Under the spotlight

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Under the spotlight: mechanisms of photobiomodulation concentrating on blue and green light.

Short title: PBM with blue and green light.

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Abstract

Photobiomodulation (PBM) describes the application of light at wavelengths ranging from 400-1100nm to promote tissue healing, reduce inflammation and promote analgesia. Traditionally, red and near-infra red (NIR) light have been used therapeutically, however recent studies indicate that other wavelengths within the visible spectrum could prove beneficial including blue and green light. This review aims to evaluate the literature surrounding the potential therapeutic effects of PBM with particular emphasis on the effects of blue and green light. In particular focus is on the possible primary and secondary molecular mechanisms of PBM and also evaluation of the potential effective parameters for application both *in vitro* and *in vivo*. Studies have reported that PBM affects an array of molecular targets, including chromophores such as signalling molecules containing flavins and porphyrins as well as components of the electron transport chain. However, secondary mechanisms tend to converge on pathways induced by increases in reactive oxygen species (ROS) production. Systematic evaluation of the literature indicated 72% of publications reported beneficial effects of blue light and 75% reported therapeutic effects of green light. However, of the publications evaluating the effects of green light, reporting of treatment parameters was uneven with 41% failing to report irradiance (mW/cm^2) and 44% failing to report radiant exposure (J/cm^2). This review highlights the potential of PBM to exert broad effects on a range of different chromophores within the body, dependent upon the wavelength of light applied. Emphasis still remains on the need to report exposure and treatment parameters, as this will enable direct comparison between different studies and hence enable the determination of the full potential of PBM.

1 Introduction

The potential application of what is now known as Photobiomodulation (PBM) was first reported by Endre Mester in 1967 at Semmelweiss University, Budapest (1). Mester shaved the backs of mice and shone a ruby red laser emitting a wavelength of 694nm on the backs of a group of mice in order to investigate carcinogenicity. To his surprise, the hair on the backs of the irradiated mice grew back faster compared with that of the non-irradiated control group. He called this phenomenon 'photobiostimulation' and to date (January 2019), over 6000 papers have been published regarding the efficacy of PBM in treating a number of ailments by inducing analgesia (2), promoting wound healing (3) and reducing inflammation (4).

PBM encompasses a broad range of different terminologies including low level laser/light therapy (LLLT), cold laser therapy and phototherapy. Whilst the term PBM is the most recent addition to this list, and is currently the preferred Medical Subject Heading Term (MeSH) which encompasses both the stimulatory and inhibitory mechanisms involved, PBM is also often called photobiomodulation therapy (PBMT) which further adds to the list of terms for the same therapy. *Figure 1* gives an overview of PBM publications so far.

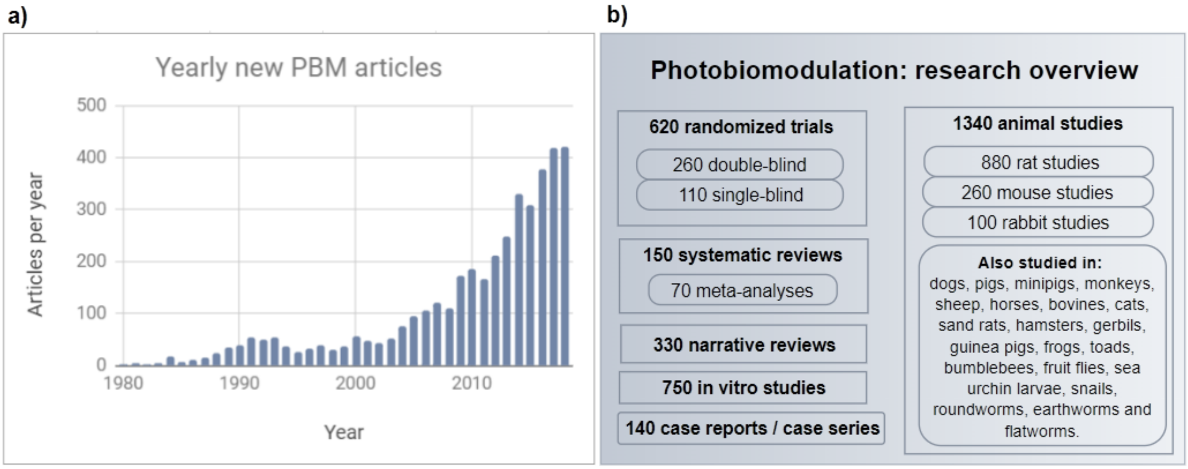

Figure 1: Preliminary PBM research overview based on a personal database of approximately 4,000 scientific articles related to PBM, compiled by manual PubMed and Google Scholar literature search using more than 80 different keywords (Supplementary file 1). (a) The amount of newly published PBM-related scientific articles has been increasing steadily during the 21st century, recently reaching a level of approximately 400 new articles per year. (b) The published research includes experimental in vitro studies and animal research. Also, a variety of randomized human trials and systematic reviews have been published so far.

Nonetheless, a growing number of observations suggests that specific wavelengths of electromagnetic radiation spanning the visible to near infra-red spectrum (400-1100nm) could lead to photo-physical and photochemical effects that can modulate major biological processes to achieve therapeutic goals such as cellular proliferation, mitochondrial function and inflammatory signalling (5) in various eukaryotic organisms, including humans. The majority of the literature reports the beneficial therapeutic effects of red and near infrared light (red: ~600-750, NIR: ~750-1100nm) in promoting tissue healing and reducing inflammation (6-14). Nevertheless, controversy still surrounds the application of PBM in practice, due to the lack of knowledge concerning how PBM elicits its molecular effects and also a poor understanding of photophysics and radiometric parameters which affect repeatability and reliability (15). The importance of reporting treatment parameters in a more consistent and reliable way has been emphasised in several articles and guidance for reporting radiometric properties has previously been published (15, 16) to little or no general avail (17-21). Indeed, those articles that have provided guidance for reporting radiometric parameters have commonly recommended the consistent reporting of up to ten key radiometric parameters (wavelength, power, irradiation time, beam area (at the skin or culture surface; this is not necessarily the same size as the aperture), radiant energy, radiant exposure, pulse parameters, number of treatments, interval between treatments and anatomical location) (22).

Whilst the majority of the literature supports the application of PBM using wavelengths between 600-1100 nm, wavelengths <600 nm are less commonly researched or reported. The use of blue light in particular (400-500 nm) is additionally surrounded by significant controversy relating to the premise that the margin between ‘safe’ blue light and potentially damaging ultraviolet (UV) light is not well defined.

UV light is divided into three discrete categories: UV-C (~100-280 nm), UV-B (~280-315 nm) and UV-A (~315-400 nm) (23). A common misconception is that all UV radiation is associated with DNA damage and mutagenesis (24). In fact, DNA damage is reportedly more efficient at UV-C and UV-B wavelengths with a peak absorption at 254 nm which corresponds to absorption by one of the nucleotide bases of DNA known as thymine, resulting in the formation of thymine dimers and rendering the DNA molecule inactive and unable to replicate. UV-A radiation on the other hand has a poor efficiency in inducing DNA damage, because it is not absorbed by native DNA or any of its bases. However, like red and NIR wavelengths , UV-A wavelengths are able to generate singlet oxygen (reactive oxygen species, ROS), and if the concentration of these radicals is in sufficient quantity, they can damage DNA (25). However, ROS in small quantities can be beneficial to cells and is commonly associated with proposed mechanisms of PBM (26). Indeed, the production of ROS is likely to be influenced by radiometric parameters, namely, wavelength, irradiance, dose and the number of photons delivered and again highlighting the importance of these parameters. Nonetheless, the use of wavelengths in PBM at 400 nm or lower should be utilised in practice with extreme caution.

In addition, another key caveat regarding the use of blue light for PBM is the low penetration depth of blue light through tissue compared with that of red or NIR light (27). Whilst blue light is cited to possess a penetration depth corresponding to an intensity decrease by 1/e (or approximately 63%) at 1mm, NIR light has a penetration depth of up to 5mm through tissue (28). However, there is a body of growing evidence supporting the use of PBM using blue light to reduce inflammation in superficial tissues (29) and promote wound healing (30), as well as being able to limit bacterial growth (31). Similarly, wavelengths within the green section of the visible spectrum (495-570 nm) have also gathered considerable interest. Published reports have indicated PBM effects for green light ranging from improved cellulite appearance (32) to reduced tissue swelling (33).

This review aims to evaluate the main primary and secondary mechanisms involved in light transduction in particular with blue and green wavelength of light. Secondly we focus on evaluation of current literature regarding the therapeutic efficacy of blue and green PBM.

2 Primary mechanisms of PBM

According to the Grotthuss–Draper law, commonly termed "the First Law of Photochemistry", photochemical reactions are dependent on the absorption of light by a system. Subsequently in this section, we provide a review of the literature of the most often proposed cellular photoacceptors (chromophores) that are reported to mediate the biological effects in PBM. We cover in particular the possible photoacceptors responsible for the transduction of blue and green wavelengths of light.

2.1 Cytochrome c oxidase

It has been proposed that PBM acts directly on the electron transport chain located in the mitochondrial membrane, specifically on the enzyme cytochrome c oxidase (CCO), also known as complex IV (34). The electron transport chain is comprised of five complexes: complex I (NADH-CoQ reductase), complex II (succinate dehydrogenase), complex III (cytochrome c reductase), cytochrome c oxidase and complex V (ATP synthase). Electrons are passed systematically down the chain of these complexes in order to generate a proton gradient to provide the activation energy for ATP synthase to catalyse the production of ATP (35). CCO is responsible for the conversion of molecular oxygen (O_2) to two molecules of water (H_2O). CCO contains two copper centres (Cu_A, Cu_B) and two hemes (cytochrome a, cytochrome a_3), which are involved in redox reactions within the enzyme.

The most widely accepted explanation for the beneficial photobiological effects of red and near-infrared light has been the "CCO theory" largely established by Tiina Karu in the 1990s. It posits that the light-cell interaction responsible for the observed PBM effects occurs initially at the redox-active copper atoms of CCO complex in the mitochondrial electron transport chain (36-39). The CCO theory was based on Karu's earlier findings in the 1980s, which showed that the position of peaks in the action spectrum measured for a variety of light-induced cellular changes (including DNA synthesis, RNA synthesis and cell attachment) were practically identical. These findings suggested that a universal cellular photoacceptor could be capable of absorbing those specific wavelengths and producing cellular changes affecting multiple cellular compartments. The observed peaks in the action spectrum were located within the blue (404 nm), red (620 and 680 nm) and near-infrared (760 and 820 nm) parts of the electromagnetic spectrum (36).

Various *in vitro* and *in vivo* studies have observed effects related to increased mitochondrial activity, including increased ATP levels, ROS levels, and mitochondrial membrane potential following irradiation. Interestingly, the time it takes for these effects to become evident varies from minutes to hours depending upon the experimental settings (40-42). Effects on mitochondrial function have also been demonstrated in animal (43, 44).

Interestingly there remains no clear understanding, however, of the exact events that occur within the electron transport chain or the enzyme CCO during light absorption to produce these effects. A multitude of hypotheses have been proposed, including photodissociation of nitric oxide (NO), changes in CCO redox properties with acceleration of electron transfer, superoxide generation and biochemical changes related to transient heating of irradiated photoacceptors (45). It has also been suggested that cytochrome c oxidation by CCO might be catalysed by red light irradiation (46). However, a later replication study failed to confirm this effect, and also raised doubts indicating that the initial positive results could have been experimental artefacts due to lack of detergent used for the CCO solubilization (47). An alternative explanation for the observed mitochondrial effects could also be an increased efficiency of CCO proton pumping (48). Regardless, the very limited amount of observations allows no firm conclusions to be made on the subject.

The hypothesis of NO photodissociation from CCO is relatively popular, and based on the understanding of the reversible inhibitory effects of NO on CCO (49, 50). There is some evidence suggesting that light can attenuate the mitochondrial inhibitory effects of NO (51) and some suggesting that NO can also inhibit the cellular effects of light (52). Light has been shown to increase NO levels in cells and blood (53). However, the evidence is not completely consistent. One experiment failed to demonstrate the protective effect of red light against NO-induced inhibition of mitochondrial respiration, but demonstrated partial protective effects with blue light (442 nm) (54). Another experiment with blue light (430 nm) recovered the mitochondrial function that had been inhibited by nitric oxide at the levels generated under septic conditions (55). Hence, demonstrating wavelengths outside the red and NIR range could be effective in modulating mitochondrial activity.

2.2 Opsins

Opsins are G-protein coupled receptors that have gained considerable interest in phototherapy research due to their excitation by blue or green light (56) (see *Figure 2*). Opsins can be divided into subcategories dependent upon the location they are expressed.

Opsin 1 (OPN1) and 2 (OPN2) expression is localised to the retina in the eye. OPN1 is expressed by cone cells, photoreceptors within the eye that recognise coloured light and can be subdivided into three types: OPN1 short wavelength (OPN1-SW), OPN1 medium wavelength (OPN1-MW) and OPN1 long wavelength (OPN1-LW). Conversely, OPN2 (rhodopsin) is expressed by rod photoreceptors, cells that recognise dim light and are important in peripheral vision (17). Three further opsins are expressed within the human body including OPN3 (encephalopsin), OPN4 (melanopsin) and OPN5 (neuropsin) all of which exhibit an absorption spectrum ranging between 380-496 nm. Notably, OPN expression has been detected throughout the body with the expression of OPN2, OPN3 and OPN5 being found in epidermal skin (57) and the expression of OPN3 in the brain (58).

