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Review Article

Vaccinium vitis-idaea L.: Chemical Contents, Pharmacological Activities

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Abstract

One of the most known species of the genus *Vaccinium* (Ericaceae) is *Vaccinium vitis-idaea* L. or lingonberry. Leaves are included in the State Pharmacopoeia of the Russian Federation (XIV-th edition) and the State Pharmacopoeia of the Republic of Belarus (II-nd edition). The aim of this review is an analysis of data about a chemical content and types of pharmacological activities of *Vaccinium vitis-idaea* L. to discuss the tendency of future investigations on this plant. The main parts of works describe researches of chemical contents of fruits as medicinal and edible plant material. The majority of researches describe results of *in vitro* experiments. A significant interest is the study of the neuroprotective activity of the *Vaccinium vitis-idaea* extracts as well as their anti-cytokine and antiapoptotic properties and metabolic effects. The main biologically active compounds are phenologlycosides, tannins, proanthocyanes, saponins etc. These results will be of great significance for the development of new drugs from this plant and use along with the fruits of other parts of the plant.

Introduction

Some well-known medicinal plants can be interesting for a detailed investigation. These plants are included in the State Pharmacopeias of different countries and have a broad medical application, but a study of qualitative and quantitative chemical compositions of the groups of substances other than those responsible for the main pharmacological effect, as well as the study of new and not well-known therapeutic effects, is promising and relevant. Many species of genus *Vaccinium* L. are known as medicinal and edible plants.

The genus *Vaccinium* comprises more than 100 species, 11 of them grow among the *flora* of Russia.[1] In a lot of countries, a pharmacopoeia species is *Vaccinium vitis-idaea* L. According to the data of The Plant List (2019), the synonyms of *Vaccinium vitis-idaea* L. are: *Myrtillus exigua* Bubani., *Rhodococcum vitis-idaea* Avrorin., *Vaccinium jesoense* Miq., *Vitis-idaea punctate* Moench., *Vitis-idaea punctifolia* Gray.[2] In different countries, this plant is also named as lingonberry (English), preiselbeere (German), airelles (French).

According to the taxonomy and phylogeny of flowering plants, worked out by A. L. Takhtajan, the genus *Vaccinium* has the following systematic positions:[3] phylum - Magnoliophyta, class - Magnoliopsida, subclass - Dilleniidae, superorder - Dillenianae, order - Ericales; family - Ericaceae, subfamily - Vaccinioideae (tribe: Oxydendreae, Vaccinieae, Gaultherieae), tribe Vaccinieae [genus: *Gaylussacia*, *Vaccinium* (including *Oxycoccus*), *Symphysia*, *Thibaudia*, *Satyria*, *Agapetes* (including *Pentapterigium*), *Didonica*, *Lateropora*, *Notopora*, *Utleya*, *Gonocalyx*, *Dimorphanthera*, *Paphia*, *Cavendishia*, *Orthaea*, *Macleania*, *Psammisia*, *Mycerinus*, *Polyclita*, *Anthopteropsis*, *Ceratostema*, *Semiramisia*, *Oreanthes*, *Siphonandra*, *Pellegrinia*, *Disterigma*, *Sphyrospermum*, *Diogenesia*, *Rusbya*, *Themistoclesia*, *Plutarchia*, *Demosthenesia*, *Anthopterus*, *Costera*].[3]

The latest version of the Angiosperm Phylogeny Group (APG) is APG IV (2016). APG uses the clades which include all taxa in the hierarchic sequence and they have only one match. The family Ericaceae matches the clade Asterids, the order Ericales.[4] *Vaccinium vitis-idaea* L. matches the clade Vaccinium.[5]

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According to S. K.Cherepanov's data[1],11 species occur in the Russian flora, among them 4 species grow in the Caucasus, 4 – in the European part of Russia, 4 – in West Siberia, 10 – in the Russian Fast East.

V. vitis-idaea L. is an evergreen subshrub with a height of 2.5-25 cm. It has round whitish hairy stems and coriaceus, obovate to elliptic leaves. Their tops are flat or daedalous, finely toothed or smooth-margin. The leaves are induplicate, 5-27 mm long and 3-12 mm wide, on a short pubescent petiole 0.5-3 mm long. The leave upper surface is dark green; the lower surface is pale green, waxy with deep-brown scattered glandular dots. Flowers have short reddish pubescent peduncles; at the ends of last-year's branches there are inflorescences in racemes, in short, but thick drooping clusters of 2-8 with a faint but pleasant smell. Calyxes are quadridentate with four short rounded reddish notches, 0.75-1.25 mm long and 0.75-1 mm wide. Corolla is bell-shaped, pale pink, 4-6.5 mm long. It has four petals. There are 8 stamens with pilose anther filaments. Fruits are globose berries carmine in *color* when ripe. Fruits are edible. *V. vitis-idaea* L.'s main bloom time is early summer and late spring (June-July). Its ripening time is September.[6]

Plants with larger leaves (10-30 mm long) occur in Europe and Asia. This variety is named *V. vitis-idaea* var. *vitis-idaea* L., *V. vitis-idaea* subsp. *vitis-idaea* or cowberry. In the North America, lingonberry or V. *vitis-idaea* var. *minus* Lodd. (*V. vitis-idaea* subsp. *minus* (Lodd.) Hultén), has leaves 5–18 mm long.[7]

Use in Traditional Medicine

Fruits of lingonberry are used as medicinal and edible plant materials. Fruits are used in jams, juices, vines, pies.[8] Other plant parts are also used in medicine.

Vaccinium vitis-idaeae L. was included in the first Russian Pharmacopoeia.[9] Leaves are included in the Russian State Pharmacopoeia (XIVth edition). At the pharmaceutical marker there is "Brusniver", a polyherbal drug. It includes *Vaccinium vitis-idaea* L. leaves (50%), herbs of *Hypericum perforatum* L. and *Bidens tripartita* L. (20% and 10%, respectively), fruits of *Rosa* spp. L. (10%). The data on clinical trials of this complex drug are insufficient. Usually, it is used as infusion for treatment of diseases of the genitourinary system, cystitis, genitourinary infection, urethritis.[10]

In the Encyclopedia of Traditional Chinese Medicine, *V. vitis-idaea* is represented as a source of 6-O-acetylarbutin, arbutin (its content in leaves is about 4%), avicularin, 2-O-caffeoyl arbutin, cyanidin-3-O-β-D-galactoside, (−)-epicatechin, hydroquinone, 4-hydroxyphenyl-β-gentiobioside, proanthocyanidin A2, procyanidin B1, B3, B7, rhodioloside. To reduce strangury and urinary disorders, leaves of the plant are used as an antitoxic agent.[11]

Leaves have astringent, antiseptic, diuretic, anti-fever, anti-inflammatory effects; fruits and leaves can show a metabolite activity, have anti-fever, reparative, analgesic, sedative, detoxifying effects. Shoots are known as a homeopathic remedy.[12] Fruits are used to treat diabetes, gastric and intesinal ulcers, liver diseases, periodontosis, hypertension, eczema, dermatophytosis, diathesis, respiratory infections, gastric and skin cancers, eye diseases, rheumatism, neurasthenia.[12,13]

Chemical Composition

In different aerial parts of *Vaccinium vitis-idaea* L., phenologlycosides, phenylpropanoids, anthocyanes, saponins have been found out by researches from different countries; and in fruits, the content of anthocyanes has been established.

Phenols, phenologlycosides, coumarins

Munich scientists Friedrich and Schoenert[14] collected *Vaccinium vitis-idaea* L. fruits and leaves from April to August. Aqueous and methanol extracts were prepared from fruits and leaves and then analyzed by thin-layer chromatography (TLC) and column chromatography (CC). It turned out impossible to isolate hydroquinone-β-D-glucopyranoside (arbutin) and hydroquinone using either polyamide or silica gel. The presence of these compounds was established by TLC after post processing of the chromatogram with diazotized sulfanilic acid and saturated sodium carbonate solution. The investigation resulted in the conclusion that *Vaccinium vitis-idaea* L. leaves contain arbutin and hydroquinone. The optimal period of harvesting is August. The authors also claim that *Vaccinium vitis-idaea* L. can hybridize with other species of the *Vaccinium* genus and form intermediate hybrid forms.

In 1979 Swiss scientists Sticher *et al.*[15] developed methods of phenolic analysis using high-performance liquid chromatography (HPLC). In *Vaccinium vitis-idaea* L. leaves they detected 3-5% of arbutin and 0.14-0.20% of hydroquinone. It was established that if the amount of hydroquinone increased, the amount of arbutin decreased. Neither methylarbutin nor hydroquinonemonomethyl were detected in the leaves.

In 2005-2006 Pyka *et al.*[16] collected *Vaccinium vitis-idaea* L. leaves which are a pharmacopoeia plant material in Poland. The leaves were air-dried. A spectrodensitometric method for the determination of arbutin was worked out by the scientists. The aqueous-methanol extract (1:1, v/v) of leaves was applied onto the chromatographic plate and detected at λ_{max} = 285 nm. The amount of arbutin in 1 g of the raw material (air-dried leaves) was 35 mg/g (2005) and 47 mg/g (2006). This method was proposed as a pharmacopoeia method (the Polish Pharmacopeia, IV-th edition).

Wang et al.[17], scientists of *Heilongjiang University* (2005), obtained an aqueous-alcohol extract from *V. vitis-idaea*. leaves. Its analysis resulted in the isolation of arbutin and coumarin fraxetin-8-O-glucoside (fraxin).

Liu *et al.*[18] (2014) collected *V. vitis-idaea* leaves in the flora areas of Turkey and Finland from the end of June to the middle of September. The leaves were collected every 10-th day and subjected to freezing with liquid nitrogen. The acetone, chloroform, aqueous-alcohol extracts from the leaves were subjected to the analytic investigation. In the obtained fractions, the entire phenolic complex, including phenolic glycosides, was analyzed. The use of HPLC resulted in the detection of arbutin and 2-O-caffeoylarbutin. The lowest amount of arbutin was detected on 30 June, the highest – on 18 July; the lowest amount of 2-O-caffeoylarbutin was registered on 29 August (9 mg/g of dry mass), the highest – on 18 July (14 mg/g of dry mass).

