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Review

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Photobiomodulation therapy assisted orthodontic tooth movement: potential implications, challenges, and new perspectives

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Abstract: Over the past decade, dramatic progress has been made in dental research areas involving laser therapy. The photobiomodulatory effect of laser light regulates the behavior of periodontal tissues and promotes damaged tissues to heal faster. Additionally, photobiomodulation therapy (PBMT), a non-invasive treatment, when applied in orthodontics, contributes to alleviating pain and reducing inflammation induced by orthodontic forces, along with improving tissue healing processes. Moreover, PBMT is attracting more attention as a possible approach to prevent the incidence of orthodontically induced inflammatory root resorption (OIIRR) during orthodontic treatment (OT) due to its capacity to modulate inflammatory, apoptotic, and anti-antioxidant responses. However, a systematic review revealed that PBMT has only a moderate grade of evidence-based effectiveness during orthodontic tooth movement (OTM) in relation to OIIRR, casting doubt on its beneficial effects. In PBMT-assisted orthodontics, delivering sufficient energy to the tooth root to achieve optimal stimulation is challenging due to the exponential attenuation of light penetration in periodontal tissues. The penetration of light to the root surface is another crucial unknown factor. Both the penetration depth and distribution of light in periodontal tissues are unknown. Thus, advanced approaches specific to orthodontic application of PBMT need to be established to overcome these limitations. This review explores possibilities for improving the application and effectiveness of PBMT during OTM. The aim was to investigate the current evidence related to the underlying mechanisms of action of PBMT on various periodontal tissues and cells, with a special focus on immunomodulatory effects during OTM.

Key words: Photobiomodulation therapy; Low-level laser therapy (LLLT); Low-intensity laser therapy (LILT); Orthodontic tooth movement; Orthodontics; Immunorthodontics

1 Introduction

The introduction of laser (light amplification by stimulated emission of radiation) technology provided researchers and clinicians with the opportunity to use light in human biology, creating new opportunities for its application in medicine (Chen et al., 2023). After more than 50 years of ongoing research, there is growing evidence regarding the clinical effects of laser light, particularly in the field of dentistry. Lasers used in phototherapy to induce photobiomodulation (PBM) therapy (PBMT) on periodontal tissues are classified as class III (those with an output power of 500 mW or less) or class IV (those with an output power of more than 500 mW) (Dompe et al., 2020).

It was previously believed that PBMT required the use of coherent laser light, but recently, light-emitting diodes (LEDs) have been serving as a cheaper alternative (Chow et al., 2009). The use of a low-power light source (lasers or LED lights) can induce a PBM effect to simulate host cells directly for the purpose of accelerating tissue healing, promoting

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angiogenesis, reducing inflammation, relieving pain, and producing analgesia (Chung et al., 2012). Clinically, PBMT entails exposure of cells or tissues to red (600–700 nm) and near infra-red (NIR, 770–1200 nm) lights.

The key mechanisms involved in the intracellular responses include the stimulation of mitochondrial metabolism and an increase in electron transport. Adenosine triphosphate (ATP) production elevated by activation of the electron transport chain and a short release of nitric oxide (NO) from its binding site on cytochrome *c* oxidase (CCO) results in increased cell respiration and transient synthesis of reactive oxygen species (ROS) which in turn promote the conversion of adenosine diphosphate (ADP) to ATP. Another hypothesis concerns the activation of light-sensitive ion channels that allow calcium ions (Ca^{2+}) to enter the cell leading to subsequent modulation of numerous signaling pathways via ROS, adenosine 3',5'-cyclic-monophosphate (cAMP), NO, and Ca^{2+} release, resulting in transcription factor production (Cronshaw et al., 2020). These transcription factors are able to promote the expression of genes associated with new protein synthesis, cell migration and proliferation, anti-inflammatory signaling, anti-apoptotic proteins, and antioxidant enzymes (de Freitas and Hamblin, 2016).

There are recent encouraging reports of the dental application of PBMT in a wide range of oral hard and soft tissues in endodontics, periodontics, pediatrics, prosthodontics, orthodontics, and maxillofacial surgery (de Freitas and Hamblin, 2016). Recently, PBMT has been studied extensively in regard to orthodontic pain management (pain reduction), tooth movement acceleration (faster alveolar bone remodeling and improved collagen deposition) during fixed mechanotherapy, bone regeneration (improved osteoblast/osteoclast activity) after rapid maxillary expansion, titanium implants (improved wound healing, attachment, and osseointegration), external root resorption control, and post-treatment retention (Nayyer et al., 2022). One of the commonly associated iatrogenic effects of fixed orthodontic treatment (OT) is the occurrence of orthodontically induced inflammatory root resorption (OIIRR), which is gaining attention concerning its prevention and treatment (Yong et al., 2022e). Based on the established mechanisms of PBMT, it is expected that the energy emitted by PBMT may act at the cellular and molecular levels to influence bone and cementum remodeling mechanisms. The biological process triggered by PBMT mentioned above can be used for improving the proliferation rate of osteoblasts, as well as cementum repair, allowing the development of new clinical approaches in orthodontics (Yong et al., 2022f).

In this review, we explore possibilities for improving the application and effectiveness of PBMT during orthodontic tooth movement (OTM). The aim was to investigate the current status of evidence related to the underlying mechanisms of action of PBMT on various periodontal tissues and cells, with a special focus on the immunomodulatory effects during OTM. The first goal of this review was to update knowledge of laser application in dentistry, mostly concerning how PBMT works at the molecular and cellular levels in relation to orthodontics. The second purpose was to raise the awareness of researchers regarding the difficulties and challenges of the application of PBMT in orthodontics. The third objective was to promote PBMT-assisted OT as an important complementary approach to treat orthodontic-related problems that goes beyond traditional methods. For future research, the working mechanisms underlying the positive effects of PBMT on OTM should be investigated.