A number of publications have explored the role of OPNs in blue light mediated PBM signalling both *in vitro* and *in vivo*. For example, *Regazetti et al*. (44) explored the effects of irradiation at 415 nm (50 J/cm²) or 465 nm (62.5 J/cm²) on the regulation of pigmentation through OPN signalling. The authors concluded that OPN3 could provide a novel target for regulating melanogenesis (59). *Oritz et al*. [45] also explored the effects of irradiation at 400 nm or 460 nm on the influence of signalling through OPN3 and OPN4 on pulmonary vaso-relaxation (60). The authors concluded that blue light induced vaso-relaxation and reduced arterial relaxation, through OPN3 and OPN4 signalling. A series of further publications have also evaluated the role of blue light in influencing opsin signalling to regenerate visual pigments (61) and promote hair regrowth (56). Notably, whilst there is a wealth of literature supporting the idea that opsin signalling influences responses both *in vitro* and *in vivo*, the molecular and cellular mechanisms of this signalling pathway are yet to be fully elucidated.

Current literature indicates that different opsins are coupled to different subtypes of G-proteins and hence induce different signalling pathways. For example OPN4 is coupled to Gq (activates the phospholipase C pathway) whilst other opsins (OPN1, OPN2, OPN3 and OPN5) are coupled to Go (inhibits adenylate cyclase), Gi (inhibits adenylate cyclase), Gt (transducing, activates phosphodiesterase 6) and Gs (activates adenylate cyclase) (62-64).

It is proposed that one downstream target of opsins is transient receptor potential (TRP) channels, particularly the TRPV1 subtype (capsaicin receptor), which has been cited to be activated by light (65). TRP channels are ligand-gated ion channels. When a stimulus is applied, the TRP channel opens and this enables a flood of calcium (Ca^{2+}) ions into the cytoplasm of the cell. In turn, Ca^{2+} then induces the activity of calcium/calmodulin dependent kinase II (CAMKII), which in turn induces the phosphorylation of the transcription factor, cAMP response element-binding protein (CREB) located in the nucleus. In turn, CREB induces a series of changes in gene transcription ultimately proposed to lead to some of the beneficial effects of PBM, seen both *in vitro* and *in vivo* (59, 64). *Figure 2* highlights the current proposed molecular mechanisms relating to how blue and green light PBM triggers opsin signalling. It has also been shown that increased activity of TRP channels induces ROS generation (66) and thus the activation of the Ras pathway, a key pathway involved in the modulation of the activity of small GTPases, ultimately leading to the modulation of calcium signalling and apoptosis (67). Hence, these mechanisms may explain current findings which indicate that blue light induces significant increases in ROS production (19, 68-72). However, evidence also suggests this may be due to the effects of blue light on mitochondrial activity, inducing increases in ROS production as a result of the stimulation of the electron transport chain (73). Therefore, whilst there is a wealth of literature suggesting that blue light induces the activity of opsins and TRP channels, the pathway that links these two complexes is yet to be elucidated. Therefore, further work is required to determine the molecular mechanisms involved.

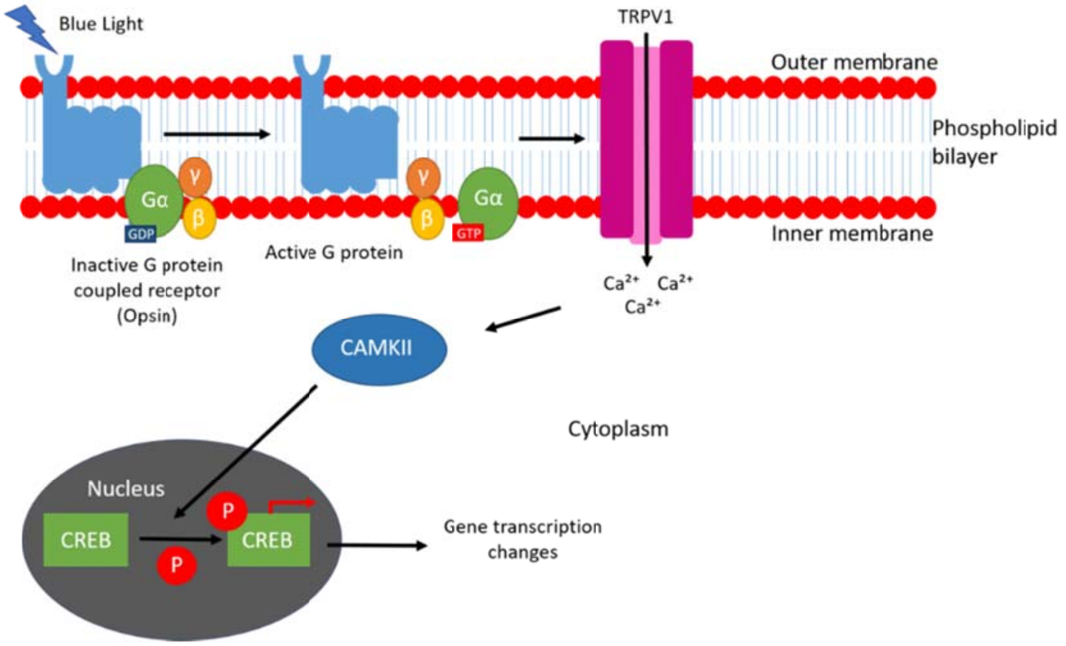

Figure 2: Possible molecular mechanism of blue light PBM in which an opsin receptor is activated by blue light, which induces a conformational change in the cis-retinaldehyde cofactor, allowing it to act as a guanine nucleotide exchange factor. This then enables the dissociation of guanosine diphosphate (GDP) from subunit Gα of the associated G protein and the binding of guanosine triphosphate (GTP). In turn this provides the activation energy to enable Gα to dissociate from Gβ and Gγ (the other subunits of the G protein) and enables signalling of Gα through a series of pathways including the cAMP and phosphatidylinositol pathways. In turn, signalling through these pathways is understood to induce the downstream activity of transient receptor protein (TRP) channels including the capsaicin receptor (TRPV1), which causes a flood of calcium ions into the intracellular space, resulting in the activation of calcium/calmodulin dependent protein kinase-II (CAMKII) and thus the phosphorylation of CREB (a transcription factor). CREB then induces a series of transcriptional events.

2.3 Flavins and flavoproteins

Blue light (400-500 nm) is known to excite flavins and flavoproteins including flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) (74). A well-characterised family of flavin containing complexes is called "cryptochromes" (75). Notably, cryptochromes have been widely documented to absorb blue light (76) and are proposed to be involved in the regulation of the circadian rhythm in mammals (77). Notably, FMN is also found within complex I of the electron transport chain and it is proposed that blue light provides the activation energy for FMN to catalyse the reduction of oxygen (O_2) to superoxide ($O_2^{-}\cdot$)(78). Hence, blue light is understood to induce increases in the levels of circulating ROS (79). Complex II is also a flavin (contains $FADH_2$) containing cytochrome (80), and also absorbs blue light (81). Hence, it is plausible that like red and NIR light, blue light could affect mitochondrial activity. Indeed, *Serrage et al* demonstrated that blue light (400-450 nm, 5.76 J/cm^2) was as effective in inducing increases in mitochondrial activity as NIR light (810 nm, 5.76 J/cm^2 (82)). However, further work is required to validate this hypothesis to determine whether blue light can modulate the activity of flavin containing complexes of the ETC.

2.4 Porphyrins

Porphyrins, a group of heterocyclic organic compounds found complexed to proteins ranging from haemoglobin (83), to cytochrome p450 enzymes (84), to complex IV of the electron transport chain (CCO) (85) are known to possess a typical Soret band at 400-420m and hence possess the ability to absorb blue light (86). Blue light of wavelengths between 400-415nm induces the π to π* transition in porphyrin rings (87). Wavelengths between 400-420nm could oxidise porphyrin containing heme groups (found within complex IV), whilst a wavelength of 450 nm could induce CuB (a component of complex IV) reduction hence inducing complex IV oxidation or reduction respectively (88).

When evaluating the influence of PBM on mitochondrial electron transport chain activity, Evgeny et al concluded that blue light application (442 nm, 30 mW/cm², 3 J/cm²) induced significant increases in complex IV activity and cell metabolic activity, compared to NO which inhibited cell responses (54). Also, Ankiri et al reported that complex IV possesses a maximal absorption at 410 nm and hence this could be due to porphyrins contained within the complex (89). Similarly, Del Olmo-Aguado et al evaluated the effects of blue light on retinal ganglion cell mitochondrial activity. The authors concluded that blue light upregulated the activities of complexes III, IV and V of the electron transport chain, but also induced significant reduction in cell viability, and induced apoptosis (90). These data indicated a possible role of blue light in affecting porphyrin-containing complexes of the electron transport chain.

Cytochrome p450s (CYPs) are also porphyrin-containing complexes that have gained interest in phototherapy research, as their activation by blue light has been cited (91). CYPs are a family of proteins that contain heme and are vital for drug metabolism. The p450 element of the cytochrome refers to the protein absorption spectra, since CYPs exhibit a maximal absorption peak at 450 nm when bound to carbon monoxide (92). CYPs are membrane bound proteins and can be located either in the endoplasmic reticulum or the inner mitochondrial membrane. Mitochondrially-located CYPs including cytochrome P450 reductase, transfer electrons from nicotinamide adenine dinucleotide phosphate (NAPDH) and thus could play a role in ETC activity (93).

Interestingly, Becker et al evaluated the effects of blue LED irradiation (453 nm, 23 mW/cm², 41.4 J/cm²) on the proliferation and gene expression of keratinocytes, and found that irradiation induced a decrease in cell proliferation. However, the authors also reported that blue light induced significant increases in the transcription of electron transport chain-related genes, cytochrome P450-related genes and also genes relevant to steroid hormone synthesis (94). Becker and colleagues also reported that genes relevant to inflammation were significantly down-regulated due to this exposure, and proposed that this may be due to the induction of steroid hormone biosynthesis via the CYPs pathway. Hence, these data provide an additional hypothesis as to how blue light PBM could affect cellular signalling.

2.5 Nitric oxide (NO)-containing compounds and nitrite reductases

In addition to the NO photodissociation hypothesis (*see Section 2.1*), there is some literature suggesting that light-mediated effects are related to the synthesis combined with, or without, the release of NO due to light exposure.

Firstly, CCO has also been shown to function as a nitrite reductase, thus being able to produce NO locally in the mitochondria. This nitrite-dependent NO synthesis in isolated mitochondria has been demonstrated to increase by yellow light (590 nm), without any concomitant increase in mitochondrial oxygen consumption (100). These data suggest that light-induced cellular effects do not necessarily have to be coupled with changes in mitochondrial respiration.

Secondly, there is also evidence that certain wavelengths of light can induce the release of NO from photolabile sources of stored NO, such as nitrosyl hemoglobin (HbNO), nitrosyl myoglobin (MbNO), S-nitrosothiols (RSNO) or dinitrosyl iron complexes (DNIC). This effect is reportedly much greater with red light (670 nm) compared with some longer wavelengths that have been examined, including 740 nm and 830 nm (101, 102). NO release from some S-nitrosothiols (RSNOs) has also been demonstrated with ultraviolet (340 nm) and green (545 nm) wavelengths of light (103). Blue light (420-453 nm) has been shown to be capable of eliciting NO release from S-nitrosoalbumin (SNO-Alb), HbNO and aqueous nitrite solutions (104) (105).

3 Secondary mechanisms of PBM

From evaluation of the possible hypotheses of the primary mechanisms of PBM, it is apparent that several pathways converge on the induction of the same signalling molecules; i.e. ROS. Therefore, this section of the review evaluates the possible effects of PBM on ROS-related pathways. It is prudent to highlight this review evaluates the effects of PBM on a number of downstream targets. PBM may modulate a variable number of these targets, dependent upon the dose of light used, the wavelength employed and also the in *vitro/in vivo* model light is applied to. The same is true for the primary mechanisms of PBM, illustrated in section 2.

3.1 Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)

ROS production instigates a signalling cascade ultimately leading to the phosphorylation of IκB, an inhibitor of the pro-inflammatory transcription factor NFκB. In its inactive state IκB is bound to NFκB in the cytoplasm, however, once phosphorylated, IκB dissociates from NFκB and is targeted to the proteasome for degradation. This then allows the translocation of free NFκB to the nucleus binding to DNA, and initiation of a series of gene transcription changes, mRNA production and potential downstream expression of key cytokines, chemokines and growth factors including interlukin-8 (IL-8), IL-6 and vascular endothelial growth factor (VEGF (106-109)).

A number of authors report the modulation of NFκB by light. For example, Chen et al reported that irradiation at 810 nm and radiant exposure of 0.003 J/cm² induced the activation of NFκB through increased ROS production induced by light (40). Similarly, Curra et al evaluated the effects of a 660 nm diode laser on NFκB protein levels using an *in vivo* hamster model of oral mucositis (110). The authors concluded that PBM reduced disease severity through the activation of the NFκB pathway. Conversely, PBM reportedly may reduce NFκB activation and subsequently reduce the expression of pro-inflammatory mediators in several diseases (111). Interestingly, de Farias Gabriel also reported that application of 660nm (4J/cm²) modulated NFκB activation leading to keratinocyte migration, resulting in improved wound healing in a rat model for oral epithelial wound healing (112). Hence, modulation of NFκB not only affects pathways related to inflammation but also those influencing wound healing.

