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Research Article

Simultaneous Determination of 78 Compounds of *Rhodiola rosea* Extract by Supercritical CO_2-Extraction and HPLC-ESI-MS/MS Spectrometry

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The plant *Rhodiola rosea* L. of family *Crassulaceae* was extracted using the supercritical CO_2-extraction method. Several experimental conditions were investigated in the pressure range of 200–500 bar, with the used volume of cosolvent ethanol in the amount of 1% in the liquid phase at a temperature in the range of 31–70°C. The most effective extraction conditions are pressure 350 bar and temperature 60°C. The extracts were analyzed by HPLC with MS/MS identification. 78 target analytes were isolated from *Rhodiola rosea* (Russia) using a series of column chromatography and mass spectrometry experiments. The results of the analysis showed a spectrum of the main active ingredients *Rh. rosea*: salidroside, rhodiolosides (B and C), rhodiosin, luteolin, catechin, quercetin, quercitrin, herbacetin, sacranoside A, vimalin, and others. In addition to the reported metabolites, 29 metabolites were newly annotated in *Rh. rosea*. There were flavonols: dihydroquercetin, acacetin, mearnsetin, and taxifolin-O-pentoside; flavones: apigenin-O-hexoside derivative, tricetin trimethyl ether 7-O-hexosyl-hexoside, tricin 7-O-glucoronyl-O-hexoside, tricin O-pentoside, and tricin-O-dihexoside; flavanones: eriodictyol-7-O-glucoside; flavan-3-ols: gallocatechin, hydroxycinnamic acid caffeoylmalic acid, and di-O-caffeoylquinic acid; coumarins: esculetin; esculin: fraxin; and lignans: hinokinin, pinoresinol, L-ascorbic acid, glucaric acid, palmitic acid, and linolenic acid. The results of supercritical CO_2-extraction from roots and rhizomes of *Rh. rosea*, in particular, indicate that the extract contained all biologically active components of the plant, as well as inert mixtures of extracted compositions.

1. Introduction

The plant *Rhodiola rosea* L. of family *Crassulaceae* is widely used in traditional medicine and traditional medical systems (Tibetan, Chinese, and Korean). Rhizomes and plant roots are mainly used for the preparation of medicinal products [1, 2].

The plant has an established popular name "golden root." The name is determined not only by the color of the rhizome but also by its high price. The main medicinal raw material of *Rh. rosea* is rhizomes with roots, which are harvested from the end of flowering until the completion of the plant's vegetation. *Rh. rosea* grows in the mountains in the north of the European part of Russia, Siberia, the Urals, the mountains of Altai, the Tien Shan and the Far East, the mountains of Western Europe, Scandinavia, Mongolia, and on the spurs of the Himalayas. Brush wood of *Rh. rosea* is located at an altitude of 1700–2200 m above sea level. Since about the 80s, *Rh. rosea* has been one of the main adaptogenic plants and competes with such well-known

adaptogens such as *Panax ginseng* and *Eleutherococcus*. Adaptogens are a pharmacological group of drugs of natural or synthetic origin, which can increase the body's resistance to various adverse environmental conditions [3–5].

Rh. rosea roots and rhizomes contain organic acids (citric, malic, oxalic, and succinic acid) and sugars (fructose, sucrose, glucose, sedoheptulose, essential oil, phenolic compounds, monoterpenes, sterols, cinnamon alcohol, and manganese) [6–8].

The active biologically active substances of *Rh. rosea* are tyrosol, salidroside, caffeic acid, gallic acid, methyl gallate, flavonoids (astragalin, kaempferol, rhodionine, rhodiosin, rhodiolinin, and rhodiolgin), and tannins of the pyrogallol group (Table 1). Monoterpenes are represented by rosiridol and its glycoside rosiridin, and sterols are represented by β-sitosterol and daucosterol. Cinnamon glycosides—rosin, rosarin, and rosavin—were isolated from the roots of *Rh. rosea* [9].

Information on the content of salidroside and rosavin in *Rh. rosea* is numerous and contradictory [10, 11]; Zang et al., 2019). Researchers still have not come to a consensus on the localization and activity of specialized biosyntheses, the nature of seasonal changes in glycoside content, and the variability in the accumulation of these substances in wild and cultivated plants [12–14].

Detailed comparative studies of the content of salidroside and rosavin in the organs of wild-growing and cultivated plants were carried out. Performed using a unified determination method showed the presence of glycosides only in the roots and caudex. The presence of rosavin and salidroside in the aerial organs (stems, leaves, inflorescences, and seeds) was not detected in any case [15].

Plants from different places of growth differed significantly in the accumulation of individual glycosides. The content of salidroside in the plant caudex varied from 9 to 20 mg/g dry weight. The largest accumulation of this glycoside was characterized by plants growing on rocks on the coast of the Barents Sea (Norway), as well as Ural plants growing on outcrops of bedrock with an insignificant soil layer. The minimum salidroside content was found in Altai plants. The highest content of rosavin (32 mg/g) was found in the caudex of plants of the subalpine ecotope in the Polar Urals, the lowest (10–12 mg/g) being in plants growing on the islands and the coast of the Barents Sea. Cultivated plants were not inferior for accumulation of rosavin to wild plants.

Differences in the accumulation of glycosides by plants of various ecotopes were revealed. So, in the Subpolar Urals, in the caudex of plants growing in faults and on ledges of rocks, more salidroside accumulates, but these plants were characterized by a low content of rosavin, 1.5–2 times less than in plants of the subalpine ecotope [15].

Cinnamic glycosides, and in particular rosavin, are believed to be the hallmark of the chemotaxonomic trait of *Rh. rosea* [16, 17]. Recently, however, literature has reported that this glycoside is present in other species of the genus *Rhodiola L*. The results confirmed the presence of rosavin in the caudex of *Rh. iremelica Boriss*. The concentration of salidroside and rosavin in the plant caudex was 7.1 ± 2.4 and 15.3 ± 2.9 mg/g, respectively. In the underground part of *Rh. quadrifida (Pall.) Fisch.* et Mey, rosavin was not detected, and the content of salidroside was about 10 mg/g dry weight [15].

In official medical practice, *Rh. rosea* root extract is intended for oral administration as a tonic and immunomodulating therapeutic agent. In the study of alcoholic extracts of *Rh. rosea*, their hepatoprotective, nootropic, cardioprotective, and antiarrhythmic properties were clearly demonstrated [18–20].

