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Review

Vaccinium Species (Ericaceae): From Chemical Composition to Bio-Functional Activities

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Abstract: The genus *Vaccinium* L. (Ericaceae) includes more than 450 species, which mainly grow in cooler areas of the northern hemisphere. *Vaccinium* species have been used in traditional medicine of different cultures and the berries are widely consumed as food. Indeed, *Vaccinium* supplement-based herbal medicine and functional food, mainly from *V. myrtillus* and *V. macrocarpon*, are used in Europe and North America. Biological studies support traditional uses since, for many *Vaccinium* components, important biological functions have been described, including antioxidant, antitumor, anti-inflammatory, antidiabetic and endothelium protective activities. *Vaccinium* components, such as polyphenols, anthocyanins and flavonoids, are widely recognized as modulators of cellular pathways involved in pathological conditions, thus indicating that *Vaccinium* may be an important source of bioactive molecules. This review aims to better describe the bioactivity of *Vaccinium* species, focusing on anti-inflammatory and endothelial protective cellular pathways, modulated by their components, to better understand their importance for public health.

Keywords: *Vaccinium* species; phytochemicals; berry; leaf; anti-inflammatory pathways; endothelial dysfunction

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1. Introduction

In recent years, *Vaccinium* species, mainly their fruits, have gained great attention for their potential health benefits. *Vaccinium* L. (Ericaceae) is a morphologically various genus of terrestrial or epiphytic shrubs and sub-shrubs, comprising approximately 450 species across Europe, North and Central America, South East and Central Africa, and Asia [1]. Deciduous or evergreen dwarf shrubs, shrubs or small trees characterize the genus, and the fruits of each variety are edible. The European flora comprises *V. corymbosum* (blueberry), *V. oxycoccos* (cranberry), *V. microcarpum*, *V. macrocarpon*, *V. vitis-idaea*, *V. uliginosum*, *V. myrtillus*, *V. arctostaphylos*, and *V. cylindraceum*. *V. corymbosum* was imported by North America, and now is cultivated in Europe for its big edible fruits [2]. *V. myrtillus* (bilberry) is a woody dwarf shrub, present in the forests of the Northern Hemisphere. It needs acid and well-drained soils for its growth, and it is considered to be an indicator of the biodiversity of forests due to its abundance.

Fruits of several *Vaccinium* species have been extensively investigated for their chemical profile. They are described as being a rich source of polyphenols and carotenoids. Nevertheless, especially due to their high content of anthocyanins, these fruits are recognized for their bioactive properties, such as prevention or treatment of cardiovascular diseases, diabetes, obesity, cancer, urinary tract infections, and aging diseases [3,4].

Polyphenols are the subject of increasing interest because of their potential beneficial effects on human health [5–9]. In fact, several epidemiological studies suggested that long term consumption of foods rich in polyphenols offered protection against the development of cardiovascular diseases, diabetes, cancers, and neurodegenerative diseases [5,6]. Polyphenols have been recognized due to their potent antioxidant activity and ability to modulate key signalling pathways of several inflammatory cytokines and enzymes [5]. Therefore, beyond these modulatory roles, their antioxidant activity related to the capacity to scavenge reactive oxygen species (ROS), or to activate cellular endogenous antioxidant systems, may be of importance in countering the oxidative stress in inflammatory diseases [5,6].

The antioxidant and anti-inflammatory activities of *Vaccinum* species are also reflected in a protective role for vascular endothelium against cardiovascular diseases linked to endothelial dysfunction [10,11].

The present review is designed to report the current knowledge on the plant species that belong to the *Vaccinium* genus, their phytochemicals, and their potential biological properties, with particular emphasis on their cardiovascular protective effects. Attention is focused on the ability of *Vaccinium* species to revert endothelial dysfunction promoted by increased oxidative stress and inflammatory status. All collected data have been obtained from different databases such as PubMed, Scopus, Sci Finder, Web of Science, Science Direct, NCBI, and Google Scholar.

2. Traditional Uses of *Vaccinium* Species

Vaccinium species are extensively used in traditional medicine. As reported in Table 1, the fruits of *V. myrtillus* are used in Europe for the treatment of stomatitis, renal stones, intestinal and liver disorders, as a remedy for fevers and coughs, and for their astringent, tonic, and antiseptic properties [12,13]. The decoction and infusion of leaves are used in south-eastern Europe to treat diabetes [14].

Table 1. Traditional uses of *Vaccinium* species.

Vaccinium	Traditional Uses	Part Used	References
V. myrtillus	Fevers and coughs	Fruits	[12]
	Antidiabetic and anti-inflammatory diabetic	Leaves	[13,14]
	Respiratory inflammations	Leaves and fruits	[15]
	Stomatitis	Fruits	[12]
	Eye inflammation	Fruits	[15]
	Intestinal and liver disorders	Fruits	[12]
	Hepatitis	Fruits	[15]
	Digestive and urinary tract disorders	Fruits	[15]
	Renal stones	Leaves and fruits	[12,15]
	Antiseptic, astringent, tonic	Fruits	[13]
	Anti-anemic	Leaves and fruits	[15]
V. vitis idaea	Antipyretic	Leaves and fruits	[15]
	Sore eyes, abscesses, toothache, thrush and snow blindness	Fruits	[16]
	Colds, coughs and sore throats	Fruits	[17]
	Anti-inflammatory properties in urinary tract	Leaves	[15]
	Respiratory system infections	Stems and leaves	[18]
	Frequent urination	Fruits	[16]
	Urinary tract infection properties	Fruits	[15]
	Kidney stones	Fruits	[15]
	Anti-inflammatory	Stems and leaves	[18]
	Wound healing, anti-rheumatic, anti-convulsant, diuretic and anti-diabetic	Leaves and fruits	[15]
V. arctostaphylos	Anti-hypertensive and anti-diabetic	Leaves and fruits	[19]
V. corymbosum	Anti-diabetic, antioxidant, and anti-inflammatory	Fruits	[20,21]
	Gastrointestinal disorders	Fruits	[22]

In Macedonia and Kosovo, the juice of *V. myrtillus* fruits are employed as anti-anemic agents, and to treat digestive and urinary tract infections, eye inflammations and hepatitis, while the infusions of leaves and fruits are used as lithontriptic and anti-anemic treatments, and for respiratory inflammations [15]. *V. vitis idaea* berries are effective in the traditional medicine of Cree Nation (Quebec) to treat frequent urination, sore eyes, abscesses, toothache, thrush and snow blindness [16]. Among the Alaska Natives, berries are also used to treat colds, coughs and sore throats [17]. From ancient times, stems and leaves have shown anti-inflammatory properties and are known for treating respiratory system infections in Chinese Traditional Medicine [18].

In Macedonia and Kosovo, an infusion of the leaves was used for their anti-rheumatic properties, as well as anti-inflammatory effects in the urinary tract, while the fruit infusion was useful for treating urinary tract infections and the presence of kidney stones. Fruits and leaves are also used as diuretic, anti-rheumatic, antipyretic, anti-diabetic and anti-convulsant medicines, as well as for wound healing [15]. *V. arctostaphylos* leaves and fruits have been utilized as anti-hypertensive and anti-diabetic agents in Iranian folk medicine [19]. In Quebec, *V. corymbosum* fruits have mainly been used to treat diabetes [20–22].

3. Phytochemicals of *Vaccinium* Fruits

Anthocyanins are present in the outer layer of fruits, together with polyphenolic compounds, and a small content was found also in pulp and seeds. Environmental factors can affect the content and composition of secondary metabolites in berries.

Growing conditions also affect the content of anthocyanins and other phenolic compounds in the berries of wild and cultivated species [23]. Prior to berry ripening, proanthocyanidins, flavonols and hydroxycinnamic acids are the major phenolic compounds. During the ripening process, flavonoid profiles vary, and anthocyanins accumulate in the skin. High levels—and a wide variety—of anthocyanins provide the red, blue, and purple colours that characterize berries of this genus.

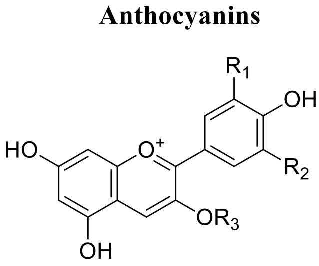
Vaccinium berries have a well-deserved reputation as potential healthy products and functional foods, supported by many studies, which have identified and quantified various bioactive phytochemicals with known benefits for human health.

Many studies have demonstrated the benefits of anthocyanin-rich extracts of *Vaccinium* species in the prevention of several diseases [24]. Nonetheless, it is important to note that their efficacy is subject to their bioavailability. Once ingested, anthocyanins are metabolized into various conjugates, which are metabolized into phenolic acid degradation products. Accumulated evidence suggests synergistic effects between all possible metabolites to explain their health-promoting properties.

An inter-individual and intra-individual variability in anthocyanins absorption, metabolism, distribution, and excretion is also evident.

Six anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, petunidin, and peonidin), which are also the most common anthocyanidin skeletons in higher plants, have been isolated from *Vaccinium* species [25]. To date, more than 35 anthocyanin glycosides have been isolated from the genus *Vaccinium*.

In *Vaccinium* berries, mono, di, or trisaccharide derivatives of delphinidin, cyanidin, peonidin, petunidin, and malvidin are common (Figure 1) [25]. The principal sugars are glucose, galactose, xylose, rhamnose, and arabinose.


Anthocyanins

	R_1	R_2	R_3
Cyanidin 3-*O*-arabinoside	OH	H	Ara
Cyanidin 3-*O*-galactoside	OH	H	Gal
Cyanidin 3-*O*-glucoside	OH	H	Glc
Cyanidin 3-*O*-glucuronide	OH	H	Glc A
Cyanidin 3-*O*-sambubioside	OH	H	Xyl(1→2)Glc
Delphinidin 3-*O*-arabinoside	OH	OH	Ara
Delphinidin 3-*O*-glucoside	OH	OH	Glc
Delphinidin 3-*O*-galactoside	OH	OH	Gal
Delphinidin 3-*O*-sambubioside	OH	OH	Xyl(1→2)Glc
Delphinidin 3-*O*-xyloside	OH	OH	Xyl
Malvidin 3-*O*-arabinoside	OCH_3	OCH_3	Ara
Malvidin 3-*O*-galactoside	OCH_3	OCH_3	Gal
Malvidin 3-*O*-glucoside	OCH_3	OCH_3	Glc
Malvidin 3-*O*-xyloside	OCH_3	OCH_3	Xyl
Peonidin 3-*O*-arabinoside	OCH_3	H	Ara
Peonidin 3-*O*-galactoside	OCH_3	H	Gal
Peonidin 3-*O*-glucoside	OCH_3	H	Glc
Petunidin 3-*O*-arabinoside	OH	OCH_3	Ara
Petunidin 3-*O*-galactoside	OH	OCH_3	Gal
Petunidin 3-*O*-glucoside	OH	OCH_3	Glc
Petunidin 3-*O*-xyloside	OH	OCH_3	Xyl

Figure 1. Anthocyanins from *Vaccinium* species [25–36].

The fruits of *V. myrtillus* are characterized by the presence of different types of anthocyanins. In particular, cyanidin 3-*O*-galactoside, cyanidin 3-*O*-glucoside, cyanidin 3-*O*-arabinoside, delphinidin 3-*O*-galactoside, delphinidin 3-*O*-arabinoside, delphinidin 3-*O*-glucoside, malvidin 3-*O*-galactoside, malvidin 3-*O*-arabinoside, malvidin 3-*O*-glucoside, petunidin 3-*O*-galactoside, petunidin 3-*O*-arabinoside, petunidin 3-*O*-acetylglucoside, peonidin 3-*O*-galactoside, and peonidin 3-*O*-arabinoside were identified [26–31].

In *V. myrtillus*, cyanidin 3-*O*-xyloside, cyanidin 5-*O*-glucoside, cyanidin 3,5-*O*-diglucoside, cyanidin 3-*O*-(6″-*O*-2-rhamnopyranpsyl-2″-O-β-xylopranosyl-β-glucopyranoside), cyanidin 3-*O*-sambubioside, delphinidin 3-*O*-sambuobiside, and peonidin-3-glycoside have also been identified [31–34].

