

UDC 549.4:581.192:582.32/.998

## HALOGENATED PHENOLIC COMPOUNDS OF NATURAL ORIGIN CONSTITUTE A RARE MINOR GROUP OF SUBSTANCES (A REVIEW)

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The composition of primary and secondary metabolites of natural origin raw materials includes major and minor compounds. Halogenated phenolic compounds are considered rare minor compounds found in natural entities. This review provides a summary of currently known halogenated phenolic compounds of natural origin.

Until the 1970s, only a few substances had been isolated and their structures determined from bacteria, fungi, and marine algae. By now, information exists on several dozen halogenated flavonoids, isoflavonoids, chromones, and depsides, isolated from bees, bacteria, fungi, algae, lichens of the genera *Lecanora*, *Punctelia*, as well as representatives of higher plants (from families *Thymelaeaceae*, *Rutaceae*, *Apiaceae*, *Fabaceae*, *Moringaceae*, and two species of the *Equisetum* L. genus). Only 17 substances have been isolated and identified from higher plants. The main substituents in halogenated compounds are chlorine, and less frequently bromine and fluorine.

Several studies have shown that the presence of halogens in a molecule significantly enhances biological activity. For most halogenated compounds, antibacterial, antifungal, antioxidant, and anticancer activities have been established. Some substances exhibit anxiolytic, neuroleptic, and cardioprotective properties, which is of practical interest for developing medications for the treatment and prevention of socially significant diseases.

*Keywords:* halogenated phenolic compounds, higher plants, lichens, microorganisms, *Equisetum* L., *Rutaceae*, *Apiaceae*, *Thymelaeaceae*, *Fabaceae*, *Moringaceae*.

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**For citing:** Kolomiets N.E. *Khimiya Rastitel'nogo Syr'ya*, 2024, no. 4, pp. 24–31. (in Russ.). DOI: 10.14258/jcprm.20240413424.

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Among the primary and secondary metabolites of natural origin raw materials, both major and minor compounds are present. Both can contribute to the manifestation of pharmacological properties, including specific ones that are of interest for creating medicinal preparations for the treatment and prevention of socially significant diseases.

Halogenated phenolic compounds are considered to be found among rarely occurring minor compounds. Until the 1970s, these substances were only known to be isolated from bacteria, fungi, and marine algae. According to some authors, their presence in these entities is linked to the high concentration of chloride and bromide ions in seawater, causing marine organisms to produce more halogenated compounds compared to terrestrial organisms. For most «marine» halogenated compounds, antibacterial and anticancer activities have been established [1].

By now, information is available on several dozen halogenated flavonoids, isoflavonoids, chromones, and depsides, isolated from bees, bacteria, fungi, algae, and lichens, as well as representatives of higher plants such as flowering plants of the *Thymelaeaceae*, *Rutaceae*, *Apiaceae*, *Fabaceae*, *Moringaceae* family, and some species of the *Equisetum* L. genus. Literature contains articles, and books, providing information on studying the chemical composition, establishing substance structures, and pharmacological properties of individual species, as well as several species within families and genera. However, despite the seemingly significant number of known substances, systematic reviews on this compound group are absent in the literature, both in terms of halogenated phenolic compounds of natural origin as a whole, and plant-derived compounds in particular. This review aims to consolidate the information presented in the literature.

The most well-known, thoroughly studied, and industrially demanded for the production of medicinal preparations (antibiotics: Neomycin®, Streptomycin®, Cipemycin®, Grisemycin®, Bottromycin®, Chloramphenicol®)

is the *Streptomyces* bacteria genus, which produces dozens of halogenated biologically active compounds, mainly containing chlorine, and less frequently bromine and fluorine [2, 3].

By the end of 2020, there was information on 127 halogen-containing compounds from a strain of *Streptomyces* sp. collected from the marine sponge *Haliclona* p. [4].

Agelolin A is a new chlorinated quinoline (Fig. 1) isolated from the fermentation of *Streptomyces* sp. Its structure was determined using spectroscopic analysis including 1D and 2D NMR, HR-ESI-MS. This compound exhibited antioxidant effects, reducing oxidative stress and genomic damage induced by the oxidative stress inducer 4-nitroquinoline-1-oxide [5]. This same compound inhibits the growth of *Chlamydia trachomatis* [6].

