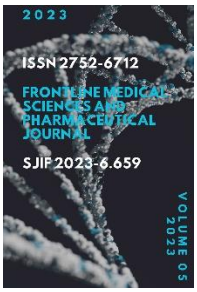
FRONTLINE MEDICAL SCIENCES AND PHARMACEUTICAL JOURNAL
(ISSN – 2752-6712)
VOLUME 03 ISSUE 03 Pages: 01-16
SJIF IMPACT FACTOR (2021: 5.14) (2022: 5.605) (2023: 6.659)
OCLC – 1272874727
Publisher: Frontline Journals




Journal Website: https://frontlinejournals.org/journals/index.php/fmspj



Research Article

# DEVELOPMENT OF TECHNOLOGY OF PRODUCTION AND QUALITY ASSESSMENT OF DRUG SUBSTANCE " DRY EXTRACT OF SCUTELLARIA ISCANDERI L. WITH SILVER NANOPARTICLES"

**Submission Date:** March 21, 2023, **Accepted Date:** March 21, 2023,
**Published Date:** March 31, 2023
**Crossref doi:** https://doi.org/10.37547/medical-fmspj-03-03-01

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## ABSTRACT

This study demonstrates the results of experimental studies aimed at the development of technology and assessment of quality of drug substance containing a dry extract of a flavonoid-containing herb and silver nanoparticles, as well as the optimal technological parameters of the phytosynthesis process and methods for the qualitative and quantitative content of biologically active substances have been developed. Phytosynthesis of silver nanoparticles was carried out using plant extracts, in which biologically active substances, flavonoids, act as an agent that reduces silver ions to nanoparticles. The optimal technology for the production of silver nanoparticles was chosen and the sample obtained at t =50 °C and the ratio of extract: silver nitrate = 1:4 was chosen as the optimal one. Additionally, the expiration date of the drug was determined for the development of regulatory documentation. During quality assessment, it was found that the quantitative content of silver nanoparticles should be at least 2 mg/g. As a result, it became

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possible to produce a substance used in the preparation of local antibacterial and antifungal drugs for the treatment of skin diseases.

## KEYWORDS

Silver nanoparticles, substance, technology, photosynthesis, dry extract, quantitative determination, authenticity, microbiological purity, expiration date.

## INTRODUCTION

In the last decades due to the intensive development of nanomedicine, it has become possible to use nanotechnology in medical practice for the modification and development of medicines, including drug substances based on nanoparticles. This development opened up great prospects for solving the most important problems in the field of medicine and pharmacy. In the pharmaceutical industry, there is a system for ensuring the quality of medicines and one of the most important parameters characterizing the quality of any substance and dosage forms is authenticity, pH, weight loss during drying, microbiological purity and quantitative determination [1,2,3].

As a result of the reforms implemented in our Republic in recent years, scientific research is being conducted in order to develop rapidly the pharmaceutical industry based on world standards, the production of drugs with high therapeutic activity based on medicinal plants. In this regard, it is important to develop a technology for a new combined substance containing silver nanoparticles and a dry extract of medicinal plants with antimicrobial and anti-inflammatory activity [4,5].

In this regard, special attention is paid to the development of technology for the production of metal nanoparticles by the "green synthesis" method, the implementation of quality assessment using modern methods of analysis, the development of regulatory documents. The production of metal nanoparticles of a specified volume, as well as physicochemical qualities, is one of the actively developing areas of nanotechnology. The synthesis of nanoscale particles that maintain their stability for a long period of time is complicated by its activity and

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reactivity. It is possible to find a solution to this problem by a qualified synthesis study, as well as by choosing the optimal stabilizer [6].

With the help of nanoparticles, it becomes possible to transport antimicrobials in a higher concentration directly to the focus of infection, while maintaining a low total dose administered to the body [7].

