ANTIMICROBIAL AND ANTIMYCOTIC PHOTODYNAMIC THERAPY (REVIEW OF LITERATURE)

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Abstract

This review highlights the possibilities of photodynamic therapy (PDT) using drugs based on chlorin e6, aluminum phthalocyanine, methylene blue as photosensitizers for bacterial and fungal pathologies. This method was developed initially to treat tumor diseases, where it had shown its high efficiency and safety. Now photodynamic therapy is actively used in the treatment of cancers of the skin, bronchi, stomach, cervix, larynx, or other regions. However, numerous studies have been carried out for the entire existence of the method, demonstrating new possibilities of its application. This review highlights a number of studies in which the efficacy and safety of antimicrobial and antimycotic PDT were studied *in vivo* and *in vitro*. It has been proven to have a positive effect on the reparative processes in the wound. An experimental study was carried out to study the effectiveness of photodynamic therapy in the treatment of peritonitis in mice. Demonstrated anti-inflammatory potential in the treatment of autoimmune diseases.

Keywords: photodynamic therapy, antibacterial therapy, autoimmune diseases, mycosis, N-methylglucamine salt of chlorine e6

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АНТИМИКРОБНАЯ И АНТИМИКОТИЧЕСКАЯ ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме

В обзоре литературы освещены возможности фотодинамической терапии (ФДТ) с использованием в качестве фотосенсибилизатора (ФС) ряда препаратов, в том числе на основе хлорина е6, фталоцианина алюминия, метиленового синего, при бактериальных и грибковых патологиях. Метод ФДТ изначально был разработан для лечения опухолевых заболеваний, в борьбе с которыми показал свою высокую эффективность и безопасность. В настоящее время ФДТ активно применяется при лечении пациентов с раком кожи, бронхов, желудка, шейки матки, гортани и других локализаций. Однако за все время существования метода были проведены многочисленные исследования, демонстрирующие новые возможности его применения. В настоящем обзоре освещен ряд научно-исследовательских работ, в которых была изучена эффективность и безопасность антимикробной и антимикотической ФДТ в экспериментах *in vivo* и *in vitro*. Выполнен обзор публикаций, посвященных изучению механизмов антимикробного действия ФДТ, а также изучающих влияние ФДТ на репаративные процессы в ране. В исследованиях, включенных в настоящий обзор, доказана высокая эффективность антимикробной и антимикотической ФДТ. Продемонстрирован противовоспалительный потенциал метода при лечении аутоиммунных заболеваний у людей.

Ключевые слова: фотодинамическая терапия, антибактериальная терапия, аутоиммунные заболевания, микозы, N-диметилглюкаминовая соль хлорина е6

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In the early 1960s, photodynamic therapy (PDT) became a new effective method developed for the treatment of patients with malignant neoplasms [1–3]. PDT is based on the ability of the photosensitizer (PS) to selectively accumulate in the tumor tissue due to the specifics of its biochemical characteristics, and, under the local influence of laser radiation of a certain wavelength, generate singlet oxygen and other active radicals that have a destructive effect on tumor tissues [4–9].

The «ideal» PS must meet a number of requirements:

- selectivity of accumulation in neoplastic tissues;
- the presence of an intense absorption band in the red or near-infrared region of the spectrum, i. e., in the so-called therapeutic window;
- the absence of aggregation in aqueous solutions, which leads to a drop in the quantum yield of generation $^1O_2$;
- no general toxicity;
- the presence of intense fluorescence, which allows simultaneous fluorescence diagnostics [10].

The disadvantage of the used PS based on hematoporphyrin derivatives, e. g.: HPD (hematoporphyrin derivative), photofrin-2, photogem, is the low absorption intensity in the photoexcitation band (625-640 nm). The significant absorption of light wave energy by the biological tissue in this spectral region determines the small depth of radiation penetration and makes it difficult to treat patients with large tumors.

Researchers are currently looking for new, more effective PSs in various classes of organic dyes, primarily among porphyrins and their synthetic analogues. Chlorins (dihydroporphyrins) are characterized by a strong increase in the intensity of the long-wave band and its shift to the red region in comparison with porphyrins [11]. Chlorin derivatives are characterized by high selectivity and short-term skin sensitization [10]. Among the chlorins, it is worth mentioning water-soluble mono-L-aspartyl chlorin e6 and other various forms of e6 chlorine, in particular, Photoditazine and Radachlorin, developed in Russia, and Photolon from Belarus [11], as well as synthetic chlorins: 5,10,15,20-tetrakis(m-hydroxyphenyl) chlorin (Temoporfin, m-THPC, Foscan) and benzoporphyrin derivatives (benzoporphyrin monoacid, ring A) [10].