The structures of the three new 3-phenylpropanoic acids (3-(3,5-dichloro-4-hydroxyphenyl)propanoic acid, 3-(3,5-dichloro-methyl ether 4-hydroxyphenyl)propanoic acid, 3-(3-chloro-4-hydroxyphenyl)propanoic acid) isolated from *Streptomyces coelicolor* were established using NMR and high-resolution ionization mass spectrometry (HRESI-MS) (Fig. 2). All substances demonstrated significant and selective antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [7].

In 2012, the isolation a few more new ones of pestalochromones from the fungal genus *Pestalotiopsis*, an ascomycete, was reported (Fig. 3): pestaloether A, pestaloether B, pestalochromone A, pestalochromone B, pestalochromone C, pestheic acid, chlorizosulochrine dehydrate, chlorizosulochrine. The authors established the structures of these compounds based on  $^1\text{H}$  и  $^{13}\text{C}$  NMR spectroscopy, correlation spectroscopy ( $^1\text{H}$ - $^1\text{H}$  COSY), and heteronuclear multiple bond correlation spectroscopy (HMBC), UV-, IR-spectroscopy, EIMS, HREI-MS. The isolated compounds exhibited moderate antifungal activity against *C. neoformans* [8].

Halogenated isoflavonoids, including 6-chlorogenistein, 6,3'-dichlorogenistein, 6,8-dichlorogenistein, 8-chlorogenistein, and 3',8-dichlorogenistein (Fig. 4), were discovered in bacteria of the *Actinoplanes* and *Streptomyces* genera [9, 10].

6,8-dichlorogenistein and 8-chlorogenistein were isolated from the *Streptomyces griseus* strain, and their structures were determined using H-NMR,  $^{13}\text{C}$ -NMR, MS spectroscopy [9].

3',8-dichlorogenistein and 8-chlorogenistein were isolated from the fermentation broth of *Actinoplanes* sp. Their structures were established using 1D and 2D NMR, HRESI-MS, ESI-MS, UV, IR-spectroscopy, and HPLC. Their antioxidant and antitumor activities against the human breast cancer cell line MDA-MB-231 were studied. The results showed that both compounds exhibited more pronounced antioxidant and antitumor activities compared to genistein. The authors demonstrated that chlorination significantly influences the biological activity of genistein, leading to its enhancement, providing important insights into the structure-activity relationship of such compounds [10, 11].

In separate publications, information about studying the pharmacological properties of halogenated chromone derivatives is provided. They have been found to possess significant anxiolytic and neuroleptic properties, stimulate the central nervous system, and have high affinity for central benzodiazepine receptors [12–15]. Halochromones have been discovered to possess antitumor properties [16–19], selective inhibitory activity against breast cancer resistance protein [17], DNA topoisomerase inhibition [16], cardioprotective effects [20], and antimicrobial activity [21].

Regarding the attachment sites of halogen atoms, based on available information about known substances with established structures, it can be inferred that in all natural halogenated structures containing up to four halogen atoms, the latter are always located in the ortho- or para-position relative to the phenolic hydroxyl group. The mechanism of phenolic compound halogenation remains unknown. It was previously demonstrated that chlorination in *Caldarimyces fumago* is carried out by a system composed of multiple enzymes. The study of chlorflavonin biosynthesis with a  $^{14}\text{C}$ -labeled carbon atom revealed that some flavonoids in fungi are formed from  $\text{C}_6\text{-C}_1$  precursors and four acetate units [22].

The information about halogenated phenolic compounds that have been found not only in microorganisms and insects but also in plants, including higher ones, is presented below.

Chlorflavonin is a dihydroxyflavone which represents a flavone substituted by chlorine at the 3' position (Fig. 5). Chlorflavonin is present in fungi of the *Aspergillus* genus (*A. candidus*, *A. campestris*), the Asian honeybee (*Apis cerana*), lichens of the *Lecanora* genus [23], endophytic fungi *Mucor irregularis* obtained from the Cameroonian medicinal plant *Moringa stenopetala* [24].

