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Multi-Targeted Non-Invasive Photoceutical Therapeutic Approach for Combat and Traumatic Soft Tissue Injuries

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ABSTRACT

Combat and soft tissue traumatic injuries pose unique challenges in terms of their severity, complexity, and thus need for the exploration of rapid, novel therapeutic interventions. Traditionally, combat injuries have been managed through invasive surgical procedures associated with potential complications and prolonged recovery times. However, advancements in non-invasive treatment modalities have opened up new possibilities for managing combat injuries more effectively and efficiently. The present article aims to provide a comprehensive overview of non-invasive, drug-free, biophysical therapeutic approaches for combat and external traumatic injuries, focusing on their benefits, efficacy, and potential applications. The non-invasive nature and favourable safety profile of photobiomodulation therapy (PBMT) make it an attractive option for combat injury management. The evidence on underlying mechanistic insights supports the efficacy of PBMT in promoting tissue repair, reducing pain, inflammation, oxidative stress, and facilitating functional recovery. In conclusion, the present review highlights the significant potential of non-invasive PBMT using dual/multi-wavelength light energy as a valuable therapeutic approach for traumatic soft tissue and combat injuries and extensively explores associated mechanistic insights. Further research on combination therapies using potential pharmacological agents in conjunction with PBMT, with optimal irradiation protocols and other energy-based healing modalities will favour the translation of potential non-invasive healing intervention for combat and traumatic injuries in clinical applications.

Keywords: Combat injuries; Combination therapy; Non-invasive; Photobiomodulation therapy; Soft tissue traumatic injuries; Wound healing

1. INTRODUCTION

Combat injury is an unfortunate reality faced by defence personnel serving in conflict zones around the world. The majority of injuries sustained in military combat are primarily caused by penetration, including gunshot wounds, explosive blasts, shrapnel, and contusions. The physical and emotional toll of combat situations can leave soldiers with severe injuries, both visible and hidden[1]. Combat and external traumatic injuries can cause physical, psychological discomfort, morbidity, mortality, and economic burden to the affected patients and health care sector. The therapeutic approach to soft tissue injuries in combat situations still represents a challenge. For decades, traditional medical interventions for combat wound care have played a crucial role in saving lives and restoring functionality during hostile conditions. However, the field of medicine is constantly evolving, and new approaches for soft tissue repair and regeneration focusing on non-invasive therapy during field operational duties have emerged. Currently, there is various innovative and groundbreaking form of treatment, which offers promising results, revolutionizing the rehabilitation process for combat injuries and significantly improving the quality of life for service members[2]. Combat and traumatic injuries vary in severity and nature, ranging from combat trauma, gunshot wounds, blast injuries, burns suffered during military conflict, frostbite, open fractures, dermal abrasions, lacerations, and traumatic brain injuries (TBI), along with post-traumatic stress disorders (Fig. 1). These injuries not only impact physical well-being but also pose significant psychological and emotional challenges. Combat-injured patients are highly susceptible to microbial infections. The repercussions of combat injuries can lead to delayed healing, infections, chronic pain, emotional suffering, limited mobility, reduced quality of life, affecting both the injured individuals, and their families. The compact injuries cause trauma, haemorrhage, infection, and sepsis resulting in myriad disorders associated with immune, mitochondrial dysfunctions, oxidative damage, and insufficient metabolisms, which can lead to multiple organ dysfunction syndrome[3]. Given the complex nature of these injuries, it is imperative to explore innovative treatment strategies to accelerate the wound repair process that can address the multifaceted needs of servicing personnel and the medicare sector.

Traditional medical interventions have made remarkable strides in treating combat injuries, specifically for acute care and surgical procedures. In the last few decades, advancements in trauma emergency medicine and rapid

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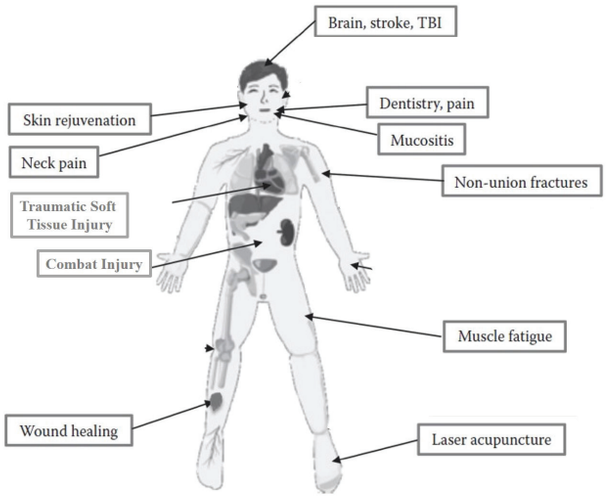

Figure 1. Image depicting various types of combat injuries, where non-invasive photobiomodulation therapy (PBMT) could promote wound healing by bioenergetic activation, inflammation & pain mitigation.

evacuation techniques have significantly increased the survival rates of soldiers injured on the battlefield. However, the traditional model of care often relies heavily on invasive interventions, such as surgeries and medication, which can have their own set of complications and limitations. The invasive therapeutic procedures, while effective in many cases, also carry inherent risks, including infections, scarring, and long recovery times. Moreover, repeated surgeries and prolonged medication use can lead to dependency, drug resistance, and undesirable side effects. These factors necessitate a paradigm shift in the strategy to combat injury treatment, and this is where non-invasive therapy plays an important and promising role.

