



# **Anthocyanin Accumulation in Berry Fruits and Their Antimicrobial and Antiviral Properties: An Overview**

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Abstract: Because of the recent global crises and lifestyle trends, anthocyanin-rich fruits are receiving more attention due to their medicinal qualities. Many studies have concluded that higher anthocyanin consumption tends to correlate with health benefits. Furthermore, research has shown great promise for anthocyanin application in treating fever and neurodegenerative processes. Once the industrial application difficulties are solved, anthocyanins might prove to be a crucial component in helping to treat the diseases that are becoming more common—viral infections and illnesses associated with aging. Fruit extracts that contain large quantities of anthocyanins have antimicrobial and antiviral (against SARS-CoV-2 virus) properties. Most of the synthesized anthocyanins in the fruit-bearing fruits are stored in the fruits. The aim of this review article is to indicate the fruit species that have the most potential for anthocyanin extraction from fruits, to overview the antimicrobial and antiviral capabilities of anthocyanin and the main sample preparation and extraction methods that preserve polyphenolic compounds and reduce the time expenditure.

Keywords: anthocyanins; antimicrobial activity; antioxidant activity; fruit; extraction



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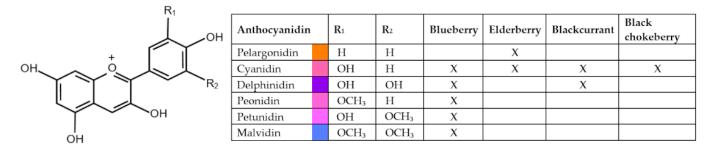
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# 1. Introduction

Due to global social and economic developments, the world's population is aging and according to the UN's data, in the next 25 years the part of the population that is 65 years and older will almost double [1]. With the rising population of senior citizens, the disorders and illnesses associated with old age are likely to increase accordingly. This is likely to be even more prevalent in economically developed countries where significant portions of the population lead a sedentary lifestyle, which is linked with various chronic damages, cardiovascular changes, metabolic disorders, and other conditions that lower the life quality and even expectancy. Illnesses that are linked with old age include ischemic heart diseases, cognitive decline disorders such as dementia and Alzheimer's disease—all of which have an extreme impact on the patient's the quality of life [2].

To mitigate the negative impact of poor lifestyle choices and minimize the discomforts that come with natural human aging, the trend of striving to live a healthier life has received more attention worldwide in recent decades. One aspect of this is an increased interest in nutraceuticals [3,4]. This growing interest results in higher production—according to research by the BBC [5], the global nutraceutical market is expected to increase from the current 2021 market value of USD 289.8 to USD 438.9 by 2026.

Phenolic compounds are a common ingredient in various nutraceutical supplements due to their positive effects on human body [6]. Phenolics are divided into two main groups, flavonoids and non-flavonoids. Research studies have shown that flavonoids have antiinflammatory and antibacterial properties. Flavonoid subclasses consist of anthocyanins, flavonols, flavonones, and isoflavones [7]. Anthocyanins are water-soluble pigments and are stored in plant cell vacuoles. Most vascular plant species contain these compounds in various quantities in most of the organs, but mainly fruits, flowers, and leaves [8,9]. Anthocyanins are found in nature as anthocyanidin–glycosides. The most common types of anthocyanidins are pelargonidin, cyaniding, delphinidin, peonidin, petunidin, and malvidin. Different anthocyanidins determine the color of the plant and range from orange to red, blue, and purple colors [10] (Figure 1).



**Figure 1.** The structural formula of six anthocyanidins commonly synthesized in the fruits that accumulate the most anthocyanins from the Ericaceae, Caprifoliaceae, Grossulariaceae, and Rosaceae families. Adapted from [11]. Highlighted are the colors of each anthocyanidin.

Because the intensity of the anthocyanin colors increases with increasing anthocyanin concentration, fruits, vegetables, and flowers that are rich in anthocyanins tend to be deep red or dark purple—such as raspberries, blueberries, elderberries, eggplants, red cabbages, and flowers such as Centaurea cyanus and et al. [12–16]. Anthocyanin color and hue varies depending on the pH—in an acidic environment anthocyanins are red, in a basic pH they become blue [17]. In a basic pH anthocyanins become less stable than in the acidic environment. Anthocyanins are sensitive not only to acidity but are also easily oxidized and are vulnerable to acylation with organic acids and complexation with metal ions. Because of this, anthocyanins are hard to use as food colorants without additional treatment or specific food technologies [18,19]. However, anthocyanins have a wide range of applications in both the food and pharmaceutical industry and also phytotherapy. They are used as an ingredient in various medicaments and supplements because they have strong anti-inflammatory, antimicrobial, and antioxidative properties and research results have linked dietary enrichment with anthocyanins to a reduced risk of gastrointestinal cancers and the inhibition of neurodegenerative diseases and cognitive decline [20]. Anthocyanins also increase the endurance and elasticity of capillaries and reduce their permeability. Additionally, they increase visual acuity and are used for some eye diseases, especially the anthocyan glycosides in bilberry [21]. It is important to note that some anthocyanins have radioprotective effects and are used for the treatment and prophylaxis of radiation sickness [22,23].

Because the proportion of senior citizens around the world is likely to increase and health-friendly consumer trends are on the rise, the positive impact of anthocyanins on human health will boost the demand for more cost-efficient anthocyanin sources. This review aims to identify the fruits that accumulate the largest quantities in their fruits and as such could be used as an efficient anthocyanin source for extraction. The data have been collected from different databases including SpringerLink, PubMed, NCBI, and Science Direct.

#### 2. Anthocyanins in Fruits

The amount of accumulated anthocyanins varies greatly depending on the source. Anthocyanin contents vary not only between plant species, cultivar, or plant organs but are also dependent on various environmental factors, plant maturity, and fruit ripeness at the time of anthocyanin content evaluation [24,25]. Accumulated anthocyanin content can vary within the species as much as between different plant species (Table 1). In the reviewed literature the common method to quantify total anthocyanin content (TAC) was by using spectrophotometry—the pH differential method. Using this method before anthocyanin

determination, the samples are incubated at room temperature, in the dark. A typical wavelength set for anthocyanin determination is 520–700 nm.

