Mitochondria and light: an overview of the pathways in the mitochondria and the metabolic disturbance that occurs when certain wavelengths are incident on the retinal pigment epithelium and skin.

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Abstract

Slightly more than half of the solar radiation that passes through the atmosphere and reaches the earth's surface is infrared. Over the past few years, many papers have been published on the possible positive effects of receiving this part of the electromagnetic spectrum. In this article we analyse the role of mitochondria in the supposed effects of infrared light based on the published literature. It is claimed that ATP synthesis is stimulated, which has a positive effect on the skin by increasing fibroblast proliferation, anchorage and the production of collagen fibres, procollagen, and various cytokines responsible for the wound healing process, such as keratinocyte growth factor. Currently there are infrared light emitting equipment whose manufacturers and centres where this service or treatment is offered claim that they are used for skin rejuvenation among other positive effects. Based on the literature review, it is necessary to deepen the scientific study of the mechanism of absorption of infrared radiation through the skin to better understand its possible positive effects, the risks of overexposure and to improve the consumer health protection .

Key words: mitochondria, R/NIR, ATP, ROS, metabolism, BK_{Ca}, cellular health.

1. Introduction

The mitochondrion, like chloroplasts, is not a cell organelle with a similar structure to the rest. It is an autonomous system that has unique characteristics in terms of having a double outer membrane, its own genetic material, being the system that generates and manages cellular energy, being the manager of cell motility, acting against free radicals and in calcium homeostasis, participating in apoptosis and proliferation and having in animals an offspring only from the female parent to the new gametes (1), i.e., no mixing of genetic material is generated. It is true that there are controversies about whether a contribution of mtDNA from the father can

be generated (2), but it seems that the results that have been obtained in this regard are research artifacts (1,3).

The genetic material is a short, non-condensed ring of DNA of which each mitochondrion has many copies. It is characterized by a high degree of variability due to the mutations that occur (4). Briefly and summarized, the catabolic pathways generated in mitochondria are as follows:

Glycolysis is the first of the metabolism reactions that requires some metals to be carried out . The anabolic ATP enzyme requires magnesium ion (Mg^{2+}) to complex the negative charges of the phosphates, thus enhancing the attack by the active centre (5–7). Another metal that acts in this part of metabolism is zinc; high levels in the medium increase the enzymatic capacity of the cycle (8,9).

The Krebs cycle is a chain of reactions essential for the cell to obtain reducing power and energy (10). Within this cycle, some metals are essential for its proper functioning, such as manganese. This metal is important in several manganese-activated enzymes, including pyruvate carboxylase, which can also be activated by other ions, such as magnesium. Therefore, adequate mitochondrial levels of Mg^{2+} are required to induce metabolism by pyruvate carboxylase in case of manganese deficiency (11).

At the end of the catabolic cascade, the respiratory chain generates energy in the form of ATP and controls body temperature in mammals (12). For heat generation, the mitochondrial respiratory chain is interrupted by the uncoupling protein type I (UCP-1) present in brown adipocytes in the neck area (13). The respiratory chain is composed of protein complexes that have heme-based organic systems as active groups (14).

Skin contains chromophores whose scattering and absorption coefficients are different for each wavelength in the ultraviolet, visible and infrared range. The most important chromophores are melanin and oxyhaemoglobin (15).

The penetration capacity of radiation is strongly dependent on wavelength. Thus, radiation with wavelengths between 405 and 505 nm (violet and blue) have the ability to penetrate to the upper dermis (16). The absorption of blue light by melanin is 80 times higher than that of red light (17), indicating that blue light is capable of generating greater changes at the molecular level than red light with respect to melatonin. Wavelengths of 595, 632, 694, 755, and 800 nm are progressively absorbed deeper into the dermis. Red light penetrates to approximately 4-5 mm depth from the surface (16). Radiation between 980 and 1064 nm penetrates the subcutaneous fat layer (18) and for longer wavelengths, there is insufficient information on their penetration into the skin and their photobiological effects (15). There has been a significant advance in the knowledge of the depth and form of light absorption in the skin thanks to Monte Carlo simulation based on the generation of different photoacoustic (PA) signals depending on the greater or lesser reactivity of the chromophores to light (19).

