Review

Low-level laser therapy in knee osteoarthritis: a narrative review

X. Zhao[1,2], X. Lou[2], B. Wu[1,2], H. Du[2], L. Li[2], Q. Zheng[2], X. Guo[2], W. Xiao[2], S. Xue[2], X. Zhang[2]

[1]School of Clinical Medicine, Shandong Second Medical University, Weifang, Shandong, China; [2]Department of Sports Medicine and Rehabilitation, Peking University Shenzhen Hospital, Shenzhen, China.

Xinyu Zhao, MM
Xinyu Lou, MM
Bing Wu, MM
Haocheng Du, MM
Lin Li, MM
Qiusheng Zheng, MM
Xin Guo, MM
Weibo Xiao, MM
Song Xue, MD
Xintao Zhang, MD

Please address correspondence to:
Song Xue
Department of Sports Medicine and Rehabilitation,
Peking University Shenzhen Hospital,
Shenzhen 518036, China.
E-mail: freexuesong@163.com

and to:
Xintao Zhang
(address as above)
E-mail: zhangxintao@sina.com

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ABSTRACT

Knee osteoarthritis (KOA) is a degenerative joint disease that affects the entire knee joint, commonly seen in the elderly, and has shown an increasing trend toward younger populations in recent years. Its main symptoms include pain, swelling, stiffness, and limited mobility; besides, severe cases can lead to disability and complete loss of function. KOA can also lead to psychological issues such as depression and anxiety, posing substantial burdens on patients, families, and society. The current treatment options include physical therapy, medications, and other conservative methods, or surgical treatment. Notably, low-level laser therapy (LLLT) is a non-invasive and safe physical treatment that has been proven to be effective for various conditions affecting the musculoskeletal, nervous, and dermatological systems. Its non-invasive nature avoids the trauma and pain associated with surgery, and it avoids potential side effects of medication. Due to its convenience, safety, and effectiveness, LLLT has been widely recognised as a strategy for treating KOA. This review comprehensively examines the mechanisms of LLLT, including its capacity to modulate synovial macrophage polarisation and regulate the expression of inflammatory factors. It also provides an in-depth analysis of the clinical efficacy of LLLT as a standalone treatment or in conjunction with other therapeutic modalities for KOA patients, drawing on evidence from cellular, animal, and patient studies over recent decades. The aim is to offer robust theoretical support for the treatment of KOA.

Introduction

Knee osteoarthritis (KOA) is a progressive degenerative joint disease characterised by the deterioration of cartilage, osteophyte formation, synovitis and subchondral bone remolding (1, 2). It ranks among the most common joint disorders globally, impacting an estimated over 654 million people worldwide, predominantly adults over the age of 40. As population ages, the incidence and prevalence of KOA are rising across general demographics (3). KOA typically manifests with symptoms including joint pain, swelling, stiffness, reduced mobility, and functional impairment. These symptoms significantly diminish patients' quality of life. Long-term consequences can lead to the reduced physical activity, complete immobilisation, disability, and mental depression. The substantial burden on both individual patients and healthcare systems underscores the medical and public health significance of KOA (4, 5). For individuals with mild symptoms, pain and other symptoms can be alleviated through exercise, weight reduction, and a healthy diet. However, if symptoms worsen, clinical treatment becomes necessary. A variety of conservative treatments are available for KOA, including intra-articular injections such as hyaluronic acid, the use of orthoses and braces, exercise therapies like balance training, and physical therapies like ultrasound, phototherapy, electrotherapy, magnetotherapy, and thermotherapy (6-8). When arthritis symptoms become severe, surgical intervention may be required. These interventions aim to alleviate symptoms, improve joint function, and delay disease progression, reflecting ongoing efforts in the medical community to address this prevalent and debilitating condition (9).

Low-level laser therapy (LLLT), which utilises light amplification by stimulated

emission of radiation (LASER) technology, also known as photobiomodulation therapy (PBMT), is a non-invasive treatment technique that utilises low-energy density lasers. LLLT has been widely applied to various conditions including nerve damage, skin issues, and KOA. It is recognised for its ability to reduce pain, inflammation, swelling, promote tissue healing and regeneration, and improve symptoms of chronic diseases (10-12). Due to its non-invasive, painless, and generally safe nature with minimal adverse effects, LLLT is gaining prominence in clinical practice (13). Despite demonstrating positive effects in the treatment of KOA, clinical research outcomes remain contentious. This paper reviews the pathogenesis of KOA, treatment methods, and the multifaceted therapeutic effects of LLLT on KOA, drawing on evidence from both *in vivo* and *in vitro* studies, with the aim of providing a theoretical basis for future research on KOA treatment (Fig. 1).

