compounds

MDPI

Review

Polyphenols in Health and Disease: Gut Microbiota, Bioaccessibility, and Bioavailability

Joaquim Bié [1,2], Bruno Sepodes [1,3], Pedro C. B. Fernandes [4,5,6,*] and Maria H. L. Ribeiro [1,7]

1 Research Institute for Medicines (i-Med), Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal
2 Centro de Investigação e Desenvolvimento em Etnobotânica (CIDE), Namaacha, Rua da Igreja, Maputo 1100, Mozambique
3 Department of Pharmacology Sciences, Pharmacy and Health Technologies, Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal
4 iBB—Institute for Bioengineering and Biosciences, Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal
5 Associate Laboratory i4HB—Institute for Health and Bioeconomy at Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais, 1049-001 Lisboa, Portugal
6 DREAMS and Faculdade de Engenharia, Universidade Lusófona de Humanidades e Tecnologias, 1749-024 Lisboa, Portugal
7 Department of Pharmaceutical Sciences and Medicines, Faculty of Pharmacy, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal
* Correspondence: pedro.fernandes@tecnico.ulisboa.pt; Tel.: +351-218-419594

Abstract: Polyphenolic compounds (PC) are among the most abundant secondary metabolites in nature. They are widely distributed in the world and can be found in fruits, cereals, tea, coffee, and beverages. Due to their structural diversity, polyphenols have many different properties and biological effects. They are resistant to the acid of the gastric tract, and very few are hydrolysed or absorbed in the stomach. Significant portions of ingested polyphenols reach the large intestine and interact with the local bacteria, the so-called gut microbiota. Epidemiological studies confirm that moderate and prolonged intake of foods rich in polyphenols could prevent the development of cancer and chronic diseases, such as cardiovascular, neurodegenerative, type 2 diabetes, and obesity. The current work aims to provide an updated overview on the nature and occurrence of polyphenols, quantification methods, bioaccessibility and bioavailability, and impact on human health, namely through interactions with the gut microbiota.

Keywords: polyphenols; gut microbiota; bioactivity; bioavailability; flavonoids

Citation: Bié, J.; Sepodes, B.; Fernandes, P.C.B.; Ribeiro, M.H.L. Polyphenols in Health and Disease: Gut Microbiota, Bioaccessibility, and Bioavailability. *Compounds* **2023**, *3*, 40–72. https://doi.org/10.3390/compounds3010005

Academic Editor: Juan C. Mejuto

Received: 4 December 2022
Revised: 31 December 2022
Accepted: 3 January 2023
Published: 5 January 2023

1. Introduction

1.1. General Aspects on Polyphenols

Polyphenols can act as antioxidants, mainly due to the electron-donating phenolic groups in their structures. Several studies have investigated the antioxidant function of polyphenols in the prevention of oxidative stress-related cellular and extracellular damage [1–6]. Polyphenols provide a variety of functions, including antioxidant, antimicrobial, anti-inflammatory, anti-angiogenic, and anti-tumour [5,7–10]. They have been identified to display various mechanisms of action in the reduction of inflammatory responses in the human body [3,5,11–13]. In line with those properties, the use of polyphenols as an intervention for the inflammatory response, especially relating to the gut microbiome, may significantly reduce the risk of disease onset [2,14–16].

Nevertheless, the bioavailability of polyphenols is significantly lower than the bioavailability of antioxidant vitamins and pro-vitamins (vitamin E, vitamin C, and

carotenoids). It depends, among other things, on molecule dimensions, level of polymerization, presence and kind of sugar in the molecule, and on the compound hydrophobicity [17,18]. The bioavailability of many dietary polyphenols is very low, mostly excreted into faeces after being transported into the gut [2,19].

Polyphenols are known for their broad-spectrum applicability in the prevention of dreadful diseases, such as cardiovascular, neurodegeneration, and cancer [7,20,21]. Enzyme-assisted modification of dietary polyphenols may improve their bioactivity, related to the role of intestinal microbiota and bioavailability [22–24]. Further detailed insight on polyphenols will be provided in the ensuing sections of this review.

1.2. Human Gut Microbiota: Composition and Role

The gastrointestinal compartment that spans over 250–400 m^2, is colonized by an estimated amount of 10 to up to 100 trillion microorganisms, most of them bacteria, the so-called gut microbiota. This bacterial load is packed into a few dm^3 of volume; hence, it classifies among the densest ecosystems known [25–27]. It has been estimated that human gut microbiota harbours 500 to 1000 species of bacteria, along with an undetermined number of other microorganisms [28], where most bacteria belong to four bacterial phyla Firmicutes (64%), Bacteroidetes (23%), Proteobacteria (8%), and Actinobacteria (3%). Firmicutes and Bacteroidetes phyla are the majority of the gut microbiota [29–31]. Recently, a massive culturing effort led to the identification of novel 264 genomes from 1520 tapped. The data were used to generate a collection termed Culturable Genome Reference that is meant to significantly improve the knowledge on the human gut microbiome [32]. A different approach, based on metagenomic analysis combined with a phylogenetic evaluation of the (meta)genomes, resulted in the identification of 4616 bacterial and 28 archaeal species, of which 66% and 31%, respectively, were uncultured [33]. The work also provided a geographic distribution of each species. Based on the data gathered, the authors organised the data in a collection termed Unified Human Gastrointestinal Genome. Moreover, the authors assembled a huge set of full-length protein sequences predicted from the almost 3×10^5 genomes analysed, and established a catalogue named Unified Human Gastrointestinal Protein. In addition to the intrinsic findings of the work, it is envisaged that the information will be paramount in improving our knowledge relating genotypes to phenotypes in the human gut microbiome. A relatively similar methodological approach was followed by Leviatan and co-workers [34]. As a major outcome of their work, a collection termed human gut microbiome genome reference set (the WIS reference set) was generated out of ~3600 genomes that belong to 2365 genera and 628 families, of which ~300 of the genomes were from unknown microbial species, most of which belong to the *Prevotella* and *Ruminococcus* genus. The novel species novel depicted lower potential antibiotic resistances than the known species. The work further established Firmicutes as the major phylum in the human gut microbiome and Bacteroidetes as the runner-up phylum.

The composition of different bacteria present in the human gut is very diverse within the population, varies within the tract of each individual, but once established is spatially conserved, and is influenced by many factors (e.g., age, health, host genetics, origin, diet, environment), and thus it can be said that each individual has its own unique profile of microbial species [29,35–38]. Recent studies have highlighted the relevant role that early gut microbiota has in human health in the long term. Hence, it has also been established that factors related to pregnancy, e.g., gestational age, delivery mode, birth weight, feeding types, antibiotic exposure, and the maternal microbiome, impact the composition of the early life gut microbiota [39]. There is some controversy regarding the timeline evolution of the profile of the microbiota from early age to adulthood [40,41]. Yet a recent study evaluated said profile within 1 to 4 months (infancy) and 6 to 10 years (childhood) allowed us to establish that there is some consistency of gut bacterial clusters in infancy, with a predominance of *Bifidobacterium* (phylum Actinobacteria) species and strains, particularly in breast-fed infants, since this abundance is reduced in formula-fed

infants. On the other hand, the number of bacterial clusters increased in childhood. Still, these profiles were shown to be influenced by several parameters, both related to pregnancy and to extrinsic factors besides already referred breastfeeding, such as birth weight, exposure to antibiotics or mode of delivery, among others [42].

The gut microbiota is involved in the absorption and biotransformation of indigestible compounds and in the synthesis of vitamins. It also plays a key role in host resistance against colonisation by pathogenic microorganisms, maintaining the energy balance, and modulating immune functions [26,43–47]. The human gut microbiota has also been shown to influence mental health, as compounds produced by the gut microbiota may reach the brain through the blood stream. Conversely, the brain may impact the gut microbiota through neuronal and endocrine pathways [48,49].

1.3. Scope of the Review

The challenge of this review is to address the demands currently faced by polyphenols; thus, it should contribute to the knowledge and application of polyphenols in health promotion and disease prevention, as well as their impact on gut microbiota and bioavailability. The review provides an updated overview of polyphenols, their classification, their identification and quantification, their properties, and the impact of biological activities on health benefits, supported with recent illustrative examples. Details on gut microbiota and bioavailability of polyphenols are also addressed in this review.

2. Polyphenols

Polyphenolic compounds (PC) are among the most extensively studied phytochemicals. Up until now, several thousand polyphenols have been identified [50]. PC are non-nutritive, secondary metabolites widespread in the plant kingdom that have a key role in vegetable growth and survival against pathogens, predators, and ultraviolet (UV) radiation [51,52].

The health benefits of dietary polyphenols have attracted much attention, mainly due to their accessibility in our daily food intake [53,54]. Moreover, PC in foods may affect the organoleptic properties, as they can contribute to the bitterness, astringency, colour, flavour, odour, and oxidative stability of foodstuff [30,55].

There is some controversy involving the nomenclature of polyphenolic compounds [50,56,57]. In fact, they are most often defined as compounds harbouring an aromatic ring with at least one hydroxyl group. The structure can vary from simple molecules to complex polymers with a high molecular weight, hence configuring a division into different groups based on the number of phenolic rings enclosed [50,56]. On the other hand, it has been suggested that the designation of "polyphenol" should be limited to the structures showing at least two phenolic moieties, notwithstanding the number of hydroxyl groups each harbours [57] (Figure 1). PC derives from two metabolic pathways: the shikimic acid pathway, in which mainly phenylpropanoids are formed, and the acetic acid pathway, in which simple phenols are formed [58]. Most PC are formed through the shikimic acid pathways, but the combination of both pathways leads to the formation of flavonoids [59]. More recently, it has been advised that polyphenols should be defined as plant secondary metabolites developed from the shikimate-derived phenylpropanoid and/or polyketide pathways, harbouring more than one phenolic moiety, and lacking nitrogen-based functional groups in their basic structure [54,57,60]. On the other hand, according to IUPAC nomenclature, phenols must depict one hydroxyl group on a benzene ring or other arene ring [54].

PC may occur either as glycosides with different sugar units associated at different positions of the polyphenol skeleton or associated with organic acids or both. Phenolic compounds, or polyphenols, constitute one of the most numerous and widely distributed groups of substances in the plant kingdom, with more than 9000 phenolic structures currently known [61]. Accordingly, they are common and diverse constituents of foods of plant origin [62–64].

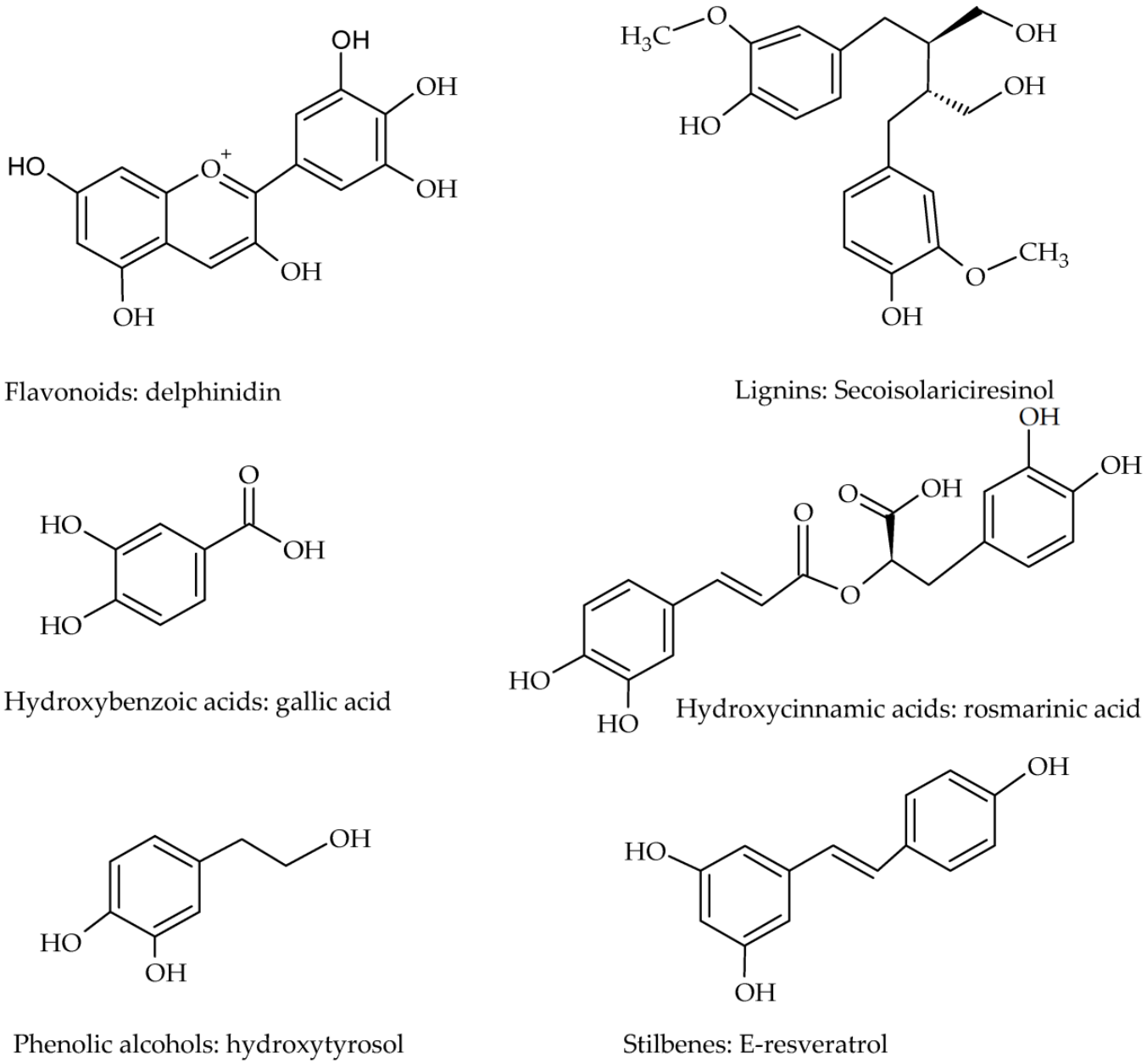

Figure 1. Basic structures of phenolic compounds.

"Polyphenol" is used to refer to flavonoids, tannins, and phenolic acids and their various chemically modified or polymerized derivatives [65].

The phenolic compounds are mainly structural components of cell walls, and most of them are toxins and antifeedants of plant defence, colouring ingredients of flowers and fruits, and antioxidants of bark and seeds [54]. The concentration of PC is influenced by many factors that include ripeness at the time of harvest, environmental factors, processing, and storage [66]. Polyphenols suppress the generation of free radicals, thus reducing the rate of oxidation by either inhibiting the formation of free radicals or deactivating the active species and precursors of free radicals [56,67]. As antioxidants, polyphenols may protect cell constituents against oxidative damage and, therefore, limit the risk of various degenerative diseases associated with oxidative stress. In fact, they have important roles in plant defence mechanisms against viruses, bacteria, fungi, and herbivores [53,68].

Polyphenols are the most abundant antioxidants in the human diet and are widespread in fruits, vegetables, cereals, olives, dry legumes, chocolate, and beverages, such as tea, coffee, and wine [68].

2.1. Classification

Polyphenols are divided into several classes according to the number of phenol rings that they contain and the structural elements that bind these rings to one another. They are classified into two main groups: flavonoids and non-flavonoids. The flavonoids can be divided into six subclasses (Figure 2): flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols [30,57,62–64,68,69]. The non-flavonoids' main subclasses are phenolic acids, lignans, and stilbenes.

The term flavonoid derives from the Latin "flavus," which means "yellow". Besides their physiological roles in plants, flavonoids have a relevant role in the human diet, where they are the most plentiful class of polyphenols, with more than 9000 different structures identified. Flavonoids are low-molecular weight compounds widely distributed in plants, especially in fruits and vegetables, although they are not considered nutrients. Accordingly, flavonoids can be found in foods and beverages such as artichokes, berries, cherries, citrus fruits, grapes, parsley, soybeans, tea, and wine, yet the richest sources are onions (up to 1.2 g/kg fresh weight) [57,66,67,70].

The carbon atoms of flavonoids are arranged in a C6–C3–C6 configuration with two aromatic rings (A and B) covalently bound to three carbon atoms, thus leading to the formation of an oxygenated heterocycle ring C (Figure 2). The vast diversity of flavonoid structures arises from the various combinations of multiple hydroxyl groups, methyl groups, glycosides, and acylated group substituents on the basic C6–C3–C6 backbone [71,72].

Flavonoids can occur in nature as glycosides, as aglycones, or as acetylated, methylated, prenylated, and sulphated derivatives. They can be ascribed to each of the six subclasses, anthocyanins, flavanols (flavan-3-ols), flavanones, flavones, flavonols, isoflavones, and according to the degree of oxidation of the central ring (ring C) and the number and position of hydroxyl groups [73–75]. Flavonoids exhibit antioxidant properties and can protect cells against oxidative damage with biological activity, depending on structural differences and glycosylation [71,76].

Isoflavones bear structural similarities to oestrogens, in particular to 17-β-oestradiol. Isoflavones depict ring B attached to ring C at the C3 position of the latter ring and exhibit hydroxyl groups in the C7 and C4' positions, akin to oestradiol. As isoflavones can bind to oestrogen receptors, they are classed as phytoestrogens. They are mostly found in legumes, e.g., chickpeas, fava beans, or soybeans. The latter is acknowledged as the most plentiful source of isoflavones, where daidzein, genistein, and glycitein, the three most important molecules of this subclass, are included. These occur mostly as glycosides through conjugation with glucose, given the heat sensibility of isoflavones. This often leads to the hydrolysis of the aglycone form during processing and storage. Given that beans are rooted in the diets of numerous cultures, isoflavones have a significant impact on human health [58,76–80].

The subclasses of flavones, flavonols, and flavanones are the most common and vastly widespread in the plant kingdom (Figure 2). Flavones and particularly their 3-hydroxy derivatives flavonols, including their glycosides and derivatives modified on all three rings, make these the largest subclasses among all polyphenols. Myricetin, kaempferol, and quercetin are among the most widespread flavonols, which are present in the skins of grapes, apples, and blueberries, among other fruits and vegetables. Over 250 glycosidic combinations have been identified for each of the two latter flavonol aglycones [45,76–78].

