Maturitas 116 (2018) 11–17

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

# Therapeutic applications of polarized light: Tissue healing and immunomodulatory effects

Jack Feehan[a,b], Soraya Patricia Burrows[a], Leonardo Cornelius[a], Alyse Malietzis Cook[a], Kathleen Mikkelsen[c], Vasso Apostolopoulos[c,*,1], Maja Husaric[a,c,d,*,1], Dimitrios Kiatos[a,c,*,1]

[a] Osteopathy Group, College of Health and Biomedicine, Victoria University, VIC, Australia
[b] Australian Institute for Musculoskeletal Science (AIMSS), University of Melbourne and Western Health, St. Albans, VIC, Australia
[c] Institute for Health and Sport, Victoria University, VIC, Australia
[d] First Year College, College of Health and Biomedicine, Victoria University, VIC, Australia

ARTICLE INFO

*Keywords:*
Polarized light therapy (PLT)
Polarized light
Photodynamic therapy (PDT)
Phototherapies
Low-level laser therapy (LLLT)
Wound healing

ABSTRACT

As the population grows and ages, non-pharmaceutical options for the treatment and management of wounds, disease and injury are required to ensure adequate care. Polarized light therapy (PLT) utilizes visible-spectrum polarized light for a number of clinical applications. The advantage of polarized light is that it is able to penetrate the skin to a depth of up to 5 cm, reaching deeper tissues involved in wound healing. PLT has been shown to accelerate the healing process for ulcers, surgical wounds and dermal burns as well as a small number of musculoskeletal injuries. As research into the histological and physiological effects of PLT is largely absent, studies related to other light therapy modalities, largely low-level laser therapy, may pave the way to identify putative mechanisms by which PLT might exert its effects. Changes to cell signalling and secretion of substances required for wound healing have been identified in response to phototherapies. The reviewed literature suggests that PLT may be efficacious in some wound and injury healing contexts, though a gap in the literature exists regarding its mechanisms of action. Future studies should fully explain the therapeutic effects of PLT and the physiological mechanisms underpinning them.

## 1. Introduction

Healing is a complex process comprising a wide variety of cell types, secreted factors and other physiological parameters. In a normal, healthy patient, the human body is capable of healing completely from a wide range of wounds and injuries. However when the system is compromized by external factors such as ageing, chronic disease or malnourishment, the healing response can be delayed, or incomplete, placing the patient at risk [1]. Despite this common problem, there are a limited number of interventions available, most of which are supportive in nature. The therapeutic use of light can be traced back to ancient Egypt. The sun god Ra was worshipped as their highest deity, and the Egyptians would bask in the sun to increase their energy levels [2]. The ancient Greeks, who were medically advanced for their time, also used sunlight to help treat illness [3], and in modern times, seasonal affective disorder is treated with bright artificial lights [4].

According to the International Commission on Illumination, light is "any radiation capable of causing a visual sensation directly" [5]. Its physical properties are described by its wavelength (i.e. the distance between the two nearest peaks in the wave), with visible light spanning from 390 to 700 nm in humans. Specific wavelengths correlate with the visual phenomenon of color when processed by the brain. Light wavelengths below this are known as ultraviolet (UV) light, and above as infrared (IR), both of which are not detectable by the human retina. In its typical setting light is incoherent or unpolarized, with individual waves travelling in all planes and directions. Polarization is achieved by passing incoherent light through specially designed filters, which allow waves travelling in the desired plane to pass and blocking those outside the desired parameter (Fig. 1). Polarized light can be of a single wavelength or polychromatic, as long as all waves travel in the same plane.

There exist a range of phototherapeutic modalities, exploiting different parts of the visible spectrum (Fig. 2). The major modalities are: UV-A and UV-B therapies, low level laser therapy (LLLT), light emitting diode (LED) therapy and IR therapies. UV therapies are often used to reduce the severity of some chronic skin conditions such as psoriasis

* Corresponding authors at: Institute for Health and Sport, Victoria University, VIC, Australia.
*E-mail addresses:* Vasso.Apostolopoulos@vu.edu.au (V. Apostolopoulos), Maja.Husaric@vu.edu.au (M. Husaric), Jim.Kiatos@vu.edu.au (D. Kiatos).
[1] These authors contributed equally.

https://doi.org/10.1016/j.maturitas.2018.07.009
Received 8 June 2018; Received in revised form 7 July 2018; Accepted 18 July 2018

