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EVALUATION OF NO-STIMULATING ACTIVITY OF *ARCTIUM LAPPA* L. AND *ARCTIUM TOMENTOSUM* MILL. CULTIVATED

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Arctium lappa L. and *Arctium tomentosum* Mill. are not only common species in nature but also widely cultivated in various countries. The chemical composition and pharmacological properties of different species of burdock have been studied fragmentarily. For cultivated species, information is sparse, and comparative studies of all plant parts within a single population are lacking.

The polysaccharide content within a single population in different morphological organs of cultivated *Arctium tomentosum* and *Arctium lappa* grown in Altai has been studied for the first time. It was found that roots dominate in the accumulation of polysaccharides, while leaves and fruits accumulate 11–12 times and 50–53 times less, respectively. The dominant components in the polysaccharide complexes of leaves and fruits are galactose and arabinose, while fructose prevails in the roots.

An endotoxin-independent study of the effects of the polysaccharide complexes of the studied species on the NO-stimulating activity of peritoneal macrophages was conducted for the first time. The results showed that polysaccharide complexes (PSCs) of leaves and fruits of both species exhibit significant NO-stimulating properties. PSCs with a defined composition, free of endotoxin impurities, can be used for detailed studies of immunomodulatory properties and further development of new safe drugs for the treatment of diseases requiring correction and regulation of the functional activity of immune cells, including antigen-presenting cells – macrophages.

Keywords: *Asteraceae, Arctium lappa, Arctium tomentosum*, polysaccharides, monosaccharide composition, molecular weight, endotoxins, macrophages, nitric oxide.

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Introduction

Arctium lappa L. and *Arctium tomentosum* Mill. are commonly found in nature. Due to their high demand in the food, para-pharmaceutical, and pharmaceutical industries, these species are cultivated in various countries [1–4]. In Russia, the roots of three burdock species – *Arctium lappa* L., *Arctium tomentosum* Mill., and *Arctium minus* (Hill) Bernh. – are used in medicine as diuretic, moderately choleretic, anti-inflammatory, and wound-healing agents [1, 3]. In China and Japan, the fruits of *Arctium lappa* L. are officially used as antidiabetic and antitumor agents [2–4].

The degree of study of the chemical composition and pharmacological properties of wild and cultivated species varies significantly; in some species, data are fragmentary or entirely absent [1–4]. Adaptogenic, antiproliferative, detoxifying, antibacterial, antiviral, antituberculous, free radical scavenging, antioxidant, anti-edema, hepatoprotective, and antimutagenic activities of extracts and tinctures of *Arctium lappa* L. have been reported [1–12]. The polysaccharide fractions of various morphological organs (leaves, roots, and fruits) of *Arctium lappa* have demonstrated antioxidant activity and the ability to regulate lipid metabolism. Cytotoxic properties have been established for lignans such as arctigenin, arctiin, and lappaol F; estrogenic properties, antioxidant and anti-inflammatory activity for arctigenin; antitumor properties for lappaol F; antitussive and immunomodulatory effects for fructans; and anti-ulcer activity for mono- and dicaffeoylquinic acids [1–12].

The pharmacological properties of *Arctium tomentosum* are poorly studied. Extracts from its leaves exhibit wound-healing, anti-exudative, antiproliferative, moderate anti-inflammatory, and analgesic activities [1–3, 13].

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The pharmacological properties and chemical composition of cultivated burdock species in Russia have not been studied, and such studies are rare globally. Thus, exploring the chemical profile, pharmacological properties, and potential mechanisms of action is of significant interest.

It is known that the roots of *Arctium lappa* are rich in polysaccharides, primarily inulin, with its content increasing in autumn [1–4]. Additionally, they contain rhamnogalacturonan, xylan, arabinan, arabinogalactan, galactan, cellulose, xyloglucan, galacturonic acid, galactose, glucose, mannose, sucrose, rhamnose, arabinose, and fructose. The leaves of *Arctium lappa* have been found to contain inulin, mucilage, rhamnose, arabinose, galactose, galacturonic acid, glucose, and mannose, while its fruits contain galactose, glucose, raffinose, rhamnose, arabinose, sorbitol, and mannitol. The composition of the polysaccharide complexes of cultivated leaves of *Arctium lappa* and the leaves and fruits of *Arctium tomentosum* has not been studied.