Scientists of the world are engaged in the creation nanoparticles of metals such as silver, copper, silicon, zirconium, aluminum, magnesium, zinc, titanium, etc. Of particular interest are the developments of silver nanoparticles preparations [8,9,10,11].

It is known that silver as a trace element is part of the body tissues, endocrine glands, brain and liver. The human body contains about 20 micrograms of silver per 100 g of dry matter. According to various data, the physiological norm of silver content ranges from 20 to 40 micrograms [12].

Currently, silver nanoparticles are mainly being developed for antibacterial use and as a disinfectant for external use. At the same time, there are works on the creation of conjugates of silver nanoparticles with cytostatic drugs [13].

When ingested into living organisms, nanoscale metal particles cause a biological response that differs from the action of the traditional ionic form of elements [14].

The scope of use of nanoscale silver can be significantly increased due to their high biocompatibility due to their synthesis using plant components [15].

The purpose of this work is development of a highly effective technology for obtaining and standardization of the drug substance containing dry extract of Scutellaria iscanderi and silver nanoparticles.

## MATERIALS AND METHODS OF RESEARCH

The aboveground part of Scutellaria Iscanderi L., collected in July in Pap district of Namangan region of the Republic of Uzbekistan (TPA 42 Uz15842845-3731-2019), was used as raw materials and water extraction based on it, and the source of silver ions is 0.01 N silver nitrate solution. Silver nanoparticles were obtained by the "Green Synthesis" method.

The study was conducted in accordance with the requirements of the State Budget of the Republic of Uzbekistan and the "General Technical

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Regulations for Medicines" Resolution of the Cabinet of Ministers of the Republic of Uzbekistan No. 365 dated October 27, 2016 [16, 17].

**Experimental part**

The phytosynthesis of silver nanoparticles is carried out using plant extracts in which biologically active substances, in particular, flavonoids, act as an agent reducing silver ions to nanoparticles. In this regard, at the first stage of our research, we had to obtain an extract with a high content of biologically active substances.

To obtain a water extract of Scutellaria Iscanderi L. with the maximum content of flavonoids, researches were carried out under various temperature conditions. The effect of temperature on the extraction of flavonoids in the water extract of Scutellaria Iscanderi L. is presented in Table 1.

**Table 1.**

**The effect of extraction temperature on the extraction of various Flavonoids**

| Flavonoids | The effect of temperature on the content of flavonoids in an aqueous extract (hydromodule 1:4) | | | |
|---|---|---|---|---|
| | 30 °C | 40 °C | 50 °C | 60 °C |
| | The content of flavonoids in the aqueous extract of Scutellaria Scutellaria Iscander L. concentration mg/g | | | |
| Apigenin | 0,015708 | 0,017768 | 0,032708 | 0,035708 |
| Quercetin | 0,050557 | 0,065557 | 0,013557 | 0,014557 |
| Routine | 0,155127 | 0,177127 | 0,227127 | 0,237127 |
| Luteolin | 0,120709 | 0,123709 | 0,130709 | 0,131709 |

As can be seen from the presented data, the maximum extraction of apigenin, quercetin, rutin and luteolin in water extract is observed at t = 60 ° C. Therefore, to obtain silver nanoparticles, it is advisable to use an extract of Scutellaria Iscanderi obtained at an extraction temperature 60 ° C.

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Next, we prepared a suspension of a water extract of the Scutellaria's Iscander with 0.01 N silver nitrate solution in various ratios. In the process of photosynthesis of nanoparticles, a change in the staining of the suspension was observed at various time intervals, which are presented in Table 2.

