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Photooxidation of tetrahydrobiopterin as the basis of vitiligo phototherapy

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The kinetics of photooxidation of tetrahydrobiopterin was investigated, the quantum yields of the formation of dihydropterin dimers were calculated when using a xenon lamp, a tunable UV laser and a UV LED as UV radiation sources. A comparative analysis of the effectiveness of these sources for the photooxidation process of tetrahydrobiopterin allowed us to conclude that the most effective for the purposes of vitiligo phototherapy are, apparently, UV LED sources with emission maxima in the region of 325 nm.

Keywords: vitiligo, tetrahydrobiopterin, melanin, oxidative stress, H_2O_2, UVB vitiligo phototherapy.

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Introduction

Biophotonics, which studies the patterns of interaction of photons with biological objects, is the fundamental basis of biomedicine and is used to study the mechanisms of biochemical processes, as well as the fundamental basis of technologies for the treatment of pathological conditions. One of the hot topics of biophotonics is associated with the study of the fundamental principles of phototherapy for dermatological diseases, since phototherapy is a non-invasive, modern method of treating these diseases. Among dermatological diseases, vitiligo is of undoubted interest, since it belongs to socially significant diseases with little-studied etiopathogenesis. The incidence of vitiligo by country ranges from 0.1% to 4.0% [1–4]. There is an increase in the incidence of this disease, which determines the relevance of this study.

Vitiligo is a dermatological disease characterized by the formation of depigmented areas of the skin due to impaired melanin biosynthesis and loss of melanocytes in the epidermis of the skin [5–7]. Until recently, several hypotheses have been considered to explain the mechanism of vitiligo occurrence: autoimmune (immune), oxidative stress, neuroendocrine, genetic and autodestruction hypothesis. It should be noted that a separate consideration of these hypotheses is not entirely justified, since there are causal relationships between all biochemical processes in the human body. Vitiligo is now considered to be the result of a complex interaction between oxidative stress and autoimmune processes in patients with a genetic predisposition [8,9].

Melanin synthesis occurs in cells — melanocytes in special organelles — melanosomes. The synthesized dark-colored melanin interacts with the proteins of the melanosomal matrix and dark-colored melanoproteins are formed, which are transferred to keratinocytes by phagocytosis [10]. One melanocyte provides with dark-colored pigments for up to 36 keratinocytes. Melanocytes are located in the basal layer of the epidermis. It has a thickness of $30-150\,\mu$m, which can be penetrated by ultraviolet UVB and UVA radiation [11,12].

The main stages of melanin biosynthesis in melanocytes are as follows: phenylalanine→ tyrosine→ dioxyphenylalanine (DOPA)→ DOPA-chrome→ · → melanin. Oxidation of the phenylalanine amino acid to tyrosine is carried out by the phenylalanine hydroxylase enzyme, which functions with the participation of the tetrahydrobiopterin coenzyme (H_4Bip). In vitiligo, melanocytes accumulate 3–5-fold excess of H_4Bip, which inhibits tyrosinase, which is a key enzyme in melanin biosynthesis [6,13–16]. Excess of H_4Bip can be easily oxidized by air oxygen (autoxidation) to form oxidized pterins and hydrogen peroxide (H_2O_2) [17,18]. Oxidized pterins, when accumulating, contribute to the photooxidation of proteins and nucleic acids [19]. Formation of oxidized derivatives of H_4Bip is accompanied by the synthesis of hydrogen peroxide, which accumulates in millimolar concentrations in the skin of patients with vitiligo [16]. Currently, the role of H_2O_2 in melanogenesis

and pathogenesis of vitiligo [9,20–22] is being actively studied.

UVB phototherapy using an excimer laser with $\lambda = 308$ nm or narrow-band lamp radiation with $\lambda = 311$ nm is the most successful treatment method for vitiligo [16,23], but the therapeutic mechanism action is not set. We proposed a hypothesis [24,25] according to which the autocatalytic cycle of excess synthesis of H_2O_2 can be broken by removing excess of H_4Bip, transforming it into dihydropterin dimers ($(H_2Ptr)_2$) under UV radiation.

