

Photobiomodulation of Aging Tissues: Optimization of Dosimetric Parameters, Optical Modeling and Biphasic Dose Response

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ABSTRACT

Aging is characterized by progressive mitochondrial dysfunction, oxidative stress, chronic inflammation and impaired tissue regeneration, all of which culminate in degenerative conditions and poor healing capacity. Photobiomodulation (PBM), which utilizes red and near-infrared light (600-1000 nm), represents an emerging, non-invasive treatment modality that can be used to regulate cellular processes for maintaining tissue homeostasis. This review aims at providing a thorough overview of PBM with regards to aging, from cell biology to optics and from clinical applications to dosimetry. In terms of cellular biology, PBM involves the absorption of photons by mitochondrial photosensitizers resulting in ATP production stimulation, ROS signaling modulation, as well as activation of signaling cascades responsible for inflammation resolution and tissue repair. Nevertheless, PBM's therapeutic effect is greatly dependent upon optical properties of aging tissues, where light scattering increases along with the change in the chromophore concentration profile affecting light fluence distribution. The biphasic dose-response relationship is of particular interest here, as it demonstrates the presence of the optimal therapeutic window in which photobiomodulation stimulates biological effects, but low and high dosages can fail to work properly. The usage of modern computational techniques like the Monte Carlo simulation of light transport is suggested as a key factor for predicting energy deposition. From a clinical point of view, photobiomodulation shows promise in dealing with chronic wounds, musculoskeletal issues, neurodegenerative diseases and aging of the skin. Generally speaking, this paper focuses on the necessity to combine biophysical and biological knowledge to advance photobiomodulation in geriatric medicine.

Keywords: Aging, Wound healing, Photobiomodulation, Tissue regeneration, Low-level laser therapy, Dosimetry.

1. Introduction

The aging process itself is very complicated biologically and entails the occurrence of deterioration in cellular physiology,

decreased regenerative capabilities and increased vulnerability to illnesses and other ailments. Such changes occur as a result of mitochondrial abnormalities, oxidative stress, chronic inflammatory response and decreased reparative properties of

tissue structures. These findings indicate that problems such as chronic wounds, joint degeneration, neurodegeneration and skin aging constitute serious issues in contemporary medicine¹.

Recent developments in photobiomodulation (PBM), formerly referred to as low-level laser therapy (LLLT), have identified it as a potential non-invasive intervention that involves modulating cellular function to promote tissue regeneration. This form of intervention involves the use of photons from red and near-infrared light ranging from 600–1000 nm to induce photochemical processes within cells, unlike other methods involving heat. On a cellular level, photons are absorbed by mitochondrial chromophores, especially cytochrome c oxidase, thereby improving electron transport, generating ATP and influencing ROS signaling².

However, while these effects appear to be significant, it should be emphasized that their effectiveness heavily relies on the interaction between light and tissue. The latter involves processes such as absorption, scattering and attenuation of optical energy, all of which may be considerably affected by aging. Such changes are mainly connected to the alteration in composition and structure of biological tissues, which include, among other things, the formation of cross-links in collagen fibers, lower content of water and differences in chromophores' distribution³.

An important feature of PBM is its biphasic dose-response pattern wherein lower dosages cause stimulation, whereas higher dosages may induce inhibition. Such non-linearity underscores the need for proper dosimetry, especially when applying PBM on geriatric patients since tissue sensitivity and optics have changed. Nevertheless, there is a lack of standardization in PBM techniques today and the ideal dosing protocol remains underdeveloped⁴.

In such cases, computational methods, especially those based on Monte Carlo simulation for photon transport, have proven to be vital tools that help better understand light propagation, fluence and energy deposition processes in biological tissue. In this regard, computer models will provide a way to predict accurately the dose distribution in target tissue layers and allow for optimization of PBM parameters for elderly patients.

Although several quantitative dosimetry schemes have been developed for PBM, no scheme that is specific to the optical properties of aged tissue and fluence attenuation has yet been established.

For this reason, this review attempts to give an integrated look at photo biomodulation processes in aged tissue in terms of biological mechanism, optics and dosimetry optimization and clinical applications. Special attention will be paid to fluence attenuation and biphasic dose-response effects on therapy efficiency. This way, the connection between biological and biophysical aspects of the problem under consideration will be made in order to facilitate the creation of new PBM protocols for geriatric patients.

2. Principles of Photo Biomodulation

Photo biomodulation (PBM), also called low-level laser therapy (LLLT), is a noninvasive treatment approach that employs light from red and near-infrared wavelengths for the modulation of biological responses without thermal effects. PBM does not rely on thermal effects but instead operates

through photochemical and photobiological processes unlike high-power laser applications that make use of thermal or ablative effects in achieving biological objectives. The basic processes involved in PBM, including mitochondrial activation, redox processes, regulation of inflammatory responses and tissue repair, are depicted schematically in (Figure 1). The mechanism of action of PBM begins with photon absorption by intracellular chromophores in the tissues leading to series of biochemistry and signaling events. As indicated in (Figure 1), photon absorption causes the activation of mitochondria, increase in ATP formation, controlled ROS formation and activation of transcription factors involved in the control of inflammation and cell proliferation. Thus, the response achieved depends on optical dose and tissue characteristics⁵.