Its structure is that of a homodimer, each of the dimers having 3 protein subunits, where subunits I and II catalyze electron and proton exchange reactions, and subunit III appears to act as a conduit to mobilize oxygen towards the active nucleus. Looking further into the copper subunits, subunit II has a double chelated copper atom (CuA) that is the electron gateway and subunit I has 12 α-helices arranged in groups of four, forming a "cloverleaf" with three cavities. One cavity houses a heme A that is bound between two histidine residues. The second cavity contains the reactor core where oxygen is reduced. This core has a second type A heme called

heme a_3, together with a histidine-bound copper, CuB. The iron of heme a_3 is on one side in direct contact with CuB and on the other side is bound to a histidine residue on its proximal side. Between the iron and CuB are the ligands of H_3O^+ (20–23). This subunit is also the buffer for reactive oxygen species produced during the process, so mutations in it increase the concentration of reactive oxygen species (ROS) that induce mutations in DNA. As a result, humans with deficiencies in this complex or mutations in it have a shorter lifespan (24).

Briefly, the detailed mechanism is a cycle in which the heme nucleus a_3 begins as an oxidized form where both copper (Cu^{2+}) and heme are assumed to be hydroxylated. An electron is then transferred and one of the protons of the hydroxides is used to generate water, reducing the copper to Cu^+. The result is a highly reactive oxygen group that attacks the second hydroxyl and generates a second water molecule. The heme is then released to bind an O_2 molecule and generate two oxidative products, superoxide and a radical on the proximal thyroxine, derived from the donation of the extra electron from copper, which is converted back to Cu^{2+}. The next step is the influx of extra hydrogen and an electron to return to the initial state of the cycle (25–28). Copper deficiencies induce a decrease in complex IV without affecting the rest of the complexes in which copper is not in their active centres. When copper intake is restored and physiological levels are regenerated, enzyme activities recover normal levels of functionality (29–32).

In addition to copper, iron is another element of relevance within the components of the respiratory chain. This metal is one of the most important for skin chromophores. Of the 40 different proteins that make up the respiratory chain, 6 have heme-type nuclei, 2 have coppers that interact in one way or another with iron, and other 6 have iron coordinated with sulphur (33). These proteins with prosthetic groups are cytochrome C, succinate dehydrogenase and cytochrome bc1. There are others that have iron as a cofactor, such as iron monooxygenases and iron dioxygenases, which are important as members of the AlkB group of ferrous dioxygenases that mediate apoptosis and cell necrosis. (34).

The sun is the most important source of energy for the Earth and represents the engine of climate as well as multiple biological processes. The radiation emitted by the sun is considered full-spectrum light, as it ranges from ultraviolet (UV) to infrared (IR), wavelengths vital for plant and animal life but also for humans. However, the whole spectrum extends to high energy radiation (i.e., cosmic, gamma and x) that is reflected or absorbed by the shielding of the atmosphere and the earth's magnetic field. The protective role of the atmosphere also extends to UV-C radiation (100-280 nm), which is completely absorbed by the stratospheric ozone layer. UV-B radiation (280-315 nm) is also largely blocked by this layer and only represents a small percentage of the UV solar radiation at the earth's surface compared to UV-A (315-400 nm), which is attenuated by air molecules and aerosols. The ratio UV-A/UV-B in sunlight is about 17 when the solar disk is close to the zenith (35) The largest amount of radiation reaching the Earth's surface is detected in the visible (39%) and IR (56%) range (36), the latter also divided into IR-A (780-1400 nm), IR-B (1400-3000 nm) and IR-C (3000 nm-1 mm). IR-A is also called near infrared radiation (NIR) and is the largest fraction in the IR range, I.e., 30% of the total solar radiation (37). The total NIR reaching the earth's surface, as in other spectral ranges, depends on astronomical, geographical and meteorological conditions. Unlike UV radiation, IR radiation is mostly direct component from the solar disk and the diffuse fraction coming from scattering with air molecules is very small (38). For this reason, when the disk is blocked by clouds or when the sun is close to the horizon, IR radiation in general and NIR in particular is considerably reduced. Figure 1 shows solar spectral irradiance at the ground in the visible and NIR ranges under different conditions