A comprehensive study of H_4Bip phototransformations that occur during vitiligo phototherapy requires further research. In this regard, the purpose of this article was to study the patterns of phototransformation of H_4Bip into dihydropterin dimers under the action of UV radiation from various light sources: xenon lamp, UV laser, and UV LED.

Materials and research techniques

Reagents. 5,6,7,8-tetrahydro-L-biopterin (H_4Bip) and other pterins from „Schirks Laboratories“ (Switzerland). Other reagents used in the article were obtained from „Sigma-Aldrich Co“ (USA).

Preparation of samples. Solutions of H_4Bip in 0.1M Tris-HCl buffer (pH 7.2) were prepared immediately before the experiment, and the concentration of H_4Bip was determined based on the molar extinction coefficient ($\varepsilon_{297} = 10200\ M^{-1}cm^{-1}$ for pH 7).

UV irradiation. Solutions of H_4Bip were irradiated with constant stirring in air in a 1 cm quartz cell using xenon lamp of a FluoroMax 4 spectrofluorimeter „Horiba Scientific“ (Japan) as a UV light source. Also, H_4Bip solutions were irradiated in a quartz cell with an optical path of 0.3 cm, using pulsed laser with wavelength tuning or LED with $\lambda_{max} = 325$ nm as a source of UV light.

Irradiation using a spectrofluorimeter was carried out under excitation at different wavelengths in the range of 300−350 nm with a spectral slit width of 20 nm for various time intervals. The dark intervals during which the spectra of the irradiated samples were recorded were 2 min. Controls without irradiation were placed in parallel to each experiment. In the dark controls, only the autoxidation of H_4Bip proceeded.

In the work we used a tunable UV laser based on a $LiLu_{0.7}Y_{0.3}F_4$ crystal doped with Ce^{3+} and Yb^{3+} ions [26,27]. As a pump source, laser based on a $LiCaAlF_6$ crystal doped by Ce^{3+} (290 nm) ions [28] was used, the excitation source for which was 266 nm radiation of the 4th harmonic of the YAG:Nd (LQ529B) „SolarLS“ laser (Belarus). The pulse duration was 10 ns at a pulse repetition rate of 10 Hz. The samples were irradiated with a laser at different wavelengths in the range of 290−330 nm.

In the work there were used LEDs 325W UVTOP (USA) based on AlGaN heterostructures, emitting at wavelength of 325 nm, the emission bandwidth is about 10 nm, and the optical output power is 0.4 mW.

The concentration of the dihydropterin dimerswas determined based on the absorption band in the region of 245 nm on the difference absorption spectra and was calculated taking into account the extinction coefficient ($\varepsilon_{245} = 27000\ M^{-1}cm^{-1}$ for pH 7.2).

Research methods The absorption spectra of dark controls and irradiated samples were recorded on a Shimadzu UV-1601 (Japan), Beckman Coulter DU650 (USA), or Cary 300 Bio („Varian“, USA) spectrophotometer. Power density ($W \cdot m^{-2}$) of radiation incident on the sample was measured with an Argus-04 „VNIIOFI“radiometer (Russia).

The reaction products were analyzed by high performance liquid chromatography (HPLC) on a Luna 5u SCX 100A „Phenomenex“ cation exchange column (USA) according to a previously developed procedure described in [25]. The column was calibrated according to the release time of witnesses — preparations of H_4Bip and its oxidized derivatives. Substances were detected using three detectors: spectrophotometric, fluorimetric, and electrochemical. The use of a column calibrated by release time of substances and three detectors made it possible to most accurately identify the reaction products, since all of them had different degrees of oxidation and fluorescence characteristics.

