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Anthocyanins and Flavonoids of *Vaccinium* L.

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Abstract: *Vaccinium* L., comprising approximately 450 species primarily in the Northern Hemisphere, is a genus of shrubs or lianas in the family Ericaceae. The berries of many species are harvested for household consumption and commercial sale. The genus produces a wide range of compounds such as anthocyanins, flavonoids, chromones, coumarins, lignans, benzoic acids, iridoids, sterols, and triterpenoids, but is best known for the production of anthocyanins and flavonoids. Extracts and isolates of anthocyanins and flavonoids from *Vaccinium* fruits or leaves showed antioxidative, anti-inflammatory, antitumor, antiviral, vasoprotective, and antifungal activities. To date, more than 116 anthocyanins and flavonoids compounds have been isolated and identified primarily from the fruits or leaves of *Vaccinium*. This article reviews phytochemistry and pharmaceutical properties of these compounds.

Keywords: anthocyanins, bioactivities, ethnobotany, flavonoids, phytochemistry, *Vaccinium* L.

INTRODUCTION

Vaccinium L. (Ericaceae) is a morphologically diverse genus of terrestrial or epiphytic shrubs and lianas, comprising approximately 450 species, which primarily occur in the cooler areas of the northern Hemisphere, although there are tropical species from areas as widely separated as Madagascar and Hawaii [1, 2]. *Vaccinium arctostaphylos* L. has been used in folk medicine as an antidiabetic and antihypertensive agent [3]. The leaves of rabbiteye blueberry (*V. virgatum* Aiton, also known as *V. ashei* Reade) have been used in a tea for diabetics among the alpine peasantry. Fruit or leaf extracts of *Vaccinium* spp. were found to induce apoptosis in cancer cells and to inhibit human leukemia [4-7] and breast [5, 8], colon [4-7, 9, 10], lung [7], and prostate [5, 11, 12] cancer cells *in vitro*. *Vaccinium* has been an important source of food and pharmaceutical ingredients coupled with have high antioxidant potential [10, 13, 14]. The berries of many *Vaccinium* species are harvested for household consumption and commercial sale, particularly of bilberry (*V. myrtillus* L.) [6, 9], rabbiteye blueberry [10], lowbush blueberry (*V. angustifolium* Aiton) [11, 12], cranberry (*V. macrocarpon* Aiton) [4, 5, 7], and highbush cultivated blueberry (*V. corymbosum* L.) [10, 15]. Today, numerous *Vaccinium* berry and leaf extract products have been developed as dietary supplements.

The chemical constituents of some of the *Vaccinium* species have been well documented. The genus produce a wide range of compounds including anthocyanins [3, 16-48], flavonoids [20-23, 28, 37, 40, 42, 46-75], coumarins [73], lignans [76], benzoic acids [77-80], iridoids [81-83], sterols

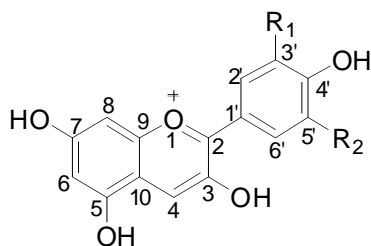
[84-87], triterpenoids [52, 55, 84, 88, 89], but are best known for the production of bioactive anthocyanins and flavonoids. To date, more than 116 anthocyanins and flavonoids compounds have been isolated and identified primarily from the fruits and leaves of *Vaccinium*. This review article focuses on the anthocyanins and flavonoids and their pharmaceutical properties.

ANTHOCYANINS

Anthocyanins are important plant pigments visible to the human eye. They belong to the widespread class of phenolic compounds collectively named flavonoids. They are glycosides of polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium or flavylium salts [90]. The sugars components of anthocyanins are usually conjugated to the anthocyanin skeleton via the C-3 hydroxyl group in ring C. The differences between individual anthocyanins relate to the number of hydroxyl groups, the nature and the number of sugars attached to the molecule, the position of this attachment, and the nature and the number of aliphatic or aromatic acids attached to the sugars in the molecule [91].

The genus *Vaccinium* has been shown to contain high levels and a wide variety of anthocyanins that provide the red, blue, purple, and black colors of these berries [92]. Many studies have been examined the contents and the composition of anthocyanins of *Vaccinium* species in the last two decades. The isolation and the structural elucidation of the individual ingredients in the anthocyanin mixtures from the extract of this genus have been the target of many investigations. The isolated anthocyanins are highly unstable and very susceptible to degradation. Their stability is affected by several factors such as PH, storage temperature, chemical structure, concentration, light, oxygen, solvents, and the presence of enzymes, proteins and metallic ions. The characterization of a mixture of anthocyanins usually involves the separation and collection of each compound, and subsequent analysis by nuclear magnetic resonance and

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Name	R ₁	R ₂
Delphinidin	OH	OH
Petunidin	OCH ₃	H
Cyanidin	OH	H
Pelargonidin	H	H
Peonidin	OCH ₃	H
Malvidin	OCH ₃	OCH ₃

Fig. (1). Chemical structure of anthocyanidins.

fast atom bombardment mass spectroscopy. For the separation and structural analysis, the use of liquid chromatography–mass spectrometry technique, which combines the separation of LC with the selectivity and sensitivity of the MS detector, permits the identification of individual compounds in the mixture of compounds [93]. The most common anthocyanidins are delphinidin, cyaniding, peonidin, petunidin and malvidin, all of them being found in *Vaccinium* berries. Galactose, glucose, arabinose, xylose, and rhamnose are the most common sugars that are bonded to anthocyanidins in mono-, di-, or trisaccharide forms. To date, a total of 41 naturally occurring anthocyanidins or aglycones were reported in the literature. In this review, the name, source and references are listed in Table 1.

Six anthocyanidins (1-6), pelargonidin, cyanidin, petunidin, delphinidin, peonidin, and malvidin were isolated from the genus *Vaccinium*, which are also the most common anthocyanidin skeletons in higher plants (Fig. 1).

The glycoside derivatives of the six anthocyanidins are the most common in nature. The following four classes of anthocyanidins glycosides are common: 3-monoside, 3-biosides, 3,5-diglycosides and 3,7-diglycosides. To date, about 35 anthocyanin glycosides have been isolated and identified from the genus *Vaccinium* (7-41). The anthocyanin glycosides include two pelargonidin glycosides, nine cyanidin glycosides, six peonidin glycosides, six delphinidin

glycosides, six petunidin glycosides, and six malvidin glycosides. Most of the anthocyanins have a monosaccharide unit attached to the C-3 position of the aglycone. Some of them have a disaccharide or trisaccharide chain at C-3 of the anthocyanins. It is well-known that the most common nature of the sugar is glucose, galactose, arabinose, rhamnose, and xylopyranose.

In the past only the 3-*O*-arabinoside (7) and 3-*O*-xyloside (8) of pelargonidin have been isolated from the berries of *V. japonicum* [32]. Cyanidin and its glycosides are present in both subgenus *Oxycoccus* (cranberries) and various sections of subgenus *Vaccinium*. Compounds cyaniding-5-*O*-glucoside (13) and cyaniding-3,5-*O*-diglucoside (14) have been reported from *V. myrtillus* containing a 5-glucoside and 3,5-diglucosides respectively. Eight disaccharides cyanidin 3-*O*-gentiobioside (15), 3-*O*-sambutioside of cyanidin (16), peonidin (22), delphinidin (28), petunidin (34) and malvidin (40), petunidin 3-*O*-rutinoside (35) and malvidin (41), and three trisaccharides cyanidin 3-*O*-(6"-*O*-2-rhamnopyranpsyl-2"-*O*- β -xylopranosyl- β -glucopyranoside) (17), peonidin (23), and delphinidin (29) have been found previously in the genus *Vaccinium* [24]. It is somewhat ironic that the blueberry contains much cyanidin compound, as cyanidin is usually associated with red flowers [94]. Recently, Ballinger *et al.* reported the extraction and purification of anthocyanins from *V. arboreum*. The compounds were identified as the 3-monoglycosides of the aglycons delphinidin, petunidin, malvidin, cyanidin, and peonidin with the sugars arabinose, galactose, and glucose (except for cyanidin and malvidin). *V. arboreum* fruit contains anthocyanins which are extremely similar to those reported for the fruits of highbush and lowbush blueberries. *V. arboreum* has at least 12 anthocyanins, while those of *V. stamineum* whose geog. range is similar to that of *V. arboreum*, has only 3 (monoglycosides of the sugars galactose, arabinose, or glucose with the aglycon cyanidin) [19]. Twenty anthocyanins were isolated from the extract of the edible blue berries of *V. padifolium* (Uveira) by a combination of chromatography techniques. They were identified as the 3-*O*- β -glucopyranosides, 3-*O*- β -galactopyranosides, 3-*O*- β -arabinopyranosides, and 3-*O*- β -sambubiosides (2"-*O*- β -xylopyranosyl-*O*- β -glucopyranosides) of delphinidin, cyanidin, petunidin, malvidin, and peonidin. Among them, 3-*O*-sambubiosides of peonidin, petunidin and malvidin are first reported as anthocyanidin disaccharides from the genus *Vaccinium*. However, petunidin (5) and Malvidin (6), and their glycosides (30-35 and 36-41, respectively) are reported in subgenus *Vaccinium* only, some non glucoside and galactoside may restrict to specific species [24].

Table 1. The Names, Sources, and References of Compounds 1-41

No.	Name	Source	References
1	Pelargonidin	<i>V. japonicum</i> (fruit)	[32]
2	Cyanidin	<i>V. × intermedium</i> (fruit)	[48]
		<i>V. myrtillus</i> (fruit)	[21, 43, 45, 46]
		<i>V. corymbosum</i> (fruit)	[46]
3	Peonidin	<i>V. padifolium</i> (fruit)	[24]
4	Delphinidin	<i>V. myrtillus</i> (leaves & fruit)	[46]
5	Petunidin	<i>V. × intermedium</i> (fruit)	[48]

Table 1. cont...

No.	Name	Source	References
6	Malvidin	<i>V. padifolium</i> (fruit)	[24]
7	Pelargonidin-3-O-arabinoside	<i>V. japonicum</i> (fruit)	[32]
8	Pelargonidin-3-O-xyloside	<i>V. japonicum</i> (fruit)	[32]
9	Cyanidin-3-O-arabinoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. × covilleum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[21, 43, 45, 46]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. padifolium</i> (fruit)	[24]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33]
		<i>V. vitis-idaea</i> (fruit)	[31, 38, 42]
		<i>V. × intermedium</i> (fruit)	[48]
		<i>V. meridionale</i> (fruit)	[47]
		<i>V. oxycoccus L.</i> (fruit)	[36]
		<i>V. stamineum L.</i> (fruit)	[30]
10	Cyanidin-3-O-galactoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. × covilleum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. padifolium</i> (fruit)	[24]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33]
		<i>V. vitis-idaea</i> (fruit)	[31, 39]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. oxycoccus L.</i> (fruit)	[36]
		<i>V. stamineum L.</i> (fruit)	[30]
11	Cyanidin-3-O-xyloside	<i>V. arctostaphylos</i> (fruit)	[97]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. myrtillus</i> (fruit)	[38, 43, 45, 46]
12	Cyanidin-3-O-glucoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20, 41]
		<i>V. corymbosum</i> (fruit)	[16, 37, 95]
		<i>V. × covilleum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. padifolium</i> (fruit)	[24]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33, 40]
		<i>V. vitis-idaea</i> (fruit)	[31]
		<i>V. × intermedium</i> (fruit)	[22, 48]

Table 1. cont...

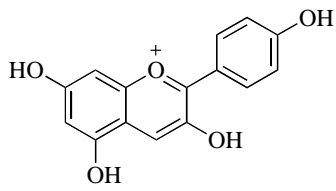
No.	Name	Source	References
		<i>V. meridionale</i> (fruit)	[47]
		<i>V. oxycoccus</i> L. (fruit)	[36]
		<i>V. stamineum</i> L. (fruit)	[30]
		<i>V. floribundum</i> (fruit)	[68]
13	Cyanidin-5-O-glucoside	<i>V. myrtillus</i> (fruit)	[98]
14	Cyanidin-3,5-O-diglucoside	<i>V. myrtillus</i> (fruit)	[98]
15	Cyanidin-3-O-gentiobioside	<i>V. padifolium</i> (fruit)	[24]
16	Cyanidin-3-O-sambubioside	<i>V. myrtillus</i> (fruit)	[27]
17	Cyanidin-3-O-(6''-O-2-rhamno-pyranosyl-2''-O-β-xylopyranosyl-β-glucopyranosides)	<i>V. myrtillus</i> (fruit)	[26]
18	Peonidin-acethyl-3-O-glucoside	<i>V. myrtillus</i> (fruit)	[99]
19	Peonidin-3-O-arabinoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. × covilleum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. padifolium</i> (fruit)	[24]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. oxycoccus</i> L. (fruit)	[36]
20	Peonidin-3-O-glucoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[41]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. × covilleum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. padifolium</i> (fruit)	[24]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. meridionale</i> (fruit)	[47]
		<i>V. oxycoccus</i> L. (fruit)	[36]
21	Peonidin-3-O-galactoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. × covilleum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. × intermedium</i> (fruit)	[22, 48]

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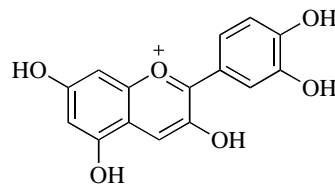
No.	Name	Source	References
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22	Peonidin-3-O-sambubioside	<i>V. padifolium</i> (fruit)	[24]
23	Peonidin-3-O-(6"-O-2-rhamnopyranosyl-2"-O- β -xylopyranosyl- β -glucopyranosides)	<i>V. padifolium</i> (fruit)	[26]
24	Delphinidin-3-O-arabinoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. virgatum = V. ashei</i> (fruit)	[20]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. \times covilleianum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. \times intermedium</i> (fruit)	[22, 48]
		<i>V. padifolium</i> (fruit)	[24]
25	Delphinidin-3-O-xyloside	<i>V. arctostaphylos</i> (fruit)	[97]
26	Delphinidin-3-O-galactoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. virgatum = V. ashei</i> (fruit)	[20]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. \times covilleianum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. \times intermedium</i> (fruit)	[22, 48]
		<i>V. padifolium</i> (fruit)	[24]
27	Delphinidin-3-O-glucoside	<i>V. macrocarpon</i> (fruit)	[69, 77]
		<i>V. angustifolium</i> (fruit)	[29]
		<i>V. virgatum = V. ashei</i> (fruit)	[20]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. \times covilleianum</i> (fruit)	[37]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. membranaceum</i> (fruit)	[96]
		<i>V. arctostaphylos</i> (fruit)	[97]
		<i>V. padifolium</i> (fruit)	[24]
		<i>V. ovatum</i> (fruit)	[96]
		<i>V. uliginosum</i> (fruit)	[33, 100]
		<i>V. vitis-idaea</i> (fruit)	[31]
		<i>V. \times intermedium</i> (fruit)	[22, 48]
		<i>V. oxycoccus L.</i> (fruit)	[36]
		<i>V. floribundum</i> (fruit)	[68]
28	Delphinidin-3-O-sambubioside	<i>V. myrtillus</i> (fruit)	[27]
29	Delphinidin-3-O-(6"-O-2-rhamnopyranosyl-2"-O- β -xylopyranosyl- β -glucopyranosides)	<i>V. padifolium</i> (fruit)	[26]
30	Petunidin-3-O-arabinoside	<i>V. myrtillus</i> (fruit)	[21]

Table 1. cont...