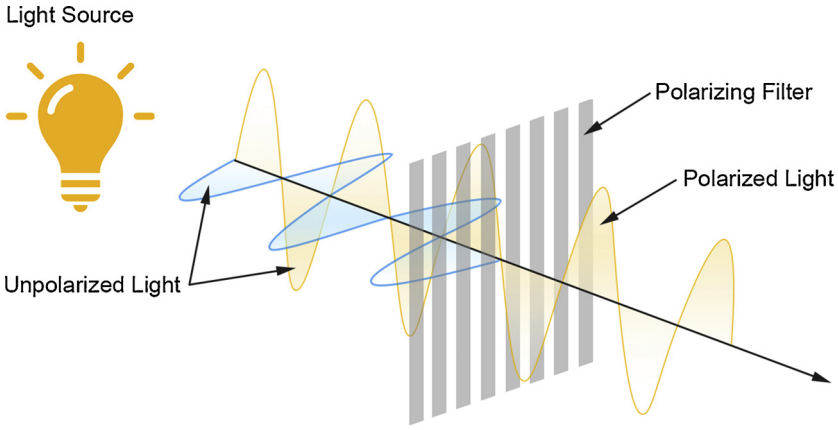


**Fig. 1.** Schematic diagram of the polarization process.

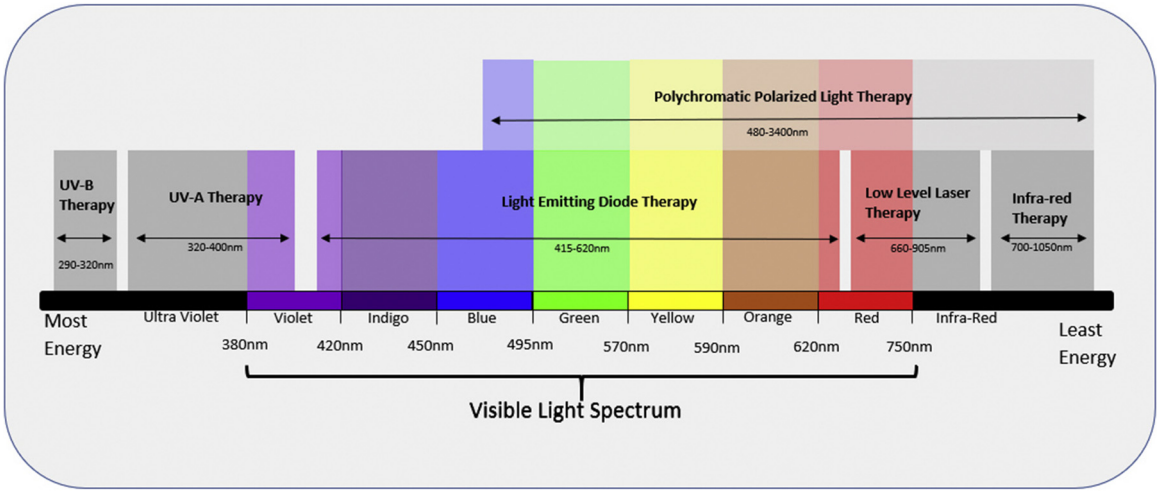


**Fig. 2.** Summary detailing the light parameters of commonly used phototherapies.

[6], and there is some evidence to support its use in atopic dermatitis [7]. UV-A therapies typically utilize light in the 320–400 nm range, and are generally considered safe for use, though due to the high energy of light in this range, burns can occur [8]. Narrow band UV-B therapy utilizes light in the 290–320 nm range. Though correct application is generally considered safe, UV-B radiation is strongly associated with development of a wide range of skin cancers and so it's use must be tightly controlled [9]. Following its invention in the 1960s, laser light has been successfully used therapeutically with much of the relevant research focused on low level laser therapy for its low risk of burns and other adverse effects. LLLT is used in a range of conditions, such as musculoskeletal injuries, pain relief and wound healing [10], and has the strongest evidence to inform its use compared to other forms of phototherapy. IR therapies utilize either "near" or "far" wavelengths in the IR light spectrum (700 nm–1050 nm), and traditionally has been used to warm premature infants in hospital due to its low energy levels. These low energy levels make IR light very safe, however it has questionable capacity for penetration, limiting its use to dermatological application. LED therapies are a newer entity, which utilize light of a single specific wavelength, typically characterized by color. The most common modalities are blue and red LED therapies, however yellow and green devices are also available. As there is little evidence surrounding its clinical use, these devices are largely limited to cosmetic applications, for conditions such as acne vulgaris. The low manufacturing cost of LED systems has prompted a number of commercial entities to begin the development and sale of these devices despite lacking evidence supporting their use.

Light therapy using broad, visible spectrum polarized light (PLT) has also gained in popularity over the past 30 years. Personalized 'at home' devices exist for many of these therapies, allowing patients to use laser or PLT devices to self-administer their own treatment. These devices are marketed as aids for the treatment of various skin conditions such as psoriasis, atopic dermatitis, acne vulgaris and vitiligo. Despite these assertions by device manufacturers, there is a dearth of evidence supporting the efficacy of PLT in many of these scenarios.

Over 3 decades ago, it was proposed that when the cell membrane phospholipid bilayer is exposed to a laser or polarized light, the random distribution of polar-headed phospholipids is replaced by a more structured configuration, possibly redistributing the biologically active proteins and enabling more efficient function [11]. Additionally, it has been suggested that PLT could also improve cellular processes such as active and passive transport, recognition of antibodies and hormones, release and reception of neurotransmitters or energy transmission and conversion [12,13], all of which may contribute to improving the healing process. More recently, it was proposed that different wavelengths cause different rates of cellular apoptosis, however the physiological mechanisms are still unclear [14].

In more recent years, the use of PLT has been proposed in the treatment of various conditions and is reported to accelerate the healing process. PLT utilizes broad spectrum, polarized light, typically within the visible, and infra-red ranges (400 nm – 3400 nm). The polarization reduces the amount of energy emitted by the light, making it safer to use, whilst still allowing it to penetrate into deeper tissues. PLT has been associated with improved outcomes in *in-vivo* models as well as in

the clinical treatment of deep dermal burns, pressure and diabetic ulcers. Expected tissue healing times are significantly decreased in comparison to standard wound care protocols. Surgical interventions are avoided and both clinicians and patients frequently express their disbelief in the positive outcomes [12,15,16]. Despite this positive evidence, qualitative measures are scarce, relying instead on expert opinion, subjective outcome measures and lacking robust controlled measures.

Very little documented research has been carried out on polychromatic spectrum PLT under experimental conditions. Most published studies involve laser treatments such as PDT, or the use of single wavelength phototherapy. It is not clear what changes occur at the molecular, cellular and physiological levels when PLT is used to treat skin lesions and wounds. Here we present the limited research that exists regarding PLT with an emphasis on dermal wound healing and musculoskeletal injuries. This review focuses on possible PLT effects occurring at the cellular level. In addition, we describe how other forms of light therapy have been shown to affect cells at the cellular level, to identify possible links between them and PLT.

