching the outcomes are indicated in the figure. Percentages were calculated over the totality of the studies and for the studies grouped per pathology

	Outcomes Reached		
	Totally	Partially	None
All Studies (n=71)	75%	5%	20%
Cancer (n=9)	56%	0%	44%
Hypertension / PAD (n=14)	64%	21%	14%
MetS (n=8)	88%	13%	0%
Diabetes (n=6)	100%	0%	0%
Dyslipidemia (n=4)	75%	25%	0%
Overweight / Obesity (n=19)	63%	5%	32%
Neurological (n=5)	100%	0%	0%
Others (n=6)	100%	0%	0%

pathologies. In this sense, PPLs can be considered valuable adjuvant interventions tailored to the patient.

To summarize the relevant clinical observations, PC and CRC patients consuming EGCG-rich green tea extract or other fresh fruit (i.e., pomegranate, annona) showed a decrease in circulating tumor markers and/or a down-regulation of local and systemic inflammation. Individuals suffering from hypertension, upon consumption of different sources of dietary PPLs, including those present in berries, reduced their systemic blood pressure and ameliorated their endothelial functions. Following PPLs usage (from berries, leaves extracts, green tea), subjects with metabolic syndrome features (including diabetes, dyslipidemia, obesity) exhibited a decrease of relevant parameters, such as improved insulin fasting, glucose and lipid metabolism, amelioration of lipidemic profile. Also, especially the daily intake of EGCG from green tea improved bones health in postmenopausal women with osteoporosis, contrasted inflammatory bowel in individuals with colitis, as well as improved cognitive functions in subjects with different neurological diseases (Table 2).

Overall, PPLs have shown a safety profile in all the clinical studies reported. However, while 75% of the PPL-based intervention in subjects with NCDs demonstrated positive and significant outcomes, and another 5% reached the proposed therapeutic outcomes partially, the remaining 20% of the studies showed only trend of improvements without reaching the statistical significance (Fig. 5). This can be due either to the small size of the cohort enrolled, or to the choice of single or few doses of PPL intervention which might have fallen below the threshold of biological effectiveness. It is worth to emphasize that reviewed studies are characterized by broad heterogeneity of active principles, matrix administered, doses, treatment duration; nonetheless, based on the encouraging clinical results showed, in the future the assessment of PPLs benefits in chronic diseases through larger cohort trials might help to better characterize the efficacy of PPL-based interventions. Also, the incorporation of PPLs into vesicles or other biocompatible carriers is under study at present, and this strategy may lead to overall improved human bioactivity of PPLs, even at lower doses.

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