

The role of near-infrared light-emitting diodes in aging adults related to inflammation

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Abstract

Traumatic and non-traumatic injuries are common complications in the aging adult. Inflammation is related to aging in older individuals and may lead to an increased risk of mortality, reduced muscle strength, and decreased mobility. Unresolved inflammation could be related to the origin of many chronic diseases associated with aging such as autoimmune and neurodegenerative diseases or tumors. With any injury to the body there is initially a process of inflammation and wound healing that in large number of cases are related with pain that increases in the following days. On the other hand, chronic inflammation in high percentage of cases are related to chronic pain, very common symptoms in aging. Chronic inflammation is associated with normal and pathological aging. Surgery, orthopedic fixation, pharmaceutical therapies and physiotherapy can be used to the treatment of the pathologies and injured area. Here we review the use of gallium arsenide (GaAs)-based near-infrared light-emitting diodes (LEDs) as a coadjutant therapy to control inflammation and wound healing. GaAs-based near-infrared LED therapy can be used alongside surgery, orthopedic fixation and pharmaceutical treatments. Studies have shown it to be an effective therapy for the treatment of inflammation and to speed wound healing. This review of clinical observations highlights the capability of GaAs-based LEDs to accelerate wound healing and avoid inflammation.

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Introduction

An LED is an electronic device component that emits light when electricity passes through it. LEDs are mostly is monochromatic, occurring at a single wavelength. The LED light spectrum output can range from ultra violet to red. The ultraviolet and blue colors are about 400 nm, while the red color is about 700 nm. LED infrared emission can be greater than 830 nm and these types of LED devices are called Infrared Emitting Diodes (IRED). LEDs function by electroluminescence, a visible light production by an exposed substance to an electrical field with non-

thermal energy generation. Gallium arsenide (GaAs) is a common semiconductor material used for near-infrared LEDs, but other semiconductors are also used. Aluminum gallium indium phosphide (AlGaInP) and other semiconductor compounds in groups III-V of the periodic table have also been utilized.

Low-level laser therapy and near-infrared LEDs have similar effects on inflammation and wound healing. Some studies have demonstrated that near-infrared LED is more efficient at speeding up wound healing compared to laser therapy [3-7]. Near-infrared (NIR) LED therapy has been shown to improve inflammation and accelerate wound healing, as well as

helping to control pain. NIR-LED devices for light therapy are affordable, portable and easy to use, unlike other light therapy sources, such as lasers or incandescent light. Furthermore, they have improved dramatically in quality since the late 1990s, when they had rather unstable power outputs and divergent wavelengths. Older generation NIR-LEDs were not able to produce a meaningful clinical reaction to tissues. A new generation of NIR LEDs, also called the “NASA LEDs”, developed by Whelan *et al.*, have a lower divergence and also a more stable power output [8].

For NIR-LEDs to be most effective it is important that they have an appropriate wavelength for the target cell. Recent literature suggests a wavelength of 830 nm for all aspects of wound healing, pain, anti-inflammatory treatment and skin rejuvenation. According to Kim *et al.*, if the wavelength is incorrect, absorption will be suboptimal and, according to the Grotthus-Draper law of photobiology, there can be no reaction without absorption.

Photon intensity, or power density (W/cm^2), should be sufficient for the retention of enough photons to achieve the desired result. If the intensity is too high, photon energy will be undesirably transformed into heat in the targeted tissue.

Finally, Kim *et al.* the fluency or dosage must be adequate (J/cm^2). According to the Bunsen-Roscoe law of reciprocity, if the power density is too low, prolonging irradiation time to achieve an ideal energy density or dose will most likely not give a good final result [9].

Traumatic head and body injury, surgical procedure, and metabolic ulcers are common in the aging population. Each of these, and a variety of other conditions prevalent in the elderly, lead to a systemic response to injury. As aging progresses, the body's ability to respond to injury decreases. Inflammation in aging is characterized by increased inflammatory cytokines, decreased adaptation and defective tissue repair. Research into coadjuvant therapies for pharmaceutical interventions needs to focus on enhancing the body's response mechanism and NIR-LEDs have shown positive results.

NIR-LED therapy has shown tremendous possibilities in anti-photo aging using non-thermal radiation. The radiation components in the NIR-LED device help improve the anti-inflammatory elements of cell rejuvenation treatments [10]. The mitochondria theory on aging states that oxidative stress, caused by mitochondria DNA mutations, is associated with decreased ATP production leading to cellular degeneration. An experiment conducted by Kokkinopoulos and his team show a significant mitochondrial shift in vitro using a 670nm light exposure and the result showed that aging related retinal inflammation can be reduced significantly with the application of light therapy of 670nm [11]. There are other NIR-LED therapy devices for anti-aging with the range of 940nm and above but more clinical research needs to be done on these devices.

Vascularized living tissue responds to injury (caused by infections, chemicals or physical agents, immune reactions and other methods) by becoming inflamed. Inflammation is intended to contain and isolate the damage, destroy microorganisms and inactivate toxins, and prepare tissues for repair and wound healing. Although inflammation is fundamentally a protective response, it can also be harmful since it can cause severe hypersensitivity reactions or an inexorable and progressive organic lesion by chronic inflammation and subsequent fibrosis. Inflammation can be modulated by different biological, chemical and physical agents. The wide variety of drugs used in the treatment of inflammation are well known, as well as physical agents, such as cold and light. The latter, in particular photomodulation through NIR-LEDs, has been demonstrated to have a positive effect in reducing inflammation and promoting the acceleration of wound healing and skin rejuvenation. NIR-LED therapeutic devices are non-coherent, which means the light intensity is consistent and can spread, covering larger areas of the tissue. NIR-LED therapies have short wavelengths and, based on our studies and literature cited, the shorter the wavelength the deeper the penetration of light to the tissues. NIR-LEDs are affordable, portable, easy to use, and continue to provide viable applications in medicine, for example, to reduce edema, the migration of inflammatory cells, and the production of inflammatory cytokines, as well as accelerating the regeneration of connective tissues. There are no known risk factors for addiction with this

type of treatment. The length of time the radiation therapy needs to be applied for optimal outcomes has yet to be determined.

Extensive review of the English and Spanish literature was performed using PubMed, BioMed, and Google Scholar scientific databases. The literature search included articles relating to light emitting diode, low level laser therapy in aging.

Inflammation and wound healing

The timeline for wound healing depends greatly on the level of inflammation. During 2009 1.8 million patients, in the United States, were discharged from hospitals for wound care and management [12] following a range of causes of injury including gait disturbances; decreased muscle mass; metabolic diseases; heart disease; and traumatic brain injury [13-29], Table 1 shows conditions that increase risks for injury in the aging. All of these may be common events in the aging population. Aging results in chronic low grade inflammation that is associated with increased risk for disease, poor physical functioning, and mortality.