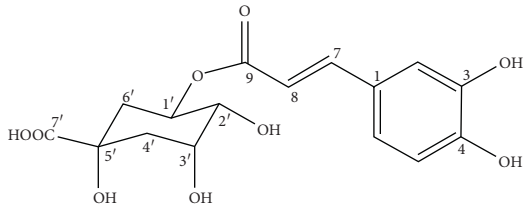
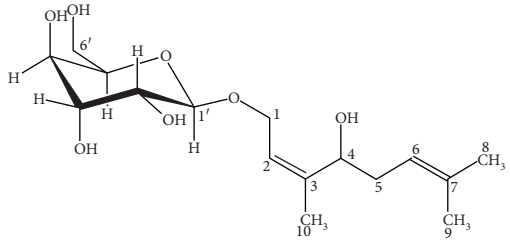
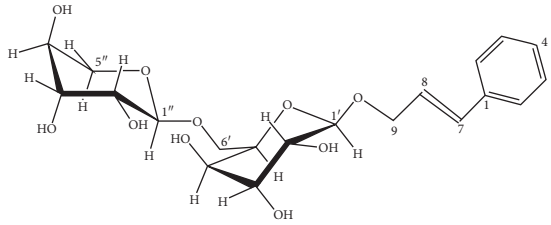
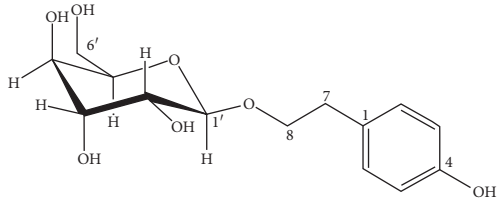
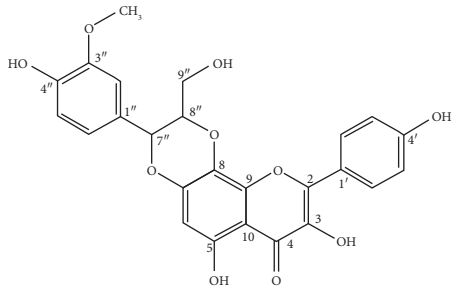
Cinnamic glycosides, also called cinnamyl glycosides and salidroside, are the main carriers of the biological activity of *Rh. rosea*, causing a positive pharmacological effect. With the presence of rosavin, rosin, and rosarin, many researchers attribute the increased biological activity of extracts of *Rh. rosea*, compared with drugs from other species of *Rhodiola*. Studies have shown the stimulating effect of drugs on the central nervous system. Of great interest is the ability of *Rh. rosea* to increase the body's resistance to the effects of various stress factors [21, 22]. *Rh. rosea* extract has immune stimulating, hepatoprotective, and antimicrobial effects [23, 24]. Studies have also been conducted on the antitumor effect of *Rh. rosea* extract [25–27].

This study considers the effectiveness of supercritical CO_2-extraction of biologically active substances from roots and rhizomes of *Rh. rosea*. Previously, the authors of this article successfully used supercritical CO_2 extraction to obtain biologically active substances from plants of the Far Eastern taiga *Panax ginseng*, *Rhododendron adamsii*, *Schisandra chinensis*, and sea cucumber which are extremely popular in traditional medicine of Southeast Asia [28, 29].

Supercritical fluid extraction (SFE) has been used since 1960s to analyze food and pharmaceutical products, isolate biologically active substances, and determine lipid levels in food and levels of toxic substances. In addition, the products do not have residues of organic solvents, which occur with conventional extraction methods, and solvents can be toxic, for example, in the case of methanol and *n*-hexane. High selectivity, easy solvent removal from the final product, and the use of moderate temperatures in the extraction process are the main attractive factors of SFE, leading to a significant increase in research for use in the food and pharmaceutical sectors [30, 31].

In Sweden, an article was published in 2009 that examined the extraction of rosavin from the roots and rhizomes of *Rh. rosea* using supercritical CO_2-extraction. In this case, water was selected as a modifier of supercritical extraction, which gave a synergistic effect on the extraction yield of rosavin [32]. In China, researchers used supercritical CO_2-extraction with ethanol modifier [33]. The purpose of this study was to extract the maximum amount of salidroside from the roots of *Rh. rosea*. The extraction conditions were chosen so that the yield of salidroside during supercritical extraction was much higher than the yield of the product when using classical extraction using a Soxhlet apparatus.

Table 1: Some of the main active compounds of *Rh. rosea*.

S. no.	Compounds	Structure
1	Chlorogenic acid: $C_{16}H_{18}O_9$	
2	Rosiridin: $C_{16}H_{28}O_7$	
3	Rosavin: $C_{20}H_{28}O_{10}$	
4	Salidroside: $C_{14}H_{20}O_7$	
5	Rhodiolin (rhodiolinin): $C_{25}H_{20}O_{10}$	

The results of SC-CO_2-extraction of from roots and rhizomes of *Rh. rosea*, in particular, indicate that when using this technology, the extract contained all biologically active components of the plant, as well as inert mixtures of extracted compositions.

2. Experimental

2.1. Materials. Ground, dried root of *Rh. rosea* was obtained from the area near Lake Baikal, Russia. All samples were morphologically authenticated according to the current standard of Russian Pharmacopeia [34]. The volume weighted mean diameter of the powder was found as 550 μm, as determined by dynamic light scattering (Hydro 2000MU Malvern Instruments Ltd.).

2.2. Chemicals and Reagents. HPLC-grade acetonitrile was purchased from Fisher Scientific (Southborough, UK), and MS-grade formic acid was purchased from Sigma-Aldrich (Steinheim, Germany). Ultrapure water was prepared from Siemens Ultra-Clear water purification system (Siemens Water Technologies, Germany), and all other chemicals were analytical grade.

2.3. Supercritical Fluid Extraction. A supercritical fluid extraction system was Thar SFE-500F-2-FMC50 (Thar Technology Inc., Pittsburgh, PA, USA) which is used in supercritical extraction. CO_2 was compressed to the required pressure using a supercritical extraction compressor (Thar SFC, USA). A hot casing string heated the extraction vessel; the temperature was regulated by a thermostat (±1°C). A

metering valve controlled the pressure. Shredded *Rhodiola* roots (50 g) were wrapped in a filter paper, charged to a one-liter extractor, and extracted with supercritical CO_2 compressed to a supercritical state at a liquid flow rate of 250 g/min. Seven SFE extracts were obtained under different pressure conditions (100–400 bar) and temperatures (31–70°C). Ethanol served as the cosolvent in all cases. The extracts were collected in a separator. The pressure and temperature of the supercritical CO_2 were optimized experimentally to achieve the maximum yield of the product during extraction.