**Table 2.**

**Effects of various technological parameters on the formation of silver nanoparticles**

| Ratio Extract + Silver Nitrate | The beginning of color change (the beginning of biosynthesis), the time after (...) min. | | The time to stop the color change after (...) min. | |
|---|---|---|---|---|
| | t=20-25 °C | t=50 °C | t=20-25 °C | t=50 °C |
| 1:1 | 10 | 8 | 40 | 38 |
| 1:2 | 12 | 10 | 45 | 42 |
| 1:3 | 13 | 10 | 50 | 48 |
| 1:4 | 14 | 11 | 55 | 53 |
| 1:5 | 14 | 12 | 60 | 58 |
| 1:6 | 16 | 14 | 65 | 62 |
| 1:7 | 17 | 16 | 70 | 65 |
| 1:8 | 18 | 17 | 75 | 73 |
| 1:9 | 18 | 17 | 80 | 78 |
| 1:10 | 20 | 18 | 90 | 88 |
| 1:15 | 22 | 20 | 120 | 115 |
| 1:20 | 24 | 21 | 180 | 175 |
| 2:3 | 13 | 10 | 50 | 48 |
| 2:5 | 15 | 12 | 55 | 52 |
| 3:4 | 10 | 8 | 40 | 38 |
| 3:5 | 12 | 10 | 52 | 48 |

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It can be seen from these tables that, depending on the ratio of extract and silver nitrate and the temperature of phytosynthesis, the color of the resulting suspension varies from yellow–brown to dark brown. As studies have shown, the most intense color change occurs at the ratio of extract: silver nitrate = 1:4.

At the same time, the beginning of color change at room temperature was observed after 14 minutes and lasted until 55 minutes from the start of mixing. Color change indicates an increase in the concentration of silver nanoparticles, as well as an increase in the particle size.

Therefore, it can be assumed that the greatest formation of nanoparticles is precisely at the ratio 1:4.

It is also known that in addition to the ratio of the extract to silver nitrate, the rate of formation and shape of nanoparticles are also affected by the temperature of biosynthesis and the pH of the suspension. The pH of the suspension in all samples varied from 5.5 to 6.2 and was stable throughout the experiment.

An increase of the biosynthesis temperature contributed to the acceleration of the nanoparticle formation. So, if the ratio of the extract : silver nitrate = 1:4, the formation of nanoparticles at room temperature begins after 14 minutes, when the temperature rises to 50 ° C, the start time of biosynthesis is reduced to 11 minutes.

Similarly, the time to stop the color change, that is, the formation of silver nanoparticles at t = 50 ° C is reduced by 5 minutes and is 50 minutes, unlike the process carried out at room temperature, at which biosynthesis ends after 55 minutes.

To standardize the substance "Extract of the herb Scutellaria Iscanderi L. dry with silver nanoparticles", external signs was determined visually. The determination of other indicators was carried out according to the methods given in SP XI.

UV spectrophotometry and mass spectrometry (ICP-MS) methods were used to determine the "Authenticity" and quantitative content.

To do this, 0.2 g of the drug is placed in a measuring flask with a capacity of 10 ml, 8 ml of water is poured and dissolved in an ultrasonic bath for 10 minutes, then the solution is brought to the mark with water, filtered through a paper filter (blue ribbon).

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2 ml of the resulting solution is placed in a test tube and 2-3 drops of diluted hydrochloric acid or sodium chloride solution are added; a white curd precipitate is formed, insoluble in nitric acid, soluble in ammonia solution (reaction to silver).

0.1 g of the drug is placed in a flask with a lapped stopper with a capacity of 25 ml, 10 ml of 70% ethyl alcohol is added and shaken for 10-15 minutes. The solution is filtered through a paper filter (blue ribbon). On the start line of the chromatographic plate "Silufol UV-254" on an aluminum substrate (or "Merck" with silica gel 60 F 254 on an aluminum substrate) with a size of (5 x 15) cm, 0.01 ml of filtrate (100 micrograms) is applied with a micropipette or a micro-syringe to the first point, to the second 0.01 ml (100 micrograms) the solution of a standard sample of apigenin in 70% ethyl alcohol is applied as a witness. The plate with the applied samples is dried in air for 15 minutes, placed in a chamber with a mixture of solvents n-butanol-acetic acid-water in a ratio of 4:2:2 and chromatographed by the ascending method. When the solvent front passes to the end of the plate, it is removed from the chamber, dried in air until the smell of solvents disappears and viewed in ultraviolet light at a wavelength of 254 nm. On the chromatogram, at the level of the witness spot, there should be a faintly colored yellow spot (apigenin).

