




## Review

# Comparison of Health-Relevant Polyphenolic Component Content and Bioavailability of Bilberry (*Vaccinium Myrtillus L.*), Blueberry (*Vaccinium Sect. Cyanococcus Rydb.*) and Chokeberry (*Aronia Melanocarpa (Michx.) Elliott*)

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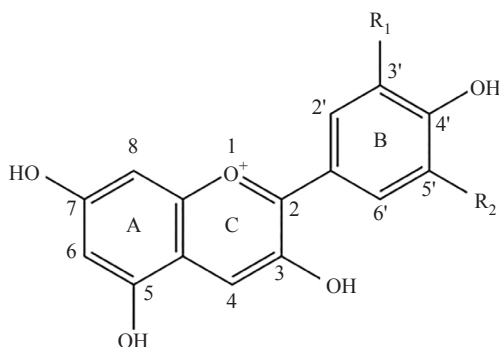
**Abstract:** The fruit-based dietary supplement business is flourishing, and many plant bioactive compounds exhibit beneficial effects on health. Polyphenols, including anthocyanins, proanthocyanidins, flavonols, phenolic acids and flavanols in bilberry, blueberry and chokeberry, are the bio-factors that determine the biological activities of the three berries. Many reports on phenolic compounds and their biological activities in berries have been published. Therefore, it is urgent to make a systematic comparison among them. We reviewed these scientific researches about phenolic substances including their compositions, contents and bioavailability from the bilberry, blueberry and chokeberry. On this basis, the phenolic compounds regarding monomer components and their contents in the three berries were systematically summarized. Variations of anthocyanidins within interspecies and different families were explained. Biological properties including biostability and bioavailability of anthocyanin and prospects for further study on berries were contained.

**Keywords:** berries, anthocyanins, proanthocyanidins, flavonols, bioavailability

## 1. Introduction

Berries are rich in antioxidant phytochemicals among fruits and vegetables [1], and are desirable fruits due to their therapeutic effects [2]. Much effort has been dedicated to uncovering their various health benefits mainly because of the complex anthocyanin profile, a great amount of anthocyanin and other therapeutic contents of flavonols, phenolic acids, flavanols, etc. [2]. Among several fruits, bilberry (*Vaccinium myrtillus L.*), blueberry (*Vaccinium spp.*) and chokeberry (*Aronia melanocarpa*) are highly consumed and contain various bioactive compounds. The reported data indicated that acidic alcohol aqueous solution is usually used in the extraction process, and evaporation could lead to partial hydrolysis of acylated anthocyanins. In the production process, special attention should be paid to maintaining the native anthocyanins profile, particularly during hot processing, and a relatively expensive column should be used to enrich anthocyanins, thus making berry anthocyanins more expensive. In such a case, market adulteration is therefore

nothing new [3-5]. Based on that, a review of the phenolic substances in berries including their compositions, contents and their related bioactivities may contribute to the development of pharmaceutical and nutritional products.



**Figure 1.** The structures of common anthocyanidins in nature

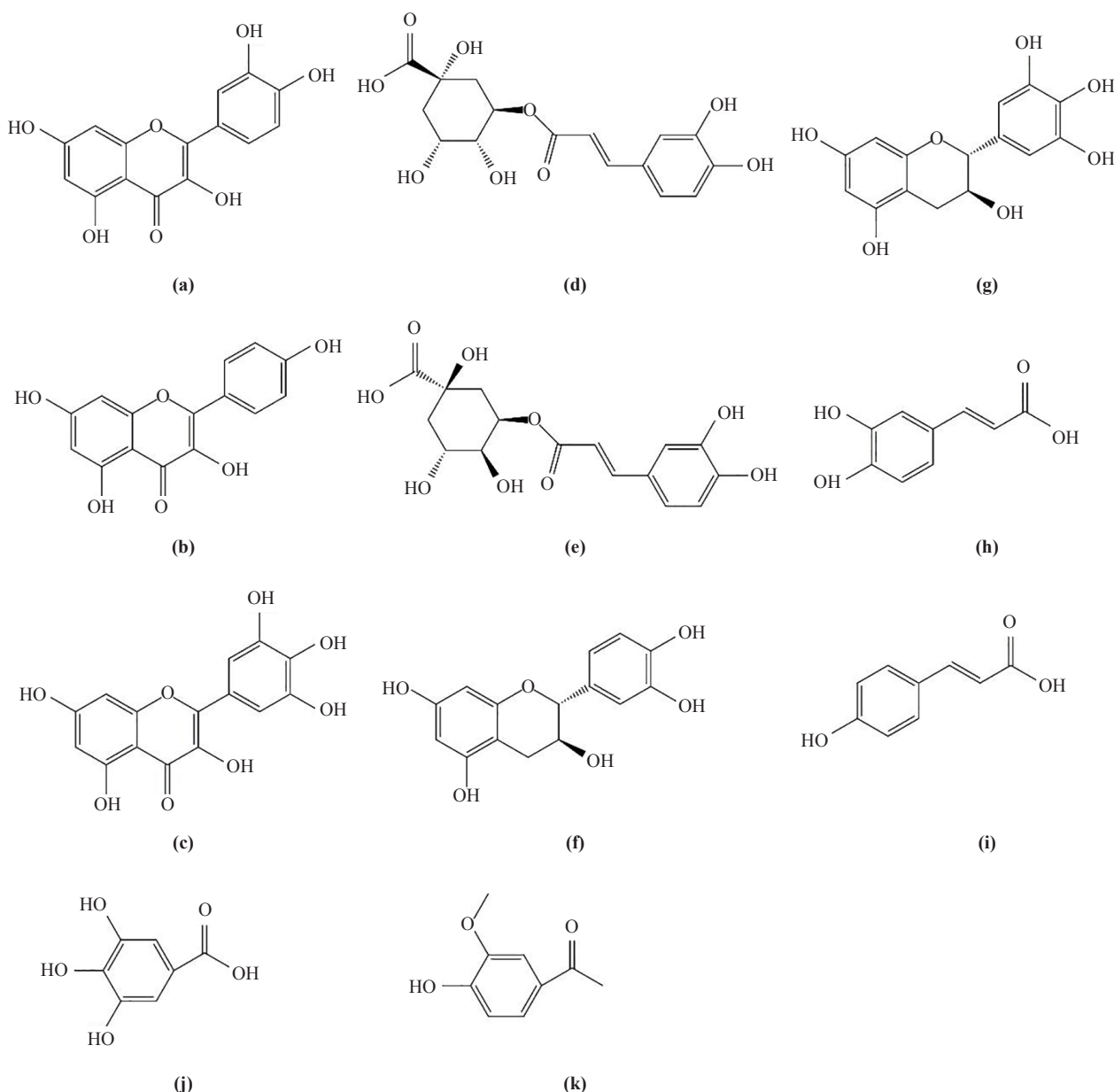
**Table 1.** The structures of common anthocyanidins in nature