Raudone *et al.*[19] (2019) published the results of the investigated phenolic profile in the several cultivars of *V. vitis-idaea* L. and the antioxidant activity of cultivars leaves. In their opinion, in the accumulation of phenolic compounds, an important role is played by such external factors as light, sun rays, temperature, type of soil, methods of cultivation, insects; and the internal factor - the genetic background. These factors and, to a greater extent, the genetic diversity, cause variability even within the same species. That was why in this work 10 different cultivars were analyzed. They were: «Sussi», «Erntekrone», «Masovia», «Koralle», «Kostromskaja rozovaja», «Sanna», «Rubin», «Kostromicka», «Erntesegen», «Erntedank»;1 subspecies (*V. vitis-idaea* subsp. *minus*) and 1 *Vaccinium vitis-idaea* L. variety (*V. vitis-idaea* var. *leucocarpum)*. Qualitative and quantitative analyses of phenolic compounds in *Vaccinium vitis-idaea* L. leaves, were carried out by HPLC Photo-Diode Array (HPLC-PDA). The analyses have resulted in the conclusion that in *Vaccinium vitis-idaea* L. leaves the main compounds are simple phenols, flavonoids, proanthocyanidines and hydroxycinnamic acids. The highest amount of arbutin (mg/g dry weight or mg/g DW)was established in the following cultivars: "Kostromskaja rozovaja" (56.968±2325.73 mg/g DW), "Rubin" (36.059±1472.12 mg/g DW) and *V. vitis-idaea* subsp. *minus* (28.708±1172.03 mg/g DW). Arbutin was the main compound in all *Vaccinium vitis-idaea* cultivars and taxa. Its quantity was about 41-78% of the total amount of phenolic compounds (Figure 1).

Flavonoids

Several flavonoids: quercetin, quercitrin, isoquercitrin and quercetin-3-arabinoside, were isolated from *Vaccinium vitis-idaea* L. leaves by Friedrich and Schöenert.[14]

Ek *et al.*[20] published data about the chemical composition of *Vaccinium vitis-idaea* L fruits, leaves and shoots collected in the west of Finland in summer and autumn of 2004. Ethanol, acetonitrile and methanol extracts were obtained by the authors. The methanol extract contained the highest amount of phenolic compounds from *Vaccinium vitis-idaea* L fruits, leaves and shoots. The ultrasound homogenisator was used for the best yield of phenolic compounds. After that the methanol extract was subjected to centrifugation. Before the analyzis by HPLC, the obtained extracts were diluted in water in the ratio of 1:2 .

According to the mass-spectrometry (MS) data and the subsequent proton nuclear magnetic resonance (proton NMR) detection of the substances, 28 compounds of the phenolic nature were detected. Ten of them referred to flavonoids: [hyperoside (quercetin-3-O-β-galactoside), isoquercitrin (quercetin-3-O-β-glucoside), quercetin-O-(hexose-deoxyhexoside), reynoutrin (quercetin-3-O-β-xyloside), quecetin-3-O-α-arabinopyranoside, avicularin (quercetin-3-O-α-arabinofuranoside), quercitrin (quercetin-3-O-α-rhamnoside), quercetin-3-O-(4"-3-hydroxy-3-methylglutaroyl)-α-rhamnoside, kaempferol-pentoside, kaempferol-deoxyhexoside, kaempferol-(3-hydroxy-3-methylglutaroyl]. The above-listed compounds

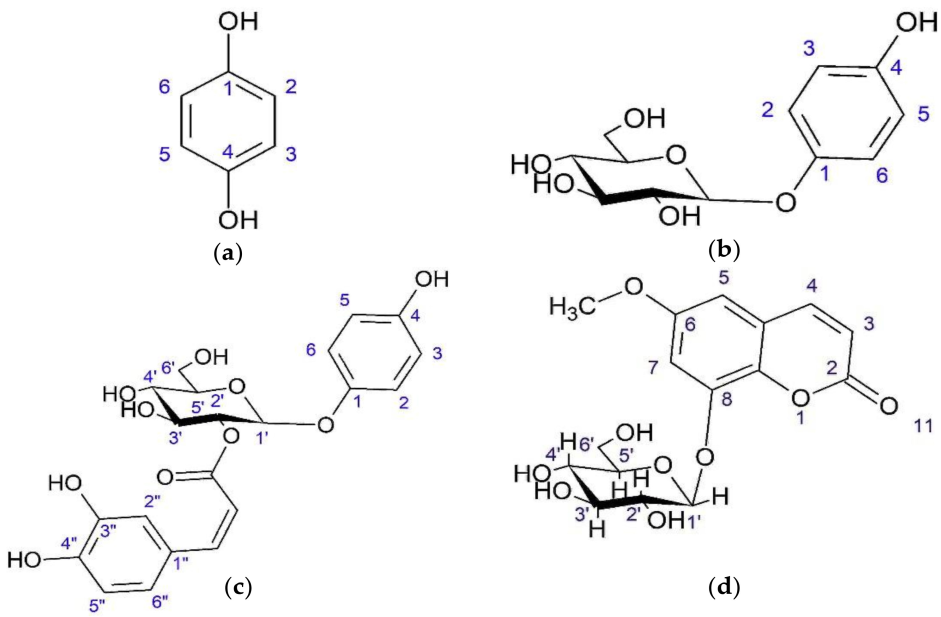


Figure 1. Phenols, phenologlycosides, coumarins from *Vaccinium vitis-idaea* L.: (**a**) hydroquinone; (**b**) arbutin; (**c**) 2-o-caffeoylarbutin; (**d**) fraxin.

were also detected in the fruits and leaves with stems.

Liu *et al.*[18] identified 12 compounds referring to flavonoids, by methods of HPLC-diode array (HPLC-DAD), HPLC-MS, gas chromatography-flame ionization detector (GC-FID), protone NMR. Ten of them were previously discovered and three were detected in this plant material for the first tme: rutin (quercetin-3-O-rutinoside), quercetin-3-O-glucuronide, kaempferol-3-O-glucuronide. The lowest total amount of flavonoids was detected on 29 August, the highest – on 12 September. In content, the main compounds in *Vaccinium vitis-idaea* L. leaves were the following: hyperoside, quercetin-3-O-arabinoside, quercetin-3-O-rhamnoside. The total amount of flavonoids was 15-20 mg/g.

Lätti *et al.*[21] identified flavonoids in *Vaccinium vitis-idaea* L. leaves. They detected the above listed compounds and also discovered 3,5,7-trihydroxy-2-(4-hydroxy-3,5-methoxyphenol)-4H-chromen-4-on (syringetin hexoside). The authors claim that when grown together, *Vaccinium myrtillus* and *Vaccinium vitis-idaea* can form a natural species hybrid *Vaccinium* x *intermedium* Ruthe.

Riihinen *et al.*[22] extracted juice from *Vaccinium vitis-idaea* L fruits collected in Finland. After the isolation of flavonoids by CC with the help of Sephadex LH-20 gel, methods of HPLC–PDA and NMR were used. Seven flavonoids such as quercetin-3-O-[4”-(3-hydroxy-3-methylglutaroyl)]-α-rhamnoside, quercetin-3-O-α-rhamnoside, quercetin-3-O-β-glucoside, quercetin-3-O-β-galactoside, quercetin-3-O-α-arabinofuranoside, quercetin-3-O-α-xylopyranoside, quercetin-3-O-α-arabinopyranoside, were identified in *Vaccinium vitis-idaea* L juice. Later the authors identified quercetin-3-O-β-galactopyranoside.[23]

Dróżdż *et al.*[24] extracted two substances from *V. vitis-idaea* fruits using ethanol (deionization water and ethanol 60:40, v/v). In the aqueous extract, the total amount of flavonoids was higher (2.55-3.53 μmole catechin equivalent to (CE)/g fresh weight of fruit) than anthocyanes (0.34-0.41 mg of cyanidin-3-glucoside equivalent to (C3G)/g fresh weight of fruit). The yield of flavonoids was twice higher when the aqueous-ethanol solvent was used.

Later the authors obtained ethanol (ethanol-water 60:40 v/v) and ethyl acetate extracts from *V. vitis-idaea* fruits cultivated in Poland.[25] The total amount of flavonoids was 53.2-67.8 μmole CE/100 g from the fruits using the ethanol-water mixture and 40.7–62.9 μmole CE/100 g using the ethyl acetate solvent.

In *V. vitis-idaea* L. fruits,[26] the portion of flavonoids is 7% of all phenols.

Raudone *et al.*[19] established that in the above listed *Vaccinium vitis-idaea* L. cultivars and taxa, the principle components of the flavonoids are hyperoside, avicularin, quercetin and, in smaller amounts, astragalin. The highest amount of hyperoside (mg/g dry weight or mg/g DW) was registered in *V. vitis-idaea* subsp. *minus* (5771.34±235.61 mg/g of DW) and *V. vitis-idaea* var. *leucocarpum* (5503.44±224.6 mg/g DW); avicularin in *V. vitis-idaea* var. *leucocarpum* (5503.44±224.68 mg/g DW; quercetin in ”Koralle” cultivar (7826.68±319.52 mg/g DW); astragalin in “Rubin” cultivar (120.60±4.92 mg/g DW) and “Kostromskaja rozovaja” (114.67±4.68 mg/g DW).

The data about flavonoids from *V. vitis-idaea* are presented in Table 1.

Proanthocyanes

Ho *et al.*[27] isolated such tannins as procyanidin B1, procyanidin B3, procyanidin A1, cinnamtannin B1, epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-catechin, epicatechin-(4β→6)-epicatechin-(4β→8, 2β→O→7)-catechin from *Vaccinium vitis-idaea* L. leaves and fruits by Morimoto’s method (1988). *In Vaccinium vitis-idaea* L. fruits, the amount of proanthocyanines was 71% of the total amount of phenols; the major compound was trimer A-type.[22] Later Riihinen *et al.*[28,29] identified (+)-catechin and (-)-epicatechin in the *Vaccinium vitis-idaea* L. fruit juice (Figure 2).