Malvidin and delphinidin derivatives represent about 75% of the total anthocyanins content of *V. corymbosum* fruits [35,36]. Cho et al. [29] reported percentages of 27–40% for delphinidin, 22–33% for malvidin, 19–26% for petunidin, 6–14% for cyanidin, and 1–5% for peonidin. Petunidin 3-*O*-glucoside has been also identified in *V. corymbosum* and *V. myrtillus* [27,31]. The 3-*O*-galactosides and 3-*O*-arabinosides of cyanidin and peonidin are the most abundant recognised anthocyanins in the fruits of *V. oxycoccos* [27,37,38].

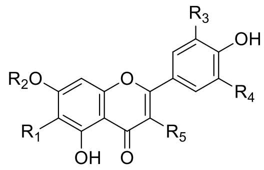
Twelve anthocyanins, namely cyanidin 3-*O*-glucoside, delphinidin 3-*O*-glucoside cyanidin 3-*O*-arabinoside, peonidin 3-*O*-arabinoside, peonidin 3-*O*-glucoside, peonidin 3-*O*-galactoside, delphinidin 3-*O*-arabinoside, delphinidin 3-*O*-galactoside, petunidin 3-*O*-galactoside, petunidin 2-*O*-glucoside, malvidin 3-*O*-galactoside, and malvidin 3-*O*-

glucoside, were isolated from the extract of the edible berries of *V. vitis-idaea* by a combination of chromatography techniques [39–44].

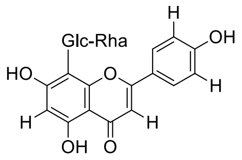
Delphinidin-3-*O*-xyloside, delphinidin-3-*O*-glucoside, malvidin-3-*O*-galactoside, malvidin-3-*O*-glucoside petunidin-3-*O*-galactoside, petunidin-2-*O*-glucoside, malvidin-3-*O*-xyloside, and petunidin-3-*O*-xyloside were isolated from *V. arctostaphylos* [45,46].

Except anthocyanins, to date, more than 50 other flavonoids (mainly flavanols and proanthocyanidins) have been isolated and identified from the genus *Vaccinium* (Figure 2) [25,28–31,40–44].

Flavonoids

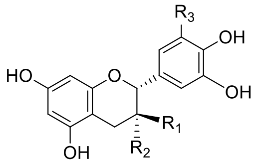


	R_1	R_2	R_3	R_4	R_5
Apigenin	H	H	H	H	H
Apigenin 7-*O*-glucuronide	H	Glc A	H	H	H
Chrysoeriol	H	H	OCH_3	H	H
Hyperoside	H	H	OH	H	*O*-Gal
Isoorientin	Glc	H	H	OH	H
Isoquercitrin	H	H	OH	H	*O*-Glc
Isorhamnetin	H	H	OCH_3	H	OH
Isorhamnetin 3-*O*-galactoside	H	H	OCH_3	H	*O*-Gal
Isorhamnetin 3-*O*-glucoside	H	H	OCH_3	H	*O*-Glc
Isorhamnetin 3-*O*-xyloside	H	H	OCH_3	H	*O*-Xyl
Kaempferol	H	H	H	H	OH
Kaempferol 3-*O*-glucoside	H	H	H	H	*O*-Glc
Kaempferol 3-*O*-glucuronide	H	H	H	H	*O*-Glc A
Kaempferol 3-*O*-rhamnoside	H	H	H	H	*O*-Rha
Laricitrin	H	H	OCH_3	OH	OH
Laricitrin 3-*O*-glucuronide	H	H	OCH_3	OH	*O*-Glc A
Luteolin	H	H	OH	H	H
Myricetin	H	H	OH	OH	OH
Myricetin 3-*O*-arabinoside	H	H	OH	OH	*O*-Ara
Myricetin 3-*O*-galactoside	H	H	OH	OH	*O*-Gal
Myricetin 3-*O*-glucoside	H	H	OH	OH	*O*-Glc
Myricetin 3-*O*-glucuronide	H	H	OH	OH	*O*-GlcA
Myricetin 3-*O*-rhamnoside	H	H	OH	OH	*O*-Rha
Myricetin 3-O-xyloside	H	H	OH	OH	*O*-Xyl
Quercetin	H	H	OH	H	OH
Quercetin 3-*O*-arabinoside	H	H	OH	H	*O*-Ara
Quercetin 3-*O*-glucoside 7-*O*-rhamnoside	H	Rha	OH	H	*O*-Glc
Quercetin 3-*O*-glucuronide	H	H	OH	H	*O*-Glc A
Quercetin 3-*O*--rhamnoside	H	H	OH	H	*O*-Rha
Quercetin 3-O-robinobioside	H	H	OH	H	*O*-Gal(6←1)Rha
Quercetin 3-*O*-xyloside	H	H	OH	H	*O*-Xyl
Rutin	H	H	OH	H	*O*-Glc(6←1)Rha
Syringetin	H	H	OCH_3	OCH_3	OH
Syringetin 3-*O*-glucoside	H	H	OCH_3	OCH_3	*O*-Glc



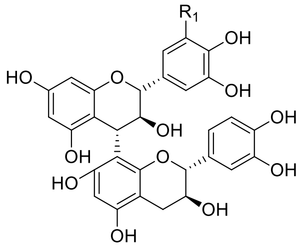
Vitexin 2-rhamnoside

Flavanols



	R_1	R_2	R_3
Catechin	OH	H	H
Epicatechin	H	OH	H
Epigallocatechin	H	OH	OH

Proanthocyanidin



	R_1
Catechin-4,8-catechin	H
Gallocatechin-4,8-catechin	OH

Figure 2. The main flavonoids identified in *Vaccinium* species [25,28–31,41].

Glycosides are usually *O*-glycosides, with the sugar moiety bound to the hydroxyl group at the C-3 or C-7 position. The most common sugar moieties include D-glucose, L-rhamnose, D-xylose, D-galactose, and L-arabinose [25].

Quercetin is the most common flavonoid isolated from *Vaccinium* species [25]. It was found in high quantities in *V. uliginosum* and *V. myrtillus* [29]; however, the richest source of quercetin is *V. oxycoccos* with 20–40 mg/100 g fresh weight [38].

Several glycosides of myricetin and quercetin were identified in *V. myrtillus*. Different studies reported the presence of myricetin 3-glucoside, myricetin 3-arabinoside, myricetin 3-*O*-rhamnoside, quercetin 3-*O*-arabinoside, quercetin 3-*O*-rhamnoside, quercetin 3-*O*-galactoside, quercetin 3-*O*-glucoside, and quercetin 3-*O*-rutinoside [28–31]. Apigenin, chrysoeriol, myricetin, myricetin-3-xyloside, quercetin 3-*O*-glucuronide, quercetin 3-*O*-xyloside, isorhamnetin 3-*O*-glucoside [41], luteolin are other flavonoids described in *V. myrtillus* [47]. Kaempferol, isorhamnetin, laricitrin, syringetin, isorhamnetin 3-*O*-galactoside, myricetin 3-*O*-glucuronide, laricitrin 3-*O*-glucoside, syringetin 3-*O*-glucoside [35,41,48], kaempferol 3-*O*-glucoside, myricetin 3-*O*-galactoside, and isorhamnetin 3-*O*-xyloside are also described [48].

The flavonoids identified in *V. oxycoccos* are mainly glycosides of quercetin and myricetin, and to a lesser extent, of kaempferol [49]. Quercetin 3-*O*-galactoside is the dominant compound, but at least 11 other glycosides are present in lower concentrations [38].

Epicatechin is the dominant constitutive unit of *V. oxycoccos*, whereas catechin and (epi)gallocatechins are present only in trace amounts [24,40].

The major flavonoids described in *V. vitis idaea* are kaempferol [41], quercetin [41,50], myricetin, myricetin 3-*O*-glucoside [44], quercetin derivatives (bond to glucose, galactose, glucuronide, rhamnose, arabinose, and xylose), kaempferol 3-*O*-rhamnoside, isorhamnetin 3-*O*-galactoside [40,51], isorhamnetin 3-*O*-glucoside, syringetin-3-*O*-glucoside, kaempferol 3-*O*-glucoside, and rutin [51].

The fruits of *V. uliginosum* are characterized by the presence of kaempferol, laricitrin [50], quercetin [50,52–54], myricetin [54], syringetin, quercetin 3-*O*-glucoside, quercetin 3-*O*-galactoside, quercetin 3-*O*-glucuronide, isorhamnetin 3-*O*-galactoside, isorhamnetin 3-*O*-glucoside, syringetin 3-*O*-glucoside, myricetin 3-*O*-galactoside, rutin [50,52], and myricetin 3-*O*-glucuronide [48].

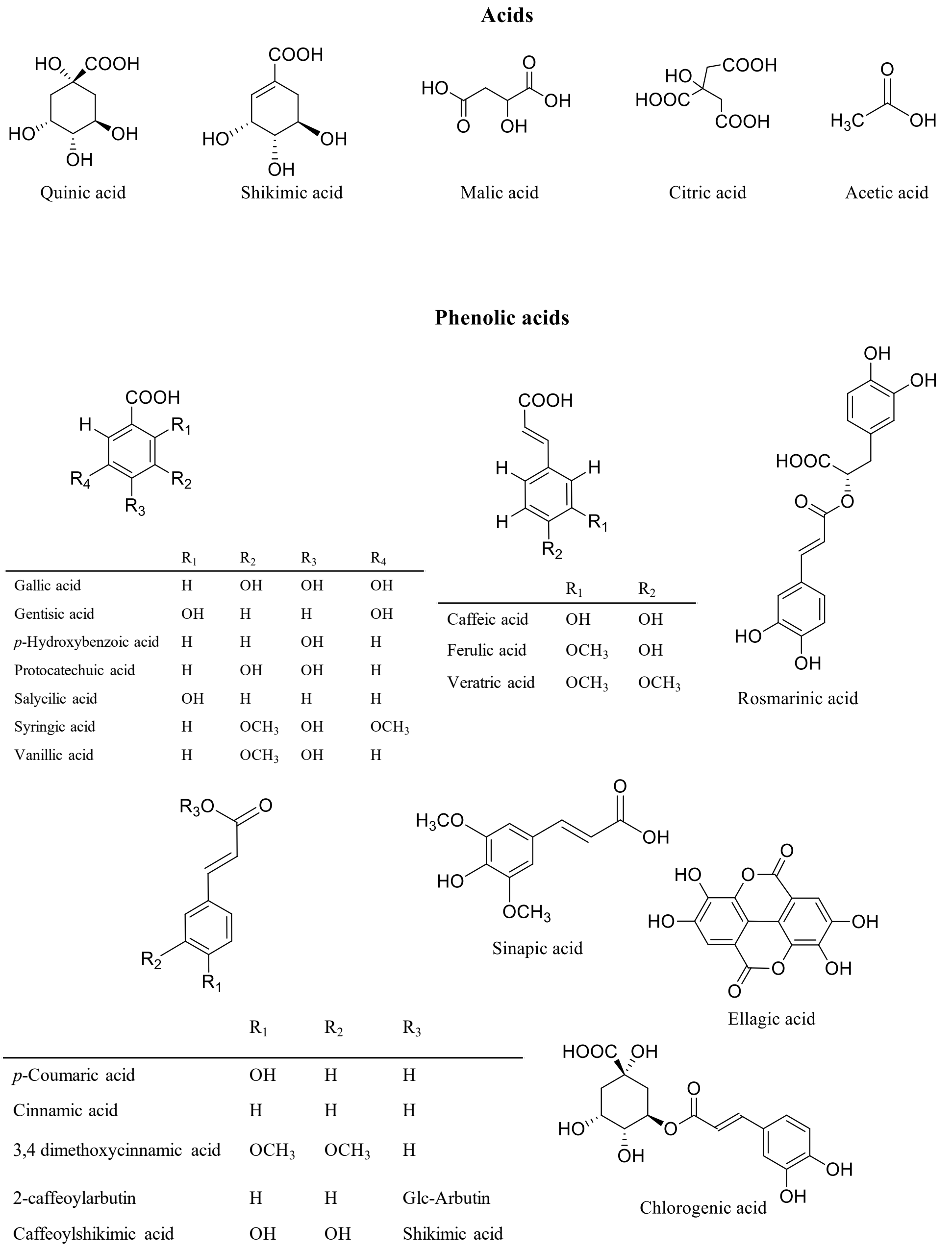
Sellappan et al. [55] described, in *V. corymbosum*, the presence of catechin, myricetin, quercetin and kaempferol, but not the presence of epicatechin.

