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Scutellaria lateriflora: The Polyphenolic Segment of the Metabolome of Aerial Organs

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Abstract—This study is a continuation of the investigation of the phenolic segment of the metabolome of *Scutellaria lateriflora*. The structural-class characterization and analysis of the distribution of polyphenolic metabolites, differing in the degree of methylation and glycosylation, in the aerial part of *S. lateriflora* introduced in the southern region of Primorskii krai are presented. The analysis showed that *S. lateriflora* predominantly accumulates nonmethylated glycosides, such as baicalein, as well as methylated flavones, including wogonin and 6-O-methylwogonin. The phenylethanoid verbascoside (caffeoyl-rutinoside dihydroxytyrosol), which is abundantly present in the plant roots, was detected in the aerial part of *S. lateriflora* in significantly lower quantities compared to flavonoids.

Keywords: *Scutellaria lateriflora*, vegetative organs, polyphenols, HPLC–MS/MS

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INTRODUCTION

The life of plants on both sides of the soil-atmosphere boundary has determined their stability and plasticity in the face of climatic fluctuations. By affecting the physiology and morphology of plants, constantly changing threats in two different habitats contributed to the formation of a chemical defense mechanism based on low-molecular-weight metabolites. Among the latter, polyphenols (PPs) of plants of the genus *Scutellaria*, in particular *S. lateriflora*, have been of scientific and practical interest for a long time (Li et al., 2012; Sherman and Joshee, 2022). The phenolic compounds of these plants mainly represented by flavones play a role in defending against physicochemical and biological damage, providing a broad adaptive potential to climate change and bioinvasion (Salam et al., 2023). Due to the presence of catechol (1,2-dihydroxybenzene) and pyrogallol (1,2,3-trihydroxybenzene) motifs in their molecules, flavones help increase plant tolerance to stresses that induce the production of reactive oxygen species (Modelli and Pshenichyuk, 2013; Pshenichyuk et al., 2015; Elkin et al., 2023a). Plants producing such molecules are often classified as medicinal (Qiao et al., 2016) or spice (Bolton et al., 2018) species. The high reactivity of such flavones is mitigated by the plant by methylating one or more hydroxyl groups, which helps prevent untimely autophagy, a process in which cells degrade their own components (Qiao et al., 2016; Elkin et al., 2018, 2023a). In some *Scutellaria* species, the polyphenolic segment of the root metabolome, along with flavones belonging to the class of phenylpropanoids, is also represented by the class of phenylethanoids (PEs). Thus, it was previously established that the majority of polyphenolic metabolites in the roots and hairy roots of *S. baicalensis* are phenylethanoids and flavonoids, which contain from two to five methoxyl groups (Elkin et al., 2023a, 2023b). Among the flavonoids of *S. lateriflora*, the most common are wogonin, 6-O-methylwogonin, and their glycosides. Phenylethanoids are represented by a number of caffeoyl-rutinoside dihydroxytyrosols (CRD), and their content is comparable to the amount of flavonoids (Elkin and Manyakhin, 2025).

To date, there are a number of publications noting the expression of genes responsible for the synthesis of certain polyphenols in various plant organs. The most representative studies are by Tuan et al. (2018) and Pei et al. (2022), which studied the expression of key genes responsible for the synthesis of polyphenols in a closely related species, the Baikal skullcap (*S. baicalensis*) and *S. lateriflora* itself. In the course of their study, the authors found that the synthesis of scutellarin, as well as its precursors (apigenin and naringenin), is localized in the aboveground organs. At the same time, the roots produce significant quantities of other characteristic metabolites, such as wogonin, baicalin, and their precursors. Another important aspect is the possibility of ascending flavonoid transport from the roots to the aboveground organs, which has been demonstrated in model plants, such as *Arabidopsis thaliana,* using exogenous administration of phenolic metabolites to the roots and their subsequent detection in the leaves (Buer et al., 2007). Such data support the hypothesis of flavonoid transport through the vascular system of the plant. In this regard, it is of interest to compare the composition of polyphenolic metabolites identified in the aboveground parts of the plant with the previously established root metabolome of polyphenolic compounds (Elkin and Manyakhin, 2025), as well as to suggest factors influencing transport depending on the growing conditions and needs of the plant organism.