of latitude, time of the day and cloudiness. As the latitude or the time of the day increases, the global solar irradiance decreases both in the visible and NIR ranges since solar rays pass through more atmospheric mass. Similarly, cloudiness decreases the irradiance reaching the ground but the extinction depends on the cloud cover and its optical properties. Figure * shows two possible cases of overcast conditions by low clouds, although with different number and characteristics of clouds droplets.

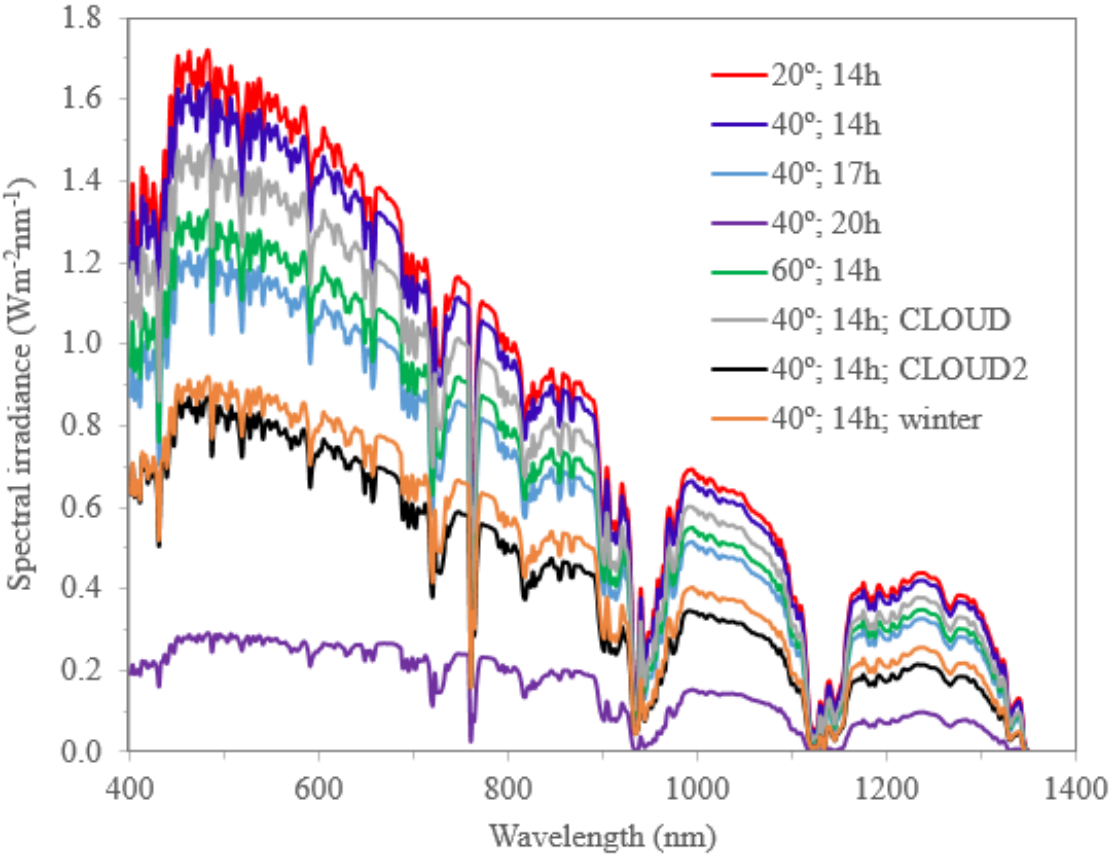

Figure 1: Solar spectral irradiance in the visible and near infrared ranges under different conditions of latitude, local time and cloudiness. Spectra referred as CLOUD and CLOUD2 are shown as examples of different overcast situations. Spectral irradiance are represented considering the incidence on a horizontal surface located at sea level.