Non-invasive therapy refers to a range of treatment modalities that aim to heal without the need for surgical intervention or pharmaceutical drugs. It harnesses the body's natural healing mechanisms using biophysical energy-based healing modalities, promoting tissue repair, pain relief, reducing inflammation, and restoring overall well-being. By utilizing non-invasive techniques, healthcare professionals can address combat injuries holistically, providing a comprehensive and personalized treatment plan for individuals[4]. The present article explores the challenges posed by combat and external traumatic injuries, examines the limitations of traditional interventions, and discusses the potential of non-invasive biophysical modalities as a transformative healing approach.

2. SOFT TISSUE INJURIES IN COMBAT SITUATIONS

Combat situations present unique challenges and risks that can lead to various types of injuries, including soft tissue injuries. It involves skin, muscles, tendons, ligaments, and other non-bony structure injuries. It can significantly impact the physical abilities, functionality, and overall well-being of combatants. Understanding the nature and prevalence of soft tissue injuries in combat situations is crucial for effective management and treatment[5].

2.1 Soft Tissue Injury Types

Soft tissue injuries are of various kinds primarily depending upon causative factors and the extent of tissue damage[6]. Table 1 shows the different types of soft tissue injuries and their properties.

Table 1. Types of soft tissue traumatic injuries and their properties

S. No.	Soft Tissue Injury	Injuries Properties
1.	Muscle Strains	Tearing/ overstretching of muscle fibers due to sudden/ excessive force.
2.	Ligament Sprains	Partial/ complete tearing of ligaments, which attach bones and stabilize joints.
3.	Contusions	Bruises resulting from direct trauma or impact to the soft tissues.
4.	Tendonitis	Inflammation and irritation of tendons, commonly caused by overuse or repetitive motion.
5.	Soft Tissue Lacerations	Deep cuts/ tears, often occurred due to sharp objects or explosive fragments.
6.	Crush Injuries	Severe compression of soft tissues between two objects, leads to tissue damage and potential complications.
7.	Burn Injuries	Owing to gunshot wounds, blast injuries

2.2 Prevalence and Impact of Soft Tissue Injuries

Soft tissue damages are among the frequently prevalent wounds in combat situations, mostly occurring alongside other traumatic injuries. It can significantly limit mobility, strength, and flexibility, affecting combat readiness and performance. Soft tissue injuries can cause significant pain, discomfort, and limitations in daily activities, hindering operational effectiveness. Chronic soft tissue injuries can lead to psychological distress, affecting the mental well-being and overall resilience of combatants[7].

2.3 Challenges in Combat-Related Soft Tissue Injury Management

Combat operations often take place in harsh environments with limited resources, complicating injury management and treatment. There is a need for quick evacuation, as the limited medical facilities in combat situations may delay definitive medical help and rehabilitation. Swift recovery and rehabilitation are crucial for combatants to return to full operational capability as soon as possible. Untreated or inadequately managed soft tissue injuries can result in chronic pain, impaired functions, and potential long-term disabilities. Understanding the nature,

mechanisms, and impact of soft tissue injuries in combat situations is essential for developing effective strategies and interventions to minimize their occurrence and optimize treatment outcomes[8]. Military healthcare professionals play a pivotal role in addressing these injuries promptly and applying suitable management techniques, ultimately enhancing the recovery process, mitigating the impact on operational readiness, and enhancing the overall well-being of combatants.

3. PHOTOBIOMODULATION THERAPY (PBMT)

PBMT is a low-power photon therapy that harnesses the potential of precise light wavelengths to modulate cellular functions and facilitate the restoration of diverse tissue damage. PBM is a non-invasive and non-thermal treatment modality, that has gained recognition and popularity in the last few decades due to its potential benefits in accelerating tissue repair, reducing inflammation, relieving pain, and improving cellular functions in a wide range of medical conditions[9,10]. The energy-based PBMT involves the application of low-power photons (optimum irradiation parameters like wavelength, energy density, etc.) to targeted areas of the body (light-tissue interaction). Penetration of NIR pulsed 810 nm and superpulsed 904 nm lasers are distinct up to the different extent of tissue layers and thereby, affecting absorption by different cellular chromophores/ photoacceptors. The absorption depth of the light greatly relies on illuminated wavelength and pulsed frequency. Depending on the penetration power of these laser wavelengths, 810 nm pulsed showed better therapeutic efficacy for superficial injury however, superpulsed 904 nm laser showed better therapeutic efficacy for both superficial as well as deep burn tissues (Fig. 2).