Table 1. Potential causes for injury of the aging adult [13-29]

Exercise and fitness	Physical Abuse	Ataxia
Oncology	Metabolic diseases	Heart disease
Arterial Ischemia	Venous disease	Dementia
Polypharmacy	Traumatic brain injury	Traumatic spinal cord injury
Surgical wounds	Tooth extractions	Traffic collisions
Medical prosthesis rejection	Catastrophic Events	Warfare
Terrorism	Bone Fracture	Ligament strain
	Skin Infection	Orthostatic changes

Inflammation and tissue response to injury is characterized by acute and chronic phases. In the acute phase, changes in vascular caliber and permeability occur with the consequent migration of leukocytes, particularly neutrophils. Increased

vascular permeability is induced in various ways, one of which is via chemical mediators such as histamine, interleukin (IL)-1, and tumor necrotic factor (TNF), as well as by the migration of leukocytes, and the release of reactive oxygen species (ROS) and proteolytic enzymes.

Both IL-1 and TNF facilitate increased vascular permeability and migration of lymphocytes, enabling the phenomena of acute inflammation and increased interstitial fluid. The application of near-infrared light on tissue in the acute phase of inflammation causes a decrease in the levels of both IL-1 and TNF- α [30,31].

During acute inflammation, the release of chemical mediators modulates vascular and cellular phenomena such as chemotaxis, leukocyte activation, phagocytosis and release of leukocyte products. An early mediator released in the area of injury is histamine, released primarily from mast cells, which causes vasodilation. Stimulation via near-infrared LEDs, or low-level lasers, has the ability to modulate the number of mast cell degranulations [32-34]. Leukocyte activation facilitates the release of pro-inflammatory molecules, such as the production of cytokines and metabolites of arachidonic acid. One of the key enzymes in the production of arachidonic acid derivatives, such as prostaglandins and thromboxanes, is cyclooxygenase-2 (COX-2). The activity of this enzyme can be decreased in areas of inflammation by stimulation with near-infrared light. Furthermore, the participation of neutrophils and macrophages in the acute stage of inflammation allows both phagocytosis to be initiated, and the release of products from phagolysosomes into the interstitial space, which can damage tissue [35,36].

Key products released primarily by macrophages are growth factors and ROS, which cause tissue damage and the inactivation of anti-proteases. Irradiation with near-infrared lasers has been shown to decrease the number of neutrophils and macrophages at the site of inflammation, and reduces ROS levels at both neutrophils and the damaged tissues [37-40]. Nitric oxide (NO) is a mediator that has some protective effects during acute phase inflammation. Some of these effects are to maintain vascular tone and reduce leukocyte recruitment. Studies have shown NO levels can be increased by stimulation with near-infrared light [41-43]. Finally, if the injurious agent can be

eliminated, the regulatory mechanisms of the inflammatory process can occur, leading to tissue regeneration. If the offending agent is not properly removed it can lead to chronic inflammation.

Chronic inflammation is a lengthy process of weeks to months, in which active inflammation, tissue destruction, and attempts at healing occur in a simultaneous manner. In contrast to acute inflammation, chronic inflammation is characterized by the infiltration of mononuclear inflammatory cells, tissue destruction, and attempts at healing by fibrosis and angiogenesis. Macrophages are the dominant and central cells in chronic inflammation; they are activated by clinical mediators such as interferon- γ , produced by T-lymphocytes. The application of near-infrared light significantly inhibits the expression of interferon- γ and IL-1 β , and decreases inflammation by changing the expression of genes encoding inflammatory cytokines [44,45]. Macrophage activation produces chemical mediators that stimulate tissue repair; in turn, some of these mediators generate ROS, NO and proteases, which further cause tissue injury. The concentration of ROS, as well as metalloproteases, may be decreased in the damaged tissue by stimulation with near-infrared light. In addition, tissue repair mediators such as transforming growth factor (TGF)- β 1 and platelet-derived growth factor (PDGF), can be modulated by light [40,46-48]. Finally, in chronic inflammation, infiltration of mononuclear cells into the tissues generates tissue destruction and attempts at healing tissue.

Aging is associated with various changes in the inflammatory response. As humans age there is an upregulation in the anti-stress responses, both cellular and molecular, that has been coined 'inflammaging'. Over time this leads to tissue damage that may lead to a decrease in effective function of the inflammatory response. Factors that may also lead to continuous low-grade inflammation in the elderly include smoking, subclinical disorders, and increased fat tissue [49]. Fat tissue may be linked to increased levels of macrophages, which are associated with cytokine production [50]. Newer studies have found a correlation between infectious history and an increased risk of heart attack, stroke, and cancer [51] suggest that infections at early ages leave an imprint in the host and inflammatory mechanisms can become flawed, and lead to further diseases during later years.

If an individual's body is adept in keeping inflammatory cytokines low, or anti-inflammatory cytokines high, they have a greater chance of attaining higher ages [52-54].

As humans age the functionality of the mitochondria decreases; both in effectiveness and by the increase of free radicals. Free radicals are known to increase pro-inflammatory signals that lead to cell death or uncontrolled cell growth has identified these mitochondrial deficiencies as a cause of chronic inflammation [55].

Diets high in red meat may also lead to an accumulation of antibodies for the Neu5Gc sugar molecule found in red meats, and enters human tissue after consumption. The human immune system sees this sugar as a foreign invader and creates antibodies. Over time, the combination of this foreign invader and the antibodies causes an inflammatory state that may become chronic [56].

Healing and tissue regeneration is the final process of tissue injury, and involves a large number of cells and chemical mediators. In tissue repair, it is known that various processes are activated to achieve tissue regeneration or healing, including the proliferation and migration of parenchymal cells of connective tissue, angiogenesis, synthesis of extracellular matrix (ECM) proteins, and tissue remodeling. The main connective tissue cells involved in tissue regeneration are fibroblasts. These cells, by stimulation with near-infrared light, can increase in activity and number. Their effects are modulated, in part, by increasing mediators such as TGF- β 1 and PDGF [57-60]. It is also known that stem cells are involved in tissue regeneration; these can also be stimulated by near-infrared light, causing an increase in both number and activity [61,62]. One of the most important factors in the process of angiogenesis - a critical component of wound healing - is vascular endothelial growth factor (VEGF). Both VEGF and angiogenesis can be stimulated by near-infrared light [63]. Tissue continuity is rebuilt by fibroblasts and endothelial cells. Fibroblasts rebuild the matrix, while endothelial cells are needed for angiogenesis. Collagen, particularly Types I and III, is needed to ensure successful wound healing. As the repair progresses, fibroblasts synthesize and deposit collagen and other ECM proteins such as decorin. Levels of these

molecules can be increased by stimulation with light [64-66]. Collagen deposition and the composition of the ECM is remodeled by metalloproteases. These enzymes generate a balance between the synthesis and degradation of molecules to achieve adequate regeneration and tissue healing. Metalloproteases can be modulated by near-infrared light [67,68].

