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Review

Human Body Photobiomodulation: History and Future Perspectives

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Abstract

Photobiomodulation (PBM) has ancient origins being Hippocrates considered the first physician who recommended to expose ulcers and wounds to sunlight for accelerating the healing process. Subsequently, at the end of the 18th century, Joseph Priestley started his photochemical rechearses, later continued by Antoine de Lavoisier who constructed the basis of modern photobiology. In 1960 Theodore Maima constructed the first laser device emitting a coherent, collimated and monochromatic (red) beam and Andre Mester, few years after, discovered the possibility to use the coherent light at low power to increase the wound healing process. Konstantin Korotov, between the 1980s and the first decade of the 2000s, realized the bioelectrographic GDV (Gas Discharge Visualization) device, a particular kind of camera able to detect and measure the energy fields inside the body. The aim of this brief report is to describe the opportunities of the PBM in the human body, both for diagnostic and therapeutical utilization.

Keywords: photobiomodulation; laser therapy; low-level laser therapy; laser; light-emitting-diode

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1. Introduction

Depending on the applications and emitted energy amounts, lasers can be classified as diagnostic, therapeutic and surgical [1–5] and, even if intense pulsed and Light-Emitted-Diodes (LED) lights, are employed since few years for therapeutic purposes, only lasers own the peculiarity of simultaneously being monochromatic, coherent, bright and directional.

In fact, radiations based on intense pulsed light and LEDs are brilliant and monocromatic, but neither coherent nor perfectly collimated and this means that, while the laser beam can be in advance dosed at the tissue level and consequently the amount of its absorption predicted, the same cannot be done with intense light lamps or LEDs. Therefore, the amount of irradiating radiation absorbed by the tissue will be at any moment different, also considering the same kind of tissue.

Laser radiation, as well as intense pulsed and LED light radiation, is composed of photons and it is therefore generally considered as not carcinogenic and/or mutagenic even if some authors don't exclude this possibility when emitted in the ultraviolet band of type A. In fact, several photobiological studies stated the short wavelengths can cause genetic mutations even in an oncogenic sense [6], even if some Authors concluded that radiation from excimer lasers is less mutagenic than UV light from Hg lamps [7].

Andre Mester, in 1967, observing the improvement of the healing process in scare rats after low-power Ruby laser irradiation [8], proposed the utilization of this procedure in medicine and started to successfully treat non-healing difficult-healing human skin and mucosal ulcers and wounds. Subsequently, many Authors studied in detail the mechanisms of action of low-energy laser irradiation in the tissues. Karu indicated mitochondria as the most cellular compo-nent sensitive to visible and near IR radiations [9] and Hamblin et al., confirming this theory, suggested as the final result the increasing of adenosine triphosphate (ATP) production, deoxyribonucleic acid (DNA) synthesis, reactive oxygen species (ROS) and nitric oxygen species (NOS) modulation and transcription factors induction [10]. Moreover, Kulbacka et al. demonstrated that visible wave-lengths, mainly blue and green, are also active in intracellular Calcium increase [11]. Low-power laser irradiation has now developed into a therapeutic procedure that is used in three main ways: to reduce inflammation, oedema, and chronic joint disorders, to promote the healing of wounds, deeper tissues, and nerves, and to treat neurological diseases and pain [12]. In 2019, Juanita Anders et al., to avoid confusion about the terminology that time adopted (LLLT, soft laser, cold laser, biostimulation, and so on), proposed only to use the term Photobiomodulation (PBM), so enhancing also that, by this technique, is possible to make both stimulation and inhibition. At the same time, these Authors affirmed that Laser and Light-Emitting-Diode (LED), at low power, have the same kind of effects in the biological tissues [13]. This was confirmed in 2018 by Heiskanen and Hamblin who enhanced the advantages of LED light in PBM including no laser safety considerations, ease of home use, ability to irradiate a large area of tissue at once, possibility of wearable devices, and much lower cost per mW [14].

2. Material and Methods

2.1. PBM in Diagnostics

Types of lasers and wavelenghts used: Excimers (126-351 nm), Diodes (445-1500 nm), Helium/Neon (632 nm)

A synthetic list of the major applications of laser in medical diagnostics, evidence-based and approved as well as only experimentally proposed, is below presented:

LASER DOPPLER: By in vivo studies of capillary microcirculation, its use is up today accepted by the entire scientific community [1,2,5,15]. One of the most important applications has been studied and reported since 1997 by Prof. E. Tomasini of the University of Ancona, who showed the "vibrometry" measurements of the oral cavity structures, obtained with lasers and useful for the study of the state of the dentition [16].