2 Laser and PBMT

2.1 Basic concepts of laser

The development of lasers triggered a medical revolution in multiple branches of medicine (Svelto et al., 2007). There are three significant characteristics of laser light that set it apart from natural light: monochromaticity, collinearity, and coherence (Ailioaie and Litscher, 2020). Due to these distinctive properties, laser light is ideal for stimulating chromophores in biological tissues that are sensitive only to certain specific wavelengths (Ailioaie and Litscher, 2020). In clinical laser practice, wavelength, power, energy, irradiation/exposure time, emission modes (continuous or pulsed), power density, and energy density are the most useful parameters and units of measurement (Ailioaie and Litscher, 2020) (Table 1).

A laser device emits light energy from stimulated photons into the irradiated target tissue that stimulates photothermal, photophysical, and/or photochemical

Table 1 Irradiation parameters

Quantity	Unit	Definition
Power	mW or W	Energy (J) per second (s), peak and average when pulsed.
Energy	mJ or J	Produced energy is obtained by multiplying the laser output power (W) by exposition time (s).
Irradiation/exposure time	s or min	The irradiation/exposure time varies significantly from a few seconds to many minutes, but is often in the range of 30–150 s.
Beam area	cm^2	The correct way to measure the beam area is to use a beam profiler and report the $1/e^2$ area.
Intensity (power density), irradiance	mW/cm^2 or W/cm^2	Irradiance is the power (W) divided by the beam area (cm^2).
Fluence (energy density)	mJ/cm^2 or J/cm^2	Calculated as power (W)×time (s)/beam area (cm^2). The tissue dose is expressed by the energy density (J/cm^2).
Dose	J/cm^2	Examined another way, the dose is the power density multiplied by time (s). The resultant dose in J/cm^2 could be the consequence of several different treatment options.
Dosage	J	Dosage (J) is the trickiest parameter in photobiomodulation (PBM) studies especially when pulsing is involved. The use of Joules is advocated to specify how much energy is delivered in a treatment, which is more important clinically. Using dosage (J) rather than dose (J/cm^2) will enable better standardization of dosages and permit comparison across different treatment regimens/protocols.

reactions at various biological levels, implicating endogenous chromophores (Ailioaie and Litscher, 2020). The effect of a laser is dependent on the light interactions in biological tissues including transmission, scattering, reflection, and absorption (Arora et al., 2021).

The penetration depth of a laser beam into tissue is governed by several factors, including the wavelength, tissue composition, and forward- and backscattering by structures and molecules present within the tissue (Keijzer et al., 1989). The success of laser treatment is determined by the selection of an appropriate laser resource for energy level quantification targeting and the correct setting of parameters (Ailioaie and Litscher, 2020).

2.2 Mechanism action of PBMT

Low-level laser therapy (formerly abbreviated as LLLT), also known as low-intensity laser therapy (LILT), was initially used in attempts to cure malignant tumors in rats (MgGuff et al., 1965). However, this term became replaced by "PBMT" because equivalent beneficial biological effects can be obtained by non-coherent LEDs with comparable parameters to low power coherent monochromatic lasers for most medical applications (Hamblin, 2016).

In PBMT, numerous wavelengths in the red (600–700 nm) and NIR (770–1200 nm) spectral regions have produced desirable results, while those in the region of 700–770 nm have been ineffective, as this region coincides with a trough in the absorption spectrum of CCO (de Freitas and Hamblin, 2016). Both absorption and scattering decline significantly as the wavelength increases, so the penetration depth of NIR is maximal at a wavelength of about 810 nm (Hamblin, 2017). At longer wavelengths, water molecules become the important absorber and the penetration depth declines (Hamblin, 2017).

In PBMT, emissive photonic fluxes from LEDs enter the cells, penetrate tissue, and initiate a cascade of photochemical reactions on specific signaling pathways due to endogenous photoreceptors. These reactions trigger molecular changes in the mitochondrial respiratory chain, inducing reduction of nitrite to NO, and enhancement of synthesis of CCO, an enzyme participating in the mitochondrial electron transport chain (Osipov et al., 2018).

Hamblin (2017) proposed that three key cellular and molecular stages are triggered when light photons are absorbed by target photoreceptors modulating cellular functions. The primary biological chromophores (termed "photoreceptors") have been identified as CCO in mitochondria (absorbing light mainly in the NIR region up to 950 nm), light-gated calcium ion channels, and opsins (particularly responding to blue or green light). Secondary effects of photon absorption in cells include increases in ATP, a brief and modest burst of

ROS generation, production of NO, and regulation of calcium levels. Moreover, PBMT can normalize the oxygen levels through two enzymatic reactions of CCO, CCO/H_2O and CCO/NO (Pruitt et al., 2022), which may play an important role in hypoxic conditions induced by orthodontic force during OTM. Tertiary effects include activation of a wide range of signaling pathways that will improve cell survival and apoptosis, increase proliferation and migration, and promote new protein synthesis (Hamblin, 2017) (Fig. 1). In vivo, PBMT has a potent anti-inflammatory effect by activating nuclear factor-κB (NF-κB) in embryonic fibroblasts, reducing pro-inflammatory cytokines in activated inflammatory cells, and decreasing markers of the M1-activated macrophage phenotype in macrophages (von Leden et al., 2013). The cellular reactions of PBMT also include the inhibition of cyclooxygenase (COX) resulting in a reduced production of prostaglandins (PGs), which act as core mediators of the acute inflammatory response (Pruitt et al., 2022). Thus, the final clinical outcomes of PBMT result not only from the direct irradiation of the tissue, but also from its secondary and tertiary effects.