MATERIALS AND METHODS

S. lateriflora plants were grown from seeds (Prairie Moon, United States) in the Nadezhdinskii district of southern Primorskii krai region. The plants were allowed to grow naturally without any additional nutrients. At the beginning of flowering, the upper third of the plants was harvested, air-dried, and crushed to a particle size of 1–2 mm. For further analysis, 5 g of plant material was divided into equal parts and extracted using three methods at a raw material : extractant ratio of 1 : 10. Dichloromethane (DCM) and 70% ethanol extracts were obtained by maceration for seven days with daily stirring. An aqueous extract was obtained by extraction in a water bath for 12 h at 50°C. The DCM extract was evaporated to dryness and redissolved in 96% ethanol. Prior to HPLC–MS/MS analysis, the extracts were centrifuged for 3 min at 15000 rpm and filtered through a PTFE filter (Phenomenex, 0.45 μm pore size, 13 mm diameter). The choice of extraction conditions was based on experience with this sample that demonstrates the absence of degradation of the analyzed metabolites under the described conditions. Extraction was performed at night.

HPLC–MS analyses of *S. lateriflora* extracts were performed at the Instrumental Centre of Biotechnology and Gene Engineering of Federal Scientific Center of the East Asia Terrestrial Biodiversity, Far Eastern Branch of the Russian Academy of Sciences. The conditions and parameters of the HPLC–MS/MS system used were described in a previous study on the polyphenol metabolome of the roots of this plant (Elkin and Manyakhin, 2025). Briefly, chromatographic separation was performed on an analytical column (Zorbax C18, 150 mm, i.d. 2.1 mm, 3.5 μm part size, Agilent Technologies, United States) with a gradient elution of 0.1% aqueous formic acid and acetonitrile. The chromatographic system was coupled with a mass spectrometer (Bruker HCT ultra PTM Discovery System, Bruker Daltonik GmbH, Bremen, Germany) equipped with an electrospray ionization source (ESI). MS analyses were performed in the negative ion mode.

RESULTS AND DISCUSSION

The aromatic nature of polyphenol molecules allows their selective detection in complex plant extracts in the UV range at 275 nm. Insets (a) and (b) (Fig. 1) show the HPLC–UV profiles of three plant extracts: (1) dichloromethane, (2) hydroalcoholic, and (3) aqueous. The HPLC–UV profiles demonstrate the simple composition of the most abundant phenolic compounds in the aboveground part of the plant. Since the PPs of the roots of *S. lateriflora* (Elkin and Manyakhin, 2025) and its genetically close relative *S. baicalensis* (Qiao et al., 2016; Elkin et al., 2023b) are known, a number of chromatographic peaks were identified by retention times, and mass spectrometric signals were decoded based on the literature. A complete list of identified phenolic metabolites, including $[M-H]^-$ values, characteristic MS^2 ions, retention times, and organ localization, is presented in the Appendix (Table 1S).

An interesting result of the extraction of the aerial part of the plant with dichloromethane is demonstrated by HPLC–UV and the total ion current profile (TIC) (Fig. 1, inset (a)). The presence of two peaks of compounds (k) and (3) in both profiles indicates the aromatic nature of these molecules containing –OH and/or –COOH groups. The parent ion with *m/z* 301 in the mass spectrum indicates the molecular weight of compound (k) of 302 Da (Appendix S1). The products of its collisional fragmentation demonstrate the presence in the molecule of a nonpolar skeleton with a mass of 122 Da acylated with caffeic acid. Its presence in the molecule of compound (k) characterizes the carboxylate anion with *m/z* 179 in the ms^2 spectrum of (k). The peak of compound (3) at 17.7 min in both profiles corresponds to the compound with ion *m/z* 269, the ms^2 spectrum of which is characteristic of baicalein (3) (Appendix C3). Extraction with nonpolar dichloromethane (DCM) of two polar compounds—(k) and (3) containing catechol and pyrogallol motifs in the structure of the molecules, respectively—requires further study and explanation.

