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Experimental Determination of the Stability of the «Flamena» Gel Pharmacological Structure under the Influence of Low-Intensity Laser Radiation

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Abstract: In modern dentistry, the problem of the prevention and treatment of peri-implantitis is relevant. Proposed methods of treating patients with peri-implantitis do not stop the pathological process with the possibility of achieving long-term remission. Liposomal complexes with dihydroquercetin make it possible to influence the pathogenetic links of the inflammatory process in periodontal tissues with the prospect of normalizing blood circulation and regeneration processes in the affected area. It has been established that the complex simultaneous effect of low-intensity laser radiation and a pharmaceutical (laserophoresis) provides the possibility of more significant penetration of the drug components into periodontal tissues. The study of the laserophoresis of the liposomal complex with dihydroquercetin in the treatment of patients with peri-implantitis is relevant. However, in the modern literature, there is a lack of studies on the effect of low-intensity laser radiation on the pharmaceutical structure of drugs based on the above-mentioned basis.

Keywords: laserophoresis; laser irradiation; dihydroquercetin; peri-implantitis

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1. Introduction

Currently, one of the most common complications in the postoperative period after dental implantation is peri-implantitis. This disease is characterized by an inflammatory process in the tissues surrounding the dental implant and is accompanied by resorption of the jawbone [1–4]. Statistically, peri-implantitis symptoms are detected in 11–28% of cases after dental implantation [4]. The prevalence of this disease has led to increased attention to the possibility of preventing and treating this complication of dental implantation. The effectiveness of various physical factors and drugs in halting the inflammatory process in peri-implantitis has been established, and therapeutic and preventive algorithms for complex rehabilitation have been proposed [5–11].

However, despite the significant number of options for rehabilitation treatment, the development of an optimal method of rehabilitation for peri-implantitis, based on the individual characteristics of the disease manifestation in each individual clinical case, remains relevant due to the numerous facts about the development of this inflammatory process [12,13].

It should be noted that there is information indicating a short period of effect of the proposed treatment of complications after implantation [14].

However, it has been established that it is possible to normalize the elastic-mechanical and functional parameters of tissue cells, activate the respiratory function of mitochondria and suppress apoptosis in deformed cells with concomitant activation of the cell membrane repair process as a result of the use of preparations based on the «Flamena» liposomal antioxidant–phospholipid complex (Russia, Reutov), which includes 3% lecithin, 4% glycine, 0.4% dihydroquercetin, 0.5% carbomer 979, 0.005% sanguiritrin and up to 100% water [15–21].

At the same time, the expediency of carrying out a physico-pharmacological effect (laserophoresis) based on the combined use of laser radiation and a drug has been proven to increase the degree of biopermeability of the gums and the amount of the drug that is dissolved as a result of this effect in the periodontal tissue compared with the application of the drug and the physical factor effect separately [22–25].

Therefore, it seems promising to develop and justify an algorithm for the treatment of patients with peri-implantitis as a result of laserophoresis with a gel based on a liposomal antioxidant–phospholipid complex. The aim of this work was to study the possibility of using Flamena along with laserophoresis in the treatment of patients with peri-implantitis. However, the primary task was to determine the stability of «Flamena» gel under the influence of low-intensity laser radiation.

2. Materials and Methods

2.1. Parameters of Laser Exposure

To determine the degree of stability of the «Flamena» gel during the experiment, the drug was irradiated with laser radiation with a wavelength of 0.80 to 0.91 μm using the "Rikta" 04/4 device (Russia, Moscow). The following radiation mode was used: a radiation power of up to 50 mW and radiation frequency of up to 1000 Hz, as well as a radiation power of up to 100 mW and a radiation frequency of up to 50 Hz with an exposure time of 5 min.

2.2. Experimental Part

During the experiment, a gel weighing 2 g was applied to a cover glass in the form of a drop 0.5 cm thick and 1.5 cm in diameter. Then, the drug samples were irradiated in various modes using a point nozzle fixed at a distance of 1 cm from the sample for 5 min (Figures 1 and A1).

«Flamena» samples were examined according to the following parameters:

1. Appearance;
2. Viscosity;
3. The quantitative content of dihydroquercetin (DHQ), as assessed via thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC);
4. The quantitative content of glycine, as assessed via TLC and spectrophotometry in ultraviolet light at 254 nm.

Study of the samples was carried out according to the provisions of the Russian State Pharmacopeia (XIV edition) [26] and the methods below.