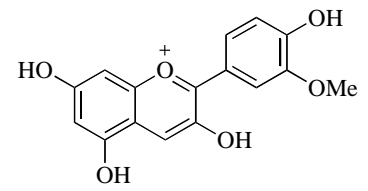
No.	Name	Source	References
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. uliginosum</i> (fruit)	[29, 33]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]
31	Petunidin-3-O-xyloside	<i>V. arctostaphylos</i> (fruit)	[101]
		<i>V. × intermedium</i> (fruit)	[48]
32	Petunidin-3-O-galactoside	<i>V. angustifolium</i> (fruit)	[29]
		<i>V. corymbosum</i> (fruit)	[18, 46, 95]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. arctostaphylos</i> (fruit)	[97]
		<i>V. padifolium</i> (fruit)	[24]
		<i>V. uliginosum</i> (fruit)	[100]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]
33	Petunidin-3-O-glucoside	<i>V. angustifolium</i> (fruit)	[29]
		<i>V. corymbosum</i> (fruit)	[18, 19, 46, 95]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. arctostaphylos</i> (fruit)	[97]
		<i>V. padifolium</i> (fruit)	[24]
		<i>V. uliginosum</i> (fruit)	[33, 100]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. oxycoccus</i> L.	[36]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]
34	Petunidin-3-O-sambubioside	<i>V. padifolium</i> (fruit)	[24]
35	Petunidin-3-O-rutinoside	<i>V. padifolium</i> (fruit)	[24]
36	Malvidin-3-O-arabinoside	<i>V. myrtillus</i> (fruit)	[21]
		<i>V. corymbosum</i> (fruit)	[18, 19, 46, 95]
		<i>V. uliginosum</i> (fruit)	[33, 100]
37	Malvidin-3-O-xyloside	<i>V. arctostaphylos</i> (fruit)	[101]
38	Malvidin-3-O-galactoside	<i>V. angustifolium</i> (fruit)	[29]
		<i>V. corymbosum</i> (fruit)	[18, 19, 46, 95]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. arctostaphylos</i> (fruit)	[97]
		<i>V. uliginosum</i> (fruit)	[40, 100]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]
39	Malvidin-3-O-glucoside	<i>V. angustifolium</i> (fruit)	[29]
		<i>V. corymbosum</i> (fruit)	[37, 95]
		<i>V. myrtillus</i> (fruit)	[17, 21]
		<i>V. arctostaphylos</i> (fruit)	[97]
		<i>V. uliginosum</i> (fruit)	[33, 40, 100]
		<i>V. vitis-idaea</i> (fruit)	[22, 48, 67]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]
		<i>V. oxycoccus</i> L. (fruit)	[36]
40	Malvidin-3-O-sambubioside	<i>V. padifolium</i> (fruit)	[24]
41	Malvidin-3-O-rutinoside	<i>V. padifolium</i> (fruit)	[24]



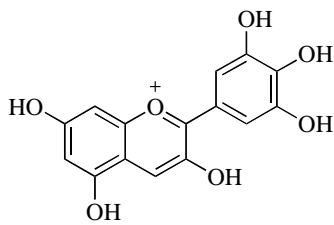
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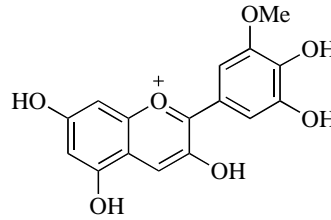
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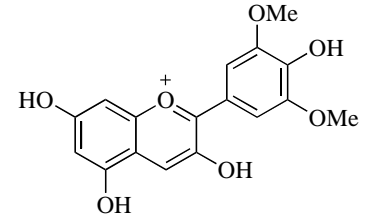
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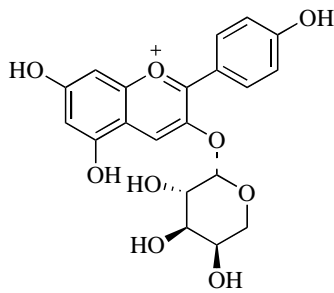
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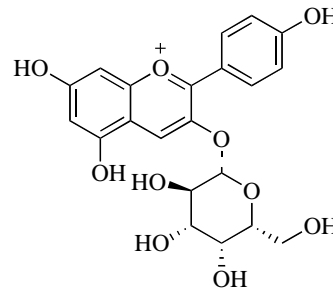
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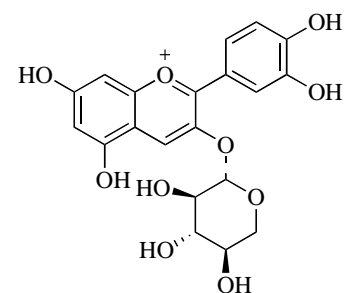
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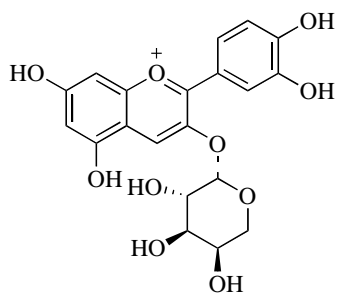
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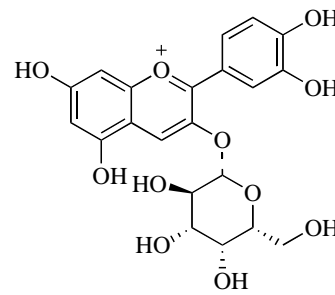
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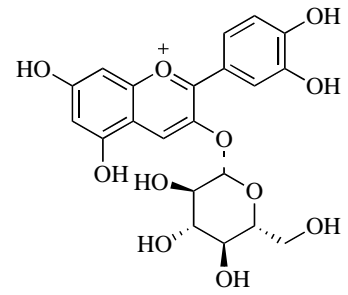
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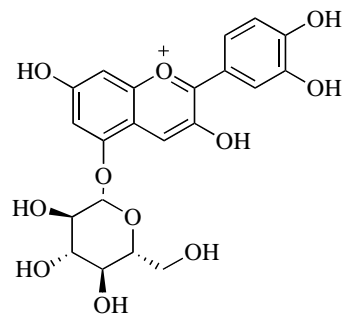
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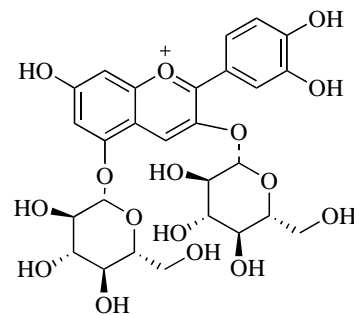
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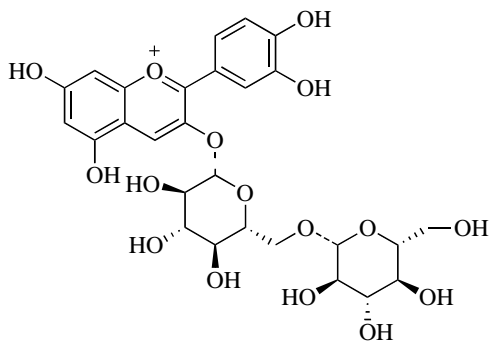
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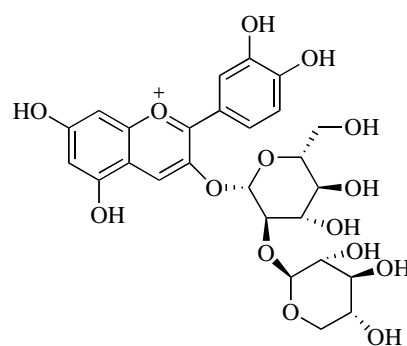
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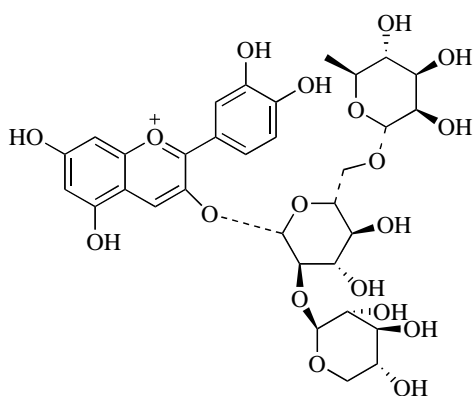
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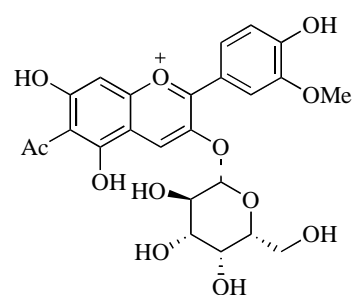
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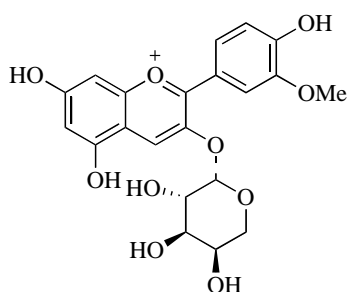
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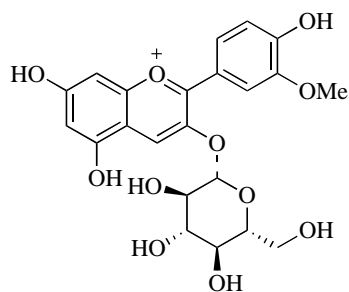
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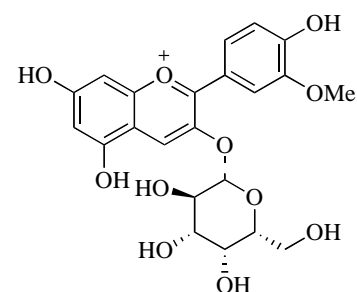
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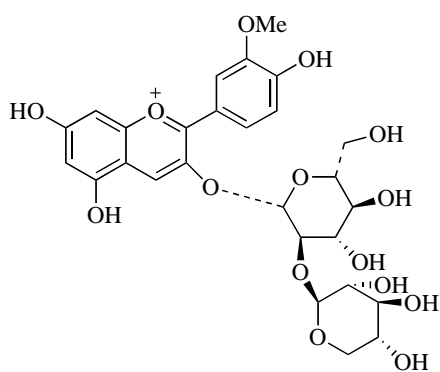
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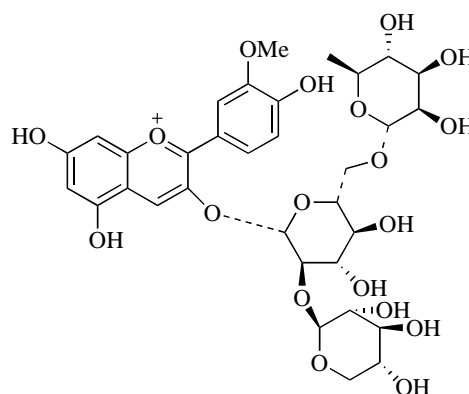
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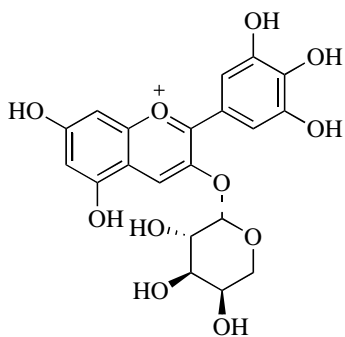
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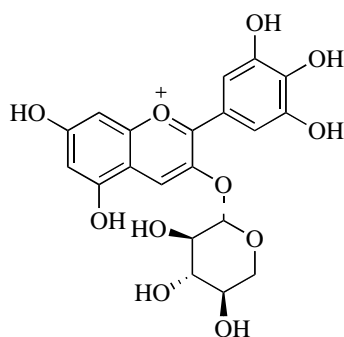
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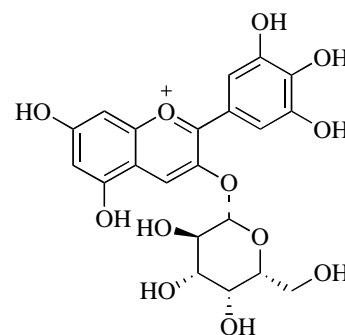
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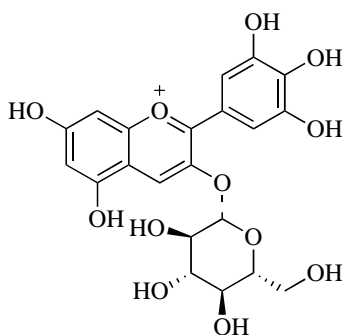
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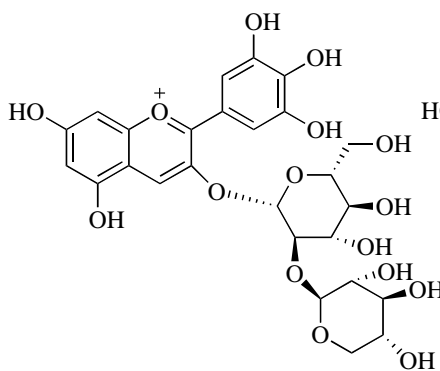
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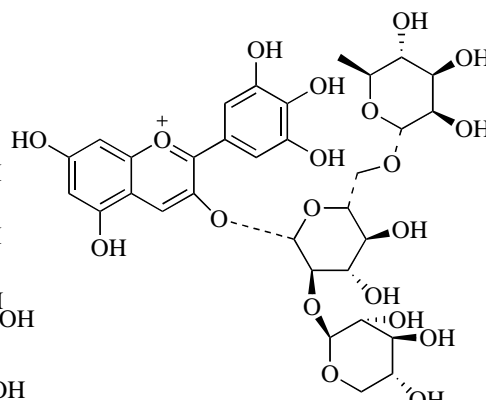
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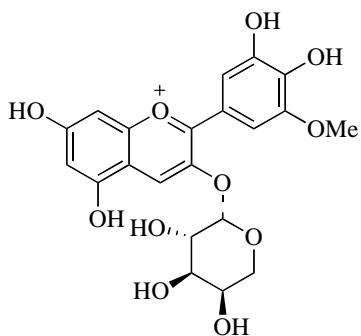
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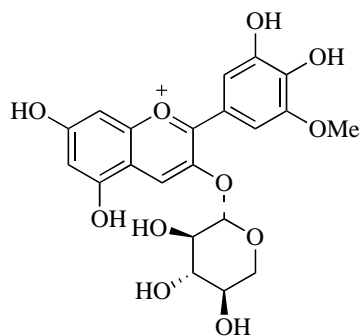
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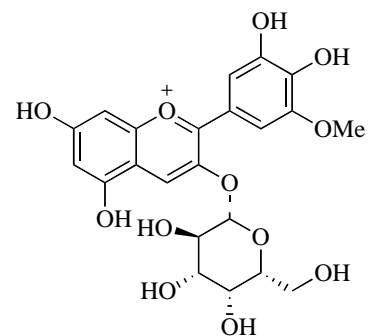
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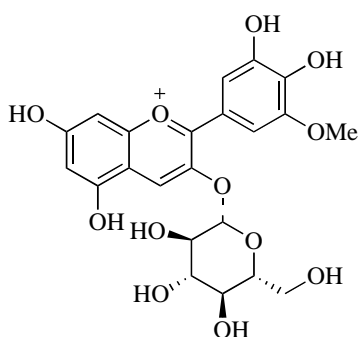
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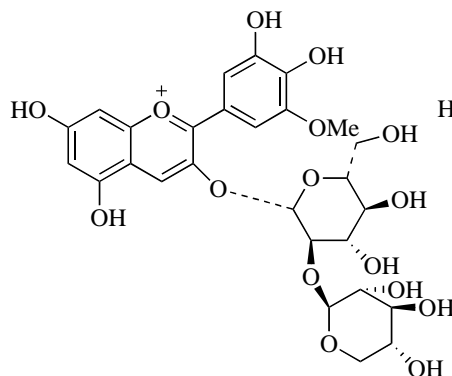
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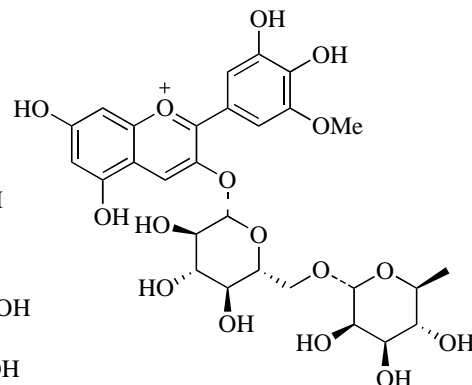
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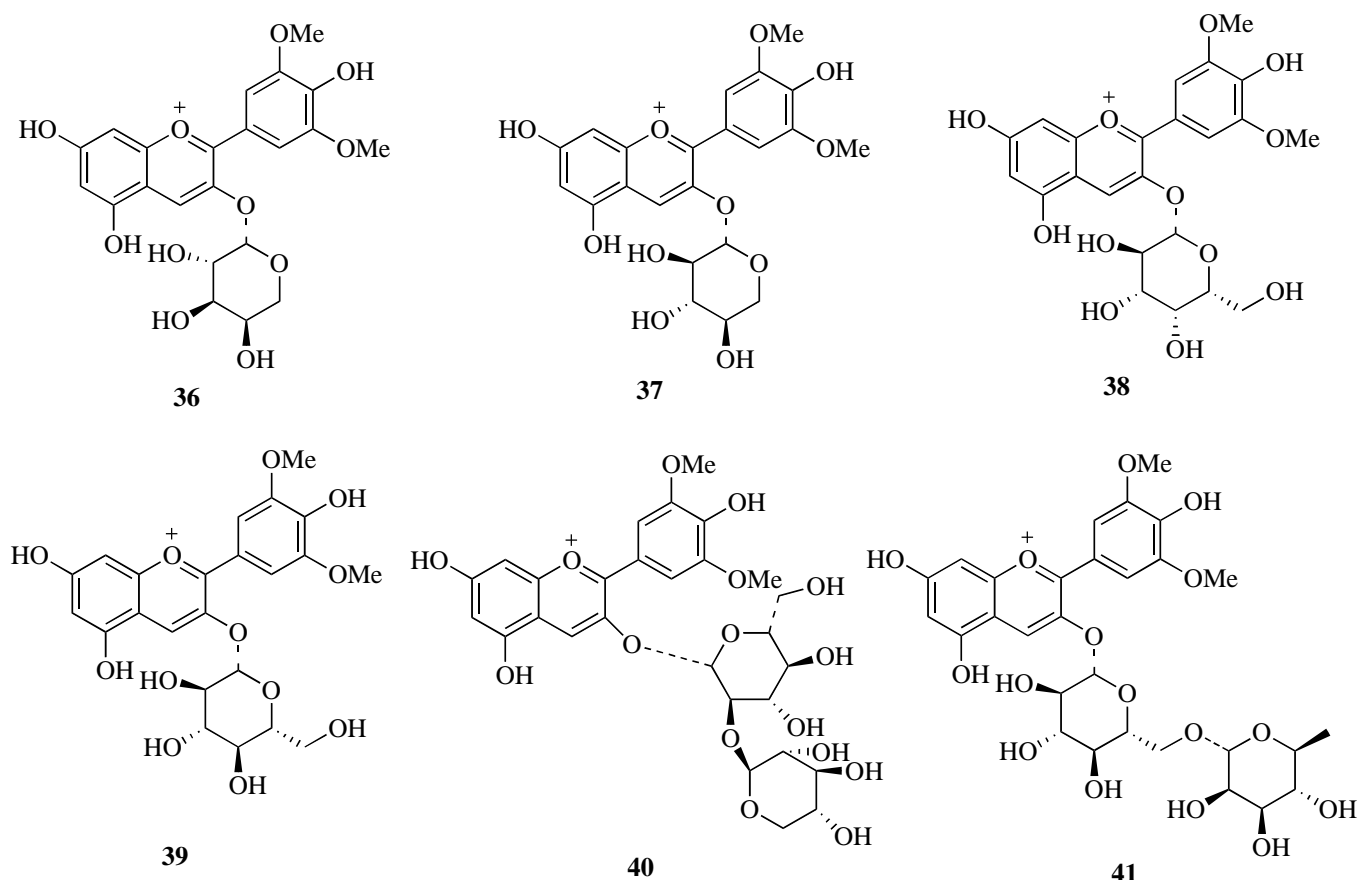
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FLAVONOIDS