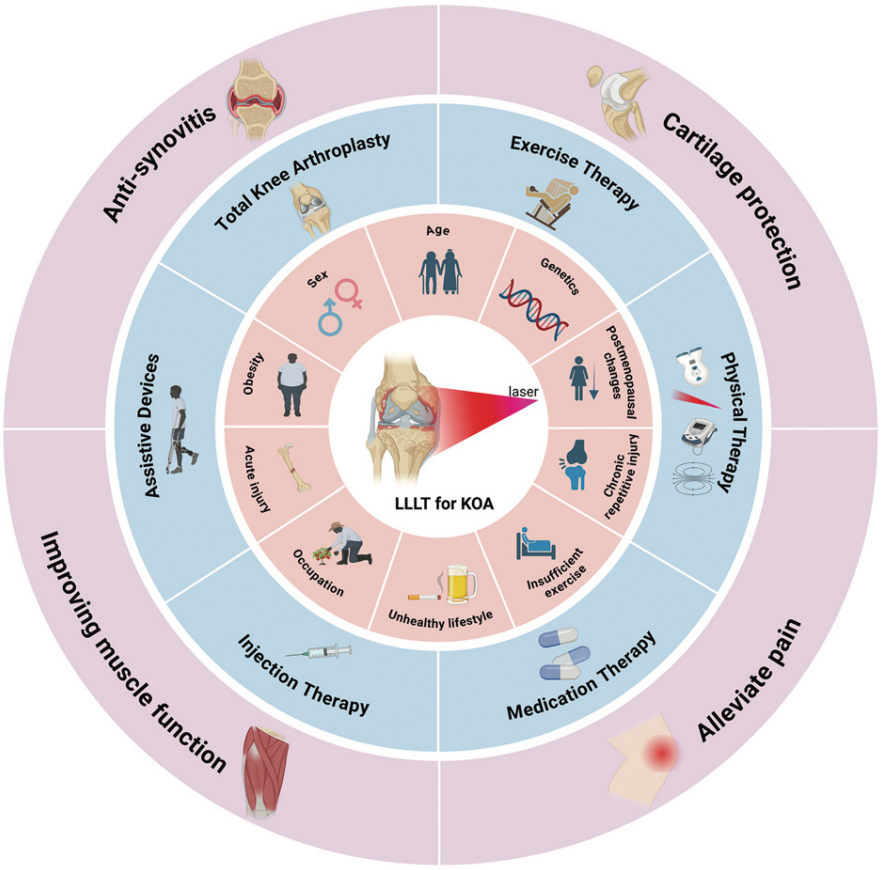

Fig. 1. Pathogenic factors of KOA, treatment methods, and the mechanism of LLLT for KOA.

Mechanisms

The pathogenesis of KOA involves the interplay of numerous intrinsic and extrinsic factors, which collectively contribute to the degeneration of knee joint cartilage and multiple structural changes within the joint (14). LLLT leverages the monochromatic, coherent, and directional properties of laser to precisely target specific tissues or cells, eliciting photobiomodulation effects for therapeutic purposes.

Pathogenesis of KOA

Epidemiological studies indicate that KOA is influenced by both intrinsic and extrinsic risk factors (1). Intrinsic factors include age, gender, genetics, and postmenopausal changes (15). Osteoarthritis (OA) progression is rarely attributable to a single gene but is more likely influenced by interactions among multiple genes. Extrinsic risk factors such as acute injuries, chronic repetitive trauma, obesity (Body Mass Index (BMI) >30), joint surgeries, and unhealthy lifestyles (smoking, alcohol consumption, etc.) significantly increase the likelihood of KOA (16-20). For instance, occupations involving frequent kneeling or squatting notably heighten the risk of KOA compared to other groups (21). Additionally, abnormal foot posture, such as a more pronated foot posture, may alter lower limb biomechanics, increase knee joint loading, and accelerate articular cartilage degeneration, thereby promoting the onset and progression of KOA (22). Within the physiological structure of the knee joint, articular cartilage stands as a primary target and initial site of damage in the onset of KOA. In addition, inflammation affects surrounding tissues including the synovium, subchondral bone, meniscus, infrapatellar fat pad, and muscles (23). Composed primarily of water (more than 70%) and an organic extracellular matrix, articular cartilage mainly includes collagen fibers, proteoglycans, and structural proteins like aggrecan (AGC) (24). The dynamic equilibrium between matrix synthesis (*e.g.* insulin-like growth factor (IGF-1) and degradation (*e.g.* interleukin-1 (IL-1), tumour necrosis factor-alpha (TNF-α), and proteases) regulates ongoing formation and degeneration of cartilage matrix (25-27). However, when the harmful effects of OA surpass the compensatory capacity of the dynamic equilibrium system, degradation of the cartilage matrix, marking the onset of KOA. Prolonged detrimental impacts perpetuate continuous damage to the knee joint, gradually eroding and depleting articular cartilage, resulting in pain, swelling, restricted joint movement, reduced physical activity, and potentially disability (1, 28).

Despite a profound understanding of the pathogenesis of KOA, current treatment strategies still face numerous challenges. Existing therapeutic approaches primarily focus on alleviating pain and improving function, yet they fail to adequately address the underlying pathological changes. Therefore, exploring new therapeutic avenues is crucial for improving long-term prognosis.

Mechanism of LLLT

Generally speaking, laser therapy utilises the monochromatic, coherent, directional, and highly focused properties of

laser to target specific tissues or cells, aiming to treat OA, alleviate symptoms, and promote rapid recovery (29). Laser therapy involves visible red and near-infrared light (390–1600 nm), which penetrate tissues effectively and exert beneficial therapeutic effects on living tissues (30). Current research on laser therapy for KOA primarily distinguishes between LLLT and high-level laser therapy (HLLT) (31).

LLLT typically refers to laser light within the visible to near-infrared spectrum (390–1100 nm) with power ≤500 mW, capable of altering biological activity without generating significant heat during tissue irradiation, thus penetrating superficial tissue layers (32). It is known for its roles in pain alleviation, inflammation reduction, swelling relief, tissue healing and regeneration promotion, and improvement of blood circulation (33). Clinically, LLLT is commonly used for musculoskeletal conditions such as OA, sports injuries, and muscle pain, as well as for skin conditions like burns and pressure ulcers, and neurological conditions such as neuropathic pain and peripheral nerve injuries, among others (34-36). While HLLT's therapeutic effects and indications largely overlap with LLLT, it may cause discomfort such as pain due to its higher laser intensity, necessitating skilled medical personnel for operation (37). Therefore, compared to HLLT, LLLT offers higher operational safety, minimal discomfort, a more comfortable and relaxing treatment experience, making it applicable across a broader range of conditions (38).

LLLT improves therapeutic effects and tissue repair through various mechanisms and biological pathways. It reduces the release of pro-inflammatory cytokines such as TNF-α and IL-6 while increasing the release of anti-inflammatory cytokine IL-10, thus exerting anti-inflammatory effects (39-43). Additionally, LLLT alleviates pain by reducing peripheral nerve sensitivity and inhibiting the release of pain mediators (44-48). It enhances local blood circulation by stimulating the release of nitric oxide, leading to microvascular dilation and improved delivery of oxygen and nutrients crucial for tissue repair (49-51). Moreover, LLLT promotes proliferation and differentiation of various cell types, including fibroblasts and myocytes, promoting tissue repair and regeneration (52-57). These synergistic mechanisms make LLLT a clinically effective treatment option across a broad spectrum of diseases and injuries.