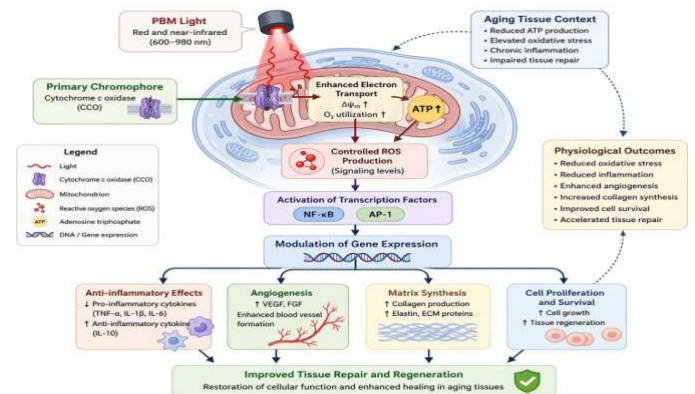


Figure 1: Mechanisms of photobiomodulation (PBM) at the cellular and molecular level. Diagrammatic representation of the basic mechanisms of PBM. Photobiomodulation involves absorption of red and near infrared light (600 - 980 nm) by mitochondrial chromophores such as cytochrome c oxidase (CCO), which leads to an increase in electron transport activity and increased levels of ATP formation. ROS formation that occurs in a controlled manner acts as signaling molecules responsible for the activation of transcription factors including NF- κ B and AP-1, thereby regulating gene expression. As a result, down-regulation of pro-inflammatory cytokines like TNF- α and IL-1 β , increased expression of anti-inflammatory cytokines such as IL-10, angiogenesis through VEGF up-regulation and stimulation of collagen synthesis take place.

2.1. Light-tissue interactions

The physics of light-tissue interaction is described by processes such as absorption, scattering, reflection and transmission. As soon as light reaches a biological sample, part of it gets absorbed due to the presence of various chromophores including melanin, hemoglobin and water, whereas the rest is subjected to scattering from tissue inhomogeneity.

As far as photobiomodulation (PBM) applications are concerned, the wavelength region from 600 to 1000 nm or an optical window, is preferable because of low levels of absorption and scattering of photons. Nevertheless, the behavior of light in tissues depends strongly on the characteristics of the latter and age-related changes may affect it dramatically⁶.

2.2. Mitochondrial photoreception

It has been widely reported that mitochondria act as the chief cellular target in PBM therapy. Cytochrome c oxidase (CCO), a crucial component in the mitochondria's electron transfer chain, serves as a prime candidate for photoacceptor. The absorption

of photon results in electron transfer, mitochondrial membrane depolarization and eventually ATP production.

Furthermore, PBM therapy contributes to the photodissociation of NO from CCO, thus ensuring better oxygen metabolism. While the involvement of CCO is well-documented, several other processes have been suggested as being responsible for photobiomodulation including photon interaction with water bound within mitochondria or other photosensitizers. As depicted in Figure 1 below, these processes suggest that PBM works via a multi-level mechanism rather than a single one^{7,8}.

2.3. Cellular and molecular responses

The primary photochemical effects triggered by PBM cause a chain reaction of other secondary cellular effects, such as

Table 1: Cellular and molecular mechanisms of photobiomodulation (PBM) and their biological importance.

Mechanism	Primary Target	Molecular/Cellular Effect	Biological Outcome	Relevance in Aging Tissues	References
Photon absorption	C y t o c h r o m e oxidase (CCO)	Activation of electron transport chain	Initiation of PBM response	Reduced efficiency in aged mitochondria → requires optimized dosing	8,10
ATP production ↑	Mitochondria	Increased oxidative phosphorylation	Enhanced cellular energy metabolism	Restores impaired bioenergetics in aged cells	11,12
ROS modulation	Mitochondria / cytoplasm	Transient increase in signaling ROS	Activation of redox-sensitive pathways	Helps rebalance oxidative stress in aging	13
Gene activation	NF-κB, AP-1	Upregulation of transcription and protein synthesis	Cell survival and proliferation	Supports regeneration in aged tissues	14
Anti-inflammatory response	Cytokines (TNF-α, IL-1β, IL-10)	↓ Pro-inflammatory, ↑ anti-inflammatory mediators	Reduced inflammation	Counteracts “inflammaging”	12
Angiogenesis	VEGF, endothelial cells	Increased vascular signaling	New blood vessel formation	Improves oxygenation in aged tissues	15,16
Collagen synthesis	Fibroblasts	Increased extracellular matrix production	Tissue remodeling and repair	Enhances skin and wound healing in elderly	17

2.4. Biphasic dose response

One of the main features of PBM therapy is the presence of the biphasic dose-response relation, which is well described by the Arndt-Schulz law. According to the law, small doses of light activate biological processes, while large doses may suppress the physiological functions of cells. Thus, the nonlinear dependency reflects the presence of a special window of therapeutic action when phototherapy shows its positive effect. At lower energies, no effects may be observed since there is no adequate response from the biological system, while at high energies, cell activation is suppressed.

Biphasic behavior is especially important in elderly patients whose metabolism and optical properties differ significantly from those in young organisms. Thus, strict regulation of all parameters of irradiation (wavelengths, irradiance, fluence and time of irradiation) is critical for success in PBM therapy¹⁸.