A. Study of the composition of samples containing liposomal emulsions using TLC.

The samples were prepared in the following way:

(1) An among of 1 mL of water was added to 1 g of the gel and stirred. Afterwards, 1 mL of 3% benzyltrimethylammonium hydroxide (Triton B (Russia)) was added. Then, the solution was stirred and filtered.

As substances, the following solutions were used:

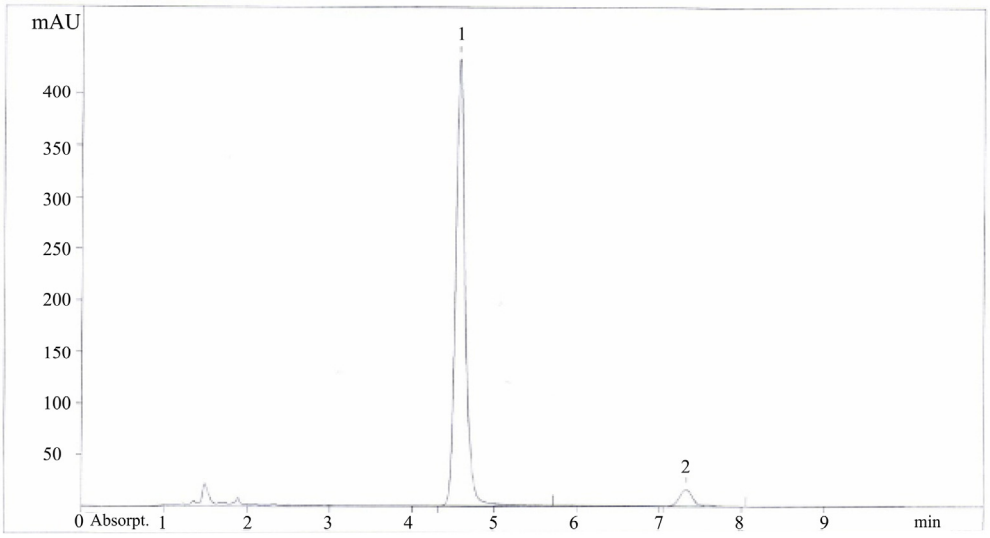
(2) Lecithin (Lipoid GmbH, Germany)—0.2 g of lecithin standard sample solution (SSO) was dissolved in 10 mL of ethanol.

(3) Dihydroquercetin (Russia)—0.05 g of DHQ SSO was dissolved in 10 mL of ethanol.

(4) Glycine (Russia)—0.75 g of glycine SSO was dissolved in 25 mL of water.

SAMPLE:
0.5053
Test tube №: 1
Volume: 1.0 µL
Dilution: 1.00
Multiplier: 1.00
Individual parameters:
Luna Phenomonex
COLUMN: 0.5x250 mm
Size:

MOBILE PHASE A:
Feed rate:
MPa



CALCULATION RESULTS
Calculation method: Customized
Standard: No

Peak	Time min	Height mAU	Area mAU*sec	Konc.	Component
1	4.571	435.31	3522.24	3522	
2	7.328	16.26	187.71	187.7	
2	9.992	451.58	3709.95	3710	

Report was generated by «MultiChrome»

Figure 1. Quantitative determination of dihydroquercetin in «Flamena» using HPLC after laser irradiation at 100 mW/50 Hz.

I. The following samples were applied to two chromatographic plates with a microsyringe:

1. Two microliters of SSO of DHQ;
2. Ten microliters of SSO of lecithin;
3. Ten microliters of SSO of glycine;
4. Ten microliters of prepared gel samples.

The plates were dried and placed in a chromatographic chamber with a mobile phase (chloroform/methanol/water in the ratio 65:25:4). After the front of the mobile phase extended 10–12 cm from the starting line, the plates were taken out and dried.

Next, one plate was sprayed with a 20% solution of sulfuric acid (Russia) in alcohol. The starting line was treated with a 4.75% solution of ninhydrin in acetone, and both plates

were placed in a drying cabinet (+105–115 °C) under a temperature of 110 °C (hysteresis 5 °C) for 5–10 min.

After drying, the reagent-treated plate was viewed in daylight (Figures 2 and A2), and the untreated plate was viewed under ultraviolet radiation (Figures 3 and A3).

