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Berry polyphenols and human health: evidence of antioxidant, anti-inflammatory, microbiota modulation, and cell-protecting effects

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Studies have revealed more positive effects of berries' components over the years, representing a growing trend in their consumption. Phenolic compounds, such as anthocyanins, flavonols, and phenolic acids occur in different concentrations depending on the berry type. Significant trends to exploit the beneficial compounds were collected, with mostly novel and environmentally friendly techniques, such as ultrasound, microwave, and high-pressure technologies. Abundant phenolic compounds present in different berries (raspberry, blueberry, goji berry, blackcurrant, strawberry, cranberry, and blackberry) were summarized based on up-to-date information and their beneficial health effects. The antioxidant, anti-inflammatory, antihypertensive, and antihyperglycemic activities *in vitro* and *in vivo* were comprehensively reviewed. Recent studies allied to *in vivo* results and positive findings to reduce oxidative stress, for example, support that berries and their functional products represent a prominent economic potential to maintain human health and function.

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Introduction

According to the Food and Agriculture Organization [1] the fruit production in 2019 was 883.42 million metric tons (mmt), in which China (246.62 mmt), India (104.17 mmt), Brazil (40.1), USA (25.3 mmt), Mexico (23.68 mmt), Turkey (23.31 mmt), Indonesia (21.45 mmt), Spain (18.32 mmt), Iran (17.46 mmt), and Italy (17.25 mmt) were the primary producers. Apart from the fruit commodities (i.e. citrus, apple, and banana), strawberry (8.89 mmt), blueberry (0.68 mmt), raspberry (0.82 mmt), blackcurrant (0.18 mmt), cranberry (0.69 mmt) and other berries (0.92 mmt) accounted for a tiny portion of the worldwide production.

In northern countries, such as in the Scandinavian countries, Canada, USA, Russia, and many other EU countries, berries' consumption is part of the daily eating habits, and the global market is expected to grow roughly 2% during 2020–2025 [2]. Berries are generally consumed as fresh fruits, but many different technological products are also widely available, in which beverages and confectioneries have grown considerably in the last years. The consumption of berries has increased because of the growing health consciousness and more processed 'berry-loaded' foods. Additionally, studies relating the chemistry of

bioactive compounds and the functionality/bioactivity of such compounds have become available [3–7]. Thus, it is clear that the scientific development and production of data are demanding and of pivotal importance for berry producers, food processors, and consumers.

Trying to ally the scientific development related to the association between the consumption of different berries and health benefits, the main objective of this review was to discuss some relevant topics for new studies that could benefit the industry and improve the local economy where the berries are found. Therefore, the dissemination of the studies already carried out with these fruits strategically important can stimulate new research lines to solidify this field and define what is still demanding in the literature concerning the bioactivities, quantity and overall recommended consumption patter of berries in the regular diet.

Berries: phenolic composition

Profile of phenolic compounds and effects of variety and geographical origin

Phenolic compounds are secondary metabolites found widely in the plant tissues, including fruits, berries, vegetables and also grains. These compounds can be classified into several groups, such are the phenolic acids, flavonoids, tannins, coumarins, lignans, stilbenes and others, as well as into different subgroups. Many of these compounds have been connected with beneficial effects on human health. However, some post-harvest and processing methods may influence their bioactivity and bioavailability.

The following sections will give an overview of the most common phenolic compounds in different berries, how the profile and quantities are influenced by environmental and processing factors, and the major health beneficial properties of berries. The phenolic profile of berries is different when species and varieties are compared [8] in Table 1 and the structure of the most common polyphenols can be observed in Figure 1. The biosynthesis of phenolic compounds is dependent on many factors, such as the plant genotype, growth conditions, developmental stage, soil, environmental conditions, and other agricultural practices, as well as abiotic and biotic stress factors [9–14].

Factors such as harvest dates, fruit position, and interactions play an important role and influence the phenolic compounds' content [15]. For instance, 27 strawberry cultivars at three ripening stages were studied by Aaby *et al.* [9], and results showed that the phenolic profile is similar. However, the quantity found within cultivars and maturity degree varies significantly, especially for glycosylated compounds (flavonols and anthocyanins). Complementarily, Panico *et al.* [16] found that strawberries from two different genotypes, namely Tudla and Maletto, present different antioxidant activity (AA) in terms of the 2,2-diphenyl-1-picrylhydrazyl free radical method (DPPH) and oxygen radical absorbance capacity assay (ORAC) and total phenolic content (TPC). Similarly, Djordjević *et al.* [17] found that the phenolic composition and AA of 13 blackcurrant varieties differ significantly. Thus, different fruit cultivars may play different roles in human nutrition, and a focus on a more nutritious variety should give light to future studies and nutritional recommendations.

The geographical origin of a certain berry species impacts the profile and quantity of bioactive compounds synthesized. Environmental factors include the soil type, water stress, climatic conditions, sunlight exposure, applied manure, fertilization practices, and harvest time are the main contributors to the biosynthesis of phenolic compounds in fruits [10,12,18]. For instance, Wu *et al.* [19] investigated the effects of leaf extracts from 73 blueberry/bilberry cultivars grown in different locations in China and found that total phenolic content, proanthocyanidins, total anthocyanins, and AA (ferric recuding antioxidant power assay, FRAP, scavenging of 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) cation, ABTS, ORAC, and DPPH) varied considerably when the geographical origin of the fruits was evaluated. The AA, individual phenolic acids, and flavonols were responsible for the differentiation between geographical origins and cultivars. Similarly, Mocan *et al.* [20] assessed the chemical composition of goji berry produced in Italy and Romania. They found that the individual phenolic composition (phenolic acids and flavonoids), bioactivity (DPPH, FRAP, ABTS, and the inhibition of tyrosinase activity) were dependent on the fruit's location was grown. The *terroir* affects the chemical composition and bioactivity of berry species. Future studies should also focus on the most appropriate locations and berry variety systematically affect the bioavailability of bioactive compounds.

Effect of processing technologies on the phenolic compounds

Berries are consumed in a fresh form only for a short time, and for the rest of the year, they are processed mostly to juices, concentrate beverages, jams/purees, and the seeds can be used to recover oil. Phenolic compounds are, in general, heat and processing sensitive compounds, and therefore, the thermal processing should be mild. At first, the berries' biological processes may decrease the TPC by degradation of specific compounds due to the naturally present polyphenol oxidase (PPO) enzyme activity that induces enzymatic browning process as soon as tissue damage of the berry occurs [40].

PPO along with the peroxidase enzyme when released from the cells may accelerate the oxidation and degradation of the polyphenols. Recently, several promising