3. Mechanisms of Photo biomodulation in Aging

The mode of action for Photo biomodulation therapy relies on several mechanisms, which include photochemical reactions, biochemical reactions and cellular actions. In the context of aging tissue, PBM acts through the restoration of bioenergetics in cells, regulation of redox signaling, modulation of the immune response and stimulation of regeneration in tissues. (Table 2) provides an overview of some of the physiological pathways involved in the action mechanism of photo biomodulation therapy, while Figure 2 describes how the optical energy distribution affects aging tissues.

increased ATP production, ROS modulation and activation of transcription factors, like NF-κB and AP-

1. In regulated amounts, ROS function as signalers, responsible for the control of gene expression, cell proliferation and adaptation to stressors⁹.

Photo biomodulation is also effective in reducing inflammatory cytokines (for instance, TNF-α and IL-1β) and stimulating anti-inflammatory cytokine production (for example, IL-10). Additionally, PBM stimulates angiogenesis through VEGF pathways and increases the activity of fibroblasts, causing an increase in collagen formation and extracellular matrix remodeling. The interrelated processes are illustrated in (Table 1) and synthesized in (Figure 1).

3.1. Mitochondrial activation and restoration of cellular bioenergetics

A major pathway in PBM is the uptake of photons at wavelengths between 600 nm and 1,100 nm into mitochondria by photo acceptors, specifically cytochrome c oxidase. This facilitates enhanced electron transport and increases mitochondrial membrane potential¹⁹.

As aging occurs, mitochondrial metabolism decreases, reducing energy levels and repair rates for tissues. PBM acts on the mitochondria to help regenerate cell division and migration as well as metabolic reactions. Also, PBM can result in the separation of NO from cytochrome c oxidase, thus facilitating oxidative phosphorylation and oxygen metabolism²⁰.

3.2. Modulation of reactive oxygen species and redox signaling

ROS have a dual impact on biological organisms, as they can act as destructive substances as well as messengers. PBM induces a controlled increase in ROS levels that will activate redox-responsive signaling pathways and transcription factors, including NF-κB and AP-1. Oxidative stress is often high in older organisms; however, their protective antioxidants may be weakened. PBM works by balancing ROS levels and improving cell adaptation as well as antioxidant activity in general. It is essential to maintain control over ROS because this process helps regulate gene expression and other functions^{21,22}.

3.3. Anti-inflammatory and immunomodulatory effects

One of the features of aging is the chronic low-grade state of inflammation in the body, called “inflammaging.” PBM downregulates the production of pro-inflammatory molecules, such as, TNF- α , IL-1 β and cyclooxygenase-2, while upregulating anti-inflammatory cytokines such as, IL-10.

Moreover, PBM regulates the activity of immune cells, mainly affecting the process of macrophage polarization and inducing the conversion of macrophages from M₁ phenotypes to M₂ phenotypes. This leads to the resolution of inflammation and remodeling of tissues, which is extremely important in cases when the body is aged^{23,24}.

3.4. Stimulation of proliferation, angiogenesis and Tissue regeneration

PBM improves the function of important cell types responsible for tissue repair, such as fibroblasts, keratinocytes, endothelial cells and stem or progenitor cells. This results in enhanced cell proliferation, migration and production of extracellular matrix, which in turn increases tissue regeneration capacity^{25,26}. Additionally, PBM induces angiogenesis by increasing the expression of growth factors like VEGF and TGF- β . Such actions increase blood flow, oxygen supply and nutrition delivery, which can be hampered in aging tissues. All of these biological mechanisms contributing to tissue regeneration are outlined in (Table 2).

Table 2: Mechanistic pathways of photobiomodulation (PBM) and their biological relevance in aging tissues.

Mechanism	Primary Target	Key Biological Effects	Relevance in Aging Tissues	References
Mitochondrial activation	Cytochrome c oxidase (CCO)	Enhanced electron transport, \uparrow ATP production, improved mitochondrial membrane potential	Restores impaired cellular bioenergetics and metabolic activity in aged cells	27
Nitric oxide photodissociation	CCO-NO complex	Release of inhibitory NO, improved oxygen utilization and respiration	Enhances mitochondrial efficiency under hypoxic or aged conditions	28
ROS modulation	Redox-sensitive signaling pathways	Transient ROS increase \rightarrow activation of NF- κ B, AP-1, antioxidant response	Rebalances oxidative stress and restores redox homeostasis	20,29,30
Anti-inflammatory regulation	Cytokines (TNF- α , IL-1 β , IL-10)	\downarrow Pro-inflammatory mediators, \uparrow anti-inflammatory cytokines	Reduces chronic inflammation (inflammaging)	31
Macrophage polarization	Immune cells (M ₁ \rightarrow M ₂)	Shift toward reparative phenotype, enhanced tissue remodeling	Promotes resolution of inflammation and healing in elderly tissues	32
Cellular proliferation	Fibroblasts, keratinocytes	\uparrow Cell proliferation, migration, collagen synthesis	Accelerates delayed wound healing in aging	33-35
Angiogenesis	VEGF, TGF- β pathways	\uparrow Neovascularization, improved blood supply	Enhances oxygen and nutrient delivery to aged tissues	36-38
Stem cell activation	Mesenchymal stem cells (MSCs)	\uparrow Differentiation and regenerative capacity	Compensates for age-related decline in stem cell function	7,39,40
Optical-tissue interaction	Tissue chromophores (melanin, Hb, water)	Light absorption, scattering, depth-dependent fluence distribution	Alters effective dose delivery in aged tissues	41-43
Biphasic dose response	Cellular metabolic response	Stimulation at optimal dose, inhibition at excessive dose	Requires precise dosimetry in geriatric applications	18,44-46

3.5. Optical and biophysical considerations in aging tissue

Moreover, besides biological factors, the success of PBM therapy is significantly dependent on the physics of light transport through tissue. With age, the physical parameters of tissue change due to alterations in collagen structure, hydration, vascularity and chromophore concentration. This impacts the optical properties of tissues by affecting absorption, scattering and anisotropy.