Another gene directly regulated by NFκB activation is cyclooxygenase-2 (COX-2). Its main role is to catalyse the conversion of arachidonic acid to prostaglandins including PGE2 (113). PGE2 has then been reported to be involved in the activation of a variety of pathways including cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) signalling (114, 115).

To stimulate activity of the cAMP pathway, PGE2 binds to prostaglandin E_2 receptor 4 (EP4). EP4 is a GPCR coupled to a stimulatory G protein (Gs). On binding, PGE_2 induces a conformational change activating Gs, which then activate adenylyl cyclase to catalyse the conversion of ATP (a second molecule whose production is increased by PBM) to cAMP (116). cAMP then induces the activation of protein kinase A (PKA) leading to the phosphorylation of transcription factors including CREB (117). Several authors have reported the effects of PBM on NFκB induced signalling. Lim et al reported that irradiation at 635 nm modulated both COX2 and PGE_2 protein expression (118). Current literature also indicates the effects of PBM on a series of signalling proteins/molecules implicated in this pathway, including CREB (119).

Another key molecule modulated by NFκB signalling is VEGF, a growth factor central to the promotion of angiogenic events (120, 121). Literature reports indicate that activation of EP4 induces the upregulation of the expression of VEGF and several authors have reported the effects of PBM on VEGF expression and activity. Tim et al concluded that 830 nm irradiation of male Wistar rats with induced bone defects induced significant increases in COX2 and VEGF expression (122), and das Neves et al also reported an increase in VEGF expression following irradiation of male Wistar rats with transverse *rectus abdominis* musculocutaneous flap at 660 nm or 830 nm (107). Cheng et al also reported application of 450nm light induced significant increases in COX2 and VEGF in a dose dependent manner (0.001-0.1J/cm²) relative to lipopolysaccharide treated microglial cells (123). Hence, the effects of blue, red and NIR light on NFκB associated pathways have been reported in a handful of studies. However, none to date have evaluated the effects of green light on these pathways. Hence, it will be prudent in the future to evaluate the wavelength and dose dependent effects of light on downstream targets of PBM.

3.2 Transforming growth factor-β (TGFβ) signalling

Transforming growth factor-β (TGF-β) molecules represent a family of growth factors in which there are three mammalian isoforms: TGF-β1, TGF-β2 and TGF-β3. They have been extensively documented for their crucial role in wound healing processes (124) and in promoting angiogenesis and fibrosis (125). They are secreted by a variety of cell types in inactive form as latent-TGF-β in which a TGF-β dimer held together by disulphide bonds is non-covalently bound to a pro-domain known as latency associated peptide (LAP). This complex is also commonly referred to as small latent complex (SLC). The dissociation of this complex to enable activation of free TGF-β can be induced by a range of activation stimuli including heat and pH changes (126, 127). Notably, one mechanism of particular interest here is that PBM could induce activation of TGF-β signalling (128-130). In a recent study Arany et al employed a laser emitting a wavelength of 904 nm with radiant exposure outputs ranging from 0.1-6 J/cm² and concluded that PBM was able to activate latent-TGFβ1 (131). It has subsequently been hypothesised that light induces an increase in levels of ROS including superoxide (O_2^-) (132) which interacts with the methionine 253 amino acid residue on LAP (133). This, in turn, then induces a conformational change in LAP, enabling its dissociation from TGF-β enabling it to bind with high affinity to its cell-surface receptors, including TGF-β receptors (TGFβRI, TGFβRII and

TGFβRIII). Notably, TGFβRIII binds TGF-β1 and then transfers it to TGFβRI and TGFβRII, which are both serine/threonine kinases. In turn, these receptors phosphorylate transcription factors including "small mothers against decentaplegic" (Smad). Once phosphorylated Smad2 and Smad3 bind Smad4, the complex then translocates to the nucleus and interacts with transcriptional coactivators including p300, a nuclear scaffolding protein. This signalling then enables the binding of the complex with the Smad binding element, leading to the transcription of multiple target genes (134).

Interestingly, several authors have also provided evidence for an increase in the activity of Smad proteins following irradiation. The Smad family is comprised of the receptor Smads (Smad-1, -2, -3, -5 and -8/-9), the inhibitory Smads (Smad-6 and -7) and the co-Smad, Smad-4. Hirata et al found that irradiation at 805 nm induced increases in phosphorylation of Smad-1/-5/-8 (135). Interestingly, Dang et al also found an increase in phosphorylated Smad proteins, specifically Smad-2 and Smad-4 following irradiation at 800 nm (136). Similarly, Yuchao et al reported application of 475nm light induced significant increases in Smad2 phosphorylation. Providing evidence that blue light may also show efficacy in modulating TGFβ signalling (137). Hence, these data indicate the possible involvement of TGF-β signalling through Smad proteins during the transduction of the molecular effects of PBM. However, other pathways are also induced by TGF-β signalling including the mitogen associated protein kinase pathway (MAPK (138)). Therefore, it will be interesting to determine how PBM, modulates TGF-β signalling through these interlinked pathways, and which wavelengths of light can induce which pathway.

3.3 Nuclear factor erythroid 2–related factor 2 (Nrf2) signalling

Nrf2 is a protein in the "basic leucine zipper protein" (bZIP) family and is implicated in regulation of the expression of antioxidant proteins (139). Increases in ROS production lead to the dissociation of Nrf2 from its inhibitor, Keap1, targeting it for degradation. This enables Nrf2 to translocate into the nucleus and induce the transcription of antioxidant genes, due to the binding of Nrf2 to antioxidant response elements (AREs). To date, only a handful of studies have evaluated the effects of PBM on Nrf2 expression and activity. Interestingly, Sohn et al reported an increase in Nrf2 gene expression following irradiation at 635 nm (140). Similarly, Trotter et al also found that application of blue light induced significant increases in Nrf2 expression *in vitro* (141). This acts as a feedback mechanism following NFkB activation so the interaction of these two pathways may be important in PBM modulation of chronic inflammatory diseases. Indeed a differential upregulation of Nrf2 may be important in such diseases. However, further work will be required to fully dissect the effects of blue and green light on Nrf2 signalling.

3.4 Mitogen activated protein kinase (MAPK) signalling

Mitogen activated protein kinases (MAPKs) are a family of serine/threonine protein kinases that play an essential role in the regulation of a diverse number of cellular activities ranging from cell signalling to cell death. There are three subgroups of MAPKs including extracellular signal regulated kinases (ERKs including ERK-1 and ERK-2), p38 MAPKs (p38α, p38β, p38γ and p38δ) and c-Jun-N-terminal kinases (JNKs including JNK-1, JNK-2 and JNK-3). The three subgroups of MAPKs are finely regulated by a series of different kinases. Their activation is initiated by first the induction of MAPK kinase kinase (MAP3K) which in turn phosphorylates MAPK kinase (MAP2K). This then finally leads to the phosphorylation and activation of the MAPKs. Each MAPK is regulated by specific kinases as described below:

3.4.1 Extracellular-regulated kinase (ERK) signalling

The activity of the ERK pathway can initially be induced by receptor tyrosine kinases including TGFβR1, a member of the TGFβ signalling pathway previously proposed to play a role in transducing the effects of PBM (131). The activation of TGFβR1 enables the downstream activation of Ras-activating protein, which catalyses the phosphorylation of inactive Ras bound to guanosine diphosphate (Ras-GDP) to form active Ras guanosine triphosphate (Ras-GTP). Ras then phosphorylates Raf, which in turn phosphorylates MEK, which ultimately induces phosphorylation of ERK, culminating in gene transcription changes that lead to proliferation, differentiation or apoptosis. Interestingly, several authors have reported the effects of PBM on signalling molecules involved in this pathway. In their study, Kim et al evaluated the response of human outer root sheath cells to PBM at wavelengths of 415 nm, 525 nm, 660 nm or 830 nm (142). Notably they found that PBM induced an increase in ERK phosphorylation.

3.4.2 p38 MAPKs

The p38 MAPK pathway is activated by an array of stimuli including inflammatory cytokines, heat shock or ligands for G-protein coupled receptors (GPCRs). These stimuli induce the activation of an array of MAP3Ks including TGFβ activated kinase-1 (TAK1). Activation of MAP3Ks enables the phosphorylation of MEK3 or MEK6. In turn, these kinases phosphorylate members of the p38 family, inducing their activation and hence a series of downstream effects including modulation of cytokine production and apoptosis (143).

Several authors have reported the effects of PBM on p38 MAPK signalling. Interestingly, both Kim et al and Chu et al concluded that red light PBM induced increased p38 phosphorylation and therefore increases in the activity of this pathway (142, 144). However, a further study concluded that following application of red light, there was a decrease in p38 phosphorylation (145). The difference in response may be due to the difference in radiant exposures employed in the different studies. For example, the authors reporting an increase in p38 phosphorylation when using a light source with a radiant exposure output of less than 12 J/cm², whilst, a radiant exposure of 18 J/cm² induced a decrease in p38 phosphorylation. Hence, this may show a biphasic dose response in which lower doses of light induce stimulatory effects whilst higher doses cause inhibitory effects. However, further work will be required to evaluate this hypothesis, particularly with reference to blue and green light.

3.4.3 c-Jun N-terminal kinase (JNK)

The JNK pathway is activated by an array of stimuli including cytokines, growth factors and the ligation of specific receptors. In turn these stimuli activate some of the same MAP3Ks induced in the p38 MAPK pathway including apoptosis signal-regulating kinase 1 (ASK1), mitogen-activated protein kinase kinase kinase (MEKK1) and mitogen-activated protein kinase kinase kinase 3 (MEKK3). In turn, these MAP3Ks can phosphorylate either MKK4 or MKK7, Mitogen-activated protein kinase kinases (MAP2Ks) specific to the JNK pathway. MKK4 and MKK7 can also activate MKK3 and 6, enabling the activation of the p38 MAPK pathway (146).

Interestingly, Silva et al explored the effects of 780 nm light at a radiant exposure of 10 J/cm² on JNK phosphorylation of mice with diet-induced obesity. They concluded that PBM induced a significant reduction in JNK phosphorylation and hence could prove useful in treating effects induced by a high fat diet (147). Similarly, in a mouse model for depression, Salehpour et al evaluated the effects of 810 nm light at a radiant exposure of 33.3 J/cm² and found that PBM induced reductions in JNK phosphorylation and other members of the MAPK signalling pathway including p38 (148). The authors also reported that treatment induced decreases in the serum levels of key pro-inflammatory cytokines, including Tumour necrosis factor-α (TNF-α). Hence, these data provide evidence that PBM could modulate JNK signalling and therefore downstream effects, including the production of pro-inflammatory cytokines. However, the effects of blue and green light on JNK signalling are yet to be explored, hence future work may endeavour to evaluate the wavelength dependent effects of PBM on the JNK pathway.

4 In vitro and in vivo application of blue and green light PBM therapy

4.1 Introduction

Whilst a number of reviews have been published detailing the possible therapeutic efficacy of red and NIR PBM (132, 158), none to date have extensively explored the effects of blue or green light either *in vitro* or *in vivo*. Hence, this section investigates the potential of blue and green light PBM in therapeutic application to determine whether these short wavelengths of light could be efficacious.

4.2 Methods

To assess literature surrounding the effects of green and blue light PBM, a systematic review of relevant literature was performed using Scopus. The Scopus database was employed as a means to undergo key word searches to provide an overview of literature regarding the effects of blue and green light PBM. Future work may endeavour to use a broader range of databases including MEDLINE and PubMed to evaluate the effects of blue and green light PBM.

The two searches outlined in *Figure 3* were performed separately and a series of key terms and wavelengths were included to refine the search. Following literature searches, the results were filtered for 'articles only' and for articles published within the past ten years (25/1/2008-25/1/2019). This timeline was selected to ensure a manageable sample of articles were included in the review, where key MeSH accepted terms were relevant to articles (including LLLT and PBM) investigated. Key words described in *Figure 3* were input into the Scopus database and systematic evaluation ensured irrelevant articles were excluded from the review. For example, those reporting the use of PBM but using biological assays including 'Alamar blue' (cell metabolic activity assay) or 'trypan blue' (a vital stain used to differentiate between live and dead cells *in vitro*) were not included as they did not specifically report the effects of blue light *in vitro* or *in vivo*. Other exclusion criteria included elimination of articles that reported the effects of lasers on remodelling tissue at a high power. For example, photoselective vaporisation commonly uses lasers emitting green light and the procedure involves the burning away of excess tissue to enable normal urine flow through the prostate (159). As PBM is commonly defined as modulation of tissue response rather than removal of tissue, these articles were excluded. Review articles were also excluded from analysis. Articles selected for review were then assessed in terms of the reporting of light properties (including wavelength, irradiance, radiant exposure, exposure time and beam area), the application of the light source (i.e. *in vitro, in vivo* or *ex vivo*) and the outcome of each study (therapeutically beneficial or harmful).