Raudone *et al.*[19] detected qualitative and quantitative contents of (+)-catechin, (-)-epicatechin, procyanidin C1, procyanidin A2 in *Vaccinium vitis-idaea* L.cultivars and taxa listed above. In “Masovia” cultivar, the amount of (+)-catechin was 2954.64±120.62mg/g (DW) and in “Kostromskaja rozovaja” it was 2273.92±92.83 mg/g (DW); (-)-epicatechin was detected in “Kostromskaja rozovaja” in the amount of 743.67±30.36 mg/g (DW) and in “Rubin” - 669.11±27.32 mg/g (DW); in V. vitis-idaea var. leucocarpum procyanidin C1 was in the amount of 4645.97±189.67 mg/g; in V. vitis-idaea subsp. Minus procyanidin A2 was in the amount of 7074.60±288.82 mg/g; in ”Erntekrone“ - 3609.57±147.36 mg/g (DW). and in “Masovia” - 3554.68±145.12 mg/g (DW).

Anthocyanes

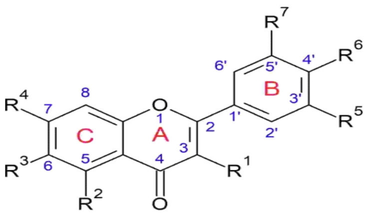
Viljanen *et al.*[30] detected such anthocyanes as cyaniding-3-glucoside, cyaniding-3-galactoside, cyaniding-3-arabinoside in *Vaccinium vitis-idaea* L. fruits by HPLC. Ek *et al.*[20] detected proanthocyanidines and cyanidines in *Vaccinium vitis-idaea* L. fruits and leaves. Anthocyanes were not detected in the leaves with shoots.

Later Dudonne *et al.*[31] confirmed these data and also added new information on the quantitatively content of each anthocyane in their total amount. Cyanidin-3-galactoside was represented by 58%, cyaniding-3-arabinoside – by 35% and cyaniding-3-glucoside – by 7% from the total amount of anthocyanes. According to the data in one of the works,[26] paeonidin-3-glucoside was also detected in the amount 4.2%. Anthocyanes are presented by 15% from the total amount of of phenols.[26]

The United States Department of Agriculture (USDA), Agricultural Research Service (ARS), Horticultural Crops Research Unit (HCRU) recommended to standardize *Vaccinium vitis-idaea* L. fruits by the amounts of the three anthocyanes described above because there are already several cases of adulteration of these valuable plant materials.[32]

Brown *et al.*[33] used 1% formic acid in methanol to extract

Table 1. Flavonoids from *Vaccinium vitis-idaea* L.



No	Name	Type of flavonoids	R¹	R²	R³	R⁴	R⁵	R⁶	R⁷	Glycoside
1	Quercetin	Flavonol quercetin	OH	OH		OH	OH	OH		
2	Quercitrin		3-O-α-L-rhamnoside	OH		OH	OH	OH		O-glycoside
3	Isoquercitrin		3-O-β-D-glucopyranoside	OH		OH	OH	OH		O-glycoside
4	Guaijaverin, quercetin-3-O-α-L-arabinoside		3-O-α-L-arabinopyranoside	OH		OH	OH	OH		O-glycoside
5	Hyperoside (quercetin-3-O-galactoside)		3-O-β-D-galactoside	OH		OH	OH	OH		O-glycoside
6	Reynoutrin (quercetin-3-O-β-D-xyloside)		3-O-β-D-xyloside	OH		OH	OH	OH		O-glycoside
7	Avicularin (quercetin-3-O-α-L-arabinofuranoside)		3-O-α-L-arabinofuranoside	OH		OH	OH	OH		O-glycoside
8	Quercetin-3-O-[4″-(3-hydroxy-3-methylglutaroyl)]-R-rhamnose		3-O-[4″-(3-hydroxy-3-methylglutaroyl)]-R-rhamnose	OH		OH	OH	OH		O-glycoside
9	Rutin (quercetin-3-rutinoside)		3-O-β-D-rutinoside	OH		OH	OH	OH		O-glycoside
10	Quercituron (quercetin 3-O-β-D-glucuronopyranoside)		3-O-β-D-glucuronopyranoside	OH		OH	OH	OH		O-glycoside
11	Isorhamnetin-3-O-glucoside	Flavonol 3-methyl-quercetin	3-O-β-D-glucopyranoside	OH		OH	OCH_3	OH		O-glycoside
12	Kaempferol-pentoside	Flavonol kaempferol	3-O-pentoside	OH		OH		OH		O-glycoside
13	Kaempferol-deoxyhexoside		3-O-hexoside	OH		OH		OH		O-glycoside
14	Kaempferol-(3-hydroxy-3-methylglutaroyl) rhamnoside		(3-hydroxy-3-methylglutaroyl)rhamnoside	OH		OH		OH		O-glycoside
15	Nicotiflorin (kaempferol-3-O-β-rutinoside)		3-O-β-rutinoside	OH		OH		OH		O-glycoside
16	Astragalin (kaempferol-3-O-β-D-glucopyranoside)		3-O-β-D-glucopyranoside	OH		OH		OH		O-glycoside
17	Kaempferol-3-O-glucuronide		3-O-β-D-glucoronopyranoside	OH		OH		OH		O-glucoside
18	Syringetin hexoside (3',5'-O-dimethylmyricetinhexoside)	Flavonol myricetin	Hexoside	OH		OH	OCH_3	OH	OCH_3	O-glycoside

anthocyanes from *Vaccinium vitis-idaea* L. fruits, then the extract was centrifuged. The residue was separated, subjected to the process of extraction again by the same solvent, and then centrifuged. All the supernatants were united and evaporated to dryness under vacuum. Then the residue was analyzed by HPLC-MS/MS. The anthocyanes were detected at the wavelength of 520 nm.

The study resulted in the identification of cyaniding-3-O-galactoside, cyaniding-3-O-glucoside, cyaniding-3-O-arabinoside. Other anthocyanes were found out

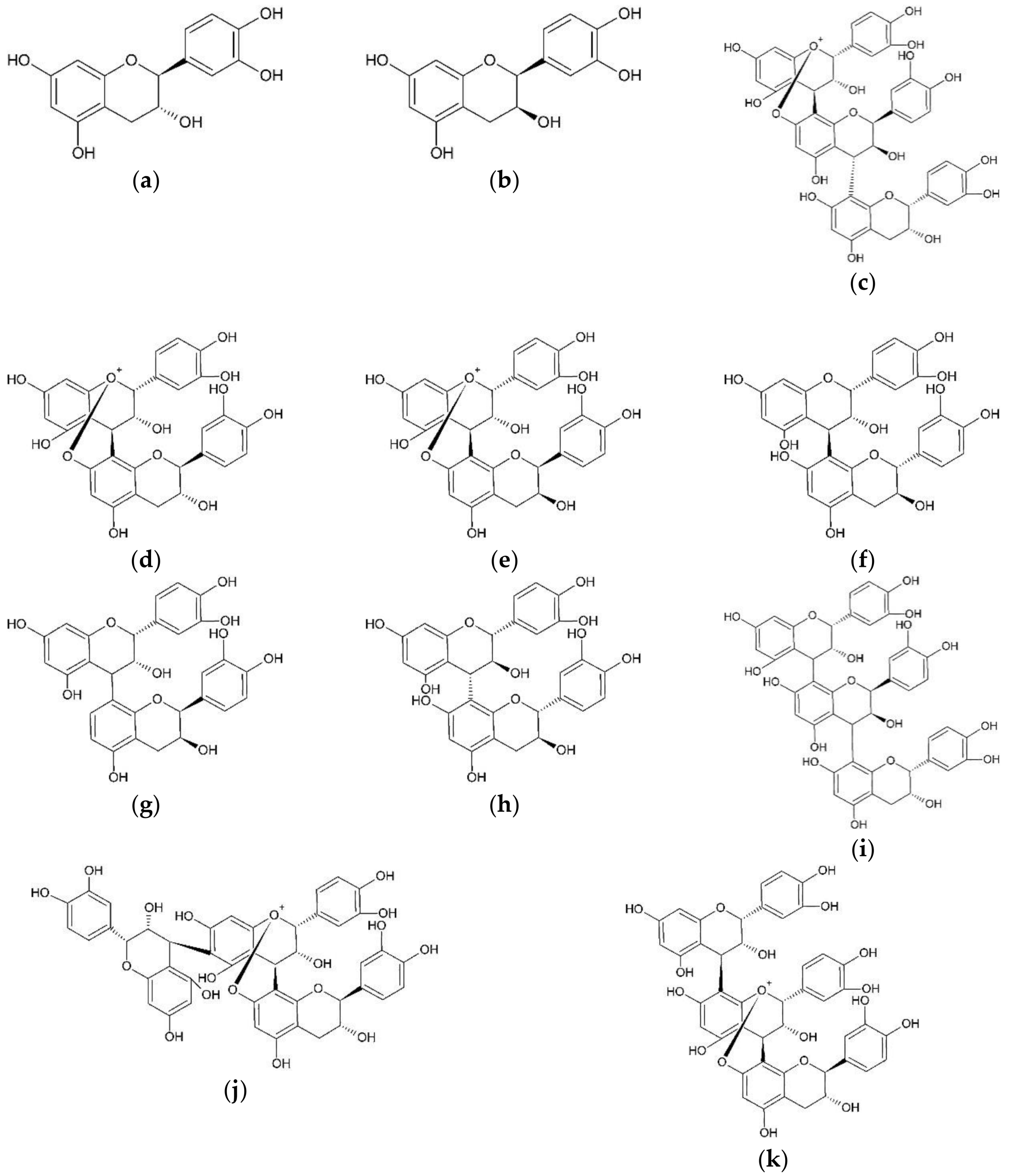


Figure 2. Proanthocyanines from *Vaccinium vitis-idaea* L.: (**a**) (+)-catechin; (**b**) (-)-epicatechin; (**c**) cinnamtannin B1; (**d**) proantocyanidin A1; (**e**) proantocyanidin A2; (**f**) proantocyanidin B1; (**g**) proantocyanidin B2; (**h**) proantocyanidin B3; (**i**) proantocyanidin C1; (**j**) epicatechin-(4β→6)-epicatechin-(4β→8, 2β→O→7)-catechin; (**k**) epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-catechin.