The pH of the drug was determined by potentiometry. From 4.5 to 6.5 (1% aqueous solution of the drug, potentiometric; SP XI, issue 1, p.113).

The loss in mass during drying was determined by the isometric method. To do this, 0.5 g of the drug (exact suspension) is dried at 60 ° C to a constant weight (SP XI, issue 1, p. 175).

It is known that medicines that are not sterilized during the production process can be contaminated with microorganisms. Based on this, a microbiological purity test was carried out at the next stage. Microbiological purity was assessed according to the requirements of the SP of the Republic of Uzbekistan. The drug must meet the requirements specified in SP XI, issue 2, p.193 and Amendment No. 2 of 29.09.2005, category 3.2.

Microbiological purity testing included preparation of various samples before testing of samples for analysis. The test was carried out under aseptic conditions in order to prevent contamination of the studied samples [18].

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Quantitative determination of microorganisms. The test was carried out by a two-layer method in Petri dishes. The 10 g sample was dissolved in a phosphate buffer solution pH 7.0 so that the final volume of the solution was 100 ml.

The quantity of aerobic bacteria. From the prepared solution, 1 ml was added into each of two test tubes with 4 ml of medium No. 1 cooled to a temperature of 45 ° C.

Detection of Escherichia coli. The test sample diluted with a sterile buffer solution of 1:10 was transferred in an amount of 10 ml (corresponding to 1 g) in 100 ml of liquid nutrient medium No. 8, mixed and incubated for 18-48 hours. Then 1 ml of the contents of the vial was transferred to 10 ml of medium No. 3. The crops were incubated for 18-24 hours. In the presence of growth, in the case of uniform turbidity of the medium in test tubes, they were transplanted to medium No. 4. The crops were incubated for 18-24 hours. On Wednesday No. 4 E. coli formed - crimson colonies with metallic luster, surrounded by crimson zones, not slimy. Colonies suspected of belonging to E. coli were microscopized on dense media. When gram-negative rods were detected in the smears , individual colonies were screened out on the medium No. 1 mown in test tubes and incubated for 18-24 hours .

Biochemical tests were used to confirm the results. Test tubes with pure culture were subcultured on Simmons agar and casein soy broth (medium No. 15), and a test for the presence of the cytochrome oxidase enzyme was also performed. After 18-24 hours of incubation, bacterial growth or its absence was noted on Simmons agar (Wednesday No. 14). Utilization of citrate was determined by the shift of the pH medium to the alkaline side (change in the color of the medium from green to blue). The presence of indole was determined by the appearance of a red ring on the surface of the soy-casein broth when Kovacs' reagent was added.

Quantitative determination of E. coli. The quantitative determination of E. coli was carried out in the same way as the quantitative determination of other enterobacteria, by subculturing from homogenate A into tubes with medium No. 3. In the case of uniform turbidity of the medium in the tubes, to confirm the presence of E. coli, each tube was inoculated with a loop onto a solid medium No. 4. Crops were incubated for 18-24 hours. The appearance of gram-negative rods characteristic of E. coli colonies on

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the media was a positive test, the absence of growth of these colonies was a negative test.