Anthocyanidins	R <sub>1</sub>	R <sub>2</sub>
Cyanidin	OH	H
Peonidin	OCH <sub>3</sub>	H
Petunidin	OH	OCH <sub>3</sub>
Malvidin	OCH <sub>3</sub>	OCH <sub>3</sub>
Delphinidin	OH	OH
Pelargonidin	H	H

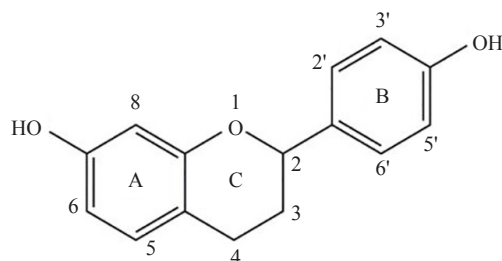
Anthocyanins (Figure 1, Table 1) are composed of anthocyanidin aglycone and a sugar moiety mainly attached at 3-position on the C-ring or less frequently at 5- or 7-position on A-ring [6-7]. More than 650 different anthocyanins [8] and 23 anthocyanidins [9] have been reported, which differ in the number of hydroxyl groups, the degree of methylation, the nature, number, and the placement of sugars attachment to anthocyanidins, as well as the type and number of aliphatic or aromatic carboxylate attached to sugars in the molecules [6, 9]. The six most prevailing anthocyanidins in nature are cyanidin (50%), delphinidin (12%), petunidin (7%), peonidin (12%), pelargonidin (12%) and malvidin (7%), which are distinguished by the number and position of the hydroxyl and methoxy groups on the B-ring (Figure 1). The glycoside derivatives that extensively exist in nature are 3-monosides, 3-biosides, 3,5- or 3,7-diglucosides, where 3-O-glucoside are very common in nature, which is 2.5 folds higher than 3,5-diglucoside. Accordingly, cyanidin-3-O-glucoside is found to be the richest [9].

There are many other bioactive substances in berries, including flavonols, procyanidins and phenolic acids. Flavonols such as quercetin, myricetin, kaempferol (Figure 2) and their derivatives (primarily glycosides) are the main representative molecules, which have been identified and quantified in literature [10]. Their pharmacological effects are available as well, for instance, the antioxidant, anti-amyloidogenic, antibacterial, antiviral, antidiabetic, anticancer, anti-inflammatory, anti-epileptic and anti-ulcer activities of myricetin [11]. Evidence suggests that quercetin could regulate key signaling pathways to prevent diseases [12]. Proanthocyanidins (Figure 3, Table 2), effective antioxidants, are important oligomeric and polymeric polyphenolic substances in berries [12]. They commonly consist of procyanidins, prodelfinidins and propelargonidins with their respective monomer as (epi)catechin, (epi)gallocatechin (Figure 2) and

(epi)afzelechin. The length of proanthocyanidins chain or molecule size can be described by the degree of polymerization (DP). Flavan-3-ol units frequently linked by C4-C8 or C4-C6 bond (B type) or by an additional C2-O-C7 or C2-O-C5 bond (A type) (Figure 3, Table 2). [13]. Phenolic acids are non-flavonoid polyphenolic components with the structure of a carboxyl group linked to the benzene ring. They are derived from two major phenolic components, benzoic and cinnamic acids [12]. Hydroxycinnamic derivatives (chlorogenic neochlorogenic, *p*-coumaric, caffeic acids, etc.) and hydroxybenzoic derivatives (gallic and vanillic acids) (Figure 2) are common phenolic acids in berries, of which chlorogenic acid and neochlorogenic acid are frequently found to be present in high levels. The therapeutic effect of chlorogenic acid on the Parkinson's and Alzheimer's diseases, and the antitumor effect of neochlorogenic acid on human gastric carcinoma cells have been documented [14-15]. Ellagic acid, abundant in berries, has been shown to lower cholesterol and blood pressure [12].



