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Determination of high quality of Echinaceae purpurae herba grown in Uzbekistan and the prospect of creating immunomodulatory medicinal products on its base

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Abstract---*As it known, immunostimulatory medicines present synthetic, biotechnological and natural substances which are able to effect on different links of the immune system and change the strength, nature and direction of immune responses. [2]. Medicinal plants and medicines made of them are valuable raw materials for producing of medicines in the treatment of various diseases related to disruption of functional activity of the immune system. Medications made of Echinaceae purpurae herba are the most widely used plant-based medicines applied in various forms of immunodeficiency. The therapeutic properties of Echinaceae purpurae are due to the unique chemical composition of all parts of the herb. Rich vitamin-mineral composition of Echinacea purpurae specifies its immunomodulatory, anti-inflammatory, antiallergenic, antimicrobial effect. Especially polysaccharides of Echinaceae purpurae have expressed pharmacological activity.* ***The aim andtask*** *of the present research is to find out and analyze the chemical-biological composition of Echinaceae purpurae. Besides, to implement into the medical practice domestic highly effective, low-toxic medicines of immunomodulatory and immunostimulatory effect on the base of medicinal plant raw material of Echinaceae purpurae herba.* ***Objective of the study****is determination of high quality of Echinaceae purpurae herba grown in Uzbekistan, and the analysis of the immunomodulatory medicinal products assortment.* ***Materials and Methods of the study.****In the present work such methods and deviceswere applied, as the method of chromato-mass-spectrometry analysis (a chromato-mass spectrometer of "Agilent Technology" company GC/MS AT 5973N), IR-spectrum(for obtained polysaccharides), ICP-MS (Inductively Coupled Plasma Mass Spectrometer) AT 7500a (for determination of heavy metal micro-composition), the method of GF XI of the issue 2 and to change № 2, dated 12.10.2005 of category 4B (for determination of microbiological purity). In the process of analysis, the State Registers of medicines and medical products of the Republic of Uzbekistan for 2019, № 23 were used as the materials. For determination ofhigh quality of Echinaceae purpurae herba raw material, such indicators as moisture content, ash content, protein, fatty acids, essential amino acids and microelements have been researched, as well as the assortment composition of immunomodulatorymedicinal products was studied, in order to create perspective medicinal products from Echinaceae purpurae herbagrown in Uzbekistan.*

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Keywords---*Echinaceae purpurae herba, immunomodulator, moisture content, ash content, protein, fatty acids, amino acids, microelements.*

I. Introduction

The recovery of immunological disorders with the help ofimmune correcting medicines is undoubtedly, as almost any disease is generally accompanied by the development of immunodeficiency conditions. [1].

Immunostimulatory medicines present synthetic, biotechnological and natural substances which are able to effecton different links of the immune system and thereby change the strength, nature and direction of immune responses. [2].

Medicinal plants and medicines made of them, which are advantageously different from their synthetic analogues by biological affinity to the body tissues, low toxicity and accessibility, are valuable raw materials for producing of medicines in the treatment of various diseases related to disruption of functional activity of the immune system of the body.

Medicinal products made of Echinaceae purpuraeare the most widely used plant-based medicines applied in various forms of immunodeficiency. The therapeutic properties of Echinaceae purpuraeare due to the unique chemical composition of all parts of the herb. Biologically active substances such as polysaccharides, flavonoids, acid derivatives of coffee acid, fats, polyacetylenes, alkylamides and various microminerals, essential oils, antioxidants, essential amino acids, vitamins are obtained from Echinaceae purpurae. Polysaccharides of Echinaceae purpurae have expressed pharmacological activity. They have a pronounced stimulating effect on phagocytic activity of blood monocytes, tissue macrophages and neutrophilic granulocytes [3-5].