Of great interest is Photoditazine, which, according to a number of authors, is an effective and safe PS of the chlorin group [11–16]. It is the N-methylglucamine salt of e6 chlorine, which has a strong absorption band in the red region of the spectrum, with a maximum of 662 nm in the range of 660–680 nm. This is the interval at which biotissues have high transmittance and fluorescence. Photoditazine obtained by chemical modification of methylfeoforbide has good water solubility, without forming aggregated forms, which is typical for preparations based on hematoporphyrin derivatives. In addition, the presence of amphiphilic properties determines its high ability to bind to the membranes of tumor cells, which provides its high photodynamic activity.

In vivo experiments showed that Photoditazine is a highly selective PS for PDT, the effectiveness of which is determined by the dose of the drug and the dose of laser irradiation. The most pronounced antitumor effect (inhibition of breast cancer tumor growth in 100% of cases, M-1 to 92.5% by day 21) in in vivo experiments on mice and rats was obtained at a dose of 5.0 mg/kg of body weight and light doses of 600 J/cm^2, which indicates a pronounced photodynamic activity of the compound. In vivo toxicity studies have shown that photoditazine is a low-toxicity compound: LD_{50} is 158 mg/kg of body weight at an average therapeutic dose of 0.8 mg/kg [17].

In recent years, PDT has been used in the treatment of purulent wounds, including those nonhealing over a long period, complicated burns, and trophic ulcers [11, 17, 18]. At the same time, the bactericidal and bacteriostatic effects of antimicrobial PDT on pathogens of infectious diseases are achieved due to generation of singlet oxygen and peroxide radicals of the PS present extracellularly and intracellularly, with the subsequent development of a cascade of phototoxic reactions.

In the study by J. Schneider et al. [19] it was shown that PDT with methylene blue and irradiation with broadband white light (400–700 nm) at a dose of 10 J/cm^2 causes inactivation of bacteriophage RNA in vitro by crosslinking it with plasma proteins. The ability of a bacterial cell to survive in vitro after oxidative stress depends on the activity of its superoxide dismutase, as in the case of E. coli strains [20], or on the amount and activity of its heat shock proteins, as in the case of mycobacteria, which produce 2 types of heat shock proteins under oxidative stress: HSP-70 and HSP-90 [21]. In this regard, the combined effect of PDT on Mycobacterium tuberculosis in vitro with sulfated aluminum phthalocyanine and laser radiation with a wavelength of 600–700 nm at a dose of 20 J/cm^2 is of interest. Viable cultures of *M. tuberculosis* were used for the study. The dynam-

ics of culture growth was estimated by the number and size of colonies every 10 days over a period of 60 days. On day 7, the cultures were exposed to PDT with sulfated aluminum phthalocyanine, hematoporphyrin, and some other PSs. The result was a distinct delay in the growth of mycobacterium colonies. In the control group (only PS and only laser exposure), no colony growth delays were observed.

In antimicrobial PDT of gram-negative bacteria, such as *Pseudomonas aeruginosa*, photodynamic activation may involve the lipopolysaccharide envelope of bacteria and proteolytic enzymes. The result in this case is a decrease in resistance to antibacterial drugs and virulence. N. Komegik et al. [22] showed that conducting antimicrobial PDT in vitro with methylene blue and laser irradiation at a dose of 74.4 J/cm^2 (helium-neon laser) significantly reduces the activity of *Pseudomonas aeruginosa* proteases and the immunogenicity of its lipopolysaccharide envelope. Incubation of *Pseudomonas aeruginosa* exposed to this variant of PDT with mononuclears of human peripheral blood showed a sharp decrease in the activity of its proteases and the immunogenicity of lipopolysaccharides, which was expressed in a significant reduction in the synthesis of pro-inflammatory cytokines (IL-1, IL6, IL-8, TNF-a, TNF-3) by the mononuclears. Inactivation of proteolytic enzymes of *Porfiromonas gingivalis* by antimicrobial PDT with methylene blue was confirmed by S. Packer [23].

Thus, PDT of infectious diseases caused by bacterial pathogens is a process of interaction of reactive oxygen species and toxic radicals with anti-stress factors of bacteria. The outcomes of the interaction can be different depending on the intensity of generation of reactive oxygen species, the activity of anti-stress proteins, antioxidant enzymes of bacteria, and *in vivo* – on the persistence of the pathogen both intra- and extracellularly, on the cellular microenvironment, and many other factors.