Detection of bacteria of the genus Salmonella. At the beginning, 10.0 g of the test sample was transferred to 100 ml of medium No. 8, stirred and incubated for 18-24 hours. If there was growth, 1 ml after stirring was transferred to 10 ml of medium No. 12 and incubated for 16-24 hours. Then, a loop transfer was made on Bismuth sulfite agar and incubated for 24-48 hours. On Bismuth sulfite agar, bacteria from the genus Salmonella formed black colonies with a characteristic metallic sheen, while the area of the medium under the colony stained black. Colonies suspected of belonging to the genus Salmonella were microscopically examined. When gram-negative rods were found in the smears, 2-3 characteristic colonies (each separately) were subcultured on three-sugar agar with iron salts (medium No. 13), applying a large amount of the culture with a loop, first on the slanted part of the agar, and then with a prick in a column, without touching the bottom of the test tube. After 24 hours of incubation, a change in color from red to yellow was noted in the culture medium column. The blackening of the medium indicated the formation of hydrogen sulfide, a typical feature of the species of the genus Salmonella. In parallel, a test for the presence of the enzyme "cytochrome oxidase" was performed using a pure culture from a slant of medium No. 1. If additional confirmation was required, appropriate biochemical and serological tests were used.

Identification of Staphylococcus aureus. The test sample, diluted with a sterile buffer solution 1:10, was transferred in an amount of 10 ml (corresponding to 1 g) in 100 ml of liquid nutrient medium No. 8, mixed and incubated for 24-48 hours. In the presence of growth, they were subcultured with a loop on medium No. 10 and incubated for 24-48 hours. Golden yellow colonies surrounded by yellow zones on medium #10 indicated the presence of S. aureus.

The quantitative determination of silver was carried out by mass spectrometry (ICP-MS) at the Central Laboratory of the State Committee for Geology and Mineral Resources of the Republic of Uzbekistan. Considering that vegetable raw materials are used in the production of the substance, the study of the shelf life was carried out by the method of natural storage [19].

Discussion of the obtained results.

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Thus, a sample obtained at t=50 °C was chosen and the ratio of extract: silver nitrate = 1:4.Given the convenience of using the substances in dry form, it was advisable to obtain our substance in the form of a dry powder. The dry substance is a powder dry, fine, amorphous powder of dark brown color, hygroscopic, slightly clumping, the smell is weak, peculiar. Well dissolve in water, water-alcohol mixtures. (20.40.50.60.70%). The pH of the preparation was 5.5.

To obtain in the form of a dry substance, 20 liters of silver nitrate 0.01 N were added to 5.0 l of liquid extract of Scutellaria Iscanderi, and after 50 minutes, a complete stop of color change from light brown to dark brown was observed. After that, the suspension was thickened using a vacuum evaporator (Circulation, vacuum evaporator, water capacity 50 l/h. Dimensions: 2000x750x4450 mm. Steam heating, water cooling. Loading - under vacuum, unloading - by gravity. Manufacturer: Czech Republic , plant "Cavalier") up to a volume of 5.0 liters. Further, using freeze drying (Type VirTis Freezemobile FM35), a dry powder was obtained. Thus, 85.6 g of a dry powder of a substance with silver nanoparticles was obtained from 5 l of a thick suspension. The weight loss during drying was 6.4±0.40%, which does not exceed 7% regulated by the regulatory documentation. The technological scheme for the production of a medicinal substance with silver nanoparticles is shown on Fig.1.

The results of the study of microbiological purity in assessing the quality of the substance "Dry Extract of Scutellaria Iscander.L. with silver nanoparticles" are presented in Table 1.

**Table 1.**

**Results of microbiological purity study**

| Requirements of regulatory documents | Results |
|---|---|
| The total number of aerobic bacteria is not more than 104 CFU/g (colonies forming units in 1 gram) | Less than 10 CFU |
| The total number of mushrooms is not more than 200 in 1 g | Less than 10 CFU |

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| | |
|---|---|
| Absence of Escherichia coli in 1 g . | Absent |
| Enterobacteria, and other g – bacteria no more than 100 in 1 g | Absent |
| Absence of Ps.aeruginosa in 1 g. | Absent |
| Absence of Salmonella in 10 g | Absent |
| Staphylococcus aureus in 1 g | Absent |

In 1 g of the preparation, the total number of aerobic bacteria, no more than 104, the total number of fungi, no more than 102, is allowed.