Microelements such as iron, calcium, selenium, silicon are found in the leaves, blooms and roots of Echinaceae purpurae. This microelements composition gives a chance to Echinaceae purpuraemedicinal products to participate in blood formation, bones, teeth, nail plates and hair formation. Such element as selenium today is included into almost all biologically active additives (BAA) as a powerful antioxidant. Together with vitamins C and E selenium links free radicals and removes them from the body. This effect prevents earlycells ageing, as well as the development of malignant tumors. Such vitamin-mineral composition of Echinaceae purpurae specifies its immunomodulatory, anti-inflammatory, antiallergenic, antimicrobial effect.

Prerequisite for the creation of new dosage forms is a marketing analysis of existing medicinal products in the market and their comparative evaluation in order to study the prospects for further development of the researched assortment.

One of the relevant tasks of modern domestic pharmacy is creation and implementation into the medical practice of domestic highly effective, low-toxic medicines of immunomodulatory and immunostimulatory effect on the base of medicinal plant raw materials.

Objective of the study

Determination of high quality of Echinaceae purpurae herbagrown in Uzbekistan, as well as the study of the immunomodulatorymedicinal products assortment in order to create perspectivemedicines from thepresent raw material.

II. Methods of the study

The subject of the study was Echinaceae purpurae herba. Determination of fatty acidcompositionwas performed by the method of chromato-mass-spectrometry analysis on chromato-mass spectrometer of “Agilent Technology” company GC/MS AT 5973N with the use of a capillary column of 30мх×0.25 mm in size with 5% phenylmethylsiloxane at a temperature of injector 280 °C, MS source temperature – 230ºC, MS quadrupole temperature – 180 ºC;at programming of

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temperature of the column thermostat from 170 to 280 °C, the temperature rise speed 10 ºC/min, the test value 1 mkl. in non-split flow mode.

Obtained proteins were determined on electro-photocolorimeter KFK-3.

IR-spectra of the obtained polysaccharides, pectin substances, hemicellulose (uronic acids, galactose, glucose, arabinose, xylose, ramnose) were taken on a Perkin-Elmer IR spectrometer, model 2000, in tablets pressed with KBr.

ICP-MS (Inductively Coupled Plasma Mass Spectrometer) AT 7500a was used to determine heavy metal micro-compositions. Device parameters: plasma power 1200 W, integration time 0.1 sec, rotation speed of peristaltic pump - 0.1 rpm/s. Other parameters of the device are set during the tuning process and are unchanged between maintenance periods. As a standard, a multi-element (27 component) standard solution with a target content 1.0 mg/l was applied.

Microbiological purity was defined according to the method of GF XI of the issue 2 and to change № 2, dated 12.10.2005 of category 4B.

In the process of analysis, the State Registers of medicines and medical products of the Republic of Uzbekistan for 2019, № 23 were used as the objects.

Experimental part

Analysis for determination of moisture content was performed by the recommended method in double repetition. The laboratory sample of the herb, after careful mixing, was scattered with a thin layer on the table and from its different sites it was taken about 5g of the herb for every determination. Every herb sample was taken by separate compositional parts from different sample sites at 3-4 intakes. The collected samples were carefully crushed in a mortar, then transferred to pre-dried and weighed bucks and closed with covers; then they were weighed on analytical scales. The herb samples were dried in a drying cabinet at 100-105ºC during 2 hours. At the end of this time, the bucks were quickly removed from the cabinet, closed with covers and placed into a desiccator for 10-15 minutes. The cooled and weighed bucks were again placed into the drying cabinet for 30 minutes, then removed, cooled and weighed. This process was repeated until achieving of constant weight.

Constant weight was considered achieved when the difference between weighing did not exceed more than 0.001.

The moisture content of the herb in% (X) was calculated by the formula:

$$X = \frac{(P_1 - P_2).100}{P}$$

Where P_1 isthe weight of the dried raw material before drying, g;

P_2 is the weight of the dried raw material after drying, g;

P –sample weight, g.

For the final result the average of two parallel definitions was taken. Discrepancies between parallel definitions did not exceed 0.3%. The results are shown in the Table 1.