PBMT presents a "biphasic dose-response" (also termed the "Arndt-Schulz curve"), where low doses produce photobiostimulation and high doses produce photobioinhibition (Huang et al., 2011). Photobiostimulation is associated with enhanced healing, whereas photobioinhibition has been found to be optimal for pain relief (Kate et al., 2018). As a result, it is widely applied in clinical practice for stimulation and wound healing (as values from 5 to 50 mW/cm^2) and relief of pain and inflammation or nerve inhibition (up to 1 W/cm^2), noting that a key consideration for clinicians is that an inappropriate dose may have the opposite therapeutic effects (Huang et al., 2011).

The use of PBMT may be an alternative treatment with good acceptance due to its well-proven characteristics, as well as being a type of therapy that can be widely used in different areas of dentistry. In

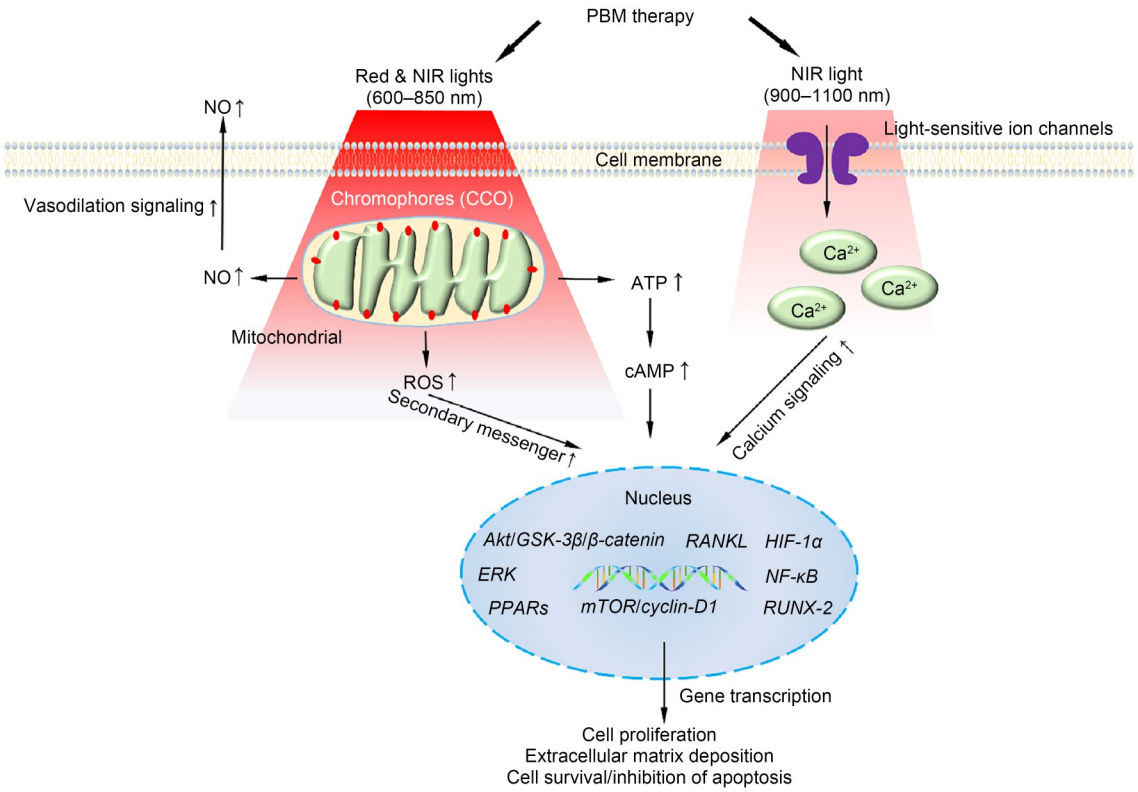

Fig. 1 Mechanisms underlying photobiomodulation (PBM) at the cellular and molecular levels. NIR: near infra-red; NO: nitric oxide; ROS: reactive oxygen species; CCO: cytochrome *c* oxidase; ATP: adenosine triphosphate; cAMP: adenosine 3', 5'-cyclic-monophosphate; *Akt*: protein kinase B; *GSK-3β*: glycogen synthase kinase-3β; *NF-κB*: nuclear factor-κB; *RANKL*: receptor activator of NF-κB ligand; *HIF-1α*: hypoxia-inducible factor-1α; *ERK*: extracellular signal-regulated kinase; *PPAR*: peroxisome proliferator-activated receptor; *mTOR*: mammalian target of rapamycin; *RUNX-2*: Runt-related transcription factor 2.

the field of periodontology, PBMT at wavelengths of 810 nm (Abidi et al., 2021) and 660 nm (Lee et al., 2018) has anti-inflammatory effects on human periodontal ligament cells (hPDLCs). Besides its non-invasive, safe, and effective properties, PBMT has been highlighted in the dental literature mainly for its pain inhibitory effects (Topolski et al., 2018) and tissue repair mechanisms (Wagner et al., 2013). These modulatory effects are the result of the capacity of PBMT to induce metabolic changes and accelerate bone resorption and neoformation, which are also necessary for OTM (Ekizer et al., 2016). This prompted us to explore its potential applications and underlying mechanisms more deeply for future "PBMT-assisted orthodontics."

3 PBMT in orthodontics

Orthodontics is a dental specialty and, like all dental procedures, may have adverse effects. The most common side effects of OT are pain, oral ulcers (Baricevic et al., 2011), white spot lesions and caries, periodontal changes, root resorption (specially termed "OIIRR"), pulpal changes, and temporomandibular disorder (TMD) (Enaia et al., 2011; Talic, 2011).