The effectiveness of PDT with Photoditazine in the treatment of purulent wounds is proved in some works.

P. I. Tolstykh et al. in 2014, in a study on mice, showed the advantage of PDT over standard local treatment of purulent wounds [24]. In each animal, a 2x2 cm skin flap was isolated in the interscapular region, after which the muscular bottom of the wound was crushed with a Kocher clamp. Then the wound was infected with 1 ml of a daily suspension of Staphylococcus aureus and purulent bacillus culture. After 48 hours, purulent inflammation developed, and then local treatment of the wound began. The experiment was conducted on 5 observation groups of 20 animals in each. In the first group (control group), the mice received therapy in the form of dressings with an aqueous solution of chlorhexidine. In the remaining groups, PDT was performed with different PSs in different dosage forms: an aqueous solution of Holosens, an aqueous solution of Photoditazine, Holosens in gel form, and Photoditazine in gel form. The evaluation of wounds included planimetric (wound size), bacteriological (results of bacteriological examination of the wound discharge), and cytological (assessment of the cellular composition of the wound wall biopsy) data of purulent wounds on days 3, 4, 5 and 10. It was found that in animals subjected to PDT, the wound area is reduced significantly faster, and cytological examination showed more pronounced signs of repair (the presence of phagocytes, macrophages, monocytes, differentiating fibroblasts), while bacteriological examination showed a more pronounced decrease in bacterial contamination. It was revealed that the most effective of the PS was Photoditazine in gel form.

Evaluation of the effectiveness of PDT with photoditazine in an experiment on a model of acute widespread fecal peritonitis (168 rats) was performed by A.V. Geinitz et al. [25]. The authors also investigated the accumulation of the drug in the inflamed peritoneum. To create a model of acute peritonitis, a modified method of V. A. Lazarenko was used, with a filtered 10% fecal suspension at a dose of 0.5 ml per 100 g. After the introduction of fecal suspension into the abdominal cavity, the rats developed a clinical picture of acute peritonitis on day 3, which was expressed in lethargy and inactivity of the animals, abdomen bloating, refusal of food and lack of stool. On day 3, the animals in all groups were subjected to surgical intervention under general intravenous anesthesia against the background of general peritonitis. The animals underwent laparotomy and abdominal sanitation. All individuals were divided into 8 groups: 6 main groups and 2 control groups. In the first control group, PS was not administered, in the second, the accumulation of Photoditazine in rats with an unchanged peritoneum was studied. The 6 main groups of animals had local fluorescence spectroscopy administered at differed time (after 30, 60, 90, 120, 150, 180 min). The study of the accumulation of the drug showed the peak of its concentration in the group in which local fluorescence spectroscopy was performed after 120 minutes.

To assess the effectiveness of PDT with Photoditazine, 65 rats were studied, 43 of which were in the main group and 22 in the control group. Both groups received gentamicin for 3 days in the postoperative period. Sanitation in the main group was performed with PDT, whereas in the control group it was done by washing the abdominal cavity with an aqueous solution of chlorhexidine until the washing water came back clean. The evaluation included data of bacteriological examination of abdominal wall smears and the number of deaths in the observation groups. No signs of peritoneal burns were found in any of the cases. The mortality rate in the main group was 9.5%, of which 50% of animals died on the first day, and the remaining 50% on the second. – In the control group, 27.3% of the rats died in the first 24 hours. All the animals

died due to the background of continuing peritonitis and increasing intoxication. Leukocytosis in the main group of rats by the end of the first day was lower by an average of 17.1% compared to the control group. The level of white blood cells on day 5 returned to normal and was 21.48% lower than in the control group. Biochemical blood parameters (creatinine, urea, total protein, ALT and AST) on the 5th –7th day were also better in rats exposed to PDT. The sterility of the abdominal cavity in the animals of the main group was determined on day 3, in the control group – on day 7, with an average contamination of all rats with E. Coli 10^7– of 10^8 microbial bodies in 1 ml of exudate.

