Review Article

On biomedical engineering techniques for efficient phototherapy

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Abstract

Background: The paper contains a mini-review of perspective techniques for the diabetic foot and different internal diseases treatment, prevention and rehabilitation by low-intense lasers and light-emitting diodes. The mechanisms of the general and specific influences of the irradiation are discussed. The latter are determined by the photo induced biochemical reactions while the former are produced by local intensification of the blood microcirculation and related physiological effects. The technical characteristics of the biomedical engineered units and the results of the treatments are presented. The specific mechanisms of the curating influence of different wave frequencies are discussed.

Keywords: diabetic foot treatment, blood microcirculation, low-level laser therapy, light-emitting diodes

Introduction

During the centuries optical radiation has been used for the therapeutic heating of surface tissues and curation of a wide set of diseases. Mostly the infrared (IR) radiation in combination with visible light (VL) of different intensities and wavelengths has been used for treatment of local skin problems, infectious diseases, skeletal, muscular and respiratory diseases, wound healing and growth stimulation.[1–3] In the prevalent cases the VL or combination of VL with IR treatment produce an enhancement in blood circulation, normalizes metabolic processes, strengthens the body's defense systems, stimulates reparative processes, and promotes the wound healing.[4–7] Expositions to VL with red/IR wavelengths improve the blood circulation in the tissues, enhance the regeneration of damaged tissues, normalizes the water balance, increase the rate of redox reactions, has a pronounced vasodilating, anti-inflammatory, analgesic, and lymph-depleting effects.[1–7] IR radiation of the wavelengths λ=0.76-400mcm penetrates into the surface tissues to a depth h~2-3cm, influences the skin thermo receptors and after 2-3minutes of the exposition causes local hyperemia accompanied by the increased blood flow and heat transfer, tissue metabolism, oxidative processes and reduce the water content in the tissues. It was shown that it is the removal of the vascular spasm and the intensification of microcirculation that underlies the therapeutic effect of VL and IR radiation in skin diseases.[6,7]

During the last decades high attention has been paid to the therapeutic use of non-destructive and non-toxic low-level laser therapy[7,8] (LLLT) and light-emitting diodes[9,10] (LED). Such treatments produce moderate changes in the temperature of the irradiated tissues below the temperature range of skin thermo receptors and evoke noticeable therapeutic effect due to photochemical and photophysical mechanisms.[1,2,11,12] The mechanisms of the action of photons are associated with cellular and sub cellular receptors, where the photo induced increase/ decrease in their activity leads to a series of reactions at different scales.[13] For example, the cellular chromophores like cytochrome C oxidase and photoactive porphyrins are responsible for the effect with absorption peaks in the near IR. Due to such mechanisms the irradiation of LEDs activates the synthesis of elastin and collagen by the cells, causes an increase of the growth factors, the remodeling of extracellular matrix, and enhanced microcirculation.[14–17] The latter is associated with activation of the mitochondrial respiration. The increase in the blood vessel diameter after the LED irradiation is confirmed by MRI,[18] and the increase in the blood flow velocity has been confirmed by the Doppler velocimetry and capillarography.[19] The activated synthesis of collagen and the release of growth factors provide a healing effect in bones, skin, cartilage, tendons and ligaments.[20] Noticeable activation of blood microcirculation promotes the rise of tissue metabolism and faster recovering after the inflammatory diseases of the skin, in the case of diabetes,[17,21] wound healing,[3,5,13,20] and pain reduction.[22]