Molecular signaling mechanisms of PBMT are depicted in Fig. 3, wherein, absorption of light through the mitochondrial complex-IV of electron transport chain i.e. cytochrome c oxidase (CCO), and non-mitochondrial cellular photoacceptors (chromophores) (transient receptor potential vanilloid (TRPV), heat-sensitive ion channels) leading to activation of a cascade of molecular and cellular events. Upon photostimulation, inhibitory nitric oxide (NO) is released from CCO, which in turn enhances its activity, which subsequently modulates various specific cellular events such as pH, intracellular calcium ion levels, mitochondrial membrane potential, ATP generation, and oxygen consumption. Absorbed light energy stimulates cellular metabolism, increases adenosine triphosphate (ATP) production, and modulates various cellular signaling pathways, ultimately helping wound repair, reducing inflammation, oxidative stress, and alleviating pain[11]. PBMT has shown efficacy in a variety of medical fields, including sports medicine, orthopedics, dermatology, dentistry, and neurology. It has been used to accelerate the healing process in soft tissue injuries, promote bone regeneration, alleviate pain in chronic conditions, improve skin conditions, enhance nerve regeneration, and restore cellular functions.

PBMT employs photons (light energy) to injured tissues and thereby enhances cellular proliferation, collagen synthesis, and angiogenesis, leading to faster repair and regeneration[10]. It can help reduce the recovery time for various injuries and surgical procedures. PBM treatment has anti-inflammatory properties and can modulate inflammatory responses by reducing pro-inflammatory cytokines and promoting the release of anti-inflammatory cytokines/ mediators[11]. PBMT has pain-relieving effects and can help reduce pain in both acute and chronic conditions. It can inhibit pain signaling pathways, stimulate endogenous opioid release, and decrease nerve sensitivity, providing

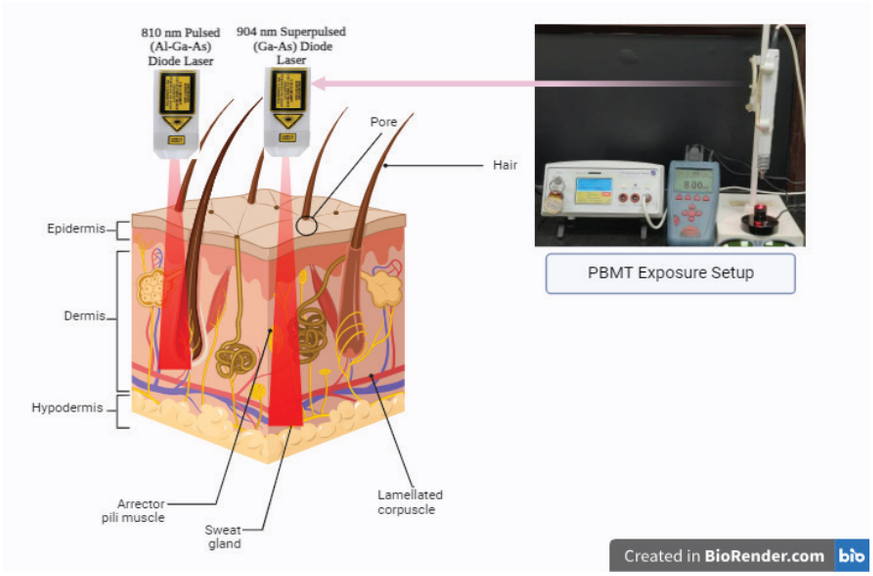

Figure 2. Image depicting distinct penetration depth of near-infrared (NIR) pulsed 810 nm and superpulsed 904 nm lasers in the skin tissue (light-tissue interaction) during photobiomodulation therapy (PBMT).

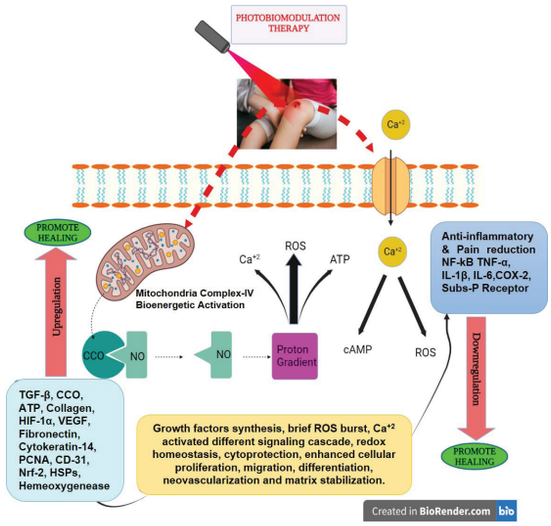

Figure 3. Schematic diagram of molecular insight of photobiomodulation mediated tissue repair & regeneration in soft tissue injuries. Light photon energy is absorbed by mitochondrial (CCO, complex-IV) and non-mitochondrial (TRPV, transient receptor potential vanilloid) cellular endogenous chromophores. After light absorption, photodissociation of inhibitory nitric oxide (NO) from CCO increases its enzymatic activity resulting in pH change, increased matrix membrane potential (MMP), ATP production, oxygen consumption, and alteration in intracellular calcium. Furthermore, TRPV (light/ heat-sensitive cation channels) facilitates the influx of Ca^{2+} ions, which subsequently modulates the effector molecules such as cAMP (cyclic AMP) and ROS. The activated effector molecules eventually regulate various transcription factors and promote the synthesis of growth factors and thereby enhancing cellular proliferation, migration, differentiation, (PCNA, cytokeratin-14, TGF-β2), angiogenesis (HIF-1α, VEGF, CD31), extracellular matrix (ECM) accumulation (collagen type 3), ECM stabilization (fibronectin), dermal hydration (AQP3), calcium homeostasis (TRPV 3, calmodulin), wound contraction (α-smooth muscle actin), bioenergetics activation (CCO, AMPK-α, ATP), cytoprotection (molecular chaperons; HSPs). In addition, PBMT also decreases oxidative stress, inflammation, and maintains redox homeostasis (TNF-α, NFkB, HO-1, COX-2, Substance P receptor). Collectively, these molecular and cellular alterations facilitate the tissue repair processes and promote healing.