Flavonoids are formed in plants from the aromatic amino acids phenylalanine and tyrosine, and malonate. The basic flavonoid structure is the flavan nucleus, which consists of 15 carbon atoms arranged in three rings ($C_6-C_3-C_6$). Which are labeled A, B, and C (Fig. 2). The various classes of flavonoids differ in the level of oxidation and pattern of substitution of the C ring, while individual compounds within a class differ in the pattern of substitution of the A and B rings. Flavonoids are among the most ubiquitous phenolic compounds found in the genus *Vaccinium*. Their structures vary based on the substituents of hydroxyl at B ring, as well as the nature and the number of sugars attached to the molecule. To date, more than 50 compounds have been isolated and identified from the genus *Vaccinium*. Flavonoid glycosides are one of the most frequently chemical constituents from *Vaccinium*. The most common

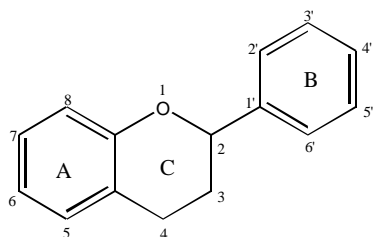


Fig. (2). Basic flavonoid structure.

sugar moieties include D-glucose, L-rhamnose, D-xylose, D-galactose, and L-arabinose. The glycosides are usually *O*-glycosides, with the sugar moiety bound to the hydroxyl group at C-3 or C-7 position. The most common flavonol in the *Vaccinium* is quercetin.

Flavone, Flavonol and their Glycosides

Flavone, flavonol and their glycosides are the main chemical constituents from genus *Vaccinium*. The glycosides are usually *O*-glycosides, with the sugar moiety bound to the hydroxyl group at the C-3 or C-7 position. A total of 45 flavonoids including flavone, flavonol and their glycosides were isolated and identified from the genus *Vaccinium* (Table 2).

A few early investigations from the leaves of *V. myrtillus* led to the isolation and identification of quercetin, quercetin 3-arabinoside, isoquercitrin, quercetin 3-rhamnoside, quercetin 3-glucoglucoside, and apparently a new quercetin arabinoside not identical with quercetin 3-arabinoside [21, 50]. It is interesting that four novel flavonols with a 3-*O*-glucuronic acid were isolated from the species *V. bracteatum*, *V. × intermedium* and *V. myrtillus* [22]. During the past decade, with improving separation, characterization and quantitative techniques, a number of flavonols and their glycosides from the fruit of *Vaccinium* have been isolated and identified. For example, Zhang *et al.*, identified 12 flavonol glycosides, quercetin-3-*O*- β -D-glucuronide (55), quercetin-3-*O*- β -D-glucuronide Me ester (56), quercetin-3-

Table 2. The Names, Sources, and References of Compounds 42-86

No.	Name	Source	References
42	Chrysin	<i>V. bracteatum</i> (leaves)	[73-75]
43	Apigenin	<i>V. bracteatum</i> (leaves)	[73-75]
		<i>V. myrtillus</i> (fruit)	[22]
44	Luteolin	<i>V. bracteatum</i> (leaves)	[73-75]
		<i>V. myrtillus</i> (fruit)	[102]
45	Chrysoeriol	<i>V. myrtillus</i> (fruit)	[22]
46	Kaempferol	<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. corymbosum</i> (leaves)	[18, 46, 95]
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. smallii</i> (leaves)	[72] [49]
		<i>V. bracteatum</i> (leaves)	[73-75]
		<i>V. uliginosum</i> (fruit)	[66]
		<i>V. vitis-idaea</i> (fruit)	[22]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. meridionale</i> Swartz (fruit)	[47]
47	Quercetin	<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. corymbosum</i> (leaves)	[18, 46, 95]
		<i>V. koreanum</i> (leaves)	[54]
		<i>V. calycinum</i> (leaves)	[53]
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. reticulatum</i> (leaves)	[53]
		<i>V. smallii</i> (leaves)	[72] [49]
		<i>V. bracteatum</i> (leaves)	[52, 56, 73, 105]
		<i>V. meridionale</i> (fruit)	[47]
		<i>V. floribundum</i> (fruit)	[68]
		<i>V. uliginosum</i> (fruit)	[23, 40, 66, 100]
		<i>V. vitis-idaea</i> (fruit)	[22, 66]
		<i>V. × intermedium</i> (fruit)	[22, 48]
48	Isorhamnetin	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. calycinum</i> (leaves)	[53]
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. reticulatum</i> (leaves)	[53]
		<i>V. × intermedium</i> (fruit)	[22, 48]
49	Quertine-3- <i>O</i> -methyl ether	<i>V. calycinum</i> (leaves)	[53]
		<i>V. reticulatum</i> (leaves)	[53]
50	Myricetin	<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[20]

Table 2. cont...