## 2. Methodology

Searches were conducted using PUBMED, CINAHL (Cumulative Index to Nursing and Allied Health Literature), The Cochrane Library, and MEDLINE using the following search terms: light therapy, phototherapy, polarization, bio stimulation, polarized light, polychromatic non-coherent light. In addition the following search terms were included in the context of light therapy – wound healing, skin wound, biostimulation, ulcer, diabetic ulcer, pressure ulcer, burns and musculoskeletal injuries. English and American English spellings of polarized and it derivatives were included. Studies from all years were included. Reference lists of reviewed articles were also assessed for other relevant articles. Inclusion criteria were peer reviewed papers and therapeutic use of polychromatic polarized light. Studies that used UV spectrum light for treatment and non-English articles which were not able to be translated were excluded. Title and abstract analysis was performed to identify appropriate studies, and full texts of included studies were assessed. In total 17 studies were found on polarized light, covering a range of topics including: ulcers, burns, wounds and musculoskeletal injuries.

## 3. Non-healing wounds

One study investigated the effects of broad spectrum PLT to patients with wounds which were resistant to normal treatment methods. PLT of 400 nm–3000 nm was applied to 30 patients, with non-healing wounds including diabetic foot ulcers, atherosclerosis obliterans, varicosities or post thrombic syndromes, decubitus ulcer and osteomyelitis. Following PLT exposure resulted in decreased wound secretions and increased epithelialization and wound closure. In addition, this led to an increased immune cell infiltration and secretion of cytokines and chemokines which was proportional to the rate of healing [12]. However, much of this research was not appropriately blinded, controlled, randomized, or statistically analysed weakening its conclusion. Nevertheless, the study demonstrated a compelling case for the possibilities of PLT application for delayed wound healing.

## 4. Dermal burns

Dermal burns, which are known to have significantly reduced potential for healing, have been studied as a target for PLT. In one study, 22 patients with burns were treated with polarized light which subjectively accelerated the healing rate and required less frequent treatments [16]. Whilst promising, the study outcome was based on subjective expert opinion, and lacked a control or sham treatment group by which to make comparisons, decreasing the applicability of the study. In rat burn models however, PLT has been shown to have a positive effect on wound healing. In fact, second degree burns created on the backs of rats were analysed and scored weekly for 3 weeks, comparing their macroscopic and histopathological properties. Macroscopically, wound closure was improved in the PLT group, as well as histopathologically significant improvement in vascularization and epithelialization. This data adds to the theory that PLT accelerates healing by affecting both the immediate and later stages of the healing process [17]. In another study, the effects of 400 nm–2000 nm PLT on the healing effects of third degree burns in rats with or without diabetes was evaluated. Diabetes is known to cause significant diminishment of a patients healing capacity. Hence, the effects of PLT over 3 weeks, was assessed in regards to inflammation, re-epithelialization, neovascularization, fibroblast proliferation and collagen fibre deposition. PLT was shown to increase collagen deposition, enhance the inflammatory response and improve vascularization of wounds. Notably, it was shown that 10.2 $J/cm^2$ to be the most effective dose, with increased doses causing effect [18].

## 5. Artificial wounds

Some studies have used artificial or surgical wounds to determine the effects of PLT on healing. One such study used a cohort of 20 patients undergoing skin grafts as a model to examine this. The donor areas for skin grafts were considered ‘standard wounds’. As each patient was to have grafts taken from skin on both thighs, they became their own control. The wounds were tended and dressed via standard hospital procedures, but one thigh was irradiated with PLT which showed vast improvement in healing [19]. The creation of standard wounds, although controlled, also introduces possible sources of error. For example, controlled surgical procedures are unlikely to generalize well to the realistic setting of pathological wounding. However, this study does provide a good baseline for future studies of real wounds by limiting the number of confounding variables that can be encountered in more realistic settings, such as infection, wound location and debris. The model of using the patient as their own control has likewise benefits and risks. It ensures even baseline variables between experimental and control subjects, meaning specific participant factors that may influence healing (e.g. individual pathology), are accounted for but does not account for a systemic mode of effect such as immunomodulation, which would have effects on bilateral wounds. Animal models can go some way to remedying this, as variables can be more tightly controlled between experimental animals. In Wistar rats the effects of LLLT and PLT on wound healing was evaluated; each rat received a single, dorsal, surgical cut, followed by 20 $J/cm^2$ and 40 $J/cm^2$ of 685 nm LLLT and 400 nm–2000 nm, and compared against untreated control group. It was noted that 20 $J/cm^2$ of PLT or LLLT caused improvements in collagen deposition and organization, and PLT additionally increased the number of myofibroblasts present [20]. A similar study used 480 nm–3400 nm PLT on full thickness skin wounds and noted statistically significant improvements in epithelialization and suggested a qualitative (but non-significant) improvement in wound healing [21]. In addition, different light parameters were assessed, such as, polarized, linearly polarized, right circularly polarized and left circularly polarized, to a 20 mm diameter wound. The wounds showed significant decrease in size after exposure to right circularly and linearly polarized light, and type 1 procollagen mRNA expression was upregulated in the right circularly polarized light group [22]. Further, right circularly and linearly polarized light groups showed increased proliferation of fibroblasts. This study provides important information regarding the physiological effects caused by right circularly polarized treatment and that an optical active material possessing a circular dichroic spectrum facilitated a biochemical reaction [22]. This study had a strong methodology, with appropriate controls and quantitative measures giving more reliable evidence in favour of PLT (Table 1).