Therapeutic effects of LLLT

LLLT has become a promising treatment method for KOA, effectively addressing the interrelated issues of inflammation, cartilage degradation, pain and function.

Anti-synovitis

In recent years, an increasing number of scholars have identified OA as a condition primarily characterised by mild synovitis dominated by macrophage infiltration (58).

Macrophages exhibit high plasticity and can polarise into pro-inflammatory M1 and anti-inflammatory M2 types (59-62). These activated macrophages release mediators that induce inflammatory and destructive responses within the OA synovium (63). Guiding synovial macrophages towards the reparative M2 phenotype has been shown to promote healing and recovery of synovitis (64). A study showed that applying LLLT (810 nm; 4 J; 2 mW/cm^2) for two consecutive days, with each treatment lasting 440 seconds significantly inhibited inflammation in bone marrow-derived macrophages (BMDMs) induced by bacterial lipopolysaccharide (LPS) and interferon-γ (IFN-γ). Specifically, the TNF-α level (p=0.013) and the IL-1β level (p=0.019) decreased significantly. Furthermore, the treatment significantly reduced macrophage polarisation towards the M1 phenotype, with the polarisation marker iNOS level decreasing from 1.000±0.077 to 0.214±0.010 (p=0.001) (65). Sun *et al*.'s research further supports the efficacy of LLLT. They found that the overactivation of M1 macrophages leads to excessive activation of astrocytes and upregulation of chondroitin sulfate proteoglycan (CSPG) expression. Alternatively, LLLT significantly inhibited the expression of glial fibrillary acidic protein (GFAP) (p<0.05), effectively alleviating the excessive activation of astrocytes and significantly downregulating CSPG levels (p<0.05) (66). These research results collectively indicate that LLLT can effectively reduce inflammatory responses and improve immune cell function, providing strong support for its future clinical applications.

LLLT effectively modulates the expression of inflammatory factors. Tomazoni *et al*. evaluated the effects of LLLT alone or in combination with topical non-steroidal anti-inflammatory drugs (NSAIDs) and/or exercise on papain-induced osteoarthritis in rats. The results showed that these treatments significantly reduced gene expression levels of IL-1β, IL-6, and TNF-α (p<0.05) and suppressed levels of prostaglandin E2 (p<0.05), effectively alleviating symptoms of synovitis. These studies indicate that LLLT demonstrates significant anti-inflammatory and recovery effects in various treatment contexts (67).

In summary, LLLT effectively manages OA-related synovitis by modulating macrophage phenotypes, suppressing inflammatory mediators (*e.g*. TNF-α, IL-1β, IL-6), and improving mitochondrial function. It shows promise in alleviating inflammation and promoting joint health.

Cartilage protection

Articular cartilage degeneration, a widespread and irreversible process, constitutes a primary factor in the onset and progression of KOA (68, 69). As the development of KOA, the balance between the anabolism and catabolism of cartilage is disrupted. Damaged chondrocytes are involved in responsive release of matrix metalloproteinases (MMPs) and other inflammatory factors, thus promoting cartilage degradation (70-72).

LLLT can reduce the production of catabolic factors such as IL-1β, MMP-3, and MMP-13 *in vitro*. Simultaneously, LLLT mitigates the loss of synthetic metabolic factors including type II collagen (Col II) and transforming growth factor-β (TGF-β) (11). Recent studies highlight the promising effects of LLLT in managing OA through its modulation of anabolic and catabolic factors.

In a rat model of KOA, LLLT applied at 808 nm with dosages of 0.8 J and 1.4 J demonstrated significant benefits. Specifically, LLLT at 1.4 J markedly enhanced chondrocyte proliferation on days 1 and 5 ($p<0.05$), while the 0.8 J dosage improved proliferation on day 3 ($p<0.05$). Additionally, LLLT treatment significantly increased the levels of extracellular matrix anabolic factors, including IL-4, IL-10, Col II, AGC, and TGF-β ($p<0.05$), and simultaneously reduced the expression of inflammatory markers and the catabolic factor IL-1β ($p<0.05$) (73). A study utilising helium-neon laser (830 nm, 1.5 J/cm^2) in a rabbit model of KOA induced by anterior cruciate ligament (ACL) transection further supports the therapeutic potential of LLLT. Administered three times weekly for eight weeks, this LLLT regimen significantly decreased levels of catabolic factors such as IL-1β, iNOS, and MMP-3 ($p<0.05$), while preserving anabolic factors like TGF-β, TIMP-1, collagen II, and glycosaminoglycans ($p<0.05$). Morphological and histological evaluations revealed that LLLT significantly mitigated cartilage damage in both the medial femoral condyle (MFC) and medial tibial plateau compared to untreated controls (74).

LLLT has been shown in animal models of KOA to effectively upregulate the anabolic markers, including IL-4, IL-10, and proteoglycans, while suppressing the expression of catabolic factors such as MMPs. These effects underscore its role in maintaining tissue health and cartilage protection (75).

Pain alleviation

Various factors can contribute to pain in patients with KOA. For instance, cartilage damage and wear can increase intra-articular friction, leading to pain. Synovial fibrosis may result in hyperalgesia, while inflammation in surrounding tissues can enhance the sensitivity of certain pain receptors, thereby exacerbating the patient's discomfort (76-78). Effective pain management in KOA is crucial not only for alleviating the condition itself but also for improving patients' quality of life and potentially mitigating physical and psychological health associated issues (79).