No.	Name	Source	References
		<i>V. corymbosum</i> (leaves)	[40]
		<i>V. myrtillus</i> (fruit & leaves)	[22]
		<i>V. floribundum</i> (fruit)	[68]
		<i>V. uliginosum</i> (fruit)	[40]
		<i>V. vitis-idaea</i> (fruit)	[67]
		<i>V. × intermedium</i> (fruit)	[22, 48]
51	Laricitrin	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. uliginosum</i> (fruit)	[66]
		<i>V. × intermedium</i> (fruit)	[22, 48]
52	Syringetin	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. myrtillus</i> (fruit)	[21, 22, 46]
		<i>V. uliginosum</i> (fruit)	[23, 66]
		<i>V. × intermedium</i> (fruit)	[22, 48]
53	Quertine-3- <i>O</i> -glucoside	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[63]
		<i>V. corymbosum</i> (leaves)	[37]
		<i>V. calycinum</i> (leaves)	[53]
		<i>V. myrtillus</i> (fruit)	[21, 22, 46]
		<i>V. reticulatum</i> (leaves)	[53]
		<i>V. arctostaphylos</i> (leaves)	[58, 106]
		<i>V. smallii</i> (leaves)	[49]
		<i>V. uliginosum</i> (fruit)	[23, 66]
		<i>V. vitis-idaea</i> (fruit)	[42, 70]
		<i>V. × intermedium</i> (fruit)	[22, 48]
		<i>V. floribundum</i> (fruit)	[68]
		<i>V. bracteatum</i> (leaves)	[51, 64]
54	Quertine-3- <i>O</i> -galactoside	<i>V. macrocarpon</i> (fruit)	[65]
		<i>V. oxycoccus</i> (fruit)	[107]
		<i>V. quadripetalis</i> (leaves)	[108]
		<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. corymbosum</i> (leaves)	[37]
		<i>V. darrowii</i> (fruit)	[109]
		<i>V. calycinum</i> (leaves)	[53]
		<i>V. myrtillus</i> (fruit & leaves)	[22]
		<i>V. reticulatum</i> (leaves)	[53]

Table 2. cont...

No.	Name	Source	References
		<i>V. smallii</i> (leaves)	[49, 72]
		<i>V. bracteatum</i> (leaves)	[51, 64]
		<i>V. uliginosum</i> (fruit)	[23, 66]
		<i>V. vitis-idaea</i> (fruit)	[42, 70]
55	Quertine-3- <i>O</i> -glucuronide	<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[63]
		<i>V. myrtillus</i> (fruit)	[22]
		<i>V. × intermedium</i> (fruit)	[48]
		<i>V. bracteatum</i> (leaves)	[64]
		<i>V. uliginosum</i> (fruit)	[23, 66]
		<i>V. vitis-idaea</i> (fruit)	[42, 70]
56	Quertine-3- <i>O</i> -glucuronide-6"-methyl ether	<i>V. bracteatum</i> (leaves)	[64]
57	Avicularine	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. koreanum</i> (leaves)	[54]
		<i>V. myrtillus</i> (fruit)	[21, 22, 46]
		<i>V. smallii</i> (leaves)	[72] [49]
		<i>V. vitis-idaea</i> (fruit)	[42, 70]
58	Quertine-3- <i>O</i> -arabinofuranoside	<i>V. × intermedium</i> (fruit)	[48]
		<i>V. macrocarpon</i> (fruit)	[69] [65]
		<i>V. bracteatum</i> (leaves)	[64]
		<i>V. koreanum</i> (leaves)	[54]
59	Quertine-3- <i>O</i> -rhamnoside	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[63]
		<i>V. corymbosum</i> (leaves)	[37, 46, 95]
		<i>V. myrtillus</i> (fruit)	[21, 22, 46]
		<i>V. smallii</i> (leaves)	[49]
		<i>V. bracteatum</i> (leaves)	[64]
		<i>V. vitis-idaea</i> (fruit)	[42, 70]
		<i>V. × intermedium</i> (fruit)	[48]
60	Quertine-3- <i>O</i> -galactoside	<i>V. macrocarpon</i> (fruit)	[4, 69]
		<i>V. smallii</i> (leaves)	[49, 72]
		<i>V. bracteatum</i> (leaves)	[64]
		<i>V. vitis-idaea</i> (fruit)	[59, 70]
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
61	Quertine-3- <i>O</i> -arabinoside	<i>V. × intermedium</i> (fruit)	[48]
		<i>V. vitis-idaea</i> (fruit)	[42, 70]
		<i>V. corymbosum</i> (leaves)	[37]

Table 2. cont...

No.	Name	Source	References
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. macrocarpon</i> (fruit)	[69]
62	Quertine-3- <i>O</i> -xyloside	<i>V. vitis-idaea</i> (fruit)	[42, 70]
		<i>V. × intermedium</i> (fruit)	[22]
		<i>V. myrtillus</i> (fruit & leaves)	[22]
		<i>V. floribundum</i> (fruit)	[68]
63	Quertine-6- <i>O</i> -glucoside	<i>V. bracteatum</i> (leaves)	[52]
64	Chrysoeriol-7- <i>O</i> -glucoside	<i>V. bracteatum</i> (leaves)	[64]
65	Flavogadorinin	<i>V. bracteatum</i> (leaves)	[64, 83, 110]
66	Quertine-3- <i>O</i> -(6"-coumaroyl)galactoside	<i>V. macrocarpon</i> (fruit)	[65]
67	Quertine-3- <i>O</i> -(6"-benzoyl)galactoside	<i>V. macrocarpon</i> (fruit)	[65]
68	3-[[4- <i>O</i> -(4-carboxy-3-hydroxy-3-methyl-1-oxobutyl)-6-deoxy- α -L-mannopyranosyl]oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-1-Benzopyran-4-one	<i>V. myrtillus</i> (fruit)	[57]
		<i>V. vitis-idaea</i> (fruit)	[22]
69	3-[[4- <i>O</i> -(4-carboxy-3-hydroxy-3-methyl-1-oxobutyl)-6-deoxy- α -L-mannopyranosyl]oxy]-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-Benzopyran-4-one	<i>V. myrtillus</i> (fruit)	[57]
		<i>V. vitis-idaea</i> (fruit)	[22]
70	Myricetin-3- <i>O</i> -arabinoside	<i>V. macrocarpon</i> (fruit)	[4, 69]
71	Isorhamnetin-3- <i>O</i> -galactoside	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. uliginosum</i> (fruit)	[23, 66]
		<i>V. vitis-idaea</i> (fruit)	[42, 70]
72	Myricetin-3- <i>O</i> -glucuronide	<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. uliginosum</i> (fruit)	[21]
		<i>V. × intermedium</i> (fruit)	[68]
73	Myricetin-3- <i>O</i> -glucoside	<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. corymbosum</i> (leaves)	[95]
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. vitis-idaea</i> (fruit)	[67]
74	Myricetin-3- <i>O</i> -xyloside	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. myrtillus</i> (fruit & leaves)	[22]
75	Laricitrin-3- <i>O</i> -glucuronide	<i>V. myrtillus</i> (fruit)	[21, 22, 46]
		<i>V. × intermedium</i> (fruit)	[68]
76	Isorhamnetin-3- <i>O</i> -glucoside	<i>V. uliginosum</i> (fruit)	[23, 66]
		<i>V. myrtillus</i> (fruit & leaves)	[22]
		<i>V. bracteatum</i> (leaves)	[64]

Table 2. cont...

No.	Name	Source	References
		<i>V. vitis-idaea</i> (fruit)	[70]
77	Syringetin-3- <i>O</i> -glucoside	<i>V. corymbosum</i> (leaves)	[46, 95]
		<i>V. myrtillus</i> (fruit & leaves)	[21, 22, 46]
		<i>V. uliginosum</i> (fruit)	[23, 66]
		<i>V. vitis-idaea</i> (fruit)	[70]
78	Kaempferol-3- <i>O</i> -glucoside	<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. corymbosum</i> (leaves)	[46, 95]
		<i>V. arctostaphylos</i> (leaves)	[58, 111]
		<i>V. myrtillus</i> (fruit)	[21]
		<i>V. vitis-idaea</i> (fruit)	[70]
79	Kaempferol-3- <i>O</i> -rhamnoside	<i>V. arctostaphylos</i> (leaves)	[58, 111]
		<i>V. vitis-idaea</i> (fruit)	[42]
80	Myricetin-3- <i>O</i> -galactoside	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. myrtillus</i> (fruit)	[21]
		<i>V. uliginosum</i> (fruit)	[23, 66]
81	Isorhamnetin-3- <i>O</i> -xyloside	<i>V. macrocarpon</i> (fruit)	[69]
		<i>V. myrtillus</i> (fruit)	[21, 62]
82	Orientin	<i>V. bracteatum</i> (leaves)	[64]
83	Vitexina	<i>V. bracteatum</i> (leaves)	[64]
84	Chrysoeriol-7- <i>O</i> -(6"- <i>O</i> - <i>p</i> -coumaroyl)- glucopyranoside	<i>V. bracteatum</i> (leaves)	[64]
85	Myricetin-3- <i>O</i> -digalactoside	<i>V. macrocarpon</i> (fruit)	[69]
86	Quertine-3- <i>O</i> -rutinoside	<i>V. bracteatum</i> (leaves)	[64]
		<i>V. angustifolium</i> (fruit)	[103, 104]
		<i>V. virgatum</i> = <i>V. ashei</i> (fruit)	[63]
		<i>V. corymbosum</i> (leaves)	[95]
		<i>V. darrowii</i> (fruit)	[109]
		<i>V. myrtillus</i> (fruit)	[21, 62]
		<i>V. arctostaphylos</i> (leaves)	[111]
		<i>V. uliginosum</i> (fruit)	[23, 66]
		<i>V. vitis-idaea</i> (fruit)	[70]
		<i>V. × intermedium</i> (fruit)	[68]

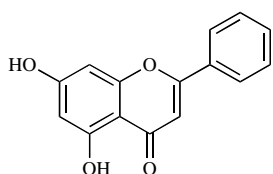
O- α -L-rhamnoside (**59**), quercetin-3-*O*- β -D-galactopyranoside (**60**), quercetin-3-*O*- α -L-arabinopyranoside (**61**), chrysoeriol-7-*O*- β -D-glucopyranoside (**64**), flavogadorinin (**65**), isorhamnetin-3-*O*- β -D-glucopyranoside (**76**), isoorientin (**81**), orientin (**82**), vitexin (**83**), and chrysoeriol-7-*O*-(6"-*O*-*p*-coumaroyl)- β -D- glucopyranoside (**84**) from the leaves of *V. bracteatum*. Compounds **56**, **64**, **65** and **84** were isolated from the *Vaccinium* for the first time, and compounds **55**, **59**, **60**, **61**, **76**, **82** and **83** were isolated from this plant for the

first time. The *p*-coumaroylglucoside of compound **84** may gradually hydrolyze in the extract to give the free acid. Compounds orientin (**82**) and vitexin (**83**) are 8-*C*-glucosylflavones in nature. The UV/Vis spectrum of the aglycone, 8-*C*-glucosylflavone, has a λ_{\max} at 541 nm in MeOH/HCl, in between that of cyanidin (at 535 nm) and delphinidin (at 546 nm). Therefore, 8-*C*-glucosylflavone appears to represent another blueing factor of flower color in addition to hydroxylation of the B-ring, acylation, co-

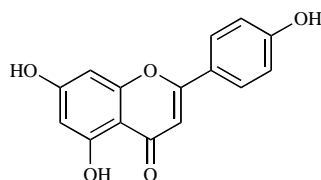
pigmentation and metal complexation [64], [94]. Vvedenskaya *et al.* isolated 22 flavonoids by UV/vis and mass spectra analyses from cranberry powder. Among them, six new constituents not previously reported in cranberry or in cranberry products were determined through NMR spectroscopy to be quercetin-3- β -glucoside (**53**), quercetin-3- α -arabinopyranoside (**61**), quercetin-3-*O*-(6''-*p*-coumaroyl)- β -galactoside (**66**), quercetin-3-*O*-(6''-benzoyl)- β -galactoside (**67**) myricetin-3- β -xylopyranoside (**74**), and 3'-methoxyquercetin-3- α -xylopyranoside (**81**). Compounds **66** and **67** represent a new class of cranberry flavonol compounds with

three conjugated components consisting of a flavonol, sugar, and carboxylic acid (benzoic or hydroxycinnamic acids). This is also the first report identifying quercetin-3-arabinoside in both furanose and pyranose forms in cranberry [69].

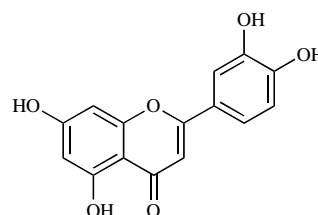
In addition, some flavonols and their derivatives were also isolated from the *V. vitis-idaea*. These compounds include kaempferol (**46**), quercetin (**47**), quercetin 3-*O*- β -D-galactoside (**54**), quercetin 3-*O*- α -L-arabinoside (**61**), and quercetin 3-*O*- α -L-rhamnopyranosyl(1 \rightarrow 6)- β -D-glucopyranoside (**85**) [22, 66].