Family	Species	Total Anthocyanin Content, mg/100 g FW	References
	Vaccinium myrtillus	159–1000	[13,14,26–29]
<b></b>	Vaccinium corymbosum	88–430	[13,30–32]
Ericaceae	Vaccinium macrocarpon	31–102	[32–34]
	Vaccinium vitis-idaea	30–50	[27,32,35]
	Lonicera caerulea	90–709	[36-39]
Caprifoliacoao	Sambucus nigra	560-924	[7,26,40-42]
Caprifoliaceae	Sambucus caerulea	149	[41]
	Sambucus ebulus	353-400	[41,43]
	Ribes rubrum	10–62	[44-47]
Grossulariaceae	Ribes nigrum	150-626	[45,46,48–50]
	Rubus idaeus	22–130	[30,45,51,52]
	Rubus fruticosus	70–180	[45,53,54]
Rosaceae	Prunus avium	50-680	[26,55–57]
	Prunus cerasus	30–150	[26,58]
	Aronia melanocarpa	280-690	[32,59–61]

Table 1. Total anthocyanin content in various fruits, expressed in mg/100 g fresh weight (FW).

From the reviewed literature in *Prunus avium, Aronia melanocarpa Sambucus nigra,* and *Vaccinium myrtillus* the largest potential total anthocyanin count was determined—up to 680, 690, 810, 1000 mg/100 g FW, respectively. *Ribes nigrum* and *Vaccinium corymbosum* accumulated slightly fewer anthocyanins—up to 380 and 430 mg/100 g FW, respectively (Table 1). Anthocyanin accumulation varies greatly even within the same species because of climate, soil, environment conditions, and different cultivars [30,49,62,63].

Among the commonly synthesized anthocyanins in plants and one that was found in large quantities in the analyzed literature in both *V. myrtillus* and *V. vitis-idaea* was cyanidin-3-*O*-galactoside (Cy-3-Gal) (Table 2). It is a compound that, similar to other anthocyanins, acts as a key antioxidant in plants. It has been found that it is capable of DPPH<sup>•</sup> and ABTS<sup>•+</sup> radical scavenging. Researchers also found that Cy-3-Gal can scavenge hydrogen peroxide and absorb radical oxygen. In the research studies it was found that Cy-3-Gal can perform its physiological functions without the presence of other compounds [60].

Table 2. Specific anthocyanin contents found in the fruits of Ericaceae family.

Anthocyanin	<i>V. myrtillus</i> (mg/100 g FW)	V. corymbosum (mg/100 g FW)	V. macrocarpon (mg/100 g FW)	<i>V. vitis-idaea</i> (mg/100 g FW)
Delphinidn-3-O-galactoside	43.7 [14] 85.7 [64] 127.1 [29] 167.1 [31]	18.74 [32] 23.4 [31]		39.3 [35]
Delphinidin-3-O-glucoside	47.7 [14] 76.6 [64] 123.8 [29] 169.1 [31]	11.23 [32] 15.4 [31]		
Cyanidin-3-O-galactoside	46.5 <b>[14]</b> 53.3 <b>[64]</b> 56.3 <b>[29]</b> 122.6 <b>[31]</b>	4.2 [31] 7.49 [32]	8.89 [32] 24.0 [33]	39.3 [35] 48.6 [32] 53.6 [64]
Delphinidin-3-O-arabinoside	85.9 [64] 97.4 [29] 152.3 [31]	9.4 [32] 24.6 [31]		
Cyanidin-3-O-glucoside	47.7 [14] 48.8 [64] 58.1 [29] 130.4 [31]	2.6 [31] 3.04 [32]	0.74 [32] 19.1 [33]	1.42 [32] 2.2 [64] 5.2 [35]
Petunidin-3-O-galactoside	14.3 [14] 18.6 [64] 50.0 [31]	11.7 [31] 14.43 [32]		

Anthocyanin	<i>V. myrtillus</i> (mg/100 g FW)	V. corymbosum (mg/100 g FW)	V. macrocarpon (mg/100 g FW)	V. vitis-idaea (mg/100 g FW)
Cyanidin-3-O-arabinoside	110.6 [31] 31.5 [14] 68.9 [64]	3.5 [31]	4.80 [32] 6.85 [33]	6.27 [32] 7.2 [35] 12.4 [64]
Petunidin-3-O-glucoside	14.0 [14] 38.7 [29] 43.7 [53] 101.9 [31]	7,03 [32] 12.4 [31]		
Cyanidin-3-O-arabinoside	31.5 [14] 37.1 [29] 68.9 [64] 110.6 [31]	3.5 [31]	4.80 [32] 6.85 [33]	6.27 [32] 7.2 [35] 12.4 [64]
Petunidin-3-O-glucoside	14.0 [14] 43.7 [53] 82.8 [29] 101.9 [31]	7,03 [32] 12.4 [31]		
Peonidin-3-O-galactoside	3.3 [53] 13.3 [31]	1.8 [31]	21.36 [32] 44.5 [33]	
Petunidin-3-O-arabinoside	14.7 [53] 23.1 [29] 23.9 [31]	9.3 [31] 12.89 [32]		
Peonidin-3-O-glucoside	16.0 [53] 36.4 [29] 56.7 [31]	2.1 [31]	4.04 [32] 7.67 [33]	4.13 [32]
Malvidin-3-O-galactoside	18.1 [53] 27.5 [31] 26.8 [33]	15.01 [32] 34.9 [31]		
Peonidin-3-O-arabinoside	3.3 [53] 4.5 [31]	1.0 [31]	9.97 [32]	
Malvidin-3-O-glucoside	34.3 [14] 49.2 [53] 67.7 [31] 92.4 [33]	11.46 [32] 31.2 [31]		
Malvidin-3-O-arabinoside	7.8 [14] 12.8 [31] 13.6 [64] 17.6 [29]	11.45 [32] 34.7 [31]		

Table 2. Cont.