(Figure 2(A)) clearly indicates that the intensity of light diminishes from maximum values at the surface to lower levels at increasing depths. Moreover, in (Figure 2(B)), it can be observed that fluence is exponentially related to depth according to the effective attenuation coefficient (μ_{eff}). Consequently, optical changes with age impact the depth of light penetration into tissue⁴⁷⁻⁴⁹.

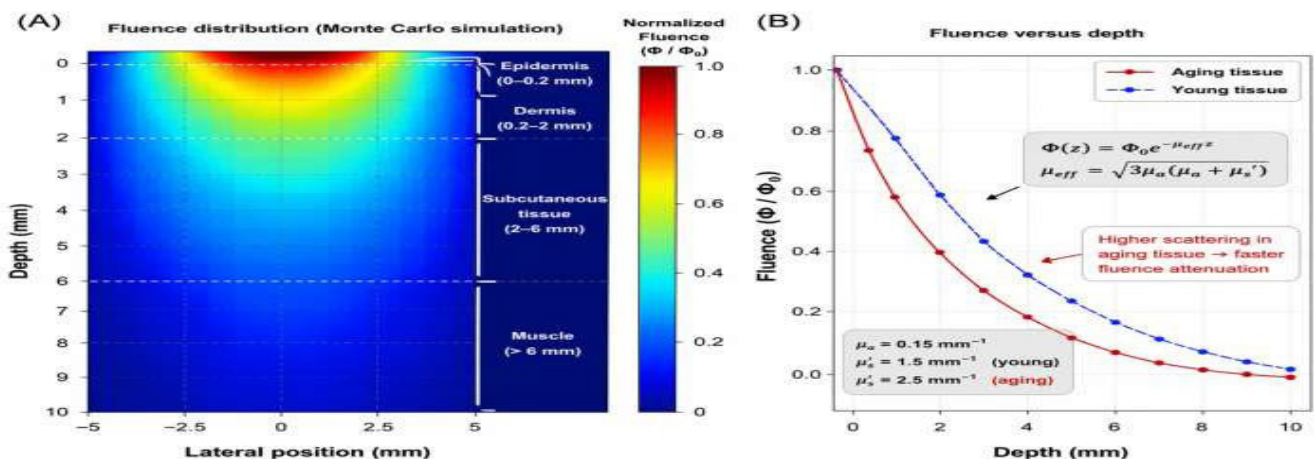


Figure 2: Penetration and fluence distribution of light used for photobiomodulation therapy in aging tissues.

Fluence distribution map obtained by Monte Carlo simulation demonstrating light intensity distribution in a multilayer tissue model, where the absorption is maximal at the surface layer while the light intensity decreases with depth.

Fluence profile as a function of depth depicting the exponential decrease in light intensity due to the effective attenuation coefficient (μ_{eff}).

3.6. Biphasic dose-response relationship

PBM exhibits a biphasic dose-response relationship response where small doses cause increased cell activity while large doses can cause inhibition, with the optimum dose giving the maximum effect. The biphasic effect of PBM is especially important during use on aged individuals who have lower metabolic abilities, hence altering their sensitivity to light. Thus, proper optimization of optical parameters is necessary for an efficient and optimized application during treatment of older individuals. Understanding the physiology of aging and using this information along with optical theory helps determine the correct treatment procedure⁵⁰⁻⁵³.

Despite considerable research into the physiological pathways involved in photobiomodulation, notable variations can be seen among various experimental setups. While a large number of researchers have observed improved mitochondrial function and ATP generation due to exposure to PBM, others have reported limited or no significant effects based on the wavelength, light intensity and biological conditions of cells^{54,55}.

In addition to the above, the involvement of cytochrome c oxidase as the main photo acceptor is also disputed, with certain researchers proposing that it could involve other molecules such as the water bound to the mitochondria or other chromophores. The differences suggest that PBM physiology varies among different tissues and ages.

Hence, there is a need for an extended mechanism that will factor in the aforementioned differences in order to achieve accurate predictions of PBM results in aging tissues.

4. Optical Interaction with Aging Tissue

The therapeutic effectiveness of PBM is regulated by both cellular responses as well as light propagation inside biological tissues. Optical changes related to aging can have a significant impact on the way in which light propagates inside biological tissues, thus impacting the amount of light that can be effectively delivered, as seen in Figure 2 below. Parameters of light propagation are highlighted in (Table 3).

4.1. Age-related changes in tissue optical properties

Tissue composition is significantly altered with the process of aging. These changes in tissue composition directly impact the optical characteristics. The changes include decreased water content, changes in the structure of collagen and changes in the concentration of chromophores such as melanin and hemoglobin. All these changes impact the basic optical parameters such as the absorption coefficient (μ_a), scattering coefficient (μ_s) and the anisotropy factor (g)⁵⁶.

Changes in the structure of collagen with the process of aging include increased collagen cross-linking and disorganization. These changes impact the scattering characteristics. Similarly, changes in tissue pigmentation and vascularization impact the

absorption characteristics^{57,58}. The changes in tissue composition with the process of aging increase the optical heterogeneity of the tissue, which impacts the propagation of photons.