A brief review of the therapy techniques

The very first mention on the heliotherapy can be found in the manuscripts of Hippocrates, but the phototherapy as a science began to form only in the 19th century, after the discovery by the British scientists J. Down and R. Blount (1877) of the therapeutic properties of ultraviolet (UV) radiation. In 1903, Danish physiotherapist N. Finsen was awarded the Nobel Prize in Physiology and Medicine for the development and widespread introduction of treatment methods, especially autoimmune and skin diseases, with the help of focused VL irradiation. Subsequently, in a large number of experimental studies, it was shown that blue light changes the biochemical composition of blood, improves the functioning of the heart and lungs, stimulates the immune system, and has an antimicrobial effect. At the beginning of the 20th century, before the discovery of antibiotics, blue light lamps were widely used in dentistry for the treatment of gum inflammation, as well as for anesthesia.[1,2] At the cellular level, blue light stimulates ATP synthesis, regulates metabolism, improves the function of external respiration, oxygen delivery and utilization in cells, and improves the conduction of nerve impulses.[1,2] As a result, at the level of the blood circulation system, a decrease in blood viscosity, strengthening of the vessel walls, improvement of microcirculation, and an increase in blood flow velocity in the main vessels are observed. The absorption of photons by endogenous photo sensitizers leads to the appearance of photodynamic effects, such as the destruction of bilirubin and elimination from the body in the form of non-toxic products. Selective absorption of blue light by low-density lipids leads to their destruction and reduction of their level in the blood. This triggers the genetic mechanism of regulation of lipid metabolism, which leads to the destruction of atherosclerotic plaques.[1,2] Red VL and IR irradiation improves blood microcirculation in small vessels, increases the rate of redox reactions, enhances the regeneration of damaged tissues, normalizes the water balance of cells, has a pronounced vasodilating, anti-inflammatory, analgesic, lymphatic drainage and anti-oedema actions, increases local and general immunity. IR radiation with a wavelength of λ=0.76–40μm penetrates into the tissues to a depth of h=2–3cm, affects the skin thermo receptors, and after 2–3minutes, causes hyperemia on the irradiated part of the body, accompanied by the increased blood flow and heat transfer, tissue metabolism, and oxidative processes and reducing the water content in the tissues. Stronger tissue heating causes the breakdown of some protein molecules with the release of biologically active substances, which leads to a generalized vascular reaction in the body, resulting in an increase in heartbeat and sweating. Infrared irradiation of large areas of the body of the animal provides a good therapeutic effect in chronic inflammatory processes and reduces the pain response. It was shown that it is the removal of vascular spasm and the intensification of microcirculation that underlies the therapeutic effect of VL radiation in skin diseases.[23,24]

Low-intensity optical radiation accelerates wound healing, has anti- inflammatory and analgesic effects, including as a post-operative analgesic, has a protective effect on cells, and prevents their death from cytotoxic factors.[7,25–29] Intensification of the microcirculation system under the action of VL+IR can be a key mechanism for wound healing[30] and pain reduction.[31] The cyto protective effect of LLLs of different wavelengths and radiation doses on the cells in culture has been shown in a number of works, including cells treated with cyanide poisons,[32] tetrodotoxin,[33] MPP+ and rotenone.[34] The cyto protective effect of LLLs and a decrease in apoptosis was recorded in neurons treated with beta-amyloids.[35,36] Despite the good reproducibility of many of the effects of LLLS on the cells in vitro, on the human body, domestic and experimental animals *in vivo*, the mechanisms of action at the cellular level are not entirely clear.[37] Recently, a lot of attention has been paid to the therapeutic use of non-destructive and non-toxic influence of LLLs and LEDs. Starting from the work,[38] in which the possibility of accelerating muscle regeneration and wound healing under the influence of a ruby laser with an intensity of J= 1 J/cm^2 was shown and confirmed,[39,40] the VL treatment in combination with IR is widely used in medical care all over the world. LED *in vivo* irradiation has a pronounced analgesic and anti-inflammatory effect, activates the body's protective reactions, normalizes water metabolism and increases the intensity of metabolism. It is important that LED radiation does not cause thermal damage to the tissues and contributes to the withdrawal of active radicals. Currently, the low-level optical radiation is determined by[41,42] the power of J=10^{-3}–10^{-1} W, with a wavelength λ =300–10600nm, frequency from f=0 (continuous) to f=5 kHz, a pulse duration t=1–500 ms, inter pulse interval t=1–500 ms, total exposure time T=10–3000 s, intensity j=0.01–10 W/cm^2, and total dose D=0.01–100 J/cm^2. Inert gases such as helium-neon (632.8nm), argon (488 and 514nm) and krypton (521, 530, 568 and 647nm), as well as a ruby laser (694nm), semiconductor laser diodes from gallium arsenide (GaAs; 904nm), aluminum-gallium arsenide (GaAlAs; 820 and 830 nm)[43] are used as a body for the lasers. Such wide variations in the treatment parameters make it difficult to standardize the experimental conditions, as well as the development, validation and implementation of appropriate therapeutic techniques.[44,45] Due to low intensity of the applied radiation and insignificant increase in the temperature of the irradiated biological object (below temperature changes to which tissue thermo receptors or the corresponding molecular receptors of cells are sensitive), that is, the practical absence of thermal effects, and the involvement of photochemical and photophysical mechanisms of action mostly.[41,46] In recent years, there has been an increasing interest in the therapeutic use of non-invasive methods, with almost no negative after-effects and contraindications, including the LEDs.[6,10,11] In this case, the mechanisms of photon action are associated with cellular and sub cellular receptors, the photo induced increase or decrease in the activity of which leads to a cascade of reactions at the cellular and tissue, and then at the organism level.[13] A brief review of reproducible results of LED therapy is given in Table 1 & 2. According to Planck's theory, the photons of a long-wave have less energy than the photons of a short-wave range of optical radiation $E=hc / \lambda$, where h is the Plank constant, c is the light speed in vacuum.