Table 1

Phenolic compounds found in different berries

Berry species	Phenolic compounds	References
Cranberry (*Vaccinium oxycoccus, Vaccinium macrocarpon*)	**Cranberry fruit** Total phenolics: 392.37 mg/100 g Total anthocyanins 3.60 mg/100 g: Cyanidin 3-*O*-galactoside 20.5 ± 1.8% Cyanidin 3-*O*-glucoside 2.3 ± 0.3% Cyanidin 3-arabinoside 19 ± 3.3% Peonidin 3-galactoside 32.7 ± 1.2% Peonidin 3-glucoside 3.5 ± 1.3% Peonidin 3-*O*-arabinoside 6.7 ± 1.2%	[21]
	Cranberry juice after spray drying Total anthocyanins: 1028.1 ± 12.4 μg/g Total phenolic content: 5415.5 ± 168.6–8218.6 ± 264.0 μg gallic acid equivalent (GAE)/g	[22]
	Extracts from cranberry pomace *Major anthocyanin compounds (μg/g powder):* Total anthocyanins: 10 800 Cyanidin 3-*O*-galactoside: 2728.93 Peonidin 3-*O*-galactoside: 3578.52 Cyanidin 3-*O*-arabinoside: 2229.26 Peonidin 3-*O*-arabinoside: 1798.04 *Major flavonol compounds (μg/g powder):* Total flavonols: 7967 Quercetin-3-*O*-galactoside: 2795.22 Myricetin-3-*O*-galactoside: 1633.78 Quercetin-3-*O*-arabinofuranoside: 1008.20 *Major phenolics:* Total phenolic content: 26,253 Chlorogenic acid: 2499.59 (−)-Epicatechin: 1137.54 *trans*-Cinnamic acid: 1528.86	[23]
Blueberry (*Vaccinium* spp.)	**Blueberry fruit** *Major anthocyanin compounds (mg/100 g fw):* Total anthocyanins: 9.8 ± 0.8 Cyanidin 3-*O*-glucoside: 8.2 ± 1 Pelargonidin 3-*O*-glucoside: 1.6 ± 0.3 *Major flavonol compounds (mg/100 g fw)*: Total flavonol content: 16 ± 1 Quercetin 3-rutinoside: 15 ± 2 Quercetin: 0.7 ± 0.1	[24]
	Blueberry juice *Major anthocyanins (mg/L):* Total anthocyanins 73.1 ± 0.08 Total phenolic content 3.35 ± 0.05 g GAE/L Malvidin-galactoside 19.0 ± 0.03 Peonidin-galactoside 4.59 ± 0.01 Petunidin-galactoside 1.27 ± 0.02 Cyanidin-galactoside 3.34 ± 0.04 Delphinidin-galactoside 4.77 ± 0.02 Malvidin-glucoside 12.8 ± 0.01 Peonidin-glucoside 4.04 ± 0.03 Cyanidin 3-*O*-glucoside 3.78 ± 0.01 Malvidin-arabinoside 10.1 ± 0.02 Petunidin-arabinoside 0.96 ± 0.04 Cyanidin-arabinoside 6.00 ± 0.00 Delphinidin-arabinoside 0.92 ± 0.00	[25]
	Blueberry dried pomace *Total phenolic content (g GAE/100 g dw)* Freeze dried: 8.6 ± 0.1 Fixed bed dried: 7.1 ± 0.8 at 40°C, 1 m/s and 5.8 ± 1.0 at 40°C, 1 m/s Cyclone dried: 7.4 ± 0.2 at 40°C, 1 m/s and 5.5 ± 0.1 at 40°C, 1 m/s	[26]

Table 1 (*Continued*)

Berry species	Phenolic compounds	References
	Extracts of blueberry powders *Anthocyanin composition (μg/100 g)* Cyanidin 3-rutinoside: 96852.80 ± 71381.73 Cyanidin 3,5-diglucoside: 25981.83 ± 965.68 Cyanidin 3-galactoside: 22331.22 ± 1093.50 Cyanidin 3-glucoside: 14964.98 ± 1479.61 Cyanidin 3-arabinoside: 12785.94 ± 1022.13 Peonidin 3-glucoside: 53710.29 ± 1676.30 Pelargonidin 3-glucoside: 45718.20 ± 2283.03 Petunidin 3-glucoside: 39121.91 ± 1223.33 Delphinidin 3-glucoside: 32524.68 ± 936.09 Delphinidin 3,5-diglucoside: 23896.39 ± 940.33 Malvidin 3-glucoside: 18364.98 ± 483.70 Malvidin 3-galactoside: 15010.95 ± 1293.31 Malvidin 3,5-diglucoside: 14458.41 ± 484.21	[27]
	Blueberry puree *Major anthocyanins* Cyanidins: 149.9 μg/mL Total anthocyanin content 423.9 μg/mL	[28]
Blackcurrant (*Ribes nigrum*)	**Dried blackcurrant skins** *Major anthocyanins* Delphinidin 3-*O*-rutinoside: 50.4% Cyanidin 3-*O*-rutinoside: 29.1% Delphinidin 3-*O*-glucoside: 20.7% Cyanidin 3-*O*-glucoside: 8.6% *Major phenolic acids (mg/100 g)* Free *p*-coumaric acid: 61.6 Caffeic acid: 35.6 Ferulic acid: 18.5 Bound *p*-coumaric acid 42.8−47.8 *Major flavonols* Myricetin 3-*O*-glucoside: 28.6–29.0% Myricetin:15.8–16.8% Quercetin 3-*O*-glucoside: 23.0–29.6% Quercetin 3-*O*-rutinoside:15.1–15.4% Quercetin: 8.2–8.5% Kaempferol-3-glucoside: 2.8% Kaempferol 3-rutinoside: 3.6–3.7% Total free flavonol: 23.0–29.5 mg/100 g *Flavonol aglycons:* Myricetin 58.3–62.6%, Quercetin 37.4–41.7% Total flavonol aglycons 26.0–27.6 mg/100 g	[29]
	Dried blackcurrant press-cake *Total phenolic content (g GAE/100 g dw)* Freeze dried: 7.0 ± 0.7 Fixed bed dried: 7.1 ± 0.8 at 40°C, 1 m/s and 5.7 ± 0.9 at 40°C, 1 m/s Cyclone dried: 7.3 ± 0.3 at 40°C, 1 m/s and 4.8 ± 0.5 at 40°C, 1 m/s	[26]
	Extracts of blackcurrant *Phenolic compounds (mg/g):* Solvent extraction: 26.32 ± 0.64 Ultrasound-assisted extraction: 34.98 ± 0.83 Microwave-assisted extraction: 40.19 ± 1.37 Main phenolic compounds: kaempferol 3-*O*-rutinoside, quercetin 3-rutinoside, cyanidin 3-*O*-glucoside and hyperoside	[30]

Table 1 (*Continued*)

Berry species	Phenolic compounds	References
	Extracts of blackcurrant powders *Anthocyanin composition (μg/100 g)* Pelargonidin 3-glucoside: 102936.30 ± 741.32 Petunidin 3-glucoside: 91318.68 ± 1524.90 Delphinidin 3-glucoside: 76135.00 ± 508.6 Delphinidin 3,5-diglucoside: 55447.28 ± 1348.64 Cyanidin 3,5-diglucoside: 63642.05 ± 288.04 Cyanidin 3-galactoside: 50969.76 ± 758.64 Cyanidin-3-glucoside: 36266.40 ± 1685.65 Cyanidin 3-rutinoside: 330616.73 ± 4189.10 Cyanidin 3-arabinoside: 30766.48 ± 1124.33 Malvidin 3-glucoside: 43656.61 ± 1064.02 Malvidin 3-galactoside: 36629.90 ± 332.21 Malvidin 3,5-diglucoside: 33650.44 ± 1761.28 Peonidin 3-glucoside: 13170.93 ± 562.3	[27]
Blackberry (*Rubus ulmifolius*)	**Blackberry fruit extract (mg/100 g fw)** Anthocyanins: 80−170 Condensed tannins: 11−30 Flavonols: 9−20 Specific compounds: cyanidin 3-*O*-glucoside, cyanidin 3-*O*-xyloside, cyanidin 3-rutinoside, cyanidin 3-*O*-(6″-malonyl-glucoside), cyanidin 3-*O*-(6″-dioxalyglucoside), chlorogenic acid derivatives, (+)-catechin, kaempferol derivatives, apigenin derivatives, quercetin, quercetin 3-rutinoside, ellagic acid pentoside, isorhamnetin hexuronide, epigallocatechin 3-*O*-syringate, chrysin, luteolin, isoquercitrin, pinocembrin, pinobanksin, syringaldehyde, caffeic acid, *p*-coumaric acid, gallic acid, sinaptic acid	[31,32]
	Blackberry fruit extract Total phenolic content 42.2 mg GAE/100 g fw Flavonoids: 17 302 μg/kg fw Phenolic acids: 13 221 μg/kg fw Resveratrol: 511 μg/kg fw Specific compounds: hydroxybenzoic acid, protocatechuic acid, caffeic acid, chlorogenic acid, naringenin, luteolin, quercetin, *p*-coumaric acid, quercetin 3-rutinoside	[33]
Goji berry (*Lycium barbarum*)	**Goji berry fruit extract (mg/kg dw)** Chlorogenic acid: 1758 Caffeic acid: 180 Ellagic acid: 1517 Ferulic acid: 54 Gallic acid:2014 *p*-Coumaric acid: 311 Syringic acid: 121 Vanillic acid: 661 Quercetin 3-rutinoside: 2980 (+)-Catechin: 2480	[34,35]
Strawberry (*Fragaria* x *ananassa*)	**Strawberry fruit extract** Total phenolic content: 40 mg GAE/100 g fw Phenolic acids: 17,275 μg/kg fw Flavonoids:13513 μg/kg fw Specific compounds: gallic acid, 4-hydroxybenzoic acid, (+)-catechin, chlorogenic acid, *p*-coumaric acid, ellagic acid, quercetin 3-rutinoside	[33]
	Strawberry fruit extracts (mg/100 g fw) Total phenolic content: 190−340 Total flavonoids: 65 Total anthocyanins: 31 Specific compounds: cyanidin 3-*O*-glucoside, pelargonidin 3-*O*-glucoside, peonidin 3-*O*-glucoside, ellagic acid derivatives, quercetin glucosides, kaempferol, (+)-catechin, ferulic acid derivative	[9,24,36]