The total ion current (2TIC) of the aqueous-alcoholic extract (Fig. 1) demonstrates the diversity of extraction products; however, it does not fully convey the complexity of the composition of compounds in the aboveground part of the plant, as observed in the ion chromatograms (IC) with ms^2 spectra and the integral mass spectra of the conditional fractions of the extract (Appendix C2–C5). The chromatographic distribution of compounds according to their polarity and mass spectra and the existing experience in the differential analysis of metabolites of plants of the genus *Scutellaria* (Elkin et al., 2018, 2023b; Elkin and Manyakhin, 2025) made it possible to determine the PPs of the aqueous-alcoholic extract of the aboveground part of *S. lateriflora*. Thus, the 2TIC profile is conditionally divided into four fractions (F): 1, car-

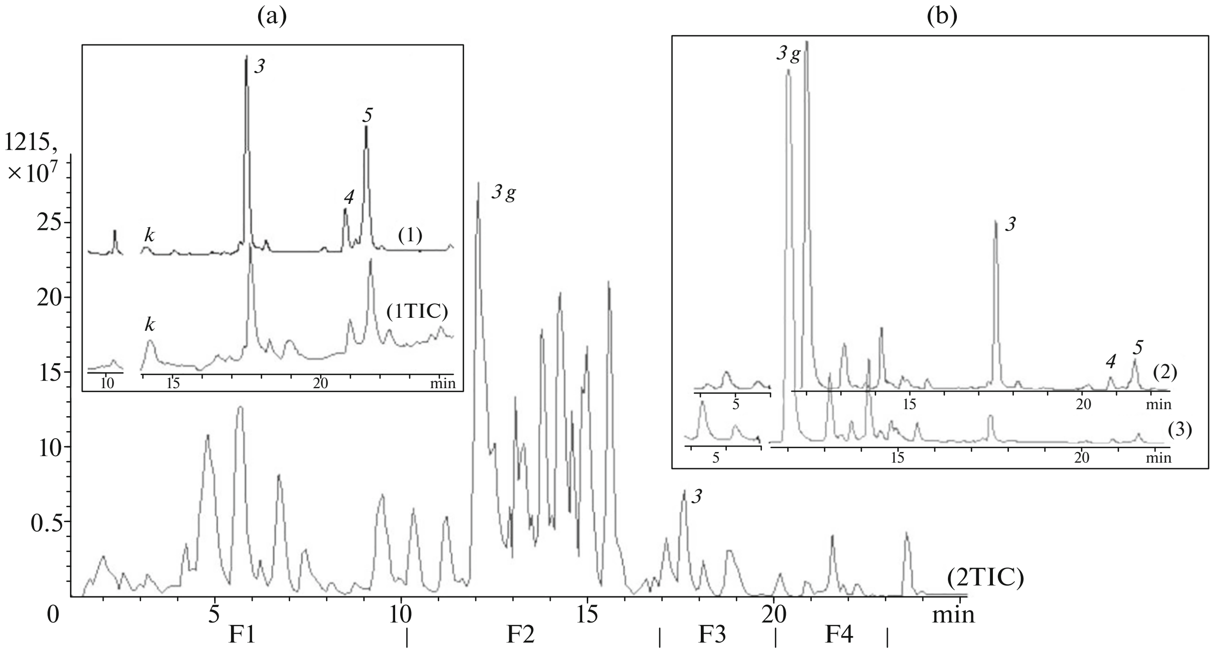

Fig. 1. Chromatogram profile of extracts: (2TIC) total ion current of 70% ethanol extract of *S. lateriflora* aerial parts. Insert (a): (1) UV and (1TIC) total ion current of dichloromethane extract. Insert (b): (2) UV of 70% ethanol extract, (3) UV of aqueous extract, 3g—7-D-glucuronic acid-5,6-dihydroxyflavone (baicalin). (k) Unknown compound. (3) 5,6,7-Tri-OH flavone (baicalein), (4) 5,7-dihydroxy-8-OMe flavone (wogonin); (5) 5,8-di-OH-6-OMe flavone (oroxylin A). F1–F4 are conditional fractions of the extract chromatogram.

bohydrates; 2, flavone glycosides; 3, unmethylated flavones; and 4, methylated flavones (Fig. 1).