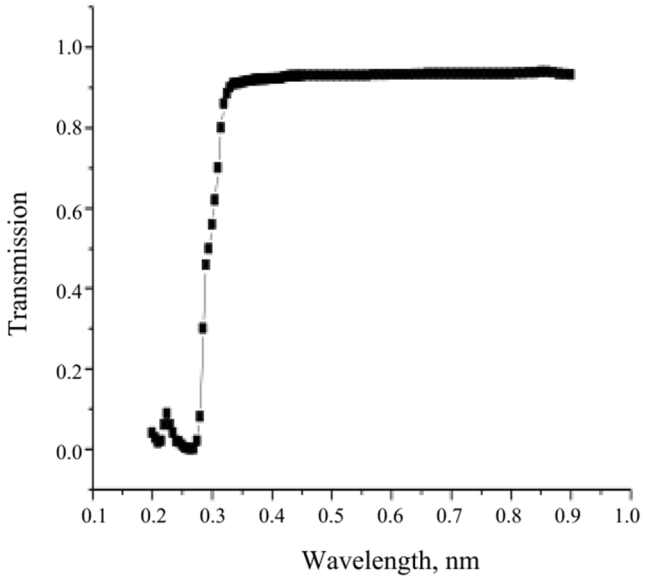


Figure 2. Spectral characteristics of the transmittance of the «Flamena» sample in the range of 200–900 nm.

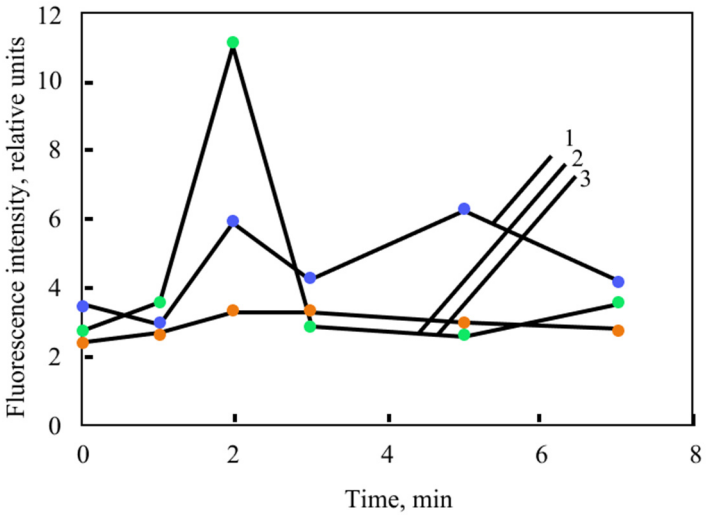


Figure 3. Fluorescence intensity on the gingival mucosa: depending on the time of laser irradiation and the rate of diffusion of «Flamena» drug molecules: 1—non-irradiated area of «Flamena»; 2—irradiated area of «Flamena»; 3—non-irradiated intact area.

Intermediate results from the first phase of the experiment are as follows:

(1) Glycine was found on the reagent-treated plate as dark spots on the starting line.

The presence of such spots confirmed the authenticity of the glycine in the studied samples. The shape of the spot allowed us to confirm the absence of a change in the content of glycine after sample laser irradiation.

(2) DHQ was detected as yellow spots on the reagent-treated plate near the finish line of the mobile phase. Under UV light, DHQ showed up as dark spots near the finish line. Based on the more blurred spot of the last sample, it can be concluded that the quantitative content of DHQ decreased.

II. The content of glycine in the sample of the drug was determined using UV–spectrophotometry.

An amount of 0.25 g of accurately weighed sample was transferred into a 250 mL volumetric flask. Then, 5 mL of water was added to the preparation and dissolved under stirring until the gel lumps disappeared. About 0.25 mL of a 3% alcohol solution of Triton X 100 was added to the resulting solution and stirred until a clear solution was obtained.

To the resulting solution, 0.75 mL of a 4.75% solution of ninhydrin in an acetone solution was added and heated in a water bath under a temperature of +95 °C for 40 min. After complete cooling, the reaction product was diluted with water to 250 mL. One hour after the start of the reaction, the drug optical density was determined with a spectrophotometer at a wavelength of 420 nm in cuvettes with an absorbing layer thickness of 1.0 mm.

At the same time, a freshly prepared 3% standard sample solution of glycine was reacted with a 4.75% solution of ninhydrin in an acetone solution, and the optical density was determined under similar conditions.