relief without the need for medications. PBM treatment can exert both local and systemic effects. It can target specific areas of the body where the light is applied, but it can also have systemic benefits by modulating cellular and biochemical processes throughout the body[10]. The field of PBM is rapidly evolving, with ongoing research and clinical trials exploring its potential applications in diverse medical conditions. The accumulated evidence supports the effectiveness and safety of PBMT, leading to its integration into clinical practice and rehabilitation settings.

4. CLINICAL EVIDENCE OF THERAPEUTIC BENEFITS OF PBMT

PBMT has gained significant attention in the field of soft tissue injuries due to its potential therapeutic benefits. Numerous clinical studies have been conducted to evaluate the efficacy of PBMT in various soft tissue injuries, providing evidence of its efficacy in promoting tissue healing, reducing pain, and improving functional outcomes. The following studies highlight some key clinical findings supporting PBMT in soft tissue injuries.

Gigo-Benato et al. (2004) evaluated studies on PBMT in post-surgical orthopedic rehabilitation and concluded that PBMT improved functional outcomes, reduced pain, and facilitated recovery in patients undergoing various orthopedic procedures[12]. A randomized controlled trial by Vieira et al. (2012) demonstrated that PBMT significantly improved isokinetic muscle performance and reduced pain in sports young women compared to the placebo group[13]. In another study, A randomized controlled trial by Kheshie et al. (2014) revealed that PBMT resulted in faster pain relief and earlier return to daily activities in patients with knee ligament sprains compared to the control group[14]. A systematic review by Huang et al. (2015) evaluated multiple studies and concluded that PBM was found to be effective in mitigating pain in patients having ankle sprains and also improved their effective performances [15].

A randomized controlled trial showed that PBMT combined with eccentric exercise therapy led to superior clinical outcomes in recreational athletes with Achilles tendinopathy compared to the placebo group[16]. A systematic review on PBM treatment in acute and chronic injuries found that PBMT accelerated healing, reduced wound size, and improved overall wound repair[10]. These studies provide substantial evidence supporting the efficacy of PBMT in promoting tissue healing, reducing pain, and improving functional activities in various soft tissue injuries. The positive results from these clinical studies highlight the potential of PBM as a valuable therapeutic option for combat-related soft tissue injuries, offering a non-invasive and effective treatment approach that can expedite the healing process and enhance the recovery

of combatants.

5. ADVANCEMENTS IN PBMT FOR COMBAT INJURIES

PBMT has shown promising effects in the treatment of combat-related soft tissue injuries. PBMT represents a promising strategy in complex wound management. As the field of PBM continues to advance, several future directions and potential applications in combat injuries are being explored. These advancements aim to improve the effectiveness, accessibility, and integration of PBM therapy into the military and other healthcare settings. The development of portable and wearable PBM devices can enhance the accessibility and usability of PBMT in combat situations. These devices can provide on-the-spot treatment and allow injured personnel to receive continuous PBMT during transportation or other critical periods. A study demonstrated the feasibility of a wearable PBM device for accelerating wound healing, indicating the potential of such devices in combat injuries[17]. Further research is needed to optimize the irradiation parameters of PBMT specifically for combat-related soft tissue injuries. This includes determining the optimal wavelength, power density, operation mode (continuous or pulsed), treatment duration, and repetition regimens of PBM sessions. By fine-tuning these parameters, the efficacy and efficiency of PBMT can be maximized. A study investigated the effects of different PBM parameters on surgical nerve repair to improve nerve regeneration, highlighting the importance of optimizing treatment parameters for desirable outcomes. Advancements in PBM technology and our understanding of individual variability in response to PBMT may facilitate personalized treatment approaches for combat injuries.

Recently, it has been reported that LED whole-body 'Light Pod' could help in reducing muscle fatigue, pain, and increasing better performance in combination with exercise (pre-conditioning and post-conditioning benefits of PBMT in combat situations)[18]. Tailoring PBMT-based healing devices on individual patient characteristics, such as wound type, severity, and patient-specific factors, can optimize treatment paradigms. A study demonstrated the potential of individualized PBMT protocols based on genetic markers for enhanced wound healing[19]. These future directions, new frontiers, and potential applications in PBMT for combat-related soft tissue injuries hold promise for improving patient outcomes in military healthcare settings. Advancements in PBMT and our understanding of individual variability in response to PBM may facilitate personalized treatment approaches for combat injuries. Continued research, technological advancements, and collaboration between clinicians, researchers, military, and medicare stakeholders are essential for translating these advancements into practical and effective solutions for combat injuries.