**Table 1**
Effects of Low level laser therapy (LLLT) on cell surface markers, chemokines, cytokines.

| Cell type/Model | Cell surface protein or molecule | Treatment | Result | Outcomes |
|---|---|---|---|---|
| Mature dendritic Cells [34] | MHC II | 810 nm LLLT | Downregulated | Anti-inflammatory effect |
| | CD86 | | Upregulated | |
| Mature dendritic Cells [35] | MHC I | 690 nm LLLT | Downregulated | Anti-inflammatory effect |
| | MHC II | | | |
| | CD 80 | | | |
| | CD86 | | | |
| | CD 40 | | Unchanged | |
| Rat Model [36] | IL-1beta | 870 nm LLLT | Decreased | Anti-inflammatory effect |
| Aortic smooth muscle cells (*in-vitro*) [37] | IL-1beta | 780 nm LLLT | Decreased | Anti-inflammatory effect |
| Mice [41] | MCP-1 | 780 nm LLLT | Decreased | Anti-inflammatory effect |
| Arthritis induced rats [40] | CCL2 | 830 nm LLLT | Decreased | Anti-inflammatory effect |
| | CCL4 | | | |
| Human monocytes [39] | CCL2 | 660 nm LLLT | Decreased | Anti-inflammatory effect |
| | CXCL10 | 808 nm LLLT | | |
| | TNF-alpha | | | |

## 6. Ulcers

Ulcers, regardless of their cause, often have poor capacity for healing, and several studies have determined whether PLT can play a role in reversing this. In a study comprising 55 patients with paired control and experimental ulcers, demonstrated significant improvement in healing with 50% of the wounds completely resolved within one week [15]. Likewise, pressure ulcers were also significantly improved in 40 patients in a randomized single-blinded control trial which used wound surface area and the pressure ulcer scale as outcome measures [23]. However, the control and experimental groups were poorly matched at baseline and wound scoring was inconsistent. Despite the promising outcomes, the differences at baseline may have skewed the results towards favourable healing with PLT. In addition, in 25 patients with venous leg ulcers were significantly reduced (wound surface area and number of ulcers) following phototherapy once a day for four weeks [24]. PLT has also been shown to be effective in ulcer prevention in an acute care setting. In fact, 10 min of PLT / day in addition to standard ulcer prevention protocols resulted in less sacral and heel ulcers of grade II and above over the two months in 23 patients compared to controls. This suggests that PLT could be an effective adjunct to normal ulcer prevention techniques in bedridden patients. This evidence, whilst preliminary, indicates that PLT has potential as a non-invasive non-pharmacological intervention in ulcer control and prevention, however robust, controlled trials are required to fully expand these findings.

## 7. Musculoskeletal injuries

Another area in which PLT has been applied clinically is the treatment of musculoskeletal injuries. Three studies have assessed the use of PLT in tendinous injuries of the lateral elbow, generally finding positive results. Tendinopathies are known to be difficult injuries which often have limited improvements to standard therapies. One study compared the effects of supervised exercise rehabilitation, Cyriax physiotherapy (a structured, unsupervised rehabilitation regimen) and PLT to patients reported pain and pain-free grip strength in these patients. It was noted that supervised physiotherapy to be the superior intervention, however, PLT did show significant improvements in all parameters [25]. PLT has also been compared to LLLT in the treatment of these patients. Fifty patients were divided into two groups and received four weeks of either LLLT or PLT in conjunction with a standard exercise program, finding no significant differences amongst the two in pain and functional improvement, though both groups showed improvement from baseline [26]. In a similar vein, PLT has been shown to be effective in treating lateral elbow epicondylalgia, decreasing patient pain and increasing function and pain-free grip strength [27]. While these studies provide positive evidence for the place of PLT in treating these conditions, all three suffer from the lack of an untreated, or standard practice control and lack of blinding of patients and practitioners. This weakens their conclusions as it is unclear whether the effects demonstrated were due to the PLT intervention, or another factor such as patient healing, placebo or chance. Nonetheless, they provide an interesting outlook of PLT's efficacy in the treatment of these stubborn injuries. Another study investigated the effect of PLT on acute ankle sprains, a common, painful injury encountered in physical therapy. They enrolled 50 participants and divided them evenly into control and experimental groups. Both groups received standard cryotherapy and the experimental group additional 5 treatments of PLT (10 min. daily, for 5 days), and patient reported pain scores, oedema and ankle range of motion (ROM) were assessed after 5 days. PLT was found to cause statistically significant improvement across all parameters when compared to control, providing strong evidence of its potential for treatment. This study had robust methodology, though was only single blinded, leaving it unable to account for placebo effect of treatment, or the psychological effects of regular contact with health care personnel [28]. Likewise, in patients with idiopathic carpal tunnel syndrome, a painful condition in the hand PLT 3 times / week for 6 min over 4 weeks, showed improvements in nocturnal pain and paraesthesia but did not report any statistical analysis or effect sizes and did not use a control group, limiting the information that can be gained from the study [29]. Overall, there is evidence that suggests that PLT can improve patient symptoms and function in tendinous and ligamentous injuries, however methodological issues with most of the studies in the area limit the applicability of this research, and more carefully controlled trials are required to fully confirm PLTs efficacy, as well as to create dose response curves and protocols. Additionally, there are no reports on the physiological mechanism for the effects of PLT in these injuries, and *in vitro* studies are required to expand on this to enable its translation into clinical practice.

## 8. Limitations

While there is a growing body of evidence demonstrating the healing potential of PLT, the body of literature remains small, and generally of low quality. Most of the identified studies had small sample sizes and generally lacked robust methodologies, including blinding and control populations. Additionally, many of the studies relied heavily on qualitative outcomes and had mixed results regarding statistically significant changes. There was also variance within the protocols of PLT application. In general, the application of PLT was similar: treatment was applied for short time frames (1–3 weeks), with some short term follow up. However, a number of differing protocols were used regarding the amount, time and frequency of application, making a comparison of results difficult. Additionally, no long-term follow up