Calculation of the quantum yield of photoreaction products. The quantum yield of dihydropterin dimer formation $(H_2Ptr)_2$ (mol/quantum) was calculated by the formula:

$$\Phi = \frac{\Delta A \times V \times N_a}{\tau \times \Delta E \times l \times In},$$

where ΔA — change in the concentration of the irradiated solution in units of optical density at 245 nm; V — volume of the irradiated solution, l; N_a — Avogadro's number, mol^{-1}; τ — irradiation time, s; l — absorbing layer thickness, cm; In — intensity of absorbed light, quantum/s; ΔE — difference between molar extinction coefficients $(H_2Ptr)_2$ and H_4Bip at 245 nm.

Results and discussion

Autoxidation of tetrahydrobiopterin

H_4Bip is a highly active reduced compound that is subjected to spontaneous autoxidation by molecular oxygen both *in vivo* and *in vitro* in aqueous solutions [17,18]. According to the literature [17,18], the first product of H_4Bip autoxidation is unstable 6,7-quinonoid dihydrobiopterin (qH_2Bip) with a lifetime of 1.5 min. Then it isomerizes into more stable dihydrobiopterin (H_2Bip) or transforms into dihydropterin (H_2Ptr) with abstraction of the side radical (dihydroxypropyl). Then, H_2Bip transforms into a fully oxidized form — biopterin (Bip), and unstable H_2Ptr is oxidized by oxygen to pterin (Ptr) or to dihydroxanthopterin