4.2. Light attenuation and fluence distribution

The propagation of light in biological tissues is affected by absorption and scattering phenomena. Consequently, there is exponential attenuation as light travels deeper into tissues. This can be characterized as follows:

$$I(z) = I_0 e^{-\mu_{eff} z} \quad \dots (1)$$

Where $I(z)$ represent light intensity at a depth z , I_0 represents incident light intensity and μ_{eff} represents effective attenuation coefficient. The effective attenuation coefficient can be characterized as follows:

$$\mu_{eff} = \sqrt{3\mu_a(\mu_a + \mu_s')} \quad \dots (2)$$

Where $\mu_s' = \mu_s(1-g)$ is the reduced scattering coefficient.

As seen from Figure 2(B), fluence falls off sharply with depth, suggesting that a substantial fraction of optical energy is lost to absorption and scattering in the outer layers of tissue. In aged tissues, the enhanced scattering effect causes even greater attenuation of the beam.

4.2. Monte carlo modeling of photon transport

Because of the complicated and heterogeneous nature of the biological tissues involved, the above models may not be adequate in the accurate description of the phenomenon. Therefore, the Monte Carlo (MC) simulation has been recognized as the gold standard in the simulation of photon transport^{59,60}.

This approach considers the simulation of the path of single photons as they experience multiple scattering and absorption. The spatial distribution of the MC simulation is presented in Figure 2(A), where the distribution of the photon fluence decreases from the surface with depth. Moreover, the MC simulation offers the possibility of simulating the realistic multi-layer model of the tissue involved. This makes the MC simulation highly appropriate for the simulation of the aging tissues involved.

4.3. Implications for PBM dosimetry in aging

The optical properties of aging tissues have significant implications for PBM dosimetry. As illustrated in Figure 2(A-B), the energy deposition becomes superficial, while the fluence at the deeper layer is greatly reduced. Hence, it is crucial for PBM protocols in geriatric medicine to consider these changes in optical properties by appropriately modifying the parameters used in PBM, including the wavelengths, power density and exposure time^{52,61}. The optical parameters relevant for light propagation and their implications in aging tissues are listed in (Table 3).

4.4. Optimization strategies

Optimization methods for dealing with the problem of light attenuation in aging tissues include:

- Utilization of long wavelength light (800-980 nm) for increased penetration
- Modification of surface fluence to account for attenuation loss at increasing depths
- Utilization of Monte Carlo based simulation models for treatment planning

- Tailored PBM therapy according to tissue or patient specificity
- All of these optimization techniques lead to greater light control and PBM efficacy.

Table 3: Optical parameters and their impact on photo biomodulation in aging tissues.

Parameter	Description	Effect in Aging Tissues	Impact on PBM	References
(μ_a) (absorption coefficient)	Light absorption by chromophores (melanin, hemoglobin, water)	Altered chromophore distribution with age	Modifies energy deposition profile	43,62,63
(μ_s) (scattering coefficient)	Photon scattering within tissue microstructure	Increased due to collagen cross-linking and structural changes	Reduces penetration depth	62,64,65
(g) (anisotropy factor)	Directionality of scattering	Slight variation with tissue aging	Influences photon propagation direction	62,66,67
(μ_{eff}) (effective attenuation coefficient)	Combined absorption and scattering effects	Increased in aging tissues	Accelerates light attenuation	67,68
(Φ) Fluence	Optical energy per unit area within tissue	Reduced at deeper layers	Limits therapeutic effectiveness in deeper tissues	68,69

5. Clinical Applications of Photobiomodulation in Geriatrics

Photobiomodulation (PBM) has become a highly prospective non-invasive method of treating various aging-related pathologies. Due to its capacity to affect mitochondrial functioning, oxidative stress and inflammation, photobiomodulation becomes an effective way to influence the most important pathological mechanisms of tissue dysfunction related to aging. The connection between biological effects caused by photo biomodulation and clinical results can be seen in (Figure 3); whereas clinical uses of PBM are described in (Table 4).

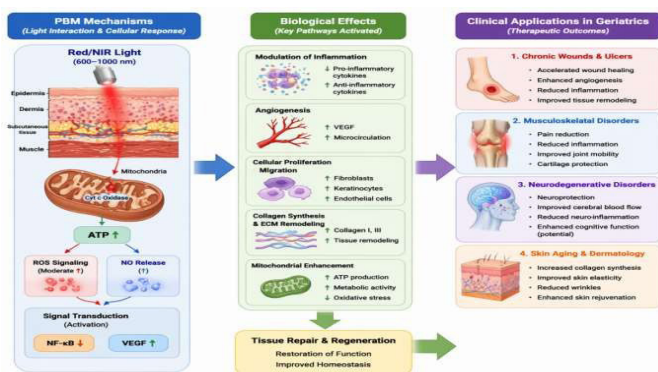


Figure 3: Photobiomodulation (PBM) applications in geriatrics medicine. Scheme illustrating the connections between the biological processes initiated via PBM and its therapeutic effects. Light activation of mitochondrial chromophores increases the production of ATP and ROS signaling, which results in regulation of inflammatory responses, neovascularization and tissue regeneration.