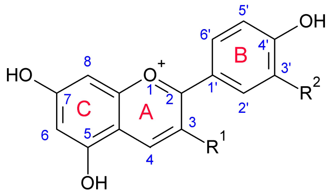
in low concentrations: cyaniding-3-O-sambubioside, pelargonidin-3-O-glucoside, paeonidin-3-O-galactoside, paeonidin-3-O-glucoside, cyanidin-3-O-xyloside, cyanidin-3-O-(6"-O-acetyl)glucoside (Table 2).

Hydroxycinnamic acids

Ek *et al.*[20] isolated 4 hydroxycinnamic acids (ferulic acid [3-methoxy-4-hydroxycinnamic acid], caffeoyl-hexose-hydroxyphenol, coumaroyl-hexose-hydroxyphenol, 2"-caffeoylarbutin] from *V. vitis-idaea* fruits, leaves and shoots. The last compound was found only in the fruits.

Hokkanen *et al.*[34] investigated chemical contents of *V. vitis-idaea* and the intermediate hybrid form *Vaccinium* x *intermedium* Ruthe L. (hybrid bilberry). The leaves with

Table 2. Anthocyanes from *Vaccinium vitis-idaea* L.



No	Name	R¹	R²
	Cyanidin-3-O-β-D-glucoside	3-O-β-D-glucopyranoside	OH
	Cyanidin-3-O-β-D-galactoside	3-O-β-D-galactoside	OH
	Cyanidin-3-O-β-D-arabinoside	3-O-β-D-arabinoside	OH
	Peonidin-3-O-β-D-glucoside	3-O-β-D-glucopyranoside	OCH_3
	Cyanidin-3-O-sambubioside (Cyanidin 3-xyloglucoside)	3-O-β-D-xylopyranosyl-(1-2)-β-D-glucopyranoside	OH
	Pelargonidin 3-glucoside (callistephin)	3-O- β -glucopyranoside	H
	Peonidin 3-O-β-D-galactoside	3-O-β-D-galactoside	OCH_3
	Cyanidin 3-O-xyloside	3-O-β-xylofuranoside	OH
	Cyanidin-3-O-(6''-acetyl)glucoside)	3-O-(6-O-acetyl-β-D-glucopyranoside)	OH

stems were collected in summer and autumn of 2005-2006 in the flora area of southern Finland. The plant materials were extracted by methanol. The analysis was carried out by ultra-performance liquid chromatography coupled with time-of-fight mass spectrometry (UPLC-TOF-MS).

In total, 51 phenolic compounds were identified. For the first time ever, caffeoyl- shikimic acid and caffeic acid, trans-chlorogenic acid, cis-chlorogenic acid, p-cumaric acid and iridoid - coumaroyl iridoid (vaccinoside) were detected. In *V. vitis-idaea* L. leaves with shoots, the contents of hydroxycinnamic acids was 24.4% from the total amount of phenolic compounds; the total amount of iridoids was 7.5%.

Ieri *et al.*[35] collected a few species of the genus *Vaccinium* (Ericaceae) including *V. vitis-idaea* in the period from 2009 to 2011, The plants were collected in the flora area of Italy, the plant materials were young and *mature* leaves of *V. vitis-idaea* L. They were used for the preparation of aqueous-glycerol-alcohol extracts which were analized then by HPLC-DAD. In these extracts the following phenolic compounds were identified: flavonoids, phenylpropanoids, phenologlycosides, coumarines. Several new flavonoids were also identified.

In the leaves and shoots, there were the following compounds: trans-5-O-caffeoyl-quinic acid (trans-chlorogenic acid), caffeoyl-hexose-hydroxyphenol, p-coumaroyl arbutin, p-coumaroyl acetyl arbutin, 2-O-caffeoyl arbutin, 4-O-caffeoyl-quinic acid (cryptochlorogenic acid), caffeoyl iridoid, coumaroyl iridoid. Coumarin – fraxetin-8-O-glucoside which had been identified before, was also found out in the leaves and shoots.

As for the content of biologically active substances in *Vaccinium vitis-idaea* L. leaves, the main group of them was represented by phenologlycosides. The main compound was arbutin, its highest amount was detected in the young leaves. The second group was represented by hydroxycinnamic acids, the third one – by flavonoids. Anthocyanes were not identified in the leaves. Previously, Ehala *et al.*[36] found out cinnamic acid (41.2 ± 2.36 μg/g of frozen berry extract) in *Vaccinium vitis-idaea* L. fruits by methods of capillary electrophoresis.

According to the data in the work by Zheng W,[37] in *V. vitis-idaea* L. berries caffeic acid was also present (6.2%). Hydroxycinnamic acids are represented by 7% from the total amount of phenolic compounds in *Vaccinium vitis-idaea* L. fruits.

Raudone *et al.*[19] established the contents of chlorogenic acid and cryptochlorogenic acid in *V. vitis-idaea* L. cultivars and taxa listed above. The highest amount of chlorogenic and cryptochlorogenic acids was in *V. vitis-idaea* var. *leucocarpum* leaves (954.03±38.95 mg/g DW and 1025.34 ± 41.86 mg/g DW, respectively).

The data about hydroxycinnamic acids from *V. vitis-idaea* are given in Table 3.

Stilbenes

Rimando *et al.*[38] published experimental data on the content of stilbenes in *V. vitis-idaea* fruits (Figure 3).

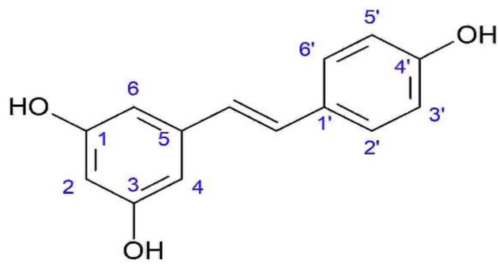
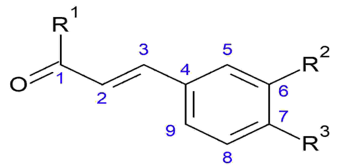


Figure 3. Stilbenes from *Vaccinium vitis-idaea* L.: Resveratrol.

Lyophilisate from fresh fruits was extracted by the mixture of methanol-acetone-acetic acid (40:40:20:0.1, v/v/v/v), then the extract was condensed under vacuum. The obtained aqueous extract was then repeatedly subjected to extraction by ethyl acetate. The ethyl acetate extracts were mixed up and evaporated to dryness under vacuum.

Table 3. Hydroxycinnamic acids from *Vaccinium vitis-idaea* L.



No	Name	R¹	R²	R³
1	Ferulic acid (4-hydroxy-3-methoxycinnamic acid)	OH	OCH_3	OH
2	Cinnamic acid	OH	H	H
3	Caffeic acid	OH	OH	OH
4	Caffeoyl-hexose-hydroxyphenol (6-O-Caffeoylarbutin)	6-O-arbutin	OH	OH
5	Coumaroyl-hexose-hydroxyphenol (4-O-E-coumaroy-larbutin)	4-O-arbutin	H	OH
6	2-O-Caffeoylarbutin	2-O-arbutin	OH	OH
7	Caffeoylshikimic acid (dactylifric acid)	3-O-4,5-dihydroxycyclohex-1-ene-1-carboxylic acid	OH	OH
8	Trans-chlorogenic acid (trans-5-caffeoyl-quinic acid	5-O-1,3,5-trihydroxycyclohex-1-carboxylic acid	OH	OH
9	Cis-chlorogenic acid (cis-5-caffeoyl-quinic acid)	5-O-cis-1,3,4-trihydroxycyclohex-1-carboxylic acid	OH	OH
10	Chlorogenic acid (3-O-caffeoylquinic acid)	trans-3-O-quinic acid	OH	OH
11	P-coumaric acid (4-hydroxycinnamic acid)	OH	H	OH
12	Coumaroyl iridoid (Vaccinoside, 10-p-trans-couma-royl-1S-monotropein)	1S-monotropein	H	OH
13	Cryptochlorogenic acid (4-O-trans-caffeoylquinic acid)	4-O-1,3,5-trihydroxycyclohex-1-carboxylic acid	OH	OH

The evaporated residue was diluted in water, and in the form of suspension it was placed into column C18 (Waters Scientific, Mississauga, ON). The process of elution was carried out, first, with water used as eluent, then with a mixture of methanol-acetone-water-formic acid (40:40:20:0.1, v/v/v/v). The fractions were analyzed by gas-liquid chromatography-mass spectrometry (GLC-MS). The amount of resveratrol was 5884 ng/g dry sample.

Ehala *et al.*[36] collected *Vaccinium vitis-idaea* L. fruits in the vicinities of Tallinn (Estonia) in 2005. The fruits were subjected to extraction by the mixtures of methanol-water (50:50 and 70:30, v/v) and ethanol-water (70:30, v/v). The obtained extracts from the fresh fruits were analyzed by capillary electrophoresis, using sodium tetraborate (pH 9.3) with 5% methanol as a buffer solution, 20 kV voltage, the temperature of 25°C and the detection at 210 nm. The analysis time was 5 minutes. The amount of trans-resveratrol in *Vaccinium vitis-idaea* L. frozen fruits was 30.00±2,8 μg/g.

Saponins

Szakiel and Mroczek[39] collected *Vaccinium vitis-idaea* L. rhizomes, stems, fruits and leaves in Poland (2004). The plant materials were shade dried at 40°C, ground and then placed into the *Soxhlet apparatus* All the parts of the plant were subjected to the sequential extraction separately using diethyl ether and methanol. Then the methanol extract was condensed, diluted in water and extracted by n-butanol.