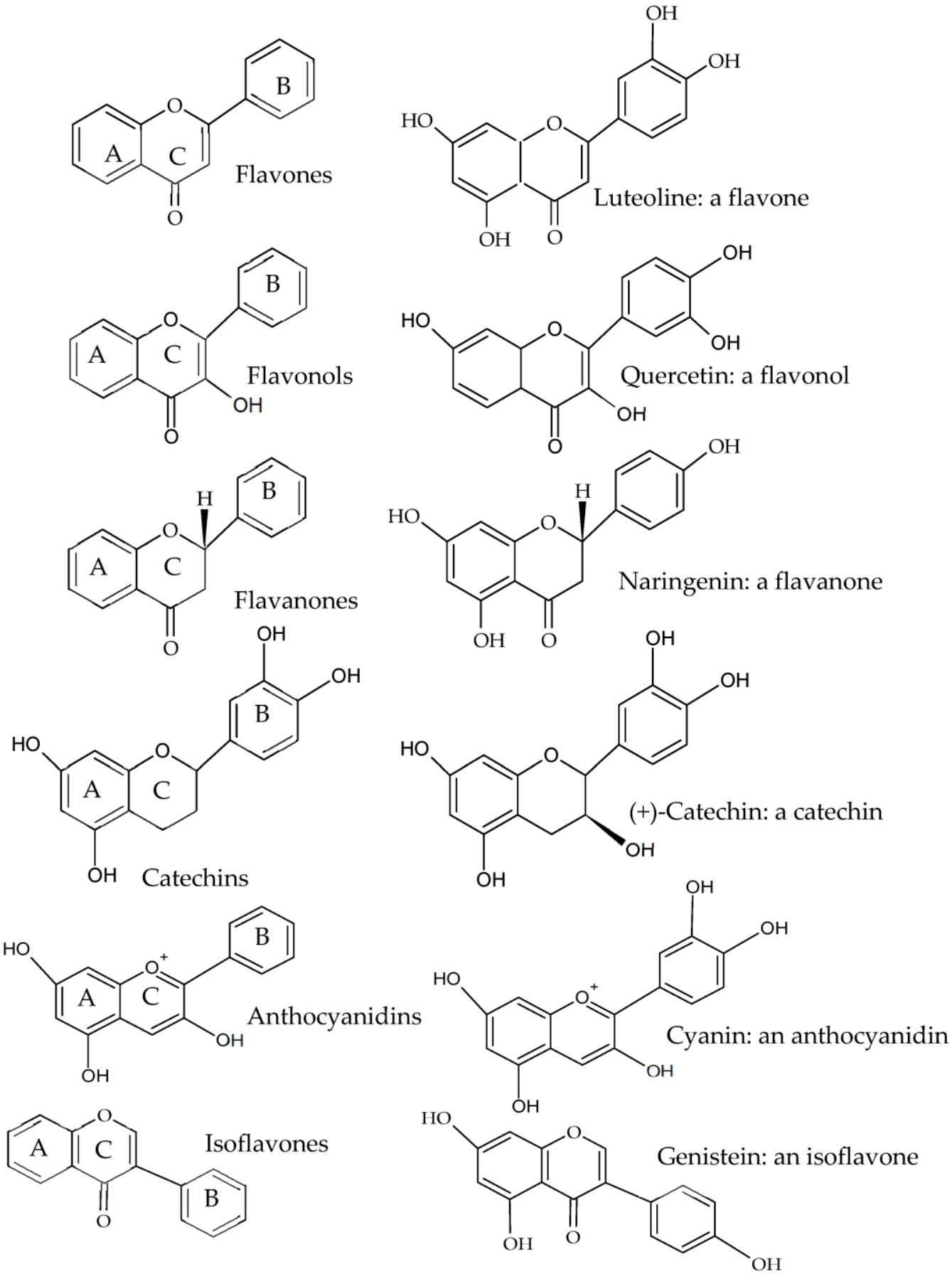

Figure 2. Subclasses of flavonoids: basic structure and a representative example.

Flavanols or flavan-3-ols, often referred to as catechins, differ from most flavonoids since they lack a double bond between C2 and C3, and a C4 carbonyl in Ring C. Combined with these features, the hydroxylation at C3 generates two chiral centres (on C2 and C3), hence four possible diastereomers [71,72,76–78].

Flavanones have a 2,3-dihydroflavone skeleton, although they lack a double bond between C2 and C3, thus conveying chirality to the former position. As an outcome, the B ring is not planar, unlike typically conjugated flavones, a feature that is supposed to influence the biological activity of flavanones. They are usually glycosylated by either a disaccharide or a glucoside at C7 to yield flavanone glycoside, and they can be found in high titres in citrus fruits, tomatoes, and some aromatic plants (e.g., mint). They contribute significantly to the daily intake of flavonoids, exceeding that of other polyphenols, and their bioavailability also surpasses that of either flavonols or flavan-3-ols [51,57,67,81].

Anthocyanidins and anthocyanins are two of the subclasses of flavonoids, where the former corresponds to the aglycone form and the latter corresponds to the glycoside form. Anthocyanidins, coloured, medium-sized molecules, are classed into 3-deoxyanthocyanidins, 3-hydroxyanthocyanidins, and O-methylated anthocyanidins, depending on the presence of hydroxy or methoxy groups bound to the ringed scaffold. Anthocyanins are often found as anthocyanidin glycosides, mostly through condensation with monosaccharides, although di- or trisaccharides may also be bound; additionally, acylated anthocyanins can also be found as an outcome of acylation with organic acids. Anthocyanins are available in several fruits and vegetables and are used as natural colourants in processed foods (red, blue, and purple pigments with low toxicity). Still, their colour is strongly influenced by structure and environmental factors, e.g., temperature, light, and pH. Most notably, anthocyanins are red in an acidic environment, yet they shift to blue or purple in an alkaline medium [71,76,82,83]. Anthocyanins have been shown to display antidiabetic, anti-inflammatory, and antimicrobial activities and to contribute to the prevention of cardiovascular and neurodegenerative diseases [83]. The health and therapeutic effects of anthocyanins are by far associated with their antioxidative activities, to which the glycosylated B-ring structure of anthocyanin strongly contributes. Anthocyanidins have higher antioxidant activity than anthocyanins, as the C-ring of the latter bears an extra sugar at C-3, opposite to the former´s single sugar [71,76,82]. However, while glycosylation decreases antioxidant activity, acylation of anthocyanins with phenolic acid has the opposite effect [71,76,82,84].

The non-flavonoid PC can be divided into two different classes of phenolic acids based on C1–C6 and C3–C6 backbones, which correspond to benzoic and cinnamic acid hydroxy derivatives, respectively, and they are often found in bound form such as amides, esters, and glycosides [85]. They have antioxidant activity as chelators and free radical scavengers, with special impact on peroxyl, hydroxyl radicals, and peroxynitrites. Hydroxybenzoic acids are mostly found bound with cell wall fractions, e.g., lignins, and to a minor extent in soluble form (conjugated with sugars or organic acids). Well-known hydroxybenzoic acids include gallic, syringic, p-hydroxybenzoic, and vanillic acids. Their titre in plants is generally low, safe for some berries and vegetables (e.g., horseradish, onions) [86]. Hydroxycinnamic acids, examples of which are caffeic acid, chlorogenic acid, coumaric acid, ferulic acid, and isoferulic acid, are found in all parts of plants; their concentration is highest in ripe fruits and vegetables. One of the most abundant hydroxycinnamic acids, chlorogenic acid, which occurs in high concentrations in coffee, is formed by the combination of caffeic and quinic acids. The bound phenolic acids can be hydrolysed by enzymes or endure acid or alkaline hydrolysis. In addition to their antioxidant role, chlorogenic acid and caffeic acid are also likely to inhibit the formation of mutagenic and carcinogenic N-nitroso compounds, therefore they are supposed to have an inhibitory effect on the N-nitrosation reaction in vitro [67,68,76].

Stilbenes are a small class of plant secondary metabolites derived from the phenylpropanoid pathway, some of which are associated with mechanisms of defence in the plant. They are found in several edible plants, e.g., some berries, grapes, and peanuts, and have a distinct structure consisting of two aromatic rings linked by an ethylene molecule. The main representative of stilbenes is resveratrol (cis and trans), which is found in high concentrations in the fresh skin of red grapes. This particular stilbene has been thoroughly studied in the last two decades, which highlighted that its intake brings health benefits due to its cardiovascular, chemopreventive, antiobesity, antidiabetic, and neuroprotective properties [67,68,87–91]. Notwithstanding, other stilbene compounds, e.g., pterostilbene, a resveratrol analogue, have been suggested to display improved neuroprotective effects as compared to resveratrol [87,92].

Lignans are plant secondary metabolites synthesised by oxidative coupling of two phenylpropane units and occur mostly in the free form, with the glycosylated form occurring sparingly; oleaginous plants, and particularly their seeds (e.g., flaxseed, sesame, linseed, and sunflower) are rich in lignans, but fibrous plants, e.g., rye, whole wheat, vegetables, and fruits are also dietary sources of lignan, albeit at minor amounts [85,93,94]. It has been shown that the gut microbiota is able to transform dietary lignans through deglycosylation and demethylation into human lignan agents such as enterodiol and enterolactone. These may act as therapeutic agents in cancer chemotherapy and neurodegenerative diseases, features that in recent years have raised major interest in lignans and synthetic derivates [57,67,95,96].

2.2. Occurrence

Natural polyphenols have been identified in a multitude of foods and plants, e.g., cereals, coffee, fruits, medicinal plants, microalgae, tea, vegetables, and wildflowers, to quote a few representative examples, to which algae, herbs and spices, and nuts can be added [52,97–102]. Some examples are given in Table 1.

Table 1. Some examples of relevant PC and related sources.

PC Class	PC Subclass	Example and Source	Reference
Flavonoids	Anthocyanins	Cyanidin/peonidin (blackberries, cranberries)	[103]
	Flavanols	Catechin, epicatechin gallate, epicatechin, epigallocatechin-3-gallate (green tea and green tea extracts)	[104]
	Flavanones	Naringenin (grapefruit), hesperetin (oranges) eriodictyol (lemons)	[105]
	Flavonols	Fisetin (strawberries, apples), rutin (green tea, apple, berries, peaches)	[106]
	Flavones	Diosmetin (vetch), tricin (rice bran)	[106]
	Isoflavones	Biochanin (red clover, soya, alfalfa sprouts, peanuts, chickpeas), daidzein (soybeans, tofu)	[106]
Non-flavonoids	Lignans	Matairesinol and secoisolariciresino (whole-grain cereals, e.g., barley, rye, and wheat)	[107]
	Phenolic acids	Caffeic acid (olives, coffee beans, fruits, potatoes, carrots), cinnamic acid (cinnamon)	[108,109]
	Stilbenes	Resveratrol (grapes, red wine)	[110]

Plant PC mostly occur in conjugated forms, where one or more sugar residues are linked to hydroxyl groups. Still, the sugar can also be bound directly to an aromatic carbon. Within sugar residues, glucose is foremost found, yet other monosaccharides, di- and oligosaccharides have also been identified. Conjugation with other compounds, e.g., acids, either carboxylic or organic, amines, and lipids, as well as binding with other phenols of occur [52,97,111].

The polyphenol composition of plants and foods is far from fully established, but consistent efforts have been made to gain detailed information and establish a database to allow for timely updates, Phenol-Explorer (http://phenol-explorer.eu/ (accessed on 5 November 2022)) [99,112,113]. Nevertheless, numerous factors, e.g., environmental factors, geographic location, ripeness at the time of harvest seasonality, and storage conditions may affect the polyphenol content of plants and foods [52,68,97,114,115].

2.3. Physical Properties

Polyphenol compounds are in part responsible for determining the sensory and nutritional characteristics of foods that contain plant components. PC display a vast diversity of physical properties depending on their structure. PC absorb strongly in the UV region of the spectrum, those coloured absorb intensely in the visible region of the spectrum. Absorption features vary depending on the PC class. Accordingly, some PCs act as pigments such as yellow (e.g., flavones, flavonols), orange (e.g., flavanones), red, blue, and purple (e.g., anthocyanins) [63,116,117]; other PC are related to food flavour (e.g., epicatechin, quercetin, resveratrol, taxifolin); and others are potent odorants, such as eugenol and vanillin, due to their volatile nature [63,118]. However, the most common flavour perceptions associated with PC are bitterness and astringency, which are often felt alongside each other, although involving different mechanisms [119], and are typically associated with condensed tannins, also termed proanthocyanidin [12,30,114,120]. Still, in a recent work involving eleven red wines and four white wines, it was reported that the total phenolic content and the polymeric tannin content displayed strong positive correlations with perceived astringency, whereas the proanthocyanidin content only showed a moderate correlation with the perceived astringency. Overall, it was suggested that polymeric flavan-3-ols are the main contributor to astringency in wines [121].

Normally PC are soluble in organic polar solvents unless they are completely glycosylated, etherified, or esterified, others are water-soluble. Typically, but not always, their solubility in water increases along with the number of hydroxyl groups [63,122].

Polyphenols are present in food both in free form and/or bound to polysaccharides and/or proteins. Notably, the intake of polyphenols present as bound compounds and their recovery in the insoluble fraction exceeds by far the proportion of free polyphenols in many foods. The content of non-extractable polyphenols (mainly hydrolysable tannins and proanthocyanidins associated with dietary fibre and proteins) in some fruits has been found to be almost ten-fold that of free polyphenols [63,115]. Structural differences between different polyphenols impact their extractability, e.g., the solubility of different polyphenols in different solvents affects the extraction efficiency and ultimately antioxidant activity, since the latter typically correlates with the titre of PC in the extracts. PC are also sensitive to temperature; hence, they may undergo unwanted reactions, e.g., Maillard reactions during processing. These matters have to be attended to throughout post-harvesting and processing and can be assessed in detail elsewhere [118,123–125].

2.4. Identification and Quantification

Different methods and techniques have been developed and implemented for the identification and quantification of polyphenols, from spectrophotometry to chromatography, capillary electrophoresis, circular dichroism, mass spectrometry, near-infrared spectroscopy (NIR), nuclear magnetic resonance (NMR), and optical rotatory dispersion. Some key advantages and limitations of key strategies for the quantification of polyphe-

nols are summarised in Table 2. Detailed insight can be found elsewhere, in reviews specifically dedicated to the analysis of PC [98,126–130].

Table 2. A brief overview on the advantages and limitations of some methods for the analysis of PC.

Technique	Advantages	Limitations
Spectrophotometry	Simple, and low-cost, can be used for the determination of the total PC titre. Colorimetric methods have been developed to estimate que titre of given classes or sub-classes of PC. Quick screening of numerous samples.	Low specificity and sensitivity.
Gas chromatography	High selectivity and specificity. Traditionally connected to an FID detector, and its connection to an MS detector vastly expands its use and eases fingerprinting profile.	Application requires volatile compounds or derivatization to improve volatility.
Thin-layer chromatography	Allows the detection and identification of multiple PC in a short analysis time.	Quantification is questionable and there is limited resolution.
High-performance liquid chromatography	The most used technique for the separation and detection of PC. Highly flexible, different types of solid and liquid phases can be used; can be connected to a vast array of detectors: e.g., UV-visible, DAD (similar to the former but enabling simultaneous measurement of multichannel absorption wavelengths), and fluorescence (limited to PC that emit fluorescence). Additionally, it is combined with tandem MS to enable high sensitivity and selectivity and eventually provides structural information.	Relatively expensive, particularly when MS is involved. Optimization of the analytical method can be time consuming.
Capillary electrophoresis	Provides a higher resolution than HPLC. Can be coupled with UV, fluorescence, amperometric, and MS detectors. Low limit of detection.	Only allows the determination of compounds that are volatile and not highly polar. Relatively new analytical technique. MS incompatibility with some types of CE.
Near infrared spectorscopy	Advanced, accurate, and non-destructive technique. Abridges visible and infrared regions (wavelength range of 780 to 2500 nm).	Relatively low dissemination. Low sensitivity and requires the development of a multivariate calibration.
Nuclear magnetic resonance	Non-destructive, high flux, and short analysis time. Easy to operate. Reproducibility and accuracy comparable to traditional chemical analysis methods.	Relatively new. Low sensitivity, unable of quantitative analysis of trace substances, and long analytical spectrum.

DAD—diode array detector; FID—flame ionization detector; and MS—mass spectrometry detector.

UV-visible spectrophotometric methods are simple, deliver results rapidly, and enables extreme parallelization, hence simultaneous evaluation of multiple samples. Therefore, they are vastly used [98]. Among these methods, the Folin–Ciocalteu assay is one of the most popular for the quantification of different classes of PC and to assess total phenolic content [131–134]. It is considered particularly suitable if gallic acid is used as a standard [135]. Although cheap and simple, Folin–Ciocalteu may overestimate PC titre as some chemicals involved in the formulation may react with compounds other than PC. Moreover, it does not allow the accurate estimation of a given PC titre without a separation method [98,136].

Hence, more specific and necessarily more complex analytical methods have been introduced, mostly relying in liquid chromatography [98,137], coupled to UV-detection and fluorescence detection in sequence for the estimation of stilbenes in grape juices [138]; fluorescence detection and UV-detection for the determination of different PC in paprika samples [139] and in apples [140], respectively; and diode array detection (DAD) for the determination of catechins, flavonoids, and phenolic acids [141], and tandem mass spectrometry [136,142], e.g., for the determination of trace and micro PC such as phenolic acids and lignans [143]. The latter detection method additionally provides structural information regarding unknown compounds. Liquid chromatography, however, often requires large volumes of solvents and lengthy separation times [144]. Thin-layer chromatography (TLC) methods, which are less complex and costly than liquid chromatography, have also been reported and enabled the simultaneous detection of several PCs in a short timeframe [98]. Gas chromatography (GC) has also been used for the quantification of PC, namely anthocyanins, flavonoids, phenolic acids, and tannins [98,126]. A major limitation of this technique is the low volatility of most PC; hence, derivatization prior to analysis to produce volatile derivatives is most often required [98,145]. Traditionally, the detection was performed by a flame ionisation detector (FID) [18,146], but coupling GC to a mass spectrometer is increasingly being used on account of the high selectivity and sensitivity [98,145]. Capillary electrophoresis (CE), a high-resolution technique where ions are separated according to their electrophoretic mobility as they flow through a capillary column, has also been used for quantification of PC [144,147]. Some recent examples include coupling CE to: UV for the determination of flavonoids in honey [148]; a diode array detector (DAD) for the determination of diverse PC in carob pekmez, a molasses-like syrup [149]; and MS [150] for the determination of flavonoids in citrus fruits. The latter deemed particularly useful to broaden the range of PC that can be directly identified [18]. Still, CE has been suggested to fail to differentiate molecules with close charge-to-mass ratios [98]. Alongside these mainstream analytical techniques, NMR [151] and NIR [152] are non-destructive methods that provide structural information besides quantification and are increasingly being used. NIR comprises a wavelength range from 780 to 2526 nm. Upon receiving this type of radiation, modifications in the vibrational and rotational modes of molecules occur. Given the uniqueness of each sample, those modes and concomitant spectra are also unique, making NIR a highly sensitive and precise method. Additionally, NIR is fast, hardly requires sample preparation, it is non-invasive, enables online or inline measurements and several parameters can be detected simultaneously. Due to the large output of variables, data processing requires multivariate statistical methods. Recent examples of the application of this technique involve the combined determination of PC and assessment of their antioxidant activity [153–155]. NMR relies on the energy that nuclei with spin quantum numbers other than zero exchange under the action of a constant and alternating magnetic field. Detection is carried out at a low field, consistent with a magnetic field strength under 0.5 T. This has a lower detection accuracy than high-field NMR, typically used in the medical area, yet the cost of the equipment is much lower, therefore enabling its dissemination. Both solid and liquid samples can be processed by NMR, which can be used to simultaneously determine more than one analyte and provide vast structural information. Accordingly, this technique has proved particularly useful in the evaluation

of complex food samples [151,156]. More recently, an altogether different approach for the separation and quantification of phenolic acids and flavonoids in tea and honey was presented, which combines chemiluminescence (CL) detection with a microfluidic environment in a microchip framework. Separation was performed in a microcolumn packed with magnetic zinc-imidazole resin. The analytes eluted were detected by a CL system using acidic $KMnO_4$ as an oxidant and HCHO to enhance CL emission [157].