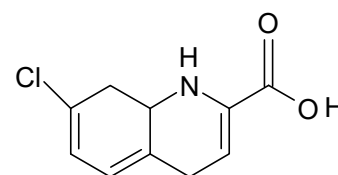


Fig. 1. Agelolin A

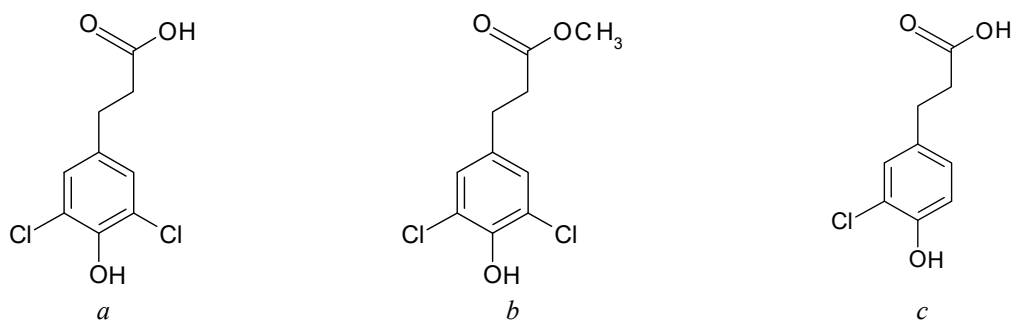


Fig. 2. 3-(3,5-dichloro-4-hydroxyphenyl)propanoic acid (a), 3-(3,5-dichloro-4-methoxyphenyl)propanoic acid (b), 3-(3-chloro-4-hydroxyphenyl)propanoic acid (c)

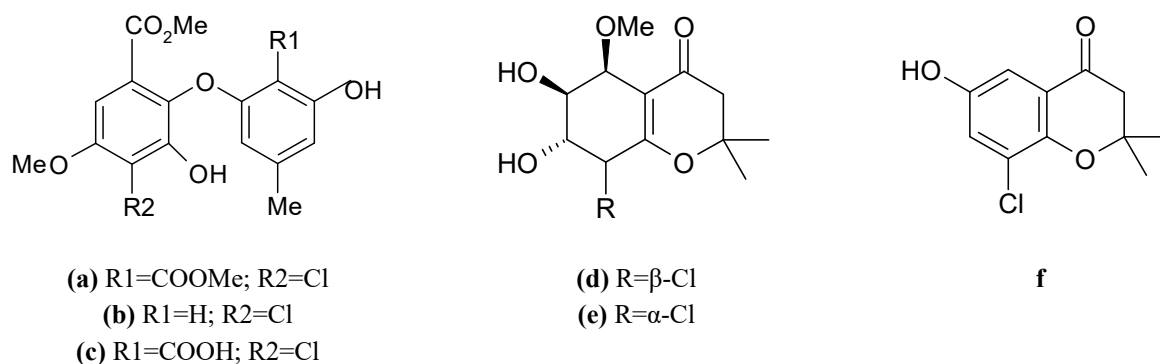


Fig. 3. pestaloether A (a), pestaloether B (b), pestalochromone A (c), pestalochromone B (d), pestalochromone C (e), pestestic acid (f), chlorizosulochrine dehydrate (g), chlorizosulochrine (i)

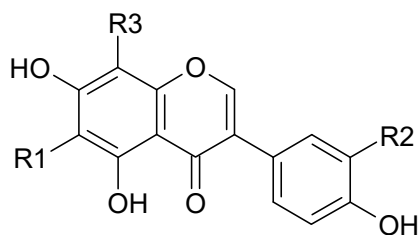


Fig. 4. 6-chlorogenistein (a), 6,3'-dichlorogenistein (b), 6,8-dichlorogenistein (c), 8-chlorogenistein (d), 3',8-dichlorogenistein (e)

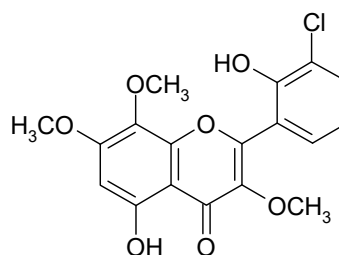


Fig. 5. Chlorflavonin

It has been established that chlorflavonin plays a role as a metabolite of *Aspergillus*. In the review of 2011, Agrawal referred to chlorflavonin as the first flavonoid-type antifungal antibiotic [25]. Besides its antifungal properties, its cytotoxic and anti-tuberculosis properties have been studied. For instance, chlorflavonin isolated from the ethyl acetate extract after three weeks of cultivation of facultative marine fungus *Aspergillus candidus* on rice medium was investigated as a potential cytotoxic agent. The compound's impact on the viability, cell cycle progression, and induction of apoptosis of therapeutically resistant prostate cancer cells (22Rv1, PC-3, LNCaP) was