Table 1 Influence of LED radiation of different wavelengths on the skin of humans and animals.[42,47]

	Color	λ(nm)	Action
1	Violet	400–420	Antibacterial. Treats psoriasis, dermatitis, vitiligo.
2	Blue	450–470	Antibacterial. Normalizes the sweat and sebaceous glands, eases seasonal affective disorders.
3	Green	520–550	Soothes reddened, inflamed skin. Eliminates red acne, erythema, skin pigmentation and age spots, narrows the capillaries.
4	Yellow and orange	580–620	Tightens and tones the skin, smooths wrinkles and folds. Reduces solar, burn and age pigmentation of the skin.
5	Red	640–690	Normalizes cellular metabolism, increases microcirculation. Stimulates collagen synthesis by cells and promotes wound healing and scars resorption.
6	IR	800–1000	Significant increase in microcirculation. Strong wound-healing and smoothing effect by activating fibroblasts and stimulating collagen synthesis not only in the skin, but also at the depth of muscle tissue. Produce analgesic and stimulating effects on muscles and joints.

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Table 2 Penetration depth (h) of optical radiation of different frequencies.[48,49]

	Short wave UV	Middle wave UV	Long wave UV	Violet	Red	Short wave IR	Middle wave IR	Long wave IR	Far IR
λ(nm)	200-250	300	360	400	700	1200	2000	2500	4·105
h(mm)	40	100	190	250	400	800	400	100	30
Reach to:	Epi-dermis only	Epider-mis only	Epider-mis and dermis	Epidermis, dermis and partially hypodermis	Epidermis, dermis and hypodermis	Dermis, hypodermis, muscles, cartilage, bones	Epidermis, dermis and partially hypoderm-mis	Epider-mis only	Epider-mis only

Therefore, LED- irradiation of skin activates the synthesis of collagen and elastin in cells, causes an increase in the content of growth factors, the formation of extracellular matrix, increased microcirculation[11,14,15,42,50–56] The latter effect is associated with the activation of the mitochondrial respiratory chain due to photo biomodulatory effects of VL. An increase in the lumen of blood vessels after the irradiation has been confirmed by tomography,[31] and an increase in blood flow velocity has been approved by the Doppler flowmetry and capillary chromatography.[56] An increase in the intensity of microcirculation leads to changes in the systemic circulation in the closed blood circulation system. Synthesis of collagen and the presence of growth factors provide a healing effect.[57] Activation of microcirculation contributes to increased tissue metabolism and improvement in inflammatory skin diseases, diabetes,[55,58] wound healing and pain reduction,[31] provides rejuvenating and smoothing effect, which is confirmed by measuring the elastic modulus of the skin before and after exposure to LED in red and IR ranges.[50] The analgesic, anti- inflammatory, and vasodilating effects of AOIs have also been noted with intravenous blood irradiation with LLEL.[56] It was also noted relaxation of the MMC of the arteries by improving cellular respiration and removal of vascular spasm, improving the rheological properties of blood, normalizing the ratio of coagulation and anticoagulation systems.