Recent studies have shown that plant-derived polysaccharides can affect the immune system by activating immune cells (macrophages, T- and B-lymphocytes, natural killer cells) and influencing the complement system. Polysaccharide molecules can initiate an immune response by binding to receptors on macrophage surfaces (e.g., Toll-like receptor 4 (TLR4), CD14, complement receptor 3 (CR3), scavenger receptor (SR), mannose receptor (MR), Dectin-1) [14]. High-molecular-weight polysaccharides (>100 kDa) are known to exhibit more pronounced immunomodulatory activity [15]. The presence of glucose, galactose, arabinose, and mannose monosaccharide residues may also be closely related to immunomodulatory activity [14, 16]. Uronic acid residues are also known to contribute to immunotropic activity [17].

NO synthase plays an important role in regulating the functions of various body systems, participating in the development of adaptive immune responses, inhibiting pathogen replication, and regulating apoptosis and cell proliferation, including macrophages, T-lymphocytes, mast cells, neutrophils, and lymphocytes [18–20].

The goal of this study was to examine the content of the polysaccharide complexes of roots, leaves and fruits of cultivated *Arctium lappa* L. and *Arctium tomentosum* Mill. and to assess their NO-stimulating properties. Such studies of all plant parts within a single population have not been described in the literature.

Materials and Methods

The cultivation of *Arctium lappa* L. and *Arctium tomentosum* Mill. raw materials was conducted in 2021 in the Altai region, Altayskoye village, at the production site of LLC «Visterra». Leaf harvesting was carried out throughout the growing season, from June to October, at 10-day intervals. The collection of leaves, fruits, and roots in October was performed only once on 07.10.21 during the fruit ripening period, combining the harvesting of all plant parts. Leaves and fruits were air-dried in shade; roots were cleaned of soil and organic impurities, slightly dried in sunlight, cut into pieces, and dried in dryers at the temperature not exceeding 60 °C.

Polysaccharide complexes were extracted twice for 3 hours at 95 °C using purified water at pH=2 with a raw material-to-extractant ratio of 1 : 30. The extract was separated from the residue by vacuum filtration, concentrated using a rotary evaporator, precipitated with 96% ethanol (1 : 4), and left for 12 hours at 4 °C. The resulting precipitate was separated from ethanol by centrifugation, dissolved in purified water, centrifuged again, and dialyzed to achieve a dialysate conductivity of less than 4 μS/cm, measured using an F3 FiveGo™ conductivity meter ("Mettler-Toledo," China). The dialyzed solution was then frozen and freeze-dried.

Polysaccharides were purified using ion-exchange chromatography with DEAE-cellulose (Cl-form, 20 × 3.5 cm) DEAE 52 («Servacel», USA) under gradient elution conditions using equal volumes (500 mL) of purified water and sodium chloride solutions (0.01, 0.1, 0.2, 0.3, 0.4, and 0.5 M) with increasing concentration. The mobile phase flow rate was 3.0 mL/min. Eluate fractions (15 mL) were collected and analyzed using the phenol-sulfuric method [21, 22]. Fractions testing positive for carbohydrates were combined, concentrated, dialyzed to remove NaCl as described above, frozen, and freeze-dried. Protein impurities were determined using the Lowry method (with pre-precipitation of protein) [23], and nucleic acid impurities were assessed by Spirin's method [23].