Many studies have reported positive effects of PBMT in the above common clinical adverse conditions in relation to OT, including reduction of orthodontic pain (Sfondrini et al., 2020; Anicic et al., 2021; Mirhashemi et al., 2021), acceleration of OTM rate (Kau et al., 2013; Yassaei et al., 2013; Shaughnessy et al., 2016; Yavagal et al., 2021), management of external root resorption (da Silva Sousa et al., 2011; Nimeri et al., 2014; al Okla et al., 2018; Khaw et al., 2018; Ng et al., 2018; Fernandes et al., 2019; Goymen and Gulec, 2020; Eid et al., 2022), mitigation of oral mucosal lesions/traumatic ulcers caused by appliances, as well as the prevention or treatment of TMD (Tunér et al., 2019; Alsarhan et al., 2022). Therefore, it seems that PBMT presents many possible and potential clinical benefits for OT and its associated side effects.

3.1 PBMT-assisted orthodontics

PBMT-assisted orthodontics refers to the application of this non-invasive therapy during OT, as it does not raise tissue temperature and stimulates biological functions in a biphasic manner using monochromatic light without causing damage (Domínguez and Velásquez, 2021).

Researchers have found different ways to speed up OTM through the stimulation of bone remodeling (Nimeri et al., 2013). The approaches fall into three broad categories: (1) biological pathways involving local or systemic drug delivery (local injections of PGs (Seifi et al., 2003), vitamin D (Kawakami and Takano-Yamamoto, 2004), osteocalcin (OCN) (Hashimoto et al., 2001) around the alveolar socket, or the administration of muscle relaxants (Uribe et al., 2014)); (2) physical or mechanical stimulation (PBMT (Doshi-Mehta and Bhad-Patil, 2012; Genc et al., 2013) or vibratory forces); and (3) surgically facilitated OT (decortication, piezocision, or cortectomies) (Fernandes et al., 2019). Based on randomized controlled trials related to PBMT-assisted OTM acceleration, the ideal range of PBMT wavelength is between 780 and 830 nm (Domínguez Camacho et al., 2020a). Individual studies have reported positive results at 809 nm (Youssef et al., 2008), 780 nm (Cruz et al., 2004), 810 nm (Yoshida et al., 2009; Doshi-Mehta and Bhad-Patil, 2012), 860 nm (Limpanichkul et al., 2006), and 980 nm (Dakshina et al., 2019). The cascade of physiological reactions triggered by applying an orthodontic force in conjunction with PBMT allows an average increase in speed of OTM of 24%–30% compared to applying force alone (Domínguez Camacho et al., 2020b).

OTM induced by orthodontic force results in a painful and sterile inflammatory adaptation process of the alveolar bone modeling (Yong et al., 2023). Different medications and techniques have been proposed to relieve pain during OT (Law et al., 2000), such as ibuprofen and naproxen sodium, chewing gum, anti-inflammatory and preemptive valdecoxib therapy, acupuncture and acupressure techniques, salicylic acetyl acid, and rofecoxib (Domínguez Camacho et al., 2020a). These alternatives can be helpful in relieving pain, but they may also slow down the rate of OTM (Bernhardt et al., 2001). The use of PBMT is able to alleviate pain, accelerate wound healing, and have a beneficial effect on inflammatory processes. Lim et al. (1995) and Harazaki et al. (1998) both showed that orthodontic pain levels were lower in PBMT group compared to control group at different treatment stages. It has further been reported that PBMT within a wavelength range of 800 to 850 nm may effectively decrease orthodontic pain, temporomandibular joint

(TMJ) pain, and TMD, at least in the short term (Eslamian et al., 2014; Panhoca et al., 2015).

Reducing orthodontic pain levels and the duration of multibracket appliance treatment would benefit patient comfort and satisfaction (Seifi et al., 2007). However, most PBMT research on OTM and the concurrent cellular reactions has been conducted in rodents (Saito and Shimizu, 1997; Yamaguchi et al., 2007; Gama et al., 2010) and rabbits (Ozawa et al., 1998; Kawasaki and Shimizu, 2000; Seifi et al., 2007). Some clinical studies have reported the relief of pain during treatment (Cruz et al., 2004; Limpanichkul et al., 2006; Youssef et al., 2008; Mistry et al., 2020), but the cellular changes that occur following laser application were not fully investigated.

3.2 Cellular and molecular mechanisms of PBMT in orthodontics

Domínguez and Velásquez (2021) proposed five fronts at which orthodontic force acts to induce OTM. Accordingly, an ideal acceleration technique should modulate all five fronts: blood vessels, non-mineralized tissues, mineralized tissues, nervous system, and immune system (Fig. 2).

At the cellular level, PBMT in the NIR region activates the primary mitochondrial photoreceptors (CCO) (Eells et al., 2004). The activation of CCO triggers different cascades of cellular responses including increased production of mitochondrial ATP (Masha et al., 2013). Increased ATP levels are then involved in promoting alveolar bone remodeling through overall elevation of metabolic activity to achieve OTM acceleration. PBMT may also promote angiogenesis, thus increasing the blood supply necessary for remodeling (Eells et al., 2003). It has been theorized that PBMT-induced ROS production may be associated with laser-induced analgesia (Ryu et al., 2010). These secondary mediators of PBMT (ROS, ATP, NO, and cAMP) can activate the cellular response via transcription factors and signaling pathways including NF-κB, receptor activator of NF-κB (RANK) ligand (RANKL), hypoxia-inducible factor-1α (HIF-1α), protein kinase B (Akt)/glycogen synthase kinase-3β (GSK-3β)/β-catenin pathway, Akt/mammalian target of rapamycin (mTOR)/cyclin-D1 pathway, extracellular signal-regulated kinase (ERK)/forkhead box protein M1 (FOXM1), peroxisome proliferator-activated receptors (PPARs), and Runt-related transcription factor 2 (RUNX-2) (de Freitas and Hamblin, 2016; Hamblin, 2018; Yong et al., 2021b, 2022a, 2022d).