Table 1 (*Continued*)

Berry species	Phenolic compounds	References
Raspberry (*Rubus idaeus*)	**Raspberry fruit/pomace extracts (μg/g fw)** Flavanols: 376 Flavonols: 58 Phenolic acids: 1160 Specific compounds: (−)-epicatechin, (+)-catechin, procyanidin B1, quercetin derivatives, kaempferol derivatives, *p*-coumaric acid, caffeic, ferulic, chlorogenic, ellagic, *p*-hydroxybenzoic, gallic and protocatechuic acids, sanguiin H-10 and H-6 isomers, lambertianin C. Anthocyanins: cyanidin 3,5-*O*-diglucoside, cyanidin 3-*O*-sophoroside, cyanidin 3-*O*-glucosyl-rutinoside, cyanidin 3-*O*-glucoside. **Raspberry pulp and juice (μg/kg fw)** Phenolic acids: 151.6 (pulp), 98.4 (juice) Flavonoids: 90.4 (pulp), 53.8 (juice) Anthocyanins: 468.8 (pulp), 371 (juice) Specific compounds: ellagic acid, ellagic acid derivative, gallic acid, quercetin-based flavonol, kaempferol-based flavonol, (+)-catechin, (−)-epicatechin, cyanidin 3-*O*-sophoroside, cyanidin 3-*O*-glucosyl-rutinoside, cyanidin 3-*O*-glucoside, cyanidin 3-*O*-rutinoside, pelargonidin 3-*O*-glucoside	[37,38] [39]

Note: fw = fresh weight, dw = dry weight.

advanced technologies were studied to prevent or reduce the enzymatic and non-enzymatic browning and polyphenol degradation processes by auto-oxidation in which the treatment efficiency is not based on thermal heat, including microwave-assisted processing [41,42], high-pressure assisted freezing [43], high-pressure processing [44], high-pressure carbon dioxide processing [45], and ultrasound technique [46]. In addition to the effects caused by increasing/decreasing temperature, some of these technologies also have a secondary effect on the PPO that produces structural changes. The conformation changes study will bring new insight into these advanced technologies and their potential for industrial application.

The food processing technologies may also affect the TPC and individual phenolic variation, in which unit operation processes preserving the product's functionality are of primary importance since ensuring safety and functionality is a more critical attribute over efficiency and profit, especially from the consumer point of view.

Debelo *et al.* [47] reviewed the effect of different general food processes on the concentration of polyphenolic compounds and the phenolics' bioactivity after the processing. Thermal treatment usually decreases the amount of phenolics following a first-order degradation. Especially in juice production, the berries' side streams, the perishable press-cake is usually utilized as a powder. Grimm *et al.* [26] compared continuous cyclone drying to conventional batch fixed-bed convective drying in bilberry, blackcurrant and cloudberry berries. The cyclone-dried press-cake had lower total phenol content than the one dried in a fixed-bed. However, the cyclone type drier had a significant advantage in separating the seeds from the peels, pulp, and stems.

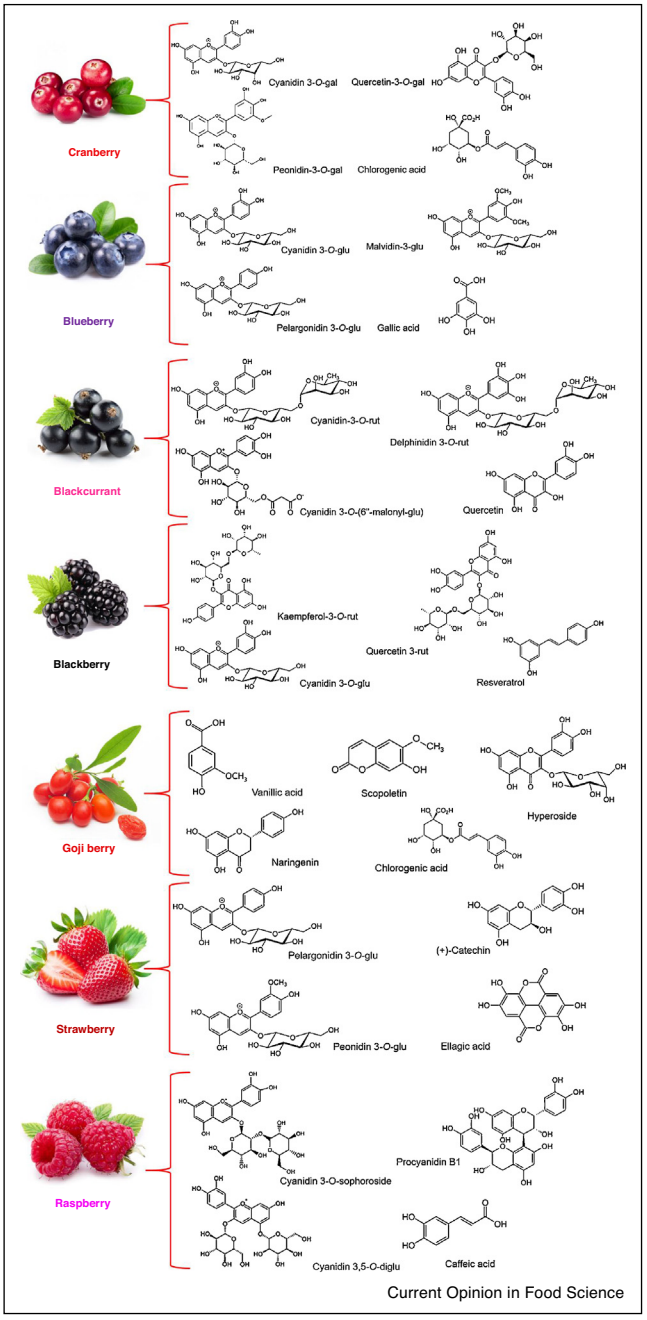
A comparison between strawberry and raspberry was made to assess the influence of different heat treatment conditions on the stability and content of phenolics [48]. The heat treatment at 93°C significantly influenced the monomeric anthocyanins and total phenolic content in strawberries, but not in raspberries which were attributed to a more stable individual anthocyanin composition. The decrease of total phenolics, anthocyanins, proanthocyanins, flavonols, and phenolic acids during storage at different temperatures (4, 25, and 45°C) was observed by Zhang *et al.* [22] using different wall materials in spray drying. All wall materials provided adequate protection of phenolics, one outstanding in the spray drying process and another during the storage conditions. The phenolics were most stable to the initial value at 25°C. Thermal processing and high hydrostatic pressure were also studied by Zhang *et al.* [28] with blueberry purees. For that specific matrix, temperatures over 90°C decreased the anthocyanin content of the product, which is somewhat high for anthocyanins, which are usually stable up to 60°C. A similar observation was made regarding the processing pressure, while the 300 MPa pressure tended to favor the liberation of anthocyanins from blueberry, especially petunidin 3-*O*-arabinoside, malvidin 3-*O*-galctoside, and malvidin 3-*O*-glucoside.

In vitro bioactivities of berries

Antioxidant activity

Several studies on berries have used chemical methods for determining *in vitro* AA [39,49–52]. In general, the *in vitro* AA determination methods found in the berries studies comprises at least one action antioxidant mechanism, such as electron transfer (e.g. DPPH scavenging activity and Folin-Ciocalteu reducing capacity — FCRC), chelation of transition metal ions (e.g. Cu^{2+} and Fe^{2+}), and H^+ ion transfer (e.g. lipid peroxidation inhibition)

Figure 1



Some typical phenolic compounds found in different berries. Note: glu: glucoside, gal: galactoside.