Methylated flavones (MFs) are represented by (4) wogonin and (5) oroxylin A, with the latter predominating (Fig. 2a), whereas their content in the roots has an inverse ratio (Elkin and Manyakhin, 2025). Conventionally taking the baicalein peak (3) as a standard, it is clear that, relative to it, MFs are most effectively extracted by DCM; their presence in the aqueous extract is, as expected, significantly lower (Fig. 1, insert (b) profile (3)). The aqueous-alcoholic (2) and aqueous (3) extracts demonstrate similarity in the composition of compounds in the UV profiles.

The ion chromatogram (IC) profiles of MFs (Fig. 2a), at first glance, confirm the species-specific nature of methylation at the hydroxyl group at the C6 atom of flavones detected in the plant roots (Elkin and Manyakhin, 2025). However, given the established differences in the PP content between organs, as well as the literature data on the possible transport of flavonoids (Buer et al., 2007), the involvement of mechanisms of movement of these compounds from the roots to the aboveground part as one of the factors complementing tissue-specific expression cannot be ruled out. Flavones with one methyl group (4) and (5) ascend from the roots to the aboveground part of the plant with a predominance of oroxylin A (5), in which the OMe group is also located at the C6 atom. This observation is also true for dimethoxy flavones (10) and (11), where the predominance of 6-OMe wogonin (11) is shown. The products of the second echelon of hydroxylation of the carbon atoms of the B ring of the flavone molecules (4) and (5), with the exception of the C4' atom, are represented in the IC by a characteristic group of ion peaks with *m/z* 299. The ratio of the methylated derivatives characterized above is also preserved in their glycosides (Fig. 2b). Due to the COO^- group of the glucuronic acid of the glycosides, the entry of not only mono-OMe flavones (*m/z* 459), but also di-OMe flavones (*m/z* 489, *m/z* 505) is noticeable in the aboveground part.

Unmethylated flavones, products of the specific 6- and 8-hydroxylation of chrysin (1), are represented practically only by baicalein (3), as can be seen from the IC ion profile at *m/z* 445 (Fig. 3a). The peaks of the IC with *m/z* 285 correspond to tetra-OH flavones by nominal mass; however, their ms^2 spectra indicate compounds of a different nature. For example, the low-efficiency peak at 12.4 min is baicalein (3), whereas the substance elutes at 17.7 min. The reason for this is the partial ion-phase hydrolysis in the ionization source of the abundant baicalin glycoside and its dimer, ion *m/z* 891. The peak at 14.6 min corresponds to the ion *m/z* 285, but paired with the abundant ion *m/z* 459 of the glycoside oroxylin A (5g), which allows us to classify it as aglycone of flavanone-oroxylin A (Elkin and Manyakhin, 2025), due to the abundant fragmentation typical of flavanones. Peaks at 21.0 and 21.8 min are also associated with flava-