Studies have been published on the use of PDT in the treatment of diseases of autoimmune pathogenesis. A. M. Shubina et al. studied the effectiveness of the method in the treatment of psoriasis [26]. The main observation group included 20 patients, the control group – 16. Photoditazine was administered to patients of the main group at a dose of 0.3 – 0.4 mg / kg of body weight, with a 30-minute laser irradiation session performed after 1.5 hours, the radiation power being 15 MW. Patients in the control group received standard treatment with calcium supplements, antihistamines, sedatives, and immunomodulators. The effectiveness was evaluated by the following signs: the appearance of new skin elements, infiltration of the skin in the affected area, itching, hyperemia, and peeling. The intensity of these signs was scored in points, 0 to 4. The result was evaluated 2 weeks and 1 month after irradiation. It was noted that in all patients who underwent PDT, itching completely disappeared after 2 weeks, the rash partially regressed, hyperemia and infiltration of psoriatic plaques disappeared in 100% of cases. After 1 month, stable therapeutic effect was found, without any cases of exacerbation observed. In the control group, such improvements were registered only in 18% of patients.

In recent years, there have been reports that PDT not only does not slow down the healing of wound defects of various origins, but also causes their accelerated regeneration [15].

In the work of E. F. Shin et al. [16], the reparative effect of PDT with the photoditazin, – amphiphilic polymer complex, was estimated. The study involved 100 patients with purulent soft tissue wounds. Depending on the treatment method, all patients were divided into two groups. The main group consisted of 50 patients who were treated with PDT in addition to the traditional method. The control group, which also included 50 patients, was administered only traditional therapy. In the main group of patients, a gel containing a Photoditazine complex with a water-soluble amphiphilic polymer immobilized on hydroxyapatite nanoparticles was applied to the wound surface. The wound was covered with a sterile polyethylene bandage for 40-50 minutes, after which the wound surface was exposed to low-intensity laser radiation with a wavelength of 661 ± 0.03 nm, power density of 1.0 W/cm^2, and an energy density of 25-30 J/cm^2.

During the surgery, the histological situation was the same in both study groups. The walls and bottom of the wound show destructive necrotic tissues abundantly infiltrated by polymorphonuclear leukocytes. In the main group, histological examination of biopsies of purulent wounds after PDT showed a faster cleaning of the wound surface from purulent necrotic/masses and the formation of granulation tissue than with the traditional treatment method. On day 7, the control group showed a reduction in the wound canal, a decrease in the volume of fibrin-necrotic masses and the degree of neutrophil infiltration. Granulation tissue was found at the border with unchanged tissues. In PDT, over the same period, there was a decrease in the volume of the fibrinous-leukocyte layer, the maturation of granulation tissue with an increase in the number of macrophages and fibroblasts. The results of morphological studies have shown that, compared with traditional treatment, laser PDT of purulent soft tissue wounds with Photoditazine in combination with an amphiphilic polymer increases the phagocytic activity of macrophages, effectively reduces bacterial contamination of tissues, and accelerates the formation and maturation of granulation tissue.

O. E. Shishkina et al. [27] compared the effectiveness of sterilization with the use of following PS: methylene blue, eosin, chlorophyllin, Photoditazine, St. John's wort oil on cultures of pathogenic microorganisms (Staphylococcus aureus, Pseudomonas Aeruginosa, Micrococcus luteus, Candida albicans, Staphylococcus epidermidis, Staphylococcus saprophyticus, Bacillus antracis, Proteus vulgaris). Cultures of microorganisms were seeded using the lawn method in Petri dishes, with each dish divided into 2 zones and the PS applied symmetrically on both sides. The exposure continued for 15 minutes. The procedure was repeated in 15 series of cultures of microorganisms. Next, one of the zones was irradiated with a laser (wavelength 660 nm in repetitively-pulsed mode, 60 s), while the second zone was covered with a light-tight sterile cloth. Then all cultures were kept for 24 hours in a thermostat, after which the results were taken into account by a semi-quantitative method. The results of the study showed that Photoditazine, methylene blue and chlorophyllin have a pronounced antibacterial effect on microbial cultures, while eosin and St. John's wort oil demonstrate relatively low effectiveness. Proteus Vulgaris and Pseudomonas Aeruginosa cultures showed high resistance. The average resistance to the use of the proposed PS was observed in fungi of Candida genus. The PDT method showed high efficiency when spore-forming flora (Bacillus subtilis strain) was exposed to it.

There are numerous studies demonstrating the antimycotic activity of the pharmaceutical [28–32].