Cyanidin-3-*O*-β-glucoside (Cy-3-Glu) is found in abundance in *V. myrtillus* (Table 2). Experiments with rats showed that Cy-3-Glu can prevent cardiac hypertrophy and diastolic dysfunction in hypertensive rats [65]. However, even though *V. myrtillus* is known for its hypertension-relieving properties, the results of the experiment showed that Cy-3-Glu supplements alone do not lower blood pressure in rats. Meanwhile experiments with *V. myrtillus* supplements did in fact ease symptoms of hypertension in rodents [66]. This could mean that the Cy-3-Glu anti-hypertensive effect is achieved only when other synergistic compounds are added.

Additionally, anthocyanins seem to be effective at inhibiting the proliferation of various human pathogens—mainly Gram-positive and Gram-negative bacteria, including *E. coli, S. aureus*, and *B. cereus* [15]. Anthocyanins damage bacteria by destroying the cell walls, cell membranes, and intercellular matrices of the affected pathogens [67].

#### 2.1. Ericaceae

Even though the Ericaceae family has many species that grow edible fruit, not many of them accumulate large amounts of anthocyanins. For example, *Arbutus unedo* (Ericaceae) fruits are a popular research subject, known for their high accumulation of arbutin—a compound with medicinal applications, but the fruit possesses a very low anthocyanin content [68], when compared with *Vaccinium* genus species (Table 2). Species of the *Vaccinium* genus are widely known to have beneficial health properties and have commonly been used as an ingredient in traditional medicine throughout Europe because of their healing properties—*Vaccinium* berries and leaves have been used to treat fever, diabetes, respiratory inflammations, common cold, and gastrointestinal disorders [65,69]. These properties are likely a result of a high polyphenolic compound, anthocyanin, and flavonoid content. Due to the accumulation of high concentrations of compounds that have relevant medicinal properties and are likely to increase in demand, it is not surprising why the species of *Vaccinium* genus are among the most researched berries in tests of plants that can be used in nutraceuticals.

European blueberries *V. myrtillus* are one of the richest natural anthocyanin sources—studies have shown that these berries contain 15 different anthocyanins, of which the most abundant are anthocyanidin- and delphinidin-based (Tables 2 and 3). *V. corymbosum* also accumulates the same 15 anthocyanins, but in lesser quantities. According to the experi-

ment results of Burdulis et al. [70], some blueberry *V. corymbosum* cultivars such as 'Coville' and 'Northland' accumulated slightly higher percentages of anthocyanin in the fruit skins than *V. myrtillus*—1.24% and 1.09%, respectively. Despite that, *V. myrtillus* fruit samples contained a larger percentage of anthocyanin in the fruit overall when compared with *V. corymbosum* cultivars. The results of this article and European Medicines Agency data [71] show that the most abundant anthocyanins in bilberries are delphinidin-3-*O*-galactoside (Del-3-Gal), constituting up to 14.9% of total anthocyanin, delphinidin-3-*O*-galactoside (Del-3-Ara), up to 15.3%, delphinidin-3-*O*-glucoside (Del-3-Glu)—up to 14.0%, cyanidin-3-*O*-arabinoside Cy-3-Ara)—13.6% and cyanidin-3-*O*-glucoside (Cy-3-Glu), comprising up to 10.1% of the total anthocyanin in bilberry fruit (Table 3). This high concentration of anthocyanins and other polyphenols is likely a result of an adaptation to store increased amounts of defensive phytochemicals as a response to high levels of environmental stress. While it is common for anthocyanins to mostly be stored in the exocarp, in *V. myrtillus* they are accumulated throughout the fruit [70]. However, a larger percentage of anthocyanins was detected in the skins of the fruit, rather than the entire fruit.

Anthocyanin	Amount, Percent of Total Anthocyanins (%)
Dephinidin-3-O-glucoside	13.7–14.0
Cyanidin-3-O-galactoside	9.0–9.2
Ćyanidin-3-O-glucoside	8.5-10.1
Cyanidin-3-O-arabinoside	7.7–13.6
Petunidin-3-O-glucoside	6.0-8.8
Peonidin-3-O-galactoside	0.6–1.1
Peonidin-3-O-arabinoside	0.5–1.0
Malvidin-3-O-glucoside	7.9–8.4
Delphinidin-3-O-galactoside	14.3–14.9
Delphinidin-3-O-arabinoside	12.1–15.3
Petunidin-3-O-galactoside	2.1–4.0
Petunidin-3-O-arabinoside	1.3–2.6
Peonidin-3-O-glucoside	0.1–3.7
Malvidin-3-O-galactoside	2.5–3.1
Malvidin-3-O-arabinoside	1.5–2.4

Table 3. Anthocyanin composition of bilberry (Vaccinium myrtillus) [64,71].

#### 2.2. *Caprifoliaceae*

Much like berries from *Vaccinium* genus, berries from the Caprifoliaceae family have historically been utilized as an ingredient of traditional medicinal remedies because of their properties. Commonly known as elderberries, *Sambucus* sp. are rich sugars, organic acids, and polyphenols—anthocyanins [12]. Because of this polyphenolic compound accumulation, they also show antioxidant activity, anti-inflammatory, and immune-stimulating properties [72]. Berries from the Caprifoliaceae family do not contain as many anthocyanins when compared with *Vaccinium* sp. berries; however, the anthocyanin composition that is accumulated differs considerably in comparison. Caprifoliaceae family plants synthesize anthocyanins that are not found in previously mentioned Vaccinium species. Most abundantly accumulated anthocyanins in *Sambucus nigra*, *S. caerulea*, and *S. ebulus* were ones that are cyanidin-based (Table 3). In research conducted by Wu and others [47] anthocyanins were extracted by using a methanol/water/acid extraction system because it was found that the use of acetone, a reagent that is commonly used in anthocyanin extraction, may cause anthocyanin conversions to pyranoanthocyanins. In total, seven anthocyanins were found in S. nigra. Four of them were the most abundant and commonly found in this species—cyanidin-O-3-sambubiosil-5-O-glucoside, cyanidin-3,5-Odiglucoside, cyanidin-3-O-sambubioside, and cyanidin-3-O-glucoside. The other three anthocyanins were cyanidin-3-O-rutinoside, pelargonidin-3-O-glucoside, and pelargonidin-3-O-sambubioside. According to the researchers, it was the first time pelargonidin-based anthocyanins were detected in S. nigra at the time. Oancea and other researchers confirmed