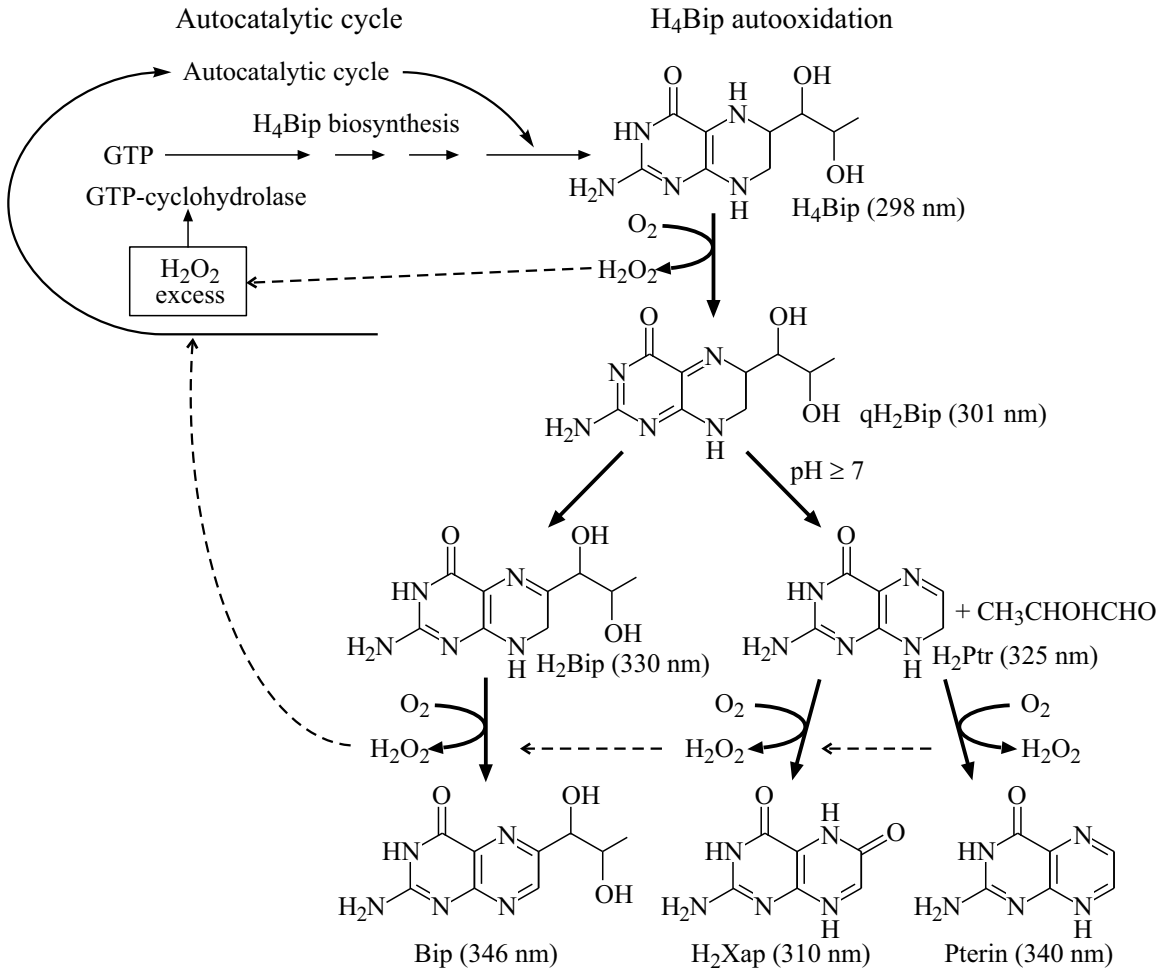

Figure 1. Scheme of autoxidation of tetrahydrobiopterin and autocatalytic cycle closure in vitiligo. The long-wavelength maxima of the absorption spectra are given in parentheses.

(H_2Xap). The sequence of H_4Bip autoxidation reactions is shown in Fig. 1. Depending on the pH of the medium, temperature, and the nature of the buffer, H_2Bip or H_2Ptr and their fully oxidized forms will predominate. In the present article, a series of experiments on autoxidation of solutions of H_4Bip $(1.6 \pm 0.2) \cdot 10^{-4}$ M in 0.1 M Tris-HCl buffer with pH 7.2 was performed. By HPLC analysis, based on the coincidence of the release times of the studied substances and the witness standards, the formation of H_2Bip (release time is 16.9 min), Bip (release time is 11.6 min) and Ptr (release time is 22.0 min) during H_4Bip autoxidation in the dark for 30 min was found. In this case, H_2Bip and Bip are formed in predominant amounts, which indicates that the oxidative transformation of H_4Bip in the dark proceeds mainly without abstraction of the side radical.

It is important to note that at each stage of the H_4Bip autoxidation process, H_2O_2 is formed, the amount of which accumulates as the process proceeds. We believe that H_4Bip *in vivo* autoxidation also leads to formation and accumulation of H_2O_2. Due to the autoxidation processes of 3–5-fold excess of H_4Bip, which occurs in vitiligo, H_2O_2 accumulates in the skin of patients with vitiligo in millimolar concentrations leading to oxidative stress. Therefore, oxidative stress takes place in melanocytes. H_2O_2, through cytokines (namely, γ-interferon), can activate the GTP-cyclohydrolase enzyme, which synthesizes an excess of H_4Bip, which then will spontaneously oxidize to form H_2O_2. We believe that in this way the autocatalytic cycle of excessive synthesis of H_2O_2 (Fig. 1), which apparently underlies the pathogenesis of vitiligo, can be triggered [24,25]. It is known that one of the functions of reactive oxygen species, in particular H_2O_2, is the induction of the immune system. Indeed, in vitiligo, humoral and cellular immunity systems are activated, leading to a decrease in the number of melanocytes producing melanin [8,9].

Photooxidation of H_4Bip

Several series of experiments were carried out on photooxidation of H_4Bip under the action of radiation from a xenon lamp. The H_4Bip solution was irradiated with UV radiation with different wavelengths in the range of 300–350 m. Each individual wavelength had a spread of 10 nm, which was provided by a spectral slit width