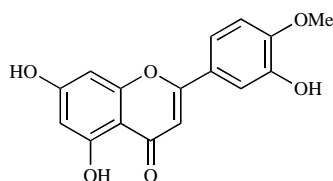
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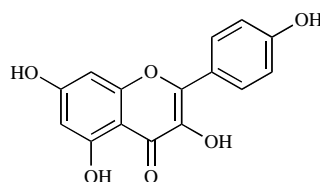
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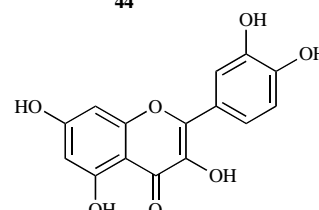
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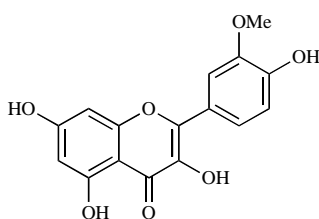
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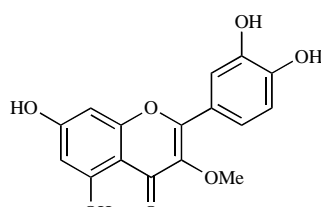
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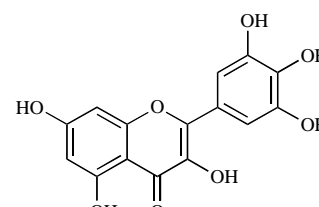
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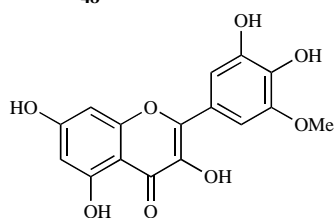
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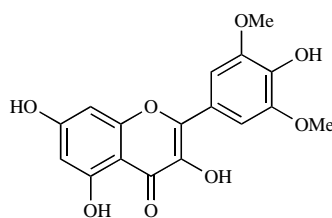
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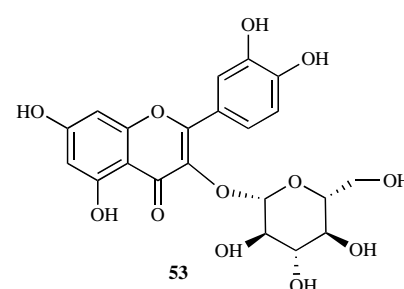
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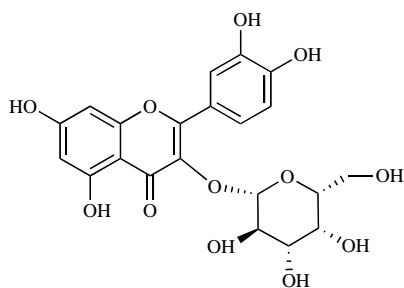
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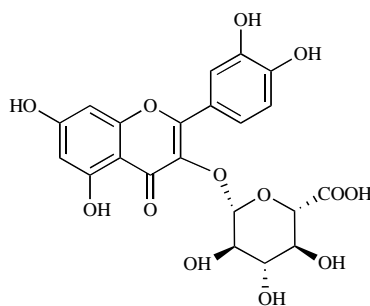
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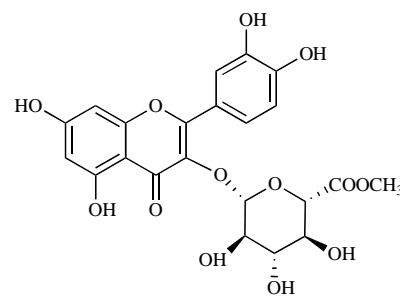
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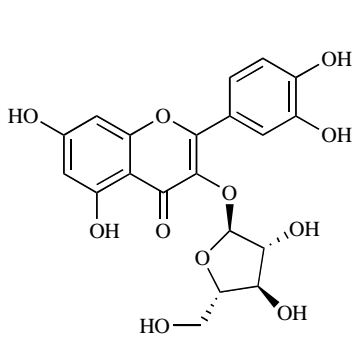
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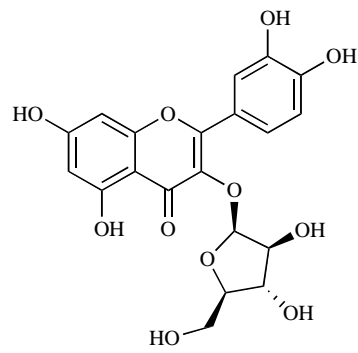
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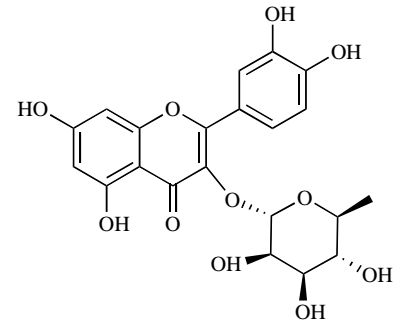
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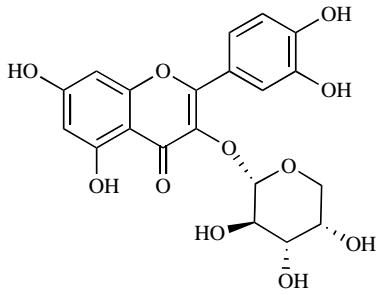
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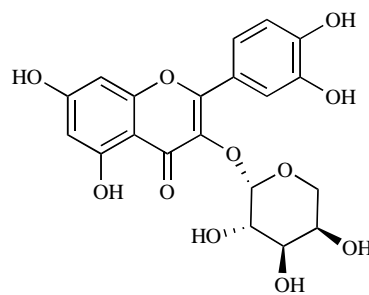
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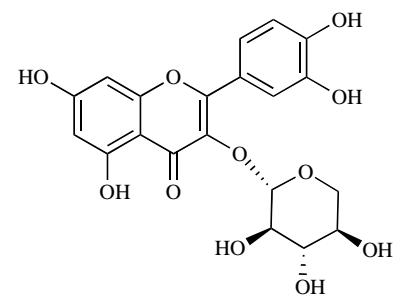
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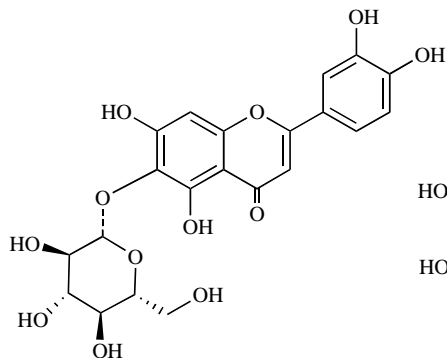
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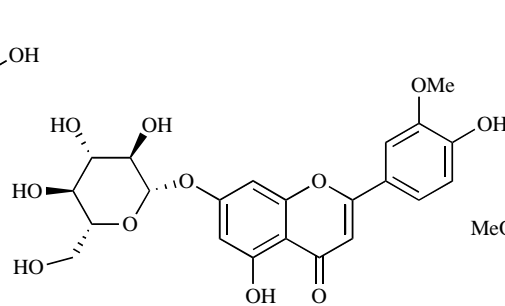
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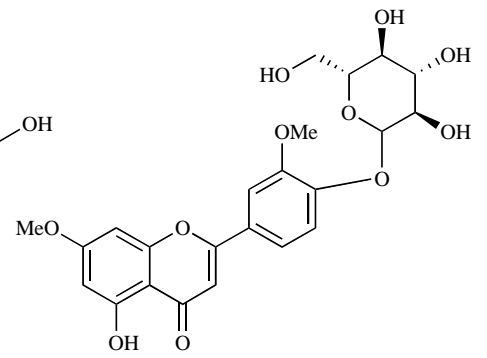
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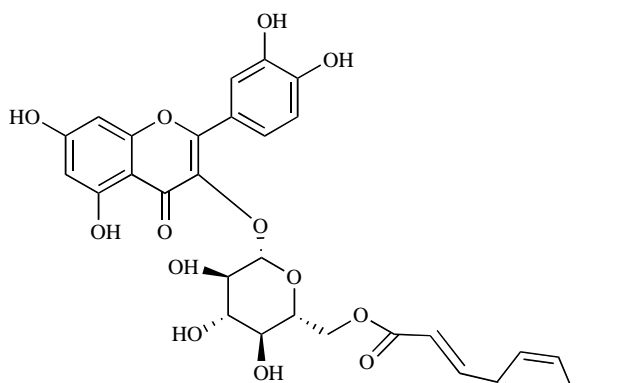
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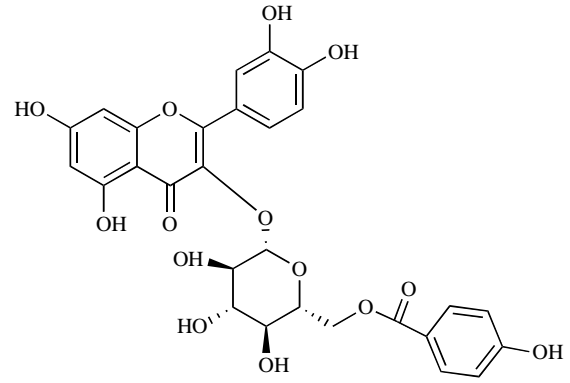
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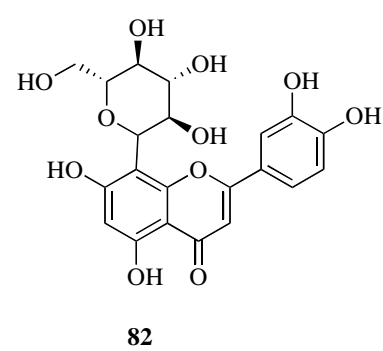
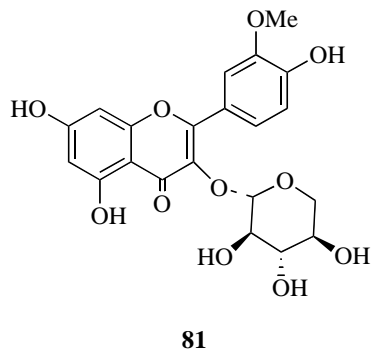
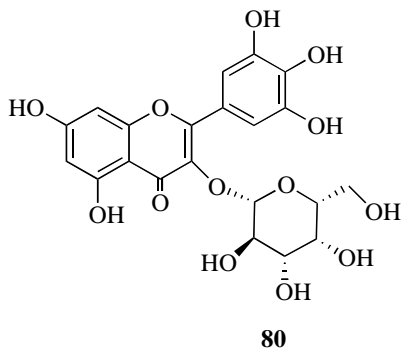
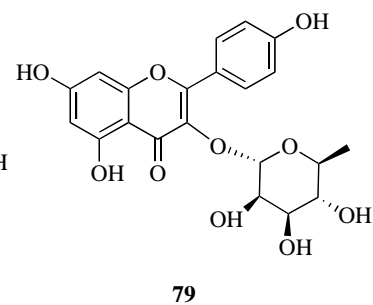
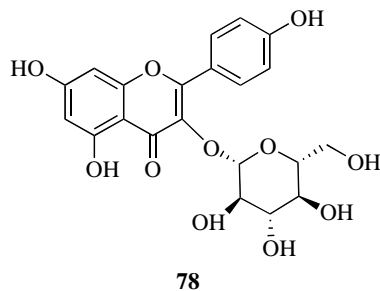
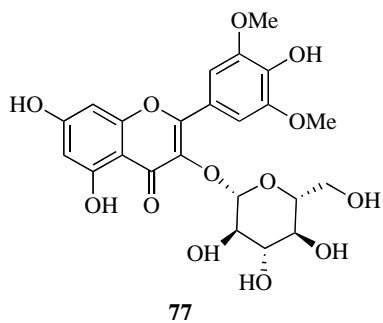
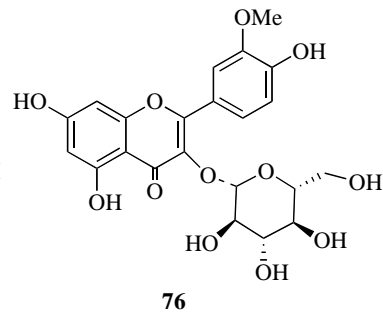
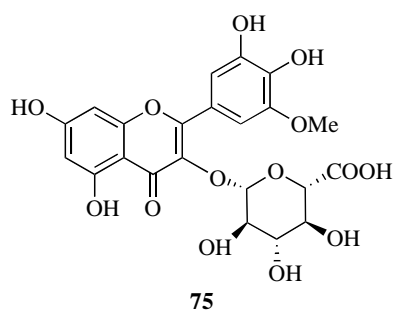
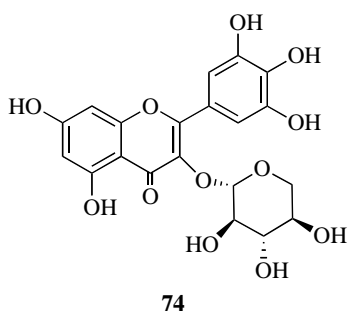
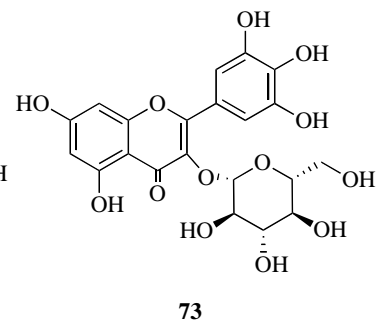
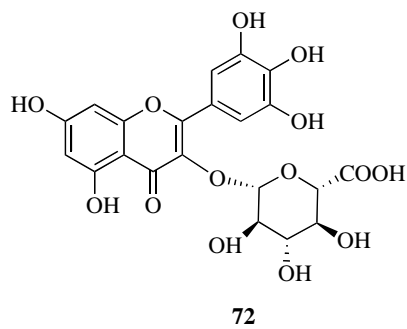
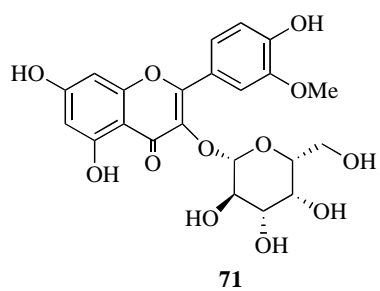
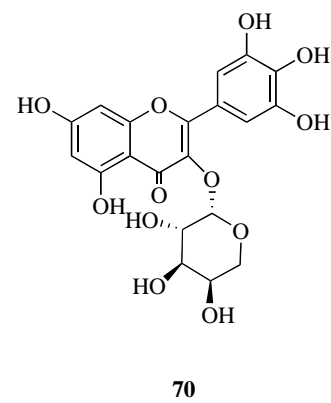
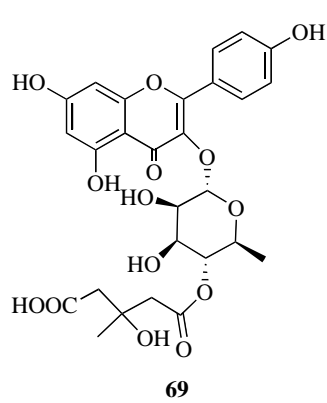
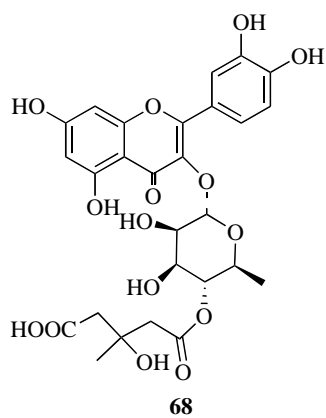
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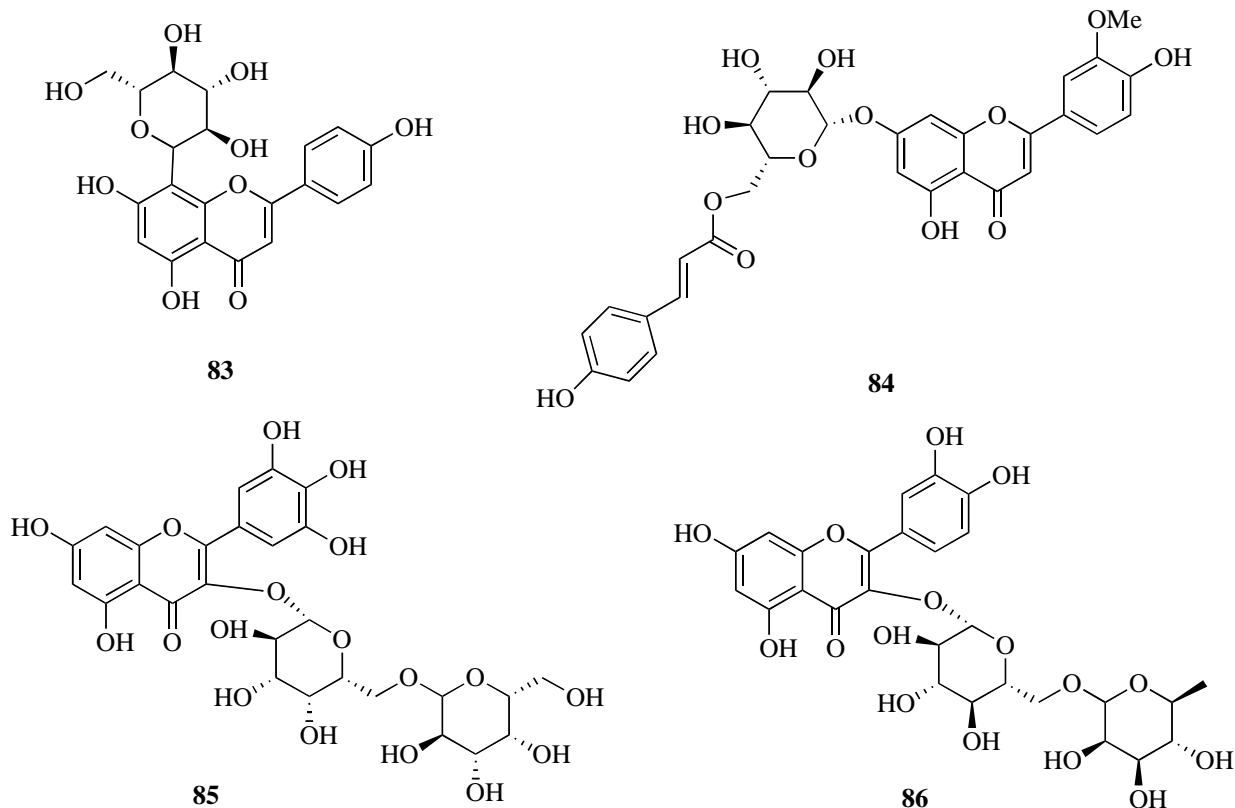