6. MULTI-TARGETED THERAPIES AND SYNERGISTIC EFFECTS WITH PBMT FOR COMBAT INJURIES

Combining PBMT with other treatment modalities in combat injury management holds the potential for synergistic effects and improved healing. Multi-targeted combination of PBMT with other modalities like physical therapy, pharmacological interventions (natural, synthetic bioagents, polymeric drug encapsulated matrices, biomaterials), and regenerative medicine (stem cell therapy) approaches may enhance tissue healing, reduce pain, and expedite functional recovery. The following section highlights some combination therapies and the synergistic effects observed when combined with PBMT in combat injuries:

Biophysical therapies and rehabilitation regimens play a vital role in the recovery of combat-related soft tissue injuries. Dos Santos et al. (2019) demonstrated that both PBMT alone and the combination of PBMT with diclofenac exhibited remarkable enhancements in functional analysis at all time intervals when compared to the injury and diclofenac-only groups. These findings suggested that PBMT, whether administered on its own or in conjunction with diclofenac, effectively lowers the inflammatory responses and enhances the walking performance of diabetic rats during the initial stages of muscle injury. Combining PBMT with pharmacological interventions can have complementary effects in combat injuries, which can enhance tissue healing, reduce pain, and expedite functional recovery. PBMT can enhance the effectiveness of pharmacological interventions and reduce the required dosage or duration of medication. This combination approach may result in better pain management and faster recovery[20]. The synergistic effects of PBMT and physical therapy were demonstrated in a study by Chow et al. (2019), where the combination led to improved repair in musculoskeletal conditions[21]. Combined treatment with PBM and non-steroidal anti-inflammatory drugs (NSAIDs) or painkillers, can have complementary effects in combat injuries. The combination of PBMT and NSAIDs resulted in improved functional recovery in peripheral nerve repair[22]. Synergistic multi-focal combination therapies in conjunction with PBMT have shown a potential pathway to enhance the healing of chronic full-thickness burn wounds[23,24].

Regenerative medicine strategies like stem cell therapy or tissue engineering, aim to promote tissue regeneration and repair. Combining PBM therapy with regenerative medicine (adipose-derived stem cells) interventions can synergistically enhance the therapeutic potential in ischemic and infected wounds of type-2 diabetic rats. PBMT can provide a favourable environment for stem cell survival and differentiation, as well as promote angiogenesis and tissue remodeling[25]. In cases where surgical intervention is required for combat injuries, combining PBMT with surgical procedures can enhance the healing process. PBMT can be used pre- and post-surgery to optimize tissue condition, reduce inflammation, and accelerate wound healing. The combination of PBMT and surgical interventions has shown promising results in various surgical specialties[26]. These combination therapies demonstrate the potential for synergistic effects when PBMT is integrated with other treatment modalities in

combat injuries. The combined approach can improve pain management, reduce inflammation, accelerate tissue healing, and enhance functional recovery. Further research and clinical trials are necessary to explore the optimal treatment duration, dosage, and sequencing of combined therapies to maximize their therapeutic effects in combat injury management. Non-invasive healing efficacy of combined PBMT approaches using binary or more different wavelengths i.e., short wavelength (red light) and long wavelength near-infrared (NIR) for combat and external traumatic injuries have been reported in many in-vivo and clinical studies[10]. A summary of the non-invasive PBMT combination therapies using dual/ multiple wavelengths for combat and external traumatic injuries along with the study outcome is outlined in Table 2.

7. CONCLUSIONS AND FUTURE PERSPECTIVE

In recent years, the management of combat and traumatic injuries has become increasingly crucial to enhancing human quality of life and extending lifespan. Therapeutic interventions for combat-impaired wounds are evolving; however, the problem persists and possesses several limitations in clinical management and dictates the search for new, promising, and cost-effective curative therapeutic interventions. This review mainly focuses on the current knowledge of recent technologies/therapies for combat and traumatic injuries, using non-invasive, energy-based biophysical healing modalities like PBMT, and combination therapy (dual/ multiple-wavelength phototherapy), which has also attracted good attention with the advancement. The optimized radiant regimens of PBMT can help in reducing pain, inflammation, augment tissue repair, promote functional recovery, and thereby facilitate the implementation of rehabilitation protocols for combat and traumatic injuries. While the efficacy of PBMT in combat, traumatic injuries has been supported and evidenced by many in-vivo, clinical studies, however, further research and advancements in PBMT are still needed. The development of phototherapy-based portable and wearable devices in operational field conditions, optimization of irradiation parameters, and exploration of combination therapies can further enhance the benefits and effectiveness of PBMT in combat injuries. Multi-focal combination therapy with PBM and other physical therapy can enhance the therapeutic healing effects. This multi-modality integration allows for a comprehensive and synergistic approach to combat, external traumatic injury management, which enhances therapeutic outcomes. The emerging therapeutic approaches for non-healing combat injuries mainly rely on multi-mode combination therapeutic approaches. The healing efficacy of multitargeted combination therapy of PBMT has shown promising effects in different preclinical and limited clinical studies. Further systematic studies are required to be conducted in this field of research as multiple pathologies associated with chronic non-healing wounds can be targeted using multifocal combination therapies. Further studies are

Table 2. Effects of the non-invasive combined dual/ multiwavelength-photobiomodulation therapy (PBMT) for combat and external traumatic injuries.