[29,31,33,39]. Methods with different mechanisms of action, media, and reaction times are recommended to obtain a broader AA assessment of complex plant extracts [53]. However, as the AA is associated with complex intrinsic and extrinsic interactions among food and organisms, *in vitro* chemistry assays are still considered useful preliminary screening studies. On the other hand, researchers unveil that the cellular antioxidant activity (CAA) assay, which reveals the antiproliferative action, is considered a useful *in vitro* analysis capable of demonstrating bioavailability issues, mainly because it is better associated with biological systems providing preliminary evidence of anticancer potential [54,55]. Moreover, chromatography techniques are usually employed in parallel to confirm the structure-activity relationship between metabolites and antioxidant potential [56]. The most common *in vitro* AA methods were investigated in different studies with berries [22,28,29,31,50–52,54,57], as well exemplified in Table 2.

Although the chemistry or antiproliferative activity against cancer cells explains the origin of *in vitro* AA, animal models and clinical trials still are considered the best protocols to be undertaken to comprehensively understand the bioaccessibility, metabolism, and functional properties of phytochemicals, nutraceutical, and foodstuffs rich in phenolics [58]. It is still necessary to develop new *in vitro* models that appropriately describe the process of absorption, distribution, and metabolism of compounds responsible for antioxidant action, considering the physiological conditions involved.

Inhibition of human-related enzymes: antihypertensive and antihyperglycemic activities

Metabolic syndrome is classified as a complex pathophysiological state that clinically manifests as a sum of interrelated risk factors (obesity, dysplipidemia, etc.) followed by a high risk of type-II diabetes and cardiovascular diseases [59]. Berries used in diets might be reflected as a reduction in sugar and fat intake, mainly ascribed to an increased intake of non-nutritive phytochemicals, mainly polyphenols. Starch hydrolysis is one of the most essential sources of postprandial glucose in the blood, involving enzymes such as salivary and pancreatic α-amylase and α-glucosidase from the intestinal apical membrane [60]. Several berry-based compounds, such as the anthocyanins (cyanidin 3-glucoside; cyanidin 3,5-glucoside; cyanidin 3-rutinoside; and peonidin 3-glucoside) exhibit competitive inhibition against porcine sourced pancreatic α-amylase, the most potent activity being showed by cyanidin 3-glucoside, an anthocyanin found in many berries. Furthermore, molecular modeling studies have shown that anthocyanins occupied the enzyme's active site by forming hydrogen bonds [61]. Nonetheless, a 50%/50% combination of gallic acid and the standard α-amylase inhibitor acarbose was shown to possess the highest α-amylase inhibitory effect, suggesting a possible synergistic effect between polyphenols and the standard drug [62]. Additionally, berries are good sources of α-glucosidase inhibitors, and berry polyphenol-rich extracts effectively inhibit this enzyme, with IC_{50} values comparable with the one of the standard drug, acarbose [63], which may direct future studies to produce bioactivity-tailored and standardized extracts to inhibit digestive enzymes. Notably, blackcurrant anthocyanin-rich

Table 2

Methods commonly used to assess the *in vitro* antioxidant activity of berries

Berries species	Antioxidant activity assay	References
Cranberry (*Vaccinium macrocarpon*)	**Cranberry juice after spray drying** FRAP: 33–51 TE μmol/g ABTS: 35–49 TE μmol/g	[22]
Blackcurrant (*Ribes nigrum*)	**Dried blackcurrant skins** DPPH: 60.7 ± 2.0% of inhibition	[29]
Raspberry (*Rubus idaeus*)	**Raspberry crude extract, phenolic and anthocyanin-rich fractions, juice crude extract, juice phenolic and anthocyanin-rich fractions** DPPH: 107.8 ± 1.5–588.9 ± 5.5 μmol TE/100 g fw; Fe^{2+} chelating activity: 5.9 ± 0.75–16.9 ± 0.23 mg EDTA/100 g fw; FRAP: 510.9 ± 5.80–1912.0 ± 1.78 μmol TE/100 g fw	[57]
Blueberry (*Vaccinium* spp.)	**Blueberry anthocyanins** PSC: 0.63 mg VcE/mg anthocyanins; CAA – HepG2 cells: 3.91 μmol QE/100 mg anthocyanins	[54]
	Blueberry puree PSC: 10.21 μg V_CE/mL blueberry puree; CAA – HepG2 cells: 43.04 μmol QE/mL blueberry puree	[28]
	Blueberry leaves aqueous extracts DPPH: 30–1998 μmol TE/g	[52]
Strawberry (*Fragaria* x *ananassa* Duch.).	**Strawberry fruit extract** DPPH: 225 μmol TE/100 fw; ABTS: 350 μmol TE/100 fw; Oxygen radical absorbance capacity (ORAC): 150 μmol TE/100 fw; Antiproliferative activity against HT-29 (294 ± 26 μg/mL), SiHa (675 ± 27 μg/mL), and HeLa (385 ± 37 μg/mL) cancer cell lines (IC_{50})	[50]
Blackberry (*Rubus ulmifolius*)	**Blackberry fruit extract** DPPH: 300 μmol TE/100 fw; ABTS: 470 μmol TE/100 fw; ORAC: 220 μmol TE/100 fw; Antiproliferative activity against HT-29 (294 ± 26 μg/mL), SiHa (290 ± 61 μg/mL), and HeLa (254 ± 35 μg/mL) cancer cell lines (IC_{50})	[50]
	Blackberry fruit extract (four different cultivars) ORAC: 2–6 mmol TE/100 g Measurement of reactive oxygen species (ROS): 34.3, 48.4, 47.0, and 37.6%.	[31]
Goji berry (*Lycium barbarum* and *Lycium chinensis*)	**Ultrasound assisted goji berry fruits aqueous extracts** DPPH (IC_{50} values): 1.29–3.00 mg/mL; ABTS (IC_{50} values): 0.39–1.10 mg/mL; Viability of C2C12 cells – levels of four oxidative stress markers: ROS generation (no effect), GSH (127.5 and 189.5%), TBARS (21.8 and 9.4%) and CARB (26.8 and 29.9%)	[51]

Note: DPPH = scavenging activity in relation to 2-diphenyl-1-picrylhydrazyl radical, ABTS = scavenging activity in relation to 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) salt diammonium cation radical, FRAP = ferric reducing antioxidant power, EDTAE = EDTA equivalent, ORAC = oxygen radical absorbance capacity, PSC = Peroxyl scavenging capacity, CAA = Cellular antioxidant activity, TE = Trolox equivalent, ROS = Reactive oxygen species, GSH = Glutathione, CARB = Lipid peroxidation and protein carbonyl levels, QE = quercetin equivalent, TBARS = Thiobarbituric acid reactive substances, V_CE = Vitamin C (V_C) equivalent, fw = Fresh weight, IC_{50} = Half-maximal inhibitory concentration.

extracts have shown to be as effective as acarbose. Furthermore, the same authors discuss possible mechanisms underlying synergistic effects between acarbose and berry polyphenols. Other studies have documented the effective inhibitory effects of kaempferol (a flavonoid found in many berries) or hesperetin against α-glucosidase [64,65]. Targeting the inhibition of angiotensin-converting enzyme I (ACE) *in vitro* might be translated into a physiological blood pressure-lowering effect. Studies have shown that berries such as cranberries might present a certain effect on the inhibition of ACE. Furthermore, purified ellagitannins from strawberry were shown to have inhibitory effect on ACE at a concentration of 50 mg/mL, while in another study several strawberry cultivars were investigated for their ACE inhibitory properties, two of them presenting moderate inhibitory potential [66,67]. Nonetheless, blackcurrant aqueous extracts exhibited ACE inhibition in a comparative study, among other berries extracts. However these effects must be further investigated by well documented *in vivo* studies in order to seek their translational value [68–70].