Effect of lasers and LEDs on pathological conditions

In our experience, inflammation caused by tooth extraction, repetitive micro-injury to the tendons, shoulder pain caused by playing golf, acute tennis elbow pain, and chronic pain of the quadriceps tendon after swimming, all saw an improved range of motion and decreased pain after treatment with 940 nm NIR LEDs. Another study looking at patient recovery after surgical procedures in various locations (Achilles tendon, shoulder, wrist, etc.) showed that infrared light increased the rate of wound healing by 25-35% [69,70].

Chronic inflammation in aging is characterized by increased inflammatory cytokines, decreased adaptation, and defective tissue repair in response to injury. Many pathologies are related with aging process are mediated by the inflammatory process and, of these, osteoarthritis is among those affecting the highest number of patients. Oshima *et al.* observed that the application of NIR-LEDs to an osteoarthritis animal model increased Type II collagen expression and decreased TNF- α expression. This therapy can decrease levels of inflammation in the osteoarthritic joints [71]. A reduction in the number of polymorphonuclear cells and signs of inflammation was also observed in the treatment of joint inflammation using near-infrared light therapy [72].

Rheumatoid arthritis is another important illness that causes significant disability. Monocyte chemoattractant protein (MCP)-1 is a key chemokine in the inflammatory status of this disease. Kuboyama *et al.* demonstrated that NIR-LED irradiation significantly reduced MCP-1 gene expression in a rheumatoid arthritis rat model, thus reducing inflammation [73]. TNF- α and IL-6 are also important mediators in rheumatoid arthritis; studies in animal arthritis models

have shown that stimulation with near-infrared light can reduce the levels of both [73,74].

Near-infrared light therapy may have potential applications as a noninvasive treatment. It has been suggested that low-level lasers and NIR-LED irradiation can modulate inflammatory processes, inhibiting edema formation, vascular permeability and hyperalgesia, and suppress inflammation in the synovial membrane [75,76]. In a recent study in an experimental tendinitis rat model, treatment with near-infrared LEDs once per day in the same location on the tendon, showed an increase in the amount of collagen Types I and III between days seven and 14. Increased collagen implies increased fiber organization and wound healing [77]. In a study of soccer players with second-degree ankle sprains, results showed that treatment with an 820 nm aluminum gallium indium phosphide (GaAlAs) diode laser, alongside conventional RICE (rest, ice, compression, and elevation), decreased edema after 24 and 48 hours with no recurrence. When range of motion in patients with tendinopathy was studied, patients treated with light therapy showed an average improvement of 32% compared to controls [78]. Xavier *et al.* studied the effects of NIR-LED therapy on Achilles tendinitis induced by collagenase in a rat model. The group treated with an 880 nm near-infrared LED showed fewer inflammatory cells arriving at the injury site, and reduced mRNA expression of IL-1 β , IL-6, TNF- α , and COX-2 [79]. NIR-LED therapy may therefore have therapeutic benefits in reducing signs of inflammation in tendinitis. Near-infrared light therapy has also been shown to reduce the pain and increase the diminished range of joint motion typically seen in tennis elbow and epicondylitis, with no bony structure involvement [80]. The application of near-infrared light also accelerates healing following tenotomy of the tendon [81].

Some studies have shown that near-infrared light therapy can reduce inflammation in injuries of the nervous tissue. Moreira *et al.* (2009) studied the effect of near-infrared light in animal models with brain injury. They observed that, during the first few hours following brain injury, low-level laser phototherapy can modulate brain levels of TNF- α , IL-1 β and IL-6. Along with other studies, this shows that stimulation with near-infrared light decreases inflammation in

injured brains while also stimulating reconnection of the injured areas [82,83].

In spinal cord lesions, it has been observed that the use of 810 nm light treatment in animal models can increase axonal numbers and decrease the activation of immune cells and cytokines [84]. Using an animal model to study a nerve lesion, NIR-LED phototherapy reduced edema, the number of mononuclear cells present in the inflammatory infiltration, and increased nerve regeneration [85]. Albarracin *et al.* found that near-infrared photobiomodulation in albino rats resulted in decreased retinal degeneration, presumably from reduced cell death, inflammation, and decreased microglia [86]. The sciatic nerve crush model was performed on mice while under anesthesia. Seven days after the operation, NIR-LED irradiation therapy (950 nm, 80 mW/cm², 2.5 J/cm²) began - applied to the skin at the site of injury - and continued for 15 days. In both the spinal cord and sciatic nerve TNF- α levels decreased, but IL-1 β and IL-10 levels did not change compared to the control [87]. Khalil *et al.* studied the role of free radicals and NO in delayed recovery in aged rats with nerve injury. The results suggest that ROS and neuronal NO contribute to delayed recovery of injured nerves in old rats. The results also raise the notion that possible interaction of free radicals with NO to form peroxynitrite might be responsible for such delayed recovery. In previous paragraphs we describe that ROS may be decreased in the damaged tissue by stimulation with near-infrared light and could be an interesting adjuvant therapy in these types of lesions [88].

Cerebrovascular disease is the third leading cause of death and the leading cause of serious long-term disability in the Western hemisphere [89]. Endothelial dysfunction is characterized by a chronic alteration of inflammatory function and markers of inflammation and the innate immune response, including C-reactive protein, IL-6 and TNF- α are linked to the occurrence of myocardial infarction and stroke in healthy elderly populations [90]. Near-infrared light therapy is an emerging technology that could be used in combination with other therapies to treat cerebrovascular disease [91]. Moreira *et al.* (2011) observed the effects of phototherapy on wound healing following cerebral ischemia by cryogenic injury. They showed that the irradiated lesions lost less tissue than the control, had a significantly higher

number of viable neurons, and the lesions of irradiated animals had fewer leukocytes and lymphocytes. They concluded that laser phototherapy was able to control brain damage, thus leading to wound healing following cryogenic injury [92]. Another study by Shen *et al.* investigated the effects of irradiation from a low-level laser applied to rat models with stroke. They observed the proliferation and differentiation of adipose tissue-derived stem cells in neuronal cells. The results of Western blot analysis indicated a significant increase in nestin and oligo-2, demonstrating that low-level laser irradiation exerts a positive effect on the differentiation of stem cells and can be employed to treat ischemic stroke to regain motor functions [93].

The inflammatory process plays an important role in some skin diseases. For some skin conditions NIR-LED therapy has shown bactericidal and anti-inflammatory effects [94-96]. As for other inflammatory skin diseases, a study performed in patients with psoriasis found anti-inflammatory effects when using 830 nm and 633 nm NIR-LED therapy [97]. In animal models of serositis it was observed that the application of near-infrared light therapy reduced inflammation in peritonitis and pleurisy by reducing inflammatory cell migration [98,99].