**Figure 2.** Some polyphenolic compounds measured in berries: (a) quercetin, (b) kaempferol, (c) myricetin, (d) chlorogenic acid, (e) neochlorogenic acid, (f) catechin, (g) gallocatechin, (h) caffeic acid, (i) *p*-coumaric acid, (j) gallic acid and (k) vanillic acid



**Figure 3.** The structures of proanthocyanidins in nature

**Table 2.** The structures of proanthocyanidins in nature

Proanthocyanidins	3	5	8	3'	5'
Procyanidin	OH	OH	H	OH	H
Prodelphinidin	OH	OH	H	OH	OH
Propelargonidin	OH	OH	H	H	H
Prorobinetinidin	OH	H	H	OH	OH
Profisetinidin	OH	H	H	OH	H
Proguibourtinidin	OH	H	H	H	H
Proapigeninidin	H	OH	H	H	H
Proluteolinidin	H	OH	H	OH	H
Procassinidin	H	H	H	H	H
Protrictetinidin	H	OH	H	OH	OH
Promelacacinidin	OH	H	OH	OH	H

Because of that, structure identification, analysis methodology, ingredients in foods and their influencing factors, postharvest processing, bioavailability and stability are dominating research topics. That's therefore what we're going to focus on in this review. Meanwhile, the (poly)phenolics of bilberry, blueberry and chokeberry have been extensively reported. However, there is a lack of comparison of phenolic compounds in the above three berries, and a systemic summary on the explanation for these discrepancies obtained in various reports and factors influencing the compositions is clearly worthwhile. Herein, the most recent investigations about the (poly)phenolics of the three berries, including anthocyanins, proanthocyanidins, flavonols, phenolic acids and flavanols, with an emphasis in comparing their compositions and contents and then explain discrepancies of the phenolic substances in materials are reviewed for the first time. Our work may contribute to the up-to-date research and development of pharmaceutical and nutritional products or promote awareness of the health-promoting properties of berries. Moreover, the biological properties of flavan-3-ols monomers and anthocyanidin-rich extracts are also given.

## 2. Botanical and chemical properties

### 2.1 Bilberry

Bilberry, a wild-type blueberry, is a perennial and low-growing shrub of the *Ericaceae* family, which grows chiefly

in Europe, North America and Asia [7, 16]. Its black or blue fruit, fleshy berry, is found to contain various secondary metabolites, such as vitamins, sugars, pectins and phenolics [17-18]. In 2012, bilberry was the 14th on the list of best-selling dietary supplements in the United States, with an estimated sale of \$3.75 million [3].

Anthocyanins, as the most widely studied class of phenolic substances of bilberry, account for content between 300 mg and 700 mg/100 g fresh weight (FW) [19]. The anthocyanin profile of bilberry is investigated to be a mixture of 15 anthocyanins including delphinidin, cyanidin, peonidin, petunidin and malvidin, while the sugar moiety attached consists of 3-O-glucoside, 3-O-arabinoside and 3-O-galactoside [5, 20]. Nearly all the anthocyanins are in glycoside forms in nature bilberry, with only a few percentages of anthocyanidins [21]. It has been reported that the percentages of delphinidin, cyanidin, malvidin, petunidin and peonidin of the total quantified anthocyanins in bilberry were 57.6%, 23.7%, 14.1%, 3.3% and 1.3%, respectively [6]. It was also found that the contents of cyanidin glycosides (170.72 mg/100 g FW, 30.26% of total anthocyanin amount) and delphinidin glycosides (171.64 mg/100 g FW) were relatively prominent, followed by malvidin glycosides (91.49 mg/100 g FW), petunidin glycosides (66.61 mg/100 g FW) and peonidin glycosides (33.71 mg/100 g FW) [22]. Cyanidins, as the most prevalent anthocyanin in berries, was identified in bilberry with merely 9-30% proportion of total observed anthocyanins [17, 23]. Nevertheless, another finding revealed the 89.01% proportion of cyanidin glycosides, followed by delphinidin glycosides (10.15%), and petunidin glycosides were demonstrated to present at low levels [24]. Regarding the sugar groups of bilberry anthocyanins growing in northern Europe, 60% were 3-O-glucosides, and the remaining 40% were about half of 3-O-galactosides and half of 3-O-arabinosides [25]. However, in *Slovenija*, the three sugars are almost equal, accounting for about 30% of total sugars [26]. With the same aglycones, 3-O-glucosides of bilberry is prone to be dominant in comparison to 3-O-galactosides and 3-O-arabinosides [5, 7, 17, 27].

Proanthocyanidins, a relatively large amount of polyphenol in bilberry, accounted for the level at 148 mg/100 g FW [20]. The contents of proanthocyanidins from monomers, dimers to polymers were reported to be at 4.1 mg/100 g FW (monomers), 37.2 mg/100 g FW (oligomers, 2-10 DP), and 53 mg/100 g FW (polymers). Bilberry proanthocyanidins are mainly composed of A-type procyanidins and prodelphinidin [28]. Ellagic acid pentoxide is the most abundant of bilberry phenolic acids (2.6 mg/g dry weight (DW)), followed by chlorogenic acid (0.71 mg/g DW). Caffeic acid, ferulic acid, ellagic acid, vanillic acid hesoside and dihydroxybenzoic acid hexoside were totally quantified to be 0.57 mg/g DW (Figure 2) [24]. Another class of phenolic compounds identified in bilberry is flavonols, among which myricetin-3-O-glucuronide (8.04 mg/100 g FW), quercetin-3-O-glucoside (5.9 mg/100 g FW), myricone-3-O-galactoside (5.59 mg/100 g FW) and myricetin-3-O-glucoside (4.65 mg/100 g FW) are found presenting at a relatively large amounts [22]. A report confirmed the presence of laricitrin-3-O-galactoside (0.49 mg/100 g FW), syringetin-3-O-glucoside (0.36 mg/100 g FW), syringetin-3-O-galactoside (0.039 mg/100 g FW), and syringetin-3-O-pentoside (0.053 mg/100 g FW). Quercetin and myricetin derivatives mainly exist in the form of 3-O-glucoside (3.04 mg and 1.04 mg/100 g FW) and 3-O-galactoside (2.44 mg and 0.88 mg/100 g FW). Isorhamnetin-3-O-glucoside/3-O-galactoside and kaempferol-3-O-rutinoside/3-O-robinobioside have been identified with their concentrations to be 0.96 mg and 0.65 mg/kg FW, 0.68 mg and 0.83 mg/kg FW, respectively [10].