Seventeen phenolic acids were identified in some varieties of *V. myrtillus* (Figure 3) [56]. Sellappan et al. [55] found gallic, *p*-coumaric, ferulic, ellagic and caffeic acids as phenolic acids in *V. corymbosum* produced in the state of Georgia (US). These results were confirmed by Taruscio et al. [30] who analysed the phenolic acids composition of *V. corymbosum* and *V. oxycoccos*. The two species have different compositions. In fact, *V. corymbosum* was characterised by the presence of chlorogenic acid as a major phenolic acid, followed by caffeic, ferulic, *p*-coumaric and traces of *p*-hydroxybenzoic acids, while *p*-coumaric acid was the principal phenolic acid of *V. oxycoccos*, followed by ferulic, chlorogenic, caffeic and *p*-hydroxybenzoic acids.

Other studies have reported *p*-coumaric, sinapic, caffeic, and ferulic acids as the main hydroxycinnamic acids identified in *V. oxycoccos* [57–59]. Ellagic acid and ellagitannins have not been detected in significant amounts [24].

Thirteen phenolic acids (gallic, protocatechuic, *p*-hydroxybenzoic, *m*-hydroxybenzoic, gentisic, chlorogenic, *p*-coumaric, caffeic, ferulic, syringic, sinapic, salicylic, and *trans*-cinnamic acids) were identified in *V. arctostaphylos*.

The dominant phenolic acids were caffeic and *p*-coumaric acids. The phenolic acid concentrations are mostly lower in *V. arctostaphylos* in comparison to the other berries of the *Vaccinium* genus [60].



	R_1	R_2	R_3	R_4
Gallic acid	H	OH	OH	OH
Gentisic acid	OH	H	H	OH
p-Hydroxybenzoic acid	H	H	OH	H
Protocatechuic acid	H	OH	OH	H
Salycilic acid	OH	H	H	H
Syringic acid	H	OCH_3	OH	OCH_3
Vanillic acid	H	OCH_3	OH	H

	R_1	R_2
Caffeic acid	OH	OH
Ferulic acid	OCH_3	OH
Veratric acid	OCH_3	OCH_3

	R_1	R_2	R_3
p-Coumaric acid	OH	H	H
Cinnamic acid	H	H	H
3,4 dimethoxycinnamic acid	OCH_3	OCH_3	H
2-caffeoylarbutin	H	H	Glc-Arbutin
Caffeoylshikimic acid	OH	OH	Shikimic acid

Figure 3. Main acids and phenolic acids in the *Vaccinium* genus [56–60].

Iridoids are a widespread group of monoterpenoids comprising a generally glycosylated cyclopentan[*c*]pyran skeleton. They are specifically produced by several botanical families and are a class of secondary metabolites that is characteristic of the Ericaceae. Iridoids from the *Vaccinium* genus have been less studied than anthocyanins and other phenolic compounds. However, iridoids have known human health benefits including anti-inflammatory, anticancer, antimicrobial, antioxidant, antispasmodic, cardioprotective, choleretic, hepatoprotective, hypoglycaemic, hypolipidemic, neuroprotective, and purgative activities [61–63].

The Figure 4 shows the main iridoids identified in *Vaccinium* species. These compounds have often been identified in mixtures and have not always been isolated. The stereochemistry of the asymmetric carbons of some of them has not been elucidated. Asperuloside, scandoside, and monotropein, and their derivatives, seem to be representative of the genus [64,65].

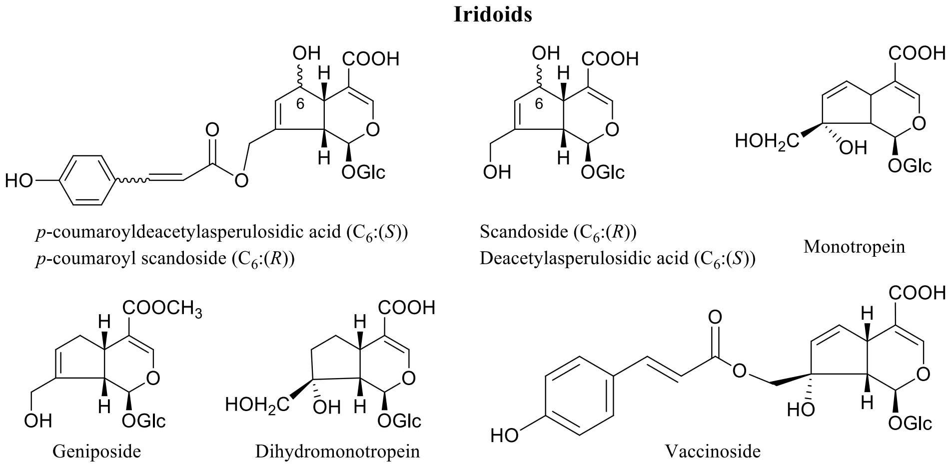


Figure 4. The chemical structures of the main iridoids isolated from *Vaccinium* species [64,65].

Heffels et al. [64] have tentatively identified, in *V. uliginosum* and *V. myrtillus*, 14 iridoid glucosides, including vaccinoside, monotropein, *p*-coumaroyl-scandoside, deacetylasperulosidic acid (C_6: (*S*)), scandoside (C_6: (*R*)), *p*-coumaroyl-deacetylasperulosidic acid, *p*-coumaroyl-monotropein, and *p*-coumaroyldihydromonotropein (C_6-C_7 hydrogenated). *V. oxycoccos* juice showed the presence of two new coumaroyl iridoid glycosides, namely 10-*p-trans*- and 10-*p-cis*-coumaroyl-1*S*-dihydromonotropein [66].

Detection and isolation of iridoids from fruits is not straightforward. Surprisingly, iridoid glycosides have not been identified in *V. corymbosum* [64,67,68], whereas scandoside, geniposide, vaccinoside, and dihydromonotropein have recently been identified in *V. corymbosum* extracts [65].

Ursolic acid, which showed to possess strong anti-inflammatory effects, is abundant in *V. oxycoccos*, which also contains two rare derivatives of ursolic acid: *cis*-3-*O*-*p*-hydroxycinnamoyl ursolic acid and *trans*-3-*O*-*p*-hydroxycinnamoyl ursolic acid [69].

Triterpenoids are the most predominant components in the cuticular wax of blueberry fruits, together with the triterpene alcohols α-amyrin, β-amyrin, and lupeol [70].

Ursolic acid was the dominant triterpene in *V. corymbosum* (southern highbush blueberry) cultivars, whereas oleanolic acid was the most abundant in northern highbush blueberry cultivars. Hentriacontan-10,12-dione was detected for the first time in *V. corymbosum* [70].

Malic, citric, and quinic acids are the non-volatile acids identified and quantified in *V. arctostaphylos* and *V. myrtillus* species. It is interesting to note that the level of malic acid in both berries increases gradually during maturation. In contrast, the level of citric and quinic acids, as well as the total acid level, decreases towards ripening in both species [71]. Citric and malic acids are the main organic acids in *V. oxycoccos* [72]. In *V. corymbosum*, the major acids (organic and phenolic) present are citric, malic, quinic, and chlorogenic acids. The minor acids, acetic and shikimic acid are present and their contribution to the total acid equivalents is 3.0% [73].

4. The Chemical Profile of *Vaccinium* Leaves

A body of scientific research studies proved the contribution of berries' consumption to the main targets of functional foods, such as health maintenance and reduced risk of some chronic diseases. However, in addition to fruits, the leaves of the *Vaccinium* species have also been used in traditional remedies (Table 1).

Leaves are considered to be by-products of berries' cultivation. Their traditional use against several diseases, such as inflammation, diabetes, and ocular dysfunction, has been almost forgotten in recent times. The scientific interest regarding the leaves' composition and beneficial properties has grown, demonstrating that leaves may be considered to be an alternative source of bioactive compounds. Analytical studies reveal that the chemical composition of leaves is similar to that of the fruits or even higher, indicating that they may be used as an alternative source of bioactive compounds for the development of functional foods, nutraceuticals, and/or food supplements.

Riihinen et al. [74] showed that red leaves of *Vaccinium* genus contain anthocyanins, which are absent in green leaves. Both green and red leaves contain proanthocyanidins, especially procyanidin. Teleszko and Wojdyło [75] analysed the phytochemical composition of fruits and leaves of several *Vaccinium* species; among them, *V. myrtillus* leaves were the first source of phenolic compounds, followed by *V. oxycoccos* leaves. The major polyphenolic group was proanthocyanidins, followed by flavonols. Proanthocyanidins, flavan-3-ols, phenolic acids and flavonols were in higher concentration than the respective fruits [76].

Proanthocyanidins were detected in small quantities in the leaves of *V. vitis-idaea* [41]. Ferlemi et al. [76,77] have detected proanthocyanidin B1/B2 and cinchonain in the leaves of *V. corymbosum*. In the same year, Wang et al. [78] identified the presence of cyanidin 3-*O*-glucoside, cyanidin 3-*O*-glucuronide, and cyanidin 3-*O*-arabinoside in the methanolic leaf extract of *V. corymbosum*, confirming that *V. corymbosum* leaves possess a higher total anthocyanins content compared to *V. virgatum* and *V. formosum* leaves.

After proanthocyanidins, flavonoids are the most important classes of constituents of *Vaccinium* leaves. Quercetin-3-*O*-glucuronide is the most abundant flavonoid (70–93% of total flavonoids) [79]. Other identified flavonoids in the leaves are quercetin-3-*O*-galactoside, quercetin-3-*O*-(4″-3-hydroxy-3-methylglutaroyl)-α-rhamnoside, quercetin-3-*O*-arabinoside, quercetin-3-*O*-glucoside, quercitrin, and quercetin, as well as three kaempferol glycosides [41,79]. In addition, Hokkanen et al. [41] have detected several other bioactive compounds in the leaves, such as flavan-3-ols, six different isomers of cinchonain, three proanthocyanidins, and two coumaroyl iridoids.

Sidorova et al. [80] investigated the flavonoids present in *V. myrtillus,* and found flavonoid C-glycosides and *O*-derivatives of apigenin and luteolin; the main ones are apigenin-7-glucuronide, vitexin-2-*O*-rhamnoside, and isoorientin. Flavonoid glycosides are represented mainly in quercetin derivatives, particularly rutin and quercetin-3-glucoside-7-rhamnoside. Isorhamnetin-3-glucoside and kaempferol-3-glucuronide were also found in the extract. Additionally, free aglycones were also present (myricetin, quercetin, luteolin and kaempferol).

The main flavonols detected in the *V. oxycoccos* leaves were hyperoside and quercetin-3-*O*-rhamnoside, together with quercetin-3-*O*-xyloside, quercetin-3-*O*-arabinoside and procyanidin A2 [66].

The green leaves of *V. vitis-idaea* have similar phytochemical profiles to those of *V. myrtillus* [41,79]. Ieri et al. [79] and Hokkanen et al. [41] have quantified the phenolic compounds in methanolic and hydroalcoholic leaf extracts of *V. vitis-idaea*. In general, hydroxycinnamic acids and flavonoids were the most abundant compounds. In the methanolic extract, the content of flavonoids was higher than that of hydroxycinnamic acids, but in the hydroalcoholic extract, the opposite was observed. In both extracts, the main acid was 2-*O*-caffeoylarbutin, which is not present in other *Vaccinium* leaves.