The compounds were separated by CC using silica gel. The compounds were eluted and then hydrolyzed by Kiliani mixture (hydrochloric acid/acetic acid/water in the ratio of 10: 35: 55, v/v/v) at 100°C for 2 hours. Then the compounds were identified by MS and GC. At all parts of *Vaccinium vitis-idaea* L. there was 3β-hydroxy-olea-12-en-28-oic acid (oleanolic acid) and its isomer 3β-hydroxy-urs-12-en-28-oic acid (ursolic acid).

In Vaccinium vitis-idaea L., the content of free triterpene acids, i.e. oleanolic acid, was the following: in fruits - 1.005%, in leaves - 0.61%, in shoots - 0.32%, in rhizomes - 0.35%. The content of ursolic acid at the lingonberry was 0.71% (fruits), 0.41% (leaves), 0.24% (shoots), 029% (rhizome).[39]

Szakiel *et al.*[40] identified triterpene acids in the young and mature leaves collected in the flora area of Finland and Poland in the August (fruits and leaves) and December (only leaves) in 2010. The plant materials were extracted with diethyl ether. The extract was then hydrolyzed with 10% NaOH in 80% MeOH at 80 °C for 3 hours. The residue was diluted with water (1:5, v/v), then the solution was neutralized with 5% CH3COOH. After that the solution was extracted with diethyl ether. The isolated triterpene acids and sterines were analyzed by TLC and identified by GC-MS. Lupeol and α-amyrin were identified by HPLC. Thus, the following compounds were identified in the young and mature leaves from Finland (**1**) and Poland (**2**) (Figures 4 and 5):

1. Neutral triterpenoids (α-amyrin, β-amyrin, betulin, cycloartanol, erythrodiol, fer-7-en-3β-ol, friedelin, lupeol, swert-9(11)-en-3β-ol, taraxasterol, urs-12-en-28-al, uvaol): their total amount was (**1**) 800.0 and (**2**) 1282.5 μg/g dry weight;
2. Triterpenic acids (oleanolic acid, ursolic acid); their total amount was (**1**) 8911.6 and (**2**) 8132.8 μg/g dry weight;
3. Steroids (campesterol, sitosterol, stigmasta-3,5-dien-7-

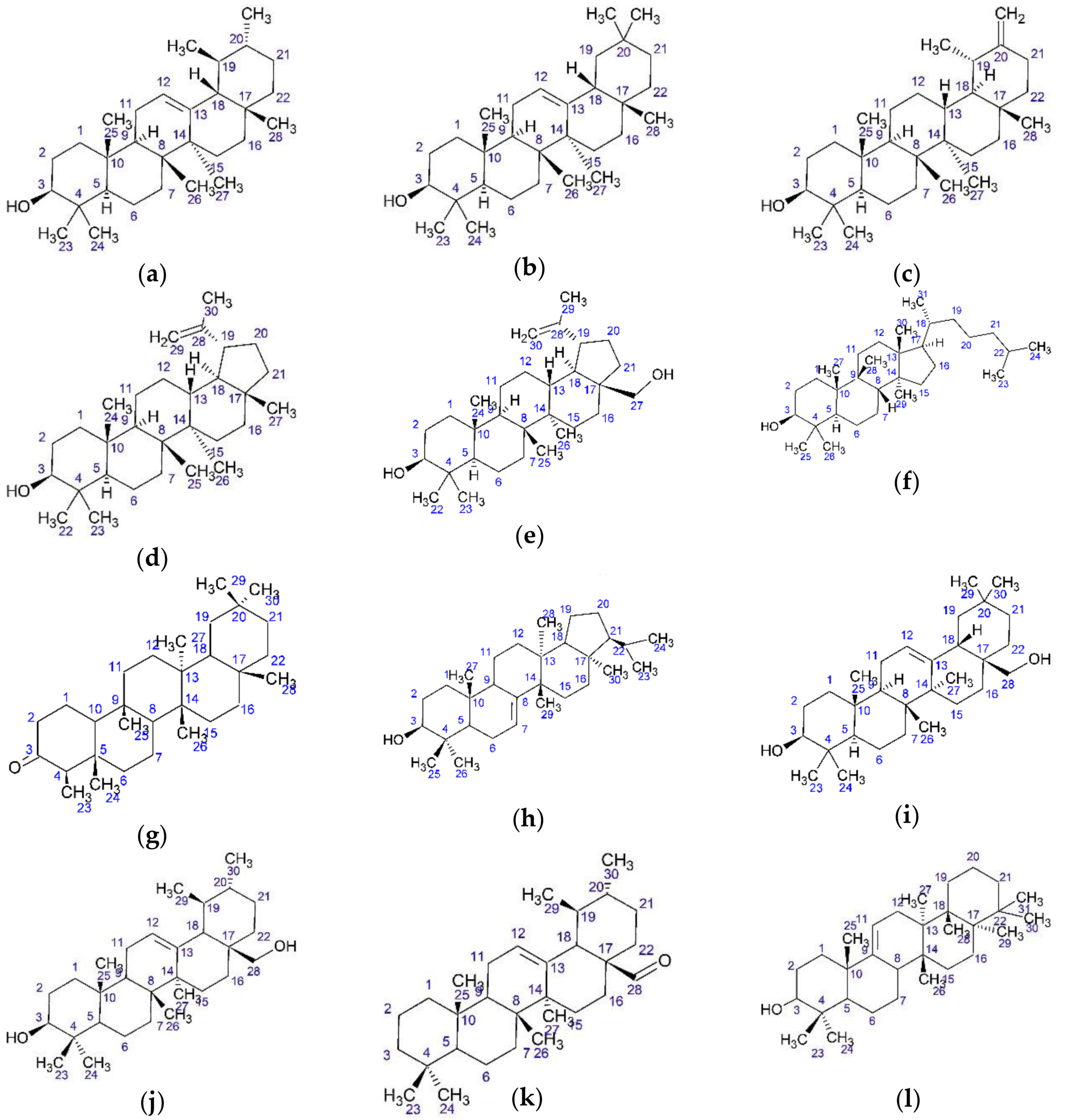


Figure 4. Triterpenes from *Vaccinium vitis-idaea* L.: (**a**) α-amyrin; (**b**) β-amyrin; (**c**) taraxasterol; (**d**) lupeol; (**e**) betulin; (**f**) cycloartanol; (**g**) friedelin; (**h**) fern-7-en-3β-ol; (**i**) erythrodiol; (**j**) uvaol; (**k**) urs-12-en-28-al; (**l**) swert-9(11)-en-3β-ol.

one, stigmasterol); their total amount was (**1**) 1591.0 and (**2**) 1813.6 μg/g dry weight;

4. Ethers (α-amyrin, β-amyrin, fern-7-en-3β-ol, taraxasterol, uvaol, oleanolic acid, ursolic acid, campesterol, sitosterol, stigmasterol); the total amount of the ethers was (**1**) 948.8 and (**2**) 431.9 μg/g dry weight.

The total amount of all saponins was the following: in the young leaves (**1**) 8446.9 μg/g dry weight and in the mature leaves 13693.9 μg/g dry weight; in the young leaves (**2**) 5732.6 and in the mature leaves 13537.09 μg/g dry weight. The plant materials were collected in August 2010. The total amount of saponins in the young leaves was (**1**) 840.4 μg/g dry weight and in the mature leaves - 14998.5 μg/g dry weight; (**2**) the young leaves contained 10514.6 μg/g and the mature leaves – 14075.5 μg/g dry weight.

Qualitative and quantitative contents of saponins depended on both – the area of collection and the time of collection. Taraxasterol was not detected in the young leaves collected in December (Finland), while it was detected in all the materials collected in the flora area of Poland. Uvaol accumulated in the young leaves collected in Finland.[40]

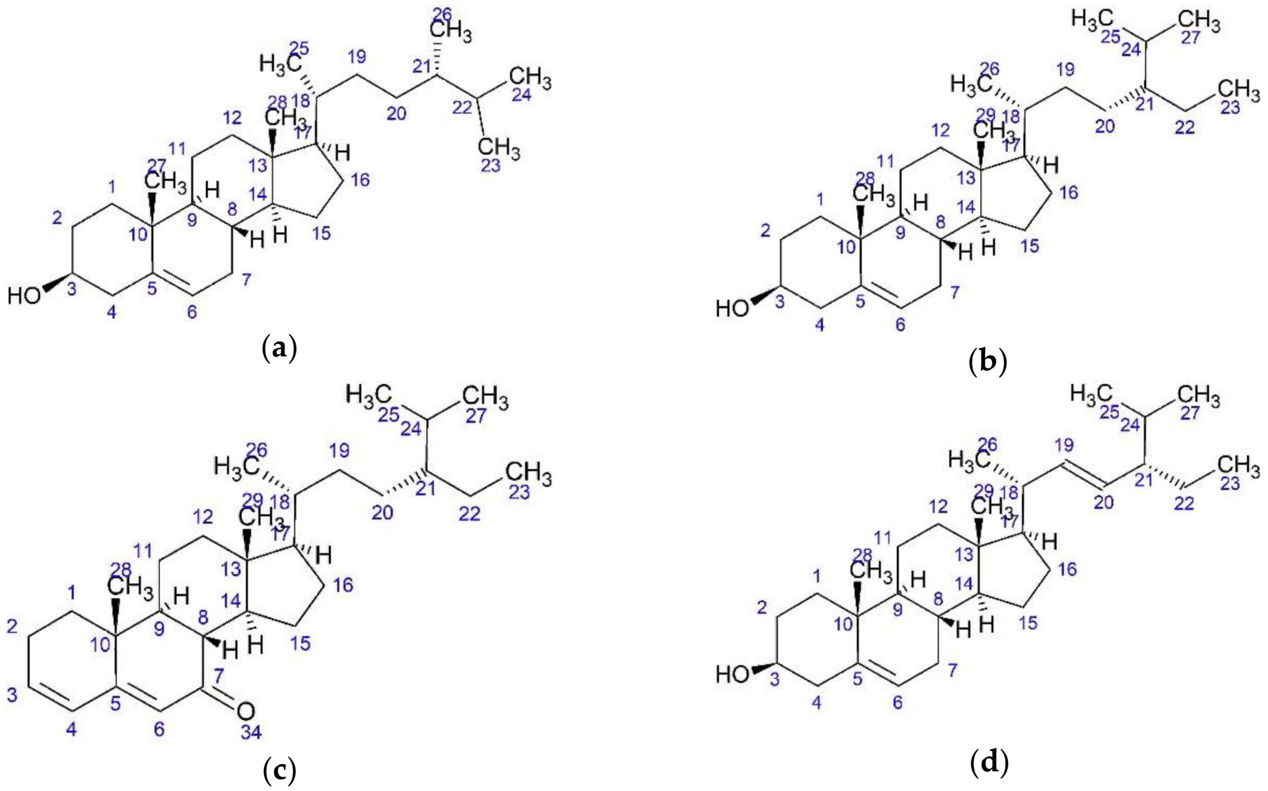


Figure 5. Steroids from *Vaccinium vitis-idaea* L.: (**a**) campesterol; (**b**) sitosterol; (**c**) stigmasta-3,5-dien-7-one; (**d**) stigmasterol.