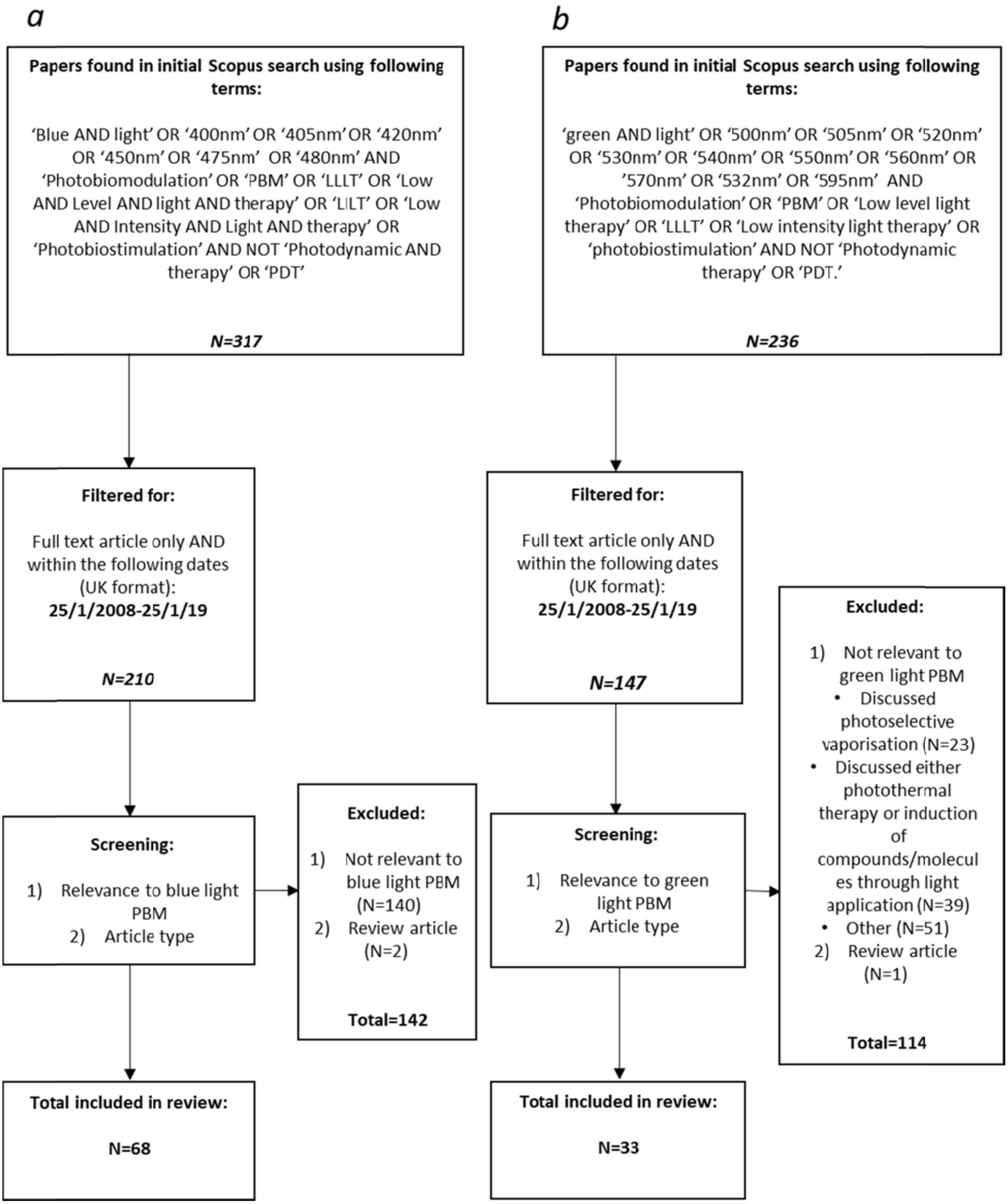

Figure 3: Flow chart describing the strategy employed to identify relevant articles illustrating the effects of a) blue light and b) green light PBM.

4.3 Results

A Scopus search was undergone to identify publications citing key words illustrated in *Figure 3* and published within the following time frame: 25/1/2008-25/1/2019. This would then enable identification of key parameters that may induce beneficial effects *in vivo*.

4.3.1 Blue light PBM

An initial search employing the Scopus database resulted in 317 articles citing the search terms described in *Figure 3a,* articles were then subsequently filtered and screened, and it was concluded that 68 articles were suitable for further review (17-21, 29-31, 64, 68-73, 79, 89, 160-210).

Of the articles reviewed, 72% (49/68) reported a positive effect following the application of blue light, with 7% (5/68) reporting negative effects and 21% (14/68) reporting no significant effect. Whilst, the majority of articles within this review reported the effects of PBM on tissue, a handful also evaluated the bactericidal effect of blue light PBM (3/68 (167, 192, 199)). Although, the mechanism of blue light in inducing bacterial cell death is not a focus of this current review, we felt it important to highlight this as a further application of PBM which has therapeutic application (211). Notably however, the parameters required to induce a bactericidal effect (>55J/cm²) are much higher than those applied to induce tissue effects (<55J/cm²). Hence, when exploring possible beneficial parameters for tissular applications, articles evaluating the antimicrobial properties of blue light were excluded.

When evaluating the recording and reporting of treatment parameters, it was found that 68% (46/68) of articles failed to report any information regarding light characterisation procedures and relied entirely on the manufacturers reported values. Of the other 22 articles, the light characterisation procedures reported were minimal, where the majority reported either analysis of power or irradiance output of a light source (12/22 (68, 73, 160, 164, 168, 169, 174, 179, 195, 197, 204, 206)). Interestingly, these figures are similar to those reported by Hadis et al in which 76% of articles evaluated failed to report the use of any light characterisation techniques (15). A series of other key parameters were also not reported in full by authors including irradiance (29%, 20/68), exposure time (34%, 23/68), radiant exposure (38%, 26/68) and beam area (82%, 56/68).

From those articles reporting parameters, median values could be calculated. For example, for those articles reporting a positive effect of PBM, a median value of radiant exposure of 7.8 J/cm² (range: 1.5-90J/cm²) was determined. In fact, 63% (17/27) of articles reporting both positive effects of PBM used radiant exposure values <10 J/cm². Interestingly, only one article reported a beneficial effect of PBM on tissue at a radiant exposure >55 J/cm² (196). For articles reporting negative effects of PBM, a median radiant exposure of 7.5 J/cm² (range: 3-183.43J/cm²) was calculated. However, of the 5 articles reporting a negative effect of PBM only 4 reported radiant exposure values, 3 of which were >30 J/cm². Interestingly of those reporting no significant effect of blue light, an average radiant exposure of 8J/cm² was reported (range: 0.378-80J/cm²). In which, 4/7 of those articles studied reported the radiant exposure utilised in experimentation. Hence, it is apparent from these findings that further work is required to gain a better understanding of the biphasic effect of blue light and also to demonstrate the importance of recording and reporting treatment parameters. *Table 1* summarises the studies evaluated in this review including the study type, reported parameters and outcomes.

Table 1: Citations identified from a review of the literature evaluating the effects of blue light PBM using the following search terms: 'Blue AND light' OR '400 nm' OR '405 nm' OR '420 nm' OR '450 nm' OR '475 nm' OR '480 nm' AND 'Photobiomodulation' OR 'PBM' OR 'LLLT' OR 'Low AND Level AND light AND therapy' OR 'LILT' OR 'Low AND Intensity AND Light AND therapy' OR 'Photobiostimulation' AND NOT 'Photodynamic AND therapy' OR 'PDT'

Citation	Light Source	Dose	Study type	Conclusion
1. **Mignon et al, 2018(19)**	**Source: LED** **Wavelength (nm):** 450, 490, 550, 650 and 850 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 30 (450 nm), 30 (490 nm), 30 (550 nm), 7 (590 nm), 60 (655 nm), 80 (850 nm) **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):** 0-250 **(dependent upon wavelength)**	*In Vitro:* Human reticular and papillary dermal fibroblasts	450nm light at 30J/cm² induced 50% reductions in cell metabolic activity. 450nm and 500nm induced stronger inhibitory effects on reticular DFs vs papillary DFs. 450nm light induced increases in intracellular ROS production. Blue and NIR light induced changes in some similar gene groups. However, more genes were downregulation following irradiation with blue light compared to NIR. Blue light also downregulated expression of genes associated with the TGF-β pathway.
2.Tani et al, 2018 (191)	**Source:** LED **Wavelength (nm):** 405, 635, 808 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 12.59 **Time (s):** 30 **Energy (J):** **Radiant exposure (J/cm²):** 0.378	*In Vitro:* human osteoblasts and human mesenchymal stromal cells.	Blue light had no significant effect on molecular signalling. 635nm light could be effective in promoting or improving bone regeneration as shown through molecular analysis.
3.Priglinger et al, 2018 (197)	**Source:** LED **Wavelength (nm):** 475, 516, 635 **Power (mW):** **Frequency (Hz):** pulsed 2.5 (pulse rate 50%) **Spot area (cm²):**	**Irradiance (mW/cm²):** 40 **Time (s):** 600 **Energy (J):** **Radiant exposure (J/cm²):** 24	*In Vitro:* Stromal Vascular fraction cells	Blue, green and red light did not have a cytotoxic effect on cells. Red and green light induced significant increases in vascular endothelial growth factor expression.
4.Falcone et al, 2018 (175)	**Source:** LED **Wavelength (nm):** 453 **Power (mW):** **Frequency (Hz):** 5% duty cycle, 100Hz **Spot area (cm²):**	**Irradiance (mW/cm²):** 10 (cw), 200 (pulsed) **Time (s):** 1800 **Energy (J):** **Radiant exposure (J/cm²):** 18	*In Vivo:* effects on inflammation and skin barrier recovery.	Reduced IL-1α following irradiation.
5.Veleska-Stevkoska and Koneski, 2018 (21)	**Source:** LED **Wavelength (nm):** 410 and 470 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):** 1.25	**Irradiance (mW/cm²):** 750 **Time (s):** 10-20 **Energy (J):** 50-100 **Radiant exposure (J/cm²):** 7.5-15	*In Vivo:* Haemostasis in oral surgery (bleeding from tooth extractions).	Blue light shortens bleeding time from extraction socket.
6. **Castellano-Pellicena et al, 2018 (17)**	**Source:** LED **Wavelength (nm):** 447, 505, 530, 655 and 850 (24 well) or 453, 656 (ex vivo) **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** **Time (s):** 1200 (24 well) **Energy (J):** **Radiant exposure (J/cm²):** 453 nm- 2, 656 nm- 30	*In vitro and ex vivo:* Keratinocytes and human skin epidermis	Blue light stimulated metabolic activity of cultured keratinocytes. Low levels of blue light reduced DNA synthesis and stimulated keratinocyte differentiation. Level of differentiation induced by blue light was reduced in opsin 3 (OPN3) knockdown, suggesting OPN3 may be Important in blue light induced restoration of barrier function.
7. **Fekrazad et al, 2018(176)**	**Source:** Laser **Wavelength (nm):** 810, 660, 532, 485, *combinations:* 810-660, 810-485, 660-532, 660-485 **Power (mW):** 30-200 (dependent on wavelength) **Frequency (Hz):** **Spot area (cm²):** 0.113-0.18	**Irradiance (mW/cm²):** 266 (blue), 266 (green) 167 (red), 1333(NIR) **Time (s):** 3-24 (dependent upon wavelength) **Energy (J):** **Radiant exposure (J/cm²):** 4 (8 for combination)	*In vitro:* Mesenchymal stem cells.	Cartilage markers were upregulated by 810nm and 810-485nm light. Red and blue-green irradiation induced expression of COL1. Blue, blue-green and green light irradiation reduced osteocalcin expression. Stimulatory effects on osteogenesis were seen for red and near infra-red lasers but green light had inhibitory effects. Blue light was not reported to induce inhibitory effects. Cons: Parameters differ considerably from one wavelength to the next, particularly when evaluating combination treatments. Making results of which wavelength is most effective questionable.
8. **Rocca et al, 2018 ~~(183)~~ (198)**	**Source:** diode laser (450 nm, 635 nm, 808 nm, Er:YAG laser (2940 nm) **Wavelength (nm):** 2940,	**Irradiance (mW/cm²):** 280 (808 nm), 280 (450 nm), 1000 (63 5nm) **Time (s):** 60 (2940 nm),	*In Vivo:* Human	The diode lasers proved more effective than the Er:YAG in reducing pain scores over a 7 day period. 635nm had the most immediate