5.1. Chronic wounds and ulcers

Chronic wounds like diabetic foot ulcers and pressure ulcers are common among geriatric patients because of poor vascularization, chronic inflammation and inability for regeneration. PBM promotes wound healing through cellular proliferation, inflammation reduction and angiogenesis by elevating levels of VEGF [70–72]. PBM has also been shown to improve wound healing by increasing the expression of vascular endothelial growth factor (VEGF), thus improving wound microcirculation. PBM has also been shown to improve wound healing by improving the inflammatory response, thus improving the transition from the inflammatory phase to the proliferative phase of wound healing⁷³.

5.2. Musculoskeletal disorders

Musculoskeletal disorders, including osteoarthritis and joint pain, are significant sources of disability in the elderly. PBM has therapeutic effects in treating musculoskeletal disorders by its anti-inflammatory and analgesic properties, which are achieved by its antioxidant properties in reducing oxidative stress and inflammatory mediators^{23,74}.

PBM also has effects in improving microcirculation and tissue oxygenation, as well as its effects in improving chondrocyte function and maintenance of the cartilaginous matrix. This makes PBM an effective adjunctive therapy in the management of geriatric musculoskeletal disorders^{21,75}.

5.3. Neurodegenerative disorders

Neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease have a significant association with mitochondrial dysfunction, oxidative stress and neurodegeneration. PBM therapy, especially transcranial PBM therapy, has shown promise as a neuroprotective therapy for neurodegenerative diseases⁷⁶.

PBM therapy increases mitochondrial activity in neurons, increases blood flow to the brain and decreases neuroinflammation. These mechanisms have shown promise in improving cognitive functions and neurological outcomes. However, more clinical studies are necessary to prove the long-term effects and treatment protocols for PBM therapy for neurodegenerative diseases.

5.4. Skin aging and dermatological applications

Skin aging is characterized by reduced collagen synthesis, decreased elasticity and degradation of skin structures. PBM has been used for therapeutic purposes in dermatology for rejuvenation and repair of tissues.

The therapeutic effects are mediated by enhanced fibroblast proliferation and collagen synthesis due to increased mitochondrial activity and growth factor secretion. PBM therapy increases microcirculation and reduces oxidative stress for improved skin texture, elasticity and dermal structures. Clinical studies have shown significant improvement in reducing wrinkles and improving skin quality after PBM therapy.

5.5. Integration of clinical evidence

Even though photo biomodulation proves to be widely applicable as a therapy tool in many clinical conditions, inconsistency in therapy parameters such as wavelength, fluence,

irradiance and exposure time is an issue. The lack of uniformity in dosimetric parameters makes comparing different clinical trials rather challenging.

As can be seen from (Figure 3), the effectiveness of the therapy is directly related to certain biological mechanisms

associated with activation, regulation of mitochondrial activity and changes in redox balance and inflammation. (Table 4) summarizes the main applications of PBM in geriatric medicine, the mechanisms that work behind each application and therapeutic effects observed.

Table 4: Clinical applications of photo biomodulation in geriatric patients.

Application	Mechanism of Action	Key Biological Targets	Clinical Outcomes	References
Chronic wounds and ulcers	↑ ATP production, ↑ VEGF, ↓ inflammation	Fibroblasts, endothelial cells, cytokines	Accelerated wound healing, enhanced angiogenesis, improved tissue remodeling	74,77
Musculoskeletal disorders	↓ oxidative stress, ↓ inflammatory mediators, ↑ microcirculation	Chondrocytes, synovial cells	Pain reduction, improved joint mobility, enhanced functional recovery	78
Neurodegenerative disorders	↑ mitochondrial function, ↑ cerebral blood flow, ↓ neuroinflammation	Neurons, microglia	Improved cognitive performance, neuroprotection, enhanced neuronal survival	79
Skin aging and dermatology	↑ fibroblast proliferation, ↑ collagen synthesis, ↑ growth factor signaling	Dermal fibroblasts, extracellular matrix	Improved skin elasticity, wrinkle reduction, dermal regeneration	80

Although PBM has shown positive results in clinical settings, its effectiveness varies among different studies. Factors such as wavelength, fluence, irradiance and exposure time are different across studies, making it hard to compare the results. Some studies show that similar parameters used in PBM therapy may produce varied results, proving that there is no clear guideline in the use of PBM therapy.

Furthermore, clinical studies may be flawed due to factors such as a small number of participants, inadequate control groups and insufficient follow-ups, leading to unreliable results. The heterogeneous characteristics of the population also make it difficult to interpret the results.

Therefore, the current studies should be improved by conducting extensive clinical studies and developing a uniform dosimetric guideline for PBM therapy.

6. Dosimetry and Therapeutic Parameters

Photo biomodulation (PBM) therapy is greatly influenced by dosimetry accuracy. Parameters such as the wavelength, irradiance, fluence, duration of exposure and frequency should be precisely manipulated in order to attain favorable physiological effects. This becomes especially significant in aged tissue owing to the presence of changes in optical properties and metabolism that affect both the penetration and biological activity of light.

One unique characteristic of photo biomodulation therapy is its dose-dependency, which can be observed through the nonlinear interaction of light energy on biological processes. The dose-response relationship is depicted in (Figure 4), whereas the dosimetric parameters involved in photo biomodulation therapy and their importance in medical practice are detailed in (Table 5).

6.1. Wavelengths

The wavelength chosen determines how deep the light can penetrate into the tissue as well as the extent of the absorbance by the chromophores. Red light (630 - 660 nm) and near infrared (800 - 980 nm) are normally used in PBM treatments⁴³. Red wavelengths of light have high absorbance and therefore are used for dermatology purposes and wound treatment; on the other hand, near infrared light has deeper penetration and hence is best used to treat internal tissues such as muscles and joints.