Study	PBMT Parameter	Experimental Model/ Clinical Study	Silent Findings	Ref.
Influence of dose and wavelengths of laser light on dermal wound healing.	Red light 685 nm and NIR 830 nm; 35 mW; 20 and 50 J/cm^2	Dermal injury in the dorsal side of rats.	In the combination group, H&E and picrosirius staining revealed increased collagen synthesis and well-organized collagen deposition.	27
Efficacy comparison between 665 nm diode laser hat and a combination of 665 nm and 808 nm diode laser scanner for hair growth	Red lights 655 nm, 3 J/cm^2; 655 nm, 2 J/cm^2; NIR plus 808 nm (Hz),1 J/ cm^2	Study on 90 patients	Improved outcomes with superior rise in terminal hair density observed in combination group treated with 655 nm and 808 nm lasers treatment in patients of androgenic alopecia.	28
Efficacy of PBMT and eccentric exercises for treatment of Achilles tendinopathy.	NIR light 820 nm, 12 sessions, irradiated 6 points around Archilles tendon; 60 mW/ cm^2 power density and 5.4 J per session.	Controlled randomized study; 52 athletes with chronic Achilles tendinopathy.	Combined therapy exhibited better outcomes and accelerated clinical recovery.	16
Combined PBMT using diode lasers of 670 nm and 810 nm for wound healing in diabetic rats.	Red light 670 nm, (500 mW, 10 J, 48 s), NIR light 810 nm, (250 mW, 12 J, 50 s)	Diabetic wound rat model.	In either diabetes or non-diabetic rats, combining irradiations did not improve the physical parameters of wound healing.	29

PBMT with single and combined lasers on mesenchymal stem cells	NIR 810 nm; red 660 nm; green 532 nm, and blue 485 nm; 4 J/cm^2; irradiation with 810 nm (3 s), 660 nm (24 s), 532 nm (15 s), 485 nm (15 s)	Mesenchymal stem cells derived from rabbit iliac bone marrow.	In general, combinations of two wavelengths performed worse compared to IR or red standalone, and notably, the combination treatment of IR-R seemed to be lower. Blue-green light pair was sometimes superior to either wavelength on its own.	30
Effects of dichromatic laser exposure on DNA of E. coli and plasmids	NIR 808 nm and red 660 nm; 100 mW; 25, 50, and 100 J/ cm^2	E. coli AB1157 and BH20	Red and dichromatic laser exposure reduced percentages of survival of cultures, however, dichromatic laser irradiation, these percentages are noticeably greater and the proportion of bacterial filaments with the highest fluency has increased.	31
Dichromatic and monochromatic laser irradiation effects on survival and morphology of Pantoea agglomerans	NIR light 808 nm and red light 660 nm; 100 mW; continues wave; 35, 70, 140 J/cm^2; 1, 2, 4 J, (10, 20, 40 s exposure)	P. agglomerans (isolated from pressure ulcers)	Monochromatic red and infrared lasers boosted bacterial survival at the same fluency, however, the dichromatic laser irradiation lowered bacterial survival in the log growth phase.	32
Effects of irradiation with dichromatic and monochromatic lasers on survival of Pantoea agglomerans	NIR light 808 and red 660 nm; 100 mW; continues wave; 35, and 140 J/cm^2; (10 and 40 s exposure)	P. agglomerans (isolated from pressure ulcers)	While monochromatic red laser exposure at low-doses promoted biofilm development and IR-light at high-doses lowered antibiotic-resistance to ampicillin, dichromatic laser exposure reduced biofilm formation.	33

Infrared, IR; Near-infrared, NIR; PBMT, Photobiomodulation.

critical to provide insights into how scientific evidence from combination therapy can be applied for the treatment of combat and traumatic soft tissue injuries in the clinical setting. In conclusion, PBMT holds great promise as a valuable therapeutic approach for combat and traumatic injuries. By addressing the unique challenges, methods of injured tissue collection at the field site, predictive markers, and considerations of combat injuries and continuing research efforts, the full potential of PBMT in combat, and traumatic injuries can be realized, leading to improved outcomes and enhanced quality of life for injured military and medicare patients.

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REFERENCES

1. Grimm, P.D.; Mauntel, T.C. & Potter, B.K. Combat and noncombat musculoskeletal injuries in the US military. *Sports Med. Arthrosc. Rev.,* 2019, **27**, 84-91. doi: 10.1097/JSA.0000000000000246.
2. Xuan, W.; Agrawal, T.; Huang, L.; Gupta, G.K. & Hamblin, M.R. Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis. *J. Biophotonics.,* 2015, **8**, 502-511. doi: 10.1002/jbio.201400069.
3. Yao, Y.M. & Zhang, H. Better therapy for combat injury. *Military Med. Res.*, 2019, **6**, 1-3. doi.org/10.1186/s40779-019-0214-9.
4. Dhaliwal, S.K.; Meek, B.P. & Modirrousta, M. M. Non-invasive brain stimulation for the treatment of symptoms following traumatic brain injury. *Front Psychiatry.*, 2015, **6**, 119. doi: 10.3389/fpsyt.2015.00119.