explored. The experiment revealed moderate cytotoxic properties of chlorflavonin [26]. Chlorflavonin from the endophytic fungus *Mucor irregularis*, infecting the plant *Moringa stenopetala*, exhibited strong inhibitory activity against *Mycobacterium tuberculosis* without cytotoxicity towards human cell lines MRC-5 and THP-1. The authors demonstrated that chlorflavonin exhibited bacteriostatic effects in monotherapy and synergistic effects with isoniazid and delamanid when used in combination [24].

Another halogenated flavonoid, 6-chlorapigenin (Fig. 6), has been found in bacteria of the *Streptomyces* genus [23] and in representatives of higher spore-bearing plants like *Equisetum arvense* [27–29].

Research conducted by A. Syrchina et al. in the late 1970s and early 1980s reported the isolation from the ether-soluble fraction of the methanol extract of *Equisetum arvense* and the establishment of the structure of 6-chloroapigenin. This was the first instance of detecting such compounds in higher plants. The structure of this compound was determined based on UV, NMR spectroscopy, MS spectrometry, Stepanov reactions, Belstein's test, reactions with aluminum chloride III, hydrochloric acid solution, and others. The authors noted that in the mass spectrum of the substance in the molecular ion region, two peaks were observed at  $m/z$  304 (100%) and 306 (39%), which is characteristic of chlorine-containing compounds with a single chlorine atom. Additionally, any chlorine-containing ion peak is always accompanied by  $M+2$ , which is approximately three times less intense, due to the 3 : 1 ratio of isotopes  $^{35}\text{Cl}$  and  $^{37}\text{Cl}$ . The presence of a chlorine atom in the molecule is also confirmed by the presence of fragment ions in the mass spectrum at  $m/z$  188, 187, 186 [27–29].

The study by N. Kolomiets et al. demonstrated the presence of two dihalogenated phenolic compounds in *Equisetum arvense* and *Equisetum x litorale* (Fig. 7) [30–32]. The structure of these compounds was determined using HPLC-MS in combination with UV spectroscopy. The nature and number of halogen atoms in the substances were determined based on the number of peaks and ion intensity ratios. Chlorine and bromine are known to exist in two stable isotopes occurring in nature in a ratio of  $^{35}\text{Cl} : ^{37}\text{Cl}$  (3 : 1) and  $^{79}\text{Br} : ^{81}\text{Br}$  (1 : 1). Therefore, ions containing chlorine and bromine manifest in mass spectrometry as two or more peaks differing by two mass units. In the mass spectra of these two analyzed compounds in the molecular ion region, three peaks were observed for  $M^+ / M^{++2} / M^{++4}$ . In APCI Positive Scan mode, the first compound exhibited peaks at  $m/z$  355/357/359, with intensity ratios of 100 : 67 : 23; for the second compound, the peaks were at  $m/z$  339/341/343, with intensity ratios of 100 : 63 : 15. In APCI Negative Scan mode, the intensity ratios for the first compound were 100 : 72 : 31, and for the second compound, 100 : 54 : 11. If bromine ions were present in the molecules of the considered substances, the intensity ratios of the peaks would be different. Subsequently, based on calculations and other assumptions, the authors suggested that the first compound is dichlorokaempferol, with chlorine atoms positioned in either the A-ring at positions 6 and 8 or the B-ring at positions 3' and 5' (location options are shown in the figure). The second chlorinated compound is identified as apigenin (338-70+2), chlorine ions in which could also be positioned in either the A-ring at positions 6 and 8 or the B-ring at positions 3' and 5' (location options are shown in the figure). Thus, the second compound is identified as dichlorapigenin [30–32].

In the late 1960s, the first halochromone, sordidone (8-chlor-5,7-dihydroxy-2,6-dimethoxychromone), was isolated from the crustose lichen *Lecanora rupicola* of the *Lecanora* genus (Fig. 8) [33–35].

