# Vaccinium Species: Composition and Activity

Subjects: Food Science & Technology

Contributor: Lorenza Trabalzini

The genus *Vaccinium* L. (Ericaceae) includes more than 450 species, which grow mainly in cooler areas of the northern hemisphere. *Vaccinium* species have been used in the traditional medicine of different cultures and the berries are widely consumed as food. Indeed, Vaccinium supplements-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 of *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.

Vaccinium species | phytochemicals | berry | leaf | anti-inflammatory pathways | endothelial dysfunction

## 1. Introduction

In recent years, *Vaccinium* species 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. *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.

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, 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][6][7][8][9]. In fact, several epidemiological studies suggested that long-term consumption of foods rich in polyphenols offers 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 signaling 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].

## 2. Traditional Uses of Vaccinium Species

Fruits and leaves of different *Vaccinium* species are extensively used in traditional medicine, as summarized in **Table 1** [12][13].

**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 blind-ness | Fruits | [16] |
| | Colds, coughs and sore throats | Fruits | [17] |
| | Anti-inflammatory of urinary tract properties | Leaves | [15] |
| | Respiratory system infections | Stems and leaves | [18] |
| | Frequent urination | Fruits | [16] |
| | Infections of urinary tract properties | Fruits | [15] |
| | Kidney stones | Fruits | [15] |
| | Anti-inflammatory | Stems and leaves | [18] |
| | Wound healing, anti-rheumatic, anti-convulsant, diuretic, anti-diabetic | Leaves and fruits | [15] |
| *V. arctostaphylos* | Anti-hypertensive, anti-diabetic | Leaves and fruits | [19] |
| *V. corymbosum* | Anti-diabetic, antioxidant, and anti-inflammatory | Fruits | [20,21] |
| | Gastrointestinal disorders | Fruits | [22] |

## 3. Phytochemicals of *Vaccinium* Fruits and Leaves

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 [14]. 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 colors 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 [15]. 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. 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 [16]. To date, more than 35 anthocyanin glycosides have been isolated from the genus *Vaccinium*.

Mono, di, or trisaccharide derivatives of delphinidin, cyanidin, peonidin, petunidin, and malvidin are common in *Vaccinium* berries [25]. The principal sugars are glucose, galactose, xylose, rhamnose, and arabinose.

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, peonidin 3-O-galactoside, and peonidin 3-O-arabinoside were identified [17][18][19][20][21][22].

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, delphinidin 3-O-sambuobiside, and peonidin-3-glycoside have also been identified [22][23][24][25].

Malvidin and delphinidin derivatives represent about 75% of the total anthocyanins content of *V. corymbosum* fruits [26][27]. Cho et al. [20] 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* [18][22]. The 3-O-galactosides and 3-O-arabinosides of cyanidin and peonidin are the most abundant recognised anthocyanins in the fruits of *V. oxycoccos* [18][28][29].

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 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 [30][31][32][33][34][35].

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* [36][37].

Except anthocyanins, to date, more than 50 other flavonoids (mainly flavanols and proanthocyanidins) have been isolated and identified from the genus *Vaccinium* [16][19][20][21][22][31][32][33][34][35].

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 [16].

Quercetin is the most common flavonoid isolated from *Vaccinium* species [16]. It was found in high quantities in *V. uliginosum* and *V. myrtillus* [20]; however, the richest source of quercetin is *V. oxycoccos* [38].

Several glycosides of myricetin (myricetin 3-glucoside, myricetin 3-arabinoside, myricetin 3-O-rhamnoside) and quercetin (quercetin 3- O-arabinoside, quercetin 3-O-ramnoside, quercetin 3-O-galactoside, quercetin 3-O-glucoside, and quercetin 3-O-rutinoside) were identified in *V. myrtillus* [28,29,30,31]. Apigenin, chrysoeriol, myricetin, myricetin-3-xyloside, quercetin 3-O-glucuronide, luteolin are other flavonoids described in *V. myrtillus* [47].

Glycosides of quercetin, myricetin, and kaempferol are the main flavonoids identified in *V. oxycoccosare* [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 [15][31].

The major flavonoids described in *V. vitis idea* are kaempferol [32], quercetin [32][38], myricetin, myricetin 3-O-glucoside [35], quercetin derivatives (bond to glucose, galactose, glucuronide, rhamnose, arabinose, and xylose), kaempferol 3-O-rhamnoside , isorhamnetin 3-O-glucoside, syringetin-3-O-glucoside, kaempferol 3-O-glucoside, and rutin [39].