More attention should be paid to the two reports mentioned above. The former confirmed a higher level of myricetin derivatives in bilberry, while the latter considered it to be quercetin derivatives. Moreover, the relative level of monomeric anthocyanin is significantly different. Reasons including growing environment, edaphic factors, and detecting conditions may explain the variation chemical composition or variation of phenolics content based on various reports. In such a case, it makes sense to rigorously screen the growing conditions for better berries.

## 2.2 Blueberry

Blueberry, one of the handful fruits native to North America, is a deciduous shrub of the *Ericaceae* family and genus *Vaccinium*. Highbush (North and South high) (*V. corymbosum* L.) and lowbush (*V. angustifolium* Aiton) are the three major species in the U.S. market [29], as well as the main commercially grown blueberries [30]. In 1980s, a large number of blueberry varieties were introduced to China, which was principally planted in northeast China. Blueberries are a major fruit commodity in U.S. with an annual output of 511 million pounds valued at \$860.1 million in 2011 [30].

Blueberry, a closely related species to bilberry in the genus *Vaccinium*, displays the analogical anthocyanins profile as bilberry [1]. The contents of anthocyanin in blueberries range from 140 mg to 820 mg/100 g FW [31], and 1.1 g to 2.6 g/100 g DW [32-33]. Anthocyanins of blueberry with 6-acetyl or non-acylated have been confirmed [19,

33-35], and the prevalent blueberry anthocyanins are indicated to be 15 major characteristic anthocyanidin glycosides, where five different aglycones (cyanidin, delphinidin, malvidin, peonidin and petunidin) are recognized with attached sugar moieties (glucose, galactose and arabinose) [32, 34, 36]. The anthocyanin profiles of all cultivars are similar, but the proportions are cultivar- and weather-dependent [1]. 12 to 27 anthocyanins were identified through the studies of different varieties of blueberry [37], which might be closely related to the varieties of blueberries, the multiple peaks in HPLC, or the different limits of detection under their conditions. Although many anthocyanins are quantified as particularly substantial, the relatively higher amount of delphinidin glycosides is confirmed, followed by cyanidin glycosides or malvidin glycosides [14, 34, 36, 38]. While peonidin glycosides, a minor amount of compounds in blueberry, sometimes are found below the detection threshold [4, 39]. Delphinidin glycosides and malvidin glycosides are frequently prevalent in the form of 3-O-glucosides and 3-O-galactosides [40]. The anthocyanin profiles of six cultivated highbush blueberry varieties and one lowbush or wild blueberry were examined, which revealed that the delphinidin glycosides are the predominant anthocyanins with the content of 45.0-74.9 mg/100 g FW, followed by malvidin glycosides (37.1-62.2 mg/100 g FW) [14]. Whereas, the malvidin glycosides of 13 blueberry cultivars, including highbush blueberries and half-high blueberries, were conferred on the greatest amount with the total average content of  $77.0 \pm 32.2$  mg/100 g FW, accounting for more than 55% of the total anthocyanin amount of all varieties, followed by delphinidin glycosides ( $53.3 \pm 24.7$  mg/100 g FW). The same report also exhibited that the total anthocyanin content and the contents of monomers (except for the malvidin-3-O-glucoside) were higher in half-high blueberries compared with the highbush blueberries, and the average proportions of total anthocyanins for the malvidin and delphinidin derivatives were lower in half-high blueberries compared with the highbush blueberries [39]. For comparison, the relative proportion of malvidin glycosides in blueberries is higher than that of cyanidin or delphinidin in bilberries [4, 39], but the cyanidin glycosides proportion of total anthocyanins in blueberry is lower (approximately 7.0%) [1, 39] than that in bilberry (9% to 33%) [17, 23, 41].

The proanthocyanidin level varies from 30 mg to 331 mg/100 g FW [28, 34, 42]. The presence of A-type procyanidins and prodelphinidins in bilberry are confirmed [28], whereas only B-type procyanidins are identified in the cultivated and wild diploid blueberry species [34], even though blueberry is a closely related species to bilberry in the genus *Vaccinium*. Procyanidins of blueberry were quantified in detail, which revealed that polymeric (DP > 10) account for 26-47% of total procyanidin amount, and dimers account for 2-10% [34]. Another work suggested that the monomers (catechin and epicatechin) accounted for only 1.0-2.2% and 2.7-4.0% of the total quantified procyanidins, highbush blueberries and lowbush blueberries contained abundant of polymeric of 71.7% to 78.4% [42]. However, different researches revealed the  $11 \pm 0.7\%$  and  $24 \pm 1.5\%$  for monomers and dimers in blueberries [14], 32.4% and 25.1% for monomers and procyanidins with DP > 8 [43].

In the analysis of flavonols, 23 flavonol glycosides from six aglycone classes, including myricetin, quercetin, laricitrin, kaempferol, isorhamnetin and syringetin, were identified and quantified in one cultivated tetraploid and six wild diploid blueberry species. Quercetin was found to be the most abundant at 14 mg/100 g FW among these 7 blueberry varieties, accounting for 68-82.4% of total quantified flavonol glycosides [34]. Myricetin content was the second, and the combined contents of quercetin derivatives and myricetin derivatives accounted for 79.9-95.1% of the total flavonol content. Isorhamnetin possessed the lowest content among these flavonols, accounting for only 0.05%-0.65% of the total flavonol content [34]. In addition, quercetin and chlorogenic acid in highbush blueberries were 8.6 mg and 126.1 mg/100 g FW, respectively, and 10.3 mg and 141.4 mg/100 g FW in half-bush blueberries [44]. A relatively detailed work about 28 wild and cultivated berry species elucidated that quercetin is mainly present in 3-O-galactoside and 3-O-rutinoside forms with the concentrations of 6.4 mg/100g FW and 2.3 mg/100 g FW, while myricetin-3-O-galactoside (1.92 mg/100 g FW) was predominant among myricetin derivatives. Isorhamnetin-3-O-rutinoside (0.71 mg/100 g FW) and kaempferol-3-O-rutinoside (0.18 mg/100 g FW), small amounts in 28 blueberries, were dominant among its derivatives. Similarly, laricitrin-3-O-glucoside and syringetin-3-O-pentoside presented in small amounts with a range of 0.29 mg to 0.5 mg/100 g FW [10].