Monosaccharide composition was determined using gas-liquid chromatography on an Agilent 7890 chromatograph with a flame ionization detector («Agilent Technologies», USA). Column: DB-5 («Agilent Technologies», USA, 0.25 mm, 30 m). The analysis was performed in a temperature range from 175 °C (1 min) to 250 °C (2 min) with the temperature increase rate of 3 °C/min. Prior to analysis, polysaccharide samples (10 mg) were hydrolyzed with 2M trifluoroacetic acid and derivatized with a silylation reagent (a mixture of trimethylchlorosilane: trimethylsilylimidazole in a 3 : 1 ratio, 100 μL) in the presence of anhydrous pyridine (200 μL) at 75 °C for 25 minutes. The resulting TMS derivatives of sugars were extracted twice with 500 μL of hexane. Monosaccharides

were identified as polyol acetates after hydrolysis for 5 hours at 100–105 °C. Polyol acetates was determined using gas-liquid chromatography on an Maestro GC 7820 chromatograph («Interlab», Russia), on an HP-5 («Agilent Technologies», USA) capillary column (0.32 mm × 30 m), in a temperature gradient from 160 °C (1 min) to 290 °C (7 °C/min). Polyol acetates was identified by performing similar procedures with known standard substances (monosaccharides: glucose, fructose, rhamnose, galactose, arabinose, xylose, mannose by «Sigma Aldrich», USA)

Molecular weight distribution was determined by high-performance size-exclusion liquid chromatography using an Ultimate 3000 chromatograph with a refractive index detector RI-101 («Dionex», «Thermo», Germany). The mobile phase was a 0.01 M sodium nitrate solution with 0.1% sodium azide in water. The column was Ultrahydrogel 250, 7.8 × 300 mm, 250 Å («Waters», USA). Sample volume: 10 μL; flow rate: 0.5 mL/min; column thermostat temperature: 30 °C. The average molecular weight (Mw) and number-average molecular weight (Mn) were calculated using pullulan standards (lot. Pulkitsa-10 Mp 342–708000 Da, PSS GmbH).

The total polysaccharide content was determined using the «Burdock Root» method described in the XIV edition of the State Pharmacopoeia of the Russian Federation [23]. The total carbohydrate content was determined by the spectrophotometric phenol-sulfur method [21].

All physical and chemical methods were validated for linearity, precision, and accuracy following pharmacopoeial requirements.

The pharmacological study was conducted *in vitro* on a model of peritoneal macrophages (MF) from mice, assessing cell proliferation and nitric oxide production, as well as sample pyrogenicity using polymyxin B.

Peritoneal macrophages were obtained from the peritoneal exudate cells of 8-10-week-old C57BL/6 mice bred in the Experimental Biological Models Department of the Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center using the Easy Sep™ Biotin Positive Selection Kit and antibodies specific to macrophage receptors Anti-Mouse F4/80 Antibody (StemCell, USA).. The study was approved by the Institute's Bioethics Committee (Protocol No. 171052020 of 18.05.2020).

The macrophages ($2.5–3\times10^6$ mL) were cultivated for 48 hours in 96-well plates at 37 °C in an atmosphere of 5% CO_2 and high humidity in RPMI 1640 medium («Sigma», USA) supplemented with 10% FBS («Hyclone», UK), 20 mM HEPES («Sigma», USA), 0.05 mM 2-mercaptoethanol («Sigma», USA), 50 μg/mL gentamicin («Sigma», USA), and 2 mM L-glutamine («Sigma», USA). The test substances were dissolved immediately before use in experiments in RPMI 1640 culture medium (Sigma, USA) and added at a rate of 20 μg/ml directly into the wells of macrophages.

NO-synthase activity of mature peritoneal macrophages was determined by measuring nitrite concentration in cell supernatants after 48 hours of cultivation with PSC or LPS (O111:B4 serotype, «Sigma», USA) using Griess reagent («Sigma-Aldrich», USA) in a 1 : 1 ratio. Optical density was measured on a Titertek Multiskan® MCC spectrophotometer («Labsystems», Finland) at 540 nm.

The endotoxin content was assessed after incubating the antibiotic polymyxin B (50 μg/mL, «Sigma», USA) with the test substances for 1 hour, followed by cell cultivation as described above.

The cytotoxic properties of the test substances were determined using a colorimetric method in a classical MTT assay (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, «Sigma», USA). MTT was added 4 hours before the end of incubation at a final concentration of 200 μg/mL. The resulting precipitate was dissolved in dimethyl sulfoxide («Sigma», USA), and the optical density (OD unit) was measured as described above.