The fruits of *V. uliginosum* are characterized by the presence of kaempferol, laricitrin [38], quercetin [38][40][41][42], myricetin [42], syringetin, quercetin 3-O-glucoside, quercetin 3-O-galactoside, quercetin 3-O-glucuronide, isorhamnetin, syringetin 3-O-glucoside, myricetin 3-O-galactoside

Sellappan et al. [43] 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* [56]. Phenolic acids including gallic, p-coumaric, ferulic, ellagic, and caffeic acids were found in *V. corymbosum* and *V. oxycoccos* [44]. *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* [45][46][47]. Ellagic acid and ellagitannins have not been detected in significant amounts [15].

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 [48].

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 [49][50][51]. In *Vaccinium* species, iridoids 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 [52][53].

Heffels et al. [52] 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-C7hydrogenated). *V. oxycoccos* juice showed the presence of two new coumaroyl iridoid glycosides, namely 10-p-trans- and 10-p-cis-coumaroyl-1S-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 [54].

Triterpenoids are the most predominant components in the cuticular wax of blueberry fruits, together with the triterpene alcohols α-amyrin, β-amyrin, and lupeol [55].

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* [55].

The non-volatile malic, citric, and quinic acids were identified and quantified in *V. arctostaphylos* and *V. myrtillus*. 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 [56]. The major acids (organic and phenolic) present in *V. corymbosum* are citric, malic, quinic, and chlorogenic acids.

In addition to fruits, the leaves of *Vaccinium* species have also been used in traditional remedies (**Table 1**). Leaves are considered by-products of berries cultivation. Their traditional use against several diseases, such as inflammation, diabetes, and ocular dysfunction, has been almost forgotten nowadays. The scientific interest regarding the leaf composition and beneficial properties grows, documenting that leaves may be considered 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.

## 4. 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][57][58][59]. High antioxidant activity has been demonstrated for *V. corymbosum* [60][61], *V. oxycoccos* [62], *V. myrtillus* [63], 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 [64][65]. As *Vaccinium* berries are edible, their consumption may be helpful for the treatment of inflammatory illnesses.

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 [66].

Indeed, many cardiovascular diseases are either a direct or indirect result of a dysfunction of the endothelium that fails to maintain body homeostasis [67][68]. Endothelial dysfunction (ED) is considered a predictor of cardiovascular events, and it is characterized by alterations in vascular tone and endothelial production of procoagulant and prothrombotic factors [67][68].

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 [69][70]. *Vaccinium* extracts have long been used in traditional medicine and appear to be promising nutraceuticals to prevent endothelial dysfunction and cardiovascular diseases.

## 4.1. Vaccinium and diabetes

Several reports indicate a potential role of *Vaccinium* in the control of diabetes, and it has been used in traditional medicine to ameliorate its symptoms [71][72][73]. Approximately 90% of 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 [74]. 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]. 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 Blueberry metabolites reduce the expression of inflammatory markers and restore the glycosaminoglycan levels increased by high glucose in *in vitro* models of diabetic ECs [75]. Moreover, malvidin, a major anthocyanin present in blueberries, decreases ROS levels, increases the enzyme activity of catalase and superoxide dismutase, and downregulates NADPH oxidase 4 (NOX4) expression in ECs exposed to high glucose levels [76], 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 levels [112], and restores 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 [77], suggesting that *Vaccinium* anthocyanin may be helpful in inhibiting diabetes-induced retinal abnormalities and preventing the development of diabetic retinopathy.

## 4.2. 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 [78].

Hydroalcoholic extracts of *V.myrtillus* leaves showed lipid-lowering activity, while *V. corymbosum* berries decreased blood cholesterol levels, thus reducing cardiovascular risk and promoting atherosclerosis prevention [79][80]. 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 [81][82][83]. Blueberries showed to induce regression of atherosclerotic plaques in arteries, and to reduce total, HDL and LDL-VLDL blood cholesterol and triglycerides, as well as the hepatic expression of bile acid synthesis genes in mice models [122, [84].

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 [15].

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 has 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 [85]. 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 [85]. In addition, Xie et al. [86] 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].

## 4.3. 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 contribute to endothelial cell activation, priming it for adhesion, infiltration, and immune cell activation [87].

