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

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. oxyccocos (cranberry), V. microcarpum, V. macrocarpon, V. vitis-idaea, V. uliginosum, V. myrtillus, V. arctostaphylos, and V. corymbosum. 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 Vaccinium 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].

| 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, antioxidat, 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 lithotriptic 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

The fruits of *V. myrtillus* are characterized by the presence of different types of anthocyanins. In particular, cyanidin 3-O-arabinoside, 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-xiloside, cyanidin 5-O-glucoside, cyanidin 3,5-O-diglucoside, cyanidin 3-O-(6”-O-2-rhamnopyranosyl-2”-O-β-xylopyranosyl-β-glucopyranoside), cyanidin 3-O-sambubioside, delphinidin 3-O-sambuobisde, 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-xylloside, delphinidin-3-O-glucoside, malvidin-3-O-galactoside, malvidin-3-O-glucoside petunidin-3-O-galactoside, petunidin-2-O-glucoside, malvidin-3-O-xylloside, and petunidin-3-O-xylloside 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**

![Flavonoids](image)

| Flavonoids          | R₁  | R₂  | R₃  | R₄  | R₅  |
|---------------------|-----|-----|-----|-----|-----|
| Apigenin            | H   | H   | H   | H   | H   |
| Apigenin 7-O-glucuronide | H   | Glc A | H   | H   | H   |
| Chrysoeriol         | H   | H   | OCH₁ | H   | H   |
| Hyperoside          | H   | H   | OH  | H   | O-Gal |
| Isoquercitrin       | Glc | H   | H   | OH  | H   |
| Isoquercetin        | H   | H   | OH  | H   | O-Glc |
| Isoquercetin 3-O-galactoside | H   | H   | OCH₁ | H   | O-Gal |
| Isoquercetin 3-O-glucoside | H   | H   | OCH₁ | H   | O-Glk |
| Isoquercetin 3-O-xylloside | H   | H   | OCH₁ | H   | O-Xyl |
| Kaempferol          | H   | H   | H   | H   | OH  |
| Kaempferol 3-O-glucoside | H   | H   | H   | H   | O-Glc |
| Kaempferol 3-O-galactoside | H   | H   | H   | H   | O-Glc A |
| Kaempferol 3-O-rhamnoside | H   | H   | H   | H   | O-Rha |
| Laricitrin          | H   | H   | OCH₁ | OH  | OH  |
| Laricitrin 3-O-galacturonide | H   | H   | OCH₁ | OH  | O-Gl A |
| Luteolin            | H   | H   | OH  | H   | H   |
| Myricetin           | H   | H   | OH  | OH  | OH  |
| Myricetin 3-O-arabinoside | H   | H   | OH  | OH  | O-Aru |
| Myricetin 3-O-galactoside | H   | H   | OH  | OH  | O-Gal |
| Myricetin 3-O-galactoside | H   | H   | OH  | OH  | O-Gk |
| Myricetin 3-O-galactoside | H   | H   | OH  | OH  | O-Gla |
| Myricetin 3-O-arabinoside | H   | H   | OH  | OH  | O-Rha |
| Myricetin 3-O-arabinoside | H   | H   | OH  | OH  | O-Xyl |
| Quercetin           | H   | H   | OH  | H   | OH  |
| Quercetin 3-O-arabinoside | H   | H   | OH  | H   | O-Aru |
| Quercetin 3-O-glucoside 7-O-rhamnoside | H   | Rha | OH  | H   | O-Glc |
| Quercetin 3-O-glucuronide | H   | H   | OH  | H   | O-Gl A |
| Quercetin 3-O-arabinoside | H   | H   | OH  | H   | O-Rha |
| Quercetin 3-O-rhamnoside | H   | H   | OH  | H   | O-Ga(6→1)Rha |
| Quercetin 3-O-xyloside | H   | H   | OH  | H   | O-Xyl |
| Rutin               | H   | H   | OH  | H   | O-Ga(6→1)Rha |
| Syringetin          | H   | H   | OCH₁ | OCH₁ | OH  |
| Syringetin 3-O-glucoside | H   | H   | OCH₁ | OCH₁ | O-Glc |

**Flavanols**

![Flavanols](image)

| Flavanols         | R₁  | R₂  |
|-------------------|-----|-----|
| Catechin          | OH  | H   |
| Epicatechin       | OH  | H   |
| Epigallocatechin  | OH  | OH  |

**Proanthocyanidin**

![Proanthocyanidin](image)

| Proanthocyanidin | R₁  |
|------------------|-----|
| Catechin-4,8-catechin | H   |
| Galloocatechin-4,8-2-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-galactoside, quercetin 3-O-glucoside, and quercetin 3-O-rutinoside [28–31]. Apigenin, chrysoeriol, myricetin, myricetin-3-xylloside, quercetin 3-O-glucuronide, quercetin 3-O-xylloside, 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-xylloside 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 hydroxycinamic 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].
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].
Heffels et al. [64] have tentatively identified, in *V. uliginosum* and *V. myrtillus*, 14 iridoid glucosides, including vaccinoside, monotropein, *p*-coumaroyl-scandoside, *deacetylasperulosidic acid* (*C₆: (S)*/, scandoside (*C₆: (R)*), *p*-coumaroyl-deacetylasperulosidic acid, *p*-coumaroyl-monotropein, and *p*-coumaroyldihydromonotropein (*C₆:C₇ hydrogenated*). *V. oxycoccus* juice showed the presence of two new coumaroyl iridoid glycosides, namely 10-*p*-trans- and 10-*p*-cis-coumaroyl-15-dihydromonotropein [66].

Detection and isolation of iridoids from fruits is not straightforward. Surprisingly, iridoid glucosides 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. oxycoccus*, 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-amyрин, β-amyрин, 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. oxycoccus* [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 procyanadin. Teleszko and Wojdylo [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. oxyccos 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, quercetin, 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. Isohamnetin-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 flavonoids detected in the V. oxyccos 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-gluicoside, quercetin-3-O-rutinoside [83], syringetin-3-O-gluicoside, and kaempferol-3-O-gluicoside [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-dicafeoylquinic acid from the leaves of *V. arctostaphyllos*.

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

Twenty different compounds, mainly phenolic acids and flavonoids, 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 7α-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 reverse 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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