The presence of enterobacteria and some other gram-negative bacteria is not allowed. Absence of Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus in 1 g of the drug and absence of Salmonella in 10 g of the drug.

Based on the results of studying the elemental composition of a dry substance with silver nanoparticles by the ICP-MC method, it is possible to calculate silver for physico-chemical, microbiological analyses.

The elemental composition of the suspension in different ratios and the dry substance was studied quantitatively. (table-2)

**Table 2**

**Quantitative content of the elemental composition of the substance**

| № | Element | Suspension | | Dry concentrated powder | |
|---|---|---|---|---|---|
| | | Mg/kg | % | mg/g | % |
| 1 | Silver | 1219,189 | 0,12% | 20 (200681,388) | 20% |

From the data in the table it can be seen that the quantitative content of silver in the liquid substance is 0.12%, and in the dry powder its content is 20%. Thus, the use of dry substance:

firstly: it is convenient for use in laboratory studies;

secondly, it is economical for further use in the production of medicines.

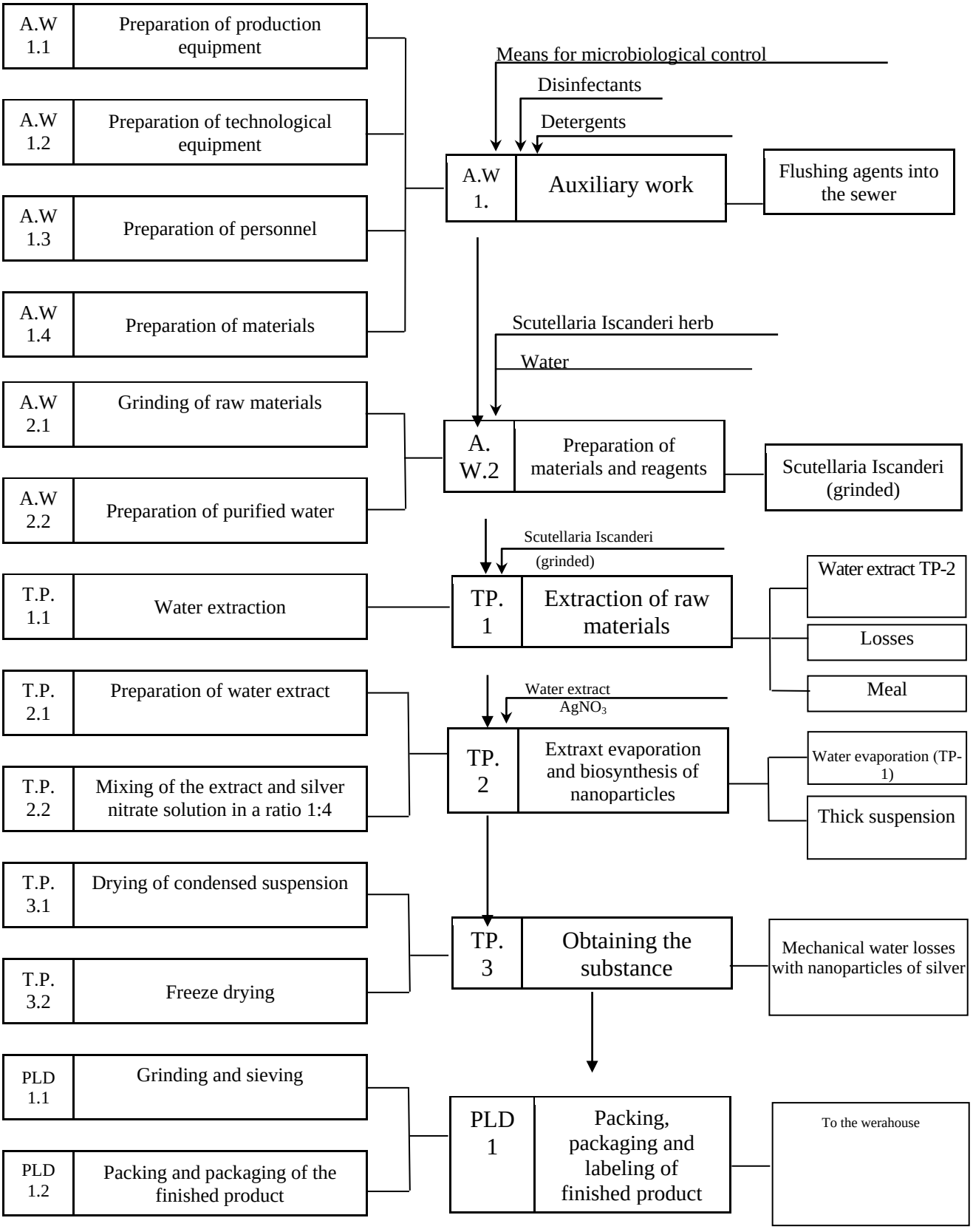


**Fig.1. Technological scheme of production of medicinal substance with silver nanoparticles**

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The storage conditions and shelf life of the developed substance, which was defined 2 years, were studied by the method of natural storage. Based on the results of physicochemical and microbiological studies, a VFS project was developed for a substance with silver nanoparticles obtained on the basis of Scutellaria Iscanderi L. extract.

Based on the results of all the physico-chemical and microbiological studies, a VFS project was developed for a substance with silver nanoparticles obtained on the basis of Scutellaria Iscanderi L. extract. On the basis of the developed VFS project, studies of the obtained substance were carried out. The results of the work carried out are presented in Table 3.

**Table 3**

**Substance Specification**

| INDICATORS | METHODS | NORMS |
|---|---|---|
| Description | **Visually**<br>Dry fine amorphous powder of dark brown color, hygroscopic, slightly clumped, the smell is weak, peculiar. | Respond |