it and identified pelargonidin anthocyanins in *S. nigra* and found that pelargonidin and delphinidin-based anthocyanins were among the major anthocyanins in the fruit [73]. However most other authors listed cyanidin anthocyanins as the most found major anthocyanins in this species [12,41,47]. However, interspecies hybrids of *Sambucus* genus might have a different anthocyanin profile entirely, containing anthocyanins that are not found in a non-hybrid specimen, for example cyanidin-xylosyl-dihexoside [74].

Lonicera caerulea is another species of anthocyanin-accumulating berries that has potential to become an efficient ingredient for super foods. These berries accumulate large amounts of secondary metabolites-among them tannins, saponins, phenolics, ascorbic acid, and other compounds that have many health benefits [74,75]. Anthocyanins are the predominant compounds and constitute from 38 up to 91% of total identified phenolic compounds. The total amount of identified anthocyanins varies widely within cultivars. The highest average amounts are found in Amphora (401 mg/100 g FW), Indigo Gem, Nimfa, Tundra, Leningradskij Velikan, and the lowest—in the fruits of Tola, Wojtek, and Iga varieties—3.83, 13.58, and 44,92 mg/100 g FW, respectively [39]. In the experiment conducted by Senica and others [76] anthocyanins were extracted from Lonicera caerulea using ultrasound-assisted methanolic extraction. It was found that the main anthocyanin in L. caerulea was cyanidin-3-O-glucoside (56.93 mg/100 g FW) (Table 4). In the analysis conducted by Khattab and others [38] it was found that there can be a considerable variation in Cy-3-Glu accumulation depending on the cultivar—Indigo gem cultivar accumulated up to 649 mg/100 g of Cy-3-glu while *Berry blue* only accumulated 342 mg/100 g FW. Peonidin-based anthocyanins were also among the major anthocyanins, while others were only found in small quantities—0.15–16.39 mg/100 g FW [39]. These findings are in line with other researchers' work—cyanidin-3-O-glucoside is a major anthocyanin while the most abundant minor anthocyanins are rutinosides [36,39] (Table 5).

Table 4. Specific anthocyanin contents found in the fruits of the Caprifoliaceae family.

Anthocyanin	<i>S. nigra</i> (mg/100 g FW)	S. caerulea (mg/100 g FW)	S. ebulus (mg/100 g FW)	L. caerulea (mg/100 g FW)
Cyanidin-3-O-galactoside	0.32 [41]			0.05–0.83 [39]
Cyanidin-3-O-glucoside	376.2 [12] 449 [41]; 739.8 [47]	2.85 [41]	0.49 [41]	33.97–56.93 [76] 342–649 [38] 3.3–230 [39]
Cyanidin-3,5-O-diglucoside	5.46 [47] 5.91 [41]; 14.34 [12]			1.39–2.38 [76] 15–31 [38] 0.4–17.6 [39]
Cyanidin-3-O-sambubioside	344.44 [41] 438.8 [12] 545.9 [47]	63.43 [41]	6.56 [41]	
Cyanidin-3-O-sambubiosil-5-O-glucoside	30.77 [12] 42.19 [41] 82.6 [47]			
Cyanidin-pentoside-hexoside	1.08 [41]	78.99 [41]	345.82 [41]	
Cyanidin-3-O-rutinoside	9.36 [41]			5.66–10.21 [76] 10.0–37.0 [38] 0.21–10.04 [39]
Pelargonidin-3-O-glucoside	1.80 [47]			2.30–5.90 [76] 5–12 [38]
Pelargonidin-dihexoside				0.82-6.29 [76]
Peonidin-3,5-O-dihexoside				13.88–18.94 [76]
Peonidin-3-O-glucoside				6.55–14.53 [76] 25.0 [38] 0.15–16.39 [39]

Anthocyanin	Amount, Percent of Total Anthocyanins (%)
Cyanidin-3-O-glucoside	71–89
Cyanidin-3-O-rutinoside	7–23
Cyanidin-3,5-O-diglucoside	2.2-0.4
Peonidin-3-O-glucoside	>0.5
Pelargonidin-3-O-rutinoside	>0.1

 Table 5. Anthocyanin composition of Lonicera caerulea fruits [38,39,76,77].