5. Bellamy, R.F. Combat trauma overview. Textbook Military Medicine, 1995, **4**, 1-42.
6. Valderrama-Molina, C.O.; Estrada-Castrillón, M.; Hincapie, J.A. & Lugo-Agudelo, L.H. Intra- and interobserver agreement on the Oestern and Tscherne classification of soft tissue injury in periarticular lower-limb closed fractures. *Colomb Med.,* 2014, **45**, 173–178.
7. Skaricic, J.; Vuletic, M.; Hrvatin, S.; Jelicic, J.; Cukovic-Bagic, I. & Juric, H. Prevalence, type and etiology of dental and soft tissue injuries in children in Croatia. *Acta. Clin. Croat.*, 2016, **55**, 209-215. doi: 10.20471/acc.2016.55.02.05.
8. Kozminski, M. Combat-related posttraumatic headache: diagnosis, mechanisms of injury, and challenges to treatment. *J. Am. Osteopath. Assoc.*, 2010, **110**, 514-519.
9. Hamblin, M.R., & Liebert, A. Photobiomodulation therapy mechanisms beyond cytochrome c oxidase. *Photobiomodul. Photomed. Laser Surg*., 2022, **40**, 75-77. doi: 10.1089/photob.2021.0119.
10. Gupta, A. Augmenting wound healing with photobiomodulation therapy. *In* Low-Level Light Therapy: Photobiomodulation, Hamblin, M.R; Ferrarsi, C.; Huang, Y.Y., Freitas, L.F. de; Carroll, J.D. (Eds.), *SPIE eBook*, USA, 2018. Pp. 135-146.
11. Mosca, R.C.; Ong, A.A.; Albasha, O.; Bass, K. & Arany, P. Photobiomodulation therapy for wound care: a potent, noninvasive, photoceutical approach. *Adv. Skin Wound. Care*, 2019, **32**, 157-167. doi: 10.1097/01.ASW.0000553600. 97572.d2.
12. Gigo-Benato, D.; Geuna, S.; de Castro Rodrigues, A.; Tos, P.; Fornaro, M.; Boux, E.; Battiston, B. & Giacobini-Robecchi, M.G. Low power laser biostimulation enhances nerve repair after end-to-side neurorrhaphy: a double-blind randomized study in the rat median nerve model. *Lasers. Med Sci*., 2004, **19**, 57–65. doi: 10.1007/s10103-004-0300-3.
13. Vieira, W.H.; Ferraresi, C.; Perez, S.E.; Baldissera, V. & Parizotto, N.A. Effects of low-level laser therapy (808 nm) on isokinetic muscle performance of young women submitted to endurance training: a randomized controlled clinical trial. *Lasers. Med Sci.*, 2012, **27**, 497–504. doi.org/10.1007/s10103-011-0984-0.
14. Kheshie, A.R.; Alayat, M.S. & Ali, M.M. High-intensity versus low-level laser therapy in the treatment of patients with knee osteoarthritis: a randomized controlled trial. *Lasers. Med Sci*., 2014, **29**, 1371–1376. doi.org/10.1007/s10103-014-1529-0.
15. Huang, Z.; Ma, J.; Chen, J.; Shen, B.; Pei, F. & Kraus, V.B. The effectiveness of low-level laser therapy for nonspecific chronic low back pain: a systematic review and meta-analysis. *Arthritis. Res. Ther*., 2015, **17**, 1-8. doi: 10.1186/s13075-015-0882-0.
16. Stergioulas, A.; Stergioula, M.; Aarskog, R.; Lopes-Martins, R. A. & Bjordal, J.M. Effects of low-level laser therapy and eccentric exercises in the treatment of recreational athletes with chronic achilles tendinopathy. *Am. J. Sports Med*., 2008, **36**, 881–887. doi.org/10.1177/0363546507312165.
17. Wang, J. & Dong, J. Optical waveguides and integrated optical devices for medical diagnosis, health monitoring and light therapies. *Sensors*., 2020, **20**, 3981. doi: 10.3390/s20143981.
18. Salehpour, F.; Mahmoudi, J.; Kamari, F.; Sadigh-Eteghad, S.; Rasta, S. H. & Hamblin, M. R. Brain Photobiomodulation Therapy: A Narrative Review. *Mol Neurobiol.,* 2018, **55**, 6601–6636. doi.org/10.1007/s12035-017-0852-4.
19. Anders, J. J.; Moges, H.; Wu, X.; Erbele, I. D.; Alberico, S. L.; Saidu, E. K.; Smith, J. T. & Pryor, B. A. In vitro and in vivo optimization of infrared laser treatment for injured peripheral nerves. *Lasers. Surg Med*., 2014, **46**, 34–45. doi.org/10.1002/lsm.22212.
20. Dos Santos, L. S.; Saltorato, J. C.; Monte, M. G.; Marcos, R. L.; Lopes-Martins, R. Á. B.; Tomazoni, S. S.; Leal-Junior, E. C. P. & de Paiva Carvalho, R. L. PBMT and topical diclofenac as single and combined treatment on skeletal muscle injury in diabetic rats: effects on biochemical and functional aspects. *Lasers. Med Sci*., 2019, **34**, 255–262. doi. org/10.1007/s10103-018-2580-z.
21. Chow, R. T.; Johnson, M. I.; Lopes-Martins, R.A. & Bjordal, J.M. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. *Lancet.*, 2009, **374**, 1897–1908. https://doi.org/10.1016/S0140-6736(09)61522-1.
22. Gigo-Benato, D.; Geuna, S. & Rochkind, S. Phototherapy for enhancing peripheral nerve repair: a review of the literature. *Muscle Nerve.*, 2005, **31**, 694–701. doi.org/10.1002/mus.20305.
23. Yadav, A.; Verma, S.; Keshri, G.K. & Gupta, A. Combination of medicinal honey and 904 nm superpulsed laser-mediated photobiomodulation promotes healing and impedes inflammation, pain in full-thickness burn. *J. Photochem. Photobiol., B* 2018, **186**, 152-158. doi: 10.1016/j.jphotobiol.2018.07.008
24. Priyadershi, A., Keshri, G.K. & Gupta, A. Effect of combination of photobiomodulation 904 nm superpulsed laser therapy and *Hippophae rhamnoides* L. on third-degree burn wound healing. *J. Cosmet. Dermatol*., 2023. doi: 10.1111/jocd.15806. Online ahead of print.
25. Ebrahimpour-Malekshah, R.; Amini, A.; Zare, F.; Mostafavinia, A.; Davoody, S.; Deravi, N.; Rahmanian, M.; Hashemi, S. M.; Habibi, M.; Ghoreishi, S. K.; Chien, S.; Shafikhani, S.; Ahmadi, H.; Bayat, S. & Bayat, M. Combined therapy of photobiomodulation