3.2.1 Effects of PBMT on blood vessels

During OTM, periodontal ligament and alveolar bone remodeling are two main alterations in response to orthodontic force. However, it is crucial to consider that there are also important alterations in the pulp

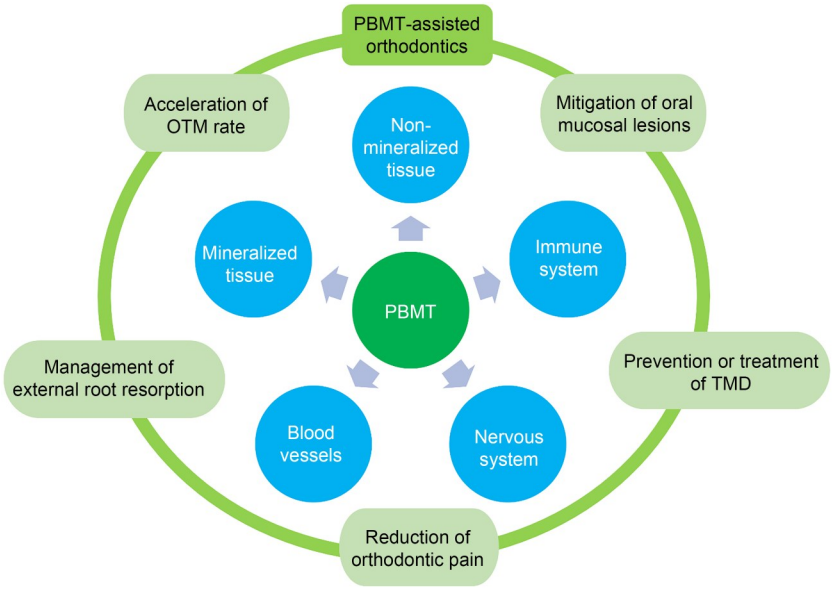

Fig. 2 Therapeutic effects in photobiomodulation therapy (PBMT)-assisted orthodontics are multifactorial, with positive reactions in blood vessels, mineralized tissues, non-mineralized tissues, nervous system, and immune system. OTM: orthodontic tooth movement; TMD: temporomandibular disorder.

and gingival tissues as a result of vascular changes of inflammatory origin. Vascularization plays a key role in OTM because both frontal and undermining alveolar bone resorptions require blood vessel supply (Yassaei et al., 2013).

PBMT in rats, particularly at 660 nm, promotes angiogenesis and decreases oral wound level of tumor necrosis factor-α (TNF-α) while increasing level of interleukin-1β (IL-1β) (Wagner et al., 2016). Cury et al. (2013) demonstrated in rats that 660 and 780 nm of PBMT have a pro-angiogenic effect through HIF-1α and vascular endothelial growth factor (VEGF) expression, as well as by a decrease in matrix metalloproteinase-2 (MMP-2). Szymanska et al. (2013) reported that vascular endothelial cells exposed to 635-nm irradiation proliferated faster than non-irradiated cells and had a decreasing VEGF level, while 830-nm irradiation decreased transforming growth factor-β (TGF-β) secretion by endothelial cells. PBMT has also been shown to stimulate angiogenesis during OT in the pulp at a wavelength of 830 nm (100 mW, 2.2 J/palatine, for 22 s/point) (Domínguez et al., 2013). PBMT using LED illumination at 5 J/cm^2 also showed favorable results regarding angiogenesis (Corazza et al., 2007). PBMT facilitates epithelial healing and new blood vessel formation through activation of the mTOR signaling pathway (Pellicioli et al., 2014) and ROS accumulation without inducing extra DNA damage (Dillenburg et al., 2014). ROS is a classical "Janus-face" mediator; beneficial at low concentrations and with brief exposures, but harmful at high concentrations and with prolonged and chronic exposures (Popa-Wagner et al., 2013). PBMT application initially reduces the production of prostaglandin E2 (PGE2) by inhibiting the tissue arachidonic acid cascade, which affects the secretion of inflammatory cytokines (Mizutani et al., 2004).

The consequences of PBMT on hypoxic cells are dependent on four classes of effects. The first class of effect is induced by enzyme CCO, which transfers light energy to the cell, triggering a series of downstream effects. The second class of effect is induced by changes in NO, ATP, and ROS levels. The third class of effect refers to downstream intracellular genetic transcription and cellular signaling to regulate cell hemeostasis in processes such as proliferation, migration, necrosis, and inflammation. The fourth class of effect is determined by the cells in the blood, where the cells are indirectly affected by bioactive molecules released from the stimulated cells (Carroll et al., 2014).