66



67





Flavan-3-ols and Proanthocyanidins

Proanthocyanidins, also known as procyanidins, are a class of flavanols. Proanthocyanidin are essentially polymer chains of flavonoids such as flavan-3-ols (catechins). The composition and content of procyanidins have been studied in common plant foods [112, 113]. The universal B-type procyanidins have a single link between structural units of catechins, whereas the rare A-type procyanidins are double linked. This unique double linked chain structure of flavonoids aroused special interest, because it was suspected to contribute to antiadhesion activity against bacteria and to the antiviral effects of these food products. Cultivated cranberry (*V. macrocarpon* Aiton) and wild lingonberry contain both A- and B-type procyanidins, whereas primary B-type procyanidins were identified in wild (*V. angustifolium* Aiton) and cultivated blueberries (*V. corymbosum* and *V. virgatum*) [114-118]. To date, four flavan-3-ols and 24 proanthocyanidins have been isolated and identified from the genus *Vaccinium* (Table 3). Recently some other reports have studied the composition and contents of proanthocyanidin of *Vaccinium* species using HPLC-MS after extraction from the leaves [119, 120].

BIOLOGICAL ACTIVITIES

Vaccinium species are rich in anthocyanins and flavonoids. Many reports have suggested that these compounds exhibit a wide range of biological activities, e.g., antioxidant, anti-inflammatory and anticancer effects (Table 4 and 5) [78, 121, 122]. Thus, they are assumed to promote health by protecting one from various degenerative diseases and diabetes as well as enhancing visual function and

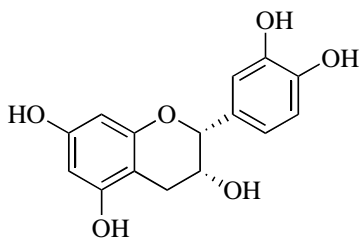
slowing the progression of neurological disorders. Consumption of flavonoid-rich plant foods has been claimed to protect against cardiovascular diseases and certain cancers, such as lung cancer [123]. It is known that the oxidation of low density lipoproteins (LDL) is associated with cardiovascular diseases, and thus flavonoids, compounds possessing antioxidant activity, are postulated to have potential benefits in the prevention of these diseases [124, 125].

BIOSYNTHESIS PATHWAYS OF ANTHOCYANINS AND FLAVONOIDS (FIG. 3) [172-173]

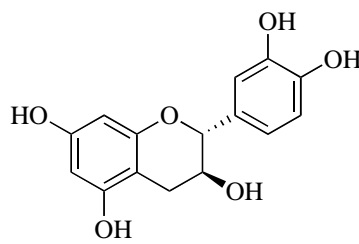
As anthocyanins and flavonoids shared a basic C₆-C₃-C₆ skeleton system, their biosynthetic precursor was thus proposed to be cinnamoyl-CoA starter unit. The chain can be extended to give naringenin chalcone by using three molecules of malonyl-CoA. Then the naringenin chalcone generates aromatic rings through the chalcone isomerase (CHI). Chalcones act as precursors for a vast range of flavonoid derivatives found throughout the plant kingdom. Most contain a six-membered heterocyclic ring, formed by Michael-type nucleophilic attack of a phenol group on to the unsaturated ketone giving a flavanone. This isomerization can occur chemically, acid conditions favouring the flavanone and basic conditions the chalcone, but in nature the reaction is enzyme catalysed and stereospecific, resulting in formation of a single flavanone enantiomer. Flavanones can then give rise to many variants on this basic skeleton, e.g. flavones, flavonols, and anthocyanidins. Modifications to the hydroxylation patterns in the two aromatic rings may occur, generally at the flavanone

Table 3. The Names, Sources, and References of Compounds 87-116

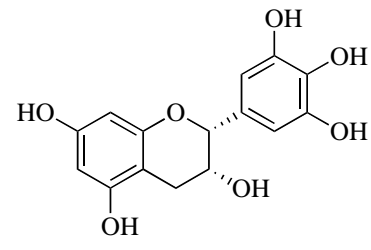
No.	Name	Source	References
87	(-)-epicatechin	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
		<i>V. vitis-idaea</i> (whole plant)	[117]
		<i>V. vitis-idaea</i> (fruit)	[42]
88	(+)-catechin	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
		<i>V. vitis-idaea</i> (whole plant)	[117]
		<i>V. vitis-idaea</i> (fruit)	[42]
89	(-)-epigallocatechin	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
		<i>V. vitis-idaea</i> (whole plant)	[117]
90	(+)-galocatechin	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
		<i>V. vitis-idaea</i> (whole plant)	[117]
91	Mururin A	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
92	Mururin B	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
93	Vaccinin A	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
94	Cinchonain Ia	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
95	Cinchonain Ib	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
96	[2R-(2 α ,3 β ,10 β)]-2,10-bis(3,4-dihydroxy phenyl)-3,4,9,10-tetrahydro-3,5-dihydroxy-2H,8H-benzo[1,2-b:3,4-b']dipyran-8-one	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
97	Kandelin A-2	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
98	Cinchonain IIb	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
99	Kandelin A-1	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
100	Cinchonain IIa	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
101	Procyanidin B-3	<i>V. vitis-idaea</i> (whole plant)	[117]
102	Procyanidin B-1	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
103	Procyanidin B-2	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
104	Procyanidin B-7	<i>V. vitis-idaea</i> (whole plant)	[117]
105	Procyanidin C-1	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
106	Proanthocyanidin A-2	<i>V. vitis-idaea</i> (whole plant)	[117]
107	Proanthocyanidin A-1	<i>V. vitis-idaea</i> (whole plant)	[117]
108	Epicatechin-(4 β →8,2 β →7)-epicatechin-(4 α →8)-epicatechin	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
109	(+)-galocatechin	<i>V. vitis-idaea</i> (whole plant)	[117]
110	Epicatechin-(4 β →8, 2 β →7)-epicatechin-(4 α →8)-catechin	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
111	Cinnamtannin D1	<i>V. vitis-idaea</i> (whole plant)	[117]
112	Cinnamtannin B1	<i>V. vitis-idaea</i> (whole plant)	[117]
113	Cinnamtannin D2	<i>V. vitis-idaea</i> (whole plant)	[117]
114	Cinnamtannin B2	<i>V. vitis-idaea</i> (whole plant)	[117]
115	Epicatechin-(4 β →8, 2 β →7)-epicatechin-(4 α →8)-epicatechin-(4 β →8)-catechin	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]
116	Epicatechin-(4 β →8, 2 β →7)-epicatechin-(4 α →8)-epicatechin-(4 β →6)-catechin	<i>V. virgatum</i> = <i>V. ashei</i> (leaves)	[63]