	808, 450, 635 **Power (mW):** 200 (635 nm), 1500 (808 nm), 500 (450nm) **Frequency (Hz):** 20 (Er:YAG) **Spot area (cm²):**	3x30 (635 nm), 60 (808 nm), 60 (450 nm) **Energy (J):** **Radiant exposure (J/cm²):** 76.43 (Er:YAG), 36 (635 nm), 50 (808 nm), 17 (450 nm)		effect, but there was no significant difference pain score using the 3 diode lasers after 7 days.
9. Wang et al, 2018 (208)	**Source:** LEDs **Wavelength (nm):** 405 **Power (mW):** 200 **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 20 **Time (s):** 900 **Energy (J):** **Radiant exposure (J/cm²):** 12	*In Vitro:* Whole blood samples (human)	No significant change in the absorption spectra exhibited by blood following irradiation.
10. Kim et al, 2017(187)	**Source:** LEDs **Wavelength (nm):** 410, 630, 830 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):**	*In Vivo:* Mouse model	Wound closure percentage over 10 days was greatest when an 830nm LED used. Increased TGF-β and collagen 1 but downregulated SMAD7.
11.Rohringer et al, 2017 (68)	**Source:** LED **Wavelength (nm):** 475, 516, 635 **Power (mW):** **Frequency (Hz):** 50% pulse rate, 2.5Hz **Spot area (cm²):**	**Irradiance (mW/cm²):** 80 **Time (s):** 600 **Energy (J):** **Radiant exposure (J/cm²):** 24	*In Vitro:* Human umbilical vein endothelial cells	Red and green light induced proliferation and migration of endothelial cells whilst blue light had no significant impact. Blue light only induced significant increases in ROS production. NOTE: irradiance and irradiation time values do not correlate with fluency. Cells irradiated at 20% confluency – may explain negative effects of blue light.
12.Wang et al, 2017 (64)	**Source:** LED array (415 nm), Filtered lamp (540 nm), Diode laser (660 nm and 810 nm) **Wavelength (nm):** 415, 540, 660, 810 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):** 4	**Irradiance (mW/cm²):** 16 **Time (s):** 188 **Energy (J):** **Radiant exposure (J/cm²):** 3	*In vitro:* human adipose-derived stem cells.	Blue and green light induce significant increases in intracellular calcium and ROS, reduce mitochondrial membrane potential, lower intracellular pH and reducing cellular proliferation. Red and NIR light have the opposite effect. Labelled fluency as irradiance. Different delivery systems may alter light delivery (coherent vs non-coherent light sources).
13.Wang et al, 2017(69)	**Source:** LED **Wavelength (nm):** 480, 560, 660 and white (400-750) **Power (mW):** 3000 **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 250 **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):**	*In vitro and in vivo:* Irradiated fertile broiler eggs and isolated skeletal muscle and satellite cells.	Green PBM promoted muscle growth and satellite cell proliferation through insulin growth factor-1 signalling in late embryogenesis.
14.Choe et al, 2017 (171)	**Source:** LED **Wavelength (nm):** 622, 535, 462 **Power (mW):** 24000 **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 16 **Time (s):** 600-1800 (daily) **Energy (J):** **Radiant exposure (J/cm²):**	*In Vitro*: HeLa cells (cancer cell line).	Blue light and high frequency ultrasound induced significant reductions in cell density when compared to red and green light combined with ultrasound. This could be beneficial in alleviating cancer cell proliferation.
15.Buscone et al, 2017 (170)	**Source:** LED **Wavelength (nm):** 453, 689 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):** 3.2	*In vitro and ex vivo:* hair growth and outer root sheath cells.	Blue light at low radiant exposure stimulate hair growth ex vivo.
16. Santos et al, 2017 (70)	**Source:** LED **Wavelength (nm):** 405 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):** 0.27	**Irradiance (mW/cm²):** 300 **Time (s):** 30-60 **Energy (J):** **Radiant exposure (J/cm²):**	*In vitro:* Subventricular zone (SVZ) cell culture.	Blue light induced transient increases in ROS, causing increased neuronal differentiation and increases retinoic acid receptor levels. The effects are heightened with the addition of light reactive nanoparticles.
17. Fekrazad et al, 2017(18)	**Source:** laser: GaAs (405 nm, 532 nm), InGaAlP (660 nm) and GaAlAs (810 nm) **Wavelength (nm):** 405, 532, 660, 810 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):** 1	**Irradiance (mW/cm²):** 200 **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):** 1.5	*In Vivo:* Male Wistar rats (n=60)	Green, blue, red and infrared light irradiation may accelerate healing process.
18.Lee et al, 2017(190)	**Source:** LED **Wavelength (nm):** 410, 630, 830 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 205 (405nm), 172 (630), 50 (830) **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):**	*In Vitro:* Keloid fibroblasts	Blue did not affect cell viability. COL1 gene and protein expression decreased significantly after irradiation with blue light and may be effective in preventing keloid formation.

		10		
19. Alba et al, 2017 (29)	**Source:** LED (470) and laser (660) **Wavelength (nm):** 470 and 660 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** **Time (s):** 180 (470), 60 (660) **Energy (J):** 6-8 **Radiant exposure (J/cm²):**	*In Vivo:* treatment of acne vulgaris	The combined use of red and blue light proved beneficial in reducing inflammation and enhancing wound healing when compared to the use of salicylic acid for treatment.
20. Mignon et al, 2017(193)	**Source:** LED **Wavelength (nm):** 400, 500, 530, 590, 655, 850 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 3-80 **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):** 2-30	*In Vitro:* Human dermal fibroblasts	The effects of blue light on cell metabolism were dramatically influenced by FBS concentration, confluency level of cells and the fluency values applied to cells.
21. Yoshimoto et al, 2017(210)	**Source:** LED **Wavelength (nm):** 465 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 30 **Time (s):** 1800 **Energy (J):** **Radiant exposure (J/cm²):** 54	*In Vitro:* Human colon cancer cells (HT-29 or HCT-116)	Blue light irradiation reduced cancer cell viability. However, this effect was reversed in an Opsin 3 (Opn3) knockdown.
22. Yuan et al, 2017(71)	**Source:** LED **Wavelength (nm):** 470 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 20 **Time (s):** 60-3600 **Energy (J):** **Radiant exposure (J/cm²):**	*In Vitro:* Bone marrow-derived mesenchymal stem cells (BMSCs)	Blue light inhibited osteogenic differentiation, induced apoptosis as a result of increased ROS production and DNA damage.
23. Monrazeri et al, 2017 (194)	**Source:** LED **Wavelength (nm):** 630, 808, 450 **Power (mW):**100 (630 nm and 808 nm), 3000 (450 nm) **Frequency (Hz):** **Spot area (cm²):** 1	**Irradiance (mW/cm²):** 100 (630 nm) **Time (s):** **Energy (J):** 48J per point **Radiant exposure (J/cm²):**	*In vivo:* Human	Combining all three wavelengths reduced abdominal girth significantly.
24. Li et al, 2016(191)	**Source:** LED **Wavelength (nm):** 630, 460 **Power (mW):**100 (630nm and 808nm), 3000 (450nm) **Frequency (Hz):** **Spot area (cm²):** 300	**Irradiance (mW/cm²):** 50 **Time (s):** 900-1800 **Energy (J):** **Radiant exposure (J/cm²):** 45-90	*In vivo:* Japanese big ear white rabbits, induced wound model (incisions in back)	Red light was more effective in promoting wound healing than blue light.
25. Khori et al, 2016 (186)	**Source:** Laser **Wavelength (nm):** 405, 532, 632 **Power (mW):** 1-3 **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** **Time (s):** 600 (10 treatments, 3 times a week) **Energy (J):** **Radiant exposure (J/cm²):**	*In vivo and in vitro:* BALB/c inbred female mice and mouse mammary carcinoma cell line (4T1).	Blue light reduced tumour volume and gene expression markers for tumorigenesis.
26. AlGhamdi et al, 2016 (161)	**Source:** laser **Wavelength (nm):** 457, 635, 355 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 25 **Time (s):** 80 **Energy (J):** **Radiant exposure (J/cm²):** 2	*In Vitro:* Melanocytes from normal human melanocytes.	PBM at all wavelengths induced the production of stage I melanosomes to the highest levels relative to control cells. In particular, red and blue laser PBM induced the highest increase in % level of stage I melanosomes. This indicates significant stimulation of melanogenesis.
27. Wang et al, 2016 (209)	**Source:** LED array (420), Filtered lamp (540), Diode laser (660, 810). **Wavelength (nm):** 420, 540, 660, 810 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):** 4	**Irradiance (mW/cm²):** 16 **Time (s):** 188 (five times, every 2 days). **Energy (J):** **Radiant exposure (J/cm²):** 3	*In Vitro:* Human adipose-derived stem cells.	Blue and green light were effective in stimulating osteoblast differentiation and increasing intracellular calcium levels than red and near infra-red light. Blue and green light could activate light-gated calcium ion channels.
28. Masson-Meyers et al, 2016(30)	**Source:** LED **Wavelength (nm):** 470 **Power (mW):** 150 **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 30 **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):** 3, 5, 10, 55	*In Vitro:* Human Dermal Fibroblasts	Blue light and radiant exposure of 5J/cm² improved wound healing, increased protein concentration and reduced IL-6 secretion significantly. There was no effect of irradiation on cell viability.
29. Ashworth et al, 2016 (164)	**Source:** LED **Wavelength (nm):** 450, 510, 660, 860 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):** **Other:** photons/cm²/s	*Ex Vivo*: Rat or mouse spinal cord slices	All four wavelengths at the highest intensity output reduced immunoreactivity.
30. Figurova et al, 2016 (178)	**Source:** LED **Wavelength (nm):** 685/470 combined **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 8 **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):** 3.36	*In Vivo*: Minipigs	Combined red and blue light therapy induced improved tissue healing relative to control groups.

31. Becker et al, 2016 (165)	**Source:** LED **Wavelength (nm):** 453 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 23 **Time (s):** 1800 **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vitro*: Melanoma cells	The effects of blue light on cell viability were dose dependent and blue light down regulated anti-inflammatory genes but upregulated genes associated with apoptosis. Significant decreases in viability were witnessed after irradiation times of 1800s.
32. Dereci et al, 2016 (173)	**Source:** LED (blue, 400-490), GaAlAs diode laser (NIR, 980nm) **Wavelength (nm):** 400-490, 980 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 12 (400-490), 200 (980) **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** 13 (400-490, 20 (980)	*In Vivo*: Wistar rats	Whilst high doses of blue light were inhibitory, low doses proved efficacious in promoting bone regeneration to similar levels to NIR light.
33. Takhtfooladi and Sharifi, 2015 (204)	**Source:** GaAlAs (680), LED (650, 450) **Wavelength (nm):** 680, 650, 450 **Power (mW):** 10 (680) **Frequency (Hz):** Pulsed (no info, 680 only) **Spot area (cm^2):** 0.4 (680), 1.5 (650, 450)	**Irradiance (mW/cm^2):** **Time (s):** 200s (680), 600s (450, 650) 14 days **Energy (J):** **Radiant exposure (J/cm^2):** 10 (680), 650 (2.4), 450 (2.4)	*In Vivo*: New Zealand rabbits	Blue and red LEDs had no significant effect on cell proliferation or myelination. Conversely, laser red light had a significant effect. This may be due to the pulsed modality of the laser light source.
34. Fekrazad et al, 2015 (177)	**Source:** laser **Wavelength (nm):** 630, 532, 425 **Power (mW): Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 50 (630 nm and 532 nm), 55 (425 nm) **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** 2	*In Vivo:* Diabetes induced male Wistar rats	All three wavelengths induced significant increases in wound healing, where red light was most effective.
35. Masson-Meyers et al, 2015 (192)	**Source:** LED or Laser **Wavelength (nm):** 405 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** 900, 1800, 14400 **Energy (J):** **Radiant exposure (J/cm^2):** 40, 54, 81, 121	*In Vitro*: Methicillin Resistant Staphylococcus Aureus (MRSA)	Both LED and laser proved efficacious in supressing bacterial growth to significant levels at all four radiant exposure values evaluated.
36. Schafer and McNeely, 2015 (199)	**Source:** LED **Wavelength (nm):** 405 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 30 **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vitro: Staphylococcus Epidermis*, *Staphylococcus Aureus* and *Propionibacterium Acnes*	The effects of blue light combined with ultrasound were dose dependent where it is proposed that bacterial cells become more susceptible to the antimicrobial effects of blue light following ultrasound application.
37. Niu et al, 2015 (195)	**Source:** LED **Wavelength (nm):** 405, 630, 660 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 161μW/cm^{2}nm (405 nm), 300μW/cm^{2}nm (630 nm), 545μW/cm^{2}nm (660 nm) **Time (s):** 600 **Energy (J):** **Radiant exposure (J/cm^2):** 1.604 (405 nm), 3.409 (630 nm), 6.538 (660 nm)	*In Vitro*: Keratinocytes	The combination of blue light, red light and curcumin was able to regulate proliferation and apoptosis of keratinocytes. Without curcumin, light did not influence cell viability.
38. AlGhamdi et al, 2015 (162)	**Source:** diode laser **Wavelength (nm):** 355, 457, 635 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 25 **Time (s):** 20-200 **Energy (J):** **Radiant exposure (J/cm^2):** 0.5-5	*In Vitro*: Melanocytes	Blue laser proved most efficacious in promoting cell proliferation and migration.
39. Pfaff et al, 2015 (196)	**Source:** LED **Wavelength (nm):** 453 **Power (mW):** **Frequency (Hz):** High (200mW/cm^2) and low (100mW/cm^2) duty cycles employed **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 100 (low), 200 (high) **Time (s):** 1800 **Energy (J):** **Radiant exposure (J/cm^2):** 90	*In Vivo*: Treatment of patients with mild Psoriasis Vulgaris (Pv).	Blue light proved to significantly reduce Pv severity at both irradiance outputs.
40. Bumah et al, 2015(167)	**Source:** LED **Wavelength (nm):** 470 **Power (mW):** 150 (18 delivered to cultures) **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 30 **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** 55	*In Vitro*: MRSA	Blue light alone is effective in supressing MRSA growth, where there was no significant difference in the effect of blue light and the combination of blue light and hyperbaric oxygen.
41. Jung et al, 2015 (183)	**Source:** LED **Wavelength (nm):** 415, 630 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** 76-615 **Energy (J):** **Radiant exposure (J/cm^2):** 5-40	*In Vitro*: Human Sebocytes	Blue and red light influence lipid production and may have beneficial effects on acne through the suppression of sebum production.
42. Teuschl et al, 2015 (206)	**Source:** LED **Wavelength (nm):** 470, 630	**Irradiance (mW/cm^2):** 50 **Time (s):** 600 (5 times, once per day)	*In Vitro*: C2C12 (myoblast), NIH/3T3 (fibroblast), BICR10	Blue light reduced cell proliferation and promoted necrosis. Red light promoted cell proliferation and