In 2013 Dovigo L. N. et al. [33] studied the effects of PDT with Photoditazine on various fungal species in vitro: C. albicans, C. glabrata, and C. Tropicalis, represented both as biofilms and as planktonic cultures. An aqueous solution of Photoditazine in various concentrations (25, 50, 75 mg/l for planktonic cultures and 75, 100, 125 mg/l for biofilms) was applied to fungal colonies. Different radiation doses were tested: 18, 25.5, 37.5 J/cm^2. All cultures were divided into experimental groups which were then exposed to different drug dosages and radiation doses. The control group consisted of intact colonies. As a result, it was found that fungal colonies in the form of biofilm are more resistant to PDT. Plankton culture C. Albicans was completely destroyed by photoditazine concentrations of 50 and 75 mg/l at a dose of 37.5 J/cm^2, while a biofilm containing this type of fungi did not significantly reduce the number of microbial bodies even at high concentrations of the drug (100 and 125 mg/l). C. glabrata and C. tropicalis were found to be more resistant to PDT in both biofilms and planktonic cultures.

Conclusion

Thus, the results of the above studies once again confirm that the effects of PDT are much wider than its antitumor action. The demonstrated anti-inflammatory component of PDT is comparable to the therapeutic effect of traditional antibacterial and antimycotic methods.

REFERENCES

1. Stranadko E. F., Kuleshov I. Yu., Karakhanov G. Ya. Photodynamic effect on pathogenic microorganisms (current state of the problem of antimicrobial photodynamic therapy). *Laser medicine*, 2010, No 14 (2), pp. 52–56. (in Russ.)
2. Yang Y., Hu Y., Wang H. Targeting antitumor immune response for enhancing the efficacy of photodynamic therapy of Cancer: recent advances and future perspectives. *Oxid Med Cell Longev*, 2016, 5274084. doi: 10.1155/2016/5274084
3. Yano T., Wang K.K. Photodynamic therapy for gastrointestinal cancer. *Photochem Photobiol*, 2020, Vol. 96 (3), pp. 517–523. doi: 10.1111/php.13206.
4. Civantos FJ, Karakullukcu B, Biel M, et al. A Review of Photodynamic Therapy for Neoplasms of the Head and Neck. *Advances in Therapy*, 2018, Vol. 35, pp. 324–340. doi: 10.1007/s12325–018–0659–3
5. Kwiatkowski S, Knap B, Przystupski D, et al. Photodynamic therapy - mechanisms, photosensitizers and combinations. *Biomed Pharmacother*, 2018, Vol. 106, pp. 1098–1107. doi: 10.1016/j.biopha.2018.07.049
6. Shen Y, Li M, Sun F, et al. Low-dose photodynamic therapy-induced increase in the metastatic potential of pancreatic tumor cells and its blockade by simvastatin. *J. Photochem Photobiol B*, 2020, Vol.207, pp. 111889. doi: 10.1016/j.jphotobiol.2020.111889
7. Mallidi S., Anbil S., Bulin A.L., et al. Beyond the barriers of light penetration: strategies, perspectives and possibilities for photodynamic therapy. *Theranostics*, 2016, Vol. 6, pp. 2458–2487. doi: 10.7150/thno.16183
8. Chilakamarthi U., Giribabu L. Photodynamic therapy: past, present and future. *Chem. Rec*, 2017, Vol. 17, pp. 775–802. doi: 10.1002/tcr.201600121.
9. Lee H.H., Choi M.G., Hasan T. Application of photodynamic therapy in gastrointestinal disorders: an outdated or re-emerging technique. *Korean. J. Intern. Med*, 2017, Vol. 32, pp. 1–10. doi: 10.3904/kjim.2016.200
10. Lukyanets E. A. Search for new photosensitizers for photodynamic therapy. *Photodynamic therapy and photodiagnostics*, 2013, Vol. 3, pp. 3–16. (in Russ.)
11. Zharova T. A. et al. Gonarthritis photodynamic therapy with chlorin e6 derivatives. *Photodiagnosis and photodynamic therapy*, 2016, Vol. 15, pp. 88–93 doi: 10.1016/j.pdpdt.2016.06.002
12. Zharova TA et al. Correlation of synovial caspase-3 concentration and the photodynamic effectiveness in the osteoarthritis treatment. *Photodiagnosis Photodyn Ther*, 2020, Vol. 30, pp. 101669. doi: 10.1016/j.pdpdt.2020.101669
13. Torchinov A.M., Umakhanova M.M., Duvansky R.A. et al. Photodynamic therapy of background and precancerous diseases of