Between 2002 and 2004, 5-chlorolecanoric acid (Fig. 9), classified as a polyphenol and depside, was discovered in acetone and methanol extracts of foliose lichens of the *Punctelia* genus (*P. pseudocoralloidea*, *P. subalbicans*, *P. subflava*) and *Flavopunctelia* genus (*Flavopunctelia soredica*) from the *Parmeliaceae* family. Identification was carried out using TLC and HPLC [36, 37].

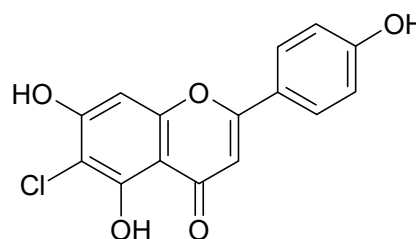


Fig. 6. 6-chlorapigenin

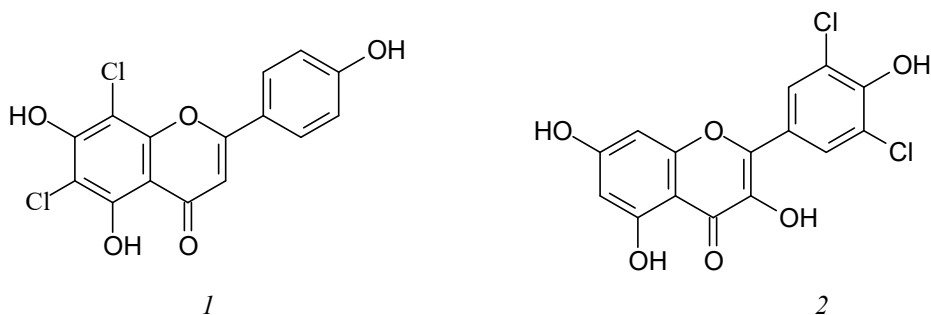


Fig. 7. dichlorapigenin (1), dichlorkaempferol (2)

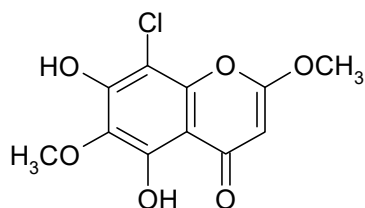


Fig. 8. Sordidon

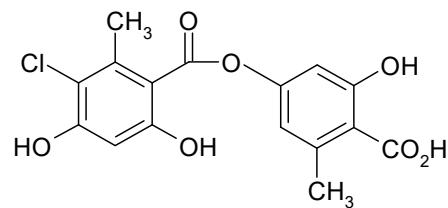


Fig. 9. 5-chlorolecanoric acid

Halochromones are found in higher plants. In 2012, 8-chlor-2-(2-phenylethyl)chromone was isolated from the ethyl acetate extract of the flower plant *Aquilaria sinensis* (*Chinese agarwood*) from the *Thymelaeaceae* family (Fig. 10). The structure was determined based on NMR, IR spectroscopy, UV spectroscopy, and MS spectroscopy. The authors suggest that the versatility of these compounds as reactive organic intermediates allows for obtaining a range of promising heterocyclic systems [38–40].

Other halogenated phenolic compounds from higher plants of the *Rutaceae* family include: chlorcumarin (Fig. 11) from the woody liana *Zanthoxylum asiaticum* (syn. *Toddalia asiatica*); chlorticol (Fig. 12) from the evergreen tree *Murraya exotica*; chlorculol (Fig. 13) from the tree / shrub *Murraya paniculata*; chlorinated coumarin (Fig. 14) from the evergreen shrub *Triphasia trifolia* [41].

Saxalin (Fig. 15) – chlorine-containing furocoumarin has been isolated from several species of the *Apiaceae* family: roots of *Angelica saxatilis*, seeds of *Cachrys pebescens*, *Ammi majus* and *Petroselinium sativum* [41–44]. Chlorinated psoralenes (Figs. 16, 17) were isolated from *Heracleum granatense*, *H.pyrenaicum*; *Prangos pabularia* [41, 45–47]. Peuchlorin (Fig. 18 a), peuchlorinin (Fig. 18 b), and peuchloridin (Fig. 18 c) were isolated from the roots of *Peucedanum arenarium* [41, 48, 49]. Only one species of the *Fabaceae* family, *Swartzia laevicarpa*, contains chlorinated isocoumarins (Fig. 19 a, b), one of which (Fig. 19 b) was later found in the flowering plant *Tovomita brasiliensis* from the *Clusiaceae* family [41, 45, 50–52].