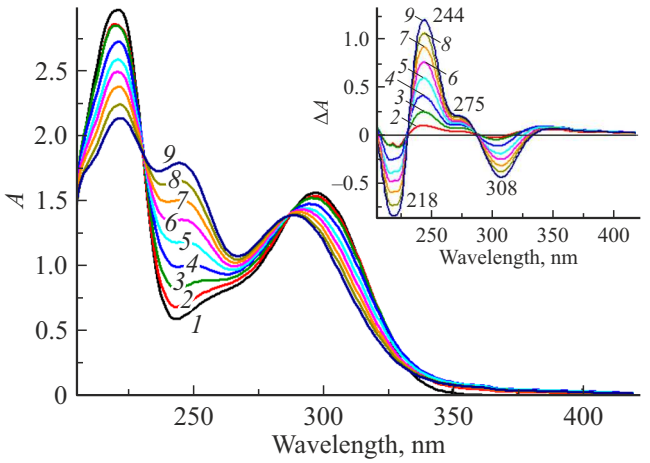

Figure 2. Change in the absorption spectra of $1.53 \cdot 10^{-4}$ M H_4Bip solution in 0.1M Tris-HCl buffer with pH 7.2 upon stepwise irradiation with 325 ± 10 nm xenon lamp of a spectrofluorimeter in the presence of atmospheric oxygen; the insertion shows the difference spectrum (difference between the irradiated and initial sample). Duration of irradiation: 0 (*1* — original spectrum), 2 min (*2*), 4 min (*3*), 6 min (*4*), 8 min (*5*), 10 min (*6*), 12 min (*7*), 14 min (*8*), 16 min (*9*).

of 20 nm in the spectrofluorimeter used by us as a UV light source. Figure 2 shows the results of an experiment on irradiating $1.53 \cdot 10^{-4}$ M H_4Bip solution with radiation with wavelength of 325 ± 10 nm (power density is 72 W·m^{-2}), while the irradiation interval and the dark interval between irradiations were 2 min. It can be seen in the difference absorption spectrum (Fig. 2, insertion) that, with irradiation, the compound with the long-wavelength absorption maximum at 308 nm decreases, and the absorption increases in the region of 244 nm and the inflection increases in the region of 275 nm. This may indicate a decrease in the intermediate intermolecular complex (quinonoid dihydropterin-dihydropterin (qH_2Ptr-H_2Ptr)) and an increase in the amount of dihydropterin dimer formed $(H_2Ptr)_2$. An intermediate intermolecular complex can be formed by donor-acceptor interactions of the benzoid form of dihydropterins (H_2Ptr or H_2Bip) with the quinonoid form of dihydropterins (qH_2 Ptr or qH_2Bip). The formed intermolecular complex obviously has absorption with a maximum at 307 nm, which was revealed by the appearance of a band at 307 nm in the spectrum of the fourth derivative of the absorption spectrum of the initial H_4Bip. It is the absorption band with a maximum at 307 nm that decreases during photooxidation of H_4Bip at all investigated wavelengths in the range of 300–350 nm.

As an example of experiments on irradiation of $1.19 \cdot 10^{-4}$ M H_4Bip solutions with tunable UV laser (light and dark intervals of 2 min) (Fig. 3), the experimental data are provided when irradiation was carried out at wavelength of 325 nm (pulse power is 64 μJ) in a square cell with an optical path length of 0.3 cm. It can be seen in Fig. 3 that, with irradiation, the absorption in the 310 nm region also decreases and the absorption increases in the 244 and 275 nm regions, which indicate the formation of $(H_2Ptr)_2$ from an intermediate intermolecular complex.

The photooxidation processes of H_4Bip were compared under irradiation with UV laser and a xenon lamp at wavelength of 325 nm. Based on the spectral data (Fig. 3), taking into account the molar extinction coefficients, it can be calculated that after 10 min of laser irradiation, 76% of H_4Bip transfers to $(H_2Ptr)_2$. Based on the spectral data (Fig. 2) it can be calculated that 37% of H_4Bip transforms into dimers after 10 min of irradiation with a xenon lamp. It can be concluded that the initial rate of the H_4Bip photooxidation process in case of using laser is higher than when using a xenon lamp. Although it must be taken into account that the power density of laser radiation is much higher than that of a xenon lamp. During phototherapy of vitiligo, excess energy can be absorbed not only by H_4Bip, but also by other photosensitizing chromophores and lead to undesirable destructive processes. Moreover, photooxidation of H_4Bip, proceeding by the radical mechanism [29–31], can be accelerated much faster than dimer formation, since formation of dimers requires an intermediate intermolecular complex (qH_2Ptr-H_2Ptr), formation of which, apparently, has diffusion limitations.