LASER SCAN MICROSCOPY: Sometimes known also as confocal laser scanning microscopy (CLSM) or laser scanning confocal microscopy (LSCM) it is able to capture multiple two-dimensional images at different depths in a sample; by its way it is possible the reconstruction of three-dimensional structures and, consequently, the reduction of the thin sectioning using instruments such as the microtome. [1]

PHOTODYNAMIC DIAGNOSIS (PDD): it allows the selective identification of neoplastic cells through an agent binding to them activated by a proper laser wavelength. It can be coupled with photodynamic therapy (PDT), when the agent (chromophore) activated by the laser selectively eliminates the neoplastic cells [1–4].

It was proposed for the first time in the world by Tom Dogherty [15] at the end of the 60s and the first centres in the world using this method were England, Germany, USA, France, Japan, Israel and Lithuania. It has not yet become widespread in routine, due to a series of inconveniences and limitations:

- Rather low fluorescence decay time of substances and variable quantities of primary and secondary fluorescence for the same substance, depending on the time of use (poor stability);
- High costs and difficult availability in many countries, where such therapies are not permitted, except at an experimental level;
- Impossibility of irradiating many deep tissues with the laser, and "shield effect" of the first most superficial layers of the substance-tissue complex which, necrotizing during irradiation, prevent the penetration of the rays to deeper levels;

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- Only relative substance-tissue selectivity, with the possibility of the photodynamic substance binding to other cells with a high mitotic index, such as liver and skin cells, in addition to neoplastic cells, and/or not binding to poorly or poorly vascularized neoplastic cells.

PDD and PDT are however mainly used for the diagnosis and therapy of skin and hollow organ tumours. Today attempts are being made to use these methods also in the treatment of skin diseases such as acne, pigmented keratosis, vitiligo, psoriasis and eczema [17–21], and in chronic osteomyelitis [1].

OPTICAL TOMOGRAPHY: it is a type of CT scan, where X-rays are replaced by laser beams which can give a three-dimensional vision of the irradiated area. [1]. During Laser Florence 2000, Prof. A. Hielscher of Columbia University in New York showed the three-dimensional images of the human body obtained with this technology which allows an accurate study of the bones and muscular systems, not yet of the fine structures.

OPTICAL BIOPSY: it allows the identification of cells undergoing malignant transformation with a simple light scan, without any invasive methods. Useful for breast cancer, but not yet used routinely. It is mainly used as a guide for traditional biopsy [1–4].

RAMAN SPECTOMETRY: It is based on the principle that each tissue has its own absorption map of the various colours. Lasers allow these maps to be traced, which change for each tissue shortly before it becomes ill [1–3,5]. It finds applications not only in medicine, but also in Criminology, where it is used in place of normal detectors, and in diagnostics for Cultural Heritage. It was also utilised to study the chemical composition of the human dental enamel and its modification after fluoride incorporation [22].

KIRLIAN SPECTOMETRY: due to every living body emits light radiation, it can be measured and influenced by laser beams, and can continue to be emitted for a more or less long period even after death. It is still at an experimental stage and is applied in the USA, Germany, the United Kingdom, France, Russia, China, India, Saudi Arabia and Japan [5].

2.2. PBM in Medical Therapy

Types of lasers and wavelengths employed: CO_2 (10200 nm), Nd:YAG (1064 nm), He/Ne (632 nm), Diodes (445-1500 nm), Excimers (126-351 nm), Pulsed light (280-1200 nm), LED (445-1100 nm).

Even if non-surgical applications of lasers have reached up today more and more popularity in the world for their great number of advantages, their progression was not so easy.

In fact, in the first years of their birth, due to the effect was less immediate and demonstrable than in surgery applications, as well as that, because their low costs, they were initially proposed only by Eastern European countries [23,24] In the United States, non-surgical physical therapies experimentations were not allowed by the pharmacological industry until Clinton presidency (1992), and the first therapeutic lasers were marketed in Europe in a wild way, including teleshopping, and without a correct information about their applications, so often ending up in the wrong hands. Fortunately in recent years, the scrupulous researches conducted according to international scientific rules [25–28], as well as the great number of clinical case studies appeared in the literature have been able to give Photobiomodulation the deserved dignity and importance.