The content of glycine in the preparation (X), as a percentage, was calculated using Formula (1):

$$X_i = \frac{D_1 \cdot a_0 \cdot 50 \cdot 100}{D_0 \cdot 50 \cdot 100} = \frac{D_1 \cdot a_0}{D_0} \quad (1)$$

where

D_1—optical density of the reaction product of the tested solution with a 4.75% solution of ninhydrin in acetone;
D_0—optical density of the reaction product of a 3% standard sample solution of glycine with a 4.75% solution of ninhydrin in acetone;
a_0—weight of a sample of a glycine SSO, g.

The content of glycine in the preparation must be at least 2.3%.

Solution preparation technique:

(1) Preparation of the glycine standard solution. About 3.0 g (with an accuracy of 0.00005 g) of a standard sample of glycine (analytical standard solution (ASO)) was placed in a 100 mL volumetric flask and dissolved in 60 mL of distilled water. Then, it was filled to the mark with water, mixed and filtered.

(2) Preparation of a 4.75% solution of ninhydrin. About 4.75 g of ninhydrin was placed in a 100 mL volumetric flask. Then, it was dissolved in 50 mL of acetone, and the solution was brought up to the mark and stirred.

(3) Preparation of 3% solution of Triton X 100 PRS. About 3 mL of Triton X 100 was placed in a 100 mL volumetric flask. Then, it was dissolved in 50 mL of 50% ethanol solution, and the solution was brought up to the mark and mixed.

B. Quantitative determination of dihydroquercetin in «Flamena»

The drug, weighing 0.5 g (accurately weighed), was placed in a 10 mL volumetric flask, to which 1.0–1.5 mL of water was added and stirred until a liquid gel was obtained. Then, 1.0–1.5 mL of a 3% solution of Triton B was added to the resulting gel. The contents were thoroughly mixed until a transparent gel appeared. A total of 2 mL of the mobile phase was added to the resulting solution and stirred until a clear liquid without gel lumps was obtained. The resulting liquid was brought to the mark with the mobile phase (the solution was not shaken to prevent foam formation).

The solution was filtered through a syringe filter with a pore size of 0.45 μm and injected into the 10 μL injector loop. Quantitative determination of dihydroquercetin in the «Flamena» gel coating was carried out using HPLC («Tscvet Yausa», Detector «Akvilon», made by SPA «Himautomatika» (Russia, Moscow)).

The analysis was carried out via HPLC.

For analysis, a liquid chromatograph equipped with a UV detector (SPA «Himautomatika», Detector—«Akvilon» (Russia, Moscow)) and a reversed-phase column («Phenomeneks Luna C_{18}» (Russia, Saint Petersburg)) was used (Table 1):

Table 1. Characteristics of the UV detector.

Column	15 mm × 4.6 mm
Sorbent	C_{18}
Analytical wavelength	290 nm
Mobile phase	Acetonitrile–2% acetic acid solution (3:7, vol)
Mobile phase flow rate	1 mL/min
Chromatogram registration time	About 15 min

The chromatogram was registered, and the peak area was calculated using the "Multichrome" program, version 3.1.1573.

Under the same conditions, chromatography of the ASO dihydroquercetin solution was carried out in parallel.

The content of dihydroquercetin as a percentage in the preparation was calculated using Formula (2):

$$A = \frac{S_1 \cdot m_2 \cdot 2}{S_2 \cdot (m_1 \cdot 40)} \quad (2)$$

where

- S_1—dihydroquercetin peak area on the chromatogram of the preparation solution;
- S_2—dihydroquercetin peak area on the chromatogram of the ASO preparation solution;
- m_1—weighed portion of the preparation, g;
- m_2—sample of ASO dihydroquercetin, g.

The content of dihydroquercetin in the preparation should be in the range 0.45 to 0.25%.

The method for preparing solutions and mobile phase was as follows.

(1) Preparation of ASO dihydroquercetin solution:

Approximately 0.01 g (accurate to 0.0001 g) of ASO of dihydroquercetin or a similar substance pre-dried at 105 °C to a constant weight was dissolved in 50 mL of mobile phase. The expiration day of the solution was 1 day.

(2) Mobile phase preparation:

To 300 mL of acetonitrile used "for liquid chromatography" or a similar solution, 700 mL of 2% acetic acid solution was added and stirred. The expiration day of the solution was 1 month.

(3) Preparation of 2% acetic acid solution:

In a volumetric flask with a 1 L capacity, 20 mL of acetic "glacial" acid was placed, and the volume was brought up to 1 L with bidistilled water and mixed. The expiration day of the solution was 1 month.