In hypoxic microenvironments induced by compressive force, mitochondria synthesize NO, which competes with and displaces oxygen for binding to CCO, leading to two negative effects: reduced ATP synthesis and increased oxidative stress, causing inflammation via NF-κB, an inflammatory "master switch" transcription factor (Carroll et al., 2014). Thus, PBMT is able to circumvent these negative effects because it releases NO from CCO, restoring ATP formation. Then, PBMT contributes to the dilation of blood vessels and improves blood circulation through the action of the signaling molecule NO released from CCO, increasing ATP synthesis and reducing oxidative stress (de Freitas and Hamblin, 2016). NO, a well-known vasodilator, acts via stimulation of soluble guanylate cyclase to form cyclic guanosine monophosphate (cGMP), which later activates protein kinase G to result in Ca^{2+} reuptake and the opening of calcium-activated potassium channels (de Freitas and Hamblin, 2016). The fall in concentration of Ca^{2+} prevents myosin light chain kinase (MLCK) from phosphorylating the myosin molecule, which causes relaxation of the smooth muscle cells in the lining of blood vessels and lymphatic vessels (Murad, 2004). Additional mechanisms have also been proposed by which NO could affect signaling pathways, including activation of iron-regulatory factors in macrophages (Drapier et al., 1993), modulation of proteins such as ribonucleotide reductase (Lepoivre et al., 1991) and aconitase (Drapier and Hibbs, 1996), stimulating ADP-ribosylation of glyceraldehyde-3-phosphate dehydrogenase (Dimmeler et al., 1992), and nitrosylation of protein sulfhydryl group (Stamler et al., 1992).

3.2.2 Effects of PBMT on non-mineralized tissues

The biological response of non-mineralized tissues during OTM includes the synthesis of collagen fibers and the proliferation of periodontal ligament (PDL) cells, PDL stem cells (PDLSCs), and fibroblasts. Also, specific biomarkers that modulate mineralized tissue remodeling (bone/cementum) must be considered (Yong et al., 2021a).

Indicators of mechanisms required to increase the turnover in periodontal fibers are the increases in expression of TGF-β, fibroblast growth factor (FGF), insulin-like growth factor-2 (IGF-2), and receptor of

IGF-1 (IGF binding protein 3 (IGFBP3)) (Saygun et al., 2008). At this point, the positive effects of PBMT start to overlap on various fronts on which the application of force has its effect. For example, PBMT results in an increase in the expression of FGF, which is a cytokine involved in angiogenesis, tissue remodeling, and stimulation of osteoblasts and osteoclasts. Kim et al. (2009) reported that PBMT at 808 nm increases fibronectin and type I collagen levels to facilitate the turnover of connective tissue during OTM. Faria et al. (2020) demonstrated that PBMT at 830 nm with 3 and 30 J/cm^2 alters B-cell lymphoma-2 (BCL-2) and caspase-6 levels to modulate cell survival and reduce DNA fragmentation in PDL cells. PDL also contains PDLSCs that can differentiate into cementum/PDL-like structures in vivo to promote repair of OIIRR (Seo et al., 2004). Gholami et al. (2022) reported that PBMT at 940 nm using a diode laser at 4 J/cm^2 improved mineralized deposition by bone morphogenetic protein-2 (BMP-2) and VEGF levels on PDLSCs. A recent systematic review indicated that PBMT can enhance the differentiation capacities of PDLSCs, but there is no agreement on the protocol (Mylona et al., 2022). In terms of the energy density applied by clinicians, it should not exceed 8 J/cm^2 when using LED devices, and 4 J/cm^2 when using lasers (Mylona et al., 2022).

3.2.3 Effects of PBMT on mineralized tissues

When orthodontic force and PBMT are applied, the periodontal ligament is no longer the only mechanotransducive organ that enables the acceleration of OTM. At that point, it is the change in alveolar bone turnover that will speed up OTM (Yoshida et al., 2009). Studies using an experimental tooth movement rat model have shown that PBMT irradiation increases the velocity of OTM by induction of the RANK/RANKL system (Fujita et al., 2008) and the *c-fms*/macrophage colony-stimulating factor (M-CSF) system (Yamaguchi et al., 2007). Kawasaki and Shimizu (2000) reported that PBMT stimulated the amount of OTM and the formation of osteoclasts on the compressed side during experimental tooth movement in vivo in rats, indicating that PBMT can accelerate OTM. However, PBMT also increases osteoblastic cell proliferation and can therefore stimulate osteogenesis and increase bone density on the compressed side during OTM (Yassaei et al., 2013), which could in turn reduce the speed of OTM.

Interaction between the mineralized structure and PBMT induces osteoblast proliferation and activates the NF-κB and RANK/RANKL/osteoprotegerin (OPG) system (Fujita et al., 2008). More osteoblasts express more circulating RANKL (Katagiri and Takahashi, 2002), which is a factor promoting osteoclastogenesis. The receptor RANK, located on the cell surface of precursors of osteoclasts, transduces signaling inside the osteoclasts. OPG, a decoy receptor with the capacity to competitively combine RANK and RANKL with RANK, inhibits osteoclastogenesis to decrease osteoclast formation. Thus, RANKL and OPG regulate alveolar bone resorption by exerting a positive or negative control on RANK on osteoclasts (Blair et al., 2007).

After application of orthodontic forces, alveolar bone resorption is induced on the compressed side by RANK signaling in osteoclast precursors. Kim et al. (2007) reported that PBMT increased the expression of both RANK and RANKL in the irradiated area around the moved tooth, which are two components necessary for the induction of tooth movement and osteoclastogenesis. Experimental evidence showed that PBMT stimulates osteoblast proliferation and induces osteoclast differentiation during OTM, and accelerates alveolar remodeling (Fujita et al., 2008). Marcos et al. (2011) showed that PBMT irradiated at 810 nm decreased the gene expression of *COX-2* and subsequently inhibited the production of PGE2 in a rat model, both of which led to pain reduction. When PBMT at 630 and 810 nm stimulates proliferation and differentiation of osteoblasts, it is accompanied by increased alkaline phosphatase (ALP) and OCN expression (Chang et al., 2019). According to Fujimoto et al. (2010), this effect can be stimulated by 1.91 J/cm^2 PBMT and be attributed to an increased expression of RUNX-2 and Osterix (Osx), although other differentiation factors, such as BMP-2, BMP-4, BMP-6, and BMP-7, might also be involved. Another major finding is that PBMT at 2 J/cm^2 irradiation influences cementoblast migration, proliferation, and differentiation, and activates MAPK signaling, depending on the pulse duration. This suggests that PBMT could be considered as an adjunctive therapy to be applied in prevention or treatments involving dental roots, such as OIIRR (Yong et al., 2022f).