Table No. 1. Results of moisture determination in dried raw material of Echinaceae purpurae herba

№	Weight of bucks g	Weight of bucks with initial sample weight, g	Sample weight, g	Results of weighting after drying, g	Dry substance, %	Average value, %
Test1	14,068	15,158	1,104	15,058	9,05	

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Test 2	15,876	16,918	1,053	16,821	9,2	9,13

Determination for ash content was performed by burning the sample in a muffle furnace at 600-800 ºC temperature during 2-3 hours until disappearing of organic substances in the ash, in the form of black particles. The ash content was determined by the difference between the mass of the pot furnace before and after calcination in the muffle expressed in percentage to the initial sample weight, by the formula:

$Z = (M_1 - M_2) * 100/H$, where

M_1- the mass of the pot furnace with the sample before drying, g;

M_2 - the mass of the pot furnace with the sample after drying, g;

H- sample weight, g.

The results are shown in the Table 2.

Table No. 2. Results of ash content determination of dried raw material of Echinaceae purpurae herba

№ Pot furnace	Weight of the pot furnace, g	Weight of the pot furnace with initial sample weight, g	Sample g	Weighting results after burning, g	Weight of ash,g	Average value, %	Ash, %
Test 1	16,903	18,290	1,387	17,117	0,15	0,15	0,15
Test 2	16,869	18,122	1,253	17,066	0,15		0,15

According to the results, the moisture of the dried raw material made 9.13% and the ash content made 0.15%.

Forextraction of proteins theraw material of Echinaceae purpurae herbawas crushed up to disruption of the cell walls,till obtaining a homogenate. Concentrated sulfuric acid H_2SO_4(ρ of 1.84 g/ sm^3) was poured into heat-resistant flasks, to the selected sample weight from the homogenate. The flasks were placed on a sandbath at the temperature of 400 ºC. At the same time, no rough boiling was permitted. Distilled water was carefully poured into the cooled flasks and quantified into a 50 ml measuring flask. After cooling, the volume in the flasks was reached to the mark and thoroughly mixed. From the measuring flask, after mineralization, for determination of protein content by nitrogen, an aliquot was taken, depending on the expected protein content. At high nitrogen content in the samples, a dilution was carried out. Distilled water was added up to the half of the volume to the taken aliquot. Then the solution was neutralized. 1 ml of Nessler 's reagent was added. The solutions in the flasks were diluted with water and mixed thoroughly. At the same time the solutions were completely clear. 15 minutes after painting, the solutions were colorimetered.

Table 3. Results of analysis on total proteinof dried raw material of Echinaceae purpurae herba

Sample	Sample weight, g	Aliquot	400 nm	Protein, %	Average value, %
Test 1	0,405	0,2	0,092	7.1	7,5
Test 2	0,412	0,2	0,098	7,6	

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The analysis of fatty acid methyl esterscomposition was performed by the method of chromato mass spectrometry.

The 5g weighted amounts were chosen twice, and multiple exhaustive extraction with toluene was carried out. Forobtaining of oil from the extracts, the solvent was removed by drying up to a constant mass in a stream of air under draft at a room temperature.

Aliquot 0.20 ml was taken from theextracted oil of the Objects 1.2 twice. 1 ml of toluene and 1 ml of the alkylating solution (trifluoroborhate in 10% methanol) were poured into the flasks. The methylation was carried out by heating on a water bath at 60 ºC temperature during 10 minutes, then cooling, adding 1 ml of distilled water, stirring, and when the phases were delaminated, the top layer was taken for the analysis.

Analysis of the obtained chromatograms and mass-spectra of methylated oil solutions testified that in the researched objects the following saturated and unsaturated fatty acids were found, which correspond to methyl esters: myristic, palmitic, linoleic, linolenic, stearic, arachidic, behenic, montanic acids.

The relative content of fatty acids methyl estersin the testingobjects 1,2 was determined bythe field of the chromatographic peak of the corresponding acid methyl ester, expressed in %, on the relation tothe sum of the fields mentioned above fatty acid methyl ester peaks. The results of the analysis are shown in the Table 4.