(4) Preparation of bidistilled water:

Purified water was distilled twice in glass. The expiration day of the solution was 15 days.

(5) Preparation of a solution of Triton B 3%:

A total of 3 mL of Triton X100 PRS was placed in a 100 mL volumetric flask. The solution was adjusted to the mark with 50% ethyl alcohol solution and mixed.

2.3. Evaluation of the Spectral Characteristics of the «Flamena» Gel Transmission

An important aspect of assessing the change in the characteristics of preparations under laser irradiation was the evaluation of changes in the spectral transmittances of the preparations and their components. An infrared laser beam was irradiated in pulsed mode at a wavelength in the range of 0.2–2.5 μm. The spectral characteristics were studied using a two-beam automated spectrophotometer, MPS-2000 «Shimadzu» (Japan, Kyoto).

These measurements were necessary for the subsequent development of recommendations on the use of the most optimal spectral ranges at which to stimulate its pharmacological action.

In addition, it was necessary to show that the indicated drug transmits low-intensity light in the optical range quite well, which ensures its direct sanogenetic effect on periodontal tissues. On the other hand, the radiation of the optical range is to some extent absorbed by the drug itself, excites its molecules, enhances photoinduced diffusion and is transported through membranes in tissues, which activates its pharmacological action and the sanogenetic effect in general.

2.4. Spectrophotometry Parameters

During the experimental substantiation of laser laserophoresis, spectral studies of the «Flamena» preparation were carried out in order to determine the intensity of the back-reflected spectral component of laser radiation and induced fluorescence in the gum tissues through the method of laser fluorescence diagnostics using the «FOTON-BIO 637» medical spectrometer (Russia, Moscow).

Main technical characteristics of the spectrometer:

Wavelength of laser radiation: 637 nm.

Spectral range of the spectrometer: 500–1000 nm.

Spectral resolution: 1 nm.

Maximum laser output power at the output of the light-guiding tool: 25 mW.

Short-term results' reproducibility: ±10%.

Measurements were made with steady contact using a light-guiding instrument with an attached single-use medical sterile light-guiding nozzle «PHOTON-BIO D» (Russia, Moscow). A total of 12 measurements were carried out.

3. Results

1. The revealed pattern of the effect of laser radiation on the gel is reflected in the following table (Table 2).

Table 2. The effect of laser radiation on the gel.

Radiation Power, (mW)	Radiation Frequency, (Hz)	Appearance	Viscosity, (cP)	DHQ Content as Assessed Using TLC	DHQ Content as Assessed Using HPLC, (%)	Glycine Content as Assessed Using TLC	Glycine Content as Assessed Using UV Spectrometry, (%)
0	0	light yellow gel	42,000	confirmed	0.42	confirmed	3.22
50	50	light yellow gel	42,000	confirmed	0.41	confirmed	3.22
50	1000	light yellow gel	42,000	confirmed	0.41	confirmed	3.21
100	50	light yellow gel	40,000	confirmed	0.37	confirmed	3.20
100	1000	light yellow gel	34,000	confirmed	0.22	confirmed	3.22

As a result of the visual observation of the «Flamena» gel appearance, no change in external indicators related to color and transparency was revealed after exposure to laser radiation.

We observed a change in the density of the drug when exposed to laser radiation with a power of 50 to 100 mW at a frequency of 50 to 1000 Hz. It was found that the content of DHA was in the range 0.42 to 0.22%, which corresponded to the norm of the active substance in the preparation despite the effect of laser radiation.

2. As a result of the experiment conducted to determine the transmittance of the drug sample in the spectral range of 200–900 nm, the following dynamics were revealed (Figure 2).

4. Discussion

The phenomena described in the Conclusion can likely be explained by the absorption of medicinal substances that displace fluorescence, including some of the protein molecules of the intercellular fluid from the tissue of the gums' mucous membrane.

The revealed pattern indicates the likely presence of pharmaceutical substance surface diffusion and an increase in its speed under the action of laser irradiation. It is impossible to exclude slower photodiffusion of fluorescent particles of proteins and other components, the oxidizing effect of singlet oxygen, and the oxidation of fluorescent components, or vice versa, the production of components with high fluorescence due to chemical oxidation reactions.

Thereby, it can be assumed that carrying out laserophoresis of the «Flamena» gel makes it possible to increase the rate of penetration of the drug through the gingival mucosa.