Modern biomedical engineering units for phototherapy

Phototherapy is successfully used in complex medical treatment of diabetic foot, angiopathy of the lower

extremities, cerebral palsy, injuries, burns, frostbite, trophic ulcers and wounds. The basis of the therapeutic effect of light is its ability:[1,2,7,27,42]

I. To normalize the work of the regulatory systems of the human body (immune, endocrine and central nervous).

II. To increase the microcirculation of blood and lymph, to increase the elasticity of the blood vessel walls, to normalize the rheological parameters of blood and its oxygen transport function.

III. The anti-inflammatory, anti-oedema, healing, analgesic, radio protective and photo reactivating effects;

IV. To accelerate the process of tissue regeneration.

V. To stimulate the formation of ATP in mitochondria that increases the bioenergetic potential of cells;

VI. To accelerate metabolic processes.

The final result of *in vivo* exposure of human body or its local regions to IR and VL is an increase in its resistance and an extension of the limits of adaptation, i.e. body resistance to various diseases and negative external factors. VL has neither contraindications or negative side effects and can be used for the treatment and prevention of the most common human diseases.

Diabetic foot treatment

The above mentioned properties of the IR and VL radiation have been used for the treatment and prevention of diabetic foot syndrome, since any pathological process starts with a non-specific phase, namely, a violation of the microcirculation of the blood and lymph. To ensure effective uniform irradiation of the lower limbs of the patient, the following biomedical engineered units have been designed (Figure 1).[59] Six small printed circuit boards with eighteen LEDs mounted on them are located in each section on the base and the rear wall. One small board is placed on the front wall of the section. On each side wall of the section there are three large printed circuit boards, each containing thirty-six LEDs. The printed circuit boards with LEDs on the base and the back wall are covered with transparent polycarbonate plates of 5mm thick, which are fixed to the support posts, that allows patients weighing up to 120kg to stand on the base of the chamber. The printed circuit boards on the side walls are protected by 2mm thick transparent polycarbonate plates.

All printed circuit boards are electrically interconnected in parallel, and connected to the power supply unit MPB-2S/500, which is powered from 220V, 50Hz and has an output voltage of 15 V DC 5A. The power supply is outside the device and is located in a separate case for maximum safety when using the device. The technical parameters of one of the modifications of the unit are given in Table 3. The acceptable colors for the treatment procedures are: IR (λ=940nm), red (λ=630nm), yellow (λ=595nm), green (λ=525nm), blue (λ=470nm), and violet (405nm). The following combinations have been approved after the clinical testing: IR+red, IR+green, IR+blue, IR+red+yellow+ green+blue+violet.[42]

Treatment of the internal diseases

This type of photonic applicators have been designed for prevention, treatment and rehabilitation of the most common human diseases: myocardial infarction, stroke, hypertension, hypotension, influenza, tuberculosis, pneumonia, bronchitis, asthma, gastric ulcer and duodenal ulcer, osteochondrosis, vascular dystonia, neuralgia, sinusitis, otitis media, arthritis, arthrosis, allergies, prostatitis, andexitis, injuries, burns, frostbite, and others needed local heating and activation of local tissues and their microcirculation. Several types of the applicators can be helpful (Figure 2). The units designed for local applications are composed of 24LEDs (Figure 2A) while the units for the distributed purposes have 120LEDs (Figure 2B). The pulsed control unit MPB-2S/80 ensures the operation of the unit in continuous, pulsed or scanning modes. The scanning is performed according to the modulation frequency of the luminous flux. Also the unit can be used for dosing of the phototherapeutic procedure according to the duration of the irradiation. The main technical parameters of the unit MPB-2S/80 are given in the Table 4. The first unit can be used for local treatment of small local areas 10x12cm, while others are applicable for the treatment of back, high and low extremities. High therapeutic effect of both units have been shown during the detailed clinical trials.[42] The same combinations of the colors for activation of the photo induced reactions in the cells and tissues with IR radiation for local heating and intensification of the microcirculation have been chosen (see §5.1).