Table 4. Composition of fatty acids of dried raw material of Echinaceae purpurae herba

Name of the fatty acid	Relative % content of fatty acidin tested objects
MyristicC14:0	1,04
PalmiticC16:0	19,84
LinoleicC18:2	43,52
LinolenicC18:3	24,81
StearicC18:0	5,29
ArachidicC19:0	1,33
BehenicC22:0	1,24
Lignoceric C24:0	1,19
Montanic C28:0	1,75

As it is seen from the data given above, the sample has a low fat content - the oil contentwas not more than 1.54%. At the same time the oil extracted from the dried sample of Echinaceae purpuraehad a rich fatty acid composition with the presence of long-chain fatty acids such as arachidic, behenic, lignoceric and montanic acids. The fatty acid composition of the oil extracted from the dried sample had unsaturated fatty acids: linoleic -43.5% and linolenic - 24.81%. Total content of unsaturated and saturated fatty acids in oil extracted from the dried sample was: saturated - 31.67%, unsaturated - 68.33% (ratio of saturated to unsaturated 1:2).

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Table 5. Results of physical and chemical composition of Echinaceae purpurae

№	Echinaceae purpurae herba	Moisture,%	Ash content, %	Nitrogen, %	Protein, %	Fat, %
1	Dried sample of Echinaceae purpurae	9,13	0,15	1,25	7,5	1,54

The exactsample weight of crushed (100 g) airy-dry raw material of Echinaceae purpurae was extracted with boiling chloroform for removing lipids, waxy compounds and other low molecular substances. Forextracting of alcohol-soluble carbohydrates, the residue of the raw material after chloroform processing was separated by filtration, and then was dried on a rotary vaporizer at a temperature of 40-50°C for removing of chloroform odor. Then the rawmaterial was extracted with boiling 82-degree alcohol twice at a ratio of 1:4, 1:3.The alcohol extracts were mixed, evaporated and analyzed by paper chromatography. The chromatography was performed by the descending method; the system of solvents of butanol-pyridine-water (6:4:3) was applied. The time of chromatographywas 16-18 hours. When time was up, the chromatograms were removed from the column and dried. Two strips were used for the analysis.Such monosaccharides as glucose and galactose were applied on the first one, and ketone metabolites as witnesses (taps), i.e. fructose and sucrose were applied on the second one. The first chromatogram was sprayed with sour aniline phthalate and dried,after which a brown spot appeared –glucose presence. The second chromatogram was sprayed with 5% urea alcohol solution, after drying blue spots appeared, confirming the presence of such ketone metabolites as fructose and sucrose.

In order to obtain water-soluble polysaccharides, the residue of the raw material after the alcohol extraction was processed with hot water on a water bath at 75 ºC-80 ºC. Extraction was carried out at a ratio of 1:5, 1:3 with constant stirring during 1.5-2 hours. The extracts were mixed and centrifuged. The centrifuged mass was evaporated to 50 ml and precipitated with alcohol (1:4). The precipitate was separated by centrifuging and was dried. The water soluble polysaccharides were extracted as an amorphous powder.

100 mg of water-soluble polysaccharides were hydrolyzed with 3 ml of 1n sulfuric acid at 100ºC during 12 hours. The hydrolysate was neutralized with$BaCO_{3,}$ then was filtered and deionized with cationite KU-2 (H^+). The mass was evaporated up to 3 ml and chromatographed in the system of solvents of butanol-pyridine-water (6:4:3). The time of chromatography was 18 hours. The chromatogramwas dried up, processed with sour aniline phthalate, after which the existence of the following monosaccharides: uronic acids, galactose, glucose, arabinoza, xylose was found out.

The raw material residue after extracting of the water soluble polysaccharides was processed with a mixture of 0.5% solutions of oxalic acid and oxalate. The precipitate was centrifuged and dried up. At hydrolysis with following chromatography of hemicellulose such monosaccharides as uronic acids, galactose, glucose, arabinose, xylose were revealed [6].

Extracted polysaccharides (PS), pectin substances (PS), hemicellulose (HMC) (uronic acids, galactose, glucose, arabinose, xylose, ramnose) were taken on IR spectrometer in the form of tablets pressed with KBr.