Metabolomics, a methodology that focuses on the qualitative and quantitative assessment of small (under 1.5 kDa) molecules and enables the comparison between samples, has been used to identify and quantify PC in foods, investigate the interaction of PC with the gastrointestinal tract, and evaluate PC role as biomarkers. Metabolomics relies on the use of analytical techniques such as NMR, electrospray ionisation-linear ion trap quadrupole-Orbitrap-mass spectrometry (ESI-LTQ-MS), high-performance liquid chromatography coupled to photodiode-array detection and electrospray ionization/ion trap mass spectrometry (HPLC-DAD-ESI-MS), ion trap with time-of-flight (IT-TOF), ultra-performance liquid chromatography-quadrupole-time of flight-mass spectrometry (UPLC-Q-TOF-MS), and gas chromatography time-of-flight mass spectrometry (GC-TOF-MS) [158,159]. In a recent example, HPLC-DAD-ESI-MS analysis enabled the identification of galloyl and caffeoyl quinic acids, ellagitannins, and ellagic acid- and flavonoid-derivatives in maqui (*Aristotelia chilensis*). Moreover, HPLC-MS analysis allowed to differentiate PC content in spring basal leaves of maqui and in vitro leaves extract, the latter missing quercetin unlike the former. The study allowed to establish maqui leaves as a sound source of PC that can ultimately be used in nutraceuticals and drugs as antioxidants, but it also allowed to define some guidelines towards the effective production of maqui leaves secondary metabolites [160]. In another recent example, ultrahigh resolution liquid chromatography orbitrap MS analysis (UHPLC-ESI-OT-MS) allowed the identification of several flavonoids and diverse phenols upon metabolite profiling of *Larrea divaricata Cav* and *L. nitida Cav* resins. The PC-rich extracts exhibited antioxidant and antibacterial activity [161]. Metabolite profiling of extracts from *Weinmannia trichosperma Cav* (Cunoniaceae) using UHPLC-ESI-OT-MS led to the identification of isoastilbin, neoisoastilbin, and neoastilbin. The titres of these flavonols were later established by HPLC, and their antioxidant activity was established. The work helped to establish the potential use of this plant as a source of valuable secondary metabolites for nutraceuticals and pharmaceutical industries [162]. Further examples, as well as detailed insight on the use of metabolomics for the identification and quantification of PC, can be found in dedicated reviews recently published [158,159,163].

Proteomics evaluates the interactions of different proteins with each other and the roles played by them within an organism [164]. Proteomics includes either two-dimensional gel-electrophoresis and isoelectric focusing (gel-based, time-consuming methods) or gel-free methods, such as time-of-flight mass spectrometry (TOF-MS), electrospray mass spectrometry (ESI-MS), and capillary electrophoresis mass spectrometry (CE-MS), and this technology has been used to gain insight on protein–PC interactions [158,159,163]. Proteomic analysis was used to establish the inhibitory effect of pentagalloyl glucose on some proteins highly expressed in neurodegenerative diseases, namely eptin-7, ataxin-2, and adenylosuccinate synthetase isozyme 2 [165]. In more recent work, proteomic analysis was used to establish a correlation between the PC expression level of peanuts and protein expression. The authors were able to observe that the overexpression of the phenylpropanoid pathway enhanced PC biosynthesis. Ultimately, the work allowed the identification of recombinant peanut lines with appealing antioxidant features [166]. Further examples and detailed insight on the use of proteomics for understanding the functional role of PC can be found in dedicated reviews recently published [158,159,163].

Proteomics and metagenomics are two of the five omics-based approaches used to study the functional activities of polyphenols, the remaining being genomics, transcriptomics, and lipidomics [167]. The whole has been termed foodomics and provides a

holistic approach in the field of food and nutrition sciences [168]. Genomics is used in the identification of polyphenol genes and thus contributes to the development of PC-rich food materials and to the evaluation of gut microbiota upon ingestion of PC [158,159].

In a recent work, genome-wide association studies (GWAS), a methodology that encompasses whole-genome resequencing of each individual in a population with high genetic diversity, enabled the identification of candidate genes for the production of several relevant PC, e.g., quercitrin, epicatechin, catechin, chlorogenic acid, and 4-O-caffeoylquinic acid, in apples. The results were envisaged to help breeders enhance the nutritional value of apples [169]. As another recent example, quantitative trait locus (QTL), a methodology that identifies the position of genes controlling quantitative traits in the genome, was used to identify the loci responsible for phenotype variance in the synthesis of phenolic compounds in Asian plum (*Prunus salicina* L.) skin and flesh. Again, the work was foreseen to assist in the development of breeding strategies towards the generation of fruit varieties with high PC titres and hence, high antioxidant activity [170]. Aiming to gain insight on the effect of quercetin on cellular functions, Atrahimovich and co-workers relied on the use of massive parallel DNA-sequencing technologies. The authors were able to establish that quercetin plays a regulatory transcription action in the expression of genes accountable for cell cycle, differentiation, and development [171]. Further examples of the use of genomics towards the elucidation of the functional activity of PC can be found elsewhere [158,159,163,172]. Transcriptomics addresses the transcription of genes in cells and transcription regulation in the cell at the RNA level and is a useful tool to understand interactions between PC and genes. As a recent example, RNA-sequencing was used during berry development to assess events related to PC accumulation that affect antioxidant capacity. Given the results, the authors suggested that the reactions underlying the modification of flavonoids, e.g., hydroxylation, methylation, and glycosylation, were noticeably activated in a specific genotype, leading to the synthesis of more biologically active flavonoid derivatives [173]. In another recent example, RNA sequencing enabled the identification of several structural and regulator genes putatively involved in the synthesis of phenolic compounds in tomato. Moreover, the authors established the key role of chalcone synthases in the control of the accumulation of phenolic compounds in tomato genotypes [174]. Further examples can be found in a recent review [163].

Lipidomics focuses on the identification of modifications in lipid metabolism and lipid-mediated signalling processes related to the regulation of cellular homeostasis [163]. A classic example involved the evaluation of the effect of supplementation of aronia-citrus PC-rich juice on lipid peroxidation markers [175]. In a more recent study, diet supplementation with PC given to a population of lactating women was shown to modulate human milk lipids [176]. Further examples of the interaction between lipidomics and PC can be found elsewhere [177]. Often, a multi-omics approach is used to study the functional activity of PC [178]. In a recent example, genomics, transcriptomics, and metabolomics were combined to provide detailed insight into chayote evolution, including aspects related to PC synthesis and profile [179]. In another recent example, transcriptomics and metabolomics were combined to identify several key metabolites, including PC, with antioxidant activities in the fruits of *Rosa roxburghii Tratt* at different developmental stages or in fruits of different genotypes and to provide insight on the mechanisms of PC synthesis [180].

3. Biological Activities of Polyphenols and Health Benefits

Oxidative stress is considered to play a pivotal role in the pathogenesis of aging and several degenerative diseases, such as atherosclerosis, cardiovascular disease, type II diabetes, and cancer. Several studies describe polyphenols as having many activities and properties, including antioxidant, anticarcinogenic, anti-inflammatory, modulators of immune system response, and protectors of the cells against free radical damage [181,182]. Body cells and tissues are continuously threatened by the damage caused by free rad-

icals and reactive oxygen species (ROS), which are produced during normal oxygen metabolism or are induced by exogenous damage. Flavonoids can act because of another mechanism, through the interaction with various enzyme systems. They have been reported to possess many useful properties, including anti-inflammatory activity, oestrogenic activity, enzyme inhibition, and antimicrobial activity [29,78]. Irrespective of their specific nature and intended role, for the biological activity of PC to be advantageously used, their structure must be preserved, and they have to be available for systemic circulation (bioavailability). The preservation of the structure strongly depends on the PC extraction and enrichment methods (e.g., classic liquid extraction, supercritical extraction, pressurised liquid extraction, membrane technology for purification) as described elsewhere [183,184], but the outcome of those treatments also impacts bioavailability, since the latter depends on the interaction with the food matrix, besides the metabolic processes mediated by the liver, intestine, and microbiota [185]. Additionally, PC metabolites produced either in vivo or in vitro may have improved biological activity [185,186]. Adequate formulations, namely through PC encapsulation [187,188] or PC conjugation [189], e.g., with gellan gum [190], and the advantageous use of synergistic effects [191–194], have been shown to increase the biological activity of PC. Despite the well-acknowledged benefits of PC in health, as neatly summarised in a recent review [7], some side effects and toxicity associated with PC consumption have also been reported [7,195,196]. These are typically associated with intakes in dosages largely exceeding what is recommended, namely in Western diets [7,195] and have been summarised as carcinogenicity/genotoxicity, the estrogenic effect of isoflavones, thyroid toxicity, interactions with pharmaceuticals, and negative nutritional effects, the latter namely through the lack of proper synergistic effects with other dietary items [7,196,197]. Specific details can be found elsewhere [7,196,197]. Still, it is highlighted that inconsistency of results in human studies are often observed, which can be ascribed to the inter-individual variability in bioavailability and bioactivity of dietary polyphenols, alongside with the heterogeneity of the populations study and the statistical approach of the studies [7,195]. Some key aspects of the impact of the biological activity of PC on human health are summarised in Table 3.

Table 3. Impact of PC biological activity in human health [97,198,199].

Antioxidant—free radical scavenging.
Anti-inflammatory—inhibition of tumour necrosis factor, modulation of enzyme activity, and impact on neurodegenerative diseases.
Anti-carcinogenic—modulation of cancer cell signalling, promotion of apoptosis.
Antidiabetic—inhibition of key enzymes that regulate glucose absorption.
Antihypertensive—decrease the oxidative sensitivity of low-density lipoproteins, increase vasodilation, and impact on cardiovascular diseases.
Anti-obesity—stimulate adipocyte apoptosis, promote lipolysis, and fat oxidation.
Antimicrobial—antibacterial activity through inactivation of efflux pump, destabilization of cytoplasmic membrane, and synergic action with antibiotics.

3.1. Antioxidant Activity

Among the notable bioactivities of PC, the antioxidant activities have been widely studied, including the scavenging of free radicals, inhibition of lipid oxidation, and reduction of hydroperoxide formation, among others. Details on the different methods to assess antioxidant activity in vitro are discussed elsewhere in a comprehensive review [200]. Transition metals can function in various oxidation processes, acting as a catalyst in the autoxidation of many biomolecules. In many cases, oxidation can be initiated by the hydroxyl radical (HO·) generated in the reaction between iron and hydrogen peroxide, known as the Fenton reaction. Metals can also generate other ROS. PC have the ability of chelating metals and controlling their prooxidant activity. Polyphenols are known to be agents that can scavenge a wide range of ROS by mechanisms that include direct scavenging of ROS, suppression of ROS formation by inhibition of

enzymes involved in their production, inducing endogenous antioxidants enzymes, regeneration of body antioxidants such as α-tocopherol and ascorbic acid, regulation of signal transduction and up-regulation or protection of cellular antioxidant defence systems. As antioxidants and anti-inflammatory agents, PC act at a local level when they act directly during passage through the gastrointestinal tract, as well as at a systemic level after their absorption [12,53,67,182,201,202]. Further details on the mechanistic action of PC as antioxidants can be found elsewhere [203].

Almost every group of flavonoids (Figure 2) can act as antioxidants. Free radicals can damage cells by lipid peroxidation, resulting in cellular membrane damage leading to swelling and eventually death. Protection mechanisms of the body include enzymes such as superoxide dismutase, catalase, and glutathione peroxidase and other non-enzymatic materials such as glutathione, ascorbic acid, and α-tocopherol. Flavonoids have an additive effect on endogenous scavenging compounds. Flavonoids are oxidised by radicals, resulting in more stable, less reactive radicals. In other words, flavonoids stabilise the ROS by reacting with the reactive compound of the radical. Some of the flavonoids can directly scavenge superoxides, whereas other flavonoids can scavenge the highly reactive oxygen-derived radical called peroxynitrite, also can chelate iron removing a causal factor for development of free radicals. Another interesting effect of flavonoids on enzyme systems is the inhibition of the metabolism of arachidonic acid [182,201]. This feature gives flavonoids anti-inflammatory and antithrombogenic properties. Selected flavonoids, namely quercetin, kaempferol, and myricetin, effectively inhibited platelet aggregation in dogs and monkeys. Several studies have been published to correlate the intake of PC through food ingestion and antioxidant activity both in vitro and in vivo, although the former largely exceeds the latter [204–206]. As an example, Zujko and Witkowska evaluated the total PC titre in different beverages (e.g., red and white wine, different teas, orange juice, beer), several types of chocolate, and several nuts and seeds (e.g., walnuts, sunflower seeds, pistachios) and determined the corresponding antioxidant potential with the ferric reducing antioxidant power (FRAP) method. It was possible to establish that in all cases the increasing PC titre resulted in increased antioxidant potential. The highest values in each class tested were observed for red wine, dark chocolate, and walnuts [207]. In another study, Lafarga and co-workers also addressed the relationship between total PC titre and antioxidant potential, using the FRAP and 2,2-diphenyl-1-picrylhydrazyl (DPPH) methods of dry and cooked pulses, e.g., lentils, faba beans, chickpeas, and soy [208]. Again, the total PC titre correlated positively with antioxidant potential with the best result being observed for faba beans. Moreover, the authors established that cooking increased total PC titre and antioxidant activity in methanolic extracts, which was attributed to cell disruption and improved extraction of polyphenols. Finally, simulated gastrointestinal digestion led to a further increase in total PC titre and antioxidant potential of the extracts evaluated, which was attributed to enhanced bioaccessibility to PC. Recently, an in vivo study demonstrated winemaking by-products from Syrah grapes, rich in anthocyanins, flavanols, flavonols, and stilbenes (Figures 1 and 2), displayed higher antioxidant activity than red wine, leading to lower very low-density lipoprotein cholesterol titres [209]. Previously, an ex vivo had demonstrated that LDL-cholesterol oxidation (ex vivo) was lower in healthy human subjects due to daily intake of daily intake of 3 g guarana seed powder containing 160 mg catechins [210]. A more recent ex vivo study showed that a nutraceutical formulation based on a polyphenolic-rich extract from winemaking by-products (Taurisolo®) displayed high oxidant power, given its action as a ROS scavenger agent. This action ultimately triggered an increase of antioxidant enzyme activities in the intracellular medium, which was tentatively related to the up-regulation of their gene expression [211]. Despite the acknowledged antioxidant role of PC, their dietary intake at high doses, e.g., through dietary supplementation, may have a deleterious effect, such as pro-oxidant activity, production of ROS and hydrogen peroxide, and oxidative stress [212]. The authors also

highlight the need for in vivo studies to corroborate information obtained in in vitro studies and rule out negative effects that are not detected in the latter.

3.2. Neurodegenerative Protective Effects

Many neurodegenerative diseases, including Alzheimer's disease, consist of damage to cellular components such as DNA, lipids, and proteins. In these conditions, oxidative stress is considered as a key regulatory factor. The oral administration of green tea polyphenols and flavonoid-related compounds has been shown to inhibit iron-induced lipid peroxide accumulation and age-related accumulation of neurotoxic lipid peroxides. Accordingly, the risk of the development of Parkinson's disease is reduced by the consumption of polyphenols in the form of green tea [213,214]. Epidemiological studies suggest that polyphenols may be effective in reversing neurodegenerative pathology and age-related declines in neurocognitive performance [35,67,215–217]. Flavonoids (Figure 2) may perform a key role in the enzyme and receptor systems of the brain, exerting significant effects on the central nervous system. Flavonoids can inhibit enzymes such as aldose reductase and phosphodiesterase and prevent neurodegenerative diseases. Preparations containing flavonoids as the main physiologically active agent have been used for centuries by physicians and lay healers as tools to tackle human disease. The release of arachidonic acid is a starting point for a general inflammatory response. Flavonoids inhibit the metabolism of arachidonic acid through the enzyme pathway, thus conveying flavonoids' anti-inflammatory and anti-thrombogenic properties [69,77,78,218,219]. The positive effects of PC (both observed and potential) in neurodegenerative diseases, including the use of PC-rich foods, have been described in a recent comprehensive review [220]. In this work, the authors highlight that the neuroprotective effect of PC can be either direct, through the action of PC that crosses the blood-brain barrier, or indirect, through PC that influence the gut microbiota. The latter rely on the two-way communication between the gut and the brain through the neural, endocrine, and immune systems, the so-called brain-gut axis, to ultimately play a neuroprotective role [220,221]. Some authors, however, suggest that care must be taken when relating the intake of PC-rich foods, e.g., walnuts with protective neurodegenerative effects [222]. Positive effects were only observed for some populations, and further studies were suggested to fully understand the mechanisms of neuroinflammation inhibition in neurodegenerative diseases. Moreover, a large number of clinical trials are needed to validate the translation of the observed effect to humans. A systematic review performed by Colizzi, using as ref. [24] studies, failed to find enough evidence that polyphenols have beneficial effects against Alzheimer's disease. The author suggested that further randomised control trials are needed for validation of the results, along with other recommendations, so that it can be conclusively stated that PC can systematically reduce the effects of Alzheimer disease [223]. Again, these conclusions highlight the need for studies abridging suitable populations, adequate control trials, and proper statistical data processing, so that generalisations can be made.

3.3. Cancer Protective Effects

PC can inhibit the metastasis of the cellular lines by different mechanisms, including the removal of carcinogenic agents, modulation of cancer cell signalling, and cell cycle progression, promotion of apoptosis, and modulation of enzymatic activities. In addition, they have anti-inflammatory effects and can modulate apoptotic processes in the vascular endothelium. PC are protective and responsible for lowering tumour growth. This type of beneficial effect was observed for various cancer sites, including the mammary glands, skin, lung, and liver, and some sites of the digestive tract such as the intestine, stomach, and mouth. Polyphenolic compounds provide chemoprevention by several identified mechanisms, such as oxidation prevention, antiproliferation, detoxification of enzymes, initiation of apoptosis or cell cycle arrest, host immune system regulation, estrogenic/antiestrogenic activity, and anti-inflammatory activity by producing alterations

in cellular signalling [67,181,215–217,224–226]. Additionally, there is increasing evidence suggesting that polyphenols are more bioavailable when considering their metabolites. In addition, this raises the question of whether host metabolites and microbial catabolites of polyphenolic compounds can retain some biological activities. In two recent reviews, the role of dietary PC in cancer management was addressed [227,228]. Some key findings are summarised in Table 4.

Table 4. Some examples of PC-rich foods in the management of different types of cancer.

Type of Cancer	Observations
Prostate cancer	Tomatoes, red wine, green tea, turmeric and pomegranate, rich in PC such as epigallocatechin gallate (EGCG) and curcumin act through the downregulation of different signal transduction pathways. Resveratrol, found in red wine and grapes inhibits dehydrotestosterone-induced progression of this type of cancer [229]. PC present in green tea, namely EGCG, suppress progression of this type of cancer through epigenetic induction of TIMP-3, an inhibitor of matrix metalloproteinases [230].
Breast cancer	Dietary intake of PC for the prevention of this type of cancer is controversial, as only high concentrations PC inhibit estrogen metabolism [231].
Lung cancer	Anthocyanin-rich haskap berry extracts were shown to decrease nitrosamine-induced DNA damage human lung epithelial cells in vitro [232].
Colorectal cancer	Djulis, a cereal crop rich in PC exhibited chemopreventive by regulating antioxidative and apoptotic pathways in rats [233]. Anthocyanins present in black raspberries and strawberries were shown to play a synergistic role in several molecular events, e.g., suppression of cytokines release, decreased oxidative stress, reduced genomic instability, and inhibiting critical pathways [234].

3.4. Antidiabetic Effects

PC have an effect on the prevention and management of type 2 diabetes. The potential of PC as antidiabetic agents may be due to its inhibitory action in the gut for glucose absorption, promotion of glucose uptake in peripheral tissue uptake, stimulation of insulin and glucagon-like peptide 1 secretion, and suppression of glucose release from liver [235,236]. Moreover, it is suggested that PC may inhibit aldose reductase, α-amylase, and α-glucosidase [235], claim that seems to be supported by recent findings [235,237,238]. Again, the antidiabetic effect of dietary polyphenols is the subject of some controversy. As reviewed in detail recently [239], some epidemiological research suggests that dietary polyphenols might control and prevent T2D, e.g., PC from grape pomace [240,241], but opposite opinions have been unveiled [239,242]. Such discrepancies have been related to major variation between different populations and measurement errors in dietary intake [239,243].