Treatment of neurological diseases

Therapeutic influence on the head needs a delicate approach. Special phototherapeutic units for the prevention and treatment of neurological diseases caused by acute or chronic cerebro vascular accident, Alzheimer's disease, Parkinson's disease, meningitis, herpes viral encephalitis, migraine, epilepsy and other brain diseases have been elaborated (Figure 3A). Such diseases are difficult to treat with drugs or other physiotherapeutic procedures. The proposed treatment cannot substitute the drug therapy prescribed, and can be used as a complimentary measure that can enhance the main treatment and accelerate the recovery. The photon units Barva- CNS are manufactured as a hat that can be adjusted to any size of the head (Figure 3A) or neck (Figure 3B). Its application allows reducing the duration of treatment of neurological diseases by 2-3 times depending on its severity, and significantly increases the efficiency of drug therapy. The first type of unit (Figure 3A) is designed for the problems caused by acute or chronic insufficient cerebro vascular blood circulation. They can also be used for treatment of the skin and hair problems like alopecia and others. The units contain 228 or 240 LEDs depending on their type and size. The most efficient combinations of colors with IR radiation are the same as in §5.1. The second type of unit (Figure 3B) is designed for the prevention and treatment of otolaryngological (sore throats, pharyngitis, laryngitis) and neurological diseases (neck osteochondrosis, etc.). The technical characteristics are similar to those presented in Table 3. The restoration of blood microcirculation in the ischemic zone allows elimination the cause of the pathology development and ensuring rapid recovery.

Table 3 Specifications of the two-channel microprocessor unit MPB-2S/500

Parameter	Value	Units
Output voltage of each channel in continuous mode	14 ± 0.3	V
Nominal value of the output current of each channel	500	mA
Adjustment range of the modulation frequency of the light flux in pulsed mode	Jan-99	Hz
The duty cycle of pulses of light flux in pulsed mode	2	
Duration of the irradiation	Jan-99	min
Supply voltage	220 ± 22	V
AC supply voltage frequency	50	Hz
Overall dimensions	220x195x70	mm

Table 4 Specifications of the unit MPB-2S/80

Parameter	Value	Units
Output voltage of each channel in continuous mode	14 ± 0.3	V
Nominal value of the output current of each channel	80	mA
Adjustment range of the modulation frequency of the light flux in pulsed mode	Jan-99	Hz
Adjustment range of the modulation frequency in the first scanning mode	10-Jan	Hz
Adjustment range of the modulation frequency in the second scanning mode	10-100	Hz
Frequency resolution in the first scanning mode	1	Hz
Frequency resolution in the second scanning mode	10	Hz
Duration of the irradiation	Jan-99	min
Supply voltage	220 ± 22	V
AC supply voltage frequency	50	Hz
Overall dimensions	195x140x50	mm