IR-spectrum of PS has absorption strips fields specific for polysaccharides. First of all, we should indicate the field of absorption 3427 sm^{-1} - an intensive wide strip showing the presence of a free hydroxyl group. The field of absorption of

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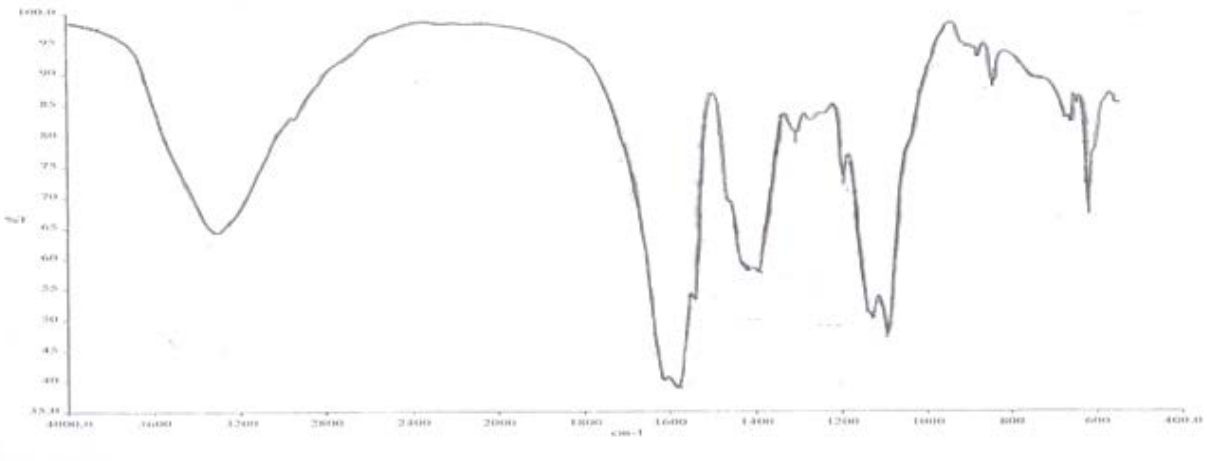
hydroxyl groups is displaced to the low-frequency field 2913 sm^{-1}, formed with the participation of hydrogen bonds. According to the acid hydrolysis data, monosaccharides include uronic acids; absorptions at 1745 sm^{-1}correspond to valence fluctuations of carbonyl of the carboxyl groups and complex ether groups (C=O).The polysaccharide contains metal ions in the carboxyl group (Na^{+}orK^{+}) expressed by intensive absorption strips in the field 1613 sm^{-1} and 1406 sm^{-1}. The following field s of absorption strips in the IR-spectrum of the polysaccharide are related to the deformational fluctuations of a number of groups: 1328 sm^{-1} and 1261 sm^{-1} (CH), 1261 sm^{-1}, 1141 sm^{-1}, 1078 sm^{-1}, 1046 sm^{-1}, 1018 $sm^{-1,}$ referring to valence fluctuations (C-C), (C-O) of pyranose cycles and (C-O-C) ether bridges. In the lower frequency fields there are absorption strips showing the presence of α-glycoside bond 830 sm^{-1} andß-glycoside bond 766 sm^{-1} (Fig.1).