During Laser Florence 2001 [3] the diode laser was successfully employed to reduce blood sugar levels in insulin-dependent diabetics by Prof. Pretidev Ramdawon and the same technique has been used for about thirty years in many Eastern European countries, in China, India and Finland [5,28]. During Laser Florence 2002 and 2003 other different groups discussed about this topic and also our team started collecting clinical cases and completed phase 2 of the experimentation, with excellent results, both on type 1 and type 2 diabetes, only changing the irradiation method. By diode lasers used during the digestion phase, we tried to avoid secondary hyperglycaemia, so maintaining the results obtained for as long as possible. In fact, the follow-up is positive as long as the patients follow the basic rules of hygiene, with regard to diet and physical activity [5,28]. During Laser Florence 2002, the effect of lasers on the healing of an experimental ulcer model was demonstrated, where the fibroblast growth factors increased by 98%.[29,30] This is a contributing factor that may explain the extremely positive clinical effect of non-surgical lasers on the healing of experimental ulcers and wounds [25–28].

It must be underlined that each effect of PBM is strictly dose-dependent [21,23]: in fact the same wavelength on the same tissue kind may induce opposite effects: lasers used to stimulate healing can also inhibit it and vice versa.

This phenomenon, known as "Arndt-Shultz Law" is useful in the case of pathological healing, such as hypertrophic scars and keloids [31,32], or for collagenopathies, such as "induratio penis plastic," also known as "La Peyronie's Syndrome" [28,33] where it has been seen that metal-sensitive collagen proteinase increases up to 80% after each laser irradiation, reaching its maximum after approximately three weeks of irradiation, while the Transforming Fibroblast Factor (TGF) remains unchanged until the third or fourth application, conducted with dosages at least double than those used to stimulate healing [34].

Lasers and pulsed light are also used in aesthetic medicine, according to the skin rejuvenation method: in these cases, an application of these radiations every 3-4 weeks, for an average of four to eight applications, is able to improve areas of dystrophic skin, reabsorbing dyschromia and small wrinkles, and giving the tissue a more toned appearance and more resistant to external insults. The Anglo-Saxon authors have carried out various histological surveys with the punch technique (which involves the use of a scalpel with a circular cutting edge called, precisely, "punch", which removes cylindrical portions of tissue), highlighting the reabsorption of damaged collagen and other skin impurities and the replacement with young collagen and revitalized tissue [35,36]. The same authors have hypothesized a mild dermo-hypodermic inflammation at the basis of these phenomena, but the same inflammation caused by violent pressure, such as slaps, does not produce the same effect. Therefore, we have proposed a totally different mechanism [37]: several in vitro studies have been shown that red light is absorbed by cellular mitochondria, near infrared light by cellular walls, as well as by tissues of complementary wavelength. Under normal conditions, activated mitochondria have the exclusive peculiarity of producing H_2O, and this triggers the subsequent process of ATP production, not only by the mitochondria themselves but by all the cellular components. The large amount of energy formed stimulates the normal cell to work to its maximum capacity. However, in case of damaged cells, the mitochondria produce H_2O_2, with a consequent increase in activated oxygen radicals, called ROS (Reactive Oxygen Species), due to the degradation of the unstable H_2O_2 itself. The small quantities of ROS "clean" the cytoplasm, putting the cell in the condition to resume its functions at its best. Larger quantities of ROS create in the tissue an inflammation with relative active hyperemia, up to a toxic dose, so causing the coupling of two oxygen ions in the mitochondria, so much so as to give an activated state called "singlet oxygen", which is cytocidal, since it causes the denaturation of the cytoplasm and cell death. The coagulation of the cytoplasm, on the other hand, prevents the cellular degeneration of severely damaged cells.

The acceleration of tissue metabolism, with consequent acceleration of cellular turnover and regeneration, would be mediated by ROS induced by light. A similar mechanism at mitochondrial level has also been proposed by several Authors [2,3], for different PBM applications, such the reabsorption of ear inflammation [4,5].

Several clinical double-blind trials have been conducted by various groups on rheumatology and sports medicine. Every year during Laser Florence the state of the art of this type of application is discussed and WHO and FDA representatives illustrate their guidelines [1–5,10].

Lasers are excellent local anti-inflammatories and, according to many authors, particularly by Russia, they have also antibacterial, antiviral, antiparasitic effects, stimulating the immune defences, principally lymphocytes [1–5,21,23,28]. Some of these actions have been verified, especially in the oral cavity [38–41], others still need confirmation by adequate experiments.