and adipose-derived stem cells synergistically improve healing in an ischemic, infected and delayed healing wound model in rats with type 1 diabetes mellitus. *BMJ Open Diabetes. Res. Care.*, **8**, e001033. doi.org/10.1136/bmjdrc-2019-001033.

26. Grissom, A. C.; Hernandez, I. A.; Kirkpatrick, T. C.; Patel, S. A.; Barros, J. A. & Stanley, E. Treating nerve injury after endodontic microsurgery using laser photobiomodulation: a report of 2 cases. *J. Endod*., 2023, **49**, 597–603. doi.org/10.1016/j.joen.2023.01.011.
27. Mendez, T. M., Pinheiro, A. L., Pacheco, M. T., Nascimento, P. M. & Ramalho, L. M. Dose and wavelength of laser light have influence on the repair of cutaneous wounds. *J. Clin. Laser. Med Surg*., 2004, **22**, 19-25. doi: 10.1089/104454704773660930.
28. Barikbin, B., Khodamrdi, Z., Kholoosi, L., Akhgri, M. R., Haj Abbasi, M., Hajabbasi, M., Razzaghi, Z., & Akbarpour, S. (2017). Comparison of the effects of 665 nm low level diode Laser Hat versus and a combination of 665 nm and 808nm low level diode Laser Scanner of hair growth in androgenic alopecia. *J. Cosmet. Laser. Ther*., 2017. doi.org/10.1080/14764172.2017.1326609.
29. Jahangiri Noudeh, Y., Shabani, M., Vatankhah, N., Hashemian, S. J. & Akbari, K. A combination of 670 nm and 810 nm diode lasers for wound healing acceleration in diabetic rats. *Photomed. Laser Surg*., 2010, **28**, 621-627. doi: 10.1089/pho.2009.2634.
30. Fekrazad, R.; Asefi, S.; Eslaminejad, M.B.; Taghiar, L.; Bordbar, S. & Hamblin, M.R. Photobiomodulation with single and combination laser wavelengths on bone marrow mesenchymal stem cells: proliferation and differentiation to bone or cartilage. *Lasers. Med Sci.*, 2019, **34**, 115-126. doi: 10.1007/s10103-018-2620-8. Epub 2018 Sep 27.
31. Martins, W.A.; Polignano, G.A.C.; Guimarães, O. R.; Geller, M.; Paoli, F. & Fonseca, A.S. Dichromatic laser radiation effects on DNA of *Escherichia coli* and plasmids. *Laser Physics.*, 2015, **25**, 045603.
32. Thomé, A.M.C.; Souza, B.P.; Mendes, J.P.M.; Cardoso, A.F.R.; Soares, L.C.; Trajano, E.T.L. & Fonseca, A.S. Dichromatic and monochromatic laser radiation effects on antibiotic resistance, biofilm formation, and division rate of *Pantoea agglomerans*. *Laser Physics.*, 2018, **28**, 065606.
33. Thomé, A. M. C.; Souza, B. P.; Mendes, J. P. M.; Soares, L. C.; Trajano, E. T. L. & Fonseca, A. S. Dichromatic and monochromatic laser radiation effects on survival and morphology of *Pantoea agglomerans. Laser Physics.*, 2017, **27**, 055602.

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