Fig. 1. IR-spectrum of water-soluble polysaccharides obtained by cold extraction



Pectin substances extracted from the plants in the main polymer chain contain acid salts of methylated (partially) polygalacturonic acids. The degree of methylation is various. Side chains usually consist of neutral monosaccharides. Besides it, hydroxyl groups can be acetylated. Pectin substances are in essence carboxypolysaccharides, where the main chain of polymer is presented by the residues, boundedwith each otherby α-1 → 4 glycosidebonds. Due to this variety, the IR-spectra of pectin substances are quite complex. First of all, we should indicate absorption strips in the field 3436 sm^{-1} 2935 sm^{-1},which correspond to the hydroxyl groups. This is a rather intense absorption strip 3436 sm^{-1}; slightly weaker are the strips (OH) of the group formed by hydrogen bonds 2923 sm^{-1}. Absorption strip in the field1749 sm^{-1} usually corresponds to the valence fluctuations of carbonyls of the carboxyl groups (C=O), as well as complex ether groups. The water absorption strip at 1639 $sm^{-1}$is revealed slightly. The fluctuations of the ionized carboxyl appear in fields 1617 sm^{-1} and 1442 sm^{-1} respectively. The presence of the methoxy group is confirmed by the absorption strip at 1367 sm^{-1}. In the interval of 1236 sm^{-1}, 1146 sm^{-1}, 1104 sm^{-1}, 1074 sm^{-1} and 1019 sm^{-1} there are weakintensive strips corresponding to the fluctuations of pyranose cycles (C-C), (C-O),(C-O-C), (C-H), (CH_2OH), (C-OH), etc. The existence of α-1→4 of glycosidebond is specific for pectin substances, which finds its reflection in IR-spectrum of the researched polymer; the strip at 890sm^{-1}shows the existence of 1→4 of glycosidebonds, and 830sm^{-1}characterizes that fact that link 1→4 is located in α - position (Fig. 2).

Fig. 2. IR-spectra of extracted pectin substances

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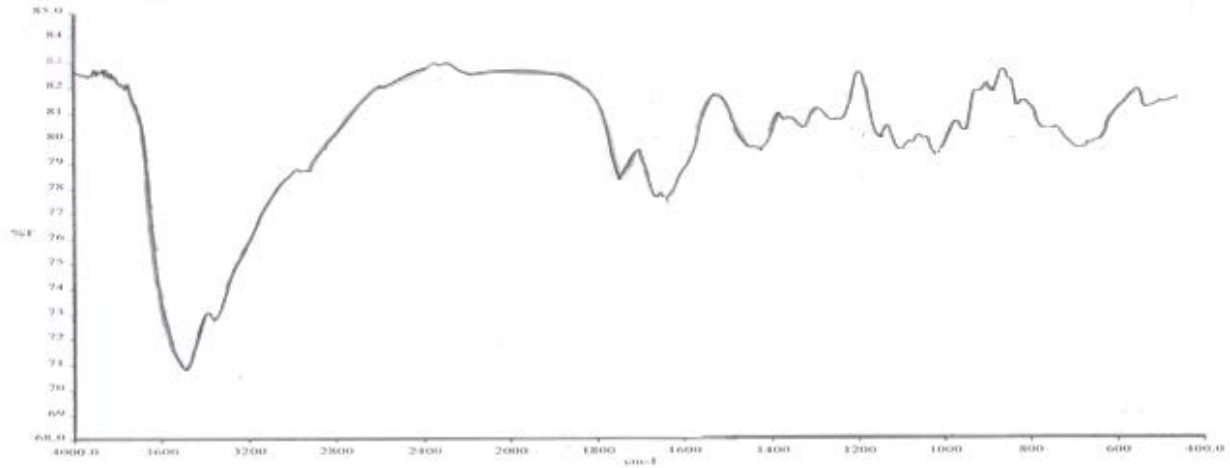
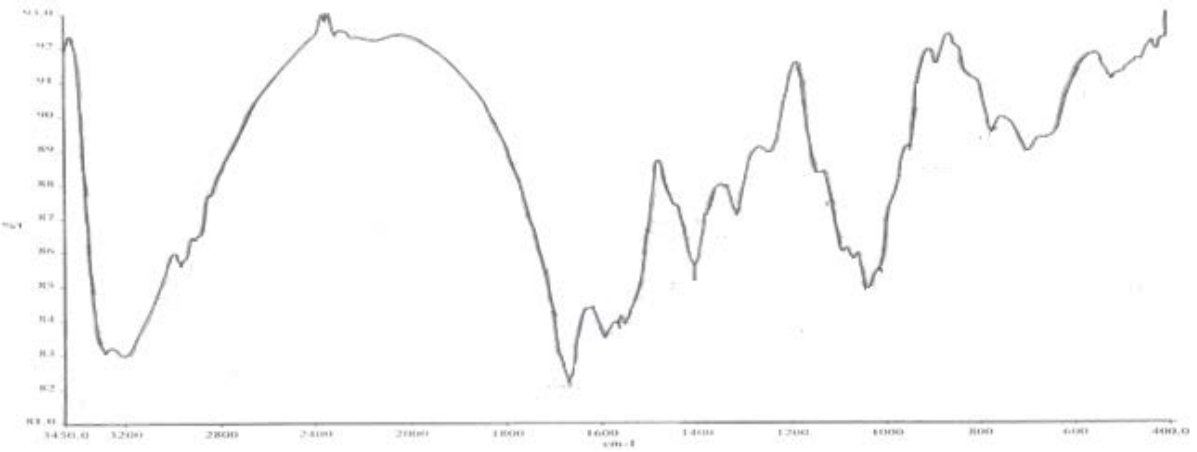