Essential oil

Radulović *et al.*[41] investigated the composition analysis of *Vaccinium vitis-idaea* L. essential oil. In its leaves 338 compounds were identified (90.4 from the total peaks area - by GLC). The main compounds were: α-terpineol (17.0%), pentacosane (6.4%), (E,E)-α-farnesene (4.9%), linalool (4.7%) and 3-hexen-1-ol (4.4%), hexadecanoic acid (4.5%), (E)-geranylacetone (4.1%), p-menthane (19.8%), farnesane (5.7%), caryophyllane (3.7%), eudesmane (3.0%), 10-epi-γ-eudesmol (3.0%) β-caryophyllen (2.9%), heptacosane (2.9%), nonacosane (2.0%) and geraniol (1.5%) (Figure 6). Monoterpenes account for 27.4 %, sesquiterpenes – for 18.7% of the total.

Organic acids and saccharides

Mikulic-Petkovsek *et al.*[42] collected 18 species including *Vaccinium vitis-idaea* L. in the central part of Slovenia . The fruits were subjected to extraction with bidistillation water at the room temperature. Then the homogenate was centrifuged. The supernatant was filtrated and analyzed by HPLC-UV. In *Vaccinium vitis-idaea* L. fruits, glucose (37.9 g/kg), fructose (29.2 g/kg) and saccharose (0.45 g/kg) were identified. As for the organic acids, in *Vaccinium vitis-idaea* L. fruits they were represented by citric acid (20.0 g/kg), mallic acid (2.7 g/kg), tartaric acid (3.379 g/kg), fumaric acid (35.6 g/kg), shikimic acid (40.9 g/kg).[42]

Pharmacological Properties

It has been established that the extracts obtained from *Vaccinium vitis-idaea,* have a wide range of pharmacological activities, including antioxidant,[27] anti-inflammatory,[43] anti-neoplastic,[44] lipid corrective,[45] neuroprotective,[46] hypoglycemic,[47] antiapoptotic,[48] antiviral[49] and antibacterial[50] types of effects.

Antioxidant activity

A significant number of experimental researches have been devoted to the investigation of antioxidant properties of *Vaccinium vitis-idaea* extracts. So, according to Ho *et al.*[27] (dedicated to the evaluation of antioxidant activity, preclinical study), the tannins obtained from *Vaccinium vitis-idaea*, have the ability to inhibit the processes of lipid peroxidation, which was confirmed by a decrease in the formation of thiobarbituric acid-active products (thiobarbituric acid reactive substances or TBARS). In this study, the inhibitory properties of *Vaccinium vitis-idaea* tannins against superoxide radical (xanthine oxidase inhibition test) have also been established.

In another study conducted by Määtta-Riihinen *et al.*[29] (dedicated to the evaluation of antioxidant activity and hypolipidemic properties, preclinical *in vitro* study), it was established that *Vaccinium vitis-idaea* ethylacetate extract contains phenolic acids, catechins, procyanidins, and phenologlycosides. These substances *in vitro* suppressed the oxidation of low-density lipoproteins, which can indirectly indicate the presence of anti-atherosclerotic and angioprotective properties of the extract.

In addition, antiradical and chelating activity is specific for

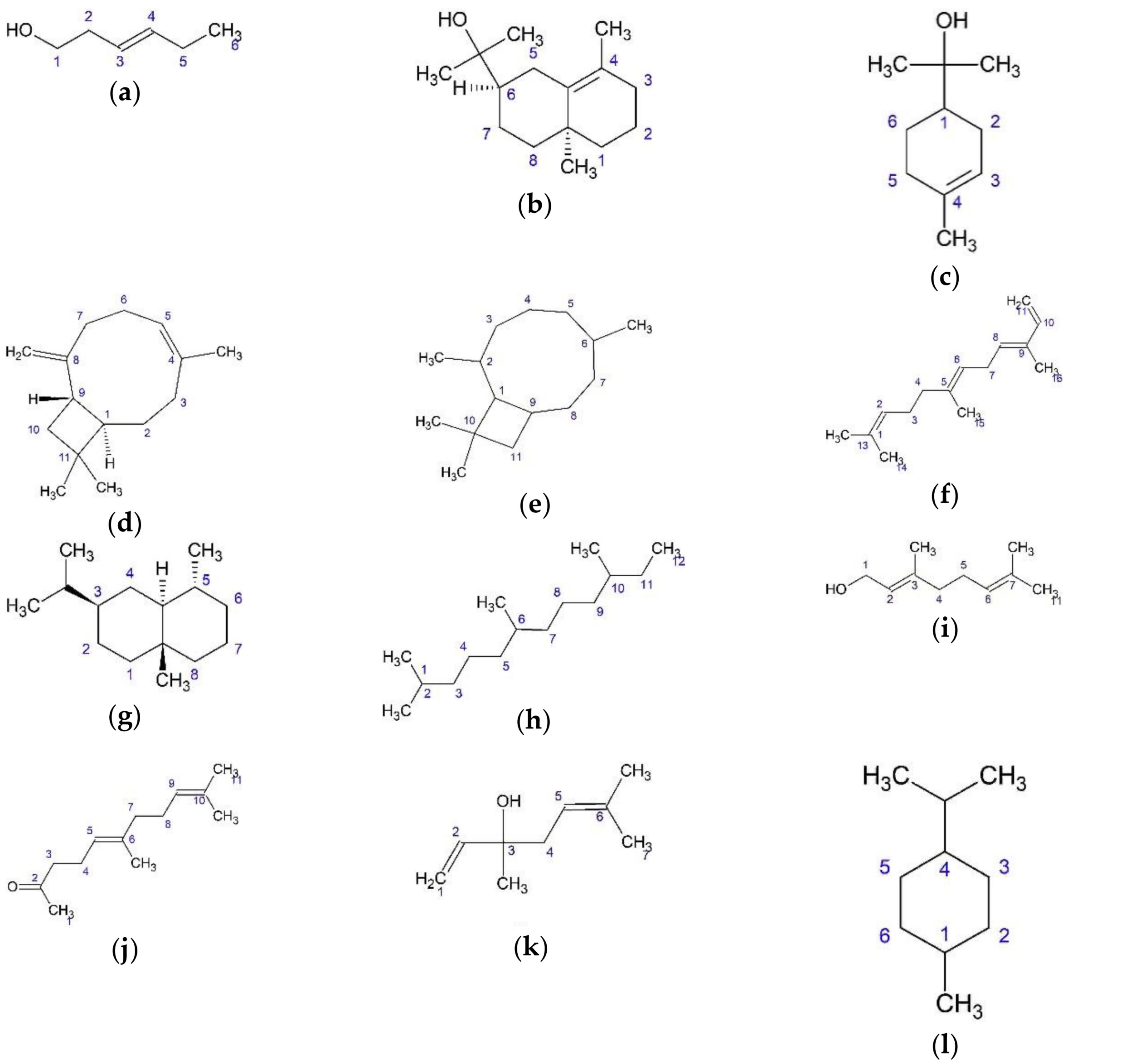


Figure 6. The main compounds of essential oil from *Vaccinium vitis-idaea* L.: (**a**) 3-hexen-1-ol; (**b**) 10-epi-γ-eudesmol; (**c**) α-terpineol; (**d**) β-caryophyllen; (**e**) caryophyllane; (**f**) E,E-α-farnesene; (**g**) eudesmane; (**h**) farnesane; (**i**) geraniol; (**j**) geranylacetone; (**k**) linalool; (**l**) p-menthane.

various extracts from *Vaccinium vitis-idaea*. Meanwhile, it was established that the ethanol extract from *Vaccinium vitis-idaea* L. leaves has scavenger properties relative to hydroxyl and ABTS-radicals (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), this extract was also characterized by the presence of metal chelating activity.[19]

The study of Wang *et al.*[51] (dedicated to the evaluation of antioxidant activity, preclinical *in vitro* study) proved *in vitro* antiradical properties of *Vaccinium vitis-idaea* L. extract against DPPH (2,2-diphenyl-1-picrylhydrazyl), peroxyl (ROO), hydroxyl (OH) and superoxide - anion radical. In this study, it was also shown that *Vaccinium vitis-idaea* extracts inhibit the activity of nuclear factor-κB (NF-kB), mitogen-activated protein kinases (MAPK) and activator protein-1 (AP-1) in mice's epidermal cell culture. In addition, an experimental study conducted by Viljanen *et al.*[52] (dedicated to the evaluation of antioxidant activity, preclinical *in vitro* study) showed that *Vaccinium vitis-idaea* L. fruit extract inhibits the oxidation of lipoprotein liposomes induced by lactalbumin.

The presence of direct antioxidant activity in the extracts obt ained from *Vaccinium vitis-idaea* L. is quite important, as it can provide the basis for the anti-apoptotic action. It was proven in the study by Isaak *et al.*[48] (dedicated to the evaluation of antioxidant activity, preclinical *in vitro* study). In this study, the standardized *Vaccinium vitis-idaea* L. extract in the *in vitro* test, dose-dependently suppressed a cascade of reactive oxygen species (ROS)-induced apoptosis reactions in human cardiomyocyte cell cultures (H_2O_2 was used as an apoptosis-induce substance), while this action was associated by the authors with a high content of anthocyanins in the analyzed extract.