The obtained data were processed using the Statistica 13.3 software package, applying the Shapiro–Wilk test to check for normality, one-way analysis of variance (ANOVA), and Dunnett's test. The results are presented as X±m, where X is the mean value and m is the standard error of the mean. The significance level was set at $p<0.05$, with a sample size of n=9.

Results

The results, presented in Table 1, show that the polysaccharide content in the leaves increases during the growing season, reaching its peak in October. The roots of both species are the leaders in polysaccharide accumulation, with differences in content between *Arctium lappa* and *Arctium tomentosum* not exceeding 10%, and in leaves and fruits not exceeding 1–2%. The polysaccharide content in the roots of both species is 11–12 times greater than in leaves and 50–53 times greater than in fruits.

To obtain information on the polysaccharide complexes (PSCs) of all morphological parts of the plants from a single population, samples collected on 07.10.2021 were selected for analysis.

Polysaccharides isolated from Arctium lappa were light, flaky powders of whitish-brown color, while those from Arctium tomentosum were beige to light beige powders. The composition of PSCs, including total carbohydrates, uronic acids, proteins, nucleic acids, monosaccharide composition, molecular weights, and polydispersity coefficients, is presented in Table 2.

All PSCs showed high carbohydrate content, low levels of protein and nucleic acid impurities, demonstrating the efficiency of the extraction method. Uronic acids (ranging from 9 to 63%) were present in all PSCs, with fruits and leaves of *Arctium tomentosum* having higher uronic acid content. The detection of high levels of uronic acids in the aboveground parts of *Arctium tomentosum* correlates with data from other authors on the content in fruits and leaves of some other plant species, for example, in *Plantago major* (up to 72%), *Tussilago farfara* (up to 67%), *Betula pendula* (up to 60%), *Cornus officinalis* (up to 46%) [17, 24–27]. Roots did not contain mannose, rhamnose, or xylose. The major monosaccharides in the fruits and leaves are galactose and arabinose, with their content being twice as high in *Arctium tomentosum* compared to *Arctium lappa*. In the roots, fructose is the predominant monosaccharide and this is not unexpected. Fructose is a product of inulin hydrolysis, which refers to the reserve nutrients that accumulate mainly in underground organs. This correlates with the data of other authors who have studied burdock roots [1, 2, 28].

The comparison of exclusion chromatography results between the two species showed that the lowest molecular weight was observed in PSC samples from the roots and leaves of *Arctium lappa* (0.88 and 1.86 kDa), while the maximum molecular weight was noted in PSC samples from the leaves of *Arctium tomentosum* (62.98 kDa). Within each species, the trends differed: for *Arctium lappa*, the molecular weight order was fruits → leaves → roots, while for *Arctium tomentosum*, the order was leaves → roots → fruits.

To compare the heterogeneity profiles of each PSC sample, the polydispersity coefficient (K) was calculated. All the studied samples were characterized as homogeneous (K = 0.01–2.14). The least homogeneous samples were PSCs from the roots of both species (K = 0.01 and 0.24) and the leaves of *Arctium lappa* (K = 0.1).

NO-synthase Activity

The results of the study on the effects of the tested complexes on nitric oxide (NO) production by peritoneal macrophages of intact mice are shown in Table 3. None of the tested samples at the studied concentration exhibited cytotoxic properties, i.e., they did not reduce macrophage proliferation.

The degree of influence on nitric oxide production by PSCs from different morphological groups varied significantly. The highest activity, comparable to lipopolysaccharide (LPS), was shown by PSCs from the leaves and fruits of *Arctium tomentosum*, *Arctium lappa*, and the roots of *Arctium lappa*. The activity ranking of the tested PSCs is as follows: PSC AT-fr > PSC AT-f > PSC AT-r > PSC AL-r > PSC AL-f > PSC AL-fr.