Chlorogenic acid, a class of hydroxycinnamic acid presents in abundance, is quantified in quite a few works, whose concentration in 6 highbush blueberries ranges from 36.3 mg to 126.1 mg/100 g FW, and ranges from 58.9 mg to 109.95 mg/100 g FW in lowbush blueberries [14]. Similarly, the chlorogenic acid contents in highbush blueberries and lowbush blueberries ranging from 50 mg to 100 mg/100 g FW are published earlier [45]. The levels of phenolic acid of 16 blueberry samples from China appeared to be slightly lower than 30 mg/100 g FW, among which, chlorogenic



acid was the richest phenolic acid, accounting for 84.4-99.2% of total phenolic acids [29]. Three major organic acids in blueberries are quinic acid, shikimic acid and citric acid, among which citric acid is the most abundant one, accounting for more than 90% of the total organic acids. Lower levels of malic acid, succinic acid and tartaric acid have been also observed in blueberries [34]. In another study, gallic acid, caffeic acid, vanillin, syringic acid, *p*-coumaric acid and ferric acid were observed in highbush blueberry juice, but quercetin and kaempferol were not detected [46].

Interspecific comparisons are made among different varieties of blueberries, indicating that the content of chlorogenic acid in lowbush blueberries are higher than that in highbush blueberries [14]. However, the total anthocyanin amounts between highbush blueberries and lowbush blueberries is controversial. Prior's work [19] elucidated the relatively higher antioxidant properties in lowbush blueberry and bilberry compared with highbush blueberry due to the higher contents of the total anthocyanin and polyphenol, but another work demonstrated that the total anthocyanin contents of the one lowbush blueberry is close to those of the other two highbush blueberries [14]. The total anthocyanin content of half-high blueberries is higher than that of highbush blueberries, but except for malvidin [35] and delphinidin [39], which are lower in half-high blueberries. Rabbiteye blueberries with relatively smaller sizes show a higher level of anthocyanins and a higher proportion of cyanidin-3-O-galactoside relative to highbush cultivars. Nevertheless, highbush cultivars account for higher percentages of delphinidin-3-O-arabinoside and malvidin-3-O-arabinoside [32]. Due to the fact that anthocyanins are mainly concentrated in the skin and outer layer of the pulp [45], the amount of peel or surface to volume ratio increases with the decrease of fruit size when given a specific volume of berries. Consequently, lowbush blueberries and rabbiteye blueberries display higher total anthocyanin content than highbush blueberries [40]. This conclusion could be used as one of the reasons to interpret the discrepancies in total anthocyanin contents of blueberries quantified in many studies [40]. However, the accumulation of anthocyanins during fruit ripening makes this result invalid [19]. Furthermore, there is likely that highbush blueberries and lowbush blueberries present the similar oligomeric procyanidins [14].

Based on the fact that the interspecies, cultivar- and weather-dependent or detecting conditions account for the significantly different polyphenol levels. Apart from growing conditions, species should also be compared to select the right species to plant. Meanwhile, the screening criteria need to be adjusted for different uses or for different therapeutic purposes, but in such a case, a more uniform quantitative approach is crucial, because only then can the reports be comparable.

### 2.3 Chokeberry

Chokeberry or wild cherry, a shrub of the *Rosaceae* family with 0.5-3 m in length, is native to the eastern of North America and is now widely cultivated in Europe and Asia. Chokeberries carry white flowers in May and bear fruits in mid-to-late summer in umbels, the berries are found to possess a diameter of 6 to 13 mm, a weight of 0.5 to 2 g [47].

The total polyphenol contents of chokeberry range from 1.1 g to 3.0 g gallic acid equivalents per 100 g FW (Folin-Ciocalteu assay), and the total anthocyanin contents are between 249 mg and 737 mg/100 g FW (cyanidin-3-O-galactoside equivalent) and  $9.06 \pm 5.06$  mg cyanidin-3-O-galactoside equivalents per g DW by liquid chromatography [48-50]. Six pure anthocyanin mixtures were used as the standards, and the HPLC results showed that the total anthocyanin content of chokeberries is 1480 mg/100 g FW [51]. The relative distribution of monomer components was analyzed by HPLC, and the obtained result demonstrated that there were four anthocyanins in the chokeberry extract, and the proportions of total anthocyanins were 47.6% (cyanidin-3-O-arabinoside), 46.4% (cyanidin-3-O-galactoside), 4.7% (cyanidin-3-O-xyloside), and 1.3% (cyanidin-3-O-glucoside), respectively [52]. Similar reports exhibited that cyanidin-3-O-arabinoside was the most abundant monomer in chokeberries with concentrations of 142.4 mg [53] or 94.1-155.3 mg/100 g DW [54]. Cyanidin-3-O-galactoside was the second most abundant monomer in chokeberries, and possessed concentrations of 25.6 mg [53] or 101-120.4 mg/100 g DW [54]. A variation was discovered that cyanidin-3-O-galactoside was predominant in chokeberries with a proportion of 65%, followed by cyanidin-3-O-arabinoside (30%). Their finding revealed that the concentrations of cyanidin-3-O-galactoside, cyanidin-3-O-arabinoside, and cyanidin-3-O-glucoside in chokeberry were 222.11 mg/100 g, 159.21 mg/100 g, and 10.87 mg/100 g FW, respectively [22]. Nevertheless, several similar results elucidated that the content of cyanidin-3-O-galactoside was higher than that of cyanidin-3-O-arabinoside [10, 47, 48, 51-55]. Trace amounts of pelargonidin-3-O-arabinoside, pelargonidin-3-O-galactoside, and cyanidin-rhamnose-pentose were also discovered [48, 51], of which pelargonidin-3-O-arabinoside was quantified to be 2 mg/100 g FW [48].