studies have been reported, leaving information as to the long-term effects of PLT scarce. Despite these flaws, the overall consensus was that PLT provided small to modest improvements, particularly at the early time points [12,15–17,19] on wounds with a greater preservation of tissue structural integrity [23,30]. However, there are still many questions remaining that need to be answered for more widespread use of PLT to be recommended. Firstly, the safety of PLT is yet to be fully evaluated. There is a case study reporting the development of a metastasized myxoid melanoma in a patient using PLT [31] however, the application of this is limited due to methodological issues. Some forms of light, most notably UV, have been associated with an increased risk of malignancy [32], and as such it is important to evaluate these, and any other, patient risks. It is important to note however, that UV therapy has been found to be a safe intervention [33], and based on the lower energy levels involved in PLT, this is likely to hold true. However, if PLT is to become a more widely used intervention full risk evaluation must be performed. There is also little evidence regarding the mechanisms by which PLT may exert its effect. There is some indication that PLT has effects on both local connective tissue cells [12,22], and has capacity to influence the immune system [12], though little information exists regarding specific, biological changes driving this. One study identified a change in the expression of procollagen mRNA [22], providing a rationale for further studies to determine changes at the molecular and cellular level (Fig. 3). While there is a complete absence of evidence supporting a biochemical or physical mechanism for the effects of PLT on cell function. However, some suggested mechanisms have been theorized about, these are yet to be substantiated (Fig. 4). These mechanisms include changes to the polarization or structure of the phospholipid membrane, increased ATP production via mitochondrial stimulation or activation of photosensitive receptors in either the cell or nuclear membranes, with resulting changes to cell physiology or gene expression. Finally, further controlled, robust studies are required to demonstrate PLTs effectiveness, as well as to establish best practice dosage protocols and dose response curves. Overall, the literature seems to indicate a generally positive effect, however significant methodological issues make definitive statements of efficacy impossible. It does however provide a direction for future research, as it holds the potential to provide a safe, cheap and effective adjunct to the standard care of a number of conditions.

## 9. Immunomodulation: a low-level laser perspective

As the immune system is most active in the acute stages of wound healing, and PLT has been shown to be most effective at this time, it is inferred that PLT may exhibit immunomodulatory effects. These questions may be answered by selectively examining the effects of PLT on immune cells. The lack of PLT research makes these questions difficult to answer, however, research published using LLLT, in which a single wavelength is used may pave the way to possible mechanisms of action for PLT.

Phototherapies, particularly LLLT, have been demonstrated to have immunomodulatory effects on mammalian cells. Chen et al., examined the effects of an 810 nm laser on murine bone-marrow derived dendritic cells (DCs), *in-vitro*. Immature DCs were matured with either lipopolysaccharide or CpG oligodeoxynucleotide, and exposed to laser light therapy, resulting in the downregulation of MHC class II and upregulation of CD86 cell surface markers. Immature DCs exposed to the same LLLT had no change. The authors concluded that LLLT has an anti-inflammatory effect on activated DCs, and suggested it was possibly mediated by cAMP and reduced NF-κB signalling [34]. In another study, mature splenic DCs, which had been treated with a photosensitizer, were treated with a 690 nm laser at a dose of 5 J/cm$^2$, and showed downregulation of cell surface markers (MHC class I, MHC class II, CD80 and CD86) and a resulting suppression of T cell activation [35]. In rats, 2 groups received wounds by scalpel (groups A and C) whilst the other 2 groups had their wounds induced by laser (groups B and D). Two of the four groups (A and B) were subject to 2 bouts of low level laser irradiation 24 h apart following their wounds (wavelength 870 nm, total irradiation time 120 s and 9.6Jcm$^2$). When comparing Group A (scalpel induced wound with LLLT) with group C (laser induced wound with no LLLT) it was clear that there was a marked decrease in the expression of IL-1β for group A. Additionally, there were slight, non-significant decreases in mRNA levels of IL-1β in Group B (laser-induced wounds with LLLT) when compared to Group D (laser induced wounds with no LLLT) [36]. Gene expression of IL-1β in Group B (laser induced wound and LLLT) was slightly lower than that of Group

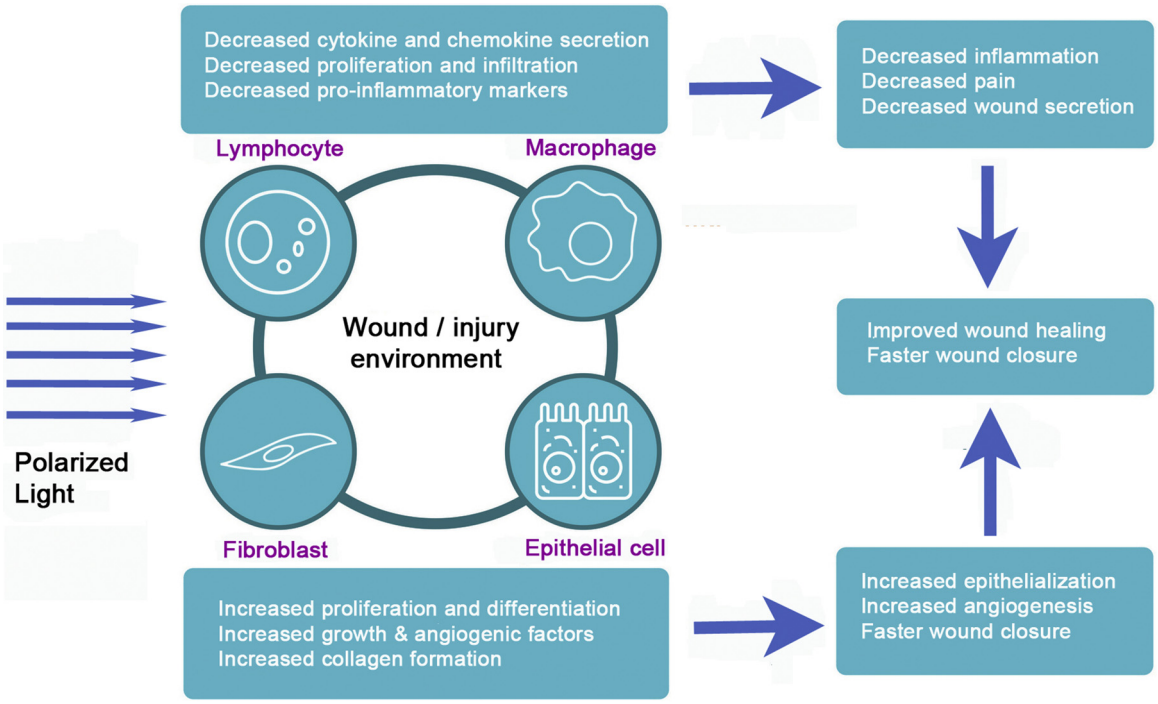


**Fig. 3.** Schematic representation of the immunomodulatory effects of polarized light leading to improved wound healing.