The advantage of this method is the cumulative effect of the pathogenetic effect of low-intensity laser radiation on periodontal tissues and the therapeutic properties of DHQ. We assume that as a result of such an impact, it will be possible to stop the inflammation process for a longer period of time due to the improved blood circulation in periodontal tissues and the stimulation of regeneration processes.

5. Conclusions

1. It was established that there were no violations of the pharmacological basis of the «Flamena» gel in the modes of exposure to laser radiation with a radiation power of up to 50 mW and a radiation frequency of up to 1000 Hz, as well as a radiation power of up to 100 mW and a radiation frequency of up to 50 Hz.
2. A significant decrease in the content of dihydroquercetin in the studied samples was revealed after exposure to laser radiation at a radiation power of up to 100 mW and a radiation power of up to 1000 Hz. This mode is not recommended for the use of «Flamena» gel for laser radiation in laserophoresis with the specified parameters.
3. The drug «Flamena» enhances the transmitted radiation due to its luminescence in the UV range. This drug does not have a pronounced absorption edge; the transmission gradually decreases in the range of 420–280 nm.
4. When «Flamena» gel was applied to gum tissue in volunteers at the beginning of laser irradiation, a short-term increase in fluorescence intensities was observed. From the third minute onwards, intense fluorescence quenching was noted due to increased penetration of the drug into tissues during laserophoresis, followed by relaxation of the fluorescence parameters for 5 min, which was absent on the intact side (Figure 3).
5. Thus, «Flamena» gel can be used for further clinical studies on the effectiveness of laserophoresis in the complex treatment of patients with peri-implantitis.

Author Contributions: Conceptualization, V.F.P.; methodology, D.V.P.; software, A.P.; validation, D.V.P., A.P. and A.K.K.; formal analysis, V.F.P.; investigation, D.V.P., V.F.P. and A.P.; resources, V.F.P.; data curation, V.F.P.; writing—original draft preparation, D.V.P.; writing—review and editing, D.V.P. and V.F.P.; visualization, A.P. and A.K.K.; supervision, V.F.P.; project administration, V.F.P. and D.V.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: There was no appeal to the Ethics Committee, because in this study we didn't carry out research conducted in humans. The standard diagnostics procedure was performed.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

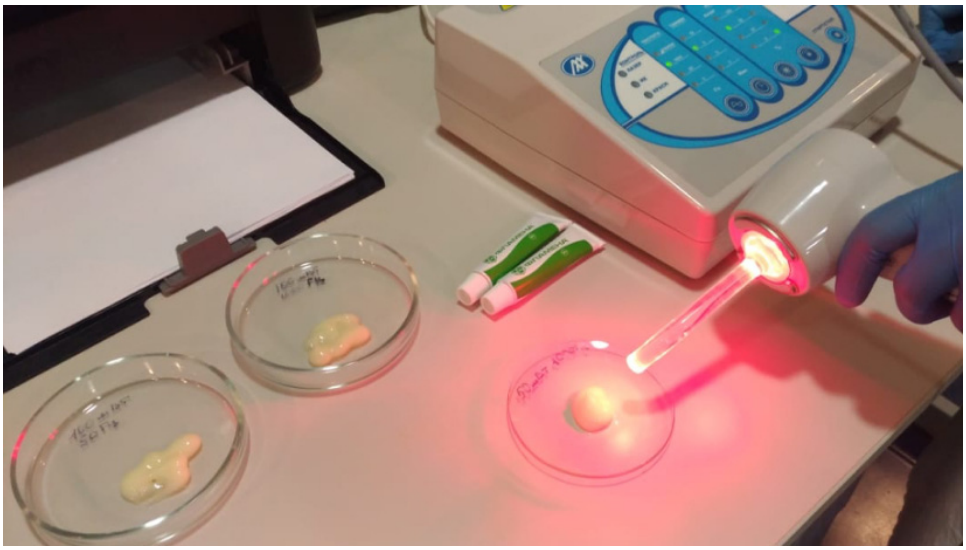

Figure A1. Methodology for the experimental stage.