The aim of this work is to seek scientific justification for the possible skin regeneration effects claimed to be produced by infrared emitting lamps through stimulation of mitochondrial metabolism, as well as information on the possible positive effects of the emitted energy freely offered to consumers by the suppliers of this equipment.

2. Materials and Methods

The criteria used for the bibliographic search were homogenized in order to have a common criterion for searching and filtering the information accessed through PubMed, ScienceDirect and Scopus. The keywords and their synonyms or derivatives "near infrared", "ROS", "mitochondria", "ATP", "NOS", "chromophore" and "BK_{Ca}" were used as search criteria. These keywords were used in combination with the inclusion criteria "retinal", "copper", "iron", "magnesium", "wavelength", "patch", "OLED", "LED", "equipment", "skin", "treatment", "effects", "irradiation", "regeneration".

Figure 1 shows the process flow diagram that has been maintained throughout the development of this manuscript.

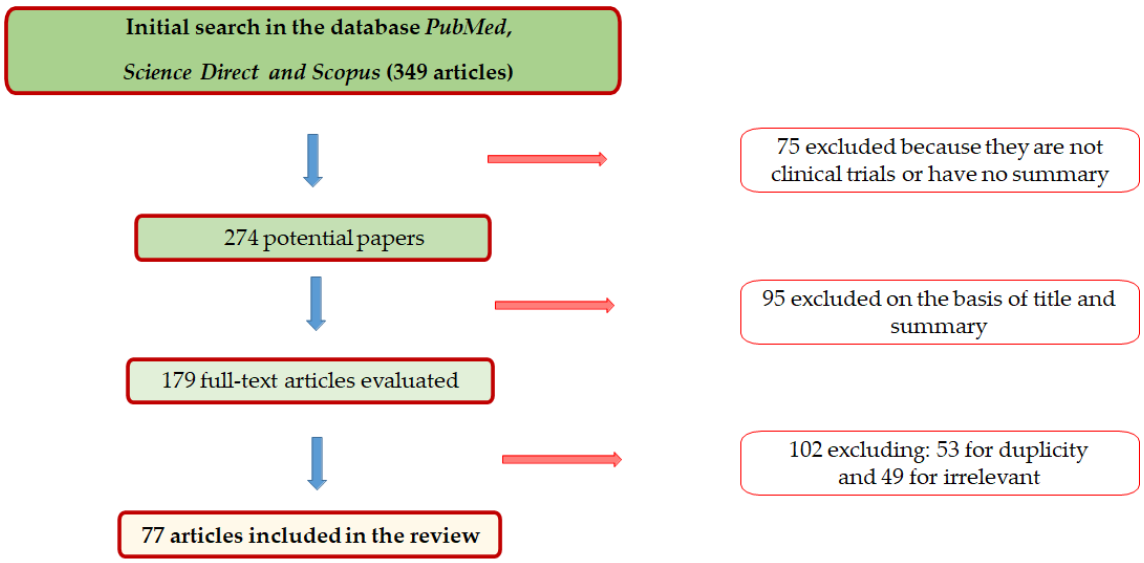

Figure 1. PRISMA(39) flow chart for literature search and selection of articles.