Near-infrared light therapy may accelerate cutaneous wound healing in different pathological conditions such as diabetes, and burned or injured skin. This accelerated process was observed in association with a photobiomodulation-related increase of healing mediators such as integrins, laminin, kinesin, TGF- β 1 and matrix metalloproteinase-2. Photobiomodulation stimulated healing, relieved pain and inflammation, restored function of tissue, and helped to control secondary infection [100-106]. The wounds of patients treated with a 670 nm, 720 nm, and 880 nm near-infrared LED unit healed twice as quickly as their counterparts not treated with near-infrared. Following tissue injury, adequate inflammatory vascular responses are essential for subsequent tissue repair. Khodr *et al.* studied the role of ROS and age in modulating the inflammatory response in acute and chronic injury conditions and the implications of this modulation for tissue repair. The results showed that antioxidant treatment had no effect on the response during early and late phases of acute inflammation in

young rats. However in old rats, the vascular response was significantly attenuated (60%) or significantly increased (40%) during the early and late phases of acute inflammation, respectively. The results suggest that ROS have a paradoxical role exerting either a positive or negative effect on the inflammatory response with age. Related with this observation, the ROS can be modulated by NIR-LED as we observe previously in the text [107]. The potential for fracture and bone injury in the aging adult is high due to gait disturbances, daily activities, age more than 75, living alone, chronic pain, metabolic diseases, and nutrition/vitamin deficits. Bone healing has also been shown to benefit from light therapy [108,109]. Pinheiro *et al.* demonstrated that bone irradiated with near-infrared light showed increased osteoblastic proliferation, collagen deposition, and bone neoformation [110]. Rats given a ligature injury at the first mandibular molar were treated with NIR-LED irradiation, and histomorphological analysis revealed decreased bone resorption, lower neutrophil migration, and lower TNF levels [111].

Pharmacological therapy is widely used to modulate inflammation and wound healing, but NIR-LED GaAs therapy is emerging as a promising non-pharmacological coadjutant treatment for these conditions. Some studies have compared the effect of light therapy with that of the most commonly used drugs for inflammation and wound healing. De Almeida *et al.* compared the effects of the topical application of sodium diclofenac with low-laser therapy on morphological aspects and the gene expression of biochemical inflammatory markers. Compared to subjects given diclofenac, those receiving light therapy showed decreased expression of COX-2 and TNF- α , and improved morphological aspects of the tissue [112]. A similar study by de Paiva Carvalho *et al.* observed that, compared with the topical and intramuscular application of diclofenac, near-infrared light therapy more effectively decreased the levels of prostaglandin E2 during the treatment of acute muscle strain injury [113]. Viegas *et al.* observed that low-level laser therapy showed a higher degree of collagen fiber organization and maturation, and a better healing pattern than that seen with the use of meloxicam, but meloxicam more effectively decreased the intensity of polymorphonuclear infiltration and edema in rat

wounds [114]. Finally, some studies have compared the effects of near-infrared light therapy with those of corticosteroids. These have observed that, compared to corticoids, light therapy increases collagen content, allows a better arrangement of the ECM, an increase in number of fibroblasts, and accelerated levels of epithelialization. Near-infrared light accelerates tissue repair even in the presence of dexamethasone [115-117]. Other physical therapy use on the treatment of wound healing is ultrasound. A study by Demir *et al.* compared the effects of laser, ultrasound, and combined laser and ultrasound treatments in experimental tendon healing. They concluded that both treatments increased tendon healing biochemical and biomechanical more than the control groups. No statistically significant difference was found between ultrasound and laser therapy and these therapies can be used successfully in the treatment of tendon healing [118].

Many diseases of the elderly, such as Alzheimer's disease, could benefit from NIR-LED therapy studies. The injury to the brain during the progression of Alzheimer's disease is also compounded by inflammation and studies should be completed to understand the effects of NIR-LED therapy on Alzheimer's inflammation [49].

Finally, aging and many pathologies related to aging, are closely associated to inflammatory processes and are the target of many therapeutic options, often with undesirable side effects. NIR-LED is emerging as an adjunctive treatment option without adverse effects, which makes it an interesting option in adult patient who frequently consume too many drugs which could help decrease, or not potentiate, adverse effects. NIR-LED can exert therapeutic effects at different stages of the inflammatory process and tissue repair. This makes it a therapeutic option of great interest for clinical application and research for its promising modulatory effects at the molecular level.

Conclusions

GaAs-based NIR-LEDs represent a novel, non-invasive, and effective coadjutant therapeutic intervention for the treatment of numerous diseases linked to inflammation and wound healing. The equipment is easy to obtain, economically more sound

than other methods of NIR radiation, can be used several times during the day, simple to use with little training, and versatile for use in many fields and locations.