ЛИТЕРАТУРА

1. Странадко Е.Ф., Кулешов И.Ю., Караханов Г.Я. Фотодинамическое воздействие на патогенные микроорганизмы (современное состояние проблемы антимикробной фотодинамической терапии) // Лазерная медицина. – 2010. – Т. 14 (2). – С. 52–56.
2. Yang Y., Hu Y., Wang H. Targeting antitumor immune response for enhancing the efficacy of photodynamic therapy of Cancer: recent advances and future perspectives // Oxid Med Cell Longev. – 2016. – 5274084. doi: 10.1155/2016/5274084
3. Yano T., Wang K.K. Photodynamic therapy for gastrointestinal cancer // Photochem Photobiol. – 2020. – Vol. 96 (3). – P. 517–523. doi: 10.1111/php.13206.
4. Civantos FJ, Karakullukcu B, Biel M, et al. A Review of Photodynamic Therapy for Neoplasms of the Head and Neck // Advances in Therapy. – 2018. – Vol. 35. – P. 324–340. doi: 10.1007/s12325–018–0659–3
5. Kwiatkowski S, Knap B, Przystupski D, et al. Photodynamic therapy - mechanisms, photosensitizers and combinations // Biomed Pharmacother. – 2018. – Vol. 106. – P. 1098–1107. doi: 10.1016/j.biopha.2018.07.049
6. Shen Y, Li M, Sun F, et al. Low-dose photodynamic therapy-induced increase in the metastatic potential of pancreatic tumor cells and its blockade by simvastatin // J. Photochem Photobiol B. – 2020. – Vol.207. – P. 111889. doi: 10.1016/j.jphotobiol.2020.111889
7. Mallidi S., Anbil S., Bulin A.L., et al. Beyond the barriers of light penetration: strategies, perspectives and possibilities for photodynamic therapy // Theranostics. – 2016. – Vol. 6. – P. 2458–2487. doi: 10.7150/thno.16183
8. Chilakamarthi U., Giribabu L. Photodynamic therapy: past, present and future // Chem. Rec. – 2017. – Vol. 17. – P. 775–802. doi: 10.1002/tcr.201600121.
9. Lee H.H., Choi M.G., Hasan T. Application of photodynamic therapy in gastrointestinal disorders: an outdated or re-emerging technique // Korean. J. Intern. Med. – 2017. – Vol. 32. – P. 1–10. doi: 10.3904/kjim.2016.200
10. Лукьянец Е.А. Поиск новых фотосенсибилизаторов для фотодинамической терапии // Фотодинамическая терапия и фотодиагностика. – 2013. – Vol. 3. – С.3–16
11. Zharova T. A. et al. Gonarthritis photodynamic therapy with chlorin e6 derivatives // Photodiagnosis and photodynamic therapy. – 2016. – Vol. 15. – P. 88–93 doi: 10.1016/j.pdpdt.2016.06.002
12. Zharova TA et al. Correlation of synovial caspase-3 concentration and the photodynamic effectiveness in the osteoarthritis treatment // Photodiagnosis Photodyn Ther. – 2020. – Vol. 30. – P. 101669. doi: 10.1016/j.pdpdt.2020.101669