A series of experiments on photooxidation of H_4Bip under the action of LED radiation with $\lambda_{max} = 325.5$ nm (power density is 2.5 W·m^{-2}) in a square cell with an optical path length of 0.3 cm was carried out. Figure 4 shows the photooxidation kinetics of the $(1.81 \cdot 10^{-4}$ M) H_4Bip solution. It can be seen that the process of dihydropterin dimers formation is similar to the process occurring under the action of UV radiation from a xenon lamp or UV laser radiation. Absorption also decreases at 305 nm in

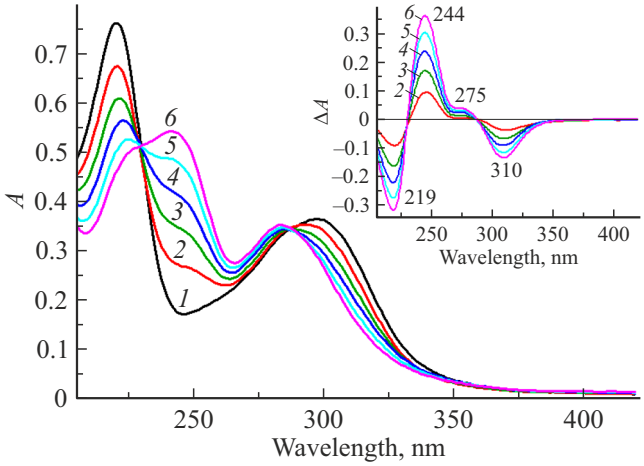

Figure 3. Change in the absorption spectra of $1.19 \cdot 10^{-4}$ M H_4Bip solution in 0.1M Tris-HCl buffer with pH 7.2 upon stepwise irradiation with 325 nm on tunable laser in the presence of atmospheric oxygen; the insertion shows the difference spectrum (difference between the irradiated and initial sample). Duration of irradiation: 0 (*1* — original spectrum), 2 min (*2*), 4 min (*3*), 6 min (*4*), 8 min (*5*), 10 min (*6*).

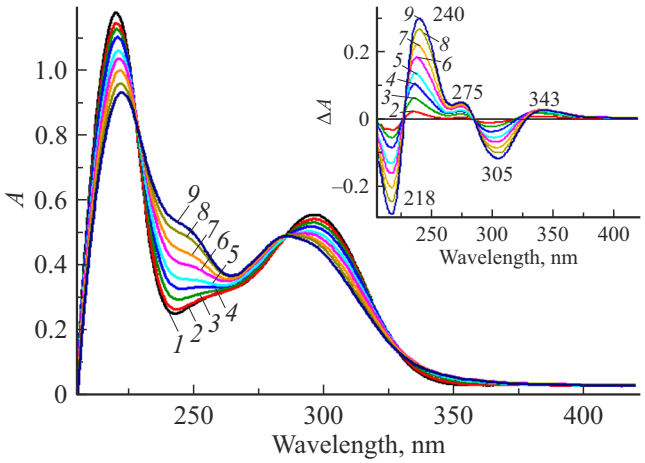

Figure 4. Change in the absorption spectra of $1.81 \cdot 10^{-4}$ M H_4Bip solution in 0.1M Tris-HCl buffer with pH 7.2 upon stepwise irradiation with 325 ± 5 nm LED in the presence of atmospheric oxygen; the insertion shows the difference spectrum (difference between the irradiated and initial sample). Duration of irradiation: 0 (*1* — original spectrum), 2 min (*2*), 4 min (*3*), 6 min (*4*), 8 min (*5*), 10 min (*6*), 12 min (*7*), 14 min (*8*), 16 min (*9*).

the absorption region of the intermediate complex, and absorption increases in the region of 240 and 275 nm, which correspond to the accumulation of $(H_2Ptr)_2$. The shift by 5 nm in the absorption region of dihydropterin dimer ($\lambda_{max} = 245$ nm) probably occurred due to the presence of small amounts (about 7%) of oxidized pterins (having absorption in the region of 230, 275 and 340 nm).