Other phenolic acids detected in the methanolic extract were chlorogenic, caffeic, *p*-coumaric and caffeoyl-shikimic acids, together with the coumaroyl quinic acid isomers [41]. Moreover, *V. vitis-idaea* leaves were characterised by coumaroyl- and caffeoyl-hexose hydroxyphenols.

The most abundant flavonoid was quercetin-3-*O*-(4″-3-hydroxy-3-methylglutaroyl)-α-rhamnoside, which represents 5–6% of total phenols in the hydroalcoholic extract and 32% of the methanolic extract.

Rutin, hyperoside, and quercitrin were also detected in significant amounts in the methanolic extract, while traces of four quercetin glycosides and kaempferol glycosides were also found. Proanthocyanidins and coumaroyl iridoids were also identified [41].

Quercetin-3-*O*-glucoside, quercetin-3-*O*-rutinoside, kaempferol-3-*O*-glucoside, and kaempferol-3-*O*-rhamnoside were identified in the leaves of *V. arctostaphylos* [45,81].

The main flavonoids detected in the leaves of *V. corymbosum* were hyperoside, isoquercetin and rutin. Other flavonoids found were: myricetin [54], quercetin-3-*O*-glucoside, quercetine-3-*O*-galactoside, quercetine-3-*O*-arabinoside [82], quercetin-3-*O*-rhamnoside [35,82,83], myricetin-3-*O*-glucoside, quercetin-3-*O*-rutinoside [83], syringetin-3-*O*-glucoside, and kaempferol-3-*O*-glucoside [35,83].

Several studies have demonstrated the role of collection time of *Vaccinium* leaves in influencing their phenolic content [79]. In fact, contrary to the fruits, the flavonoid content increases during the development of the leaves, while hydroxycinnamic acid content strongly decreases [84]. Previously, Riihinen et al. [74] have indicated that the red leaves of *V. corymbosum* have higher quantities of quercetin and kaempferol, as well as of ferulic, caffeic and *p*-coumaric acid, than green leaves. The main bioactive compounds of *V. myrtillus* leaves are hydroxycinnamic acids, especially chlorogenic acid [41,79]; its concentration ranges from 59 to 74% of the total hydroxycinnamic acids [79]. Sidorova et al. [80] also reported the presence of rosmarinic acid, caffeoylquinic acid, *p*-coumaric and ferulic acid. Hokkanen et al. [41] analysed the methanolic extract of *V. myrtillus* leaves and identified thirty-five compounds. Other than the abundant chlorogenic acid and its isomers, caffeoyl-shikimic acid, feruloylquinic acid isomer, and traces of caffeic acid were found.

In addition, Neto et al. [85] have performed an HPLC-MS analysis of the phenolic profile of *V. oxycoccos* leaves; the phenolic acids are mainly chlorogenic and neo-chlorogenic acid, as well as 3-*O*- and 5-*O*-coumaroylquinic acids. Mzhavanadze et al. [86] reported the isolation of caffeic, chlorogenic, neochlorogenic, 3- and 5-*p*-coumaroylquinic acids, and 3,5-dicaffeoylquinic acid from the leaves of *V. arctostaphylos*.

Continuing the investigation of the qualitative composition of the leaves, they have isolated six phenolic substances: cryptochlorogenic (4-caffeoyl-quinic) acid, arbutin, rosmarinic acid, caffeoylarbutin, 1-*p*-coumaroylgalactoglucose, and *p*-coumaroylarbutin.

Twenty different compounds, mainly phenolic acids and flavonols, were identified in the red dried leaves of *V. corymbosum* by Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometry (LC/ESI-MS/MS) and High-Performance Liquid Chromatography-Diode-Array Detection (HPLC-DAD) [76,77]. Interestingly, these two groups were in almost equal concentration in the crude extract (chlorogenic acid and quercetin-3-*O*-galactoside); as in *V. myrtillus* leaves, the most abundant compound was chlorogenic acid. LC-MS analysis showed the presence of quinic and caffeic acid.

Even though the triperpenes in the leaves comprised only the 4–6% of those in the respective fruits, several compounds were identified in the diethyl ether leaf extract. The principal compound was β-amyrin, followed by oleanane- and ursane-type triterpenes. The triterpene oleanolic and ursolic acids were also identified [87].

Two coumaroyl iridoid isomers (*trans*- and *cis*- form) previously documented in *V. oxycoccos* fruits were also reported in the leaves [66]. In *V. vitis ideae* coumaroyl, iridoids were quantified in small concentrations [41]. The three iridoids found in the leaf extracts of *V. corymbosum* are identical to those found in the fruit. However, it should be noted that a fourth iridoid, vaccinoside (monotropein-10-trans-*p*-coumarate), was detected in fresh leaves but not in dried leaves [65].

5. Biological Properties of *Vaccinium* Species

Many biological properties have been reported for extracts and derivatives of different *Vaccinium* species, and the anti-inflammatory, antioxidant, anti-carcinogenic, cardiovascular and neurodegenerative protective effects have been extensively described [11,88–90]. High antioxidant activity has been demonstrated for *V. corymbosum* [76,91], *V. oxycoccos* [92], *V. myrtillus* [93], and many others. This activity appears to be linked to cultivar, genotype, growing site, cultivation techniques and conditions, processing, and storage.

Similarly, in different anti-inflammatory tests, *Vaccinium* exhibited high anti-inflammatory activity [11]. High concentrations of anthocyanins (such as cyanidin, delphinidin and malvidin) and flavonoids (such as astragalin, hyperoside, isoquercitrin, and quercitrin) appear to be related to the anti-inflammatory and antioxidant activities ascribed to these berries [94,95]. Considering that berries of *Vaccinium* are edible, their consumption may be helpful for the treatment of inflammatory illnesses.

In this review, we will focus on the activity of *Vaccinium* extracts and derivatives in cardiovascular diseases, closely associated with the inflammation processes and oxidative stress. The vascular endothelium occupies a catalogue of functions that contribute to the homeostasis of the cardiovascular system. Endothelial cells (ECs) play a variety of roles, including the control of tone regulation, blood coagulation and vascular permeability, and local regulation of coagulative, immune and inflammatory stimuli [96].

Indeed, many cardiovascular diseases are either a direct or indirect result of a dysfunction of the endothelium that fails to maintain body homeostasis [97,98]. Endothelial dysfunction (ED) is considered as a predictor of cardiovascular events, and it is characterized by alterations in vascular tone and endothelial production of procoagulant and prothrombotic factors [97,98].

Several risk factors including smoking, obesity, insulin resistance, diabetes, hypercholesterolemia, and physical inactivity have been described for ED. In addition, ED occurs with aging, as a consequence of senescence processes [99,100]. *Vaccinium* extracts have long been used in traditional medicine and appear to be promising nutraceuticals to prevent endothelial dysfunction and cardiovascular diseases.

5.1. *Vaccinium and Diabetes*

Several reports indicate a potential role of *Vaccinium* in the control of diabetes, and it has been used in traditional medicine for centuries to ameliorate its symptoms [101–103]. Approximately 90% of the diabetic patients have type 2 diabetes that is characterized by peripheral insulin resistance and by a reduction in the number and the activity of pancreatic β-cells [104]. Anthocyanins from *Vaccinium* have potential in terms of lowering the risk of developing various chronic diseases due to their ability to regulate energy metabolism as well as through their anti-inflammatory and anti-oxidative effects [11]. Furthermore, anthocyanins inhibit the activities of α-glucosidase and pancreatic α-amylase, important targets for some antidiabetic drugs [105–107]. Phenolic compounds affect key pathways of carbohydrate metabolism and hepatic glucose homeostasis including glycolysis, glycogenesis, and gluconeogenesis, which are usually impaired in diabetes.

In addition, *Vaccinium* extracts and derivatives protect pancreatic β-cells from glucose-induced oxidative stress, increase insulin secretion, possess glucose-lowering effects, restore glutathione concentration, inhibit DPP-4, enhance insulin response, and attenuate the secretion of glucose-dependent insulinotropic polypeptide and GLP-1 [80,106,108,109]. Blueberry metabolites reduce the expression of inflammatory markers and restore the glycosaminoglycan levels increased by high glucose in in vitro models of diabetic ECs [110]. Moreover, malvidin, a major anthocyanin present in blueberries, decreases reactive oxygen species levels, increases the enzyme activity of catalase and superoxide dismutase, and downregulates NADPH oxidase 4 (NOX4) expression in ECs exposed to high glucose levels [111], indicating a protective role against diabetes-induced oxidative stress. In similar models, this compound also reduces vascular endothelial growth factor (VEGF) up-regulation, ICAM-1 expression, and NF-κB (p65) levels [112]. In addition, malvidin has been shown to be able to restore PI3K and Akt levels, which are reduced by high glucose [113].

These observations are also confirmed in the retina of diabetic rats, where blueberry anthocyanins reduce oxidative stress, vascular endothelial growth factor (VEGF) and interleukin 1β (IL-1β) expression, and activate the Nrf2-related/heme oxygenase 1 (Nrf2/HO-1) signalling pathway [114], suggesting that *Vaccinium* anthocyanin may be helpful in inhibiting diabetes-induced retinal abnormalities and preventing the development of diabetic retinopathy.

5.2. *Vaccinium* and Atherosclerosis

Atherosclerosis is one of the major causes of cardiovascular diseases and is characterized by the accumulation of lipids and fibrous plaques in the large arteries, which may lead to heart attacks, strokes, and peripheral vascular diseases [115].

Cignarella et al. [116] tested a dried hydroalcoholic extract of *V. myrtillus* leaves showing a lipid-lowering activity with decrease of 39% of the triglycerides in the blood of dyslipidemic animals. Similarly, *V. corymbosum* berries decreased blood cholesterol levels, thus reducing cardiovascular risk and promoting atherosclerosis prevention [117,118]. In addition, consumption of cranberry anthocyanins improved lipid profiles, increasing HDL and decreasing LDL in rats, hamsters fed a high-fat diet and hypercholesterolemic swine [119–121]. Wu et al. [122] showed that blueberries induce a regression of atherosclerotic plaques in arteries. In this manuscript, the apolipoprotein-E deficient (apoE$-/-$) mice were fed either a control diet or an enriched diet supplemented with 1% freeze-dried wild blueberries for 20 weeks. The plaques, measured at two sites, were 39 and 58% smaller in the mice fed blueberries compared to those fed the control diet, and these effects were associated with the reduction in biomarkers of lipid peroxidation in the liver, such as F2-isoprostane [122]. Similarly, Matziouridou et al. [123] showed that in Apoe$-/-$ mice fed either a low-fat diet or high-fat diet, with or without lingonberries, the size of the atherosclerotic plaques, the total, HDL and LDL-VLDL blood cholesterol, and triglycerides, as well as the hepatic gene expression of bile acid synthesis genes (cholesterol 7 α-hydroxylase (Cyp7a1), sterol 12α-hydroxylase (Cyp8b1)) were reduced.

Although published animal studies primarily focused on the specific cardiovascular disease risk factors or biomarkers, and the antioxidant and anti-inflammatory effects, of *Vaccinium* and its derivatives, clinical data have also been published [10]. Indeed, good results were also observed with cranberry juice in obese men, and hyper-triglyceridemic or diabetic patients [24].

The molecular mechanisms of atheroprotective effects of *Vaccinium* are not completely understood and are often associated with antioxidant and anti-inflammatory activities. In fact, the protective activity in atherosclerosis development have been associated with the reduction in oxidative stress, inhibition of inflammation, and regulation of cholesterol accumulation and trafficking [10].

In apoE$-/-$ mice, the treatment with 1% wild blueberries for 20 weeks modulated gene expression and protein levels of scavenger receptors CD36 and SR-A, the principal receptors responsible for the binding and uptake of modified LDL in macrophages [124].