From the general search of the articles used, only those published during the 10 years prior to the date of the search were considered (with exceptions, such as legislation, guidelines or references to well-established theories). In addition, all publications dealt with infrared solar radiation and its impact on living beings, focusing on the effects on humans. We considered both exposures to sunlight and to artificial sources, such as large equipment for treating entire areas, as well as small equipment for treatment of specific areas. Regarding the radiant source, equipment where the illumination is generated by LED, laser and other specific sources have been included. Natural and artificial exposures for indoor, outdoor, therapeutic and workplace treatment and regeneration purposes were considered. Finally, all articles had to be originally written in English or with an official version published in English, with the exception of laws or guidelines taken or to be taken into account for the elaboration of this review that are in the language of the country in which they were published.

Regarding the exclusion criteria considered for the elaboration of the work, publications that did not have the keywords "wavelength" or "mitochondria" were excluded.

3. Results:

3.1 Spectral sensitivity on retin and skin:

At the retinal level, it has been described that the use light at 670 nm for 5 minutes per day generates or induces an increase in the regeneration of retinal tissue cells (40–44). Despite reaching the same conclusion, there are two approaches to explain how this effect develops. One theory indicates that the regeneration is due to the action of NIR on complex IV of the respiratory chain (45), whereas the other theory indicates that the mechanism is through viscosity change (40).

According to the first mentioned theory, there is a change in the excited states of the copper A (diatomic CuA) and copper B (mono-atomic CuB) atoms of the respiratory chain when they are excited with 670 nm radiation. One of the underpinnings of this theory is that when the retina is exposed to 420 nm (blue light) or 670 nm radiation, no change in the ratio of oxidized to

unoxidized hemoglobin is observed at the second wavelength, but a significant increase in total hemoglobin concentration is detected. This fact partly supports the proposal that the application of 670 nm reduces the redox state of complex IV (Oxidase C or COX) of the respiratory chain (41).

It should be noted that the chromophore formed by copper A (CuA) of COX contributes 85% of the absorbance at a wavelength of 830 nm generating its reduction, which is enhanced if melatonin is present in the medium. This band is known to be predominant when CuA is oxidized because it is non-existent when CuA is completely reduced (46). When CuB is in the reduced state, the maximum absorption is detected at 443.5 nm (blue) and 603.3 nm (orange)(47). Therefore, it can be indicated that infrared can vary the redox states of complex IV, but especially in CuA if radiation at 830 nm is incident on it.

Recent studies have further explored the use of 670 nm wavelength for retinal regenerative medicine. With this wavelength and an application for 3 minutes per day (preferably in the morning), a significant improvement in retinal cell regeneration with an increase in ATP is achieved. The most likely mechanism is described as the change in viscosity/pumping of nutrients and waste metabolites due to temperature changes between the fluid layers in the cytoplasm and mitochondria by the long wavelengths (40,48). The retina has a high concentration of mitochondria, so it is important to maintain their health and function by removing ROS generated by metabolic processes and increasing ATP. Normally, the goal is to achieve an amount of 40 mW/cm^2 (49,50) but recent research has arrived at an estimate of approximately 8 mW/cm^2 (40).

The therapeutic use of infrared radiation is aimed at generating ROS and increasing ATP generation. This increase in ATP is supposed to be achieved by the excitation of Cytochrome C Oxidase generated by the jet of photons arriving in the near-infrared (51).

Ferrous(ic) groups absorb at a wavelength between 508 nm and 593 nm depending on the organic structure in which they are complexed (52) but do not absorb infrared radiation as they reflect it completely. The target of infrared action is the system formed between the organic part and the copper atoms at complex IV. It has been shown, using exsanguinated mouse and cat brains, that the copper cytochrome oxidase has an absorption maximum wavelength between 830 nm and 920 nm (53) in NIR. It should be noted that in tissues perfused with blood, the cytochrome is not correctly detected due to the masking by oxyhemoglobin in the red blood cells (53).