Hemicelluloses extraction is connected with their extraction with alkaline solutions, resulting to the removal of methoxyl and acetylated groups. In addition, the alkali effect results to the partial destruction of the polymer. In the IR-spectrum of hemicellulose, obtained from Echinaceae purpurae herba, free hydroxyl group 3435 $sm^{-1}$is also well revealed; hydroxyl groups formed by hydrogen bonds are revealed at 2924 sm^{-1}. The low intensity absorption strip at 1745 sm^{-1}corresponds to the fluctuations of the carbonyl (C=O) of the carboxyl group. In the field 1626 $sm^{-1}$and 1412 sm^{-1}there are absorption strips of the metal-ionized carboxyl group. The following fields of absorption 1331 sm^{-1}, 1261 sm^{-1}, 1078 sm^{-1}, 1020 $sm^{-1}$are also related to fluctuations the pyranose cycles (-C-C-), (-C-O-), (CH), (CH2), (CH_2OH), etc. These fluctuations can be both valence and deformational. (Fig. 3)

Fig. 3. IR-spectra of extracted hemicelluloses



The obtained IR-spectroscopic data show the presence of monosaccharides in the composition ofextracted polysaccharides, such ketone metabolites as fructose, sucrose, galactose, arabinose, glucose, xylose and uronic acids. IR-spectroscopy data are confirmed by chromatography methods of polysaccharide analysis.

For determination of micro-composition of heavy metals, the exact mass of the sample (0.5 g) from the object was decomposed in the mixture of nitric and perchloric acids (8ml: 2ml) in a “Milestone” microwave oven at power programming from 250 to 500 W and temperature from 180 to 220ºC. The obtained solution was proportionally poured into a 100 ml measuring flask and then used for direct input into the spray chamber of the device. The results of the

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spectral method of Echinaceae purpurae herba study revealed such vital elements as potassium, calcium, magnesium, iron, sodium, etc. The obtained results are shown in the Table 6.

Table 6. Element composition of Echinaceae purpurae herba

№	Elements	Content in the herb, mg/kg	№	Elements	Content in the herb, mg/kg
1	Li	4,70	13	Co	2,20
2	Be	0,11	14	Ni	18,00
3	Na	240,00	15	Cu	15,00
4	Mg	6900,00	16	Zn	19,00
5	Al	900,00	17	S	27,00
6	P	100,00	18	Br	19,00
7	K	18000,00	19	Sr	560,00
8	Ca	15000,00	20	Mo	1,30
9	Cr	20,00	21	Ag	6,60
10	Mn	100,00	22	Se	1,10
11	Fe	2600,00	23	Au	0,04
12	I	1,50	24	Si	61,00

Determination of microbiological purity of the raw material obtained from the dried Echinaceae purpurae herba, grown in Uzbekistan, was performed in the Laboratory of Microbiology at the Testing Center of Medical Products at " Scientific Center of Medicines Standardization" LLC, according to the method of GF XI of the edition 2 and amendment No. 2, dated 12.10.2005 category 4B, by the indicator "Microbiological purity". It should be noted that in leading foreign pharmacopoeias the test for microbiological purity in ND is generally not performed, but it is necessarily assumed. It is connected with the fact that all medicinal products in the developed countries are produced in accordance with GMP requirements, where the control of microbiological purity is strictly mandatory.