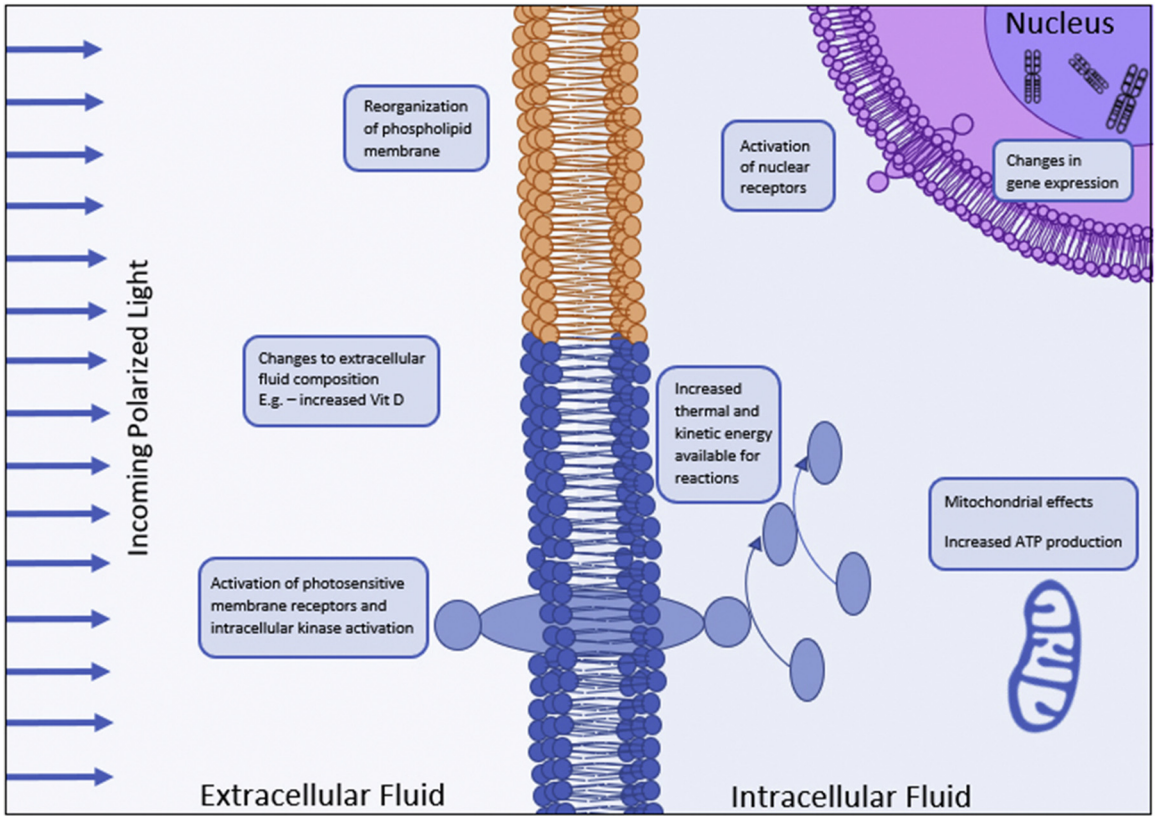


**Fig. 4.** Summary of the possible physiological mechanisms of polarized light therapy.

C (scalpel induced wound and no LLLT) but not significantly different. Likewise, in porcine aortic smooth muscle cells, IL-1β gene expression was also reduced within the first half hour following LLLT treatment (780 nm with 1–2 J/cm$^2$) [37]. Moreover, the effects of light-emitting diode therapy (LEDT) showed that LEDT induced pro-inflammatory cytokines (TNF-α and IL-1β) in an acute time frame but switched to anti-inflammatory (IL-10) post 5 days LEDT exposure [38].

The effects of a single bout of LLLT (660 nm at 1–2 J/cm$^2$) to human monocyte cell line (THP-1) showed that CCL2 mRNA expression was enhanced 24 h' post irradiation, although exposure at 3 J/cm$^2$ LLLT suppressed CCL2 expression in THP-1 cells [39]. This result suggests that at differing doses, LLLT can be a potent enhancer or suppressor of pro-inflammatory cytokines and chemokines in human monocytes. This study also showed that 1 J/cm$^2$ LLLT induced CCL2 and CXCL10 protein expression whereas higher doses of 2 J/cm$^2$ and 3 J/cm$^2$ did not. In rats with collagen-induced arthritis, LLLT upregulated the expression of CCL2 and CCL4 in the synovial tissues, resulting in the enhancement of healing [40]. Additionally, in another study it was noted that infrared LLLT of 780 nm at 10 J/cm$^2$ administered across three sessions markedly reduced MCP-1 levels, and may have a beneficial effect on surgical wounds [41]. Although it is not possible to automatically extrapolate the results of this *in vitro* experiment to intact living organisms, the data is suggestive that the immunomodulatory effect of LLLT on monocyte polarization could be a potential treatment for allergic or auto-immune diseases and at a different dose could also be used to promote inflammation and immune response to pathogenic stimuli.