The application of 670 nm pulsed wavelength is mostly absorbed by the water of the cellular internal contents with a relatively residual incidence of these photon beams on complex IV of the cellular respiratory chain. The water is distributed in the form of nanosized monolayers (48,54). Pulsed infrared light strikes on these sheets, causing them to expand and in turn generating a decrease in their viscosity (55,56) . These changes generated during the pulses cause the cells to expand and contract, which ultimately induces the entry of intercellular fluid as if they were sponges, sucking up the medium during the dark phase generated by the laser flicker (57). Ultimately, the physical mechanism of uptake is transmembrane convection. This effect explains how HeLa cells absorb chemotherapeutic substances from the medium when irradiated with pulsed light at 670nm (57). Therefore, in the end, the mechanism by which ATP is increased and ROS is reduced is only induced by the increased substrate availability and the increased elimination of toxic substances. It is not known whether this theory considers that enzyme capacity is saturable and this fact can be taken into account to demonstrate its importance in the mechanism.

Mitochondria have several mechanisms to increase ATP anabolism and reduce wavelength-independent ROS, one of which is the use of ATP-sensitive K+ channels highly present in cardiac and brain tissue. These channels can decrease ROS concentration when they remain closed (58–60). The state of opening or closing is considered to depend on the pH of the matrix, the alkaline state being an inducer (61) of the internal Mg^{2+} concentration and the intracellular ATP/ADP equilibrium (62). These channels are important as they act as sensors that reduce the amount of ROS when it increases locally in the cell cytosol (63). The large-conductance calcium- and voltage-activated K+ channel (BK_{Ca}) is indirectly activated by the action of light at 670 nm, by increasing nitrogen monoxide (NO) levels (64,65). These BK_{Ca} channels are involved in modulating cellular Ca^{2+} and K^{+} levels. In therapeutics, BK_{Ca} activation is used to palliate the damage caused by cardiac reperfusion after an ischemic state (66).

When the tissue is perfused again, what is called ischemia-reperfusion (I/R) damage, an overload of ROS and calcium in the mitochondria is detected. Activation of BK_{Ca} with agonists during reperfusion, reduces ROS levels and on the other induces stabilization of calcium levels, which prevents or delays the opening of the mitochondrial permeability transition pore (mPTP). The mPTP are the initiators of cell apoptosis due to irreparable internal damage. ATP levels remain stable because there is no collapse in the polarization of the mitochondrial membrane. (67). Among the activators proposed to prevent I/R damage, NO stands out as a good activator, either directly or indirectly through the activation of the guanosine monophosphate cycle (cGMP). (68,69). As a summary, light incidence at 670 nm induces an increase in NO that increases vasodilation and the opening of BK_{Ca} channels that stabilize cellular Ca^{2+} levels and reduce ROS (67).

In the skin, BK_{Ca} has been reported at the level of fibroblasts, which are excitable with NO (70,71). Its existence suggests that at the dermal level in the skin the same occurs as in cardiac tissue after revascularization when NO is used as a channel modulator. When R/NIR is applied, NO levels increase inducing vasodilatation that triggers the BK_{Ca} cascade. This cascade ultimately helps to remove ROS from the cell cytoplasm and maintains or increases ATP levels by stabilizing mitochondrial membrane potentials.

3.2 Published studies on the effects of red and IRa absorption.

There are many studies that justify the effects generated when cells are irradiated with wavelengths in the infrared range. It has been observed that exposure to IR not only produces mitochondrial improvements, but also acts on structures as essential to the cell as DNA. This increase in DNA synthesis promotes mitosis and cell regeneration. If fibroblast and keratinocyte cell cultures are irradiated, a proliferation that enhances their regeneration is demonstrated. Regeneration of fibroblasts and keratinocytes is essential for skin recovery in patients who have suffered burns, enhancing the natural regeneration of their own tissues as well as the implants that can be performed in these patients. Table 1 shows a selection of publications demonstrating the effects of radiation on cells and tissues. (72–76)

Table 1. Summary of articles on the effect of infrared radiation. Research since 2000 is included because of its relevance.