6.2. Power density (Irradiance)

Irradiance, which is measured in mW/cm², describes how quickly energy can be administered to the tissue. This factor becomes important because very low irradiance would not have any effect on the cells, while high irradiance can cause inhibition.

The importance of the irradiance level should be taken into account together with the duration of exposure, because it will define the amount of energy. In that regard, it becomes important to optimize the irradiance level in order to remain within the therapeutic range.

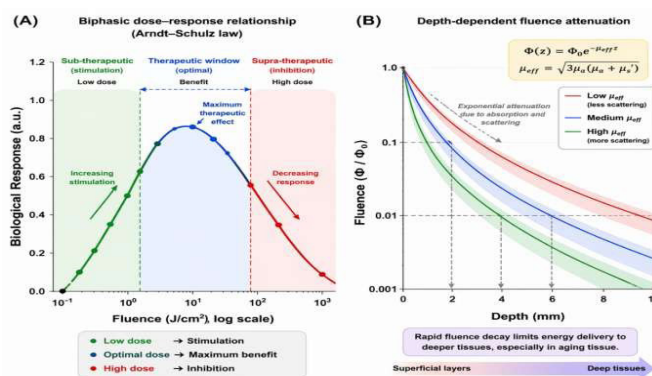


Figure 4: Biphasic nature of the dose response and depth-dependent fluence attenuation for photo biomodulation.

A biphasic nature of the dose-response relationship with demonstration of the Arndt-Schulz law and optimal therapeutic window.

Depth-dependent fluence attenuation with exponential decrease of intensity as a result of light absorption and scattering.

6.3. Fluence (Energy density)

Fluence or the amount of energy per unit area (J/cm²) is another very important factor in PBM therapy and is calculated as follows:

$$Fluence = Power\ density \times Time / Area \dots (3)$$

Typical values for fluence are in the 1-10 J/cm² range for superficial treatments and in the 50–100 J/cm² range for deep tissues. Nevertheless, due to the absorption and scattering process, surface fluence does not indicate energy delivery into deeper tissue levels.

As shown in **(Figure 4(B))**, fluence is an exponentially declining function of depth, thus resulting in less energy available at the targeted areas. Hence, the dosage at the surface should be increased to overcome this effect, especially in aged tissues with higher levels of scattering.

6.4. Exposure time

Exposure time affects the overall dose of energy that is applied to the tissue and needs to be controlled along with the density of power⁴⁶. Too much exposure will decrease the effectiveness of the dose; too little exposure can render results ineffective as well. The exposure time varies in the clinical setting from several seconds to several minutes depending on the treatment process.

Table 5: Important photo biomodulation dosimetry parameters and ranges.

Parameter	Definition	Typical Range	Clinical Relevance	References
Wavelength (nm)	Light spectral range used for PBM	630–660 (superficial), 800–980 (deep)	Determines penetration depth and chromophore absorption	81
Power density (mW/cm ²)	Power delivered per unit area	5–500 mW/cm ²	Controls rate of energy delivery and cellular stimulation	44
Fluence (J/cm ²)	Energy delivered per unit area	1–10 (superficial), 10–100 (deep)	Determines therapeutic dose and effectiveness	82
Exposure time (s–min)	Duration of irradiation	Seconds to minutes	Influences total delivered energy	33
Treatment frequency	Number of sessions	2–5 sessions/week	Determines cumulative therapeutic response	83

6.6. Optimal dosage and modeling approach

With the complications associated with light transport through biological tissues in aging, it is essential to use simulation techniques for optimizing the dosimetry procedure. By means of simulations based on the Monte Carlo technique, fluence distribution and energy deposition in layered tissues can be accurately predicted.

It makes it possible to develop a mathematical model describing the relationship between irradiation parameters at the surface and dose delivery in tissues. It can be used to develop individual photobiomodulation programs.

7. Challenges and Limitations of Photo Biomodulation in Geriatrics

Although there is increasing interest in PBM as a potential treatment for age-related diseases, several obstacles exist that inhibit its broad application and reproducibility in clinical practice, especially among older adults.

7.1. Inconsistency of protocols

A major challenge associated with photo biomodulation (PBM) therapy includes the inconsistency of treatment protocols. There is considerable variation in important parameters such as wavelength, power density, fluence and time duration of treatments in various research papers and studies³³. In addition, the biphasic nature of PBM's dose response effect implies that underdosing or overdosing can be detrimental to the treatment process. Establishing reliable protocols, therefore, is essential in order to ensure effective PBM treatment.

7.2. Variations in light penetration depth

However, penetration depth affects the effectiveness of PBM and its optical characteristics determine the ability of light to penetrate tissues. In Section 4 and **(Figure 2)** below, it was shown that the intensity of light penetrates tissues with exponential decay because of absorption and scattering.

6.5. Dose response and therapeutic window for PBM

The effect of PBM follows a biphasic dose response, wherein the effect rises with increasing dose up to a certain optimum point and then falls off. The curve for such a response is shown in **(Figure 4(A))**. For low doses, the effect is one of enhancing cellular activity and aiding tissue repair. For optimum doses, maximum effects can be attained. If higher doses are applied, the effect may be one of decreased cellular activity or inhibition.

It is necessary to determine the proper therapeutic window for each application of PBM, especially in older tissues with different cellular sensitivities and optical properties.