## 2.3. Grossulariaceae

The Grossulariaceae family only consists of a single genus—*Ribes* [78]. In Europe the most widely grown species from this genus are blackcurrant (Ribes nigrum) and redcurrant (*Ribes rubrum*) and are among the most grown berries in the region [79]. Currants, both red and black, are commonly used to make jams, syrups, and juices. In the United States of America, the cultivation of blackcurrants used to be banned until around 1980 due to fears of spreading fungal pathogen Cronartium ribicola which caused financial losses to lumber industry sector. Since then, new cultivars were selected that do not spread this pathogen and as such the restrictions were lifted, granting more opportunities to research the species more widely [80]. Black currants especially are very rich in anthocyanins as indicated by their saturated dark color [48]. Ribes rubrum, however, accumulates different anthocyanins in comparison (Table 6), and lesser quantities of said anthocyanins which can also be determined by the difference in the color. The total anthocyanins content of Ribes rubrum in the study in [23] was 63 mg/100 g FW, much higher than that reported by the authors of [36,37,41]. Significant differences in total anthocyanin content can be attributed to the variety of wild red currants. The major anthocyanins in *Ribes nigrum* are both rutinosides with different anthocyanidins—cyanidin-3-O-rutinoside and delphinidin-3-O-rutinoside, accumulated up to 138.81 mg/100 g FW and 311.42 mg/100 g FW, respectively. A similar anthocyanin composition can be found in other researchers' work as well [81]. However, in red currant R. rubrum delphinidin-based anthocyanin delphinidin-3-O-sambubioside is only a minor anthocyanin and all major anthocyanins are cyanidin-based, the most abundant being cyanidin-3-O-xylosylrutinoside and cyanidin-3-sambubioside, neither of which were detected in *R. nigrum*. Other researchers have also detected cyanidin-3-Oxylosylrutinoside as a major anthocyanin in *R. rubrum*; this anthocyanin was not present in R. nigrum or any other analyzed fruit in that research, including blueberries, bilberries, and cranberries [82].

Table 6. Specific anthocyanin contents found in fruits from Grossulariaceae family.

Anthocyanin	Ribes nigrum (mg/100 g FW)	Ribes rubrum (mg/100 g FW)
Delphinidin-3-O-glucoside	39.64 [48] 37.2 [64] 44.33 [83] 52.88 [84] 113.21 [47]	
Delphinidin-3-O-rutinoside	91.6 [53] 109.93 [83]; 157.58 [84] 194.17 [48] 311.42 [47]	
Cyanidin-3-O-glucoside	8.52 [83] 16.5 [64] 16.68 [48] 28.56 [47] 39.42 [84]	0.16 [47] 2.52 [85]
Cyanidin-3-O-rutinoside	20.78 [83] 89.0 [64] 133.71 [48] 138.83 [47] 138.81 [84]	1.61 [47] 3.68 [85]
Cyanidin-3-O-sambubioside		3.39 [47]
Delphinidin-3-O-sambubioside		0.10 [47]
Cyanidin-3-O-sophoroside		0.11 [47]
Cyanidin-3-O-glucosylrutinoside		0.49 [47]
Cyanidin-3-O-xylosylrutinoside		6.93 [47]
Petunidin-3-O-rutinoside	0.1 [64] 4.15 [47] 5.67 [84]	
Petunidin-3-O-glucoside	3.97 [84] T [47]	
Pelargonidin-3-O-rutinoside	1.20 [84] 2.22 [47]	
Peonidin-3-O-glucoside	2.64 [84] T [47]	
Peonidin-3-O-rutinoside	1.2 [64] 2.94 [84] 0.77 [47]	

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T—trace.

#### 2.4. Rosaceae

Fruits from the Rosaceae family are a valuable addition to the daily diet not only because of their high nutritional value, but also because of their antioxidative properties [86]. The beneficial health effects are not only physical—other researchers also found that Rubus sp. fruits can have neuroprotective effects as well—the ingestion of blackberry metabolites in rodents reduced brain neurodegenerative processes and injections of Prunus avium extracts had positive results in reducing learning impairments and memory deficits in mice [87,88]. These effects are in line with other high anthocyanin concentrationaccumulating fruit health impacts. One of the fruits in this family—Aronia melanocarpa, which originates from North America but is widely spread in Europe nowadays—is one of the richest fruits in polyphenolic compounds and most of these accumulated compounds are anthocyanins [89]. Aronia melanocarpa accumulates lower amounts of cyanidin-3-Oglucoside when compared with Rubus fruticosus and Rubus idaeus but is rich in cyanidin-3-O-galactoside, and cyanidin-3-arabinoside which are not commonly found in fruits of other species from Rosaceae family (Table 7). Blackberry (Rubus fruticosus) also contains high levels of anthocyanins—especially cyanidin-3-O-glucoside (111.3–122.54 mg/100 g FW), which makes up around 89% of the total anthocyanin content in the fruit (Table 8). This anthocyanin has been detected in comparable concentrations in *V. myrtillus*. The other major anthocyanin in blackberry is cyanidin-3-O-sophoroside and some researchers have also found cyanidin-3-O-rutinoside, neither of which is present in V. myrtillus. Major anthocyanins in red raspberry (Rubus idaeus) are mostly cyanidin- or pelargonidin-based. The main anthocyanin in R. idaeus is cyanidin-3-O-sophoroside, which was found in concentrations up to 63.86 mg/100 g FW. Red raspberry accumulates less anthocyanins than blackberry overall, which is also indicated by the reduced color saturation of the fruit. Sweet cherry (*Prunus avium*) accumulates only a small amount of anthocyanins, the major one being peonidin-3-O-rutinoside, only making up 16.2 mg of 100 g of fresh fruit weight. However, sour cherry (Prunus cerasus), while not accumulating large amounts of most anthocyanins—concentrations reaching up to 13 or 16 mg/100 g of FW— was found in some cases to accumulate substantial amounts of cyanidin-3-O-glucosylrutinsoide—up to 235.1 mg/100 g FW during the analysis conducted in Italy. The only other major anthocyanin in *Prunus cerasus* that was found in the analyzed research was peonidin-3-Orutinoside, which was noted in concentrations reaching up to 68.1 mg/100 g FW.