Anti-inflammatory activity

Several *in vitro* studies have focused on the role of bioactive compounds present in berries in exerting anti-inflammatory activity. Most of these have been

undertaken using bioactive compounds-enriched extracts from berries or fermented berries beverages. A number of the phytochemicals found in berries have been shown to reduce chronic inflammatory conditions and associated side-effects by modulating the levels of inflammatory markers. Endotoxin lipopolysaccharide (LPS) is used to stimulate innate immunity by regulating the production of various inflammatory mediators (including TNF-α, IL-1β, IL-6, and IL-8) in monocytes/macrophages [71]. A polyphenol-enriched extract from strawberries displayed significant inhibition of IL-8 secretion in TNF-α-treated human gastric epithelial cells by dampening the NF-κB signaling [72]. In addition, the ellagic acid-enriched extracts from strawberries also imparted an anti-inflammatory effect by reducing TNF-α, IL-1β, and iNOS expressions by inactivating MAPKs signaling in murine macrophage RAW 264.7 cells [73]. Phenolic-enriched extracts from cranberry used to treat LPS-stimulated intestinal Caco-2/15 cells inhibited the release of pro-inflammatory cytokines (TNF-α and IL-6) by activating Nrf2 signaling [74].

Collectively, the *in vitro* studies reported here indicated that blueberry extracts possess an ability to modulate inflammatory markers in various cell types exposed to a variety of stressors via an antioxidative pathway [75–77]. In another *in vitro* study, anthocyanins-enriched fractions from fermented blueberry-blackberry beverages inhibited starch-degrading enzyme α-glucosidase, and dipeptidyl peptidase-IV activity in LPS-stimulated murine macrophages [78]. All *in vitro* studies have evaluated the anti-inflammatory effects of berries extracts, and therefore, the anti-inflammatory mechanisms of berries extracts have not been thoroughly explored.

Bioactivities of berries *in vivo*

Antioxidant activity

Fruits like berries may be an important component of a healthy diet because of their great content of phenolic acids and flavonoids, especially anthocyanins. These compounds exert *in vivo* antioxidant activity [79–81], such as in, rats [3,4,82,83], or humans [84,85]. These studies approach different conditions and diseases related to life style and try to associate the beneficial effects of different berries on different circumstances, such as dyslipidemia with blackberry, cranberry, and chokeberry [84], aging with strawberry [3] and goji berry [86], hypertension with blueberry [87], liver disorders with cranberry [83,88], depression with blackberry [4], metabolic syndrome [85], type-II diabetes and cardiovascular diseases with blueberry [85].

In general, recent studies assessed the performance of antioxidant defense systems through the dosage of hepatic [3], cerebral [4] and plasmatic [3,83] levels of the following biomarkers: protein carbonyl [3], glutathione, GSH [83], malondialdehyde, MDA, thiobarbituric acid reactive substances, TBARS [82,83], glutathione peroxidase, GPx [3,4,89], glutathione reductase, GR [3], superoxide dismutase, SOD [3,4,83], catalase, CAT [4,83,89], TBARS [4,82] and reactive oxygen species, ROS [3,4]. In this sense, Park *et al.* [89] revealed that supplementation with 30 g of freeze-dried black raspberry for four weeks increased CAT and GPx activities on plasma of health male smokers, thus decreasing cigarette smoke-induced oxidative stress. Moraes *et al.* [31] evidenced the antioxidant effects of berries since extracts of blackberry reduced the ROS generation by *Caenorhabditis elegans* worms by 34.3–48.4%. Overall, these recent findings associate the improvement of the evaluated parameters and protective effects with the AA and phenolic composition (i.e. cyanidin 3-*O*-glucoside, chlorogenic acid, catechin, gallic acid, and quercetin 3-*O*-rutinoside) of berries fruit [4,80,84,90]. In fact, as well stressed by Battino [91], phenolic compounds found in berries have the ability to modulate the expression of several genes and proteins involved in apoptosis, inflammation, antioxidant defense, lipid metabolism, and mitochondrial biogenesis.

For instance, an *in vivo* study using rats pointed out that the strawberry intake increased in 16.9%–55.9% the antioxidant enzyme activities (GPx, GR, SOD and CAT), mitochondrial biomass and functionality, and decreased 17.8% of ROS levels and up to 47.4% of plasma biomarkers of protein, lipid, and DNA damage. Polyphenols from strawberry have been proposed as activators of the AMP-activated protein kinase (AMPK) signaling pathway. This might explain the relationship between the consumption of polyphenol-rich foods and the slowdown of the advancement of oxidative stress and aging [3]. Moreover, antioxidant properties of cranberry peel intake ameliorating steatosis and inflammatory biomarkers in the rat's liver, decreasing serum and liver triacylglyceride contents, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, as well as reducing tumor necrosis factor-alpha (TNFα) and transforming growth factor-beta (TGFβ) levels in serum [88].

In healthy human volunteers, juice consumption with blueberry, cranberry, chokeberry, and apple for 21 days resulted in a decrease of 30% in low-density lipoprotein (LDL) cholesterol levels and increased by up to 20% the high-density lipoprotein (HDL) cholesterol and total antioxidant status. Thus, it seems that the regular intake of berries positively impacts lipid profile in human models [84]. Additionally, Curtis *et al.* [85] observed that the intake of blueberries (150 g/day) for 6 months by overweight and obese adults, improved endothelial function, elevated HDL cholesterol and total concentrations of anthocyanin-derived phenolic acid metabolites in serum and 24-hour urine. This study proposed a reduction of 12–15% in cardiovascular diseases risk with the blueberry consumption daily.

In summary, these researches shed light on the health-promoting effects of berries intake, which open avenues to exploit their use in preparing nutraceuticals and functional foods with beneficial effects against diseases and disorders related to oxidative stress.

Antihypertensive and antihyperglycemic activities

As we have shown above, berry bioactive, including anthocyanins and chlorogenic acids, are recognized for their inhibitory effects on carbohydrate digestions and consequently glucose absorption. Several animal and human studies have shown the positive effects of anthocyanins and other berry polyphenols on the postprandial plasma glucose curve [92]. However, substantial heterogeneity can be seen in these studies using various berries (blueberry, lingonberry, blackcurrant, cranberry, raspberry, cloudberry, and chokeberry) or berry combinations, methods of administration, and peculiarities of each study [92]. Simultaneously, 150 g whole berry-puree consisting of a mixture of equal amounts of strawberries, bilberries, cranberries, and blackcurrants significantly reduced the postprandial insulin response in healthy women [93].

Berries, such as blueberries and chokeberries, effectively reduce blood pressure via inhibition of ACE, *in vivo*. Particularly, feeding blueberries for spontaneously hypertensive stroke-prone rats led to a lowering blood pressure effect which was partially ascribed to inhibition of ACE activity [94]. Additionally quercetin, an ubiquitous flavonoid found in berries have shown antihypertensive activity (162 mg/day) in overweight-to-obese patients with prehypertension and stage I hypertension [67,95]. Concerning phenolic acids, Agunloye *et al.* [96] have shown that caffeic and clorogenic acids (10 and 15 mg/kg/day) administered to cyclosporine induced hypertensive rats present the ability to decrease systolic blood pressure, heart rate, and ACE activity.

Anti-inflammatory activity

In vivo studies are essential to understand the in-use potential and activities of berries. Table 3 summarizes the animal and human studies that have demonstrated the potential for using berry extracts (i.e. freeze-dried powder, concentrated fruit extracts/purees, or beverages) to modulate pro-inflammatory markers, antioxidant enzymes, and signaling pathways. Various in *vivo* studies (mice and humans) have demonstrated the anti-inflammatory effects of berries. For example, Glisan *et al.* [97] reported a significant anti-inflammatory activity of cranberry (0.8% w/w cranberry extract in diet) against high-fat-diet-induced hepatic inflammation and histological severity of nonalcoholic fatty liver disease (33% decrease in area, 29% decrease in lipid droplet size); and hepatic protein levels of TNF-α and C-C chemokine ligand 2 were reduced by 28% and 19%, respectively. Song *et al.* [98] examined and reported on the anti-inflammatory properties of blueberry anthocyanins using a streptozotocin-induced rat diabetes model. Blueberry anthocyanins, at 20, 40, and 80 mg/kg were given orally for about 12 weeks, significantly decreased vascular endothelial growth factor and Interleukin-1β in the serum of diabetes rats. However, a significant increase in GSH content and GPx activity was observed with hosts provided blueberry anthocyanins.