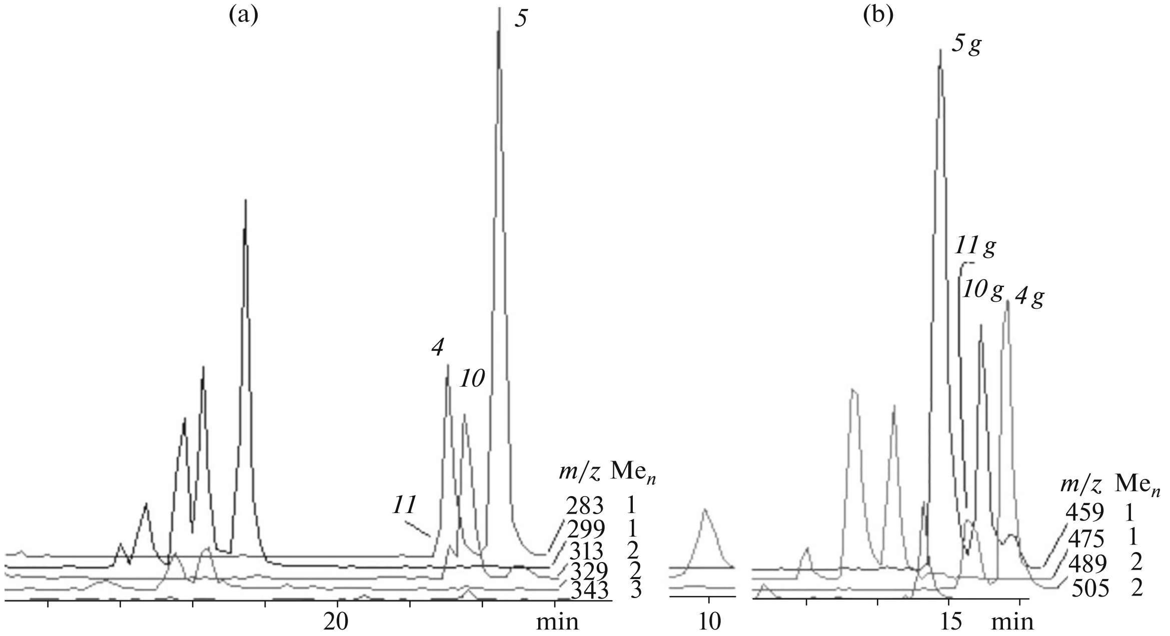

Fig. 2. Ion chromatograms of the most abundant methylated (a) flavones and (b) glycosides; (11) 5,8-di-OH-5,7-di-OMe flavone; (4) wogonin; (10) 5,7-di-OH-6,8-di-OMe flavone; (5) oroxylin A; (g) glycoside.

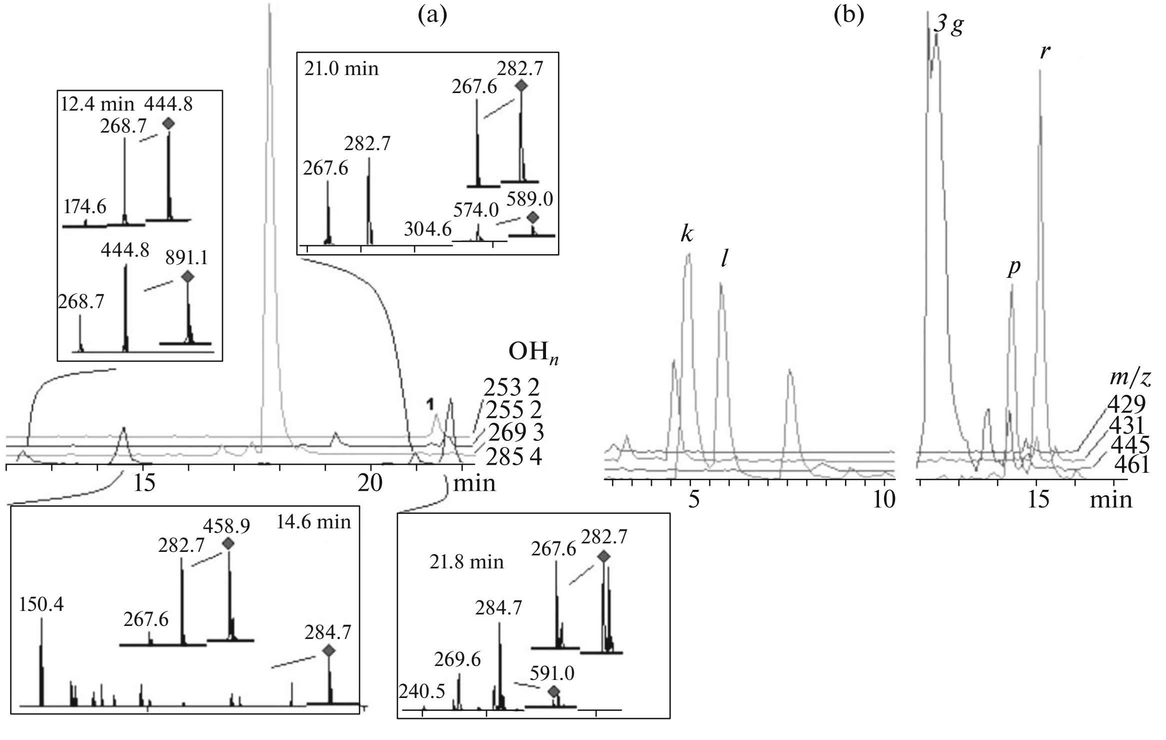

Fig. 3. Ion chromatograms of (a) unmethylated flavones and (b) their glycosides; (3) baicalein; (1) chrysin; (k, l) glycosides of tetra-OH flavones; (3g) baicalin; (p) ^{13}C isotope peak of oroxylin A glycoside; (r) form of flavonone–wogonin glycoside (4og).

nones, following the shoulder of flavones (4) and (5) and partly with ^{13}C isotopic molecules.