Animal pain behaviour tests have demonstrated the pain-relieving effects of LLLT. In a study using a MIA-KOA model in rats, LLLT at 904 nm was administered three times a week for a total of 8 weeks. The results indicated that LLLT significantly improved pain threshold and spontaneous pain symptoms ($p<0.001$) and effectively regulated the activity of serum neutrophils ($p<0.001$). Moreover, LLLT prevented the decrease in superoxide dismutase (SOD) levels ($p<0.05$) and reduced the levels of non-protein thiols in the serum ($p<0.05$), indicating that it mitigated oxidative stress damage in serum and spinal cord samples by enhancing antioxidant capacity (80). Another interesting experiment involved a study with 17 dogs diagnosed with OA and exhibiting pain symptoms. Each dog received LLLT once a week for 6 weeks. Assessments were performed using the Canine Brief Pain Inventory (CBPI), Visual Analogue Scale (VAS), and the Colorado State University Canine Chronic Pain Scale. The results showed a significant reduction in CBPI scores before and after treatment (11.8±3.6 *vs.* 4.4±4.0, $p<0.001$) and a significant decrease in VAS scores (7.7±0.8 *vs.* 3.4±1.4, $p<0.001$), with these scores continuing to decline over time. This indicates that LLLT helps to reduce the use of analgesics and enhances the quality of life for dogs with OA (81). These experimental results demonstrate that LLLT has a significant alleviating effect on pain caused by KOA, suggesting that LLLT may be an important tool for the treatment of KOA.

Muscle function improvement

Research indicates asymmetry in quadriceps muscle mass, biomechanical characteristics, and performance among KOA patients. Increasing quadriceps strength enhances knee joint stability, reduces abnormal knee joint movements, and alleviates intra-articular pressure. These effects help reduce cartilage wear and inflammation, and also decrease the risk of pain and injury during movement (82).

In a study, 47 participants received LLLT with either an 808 nm or 660 nm wavelength, administered three times per week for 8 weeks. The results indicated that both treatment groups showed significant improvements in knee extensor and flexor muscle strength compared to the control group. The 808 nm wavelength LLLT demonstrated a more pronounced effect on improving knee extensor strength ($p=0.009$, d=0.67). Additionally, the 660nm group showed significant improvement in the 30-second sit-to-stand test ($p=0.006$, d=0.49). These findings suggest that LLLT effectively enhances muscle strength and physical function, with the 808nm wavelength LLLT particularly excelling in improving knee extensor strength (83). A similar conclusion was reached in a study conducted a few years ago. The study involved 51 patients with KOA) who received LLLT with a wavelength of 808±10 nm and a power of 50 mW, applied bilaterally to the quadriceps for 30 minutes per session. Post-intervention measurements using an isokinetic dynamometer revealed significant increases in knee extensor strength, including peak torque, concentric, and eccentric contractions ($p<0.05$). Additionally, LLLT significantly reduced knee pain by 54% and improved timed five-chair stands and walking speed ($p<0.05$). These improvements contribute to joint stability and facilitate the recovery of daily activities, playing a crucial role in the patients' clinical and functional rehabilitation (84).

In summary, LLLT targeting the quadriceps in patients with KOA can provide direct benefits, including enhancing quadriceps strength, reducing knee pain, and restoring physical function. Therefore, LLLT should be incorporated into rehabilitation programmes as an effective non-invasive treatment option to improve muscle strength and functional performance in KOA patients.

Clinical application

Over the past three decades, numerous randomised controlled trials have assessed the efficacy of LLLT in patients with KOA, with varying types of lasers, parameters, and assessment methods (Table I). The earliest clinical trial of LLLT for KOA was conducted in 1992 by Stelian et al. This study involved 50

Table I. Clinical research on low-level laser therapy for knee osteoarthritis.