Berries are most well-known and touted for delivering potent dietary antioxidants; however, limited data are available about their potential anti-inflammatory effects in humans. In one study, Edirisinghe *et al.* [106] supplemented overweight adults who consumed a high-carbohydrate, moderate-fat meal with 305 g of strawberry beverage intake daily for 7 days in a cross-over design. Results indicated the strawberry beverage consumption significantly attenuated the postprandial inflammatory response measured by high-sensitivity C-reactive protein (CRP) and interleukin-6, two major biomarkers of *in vivo* inflammation. In another study, Chew *et al.* [110] investigated the effects of consuming 450 mL/day of cranberry beverage for 8 weeks in a randomized, double-blind, placebo-controlled, parallel design trial on overweight or obese adults with abdominal adiposity. Blood and urine biochemical parameters were measured at baseline and after the intervention. Specifically, after 8 weeks of cranberry beverage consumption, fasting CRP and serum insulin were significantly decreased, and HDL cholesterol was increased compared to the placebo group.

The *in vivo* evidences support berries' purported ability and their derived products to confer properties that favorably exert anti-inflammatory benefits. The clinical trials demonstrating these effects used traditional cross-over or parallel study designs, while several questions remain in order to provide specific dietary recommendations, including optimal dose, delivery mode, timing and frequency of intake in different populations, and further investigations are required to clarify, confirm and optimize benefit effects in human.

Microbiota modulation

The gut microbiota comprises bacteria, fungi, viruses, protozoa, and archaebacteria present in the intestinal tract [111]. A diet rich in carbohydrates, fats, and proteins of animal origin, combined with a low fiber intake, can decrease the presence of beneficial microbiota as *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Lactobacillus* spp., *Bifidobacterium* spp., *Clostridium* cluster XIVa [112]. On the other hand, a diet rich in bioactive compounds can promote many health benefits, such as modulating the gastrointestinal tract beneficial microbiota, inhibiting negative bacteria proliferation.

The intestinal microflora is formed mainly by *Firmicutes* and *Bacteroidetes*, representing about 90% of its composition. The remainder consists of Proteobacteria,

Table 3

***In vivo* effects of berries on inflammation markers**

Berries species	Route of administration - dose	Results	References
Strawberry	Oral – 2.35% freeze-dried strawberry in diet for 10 weeks	Significant decrement in endothelial-dependent vasorelaxation and blood pressure, and expression of NOX2 and inhibitor-κB kinase in diabetic db/db mice	[99]
Strawberry	Oral – 2.5 or 5.0% freeze-dried strawberry in diet for 37 days	Significant decrement in disease activity index, colon shortening and spleen enlargement, proinflammatory immune cells in DSS-treated male CD-1 mice	[100]
Cranberry	Oral – gavaged daily 200 mg/kg cranberry extract for 8 weeks	Significant decrement in liver weight and triglyceride accumulation, hepatic oxidative stress and inflammation and hyperinsulinaemia in high fat/high sucrose-fed C57BL/6J mice	[5]
Cranberry	Oral – 1.5% freeze-dried strawberry in diet for 37 days	Significant decrement in colon shortening, disease activity, histologic score, pro-inflammatory cytokine (IL-1β, IL-6 and TNF-α) in DSS-treated male CD-1 mice	[101]
Cranberry	Oral – 0.8% cranberry extract in in diet for 10 weeks	Significant decrement in plasma alanine aminotransferase, histological severity, hepatic TNF-α, C-C chemokine ligand 2, TLR4 and NF-κB in high fat-fed obese C57BL/6J mice	[97]
Blueberry	Oral – 10% blueberry powder in in diet for 8 weeks	Significant decrement in ileal villus height, pro-inflammatory cytokine (IL-1β and TNF-α), hepatic insulin receptor substrate 1 in high-fat-diet-fed male Wistar rats	[102]
Blueberry	Oral – gavaged daily 20, 40, and 80 mg/kg blueberry anthocyanins for 12 weeks	Significant decrement in blood glucose, MDA and ROS levels, VEGF and IL-1β in the serum; and increase in GSH and GPx, and Nrf2 and HO-1 in streptozotocin-induced rat diabetes model	[98]
Blueberry	Oral – gavaged daily 12.5 mg/kg blueberry fruit extract for 2 weeks	Significant decrement in paw volume increase, joint pathology and the soft tissue edema in the hind paw, synovitis and cartilage damage, COX2 and iNOS expressions and neutrophils Infiltration, and pro-inflammatory cytokine (IL-1β, IL-6 and TNF-α) in collagen-induced Wistar rat arthritis model	[103]
Blueberry	Oral – gavaged daily 100 or 200 mg/kg blueberry anthocyanins for 4 weeks	Significant decrement in MDA and protein carbonyl content of liver, MCP1, IL-1β, MIP-2 contents and Colagen III and α-SMA in CCl_4-treated male C57BL/6J mice	[104]
Blackberry or Blueberry	Oral – 200 mg/kg diet of blackberry or blueberry anthocyanins in diet for 12 weeks	Significant decrement in body weight gain, serum and hepatic lipid levels, pro-inflammatory cytokine (IL-6 and TNF-α); and increase in SOD and GPx activities in high-fat-diet-fed C57BL/6 mice	[105]
Strawberry	Oral – strawberry beverage (305 g/day) daily for 7 days	Significant decrement in postprandial inflammatory response (high-sensitivity CRP and IL-6) in consumed a high-carbohydrate, moderate-fat meal overweight adults	[106]
Blueberry	Oral – 22 g freeze-dried blueberry powder daily for 8 weeks	Significant decrement in blood biomarkers of 8-OHdG in postmenopausal women with pre- and stage 1-hypertension	[107]
Blueberry	Oral – 250 g of blueberries daily for 6 weeks and 375 g given 1 hour before 2.5 hour of running	Significant decrement in blood F_2-isoprostanes and urine 5-OHMU; increase in plasma IL-10 and NK cell counts after 2.5 hour of running in well-trained subjects	[108]
Blueberry	Oral – 25 g of freeze-dried blueberries powder daily for 6 weeks	Significant decrement in the levels of endogenously oxidized DNA bases and the levels of H_2O_2-induced DNA damage in male middle-aged volunteers	[109]
Cranberry	Oral – 450 mL of cranberry extract beverage daily for 8 week	Significant decrement in endothelin-1, nitric oxide and fasting CRP in overweight or obese adults with abdominal adiposity	[110]

Note: ROS = reactive oxygen species, MDA = malondihaldehyde, SOD = superoxide dismutase, CRP = C-reactive protein, DSS = dextrane sulfate sodium, GPx = glutathione peroxidase, IL = interleukin, GSH = glutathione, TNF = tumor necrosis factor, SMA = smooth muscle actin, VEGF = vascular endothelial growth factor.

Actinobacteria, Fusobacteria, and Verrumicrobia [113]. The *Firmicutes*/*Bacteroidetes* balance is fundamental for microbial balance and homeostasis, consequently, the health status. This proportion will depend on dietary habits and age, immunological status, lifestyle, and antibiotic usage, among other hosts' habits.

The dysbiosis, or the impairment of the gut microbiota's eubiotic status, is represented by an imbalance in a normal microbial ecosystem's density or diversity. This imbalance may be responsible for many diseases such as diabetes, obesity, immunological and neurological diseases, inflammatory bowel disease, among others [113]. Furthermore, a diet rich in fat might sway directly the dysbiosis process, inducing to enhancement circulating lipopolysaccharide and serum hepatic lipids, as well as gut barrier dysfunction. In this sense, the higher *Firmicutes*/*Bacteroidetes* ratio correlates with obesity and increased body weight [114].

According to Moorthy *et al.* [115], polyphenols are considered the 'new' prebiotics. The more recent definition of prebiotics is '*a substrate that is selectively utilised by host microorganisms and conferring a health benefit*' [116]. Moorthy *et al.* [115] reported significant modulation of gut microbiota associated with the consumption of polyphenols.