The tests were carried out under sterile box conditions, at a room temperature 21ºC and humidity 68%. The test results are shown in the Table 7.

Table7. Results of determination on microbiological purity of Echinaceae purpurae herba

Indicators	Requirements of ND	Results of analysis	Correspondence with the requirements of ND
Total number of aerobic bacteria (1 g)	Must be less than 10^5 /1 gram (total)	800 KOE	Corresponds

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Total number of yeast and mold fungi (in 1 g)	Must be less that10^4/1 gram	1000 KOE	Corresponds
Escherichia coli (in1 gor 1 ml)	Must be absent	Absent	Corresponds
Enterobacteria and other gram-negative bacteria	Must be less than10^3/1 gram	Absent	Corresponds
Salmonella (in 10 g or 10 ml)	Must be absent	Absent	Corresponds

Proceeding from the obtained results of the study on the Echinaceaepurpurae herb sample for microbiological purity, we may see the correspondence of the sample with the requirements of ND(the indicator “Microbiological purity”).

According to the data of the State Register of medicines and medical products of the Republic of Uzbekistan for 2019, the pharmaceutical market is presented by 86 medicinal products of immunomodulatory and immunostimulatory effect. This research work is based on the study of qualitative and quantitative indicators of 86 assortment items for 2019. The results of the analysis of the medicines assortment are systematized and presented in the Table 8. At the same time, each analyzed indicator is presented both in quantitatively and percentage shares on average from the total amount. The largest share of 64% is represented by the medicinal products of the CIS countries pharmaceutical producers, 29% of the foreign countries and 7% of the local producers of the total assortment.

86 assortment items are represented by 10 dosage forms such as injections, tablets, suppositories, capsules, solutions for oral use, solutions for topical application, gel for external application, eye drops, collections. Injectable solutions have a leadership of 37.2%, tablet forms are 23.3%, suppositories are 9.4%, nasal solutions are 9.4%, encapsulated forms are 7.1%, nasal solutions are 9%, solutions for oral useare 8.1%, solutions for topical application are 2.2%, gel forexternal application are 1.1%, eye drops - 1.1%, collections - 1.1%. The largest share by the source of origin of the above-mentioned dosage forms is presentedbythe medicinal products of non-plant origin - 90.7% [7, 8].

Table 8. Assortment analysis of immunomodulatory and immunostimulatorymedicinal products

Total amount	**Positions**	**Percentage**	**Update index**
	86	100	8/86=0,09
Countries-manufactures			
CIS countries	55	64	4/55=0,07
Foreign countries	25	29	3/25=0,12
Uzbekistan	6	7	1/6=0,16
Dosage form			
Solutions for injection	32	37,2	-
Tablets	20	23,3	3/20=0,15

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Suppositories	8	9,4	2/8=0,25
Nasal solutions	8	9.4	-
Capsules	6	7,1	1/6=0,16
Solutionsfororal use	7	8,1	2/7=0,28
Solutions for topical application,	2	2,2	2/2=1
Gel for external application	1	1,1	1/1=1
Eye drops	1	1,1	1/1=1
Collections	1	1,1	1/1=1
Source of origin			
Plant origin	8	9,3	3/8=0,375
Non-plant origin	78	90,7	5/78=0,064

III. CONCLUSION

On the base of the assortment analysis of immunomodulatory and immunostimulatory medicinal products registered in the Republic of Uzbekistan in 2019 it is found out that the assortment of the above-mentioned medicinal products is characterized by varietyof both countries-manufacturersand dosage forms.

Besides, it has been established that among immunomodulators and immunostimulators the share of these medicinal products import made93 % from the total amount of this pharmacological group. The largest share by the source origin of the above-mentioned medicines comes for medicinal products of non-plant origin - 90.7%. Thus, the creation andimplementation into the production of medicinal products based on the local medicinal plant raw materials is considered to be very relevant.

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