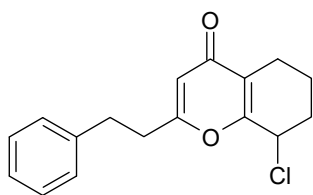


Fig. 10. 8-chlor-2-(2-phenylethyl)chromon

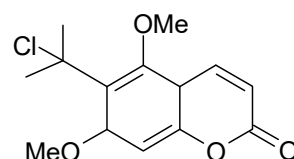


Fig. 11. Chlorcumarin

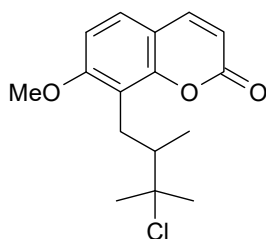


Fig. 12. Chlorticol

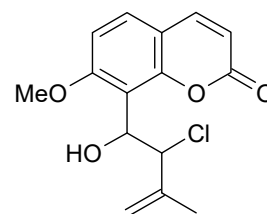


Fig. 13. Chlorculol

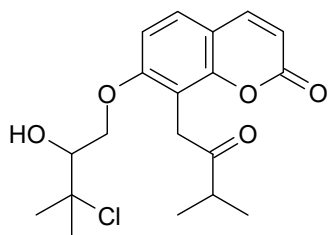


Fig. 14. Chlorinated coumarin

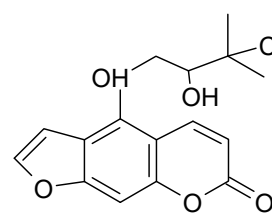


Fig. 15. Saxalin

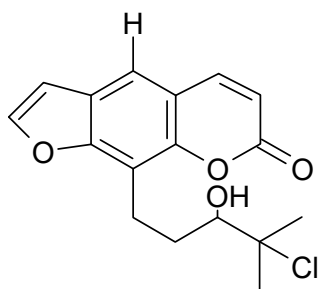


Fig. 16. Chlorinated psoralen

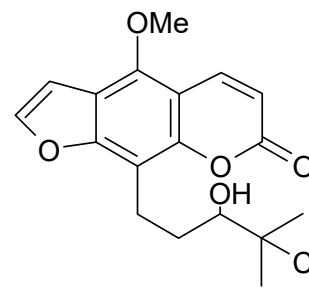


Fig. 17. Chlorinated psoralen

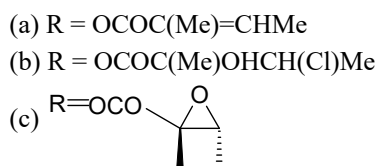
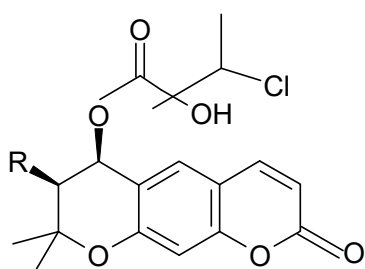


Fig. 18. Peuchlorin (a), peuchlorinin (b), peuchloridine (c)

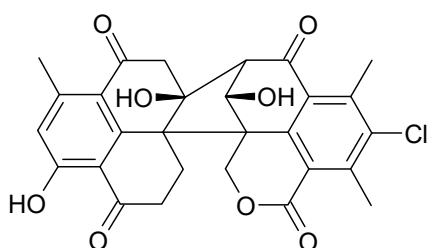


Fig. 19. Chlorinated isocoumarins

Thus, the information presented in this review shows a significant diversity of halogenated phenolic compounds (over 100) found in simple organisms, primarily marine inhabitants. To date, only 17 representatives of halogenated phenolic compounds have been discovered in plants, including higher ones (*Equisetaceae*, *Thymelaeaceae*, *Rutaceae*, *Apiaceae*, *Moringaceae*, *Fabaceae*). Their metabolism and the reasons for their production in plants require further study.

#### Funding

This work was supported funding Siberian State Medical University and Kemerovo State Medical University. No additional grants to carry out or direct this particular research were obtained.

#### Conflict of Interest

The author of this work declares that she has no conflicts of interest.

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Received October 19, 2023

Revised December 8, 2023

Accepted June 10, 2024

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