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. [88] 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 nonsmoker subjects [89][90], improved endothelial function over six weeks in subjects with metabolic syndrome [91], and improved endothelium-dependent vasodilation in hypercholesterolemic individuals through the induction of the NO-cGMP signaling pathway [92].

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 [93]. Blueberry consumption was also able to protect endothelial function in obese Zucker rats, through the attenuation of local inflammation in perivascular adipose tissue (PVAT) 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 [94]. Finally, in hypoperfusion-reperfusion experiments in rats, the administration of the extract of *V. 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 cells (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 [95]. 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 [96]. 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 [97].

This entry reports chemical composition of fruits and leaves of Vaccinium species and overviews 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 evidences 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.

## 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.
4. Abreu, O.A.; Barreto, G.; Prieto, S. Vaccinium (Ericaceae): Ethnobotany and pharmacological potentials. Emir. J. Food A 2014, 26, 577–591.
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.
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.
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.
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.
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.
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.
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.
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. 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.
15. 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.
16. Su, Z. Anthocyanins and flavonoids of Vaccinium, L. Pharm. Crops 2012, 3, 7–37.

17. Gao, L.; Mazza, G. Quantitation and distribution of simple and acylated anthocyanins and other phenolics in blueberries. J. Food Sci. 1994, 59, 1057–1059.
18. Beattie, J.; Crozier, A.; Duthie, G.G. Potential health benefits of berries. Curr. Nutr. Food Sci. 2005, 1, 71–86.
19. 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.
20. 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.
21. 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.
22. 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.
23. Suomalainen, H.; Keranen, A.J.A. The first anthocyanins appearing during the ripening of blueberries. Nature 1961, 191, 498–499.
24. Cabrita, L.; Froystein, N.A.; Andersen, O.M. Anthocyanin trisaccharides in blueberries of Vaccinium padifolium. Food Chem. 2000, 69, 33–36.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.

30. Andersen, O.M. Chromatographic separation of anthocyanins in cowberry (lingonberry) Vaccinium vites-idaea L. J. Food Sci. 1985, 50, 1230–1232.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. 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.

37. Nickavar, B.; Amin, G.; Salehi-Sormagi, M.H. Anthocyanins from Vaccinium arctostaphylos berries. Pharm. Biol. 2004, 42, 289–291.

38. 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.

39. 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.

40. Cui, Z.H.; Yuan, C.S. Flavones of Vaccinium uliginosum fruits. Fitoterapia 1992, 63, 283.

41. 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.

42. 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.

43. Li, R.; Wang, P.; Guo, P.; Wang, Z.Y. Anthocyanin composition and content of the Vaccinium uliginosum berry. Food Chem. 2011, 125, 116–120.
44. 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.
45. 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.
46. 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.
47. 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.
48. 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.
49. 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.
50. Dinda, B.; Debnath, S.; Harigaya, Y. Naturally occurring iridoids. A review, part 1. Chem. Pharm. Bull. 2007, 55, 159–222.
51. 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.
52. 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.
53. 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.
54. 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.
55. 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.
56. 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.

57. 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.
58. 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.
59. 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.
60. 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.
61. 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.
62. 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.
63. 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.
64. 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.
65. 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.
66. Yao, Y.; Vieira, A. Protective activities of Vaccinium antioxidants with potential relevance to mitochondrial dysfunction and neurotoxicity. Neurotoxicology 2007, 28, 93–100.
67. 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.
68. 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.

69. Marziano, C.; Genet, G.; Hirschi, K.K. Vascular endothelial cell specification in health and disease. Angiogenesis 2021.

70. Matsuzawa, Y.; Lerman, A. Endothelial dysfunction and coronary artery disease: Assessment, prognosis, and treatment. Coron. Artery Dis. 2014, 25, 713–724.

71. 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.

72. 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.

73. 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.

74. 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.

75. 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.

76. 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.

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. Basu, A.; Lyons, T.J. Strawberries, blueberries, and cranberries in the metabolic syndrome: Clinical perspectives. J. Agric. Food Chem. 2012, 60, 5687–5692.

83. 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.
84. 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.
85. 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.
86. 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.
87. 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.
88. 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.
89. 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.
90. 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.
91. 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.
92. 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.
93. 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.

94. 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.
95. 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.
96. 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.
97. 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.
98. 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.
99. 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.
100. 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.
101. 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.
102. 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.