Author. year	Sample size	Types of lasers	Wavelength (nm)	Output power (mW)	Power density (mW/cm2)	Energy per point (J)	Energy density (J/cm2)	Points	Treatment time; frequency; session	Assesment time	Assessment method	Effect	Reference
Stelian *et al*. 1992	50	/	830	18-75	8-34	/	5. 1	/	15min; 2/d; 20	Before and after treatment	SF-MPQ; PPI; VAS; DIQ	Both groups pain↓functional ability↑	(85)
Bülow *et al*. 1994	29	Ga-Al-As	830	25-270	11-122	/	5. 6	/	15min; 3/w; 9	Before, during, and after treatment	VAS; analgesic demand; palpation tenderness; isokinetic	No significant differences	(88)
			/	/	/	/	/	/					
Gur *et al*. 2003	90	Ga-As	904	10	10	/	/	/	5min; 5/w; 10	Before and after treatment	VAS; WOMAC; active knee flexion; duration of morning stiffness; pain-free walking distance and duration	VAS↓↓ SKFS↑	(94)
			904	11. 2	11. 2	/	/	/	3min; 5/w; 10				
Tascioglu *et al*. 2004	60	Ga-Al-As	830	50	/	3	/	5	10min; 5/w; 10	Before treatment; 1 week, 6 months after treatment	VAS; WOMAC	No impact on pain	(89)
Yurtkuran *et al*. 2007	52	/	904	4	10	0.48	/	/	20min; 5/w; 10	Before and after treatment; 3 months after treatment	VAS; 50-foot walk test; KC; MTS; WOMAC; NHP	Swelling around the joints↓	(116)
Hegedus *et al*. 2009	/	Ga-Al-As	830	50	/	6	/	8	?; 2/w; 8	Before and after treatment; 2 months after treatment	Thermography; joint flexion; joint circumference; pressure sensitivity; VAS	Pain↓ microcirculation in the irradiated area↑	(86)
Fukuda *et al*. 2011	47	Ga-As	904	60	120	3	6	9	50s/point; 3/w; 9	Before and after treatment	TUG; VNPS; Lequesne	Short-term pain↓ functional ability↑	(117)
Hsieh *et al*. 2012	72	/	890	6240	34. 7	/	41. 6	8	40min; 3/w; 6	Before, during, and after treatment	WOMAC; timed stair climb; 10-meter fast walk; chair stand time	No significant differences	(118)
Gworys *et al*. 2012	94	MLS	810	400	634. 9	8	12. 7	12	20s/point; 5/w; 10	Before and after treatment	Lequesne; Modified Laitinen; VAS	All groups knee joint function↑ pain↓ Group II exhibited the greatest improvement	(119)
			808+905	1100	/	12. 4	4. 21	12					
Soleim anpour *et al*. 2014	18	Ga-Al-As	808+905 810 810	1100 50 30	/ 50 17	6. 6 6 10	3. 28 46 46	12 / /	?; 3/w; 36	Before and after treatment	VAS	Both groups pain↓	(120)
Alghadir *et al*. 2014	40	Ga-As	850	50	/	6	48	8	60s/point; 2/w; 8	Before and after treatment	VAS; WOMAC	Pain↓↓ knee joint function	(121)
Al Rashoud *et al*. 2014	49	Ga-Al-As	830	30	/	1. 2	/	5	40s/point; ?; 9	Before, during, and after	VAS; SKFS	VAS↓↓ SKFS↑↑	(87)
Hinman *et al*. 2014	282	/	/	10	/	0.2	/	≤ 6	20min; 1-2/w; 8-12	Before and after treatment, follow-up for one year	VAS; WOMAC	At 12 weeks pain↓ no improvement was observed at 1 year	(122)
Helianthi *et al*. 2014	62	Ga-Al-As	785	50	25	4	2	5	80s/point; 2/w; 10	Before, during, and after treatment	VAS; Lequesne	VAS↓↓ Lequesne↓↓	(123)
S *et al*. 2017	34	/	905	25	/	1. 5	/	8	60s/point; 3/w; 12	Before treatment, 4 to 8 weeks after treatment	Joint space width; CTX-II; MMP-3/8 /13 ; VAS	Pain↓↓ cartilage thickness↑↑ biochemical changes	(124)
Vassão *et al*. 2020	62	/	808	100	2000	4	91	14	40s/point; 2/w; 16	Before and after treatment	WOMAC; Lequesne; 1RM; SAPO	Pain↓ function↑ muscle strength↑	(125)
Zhao *et al*. 2021	392	/	10.6μm	160-180	/	/	61. 2-68. 8	2	30min; 3/w; 12	Before and after treatment	WOMAC	Pain↓ function↑	(126)
Alqualo-Costa *et al*. 2021	168	Ga- As	904	40	/	3	/	9	40-50min; 3/w; 12	Before and after treatment; 3 to 6months post-treatment	VAS; TUG; sit and lift; Lequesne; WOMAC; pressure pain threshold; conditioned pain modulation; isokinetic muscle strength	Intensity of pain at rest↓ better than interfering electricity	(127)
Ahmad *et al*. 2023	34	/	830	400	/	/	10-12	/	15min; 1/w; 12	Before and after treatment	KOOS; NPRS; active knee flexion; TUG	Both groups' KOOS↑ NPRS↓ active knee flexion↑ TUG↑	(128)
Pinto *et al*. 2022	31	/	830	400	/	/	/	/	?; 2/w; 10	Before and after treatment	VAS; QOL; serum/urine analysis	Short and medium term pain↓QOL↑	(129)
Alfredo *et al*. 2022	43	Ga-As	904	60	/	3	/	9	?; 3/w; 9	Before and after treatment; 8 weeks to 6 months post-treatment	VAS; Lequesne; TUG; ROM; muscle strength; WOMAC; medication intake and relief	Pain↓ disability↓ medication intake↓	(130)
Elboim-Gabyzon *et al*. 2023	40	/	/	100	/	/	8	5	15min; 2/w; 6	Before and after treatment	VAS; WOMAC; TUG; 100MW	Pain↓↓ physical function↑↑	(131)
Jankaew *et al*. 2023	47	/	810	300	/	5. 76	/	6	15min; 3w; 24	Before treatment; 1 week after treatment	30s sit-to-stand test; 40-meter fast-paced walk; stair climbing; TUG	The functional tests↑ muscle strength↑ function↑ 808nm group's function of knee extensor muscles↑	(83)
		/	660	300	/	5. 76	/	6	15min; 3w; 25				

*SF-MPQ: Short-Form McGill Pain Questionnaire, used to assess the intensity and type of pain; PPI: pain pressure threshold, is used to assess the severity of pain; VAS: Visual Analogue Scale; VNPS: Verbal Numerical Pain Scale; NPRS: Numeric Pain Rating Scale, used to assess the severity of pain; DIQ: Disability Index Questionnaire; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, used to assess symptoms and function in osteoarthritis patients; KC: knee circumference; MTS: Medial Tenderness Score; NHP: Nottingham Health Profile, used to assess the quality of life and overall health status of patients with chronic diseases; TUG: timed up and go; Lequesne's Index, used to assess pain and function in osteoarthritis of the hip and knee; SKFS: Saudi Knee Function Score; SAPO: posture evaluation software; 1-RM: One-Repetition Maximum; KOOS: Knee injury and Osteoarthritis Outcome Score, used to assess the condition and outcome of knee injuries and osteoarthritis; QOL: quality of life; ROM: range of motion; 100 MW: 100 - meter walk test.

KOA patients who received 830 nm wavelength LLLT. The laser was applied to both sides of the knee for 15 minutes, twice daily, over a period of 10 days. Pain was assessed using the Short McGill Pain Questionnaire, current pain intensity, and the VAS before and after the intervention, while function was evaluated using the Disability Index Questionnaire. The results indicated that the treatment group experienced over a 50% reduction in pain ($p<0.05$) and significant improvement in function ($p<0.05$), whereas the placebo group showed no notable improvements in either pain or function (85). This study was the first to demonstrate the effectiveness of LLLT in alleviating pain and disability in patients with KOA. Another study also confirmed the bioregulatory effects of LLLT on pain and microcirculation in patients with KOA. This study employed LLLT (830 nm, 50 mW, 6 J/point) for a 4-week intervention in patients with mild to moderate KOA. The results showed significant improvements post-LLLT in patients' pain (before treatment: 5.75; after treatment: 1.18), pressure sensitivity (before treatment: 2.33; after treatment: 0.77). Additionally, thermographic measurements indicated improved circulation, with temperatures rising by at least 0.5 °C compared to initial values (86). Another similar study demonstrated that applying LLLT to specific acupoints for 6 months can effectively alleviate pain in patients with KOA and improve their quality of life. Moreover, this improvement was maintained at 6 months post-intervention (95 % confidence interval: -34 to -7; $p=0.006$) (87).