3.5. Cardiovascular Effects

Cardiovascular diseases, including coronary artery diseases, stroke, heart failure, and hypertension, are the first cause of death globally [244]. Many naturally occurring compounds and foods are promoted for the prevention of such diseases; studies have demonstrated that consumption of PC reduces the risk of major cardiovascular events. A broad range of epidemiological studies and human trials have shown that a diet rich in polyphenols, based on balanced consumption of tea, vegetables, fruits, and cocoa, increases the likelihood of cardiac safety [11,52,67,226,245–247]. For instance, epidemiological studies summarised in a meta-analysis have suggested that there was an 11% reduction in the risk of cardiovascular disease by having 3 cups of tea per

day [248,249]. In addition, it has been proposed that the antioxidant properties of polyphenols might protect vascular endothelial function against the deleterious consequences of the oxidation of low-density lipoproteins (LDLs), as oxidised LDL can impair endothelium-dependent vasorelaxation. PC play a meaningful role in reducing cardiovascular diseases through an improvement in vascular function and a modulation of inflammation [11,52,67,226,245–247].

3.6. Obesity

Numerous clinical interventions have investigated the effects of polyphenol-rich intake on anthropometric variables, namely weight, body mass index (BMI), waist circumference, and body fat mass. Clearly, clinical studies pointed towards significant beneficial effects; the studies confirmed a significant reduction in body weight, BMI, waist circumference, and body fat mass in men who took a green tea extract compared with the control group. There are several potential mechanisms whereby polyphenols may influence body weight and composition. According to the prevailing hypothesis, polyphenols enhance energy expenditure, affect sympathetic nervous system activity, and stimulate the oxidation of fat [75,250–252]. The anti-obesity role of dietary polyphenols has been reviewed recently [251,253], where the contribution of several foods is highlighted through several studies. The most significant foods for said role were: green tea extracts, rich in EGCG, epicatechin, epigallocatechin, and epicatechin-gallate; berries, rich in anthocyanins; onions, rich in quercetin; and soybeans, rich in isoflavones. In a recent work, involving the intake of PC-rich foods by Iranian women, significant negative associations were observed between: stilbenes and lignans intake and BMI; beverages containing phenolic acids and hip circumference; total polyphenols intake and weight-to-hip ratio; stilbenes intake and cholesterol level [254]. Again, it should be highlighted that some results in the literature are conflicting, and ascribe this to disparate study designs and lengths, variation of population and diversity of the dietary polyphenols used [251].

3.7. Antimicrobial Activity

Polyphenols have been demonstrated to have potential antibacterial, antifungal, and antiviral activities [75,215,218,255]. Indirectly, they affect the growth of some Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas fluorescens* [67,225,235,256]. EGCG, extracted from green tea, was shown to bind directly to the peptidoglycan from *Staphylococcus aureus*, impairing cell integrity and destroying the osmotic protection of the cell wall. Moreover, EGCG inhibited penicillinase activity [257]. Antimicrobial activity has also been ascribed to flavonoids (Figure 2), and the structures of flavonoids having properties of antifungal, antiviral, and antibacterial activity have been isolated and identified [69,77,78,218,219]. Green tea leaves, rich in EGCG, exhibited a minimum inhibitory concentration (MIC) of 125 μg/mL in the case of multidrug-resistant (MDR) *E. coli*, MDR *S. aureus* and their reference strains [258]. The antimicrobial role of green tea against MDR *E. coli* was further reinforced in a more recent work [259]. Curiously, the size of green tea particles was shown to be a key parameter for their antimicrobial activity, which was absent for those exceeding nano sizes. The authors also noticed that EGCG correlated positively with an antibacterial effect against oral microflora [260]. In another study, juices from cranberry, Japanese quince, and sea buckthorn displayed antimicrobial activity against several Gram-positive and Gram-negative bacteria, which was associated with their high content of PC. Wild rose, chokeberry, both rich in flavonoids, and elderberry juices, rich in anthocyanins, displayed activity mostly against antimicrobial activity only against Gram-positive strains tested (safe for *Enterococcus faecalis* and *Clostridium perfringens*) [261]. Studies have proven antifungal activity against pathogens, such as *Aspergillus*, *Candida*, *Cladosporium*, and *Penicillium* genera [218]. Despite the well-established antimicrobial role played by PC, due to their

structural diversity (Figure 1), the mechanisms underlying their activities have not yet been fully resolved [262].

4. Gut Microbiota and Polyphenols

Flavonoids have been shown to strongly interact with the gut microbiota [150]. Within flavonoids, the ubiquitous flavonols have been more extensively studied, with their consumption estimated at ~25 mg/d in the United States [263]. Only about 5–10% of the total flavonoids in the suggested intake of 1 g/day around the world are absorbed in the upper digestive system; the non-absorbed flavonoids interact with the gut microbiota. An outcome of such interaction is the formation of common phenolic intermediates such as phenyl propionic, phenylacetic, and benzoic acids with different levels of hydroxylation [67,264–266]. The metabolization of dietary polyphenols, hence including flavonoids, has exhibited noticeable inter-individual variability [264,265]. The individual ability to generate a specific polyphenol metabolite profile is suggestive of specific microbiota enterotypes, with enthralling implications on immune function [22,51,267,268].

Bacterial metabolism often decreases the activity of dietary compounds, yet occasionally it may improve some properties [269]. Typically, the absorption of flavonoid glycosides involves lactase phloridzin hydrolase (LPH) in the brush border of the small intestine epithelial cells that cleaves the glycoside and enables the release of the aglycone, which then migrates to the epithelial cells by passive diffusion. Another hydrolytic step is mediated by cytosolic α-glucosidase within epithelial cells, the resulting aglycone then enters the epithelial cells [35]. Glycosylated flavonoids are more available than aglycones. Flavonoids and their metabolites that are able to reach the colon interact with the gut microbiota by inhibiting the growth of some pathogens and promoting the growth of beneficial genera such as *Lactobacillus* and *Bifidobacterium* [37,77,266,268,270,271].

The positive impact of PC can also be associated with anti-inflammatory metabolites (e.g., ellagic acid) produced by the gut microbiota that contribute to decreasing the symptoms of inflammatory bowel diseases. Alongside, fatty acids are also produced, stimulating the growth of acid-forming bacteria that contribute to improving intestinal conditions. Overall, these positive aspects are suggestive of a synergy between the impacts of their metabolites on the enhancement of favourable microbial diversity, whereas pathogenic organisms and other health-threatening factors are inhibited [272–274]. Key issues on the impact of PC in gut microbiota are summarized in Table 5.

Table 5. Gut microbiota and PC: a summary of key issues [22,275].

Low level of adsorption, gut microbiota can metabolize PC, and easing their absorption and increasing bioactivity.
Modulation of microbial environment, prebiotic role, and decreased pathogen colonization in the gut.
Production of PC-related beneficial metabolites.
Polyphenols-gut microbiota interplay on brain neuromodulation and impact on neurodegenerative diseases.

5. Bioavailability of Polyphenols

The commonly accepted definition of bioavailability is the proportion of the nutrient that is digested, absorbed, and becomes available for use at the site of action. Due to the vast diversity of their chemical structures, it is difficult to estimate the total polyphenol content in foods. Moreover, besides food sources, the positive impact of phenolic compounds on health depends also on their stability and on host issues. The former relates to the raw material processing methods and nature of the matrix used for incorporation; the latter relates to the microbiota and digestive enzymes. Bioavailability varies greatly among different polyphenols. According to Shivashankara and Acharya, bioavailability can be ranked in the following order: isoflavones > flavanols > flavanones > flavonols > anthocyanins [276]. Additionally, high bioavail-

ability of polyphenols does not necessarily correlate positively with high polyphenol concentrations in food, with poor bioavailability resulting in decreased bioefficacy and health effects [17,29,65,68,112,219,277].

The level of biotransformation endured by a PC in the gastrointestinal tract is determined by two factors: one is structure-specific since the scaffold of the polyphenol will only allow for some biotransformation to be performed by intestinal enzymes and gut microbiota species; the second factor relates to the individual diversity of intestinal microbiota, for while a set of biotransformations (e.g., deglycosylations) can be performed by a wide array of gut microbial species and genera, others require particular enzymes that are only expressed by given species or strains [29,36–38,266,268,270,278]. The ubiquity of deglycosylation is relevant in food matrices, since the presence of a glucose residue in aglycones strongly reduces both the bioaccessibility and bioavailability of phytochemicals. Additionally, bioaccessibility can be compromised in some classes of polyphenols (e.g., catechins) that can form oligomers, also called proanthocyanidins [29,36,38,266,278].

The in vivo effects of PC depend on their bioaccessibility and bioavailability after ingestion, together with their concentration. Bioavailability, or the fraction of the compound that is digested, absorbed, and metabolized, depends heavily on estimates of the amount of antioxidant absorbed [246]. Bioaccessibility is commonly defined as the amount of an ingested nutrient that is available for absorption in the gut after digestion [279]. It is well established that the physical state of the food matrix is paramount in the release, mass transfer, accessibility, and biochemical stability of many food components, including PC. PC may interact with other food components in the gut by binding to macromolecules such as fibre and forming chemical complexes and colloidal structures that reduce or improve their bioavailability [36,246,266].

The aglycones can be absorbed from the small intestine. However, most polyphenols are present in food in the form of esters, glycosides, or polymers that cannot be absorbed in their native form. Instead, they must undergo hydrolysis by either intestinal enzymes or the colonic microflora prior to their absorption. Overall, gut microbiota influences the composition the bioavailability of PC and the PC influences the composition of gut microbiota. A fraction of the PC can be degraded by the gut microbiota, and simple aromatic acids are delivered as the outcome. Throughout absorption, PC are conjugated in the small intestine and in the liver, a process that includes methylation, sulfation, and glucuronidation, and ultimately increases the hydrophilicity and facilitates the urinary elimination [66,266].

The structural differences between individual compounds affect their bioavailability. Hence, polyphenols that are not absorbed in the small intestine arrive in the colon and are thus available for biotransformation by the resident microbiota [66,67]. On the other hand, passive diffusion of polyphenols into the gut wall is a relatively poor mass transfer mechanism since most polyphenols are likely too hydrophilic to penetrate the gut wall. Given that the pH of the small intestine varies within 5 to 8, the ionisation state, hence pKa, of the compound influences passive diffusion, a mechanism also affected by molecular weight and the number of hydrogen-bonding acceptor/donor [66,280–282]. Overall, it can be suggested that only PC displaying low molecular weights and an adequate hydrophobic and neutral charge are likely to be transported by passive diffusion [280,282]. Otherwise, the membrane carriers that could be involved in polyphenol absorption have not been identified. So far, the sole active transport mechanism that has been described is a Na-dependent saturable transport mechanism involved in cinnamic and ferulic acid absorption in the rat jejunum [66,283].

Since flavonoids occur predominantly as glycosides (except flavonols) of hydrophilic nature, are not well absorbed in the intestine, their bioavailability is fairly low. This low bioavailability, coupled with instability, oxidative degradation, and metabolic transformation, lower their bioactivity and limits their use as drugs or nutraceuticals. Recently, considerable attention is being given to improve flavonoids' bioavailability through microencapsulation, nano delivery systems, and microemulsions, among others. The

absorption of flavonoids' glycosides in the stomach is very poor; although possible for some flavonoids, such as quercetin and daidzein, most flavonoids resist acid hydrolyses in the stomach. Polyphenols linked to a rhamnose moiety must reach the colon and be hydrolysed by rhamnosidases of the microflora before absorption [66,267].

Prebiotics refer to a substrate that is selectively utilised by host microorganisms to confer a health benefit. Thus, it refers to compounds that are non-digested by human digestive enzymes that regulate positively the composition and activity of intestinal microbiota. The new definition of prebiotics led to an increase in the list of compounds considered prebiotics, not only the dietary fibres that were traditionally considered as prebiotics, but also many molecules, including polyphenols. Some key issues on the bioavailability of PC are summarised in Table 6.

Table 6. Some key issues on the bioavailability of PC.

Bioavailability of PC
Bioavailability is deeply influenced by the vast diversity of chemical structures of PC.
High PC titre in food does not necessarily correlate with high bioavailability.
Biotransformations promoted by the gut microbiota impact on bioavailability.
Bioavailability conditions the efficacy for the intended goal of a given PC.
Bioavailability is influenced by absorption and metabolism.

6. Conclusions

PC abridge a wide diversity of compounds that are vastly distributed in fruits cereals and beverages. They play important roles in human health, mainly the consumption of food rich in PC is related with many human health benefits, mostly due to the antioxidant activity. Several analytical methods have been developed for the identification, quantification, and evaluation of the bioactivity of PC. This has contributed to expanding the range of PC and derived metabolites currently known. It has been established that although PC are available in many diets, the health benefits depend not only on the amount and nature of PC ingested but also on its bioavailability and bioaccessibility.

The limited bioavailability of PC present in food from fruit and vegetable matrices is determined by their low bioaccessibility in the small intestine due to the physical and chemical interactions of the PCs with the indigestible polysaccharides of cell walls. The gut microbiota plays an important role in the bioavailability and bioaccessibility of PC.

Despite dedicated research efforts over the past 20 years on the impact of PC on human health, further work is required to further ascertain the usefulness of PC in the diet towards improvements in human health. The diversity of molecular structures hampers the study of PC, in particular full insight on structure-activity relationships in most pathologies; additionally, there is a scarcity of data on bioavailability and bioaccessibility. Both of these matters have been acknowledged, and further dedicated efforts are foreseen in the near future to fill this gap. Additionally, since some inconsistencies have been observed in epidemiological studies aimed to the impact of dietary polyphenols on health, standard guidelines for the statistical approach to address this matter are to be implemented. Improved methods to access oxidative damage in vivo are needed, as are those to collect data on adsorption and excretion and thus gain a clearer picture on the fate of PC and their metabolites resulting from interaction with gut microbiota. Interactions between PC and receptor molecules, namely within the treatment of diseases, need further highlighting. Recent findings on the microbiota-gut-brain-axis and the impact of PC on the microbiota suggest that PC can be the basis for therapeutics against brain degeneration. Methodologies to improve bioavailability/bioaccessibility, stability, and protection of PC against oxidative damage and unwanted metabolization as to allow formulations that enable the use of PC as drugs and/or nutraceuticals is needed. As options to overcome poor bioavailability, should this be further confirmed as a limiting step for therapeutic action, improved formulations, e.g., nanoparticle-based using smart hydrogels, and rational design of analogues to produce drugs from natural

PC are also likely approaches to be undertaken, albeit coupled with monitoring to rule out the potential toxicity of the developed formulations/molecules.

Author Contributions: All authors have substantially contributed to the conceptualization, methodology, resources, writing—original draft preparation, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by FCT—FOUNDATION FOR SCIENCE AND TECHNOLOGY, I.P., project UID/DTP/04138/2021 and UID/BIO/04565/2020.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. Annunziata, G.; Maisto, M.; Schisano, C.; Ciampaglia, R.; Daliu, P.; Narciso, V.; Tenore, G.C.; Novellino, E. Colon Bioaccessibility and Antioxidant Activity of White, Green and Black Tea Polyphenols Extract after In Vitro Simulated Gastrointestinal Digestion. *Nutrients* **2018**, *10*, 1711. [CrossRef] [PubMed]
2. Kawabata, K.; Yoshioka, Y.; Terao, J. Role of Intestinal Microbiota in the Bioavailability and Physiological Functions of Dietary Polyphenols. *Molecules* **2019**, *24*, 370. [CrossRef] [PubMed]
3. Fakhri, S.; Abbaszadeh, F.; Moradi, S.Z.; Cao, H.; Khan, H.; Xiao, J. Effects of Polyphenols on Oxidative Stress, Inflammation, and Interconnected Pathways during Spinal Cord Injury. *Oxidative Med. Cell. Longev.* **2022**, *2022*, 8100195. [CrossRef] [PubMed]
4. Rudrapal, M.; Khairnar, S.J.; Khan, J.; Bin Dukhyil, A.; Ansari, M.A.; Alomary, M.N.; Alshabrmi, F.M.; Palai, S.; Deb, P.K.; Devi, R. Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights Into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action. *Front. Pharmacol.* **2022**, *13*, 806470. [CrossRef] [PubMed]
5. Gasmi, A.; Mujawdiya, P.K.; Noor, S.; Lysiuk, R.; Darmohray, R.; Piscopo, S.; Lenchyk, L.; Antonyak, H.; Dehtiarova, K.; Shanaida, M.; et al. Polyphenols in Metabolic Diseases. *Molecules* **2022**, *27*, 6280. [CrossRef] [PubMed]
6. Kruk, J.; Aboul-Enein, B.H.; Duchnik, E.; Marchlewicz, M. Antioxidative properties of phenolic compounds and their effect on oxidative stress induced by severe physical exercise. *J. Physiol. Sci.* **2022**, *72*, 19. [CrossRef]
7. Cory, H.; Passarelli, S.; Szeto, J.; Tamez, M.; Mattei, J. The Role of Polyphenols in Human Health and Food Systems: A Mini-Review. *Front. Nutr.* **2018**, *5*, 87. [CrossRef]
8. Wang, Z.-F.; Liu, J.; Yang, Y.-A.; Zhu, H.-L. A Review: The Anti-inflammatory, Anticancer and Antibacterial Properties of Four Kinds of Licorice Flavonoids Isolated from Licorice. *Curr. Med. Chem.* **2020**, *27*, 1997–2011. [CrossRef]
9. Azeem, M.; Hanif, M.; Mahmood, K.; Ameer, N.; Chughtai, F.R.S.; Abid, U. An insight into anticancer, antioxidant, antimicrobial, antidiabetic and anti-inflammatory effects of quercetin: A review. *Polym. Bull.* **2022**, 1–22. [CrossRef]
10. Tatipamula, V.B.; Kukavica, B. Phenolic compounds as antidiabetic, anti-inflammatory, and anticancer agents and improvement of their bioavailability by liposomes. *Cell Biochem. Funct.* **2021**, *39*, 926–944. [CrossRef]
11. Tangney, C.C.; Rasmussen, H.E. Polyphenols, Inflammation, and Cardiovascular Disease. *Curr. Atheroscler. Rep.* **2013**, *15*, 324. [CrossRef]
12. Hussain, T.; Tan, B.; Yin, Y.; Blachier, F.; Tossou, M.C.; Rahu, N. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? *Oxid. Med. Cell. Longev.* **2016**, *2016*, 7432797. [CrossRef] [PubMed]
13. Yahfoufi, N.; Alsadi, N.; Jambi, M.; Matar, C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients* **2018**, *10*, 1618. [CrossRef] [PubMed]
14. Li, H.; Christman, L.M.; Li, R.; Gu, L. Synergic interactions between polyphenols and gut microbiota in mitigating inflammatory bowel diseases. *Food Funct.* **2020**, *11*, 4878–4891. [CrossRef] [PubMed]
15. Shandilya, S.; Kumar, S.; Jha, N.K.; Kesari, K.K.; Ruokolainen, J. Interplay of gut microbiota and oxidative stress: Perspective on neurodegeneration and neuroprotection. *J. Adv. Res.* **2021**, *38*, 223–244. [CrossRef]
16. Molinari, R.; Merendino, N.; Costantini, L. Polyphenols as modulators of pre-established gut microbiota dysbiosis: State-of-the-art. *Biofactors* **2021**, *48*, 255–273. [CrossRef]
17. Manach, C.; Williamson, G.; Morand, C.; Scalbert, A.; Rémésy, C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* **2005**, *81*, 230S–242S. [CrossRef]
18. Kontogianni, V.G. Chapter 8—Novel Techniques Towards the Identification of Different Classes of Polyphenols. In *Polyphenols in Plants*; Watson, R.R., Ed.; Academic Press: San Diego, CA, USA, 2014; pp. 159–185; ISBN 978-0-12-397934-6.
19. Ray, S.K.; Mukherjee, S. Evolving Interplay Between Dietary Polyphenols and Gut Microbiota—An Emerging Importance in Healthcare. *Front. Nutr.* **2021**, *8*, 634944. [CrossRef]