Anthocyanin	<i>Rubus idaeus</i> (mg/100 g FW)	<i>Rubus fruticosus</i> (mg/100 g FW)	<i>Prunus avium</i> (mg/100 g FW)	<i>Prunus cerasus</i> (mg/100 g FW)	Aronia melanocarpa (mg/100 g FW)
Pelargonidin-3-O-sophoroside	8.77 [90]				
Cyanidin-3-O-rutinoside	10.53 [90] 4.1 [52]	4.66 [91] 31.9 [54]	13.5 [55] 52 [92] 64.16 [93] 66.81 [94]	4.9 [58] 7.3 [95] 17.11 [93]	
Cyanidin-3-2-glucosylrutinoside	11.9 [52]	19.3 [54]			
Pelargonidin-3-O-glucoside	4.23 [90]		N.D. [93]		
Cyanidin-3-O-glucoside	11.5 [52] 25.12 [90] 43.61 [96]	111.3 <b>[54]</b> 122.54 <b>[91]</b>	2.3 [55] 5.26 [93] 8.02 [92] 8.85 [94]	2.91 [93] 4.5 [97] 5.3 [95]	1.69 [32] 5.62 [98] 37.6 [47]
Delphinidin-3-O-glucoside	2.88 [90]				
Pelargonidin-3-O-rutinoside			0.4 [92] 1.08 [55] 1.48 [93] 3.40 [94]	N.D. [93]	
Peonidin-3-O-rutinoside			0.9 [92] 2.89 [94] 3.84 [93] 16.2 [55]	2.47 [93] 68.1 [95]	

Table 7. Specific anthocyanin contents found in the fruits of Caprifoliaceae family.

Anthocyanin	<i>Rubus idaeus</i> (mg/100 g FW)	<i>Rubus fruticosus</i> (mg/100 g FW)	<i>Prunus avium</i> (mg/100 g FW)	<i>Prunus cerasus</i> (mg/100 g FW)	Aronia melanocarpa (mg/100 g FW)
Cyanidin-3-O-galactoside					100.68 [98] 125.63 [32] 989.7 [47]
Cyanidin-3-O-glucosylrutinsoide			N.D. [93]	16.5 [58] 43.82 [93] 235.1 [95]	
Cyanidin-3-O-arabinoside		0.41 [91]			46.58 [98] 142.43 [32] 399.3 [47]
Cyanidin-3-O-xyloside		6.37 [91]			4.69 [32] 5.14 [98] 51.5 [47]
Malvidin-3-O-glucoside	3.64 [90]				
Cyanidin-3-O-xylosyl-6-rutinoside		3.6 [54]			
Cyanidin-3-O-glucorutinoside	11.58 [90]				
Cyanidin-3-O-sambubioside		1.8 [54]			
Cyanidin-3-O-sophoroside	11.46 [96] 44.7 [52] 63.86 [90]	35.3 [54]	N.D. [93]	4.91 [93] 39.2 [95]	

#### Table 7. Cont.

Table 8. Anthocyanin composition of blackberry (Rubus fruticosus) [54,91,99].

Anthocyanin	Amount, Percent of Total Anthocyanins (%)
Cyanidin-3-O-glucoside	90.72
Cyanidin-3-O-xyloside	3.44
Cyanidin-3-O-malonylglucoside	2.97
Cyanidin-3-O-dioxalylglucoside	2.04
Cyanidin-3-O-sambubioside	0.84

#### 3. Viability of Anthocyanins in an Antimicrobial and Antiviral Role

Since the start of the severe acute respiratory syndrome—coronavirus 2 (SARS-CoV-2) pandemic, increased infection rates and lockdowns have resulted not only in a global economic downturn, but have also caused immense harm to people's health, small businesses, livelihoods, and health. SARS-CoV-2 can cause long-term harm to lung tissues via excessive inflammation because of the "cytokine storm"—the overproduction of pro-inflammatory cytokines as an exaggerated immune response to the infection [100]. The overstimulated inflammatory response has also been called an "inflammatory cascade" by other researchers and can result in damage not only to the respiratory system, but also the urogenital, neural, and circulatory systems [101]. A significant portion of COVID-19 patients were also diagnosed with coinfections, most of which appear to be bacterial, caused by pathogens such as Streptococcus pneumoniae, Escherichia coli, and Staphylococcus aureus; viral and fungal infections (such as *Aspergillus* sp.) were less prevalent [102]. Because of the severity of impact caused by the COVID-19 and the control measures taken against it, the public's attention was drawn to finding effective ways to prevent and cure diseases. It is now quite clear that the pandemic and the governments' response to it caused a disproportionately large amount of damage to lower socioeconomic segments of society [103]. The traditionally high cost of antiviral medication coupled with a disparity in the negative impact distribution raises a difficult question—how to protect the low-income strata of society against viral and microbial infections? Knowing that anthocyanins generally have a positive impact on health, could anthocyanin-rich fruits be a viable element in finding the solution?

Research into the antiviral effects of anthocyanin has surged since the start of the pandemic. By using in silico techniques, it is possible to virtually test the possibility of establishing a bond between molecules. One such virtual research tested the inhibitory capabilities of anthocyanins against SARS-CoV-2 virus by using molecular docking [104]. The research showed that from 118 tested anthocyanins, theoretically delphinidin-3-*O*-glucosyl-glucoside, cyanidin-3-*O*-glucosyl-rutinoside, cyanidin-3-(p-coumaroyl)-diglucoside-5-glucoside), and delphinidin-3-(p-coumaroylrutinoside) are the most promising; however, this remains to be tested. In another similar research where the theoretical inhibitory capabilities of anthocyanins against SARS-CoV-2 protease and spike glycoprotein were tested via molecular docking (AutoDock Tools 1.5.4), 18 anthocyanins that are commonly found in foods were chosen for the experiment [105]. The results showed that cyanidin-3-arabinoside pelargonidin-3-glucoside, pelargonidin 3-rhamnoside, and cyanidin-7-arabinoside did not show hepatocellular toxicity and blocked SARS-CoV-2 from bonding with host cell receptors. The author concluded that cyanidin-3-arabinoside showed potent inhibition of the virus, and that its consumption could be crucial in infection prevention. *V. myrtillus* and *A. melanocarpa* contain high amounts of this anthocyanin (Tables 2 and 7), and based on these in silico results, appear to be promising source of extracts for testing SARS-CoV-2 inhibition in vitro.