V. Ovsiannikov also proposed the "endovenous PBM" [42], where a fibre optic laser is inserted into a venous cannula needle on a brachial vein, with irradiation of all intracorporeal blooding, with the aim to increase number and activity of lymphocytes and all cellular blood components, the oxygen pressure in the blood and positively influence all the hemato-chemical parameters; this technique is also called “photo-dialysis”.

Toshio Oshiro [1,2] used lasers at the level of reflexogenic points controlling all the micro-vasomotory activity of the affected half-body; he checked tele-thermographically the patient’s map before irradiation, highlighting hypo-perfusion of the damaged areas, and demonstrated how them normalise after laser application. At a practical clinical level, this therapy is applied to all types of inflammation and pathologies where there is local hypoperfusion.

This may also accelerate venous-lymphatic drainage of tissues, particularly in zones subject to stasis, such as the lower limbs; moreover, it facilitates the “restitutio ad integrum” of areas subjected to acute trauma, such as sports injuries.

N. Wise [3] used laser as “anti-stress” on some transcranial points, called by ancient civilization called “Chakra”. Transcranial laser therapy has also been proposed for the treatment of the aftermath of cerebral strokes, and is being tested for Alzheimer’s disease, insomnia, anxiety and depression, and many other diseases of Central Nervous System [41,43]

J. Anders et Al [13] demonstrated the in vitro regeneration, increased growth and reproduction of nerve fibres, linking to the discovery of Levi-Montalcini. The possibility of central and peripheral nerve fibres regeneration, confirmed by S. Rockhind, Y. Asagai and many other Authors [44,45] who presented it in different editions of Laser Florence, has allowed for the effective treatment of lesions of the peripheral nervous system, such as trigeminal, post-herpetic, facial and post-avulsion neuralgia, as well as traumatic lesions of the central nervous system [5,21,28,41], such as tetraplegia and paraplegia, both spastic and flaccid, including those with “complete lesion”, as myelic lesion is often defined, with an exclusively presumptive diagnosis. Attempts have also been made to treat degenerative diseases of the central nervous system, such as multiple sclerosis and of its variants (amyotrophic lateral sclerosis, demyelinating leukodystrophy), with positive but transitory results, lasting a few months [41–45]. Y. Asagai successfully treated neonatal cerebral palsy, due to the effects of the atomic bombs of the Second World War [36] These applications of lasers on the central and peripheral nervous system are continuously evolving positively, and allow the treatment of lesions previously defined as incurable [41–45]. A meta-analysis of laser treatments for neck pain was published in the Lancet, which highlighted how treatment with different types of lasers should be considered the elective therapy for this syndrome, regardless of the causes [46].

2.3. PBM in Dentistry and Stomatology

One of the most important application of PBM in this field is represented by Paediatric Dentistry, where the pain control and discomfort may contribute to enhance the compliance of little patients.

Fornaini et Al, in a literature review, analysed nineteen studies about PBM for prevention and treatment of oral mucositis associated with oncotherapy (chemotherapy, radiation, and transplants), for postsurgical oral pain and for pulpotomies, stating that all these studies reported therapeutic benefits without adverse effects and concluding that PBM therapy is a safe and effective treatment modality for various clinical applications in pediatric dentistry [47].

Orthodontics is one of the dental fields where most of the scientific papers regarding the use of PBMT were published.

Caccianiga et al., in 2021, investigated by a randomized clinical trial on 30 patients the effect of a LED with a combination of wavelengths from 450 to 835 nm on Pain Reduction during Rapid Palatal Expansion (RPE), and they concluded that PBM is efficient in reducing the intensity and the time of pain felt by young patients that undergo RPE [48]

Levrini et al., in 2022, performed a retrospective study on 376 patients treated with Invisalign® clear aligners in association with OrthoPulse® (continuous 850-nmwavelength, generating an average daily energy density of 9.5 J/cm^2) prescribed for 10 min a day for the entire duration of the orthodontic treatment and results showed that in the treated group the average number of additional aligners represented 66.5% of the initial aligners. In contrast, 103.4% of the initially planned aligners were needed in the control group [49].

Kalhori et al, in a literature review on Oral Medicine, stated that PBM has a positive effect on the treatment of oral lichen planus, recurrent aphthous stomatitis, hyposalivation, pemphigus vulgaris, recurrent herpes simplex, burning mouth syndrome, bisphosphonate-related osteonecrosis of the jaw, trigeminal neuralgia, facial nerve paralysis, geographic tongue, and chronic sinusitis, concluding that it can be effective (as an alternative treatment or in combination with other therapies) in improving symptoms or in the complete treatment of oral diseases [50].