	Power (mW): 1000 **Frequency (Hz):** **Spot area (cm^2):**	**Energy (J):** **Radiant exposure (J/cm^2):** 30	(keratinocytes)	increased rate of wound healing.
43. Hadis et al, 2015(181)	**Source:** LED **Wavelength (nm):** 400-900 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 3.5 **Time (s):** 15-120 **Energy (J):** **Radiant exposure (J/cm^2):** 0.05-0.42	*In Vitro:* Dental Pulp cells (DPCs)	Blue light had no significant effect on DPCs whilst wavelengths of 625nm, 660nm, 789nm and 800nm induced significant increases in mitochondrial activity. Particularly after 24hrs and irradiation periods of 30s.
44. De Sousa et al, 2015 (31)	**Source:** LED **Wavelength (nm):** 450 **Power (mW):** 70 **Frequency (Hz):** **Spot area (cm^2):** 0.00785	**Irradiance (mW/cm^2):** **Time (s):** 0-343 **Energy (J):** **Radiant exposure (J/cm^2):** 3-24	*In Vitro:* *Staphylococcus aureus, Pseudomonas aeruginosa*	Blue light inhibited bacterial growth at fluency values greater than 6J/cm^2.
45. Gold et al, 2014 (180)	**Source:** LEDs **Wavelength (nm):** 405-460 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vivo:* Human	Induced a reduction in acne vulgaris inflammatory lesions. Did induce increases in skin temperature up to 41^{o}c.
46. Schoenly et al, 2014(200)	**Source:** laser **Wavelength (nm):** 400 **Power (mW):** **Frequency (Hz):** 60ns laser pulse **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** <8	*In Vitro:* Human teeth	Removal of calculus is thickness dependent and can occur at radiant exposure <5J/cm^2
47. Buravlev et al, 2014 (73)	**Source:** LED **Wavelength (nm):** 442 **Power (mW):** 70 **Frequency (Hz):** **Spot area (cm^2):** 0.00785	**Irradiance (mW/cm^2):** **Time (s):** 30-300 **Energy (J):** **Radiant exposure (J/cm^2):** 30	*In Vitro:* Mitochondria isolated from male albino rat livers.	Blue light restored nitric oxide inhibited rates of respiration to normal. It is hypothesised blue light irradiation induces photolytic destruction of nitrosyl complexes that inhibit the activities of complex I and III of the electron transport chain.
48. Sinclair et al, 2014 (203)	**Source:** LED **Wavelength (nm):** 465, 574 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 0.0848 (blue), 0.0185 (yellow) **Time (s):** 2700 **Energy (J):** **Radiant exposure (J/cm^2):** **Other:** 68 lux, 1.21xphotons/cm^2/s	*In Vivo:* Patients with traumatic brain injury (TBI)	Blue light is effective in alleviating fatigue and daytime sleeping following TBI
49. Hochman et al, 2014 (182)	**Source:** LED (470 nm and 660 nm) and Laser (660 nm and 808 nm, no details of laser source) **Wavelength (nm):** 470, 660, 808 **Power (mW):** 100 (808nm, 660nm Laser) and 350 (470nm and 660nm LED). **Frequency (Hz):** **Spot area (cm^2):** 0.5 (LED), 0.028 (laser)	**Irradiance (mW/cm^2):** **Time (s):** 114 (LED), 396 (laser) **Energy (J):** 40 (both) **Radiant exposure (J/cm^2):** 80 (LED), 1429 (laser)	*In Vivo:* Skin of adult male Wistar rats.	Infrared (808nm) laser irradiation enhances neuropeptide secretion in healthy rat skin, whilst other sources of light and wavelengths had no significant impact.
50. Dungel et al, 2014(174)	**Source:** LED **Wavelength (nm):** 470, 629 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 50 **Time (s):** 600 **Energy (J):** **Radiant exposure (J/cm^2):** 30	*In Vivo*: Sprague-Dawley rats	Both wavelengths promoted angiogenesis, improved tissue perfusion, reduced tissue necrosis and therefore promoted wound healing.
51. KazemiKhoo and Ansari et al, 2014 (185)	**Source:** Optical fiber **Wavelength (nm):** 405, 632.8 **Power (mW):** 1.5 **Frequency (Hz):** **Spot area (cm^2):** 0.01	**Irradiance (mW/cm^2):** **Time (s):** 1800 (every other day, 14 sessions) **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vivo*: Intravascular laser irradiation of blood in type 2 diabetic patients and measurements of changes in blood sugar.	Both wavelengths induced significant decreases in blood sugar levels.
52. Burvalev et al, 2014 (168)	**Source:** Laser (442 nm, 532 nm) and LED (650 nm) **Wavelength (nm):** 442, 532, 650 **Power (mW):** 20 **Frequency (Hz):** **Spot area (cm^2):** 1.57	**Irradiance (mW/cm^2):** 30 **Time (s):** 30-300 **Energy (J):** **Radiant exposure (J/cm^2):** 3-31	*In Vitro*: Mitochondria isolated from rat liver.	Laser of mitochondria at 442nm restored mitochondrial respiration inhibited by NO. Blue light also restored complex IV activity but not complexes I-III. Other wavelengths had no significant effect.
53. Turrioni et al, 2013(207)	**Source:** **Wavelength (nm):** 450, 630, 850 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vitro:* Human dentin	All three wavelengths passed through the dentin barrier. LED power loss and transmittance varied dependent upon dentin thickness and wavelength.

54. Kazemi Khoo et al, 2013(184)	**Source:** laser **Wavelength (nm):** 405 **Power (mW):** 1.5 **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** 1800 **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vivo:* Human diabetic patients	Resulted in modulation of metabolites associated with type 2 diabetes following intravenous PBM.
55. Cheon et al, 2013 (79)	**Source:** LED **Wavelength (nm):** 470, 525, 633 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 3.55 (470nm), 4.02 (525nm) and 6.78 (633nm) **Time (s):** 3600 (9 days) **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vivo*: Sprague Dawley rats and histological analysis	Blue and green light promoted wound healing significantly. Red light promoted collagen production.
56. Burvalev et al, 2013 (169)	**Source:** HeCd laser (442 nm) diode pumped solid state laser (532 nm) and LED (650 nm) **Wavelength (nm):** 442, 532, 650 **Power (mW):** 20 **Frequency (Hz):** **Spot area (cm^2):** 1.57	**Irradiance (mW/cm^2):** **Time (s):** 30-300 (1 treatment) **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vivo*: Lipopolysaccharide B was applied through intraperitoneal injection to outbred albino rats. Mitochondria were then isolated from rat liver.	Blue light induced a 40% increase in mitochondrial respiration from LPS treated animals at a dose of 6J/cm^2
57. Kushibiki et al, 2013 (72)	**Source:** Laser **Wavelength (nm):** 405, 664, 808 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 100 **Time (s):** 60-120 **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vitro*: mouse preadipocytes (3T3-L1), prechondrocytes (ATDC5), myoblasts (C2C12), mesenchymal stromal cells (KUSA-A1), lung cancer cells (LLC), insulinoma cells (MIN6), fibroblasts (NIH-3T3), human cervix adenocarcinoma cells (HeLa), macrophages differentiated from lymphocytes (THP-1) after treatment with phorbol ester, and rat basophilic leukemia cells (RBL-2H3)	After blue light irradiation, intracellular ROS production was significantly increased in all cell types whilst red and near infra-red light had no significant effect.
58. Fushimi et al, 2012(179)	**Source:** LED **Wavelength (nm):** 456, 518, 638 **Power (mW):** 7560 (638nm), 6930 (456 nm) and 6840 (518 nm) **Frequency (Hz):** **Spot area (cm^2):** 30	**Irradiance (mW/cm^2):** 0.75 (638 nm), 0.25 (456 nm) and 0.17 (518 nm) **Time (s):** 1200 **Energy (J):** **Radiant exposure (J/cm^2):** 0.6 (638 nm), 0.3 (456 nm), 0.2 (518 nm)	*In Vivo and in vitro:* Induced wound model in ob/ob mice	LED irradiation induced significant increases in growth factor and cytokine secretion. Green LEDs promote wound healing by inducing migratory and proliferative mediators.
59. Lavi et al, 2012(189)	**Source:** LED **Wavelength (nm):** 400-505, 600-800 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 30 (600-800 nm), 10 (400-505 nm) **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vitro:* Sperm membranes	Visible (especially blue) light induce increase in ROS production in isolate sperm isolated plasma membranes
60. Adamskaya N et al, 2011(160)	**Source:** LED **Wavelength (nm):** 470, 630 **Power (mW):** 1000 **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 50 **Time (s):** 600 **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vivo:* Induced wound model (excision wound on dorsum), Sprague Dawley rats	Blue light was effective in inducing wound healing and promoting keratin expression.
61. Shuvaeva et al, 2011(202)	**Source:** laser **Wavelength (nm):** 473, 650 **Power (mW):** 20 **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 20 **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):**	*In vivo:* WKY and SHR rats	Irradiation with red light proved more effective than blue light in augmenting the constrictive effects of Norepinephrine on pial arteries. However both exerted a significant difference relative to the control.
62. Bonatti et al, 2011(166)	**Source:** LED **Wavelength (nm):** 470 **Power (mW):** 100 **Frequency (Hz):** **Spot area (cm^2):** 0.8	**Irradiance (mW/cm^2):** 125 **Time (s):** 60-180 **Energy (J):** 6, 12, 18 **Radiant exposure (J/cm^2):** 59.87, 122.3, 183.43	*In vitro:* Keloid and skin fibroblasts, human	Reduced skin fibroblasts following irradiation at 183.43J/cm^2 but induced no significant effect on keloid fibroblast number.
63. Ankri et al, 2010(89)	**Source:** LED **Wavelength (nm):** 400-830 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):**	Computational model of human dermis: photon migration model	480nm may be useful for treating infected wounds whilst 780nm has a higher penetration depth and therefore may be useful for wound healing.
64. De Sousa et al, 2010(172)	**Source:** LED **Wavelength (nm):** 700,	**Irradiance (mW/cm^2):** 7.46 (700 nm), 3.98 (530 nm),	*In Vivo and In vitro:* Male Wistar rats with	Green and red LEDs induced increases in fibroblast number relative to the

	530, 460 **Power (mW):** 15 (700nm), 8 (530nm), 22 (460nm) **Frequency (Hz):** **Spot area (cm²):** 2.01	10.94 (460 nm) **Time (s):** 668 (700 nm), 1250 (530 nm), 456 (460 nm) **Energy (J):** **Radiant exposure (J/cm²):** 10	excisional wound, followed by histological analysis.	control.
65. Ankri et al, 2010(163)	**Source:** LED **Wavelength (nm):** 400-800 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 130 **Time (s):** 300 **Energy (J):** **Radiant exposure (J/cm²):**	*In vitro:* Sperm and endothelial cells	Illumination induced increase in NO concentration, particularly blue light.
66. Kushibiki et al, 2010(188)	**Source:** LED **Wavelength (nm):** 405 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 100 **Time (s):** 180 **Energy (J):** **Radiant exposure (J/cm²):**	*In vitro:* Prechondrogenic cells	Intracellular ROS increased and mRNA levels relating to chondrogenesis were elevated.
67. Sebbe et al, 2009(201)	**Source:** LED **Wavelength (nm):** 472 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 1.26-4.73 **Time (s):** 8-24h **Energy (J):** **Radiant exposure (J/cm²):**	*In vivo:* Male Wistar rats.	Increased bilirubin degradation, important for neonatal jaundice.
68. Tamarova et al, 2009 (205)	**Source:** LED **Wavelength (nm):** 480-3400 (range of source, evaluated 'red, orange, yellow, blue, green, violet') **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 40 **Time (s):** 600 **Energy (J):** **Radiant exposure (J/cm²):** 2.4 (per minute)	*In vivo:* Male albino rats with area of pain induced by saline injection	Red light was more effective in inducing an analgesic effect. However, all colours induced significant increases in analgesia relative to control.

4.3.2 Green light PBM

A second Scopus database search was undertaken to evaluate the effects of green light PBM using the terms described in *Figure 3b.* An initial search resulted in 236 articles being identified and these articles were subsequently screened for suitability, which then identified 32 relevant articles for further review (18, 32, 33, 64, 68, 69, 79, 164, 168, 171, 176, 177, 186, 197, 205, 209, 212-227).

When evaluating the outcomes of studies reporting the effects of PBM it was found that 75% (24/32) reported a beneficial effect of green light, whilst 9% (3/32) reported negative effects and 16% (5/32) reported no significant response. Interestingly, this review also included an article evaluating the effect of green light PBM on microbial cell death (219) with high radiant exposures also being used (≤172.8 J/cm²). These findings further support the use of other visible wavelengths of light in applications other than modulation of tissue response. As described previously this article was also excluded from evaluation of parameters for suitable application to tissue PBM.