2.4. Liquid Chromatography. HPLC was performed using Shimadzu LC-20 Prominence HPLC (Shimadzu, Japan), equipped with an UV-sensor and a Shodex ODP-40 4E reverse phase column to perform the separation of multicomponent mixtures. The gradient elution program was as follows: 0.01–4 min, 100% A; 4–60 min, 100–25% A; and 60–75 min, 25–0% A; control washing 75–120 min 0% A. The entire HPLC analysis was done with a DAD detector at wavelengths of 230 ηm and 330 ηm; the temperature corresponded to 17°C. The injection volume was 1 ml.

2.5. Mass Spectrometry. MS analysis was performed on an ion trap amaZon SL (Bruker Daltoniks, Germany) equipped with an ESI source in the negative ion mode. The optimized parameters were obtained as follows: ionization source temperature, 70°C; gas flow, 4l/min; nebulizer gas (atomizer), 7.3 psi; capillary voltage, 4500 V; end plate bend voltage, 1500 V; fragmentary, 280 V; and collision energy, 60 eV. An ion trap was used in the scan range m/z 100–1.700 for MS and MS/MS. The capture rate was one spectrum/s for MS and two spectra/s for MS/MS. Data collection was controlled by Windows software for Bruker Daltoniks. All experiments were repeated three times. A two-stage ion separation mode (MS/MS mode) was implemented.

3. Results and Discussion

Several experimental conditions were investigated in the pressure range 200–500 bar, with the used volume of cosolvent ethanol in the amount of 1% in the liquid phase at a temperature ranging 31–70°C. Ethanol was used as the modifier due to its high solubility in CO_2 and high polarity and ability to disturb solute-plant matrix bonding. As a result of using a wide range of pressures and temperatures empirically, the most efficient extraction conditions were found for extracting target analytes from the *Rh. rosea* roots. The most effective extraction conditions are pressure 350 bar and temperature 60°C (Figure 1).

Obtaining chemical profiles is an extremely important result in the biological analysis system. In this work, we used the HPLC-ESI-MS/MS method with additional ionization and analysis of fragmented ions. High accuracy mass spectrometric data were recorded on an ion trap amaZon SL (Bruker Daltoniks) equipped with an ESI source in the negative ion mode. The two-stage ion separation mode (MS/MS mode) was implemented.

Figure 2 shows the distribution density of the analyzed chemical profiles in the ion chromatogram of the *Rh. rosea* supercritical CO_2-extract, realized by mass spectrometry in the two-stage ion separation mode (MS/MS mode).

Visually, a rather high-density distribution of the target analytes in the analyzed extract was observed. All the chemical profiles of the samples were obtained by the HPLC-ESI-MS/MS method. A total of 300 peaks were detected in the chromatogram. By comparing the m/z values, the RT and the fragmentation patterns with the MS^2 spectral data taken from the literature [2, 17, 35–50] or to search the data bases (MS2T, MassBank, HMDB). 78 metabolites were putatively identified as phenols, aromatic compounds, phenyl alkanoids, flavonoids, monoterpenoids, acyclic alcohol glycosides, anthocyanins etc. In addition to the reported metabolites, a number of metabolites were newly annotated in *Rh. rosea.*

A unifying system table consists of the molecular masses of the target analytes isolated from the supercritical CO_2-extract of *Rh. rosea* for ease of identification (Table 2).

The CID spectrum (collision induced dissociation spectrum) in negative ion modes of Rhodioloside B from *Rh. rosea* is shown in Figure 3**.**

The $[M-H]^-$ ion produced two fragments with m/z 447.00 and m/z 219.49 **(**Figure 3**).** The fragment ion with m/z 447.00 yields a daughter ion at m/z 314.98. The interpretation of the observed MS/MS spectra in comparison with those found in the literature was the main tool for putative identification of polyphenols. It was identified in the bibliography in extracts from *Rh. rosea* [50], from *Rhodiola crenulata* [35].

The CID spectrum in the negative ion mode of luteolin-7-O-α-L-rhamnoside from *Rh. rosea* is shown in Figure 4.

The $[M-H]^-$ ion produced fragment with m/z 284.93 (Figure 5). The fragment ion with m/z 284.93 yields a daughter ion at m/z 283.93.

It was identified in the bibliography in extracts from *Rhodiola crenulata* [35]. The CID spectrum in the positive ion mode of catechin from *Rh. rosea* is shown in Figure 5. The $[M+H]^+$ ion produced fragments with m/z 273.14 and m/z 217.09 (Figure 5). It was identified in the bibliography in extracts from *Rh. rosea* [50], from strawberry, cherimoya [36], and pear [45].

We isolated 78 target analytes from *Rhodiola rosea L.* (*Crassulaceae)* using a series of column chromatography and mass spectrometry experiments. The structures were elucidated using the data of stepwise fragmentation of ions during MS/MS spectrometry and compared with spectroscopic data in the literature. It is accepted that glycosides of cinnamon alcohol, and in particular Rosavin, are a distinctive chemotaxonomic sign of *Rh. rosea* [17]. However, lately, information has appeared in the literature on the presence of this glycoside in other species of the genus *Rhodiola L.* [15]. Thus, we can summarize the research that the supercritical extraction of the roots of *Rh.*