Antibacterial activity

In addition to antioxidant properties - a "classic" type of pharmacological activity for natural origin objects - *Vaccinium vitis-idaea* L. extracts are characterized by the presence of antibacterial properties. Ho *et al.*[53] provides evidence that tannins isolated from *Vaccinium vitis-idaea* L. (epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-catechin) showed antimicrobial activity against *Porphyromonas gingivalis* and *Prevotella intermedia* - pathogens of periodontal infections. At the same time, the test objects were only slightly inferior in terms of the therapeutic effect of the tetracycline, the antibiotic that is most widely used for the treatment of infectious periodontitis.

Besides, the work carried out by Toivanen *et al.*,[54] (dedicated to the evaluation of antibacterial activity, preclinical study) demonstrated a high level of antimicrobial activity (comparable to the referent - streptavidin) of *Vaccinium vitis-idaea* L. extract in relation to *Neisseria meningitidis* Pili. This study also provides data on the potential mechanism of action of the studied extract. So, apparently, the antibacterial activity of *Vaccinium vitis-idaea* L. berries extract is associated with the inhibition of adhesion of *Neisseria meningitidis* Pili to human epithelial cells.

In addition to *Vaccinium vitis-idaea* L. berries extract, the extract obtained from *Vaccinium vitis-idaea* leaves, has also antibacterial properties. That was proved in the study by Wojnicz *et al.*[50] (devoted to the evaluation of antibacterial activity, preclinical study) where the aqueous extract from *Vaccinium vitis-idaea* L. leaves, had a bactericidal effect on *E. coli* strain isolated from urine of the patients suffering from bacterial pyelonephritis.

Vaccinium vitis-idaea L. extracts have also antitussive and mucolytic effects, which make these objects effective means of adjuvant therapy of upper respiratory tract infections.[17] In this case, the antimicrobial effect of *Vaccinium vitis-idaea* L. extracts can be associated with suppression of bacterial hemagglutinin expressio.[55] It is important that the endophytes of *Vaccinium vitis-idaea* have an antimicobacterial activity (strains of such bacteria as *Mycobacterium aurum*, *M. tuberculosis* H37Rv), which opens up certain prospects for the use of herbal medicines based on *Vaccinium vitis-idaea* L., in the treatment of one of the main infectious causes of mortality in the world – tuberculosis.[56]

Antifungal and antiviral activities

In addition to antibacterial activity, the extracts obtained from *Vaccinium vitis-idaea* L., are characterized by the presence of antifungal and antiviral properties. Cioch *et al.*[57] show the fungicidal activity of *Vaccinium vitis-idaea* L. fruit extract against pathogenic fungi of the *genera Aspergillus*; *Penicillium* and *Saccharomyces*. (antifungal and antiviral activity, preclinical study) The study by Ermis *et al.*[58] (antifungal properties, preclinical study) demonstrated the fungicidal activity of *Vaccinium vitis-idaea* L. fruits, which, when powdered, acted as a dietary supplement to commercial juices with reduced sugar content, against pathogenic fungi *Absidia glauca*, *Penicillium brevicompactum*, *Saccharomyces cerevisiae* and *Zygosaccharomyces bailii*.

A study conducted by Nikolaeva-Glomb *et al.*[49] (antiviral properties, preclinical study) revealed a high level of antiviral activity of *Vaccinium vitis-idaea* L. fruit extract. In the course of this study, it was established that *in vitro* methanolic *Vaccinium vitis-idaea* L. fruit extract inhibited the replication of highly common and virulent pathogens: poliovirus type 1 (PV-1) and Coxsackie B1 virus (CV-B1), human respiratory syncytial virus A2 (HRSV-A2) and influenza A / H3N2.

Neuroprotective activity

The neuroprotective properties of some plant extracts are widely known, for example, *Ginkgo biloba* extract (Egb 761) and drugs based on it, which opens up the prospect of finding effective neuroprotectors among products of natural origin.[59] In this regard, a number of experimental studies on the evaluation of the neuroprotective activity of extracts from *Vaccinium vitis-idaea* were conducted.

Kelly *et al.*[46] (devoted to the evaluation of neuroprotective activity, preclinical study) report that *Vaccinium vitis-idaea* L. fruit extract has a pronounced neuroprotective effect under conditions of experimental glutamate-mediated excitotoxicity and β-amyloid-related neurotoxicity, which in turn opens up certain prospects for the application of these extracts in the treatment of neurodegenerative brain diseases such as Alzheimer's and Parkinson's diseases. At the same time, for *Vaccinium vitis-idaea* L extracts, a complex mechanism of action is implied, which includes regulation of calcium concentration and NF-kB signaling pathway, restoration of the mitochondrial membrane potential, reduction of cytokine activity (tumor necrosis factor alpha, TNF-α). In addition, in the culture of cortical cells, *Vaccinium vitis-idaea* L extract reduced glutamate-mediated excitotoxicity.[60]

Anti-inflammatory and immunotropic activity

Due to the presence of proven anti-cytokine properties in *Vaccinium vitis-idaea* L. extracts, the evaluation of the anti-inflammatory and immunotropic potential of these objects is promising. That was studied by Shaikh *et al.*[43] (preclinical study, *in vitro*) The experiments performed by Shaikh *et al.* (2015) made it possible to establish cyclooxygenase (COX)-inhibiting properties of *Vaccinium vitis-idaea* L. extract and, in addition, the anticytokine properties of this object were confirmed. This assumes a high therapeutic efficacy of the studied extract in the treatment of both acute and sluggish current chronic inflammatory processes.

In the work carried out by Vogl *et al.*[61] (devoted to the evaluation of anti-inflammatory action mechanism, preclinical study) it was shown that *Vaccinium vitis-*

idaea L fruits extract *in vitro* suppresses the formation of interleukin-8, E-selectin and tumor necrosis factor – α, as well as promotes the activation of the peroxisome proliferator-activated receptors (PPARa and PPARγ), which may indicate the anti-inflammatory properties of *Vaccinium vitis-idaea* extracts, the presence of which was the basis for the use of these extracts in the treatment of inflammatory diseases of the gastrointestinal and urogenital tracts. Besides, the anti-inflammatory action of *Vaccinium vitis-idaea* L extracts, in particular a fruit extract, may be based on a decrease in vascular permeability, suppression of exudation and inflammatory edema, realized by inhibiting the activity of enzymes of the metalloproteinase family, which, in turn, has been proven in the work by Kondo *et al.*[62] (devoted to the evaluation of anti-inflammatory action mechanism, preclinical study).

Cytotoxic activity

Among the drugs based on plant extracts, there are not only drugs for the treatment of various types of brain diseases - neuroprotectors - but also antineoplastic drugs intended for the treatment of cancer.

In the study by Du *et al.*[63] (devoted to the evaluation of anti-proliferative properties preclinical study), an anti-cancer activity of 4-[(Tetrahydro-2H-pyran-2-yl) oxy] phenol was established. This is an analogue of hydroquinone, identified as one of the active components in the extracts obtained from *Vaccinium vitis-idaea,*

In the C26 cell culture of colon cancer 4-[(Tetrahydro-2H-pyran-2-yl) oxy], phenol activated apoptosis by suppressing the activity of antiapopotic B-cell lymphoma 2 (Bcl-2) proteins and activating proapoptotic Bax proteins and, accordingly, the caspase-dependent pathway of apoptosis.

Antineoplastic activity

The work carried out by Misikangas *et al.*[64] (anti-cancer action, preclinical *in vivo* study), showed that adding food enriched with the powder of *Vaccinium vitis-idaea* L berries to the diet of animals, reduces the growth of malignant colon carcinomas in mice by more than 60% ($p<0.05$) relative to the control group. At the same time, researchers associate the anticancer activity of this nutrient with a decrease in the activity of oncogenes, such as: β-catenin, cyclin D1, adenosine deaminase, ecto-5-nucleotidase and prostaglandin E2 (in the case of affinity for EP4 receptors). In the study by Fan *et al.*[65] (radioprotective properties, preclinical *in vivo* study) the radioprotective effect of anthocyanins extracted from *Vaccinium vitis-idaea* L fruits. It is expressed in the restoration of all hematopoiesis sprouts, normalization of phagocytic activity in animals, in conditions of acute radiation exposure, which, in turn, can also be a reference to antineoplastic properties of the extracts obtained from *Vaccinium vitis-idaea* L.

Hypoglycemic activity

In addition to the above listed types of pharmacological activity, *Vaccinium vitis-idaea* L. extracts are characterized by the presence of hypoglycemic properties.

In the current conditions of extreme prevalence of insulin-resistant diabetes mellitus and the practical absence of safe and cost-effective methods for pharmacocorrection of this type of diabetes, the use of *Vaccinium vitis-idaea* L. extracts can be an effective alternative method for treating hyperglycemic conditions. The work carried out by Eid *et al.*[66] (hypoglycemic action, preclinical *in vivo* study), demonstrated a significant potential for glycemic control of *Vaccinium vitis-idaea* L. in C57BL / 6 mice under conditions of insulin resistant diabetes. At the same time, the potential mechanisms of the hypoglycemic action of the studied object, including an increase in the activity of glucose-transporting metabolic systems (GLUT-4), 5' adenosine monophosphate-activated protein kinase (AMPK) and serine/threonine-specific protein kinase (Akt) in skeletal muscles, were established. In addition, AMPK-activating properties of extracts from *Vaccinium vitis-idaea* were proven in the study by Eid *et al.*[67] (hypoglycemic action mechanisms evaluation, preclinical *in vivo* study), hereby it was found out that activation of AMPA in striated muscle caused by the use of *Vaccinium vitis-idaea* L. berries, was not accompanied by the dissociation of electron transfer reactions in the mitochondrial respiratory chain, therefore the risk of hyperlactataemia when using products based on *Vaccinium vitis-idaea,* is minimal, which distinguishes this object from those traditionally used in insulin-resistant diabetes activators of AMPK, for example, metformin.