## 10. Conclusion and future prospects

Many of the studies included in this review suffered from flawed methodology, weakening the recommendations that can be made from this review. Overall however, the evidence is largely favourable of PLT as a therapy in a range of conditions, with a strong safety profile, and unanimously beneficial effects reported. However, before PLT can be confidently recommended for regular medical use, research with robust methodologies must be done in both healthy and pathological settings to fully understand its effects. Dose response trails must also be performed to find the most effective protocols for treatment of the various conditions identified. Additionally, studies with long term follow up should be employed to fully validate the long-term efficacy and safety profile of PLT. As an adjunct to this, *in vitro* studies on the effects of PLT on the various cell types involved in the healing process should be performed to provide plausible therapeutic mechanisms and targets. Overall, PLT is an exciting therapy with large potential for utilization in a range of conditions, however a deeper understanding of its biological mechanisms and physiological effects is essential for its translation into commonplace medical use.

## Contributors

Jack Feehan contributed to the drafting of the article, and edited and reviewed the draft.

Soraya Patricia Burrows contributed to the drafting of the article.

Leonardo Cornelius contributed to the drafting of the article.

Alyse Malietzis Cook contributed to the drafting of the article.

Kathleen Mikkelsen contributed to the drafting of the article, and edited and reviewed the draft.

Vasso Apostolopoulos contributed to the drafting of the article, and edited and reviewed the draft.

Maja Husaric contributed to the drafting of the article, and edited and reviewed the draft.

Dimitrios Kiatos contributed to the drafting of the article, and edited and reviewed the draft.

## Conflict of interest

The authors have no conflict of interest to declare.

## Funding

No funding was received specifically for the preparation of this review.

## Ethical approval

No ethics was required for this review article.

## Provenance and peer review

This article has undergone peer review.

## Acknowledgements

The authors would like to thank the Immunology program in the Centre for Chronic Disease and the College of Health and Biomedicine for support and discussions. VA would like to thank the Victoria University College of Health and Biomedicine start-up funds and the Centre for Chronic Disease, Victoria University for financial support. KM was supported by the Vice Chancellors Victoria University Scholarship and JF by the University of Melbourne Postgraduate Scholarship. Finally, the authors thank Myfanwy Thewlis for the production of the figures.