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References

1. Khatami M. Inflammation, aging, and cancer: tumoricidal versus tumorigenesis of immunity: a common denominator mapping chronic diseases. *Cell Biochem Biophys*. 2009;55(2):55-79.
2. Rottenberg Y, Jacobs JM, Stessman J. Prevalence of pain with advancing age brief report. *J Am Med Dir Assoc*. 2015;16(3):264.
3. Pagan MT, de Oliveira FA, Oliveira RC, Sant'Ana AC, de Rezende ML, Greggi SL, et al. Laser and light-emitting diode effects on pre-osteoblast growth and differentiation. *Lasers Med Sci*. 2014;29(1):55-9.
4. Oliveira Sampaio SC, de C Monteiro JS, Cangussú MC, Pires Santos GM, dos Santos MA, dos Santos JN, et al. Effect of laser and LED phototherapies on the healing of cutaneous wound on healthy and iron-deficient Wistar rats and their impact on fibroblastic activity during wound healing. *Lasers Med Sci*. 2013;28(3):799-806.
5. El-Bialy T, Alhadlaq A, Felemban N, Yeung J, Ebrahim A, H Hassan A. The effect of light-emitting diode and laser on mandibular growth in rats. *Angle Orthod*. 2015;85(2):233-8.
6. Dall Agnol MA, Nicolau RA, de Lima CJ, Munin E. Comparative analysis of coherent light action (laser) versus non-coherent light (light-emitting diode) for tissue repair in diabetic rats. *Lasers Med Sci*. 2009;24(6):909-16.
7. Klebanov GI, Shuraeva Nlu, Chichuk TV, Osipov AN, Vladimirov IuA. Comparison of the effects of laser and light-emitting diodes on lipid peroxidation in rat wound exudate. *Biofizika*. 2006;51(2):332-9.
8. Whelan HT, Houle JM, Whelan NT, Donohoe DL, Cwiklinski J, Schmidt MH, et al. NASA light-emitting diode medical program-progress in space flight and terrestrial applications. *Space Technology and Applications International Forum*. 2000;504:37-43.
9. Kim WS, Calderhead RG. Is light-emitting diode phototherapy (LED-LLLT) really effective? *Laser Ther*. 2011;20(3):205-15.
10. Pinar Avci, Asheesh Gupta, Magesh Sadasivam, Daniela Vecchio, Zeev Pam, Nadav Pam, Michael R Hamblin: Low-level laser (light) therapy (LLLT) in skin: stimulating, healing, restoring *Semin Cutan Med Surg*. 2014 August 8. Published in final edited form as: *Semin Cutan Med Surg*. 2013;32(1):41-52.
11. Kokkinopoulos I1, Colman A, Hogg C, Heckenlively J, Jeffery G. Age-related retinal inflammation is reduced by 670 nm light via increased mitochondrial membrane potential. *Neurobiol Aging*. 2013;34(2):602-9.
12. Crane NJ, Elster EA. Vibrational spectroscopy; a tool being developed for the noninvasive monitoring of wound healing. *J Biomed Opt*. 2012; 17(1):010902.
13. Kallinen M, Markku A. Agingin, physical activity and sports injuries. An overview of common sports injuries in the elderly. *Sports Med*. 1995;20(1):41-52.
14. Murphy K, Waa S, Jaffer H, Sauter A, Chan A. A literature review of findings in physical elder abuse. *Can Assoc Radiol J*. 2013;64(1):10-4.
15. Nakajima K, Anzai E, Iwakami Y, Ino S, Yamashita K, Ohta Y. Measuring gait pattern in elderly individuals by using a plantar pressure measurement device. *Technol Health Care*. 2014;22(6):805-15.
16. Gazibara T, Pekmezovic T, Tepavcevic DK, Tomic A, Stankovic I, Kostic VS et al. Circumstances of falls and fall-related injuries among patients with Parkinson's disease in an outpatient setting. *Geriatr Nurs*. 2014;35(5):364-9.
17. Czernuszenko A. Risk factors for falls in post-stroke patients treated in a neurorehabilitation ward. *Neurol Neurochir Pol*. 2007;41(1):28-35.
18. Gerasimchuk PA, Kisil' PV, Vlasenko VG, Pavlyshin AV. Endothelial dysfunction indicators in patients with diabetic foot syndrome. *Vestn Ross Akad Ned Nauk*. 2014;5-6:107-10.
19. Mitchell RJ, Lord SR, Harvey LA, Close JC. Obesity and falls in older people: mediating effects of disease, sedentary behavior, mood, pain, and medication use. *Arch Gerontol Geriatr*. 2015;60(1):52-8.
20. Gist S, Tio-Matos I, Falzgraf S, Cameron S, Beebe M. wound care in the geriatric client. *Clin Interv Aging*. 2009;4:286-7.
21. Lohr NL, Ninomiya JT, Warltier DC, Weihrauch D. Far red/near infrared light treatment promotes femoral artery collateralization in the ischemic hindlimb. *J Mol Cell Cardiol*. 2013;62:36-42.
22. Naeser MA, Zafonte R, Kregel MH, Martin PI, Frazier J, Hamblin MR, et al. Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: open-protocol study. *J Neurotrauma*. 2014;31(11):1008-17.
23. Con J, Friese RS, Long DM, Zangbar B, O'Keeffe T, Joseph B, et al. Falls from ladders; age matters more than height. *J Surg Res*. 2014;191(2):262-7.
24. Mosenthal AC, Livingston DH, Lavery RF, Knudson MM, Lee S, Morabito D, et al. The effect of age on functional outcome in mild traumatic brain injury; 6-

- month report of a prospective multicenter trial. *J Trauma*. 2004;56(5):1042-8.
25. Xai ZS, Huang JM, Zhuang XR, Chen SB, Wu SQ, Yao ZD, et al. Case-control stud on suture-assisted locking plate for the treatment of proximal humeral fractures in elderly. *Zhongguo Gu Shang*. 2014;27(12):1015-8.
 26. Liu JJ, Ruan HJ, Wang JG, Fan CY, Zeng BF. Double-column fixation for type C fractures of the distal humerus in the elderly. *J Shoulder Elbow Surg*. 2009;18(4):646-51.
 27. Diaz-Garcia RJ, Oda T, Shauver MJ, Chung KC. A systematic review of outcomes and complications of treating unstable distal radius fractures in the elderly. *J Hand Surg am*. 2011;36(5):824-35.
 28. Holt G, Smith R, Duncan K, Hutchison JD, Gregori A, Reid D. Outcome ater sequential hip fracture in the elderly. *J Bone Joint Surg Am*. 2012;94(19):1801-8.
 29. Siennicki-Lantz A, Elmståhl. Phenomenon of declining blood pressure in elderly-high systolic levels are undervalued with Korotkoff method. *BMC Geriatr* 2011;11:57.
 30. Fernandes KP, Alves AN, Nunes FD, Souza NH, Silva JA Jr, Bussadori SK, et al. Effect of photobiomodulation on expression of IL-1 β in skeletal muscle following acute injury. *Lasers Med Sci*. 2013;28(3):1043-6.
 31. Mesquita-Ferrari RA, Martins MD, Silva JA Jr, da Silva TD, Piovesan RF, Pavesi VC, et al. Effects of low-level laser therapy on expression of TNF- α and TGF- β in skeletal muscle during the repair process. *Lasers Med Sci*. 2011;26(3):335-40.
 32. Vasheghani MM, Bayat M, Rezaei F, Bayat A, Karimipour M. Effect of low-level laser therapy on mast cells in second-degree burns in rats. *Photomed Laser Surg*. 2008;26(1):1-5.
 33. Khoshvaghti A, Zibamanzarmofrad M, Bayat M. Effect of low-level treatment with an 80-Hz pulsed infrared diode laser on mast-cell numbers and degranulation in a rat model of third-degree burn. *Photomed Laser Surg*. 2011;29(9):597-604.
 34. Sawasaki I, Geraldo-Martins VR, Ribeiro MS, Marques MM. Effect of low-intensity laser therapy on mast cell degranulation in human oral mucosa. *Lasers Med Sci*. 2009;24(1):113-6.
 35. Albertini R, Aimbire F, Villaverde AB, Silva JA Jr, Costa MS. COX-2 mRNA expression decreases in the subplantar muscle of rat paw subjected to carrageenan-induced inflammation after low level laser therapy. *Inflamm Res*. 2007;56(6):228-9.
 36. Pires D, Xavier M, Araújo T, Silva JA Jr, Aimbire F, Albertini R. Low-level laser therapy (LLLT; 780 nm) acts differently on mRNA expression of anti- and pro-inflammatory mediators in an experimental model of collagenase-induced tendinitis in rat. *Lasers Med Sci*. 2011;26(1):85-94.
 37. Dos Santos SA, Alves AC, Leal-Junior EC, Albertini R, Vieira Rde P, Ligeiro AP, et al. Comparative analysis of two low-level laser doses on the expression of inflammatory mediators and on neutrophils and macrophages in acute joint inflammation. *Lasers Med Sci*. 2014;29(3):1051-8.
 38. Alves AC, Vieira R, Leal-Junior E, dos Santos S, Ligeiro AP, Albertini R, et al. Effect of low-level laser therapy on the expression of inflammatory mediators and on neutrophils and macrophages in acute joint inflammation. *Arthritis Res Ther*. 2013;15(5):R116.
 39. Huang YY, Nagata K, Tedford CE, McCarthy T, Hamblin MR. Low-level laser therapy (LLLT) reduces oxidative stress in primary cortical neurons in vitro. *J Biophotonics*. 2013;6(10):829-38.
 40. Fujimaki Y, Shimoyama T, Liu Q, Umeda T, Nakaji S, Sugawara K. Low-level laser irradiation attenuates production of reactive oxygen species by human neutrophils. *J Clin Laser Med Surg*. 2003;21(3):165-70.
 41. Poyton RO, Ball KA. Therapeutic photobiomodulation: nitric oxide and a novel function of mitochondrial cytochrome c oxidase. *Discov Med*. 2011;11(57):154-9.
 42. Ball KA, Castello PR, Poyton RO. Low intensity light stimulates nitrite-dependent nitric oxide synthesis but not oxygen consumption by cytochrome c oxidase: Implications for phototherapy. *J Photochem Photobiol B*. 2011;102(3):182-91.
 43. Mitchell UH, Mack GL. Low-level laser treatment with near-infrared light increases venous nitric oxide levels acutely: a single-blind, randomized clinical trial of efficacy. *Am J Phys Med Rehabil*. 2013;92(2):151-6.
 44. Dvashi Z, Sar Shalom H, Shohat M, Ben-Meir D, Ferber S, Satchi-Fainaro R, et al. Protein phosphatase magnesium dependant 1A governs the wound healing-inflammation-angiogenesis cross talk on injury. *Am J Pathol*. 2014;184(11):2936-50.
 45. Pereira da Silva L, Miguel Neves B, Moura L, Cruz MT, Carvalho E. Neurotensin decreases the proinflammatory status of human skin fibroblasts and increases epidermal growth factor expression. *Int J Inflamm*. 2014;2014:248240.
 46. Bracey NA, Gershkovich B, Chun J, Vilaysane A, Meijndert HC, Wright JR Jr, et al. Mitochondrial NLRP3 protein induces reactive oxygen species to promote Smad protein signaling and fibrosis independent from the inflammasome. *J Biol Chem*. 2014;289(28):19571-84.
 47. Jiang L, Dai Y, Cui F, Pan Y, Shang H, Xiao J, et al. Expression of cytokines, growth factors and apoptosis-related signal molecules in chronic pressure ulcer wounds healing. *Spinal Cord*. 2014;52(2):145-51.
 48. Moura Júnior Mde J, Arisawa EÂ, Martin AA, Carvalho JP, da Silva JM, Silva JF, et al. Effects of low-power LED and therapeutic ultrasound in the tissue healing and inflammation in a tendinitis experimental model in rats. *Lasers Med Sci*. 2014;29(1):301-11.
 49. Licastro F, Candore G, Lio D, Porcellini E, Colonna-Romano G, Franceschi C, et al. Innate immunity and