Yamaguchi et al. (2010) showed in their rat model that increments in the expression of MMP-9, cathepsin

K, and subunits of integrin are detectable after PBMT application, facilitating the velocity of OTM. Yamaguchi et al. (2007) also reported that PBMT can increase M-CSF and *c-fms* on the compressed side and may also increase osteoclastogenesis leading to tooth movement. Additional PBMT shortened the duration of OTM by accelerating OTM during molar intrusion by modulating the levels of cytokines (IL-1β, IL-6, and IL-8) in irradiated areas, which were elevated in comparison to non-irradiated lesions throughout the entire experimental period (Fernandes et al., 2019). Taken together, these in vivo and in vitro findings point to a potential favorable effect of PBMT on accelerating the rate of OTM via positive effects on mineralized tissue remodeling.

3.2.4 Effects of PBMT on the nervous and immune systems

PBMT applied along with orthodontic force is also used to impact the nervous system to aid in pain management. One proposed hypothesis involves a conduction block of central and peripheral nerve fibers to increase the release of endorphins (de Freitas and Hamblin, 2016). This process includes the absorption of mitochondria leading to vasodilation, stimulation of cell division, release of NO, a rise in cortisol levels, accumulation of intracellular calcium, activity of the antioxidant enzyme superoxide dismutase, and new protein synthesis (Domínguez Camacho et al., 2020a; Yong et al., 2022b, 2022c). Yan et al. (2011) postulated that PBMT could suppress afferent fiber signaling as well as modulate synaptic transmission to dorsal horn neurons, including inhibition of substance P, which can contribute to long-term pain suppression. Chan et al. (2012) applied PBMT by 0.30–0.45 J/cm^2 in their clinical trial and demonstrated its efficacy on pulpal analgesia of premolar teeth by suppressing the intradental nerve response to electrical and mechanical stimuli.

It has also been reported that, when absorbed by nociceptors, PBMT with an irradiance higher than 300 mW/cm^2 can inhibit Aδ and C pain fibers, decrease conduction velocity, reduce the compound action potential amplitude, and suppress neurogenic inflammation (Carroll et al., 2014). PBM light can block anterograde transport of ATP-rich mitochondria in dorsal root ganglion neurons. This inhibition is entirely reversible within 48 h (Yan et al., 2011). However, more research is needed to fully characterize this complex mechanism of action (NIR light exerts a protective effect on neurons, but the mechanisms are still not fully understood).

Depending on the various energy densities reaching the tissue or cell, PBMT may activate immune cells (Viegas et al., 2007; Moriyama et al., 2009). Macrophages are important antigen-presenting cells that play a role in the induction of the primary immune response. The M1 profile is characterized by the production of high levels of pro-inflammatory cytokines (such as IL-6, TNF-α, and COX-2), low levels of anti-inflammatory cytokines, strong microbicidal activity, high ROS generation, and promotion of the Th1 immune response (Labonte et al., 2014). In contrast, the M2 profile is characterized by the production of high levels of anti-inflammatory cytokines to attenuate the effects of the M1 population as well as enzymes and growth factors that stimulate tissue remodeling and regeneration, and expression of the Th2 immune response (Martinez et al., 2009).

Chen et al. (2014) reported that PBMT at 660 nm and 1 J/cm^2 promoted optimal M1 polarization of monocytes. This effect was concomitant with histone modification at the *TNF-α* gene locus and mitochondrial biogenesis (Chen et al., 2014). According to a study by de Brito Sousa et al. (2020), PBMT irradiated at 660 nm and 17.5 J/cm^2 decreased the gene expression of the macrophage inflammatory protein-1α (MIP-1α, also known as C-C motif chemokine ligand 3 (CCL3)), MIP-2α (also known as C-X-C motif chemokine ligand 2 (CXCL2)), and TNF-α to modulate the expression of the M1-related markers. This indicates important inhibitory effects in the promotion, migration, and activation of monocytes and neutrophils in the initial stage of inflammation (de Brito Sousa et al., 2020). M1-related immunoregulation is important for the pathogenesis of inflammation in autoimmune conditions. Hence, PBMT regulation of M1-related immunological factors could be useful to promote control of autoimmune conditions. On the other hand, Liao et al. (2021) reported that NIR irradiated at high energy density (30–360 J/cm^2) epigenetically regulates macrophage M2 polarization, resulting in anti-inflammatory effects by TGF-β1. Thus, NIR irradiation not only alters the homeostasis between M1 and M2 macrophages, but also decreases the M1-mediated defense mechanism in unstimulated macrophages.

4 Challenges and difficulties of PBMT-assisted orthodontics

4.1 What is the exact energy density applied to the tooth root?

For PBMT, selection of the correct irradiation parameter determines the effectiveness of the treatment outcome because of the "biphasic dose-response" (Lanzafame et al., 2007; Su et al., 2020). Goulart et al. (2006) observed that a high intensity of laser therapy decreased the rate of tooth movement, while a low intensity had the opposite effect by a dog model. As noted previously, different wavelengths have been reported to have distinct biological effects and mechanisms. Therefore, determining the optimal irradiation parameter for each range of wavelengths in the red-to-NIR region is critical (Salehpour et al., 2018). Besides, the energy and power densities reaching the tissue are the key parameters influencing the therapeutic effects of PBMT. Na et al. (2018) found that the responses of PBMT on osteoblasts, osteoclasts, and osteocytes differ under different energy densities. The "biphasic dose-response" indicates that the energy density must exceed a certain threshold to stimulate any biological effects (Mester et al., 1978). If so, after light attenuation in various tissues, the power density must be high enough to reach the depth of the cellular components responsible for tooth movement or OIIRR (Hamblin et al., 2015). When sufficient energy density reaches the tooth root, it is possible that excessive energy density may be detrimental to the gingiva or alveolar bone. Thus, the exact calculation and the effectiveness of energy density are critical issues for orthodontics that remain unresolved.