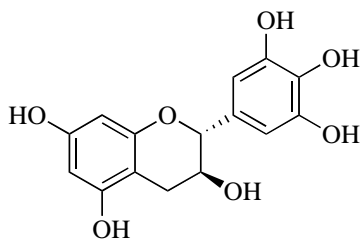
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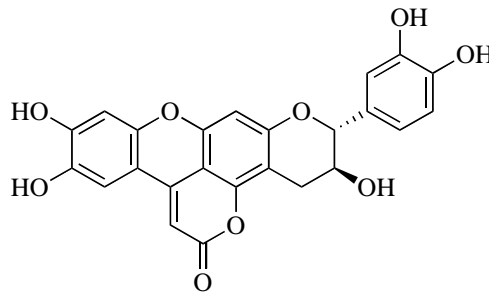
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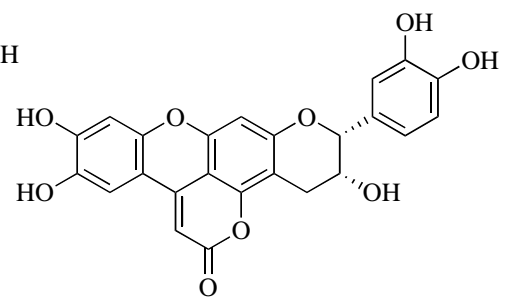
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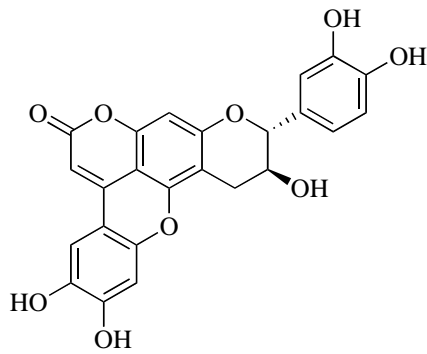
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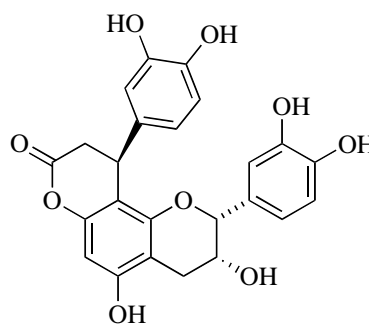
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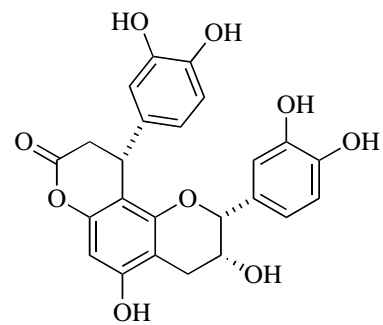
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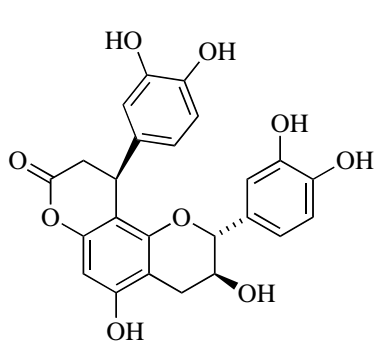
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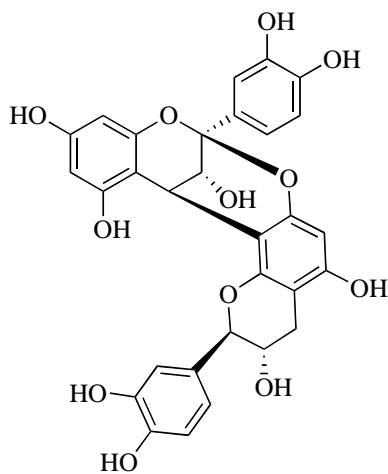
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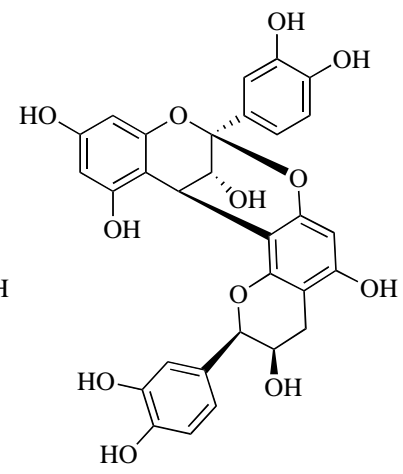
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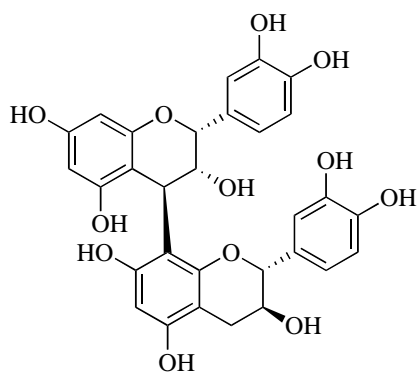
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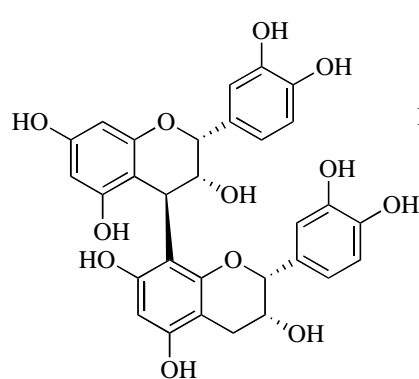
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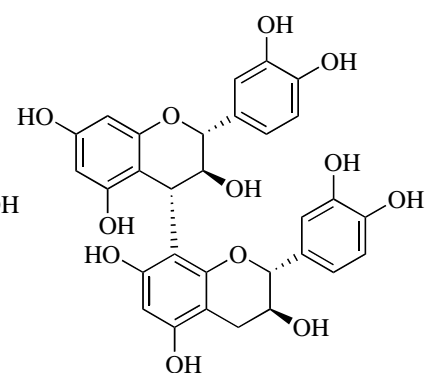
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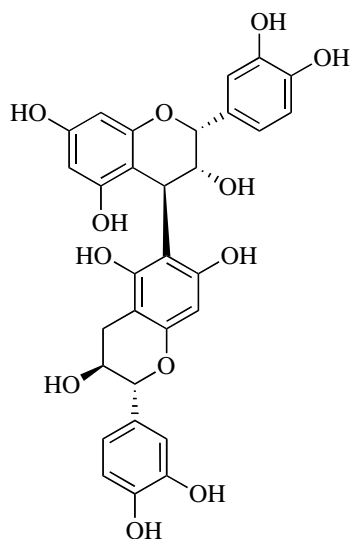
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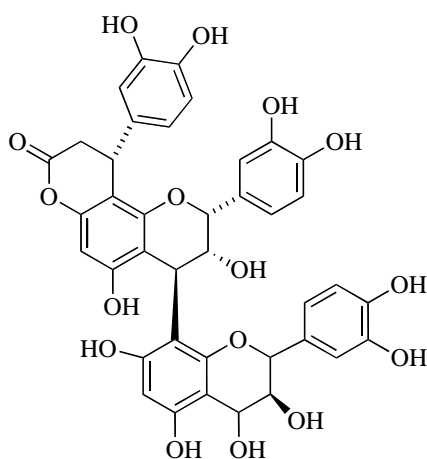
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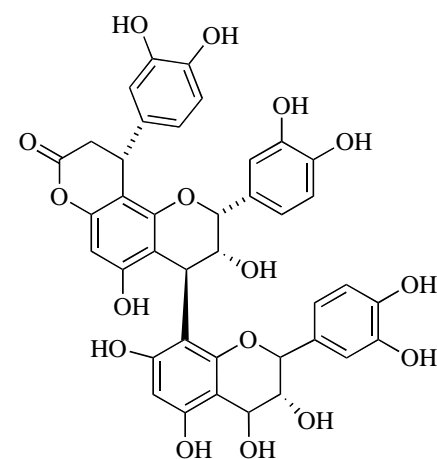
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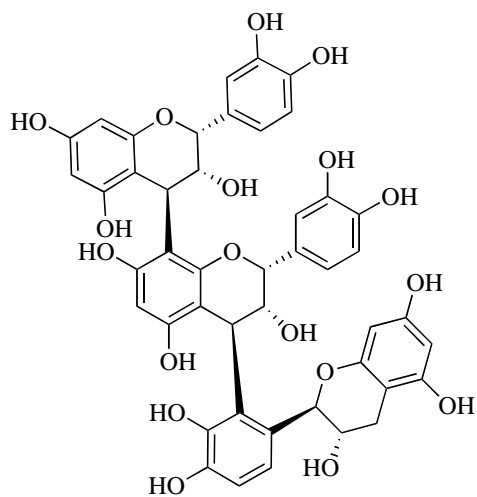
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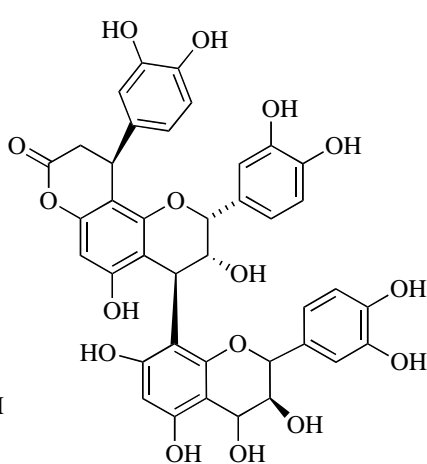
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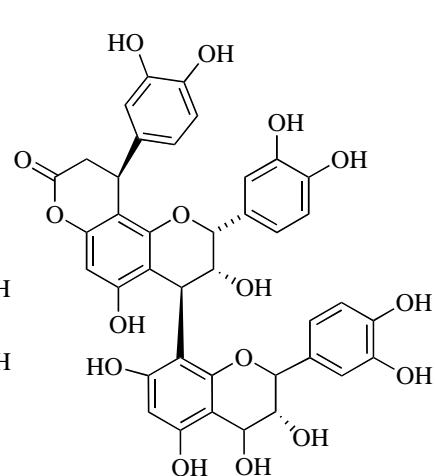
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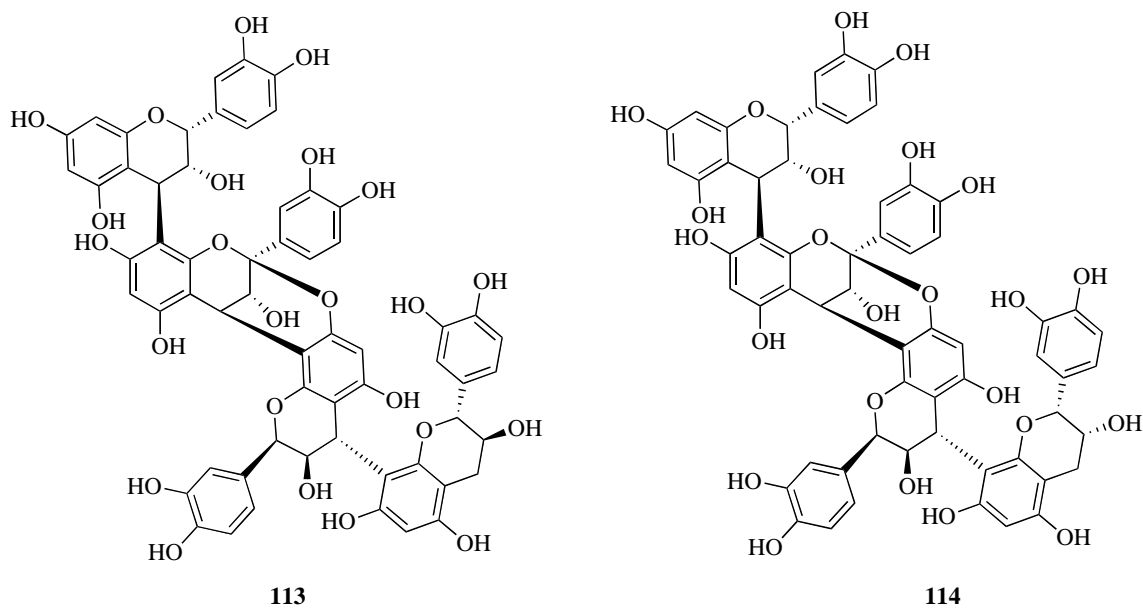
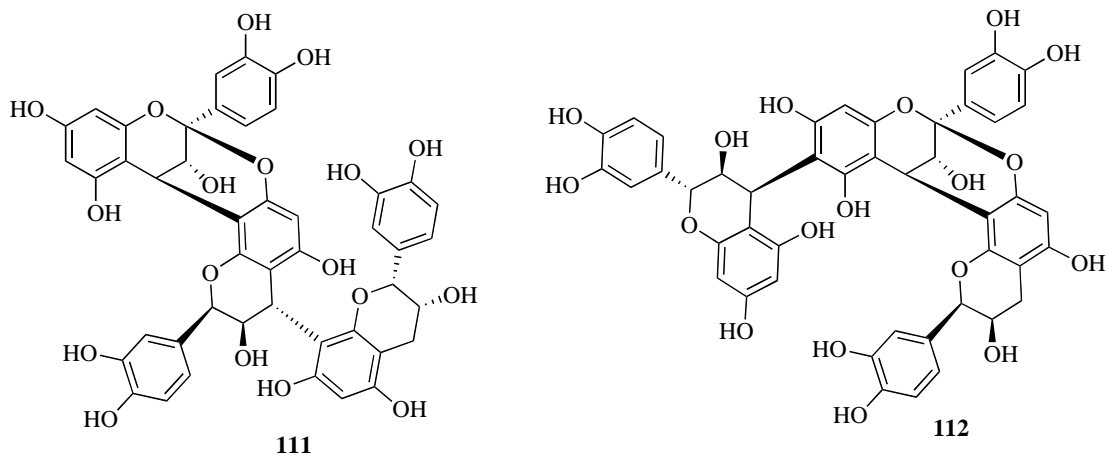
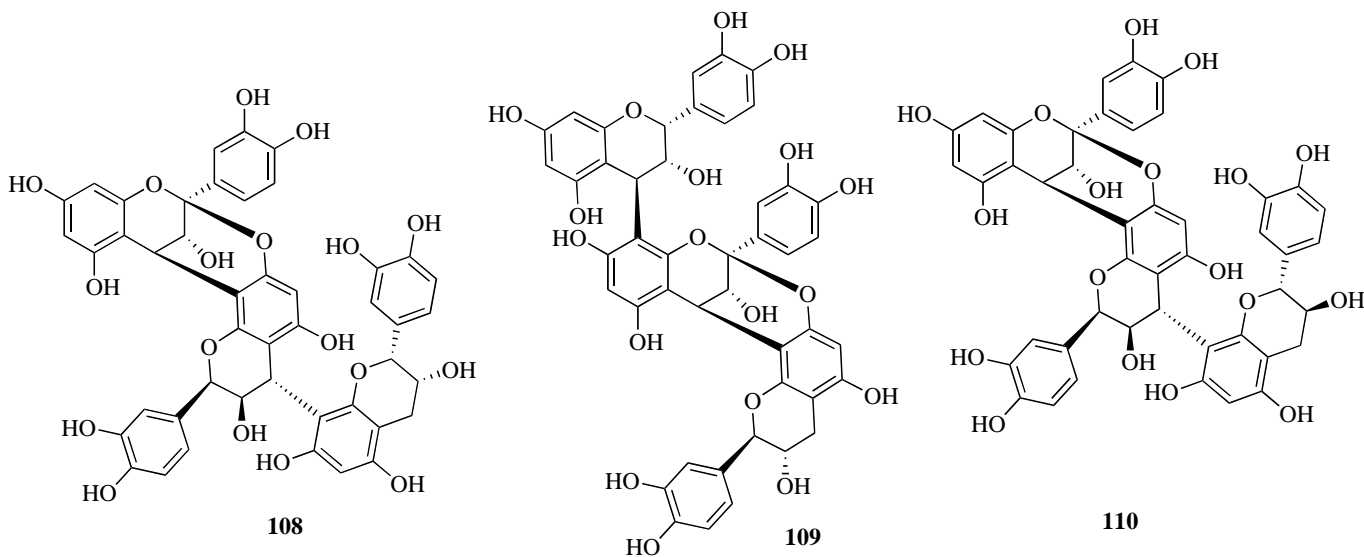
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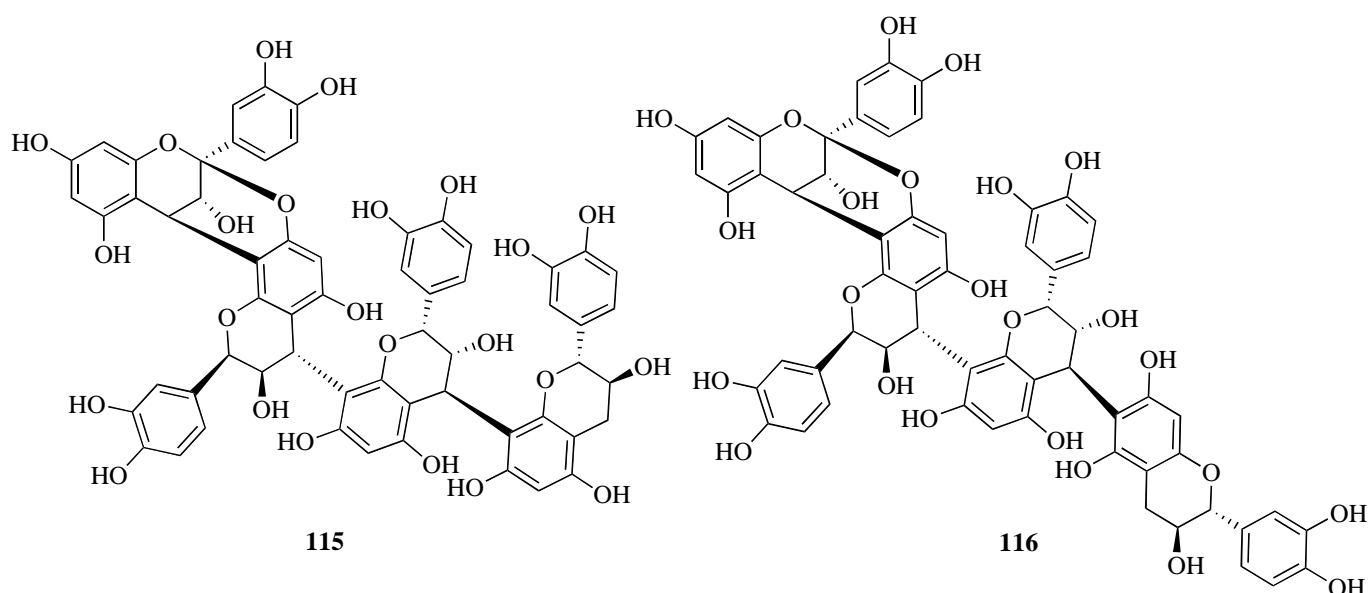