20. Potì, F.; Santi, D.; Spaggiari, G.; Zimetti, F.; Zanotti, I. Polyphenol Health Effects on Cardiovascular and Neurodegenerative Disorders: A Review and Meta-Analysis. *Int. J. Mol. Sci.* **2019**, *20*, 351. [CrossRef]
21. Obrenovich, M.; Li, Y.; Tayahi, M.; Reddy, V.P. Polyphenols and Small Phenolic Acids as Cellular Metabolic Regulators. *Curr. Issues Mol. Biol.* **2022**, *44*, 4152–4166. [CrossRef]
22. Rodríguez-Daza, M.C.; Pulido-Mateos, E.C.; Lupien-Meilleur, J.; Guyonnet, D.; Desjardins, Y.; Roy, D. Polyphenol-Mediated Gut Microbiota Modulation: Toward Prebiotics and Further. *Front. Nutr.* **2021**, *8*, 689456. [CrossRef] [PubMed]
23. Polia, F.; Pastor-Belda, M.; Martínez-Blázquez, A.; Horcajada, M.-N.; Tomás-Barberán, F.A.; García-Villalba, R. Technological and Biotechnological Processes To Enhance the Bioavailability of Dietary (Poly)phenols in Humans. *J. Agric. Food Chem.* **2022**, *70*, 2092–2107. [CrossRef] [PubMed]
24. Visvanathan, R.; Williamson, G. Review of factors affecting citrus polyphenol bioavailability and their importance in designing in vitro, animal, and intervention studies. *Compr. Rev. Food Sci. Food Saf.* **2022**, *21*, 4509–4545. [CrossRef] [PubMed]
25. Wekerle, H. Brain Autoimmunity and Intestinal Microbiota: 100 Trillion Game Changers. *Trends Immunol.* **2017**, *38*, 483–497. [CrossRef] [PubMed]
26. Thursby, E.; Juge, N. Introduction to the human gut microbiota. *Biochem. J.* **2017**, *474*, 1823–1836. [CrossRef]
27. Valdes, A.; Walter, J.; Segal, E.; Spector, T.D. Role of the gut microbiota in nutrition and health. *BMJ* **2018**, *361*, k2179. [CrossRef]
28. Eisenstein, M. The hunt for a healthy microbiome. *Nature* **2020**, *577*, S6–S8. [CrossRef]
29. Hogervorst Cvejić, J.; Atanacković Krstonošić, M.; Bursać, M.; Miljić, U. Chapter 7—Polyphenols. In *Nutraceutical and Functional Food Components*; Galanakis, C.M., Ed.; Academic Press: Cambridge, MA, USA, 2017; pp. 203–258, ISBN 978-0-12-805257-0.
30. Tsimogiannis, D.; Oreopoulou, V. Chapter 16—Classification of Phenolic Compounds in Plants. In *Polyphenols in Plants*, 2nd ed.; Watson, R.R., Ed.; Academic Press: Cambridge, MA, USA, 2019; pp. 263–284, ISBN 978-0-12-813768-0.
31. Falalyeyeva, T.; Chornenka, N.; Cherkasova, L.; Tsyryuk, O.; Molchek, N.; Kovalchuk, O.; Kyriachenko, Y.; Ostapchenko, L.; Kobyliak, N. Gut Microbiota Interactions With Obesity. In *Comprehensive Gut Microbiota*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 201–219.
32. Zou, Y.; Xue, W.; Luo, G.; Deng, Z.; Qin, P.; Guo, R.; Sun, H.; Xia, Y.; Liang, S.; Dai, Y.; et al. 1,520 reference genomes from cultivated human gut bacteria enable functional microbiome analyses. *Nat. Biotechnol.* **2019**, *37*, 179–185. [CrossRef]
33. Almeida, A.; Nayfach, S.; Boland, M.; Strozzi, F.; Beracochea, M.; Shi, Z.J.; Pollard, K.S.; Sakharova, E.; Parks, D.H.; Hugenholtz, P.; et al. A unified catalog of 204,938 reference genomes from the human gut microbiome. *Nat. Biotechnol.* **2020**, *39*, 105–114. [CrossRef]
34. Leviatan, S.; Shoer, S.; Rothschild, D.; Gorodetski, M.; Segal, E. An expanded reference map of the human gut microbiome reveals hundreds of previously unknown species. *Nat. Commun.* **2022**, *13*, 3863. [CrossRef]
35. Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J.P.E.; Tognolini, M.; Borges, G.; Crozier, A. Dietary (Poly)phenolics in Human Health: Structures, Bioavailability, and Evidence of Protective Effects Against Chronic Diseases. *Antioxid. Redox Signal.* **2012**, *18*, 1818–1892. [CrossRef] [PubMed]
36. Ashley, D.; Marasini, D.; Brownmiller, C.; Lee, J.A.; Carbonero, F.; Lee, S.-O. Impact of Grain Sorghum Polyphenols on Microbiota of Normal Weight and Overweight/Obese Subjects during In Vitro Fecal Fermentation. *Nutrients* **2019**, *11*, 217. [CrossRef] [PubMed]
37. Kumar Singh, A.; Cabral, C.; Kumar, R.; Ganguly, R.; Kumar Rana, H.; Gupta, A.; Rosaria Lauro, M.; Carbone, C.; Reis, F.; Pandey, A.K. Beneficial Effects of Dietary Polyphenols on Gut Microbiota and Strategies to Improve Delivery Efficiency. *Nutrients* **2019**, *11*, 2216. [CrossRef] [PubMed]
38. van Duynhoven, J.; Vaughan, E.E.; Jacobs, D.M.; Kemperman, R.A.; van Velzen, E.J.J.; Gross, G.; Roger, L.C.; Possemiers, S.; Smilde, A.K.; Doré, J.; et al. Metabolic fate of polyphenols in the human superorganism. *Proc. Natl. Acad. Sci. USA* **2010**, *108*, 4531–4538. [CrossRef]
39. Sarkar, A.; Yoo, J.Y.; Valeria Ozorio Dutra, S.; Morgan, K.H.; Groer, M. The Association between Early-Life Gut Microbiota and Long-Term Health and Diseases. *J. Clin. Med.* **2021**, *10*, 459. [CrossRef] [PubMed]
40. Yatsunenko, T.; Rey, F.E.; Manary, M.J.; Trehan, I.; Dominguez-Bello, M.G.; Contreras, M.; Magris, M.; Hidalgo, G.; Baldassano, R.N.; Anokhin, A.P.; et al. Human gut microbiome viewed across age and geography. *Nature* **2012**, *486*, 222–227. [CrossRef] [PubMed]
41. Ringel-Kulka, T.; Cheng, J.; Ringel, Y.; Salojärvi, J.; Carroll, I.; Palva, A.; De Vos, W.M.; Satokari, R. Intestinal Microbiota in Healthy U.S. Young Children and Adults—A High Throughput Microarray Analysis. *PLoS ONE* **2013**, *8*, e64315. [CrossRef]
42. Ou, Y.; Belzer, C.; Smidt, H.; de Weerth, C. Development of the gut microbiota in healthy children in the first ten years of life: Associations with internalizing and externalizing behavior. *Gut Microbes* **2022**, *14*, e2038853. [CrossRef]
43. Frazier, T.H.; DiBaise, J.K.; McClain, C.J. Gut Microbiota, Intestinal Permeability, Obesity-Induced Inflammation, and Liver Injury. *J. Parenter. Enter. Nutr.* **2011**, *35*, 14S–20S. [CrossRef]
44. Koppel, N.; Rekdal, V.M.; Balskus, E.P. Chemical transformation of xenobiotics by the human gut microbiota. *Science* **2017**, *356*, 6344. [CrossRef]
45. Khan, J.; Deb, P.; Priya, S.; Medina, K.; Devi, R.; Walode, S.; Rudrapal, M. Dietary Flavonoids: Cardioprotective Potential with Antioxidant Effects and Their Pharmacokinetic, Toxicological and Therapeutic Concerns. *Molecules* **2021**, *26*, 4021. [CrossRef] [PubMed]

46. Murota, K.; Nakamura, Y.; Uehara, M. Flavonoid metabolism: The interaction of metabolites and gut microbiota. *Biosci. Biotechnol. Biochem.* **2018**, *82*, 600–610. [CrossRef] [PubMed]
47. Sterling, K.G.; Dodd, G.K.; Alhamdi, S.; Asimenios, P.G.; Dagda, R.K.; De Meirleir, K.L.; Hudig, D.; Lombardi, V.C. Mucosal Immunity and the Gut-Microbiota-Brain-Axis in Neuroimmune Disease. *Int. J. Mol. Sci.* **2022**, *23*, 13328. [CrossRef] [PubMed]
48. Sani, G.; Manchia, M.; Simonetti, A.; Janiri, D.; Paribello, P.; Pinna, F.; Carpiniello, B. The Role of Gut Microbiota in the High-Risk Construct of Severe Mental Disorders: A Mini Review. *Front. Psychiatry* **2021**, *11*, 585769. [CrossRef]
49. Järbrink-Sehgal, E.; Andreasson, A. The gut microbiota and mental health in adults. *Curr. Opin. Neurobiol.* **2020**, *62*, 102–114. [CrossRef]
50. Stagos, D. Antioxidant Activity of Polyphenolic Plant Extracts. *Antioxidants* **2020**, *9*, 19. [CrossRef]
51. Nazzaro, F.; Fratianni, F.; de Feo, V.; Battistelli, A.; da Cruz, A.G.; Coppola, R. Chapter Two—Polyphenols, the New Frontiers of Prebiotics. In *Advances in Food and Nutrition Research*; da Cruz, A.G., Prudencio, E.S., Esmerino, E.A., da Silva, M.C., Eds.; Academic Press: Cambridge, MA, USA, 2020; Volume 94, pp. 35–89, ISBN 1043-4526.
52. Durazzo, A.; Lucarini, M.; Souto, E.B.; Cicala, C.; Caiazzo, E.; Izzo, A.A.; Novellino, E.; Santini, A. Polyphenols: A concise overview on the chemistry, occurrence, and human health. *Phytother. Res.* **2019**, *33*, 2221–2243. [CrossRef]
53. Papuc, C.; Goran, G.V.; Predescu, C.N.; Nicorescu, V.; Stefan, G. Plant Polyphenols as Antioxidant and Antibacterial Agents for Shelf-Life Extension of Meat and Meat Products: Classification, Structures, Sources, and Action Mechanisms. *Compr. Rev. Food Sci. Food Saf.* **2017**, *16*, 1243–1268. [CrossRef]
54. Zhang, L.; Han, Z.; Granato, D. Polyphenols in foods: Classification, methods of identification, and nutritional aspects in human health. *Adv. Food Nutr. Res.* **2021**, *98*, 1–33. [CrossRef]
55. Cvejić, J.; Atanacković Krstonošić, M.; Mikulić, M.; Miljić, U. Chapter 7—Polyphenols. In *Nutraceutical and Functional Food Components*, 2nd ed.; Galanakis, C.M., Ed.; Academic Press: Cambridge, MA, USA, 2022, pp. 243–312, ISBN 978-0-323-85052-0.
56. El Gharras, H. Polyphenols: Food sources, properties and applications—A review. *Int. J. Food Sci. Technol.* **2009**, *44*, 2512–2518. [CrossRef]
57. Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. Plant Polyphenols: Chemical Properties, Biological Activities, and Synthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 586–621. [CrossRef] [PubMed]
58. Zuiter, A. Proanthocyanidin: Chemistry and Biology: From Phenolic Compounds to Proanthocyanidins. In *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering*; Elsevier: Amsterdam, The Netherlands, 2014. [CrossRef]
59. Wiciński, M.; Gębalski, J.; Mazurek, E.; Podhorecka, M.; Śniegocki, M.; Szychta, P.; Sawicka, E.; Malinowski, B. The Influence of Polyphenol Compounds on Human Gastrointestinal Tract Microbiota. *Nutrients* **2020**, *12*, 350. [CrossRef]
60. Rasouli, H.; Farzaei, M.H.; Khodarahmi, R. Polyphenols and Their Benefits: A Review. *Int. J. Food Prop.* **2017**, *20*, 1700–1741. [CrossRef]
61. Fini, E.H.; Ayat, S.; Pahlavan, F. Phenolic Compounds in the Built Environment. In *Phenolic Compounds-Chemistry, Synthesis, Diversity, Non-Conventional Industrial, Pharmaceutical and Therapeutic Applications*; IntechOpen: London, UK, 2022.
62. Bravo, L. Polyphenols: Chemistry, Dietary Sources, Metabolism, and Nutritional Significance. *Nutr. Rev.* **1998**, *56*, 317–333. [CrossRef] [PubMed]
63. Belščak-Cvitanović, A.; Durgo, K.; Huđek, A.; Bačun-Družina, V.; Komes, D. Overview of polyphenols and their properties. In *Polyphenols: Properties, Recovery, and Applications*; Galanakis, C.M., Ed.; Woodhead Publishing: Sawston, UK, 2018; pp. 3–44. [CrossRef]
64. Singla, R.K.; Dubey, A.K.; Garg, A.; Sharma, R.K.; Fiorino, M.; Ameen, S.M.; Haddad, M.A.; Al-Hiary, M. Natural Polyphenols: Chemical Classification, Definition of Classes, Subcategories, and Structures. *J. AOAC Int.* **2019**, *102*, 1397–1400. [CrossRef] [PubMed]
65. Williamson, G. The role of polyphenols in modern nutrition. *Nutr. Bull.* **2017**, *42*, 226–235. [CrossRef]
66. Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C.; Jiménez, L. Polyphenols: Food sources and bioavailability. *Am. J. Clin. Nutr.* **2004**, *79*, 727–747. [CrossRef]
67. Pérez-Chabela, M.L.; Hernández-Alcántara, A.M. Chapter 8—Agroindustrial Coproducts as Sources of Novel Functional Ingredients. In *Food Processing for Increased Quality and Consumption*; Grumezescu, A.M., Holban, A.M., Eds.; Academic Press: Cambridge, MA, USA, 2018; pp. 219–250, ISBN 978-0-12-811447-6.
68. D'Archivio, M.; Filesi, C.; Di Benedetto, R.; Gargiulo, R.; Giovannini, C.; Masella, R. Polyphenols, dietary sources and bioavailability. *Ann. Ist. Super. Sanita* **2007**, *43*, 348–361.
69. Jiang, W.; Hu, M. Mutual interactions between flavonoidsand enzymatic and transporter elements responsible for flavonoiddisposition via phase II metabolic pathways. *RSC Adv.* **2012**, *2*, 7948–7963. [CrossRef]
70. Kozłowska, A.; Szostak-Węgierek, D. Flavonoids—Food Sources, Health Benefits, and Mechanisms Involved. In *Bioactive Molecules in Food*; Springer: Cham, Switzerland, 2018; pp. 1–27.
71. Kesavan, P.; Banerjee, A.; Banerjee, A.; Murugesan, R.; Marotta, F.; Pathak, S. Chapter 17—An Overview of Dietary Polyphenols and Their Therapeutic Effects. In *Polyphenols: Mechanisms of Action in Human Health and Disease*, 2nd ed.; Watson, R.R., Preedy, V.R., Zibadi, S., Eds.; Academic Press: Cambridge, MA, USA, 2018; pp. 221–235, ISBN 978-0-12-813006-3.
72. Donovan, J.L.; Manach, C.; Faulks, R.M.; Kroon, P.A. Absorption and Metabolism of Dietary Plant Secondary Metabolites. In *Plant Secondary Metabolites*; John Wiley & Sons: Hoboken, NJ, USA, 2006; pp. 303–351; ISBN 9780470988558.