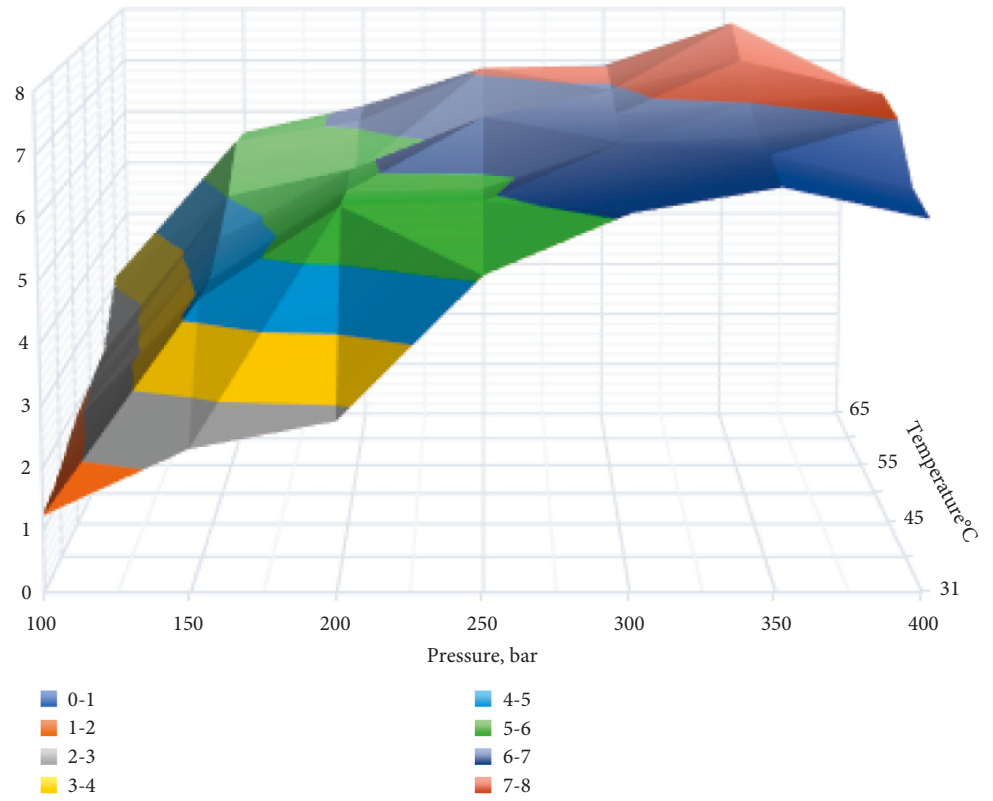


Figure 1: The effect of pressure and temperature on extraction efficiency of total yield of biologically active compounds (mg/g of extractable substance).

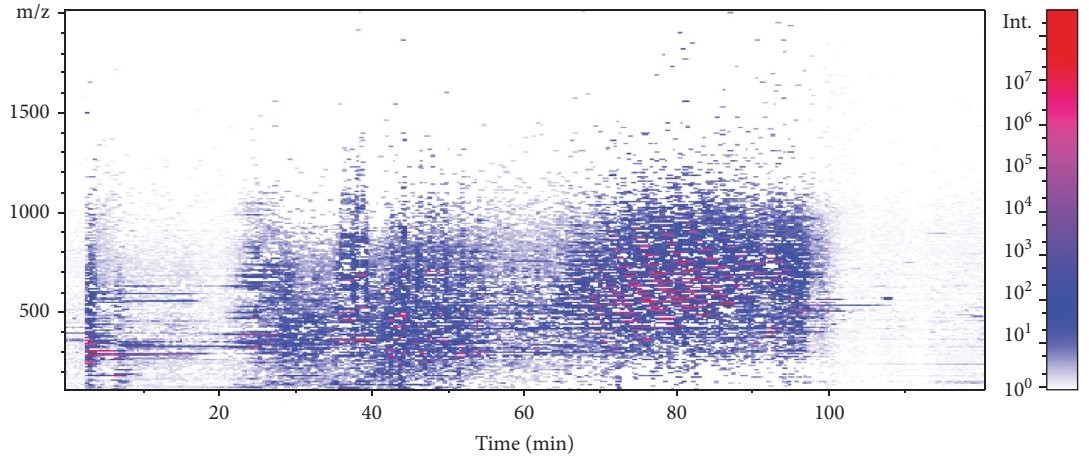


Figure 2: Distribution density of the analyzed chemical profiles in the ion chromatogram of *Rh. rosea* supercritical CO_2-extract.

rosea gives an extract that is extremely effective in terms of the composition of biologically active substances, which should find further application in both pharmacological, medical, and perfumery developments. In this regard, research on the development of a technology for obtaining supercritical drugs from rhizomes and roots of *Rh. rosea*, containing a complex of biologically active substances of this plant, and the development of modern drugs on their basis, presented primarily in the form of solid dosage forms, are relevant.

Table 2: Polyphenols and other substances identified from the SC-CO_2 extracts of *Rh. rosea*.

No.	Compound group	Identification	Formula	Calculated mass	Observed mass $[M-H]^-$	Observed mass $[M+H]^+$	Observed mass $[M+Na]^+$	MS/MS stage 1 fragmentation	MS/MS stage 2 fragmentation	References
					Polyphenols					
1	Flavonol	Acacetin [linarigenin; buddleoflavonol]	$C_{16}H_{12}O_5$	284.2635	—	285	—	240	212; 183; 165	*Mentha* [51]; *Ocimum* [41]
2	Flavonol	Kaempferol	$C_{15}H_{10}O_6$	286.2363	—	287.11	—	269; 189; 133	213; 119	*Rhodiola sachalinensis* [52, 53]; *Rhodiola crenulata* [35, 54]; *Rhodiola sacra* [55]; *Impatiens glandulifera Royle* [56]
3	Flavonol	Quercetin	$C_{15}H_{10}O_7$	302.2357	—	303.09	—	123; 147; 201; 233; 256	135; 175; 201	*Rhodiola rosea* [57]; *Rhodiola dumulosa* [58]; *Rhodiola crenulata* [35, 59]; *Impatiens glandulifera Royle* [56]; *Eucalyptus* [42]; *Triticum* [43]
4	Flavonol	Herbacetin (3, 5, 7, 8-tetrahydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one)	$C_{15}H_{10}O_7$	302.2357	—	303.08	—	285	212; 268	*Rhodiola rosea* [3, 60–62]; *Rhodiola crenulata* [35]; *Ocimum* [41]
5	Flavonol	Dihydroquercetin (taxifolin; taxifoliol)	$C_{15}H_{12}O_7$	304.2516	—	305.1	—	287; 269; 249; 231; 217; 147	269; 227; 213; 173; 161	*Larix dahurica* [63]; *Eucalyptus* [42]; *Vitis vinifera* [37]
6	Flavonol	Herbacetin 8-methyl ether	$C_{16}H_{12}O_7$	316.2623	—	317.06	—	298; 183; 112	279; 228; 129	*Rhodiola crenulata* [35]; *Rhodiola dumulosa* [64]
7	Flavonol	Gossypetin (articulatidin; equisporol; 8-methoxy-hydroxyquercetin)	$C_{15}H_{10}O_8$	318.2351	—	319.03	—	300.97	228; 166; 110	*Rhodiola rosea* [3, 62]
8	Flavonol	Mearnsetin	$C_{16}H_{12}O_8$	332.2617	—	333.1	—	317; 292; 195	221; 183	*Eucalyptus* [42]
9	Flavonol	Rhodalin (herbacetin-8-O-beta-D-xylopyranoside)	$C_{20}H_{18}O_{11}$	434.3503	—	434.96	—	389.90; 266.93	308; 345; 267; 167	*Rhodiola rosea* [17]
10	Flavonol	Taxifolin-O-pentoside	$C_{20}H_{20}O_{11}$	436.371	—	436.99	—	391; 285; 177	352; 269; 173	*Vitis vinifera* [37]
11	Flavonol	Quercitrin (quercetin 3-L-rhamnoside; quercetrin)	$C_{21}H_{20}O_{11}$	448.3769	—	448.90	—	302.95	169; 303	*Lotus japonicus* [65]; *Rhodiola rosea* [62]; *Rhodiola crenulata* [35, 59]

Table 2: Continued.