Exploration of treatment parameters revealed that 72% (23/32) articles failed to report any characterisation protocols or relied entirely upon the parameters stated by the manufacturer. In fact, only one article reported the use of beam profiling to accurately calculate beam area and to provide representative images of the distribution of spectral irradiance (214). Similar to reports in section 4.3.1, a series of key parameters were also not always reported including irradiance (41%, 13/32), radiant exposure (44%, 14/32) and beam area (66%, 21/32). In the articles reporting treatment parameters, median treatment values were also determined. In the articles reporting a positive effect of green light PBM, there was a median radiant exposure output of 4 J/cm² (range: 0.00362-30J/cm²). Interestingly, it was also found that the most commonly employed wavelength used in these studies was 532 nm, and 35% (11/32) of studies reported the use of this wavelength. Further information detailing parameters and study types employed by authors reviewing the effects of green light PBM are provided in *Table 2.*

Table 2: Citations identified from a review of the literature evaluating the effects of green and yellow light PBM using the following search terms: ‘green AND light’ OR ‘500 nm’ OR ‘505 nm’ OR ‘520 nm’ OR ‘530 nm’ OR ‘540 nm’ OR ‘550 nm’ OR ’560 nm’ OR ’570 nm’ OR ‘532 nm’ OR ‘595 nm’ AND ‘Photobiomodulation’ OR ‘PBM’ OR ‘Low level light therapy’ OR ‘LLLT’ OR ‘Low intensity light therapy’ OR ‘photobiostimulation’ AND NOT ‘Photodynamic therapy’ OR ‘PDT.’

Citation	Light Source	Dose	Study type	Conclusion
1. Priglinger et al, 2018 (197)	**Source:** LED cluster lamp **Wavelength (nm):** 475, 516, 635 **Power (mW):** **Frequency (Hz):** 2.5 (pulsed, 50% rate) **Spot area (cm²):**	**Irradiance (mW/cm²):** 40 **Time (s):** 120-300 **Energy (J):** **Radiant exposure (J/cm²):** 24	*In Vitro:* Adipose tissue derived stromal vascular fraction cells.	Green and red light resulted in increased vascular tube formation and increased concentration vascular endothelial growth factor (VEGF) concentration. Blue light had no significant effect.
2. Askhadulin et al, 2018 (213)	**Source:** Laser **Wavelength (nm):** 365, 525, 635 **Power (mW):** 1-2 **Frequency (Hz):** 80 (635 nm) **Spot area (cm²):** 8 (635 nm)	**Irradiance (mW/cm²):** 5000 (635 nm) **Time (s):** 120 (365 nm, 635 nm) 300 (525nm) , 6 sessions of each **Energy (J):** **Radiant exposure (J/cm²):**	*In Vivo:* Human	Reduced ulcer healing time and adapted physiological responses ultimately preventing relapse.
3. Fekrazad et al, 2018 (176)	**Source:** Laser **Wavelength (nm):** 810, 660, 532, 485, *combinations:* 810-660, 810-485, 660-532, 660-485 **Power (mW):** 30-200 (dependent on wavelength) **Frequency (Hz):** **Spot area (cm²):** 0.113-0.18	**Irradiance (mW/cm²):** 266 (blue), 266 (green) 167 (red), 1333(NIR) **Time (s):** 3-24 (dependent upon wavelength) **Energy (J):** **Radiant exposure (J/cm²):** 4 (8 for combination)	*In vitro:* Mesenchymal stem cells.	Cartilage markers were upregulated by 810nm and 810-485nm light. Red and blue-green irradiation induced expression of COL1. Blue, blue-green and green light irradiation reduced osteocalcin expression. Stimulatory effects on osteogenesis were seen for red and near infra-red lasers but green light had inhibitory effects. Blue light was not reported to induce inhibitory effects.
4. Oh et al, 2018 (225)	**Source:** LED **Wavelength (nm):** 630, 595, 480, 410 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 5.47 (410 nm), 13.2 (480 nm), 5.8 (595 nm), 8.63 (630 nm) **Time (s):** 410nm: 181.2-1816.8 480nm:69.6-742.2 595nm:151.2-1706.4 630nm:93-1146 **Energy (J):** **Radiant exposure (J/cm²):** 1-10	*In Vitro:* Human umbilical vein endothelial cells (HUVEC)	Irradiation at 630nm induced increases in cell proliferation, NO secretion and eNOS expression from HUVECs. Only evaluated effects on proliferation using other wavelengths where no significant change was witnessed.
5. Rohringer et al, 2017 (68)	**Source:** LED **Wavelength (nm):** 475, 516, 635 **Power (mW):** **Frequency (Hz):** 50% pulse rate, 2.5Hz **Spot area (cm²):**	**Irradiance (mW/cm²):** 80 **Time (s):** 600 **Energy (J):** **Radiant exposure (J/cm²):** 24	*In Vitro:* Human umbilical vein endothelial cells	Red and green light induced proliferation and migration of endothelial cells whilst blue light had no significant impact. Blue light only induced significant increases in ROS production.
6. **Wang et al, 2017(64)**	**Source:** LED array (415 nm), Filtered lamp (540 nm), Diode laser (660 nm and 810 nm) **Wavelength (nm):** 415, 540, 660, 810 **Power (mW):** **Frequency (Hz):** **Spot area (cm²):** 4	**Irradiance (mW/cm²):** 16 **Time (s):** 188 **Energy (J):** **Radiant exposure (J/cm²):** 3	*In vitro:* human adipose-derived stem cells.	Blue and green light induce significant increases in intracellular calcium and ROS, reduce mitochondrial membrane potential, lower intracellular pH and reducing cellular proliferation. Red and NIR light have the opposite effect. Blue and green light inhibit proliferation through activation of TRPV1.
7. **Baek et al, 2017 (214)**	**Source:** laser **Wavelength (nm):** 532 **Power (mW):** 300 **Frequency (Hz):** 0.2 (1s) **Spot area (cm²):** diameter 1mm	**Irradiance (mW/cm²):** **Time (s):** 10-300 **Energy (J):** **Radiant exposure (J/cm²):**	*In vitro:* vascular smooth muscle cells	Inhibited platelet derived growth factor-BB induced proliferation and migration. Also induced apoptosis via the p38 MAPK pathway.
8. **Wang et al, 2017 (69)**	**Source:** LED **Wavelength (nm):** 480, 560, 660 and white (400-750) **Power (mW):** 3000 **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** 250 **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):**	*In vitro and in vivo*: fertile broiler eggs were irradiated and satellite cells were isolated.	Green light promoted muscle growth and satellite cell proliferation which may be due to an increase in signalling through the insulin growth factor (IGF-1) pathway.

9. **Choe et al, 2017 (171)**	**Source:** LED **Wavelength (nm):** 622, 535, 462 **Power (mW):** 24000 **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 16 **Time (s):** 600-1800 (daily) **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vitro*: HeLa cells (cancer cell line).	Blue light and high frequency ultrasound induced significant reductions in cell density when compared to red and green light combined with ultrasound. This could be beneficial in alleviating cancer cell proliferation. Green light also drove decreases in cell density but not significantly.
10. **Fekrazad et al, 2017(18).**	**Source:** laser: GaAs (405 nm, 532 nm), InGaAlP (660 nm) and GaAlAs (810 nm) **Wavelength (nm):** 405, 532, 660, 810 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):** 1	**Irradiance (mW/cm^2):** 200 **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** 1.5	*In Vivo:* Male Wistar rats (n=60)	Green, blue, red and infrared light irradiation may accelerate healing process.
11. Moskvin et al, 2017 (222)	**Source:** LAMSIK® device, external pulsed laser (635), intravenous laser blood illumination (ILBI, 365-405 nm and 520-525 nm) **Wavelength (nm):**635, 365-405, 520-525 **Power (mW):** 40000 (635 nm) **Frequency (Hz):** pulsed 635nm **Spot area (cm^2):** 8 (635 nm)	**Irradiance (mW/cm^2):** **Time (s):** 12 sessions, 120s (per point, 635 nm), 120s (365-405 nm), 300s (520-525 nm) 6 sessions each alternate. **Energy (J):** **Radiant exposure (J/cm^2):**	*In vivo:* Treatment of patients with chronic venous diseases	Reduced time for wound cleansing, stimulates proliferation and epithelialisation processes.
12. **Khori et al, 2016 (186)**	**Source:** Laser **Wavelength (nm):** 405, 532, 632 **Power (mW):** 1-3 **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** 600 (10 treatments, 3 times a week) **Energy (J):** **Radiant exposure (J/cm^2):**	*In vivo and in vitro:* BALB/c inbred female mice and mouse mammary carcinoma cell line (4T1).	Blue light reduced tumour volume and gene expression markers for tumorigenesis.
13. **Roche et al, 2017 (226)**	**Source:** laser diodes **Wavelength (nm):** 532 **Power (mW):** 17 (per diode, 170 total) **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 0.03 **Time (s):** 1800 (3 times weekly) **Energy (J):** **Radiant exposure (J/cm^2):** 0.03 (per treatment), 0.36 (in total) calculations appear wrong.	*In Vivo:* Obese but otherwise healthy individuals, RCT	Reduced circumference of hips, waist and upper abdomen when applied to individuals with a body mass index (BMI) between 30-40kg/m^2
14. **Khurana et al, 2017 (218)**	**Source:** Qs Nd:YAG laser **Wavelength (nm):** 1064, 532 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** 9.3 (1064nm), 5 (532nm)	*In Vivo:* Case study, patient with Fusarium solani infection on toe nail	Application of PBM with sequential use of either wavelength cured infection and promoted healthy toe nail growth
15. **Wang et al, 2016 (209)**	**Source:** LED array (420), Filtered lamp (540), Diode laser (660, 810). **Wavelength (nm):** 420, 540, 660, 810 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):** 4	**Irradiance (mW/cm^2):** 16 **Time (s):** 188 (five times, every 2 days). **Energy (J):** **Radiant exposure (J/cm^2):** 3	*In Vitro:* Human adipose-derived stem cells.	Blue and green light were effective in stimulating osteoblast differentiation and increasing intracellular calcium levels than red and near infra-red light. Blue and green light could activate light-gated calcium ion channels.
16. Ashworth et al, 2016 (164)	**Source:** **Wavelength (nm):**450, 510, 660, 860 **Power (mW): Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** **Other:** 1.93x, 3.85x, 7.70xphotons/cm^2/s	*Ex vivo:* adapted mouse spinal cord organotypic culture model	Red and near infra-red light are effective antioxidant therapies for spinal cord injury.
17. Merigo et al, 2016 (221)	**Source:** KTP laser **Wavelength (nm):**532 **Power (mW):** 780 **Frequency (Hz):** **Spot area (cm^2):** 2.4	**Irradiance (mW/cm^2):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** 4 **Other:**	*In vitro:* Primary bone marrow stromal cells	Green light induces osteogenic differentiation of bone marrow stromal cells.
18. O'Connor et al, 2016 (224)	**Source:** diode laser **Wavelength (nm):**405, 532, 635 **Power (mW):** 17.5 **Frequency (Hz):** **Spot area (cm^2):** 1.413	**Irradiance (mW/cm^2):** 12.2 **Time (s):** 300 **Energy (J):** 0.0051748 **Radiant exposure (J/cm^2):** 0.003662 **Other:** Calculations wrong should be 3.66J/cm^2 and 5.1748J	*In Vivo:* C57BL6 mice treated with light and/or Mesenchymal Stem cells	405, 532, and 635 induced increases in mitochondrial activity and reduced apoptosis. Endothelial proliferation increased in response to 635 nm light and combined effects of MSC and the 405 nm wavelength. Reduced TGF-β levels were induced by 532 nm alone and when combined with MSC.
19.	**Source:** laser	**Irradiance (mW/cm^2):** 50 (630nm and	*In Vivo:*	All three wavelengths