CD36 and SR-A were found to be lower in peritoneal macrophages of blueberry-fed mice, and fewer ox-LDL-induced foam cells were formed, probably through a mechanism involving PPARγ [124]. In addition, Xie et al. [125] demonstrated that blueberry consumption increased the levels of the cholesterol transporter ABCA1, indicating that blueberries may facilitate cholesterol efflux and lowering cholesterol accumulation. Overall, it has been shown that blueberry consumption increased PPARα, PPARγ, ABCA1 and fatty acid synthase expression, while reducing SREBP-1 levels [10].

Although several sources of experimental evidence support the atheroprotective effects of *Vaccinium*, further and more in-depth studies are needed to completely elucidate the molecular mechanisms underlying this activity.

5.3. *Vaccinium* and Endothelial Dysfunction

Endothelial dysfunction is an early predictor of cardiovascular diseases, and it is well known that oxidative stress and low grade of inflammation contributes to endothelial cell activation, priming it for adhesion, infiltration, and immune cell activation [126].

In this context, data from the literature indicate that *Vaccinium* extracts and derivatives may prevent or delay cardiovascular diseases due to their capability to revert endothelial dysfunction. Very recently, Curtis et al. [127] showed that one cup of blueberries/day, for six months, promotes 12–15% reductions in cardiovascular disease risk, demonstrating that higher intakes of blueberries improve markers of vascular function and ameliorate lipid status. Similarly, the intake of blueberry acutely improved peripheral arterial dysfunction in smoker and in non-smoker subjects [128,129], improved endothelial function over six weeks in subjects with metabolic syndrome [130], and improved endothelium-dependent vasodilation in hypercholesterolemic individuals through the induction of the NO-cGMP signaling pathway [131].

In animal models, blueberry anthocyanin-enriched extracts were shown to be able to increase Bcl-2 protein expression, as well as to decrease interleukin 6, malondialdehyde, endothelin 1, and angiotensin II levels and to reduce Bax protein expression after rat exposure to fine particulate matter [132]. Blueberry consumption was also able to protect endothelial function in obese Zucker rats, through the attenuation of local inflammation in perivascular adipose tissue (PVAT) [133]. In diabetic rats, the *Vaccinium* treatment decreased markers of diabetic retinopathy, such as retinal VEGF expression and degradation of zonula occludens-1, occludin and claudin-5 [134]. Finally, in experiments of hypoperfusion-reperfusion in rats, the administration of the extract of *Vaccinium myrtillus* protected pial microcirculation by preventing vasoconstriction, microvascular permeability, and leukocyte adhesion [135].

The endothelium protective role of *Vaccinium* has also been reported in in vitro experimental models. Human aortic endothelial cell (HAECs) treated with palmitate exhibited elevated ROS levels, and increased expression of several markers of endothelial dysfunction including NOX4, chemokines, adhesion molecules, and IκBα.

The effects of palmitate were ameliorated in HAECs previously treated with blueberry metabolites [136]. In human umbilical vein endothelial cells (HUVEC), pterostilbene, an active constituent of blueberries, is able to induce a concentration-dependent nitric oxide release via endothelial nitric oxide synthase (eNOS) phosphorylation, mediated by activation of the PI3K/Akt signaling pathway [137]. Similarly, blueberry anthocyanins protect endothelial cells from oxidative deterioration by decreasing the levels of ROS and Xanthine Oxidase -1 (XO-1) and increasing the levels of superoxide dismutase and HO-1 [138].

6. Conclusions and Future Perspectives

The fruits and leaves of different *Vaccinium* species have been used for a long time in the traditional medicine of different cultures to treat several diseases including renal, gastrointestinal and liver disorders, respiratory system infections, cough, fever, diabetes, and convulsions. Biological studies support traditional uses since many *Vaccinium* components exhibit important biological properties, including antioxidant, antitumor, anti-inflammatory, antidiabetic and endothelium protective activities. In particular, the high antioxidant and anti-inflammatory activity of *Vaccinium* has been related to the high content in polyphenols, anthocyanins, and flavonoids.

In addition, *Vaccinium* extracts appear to be safe and mostly lacking in side effects, with the exception of a few case reports, without statistical significance, describing an aspirin-like effect (increased bleeding) [139,140].

Herein, we reported the chemical composition of fruits and leaves of *Vaccinium* species and provided an overview of their biological properties, focusing on the activity of *Vaccinium* extracts and derivatives in cardiovascular diseases and endothelial dysfunctions, closely associated with inflammation processes and oxidative stress.

Many studies indicate that *Vaccinium* is an important source of bioactive molecules that appear to satisfy all the requirements to develop drugs and nutraceuticals against endothelial dysfunction, thus preventing cardiovascular disease onset and progression. Well-designed and specific clinical trials are necessary in order to explore the intriguing potential of *Vaccinium* in the treatment of metabolic syndrome and in cardiovascular protection.

In conclusion, as fruits and leaves of *Vaccinium* species represent a rich source of phenolic compounds with a high biological potential, they can serve as commercial sources of specific compounds or fractions for pharmaceutics, cosmetics and natural product markets. However, because of the wide variety of constituents that characterizes the chemical profile of *Vaccinium* species, their possible interactions with other constituents, and the complexity of their metabolism, further and more in-depth studies will be necessary to better define and characterize the contribution of each single active component, possible synergisms between the different compounds, and the molecular mechanisms underlying their biological effects.

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References

1. Kloet, V.E. Manual of the flowering plants of Hawaii. *Bishop Museum Spec. Publ.* **1990**, *83*, 591–595.
2. Tutin, T.G.; Heywood, V.H.; Burges, N.A.; Valentine, D.H.; Walters, S.M.; Webb, D.A. *Flora Europea*; Cambridge University Press: Cambridge, UK, 1972; Volume 3, pp. 12–13.
3. Colak, N.; Primetta, A.K.; Riihinen, K.R.; Jaakola, L.; Jiři Grúz, J.; Strnad, M.; Torun, H.; Ayaz, F.A. Phenolic compounds and antioxidant capacity in different-colored and non-pigmented berries of bilberry (*Vaccinium myrtillus* L.). *Food Biosci.* **2017**, *20*, 67–78. [CrossRef]
4. Abreu, O.A.; Barreto, G.; Prieto, S. *Vaccinium* (*Ericaceae*): Ethnobotany and pharmacological potentials. *Emir. J. Food A* **2014**, *26*, 577–591. [CrossRef]
5. Esposito, D.; Chen, A.; Grace, M.H.; Komarnytsky, S.; Lila, M.A. Inhibitory effects of wild blueberry anthocyanins and other flavonoids on biomarkers of acute and chronic inflammation in vitro. *J. Agric. Food Chem.* **2014**, *62*, 7022–7028. [CrossRef]
6. Donnini, S.; Finetti, F.; Lusini, L.; Morbidelli, L.; Cheynier, V.; Barron, D.; Williamson, G.; Waltenberger, J.; Ziche, M. Divergent effects of quercetin conjugates on angiogenesis. *Br. J. Nutr.* **2006**, *95*, 1016–1023. [CrossRef]
7. Tenuta, M.C.; Deguin, B.; Loizzo, M.R.; Dugay, A.; Acquaviva, R.; Malfa, G.A.; Bonesi, M.; Bouzidi, C.; Tundis, R. Contribution of flavonoids and iridoids to the hypoglycaemic, antioxidant, and nitric oxide (NO) inhibitory activities of *Arbutus unedo* L. *Antioxidants* **2020**, *9*, 184. [CrossRef] [PubMed]
8. Brindisi, M.; Bouzidi, C.; Frattaruolo, L.; Loizzo, M.R.; Tundis, R.; Dugay, A.; Deguin, B.; Cappello, A.R.; Cappello, M.S. Chemical profile, antioxidant, anti-inflammatory, and anti-cancer effects of Italian *Salvia rosmarinus* spenn. methanol leaves extracts. *Antioxidants* **2020**, *9*, 826. [CrossRef]
9. Brindisi, M.; Bouzidi, C.; Frattaruolo, L.; Loizzo, M.R.; Cappello, M.S.; Dugay, A.; Deguin, B.; Lauria, G.; Cappello, A.R.; Tundis, R. New Insights into the antioxidant and anti-inflammatory effects of Italian *Salvia officinalis* leaf and flower extracts in lipopolysaccharide and tumor-mediated inflammation models. *Antioxidants* **2021**, *10*, 311. [CrossRef]
10. Wu, X.; Wang, T.T.Y.; Prior, R.L.; Pehrsson, P.R. Prevention of atherosclerosis by berries: The case of blueberries. *J. Agric. Food Chem.* **2018**, *66*, 9172–9188. [CrossRef]
11. Kalt, W.; Cassidy, A.; Howard, L.R.; Krikorian, R.; Stull, A.J.; Tremblay, F.; Zamora-Ros, R. Recent research on the health benefits of blueberries and their anthocyanins. *Adv. Nutr.* **2020**, *11*, 224–236. [CrossRef]
12. Kemper, K.J. Bilberry (Vaccinium myrtillus). *Longwood Herb. Task Force* **1999**, *20115386*, 55–71.
13. Morazzoni, P.; Bombardelli, E. *Vaccinium myrtillus* L. *Fitoterapia* **1996**, *68*, 3–29.
14. Frohne, D. *Heidelbeerblätter*; Teedrogen., M.W., Ed.; Wissenschaftliche Verlagsgesell: Stuttgart, Germany, 1990; pp. 217–219.
15. Mustafa, B.; Hajdari, A.; Pieroni, A.; Pulaj, B.; Koro, X.; Quave, C.L. A cross-cultural comparison of folk plant uses among Albanians, Bosniaks, Gorani and Turks living in south Kosovo. *J. Ethnobiol. Ethnomed.* **2015**, *12*, 11–39. [CrossRef]
16. Leduc, C.; Coonishish, J.; Haddad, P.; Cuerrier, A. Plants used by the Cree Nation of Eeyou Istchee (Quebec, Canada) for the treatment of diabetes: A novel approach in quantitative ethnobotany. *J. Ethnopharmacol.* **2006**, *105*, 55–63. [CrossRef] [PubMed]
17. Kari, P.R. *Upper Tanana Ethnobotany*; Alaska Historical Commission: Anchorage, Alaska, 1985.
18. *Standard for the Plant Drug of Heilongjiang Province*; Heilongjiang Provincial Drug Administration: Harbin, China, 2001; p. 198.
19. Mozaffarian, V. Identification of medicinal and aromatic plants of Iran. *Farhang Moaser Tehran* **2013**, 391–392.
20. Pervin, M.; Hasnat, M.A.; Lim, B.O. Antibacterial and antioxidant activities of *Vaccinium corymbosum* L. leaf extract. *Asian Pac. J. Trop. Dis.* **2013**, *3*, 444–453. [CrossRef]