## References

[1] S. Guo, L.A. DiPietro, Factors affecting wound healing, J. Dent. Res. 89 (2010) 219–229.
[2] D.T. Mc Coy, Egyptian Mythology for Smart People, (2017).
[3] A.H. Coulter, Alternative and Complementeray Therapies 92003, (2018).
[4] J.W. Stewart, F.M. Quitkin, M. Terman, J.S. Terman, Is seasonal affective disorder a variant of atypical depression? Differential response to light therapy, Psychiatry Res. 33 (1990) 121–128.
[5] CIE S. 017/E: 2011 2011 ILV: International Lighting Vocabulary. Commission Internationale de l Éclairage.
[6] R.K. Singh, K.M. Lee, M.V. Jose, M. Nakamura, D. Ucmak, B. Farahnik, et al., The patient's guide to psoriasis treatment. Part 1: UVB phototherapy, Dermatol. Ther. (Heidelb) 6 (2016) 307–313.
[7] M. Hannuksela, J. Karvonen, M. Husa, R. Jokela, L. Katajamäki, M. Leppisaari, Ultraviolet light therapy in atopic dermatitis, Acta Derm.-Venereol. Suppl. 114 (1985) 137–139.
[8] E.C. Siegfried, M.S. Stone, K.C. Madison, Ultraviolet light burn: a cutaneous complication of visible light phototherapy of neonatal jaundice, Pediatr. Dermatol. 9 (1992) 278–282.
[9] H. Slaper, A. Schothorst, Risk evaluation of UVB therapy for psoriasis: comparison of calculated risk for UVB therapy and observed risk in PUVA-treated patients, Photo-dermatology 3 (1986) 271–283.
[10] L.J. Walsh, The current status of low level laser therapy in dentistry, part 1. Soft tissue applications, Aust. Dent. J. 42 (1997) 247–254.
[11] I. Kertesz, M. Fenyö, E. Mester, G. Bathory, Hypothetical physical model for laser biostimulation, Opt. Laser Technol. 14 (1982) 31–32.
[12] M. Fenyo, Theoretical and experimental basis of biostimulation, Opt. Laser (1984) 4.
[13] T. Kubasova, M. Horváth, K. Kocsis, M. Fenyö, Effect of visible light on some cellular and immune parameters, Immunol. Cell Biol. 73 (1995) 239.
[14] L. Helander, H.E. Krokan, A. Johnsson, O.A. Gederaas, K. Plaetzer, Red versus blue light illumination in hexyl 5-aminolevulinate photodynamic therapy: the influence of light color and irradiance on the treatment outcome in vitro, J. Biomed. Opt. 19 (2014) 088002.
[15] P. Iordanou, G. Baltopoulos, M. Giannakopoulou, P. Bellou, E. Ktenas, Effect of polarized light in the healing process of pressure ulcers, Int. J. Nurs. Pract. 8 (2002) 49–55.
[16] S. Monstrey, H. Hoeksema, H. Saelens, K. Depuydt, M. Hamdi, K. Van Landuyt, et al., A conservative approach for deep dermal burn wounds using polarised-light therapy, Br. J. Plast. Surg. 55 (2002) 420–426.
[17] C.A. Karadag, M. Birtane, A.C. Aygit, K. Uzunca, L. Doganay, The efficacy of linear polarized polychromatic light on burn wound healing: an experimental study on rats, J. Burn Care Res. 28 (2007) 291–298.
[18] P.C. Oliveira, A.L.B. Pinheiro, I.C. de Castro, J.A. Reis Junior, M.P. Noia, C. Gurgel, et al., Evaluation of the effects of polarized light (λ400–200 nm) on the healing of third-degree burns in induced diabetic and nondiabetic rats, Photomed. Laser Surg. 29 (2011) 619–625.
[19] S. Monstrey, H. Hoeksema, K. Depuydt, Van Maele, K. Van Landuyt, P. Blondeel, The effect of polarized light on would healing, Eur. J. Plast. Surg. 24 (2002) 377–382.
[20] A.L.B. Pinheiro, D.H. Pozza, M.G.D. Oliveira, R. Weissmann, L.M.P. Ramalho, Polarized light (400–2000 nm) and non-ablative laser (685 nm): a description of the wound healing process using immunohistochemical analysis, Photomed. Laser Ther. 23 (2005) 485–492.
[21] P. Iordanou, E.G. Lykoudis, A. Athanasiou, E. Koniaris, M. Papaevangelou, T. Fatsea, et al., Effect of visible and infrared polarized light on the healing process of full-thickness skin wounds: an experimental study, Photomed. Laser Surg. 27 (2009) 261–267.
[22] K. Tada, K. Ikeda, K. Tomita, Effect of polarized light emitting diode irradiation on wound healing, J. Trauma 67 (2009) 1073–1079.
[23] A. Durovic, D. Maric, Z. Brdareski, M. Jevtic, S. Durdevic, The effects of polarized light therapy in pressure ulcer healing, Vojnosanit. Pregl. 65 (2008) 906–912.
[24] L. Medenica, M. Lens, The use of polarised polychromatic non-coherent light alone as a therapy for venous leg ulceration, J. Wound Care 12 (2003) 37–40.
[25] D. Stasinopoulos, I. Stasinopoulos, Comparison of effects of cyriax physiotherapy, a supervised exercise programme and polarized polychromatic non-coherent light (bioptron light) for the treatment of lateral epicondylitis, Clin. Rehabil. 20 (2006) 12–23.
[26] D. Stasinopoulos, I. Stasinopoulos, M. Pantelis, K. Stasinopoulou, Comparing the effects of exercise program and low-level laser therapy with exercise program and polarized polychromatic non-coherent light (bioptron light) on the treatment of lateral elbow tendinopathy, Photomed. Laser Surg. 27 (2009) 513–520.
[27] D. Stasinopoulos, The use of polarized polychromatic non-coherent light as therapy for acute tennis elbow/lateral epicondylalgia: a pilot study, Photomed. Laser Ther. 23 (2005) 66–69.
[28] D. Stasinopoulos, C. Papadopoulos, D. Lamnisos, I. Stasinopoulos, The use of bioptron light (polarized, polychromatic, non-coherent) therapy for the treatment of acute ankle sprains, Disabil. Rehabil. 39 (2017) 450–457.
[29] D. Stasinopoulos, I. Stasinopoulos, M. Johnson, Treatment of carpal tunnel syndrome with polarized polychromatic noncoherent light (bioptron light): a preliminary, prospective, open clinical trial, Photomed. Laser Ther. 23 (2005) 225–228.
[30] J. Verbelen, Use of polarised light as a method of pressure ulcer prevention in an adult intensive care unit, J. Wound Care 16 (2007) 145–150.
[31] M. Ulamec, A. Soldo-Belic, M. Vucic, M. Buljan, B. Kruslin, D. Tomas, Melanoma with second myxoid stromal changes after personally applied prolonged photo-therapy, Am. J. Dermatopathol. 30 (2008) 185–187.
[32] J. D'Orazio, S. Jarrett, A. Amaro-Ortiz, T. Scott, UV radiation and the skin, Int. J. Mol. Sci. 14 (2013) 12222–12248.
[33] E. Lee, J. Koo, T. Berger, UVB phototherapy and skin cancer risk: a review of the literature, Int. J. Dermatol. 44 (2005) 355–360.
[34] A.C. Chen, Y.Y. Huang, S.K. Sharma, M.R. Hamblin, Effects of 810-nm laser on murine bone-marrow-derived dendritic cells, Photomed. Laser Surg. 29 (2011) 383–389.
[35] D.E. King, H. Jiang, G.O. Simkin, M.O. Obochi, J.G. Levy, D.W. Hunt, Photodynamic alteration of the surface receptor expression pattern of murine splenic dendritic cells, Scand. J. Immunol. 49 (1999) 184–192.
[36] I.S. Sayed, A. Saafan, F.K. Abdel-Gawad, T.A. Harhash, M.A. Abdel-Rahman, Effect of low- level laser therapy on gene expression of vascular endothelial growth factor and interleukin-1 ß in scalpel-induced and laser-induced oral wounds in rats, J. Dent. Lasers (2015) 1.
[37] L. Gavish, L. Perez, S.D. Gertz, Low-level laser irradiation modulates matrix metalloproteinase activity and gene expression in porcine aortic smooth muscle cells, Lasers Surg. Med. 38 (2006) 779–786.
[38] D.F. Martins, B.L. Turnes, F.J. Cidral-Filho, F. Bobinski, R.F. Rosas, L.G. Danielski, et al., Light-emitting diode therapy reduces persistent inflammatory pain: role of interleukin 10 and antioxidant enzymes, Neuroscience 324 (2016) 485–495.
[39] C.H. Chen, C.Z. Wang, Y.H. Wang, W.T. Liao, Y.J. Chen, C.H. Kuo, et al., Effects of low-level laser therapy on M1-related cytokine expression in monocytes via histone modification, Mediat. Inflamm. (2014) 2014625048.
[40] L. Zhang, J. Zhao, N. Kuboyama, Y. Abiko, Low-level laser irradiation treatment reduces CCL2 expression in rat rheumatoid synovia via a chemokine signaling pathway, Lasers Med. Sci. 26 (2011) 707–717.
[41] T.Y. Fukuda, M.M. Tanji, J.F. de Jesus, S.R. da Silva, M.N. Sato, H. Plapler, Infrared low-level diode laser on serum chemokine MCP-1 modulation in mice, Lasers Med. Sci. 28 (2013) 451–456.