Fekrazad et al, 2015 (177)	**Wavelength (nm):** 630, 532, 425 **Power (mW): Frequency (Hz):** **Spot area (cm^2):**	532nm), 55 (425nm) **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** 2	Diabetes induced male Wistar rats	induced significant increases in wound healing, where red light was most effective.
20. **Na, C-S et al, 2015 (223)**	**Source:** laser diodes **Wavelength (nm):** 532, 658 **Power (mW):** 30 (532 nm), 60 (658 nm) **Frequency (Hz):** 20 **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** 180 **Energy (J):** **Radiant exposure (J/cm^2):** **Other:**	*In vivo:* rat model with induced middle cerebral artery occlusion (MCAO)	Decrease in Bax and cytochrome c levels in hippocampus, increase in hemoglobin, haematocrit, total white blood cell, neutrophil, lymphocyte, monocyte and erythrocyte counts.
21. Burvalev et al, 2014 (168)	**Source:** Laser (442 nm, 532 nm) and LED (650 nm) **Wavelength (nm):** 442, 532, 650 **Power (mW):** 20 **Frequency (Hz):** **Spot area (cm^2):** 1.57	**Irradiance (mW/cm^2):** 30 **Time (s):** 30-300 **Energy (J):** **Radiant exposure (J/cm^2):** 3-31	*In Vitro*: Mitochondria isolated from rat liver.	Laser of mitochondria at 442nm restored mitochondrial respiration inhibited by NO. Blue light also restored complex IV activity but not complexes I-III. Other wavelengths had no significant effect.
22. Kuboyama et al, 2014 (33)	**Source:** LED **Wavelength (nm):** 570 and 940 **Power (mW): Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm^2):** 5 (24 sessions) **Other:**	*In Vivo:* DBA/1 LacJ male mice with collagen induced arthritis	Reducing swelling induced by both wavelengths. 940nm irradiation induced significant reduction in circulating levels of IL-1β, IL-6 and MMP-3.
23. **Cheon et al, 2013 (79)**	**Source:** LED **Wavelength (nm):** 470, 525, 633 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 3.55 (470 nm), 4.02 (525 nm) and 6.78 (633 nm) **Time (s):** 3600 (9 days) **Energy (J):** **Radiant exposure (J/cm^2):**	*In Vivo*: Sprague Dawley rats and histological analysis	Blue and green light promoted wound healing significantly. Red light promoted collagen production.
24. **De Sousa et al, 2013 (215)**	**Source:** laser (660 nm, and 790nm), LED (700 nm, 530 nm and 460 nm) **Wavelength (nm):** 660, 790, 700, 530, 460 **Power (mW):** 60 (660 nm), 50 (790 nm), 15 (700 nm), 8 (530 nm), 22 (460 nm)**Frequency (Hz):** **Spot area (cm^2):** 0.03	**Irradiance (mW/cm^2):** 1911 (660 nm), 1592 (790 nm), 7.46 (700 nm), 8 (530 nm), 22 (460 nm) **Time (s):** 168 (660 nm), 200 (790 nm), 668 (700 nm), 1250 (530 nm), 456 (460 nm) (every other day, 7 days) **Energy (J):** **Radiant exposure (J/cm^2):** 10 **Other:**	*In Vivo:* Male Wistar rats wound model and stained for histological evaluation.	530nm, 700nm, 790nm and 660nm induced significant increases in angiogenesis.
25. **Tamarova et al, 2009 (205)**	**Source:** LED **Wavelength (nm):** 480-3400 (range of source, evaluated 'red, orange, yellow, blue, green, violet') **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 40 **Time (s):** 600 **Energy (J):** **Radiant exposure (J/cm^2):** 2.4 (per minute)	*In vivo:* Male albino rats with area of pain induced by saline injection	Red light was more effective in inducing an analgesic effect. However, all colours induced significant increases in analgesia relative to control.
26. Jackson et al, 2013 (32)	**Source:** laser diodes (Erchonia GL scanner) **Wavelength (nm):** 532 nm (6 diodes) **Power (mW):** 17 per diode, 125 total (sham 1.25) **Frequency (Hz):** **Spot area (cm^2):** 516 (target area)	**Irradiance (mW/cm^2):** **Time (s):** 900 (two weeks once every 2-3 days). **Energy (J):** **Radiant exposure (J/cm^2):** **Other:**	*In Vivo:* Human laser irradiation to improve cellulite appearance	532nm improved cellulite appearance on thighs and buttocks.
27. **Kim et al, 2013 (219)**	**Source:** **Wavelength (nm):** 425, 525, 625 **Power (mW):** **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 6 **Time (s):** 3600-28800 **Energy (J):** **Radiant exposure (J/cm^2):** 21.6-172.8 **Other:**	*In Vitro:* *Staphylococcus. Aureus, Escherichia. Coli, Porphyromonas. gingivalis*	No bactericidal effect induced by red light. Blue and green light were bactericidal where green light also killed *S.aureus*.
28. Fushimi et al, 2012 (217)	**Source:** LED **Wavelength (nm):** 63 8nm, 456nm, 518nm **Power (mW):** 2520 (638 nm), 2310 (456 nm), 2500 (518 nm): in vivo. 7560 (638 nm), 6930 (456 nm), 6840 (518 nm): in vitro **Frequency (Hz):** **Spot area (cm^2):**	**Irradiance (mW/cm^2):** 0.25: in vivo 0.75 (638 nm), 0.25 (456 nm), 0.17 (518 nm): in vitro **Time (s):** 1200 **Energy (J):** **Radiant exposure (J/cm^2):** 0.3: in vivo 0.6 (638 nm), 0.3 (456 nm), 0.2 (518 nm). **Other:**	*In Vivo:* Mice *In Vitro:* Fibroblasts and HaCat keratinocytes	Green light decreased wound size. Green and red light accelerated reepithelialisation. Green light induced increases in leptin, IL-8 and VEGF. Keratinocyte migration enhanced by red and green light.
29. **Li et al, 2011 (220)**	**Source:** laser (Nd:YAG) **Wavelength (nm):** 532 nm **Power (mW):** 40	**Irradiance (mW/cm^2):** **Time (s):** 300 **Energy (J):**	*In Vitro:* Vascular smooth muscle cells (VMSCs)	Low intensity laser can prevent VMSC proliferation through induction of

	Frequency (Hz): pulsed at 'double frequency' **Spot area (cm²):** 0.32	**Radiant exposure (J/cm²):** **Other:**		increases in markers for apoptosis.
30. **De Sousa et al, 2010 (216)**	**Source:** LED **Wavelength (nm):** 700, 530, 460 **Power (mW):** 15 (700 nm), 8 (530 nm), 22 (460 nm) **Frequency (Hz):** **Spot area (cm²):**	**Irradiance (mW/cm²):** **Time (s):** every other day 7 days **Energy (J):** **Radiant exposure (J/cm²):** 10 **Other:**	*In Vivo:* Wistar rats and fibroblasts grown from biopsy	Green and red light induced significant increases in fibroblast number.
31. **Al-Watban et al, 2009 (212)**	**Source:** laser diode **Wavelength (nm):** 532, 633, 670, 810, 980 **Power (mW):** 143 (532 nm), 140 (633 nm), 120 (670 nm), 200 (810 nm), 200 (980 nm) **Frequency (Hz):** **Spot area (cm²):** 7 (532 nm), 9 (633 nm), 5.25 (670 nm), 9 (810 nm), 9 (980 nm)	**Irradiance (mW/cm²):** 20.4 (532 nm), 15.56 (633 nm), 22.86 (670 nm), 22.22 (810 nm and 980nm). **Time (s):** 532nm: 246-1470 633nm: 324-1926 670nm:216-1314 810nm:228-1350 980nm:450-1350 three times per week **Energy (J):** **Radiant exposure (J/cm²):** 5, 10, 20, 30 (532 nm, 633 nm, 670 nm, 810) 10, 20, 30 (980 nm) **Other:**	*In Vivo:* Wound healing in diabetic Sprague-Dawley rats	PBM accelerated burn healing, particularly visible lasers. Response was dose dependent where highest increase in healing was induced at 30J/cm² by green light but 20J/cm² by red light.
32. Tierney and Hanke, 2009 (227)	**Source:** Diode laser **Wavelength (nm):** 532 and 940 **Power (mW):** **Frequency (Hz):** pulse duration: 60ms (532 nm) and 21ms (940 nm) **Spot area (cm²):** spot size: 1mm	**Irradiance (mW/cm²):** **Time (s):** **Energy (J):** **Radiant exposure (J/cm²):** 15 (532 nm) and 100 (940 nm) **Other:**	*In Vivo:* RCT, humans with facial telangiectasias	Both wavelengths proved effective in treating facial telangiectasias, but 940nm proved more effective as well as inducing fewer/milder side effects.

4.4 Discussion

It is apparent from this literature review, that whilst the majority of articles reported a positive effect of blue (72%) and green (75%) light PBM, further work is required to demonstrate the importance of the correct recording and reporting of treatment parameters. In fact, in this review 69% of all articles failed to report any means of measuring the output of their light source. While a number of studies have highlighted the importance of proper and thorough reporting and recording of treatment parameters (15, 228, 229), it appears these guidelines are yet to be fully implemented in practice. Future efforts are therefore required to ensure the correct reporting of parameters, to enable comparison PBM studies and therefore enable identification of beneficial parameters for therapeutic application.

Furthermore this literature review has revealed that for articles reporting the beneficial effects of both, green or blue light application, the majority of publications employed radiant exposures <10 J/cm² (66%, 26/39, excluding articles that did not report radiant exposure values). Interestingly, the beneficial effects of blue and green light included promotion of wound healing (29), reduced inflammation (175), reduction of symptoms in acne (29, 183) and reduced bleeding time following tooth extraction (21) to name a few. The full range of applications of blue and green light found in this review are described in Table 1 and Table 2 respectively. A handful of authors also reported on the biphasic dose response of light (19, 230). For example, *Masson-Meyers et al* investigated the effect of blue light on wound healing *in vitro* using human dermal fibroblast (230). The authors utilised a scratch assay to inflict a 'wound' on cell cultures and following this irradiated cells at 470nm (30 mW/cm², 3-55 J/cm²) and evaluated the effect of irradiation on a series of markers for wound healing. The authors reported that at fluence values of 3, 5 and 10 J/cm², irradiation significantly reduced the secretion of IL-6, a key pro-inflammatory cytokine, increased overall protein production (as a marker for transcription and translational activity) and had no significant impact on wound healing. They also found that irradiation induced mean increases in basic fibroblast growth factor (bFGF) levels, however, this was not significant. Conversely, when utilising a fluency value of 55 J/cm², the authors found that irradiation did significantly reduce rate of wound healing. These data suggest that lower doses of blue light could prove beneficial in inducing decreases in inflammation and promoting gene expression. This theory is in agreement with the 'Arndt-Schulz law' in which the application of a stimulus is only beneficial within a relatively narrow therapeutic window. Outside this window a stimulus can either have no effect or induce bioinhibition (231). Interestingly, previous articles have also suggested that 453 nm light is non-toxic up to 500 J/cm², when applied to human skin cells (232). Hence, future work may prioritise the study of the biphasic effect of various wavelengths of blue and green light on cells isolated from different sources in the human body.

This review, has also provided evidence for alternative applications of PBM, in which visible light could not only modulate tissue response but also exert antimicrobial properties. Notably the majority of articles citing the antibacterial properties of light use high radiant exposures (>55 J/cm² (167, 192, 219)) and these levels could potentially be toxic to eukaryotic cells. Comparatively, de Sousa et al reported that 450 nm light inhibited bacterial growth (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) at doses as low as 6 J/cm² (31). Hence, future work may endeavour to determine parameters of visible light required to modulate tissue response whilst also inhibiting bacterial growth.

However, it is prudent to highlight one limitation of this review in which radiant exposure values were used to compare literature currently published. Radiant exposure is an important parameter as it takes into consideration a number of other key parameters including irradiance and enables initial establishment of a possible therapeutic window in which blue and green light could induce beneficial effects *in vivo*. However, it is also unreliable as it assumes there is an inverse correlation between both irradiance and exposure time (15). Hence, it is important that authors report all treatment parameters values utilised in studies. This will therefore ensure reliable comparison of current literature and provide further detail as to the parameters that may induce beneficial effects clinically. Future work may also endeavour to evaluate the possible parameter combinations that may induce a beneficial effects within this therapeutic window.

5 Conclusions

This review has provided examples of the wide range of possible targets for various wavelengths of light employed in PBM. These ranged from the application of blue and green light to modulate opsin signalling (17) to the application of red and NIR light to induce cytochrome c oxidase activity (231). We provide evidence for the idea that the majority of these primary mechanisms converge on their ability to modulate ROS production. It has been proposed that small increases in ROS production can induce beneficial effects including increases in cell proliferation, whilst large increases can induce apoptosis signalling pathways (26). Literature currently suggests that light application to ‘healthy’ cells and tissue induces small increases in ROS production (70), whilst PBM can induce decreases in ROS production in inflamed tissue (111, 233). Hence, PBM could plausibly be applied both as a preventive measure, as well as a means to modulate inflammation in disease. However, further work is required to validate this hypothesis.

We also report how PBM induces the activity of downstream signalling pathways, which are modulated by this ROS production. Current literature also demonstrates the wavelength dependent effects of PBM on downstream signalling pathways, where red and NIR light have been proposed to increase the activity of TGF-β signalling (131), whilst blue light has been shown to inhibit the same pathway (234). It will therefore be important in the future to evaluate the wavelength dependent effects of PBM on downstream signalling pathways to provide further indications as to which wavelengths are beneficial for the resolution of different diseases and disorders.

This review is also the first report, to our knowledge, which systematically reviews the current literature evaluating the effects of green and blue light PBM both *in vitro* and *in vivo*. We provide evidence that application of blue or green light PBM could have beneficial effects. However, it is apparent that to date, the majority of authors have not appropriately recorded and reported their parameters, meaning that firm conclusions cannot be drawn regarding the optimum parameters to be applied therapeutically.

Overall we conclude that PBM exhibits the ability to modulate the activity of an array of signalling pathways, ultimately inducing the beneficial effects seen *in vitro* and *in vivo*. However, further work is required to ensure that experimental studies carry out rigorous spectral characterisation to enable improved reproducibility.

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7 Conflicts of interest

MRH declares the following potential conflicts of interest.

Dr Hamblin is on the following Scientific Advisory Boards

Transdermal Cap Inc, Cleveland, OH

BeWell Global Inc, Wan Chai, Hong Kong

Hologenix Inc. Santa Monica, CA

LumiThera Inc, Poulsbo, WA

Vielight, Toronto, Canada

Bright Photomedicine, Sao Paulo, Brazil

Quantum Dynamics LLC, Cambridge, MA

Global Photon Inc, Bee Cave, TX

Medical Coherence, Boston MA

NeuroThera, Newark DE

JOOVV Inc, Minneapolis-St. Paul MN

AIRx Medical, Pleasanton CA

FIR Industries, Inc. Ramsey, NJ

UVLRx Therapeutics, Oldsmar, FL

Ultralux UV Inc, Lansing MI

Illumiheal & Petthera, Shoreline, WA

MB Lasertherapy, Houston, TX

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Dr Hamblin is a stockholder in

Global Photon Inc, Bee Cave, TX

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