Relevant information on the biological interaction of IR wavelengths	Ref.
Biological tissues are transparent to wavelengths from 650 nm to 925 nm. Absorption by deoxyhemoglobin < 790 nm. Absorption by oxyhemoglobin > 790 nm.	(72)
Wavelengths from 630 nm to 638 nm increase ATP levels.	(73)
Maximun ATP production is 810 nm by mitochondrial complex-IV.	(48)

The 632.8 nm wavelength stimulates keratinocyte cell proliferation and growth factor macrophage secretion.	(76–78)
The 660 nm wavlength regulates the levels of fibroblastic growth factor.	(75,76,79)
812–846 nm is the wavelength range to enhance DNA synthesis.	(74)
780 nm can stimulate proliferation of keratinocyte cultures.	(80,81)
860 nm can stimulate proliferation of fibroblast cultures.	(82)
Wavelengths 680 nm, 730 nm and 880 nm repair damage tissues including DNA structures.	(83)
Wavelengths longer than 950 nm are absorbed by water and can cause an increase in skin temperature.	(84)

There is highly relevant scientific evidence on skin regeneration with OLED, LED and laser systems (Table 2). Of all of them, it is important highlight the thin film OLED and LED systems (80,81) since they are portable, easy to handle, no thicker than a healing dressing and are inexpensive to manufacture. These types of systems are very interesting for both focal and generalised organic recovery treatments, as they do not generate damage nor are they pharmacological treatments with the adverse effects that these entail.

Table 2. Different uses of waves on damaged tissues with the aim of regeneration.

Equipment used in scientific experiments (since 2017)	Results	Ref.
Ultra-slim OLED with thickness around 6 μm. Emission at 630 nm, 650 nm, 670 nm and 690 nm during around 100 h.	Regeneration artificial skin by up 70%. Better results with 670 nm use during 10 min at 3 J/cm² every 48 h.	(85)
Green LED at 520 ± 30 nm, 180 mW; 240 J/cm²; and Red LED at λ630 ± 10 nm, 300 mW; 36 J/cm².	Better re-epithelialisation in the red-light group between 14 and 21 days after the start of treatment.	(86)
LED with a weight of 5 g and a thickness of 0.1 mm; emission wavelength: 470, 530, 633 nm; power density levels 0–20 mW/cm².	Low driving temperature and uniform heat distribution, without thermal or inflammatory tissue damage. With excellent performance in the wound healing test and an effective fibroblast proliferation stimulation and fibroblast migration	(87)
Laser every day during 7 days at 655 nm, 150 mW, 2 J/cm² at the bed of the ulcer and infrared 808 nm, 200 mW, 6 J/cm2 to irradiate ulcer margins.	Patients treated with lasers required less skin ingestion than those treated with classic dressings.	(88)
Laser at 670 nm, 9 mW, 0.031 W/cm², applied every 48 hours, total dose of 16 J/cm² in mice skin.	On day 21, an increase in LTCD8+ and a decrease in CD68+ was observed. In addition, neo angiogenesis was observed at the end of treatment with increased CD31+, CD8+, NG2+ and alpha actin positive smooth muscle pericytes.	(89)

3.3 Commercially available non-health user access equipment.

There is equipment on the market designed to treat specific areas of the body as well as large areas of the body. They range from large panels of more than one meter in length where red and infrared LEDs are combined to small, portable systems such as slippers with built-in LEDs. Among the equipment described in Table 3, the face mask (manufacturer 9) stands out, in which there is not only red radiation, but also radiation of wavelengths corresponding to blue, green, yellow and violet can be applied. This product is sold asa comprehensive skin care system, as it treats the area with all the wavelengths that photobiology defines as enhancing cell regeneration and rejuvenation.

Table 3. Summary of easily accessible equipmentfor consumers to purchase online and at a cheap price.