- inflammation in aging: a key for understading age-related diseases. *Immun Ageing*. 2005;2:8.
50. Curat CA, Miranville A, Sengenès C, Diehl M, Tonus C, Busse R, et al. From blood monocytes to adipose tissue-resident macrophages: induction of diapedesis by human mature adipocytes. *Diabetes*. 2004;53:1285-92.
 51. Finch CE, Crimmins EM. Inflammatory exposure and historical changes in human life-spans. *science*. 2004;305:1736-9.
 52. Bonafe M, Olivieri F, Cavallone L, Giovagnetti S, Mayegiani F, Cardelli M, et al. A gender-dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. *Eur J Immunol*. 2001;31:2357-61.
 53. Lio D, Scola L, Crivello A, Colonna-Romano G, Candore G, Bonafe M, et al. Gender-specific association between -1082 IL-10 promoter polymorphism and longevity. *Genes Immun*. 2002;3:30-3.
 54. Lio D, Scola L, Crivello A, Colonna-Romano G, Candore G, Bonafe M, et al. Inflammation, genetics, and longevity: further studies on the protective effects in men of IL-10-1082 promoter SNP and its interaction with TNF-alpha-308 promoter SNP. *J Med Genet*. 2003;40:296-9.
 55. Dinarello CA. A clinical perspective of IL-1 β as the gatekeeper of inflammation. *Eur J Immunol*. 2001;4195:1203-17.
 56. Samraj AN, Pearce OM, Läubli H, Crittenden AN, Bergfeld AK, Banda K, et al. A red meat-derived glycan promotes inflammation and cancer progression. *Proc Natl Acad Sci USA*. 2015;112(2):542-7.
 57. Taniguchi D, Dai P, Hojo T, Yamaoka Y, Kubo T, Takamatsu T. Low-energy laser irradiation promotes synovial fibroblast proliferation by modulating p15 subcellular localization. *Lasers Surg Med*. 2009;41(3):232-9.
 58. Vinck EM, Cagnie BJ, Cornelissen MJ, Declercq HA, Cambier DC. Increased fibroblast proliferation induced by light emitting diode and low power laser irradiation. *Lasers Med Sci*. 2003;18(2):95-9.
 59. Byrnes KR, Barna L, Cenault VM, Waynant RW, Ilev IK, Longo L, et al. Photobiomodulation improves cutaneous wound healing in an animal model of type II diabetes. *Photomed Laser Surg*. 2004;22(4):281-90.
 60. Hakki SS, Bozkurt SB. Effects of different setting of diode laser on the mRNA expression of growth factors and type I collagen of human gingival fibroblasts. *Lasers Med Sci*. 2012;27(2):325-31.
 61. Wu HP, Persinger MA. Increased mobility and stem-cell proliferation rate in *Dugesia tigrina* incuded by 88nm light emitting diode. *J Photochem Photobiol B*. 2011;102(2):156-60.
 62. Li WT, Chen CW, Huang PY. Effects of low level light irradiation on the migration of mesenchymal stem cells derived from rat bone marrow. *Conf Proc IEEE Eng Med Biol Soc*. 2013;2013:4121-4.
 63. Salate AC, Barbosa G, Gasper P, Koeko PU, Parizotto Na, Benze BG, et al. Effect of In-Ga-Al-P diode laser irradiation on angiogenesis in partial ruptures of Achilles tendon in rats. *Photomed Laser Surg*. 2005;23(5):470-5.
 64. Silveira PC, Silva LA, Freitas TP, Latini A, Pinho RA. Effects of low-power laser irradiation (LPLI) at different wavelengths and doses on oxidative stress and fibrogenesis parameters in an animal model of wound healing. *Lasers Med Sci*. 2011;26(1):125-31.
 65. Fiório FB, Albertini R, Leal-Junior EC, de Carvalho Pde T. Effect of low-level laser therapy on types I and III collagen and inflammatory cells in rats with induced third-degree burns. *Lasers Med Sci*. 2014;29(1):313-9.
 66. De Souza TO, Mesquita DA, Ferrari RA, Dos Santos Pinto D Jr, Correa L, Bussadori SK, et al. Phototherapy with low-level laser affects the remodeling of types I and III collagen in skeletal muscle repair. *Lasers Med Sci*. 2011;26(6):803-14.
 67. Guerra Fda R, Vieira CP, Almeida MS, Oliveira LP, de Aro AA, Pimentel ER. LLLT improves tendon healing through increase of MMP activity and collagen synthesis. *Lasers Med Sci*. 2013;28(5):1281-8.
 68. Casalechi HL, Leal-Junior EC, Xavier M, Silva JA Jr, de Carvalho Pde T, Aimbire F, et al. Low-level laser therapy in experimental model of collagenase-induced tendinitis in rats: effects in acute and chronic inflammatory phases. *Lasers Med Sci*. 2013;28(3):989-95.
 69. Hsin, J. Weston, J. Treating sports-related injury and pain with light. *Practical Pain Management*. 2006;6(7).
 70. Bjordal JM, Couppé C, Ljunggren E. Low level laser therapy For tendinopathy. Evidence of a dose-response pattern. *Physical Therapy Reviews*. 2001;6:91-9.
 71. Oshima Y, Coutts RD, Badlani NM, Healey RM, Kubo T, Amiel D. Effect of light-emitting diode (LED) therapy on the development of osteoarthritis (OA) in a rabbit model. *Biomed Pharmacother*. 2011;65(3):224-9.
 72. Pallotta RC, Bjordal JM, Frigo L, Leal Junior EC, Teixeira S, Marcos RL et al. Infrared (810-nm) low-level laser therapy on rat experimental knee inflammation. *Lasers Med Sci*. 2012;27(1):71-8.
 73. Kuboyama N, Abiko Y. Reduction of monocyte chemoattractant protein-1 expression in rheumatoid arthritis rat joints with light-emitting diode phototherapy. *Laser Ther*. 2012;21(3):177-81.
 74. Araki H, Imaoka A, Kuboyama N, Abiko Y. Laser reduction of interleukin-6 expression in human synoviocytes and rheumatoid arthritis rat joints by linear polarized near infrared light (Superlizer) irradiation. *Laser Ther*. 2011;20(4):293-300.
 75. De Moraes NC, Barbosa AM, Vale ML, Villaverde AB, de Lima CJ, Cogo JC, et al. Anti-inflammatory effect of low-level laser and light-emitting diode in zymosan-