In general, we believe that UV irradiation of depigmented areas of the skin of patients with vitiligo can remove excess of H_4Bip and thereby break the autocatalytic cycle of synthesis of excess of H_2O_2, which will help prevent further development of the pathological process.

Calculation of quantum yields of dihydropterin dimer formation

In the article [25] the quantum yields were calculated and the action spectrum of UV radiation of a xenon lamp in the reaction of dihydropterin dimers formation was plotted. It was shown that the UV action spectrum maximum and quantum yields differed by less than a factor of 2 in the wavelength range of 300−325 nm, which indicates the applicability of these wavelengths for the photooxidation of H_4Bip and its conversion into dihydropterin dimers. Calculation of the quantum yields of dimer formation under the action of UV laser and building of the action spectrum based on the obtained data also showed that the most effective in the reaction of dimer formation is radiation in the region of 300−325 nm. Since irradiation at 308 and 311 nm in the UVB region (280−315 nm) captures the region of protein inactivation and thus can have a destructive effect on cells [32,33], our attention was focused on the study of the longest wavelength UV light (325 nm), included in the action spectrum of the photodimerization reaction. Quantum yields were calculated for the formation reaction of dihydropterin dimers under irradiation with wavelength of 325 nm in the initial irradiation period. For a xenon lamp it was $(1.0 \pm 0.3) \cdot 10^{-2}$, for UV laser — $(1.5 \pm 0.3) \cdot 10^{-2}$ and for LED — $(3.8 \pm 0.7) \cdot 10^{-2}$. Consequently, quantum yields for all sources are represented by values of the same order.

With an increase in the pulse power in UV laser from 10 to 100 μJ, the quantum yields of the dihydropterin dimers formation decrease approximately by a factor of 5 in the studied wavelength range. Due to the high concentration of energy in a narrow spectral range (and for pulsed lasers, in the time interval), laser light sources provide the advantage of high selectivity in the impact on a particular biochemical process. However, the high pulsed power characteristic of short-pulse lasers may be a factor limiting the use of pulsed radiation in low-intensity laser therapy techniques.

Conclusion

With UV phototherapy of vitiligo, the autocatalytic cycle of accumulation of H_2O_2 will obviously be broken due to removal of a 3−5-fold excess of H_4Bip in the form of dihydropterin dimers. Such UV phototherapy will contribute to the restoration of the melanogenesis process. Successful restoration of melanogenesis also requires removal of excess of H_2O_2, which is formed in millimolar concentrations in vitiligo-affected melanocytes and creates oxidative stress. Under these conditions, the autocatalytic cycle of excess synthesis of H_2O_2 [25] can start. In this regard, the best results in vitiligo therapy can be obtained when, simultaneously with UV phototherapy, designed to remove excess of H_4Bip, antioxidant therapy is used to remove H_2O_2 and prevent its accumulation in melanocytes. Good results of complex therapy are achieved with the use of UVB phototherapy and pseudocatalase, which decomposes H_2O_2 [16,23]. Apparently, it is possible to use nanoparticles with antioxidant properties [34]. Further development of work in this direction is necessary to improve the methods of phototherapy for vitiligo using various sources of UV radiation. In order to optimize UV phototherapy, UV radiation in the 325 nm region should obviously be used, since this will not affect numerous proteins that can be inactivated by irradiation in the 310 nm region. Among UV sources for vitiligo phototherapy, LED sources seem to be the most suitable, having the highest quantum yield in the dimerization reaction. They are the cheapest and most durable, can be designed in the form of LED matrix according to the size of the depigmented skin area and provide the radiation dose necessary for low-intensity UV phototherapy.

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Conflict of interest

The authors declare that they have no conflict of interest.

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