Commonly occurring anthocyanins such as cyanidin-3-*O*-glucoside and peonidin-3-*O*-glucoside extracted from anthocyanin rich black rice were tested in vitro as a treatment to suppress the previously mentioned harmful heightened inflammatory immune response to SARS-CoV-2 virus by inhibiting the NLRP3 inflammasome antiviral response [106]. It was found that concentrations 1.25  $\mu$ g/mL of Cy-3-Glu, and 1.25–10  $\mu$ g/mL of Peo-3-Glu significantly suppressed the inflammation gene expression by blocking the NLRP3 inflammasome pathway and inhibited the inflammatory cytokine levels, confirming that these anthocyanins possess the anti-inflammatory properties and could be adapted in nutraceutical use. Both anthocyanins are found in large quantities in *V. myrtillus*, while individually Cy-3-Glu is abundant in *S. nigra*, and Peo-3-Glu in *L. caerulea* (Tables 2 and 4), which could indicate that individual fruit extracts or their mixtures could be at least as effective.

Anthocyanin-accumulating fruits have frequently been studied for their antimicrobial purposes. Extracts from fruits that synthesize anthocyanins can be effective at halting the proliferation or destruction of harmful bacteria without harming the intestinal microfauna [107]. However, the findings of such experiments usually differ quite significantly—while some experiments only found light antibacterial effects such as a reduced rate of proliferation of contaminants, other researcher teams found anthocyanin extracts to be comparable in effectiveness to simple antibiotics such as tetracycline and ampicillin [108]. Species of Vaccinium genus are among the highest anthocyanin content-accumulating fruits and as such there has been a lot of research completed seeking to determine antimicrobial capabilities of anthocyanin-rich fruit extracts obtained from these species. In an experiment where V. myrtillus and V. corymbosum fruit and fruit skins extracts were tested for inhibitory effects against Gram-positive, Gram-negative bacteria, and yeast strains using the agar diffusion assay [109], it was determined that there was no significant difference between the inhibitory effects of fruit and fruit skin extracts and inhibited growth was observed in Gram-positive strains of Listeria monocytogenes, Staphylococcus aureus, Bacillus subtilis, and Enterococcus faecalis and these Gram-negative strains: Citrobacter freundii, Escherichia coli, Pseudomonas aeruginosa, and Salmonella enterica. In these bacteria strains C. freundii and *E. faecalis* were the most sensitive. *E. coli* was the most resistant bacteria in this experiment. Fruit extracts showed no significant effect against the tested yeast strains. Anthocyanin ineffectiveness against fungi was also found in the experiment conducted by Salamon and others [110]—where anthocyanin extracts of V. myrtillus and Aronia melanocarpa showed no antimycotic activity against Candida albicans and no antimicrobial inhibitory effects against E. coli and Staphylococcus aureus.

However, the findings in other experiments, even when similar species were tested, seem to vary quite significantly—the results of the Burdulis [70] experiment where *V. myrtillus* and *V. corymbosum* fruit and fruit skin extracts were tested for bacteria inhibitory properties showed that the extracts were more effective against the Gram-negative bacteria when compared with Gram-positive. A significant difference between fruit and fruit skin extract effectiveness was not established. Even more polarized results were observed in the experiment where several species of berries were tested for bacteria-inhibiting properties, including various Vaccinium species [111]. In this experiment most berry extracts had little to no effect in Gram-positive bacteria inhibition while being effective against Gram-negative bacteria. In contrast, the results of the Bobinaite et al. [112] experiment where *Rubus* sp. extracts were tested against Gram-positive and Gram-negative pathogens, the results were contrary—Gram-positive bacteria were more affected than Gram-negative pathogens; however, due to the insufficient number of Gram-negative species tested, no concrete conclusions about the resistance of Gram-negative bacteria to anthocyanin-rich extracts of *Rubus* sp. berries were made. The differences in the anthocyanin effect against Gram-positive and Gram-negative bacteria can been explained as result of differences in the cell wall structure, with the outer membrane of the Gram-negative bacteria acting as a hardly penetrable barrier for hydrophilic substances. However, some anthocyanins, such as malvidin-based anthocyanins, are more hydrophobic than others; therefore, their transport through membranes is more intensive. Because of these properties, it is possible that these anthocyanins may have an increased effect against Gram-negative bacteria than others.

Most of the research articles regarding microbe growth inhibition have focused on the anthocyanin-accumulating fruit extracts and there is very little information about the antimicrobial effects on pathogens of pure anthocyanins, even though some anthocyanin rich fruits show little or no antimicrobial properties—such as, for example *Sambucus nigra* [110]. One of the few research studies conducted to determine the pure polyphenolic compound effect on microorganisms was conducted by R. Puupponen-Pimiaand and others [111]. In this research it was found that the pure anthocyanidins delphinidin and cyanidin were effective at inhibiting the growth of *E. coli*. Pure cyanidin-3-*O*-glucoside only showed bacteriostatic effects. The strongest bacteria proliferation inhibition was observed when anthocyanin-rich berry extracts were used. Blueberries and raspberries showed the strongest antibacterial activity. Nohynek and others [113] mention in their conclusions that it is very likely that the strongest anthocyanin antimicrobial effects are observed only when weak organic acids, tannins, phenolic acids, and mixtures of these compounds are also involved; therefore, chemically complex compounds need extensive research to discover the full antimicrobial potential of anthocyanins.

#### 4. Effects of Processing and Extraction on Anthocyanins

An improvement in processing and extraction methods is of increasingly high importance due to the growing focus on ecology and sustainability. Adapting extraction and processing methodologies to anthocyanins can be challenging because, as mentioned before, anthocyanins are highly unstable, and their color and structure can be affected by various factors including light, acidity, and temperature [17]. Because of this instability, the processing of anthocyanin-rich material is an extremely important step that influences the anthocyanin extraction rate and output. The traditional way to extract anthocyanins is by using acidified organic solvents for example acetone, ethanol, or methanol and long extraction times to ensure that anthocyanins and other phenolics transfer from the plant cells into the solvent [114,115]. Scientists have come up with many ways to improve upon the classical method to reduce the waste, toxicity, and time required for the procedure. An alternative method that is more ecological than the traditional organic solvent extraction is utilizing the supercritical carbon dioxide technology (SC-CO<sub>2</sub>). The use of the SC-CO<sub>2</sub> results in extracts that do not contain any hazardous solvents and preserves the bioactive compounds—both hydrophilic and hydrophobic [116,117]. Additionally, when fruit industrial byproducts are used as raw materials, it was observed that  $SCE-CO_2$  has a high selectivity for high-value compound extraction [118]. Consequently, this method is both safe and suited to use for creating functional food products.