Among the blueberry, bilberry and other vegetables and fruits, the highest total procyanidin content in purified extracts with respect to chokeberry are at 663 mg/100 g FW. [42, 51]. Normal-phase HPLC quantified as (+)-catechin equivalent explained that the contents of procyanidin in chokeberry were between 1.1 mg and 4.6 mg/g DW [47-48], and the content of polymeric procyanidins is higher than that of nonpolymeric procyanidins, accounted for 45-99% of the total procyanidins [47-48]. Using cocoa and blueberry proanthocyanidins as equivalents, the procyanidin content quantified by normal-phase HPLC in chokeberries is 6.64 mg/g FW, and 81.7% of total procyanidins are polymers [42, 51]. Similar results also indicated that the means degree of polymerization of procyanidins in chokeberries ranges from 15 to 29 [47, 56]. B-type and non-acylated procyanidins in chokeberries are found to be almost exclusively (-)-epicatechin units (98.5%) [47].

The fact that quercetin derivatives are the primary contributor to the total flavonol content is observed, and the concentrations of quercetin and quercetin derivatives are quantified to be ranging from 26 mg to 71 mg/100 g FW. Quercetin derivatives are predominant in the form of 3-O-galactoside (6.56 mg/100 g FW), followed by 3-O-glucoside (4.38 mg/100 g FW), 3-O-rutinoside (4.24 mg/100 g FW), 3-O-vicianoside (3.64 mg/100 g FW), 3-O-robinobioside (2.96 mg/100 g FW) and 3-O-dihexosides (3.3 mg/100 g FW) [10, 57]. Other flavonol components including myricetin, isorhamnetin and kaempferol are observed in chokeberries with their total flavonol content as 0.4 mg/100 g FW. Different from blueberries and bilberries, laricitrin and syringetin glycosides are not detected in chokeberries [10]. Hydroxycinnamic acid (chlorogenic and neochlorogenic acids), major non-flavonoid polyphenols, are contained in chokeberries ranging from 5.2 mg to 17.3 mg/g FW [58]. Meanwhile, chlorogenic and neochlorogenic acids were analyzed in other works, in a ratio of about 1:1 [47-48], ranging from 72-96.6 mg/100 g FW to 59.3-79.1 mg/100 g FW [58]. Chlorogenic acid, neochlorogenic acid [48] and malic acid [59] are the three main phenolic acids in chokeberries, of which chlorogenic and neochlorogenic acids account for 7.5% of the total polyphenols [47], and there is also a small amount of vanillic acid and rutin hydrate [60].

It is worth pointing out that the reasons for the high variation in the percentage of polymeric procyanidins and content of flavonol and phenolic acid in these reported data about the three berries may be the differences in raw materials, treatment methods or the quantitative methods. Anthocyanins, as the main active substance in the three berries, vary on the monomer structure and relative abundance, but species-dependent between bilberry and blueberry is noticeable. Therefore, it is possible to find plants rich in more active substances through their relatives.

## **2.4 Factors influencing anthocyanin compositions and contents**

Considerable variations are observed among these published results with respect to the total bioactive substances and relative distributions, and these discrepancies might result from many factors including genotypes, environmental factors, growth conditions, maturity, storage conditions (pH, light, co-pigment, self-associating, metal ion, enzyme, oxygen, etc.) and even extraction and analysis methods, etc. [7, 14, 61] For bilberries, it is indicated that climatic factors and annual fluctuations have a greater impact on anthocyanin biosynthesis and degradation than nitrogen availability [62]. The content of bilberry anthocyanidins increases during the ripening process [7, 63-64], and subsequently exhibits a slight decrease 10-30 days before harvest [63]. Anthocyanins accumulate speedily and acetylation ratio increases at the condition of a higher temperature [65], whereas an opponent finding demonstrates that high temperatures could lead to anthocyanin degradation and inhibit their biosynthetic pathway [63]. However, plants are grown in cold climates often contain higher level of phenolic components and possess stronger antioxidant capacities due to their strategies against oxidative stress [57]. Higher anthocyanin amounts and an increase in the number of hydroxyl groups occur for bilberries in the northern latitude of Europe [65]. A more detailed report exhibits that the anthocyanin content of southern bilberries is lower than that in northern and central regions. Delphinidin glycosides are mainly distributed in northern bilberries, and cyanidin glycosides are mainly distributed in southern bilberries [41]. Studies related to altitude give controversial results. For example, at an altitude range of about 650 m, anthocyanin content in European bilberries increases with altitude [66], while delphinidin mainly increases at an altitude above 1500 m [67]. However, another finding represents that within the altitude range of 800-1500 m, the anthocyanin content is prone to decrease with the increase in altitude [68]. Therefore, to further explore the relationship between altitude and anthocyanin content of bilberries, environmental factors such as light intensity, light quality and temperature should be considered to interpret the results [25, 69-70].