The high antioxidant capacity of berries is directly related to polyphenols, particularly anthocyanins, hydroxybenzoic

acids, hydroxycinnamic acids, and flavonols, and proanthocyanidins. These compounds have a high metal-binding capacity and limit free iron availability by iron chelation, contributing to minimizing the production of iron-promoted radicals (Fenton reaction), partly explaining their potent antioxidant effect [117]. However, the bioavailability of polyphenols is limited, and they are poorly absorbed in the gut tract. It is estimated that only 5–10% of the total intake is absorbed in the small intestine [115]. The remaining can reach the large intestinal lumen, where they may be subjected to the gut microbial community enzymatic activities [118].

Among polyphenols, quercetin and resveratrol are among the most studied and capable of promoting beneficial health effects. Phenolic compounds are not considered micronutrients, but their bioactive properties confer them antimicrobial, antioxidant, anticancer, anti-inflammatory, and immunomodulatory effects [113]. Quercetin, a free radical scavenger and directly inhibitor of oxidation processes, is present in many berries. It can alter antioxidant defense as an effective antioxidant for protecting biomolecules against ROS. Then, quercetin may exert protective effects against diabetes, cardiovascular disorders, inflammation, cancer, and nerve and vision damage [119]. However, its bioavailability is low, around 5.3%, and, upon reaching the intestine, the endogenous microflora is not negatively affected in the gut [120].

Some berries are also a source of resveratrol (3,5,4′-trihydroxy-*trans*-stilbene). Studies have shown an increase in the *Bacteriodetes/Firmicutes* ratio associated with resveratrol consumption [121] with an expressive increase of *Parabacteroides*, *Bilophila*, *Akkermansia*, and a decrease of *Lachnospiraceae*. Lund and Pantuso [122] verified the increase of resveratrol permeability in Caco-2 cells in 350% when administered in combination with curcumin, quercetin, and piperine.

Upon reaching the gastrointestinal tract, the existing microbiota plays an essential role in the metabolism of polyphenols. The microbiota can catabolize flavonoids that have not been absorbed into smaller molecules, such as phenolic and aromatic acids, which can then be absorbed by the intestinal villi [123]. On the other hand, anthocyanins' presence can alter the gut microbiota's composition and functionality [5,6]. However, this bilateral relationship is still not well known [123–125].

The gut microbiota can also be modulated by polyphenols that promote the increase of symbiotic bacteria involved in the attenuation of dysbiosis disorders. Short-chain fatty acids (SCFA) are an example of microbiota biosynthesized products. SCFA, a subset of saturated fatty acids containing six or fewer carbon molecules, are the primary metabolites from homeostatic gut microbiota and are a source of energy for colonocytes [7,117]. Acetate, propionate, and butyrate are the principal SCFAs produced in the gut, representing 95% of the total [126]. The SCFAs presence also plays a function of protecting the colonic health. They improve the gut barrier by maintaining its lining [127]. The disruption of this barrier can promote an inflammatory state by the intestinal permeability increase, allowing the passage of harmful substances, such as bacterial LPS, as shown in Figure 2. In this context, prevention of gut microbiota dysbiosis as well as the preservation of the gut epithelial barrier function are fundamental for the handling of metabolic disorders and of metabolic endotoxemia associated to obesity [128,129].

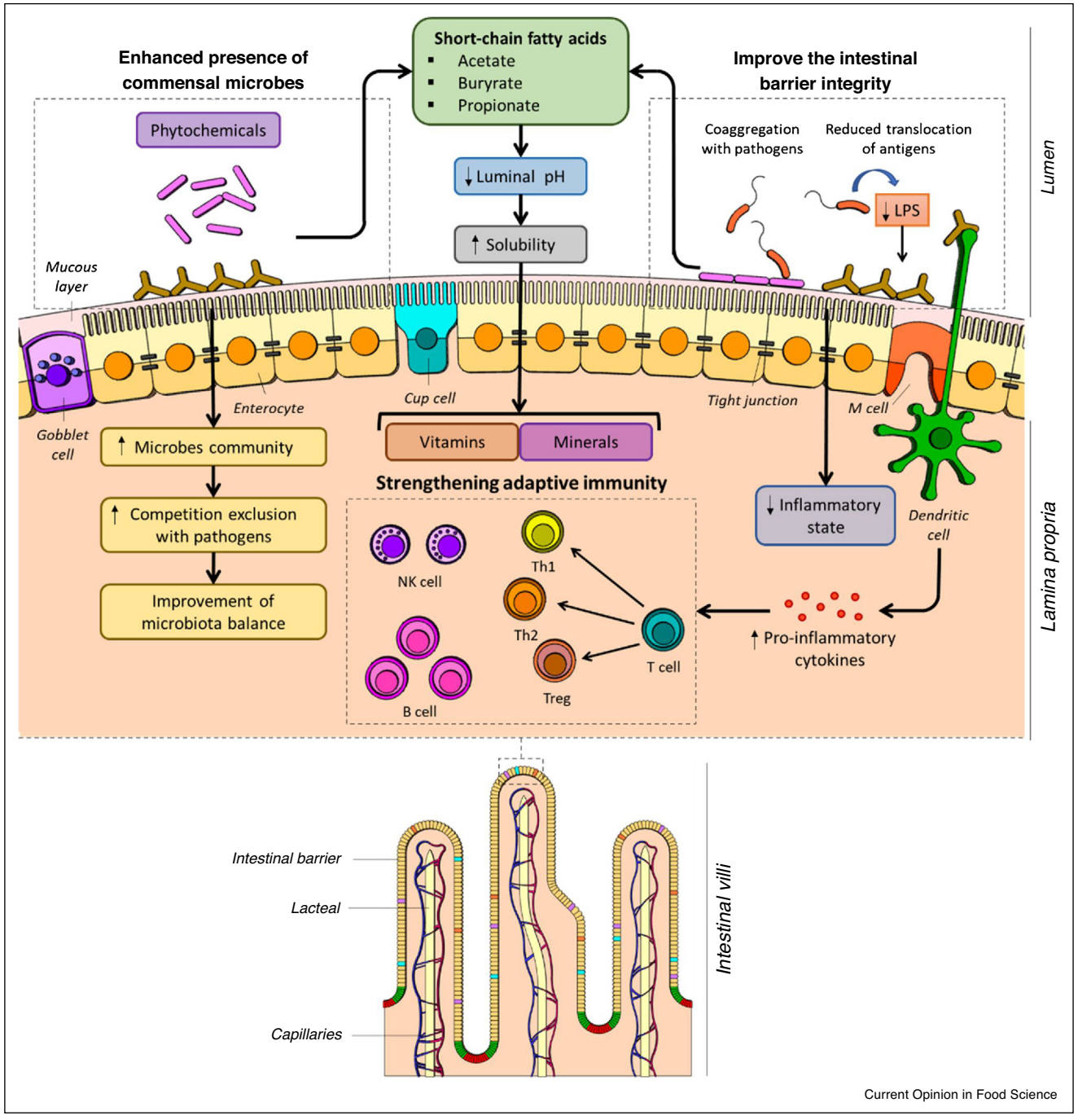
The presence of long-chain oligosaccharides that are not hydrolyzed in the small intestine can reach the colon and be metabolized by specific bacteria as the probiotic *Bifidobacterium longum* and secret formate *in vitro* assay using cranberries [130]. The formate production can increase adenosin triphosphate (ATP) production, which is beneficial for the xyloglucan metabolism [117].

The decrease of the inflammatory state can be given by the reduction of 2-cyclooxygenase (COX-2) caused by the presence of proanthocyanidins from cranberry, as demonstrated by Madrigal-Carballo *et al.* [131], which studied *in vitro* LPS-stimulated macrophages. In a study conducted by Anhê *et al.* [124], the cranberry extract decreased ROS-induced lipid peroxidation in the liver, decreasing the inflammatory status.

Concerning the gut epithelial barrier, this may have its permeability increased due to a dysfunction, resulting in increased inflammatory response. Among chronic inflammatory conditions, such as inflammatory bowel diseases, a non-standard immune response and excessive pro-inflammatory presence, such as cytokines, contribute to decreased intestinal cells' barrier function [132]. The same authors found that the presence of anthocyanins and their catabolites inhibited dysfunction caused by cytokines in Caco-2 cells.