No.	Compound group	Identification	Formula	Calculated mass	Observed mass $[M-H]^-$	Observed mass $[M+H]^+$	Observed mass $[M+Na]^+$	MS/MS stage 1 fragmentation	MS/MS stage 2 fragmentation	References
12	Flavonol	Rhodiolatuntoside	$C_{21}H_{20}O_{11}$	448.3769	—	450.92	—	332.90	200.89; 154.87	*Rhodiola sachalinensis* [66]; *Rhodiola crenulata* [67]
13	Flavonol	Rhodiolinin (rhodiolin)	$C_{25}H_{20}O_{10}$	480.4203	—	480.95	—	401; 313; 233; 173	357; 313; 269; 233; 145	*Rhodiola rosea* [2, 16]; *Rhodiola sachalinensis* [52, 53, 68]; *Rhodiola crenulata* [69]
14	Flavonole glycoside	Kaempferol-3-xylosyl-glycoside	$C_{26}H_{28}O_{15}$	580.4915	—	581.09	—	331; 509; 469; 375; 243	330.89; 287.99; 141.74	*Rhodiola rosea* [61]
15	Flavonole glycoside	Rhodiosin	$C_{27}H_{30}O_{16}$	610.5175	—	610.82	—	303; 449	169	*Rhodiola rosea* [2, 16, 70, 71]; *Rhodiola sachalinensis* [52, 68]; *Rhodiola crenulata* [69]
16	Flavonole glycoside	Rhodiolgidin	$C_{27}H_{30}O_{17}$	626.5179	—	627.30	—	344.78	344.7	*Rhodiola rosea* [3, 17]; *Rhodiola crenulata* [35]
17	Flavan-3-ol	Catechin	$C_{15}H_{14}O_6$	290.2681	—	291.97	—	250	227	*Rhodiola rosea* [50]; *Rhodiola crenulata* [35]; strawberry, cherimoya [36]; pear [45]
18	Flavan-3-ol	Epicatechin ((2R,3R)-2-(3,4-dihydroxyphenyl)-3,5,7-chromanetriol)	$C_{15}H_{14}O_6$	290.2681	—	291.1	—	261; 273; 217; 173; 163	243; 191; 173; 143	*Rhodiola rosea* [50]; *Rhodiola crenulata* [35]; *Rhodiola kirilowii* [72]
19	Flavan-3-ol	Gallocatechin ((+)-gallocatechin)	$C_{15}H_{14}O_7$	306.27	305.06	—	—	179; 168; 261	124	Red wine [73]; *Licania ridigna* [74]
20	Flavan-3-ol	(-)-Epicatechin gallate	$C_{22}H_{18}O_{10}$	442.3723	—	443.01	—	363.12	319.16	*Rhodiola rosea* [39]; *Rhodiola crenulata* [35, 75]; *Rhodiola kirilowii* [50, 76]
21	Flavanone	Eriodictyol-7-O-glucoside (pyracanthoside; miscanthoside)	$C_{21}H_{22}O_{11}$	450.3928	—	451.00	—	333; 433; 155	288; 201	*Impatiens glandulifera Royle* [56]
22	Flavone	Luteolin	$C_{15}H_{10}O_6$	286.2363	285.02	—	—	241; 168; 124	124.02	*Rhodiola crenulata* [35, 54]; *Rhodiola kirilowii* [72]; *Rhodiola sachalinensis* [53, 77]

Table 2: Continued.

No.	Compound group	Identification	Formula	Calculated mass	Observed mass $[M-H]^-$	Observed mass $[M+H]^+$	Observed mass $[M+Na]^+$	MS/MS stage 1 fragmentation	MS/MS stage 2 fragmentation	References
23	Flavone	Tricin	$C_{17}H_{14}O_7$	330.2889	329.18	—	—	299; 311; 229; 171	211.04; 125.14	*Triticum aestivum L.* [77, 78]; *Rhodiola rosea* [61, 79]; *Rhodiola sacra* [55]; *Rhodiola sachalinensis* [53]; *Rhodiola crenulata* [59]
24	Flavone	Luteolin-7-O-*α*-L-rhamnoside	$C_{21}H_{20}O_{10}$	432.3775	430.99	—	—	284.93	283.93	*Rhodiola crenulata* [35];
25	Flavone	Tricin 7-O-glucoside	$C_{23}H_{24}O_{12}$	492.4295	—	493.11	—	401; 292; 201	383; 329; 280; 156	*Rhodiola rosea* [61, 70, 79]; *Rhodiola crenulata* [59]
26	Flavone	Apigenin-O-hexoside derivative	$C_{26}H_{25}O_{12}$	529.4695	—	531.08	—	433; 485; 243; 177	399; 310	*Strawberry* [36]
27	Flavone	Tricetin trimethyl ether, 7-O-hexoside malonylated	$C_{27}H_{28}O_{15}$	592.5022	591.23	—	—	533; 437; 323	197.01	*Triticum aestivum L.* [77]
28	Flavone	Tricin, 7-O-glucoronyl-O-hexoside	$C_{29}H_{32}O_{18}$	668.5536	—	669.13	—	419; 375; 271	375; 243; 171	*Triticum aestivum L.* [77]
29	Flavone	Tricin trimethyl ether, 7-O-hexosyl-hexoside	$C_{30}H_{36}O_{17}$	668.5966	—	669.01	—	419; 557; 331; 287	375; 331; 215	*Triticum aestivum L.* [77]
30	Flavone	Tricin, O-pentoside; O-dihexoside	$C_{35}H_{44}O_{21}$	800.7113	—	801.24	—	409; 655; 509; 252	—	*Triticum aestivum L.* [77]
31	Hydroxycinammic acid	Ferulic acid	$C_{10}H_{10}O_4$	194.184	—	195.07	—	176.8	—	*Rhodiola crenulata* [35]; *Triticum* [43]
32	Hydroxycinammic acid	Caffeoylmalic acid	$C_{13}H_{12}O_8$	296.2296	—	297.09	—	279; 211; 163	265; 163; 135	Strawberry [36]
33	Cinnamate ester	4-O-*p*-Coumaroylquinic acid	$C_{16}H_{18}O_8$	338.3098	—	338.94	—	189; 151	—	Pear [45]
34	Cinnamic alcohol glycoside)	Rosin (trans-cinnamyl O-beta-D-glycopyranoside)	$C_{15}H_{20}O_6$	296.3157	—	297.06	—	255; 179; 115	215; 110	*Rhodiola rosea* [16, 49, 80]; *Rhodiola crenulata* [35]; *Rhodiola sachalinensis* [53]
35	Cinnamic alcohol glycoside	Triandrin	$C_{15}H_{20}O_7$	312.3151	—	313.21	—	268.14	240; 211; 193	*Rhodiola crenulata* [35, 54]; *Rhodiola rosea* [10, 81]
36	Cinnamic alcohol glycoside	Sachaliside 1	$C_{15}H_{20}O_7$	312.3151	311.13	—	—	309.08; 182.96	247.08; 119.01	*Rhodiola rosea* [9]
37	Cinnamic alcohol glycoside	*p*-Hydroxyphenacyl-*β*-D-glucopyranoside	$C_{14}H_{18}O_8$	314.2879	—	314.97	—	294; 163	—	*Rhodiola crenulata* [35, 82];

Table 2: Continued.