The blueberries, in the course of maturation, contain the highest total anthocyanin content among the



developmental stages, and the total anthocyanin amount of the skin is 4-fold of that in mature berries, and 37-fold in pulp. There is also an obvious accumulation of malvidin glycosides during developmental stages [71]. Additionally, the proportions of monomeric anthocyanidins and levels of glycosylation of blueberries from different geographical locations within the same genus might be substantial differences [1]. For instance, the summer days are much longer at high altitudes than at low latitudes, which causes an impact on the phytochemical compositions and contents of fruits [72].

As for chokeberries, the variation of phenolic contents in different growing seasons is triggered by climatic conditions. It has been discovered that the average monthly temperature and sunshine time exert a positive effect on the phenol content in chokeberries, while the relative environmental humidity has a negative effect on the total phenol content [5, 8]. The content of proanthocyanidin soars gradually during fruit ripening and increases slightly in late ripening. Anthocyanin biosynthesis begins at the early stage of fruit ripening and reaches the highest level in mature fruits [73]. In comparison with sun-drying and oven-drying, freeze-drying is a method to maintain the high level of bioactive compounds in the extract of chokeberries [60]. During the processing, DMSO with high polarity is considered to be the most effective extraction solvent [74]. In a word, these factors mentioned above might be the reasons to interpret the discrepancies in total anthocyanin contents.

## 2.5 Bioavailability and biostability of anthocyanins

The nutraceutical importance of anthocyanins has been widely demonstrated in vitro, but the benefits of anthocyanins obtained in vitro may not be in accordance with those in vivo. For example, one study illustrates that polyphenols of chokeberries can prevent cardiovascular disease by lowering cholesterol and blood pressure, but there is no consistent result in vivo [75]. Previous studies have found that anthocyanins are poorly absorbed in the stomach and small intestine after oral administration (about 10-50 nM), reaching the maximum plasma concentration (1-120 nmol/L) at about 1.5 h, urine recovery is below 1%, and the excretion is around 0.005% [76], a low recovery rate (less than 27%) in the ileal fluids also indicates the poor availability of anthocyanins in the intestine [77]. At the same time, the concentrations of polyphenols and their metabolites in systemic circulation and peripheral tissues are lower than those required for cell culture and in vitro studies [78], which may explain the difference in antioxidant activity obtained in vitro and in vivo [79]. Additionally, anthocyanins are unstable during the gastro-intestinal digestion, and the bioavailability of anthocyanins is observed in the range of 0.26-1.8% [55]. Studies on the bioavailability of anthocyanins reveal that anthocyanins in small amounts are absorbed in the circulation and eliminated with the urine, and anthocyanins in large amounts are found in the gastrointestinal tract. In vitro gastrointestinal digestion shows that blueberry (*Vaccinium SPP.*) phenolic compounds are relatively stable in the gastric environment, while anthocyanins are unstable in the intestinal environment (weak alkalinity condition) with a recovery rate of 3.4%, and the bioavailability of anthocyanins simulated with dialysis bag is 1.9% [80]. Similar results are also obtained in bilberry, the low bioavailability of bilberry anthocyanins is in accordance with a study of mulberry anthocyanins, whose recovery rate is 0.34% [81]. However, another study about in vitro intestinal digestion of the wild blueberry anthocyanins (*v. angustifolium*) demonstrates that the anthocyanins content only decreases by 15% in comparison with non-digested samples [82]. The bioavailability and biological stability of one polyphenol and another vary greatly, depending on their dietary sources [83]. A previous work indicated that all bilberry anthocyanins except peonidin 3-O- $\alpha$ -L-arabinoside were detectable in the rat blood plasma. The plasma concentration of anthocyanins as a whole reached the maximum level of 1.2  $\mu$ M at 15 min after oral administration of 400 mg/kg bilberry extract (153.2 mg/kg as anthocyanins) and then decreased with time. Uptake and decay profiles of each anthocyanin in the plasma were almost the same for all anthocyanins except a few with their maximum after 30 min. Among the anthocyanins carrying the same aglycone, the plasma level after 15 min of oral administration was as follows: galactoside > glucoside > arabinoside. Plasma clearance of anthocyanins after intravenous administration clearly showed that arabinoside disappeared more rapidly than glucoside and galactoside. On the other hand, when anthocyanins carrying the same sugar moiety were compared, the half disappearance time of plasma anthocyanins was in the following order: delphinidin > cyanidin > petunidin = peonidin > malvidin. Accordingly, we believe that the varieties of blueberry anthocyanins also affect their bioavailability and biological stability. Due to the instability in gastro-intestinal environment and low plasma bioavailability, enhancing the biostability absorption and transport efficiency of anthocyanins is also a challenging issue.

The glycosyl groups on anthocyanins increase their stability and water solubility, resulting in low bioavailability and limited passive diffusion of anthocyanins. These properties are not conducive to drug development [84]. Therefore,

it is clearly a task to improve the digestive stability after oral administration. To solve this problem, a new concept from the field of nanotechnology called “nano-chemoprevention” has been used to address the challenge of malabsorption, especially for oral delivery [85]. Recently, a detailed review on different nano/microencapsulation methods, directed towards bioavailability and biostability, is published [86]. Other studies, for example, reveal that polysaccharide-based nanostructured polymers, maltodextrin and Arabic gum, or microcapsules coated with chitosan or sodium alginate have been shown to successfully solve the problem of poor stability [87]. Meanwhile, Nano-pelargonidin at a nearly 10-fold reduced dose obviously enhances protection for therapeutic management of mitochondrial dysfunction [88], which is discovered to increase 10-fold protective effect for the prevention of alloxan-induced DNA damage [89]. Recently, protein-polyphenol (blueberry extracts) particles as a delivery vehicle are demonstrated more stable during gastrointestinal digestion [90]. Not only that, stable interaction between polyphenols and protein preserves even enhances the effective bioactivity of polyphenols without diminishing protein functionality [91-92]. However, these in vitro studies are still insufficient, in vivo studies are still necessary to further prove these obtained findings.