Proper material preparation can be highly beneficial to optimize the extraction—reducing particle size by using homogenizers to crush and chop raw material hulls/pomace/fruits

is one of the simplest and effective ways to increase the extraction rate [119]. Using an ultrasound to damage the plant cell walls is also an effective way to reduce the overall extraction time as found by various researchers and reduce the use of toxic solvents, since ultrasonic-assisted extraction can be performed using water extraction [98,120]. However, using ultrasonic waves may generate free radicals and as such degrade the anthocyanins, requiring the ultrasonication process to be optimized beforehand to avoid negative consequences. Freeze drying is among the newer methods used in phenolic compound material preparation and was found to be highly beneficial because it does not damage phenolics and anthocyanins since the use of water, high pressure, and temperatures are avoided [110]. Raising temperatures above 35 °C can degrade the anthocyanins [119] but raising the temperatures to 80–140 °C can decrease the total extraction time and using pressurized liquid extraction (PLE or accelerated solvent extraction ASE) resulted in both faster extraction and extracts with higher antioxidant capacity, though anthocyanin degradation to chalcone was also observed. A possible explanation for the increased antioxidant capacity could be the formation of Maillard reaction products which possess high antioxidant capacity [121]. Another innovative method of fruit pretreatment is the application of pulsed electric fields (PEF). The researchers found that by using the PEF technology it is possible to improve the anthocyanin content in both juices and the byproduct—press cake. The main principle of this method is utilization of square wave high-voltage pulse generator to soften the fruit tissue by making the cell membranes more permeable. Such a pre-treatment has an additional positive effect of increasing the juice yield in blueberries—by 32% [122]; comparable results were observed by another team of scientists with raspberries-juice yields increased up to 25% [123]. In the experiments conducted with the blueberry juice and press cakes it was concluded that the use of low field strength and high energy input enhanced the antioxidant activity in blueberry juice, while further increases in the field strength improved the antioxidant activity in the blueberry press cakes [122,124]. PEF pretreated samples with 10 kJ/kg at 3 kV/cm energy input resulted in a 55–60% anthocyanin content increase and antioxidant capacity increase up to 41% when compared with untreated samples [122,124]. Similar results were observed in raspberries where even the lowest intensity pulsed electric field treatment set to 6 kJ/kg at 1 kV/cm increased the total anthocyanin content by more than 25% [123].

#### 5. Conclusions

In a world plagued by illnesses caused by unhealthy lifestyle, and aging societies burdened by diseases associated with old age, fruits that accumulate large amounts of anthocyanins are often called super foods for their nutritional value and potential as a food supplement or even possible medicament for such conditions. From the reviewed articles studying fruit species from various families, several fruits stand out for their high anthocyanin content. In the Ericaceae family it is *Vaccinium myrtillus*, which has historically been widely studied in anthocyanin-related studies and is highly regarded for accumulating anthocyanins. *Sambucus nigra* (Caprifoliaceae) was also found to accumulate large quantities of anthocyanins and appears to be an especially promising fruit for Cy-3-Glu extraction because of its vast capability to accumulate this particular anthocyanin extraction—*Aronia melanocarpa* and *Prunus avium*. Fruit species from Grossulariaceae family appear to have noticeably lower anthocyanin accumulation.

The severe consequences of the COVID-19 pandemic, lack of effective prevention methods, and medicine forced researchers to investigate alternatives. The studies of anthocyanins as elements in viral infection prevention or even treatment have shown promising results for the prospect that anthocyanins can be a healthy alternative to, or a component in antiviral medication—even commonly occurring anthocyanins such as Cy-3-Glu and Pel-3-Glu can be effective at suppressing the harmful inflammatory reaction during

viral infections. Because the recently published research on anthocyanin antiviral effects is not very numerous, more research will be required to formulate definite conclusions.

Different anthocyanins are dominant in different families, and this appears to have an effect on the antimicrobial properties of the fruit. In the reviewed articles the conclusions about anthocyanin extract effects were varied—both Gram-positive and Gram-negative bacteria appear to be affected by anthocyanins, but more research is needed to draw strong conclusions about Gram-positive and Gram-negative bacteria sensitivity. *E. coli* appeared to be resistant to the anthocyanin extracts; none of the anthocyanin-rich extracts had a significant effect against the fungi. Variation of antibacterial effectiveness is attributed to the ease of transport through the cell membrane—hydrophobic anthocyanins such as malvidin should be more effective than more hydrophilic ones. This, however, is hard to prove due to a lack of research on individual anthocyanin antimicrobial effects. Most of the researchers consider anthocyanins as a crucial fragment that requires a complex mixture of bioactive compounds and their synergy to maximize the beneficial properties.

Traditional anthocyanin extraction requires lots of chemical solvents and takes a very long time to complete. To minimize the environmental impact and production cost and for anthocyanin extracts to be suitable for dietary or medical implementation, the use of toxic solvents and extraction duration should be reduced as much as possible. For this purpose, innovative extraction methods are employed, such as accelerated solvent extraction (ASE) and supercritical carbon dioxide technology (SC-CO<sub>2</sub>). Many pretreatment methods are utilized to damage cell walls and membranes without negatively affecting the sensitive anthocyanin compounds. Among the successfully implemented ones are lyophilization, ultrasonication, and pulsed electric fields (PEF). However, these pretreatment methods require optimization for specific fruit species to be effective and must be combined with innovative extraction methods to have the highest positive effect on extraction yield.

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