Some beneficial effects of berry consumption may be related to the more pronounced growth of beneficial bacteria in the gut, such as probiotics. Studies have demonstrated an effect against obesity, as mentioned by Cao *et al.* [133], where the consumption of blueberry, black raspberries, and lingonberries increased the count of *Bifidobacterium*, some subspecies of *Lactobacillus* and *Bacteroidetes* and showed anti-obesity activity. In this sense, the ability to increase the immunomodulatory property inducing the selectively of these microorganisms present in the gut microbiota was described by Ballan *et al.* [134]. According to the researchers, these microorganisms might also enhancement the phagocytic activity and modulate the production of natural killer cell

Figure 2



Main mechanisms of the action of phytochemicals, such as anthocyanins, chlorogenic acid, epicatechin found in berries. Note: LPS – lipopolysaccharide; M cell – microfold cell; NK cells – natural killer cell; Th1 – type 1 T helper cell; Th2 – type 2 T helper cell; Th17 – type 17 T helper cell; Treg – regulatory T cell.

function, dendritic cell activity improving the immune response through regulatory T cell (Treg) or effector as T helper cells (Th1, Th2 or Th17). On the other hand, although the accurate mechanism of Treg function remain still unsure, these cells may promote regulatory effects on other immune cell types as B lymphocytes also known as B cells [135]. Besides, the ability to protect the gut barrier integrity of the host is fundamental for commensal micro-organisms [136]. In this way, these features involve aggregation to pathogenic micro-organisms, the

Table 4

Effects of berry consumption on the microbiota modulation

Berry	Compounds involved	Microorganisms	Effect associated	Reference
Berry mixture (blueberries, blackberries, raspberries, Portuguese crowberry and strawberry tree fruit)*	Polyphenols	Expansion of the family *Proteobacteria* and decrease of *Erysipelotrichaceae*	Blood pressure regulation and anti-inflammatory	[125]
Blueberry (purified extract)	Anthocyanins (malvidin 3-*O*-glucoside, malvidin 3-*O*-galactoside, petunidin 3-*O*-glucoside)	Relative abundance of *Bifidobacterium*	Prebiotic activity with associated health benefits	[137]
Blueberry (polyphenol extract)*	Polyphenols	Increase of *Bifidobacterium*, *Desulfovibrio*, *Adlercreutzia*, *Helicobacter*, *Flexispira*, and *Prevotella*	Suppression of the body weight gain	[138]
Blueberry powder*	Polyphenols	Increase of *Gammaproteobacteria*	Protect against a high-fat diet-induced inflammation by reducing TNF-α and IL-1β levels	[102]
Blueberry pomace (fermented product)**	Polyphenols	Inhibiting *Escherichia coli*, *Enterococcus* and the ratio of *Firmicutes* and *Bacteroidetes*, increase of *Bifidobacterium*, *Ruminococcus*, and *Akkermansia*	Increase of SCFAs, especially acetic, butyric and lactic acids	[139]
Blueberry anthocyanin extract (encapsulated)**	Anthocyanins	Increase of *Bacteroidetes*	Biosynthesis of SCFAs	[105]
Cranberry (whole cranberry powder)*	Polyphenols	Decrease in the abundance of *Firmicutes* and increase in *Bacteroidetes*	Weight loss, increase in secondary bile acids and decrease in SCFAs	[7]
Cranberry (by-products/ pomace)***	Polyphenols	Increase in *Bifidobacterium*, unclassified_*Rikenellaceae*, and *Faecalibacterium*	More studies are needed, but was observed SCFAs-producing	[140]
Black raspberry*	Anthocyanins	Increase of *Akkermansia* and *Desulfovibrio* and decreased abundance of *Clostridium* and *Acetanaerobacterium*	Could inhibit gut inflammation by increasing the anti-inflammatory bacteria	[141]
Black raspberry*	Polyphenols	Increase in *Bacteroides*, *Butyricimonas*, *Mucispirillum*, and *Ruminococcus*	Glucose control associated with an increase in short-chain fatty acids	[142]
Goji berry*	Polyphenols	Increases in *Bifidobacteria*	Decreases in the contents of ω-6 polyunsaturated long-chain fatty acids (PUFA), inhibition of urease activity and anabolism of amino acids in the colon	[143]
Goji berry**	Polyphenols	Increase of genera *Bacteroides*, *Bifidobacterium*, *Phascolarctobacterium*, *Clostridium*XlVb, *Prevotella* and *Collinsella*	Production of SCFAs	[144]
Goji berry*	Polyphenols	Increase in microbiota diversity	Production of SCFAs	[145]
Goji berry*	Polyphenols	Increase of *Akkermansia*, *Lactobacillus*, and *Prevotellaceae*	Enhance the innate immunity	[146]
Blackberry**	Rutin, coumarin, 2,4,6-trihydroxybenzaldehyde	Not identified	Increase of the glucose consumption in HepG2 cells	[147]
Strawberry*	Anthocyanins	Decrease the abundance of *Verrucomicrobia and* increase the abundance of *Bifidobacterium*	Control of diabetes	[99]

Note: SCFA = short chain fatty acids, TNF = tumor necrosis factor, IL = interleukin, *study in animals, **study *in vitro*, ***study in pasture-raised broiler chickens.

inhibition of gut epithelium adhesion and the synthesis of antimicrobial substances (Figure 2).

Table 4 presents some recent studies involving berries consumption and their modulating effects on the intestinal microbiota. Some studies were carried out using by-products from the juices and jams manufacture, demonstrating the functional potential of the material that would be discarded.

Other nontraditional berries are also studied. According to Massa *et al.* [148], phenolics present in jabuticaba (fruit native from the Brazilian Atlantic forest), specially cyanidin 3-*O*-glucoside, gallic acid, hesperidin, catechin,

epicatechin gallate, procyanidin, rutin, epicatechin, and epicatechin gallate, improved the growth of *Lactobacillus* and *Bifidobacterium* species, decreased the pH of the gut, increased lactic acid, and SCFA production, indicating prebiotic effects. Inada *et al.* [149] studied the by-product of jabuticaba (peel and seed). They observed cyanidin 3-*O*-glucoside, ellagic acid, and gallic acid and verified an increase of phenolics bioaccessibility in an *in vitro* study.

Sea buckthorn berries (*Hippophae rhamnoides*), originated from Central Asia and Europe, have been recognized for their antioxidant, cytoprotective, immunomodulatory, and cardioprotective properties [150]. The same authors investigated the effect of polyphenol rich sea buckthorn berries juice on colonic microbial composition and diversity using *in vitro* simulated gut model made an *in vitro* study, and the data demonstrated the presence of sea buckthorn pulp enhanced the counts of total bacteria, lactic acid bacteria, and *Entrococcus* sp.

Despite the advance in the number of studies involving the consumption of berries and microbiota modulation, preclinical and clinical studies are still needed to prove the physiological responses of bioactive compounds for each human individual [117]. Many studies have still been carried out *in vitro* or *in vivo* (using animals), and little is known about any possible effects on humans. Some anthropometric measures, such as body weight, waist circumference, hip circumference, and clinical markers [CRP, TNFα, IL-6, IL-1β, blood pressure, glucose, total cholesterol (TC), triacylglycerides (TAG), HDL and LDL; other markers - bile acid and fecal pH] and the real effect of polyphenols on the human intestinal microbiota remains to be evaluated [115]. Most research evaluation time is relatively short, around 4–6 weeks, not revealing the possible effects of long-term consumption.

The methodologies used are quite different. *In vitro* and *in vivo* studies using animals represent the most used techniques today. Thus, it is difficult to compare the methodologies and group the effects on the human intestinal microbiota. In general, it is almost consensus among studies the increase of beneficial bacteria such as *Bacteroidetes* and decrease of *Firmicutes* and the production of short-chain fatty acids (SFCA).

Concluding remarks

The current review brings relevant topics concerning the primary evidence on the bioactivities of different berries, from phenolic composition to anti-inflammatory, antioxidant, anti-hypertensive, anti-hyperglycemic and cell-protecting effects. Taken altogether, more *in vivo* data are required to understand the mechanisms of action, while clinical trials using different characteristics (i.e. gender, age, pre-existence of diseases) should be performed so new information on the bioactivity of berries can be unveiled. These results and evidences will be the basis for a possible increase in consumption, which may trigger the primary production of berries and processing companies to develop and optimize processes.

Conflict of interest statement

Nothing declared.

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