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**Table 4. Biological Activities of *Vaccinium* L. as Revealed by *In Vitro* Studies**

Bioactivities	Description	References
Antioxidant Activities	Inhibited over 90% of the formation of methyl linoleate hydroperoxides by cranberry phenolics at concentration as low as 500 $\mu\text{g/mL}$	[126]
	Inhibited lipid peroxidation, as well as protein and lipid oxidation in liposomes	[127-129]
	Showed to possess radical scavenging capacity in various <i>in vitro</i> models using assays of the oxygen radical absorbance capacity (ORAC), the total oxidant scavenging capacity (TOSC), and the free radical scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical as well as antioxidant capacities inhibiting oxidation of methyl linoleate, liposomers, and human LDL. The most striking antioxidant activity is cyaniding 3-galactose. DPPH assays showed that it was more effective than flavonol glycoside and the standards in scavenging free radicals, with an EC_{50} of 7.7 μM compared to 17.3 μM for myricetin 3-arabinoside and 30 μM for trolox standard	[4, 130, 131]
	Increased plasma antioxidant status, protected RBC against hemolysis	[126, 132]
	Showed protective effects on PC12 cells damage and chronic diseases associated with oxidative stress	[133]
	Showed neuro and mitochondrio-protective effect	[134]
	Showed antioxidative activity under the used assay conditions towards prevention of oxidative DNA damage	[135]
Cytotoxicities	Inhibited proliferation of MCF-7, MDA-MB-231 and MDA-MB-435 breast cancer cells	[4, 8, 126, 127]
	Inhibited the induction of ornithine decarboxylase, an enzyme involved in tumor proliferation, and induce quinine reductase, an enzyme that can inactivate certain carcinogens	[136]
	Exhibited the human colon tumor cell lines Caco-2, HT-116, and HT-29	[10, 137, 138]
	Exhibited the anticancer effects on DLD-1 and COLO205 cells	[139]
	Inhibited matrix metalloproteinase activity in DU145 human prostate cancer cells	[140]
	Exhibition of anticancer capability in human lung and leukemia cells	[105]
	Modulated the expression of cyclooxygenase-2 (COX-2) and I κ B α in human colon cancer cells	[141]
	Inhibitory effect on activator protein-1, nuclear factor- κ B, and mitogen-activated protein kinases activation	[105, 142]

Table 4. cont...

Bioactivities	Description	References
Antimicrobial Activities	Exhibited selective antibacterial activity against the bacterial strains	[143-146]
	Prevented the urinary tract infections	[143]
	Showed potential inhibitory effect against bacteria involved in dental caries and periodontal diseases	[147, 148]
	Exhibited potent biological activity by inhibiting adherence of uropathogenic isolates of P-fimbriated <i>Escherichia coli</i> bacteria to cellular surfaces containing α -Gal(1 \rightarrow 4)- β -Gal receptor sequences similar to those on epithelial cells in the urinary tract	[149, 150]
	Inhibit the adsorption of phage T4 to its bacterial host cells and prevented the replication of rotavirus in its monkey kidney (MA-104) host cells	[151]
Antidiabetic Activities	Cinchonain Ib has an insulinotropic effect and can be used for managing type 2 diabetes	[152]
	Extracts of the Canadian blueberry contain active principles with insulin-like and glitazone-like properties, while conferring protection against glucose toxicity	[153]
Antinociceptive Activities	Extract from <i>V. corymbosum</i> displayed significantly antinociceptive activity	[154]
Antiinflammatory Activities	Extract from <i>V. corymbosum</i> , <i>V. vitis-idaea</i> , and <i>V. microcarpon</i> displayed significantly anti-inflammatory activity	[154,155]
Antiviral Activities	Extract from blueberry displayed significantly antinociceptive activity	[156]
Vasoprotective Activities	Anthocyanin-rich extract from bilberry showed direct vasoactive and vasoprotective properties	[157]

Table 5. Biological Activities of *Vaccinium L*. as Revealed by *In Vivo* Studies

Model	Description	References
Mice	Anthocyanins from bilberry alleviated pruritus in a mouse model of chronic allergic contact dermatitis	[158]
Rats	Flavonoids from fruit residues of <i>V. vitis-idaea</i> could lower serum uric acid and protect kidney in adenine-reduced hyperuricemia	[132]
Mice	Anthocyanins from bilberry showed protective effect on gastric ulcer	[159]
Mice	The bilberry fruit extract, in a dose dependent manner, induced the resolution of liver fibrosis by decreasing oxidative stress and inactivating HSCs via down-regulation of fibrogenic cytokines, TGF- β 1 and TNF- α	[160]
Rats and Mice	Anthocyanins from bilberry provided moderate protection against Dox-induced cardiac and hematopoietic damage	[161]
Mice	Blueberry extract showed antinociceptive activity	[162]
Mice	Bilberry extract showed protective effective against endotoxin-induced uveitis	[163]
Mice	Anthocyanins from lowbush blueberry showed hypoglycemic activity	[164]
Mice	Bilberry extract played an important role in protecting against restraint stress-induced liver damage by both scavenging free radicals activity and lipid peroxidase inhibitory effect	[165]
Mice	Bilberry extract reduced the degree of oxidative stress and kidney damage induced by KBrO ₃	[166]
Mice	<i>V. oxycoccos</i> berries extract showed preventive effect on acetic acid-induced colitis	[167]
Mice	<i>V. ashei</i> berries extract showed improvement performance in memory tasks and had protective effects on brain DNA	[168]
Mice	extract of <i>V. myrtillus</i> significantly decrease the level of glucose and fructosamine in alloxan induced NOD	[169]
Rats	Anthocyanosides from <i>V. myrtillus</i> appear to be effective in preventing the increase in capillary filtration of albumin (CFA) and the failure of lymphatic uptake of interstitial albumin	[170]
Mice	Extract from <i>V. ashei</i> produced antinociceptive effects	[162]
Mice	Extract from <i>V. corymbosum</i> did not induce <i>in vivo</i> DNA damage in peripheral blood cells of 12-day old female or male Swiss mice but the micronucleus assay indicated that the extract presented clastogenic or aneugenic effects	[171]

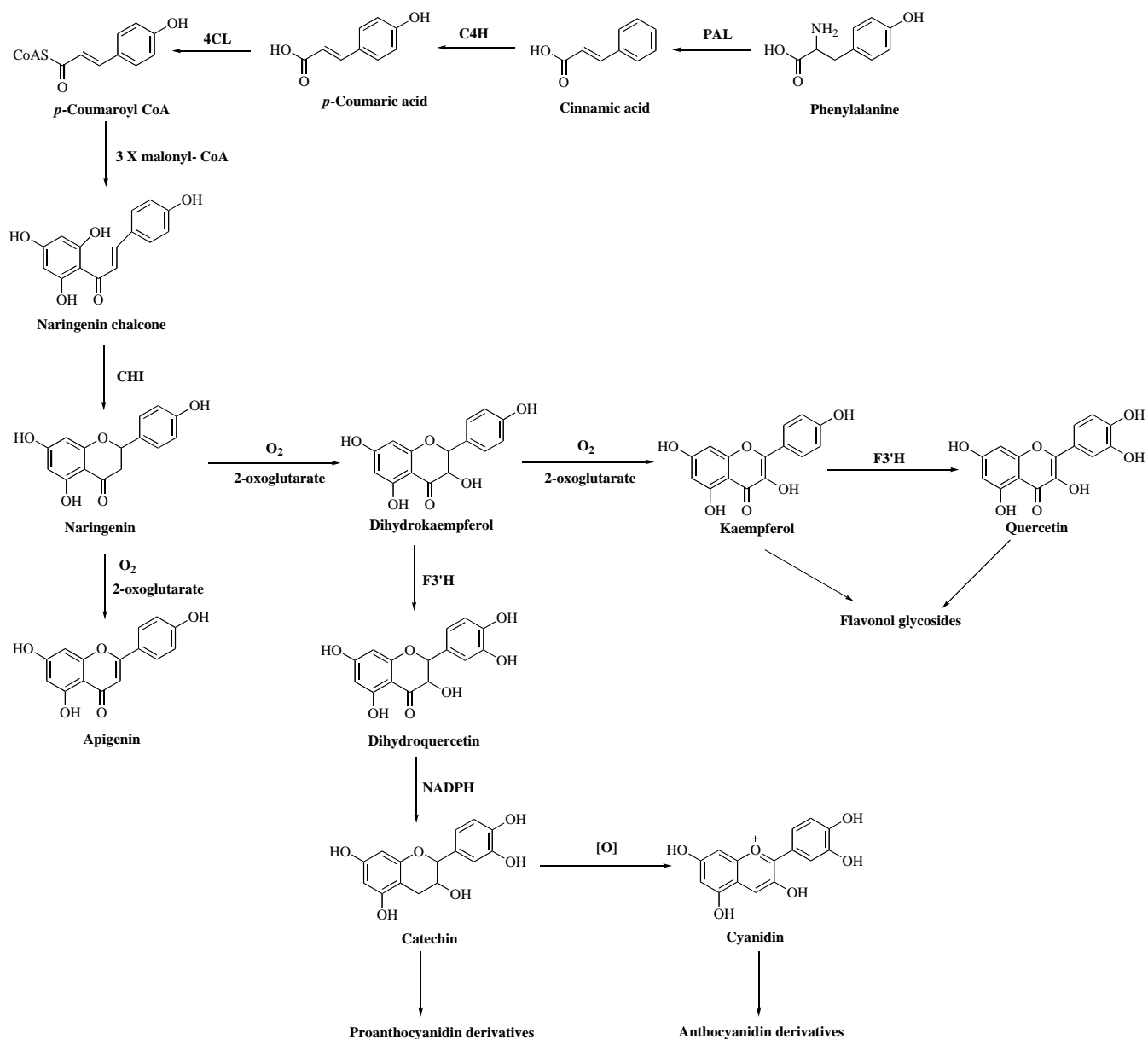


Fig. (3). Biosynthesis pathway of anthocyanidins and flavonoids.

or dihydroflavonol stage, and methylation, glycosylation, and dimethylallylation are also possible, increasing the range of compounds enormously.

CONCLUSIONS

The chemical constituents of the genus *Vaccinium* are best known for the production of anthocyanins and flavonoids which represent a class of important antioxidants, anti-inflammatory, antitumor, antiviral vasoprotective, and antifungal. A significant role of anthocyanins and flavonoids that have been under very active research recently, is their possible beneficial influence on human health. Anthocyanins and flavonoids have been found to own potent antioxidant and free radical scavenging activities *in vitro*. There is growing evidence from human consumption studies supporting a protective role of flavonoids in cardiovascular diseases and cancer. In recent years, many papers have been

published on the *in vitro* antioxidant activity of anthocyanins and flavonoids and their other functions, as well as studies assessing the correlation between their antioxidant capacity and chemical structure. Some of the extract and individual compounds isolated from the genus *Vaccinium* have showed apparently biological activities. For example, the extract of bog whortleberry were excellent antioxidants (inhibition > 90%) against the oxidation of human LDL at both concentration (2.5 and 7.5 $\mu\text{g}/\text{mL}$) and the extract of fruit or leaf extracts of *Vaccinium* spp., were found to induce apoptosis in cancer cells and to inhibit human leukemia and breast, colon, lung, and prostate cancer cells *in vitro*. However, because of the wide variety of different flavonoids, their possible interactions with other substances, and the complexity of their metabolism in the human system, more research in this area is still needed. As the leaves and fruits of *Vaccinium* species are a rich source of phenolic compounds, they can in the future serve as a commercial

source of specific compounds or fractions for pharmaceuticals, cosmetics and natural product markets.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

CFA	=	Capillary filtration of albumin
CHI	=	Chalcone isomerase
COX-2	=	Cyclooxygenase-2
DPPH	=	2,2-Diphenyl-1-picrylhydrazyl
HSCs	=	Hematopoietic stem cells
I κ B α	=	Inhibitor Kappa B alpha
LDL	=	Low density lipoproteins
NOD	=	Non-obese diabetic
RBC	=	Red blood cells
RRAC	=	Oxygen radical absorbance capacity
TGF- β 1	=	Transforming growth factor-beta-1
TNF- α	=	Tumor necrosis factor-alpha
TOSC	=	Total oxidant scavenging capacity

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