However, some studies still indicate that the effectiveness of LLLT for KOA intervention is not significant, with variations in treatment results. As early as 1994, Bülow *et al*. conducted LLLT on 29 KOA patients, with 9 sessions over 3 weeks, each lasting 15 minutes, targeting the tender points around the joints. The results after the intervention showed no significant differences in the effect variables at the pre-treatment, mid-treatment, and post-treatment stages (88). Another study found that LLLT is ineffective for managing pain in KOA. In this study, 60 KOA patients were randomly assigned to three groups: a placebo group, a 3 J/point group, and a 1.5 J/point LLLT group. Patients received 10 treatments over 2 weeks. Assessments using the WOMAC subscales showed no significant differences in pain scores between groups at any time point (89) .

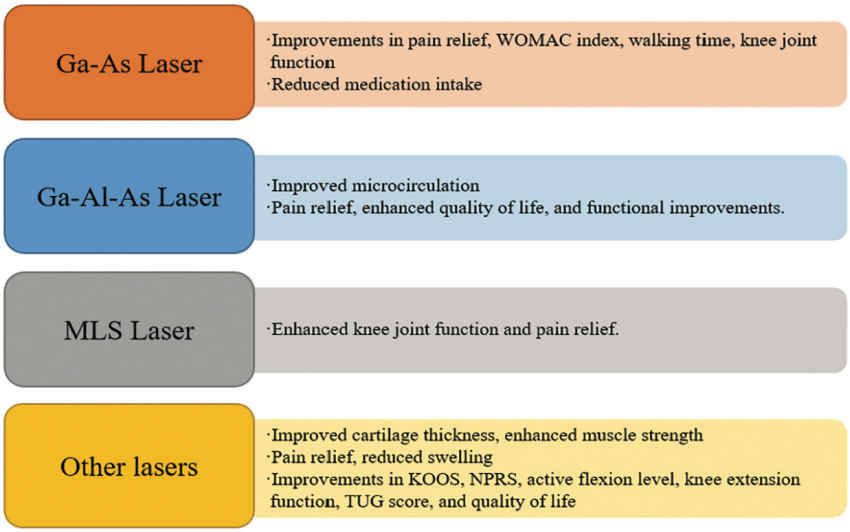

Fig. 2. Summary of LLLT demonstrated in this review, including statistical improvements of them.

Variability in the efficacy of LLLT for treating KOA may stem from inconclusive findings regarding to the optimal laser parameters for KOA treatment. According to the recommendations from the World Association for Laser Therapy (WALT), optimal irradiation for knee joints should adhere to doses of ≥4 J/point (average power: 5–500 mW) and/or ≥1 J/point (average power: 5–500 mW, peak power >1,000 mW) at wavelengths of 780–860 nm and/or 904 nm (90). A meta-analysis included 22 randomised controlled trials on LLLT for patients with KOA. Overall, LLLT significantly reduced pain compared to placebo at the end of treatment (mean difference of 14.23 mm VAS; 95% CI [7.31–21.14]). During follow-up 2–4 weeks after treatment, the recommended dose of LLLT intervention achieved peak pain relief (mean difference of 31.87 mm VAS; 95% CI [18.18–45.56]) and also significantly reduced disability. In summary, LLLT using wavelengths of 785-860 nm with 4–8 J per treatment point and 904 nm with 1–3 J per treatment point effectively alleviates pain and disability in KOA (91).

The site of irradiation may also directly influence treatment efficacy. Feng *et al*. investigated the effects of light source characteristics, such as divergence angle, wavelength, and irradiation position, on the dosage of LLLT treatment. The study results indicated that both the divergence angle and wavelength of the light source significantly affect the treatment dose. The optimal irradiation position is on both sides of the patella, as this location allows LLLT to achieve the maximum dose by the time it reaches the joint cartilage (92).

Furthermore, the effectiveness of LLLT may vary depending on the type of laser used and the duration of exposure. Various types of lasers, such as semiconductor lasers (including GaAs and Ga-Al-As lasers) and CO_2 lasers, have been summarised briefly regarding to their therapeutic effects, as depicted in Figure 2.

Combined with other treatment approaches

LLLT is commonly used as an adjunctive treatment in comprehensive care for KOA, often in combination with other therapies such as rehabilitation exercises and physical therapy. This combined approach has been shown to potentially enhance therapeutic outcomes (93).

Numerous clinical trials have investigated the therapeutic effects of LLLT in combination with other treatment modalities for KOA, such as exercise therapy, electrical stimulation, and so on (Table II). A 2003 study investigated the effects of LLLT combined with

Table II. Clinical research on low-level laser therapy combined with other treatment approaches.