4.2 What is the real penetration depth of light applied in orthodontics?

Another important issue is the real penetration depth of PBMT in the related periodontal structures in orthodontics. Light penetration in tissues is determined by several optical parameters such as wavelength, irradiance, exposure time, beam spot, and pulse mode (Henderson and Morries, 2015). In skin (epidermis), the red-light spectrum (600–660 nm) is usually applied due to the low penetration depth (about 1–2 mm (Avci et al., 2013)) of light required, whereas NIR light is applied to deep tissue (about 1–3 mm) due to its higher penetration depth than red laser light (Anders and Wu, 2016). Su et al. (2020) reported that an 830-nm laser was more suitable than a 660-nm laser for deeper tissues such as the attached gingiva stimulation, suggesting that the real required power density on the attached gingiva can be reached by radiating NIR laser light from the outside (Na et al., 2018). Furthermore, the significant difference in light attenuation between soft and hard tissues indicates the need for reassessment of PBMT parameters when treating different orthodontic-related tissues such as gingiva, alveolar bone, and tooth root. Only in this manner can optimal clinical outcomes be precisely controlled and achieved. However, exact data regarding light penetration and distribution during PBMT in periodontal hard and soft tissues under real clinical conditions have been lacking. Moreover, the real distribution or value of laser irradiation when the light penetrates to the tooth root region has not been studied at all. Therefore, it should be emphasized that the quantitative re-measurement of energy density penetration to these periodontal structures should be performed to help increase the efficiency of evidence-based clinical research (Su et al., 2020).

4.3 What other exact parameters should be tested in PBMT-assisted orthodontics?

Also, new studies are needed to measure the effects of power density and application time of PBMT on the rate of tooth alignment. The exact parameters of optical spot size at surface tissue, irradiance, radiant exposure, total energy delivered, operator technique, and clinical outcomes should be systematically evaluated. Testing these important variables on large and varied treatment groups will provide insights into the threshold levels and energy optimal for the general population of orthodontic patients (Fig. 3).

5 Conclusions, unanswered questions, and further research

PBMT boosts energy by inducing self-organizing phenomena and tissue repair, alleviating physical pain or symptoms, and regulating the interplay of oxidative stress. In the field of orthodontics, PBMT has been used to prevent pathological conditions associated with orthodontics throughout the clinical treatment period.

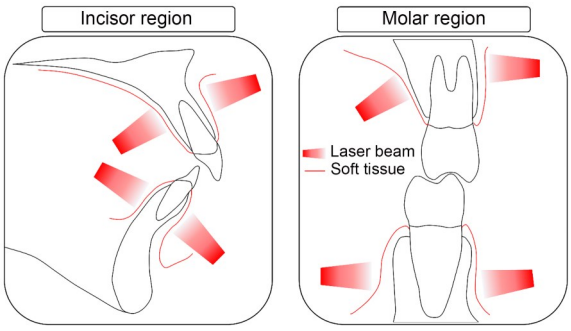

Fig. 3 Different regions of interest for light delivery to achieve photobiomodulation therapy (PBMT). The core concern is that the real energy density and penetration depth required for the light to reach the tooth root are currently unknown.

The therapeutic effects in PBMT-assisted orthodontics should be considered multifactorial, with positive reactions in blood vessels, mineralized tissues, non-mineralized tissues, nervous system, and immune system.

PBMT regulates OTM and alveolar bone remodeling at the same time, with the proper parameters. It has also been reported to induce an innovative modulation of immune cells related to OTM. Because cementoblasts interact with PBMT, application of red to NIR lights for OIIRR is highly attractive. The main problem so far is deciding the approach and the dose delivered to accomplish beneficial effects.

In this review, we have highlighted the difficulties and challenges of studying PBMT in orthodontics. PBMT-assisted OT still has not attained widespread acceptance, largely due to uncertainty about not only the molecular and cellular mechanisms of its action, but also the penetration depth and the real energy density that reaches the tooth root. As for research regarding OIIRR, whether PBMT effectively reaches the tooth root and what dose is delivered needs to be assessed. Moreover, the light parameters applied should be optimized by considering how the absorption of the light within the different target tissue decays, while maintaining the safety of all the host tissues. Careful attention to parameters is crucially important.

Future research should be carefully designed to reveal as completely as possible the cellular and molecular regulatory mechanisms underlying PBMT in the field of orthodontics. Such developments will serve to optimize the applied PBMT protocols to ensure the efficacy and safety of PBMT in conjunction with OT, in so-called PBMT-assisted orthodontics.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

Writing – original draft: Jiawen YONG and Sabine GRÖGR. Writing – review & editing: Julia VON BREMEN, Márcia MARTINS MARQUES, Andreas BRAUN, and Sabine RUF. Project administration and supervision: Xiaoyan CHEN, Sabine RUF, and Qianming CHEN. Conceptualization, data curation, and figures and tables processing: Jiawen YONG, Sabine GRÖGR, and Xiaoyan CHEN. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Jiawen YONG, Sabine GRÖGER, Julia VON BREMEN, Márcia MARTINS MARQUES, Andreas BRAUN, Xiaoyan CHEN, Sabine RUF, and Qianming CHEN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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