Manufacturer	Equipment structure	Effects

1	Curved panel, supported on a hanger, with tubes to irradiate the user from above.	Reduction of skin wrinkles, softer and firmer feel skin, youthful look, stronger and healthy-looking hair and nails, increase new capillaries generation.
2	Mercury vapor lamps emiting infrared	Skin resurfacing
3	Pad for near-infrared irradiation from the lower zone.	Induces irradiances that penetrate 10 times more than the heat emitted by traditional pads (around 6 cm). Reduces lactic acid, increases blood flow and reduces inflammation.
4	LED flat panel with combination of red (660 nm) and infrared (850 nm) light	Reduction of skin wrinkles, softer and firmer skin, youthful appearance, stronger and healthier looking hair and nails, increased generation of new capillaries.
5	Infrared LED emitting helmet (650 nm)	System designed to regenerate hair in people with alopecia and for those who do not have alopecia can increase the volume and density of hair. Increases blood flow.
6	Flexible foil and band to transform armchairs into 850 and 660 nm emitters.	Weight loss, reduces joint pain, treats inflammation, helps with obesity, relaxes, 30 min/day gives the same effect as walking 1 h, 30 min swimming or yoga, burns 3000 calories, 200 sit-ups and 2500 vibration.
7	Ceiling pendant panel with LEDs at wavelengths of 660 nm and 850 nm.	Increases collagen levels in the skin, improves muscle pain, relieves stiffness, improves joint pain, swelling, arthritis, easy and painless treatment, improves skin and rejuvenates it.
8	Ultrasound, EMS and infrared, no information on technical characteristics is provided.	For facial and body beauty, EMS slimming treatment, infrared skin rejuvenation, improve skin texture, anti-wrinkle, quickly and effectively reduce and relieve severe chronic back pain and other types of body pain, regulate internal secretion and accelerate fat consumption.
9	Infrared house slippers. 45 LEDs at 660 nm and 45 LEDs at 880nm. Max. time use 40 min.	Used in tendonitis, plantar fasciitis, hell pain, nerve irritation, hell spurs and arthritis.
10	Full face and neck mask with led phototherapy in all colors, red at 660nm, blue at 470nm and 500nm, green at 550nm, yellow at 580nm, purple or violet at 420nm. Max. time use 15 min.	Improves skin elasticity, reduces and prevents wrinkles, helps fight oily areas, reduces pores, reduces scars, evens skin tone, improves circulation, inhibits melanin pigment formation. Boost immune system, accelerate blood circulation. Temporary relief of pain and stiffness, improves sleep quality. Helps activate collagen, facilitates skin collagen growth, promotes excretion of skin bacteria. Increases oxygen to lock in skin moisture.

4. Conclusiones.

- The review has brought together three possible mechanisms of action put forward by different researchers. The variation of the volume/viscosity, the excitation of the copper of the respiratory chain and the increase of the amount of NO that modifies the opening/closing state of the BKCa channels.
- After analyzing the scientific literature on this subject, the mechanism of action at the mitochondrial level and on the respiratory chain is not clear and its study should be a priority objective. The different types of equipment emitting infrared radiation can be purchased by consumers without any control or information on the energy emitted . Therefore, further studies are needed on which of the three possible mechanisms of extra ATP generation and ROS reduction inside the cell after the incidence of red/infrared radiation.

- Health authorities should consider making it compulsory for the suppliers of these machines to warn consumers of risk situations such as, for example, people with very damaged or blemished skin and therefore with cells with a possible high level of mutations.
- Whatever the main mechanism, the important thing is that infrared irradiation generates significant improvements at the tissue level in skin fibroblasts and keratinocytes. It has been demonstrated that in the end the cellular profile is improved due to a decrease in NOS and an increase in ATP.
- Presence of iron as a cofactor in such important processes as the induction of cell apoptosis by necrosis has to be considered of high importance when photobiological therapies are proposed. The change of state from ferric to ferrous and vice versa can be the reason for the activation or inactivation of this mechanism, which is crucial for tumour processes. In the case of mutagenic stem cells it would be important to activate this mechanism to induce their destruction earlier to resolve localised tumours as well as to prevent metastasis.

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