Author. year	Combination	Sample size	Wavelength (nm)	Output power (mW)	Power density (mW/cm2)	Energy per point (J)	Energy density (J/cm2)	Points	Treatment time; frequency; session	Assesment time	Assessment method	Effect	Reference
Gur *et al*. 2003	exercise	90	904	10	/	/	/	/	3min; ?; 10	Before, during, and after treatment	VAS; degree of active knee flexion; duration of morning stiffness; Pain-free walking distance and duration; WOMAC	All parameters↑↑ the application at different doses and durations did not affect the results	(94)
			904	11. 2	/	/	/	/	5min; ?; 11				
Alfredo *et al*. 2012	exercise	40	904	60	/	3	6	9	50s/point; 3/w; 9	Before and after treatment	VAS; Lequesne; WOMAC; ROM; strength	Pain↓ function↑ mobility↑	(132)
Kheshie *et al*. 2014	exercise	53	830	800	25. 6	/	50	/	32min33s; 2/w; 12	Before and after treatment	VAS; WOMAC	VAS↓ WOMAC↓	(133)
Al Rashoud *et al*. 2014	exercise	49	830	30	/	1. 2	4	5	40s/point; ?; 9	Before and after treatment	VAS	Pain↓ QOL↑	(87)
de Paula Gomes *et al*. 2018	exercise	60	905+875+640	/	/	7. 85	/	3	?; 2/w; 10	Before and after treatment	WOMAC; LEFS; NRPS; PPT; FRT	The combination of LLLT and exercise pain↓↓	(134)
Alfredo *et al*. 2018	exercise	40	904	/	/	3	/	/	?; 3/w; 10	Before and after treatment	VAS; Consumption of paracetamol; WOMAC; Lequesne	All parameters improved and maintained for six months	(135)
de Matos Brunelli Braghi*et al*. 2019	exercise	60	808	100	/	5. 6	200	10	56s/point; 2/w; 15	Before and after treatment	WOMAC; Spatiotemporal gait variables	All outcomes improved gait variables↑↑	(136)
de Paula Gomes *et al*. 2020	exercise	100	904	40	/	6	/	8	?; ?; ?	Before, during, and after treatment	WOMAC; NRPS; Pressure Pain Threshold; Borg; 30s Sit-to-Stand Test	With the exception of the tenderness threshold, all variables showed significant improvement over time	(137)
Vassão *et al*. 2021	exercise	36	808	100	2000	4	91	14	40s/point; 2/w; 16	Before and after treatment	WOMAC; Serum biomarker concentrations (IL-1β□IL-6□IL-8□IL-10 e TNF-α and CTX-II)	WOMAC function↑ IL-10 levels↑	(138)
Jorge *et al*. 2023	exercise	127	808	100	33. 3	6	/	8	?; 3/w; 24	Before and after treatment, 3 to 6 months after treatment	VAS; QOL; WOMAC	Pain↓ physical function↑ QOL↑	(139)
Ip *et al*. 2015	PT	100	810	/	20	/	3. 6	5	180s; 3/w; 36	Before and after treatment	Occurrence of TKA	The occurrence of TKA↓	(95)
Robbins *et al*. 2022	static stretching	145	904	40	/	3	/	9	?; 3/w; 9	Before and after treatment	VAS; WOMAC; Lequesne; TUG; KROM for knee flexion goniometry	Pain↓ self-reported symptoms↓ mobility↑ function↑	(140)
Paolillo *et al*. 2018	exercise; ultrasound therapy	35	808	100	10	/	7	5	15min; ?; ?	Before and after treatment	30s Sit-to-Stand Test; Pressure Pain Threshold	With or without exercise; pain↓ physical function↑	(141)
Ip *et al*. 2015	hyaluronic acid injection	140	810	/	20	5. 4	/	/	180s; 3/w; 18	Before and after treatment	Occurrence of TKA	The life of the knee joint↑ the need for joint replacement↓	(142)
Melo *et al*. 2015	electrical stimulation	45	810	200	/	4-6	0.218	6	20-30s/point; 8w; ?	Before and after treatment	US; 6MWT; TUG	LLLT did not enhance the effect of electrical stimulation on the assessed parameters	(96)
de Oliveira Melo *et al*. 2016	electrical stimulation	45	810	200	/	4-6	0.218	6	180s; 2/w; 16	Before and after treatment	US; electrical activity of knee extensor muscles; torque; WOMAC	Health and electrical activity↑	(97)
Huang *et al*. 2021	acupuncture	82	808±10	≤ 300	/	3	/	/	10s/point; three days postoperatively; 6	Day 1/2/3 after TKA	Flection; stiff	Recovery of physical functions↑	(143)

*LEFS: Lower Extremity Functional Scale, used to evaluate lower extremity function; PPT: pressure pain threshold; FRT: functional reach test, used to assess balance and walking ability; TKA: total knee arthroplasty; 6 MWT: 6-minute walk test; US: ultrasound.

exercise on 90 patients with KOA. The participants were randomly assigned to three groups: a 3 J LLLT + exercise group, a 2 J LLLT + exercise group, and a placebo laser + exercise group, with each group receiving 10 sessions of LLLT treatment. The exercise regimen consisted of 90 daily repetitions of straight leg raises as an isometric quadriceps exercise, and the intervention lasted for a total of 14 weeks. The results showed significant improvements in all parameters (such as pain, function, and quality of life) in both LLLT groups compared to baseline ($p<0.01$) (94). Patients with advanced KOA may require total knee arthroplasty (TKA), which not only involves surgical pain but also adds to the economic burden. A study suggests that combining LLLT with conventional physical therapy may help reduce the incidence of TKA. In the study, 100 elderly patients with bilateral symptomatic KOA received either conventional physical therapy or conventional physical therapy combined with LLLT. After a 6-year follow-up, the results showed that the combined treatment group benefited significantly from the treatment: during the follow-up period, only one patient in the combined treatment group underwent TKA, while nine patients in the conventional physical therapy group underwent the procedure. The need for TKA was significantly reduced in the combined treatment group compared to the conventional physical therapy group ($p<0.05$). Therefore, the researchers recommend incorporating LLLT into the standard conservative treatment regimen for symptomatic KOA to help patients avoid surgical intervention (95). In addition to exercise therapy, LLLT combined with hyaluronic acid injections has shown positive effects for patients with KOA. Futhermore, combining LLLT with conservative treatments such as electrical stimulation (96, 97) or acupuncture (98).

Some studies have also highlighted the efficacy of combining LLLT with other conservative treatments in animal models of KOA. A study investigated the effects of LLLT combined with aerobic exercise training on a rat model of KOA. The intervention started in the fourth week after successful modelling, with LLLT applied at two points on both the medial and lateral sides of the knee, three times a week. Aerobic exercise training was conducted on a treadmill at a speed of 16 meters per minute for 50 minutes per day, with a total intervention duration of 8 weeks. The results showed that the combined intervention significantly reduced the fibrous tremor and irregular morphology of the joint surface and chondrocytes. The degenerative process measured by the OARSI score was lower (1.61±0.24, 95% CI 1.88–0.55, $p<0.0001$), and cartilage thickness increased. Furthermore, compared to the untreated KOA rat model group, the expression levels of IL-1β, caspase-3, and MMP-13 were reduced in all treatment groups (93). These results indicate that LLLT combined with aerobic exercise training can effectively prevent cartilage degeneration and modulate the inflammatory process induced by KOA. Another study investigated the efficacy of LLLT combined with chondroitin sulfate and glucosamine sulfate (CS/Gl) in a rat model of KOA. Following the induction of the model, CS/Gl treatment was administered continuously for 29 days, starting 48 hours after modelling, followed by LLLT (808 nm, 50 mW). The results showed that, compared to treatment with the drug alone, the combination of CS/Gl and LLLT significantly reduced IL-1β protein expression ($p=0.0359$) while increasing IL-10 ($p=0.028$) and Col II immunoexpression ($p=0.0204$) (99). In summary, these studies collectively suggest that combining LLLT with exercise training or drug therapy may synergistically promote tissue healing and regeneration while reducing inflammation, potentially augmenting their individual therapeutic effects on KOAhas been shown to improve pain and physical function in patients with KOA.