73. De Rijke, E.; Out, P.; Niessen, W.M.A.; Ariese, F.; Gooijer, C.; Brinkman, U.A.T. Analytical separation and detection methods for flavonoids. *J. Chromatogr. A* **2006**, *1112*, 31–63. [CrossRef]
74. Yamagata, K. Metabolic Syndrome: Preventive Effects of Dietary Flavonoids. *Stud. Nat. Prod. Chem.* **2018**, *60*, 1–28. [CrossRef]
75. Amiot, M.J.; Riva, C.; Vinet, A. Effects of dietary polyphenols on metabolic syndrome features in humans: A systematic review. *Obes. Rev.* **2016**, *17*, 573–586. [CrossRef] [PubMed]
76. Tsao, R. Chemistry and Biochemistry of Dietary Polyphenols. *Nutrients* **2010**, *2*, 1231–1246. [CrossRef]
77. Hollman, P.; Katan, M. Absorption, metabolism and health effects of dietary flavonoids in man. *Biomed. Pharmacother.* **1997**, *51*, 305–310. [CrossRef]
78. Nijveldt, R.J.; van Nood, E.; van Hoorn, D.E.C.; Boelens, P.G.; van Norren, K.; van Leeuwen, P.A.M. Flavonoids: A review of probable mechanisms of action and potential applications. *Am. J. Clin. Nutr.* **2001**, *74*, 418–425. [CrossRef]
79. Křížová, L.; Dadáková, K.; Kasparovska, J.; Kašparovský, T. Isoflavones. *Molecules* **2019**, *24*, 1076. [CrossRef] [PubMed]
80. Herrero, M.; Plaza, M.; Cifuentes, A.; Ibáñez, E. 4.08—Extraction Techniques for the Determination of Phenolic Compounds in Food. In *Comprehensive Sampling and Sample Preparation*; Pawliszyn, J., Ed.; Academic Press: Oxford, UK, 2012; pp. 159–180, ISBN 978-0-12-381374-9.
81. Shao, Y.; Bao, J. 8—Rice Phenolics and Other Natural Products. In *Rice*, 4th ed.; Bao, J., Ed.; AACC International Press: Washington, DC, USA, 2019; pp. 221–271, ISBN 978-0-12-811508-4.
82. Khoo, H.E.; Azlan, A.; Tang, S.T.; Lim, S.M. Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food Nutr. Res.* **2017**, *61*, 1361779. [CrossRef] [PubMed]
83. Mattioli, R.; Francioso, A.; Mosca, L.; Silva, P. Anthocyanins: A Comprehensive Review of Their Chemical Properties and Health Effects on Cardiovascular and Neurodegenerative Diseases. *Molecules* **2020**, *25*, 3809. [CrossRef]
84. Mannino, G.; Gentile, C.; Ertani, A.; Serio, G.; Bertea, C. Anthocyanins: Biosynthesis, Distribution, Ecological Role, and Use of Biostimulants to Increase Their Content in Plant Foods—A Review. *Agriculture* **2021**, *11*, 212. [CrossRef]
85. Kumar, M.; Dahuja, A.; Tiwari, S.; Punia, S.; Tak, Y.; Amarowicz, R.; Bhoite, A.G.; Singh, S.; Joshi, S.; Panesar, P.S.; et al. Recent trends in extraction of plant bioactives using green technologies: A review. *Food Chem.* **2021**, *353*, 129431. [CrossRef]
86. Murkovic, M. PHENOLIC COMPOUNDS. In *Encyclopedia of Food Sciences and Nutrition*; Elsevier: Amsterdam, The Netherlands, 2003; pp. 4507–4514.
87. Reinisalo, M.; Kårlund, A.; Koskela, A.; Kaarniranta, K.; Karjalainen, R.O. Polyphenol Stilbenes: Molecular Mechanisms of Defence against Oxidative Stress and Aging-Related Diseases. *Oxidative Med. Cell. Longev.* **2015**, *2015*, 340520. [CrossRef] [PubMed]
88. El Khawand, T.; Courtois, A.; Valls, J.; Richard, T.; Krisa, S. A review of dietary stilbenes: Sources and bioavailability. *Phytochem. Rev.* **2018**, *17*, 1007–1029. [CrossRef]
89. Goufo, P.; Singh, R.K.; Cortez, I. A Reference List of Phenolic Compounds (Including Stilbenes) in Grapevine (*Vitis vinifera* L.) Roots, Woods, Canes, Stems, and Leaves. *Antioxidants* **2020**, *9*, 398. [CrossRef]
90. Arbo, B.D.; André-Miral, C.; Nasre-Nasser, R.G.; Schimith, L.E.; Santos, M.G.; Costa-Silva, D.; Muccillo-Baisch, A.L.; Hort, M.A. Resveratrol Derivatives as Potential Treatments for Alzheimer's and Parkinson's Disease. *Front. Aging Neurosci.* **2020**, *12*, 103. [CrossRef] [PubMed]
91. Benbouguerra, N.; Hornedo-Ortega, R.; Garcia, F.; El Khawand, T.; Saucier, C.; Richard, T. Stilbenes in grape berries and wine and their potential role as anti-obesity agents: A review. *Trends Food Sci. Technol.* **2021**, *112*, 362–381. [CrossRef]
92. Kim, H.; Seo, K.-H.; Yokoyama, W. Chemistry of Pterostilbene and Its Metabolic Effects. *J. Agric. Food Chem.* **2020**, *68*, 12836–12841. [CrossRef]
93. Gabriela, M.I.; Girish, G. Fruit Processing By-Products: A Rich Source for Bioactive Compounds and Value Added Products. In *Food Processing By-Products and their Utilization*; John Wiley & Sons: Hoboken, NJ, USA, 2017; pp. 11–26. [CrossRef]
94. Zálešák, F.; Bon, D.J.-Y.D.; Pospíšil, J. Lignans and Neolignans: Plant secondary metabolites as a reservoir of biologically active substances. *Pharmacol. Res.* **2019**, *146*, 104284. [CrossRef]
95. Reddy, V.P.; Aryal, P.; Robinson, S.; Rafiu, R.; Obrenovich, M.; Perry, G. Polyphenols in Alzheimer's Disease and in the Gut–Brain Axis. *Microorganisms* **2020**, *8*, 199. [CrossRef]
96. Senizza, A.; Rocchetti, G.; Mosele, J.I.; Patrone, V.; Callegari, M.L.; Morelli, L.; Lucini, L. Lignans and Gut Microbiota: An Interplay Revealing Potential Health Implications. *Molecules* **2020**, *25*, 5709. [CrossRef]
97. Li, A.-N.; Li, S.; Zhang, Y.-J.; Xu, X.-R.; Chen, Y.-M.; Li, H.-B. Resources and Biological Activities of Natural Polyphenols. *Nutrients* **2014**, *6*, 6020–6047. [CrossRef]
98. Xu, C.-C.; Wang, B.; Pu, Y.-Q.; Tao, J.-S.; Zhang, T. Advances in extraction and analysis of phenolic compounds from plant materials. *Chin. J. Nat. Med.* **2017**, *15*, 721–731. [CrossRef] [PubMed]
99. Perezjimenez, J.; Neveu, V.; Vos, F.; Scalbert, A. Identification of the 100 richest dietary sources of polyphenols: An application of the Phenol-Explorer database. *Eur. J. Clin. Nutr.* **2010**, *64*, S112–S120. [CrossRef] [PubMed]
100. Shahidi, F.; Ambigaipalan, P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects—A review. *J. Funct. Foods* **2015**, *18*, 820–897. [CrossRef]
101. Besednova, N.; Andryukov, B.; Zaporozhets, T.; Kryzhanovsky, S.; Kuznetsova, T.; Fedyanina, L.; Makarenkova, I.; Zvyagintseva, T. Algae Polyphenolic Compounds and Modern Antibacterial Strategies: Current Achievements and Immediate Prospects. *Biomedicines* **2020**, *8*, 342. [CrossRef] [PubMed]

102. Meccariello, R.; D'Angelo, S. Impact of Polyphenolic-Food on Longevity: An Elixir of Life. An Overview. *Antioxidants* **2021**, *10*, 507. [CrossRef] [PubMed]
103. Fang, J. Classification of fruits based on anthocyanin types and relevance to their health effects. *Nutrition* **2015**, *31*, 1301–1306. [CrossRef]
104. Asakura, H.; Kitahora, T. Antioxidants and Polyphenols in Inflammatory Bowel Disease: Ulcerative Colitis and Crohn Disease. In *Polyphenols: Prevention and Treatment of Human Disease*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 279–292. [CrossRef]
105. Kumar, Y.; Bhatia, A. Polyphenols and Skin Cancers. In *Polyphenols in Human Health and Disease*; Elsevier: Amsterdam, The Netherlands, 2014; pp. 643–653.
106. Panche, A.N.; Diwan, A.D.; Chandra, S.R. Flavonoids: An overview. *J. Nutr. Sci.* **2016**, *5*, e47. [CrossRef]
107. Barakat, R.; Park, C.J.; Perez, P.A.; Chiu, K.; Ko, C. Female Antiestrogens. In *Encyclopedia of Reproduction*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 740–747.
108. Espíndola, K.M.M.; Ferreira, R.G.; Narvaez, L.E.M.; Rosario, A.C.R.S.; Da Silva, A.H.M.; Silva, A.G.B.; Vieira, A.P.O.; Monteiro, M.C. Chemical and Pharmacological Aspects of Caffeic Acid and Its Activity in Hepatocarcinoma. *Front. Oncol.* **2019**, *9*, 541. [CrossRef]
109. Lee, H.-G.; Jo, Y.; Ameer, K.; Kwon, J.-H. Optimization of green extraction methods for cinnamic acid and cinnamaldehyde from Cinnamon (Cinnamomum cassia) by response surface methodology. *Food Sci. Biotechnol.* **2018**, *27*, 1607–1617. [CrossRef]
110. Kasiotis, K.M.; Pratsinis, H.; Kletsas, D.; Haroutounian, S.A. Resveratrol and related stilbenes: Their anti-aging and anti-angiogenic properties. *Food Chem. Toxicol.* **2013**, *61*, 112–120. [CrossRef]
111. Kondratyuk, T.P.; Pezzuto, J.M. Natural Product Polyphenols of Relevance to Human Health. *Pharm. Biol.* **2004**, *42*, 46–63. [CrossRef]
112. Mrduljaš, N.; Krešić, G.; Bilušić, T. Polyphenols: Food Sources and Health Benefits. In *Functional Food*; Hueda, M.C., Ed.; IntechOpen: Rijeka, Croatia, 2017; pp. 23–41. ISBN 978-953-51-3440-4.
113. Zeb, A. A comprehensive review on different classes of polyphenolic compounds present in edible oils. *Food Res. Int.* **2021**, *143*, 110312. [CrossRef] [PubMed]
114. Cutrim, C.S.; Cortez, M.A.S. A review on polyphenols: Classification, beneficial effects and their application in dairy products. *Int. J. Dairy Technol.* **2018**, *71*, 564–578. [CrossRef]
115. Visioli, F.; Alarcon-De-La-Lastra, C.; Andres-Lacueva, C.; Aviram, M.; Calhau, C.; Cassano, A.; D'Archivio, M.; Faria, A.; Favé, G.; Fogliano, V.; et al. Polyphenols and Human Health: A Prospectus. *Crit. Rev. Food Sci. Nutr.* **2011**, *51*, 524–546. [CrossRef] [PubMed]
116. Pinto, T.; Vilela, A. Healthy Drinks with Lovely Colors: Phenolic Compounds as Constituents of Functional Beverages. *Beverages* **2021**, *7*, 12. [CrossRef]
117. Stavenga, D.G.; Leertouwer, H.L.; Dudek, B.; van der Kooi, C.J. Coloration of Flowers by Flavonoids and Consequences of pH Dependent Absorption. *Front. Plant Sci.* **2021**, *11*, 600124. [CrossRef]
118. Saffarionpour, S.; Ottens, M. Recent Advances in Techniques for Flavor Recovery in Liquid Food Processing. *Food Eng. Rev.* **2017**, *10*, 81–94. [CrossRef]
119. Lee, C.B.; Lawless, H.T. Time-course of astringent sensations. *Chem. Senses* **1991**, *16*, 225–238. [CrossRef]
120. Ma, W.; Guo, A.; Zhang, Y.; Wang, H.; Liu, Y.; Li, H. A review on astringency and bitterness perception of tannins in wine. *Trends Food Sci. Technol.* **2014**, *40*, 6–19. [CrossRef]
121. Choi, K.-O.; Lee, D.; Park, S.; Im, D.; Hur, Y. Correlations Between Phenolic Composition and Perceived Astringency of Wines. *Appl. Sci.* **2020**, *10*, 8020. [CrossRef]
122. Lattanzio, V.; Kroon, P.A.; Quideau, S.; Treutter, D. Plant Phenolics– Secondary Metabolites with Diverse Functions. In *Recent Advances in Polyphenol Research*; Wiley-Blackwell: Oxford, UK; pp. 1–35.
123. Routray, W.; Orsat, V. Preparative Extraction and Separation of Phenolic Compounds. In *Natural Products*; Springer: Berlin/Heidelberg, Germany, 2013; pp. 2013–2045. [CrossRef]
124. Sridhar, A.; Ponnuchamy, M.; Kumar, P.S.; Kapoor, A.; Vo, D.-V.N.; Prabhakar, S. Techniques and modeling of polyphenol extraction from food: A review. *Environ. Chem. Lett.* **2021**, *19*, 3409–3443. [CrossRef] [PubMed]
125. Albuquerque, B.R.; Heleno, S.A.; Oliveira, M.B.P.P.; Barros, L.; Ferreira, I.C.F.R. Phenolic compounds: Current industrial applications, limitations and future challenges. *Food Funct.* **2020**, *12*, 14–29. [CrossRef] [PubMed]
126. Khoddami, A.; Wilkes, M.A.; Roberts, T.H. Techniques for Analysis of Plant Phenolic Compounds. *Molecules* **2013**, *18*, 2328–2375. [CrossRef] [PubMed]
127. Sik, B.; Székelyhidi, R.; Lakatos, E.; Kapcsándi, V.; Ajtony, Z. Analytical procedures for determination of phenolics active herbal ingredients in fortified functional foods: An overview. *Eur. Food Res. Technol.* **2021**, *248*, 329–344. [CrossRef]
128. Stalikas, C.D. Extraction, separation, and detection methods for phenolic acids and flavonoids. *J. Sep. Sci.* **2007**, *30*, 3268–3295. [CrossRef]
129. Huang, Y.; Jansen, O.; Frédérich, M.; Mouithys-Mickalad, A.; Nys, G.; Servais, A.-C.; Crommen, J.; Jiang, Z.; Fillet, M. Capillary electrophoresis, high-performance liquid chromatography, and thin-layer chromatography analyses of phenolic compounds from rapeseed plants and evaluation of their antioxidant activity. *J. Sep. Sci.* **2019**, *42*, 609–618. [CrossRef]
130. Wang, Z.-F.; You, Y.-L.; Li, F.-F.; Kong, W.-R.; Wang, S.-Q. Research Progress of NMR in Natural Product Quantification. *Molecules* **2021**, *26*, 6308. [CrossRef]

131. Sánchez-Rangel, J.C.; Benavides, J.; Heredia, J.B.; Cisneros-Zevallos, L.; Jacobo-Velázquez, D.A. The Folin–Ciocalteu assay revisited: Improvement of its specificity for total phenolic content determination. *Anal. Methods* **2013**, *5*, 5990–5999. [CrossRef]
132. Bezuneh, T.T.; Kebede, E.M. UV—Visible Spectrophotometric Quantification of Total Polyphenol in Selected Fruits. *Int. J. Nutr. Food Sci.* **2015**, *4*, 397. [CrossRef]
133. Min, K.; Freeman, C.; Kang, H.; Choi, S.-U. The Regulation by Phenolic Compounds of Soil Organic Matter Dynamics under a Changing Environment. *BioMed Res. Int.* **2015**, *2015*, 825098. [CrossRef]
134. Akomeng, N.; Adusei, S. Organic solvent extraction and spectrophotometric quantification of total phenolic content of soil. *Heliyon* **2021**, *7*, e08388. [CrossRef] [PubMed]
135. Bastola, K.P.; Guragain, Y.N.; Bhadriraju, V.; Vadlani, P.V. Evaluation of Standards and Interfering Compounds in the Determination of Phenolics by Folin-Ciocalteu Assay Method for Effective Bioprocessing of Biomass. *Am. J. Anal. Chem.* **2017**, *08*, 416–431. [CrossRef]
136. Birsan, R.I.; Wilde, P.; Waldron, K.W.; Rai, D.K. Recovery of Polyphenols from Brewer's Spent Grains. *Antioxidants* **2019**, *8*, 380. [CrossRef] [PubMed]
137. Tzima, K.; Brunton, N.; Rai, D. Qualitative and Quantitative Analysis of Polyphenols in Lamiaceae Plants—A Review. *Plants* **2018**, *7*, 25. [CrossRef] [PubMed]
138. López-Hernández, J.; De Quirós, A.R.-B. Trans-Stilbenes in Commercial Grape Juices: Quantification Using HPLC Approaches. *Int. J. Mol. Sci.* **2016**, *17*, 1769. [CrossRef]
139. Campmajó, G.; Rodríguez-Javier, L.R.; Saurina, J.; Núñez, O. Assessment of paprika geographical origin fraud by high-performance liquid chromatography with fluorescence detection (HPLC-FLD) fingerprinting. *Food Chem.* **2021**, *352*, 129397. [CrossRef]
140. Liaudanskas, M.; Viškelis, P.; Jakštas, V.; Raudonis, R.; Kviklys, D.; Milašius, A.; Janulis, V. Application of an Optimized HPLC Method for the Detection of Various Phenolic Compounds in Apples from Lithuanian Cultivars. *J. Chem.* **2014**, *2014*, 542121. [CrossRef]
141. Dimcheva, V.; Kaloyanov, N.; Karsheva, M.; Funeva-Peycheva, M.; Stoilova, N. HPLC-DAD method for simultaneous determination of natural polyphenols. *Open J. Anal. Bioanal. Chem.* **2019**, *3*, 39–43. [CrossRef]
142. López-Fernández, O.; Domínguez, R.; Pateiro, M.; Munekata, P.E.; Rocchetti, G.; Lorenzo, J.M. Determination of Polyphenols Using Liquid Chromatography–Tandem Mass Spectrometry Technique (LC–MS/MS): A Review. *Antioxidants* **2020**, *9*, 479. [CrossRef]
143. Wang, D.; Zhang, L.; Yu, L.; Ma, F.; Li, P. Simultaneous Quantification of Trace and Micro Phenolic Compounds by Liquid Chromatography Tandem-Mass Spectrometry. *Metabolites* **2021**, *11*, 589. [CrossRef]
144. Przybylska, A.; Gackowski, M.; Koba, M. Application of Capillary Electrophoresis to the Analysis of Bioactive Compounds in Herbal Raw Materials. *Molecules* **2021**, *26*, 2135. [CrossRef] [PubMed]
145. Viñas, P.; Campillo, N. Chapter 17—Gas Chromatography: Mass Spectrometry Analysis of Polyphenols in Foods. In *Polyphenols in Plants*, 2nd ed.; Watson, R.R., Ed.; Academic Press: Cambridge, MA, USA, 2019; pp. 45–58, ISBN 978-0-12-813768-0.
146. Ujowundu, F.; Ukoha, A.; Ojiako, A.; Nwaoguikpe, R. Gas Chromatographic Characterization of the Flavonoids, Alkaloids, Saponins, and Tannins Isolated from C. Dolichopentalum Leaves. *J. Chem. Pharm. Res.* **2015**, *7*, 1094–1103.
147. López-Yerena, A.; Domínguez-López, I.; Vallverdú-Queralt, A.; Pérez, M.; Jáuregui, O.; Escribano-Ferrer, E.; Lamuela-Raventós, R. Metabolomics Technologies for the Identification and Quantification of Dietary Phenolic Compound Metabolites: An Overview. *Antioxidants* **2021**, *10*, 846. [CrossRef] [PubMed]
148. Tu, J.-Q.; Zhang, Z.-Y.; Cui, C.-X.; Yang, M.; Li, Y.; Zhang, Y.-P. Fast Separation and Determination of Flavonoids in Honey Samples by Capillary Zone Electrophoresis. *Kem. Ind.* **2017**, *66*, 129–134. [CrossRef]
149. Şanlı, S.; Güneşer, O.; Kılıçarslan, S.; Şanlı, N. Screening of eighteen polyphenolic compounds in different carob pekmez by green capillary electrophoresis method. *SN Appl. Sci.* **2020**, *2*, 576. [CrossRef]
150. Zhen, X.-T.; Zhu, S.-C.; Shi, M.-Z.; Yu, Y.-L.; Yan, T.-C.; Yue, Z.-X.; Gu, Y.-X.; Zheng, H.; Cao, J. Analysis of flavonoids in citrus fruits by capillary zone electrophoresis coupled with quadrupole time-of-flight mass spectrometry using chemometrics. *J. Food Compos. Anal.* **2021**, *106*, 104275. [CrossRef]
151. Cao, R.; Liu, X.; Liu, Y.; Zhai, X.; Cao, T.; Wang, A.; Qiu, J. Applications of nuclear magnetic resonance spectroscopy to the evaluation of complex food constituents. *Food Chem.* **2021**, *342*, 128258. [CrossRef]
152. Bittner, L.K.; Schonbichler, S.A.; Bonn, G.K.; Huck, C. Near Infrared Spectroscopy (NIRS) as a Tool to Analyze Phenolic Compounds in Plants. *Curr. Anal. Chem.* **2013**, *9*, 417–423. [CrossRef]
153. Xia, F.; Li, C.; Zhao, N.; Li, H.; Chang, Q.; Liu, X.; Liao, Y.; Pan, R. Rapid Determination of Active Compounds and Antioxidant Activity of Okra Seeds Using Fourier Transform Near Infrared (FT-NIR) Spectroscopy. *Molecules* **2018**, *23*, 550. [CrossRef]
154. Alfieri, M.; Cabassi, G.; Habyarimana, E.; Quaranta, F.; Balconi, C.; Redaelli, R. Discrimination and prediction of polyphenolic compounds and total antioxidant capacity in sorghum grains. *J. Near Infrared Spectrosc.* **2019**, *27*, 46–53. [CrossRef]
155. de Lima, A.B.S.; Batista, A.S.; Santos, M.R.C.; Rocha, R.D.S.D.; da Silva, M.V.; Ferrão, S.P.B.; de Almeida, V.V.S.; Santos, L.S. Spectroscopy NIR and MIR toward predicting simultaneous phenolic contents and antioxidant in red propolis by multivariate analysis. *Food Chem.* **2021**, *367*, 130744. [CrossRef] [PubMed]