Ion chromatograms of unmethylated flavone glycosides show a similar pattern, also with a clear predominance of baicalin (3g), peak m/z 445 (Fig. 3b). However, the shape of the diffuse doublet peak raises the question of its cause. Screening of the ms^2 spectra along the contour of the IC peak at m/z 445 indicates

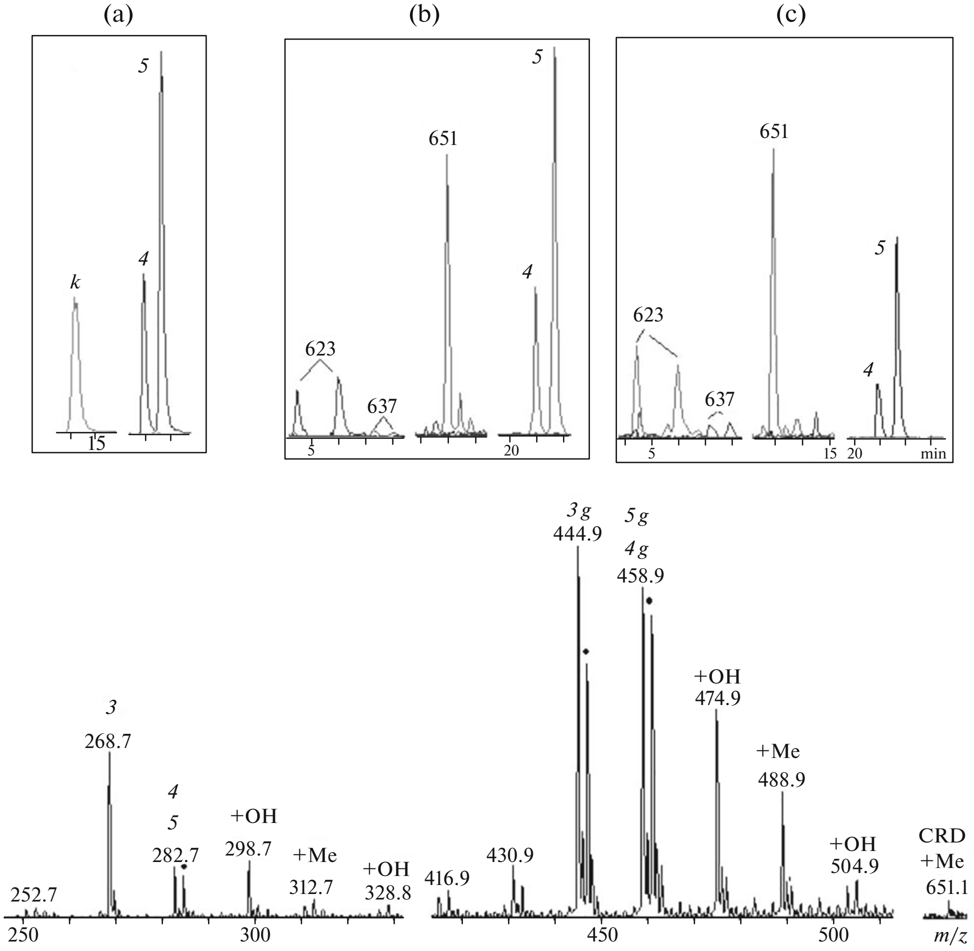

Fig. 4. Integral mass spectrum of polyphenols in the aqueous–alcoholic extract of *S. lateriflora* aerial parts. Sector *m/z* 250–330, unmethylated and sector *m/z* 420–510, methylated glycosides of flavones; CRD, ion *m/z* 651 of di-OMe verbascoside. (•) Ions with a noticeable proportion of flavonones. +OH and +OMe, ions of subsequent oxidation and methylation of flavones (3), (4), and (5). Inserts: 2D–ion chromatograms of phenylethanoids (nominal ion masses $[M-H]^-$ 623, 637, 651) with LC-UV peaks of compounds (k), (4), (5) in extracts of the aerial parts of *S. lateriflora*: (a) dichloromethane, (b) 70% ethyl alcohol, (c) water.