Safety and feasibility

LLLT has garnered considerable attention as a therapeutic approach, extensively researched and validated for its feasibility and safety(100-102). Patients typically experience minimal discomfort or pain during treatment, and there are no reports of significant side effects or complications associated with LLLT. Due to its non-invasive and non-traumatic nature, LLLT offers a safer alternative to pharmacological pain management, avoiding the side effects commonly associated with analgesic medications (101). In conclusion, LLLT stands as a non-invasive, safe, and effective treatment option that holds promise for patients with KOA, warranting further promotion and application in clinical practice.

Discussion

This review conducted a comprehensive study of the effects of LLLT across various levels of biological organisation, from cellular mechanisms to animal models, and ultimately to clinical outcomes in patients with KOA. Our analysis highlights the multifaceted impact of LLLT, which alleviates synovitis by modulating inflammation and promoting cellular repair. It also protects joint cartilage by balancing synthesis and degradation processes, thereby slowing the progression of KOA. Furthermore, LLLT helps reduce pain by modulating spinal cord sensitisation and nerve conduction, while enhancing the strength and stability of the knee extensors to minimise abnormal movement. These combined effects ultimately improve the quality of life for KOA patients. Additionally, LLLT can be effectively integrated with other treatment modalities, such as exercise, intra-articular injections, and medication, to alleviate KOA symptoms and reduce the incidence of TKA, thus avoiding surgical trauma and discomfort. This systematic exploration of the effects of LLLT at different levels provides a solid foundation for understanding its therapeutic potential and for guiding future research and clinical applications.

In 1967, Dr Endre Mester demonstrated that LLLT could promote wound healing in mouse skin (103, 104). Since then, LLLT has also shown its ability to promote healing and tissue regeneration in many medical fields. For example, in the treatment of oral diseases, LLLT has been used as an adjunct therapy for periodontitis, reducing the levels of inflammatory factors such as IL-1β, IL-

6, TNF-α and MMPs, and promoting gum tissue repair. Chronic low-grade inflammation may also be regulated by regulating GLUT1/mTOR aging-related pathways (105, 106). In diseases of the skin system, LLLT stimulates cell proliferation and accelerates collagen synthesis through the NF-κB signalling pathway, promoting wound healing and reducing scarring (107, 108). In addition, LLLT stimulates complex IV (cytochrome C oxidase) of the mitochondrial respiratory chain, which accelerates cell metabolism and ATP production, promotes vasodilation through the release of nitric oxide, and regulates transcription factors associated with cell growth and tissue repair (109, 110). In addition, LLLT also has the advantages of being non-invasive, easy to accept, with few side effects, easy to operate, and has shown high cost-effectiveness in the treatment of a variety of diseases (111-114). It is important to note that, although existing research suggests that LLLT may help reduce oxidative stress, studies in this area remain limited (80, 115). Future research should focus on the potential of LLLT to improve oxidative stress in KOA patients, aiming to provide a more comprehensive treatment plan and theoretical foundation for KOA management.

Differing from previous literature, this study synthesises the mechanisms of LLLT for KOA by integrating evidence from both *in vitro* and *in vivo* experiments. It encompasses the role of LLLT in clinical applications and evaluates its safety and feasibility. This comprehensive evaluation provides a more complete theoretical foundation for the treatment of KOA, an area that has not been sufficiently explored in prior reviews. Although earlier studies uniformly indicate that LLLT demonstrates positive effects in various clinical trials, discrepancies among the findings persist, potentially attributable to variations in treatment parameters or research designs. Thus, our study underscores the necessity for further standardisation of treatment protocols.

Based on current research findings, it is recommended to incorporate LLLT as an adjunctive treatment in the rehabilitation plans for patients with KOA, and to further explore its combined effects with other therapeutic approaches. Importantly, given the current lack of clarity regarding the optimal parameters for LLLT in the treatment of KOA, it is recommended that individualised assessments be conducted within the range of the guideline-based best parameters provided by the World Association for Laser Therapy. This approach is intended to determine the most effective treatment plan for achieving superior therapeutic outcomes (90).

The clinical implications of our research findings suggest that LLLT may play a significant role in the treatment of KOA, potentially complementing or even replacing traditional pharmacological treatments. Consequently, there is a future need to develop more standardised and detailed treatment protocols, including explicit treatment parameters and evaluation criteria. Additionally, conducting multi-center, large-scale clinical trials with long-term interventions and follow-ups should be pursued to reduce research heterogeneity, enhance the scientific rigor and effectiveness of the data, and strengthen the evidence base. Furthermore, investigating whether LLLT has similar effects on other types of joint diseases or pain management could help broaden its application and provide further support for its use in a wider range of clinical settings. Through more rigorous and comprehensive future research, we can integrate LLLT into routine clinical care, offering patients a safer and more effective alternative.

Conclusions

In conclusion, this study indicates that LLLT is a safe and non-invasive alternative treatment for KOA, effectively reducing pain, enhancing function, and minimising discomfort associated with surgery. Evidence from both *in vivo* and *in vitro* studies shows that LLLT works by modulating inflammatory mediators and cells, with specific wavelengths significantly affecting inflammatory factors such as IL-1β and IL-6, as well as inflammatory cells like macrophages and neutrophils. As a therapeutic approach, LLLT has demonstrated positive effects in both *in vivo* and *in vitro* settings. Future research should focus on optimising the parameters and protocols of LLLT to enhance its efficacy in treating KOA.

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