No.	Compound group	Identification	Formula	Calculated mass	Observed mass $[M-H]^-$	Observed mass $[M+H]^+$	Observed mass $[M+Na]^+$	MS/MS stage 1 fragmentation	MS/MS stage 2 fragmentation	References
38	Cinnamic alcohol glycoside	(2E)-3-(4-methoxyphenyl)-2-propen-1-yl-beta-D-glycopyranoside	$C_{16}H_{22}O_7$	326.3417	325.09	—	—	182.99	119.09	*Rhodiola rosea* [9]
39	Cinnamic alcohol glycoside	Coniferin	$C_{16}H_{22}O_8$	342.3411	—	343.01	—	240; 301; 129	240; 183	*Rhodiola crenulata* [35, 54]
40	Phenylpropanoid (cinnamicacid derivative glycoside)	Chlorogenic acid (3-O-caffeoylquinic acid)	$C_{16}H_{18}O_9$	354.3087	—	355.04	—	335; 285; 203	200.0	*Rhodiola rosea* [2]; *Eucalyptus* [42]; *Triticum* [43];
41	Cinnamic alcohol glycoside	Rosavin (trans-cinnamil O-(6′-O-alpha-L-arabinopyranosyl-beta-D-glycopyranoside)	$C_{20}H_{28}O_{10}$	428.4303	—	—	451.00	333; 155; 201	200.94	*Rhodiola rosea* [16, 49, 83]; *Rhodiola crenulata* [84]; *Rhodiola sachalinensis* [53]; *Rhodiola quadrifida* [2, 85]
42	Cinnamic alcohol glycoside	Rosarin (trans-cinnamyl O-(6′-O-alpha-L arabinofuranosyl-beta-D-glycopyranoside)	$C_{20}H_{28}O_{10}$	428.4303	—	429.01	—	285; 199	384; 328; 230; 159	*Rhodiola rosea* [9, 16, 49, 83]; *Rhodiola sachalinensis* [53]
43	Phenylpropanoid (cinnamic acid derivative)	Di-O-caffeoylquinic acid	$C_{25}H_{24}O_{12}$	516.4509	—	516.86	—	352; 431; 276	200; 135	*Pear* [45]
44	Gallic acid derivative	6-O-galloyl-salidroside	$C_{21}H_{24}O_{11}$	452.4087	—	453.09	—	435; 209; 336	226; 336; 417	*Rhodiola crenulata* [35, 54]; *Rhodiola rosea* [39]
45	Gallic acid derivative	1,2,6-Tri-O-galloyl-beta-D-glucoside	$C_{27}H_{24}O_{18}$	636.4687	—	637.28	—	507; 566; 620; 488; 366; 189	—	*Rhodiola rosea* [39]
46	Anthocyanidin	Pelargonidin-3-glucoside (callistephin)	$C_{21}H_{21}ClO_{10}$	468.8444	—	469.88	—	357.05	247.00	*Triticum* [43]
47	Anthocyanidin	Pelargonidin (3-O-(6-O-malonyl-beta-D-glucoside))	$C_{24}H_{23}O_{13}$	519.4388	—	520.10	—	433; 184	307; 163	*Gentiana lutea* [86]; wheat [87]
48	Proanthocyanidin	Proanthocyanidin B1 (procyanidin B1; procyanidin dimer B1)	$C_{30}H_{26}O_{12}$	578.5202	577.21	579.07	—	197; 254; 351; 393; 407; 421	196.94; 133.04; 182.93	Pear [45]; *Eucalyptus* [42]
49	Anthocyanidin	Cyanidin-3-(3″,6″-dimalonylglucoside)	$C_{27}H_{24}O_{17}$	620.4773	—	621.17	—	619; 432; 264	601; 518; 419	Wheat [87]
50	Anthocyanidin	Pelargonidin (3-O-(6-O-malonyl-beta-D-glucoside)-5-beta-D-glucoside	$C_{30}H_{33}O_{18}$	681.5812	—	682.10	—	515.58; 353.14	351; 295; 173	*Gentiana lutea* [86]

Table 2: Continued.