21. Pervin, M.; Hasnat, M.A.; Lim, J.H.; Lee, Y.M.; Kim, E.O.; Um, B.H.; Lim, B.O. Preventive and therapeutic effects of blueberry (*Vaccinium corymbosum*) extract against DSS-induced ulcerative colitis by regulation of antioxidant and inflammatory mediators. *J. Nutr. Biochem.* **2016**, *28*, 103–113. [CrossRef] [PubMed]
22. Branning, C.; Hakansson, A.; Ahrne, S.; Jeppsson, B.; Molin, G.; Nyman, M. Blueberry husks and multi-strain probiotics affect colonic fermentation in rats. *Br. J. Nutr.* **2009**, *101*, 859–870. [CrossRef]
23. Karppinen, K.; Zoratti, L.; Nguyenquynh, N.; Häggman, H.; Jaakola, L. Molecular and metabolic mechanisms associated with fleshy fruit quality. *Front. Plant Sci.* **2016**, *7*, 657.
24. Blumberg, J.B.; Camesano, T.A.; Cassidy, A.; Kris-Etherton, P.; Howell, A.; Manach, C.; Ostertag, L.M.; Sies, H.; Skulas-Ray, A.; Vita, J.A. Cranberries and their bioactive constituents in human health. *Adv. Nutr.* **2013**, *4*, 618–632. [CrossRef]
25. Su, Z. Anthocyanins and flavonoids of *Vaccinium*, L. *Pharm. Crops* **2012**, *3*, 7–37. [CrossRef]
26. Gao, L.; Mazza, G. Quantitation and distribution of simple and acylated anthocyanins and other phenolics in blueberries. *J. Food Sci.* **1994**, *59*, 1057–1059. [CrossRef]
27. Beattie, J.; Crozier, A.; Duthie, G.G. Potential health benefits of berries. *Curr. Nutr. Food Sci.* **2005**, *1*, 71–86. [CrossRef]
28. Borges, G.; Degeneve, A.; Mullen, W.; Crozier, A. Identification of flavonoid and phenolic antioxidants in black currants, blueberries, raspberries, red currants, and cranberries. *J. Agric. Food Chem.* **2010**, *58*, 3901–3909. [CrossRef] [PubMed]
29. Cho, M.J.; Howard, L.R.; Prior, R.L.; Clark, J.R. Flavonoid glycosides and antioxidant capacity of various blackberry, blueberry, and red grape genotypes determined by high-performance liquid chromatography/mass spectrometry. *J. Sci. Food Agric.* **2004**, *84*, 1771–1782. [CrossRef]
30. Taruscio, T.G.; Barney, D.L.; Exon, J. Content and profile of flavanoid and phenolic acid compounds in conjunction with the antioxidant capacity for a variety of northwest *Vaccinium* berries. *J. Agric. Food Chem.* **2004**, *52*, 3169–3176. [CrossRef] [PubMed]
31. Zheng, W.; Wang, S.Y. Oxygen radical absorbing capacity of phenolics in blueberries, cranberries, chokeberries, and lingonberries. *J. Agric. Food Chem.* **2003**, *51*, 502–509. [CrossRef]
32. Suomalainen, H.; Keranen, A.J.A. The first anthocyanins appearing during the ripening of blueberries. *Nature* **1961**, *191*, 498–499. [CrossRef]
33. Cabrita, L.; Froystein, N.A.; Andersen, O.M. Anthocyanin trisaccharides in blueberries of *Vaccinium padifolium*. *Food Chem.* **2000**, *69*, 33–36. [CrossRef]
34. Du, Q.; Jerz, G.; Winterhalter, P. Isolation of two anthocyanin sambubiosides from bilberry (*Vaccinium myrtillus*) by high-speed counter-current chromatography. *J. Chromatogr. A* **2004**, *1045*, 59–63. [CrossRef]
35. Spela, M.; Tomaz, P.; Lea, G.; Darinka, K.; Andreja, V.; Natasa, P.U.; Veronika, A. Phenolics in Slovenian bilberries (*Vaccinium myrtillus* L.) and blueberries (*Vaccinium corymbosum* L.). *J. Agric. Food Chem.* **2011**, *59*, 6998–7004.
36. Scibisz, I.; Mitek, M. Influence of freezing process and frozen storage on anthocyanin contents of highbush blueberries. *Food Sci. Technol. Qual.* **2007**, *5*, 231–238.
37. Wu, X.; Prior, R.L. Systematic identification and characterization of anthocyanins by HPLC-ESI-MS/MS in common foods in the United States: Fruits and berries. *J. Agric. Food Chem.* **2005**, *53*, 2589–2599. [CrossRef] [PubMed]
38. Pappas, E.; Schaich, K.M. Phytochemicals of cranberries and cranberry products: Characterization, potential health effects, and processing stability. *Crit. Rev. Food Sci. Nutr.* **2009**, *49*, 741–781. [CrossRef]
39. Andersen, O.M. Chromatographic separation of anthocyanins in cowberry (lingonberry) *Vaccinium vites-idaea* L. *J. Food Sci.* **1985**, *50*, 1230–1232. [CrossRef]
40. Ek, S.; Kartimo, H.; Mattila, S.; Tolonen, A. Characterization of phenolic compounds from lingonberry (*Vaccinium vitis-idaea* L.). *J. Agric. Food. Chem.* **2006**, *54*, 9834–9842. [CrossRef] [PubMed]
41. Hokkanen, J.; Mattila, S.; Jaakola, L.; Pirttila, A.M.; Tolonen, A. Identification of phenolic compounds from lingonberry (*Vaccinium vitis-idaea* L.), bilberry (*Vaccinium myrtillus* L.) and hybrid bilberry (*Vaccinium x intermedium* Ruthe, L.) leaves. *J. Agric. Food Chem.* **2009**, *57*, 9437–9447. [CrossRef] [PubMed]
42. Laetti, A.K.; Riihinen, K.R.; Jaakola, L. Phenolic compounds in berries and flowers of a natural hybrid between bilberry and lingonberry (*Vaccinium intermedium* Ruthe). *Phytochemistry* **2011**, *72*, 810–815. [CrossRef]
43. Madhavi, D.L.; Bomser, J.; Smith, M.A.L.; Singleton, K. Isolation of bioactive constituents of *Vaccinium myrtillus* (bilberry) fruits and cell cultures. *Plant Sci.* **1998**, *131*, 95–103. [CrossRef]
44. Pan, Y.F.; Qu, W.J.; Li, J.G.; Gu, Y.B. Qualitative and quantitative analysis of flavonoid aglycones from fruit residue of *Vaccinium vitis-idaea* L. by HPLC. *Nat. Prod. Res. Develop.* **2005**, *17*, 641–644.
45. Latti, A.K.; Kainulainen, P.S.; Hayirlioglu-Ayaz, S.; Ayaz, F.A.; Riihinen, K.R. Characterization of anthocyanins in Caucasian blueberries (*Vaccinium arctostaphylos* L.) native to Turkey. *J. Agric. Food Chem.* **2009**, *57*, 5244–5249. [CrossRef] [PubMed]
46. Nickavar, B.; Amin, G.; Salehi-Sormagi, M.H. Anthocyanins from *Vaccinium arctostaphylos* berries. *Pharm. Biol.* **2004**, *42*, 289–291. [CrossRef]
47. Witzell, J.; Gref, R.; Näsholm, T. Plant-part specific and temporal variation in phenolic compounds of boreal bilberry (*Vaccinium myrtillus*) plants. *Biochem. Syst. Ecol.* **2003**, *31*, 115–127. [CrossRef]
48. Laaksonen, O.; Sandell, M.; Kallio, H. Chemical factors contributing to orosensory profiles of bilberry (*Vaccinium myrtillus*) fractions. *Eur. Food Res. Technol.* **2010**, *231*, 271–285. [CrossRef]

49. Cesoniene, L.; Daubaras, R.; Jasutiene, I.; Vencloviene, J.; Miliauskiene, I. Evaluation of the biochemical components and chromatic properties of the juice of *Vaccinium macrocarpon* Aiton and *Vaccinium oxycoccos* L. *Plant Food Hum. Nutr.* **2011**, *66*, 238–244. [CrossRef]
50. Cui, Z.H.; Yuan, C.S. Flavones of *Vaccinium uliginosum* fruits. *Fitoterapia* **1992**, *63*, 283.
51. Lehtonen, H.M.; Lehtinen, O.; Suomela, J.P.; Viitanen, M.; Kallio, H. Flavonol glycosides of sea buckthorn (*Hippophae rhamnoides* ssp. sinensis) and lingonberry (*Vaccinium vitis-idaea*) are bioavailable in humans and monoglucuronidated for excretion. *J. Agric. Food Chem.* **2010**, *58*, 620–627. [CrossRef]
52. Latti, A.K.; Jaakola, L.; Riihinen, K.R.; Kainulainen, P.S. Anthocyanin and flavonol variation in bog bilberries (*Vaccinium uliginosum* L.) in Finlan. *J. Agric. Food Chem.* **2009**, *58*, 427–433. [CrossRef] [PubMed]
53. Li, R.; Wang, P.; Guo, P.; Wang, Z.Y. Anthocyanin composition and content of the *Vaccinium uliginosum* berry. *Food Chem.* **2011**, *125*, 116–120. [CrossRef]
54. Yang, G.X.; Fan, H.L.; Zheng, Y.N.; Li, Y.D. Separation and identification of the flavonoids in the fruit of *Vaccinium uliginosum* L. blueberry. *J. Jilin. Agric. Univ.* **2005**, *27*, 643–644.
55. Sellappan, S.; Akoh, C.C.; Krewer, G. Phenolic compounds and antioxidant capacity of Georgia-grown blueberries and blackberries. *J. Agric. Food Chem.* **2002**, *50*, 2432–2438. [CrossRef] [PubMed]
56. Zadernowski, R.; Naczk, M.; Nesterowicz, J. Phenolic acid profiles in some small berries. *J. Agric. Food Chem.* **2005**, *53*, 2118–2124. [CrossRef]
57. Wang, C.; Zuo, Y. Ultrasound-assisted hydrolysis and gas chromatography-mass spectrometric determination of phenolic compounds in cranberry products. *Food Chem.* **2011**, *128*, 562–568. [CrossRef] [PubMed]
58. Zhang, K.; Zuo, Y. GC-MS determination of flavonoids and phenolic and benzoic acids in human plasma after consumption of cranberry juice. *J. Agric. Food Chem.* **2004**, *52*, 222–227. [CrossRef] [PubMed]
59. Zuo, Y.; Wang, C.; Zhan, J. Separation, characterization, and quantitation of benzoic and phenolic antioxidants in American cranberry fruit by GC-MS. *J. Agric. Food Chem.* **2002**, *50*, 3789–3794. [CrossRef]
60. Ayaz, F.A.; Hayirlioglu-Ayaz, S.; Gruz, J.; Novak, O.; Strnad, M. Separation, characterization, and quantitation of phenolic acids in a little-known blueberry (*Vaccinium arctostaphylos* L.) fruit by HPLC-MS. *J. Agric. Food Chem.* **2005**, *53*, 8116–8122. [CrossRef] [PubMed]
61. Dinda, B.; Debnath, S.; Harigaya, Y. Naturally occurring iridoids. A review, part 1. *Chem. Pharm. Bull.* **2007**, *55*, 159–222. [CrossRef] [PubMed]
62. Tundis, R.; Loizzo, M.R.; Menichini, F.; Statti, G.A.; Menichini, F. Biological and pharmacological activities of iridoids: Recent developments. *Mini Rev. Med. Chem.* **2008**, *8*, 399–420. [CrossRef]
63. Wang, C.; Gong, X.; Bo, A.; Zhang, L.; Zhang, M.; Zang, E.; Zhang, C.; Li, M. Iridoids: Research advances in their phytochemistry, biological activities, and pharmacokinetics. *Molecules* **2020**, *25*, 287. [CrossRef]
64. Heffels, P.; Müller, L.; Schieber, A.; Weber, F. Profiling of iridoid glycosides in *Vaccinium* species by UHPLC-MS. *Food Res. Int.* **2017**, *100*, 462–468. [CrossRef]
65. Tenuta, M.C.; Malfa, G.A.; Marco, B.; Rosaria, A.; Loizzo, M.R.; Dugay, A.; Bouzidi, C.; Tomasello, B.; Tundis, A.; Deguin, B. LC-ESI-QTOF-MS profiling, protective effects on oxidative damage, and inhibitory activity of enzymes linked to type 2 diabetes and nitric oxide production of *Vaccinium corymbosum* L. (Ericaceae) extracts. *J. Berry Res.* **2020**, *10*, 603–622. [CrossRef]
66. Turner, A.; Chen, S.N.; Nikolic, D.; van Breemen, R.; Farnsworth, N.R.; Pauli, G.F. Coumaroyl iridoids and a depside from cranberry (*Vaccinium macrocarpon*). *J. Nat. Prod.* **2007**, *70*, 253–258. [CrossRef]
67. Leisner, C.P.; Kamileen, M.O.; Conway, M.E.; O.'Connor, S.E.; Buell, C.R. Differential iridoid production as revealed by a diversity panel of 84 cultivated and wild blueberry species. *PLoS ONE* **2017**, *12*, e0179417.
68. Ma, C.; Dastmalchi, K.; Flores, G.; Wu, S.B.; Pedraza-Peñalosa, P.; Long, C.; Kennelly, E.J. Antioxidant and metabolite profiling of North American and neotropical blueberries using LC-TOF-MS and multivariate analyses. *J. Agric. Food Chem.* **2013**, *61*, 3548–3559. [CrossRef]
69. Kondo, M.; MacKinnon, S.L.; Craft, C.C.; Matchett, M.D.; Hurta, R.A.; Neto, C.C. Ursolic acid and its esters: Occurrence in cranberries and other *Vaccinium* fruit and effects on matrix metalloproteinase activity in DU145 prostate tumor cells. *J. Sci. Food Agric.* **2011**, *91*, 789–796. [CrossRef]
70. Chu, W.; Gao, H.; Cao, S.; Fang, X.; Chen, H.; Xiao, S. Composition and morphology of cuticular wax in blueberry (*Vaccinium* spp.) fruits. *Food Chem.* **2017**, *219*, 436–442. [CrossRef]
71. Ayaz, F.A.; Kadioglu, A.; Bertoft, E.; Acar, C.; Turna, I. Effect of fruit maturation on sugar and organic acid composition in two blueberries (*Vaccinium arctostaphylos* and *V. myrtillus*) native to Turkey. New Zealand. *J. Crop Hort. Sci.* **2001**, *29*, 137–141. [CrossRef]
72. Huopalahti, R.; Järvenpää, E.P.; Katina, K. A novel solid-phase extraction-hplc method for the analysis of anthocyanin and organic acid composition of finish cranberry. *J. Liquid Chrom. Related Technol.* **2000**, *23*, 2695–2701. [CrossRef]
73. Kalt, W.; McDonald, J.E. Chemical composition of lowbush blueberry cultivars. *J. Am. Soc. Hort. Sci.* **1996**, *121*, 142–146. [CrossRef]
74. Riihinen, K.; Jaakola, L.; Karenlampi, S.; Hohtola, A. Organ-specific distribution of phenolic compounds in bilberry (*Vaccinium myrtillus*) and "northblue" blueberry (*Vaccinium corymbosum* × *V. angustifolium*). *Food Chem.* **2008**, *110*, 156–160. [CrossRef]