For instance, in older tissues, the amount of light that reaches muscle, joint and neural tissues reduces greatly because of greater scattering and heterogeneous nature of the tissues.

7.3. Patient-specific biological response

Individual biological reactions to PBM also differ greatly depending on the age of the person, their skin color, tissue type, vascular structure, metabolism and health status. When applied to elderly patients, additional variables such as decreased mitochondria performance, poor microcirculation and abnormal immunity affect the results. The unique nature of individual biological reactions to PBM poses challenges for creating standardized PBM treatment regimens.

7.4. Limitations in clinical evidence

While there have been multiple studies documenting positive effects of PBM, the quality and reliability of clinical evidence are highly inconsistent. Different studies have different designs, sample sizes, treatment protocols and evaluation criteria. This makes it difficult to draw conclusions from clinical findings.

Moreover, there are no large-scale randomized control trials that specifically deal with geriatric patients. This makes it impossible to develop guidelines for the use of PBM therapy in geriatrics.

7.5. Limitations of dosimetric and modeling strategies

Although dosimetric modeling techniques like Monte Carlo calculations offer much information about the interaction of light and energy in biological tissue, they too carry certain limitations. This is due to the fact that some models use simplistic assumptions regarding the shape of biological tissue and the optical parameters used in calculations.

The limitation becomes more pronounced in the case of aged tissues, which have greater structural heterogeneity than healthy

tissue. In addition, the adoption of modeling methods for clinical applications is still limited.

7.6. Need for personalized and adaptive PBM treatments

Taking into account the interaction of all those factors, such as optical variability, biological differences and dependency on doses, the trend towards personalized therapy is increasingly required. Adaptive methods of PBM treatments based on patient-specific data may help to achieve a higher accuracy of treatment.

The development of PBM protocols using computational simulations, imaging and biosensors is an interesting area that may lead to the design of individually optimized PBM therapy regimens.

Although photo biomodulation shows significant therapeutic potential, several fundamental challenges limit its clinical translation, particularly in aging populations. One of the primary issues is the lack of standardized dosimetric parameters, as variations in wavelength, power density and exposure time can lead to inconsistent biological responses due to the biphasic dose-response effect.

Another critical limitation lies in the uncertainty of light penetration depth in aged tissues. Increased scattering and altered optical properties reduce the amount of energy reaching deeper tissue layers, making it difficult to ensure adequate dose delivery at the target site.

Moreover, current computational models, including Monte Carlo simulations, often rely on simplified assumptions regarding tissue homogeneity and optical properties. These assumptions may not accurately represent the structural complexity and heterogeneity of aging tissues, leading to discrepancies between simulated and real biological outcomes.

In addition, patient-specific variability, including differences in skin pigmentation, vascularization and metabolic activity, significantly affects PBM response. This variability highlights the limitation of generalized treatment protocols and underscores the need for personalized PBM approaches.

Therefore, future research should focus on integrating advanced multiphysics modeling, real-time feedback systems and patient-specific data to improve the accuracy, reproducibility and clinical applicability of PBM therapy.

8. Conclusion and Future Perspectives

Photo biomodulation therapy (PBM) is becoming increasingly popular as an innovative noninvasive technology designed to treat the negative changes associated with aging at the cellular level, affecting such processes as mitochondrial function, oxidation and inflammation response.

The present review reveals the importance of the interplay between photo biomodulation mechanisms, interactions between light and tissue structures and accurate calculation of energy doses in achieving effective treatment of tissue dysfunctions associated with aging. Aging is characterized by numerous physiological changes in tissues, leading to their decreased permeability to light. As a consequence, traditional protocols based on photo biomodulation mechanisms used for healthy tissues cannot be effectively used for elderly patients.

One of the fundamental aspects of PBM technology is the presence of a dose-response curve showing the existence

of an optimum range where the treatment effect is observed. Insufficient energy levels cannot produce any biological effect, while overexposure can have a destructive nature.

Innovative computational methods, especially those involving photon transport modeling with Monte Carlo calculations, are valuable means of analyzing light propagation and energy transfer through complicated and heterogeneous biological materials. Thus, incorporating such computational techniques with experimental or clinical data will play an important role in increasing the effectiveness and reproducibility of PBM therapy.

Although PBM shows a great potential to improve health care, there are still some problems related to the absence of uniform protocols, the heterogeneity of clinical data and the biological specificity of aging tissues that have to be solved. To achieve this goal, it is necessary to create scientifically proven guidelines and personalized treatment options based on the optical properties of biological tissue.

Further research must involve the use of Multiphysics modeling, as well as dosimetry and sensor feedback control in order to provide personalized PBM therapy. Besides, it is necessary to conduct large-scale controlled clinical trials to validate treatment protocols and ensure their efficacy.

In summary, the effective implementation of PBM into mainstream medical practice for elderly patients will require an interdisciplinary effort that involves biology, optics and mathematical modeling. Through the integration of these disciplines, PBM can evolve from an empirical form of therapy to one that is precisely engineered for each individual patient.

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9.2. Conflict of interest

The author declares that there is no conflict of interest related to the publication of this paper.

9.3. Ethics approval

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9.4. Consent to participate

Not applicable.

9.5. Data availability

This study generated no datasets.

9.6. Author's contributions

Author alone contributed to the conception, review of literature, analysis and writing of this manuscript.

9.7. Consent for publication

Not applicable.

9.8. AI tools involved

AI tools have only been used for enhancing language and

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