It is quite important that, in addition to the directly hypoglycemic effect, *Vaccinium vitis-idaea* L. extracs exhibit a pleiotropic pharmacological action in diabetes mellitus. So, in the work by Reichert *et al.*[68] (devoted to the evaluation of pleiotropic hypoglycemic properties preclinical study) it was shown that the use of *Vaccinium vitis-idaea* L. fruits in experimental diabetes mellitus, contributed to the reduction of *central* nervous system complications in diabetes mellitus. The study by Zhu *et al.*[45] (devoted to the evaluation of hypoglycemic properties preclinical study) demonstrated that while using *Vaccinium vitis-idaea* L., there is a decrease in the concentration of low density lipoprotein (LDL) and an increase in the high density lipoprotein (HDL) fraction in the *blood serum*. It should be notified that the hypoglycemic properties of *Vaccinium vitis-idaea* L. extracts were confirmed by clinical data.[69] The *in vitro* studies also confirm the presence of hypoglycemic activity in *Vaccinium vitis-idaea* L. Thus, the work by Quek and Henry[70] (hypoglycemic properties preclinical *in vivo* study), shows that crushed *Vaccinium vitis-idaea* L. fruits improve glycemic control by reducing the breakdown of complex carbohydrates to monosaccharides. In addition, a high hypoglycemic activity of *Vaccinium vitis-idaea* L., has been confirmed in a number of clinical studies.

According to Rokka *et al.*[71] (hypoglycemic properties clinical study), the use of powdered *Vaccinium vitis-idaea* L. berries in 9 healthy volunteers at the median age of 35 years (20-54 years), contributed to a significant decrease in basal blood glucose levels. Hypoglycemic effect is associated with the modulation of the PPARγ function and, as a result, the elimination of insulin resistance.

Meanwhile, two studies conducted by Törrönen *et al.*[72] and Törrönen *et al.*[73] (hypoglycemic properties clinical study), reported a decrease in postprandial glucose levels and insulin secretion in healthy female volunteers. However, it should be notified that in the first case, the patients received 150 g of *Vaccinium vitis-idaea* L. in the form of berry puree, and in the second case, the therapy was carried out with a multi-component polyphenolic composition, which included equal amounts of strawberries, blueberries, cranberries and black currants.

The summarized data characterizing the spectrum of the pharmacological activity of *Vaccinium vitis-idaea* L., are presented in Table 4.

Table 4. Types of pharmacological activity of *Vaccinium vitis-idaea* L.

Pharmacological activity	Extract	Type of study	The dose/concentration IC_{50} range for *in vitro* tests	Methods	Ref.
Antioxidant, chellating	Tanins	Preclinical	IC_{50} – 7.76-630.0	Thiobarbituric acid test, oxidase inhibition test, cytochrome C test	27
	Ethyl acetate extract	Preclinical	IC_{50} – 13.0-86.0	DPPH-test, oxidation of methyl linoleate emulsion test, LDL oxidation test	28
	Ethanol extract	Preclinical	Inhibition percent – 12.08-88.5%	ABTS Radical inhibition test, Ferric Reducing Antioxidant Power test, Ferrous Ions Chelating Activity test	19
Antiapoptotic	Standardized extract	Preclinical	20 nmol/L	Hydrogen peroxyde induced apoptosis of H9c2 cells	48
Anti-inflammatory	Aqueous extract of fruits	Preclinical	1 mg/ml	Carrageenan and Phorbol Myristate Acetate induced edema	43
	Berries	Preclinical	Not indicated	DU145 prostate tumor cells.	62
Antineoplastic	(4-[(Tetrahydro-2H-pyran-2-yl) oxy] phenol)	Preclinical	2.5, 5, 10, 20 or 40 µg/ml	Inhibition of C26 murine colon carcinoma cell proliferation	63
	Berries Powder	Preclinical	10%	Multiple intestinal neoplasia/+ mice biological model	64
Radioprotective	Aqueous extract of fruits	Preclinical	50, 100, 200 mg/kg	Irradiation γ-radiation (6 Gy), at a dose rate of 1.01 Gy/min	65
Hypolipidemic	Lingonberry juice	Clinical	2.1 mg/day	Hypolipidemic activity investigated on patients with diabetes mellitus	45
	Lingonberry juice cocktail		69.5 mg/day		
	Lingonberry drink		375 mg/day		
	Lingonberry juice		24.8 mg/day		
Neuroprotective	Aqueous extract of fruits	Preclinical	25 mg/kg; 50 mg/kg	Transgenic model of Alzheimer disease	46
	Berries Powder	Preclinical	125, 250 and 500 mg/kg	Streptozotocin induced diabetes mellitus	68
Hypoglycemic	Berries Powder	Preclinical	125, 250 and 500 mg/kg	Dietary mouse model / diet-induced obesity	66
	Berries Powder	Clinical	Not indicated	Activity investigated on 9 healthy volunteers, glucose control	71
	Berries puree	Clinical	150 g	Activity investigated on healthy femalevolunteers, postprandial glucose control	72
	Berries (in combination)	Clinical	Not indicated	Activity investigated on healthy female volunteers, postprandial glucose and insulin control	73
Antiviral	Methanol extract of fruits	Preclinical	Not indicated	*In vitro* antiviral tests	49
Antibacterial	Tanins	Preclinical	0.5%	Agar dilution method	53
	Aqueous extract of fruits		0.5–8 µg/ml	Dot Binding and Binding Inhibition Assay	54
	Aqueous extract of leaves		0.125-20 mg/ml	Agar dilution test	50
Antifungal	Methanol, aqueous and ethanol extracts	Preclinical	Not indicated	Diffusion paper-disc assay	57

Discussion

The analysis of the literature data made it possible to arrive at the conclusion that *Vaccinium vitis-idaea* L. is a polymorphic species growing all over the area of Russia and it is a species typical of European countries. It also occurs in the USA. When grown together, *Vaccinium myrtillus* and *Vaccinium vitis-idaea* can form a natural infraspecies hybrid *Vaccinium* x *intermedium* Ruthe. *Vaccinium vitis-idaea* L. leaves are a pharmacopoeia medicinal plant material in Russia and in the Republic of Belarus.

The main biologically active compounds of lingonberry are phenylpropanoids, simple phenols such as arbutin and hydroquinone as the main components, flavonoids, proanthocyanidines, anthocyanidines, catechins, saponins, etc. The majority of works describe chemical contents of fruits because berries are used as a medicinal and edible plant material. Several authors claim that the chemical contents depend on cultivars of *Vaccinium vitis-idaea* L., the time of harvesting and the flora area. The quality control of *V. vitis-idaea* raw materials is carried out only by the total amount of phenologlycosides. Metabolomics research and developing the standardized finger prints plants from different habitats and different growing season are the actual future aim.

The analysis of the types of the pharmacological activity of *Vaccinium vitis-idaea* extracts, made it possible to establish that the majority of studies in which the biological activity of this plant is studied, are limited to the works performed *in vitro*. Thus, despite a sufficient number of researches devoted to the evaluation of the antioxidant activity of *Vaccinium vitis-idaea* extracts, all of them are usually focused on the evaluation of antiradical and chelating properties of these objects.

Meanwhile, the undoubted scientific and practical interest can be presented by the study of the effect of *Vaccinium vitis-idaea* L. extracts on the processes of peroxidation *in vivo*, with the assessment of changes in the activity of endogenous antioxidant enzymes such as superoxide dismutase, catalase, enzymes of glutathione series (glutathione peroxidase, glutathione-s-transferase), and also with the determination of the concentration of lipid peroxidation products (TBARS). Taking into account the fact that an oxidative stress is a “universal” pathophysiological process and underlies pathogenesis of a number of diseases, *in vivo* evaluation of the antioxidant activity of *Vaccinium vitis-idaea* L. extracts, will significantly expand the therapeutic potential of drugs obtained from *Vaccinium vitis-idaea* L.. The study of the neuroprotective activity of *Vaccinium vitis-idaea* extracts is also of significant interest. Thus, the established anti-cytokine and antiapoptotic properties in combination with the ability of these extracts to reduce the cytotoxicity of β-amyloid may be a prerequisite for the use of *Vaccinium vitis-idaea* extracts in the treatment of a number of progressive neurodegenerative diseases. That requires, however, a more detailed study. Hereby, this type of pharmacological activity (AMPK activation), opens up certain perspectives of medicines based on the application of *Vaccinium vitis-idaea* L.: correction of muscle fatigue and *ischemic/hypoxic* state. It can also be important to study various aspects of the possible mechanisms of action of these extracts. It may be appropriate to assess the effect of *Vaccinium vitis-idaea* L. extracts on the activity of metabolic transport systems (various subclasses of GLUT), PPAR, caspases and other effectors.

Conclusion

The carried out analysis of the literature data on the chemical contents and pharmacological studies of *Vacciniumvitis-idaea* L. revealed unresolved issues. There are other groups of natural compounds, such as polysaccharides, phenylpropanoids, tannins, the quantitative contents of which is has not been mentioned in the literature. The main part of the work contains the results of *Vaccinium vitis-idaea* L. fruits research. Such parts of the plant as leaves, are not fully investigated, though they have been used for a long time in traditional medicine. In addition, according to the above presented data, the flora area affects both the qualitative and quantitative composition of biologically active compounds.

There are no reliable data on the regularity of accumulation of biologically active substances in various habitats. The neuroprotective effect is a potentially new type of activity. In most studies, the activity of *Vitis-idaea* extracts is tested *in vitro*. In the absence of *in vivo* test results, it cannot be considered sufficient. In addition, it seems scientifically justified to study the mechanisms of action, extracts from lingonberries. Thus, it is possible to study the mechanisms of implementation of cerebrotropic, diuretic and antioxidant types of activity, with the establishment of specific pharmacotherapeutic targets at the molecular level. It is also advisable to further evaluate the hypoglycemic and hypolipidemic properties of extracts, while their PPAR – agonistic activity is seen as interesting, which can serve as a prerequisite for the creation of drugs with polyvalent pharmacological activity.

All these aspects establishe the high interest for future investigations *Vaccinium vitis-idaea* L. as a source of natural drugs with wide range of activities.

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Conflict of Interest

The authors declare they have no conflict of interest.

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