156. Olmo-Cunillera, A.; López-Yerena, A.; Lozano-Castellón, J.; Tresserra-Rimbau, A.; Vallverdú-Queralt, A.; Pérez, M. NMR spectroscopy: A powerful tool for the analysis of polyphenols in extra virgin olive oil. *J. Sci. Food Agric.* **2020**, *100*, 1842–1851. [CrossRef] [PubMed]
157. Bagheri, N.; Al Lawati, H.A.; Hassanzadeh, J. Simultaneous determination of total phenolic acids and total flavonoids in tea and honey samples using an integrated lab on a chip device. *Food Chem.* **2020**, *342*, 128338. [CrossRef] [PubMed]
158. Si, W.; Zhang, Y.; Li, X.; Du, Y.; Xu, Q. Understanding the Functional Activity of Polyphenols Using Omics-Based Approaches. *Nutrients* **2021**, *13*, 3953. [CrossRef]
159. Zhang, W.; Qi, S.; Xue, X.; Al Naggar, Y.; Wu, L.; Wang, K. Understanding the Gastrointestinal Protective Effects of Polyphenols using Foodomics-Based Approaches. *Front. Immunol.* **2021**, *12*, 671150. [CrossRef]
160. Crisóstomo-Ayala, K.A.; Sabater-Jara, A.B.; Manriquez, C.P.; Ferreres, F.; Gil-Izquierdo, Á.; Pedreño, M.Á.; de la Torre, M.H.; Sanchez-Olate, M.; Leal, D.G.R. Comparative Study of Metabolomic Profile and Antioxidant Content of Adult and In Vitro Leaves of *Aristotelia chilensis*. *Plants* **2022**, *11*, 37. [CrossRef]
161. Gómez, J.; Simirgiotis, M.; Manrique, S.; Piñeiro, M.; Lima, B.; Bórquez, J.; Feresin, G.; Tapia, A. UHPLC-ESI-OT-MS Phenolics Profiling, Free Radical Scavenging, Antibacterial and Nematicidal Activities of "Yellow-Brown Resins" from *Larrea* spp. *Antioxidants* **2021**, *10*, 185. [CrossRef]
162. Barrientos, R.E.; Fernández-Galleguillos, C.; Pastene, E.; Simirgiotis, M.; Romero-Parra, J.; Ahmed, S.; Echeverría, J. Metabolomic Analysis, Fast Isolation of Phenolic Compounds, and Evaluation of Biological Activities of the Bark From *Weinmannia trichosperma* Cav. (Cunoniaceae). *Front. Pharmacol.* **2020**, *11*, 780. [CrossRef]
163. Yan, S.; Bhawal, R.; Yin, Z.; Thannhauser, T.W.; Zhang, S. Recent advances in proteomics and metabolomics in plants. *Mol. Hortic.* **2022**, *2*, 17. [CrossRef]
164. Aslam, B.; Basit, M.; Nisar, M.A.; Khurshid, M.; Rasool, M.H. Proteomics: Technologies and Their Applications. *J. Chromatogr. Sci.* **2017**, *55*, 182–196. [CrossRef]
165. Mendonca, P.; Taka, E.; Soliman, K.F.A. Proteomic analysis of the effect of the polyphenol pentagalloyl glucose on proteins involved in neurodegenerative diseases in activated BV-2 microglial cells. *Mol. Med. Rep.* **2019**, *20*, 1736–1746. [CrossRef] [PubMed]
166. Muralidharan, S.; Poon, Y.Y.; Wright, G.C.; Haynes, P.A.; Lee, N.A. Quantitative proteomics analysis of high and low polyphenol expressing recombinant inbred lines (RILs) of peanut (*Arachis hypogaea* L.). *Food Chem.* **2021**, *334*, 127517. [CrossRef] [PubMed]
167. Yang, F.; Xie, C.; Li, J.; Ma, R.; Dang, Z.; Wang, C.; Wang, T. Foodomics technology: Promising analytical methods of functional activities of plant polyphenols. *Eur. Food Res. Technol.* **2021**, *247*, 2129–2142. [CrossRef]
168. Xu, Y.-J. Foodomics: A novel approach for food microbiology. *TrAC Trends Anal. Chem.* **2017**, *96*, 14–21. [CrossRef]
169. McClure, K.A.; Gong, Y.; Song, J.; Vinqvist-Tymchuk, M.; Palmer, L.C.; Fan, L.; Burgher-MacLellan, K.; Zhang, Z.; Celton, J.-M.; Forney, C.F.; et al. Genome-wide association studies in apple reveal loci of large effect controlling apple polyphenols. *Hortic. Res.* **2019**, *6*, 107. [CrossRef]
170. Valderrama-Soto, D.; Salazar, J.; Sepúlveda-González, A.; Silva-Andrade, C.; Gardana, C.; Morales, H.; Battistoni, B.; Jiménez-Muñoz, P.; González, M.; Peña-Neira, Á.; et al. Detection of Quantitative Trait Loci Controlling the Content of Phenolic Compounds in an Asian Plum (*Prunus salicina* L.) F1 Population. *Front. Plant Sci.* **2021**, *12*, 679059. [CrossRef]
171. Atrahimovich, D.; Samson, A.O.; Barsheshet, Y.; Vaya, J.; Khatib, S.; Reuveni, E. Genome-wide localization of the polyphenol quercetin in human monocytes. *BMC Genom.* **2019**, *20*, 606. [CrossRef]
172. Sorrenti, V.; Fortinguerra, S.; Caudullo, G.; Buriani, A. Deciphering the Role of Polyphenols in Sports Performance: From Nutritional Genomics to the Gut Microbiota toward Phytonutritional Epigenomics. *Nutrients* **2020**, *12*, 1265. [CrossRef]
173. Ismail, A.; Darwish, A.G.; Park, M.; Gajjar, P.; Tsolova, V.; Soliman, K.F.A.; El-Sharkawy, I. Transcriptome Profiling During Muscadine Berry Development Reveals the Dynamic of Polyphenols Metabolism. *Front. Plant Sci.* **2022**, *12*, 818071. [CrossRef]
174. Sacco, A.; Raiola, A.; Calafiore, R.; Barone, A.; Rigano, M.M. New insights in the control of antioxidants accumulation in tomato by transcriptomic analyses of genotypes exhibiting contrasting levels of fruit metabolites. *BMC Genom.* **2019**, *20*, 43. [CrossRef]
175. García-Flores, L.A.; Medina, S.; Oger, C.; Galano, J.-M.; Durand, T.; Cejuela, R.; Martínez-Sanz, J.M.; Ferreres, F.; Gil-Izquierdo, Á. Lipidomic approach in young adult triathletes: Effect of supplementation with a polyphenols-rich juice on neuroprostane and F_2-dihomo-isoprostane markers. *Food Funct.* **2016**, *7*, 4343–4355. [CrossRef] [PubMed]
176. Miranda, A.R.; Cortez, M.V.; Scotta, A.V.; Soria, E.A. Dietary Intake of Polyphenols Enhances Executive/Attentional Functioning and Memory with an Improvement of the Milk Lipid Profile of Postpartum Women from Argentina. *J. Intell.* **2022**, *10*, 33. [CrossRef]
177. Reis, A.; de Freitas, V. When polyphenols meet lipids: Challenges in membrane biophysics and opportunities in epithelial lipidomics. *Food Chem.* **2020**, *333*, 127509. [CrossRef] [PubMed]
178. Li, J.; Wang, Y.; Suh, J.H. Multi-omics approach in tea polyphenol research regarding tea plant growth, development and tea processing: Current technologies and perspectives. *Food Sci. Hum. Wellness* **2022**, *11*, 524–536. [CrossRef]
179. Fu, A.; Wang, Q.; Mu, J.; Ma, L.; Wen, C.; Zhao, X.; Gao, L.; Li, J.; Shi, K.; Wang, Y.; et al. Combined genomic, transcriptomic, and metabolomic analyses provide insights into chayote (Sechium edule) evolution and fruit development. *Hortic. Res.* **2021**, *8*, 35. [CrossRef] [PubMed]

180. Li, N.; Jiang, L.; Liu, Y.; Zou, S.; Lu, M.; An, H. Metabolomics Combined with Transcriptomics Analysis Revealed the Amino Acids, Phenolic Acids, and Flavonol Derivatives Biosynthesis Network in Developing *Rosa roxburghii* Fruit. *Foods* **2022**, *11*, 1639. [CrossRef]
181. Niedzwiecki, A.; Roomi, M.W.; Kalinovsky, T.; Rath, M. Anticancer Efficacy of Polyphenols and Their Combinations. *Nutrients* **2016**, *8*, 552. [CrossRef]
182. Chandrasekara, A.; Shahidi, F. Bioaccessibility and antioxidant potential of millet grain phenolics as affected by simulated in vitro digestion and microbial fermentation. *J. Funct. Foods* **2012**, *4*, 226–237. [CrossRef]
183. Debelo, H.; Li, M.; Ferruzzi, M.G. Processing influences on food polyphenol profiles and biological activity. *Curr. Opin. Food Sci.* **2020**, *32*, 90–102. [CrossRef]
184. Kelly, N.; Kelly, A.; O'Mahony, J. Strategies for enrichment and purification of polyphenols from fruit-based materials. *Trends Food Sci. Technol.* **2019**, *83*, 248–258. [CrossRef]
185. Di Lorenzo, C.; Colombo, F.; Biella, S.; Stockley, C.; Restani, P. Polyphenols and Human Health: The Role of Bioavailability. *Nutrients* **2021**, *13*, 273. [CrossRef] [PubMed]
186. Castro, P.; Mendoza, L.; Vásquez, C.; Pereira, P.C.; Navarro, F.; Lizama, K.; Santander, R.; Cotoras, M. Antifungal Activity against Botrytis cinerea of 2,6-Dimethoxy-4-(phenylimino)cyclohexa-2,5-dienone Derivatives. *Molecules* **2019**, *24*, 706. [CrossRef] [PubMed]
187. Munin, A.; Edwards-Lévy, F. Encapsulation of Natural Polyphenolic Compounds; a Review. *Pharmaceutics* **2011**, *3*, 793–829. [CrossRef] [PubMed]
188. Zhang, L.; McClements, D.J.; Wei, Z.; Wang, G.; Liu, X.; Liu, F. Delivery of synergistic polyphenol combinations using biopolymer-based systems: Advances in physicochemical properties, stability and bioavailability. *Crit. Rev. Food Sci. Nutr.* **2019**, *60*, 2083–2097. [CrossRef]
189. Cirillo, G.; Curcio, M.; Vittorio, O.; Iemma, F.; Restuccia, D.; Spizzirri, U.G.; Puoci, F.; Picci, N. Polyphenol Conjugates and Human Health: A Perspective Review. *Crit. Rev. Food Sci. Nutr.* **2013**, *56*, 326–337. [CrossRef]
190. Mundlia, J.; Ahuja, M.; Kumar, P. Enhanced biological activity of polyphenols on conjugation with gellan gum. *Int. J. Polym. Mater. Polym. Biomater.* **2020**, *70*, 712–729. [CrossRef]
191. Paluch, E.; Okińczyc, P.; Zwyrzykowska-Wodzińska, A.; Szperlik, J.; Żarowska, B.; Duda-Madej, A.; Bąbelewski, P.; Włodarczyk, M.; Wojtasik, W.; Kupczyński, R.; et al. Composition and Antimicrobial Activity of *Ilex* Leaves Water Extracts. *Molecules* **2021**, *26*, 7442. [CrossRef]
192. Mitra, S.; Tareq, A.M.; Das, R.; Bin Emran, T.; Nainu, F.; Chakraborty, A.J.; Ahmad, I.; Tallei, T.E.; Idris, A.M.; Simal-Gandara, J. Polyphenols: A first evidence in the synergism and bioactivities. *Food Rev. Int.* **2022**, 1–23. [CrossRef]
193. Ramata-Stunda, A.; Petriņa, Z.; Valkovska, V.; Borodušķis, M.; Gibnere, L.; Gurkovska, E.; Nikolajeva, V. Synergistic Effect of Polyphenol-Rich Complex of Plant and Green Propolis Extracts with Antibiotics against Respiratory Infections Causing Bacteria. *Antibiotics* **2022**, *11*, 160. [CrossRef]
194. Skroza, D.; Šimat, V.; Vrdoljak, L.; Jolić, N.; Skelin, A.; Čagalj, M.; Frleta, R.; Mekinić, I.G. Investigation of Antioxidant Synergisms and Antagonisms among Phenolic Acids in the Model Matrices Using FRAP and ORAC Methods. *Antioxidants* **2022**, *11*, 1784. [CrossRef]
195. Ruskovska, T.; Maksimova, V.; Milenkovic, D. Polyphenols in human nutrition: From the in vitro antioxidant capacity to the beneficial effects on cardiometabolic health and related inter-individual variability—An overview and perspective. *Br. J. Nutr.* **2020**, *123*, 241–254. [CrossRef] [PubMed]
196. Mennen, L.I.; Walker, R.; Bennetau-Pelissero, C.; Scalbert, A. Risks and safety of polyphenol consumption. *Am. J. Clin. Nutr.* **2005**, *81*, 326S–329S. [CrossRef] [PubMed]
197. Rojo, M.; Garrosa, M.; Jiménez, P.; Girbés, T.; Garcia-Recio, V.; Cordoba-Diaz, M.; Cordoba-Diaz, D. Unexpected Toxicity of Green Tea Polyphenols in Combination with the *Sambucus* RIL Ebulin. *Toxins* **2020**, *12*, 542. [CrossRef] [PubMed]
198. Zhang, Z.; Li, X.; Sang, S.; McClements, D.J.; Chen, L.; Long, J.; Jiao, A.; Jin, Z.; Qiu, C. Polyphenols as Plant-Based Nutraceuticals: Health Effects, Encapsulation, Nano-Delivery, and Application. *Foods* **2022**, *11*, 2189. [CrossRef]
199. Xie, Y.; Chen, J.; Xiao, A.; Liu, L. Antibacterial Activity of Polyphenols: Structure-Activity Relationship and Influence of Hyperglycemic Condition. *Molecules* **2017**, *22*, 1913. [CrossRef]
200. Miguel-Chávez, R.S. Phenolic Antioxidant Capacity: A Review of the State of the Art. *Phenolic Compd.-Biol. Act.* **2017**, *8*, 59–74. [CrossRef]
201. Zhou, Z.-Q.; Xiao, J.; Fan, H.-X.; Yu, Y.; He, R.-R.; Feng, X.-L.; Kurihara, H.; So, K.-F.; Yao, X.-S.; Gao, H. Polyphenols from wolfberry and their bioactivities. *Food Chem.* **2016**, *214*, 644–654. [CrossRef]
202. Faller, A.; Fialho, E. Polyphenol content and antioxidant capacity in organic and conventional plant foods. *J. Food Compos. Anal.* **2010**, *23*, 561–568. [CrossRef]
203. Costa, M.; Sezgin-Bayindir, Z.; Losada-Barreiro, S.; Paiva-Martins, F.; Saso, L.; Bravo-Díaz, C. Polyphenols as Antioxidants for Extending Food Shelf-Life and in the Prevention of Health Diseases: Encapsulation and Interfacial Phenomena. *Biomedicines* **2021**, *9*, 1909. [CrossRef]
204. Martins, N.; Barros, L.; Ferreira, I.C. In vivo antioxidant activity of phenolic compounds: Facts and gaps. *Trends Food Sci. Technol.* **2016**, *48*, 1–12. [CrossRef]

205. Fernandez-Panchon, M.S.; Villano, D.; Troncoso, A.M.; Garcia-Parrilla, M.C. Antioxidant Activity of Phenolic Compounds: From In Vitro Results to In Vivo Evidence. *Crit. Rev. Food Sci. Nutr.* **2008**, *48*, 649–671. [CrossRef] [PubMed]
206. Hu, W.; Sarengaowa; Guan, Y.; Feng, K. Biosynthesis of Phenolic Compounds and Antioxidant Activity in Fresh-Cut Fruits and Vegetables. *Front. Microbiol.* **2022**, *13*, 906069. [CrossRef] [PubMed]
207. Zujko, M.E.; Witkowska, A.M. Antioxidant Potential and Polyphenol Content of Beverages, Chocolates, Nuts, and Seeds. *Int. J. Food Prop.* **2014**, *17*, 86–92. [CrossRef]
208. Lafarga, T.; Villaró, S.; Bobo, G.; Simó, J.; Aguiló-Aguayo, I. Bioaccessibility and antioxidant activity of phenolic compounds in cooked pulses. *Int. J. Food Sci. Technol.* **2019**, *54*, 1816–1823. [CrossRef]
209. de Oliveira, W.P.; Biasoto, A.C.T.; Marques, V.F.; dos Santos, I.M.; Magalhães, K.; Correa, L.C.; Negro-Dellacqua, M.; Miranda, M.S.; de Camargo, A.C.; Shahidi, F. Phenolics from Winemaking By-Products Better Decrease VLDL-Cholesterol and Triacylglycerol Levels than Those of Red Wine in Wistar Rats. *J. Food Sci.* **2017**, *82*, 2432–2437. [CrossRef] [PubMed]
210. Yonekura, L.; Martins, C.A.; Sampaio, G.R.; Monteiro, M.P.; César, L.A.M.; Mioto, B.M.; Mori, C.S.; Mendes, T.M.N.; Ribeiro, M.L.; Arçari, D.P.; et al. Bioavailability of catechins from guaraná (*Paullinia cupana*) and its effect on antioxidant enzymes and other oxidative stress markers in healthy human subjects. *Food Funct.* **2016**, *7*, 2970–2978. [CrossRef]
211. Annunziata, G.; Capó, X.; Quetglas-Llabrés, M.; Monserrat-Mesquida, M.; Tejada, S.; Tur, J.; Ciampaglia, R.; Guerra, F.; Maisto, M.; Tenore, G.; et al. Ex Vivo Study on the Antioxidant Activity of a Winemaking By-Product Polyphenolic Extract (Taurisolo®) on Human Neutrophils. *Antioxidants* **2021**, *10*, 1009. [CrossRef]
212. Granato, D.; Mocan, A.; Câmara, J.S. Is a higher ingestion of phenolic compounds the best dietary strategy? A scientific opinion on the deleterious effects of polyphenols in vivo. *Trends Food Sci. Technol.* **2020**, *98*, 162–166. [CrossRef]
213. Malar, D.S.; Prasanth, M.I.; Brimson, J.M.; Sharika, R.; Sivamaruthi, B.S.; Chaiyasut, C.; Tencomnao, T. Neuroprotective Properties of Green Tea (*Camellia sinensis*) in Parkinson's Disease: A Review. *Molecules* **2020**, *25*, 3926. [CrossRef]
214. Truong, V.-L.; Jeong, W.-S. Cellular Defensive Mechanisms of Tea Polyphenols: Structure-Activity Relationship. *Int. J. Mol. Sci.* **2021**, *22*, 9109. [CrossRef]
215. Mutha, R.E.; Tatiya, A.U.; Surana, S.J. Flavonoids as natural phenolic compounds and their role in therapeutics: An overview. *Futur. J. Pharm. Sci.* **2021**, *7*, 25. [CrossRef] [PubMed]
216. Vauzour, D.; Rodriguez-Mateos, A.; Corona, G.; Oruna-Concha, M.J.; Spencer, J.P.E. Polyphenols and Human Health: Prevention of Disease and Mechanisms of Action. *Nutrients* **2010**, *2*, 1106–1131. [CrossRef] [PubMed]
217. Singh, M.; Arseneault, M.; Sanderson, T.; Murthy, V.; Ramassamy, C. Challenges for Research on Polyphenols from Foods in Alzheimer's Disease: Bioavailability, Metabolism, and Cellular and Molecular Mechanisms. *J. Agric. Food Chem.* **2008**, *56*, 4855–4873. [CrossRef] [PubMed]
218. Cushnie, T.P.T.; Lamb, A.J. Antimicrobial activity of flavonoids. *Int. J. Antimicrob. Agents* **2005**, *26*, 343–356. [CrossRef] [PubMed]
219. Palafox-Carlos, H.; Ayala-Zavala, J.F.; González-Aguilar, G.A. The Role of Dietary Fiber in the Bioaccessibility and Bioavailability of Fruit and Vegetable Antioxidants. *J. Food Sci.* **2011**, *76*, R6–R15. [CrossRef]
220. Yan, L.; Guo, M.-S.; Zhang, Y.; Yu, L.; Wu, J.-M.; Tang, Y.; Ai, W.; Zhu, F.-D.; Law, B.Y.-K.; Chen, Q.; et al. Dietary Plant Polyphenols as the Potential Drugs in Neurodegenerative Diseases: Current Evidence, Advances, and Opportunities. *Oxidative Med. Cell. Longev.* **2022**, *2022*, 5288698. [CrossRef]
221. Askarova, S.; Umbayev, B.; Masoud, A.-R.; Kaiyrlykyzy, A.; Safarova, Y.; Tsoy, A.; Olzhayev, F.; Kushugulova, A. The Links Between the Gut Microbiome, Aging, Modern Lifestyle and Alzheimer's Disease. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 104. [CrossRef]
222. Tan, B.; Wang, Y.; Zhang, X.; Sun, X. Recent Studies on Protective Effects of Walnuts against Neuroinflammation. *Nutrients* **2022**, *14*, 4360. [CrossRef]
223. Colizzi, C. The protective effects of polyphenols on Alzheimer's disease: A systematic review. *Alzheimer's Dement. Transl. Res. Clin. Interv.* **2018**, *5*, 184–196. [CrossRef]
224. Zhou, Y.; Zheng, J.; Li, Y.; Xu, D.-P.; Li, S.; Chen, Y.-M.; Li, H.-B. Natural Polyphenols for Prevention and Treatment of Cancer. *Nutrients* **2016**, *8*, 515. [CrossRef]
225. Ferrazzano, G.F.; Amato, I.; Ingenito, A.; De Natale, A.; Pollio, A. Anti-cariogenic effects of polyphenols from plant stimulant beverages (cocoa, coffee, tea). *Fitoterapia* **2009**, *80*, 255–262. [CrossRef] [PubMed]
226. Scalbert, A.; Williamson, G. Dietary Intake and Bioavailability of Polyphenols. *J. Nutr.* **2000**, *130*, 2073S–2085S. [CrossRef] [PubMed]
227. Briguglio, G.; Costa, C.; Pollicino, M.; Giambò, F.; Catania, S.; Fenga, C. Polyphenols in cancer prevention: New insights (Review). *Int. J. Funct. Nutr.* **2020**, *1*, 9. [CrossRef]
228. Wu, X.; Li, M.; Xiao, Z.; Daglia, M.; Dragan, S.; Delmas, D.; Vong, C.T.; Wang, Y.; Zhao, Y.; Shen, J.; et al. Dietary polyphenols for managing cancers: What have we ignored? *Trends Food Sci. Technol.* **2020**, *101*, 150–164. [CrossRef]
229. Jang, Y.-G.; Go, R.-E.; Hwang, K.-A.; Choi, K.-C. Resveratrol inhibits DHT-induced progression of prostate cancer cell line through interfering with the AR and CXCR4 pathway. *J. Steroid Biochem. Mol. Biol.* **2019**, *192*, 105406. [CrossRef] [PubMed]
230. Deb, G.; Shankar, E.; Thakur, V.S.; Ponsky, L.E.; Bodner, D.R.; Fu, P.; Gupta, S. Green tea-induced epigenetic reactivation of tissue inhibitor of matrix metalloproteinase-3 suppresses prostate cancer progression through histone-modifying enzymes. *Mol. Carcinog.* **2019**, *58*, 1194–1207. [CrossRef]