### 3. Discussion and conclusions

Characteristic compositions of blueberry, bilberry and chokeberry and their health benefits are reviewed based on the literatures [93-102]. However, in fact, considerable variations in the characteristic compositions and contents of berry materials, whether within interspecies or among different families, have not been reviewed before. In addition, the factors affecting the components and contents of bilberry, blueberry and chokeberry have not been discussed in detail. In this context, we compare the (poly)phenolic compositions and contents within interspecies and among the different berries, and explain the differences in various discoveries. Since a diverse range of potential health effects has been summarized, here we focus on the countermeasures to solve the poor biostability and low bioavailability of anthocyanins.

In bilberry, blueberry and chokeberry, the content of flavonols and their derivatives is the most eminent in chokeberry (267 mg/100 g FW), followed by those in highbush blueberry (186 mg/100 g FW) and bilberry (114 mg/100 g FW) [10]. Quercetin aglycones are dominant among the flavonol derivatives in chokeberry and blueberry, accounting for 98% and 72% of the total flavonols [10]. The flavonol content of syringetin and laricitrin aglycones in highbush blueberry and bilberry is as high as 8% of the total flavonol content, whereas syringetin and laricitrin derivatives are not contained in chokeberry [10]. Interestingly, myricetin aglycones are found to be significantly concentrated in genus *Vaccinium* berries of blueberry and bilberry, but rarely in chokeberry. Glycosides of kaempferol and isorhamnetin have been uniformly detected in traces in bilberry, blueberry and chokeberry [10]. In terms of phenolic acids and their derivatives, bilberry contains a relatively low level of chlorogenic acid, and no neochlorogenic acid is detected [24]. The content of phenolic acids in chokeberry (131-243 mg/100 g FW) is higher than that in blueberry (40-100 mg/100 g FW), and both of them contain a large proportions of chlorogenic acid and neochlorogenic acid [14, 45]. When it comes to anthocyanins, it is found that the compositions of monomeric anthocyanin in chokeberry are relatively simple and mainly composed of cyanidin glycosides [22]. However, anthocyanins in blueberry and bilberry are generally composed of delphinidin, cyanidin, petunidin, peonidin, and malvidin bonded to glucose, galactose, or arabinose via 3-O-glycosylated [5, 20, 32, 34, 36]. The anthocyanins profiles of blueberry and bilberry are similar, but the contents of monomer anthocyanins varied considerably. The content of malvidin derivatives in blueberry is significant, accounting for 41-43% of the total anthocyanins, but only about 13% in bilberry. The content of peonidin derivatives in bilberry is the least, accounting for 1.3%-6.3% of the total anthocyanin content [22], while peonidin glycosides in blueberry are detected only in trace amounts [4, 39]. The comparisons of procyanidins in bilberry, blueberry and chokeberry emerge that B-type and non-acylated procyanidins are principally found in chokeberry and blueberry. The procyanidins in chokeberry is the most abundant [28, 42, 51], of which are mainly (-)-epicatechin (98.5%) and largely composed of polymers (DP > 10) [42, 48, 51]. Blueberry contains (+)-catechin and (-)-epicatechin, with a range of 26-78% polymers [28, 34]. Different from chokeberry and blueberry, bilberry is revealed to contain A-type procyanidins and prodelfinidin and approximately 56% of polymers [28].

The relative distributions and contents of the bioactive substances in bilberry, blueberry and chokeberry are summarized as follows: the content of bilberry phenolic acids is relatively low, but the proanthocyanidin profile is relatively complex, with the presence of A-type procyanidins and prodelfinidin. The content of blueberry anthocyanins

is relatively higher than the cyanidin and delphinidin glycosides dominated among the monomeric anthocyanin, and thus the antioxidant activity of blueberry is enhanced. The diversity of monomeric anthocyanins from chokeberry is relatively low, and is mainly cyanidin-3-O-galactoside. The contents of phenolic acids and flavonols in chokeberry are higher than those in blueberry, and the content of procyanidins is the most abundant. Blueberry and bilberry are comprised of the same anthocyanidin aglycones. But the contents of cyanidin and delphinidin glycosides in blueberry are lower than those in bilberry, while the contents of flavonols and phenolic acids in blueberry are relatively higher than those in bilberry.

*In vitro and ex vivo* pharmacological studies indicate the potential application prospects of the three berries in the food industry. While engaging in cellular and animal research is dominating, human clinical studies are lacking. Therefore, providing conclusive evidence of efficiency by designing intervention trials is considered necessary. As stated above, the chemical composition of berries is closely associated with cultivar/variety, weather/climate, planting area (e.g., altitude and latitude), ripeness and postharvest processing (e.g., storage and processing). Our work reveals that different species, cultivar, growing area and process may be carefully selected for specific utilization. But a previous study illustrated that the effect of postharvest processing is negligible relative to cultivar/variety [103], the influencing factor of different species and cultivar should probably be attended to. However, considering the poor absorption and low plasma concentration of anthocyanidins, it is worth continuing to improve the biostability and bioavailability of anthocyanidins. Furthermore, limited information is provided in scientific research about the mechanism of interaction between phenolic components and their effective bioactivities or biostability in food. In such a case, further studies are still necessary to elucidate the interactions with other compounds that may affect the bioactivities of polyphenolics. Meanwhile, anthocyanins and other polyphenolics are often used in complex form but monomers, as well as environmentally surrounded by lipids, proteins and carbohydrates, which lead that the contribution of different individual polyphenolics in berries to their bioactivities and the synergistic and antagonistic effects of polyphenolic between polyphenolic compounds and other active or inactive substances are strongly encouraged to be further investigated.

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## Conflict of interest

The authors declare no conflicts of interest.

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