75. Teleszko, M.; Wojdyło, A. Comparison of phenolic compounds and antioxidant potential between selected edible fruits and their leaves. *J. Funct. Foods* **2015**, *14*, 736–746. [CrossRef]
76. Ferlemi, A.V.; Mermigki, P.G.; Makri, O.E.; Anagnostopoulos, D.; Koulakiotis, N.S.; Margarity, M.; Tsarbopoulos, A.; Georgakopoulos, C.D.; Lamari, F.N. Cerebral area differential redox response of neonatal rats to selenite-induced oxidative stress and to concurrent administration of highbush blueberry leaf polyphenols. *Neurochem. Res.* **2015**, *40*, 2280–2292. [CrossRef]
77. Ferlemi, A.V.; Lamari, F.N. Berry leaves: An alternative source of bioactive natural products of nutritional and medicinal value. *Antioxidants* **2016**, *5*, 17. [CrossRef]
78. Wang, L.J.; Wu, J.; Wang, H.X.; Li, S.S.; Zheng, X.C.; Du, H.; Xu, Y.J.; Wang, L.S. Composition of phenolic compounds and antioxidant activity in the leaves of blueberry cultivars. *J. Funct. Foods* **2015**, *16*, 295–304. [CrossRef]
79. Ieri, F.; Martini, S.; Innocenti, M.; Mulinacci, N. Phenolic distribution in liquid preparations of *Vaccinium myrtillus* L. and *Vaccinium vitis idaea* L. *Phytochem. Anal.* **2013**, *24*, 467–475. [CrossRef] [PubMed]
80. Sidorova, Y.; Shipelin, V.; Mazo, V.; Zorin, S.; Petrov, N.; Kochetkova, A. Hypoglycemic and hypolipidemic effect of *Vaccinium myrtillus* L. leaf and *Phaseolus vulgaris* L. seed coat extracts in diabetic rats. *Nutrition* **2017**, *41*, 107–112. [CrossRef] [PubMed]
81. Mzhavanadze, V.V. Kaempferol glycosides from the leaves of the Cancasian bilberry, *Vaccinium arctostaphylos*. *Soobshch Akad Nauk Gruz SSR* **1971**, *62*, 445–447.
82. Kader, F.; Rovel, B.; Girardin, M.; Metche, M. Fractionation and identification of the phenolic compounds of highbush blueberries (*Vaccinium corymbosum* L.). *Food Chem.* **1996**, *55*, 35–40. [CrossRef]
83. Scibisz, I.; Mitek, M. Antioxidant activity and phenolic compound content in dried highbush blueberries (*Vaccinium corymbosum* L.). *Zywnosc* **2006**, *13*, 68–76.
84. Martz, F.; Jaakola, L.; Julkunen-Tiitto, R.; Stark, S. Phenolic composition and antioxidant capacity of bilberry (*Vaccinium myrtillus*) leaves in Northern Europe following foliar development and along environmental gradients. *J. Chem. Ecol.* **2010**, *36*, 1017–1028. [CrossRef]
85. Neto, C.C.; Salvas, M.R.; Autio, W.R.; van den Heuvel, J.E. Variation in concentration of phenolic acid derivatives and quercetin glycosides in foliage of cranberry that may play a role in pest deterrence. *J. Am. Soc. Hortic. Sci.* **2010**, *135*, 494–500. [CrossRef]
86. Mzhavanadze, V.V.; Targamadze, I.L.; Dranik, L.I. Phenolic compounds of the leaves of *Vaccinium arctostaphylos*. *Chem. Nat. Comp.* **2004**, *8*, 125–126. [CrossRef]
87. Szakiel, A.; Paczkowski, C.; Huttunen, S. Triterpenoid content of berries and leaves of bilberry *Vaccinium myrtillus* from Finland and Poland. *J. Agric. Food Chem.* **2012**, *60*, 11839–11849. [CrossRef]
88. Ramassamy, C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: A review of their intracellular targets. *Eur. J. Pharmacol.* **2006**, *545*, 51–64. [CrossRef]
89. Miller, K.; Feucht, W.; Schmid, M. Bioactive compounds of strawberry and blueberry and their potential health effects based on human intervention studies: A brief overview. *Nutrients* **2019**, *11*, 1510. [CrossRef] [PubMed]
90. Mantzorou, M.; Zarros, A.; Vasios, G.; Theocharis, S.; Pavlidou, E.; Giaginis, C. Cranberry: A promising natural source of potential nutraceuticals with anticancer activity. *Anticancer Agents Med. Chem.* **2019**, *19*, 1672–1686. [CrossRef] [PubMed]
91. Del Bó, C.; Riso, P.; Campolo, J.; Møller, P.; Loft, S.; Klimis-Zacas, D.; Brambilla, A.; Rizzolo, A.; Porrini, M. A single portion of blueberry (*Vaccinium corymbosum* L.) improves protection against DNA damage but not vascular function in healthy male volunteers. *Nutr. Res.* **2013**, *33*, 220–227. [CrossRef]
92. Vinson, J.A.; Bose, P.; Proch, J.; Al Kharrat, H.; Samman, N. Cranberries and cranberry products: Powerful in vitro, ex vivo, and in vivo sources of antioxidants. *J. Agric. Food Chem.* **2008**, *56*, 5884–5891. [CrossRef] [PubMed]
93. Yao, Y.; Vieira, A. Protective activities of *Vaccinium* antioxidants with potential relevance to mitochondrial dysfunction and neurotoxicity. *Neurotoxicology* **2007**, *28*, 93–100. [CrossRef] [PubMed]
94. Torri, E.; Lemos, M.; Caliari, V.A.L.; Kassuya, C.; Bastos, J.K.; Andrade, S.F. Anti-inflammatory and antinociceptive properties of blueberry extract (*Vaccinium corymbosum*). *J. Pharm. Pharmacol.* **2007**, *59*, 591–596. [CrossRef] [PubMed]
95. Pereira, S.R.; Pereira, R.; Figueiredo, I.; Freitas, V.; Dinis, T.C.; Almeida, L.M. Comparison of anti-inflammatory activities of an anthocyanin-rich fraction from Portuguese blueberries (*Vaccinium corymbosum* L.) and 5-aminosalicylic acid in a TNBS-induced colitis rat model. *PLoS ONE* **2017**, *12*, e0174116. [CrossRef] [PubMed]
96. Marziano, C.; Genet, G.; Hirschi, K.K. Vascular endothelial cell specification in health and disease. *Angiogenesis* **2021**. [CrossRef]
97. Matsuzawa, Y.; Lerman, A. Endothelial dysfunction and coronary artery disease: Assessment, prognosis, and treatment. *Coron. Artery Dis.* **2014**, *25*, 713–724. [CrossRef] [PubMed]
98. Daiber, A.; Steven, S.; Weber, A.; Shuvaev, V.V.; Muzykantov, V.R.; Laher, I.; Li, H.; Lamas, S.; Münzel, T. Targeting vascular (endothelial) dysfunction. *Br. J. Pharmacol.* **2017**, *174*, 1591–1619. [CrossRef]
99. Alfaras, I.; Di Germanio, C.; Bernier, M.; Csiszar, A.; Ungvari, Z.; Lakatta, E.G.; de Cabo, R. Pharmacological strategies to retard cardiovascular aging. *Circ. Res.* **2016**, *118*, 1626–1642. [CrossRef]
100. Mensah, G.A.; Wei, G.S.; Sorlie, P.D.; Fine, L.J.; Rosenberg, Y.; Kaufmann, P.G.; Mussolino, M.E.; Hsu, L.L.; Addou, E.; Engelgau, M.M.; et al. Decline in cardiovascular mortality: Possible causes and implications. *Circ. Res.* **2017**, *120*, 366–380. [CrossRef]
101. Cravotto, G.; Boffa, L.; Genzini, L.; Garella, D. Phytotherapeutics: An evaluation of the potential of 1000 plants. *J. Clin. Pharm. Ther.* **2010**, *35*, 11–48. [CrossRef] [PubMed]