No.	Compound group	Identification	Formula	Calculated mass	Observed mass $[M-H]^-$	Observed mass $[M+H]^+$	Observed mass $[M+Na]^+$	MS/MS stage 1 fragmentation	MS/MS stage 2 fragmentation	References
51	Coumarin	Esculetin (cichorigenin; esculetin)	$C_9H_6O_4$	178.1415	—	179.02	—	147.01	119.03	*Ledum palustre* [38]; *Vitis vinifera* [37]
52	Coumarin	Esculin (esculin; esculoside; polichrome)	$C_{15}H_{16}O_9$	340.2821	—	340.91	—	133; 283; 322	175; 133	Dog plasma [38]; rat plasma [88]
53	Coumarin glucoside	Fraxin (Fraxetin-8-O-glucoside)	$C_{16}H_{18}O_{10}$	370.3081	—	370.97	—	356; 193; 123	207.02	Dog plasma [38]; rat plasma [88]
54	Lignan	Hinokinin	$C_{20}H_{18}O_6$	354.3533	—	355.01	—	337; 283; 203	239; 133	*Triticum aestivum L.* [89]; *Bursera simaruba* [90]
55	Lignan	Pinoresinol	$C_{20}H_{22}O_6$	358.3851	—	359.02	—	341; 187	323; 187	*Triticum aestivum* L. [78]; *Eucommia cortex* [47]
56	Aryl-beta-glycoside	Arbutin	$C_{12}H_{16}O_7$	272.2512	—	273.17	—	217; 163	161.09	Strawberry, blueberry, pear [91]; pear [45]
					Others					
57	Natural water-soluble vitamin	L-ascorbic acid	$C_6H_8O_6$	176.1241	—	176.98	—	145.00	117.03	Strawberry, lemon, papaya [36]
58	Aldaric acid	Glucaric acid (D-glucaric acid)	$C_6H_{10}O_8$	210.1388	—	211.01	—	192; 115	129.05	Cherimoya, papaya [36]
59	Monobasic saturated carboxylic acid	Palmitic acid (hexadecanoic acid; palmitate)	$C_{16}H_{32}O_2$	256.4241	—	257.02	—	237; 137	221; 125	*Salviae* [44]
60	Acyclic alcohol nitrile glycoside	Heterodendrin ((2R)-2-(β-D-glucopyranosyloxy)-3-methylbutanenitrile)	$C_{11}H_{19}O_6N$	261.2717	—	263.96	—	155; 228	—	*Rhodiola crenulata* [35]
61	Monobasic saturated carboxylic acid	Linolenic acid (alpha-linolenic acid; linolenate)	$C_{18}H_{30}O_2$	278.4296	—	279.1	—	261; 243; 187; 123	173; 131	*Salviae* [44]; rice [48]
62	Phenylethane glycoside	Picein (ameliaroside; salicinerin; salinigrin; piceoside)	$C_{14}H_{18}O_7$	298.2901	—	299	—	271; 211; 179	254; 225; 197	*Rhodiola rose* [9]; *Rhodiola crenulata* [82]
63	Phenylethane glycoside	Salidroside (2-(4-hydroxyphenyl) ethyl β-D-glucopyranoside)	$C_{14}H_{20}O_7$	300.3044	—	301.15	—	240; 201	183; 110	*Rhodiola crenulata* [35, 54]; *Rhodiola rosea* [1, 92, 93]; *Rhodiola sachalinensis* [53]; *Rhodiola kirilowii* [2]
64	Phenylethane glycoside	Icariside D2	$C_{14}H_{20}O_7$	300.3044	—	301.06	—	240; 201; 135	183; 113	*Rhodiola rosea* [39]; *Rhodiola crenulata* [54, 82]; *Rhodiola sacra* [55];
65	Acyclic alcohol glycoside	Creoside II	$C_{14}H_{26}O_7$	306.352	—	307.99	—	199; 255	—	*Rhodiola crenulata* [35, 54]

Table 2: Continued.

No.	Compound group	Identification	Formula	Calculated mass	Observed mass $[M-H]^-$	Observed mass $[M+H]^+$	Observed mass $[M+Na]^+$	MS/MS stage 1 fragmentation	MS/MS stage 2 fragmentation	References
66	Phenylethane glycoside	Viridoside	$C_{15}H_{22}O_7$	314.331	—	315.04	337.11	319.13; 209.08	151; 207; 262; 301	*Rhodiola viridula* [94]; *Rhodiola rosea* [83]; *Rhodiola crenulata* [35]; *Rhodiola sachalinensis* [53]
67	Acyclic alcohol glycoside	Rosiridin (3,7-dimethylocta-2,6-diene-1,4-diol; 1-O-beta-D-glucopyranoside)	$C_{16}H_{28}O_7$	332.3893	—	333.02	—	247; 175	181.93	*Rhodiola crenulata* [35]; *Rhodiola rosea* [2, 17, 49]; *Rhodiola sachalinensis* [95]
68	Acyclic alcohol glycoside	Rhodioloside A	$C_{16}H_{28}O_8$	348.3887	—	349.02	371.03	271; 281; 305; 331; 257; 231; 219; 167; 141	268; 256; 243; 229; 215; 193; 143	*Rhodiola rosea* [1, 92]; *Rhodiola crenulata* [35]
69	Acyclic alcohol glycoside	Rhodioloside D	$C_{16}H_{30}O_8$	350.4046	—	351.06	—	258; 220; 131	257; 141	*Rhodiola rosea* [1, 83, 92]; *Rhodiola crenulata* [35]
70	Tetracyclic diterpenoid	Grayanotoxin II	$C_{20}H_{32}O_5$	352.4651	—	353.04	—	335; 282; 203	315; 245; 113	Grayanotoxins [96]
72	Benzidine glycoside	Phenylmethyl (6-O-alpha-L-arabinopyranosyl-beta-D-glycopyranoside)	$C_{18}H_{26}O_{10}$	402.3930	—	402.86	—	343; 283; 175	283	*Rhodiola rosea* [83]; *Rhodiola sachalinensis* [53]
73	Acyclic alcohol glycoside	Rhodiooctanoside	$C_{19}H_{36}O_{10}$	424.4831	—	424.94	—	290.96	173; 261	*Rhodiola crenulata* [35, 54]; *Rhodiola kirilowii* [97]; *Rhodiola sacra* [98]
74	Phenylethane glycoside	Mongrhoside	$C_{20}H_{30}O_{11}$	446.4456	—	446.65	—	243; 379; 311	174.84	*Rhodiola rosea* [83]
75	Acyclic alcohol glycoside	Creoside V	$C_{21}H_{38}O_{10}$	450.5204	—	473.15	—	471; 254; 401	463.61	*Rhodiola crenulata* [35];
76	Hydroxy acid	Ursolic acid	$C_{30}H_{48}O_3$	456.7003	—	457.17	—	412; 307	368; 269	*Ocimum* [41]; pear [45]
77	Acyclic alcohol glycoside	Rhodioloside E	$C_{21}H_{38}O_{11}$	466.5198	—	467.95	—	399.94; 265; 332	331.88	*Rhodiola rosea* [1, 92]; *Rhodiola crenulata* [35, 54]; *Rhodiola sachalinensis* [13]; *Rhodiola sacra* [55]
78	Acyclic alcohol glycoside	Rhodioloside B	$C_{22}H_{38}O_{12}$	494.5299	493.22	—	517.97	447; 220	314.98	*Rhodiola rosea* [1, 92]; *Rhodiola crenulata* [35]