- induced arthritis. *Photomed Laser Surg.* 2010;28(2):227-32.
76. Amano A, Miyagi K, Azuma T, Ishihara Y, Katsube S, Aoyama I, et al. Histological studies on the rheumatoid synovial membrane irradiated with a low energy laser. *Lasers Surg Med.* 1994;15(3):290-4.
 77. Carrinho PM, Renno AC, Koeke P, Salate AC, Parizotto NA, Vidal BC. Comparative study using 685-nm and 830-nm lasers in the tissue repair of tenotomized tendons in the mouse. *Photomed Laser Surg.* 2006;24(6):754-8.
 78. Stergioulas A. Low-level laser treatment can reduce edema in second degree ankle sprains. *J Clin Laser Med Surg.* 2004;22(2):125-8.
 79. Xavier M, David DR, de Souza RA, et al. Anti-inflammatory effects of low-level light emitting diode therapy on Achilles tendinitis in rats. *Lasers Surg Med.* 2010;42(6):553-8.
 80. Simunovic Z, Trobonjaca T, Trobonjaca Z. Treatment of medial and lateral epicondylitis - tennis and golfer's elbow with LLLT: a multicenter double blind, placebo-controlled clinical study on 324 patients. *J Clin Laser Med Surg.* 1998;16(3):145-51.
 81. Casalechi HL, Nicolau RA, Casalechi VL, Silveira L Jr, De Paula AM, Pacheco, MT. The effects of low-level emitting diode on the repair process of Achilles tendon therapy on rats. *Lasers Med Sci.* 2009;24(4):659-65.
 82. Moreira MS, Velasco IT, Ferreira LS, Ariga SK, Barbeiro DF, Meneguzzo DT, et al. Effect of phototherapy with low intensity laser on local and systemic immunomodulation following focal brain damage in rat. *J Photochem Photobiol B.* 2009;97(3):145-51.
 83. Xuan W, Agrawal T, Huang L, Gupta GK, Hamblin MR. J Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis. *Biophotonics.* 2014;9999(9999).
 84. Byrnes KR, Waynant RW, Ilev IK, Wu X, Barna L, Smith K, et al. Light promotes regeneration and functional recovery and alters the immune response after spinal cord injury. *Lasers Surg Med.* 2005;36(3):171-85.
 85. Serafim KG, Ramos Sde P, de Lima FM, Carandina M, Ferrari O, Dias IF, et al. Effects of 940 nm light-emitting diode (LED) on sciatic nerve regeneration in rats. *Lasers Med Sci.* 2012;27(1):113-9.
 86. Albarracin R, Eells J, Valter K. Photobiomodulation protects the retina from light-induced photoreceptor degeneration. *Invest Ophthalmol Vis Sci.* 2011;52(6):3582-92.
 87. Cidral-Filho FJ, Martins DF, Moré AO, Mazzardo-Martins L, Silva MD, Carginin-Ferreira E, et al. Light-emitting diode therapy induces analgesia and decreases spinal cord and sciatic nerve tumour necrosis factor- α levels after sciatic nerve crush in mice. *Eur J Pain.* 2013;17(8):1193-204.
 88. Khalil Z, Khodr B. A role for free radicals and nitric oxide in delayed recovery in aged rats with chronic constriction nerve injury. *Free Radic Biol Med.* 2001;31(4):430-9.
 89. Brott T, Bogousslavsky J. Treatment of acute ischemic stroke. *N Engl J Med.* 2000;343(10):710-22.
 90. Guarner V, Rubio-Ruiz ME. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. *Interdiscip Top Gerontol.* 2015;40:99-106.
 91. Schellinger PD, Kohrmann M. Near-infrared laser treatment of acute stroke: from bench to bedside. *Nervenarzt.* 2012;83(8):966-974.
 92. Moreira MS, Velasco IT, Ferreira LS, Ariga SK, Abatepaulo F, Grinberg LT, et al. Effect of laser phototherapy on wound healing following cerebral ischemia by cryogenic injury. *J Photochem Photobiol B.* 2011;105(3):207-15.
 93. Shen CC, Yang YC, Chiao MT, Chan SC, Liu BS. Low-level laser stimulation on adipose-tissue-derived stem cell treatments for focal cerebral ischemia in rats. *Evid Based Complement Alternat Med.* 2013;2013:594906.
 94. Riddle CC, Terrell SN, Menser MB, Aires DJ, Schweiger ES. A review of photodynamic therapy (PDT) for the treatment of acne vulgaris. *J Drugs Dermatol.* 2009;8(11):1010-9.
 95. Barolet D, Boucher A. Radiant near infrared light emitting diode exposure as skin preparation to enhance photodynamic therapy inflammatory type acne treatment outcome. *Lasers Surg Med.* 2010;42(2):171-8.
 96. Sadick N. A study to determine the effect of combination blue (415 nm) and near-infrared (830 nm) light-emitting diode (LED) therapy for moderate acne vulgaris. *J Cosmet Laser Ther.* 2009;11(2):125-8.
 97. Ablon G. Combination 830-nm and 633-nm light-emitting diode phototherapy shows promise in the treatment of recalcitrant psoriasis: preliminary findings. *Photomed Laser Surg.* 2010;28(1):141-6.
 98. Correa F, Lopes Martins RA, Correa JC, Iversen VV, Joenson J, Bjordal JM. Low-level laser therapy (GaAs $\lambda = 904$ nm) reduces inflammatory cell migration in mice with lipopolysaccharide-induced peritonitis. *Photomed Laser Surg.* 2007 Aug;25(4):245-9.
 99. Lopes-Martins RA, Albertini R, Martins PS, Bjordal JM, Faria Neto HC. Spontaneous effects of low-level laser therapy (650 nm) in acute inflammatory mouse pleurisy induced by carrageenan. *Photomed Laser Surg.* 2005;23(4):377-81.
 100. Rezende SB, Ribeiro MS, Núñez SC, Garcia VG, Maldonado EP. Effects of a single near-infrared laser treatment on cutaneous wound healing: biometrical and histological study in rats. *J Photochem Photobiol B.* 2007;87(3):145-53.
 101. Whelan HT, Smits RL Jr, Buchman EV, Whelan NT, Turner SG, Margolis DA, et al. Effect of NASA light-