102. Martineau, L.C.; Couture, A.; Spoor, D.; Benhaddou-Andaloussi, A.; Harris, C.; Meddah, B.; Leduc, C.; Burt, A.; Vuong, T.; Mai Le, P.; et al. Anti-diabetic properties of the Canadian lowbush blueberry *Vaccinium angustifolium* Ait. *Phytomedicine* **2006**, *13*, 612–623. [CrossRef]
103. Chan, S.W.; Chu, T.T.W.; Choi, S.W.; Benzie, I.F.F.; Tomlinson, B. Impact of short-term bilberry supplementation on glycemic control, cardiovascular disease risk factors, and antioxidant status in Chinese patients with type 2 diabetes. *Phytother. Res.* **2021**. [CrossRef]
104. Shahcheraghi, S.H.; Aljabali, A.A.A.; Al Zoubi, M.S.; Mishra, V.; Charbe, N.B.; Haggag, Y.A.; Shrivastava, G.; Almutary, A.G.; Alnuqaydan, A.M.; Barh, D.; et al. Overview of key molecular and pharmacological targets for diabetes and associated diseases. *Life Sci.* **2021**, *278*, 119632. [CrossRef]
105. McDougall, G.J.; Shpiro, F.; Dobson, P.; Smith, P.; Blake, A.; Stewart, D. Different polyphenolic components of soft fruits inhibit alpha-amylase and alpha-glucosidase. *J. Agric. Food Chem.* **2005**, *53*, 2760–2766. [CrossRef]
106. Bljajić, K.; Petlevski, R.; Vujić, L.; Čačić, A.; Šoštarić, N.; Jablan, J.; Saraiva de Carvalho, S.; Zovko Končić, M. Chemical composition, antioxidant and α-glucosidase-inhibiting activities of the aqueous and hydroethanolic extracts of *Vaccinium myrtillus* leaves. *Molecules* **2017**, *22*, 703. [CrossRef]
107. Karcheva-Bahchevanska, D.P.; Lukova, P.K.; Nikolova, M.M.; Mladenov, R.D.; Iliev, I.N. Effect of extracts of bilberries (*Vaccinium myrtillus* L.) on amyloglucosidase and α-glucosidase activity. *Folia Med.* **2017**, *59*, 197–202. [CrossRef]
108. Li, H.; Park, H.M.; Ji, H.S.; Han, J.; Kim, S.K.; Park, H.Y.; Jeong, T.S. Phenolic-enriched blueberry-leaf extract attenuates glucose homeostasis, pancreatic beta-cell function, and insulin sensitivity in high-fat diet-induced diabetic mice. *Nutr. Res.* **2020**, *73*, 83–96. [CrossRef] [PubMed]
109. Cásedas, G.; Les, F.; Gómez-Serranillos, M.P.; Smith, C.; López, V. Anthocyanin profile, antioxidant activity and enzyme inhibiting properties of blueberry and cranberry juices: A comparative study. *Food Funct.* **2017**, *8*, 4187–4193. [CrossRef]
110. Cutler, B.R.; Gholami, S.; Chua, J.S.; Kuberan, B.; Anandh Babu, P.V. Blueberry metabolites restore cell surface glycosaminoglycans and attenuate endothelial inflammation in diabetic human aortic endothelial cells. *Int. J. Cardiol.* **2018**, *261*, 155–158. [CrossRef]
111. Huang, W.; Yao, L.; He, X.; Wang, L.; Li, M.; Yang, Y.; Wan, C. Hypoglycemic activity and constituents analysis of blueberry (*Vaccinium corymbosum*) fruit extracts. *Diabetes Metab. Syndr. Obes.* **2018**, *11*, 357–366. [CrossRef]
112. Huang, W.; Yan, Z.; Li, D.; Ma, Y.; Zhou, J.; Sui, Z. Antioxidant and anti-inflammatory effects of blueberry anthocyanins on high glucose-induced human retinal capillary endothelial cells. *Oxidative Med. Cell Longev.* **2018**, *2018*, 1862462. [CrossRef] [PubMed]
113. Huang, W.; Hutabarat, R.P.; Chai, Z.; Zheng, T.; Zhang, W.; Li, D. Antioxidant blueberry anthocyanins induce vasodilation via PI3K/Akt signaling pathway in high-glucose-induced human umbilical vein endothelial cells. *Int. J. Mol. Sci.* **2020**, *21*, 1575. [CrossRef]
114. Song, Y.; Huang, L.; Yu, J. Effects of blueberry anthocyanins on retinal oxidative stress and inflammation in diabetes through Nrf2/HO-1 signaling. *J. Neuroimmunol.* **2016**, *301*, 1–6. [CrossRef] [PubMed]
115. Jafarizade, M.; Kahe, F.; Sharfaei, S.; Momenzadeh, K.; Pitliya, A.; Tajrishi, F.Z.; Singh, P.; Chi, G. The role of interleukin-27 in atherosclerosis: A contemporary review. *Cardiology* **2021**, *19*, 1–13. [CrossRef]
116. Cignarella, A.; Nastasi, M.; Cavalli, E.; Puglisi, L. Novel lipid-lowering properties of *Vaccinium myrtillus* L. leaves, a traditional antidiabetic treatment, in several models of rat dyslipidaemia: A comparison with ciprofibrate. *Thromb. Res.* **1996**, *84*, 311–322. [CrossRef]
117. Basu, A.; Lyons, T.J. Strawberries, blueberries, and cranberries in the metabolic syndrome: Clinical perspectives. *J. Agric. Food Chem.* **2012**, *60*, 5687–5692. [CrossRef]
118. Prior, R.L.; Wu, X.; Gu, L.; Hager, T.; Hager, A.; Wilkes, S.; Howard, L. Purified berry anthocyanins but not whole berries normalize lipid parameters in mice fed an obesogenic high fat diet. *Mol. Nutr. Food Res.* **2009**, *53*, 1406–1418. [CrossRef] [PubMed]
119. Kalt, W.; Foote, K.; Fillmore, S.A.; Lyon, M.; Van Lunen, T.A.; McRae, K.B. Effect of blueberry feeding on plasma lipids in pigs. *Br. J. Nutr.* **2008**, *100*, 70–78. [CrossRef]
120. Zagayko, A.L.; Kolisnyk, T.Y.; Chumak, O.I.; Ruban, O.A.; Koshovyi, O.M. Evaluation of anti-obesity and lipid-lowering properties of *Vaccinium myrtillus* leaves powder extract in a hamster model. *J. Basic Clin. Physiol. Pharmacol.* **2018**, *29*, 697–703. [CrossRef] [PubMed]
121. Peixoto, T.C.; Moura, E.G.; de Oliveira, E.; Soares, P.N.; Guarda, D.S.; Bernardino, D.N.; Ai, X.X.; Rodrigues, V.D.S.T.; de Souza, G.R.; da Silva, A.J.R.; et al. Cranberry (*Vaccinium macrocarpon*) extract treatment improves triglyceridemia, liver cholesterol, liver steatosis, oxidative damage and corticosteronemia in rats rendered obese by high fat diet. *Eur. J. Nutr.* **2018**, *57*, 1829–1844. [CrossRef]
122. Wu, X.; Kang, J.; Xie, C.; Burris, R.; Ferguson, M.E.; Badger, T.M.; Nagarajan, S. Dietary blueberries attenuate atherosclerosis in apolipoprotein E-deficient mice by upregulating antioxidant enzyme expression. *J. Nutr.* **2010**, *140*, 1628–1632. [CrossRef]
123. Matziouridou, C.; Marungruang, N.; Nguyen, T.D.; Nyman, M.; Fåk, F. Lingonberries reduce atherosclerosis in $Apoe^{-/-}$ mice in association with altered gut microbiota composition and improved lipid profile. *Mol. Nutr. Food Res.* **2016**, *60*, 1150–1160. [CrossRef]
124. Xie, C.; Kang, J.; Chen, J.R.; Lazarenko, O.P.; Ferguson, M.E.; Badger, T.M.; Nagarajan, S.; Wu, X. Lowbush blueberries inhibit scavenger receptors CD36 and SR-A expression and attenuate foam cell formation in ApoE-deficient mice. *Food Funct.* **2011**, *2*, 588–594. [CrossRef]

125. Xie, C.; Kang, J.; Chen, J.R.; Nagarajan, S.; Badger, T.M.; Wu, X. Phenolic acids are in vivo atheroprotective compounds appearing in the serum of rats after blueberry consumption. *J. Agric. Food Chem.* **2011**, *59*, 10381–10387. [CrossRef]
126. Heitzer, T.; Schlinzig, T.; Krohn, K.; Meinertz, T.; Münzel, T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. *Circulation* **2001**, *104*, 2673–2678. [CrossRef]
127. Curtis, P.J.; van der Velpen, V.; Berends, L.; Jennings, A.; Feelisch, M.; Umpleby, A.M.; Evans, M.; Fernandez, B.O.; Meiss, M.S.; Minnion, M.; et al. Blueberries improve biomarkers of cardiometabolic function in participants with metabolic syndrome-results from a 6-month, double-blind, randomized controlled trial. *Am. J. Clin. Nutr.* **2019**, *109*, 1535–1545. [CrossRef] [PubMed]
128. Del Bo', C.; Porrini, M.; Fracassetti, D.; Campolo, J.; Klimis-Zacas, D.; Riso, P. A single serving of blueberry (*V. corymbosum*) modulates peripheral arterial dysfunction induced by acute cigarette smoking in young volunteers: A randomized-controlled trial. *Food Funct.* **2014**, *5*, 3107–3116. [CrossRef]
129. Del Bo', C.; Deon, V.; Campolo, J.; Lanti, C.; Parolini, M.; Porrini, M.; Klimis-Zacas, D.; Riso, P. A serving of blueberry (*V. corymbosum*) acutely improves peripheral arterial dysfunction in young smokers and non-smokers: Two randomized, controlled, crossover pilot studies. *Food Funct.* **2017**, *8*, 4108–4117. [CrossRef]
130. Stull, A.J.; Cash, K.C.; Champagne, C.M.; Gupta, A.K.; Boston, R.; Beyl, R.A.; Johnson, W.D.; Cefalu, W.T. Blueberries improve endothelial function, but not blood pressure, in adults with metabolic syndrome: A randomized, double- blind, placebo-controlled clinical trial. *Nutrients* **2015**, *7*, 4107–4123. [CrossRef] [PubMed]
131. Zhu, Y.; Xia, M.; Yang, Y.; Liu, F.; Li, Z.; Hao, Y.; Mi, M.; Jin, T.; Ling, W. Purified anthocyanin supplementation improves endothelial function via NO-cGMP activation in hypercholesterolemic individuals. *Clin. Chem.* **2011**, *57*, 1524–1533. [CrossRef] [PubMed]
132. Wang, Z.; Pang, W.; He, C.; Li, Y.; Jiang, Y.; Guo, C. Blueberry anthocyanin-enriched extracts attenuate fine particulate matter (PM 2.5)-induced cardiovascular dysfunction. *J. Agric. Food Chem.* **2017**, *65*, 87–94. [CrossRef] [PubMed]
133. Vendrame, S.; Tsakiroglou, P.; Kristo, A.S.; Schuschke, D.A.; Klimis-Zacas, D. Wild blueberry consumption attenuates local inflammation in the perivascular adipose tissue of obese Zucker rats. *Appl. Physiol. Nutr. Metab.* **2016**, *41*, 1045–1051. [CrossRef] [PubMed]
134. Kim, J.; Kim, C.S.; Lee, Y.M.; Sohn, E.; Jo, K.; Kim, J.S. *Vaccinium myrtillus* extract prevents or delays the onset of diabetes-induced blood-retinal barrier breakdown. *Int. J. Food Sci. Nutr.* **2015**, *66*, 236–242. [CrossRef] [PubMed]
135. Mastantuono, T.; Starita, N.; Sapio, D.; D'Avanzo, S.A.; Di Maro, M.; Muscariello, E.; Paterni, M.; Colantuoni, A.; Lapi, D. The Effects of *Vaccinium myrtillus* extract on hamster pial microcirculation during hypoperfusion-reperfusion injury. *PLoS ONE* **2016**, *11*, e0150659. [CrossRef] [PubMed]
136. Bharat, D.; Cavalcanti, R.R.M.; Petersen, C.; Begaye, N.; Cutler, B.R.; Assis Costa, M.M.; Gomes Ramos, R.; Ferreira, M.R.; Li, Y.; Bharath, L.P.; et al. Blueberry metabolites attenuate lipotoxicity-induced endothelial dysfunction. *Mol. Nutr. Food Res.* **2018**, *62*, 1–17. [CrossRef]
137. Park, S.H.; Jeong, S.; Chung, H.T.; Pae Pterostilbene, H.E. An active constituent of blueberries, stimulates Nitric Oxide production via activation of endothelial nitric oxide synthase in human umbilical vein endothelial cells. *Plant Foods Hum. Nutr.* **2015**, *70*, 263–268. [CrossRef] [PubMed]
138. Huang, W.; Zhu, Y.; Li, C.; Sui, Z.; Min, W. Effect of blueberry anthocyanins malvidin and glycosides on the antioxidant properties in endothelial cells. *Oxidative Med. Cell. Longev.* **2016**, *2016*, 1591803. [CrossRef]
139. Morgan, K.M.; Loloi, J.; Songdej, N. Cranberry supplementation as a cause of major intraoperative bleeding during vascular surgery due to aspirin-like platelet inhibition. *Blood Coagul. Fibrinolysis* **2020**, *31*, 402–404.
140. Izzo, A.A.; Hoon-Kim, S.; Radhakrishnan, R.; Williamson, E.M. A critical approach to evaluating clinical efficacy, adverse events and drug interactions of herbal remedies. *Phytother. Res.* **2016**, *30*, 691–700. [CrossRef] [PubMed]