uterine cervi with photosensitisers of chlorine raw. *Photodiagnosis and Photodynamic Therapy*, 2008, Vol. 5(S1), pp. 45.
14. Turubanova VD, Balalaeva IV Immunogenic cell death induced by a new photodynamic therapy based on photosens and photodithazine. *J Immunother Cancer*, 2019, Vol. 16, pp. 350. doi: 10.1186/s40425–019–0826–3
15. Duvansky V. A., Dzagnidze N. S., Biserov O. V. et al. Microcirculation of purulent wounds according to laser Doppler flowmetry data. *Laser medicine*, 2007, Vol. 11 (1), pp. 46–49. (in Russ.)
16. Shin E. F., Yeliseenko V. I., Sorokaty A. A. Effects of photodynamic therapy with Photodithazine combined with amphiphilic polymers on reparative processes. *Laser medicine*, 2017, Vol. 21 (3), pp. 31–35. (in Russ.)
17. Tolstykh M. P. The problem of complex treatment of purulent wounds of various origins and trophic ulcers. Dissertation of the candidate of medical sciences. M. P. Tolstykh, M., 2002, pp. 42. (in Russ.)
18. Tolstykh P. I., Tamrazova O. B., Pavlenko V. V. et al. Long-term nonhealing wounds and ulcers (pathogenesis, clinic, treatment). *Laser medicine,* 2009, Vol. 13 (4), pp. 112–123. (in Russ.)
19. Sieber F., Brien J. et al. Antiviral activity of merocyanine 540. *Photochem. Photobiol*, 1987, Vol. 46(5), pp. 707–711.
20. Dukan S., Nustrom T. Oxidative stress defense and deterioration of growth-arrested Escherichia coli cells. *J. Biol. Chem*, 1999, Vol. 274(37), pp. 26027–26032.
21. Zugel U., Kaufmann S. Role of heat shock proteins in protection from and pathogenesis of infectious diseases. *Clin. Microbiol. Rev,* 1999, Vol. 12(1), pp. 19–39.
22. Komerik N., Wilson M., Poole S. The effect of photodynamic action on two virulence factors of gram-negative bacteria. *Photochem. Photobiol*, 2000, Vol. 72 (5), pp. 676–680.
23. Packer S., Bhatti M., Burns T. et. al. *Lasers in medical Science*, 2000, Vol. 15 (1), 24–30.
24. Tolstykh P. I., Solov'eva A. B., Derbenev V. A. et al. A comparative effectiveness of various pharmaceutical forms of sensitizers applied in photodynamic therapy for purulent wounds. *Laser medicine*, 2014, Vol. 18 (2), pp. 8–12. (in Russ.)
25. Geynitz A.V., Mustafajev R. D., Tikhov G. V., Kizevadze R. I. Photodynamic therapy in treating peritonitis (experimental study). *Laser medicine*, 2012, Vol. 16 (2), pp. 58–62. (in Russ.)
26. Shubina a.m., Kaplan M. A. Potential of photodynamic therapy with the use of photosensitizer photoditazin for the treatment of psoriasis. *Russian biotherapeutic journal*, 2005, Vol. 4 (3), pp. 76–79. (in Russ.)
27. Shishkina O. E., Butakova L. Yu., Ivanchenko Yu. O., Antonov S. S. Microbiological backgrounding of photosensitizer effectiveness in photodynamic therapy. *Laser medicine*, 2013, Vol. 17 (1), pp. 35–37. (in Russ.)
28. Carmello JC, Dovigo LN, Mima EG. et al. Correction: In vivo evaluation of photodynamic inactivation using Photodithazine against Candida albicans. *Photochem Photobiol Sci*, 2017, Vol.16 (8), pp. 1336–1337. doi: 10.1039/c7pp90027a
29. Carmello JC, Alves F, Mima EGO. et al. Corrigendum to "Photoinactivation of single and mixed biofilms of Candida albicans and non-albicans Candida species using Photodithazine. *Photodiagn. Photodyn. Ther*, 2017, Vol.17, pp. 194–199.
30. Alves F, Carmello JC, Mima EGO. et al. Photodithazine-mediated antimicrobial photodynamic therapy against fluconazole-resistant Candida albicans in vivo. *Medical Mycology*, 2019, Vol. 57(5), pp. 609–617.
31. Panariello BHD, Klein MI, Alves F. et al. DNase increases the efficacy of antimicrobial photodynamic therapy on Candida albicans biofilms. *Photodiagnosis Photodyn Ther*, 2019, Vol. 27, pp. 124–130. doi: 10.1016/j.pdpdt.2019.05.038.
32. Janeth Rimachi Hidalgo K, Cabrini Carmello J, Carolina Jordão C. et al. Antimicrobial Photodynamic Therapy in Combination with Nystatin in the Treatment of Experimental Oral Candidiasis Induced by Candida albicans Resistant to Fluconazole.
13. Torchinov A.M., Umakhanova M.M., Duvansky R.A. et al. Photodynamic therapy of background and precancerous diseases of uterine cervi with photosensitisers of chlorine raw // Photodiagnosis and Photodynamic Therapy. – 2008. – Vol. 5(S1). – C. 45.