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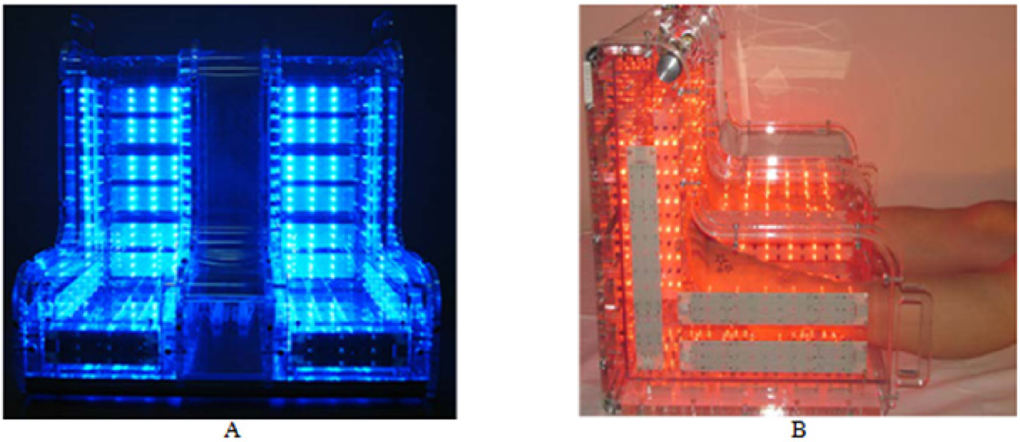
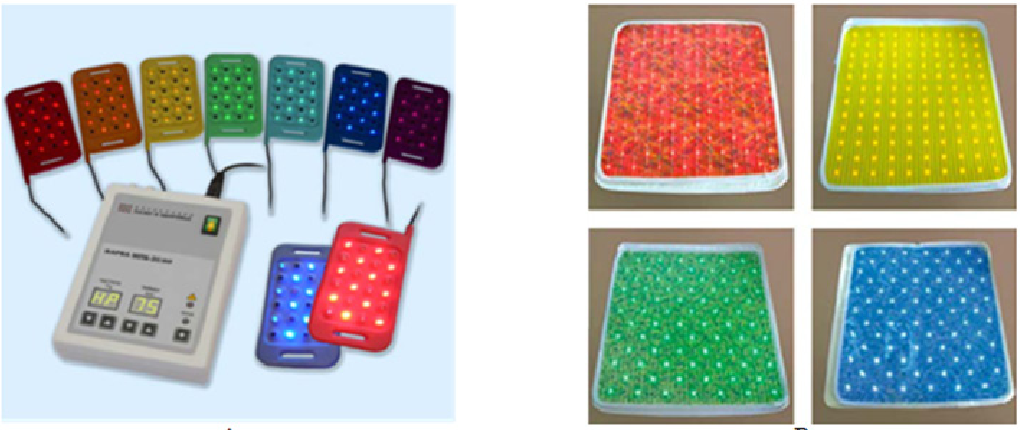


A B

Figure 1 The biophotonic device Barva-CDC for the diabetic foot treatment: A – general view of the unit with UV light turned on, B – feet location in the unit with IR+red light turned on.



A B

Figure 2 Combined applicators for biophotonic therapy of local (A) and distributed (B) areas of the body.

A B

Figure 3 The photon units Barva-CNS for applications on head (A) and neck (B) with red color VL irradiation.

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Conclusion

The valuable database of the experimental data on positive therapeutic effect of the IR and VL irradiation in strengthening the organism, prevention and treatment of many internal diseases like stroke, myocardial infarction, hypertension, pneumonia, bronchitis, asthma, ulcers, osteochondrosis, neuralgia, sinusitis, arthritis, arthrosis, injuries, burns and others stimulates the deeper data analysis and classification, understanding the mechanisms of the therapeutic effects. Among them, the intensification of local microcirculation in the irradiated tissues and the photo induced biochemical reactions with active participation of cellular chromophores like cytochrome C oxidase and photoactive porphyrins.[1,2,7,27,42] the main therapeutic mechanism is connected with fast restoration of blood microcirculation in the ischemic zone, that promotes elimination the cause of the problem/disease development and ensures rapid recovery. The applied IR+VL treatment does not substitute the individual drug therapy prescribed by a doctor, but can be used as a complimentary synergetic measure that enhances the treatment, preventive or rehabilitation measures, and accelerate the general recovery and improvement of the organism.

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Conflicts of interest

Author declares that there is no conflict of interest.

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