Matarese et al. in their recent RCT showed that PBM associated with conventional treatment of scaling and root planning improved clinical parameters such as probing depth and clinical attachment loss significantly more than conventional treatment alone, maintaining the result until

1 year of follow-up [51] ; similar results were reported by Mokeem in a recent systematic review [52].

PBM protocols have recently also been proposed by literature to reduce pain intensity and improve maximum mouth opening in patients with acute and chronic temporomandibular joint disorders who do not respond to other treatments. The data are reported in the literature for which the PBM approach is probably more effective for the treatment of joint dysfunctions with respect to problems related to masticatory muscles [53].

PBM has been proposed also for the application on pulp treatment procedures. Fernandes et al. described the improvement in radiographical success rate at different times of evaluation until the 18-month follow-up by adding PBM to calcium hydroxide [54]. Also, Ansari et al. reported similar results by adding PBM to a calcium-enriched mixture [55] while Kuo et al. compared diode application and sodium hypochlorite reporting positive results without a significant statistical difference [56].

Fornaini et al, in a narrative review of the literature, describing the advantages of using LED PBM in dentistry. In fact, in the case of treating a large area of tissue, the absence of collimation, a characteristic of laser, allows simultaneous irradiation of LED light all the surface, so saving time for the operator. Moreover, LED technology is elementary and con-sequently also the cost when compared to laser devices. Third, from a safety point of view, LED is free of risk, particularly for eyes, and so it does not require particular rules, such as glass, which is instead observed with laser utilisation [57].

3. Discussion

3.1. PBM of Stem Cells

From 1999 until 2004, in Bethesda University (USA), 18 different types of lasers with different combination of dosage parameters had been tested to obtain stem cells from different types of tissues without adding exogen growth factors in irradiated cellular cultures [58]. Starting with the irradiation of cells derivative from the yellow fish's spinal cord, stem cells have been obtained from any type of human tissue, including adipose tissue resulting from liposuction. It was established a "window" of wavelengths and a dosage range that stimulates the formation, proliferation, differentiation and migration of stem cells in vitro. There is a worldwide patent on this discovery, and in 2006 it was published. Uri Oron has demonstrated the total reconstruction of rabbit's infarcted myocardium [2], after treatment with stem cells and laser. Shimon Rockhind obtained with the same system the reconstruction of peripheral nerves of the rats [2,43].

3.2. The "at Home" PBM

PBM therapy, as before described, is a non-invasive therapy already described as useful for the management of this complication; unfortunately, the limiting factor of this kind of treatment consists on the needing, for the patients, to go to the therapist at least twice/three times weekly for treatments of some minutes, and this factor may negatively influence the compliance of the patient toward the therapy.

Due to the reduced size and the belonging to the class I laser according to the ANSI classification, of the "at-home PBM" laser device, it may be self-administered at home by the patient, and this represents a great and innovative possibility to manage the treatment of this kind of diseases. The availability on the market of these new, cheap, small, and usable at home by the patients themselves PBM appliances might be included in standard therapy for this kind of problem, giving the possibility to the patients to receive PBM treatment also daily; having the patient only a time setting as part of the device, the danger of over treating is reduced [59].

The utilization of these "auto-administered PBM" devices reached a great popularity during COVID pandemic for the treatment, even only symptomatic, of many chronic diseases in oncologic patients without going to hospitals, thus avoiding the risk of infection in this kind of compromised people [60].

Several authors described the successful utilisation of this "at home PBM" in the treatment of temporo-mandibular diseases pain reduction [61], neuronal disorders occurring in the oral district [62], Bell's palsy [53] and also diabetic foot ulcers [64,65].

A limit of this kind of devices is represented by the size that, even small, cannot be intra-orally used and, for this reason, several clinicians proposed the marketing of a new family of appliances based on LED technology and able to be used also inside the mouth [57].

4. Conclusions

Photobiomodulation is a field of medicine that should require a specific specialization [66] due to the physic principles knowledge, necessary to use laser devices in different clinical situation, with correct parameters and without the risks of over-irradiation and by observing the safety rules. The situation may be related to the radiology: when X-rays were born, they were overused, subsequently eliminated as considered dangerous and finally accepted and systematically classified as new specialty, radiology. Up today, laser photobiomodulation is successfully used for a great number of diseases. For this reason, we proposed to train a new generation of "users" by means of the creation of a new medical specialty "laserology" , able to give it the right dignity and importance [38,67,68].

Conflicts of Interest: Authors declare they have no conflict of interest.

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