When cultivated with peritoneal macrophages of intact C57BL/6 mice, PSCs isolated from the leaves and fruits of both plant species stimulated NO production 20 times, nearly reaching the level of the mitogen-activated control (Control 2). PSCs from the roots of both species demonstrated varying activity: NO-stimulating properties of PSC AT-r were similar to those of PSCs from the leaves and fruits, whereas PSC AL-r increased nitrite secretion only 4.7 times, which was four times lower than Control 2.

It is known that plant-derived extracts may contain endotoxin (lipopolysaccharide, LPS), which also enhances nitric oxide production but has undesirable significant pyrogenic effects [29]. To evaluate the degree of purification of the tested substances from LPS, experiments were conducted using polymyxin B, which directly binds to endotoxin and thereby blocks its stimulating effect [30].

Table 1. Total Polysaccharide Content, %

Group of Bioactive Substances	Species / Morphological Part	Content, % of Absolutely Dry Raw Material				
		June	July	August	September	October
Total polysaccharides recalculated as fructose	AL / leaves	4.39±0.07*	4.74±0.07*	4.68±0.07*	4.32±0.07*	7.74±0.10
	AT / leaves	4.30±0.07*	4.39±0.07*	4.58±0.07*	4.87±0.07*	7.86±0.10
	AL / roots	–	–	–	–	93.47±7.2
	AT / roots	–	–	–	–	87.74±6.5
	AL / fruits	–	–	–	–	1.75±0.08
	AT / fruits	–	–	–	–	1.73±0.12

Note: AL – *Arctium lappa*; AT – *Arctium tomentosum*; * – monthly average of three determinations of total polysaccharides.

Table 2. Characteristics of Polysaccharide Complexes

Species	Composition (%)	Mw (kDa) / Mn (kDa) / K
leaves		
Arctium lappa	Carbohydrates: 90.1±1.4; Uronic acids: 63.11±4.6; Glucose: 5.34±0.5; Galactose: 7.32±0.7; Xylose: 0.30±0.03; Arabinose: 8.62±0.7; Rhamnose: 2.71±0.22; Mannose: 2.2±0.2; Protein: 2.49±0.2; Nucleic acids: 0.003±0.0001	1.86±0.1 / 18.62±0.8 / 0.1
Arctium tomentosum	Carbohydrates: 95.5±1.9; Uronic acids: 52.48±3.9; Glucose: 3.63±0.3; Galactose: 19.22±0.92; Xylose: 0.71±0.05; Arabinose: 11.23±0.9; Rhamnose: 4.43±0.4; Mannose: 3.8±0.3; Protein: 4.3±0.21; Nucleic acids: 0.003±0.0002	62.98±3.3 / 29.40±1.4/ 2.14
roots		
Arctium lappa	Carbohydrates: 94.32±4.6; 11.21±0.5; Fructose: 73.2±3.4; Glucose: 6.43±0.2; Galactose: 1.32±0.04; Arabinose: 2.16±0.1; Protein: 3.1±0.14; Nucleic acids: 0.002±0.0001	0.88±0.03 / 74.58±3.3 / 0.01
Arctium tomentosum	Carbohydrates: 96.8±4.5; Uronic acids: 10.42±0.3; Fructose: 74.4±3.4; Glucose: 6.63±0.3; Galactose: 1.55±0.08; Arabinose: 3.1±0.1; Protein: 3.44±0.12; Nucleic acids: 0.002±0.0001	11.33±0.4 / 46.36±2.1/ 0.24
fruits		
Arctium lappa	Carbohydrates: 90.18±1.9; Uronic acids: 56.5±2.9; Glucose: 5.5±0.5; Galactose: 13.67±0.8; Xylose: 0.34±0.02; Arabinose: 9.01±0.6; Rhamnose: 1.95±0.19; Mannose: 2.50±0.2; Protein: 2.40±0.13; Nucleic acids: 0.0032±0.0003	36.72±1.4 / 33.65±1.3 / 1.09
Arctium tomentosum	Carbohydrates: 94.25±1.8; Uronic acids: 51.6±2.7; Glucose: 3.88±0.3; Galactose: 18.84±0.7; Xylose: 0.68±0.04; Arabinose: 10.86±0.7; Rhamnose: 3.67±0.3; Mannose: 4.0±0.4; Protein: 3.73±0.27; Nucleic acids: 0.0028±0.0003	7.61±0.3 / 3.65±0.1 / 2,1

Note: Mw – weight-average molecular weight; Mn – number-average molecular weight;K – polydispersity index (homogeneity coefficient).