231. Poschner, S.; Maier-Salamon, A.; Thalhammer, T.; Jäger, W. Resveratrol and other dietary polyphenols are inhibitors of estrogen metabolism in human breast cancer cells. *J. Steroid Biochem. Mol. Biol.* **2019**, *190*, 11–18. [CrossRef]
232. Amararathna, M.; Hoskin, D.; Rupasinghe, H.V. Anthocyanin-rich haskap (*Lonicera caerulea* L.) berry extracts reduce nitrosamine-induced DNA damage in human normal lung epithelial cells. *Food Chem. Toxicol.* **2020**, *141*, 111404. [CrossRef]
233. Lee, C.-W.; Chen, H.-J.; Xie, G.-R.; Shih, C.-K. Djulis (Chenopodium Formosanum) Prevents Colon Carcinogenesis via Regulating Antioxidative and Apoptotic Pathways in Rats. *Nutrients* **2019**, *11*, 2168. [CrossRef]
234. Chen, T.; Shi, N.; Afzali, A. Chemopreventive Effects of Strawberry and Black Raspberry on Colorectal Cancer in Inflammatory Bowel Disease. *Nutrients* **2019**, *11*, 1261. [CrossRef]
235. Kim, Y.; Keogh, J.B.; Clifton, P.M. Polyphenols and Glycemic Control. *Nutrients* **2016**, *8*, 17. [CrossRef] [PubMed]
236. Domínguez Avila, J.A.; Rodrigo García, J.; González Aguilar, G.A.; De La Rosa, L.A. The Antidiabetic Mechanisms of Polyphenols Related to Increased Glucagon-Like Peptide-1 (GLP1) and Insulin Signaling. *Molecules* **2017**, *22*, 903. [CrossRef] [PubMed]
237. Kalita, D.; Holm, D.G.; LaBarbera, D.V.; Petrash, J.M.; Jayanty, S.S. Inhibition of α-glucosidase, α-amylase, and aldose reductase by potato polyphenolic compounds. *PLoS ONE* **2018**, *13*, e0191025. [CrossRef] [PubMed]
238. Maradesha, T.; Patil, S.M.; Al-Mutairi, K.A.; Ramu, R.; Madhunapantula, S.V.; Alqadi, T. Inhibitory Effect of Polyphenols from the Whole Green Jackfruit Flour against α-Glucosidase, α-Amylase, Aldose Reductase and Glycation at Multiple Stages and Their Interaction: Inhibition Kinetics and Molecular Simulations. *Molecules* **2022**, *27*, 1888. [CrossRef] [PubMed]
239. Sun, C.; Zhao, C.; Guven, E.C.; Paoli, P.; Simal-Gandara, J.; Ramkumar, K.M.; Wang, S.; Buleu, F.; Pah, A.; Turi, V.; et al. Dietary polyphenols as antidiabetic agents: Advances and opportunities. *Food Front.* **2020**, *1*, 18–44. [CrossRef]
240. Campos, F.; Peixoto, A.F.; Fernandes, P.A.R.; Coimbra, M.A.; Mateus, N.; de Freitas, V.; Fernandes, I.; Fernandes, A. The Antidiabetic Effect of Grape Pomace Polysaccharide-Polyphenol Complexes. *Nutrients* **2021**, *13*, 4495. [CrossRef]
241. Cattivelli, A.; Conte, A.; Martini, S.; Tagliazucchi, D. Cooking and In Vitro Digestion Modulate the Anti-Diabetic Properties of Red-Skinned Onion and Dark Purple Eggplant Phenolic Compounds. *Foods* **2022**, *11*, 689. [CrossRef]
242. Nettleton, J.A.; Harnack, L.J.; Scrafford, C.G.; Mink, P.J.; Barraj, L.M.; Jacobs, D.R. Dietary Flavonoids and Flavonoid-Rich Foods Are Not Associated with Risk of Type 2 Diabetes in Postmenopausal Women. *J. Nutr.* **2006**, *136*, 3039–3045. [CrossRef]
243. Talaei, M. Role of phytoestrogens in prevention and management of type 2 diabetes. *World J. Diabetes* **2015**, *6*, 271–283. [CrossRef]
244. Roth, G.A.; Mensah, G.A.; Johnson, C.O.; Addolorato, G.; Ammirati, E.; Baddour, L.M.; Barengo, N.C.; Beaton, A.Z.; Benjamin, E.J.; Benziger, C.P.; et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. *J. Am. Coll. Cardiol.* **2020**, *76*, 2982–3021. [CrossRef]
245. Ghosh, D.; Scheepens, A. Vascular action of polyphenols. *Mol. Nutr. Food Res.* **2009**, *53*, 322–331. [CrossRef] [PubMed]
246. Stoclet, J.-C.; Chataigneau, T.; Ndiaye, M.; Oak, M.-H.; El Bedoui, J.; Chataigneau, M.; Schini-Kerth, V.B. Vascular protection by dietary polyphenols. *Eur. J. Pharmacol.* **2004**, *500*, 299–313. [CrossRef] [PubMed]
247. Abbas, M.; Saeed, F.; Anjum, F.M.; Afzaal, M.; Tufail, T.; Bashir, M.S.; Ishtiaq, A.; Hussain, S.; Suleria, H.A.R. Natural polyphenols: An overview. *Int. J. Food Prop.* **2017**, *20*, 1689–1699. [CrossRef]
248. Peters, U.; Poole, C.; Arab, L. Does Tea Affect Cardiovascular Disease? A Meta-Analysis. *Am. J. Epidemiol.* **2001**, *154*, 495–503. [CrossRef] [PubMed]
249. Arab, L.; Khan, F.; Lam, H. Tea consumption and cardiovascular disease risk. *Am. J. Clin. Nutr.* **2013**, *98*, 1651S–1659S. [CrossRef]
250. Rondanelli, M.; Riva, A.; Petrangolini, G.; Allegrini, P.; Perna, S.; Faliva, M.; Peroni, G.; Naso, M.; Nichetti, M.; Perdoni, F.; et al. Effect of Acute and Chronic Dietary Supplementation with Green Tea Catechins on Resting Metabolic Rate, Energy Expenditure and Respiratory Quotient: A Systematic Review. *Nutrients* **2021**, *13*, 644. [CrossRef]
251. Boccellino, M.; D'Angelo, S. Anti-Obesity Effects of Polyphenol Intake: Current Status and Future Possibilities. *Int. J. Mol. Sci.* **2020**, *21*, 5642. [CrossRef]
252. Akhlaghi, M.; Ghobadi, S.; Hosseini, M.M.; Gholami, Z.; Mohammadian, F. Flavanols are potential anti-obesity agents, a systematic review and meta-analysis of controlled clinical trials. *Nutr. Metab. Cardiovasc. Dis.* **2018**, *28*, 675–690. [CrossRef]
253. Singh, M.; Thrimawithana, T.; Shukla, R.; Adhikari, B. Managing obesity through natural polyphenols: A review. *Future Foods* **2020**, *1–2*, 100002. [CrossRef]
254. Aali, Y.; Ebrahimi, S.; Shiraseb, F.; Mirzaei, K. The association between dietary polyphenol intake and cardiometabolic factors in overweight and obese women: A cross-sectional study. *BMC Endocr. Disord.* **2022**, *22*, 120. [CrossRef]
255. Bahadoran, Z.; Mirmiran, P.; Azizi, F. Dietary polyphenols as potential nutraceuticals in management of diabetes: A review. *J. Diabetes Metab. Disord.* **2013**, *12*, 43. [CrossRef]
256. Scalbert, A.; Manach, C.; Morand, C.; Rémésy, C.; Jiménez, L. Dietary Polyphenols and the Prevention of Diseases. *Crit. Rev. Food Sci. Nutr.* **2005**, *45*, 287–306. [CrossRef]
257. Zhao, W.-H.; Hu, Z.-Q.; Hara, Y.; Shimamura, T. Inhibition of Penicillinase by Epigallocatechin Gallate Resulting in Restoration of Antibacterial Activity of Penicillin against Penicillinase-Producing *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* **2002**, *46*, 2266–2268. [CrossRef] [PubMed]

258. Parvez, A.K.; Saha, K.; Rahman, J.; Munmun, R.A.; Rahman, A.; Dey, S.K.; Rahman, S.; Islam, S.; Shariare, M.H. Antibacterial activities of green tea crude extracts and synergistic effects of epigallocatechingallate (EGCG) with gentamicin against MDR pathogens. *Heliyon* **2019**, *5*, e02126. [CrossRef] [PubMed]
259. Giri, K.; Shrestha, B.K.; Shakya, J.; Sah, S.N.; Khanal, H. Antibacterial effect of green tea extract against multi drug resistant Escherichia coli isolated from urine sample of patients visiting tertiary care hospital of Eastern Nepal. *Int. J. Appl. Sci. Biotechnol.* **2020**, *8*, 45–51. [CrossRef]
260. Gopal, J.; Muthu, M.; Paul, D.; Kim, D.-H.; Chun, S. Bactericidal activity of green tea extracts: The importance of catechin containing nano particles. *Sci. Rep.* **2016**, *6*, 19710. [CrossRef]
261. Nowak, D.; Gośliński, M.; Kłębukowska, L. Antioxidant and Antimicrobial Properties of Selected Fruit Juices. *Plant Foods Hum. Nutr.* **2022**, *77*, 427–435. [CrossRef]
262. Wang, X.; Qi, Y.; Zheng, H. Dietary Polyphenol, Gut Microbiota, and Health Benefits. *Antioxidants* **2022**, *11*, 1212. [CrossRef]
263. Sampson, L.; Rimm, E.; Hollman, P.C.; de Vries, J.H.; Katan, M.B. Flavonol and Flavone Intakes in US Health Professionals. *J. Am. Diet. Assoc.* **2002**, *102*, 1414–1420. [CrossRef]
264. Feliciano, R.P.; Mills, C.E.; Istas, G.; Heiss, C.; Rodriguez-Mateos, A. Absorption, Metabolism and Excretion of Cranberry (Poly)phenols in Humans: A Dose Response Study and Assessment of Inter-Individual Variability. *Nutrients* **2017**, *9*, 268. [CrossRef]
265. Li, Q.; Van de Wiele, T. Gut microbiota as a driver of the interindividual variability of cardiometabolic effects from tea polyphenols. *Crit. Rev. Food Sci. Nutr.* **2021**, 1–27. [CrossRef] [PubMed]
266. Crozier, A.; Del Rio, D.; Clifford, M.N. Bioavailability of dietary flavonoids and phenolic compounds. *Mol. Asp. Med.* **2010**, *31*, 446–467. [CrossRef] [PubMed]
267. Maaliki, D.; Shaito, A.A.; Pintus, G.; El-Yazbi, A.; Eid, A.H. Flavonoids in hypertension: A brief review of the underlying mechanisms. *Curr. Opin. Pharmacol.* **2019**, *45*, 57–65. [CrossRef] [PubMed]
268. Rodríguez-Daza, M.-C.; Roquim, M.; Dudonné, S.; Pilon, G.; Levy, E.; Marette, A.; Roy, D.; Desjardins, Y. Berry Polyphenols and Fibers Modulate Distinct Microbial Metabolic Functions and Gut Microbiota Enterotype-Like Clustering in Obese Mice. *Front. Microbiol.* **2020**, *11*, 2032. [CrossRef]
269. Duda-Chodak, A.; Tarko, T.; Satora, P.; Sroka, P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: A review. *Eur. J. Nutr.* **2015**, *54*, 325–341. [CrossRef] [PubMed]
270. Rechner, A.R.; Smith, M.A.; Kuhnle, G.; Gibson, G.R.; Debnam, E.S.; Srai, S.K.S.; Moore, K.P.; Rice-Evans, C.A. Colonic metabolism of dietary polyphenols: Influence of structure on microbial fermentation products. *Free Radic. Biol. Med.* **2004**, *36*, 212–225. [CrossRef]
271. Plamada, D.; Vodnar, D.C. Polyphenols—Gut Microbiota Interrelationship: A Transition to a New Generation of Prebiotics. *Nutrients* **2022**, *14*, 137. [CrossRef]
272. Cardona, F.; Andrés-Lacueva, C.; Tulipani, S.; Tinahones, F.J.; Queipo-Ortuño, M.I. Benefits of polyphenols on gut microbiota and implications in human health. *J. Nutr. Biochem.* **2013**, *24*, 1415–1422. [CrossRef]
273. Mukherjee, C.; Chakraborty, S. Study of dietary polyphenols from natural herbal sources for providing protection against human degenerative disorders. *Biocatal. Agric. Biotechnol.* **2021**, *33*, 101956. [CrossRef]
274. Rajha, H.N.; Paule, A.; Aragonès, G.; Barbosa, M.; Caddeo, C.; Debs, E.; Dinkova, R.; Eckert, G.P.; Fontana, A.; Gebrayel, P.; et al. Recent Advances in Research on Polyphenols: Effects on Microbiota, Metabolism, and Health. *Mol. Nutr. Food Res.* **2021**, *66*, 2100670. [CrossRef]
275. Corrêa, T.A.F.; Rogero, M.M.; Hassimotto, N.M.A.; Lajolo, F.M. The Two-Way Polyphenols-Microbiota Interactions and Their Effects on Obesity and Related Metabolic Diseases. *Front. Nutr.* **2019**, *6*, 188. [CrossRef] [PubMed]
276. Shivashankara, K.S.; Acharya, S.N. Bioavailability of Dietary Polyphenols and the Cardiovascular Diseases. *Open Nutraceuticals J.* **2010**, *3*, 227–241. [CrossRef]
277. Del Rio, D.; Costa, L.; Lean, M.; Crozier, A. Polyphenols and health: What compounds are involved? *Nutr. Metab. Cardiovasc. Dis.* **2010**, *20*, 1–6. [CrossRef] [PubMed]
278. Marín, L.; Miguélez, E.M.; Villar, C.J.; Lombó, F. Bioavailability of Dietary Polyphenols and Gut Microbiota Metabolism: Antimicrobial Properties. *BioMed. Res. Int.* **2015**, *2015*, 905215. [CrossRef] [PubMed]
279. Hedrén, E.; Diaz, V.; Svanberg, U. Estimation of carotenoid accessibility from carrots determined by an in vitro digestion method. *Eur. J. Clin. Nutr.* **2002**, *56*, 425–430. [CrossRef]
280. Kobayashi, S.; Shinohara, M.; Nagai, T.; Konishi, Y. Transport Mechanisms for Soy Isoflavones and Microbial Metabolites Dihydrogenistein and Dihydrodaidzein Across Monolayers and Membranes. *Biosci. Biotechnol. Biochem.* **2013**, *77*, 2210–2217. [CrossRef]
281. Rastogi, H.; Jana, S. Evaluation of physicochemical properties and intestinal permeability of six dietary polyphenols in human intestinal colon adenocarcinoma Caco-2 cells. *Eur. J. Drug Metab. Pharmacokinet.* **2014**, *41*, 33–43. [CrossRef]

282. Truzzi, F.; Tibaldi, C.; Zhang, Y.; Dinelli, G.; D′amen, E. An Overview on Dietary Polyphenols and Their Biopharmaceutical Classification System (BCS). *Int. J. Mol. Sci.* **2021**, *22*, 5514. [CrossRef]
283. Margină, D.; Ungurianu, A.; Purdel, C.; Nițulescu, G.M. Natural Remedies for a Healthy Heart: The Evidence-Based Beneficial Effects of Polyphenols. In *Plant Secondary Metabolites: Physico-Chemical Properties and Therapeutic Applications*; Sharma, A.K., Sharma, A., Eds.; Springer: Singapore, 2022; pp. 141–190, ISBN 978-981-16-4779-6.