the co-elution of baicalin (3g) with a disaccharide, presumably a sterol with a molecular weight of 582 Da eluting with a trace at 12.6 min (Appendix C4). An argument in favor of the nonaromatic nature of the disaccharide aglycone is the symmetrical shape of the baicalin (3g) peak by HPLC–UV (2) (Fig. 1, inset (b)). Peaks (l) and (k) on the profile of ions *m/z* 461, judging by the ms^2 spectra and retention times, should be assigned to the group of glycosides of tetra-OH flavones of the second echelon of hydroxylation (Appendix C5). The flavones themselves presumably produce the very weak ion signals at *m/z* 269 shown in the IC before and after the baicalein peak (3) (Fig. 3a). The ion peaks at *m/z* 461 (p) and (r) are due to flavonone satellites and, in part, to ^{13}C isotopic molecules of the glycoside oroxylin A (5g) and wogonin (4g). The ion at *m/z* 461 at 7.7 min, judging by the ms^2 spectrum, has a different origin (Appendix C5). The final spectrum of the eluted flavonoids from the aboveground parts of *S. lateriflora* is clearly illustrated by the integrated mass spectrum (Fig. 4). In total, their glycosides dominate over the flavone-aglycones themselves; however, the share of the latter remains quite noticeable, and the question of the peculiarities of transport of weakly polar methylated flavones from the roots by water remains open.

It was expected that, due to its water solubility, verbascoside, previously found in significant quantities among the PPs of the roots, would also predominate in the aboveground part of the plant (Yang et al., 2023); however, in the integral mass spectrum of fraction 1 (Appendix C5), no $[M-H]^-$ *m/z* 623 ions were found. In addition to the CRDs themselves, the plant roots produce a spectrum of their derivatives: methylated, acetylated, and glycosylated, with a predominance of di-OMe esters, ion *m/z* 651 (Elkin and Manyakhin, 2025). Using selective ion chromatograms of CRD isomers from three extracts of the aboveground part of the plant showed the presence of a small amount of two of their isomers, as well as a noticeable content of di-OMe esters, ion *m/z* 651 (Fig. 4, inserts (b) and (c)). The comparable content of CRD isomers is of interest. Isoverbascoside, an ion with *m/z* 623 at 6 min (acylated at the C-6 glucose atom with caffeic acid), has a comparable content to verbascoside. In the roots, the proportion of this isomer is several times lower. Whether this observation is due to changes in the molecular structure remains unclear. More interesting is the reason why the polar, water-soluble verbascoside does not migrate from the roots to the aboveground part of the plant.

CONCLUSIONS

Differential evaluation of polyphenolic metabolites from the vegetative part of *S. lateriflora* by derivative types reveals a high content of unmethylated glycosides (baicalein) and methylated (wogonin and 6-OMe wogonin) flavones. The need of the plant for baicalein may be related to the need urgently to counter the risk of bioinvasion. Methylated flavones perform at least a dual function: creating a hydrophobic barrier and stabilizing the highly reactive catechol and pyrogallol fragments of flavonoid molecules until their activity becomes necessary to protect the plant from damaging factors. Among the many phenylethanoloid derivatives, water-soluble verbascosides are found in the aboveground parts of plants in lower concentrations than flavonoids. The reasons for this distribution are not yet fully understood from a plant physiology perspective, given that verbascosides are present in significant quantities in the root system. The data obtained confirm that the distribution of polyphenolic metabolites in *S. lateriflora* is determined by both organ-specific synthesis and probable metabolite transport, which is consistent with previously published data for this and related species. The characteristic composition of metabolites of the aboveground organs, including the predominance of 6-OMe flavones, probably reflects the activity of specific O-methyltransferases functioning predominantly in this tissue. The results suggest that the composition of polyphenolic metabolites of *S. lateriflora* introduced in the southern Primorskii krai region may reflect the influence of regional conditions on the regulation of transport and local synthesis of flavonoids.

SUPPLEMENTARY INFORMATION

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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