14. Turubanova VD, Balalaeva IV Immunogenic cell death induced by a new photodynamic therapy based on photosens and photodithazine // J Immunother Cancer. – 2019. – Vol. 16 – P. 350. doi: 10.1186/s40425–019–0826–3
15. Дуванский В.А., Дзагнидзе Н.С., Бисеров О.В., Мараев В.В., Гаджиев Э.А. Микроциркуляция гнойных ран по данным лазерной допплеровской флоуметрии // Лазерная медицина. – 2007. – Т. 11(1). – С. 46–49.
16. Шин Е.Ф., Елисеенко В.И., Сорокатый А.А. Влияние фотодинамической терапии с фотодитазином, комплексированным с амфифильными полимерами на репаративные процессы // Лазерная медицина. – 2017. – Т. 21(3). – С. 31–35.
17. Толстых М.П. Проблема комплексного лечения гнойных ран различного генеза и трофических язв: автореф. дис... канд. мед. наук // М.П. Толстых. – М., 2002. – 42 с.
18. Толстых П.И., Тамразова О.Б., Павленко В.В., Кулешов И.Ю., Толстых М.П. Длительно не заживающие раны и язвы (патогенез, клиника, лечение) // Лазерная медицина. – 2009. – Т. 13(4). – С. 112–123.
19. Sieber F., Brien J. et al. Antiviral activity of merocyanine 540 // Photochem. Photobiol. – 1987. – Vol. 46(5). – P. 707–711.
20. Dukan S., Nustrom T. Oxidative stress defense and deterioration of growth-arrested Escherichia coli cells // J. Biol. Chem. – 1999. – Vol. 274(37). - P. 26027–26032.
21. Zugel U., Kaufmann S. Role of heat shock proteins in protection from and pathogenesis of infectious diseases // Clin. Microbiol. Rev. – 1999. – Vol. 12(1). – P. 19–39.
22. Komerik N., Wilson M., Poole S. The effect of photodynamic action on two virulence factors of gram-negative bacteria // Photochem. Photobiol. – 2000. – Vol. 72 (5). – P. 676–680.
23. Packer S., Bhatti M., Burns T. et. al. // Lasers in medical Science. – 2000. – Vol. 15. – Iss. 1. – P. 24–30.
24. Толстых П.И. , Соловьева А.Б. , Дербенев В.А., Спокойный А.Л., Аксенова Н.А. , Тимашев П.С. , Кузнецов Е.В. Берлин А.А., Осокин В.В. , Иванков М.П. Сравнительная эффективность лекарственных форм сенсибилизаторов // Лазерная медицина. – 2014. – Т. 18(2). – С. 8–12.
25. Гейниц А.В., Мустафаев Р.Д., Тихов Г.В., Кизевадзе Р.И. Фотодинамическая терапия в лечении перитонита (экспериментальное исследование) // Лазерная медицина. – 2012. – Т. 16 (2). – С. 58–62
26. Шубина А. М., Каплан М. А. Возможности фотодинамической терапии с использованием фотосенсибилизатора фотодитазин для лечения псориаза // Российский биотерапевтический журнал. – 2005. – Т.4 (3). – С. 76–79.
27. Шишкина О.Е., Бутакова Л.Ю., Иванченко Ю.О., Антонов С.С. Микробиологическое обоснование эффективности фотосенсибилизаторов при фотодинамической терапии // Лазерная медицина. – 2013. – Т. 17(1). – С. 35–37.
28. Carmello JC, Dovigo LN, Mima EG. et al. Correction: In vivo evaluation of photodynamic inactivation using Photodithazine against Candida albicans // Photochem Photobiol Sci. – 2017. – Vol.16 (8). – P. 1336–1337. doi: 10.1039/c7pp90027a
29. Carmello JC, Alves F, Mima EGO. et al. Corrigendum to "Photoinactivation of single and mixed biofilms of Candida albicans and non-albicans Candida species using Photodithazine // Photodiagn. Photodyn. Ther. – 2017. – Vol.17. – P. 194–199.
30. Alves F, Carmello JC, Mima EGO. et al. Photodithazine-mediated antimicrobial photodynamic therapy against fluconazole-resistant Candida albicans in vivo // Medical Mycology – 2019. – Vol. 57(5). – P. 609–617
31. Panariello BHD, Klein MI, Alves F. et al. DNase increases the efficacy of antimicrobial photodynamic therapy on Candida albi-

Pharmaceuticals (Basel, Switzerland), 2019, Vol. 12 (8), pp. 140. doi: 10.3390/ph12030140.

33. Dovigo LN, Carmello JC, Carvalho MT. et al. Photodynamic inactivation of clinical isolates of Candida using Photodithazine. *Biofouling*, 2013, Vol. 29, pp. - 1057–1067.

cans biofilms // Photodiagnosis Photodyn Ther. – 2019. – Vol. 27. – P. 124–130. doi: 10.1016/j.pdpdt.2019.05.038.

32. Janeth Rimachi Hidalgo K, Cabrini Carmello J, Carolina Jordão C. et al. Antimicrobial Photodynamic Therapy in Combination with Nystatin in the Treatment of Experimental Oral Candidiasis Induced by Candida albicans Resistant to Fluconazole // Pharmaceuticals (Basel, Switzerland). – 2019. – Vol. 12 (8). – P. 140. doi: 10.3390/ph12030140.

33. Dovigo LN, Carmello JC, Carvalho MT. et al. Photodynamic inactivation of clinical isolates of Candida using Photodithazine // Biofouling. – 2013. – Vol. 29 – P. - 1057–1067.