- emitting diode irradiation on wound healing. *J Clin Laser Med Surg.* 2001;19(6):305-14.
102. Danno K, Mori N, Toda K, Kobayashi T, Utani A. Near-infrared irradiation stimulates cutaneous wound repair: laboratory experiments on possible mechanisms. *Photodermatol Photoimmunol Photomed.* 2001;17(6):261-5.
 103. Güngörmüş M, Akyol UK. Effect of biostimulation on wound healing in diabetic rats. *Photomed Laser Surg.* 2009;27(4):607-10.
 104. Oliveira PC, Meireles GC, dos Santos NR, de Carvalho CM, de Souza AP, dos Santos JN, et al. The use of light photobiomodulation on the treatment of second-degree burns: a histological study of a rodent model. *Photomed Laser Surg.* 2008;26(4):289-99.
 105. Meirelles GC, Santos JN, Chagas PO, Moura AP, Pinheiro AL. A comparative study of the effects of laser photobiomodulation on the healing of third-degree burns: a histological study in rats. *Photomed Laser Surg.* 2008;26(2):159-66.
 106. Min PK, Goo BL. 830 nm light-emitting diode low level light therapy (LED-LLLT) enhances wound healing: a preliminary study. *Laser Ther.* 2013;22(1):43-9.
 107. Khodr B¹, Khalil Z. Modulation of inflammation by reactive oxygen species: implications for aging and tissue repair. *Free Radic Biol Med.* 2001;30(1):1-8.
 108. Barbos Pinheiro AL, Limeira Júnior Fde A, Márquez Gerbi ME, Pedreira Ramalho LM, Marzola C, Carneiro Ponzi EA, et al. Effect of 830-nm laser light on the repair of bone defects grafted with inorganic bovine bone and decalcified cortical osseous membrane. *J Clin Laser Med Surg.* 2003;21(6):383-8.
 109. Liu X, Lyon R, Meier HT, Thometz J, Haworth ST. Effect of lower-level laser therapy on rabbit tibial fracture. *Photomed Laser Surg.* 2007;25(6):487-94.
 110. Pinheiro AL, Gerbi ME. Photoengineering of bone repair processes. *Photomed Laser Surg.* 2006;24(2):169-78.
 111. Carvalho AS, Napimoga MH, Coelho-Campos J, Silva-Filho VJ, Thedei G. Photodynamic therapy reduces bone resorption and decreases inflammatory response in an experimental rat periodontal disease model. *Photomed Laser Surg.* 2011;29(11):735-40.
 112. De Almeida P, Lopes-Martins RÁ, Tomazoni SS, Albuquerque-Pontes GM, Santos LA, Vanin AA, et al. Low-level laser therapy and sodium diclofenac in acute inflammatory response induced by skeletal muscle trauma: effects in muscle morphology and mRNA gene expression of inflammatory markers. *Photochem Photobiol.* 2013;89(2):501-7.
 113. De Paiva Carvalho RL, Leal-Junior EC, Petrellis MC, Marcos RL, de Carvalho MH, De Nucci G, et al. Effects of low-level laser therapy (LLLT) and diclofenac (topical and intramuscular) as single and combined therapy in experimental model of controlled muscle strain in rats. *Photochem Photobiol.* 2013;89(2):508-12.
 114. Viegas VN, Abreu ME, Viezzer C, Machado DC, Filho MS, Silva DN, et al. Effect of low-level laser therapy on inflammatory reactions during wound healing: comparison with meloxicam. *Photomed Laser Surg.* 2007;25(6):467-73.
 115. Gál P, Mokrý M, Vidinský B, Kilík R, Depta F, Harakalová M, et al. Effect of equal daily doses achieved by different power densities of low-level laser therapy at 635 nm on open skin wound healing in normal and corticosteroid-treated rats. *J Lasers Med Sci.* 2009;24(4):539-47.
 116. Reis SR, Medrado AP, Marchionni AM, Figueira C, Fracassi LD, Knop LA. Effect of 670-nm laser therapy and dexamethasone on tissue repair: a histological and ultrastructural study. *Photomed Laser Surg.* 2008;26(4):307-13.
 117. Pessoa ES, Melhado RM, Theodoro LH, Garcia VG. A histologic assessment of the influence of low-intensity laser therapy on wound healing in steroid-treated animals. *Photomed Laser Surg.* 2004;22(3):199-204.
 118. Demir H, Menku P, Kirnap M, Calis M, Ikizceli I. Comparison of the effects of laser, ultrasound, and combined laser + ultrasound treatments in experimental tendon healing. *Lasers Surg Med.* 2004;35(1):84-9.