Table 3. NO-Stimulating Activity (X ± m)

Test Sample	Concentration (μg/mL)	Proliferation (OD Units × 10^{-3})	Nitrite Concentration (μM)	
			Incubation without Polymyxin B	Incubation with Polymyxin B
Medium (Control 1)	–	672±4	3.73±0.08	3.42±0.28
LPS (Control 2)	0.1	658±6	68.12±0.52*	4.16±0.14■▲
PSC AL-f	20	641±6	74.05±0.68*	77.91±0.53■♦
PSC AL-r	20	653±7	17.50±0.20*●	2.08±0.44■▲♦
PSC AL-fr	20	638±6	73.18±0.66*	76.47±0.51■♦
PSC AT-f	20	696±9	77.06±0.37*	77.43±0.75■♦
PSC AT-r	20	692±9	73.13±0.68*	7.09±0.46■▲♦
PSC AT-fr	20	698±9	78.10±0.35*	78.52±0.78■♦

Note: * – significant difference compared to medium without polymyxin B; ■ – significant difference compared to medium with polymyxin B; ▲ – significant difference compared to incubation of each substance without polymyxin B; ● – significant difference compared to LPS without polymyxin B; ♦ – significant difference compared to LPS with polymyxin B, $p<0.05$, n=5; AL-f – *Arctium lappa* leaves; AT-f – *Arctium tomentosum* leaves; AL-r – *Arctium lappa* roots; AT-r – *Arctium tomentosum* roots; AT-fr – *Arctium tomentosum* fruits; AL-fr – *Arctium lappa* fruits.

The treatment of the samples with polymyxin B showed that PSCs from the leaves and fruits contained no endotoxin impurities, as nitrite production remained unchanged regardless of the cultivation conditions. Samples from the roots contained LPS impurities, as the antibiotic reduced their NO-stimulating properties almost to the level of the intact control: an 8.4-fold decrease for PSC AL-r and a 10.3-fold decrease for PSC AT-r. This may be due to the high polysaccharide content in the roots of both species, which poses contamination risks during drying and/or improper storage of raw materials, requiring further investigation.

Regarding the potential contribution of the monosaccharide composition on the stimulation of NO-production by macrophages, it should be noted that the probable contribution of the major components of the polysaccharide complexes of fruits and leaves – galactose (Gal) and arabinose (Ara) – is important. Indirectly, our conclusion is confirmed by the studies of Yin et al. [14], who suggested that Ara, Man, Xyl and Gal are the most important monosaccharides that promote macrophage-stimulating activity. Similar conclusions were made by Wang et al., who studied the monosaccharide composition and biological activity of polysaccharides isolated from mushrooms [31]. This preliminary conclusion requires further detailed investigation.

Conclusions

The polysaccharide content within a single population has been studied in various morphological organs of *Arctium tomentosum* and *Arctium lappa* cultivated in the Altai region for the first time. It was established that the roots dominate in polysaccharide accumulation, while leaves and fruits contain significantly less polysaccharides 11–12 times and 50–53 times less, respectively. The dominant components in the polysaccharide complexes of leaves and fruits are galactose and arabinose, while fructose is predominant in the roots. For the first time, an endotoxin-independent study of the effects of polysaccharide complexes on the NO-stimulating activity of peritoneal macrophages was conducted. The results showed that the polysaccharide complexes of the leaves and fruits of both species exhibit significant NO-stimulating properties. The contribution of individual monosaccharides to the observed activity requires further study. PSCs with a defined composition, free of endotoxin impurities, can be used for detailed studies of immunomodulatory properties and the further development of new safe drugs for the treatment of diseases requiring correction and regulation of the functional activity of immune cells, including antigen-presenting cells such as macrophages.

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

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