| Authenticity | 1. Qualitative reaction with diluted hydrochloric acid or sodium chloride solution (for silver). A white curd precipitate is formed.<br>2. Foreign impurities (TLC)<br>On the chromatogram, there should be a weakly colored spot (apigenin) at the level of the witness spot. | Respond<br>Respond |
| pH | SP XI<br>In a range of 4,5 to 6,5 | 5,5 |
| Weight loss during drying | SP XI | 6,4 % |

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| | | |
|---|---|---|
| | No more 7,0% | |
| Microbiological purity | SP XI and Changes No. 2 Category 3.2 | Respond |
| Quantitative determination of silver | Mass spectroscopy (ICP-MS) At least 2000 mcg/g | 2 mg/g |
| Packaging | In accordance with the TPM | |
| Marking | In accordance with the TPM | |
| Transportation | In accordance with GOST 17768-90 | |
| Keeping | In a dry place, protected from light, at a temperature not exceeding 25 ° C | |
| Expiration date | 2 years | |

As can be seen from Table-3, that in terms of its qualitative and quantitative characteristics, the substance complies with the standards presented in the RD. This technology was tested in industrial conditions in the Institute of Plant Chemistry named after S. Y. Yunusov of the Academy of Sciences of the Republic of Uzbekistan.

## CONCLUSION

For the first time, the method of "Green Synthesis" based on local raw materials has been used as an optimal technology for obtaining a medicinal substance with silver nanoparticles.

Sample obtained at t=50 °C and in the ratio extract: silver nitrate = 1:4 was selected as the optimal way of phytosynthesis of silver nanoparticles. Taking into account the convenience of using substances in dry form, a substance in the form of a dry powder was obtained. Thus, 85.6 g of dry powder of the substance with silver nanoparticles was obtained from 5 liters of suspension. This technology was tested in industrial conditions in the Institute of Plant Chemistry named after S. Y. Yunusov of the Academy of Sciences of the Republic of Uzbekistan.

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OCLC – 1272874727
Publisher: Frontline Journals


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