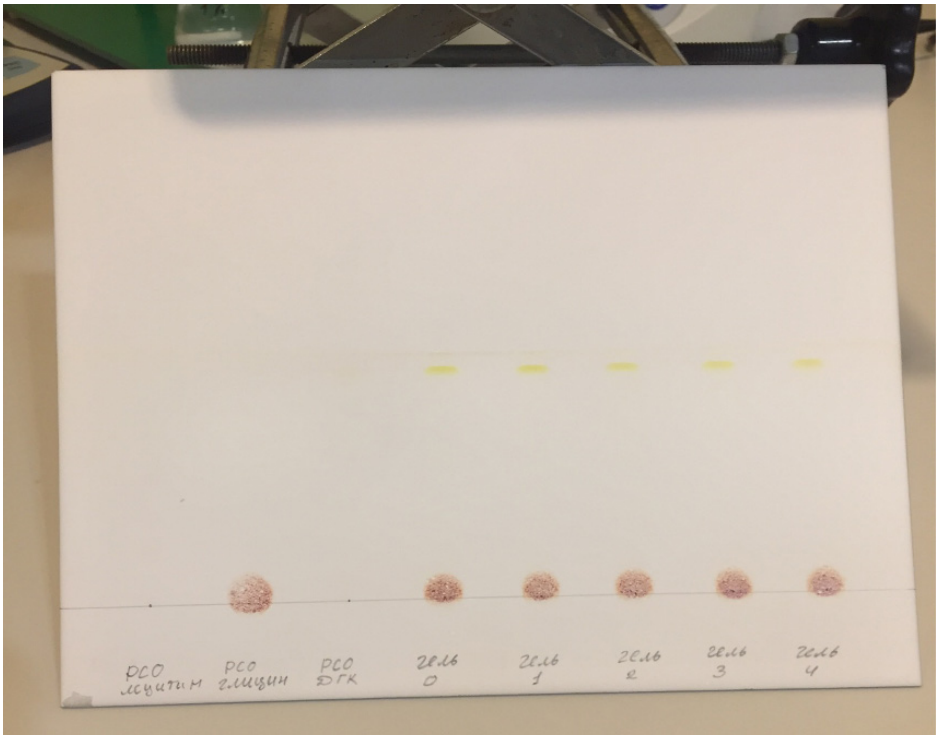

Figure A2. Treated plate in daylight.

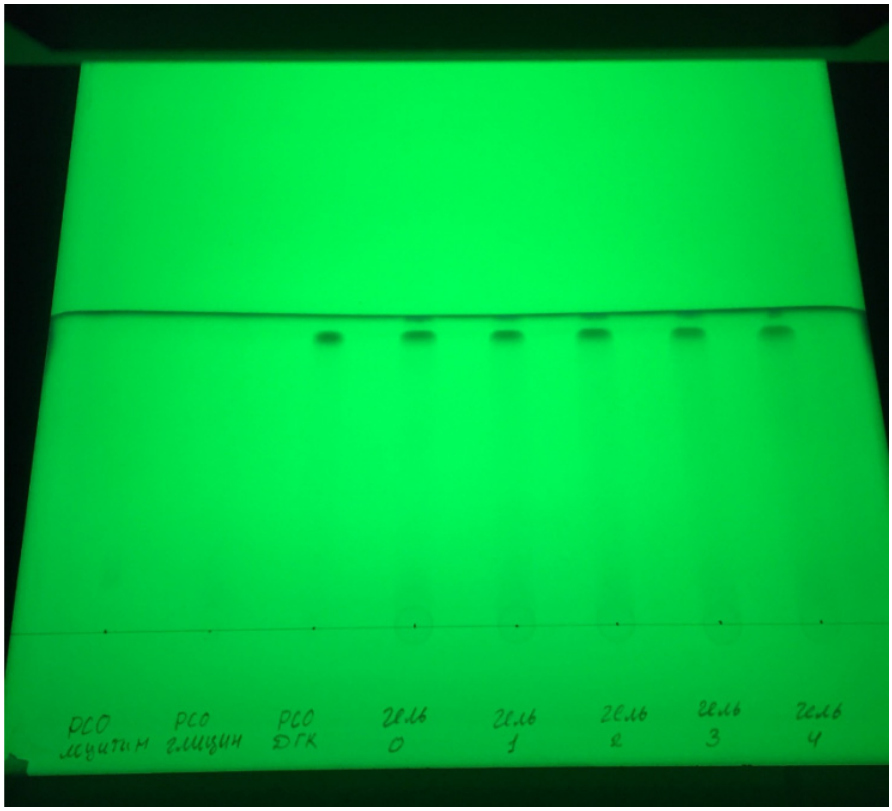

Figure A3. Untreated plate under ultraviolet radiation.

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