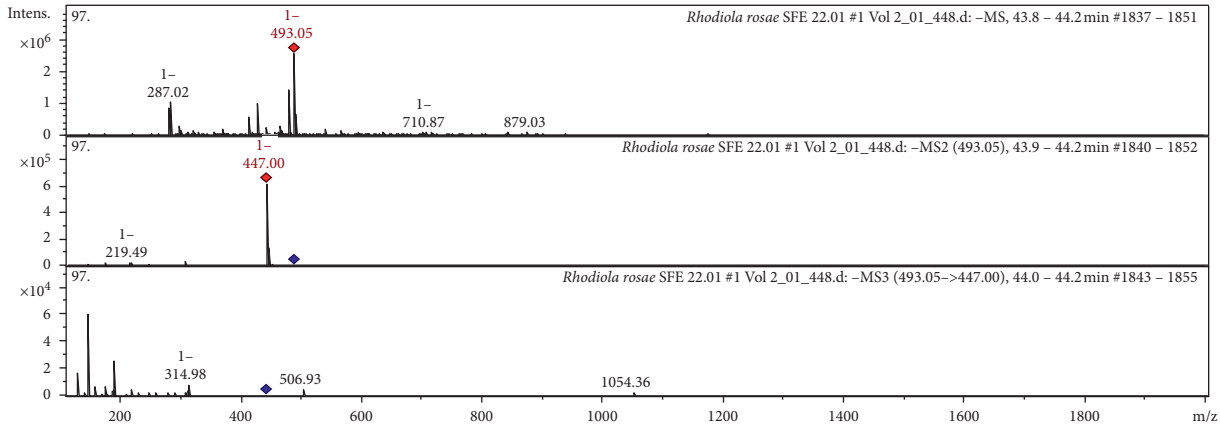


Figure 3: CID spectrum of the rhodioloside B from *Rh. rosea*, *m/z* 493.05.

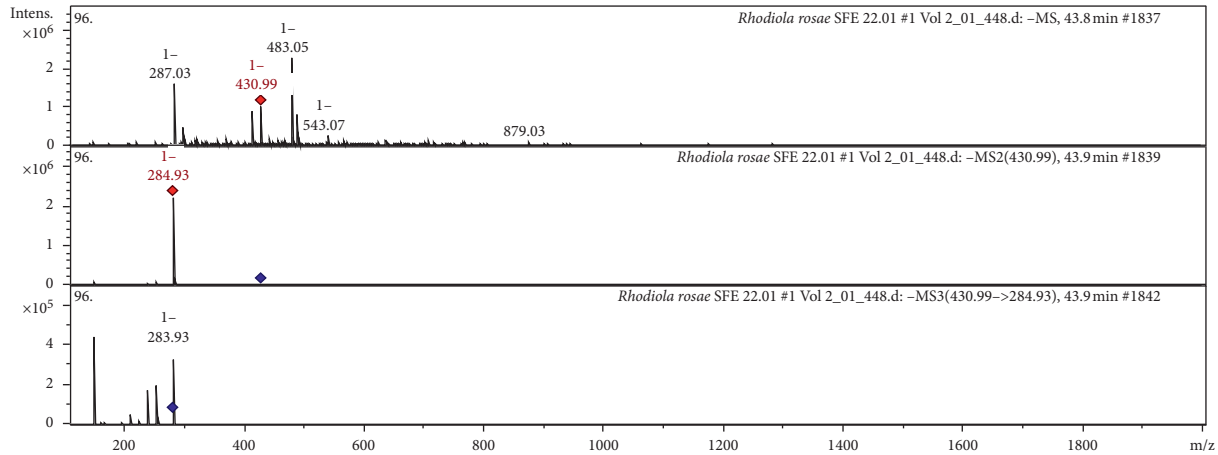


Figure 4: CID spectrum of luteolin-7-O-α-L-rhamnoside from *Rh. rosea*, *m/z* 430.99.

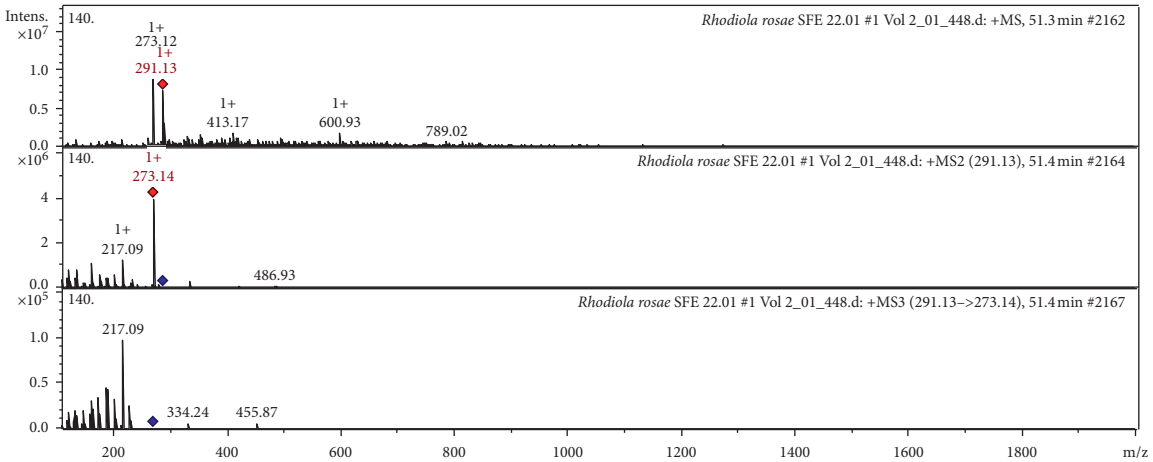


Figure 5: CID spectrum of catechin from *Rh. rosea*, *m/z* 291.13.

4. Conclusions

The *Rhodiola rosea* L. family *Crassulaceae* contains a large number of polyphenolic compounds and other biologically active substances. In this work, we tried to conduct a comparative metabolomic study of biologically active substances of *Rh. rosea* obtained from the area near Lake Baikal, Russia. HPLC in combination with a Bruker Daltoniks ion trap (tandem mass spectrometry) was used to identify target analytes in extracts.

The results showed the presence of 78 polyphenols and other compounds corresponding to the *Rhodiola rosea* family *Crassulaceae L.* species. In addition to the reported metabolites, 29 metabolites were newly annotated in *Rh. rosea*. There were flavonols: dihydroquercetin, acacetin, mearnsetin, and taxifolin-O-pentoside; flavones: apigenin-O-hexoside derivative, tricetin trimethyl ether 7-O-hexosyl-hexoside, tricin 7-O-glucoronyl-O-hexoside, and tricin O-pentoside and O-dihexoside; flavanone: eriodictyol-7-O-glucoside; flavan-3-ol gallocatechin; hydroxycinnamic acid; caffeoylmalic acid; di-O-caffeoylquinic acid; coumarins: esculetin; esculin, fraxin; lignans: hinokinin, pinoresinol, L-ascorbic acid, glucaric acid, palmitic acid, linolenic acid, etc.

The findings may support future research into the production of various pharmaceutical and dietary supplements containing *Rh. rosea* extracts. A wide variety of biologically active compounds opens up rich opportunities for the creation of new drugs and biologically active additives based on extracts from family *Crassulaceae*.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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