Fundamental Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Fundamental Research

journal homepage: http://www.keaipublishing.com/en/journals/fundamental-research/

Review

Cryotherapy and thermotherapy in the management of osteoarthritis and rheumatoid arthritis: A comprehensive review

Yuming Yao[a,1], Wenqing Xie[a,1], Michael Opoku[a], Djandan Tadum Arthur Vithran[a], Zhou Li[b,*], Yusheng Li[a,c,*]

[a] Department of Orthopedics, Xiangya Hospital, Central South University, Changsha 410008, China
[b] Beijing Institute of Nanoenergy and Nanosystems, Chinese Academy of Sciences, Beijing 101400, China
[c] National Clinical Research Center for Geriatric Disorders, Department of Geriatrics, Xiangya Hospital, Central South University, Changsha 410008, China

ARTICLE INFO

Article history:
Received 23 May 2024
Received in revised form 30 June 2024
Accepted 30 July 2024
Available online xxx

Keywords:
Cryotherapy
Thermotherapy
Contrast therapy
Osteoarthritis
Rheumatoid arthritis

ABSTRACT

As non-pharmacological options for osteoarthritis (OA) and rheumatoid arthritis (RA), cold and heat therapies manipulate local temperatures to improve symptoms and promote functional recovery. Cryotherapy reduces acute pain and inflammation by lowering temperatures, while thermotherapy elevates body temperature to enhance blood circulation and tissue repair. Contrast therapy combines the benefits of cold and heat treatments, alternating between them to boost blood flow and relieve pain. This review analyzes the existing literature, highlighting the potential benefits of these treatments in alleviating symptoms of patients with OA and RA, while emphasizing the importance of developing personalized treatment plans in clinical practice. Although specific recommendations for the application of cold and heat therapies vary across major clinical guidelines, their cautious use tailored to individual patient circumstances is generally considered beneficial. Further, with the emergence of new cold and heat therapy devices and materials, such as wearable devices and applications of nanotechnology, more possibilities for physical therapy in arthritis are available now. These innovative technologies are expected to enhance the precision, safety, and convenience of treatments. However, current research on cold and heat therapies still has limitations, including small sample sizes and a lack of long-term follow-up data. Future research needs to further validate the efficacy and safety of these treatment methods through large-scale, high-quality clinical trials, and probe their role in the comprehensive management of OA and RA.

1. Introduction

The term arthritis originates from the Greek word for “joint disease” and is defined as acute or chronic joint inflammation usually accompanied by pain and structural damage [1]. The most common type of non-inflammatory arthritis is osteoarthritis (OA), also known as degenerative joint disease. OA is one of the most common joint disorders worldwide, with the primary symptoms including joint pain and functional impairment [2,3]. The knee is the most commonly affected joint, followed by the hands and hip joints [4]. This disease not only causes pain and functional loss in patients, but also imposes a severe burden on society and the economy [2]. According to 2021 data, more than 22% of adults over the age of 40 years worldwide suffer from knee osteoarthritis (KOA), with the total number of OA cases estimated to exceed 500 million [5]. The 2019 Global Burden of Disease report showed that from 1990 to 2019, the number of disabilities caused by OA increased by 114.5% [6]. With aging populations, increasing obesity rates, and joint injuries, the incidence of OA is expected to continue to increase [4]. Rheumatoid arthritis (RA) is an autoimmune disease characterized by progressive damage to the joints and surrounding soft tissues [7]. This disease not only exacerbates disability in patients, but may also lead to premature death, resulting in a substantial socioeconomic burden. Globally, the prevalence of RA varies significantly, ranging from about 0.25% to 1% [8]. This condition can affect people of all ages but is more commonly diagnosed in individuals over 40 years of age, with women being two to three times more likely to develop the disease than men [9].

OA is a whole-joint disease involving changes in the articular cartilage, subchondral bone, ligaments, joint capsule, synovium, and periarticular muscle structures [10,11]. The pathogenesis of OA involves various factors, including mechanical, inflammatory, and metabolic aspects, with a key role played by the activation of matrix metalloproteinases (MMPs) [2,4]. Specifically, MMPs produced by chondrocytes initiate the degradation of joint cartilage, leading to the narrowing of joint spaces and the accumulation of cartilage degradation products,

* Corresponding authors.
E-mail addresses: zli@binn.cas.cn (Z. Li), liyusheng@csu.edu.cn (Y. Li).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.fmre.2024.07.008

Please cite this article as: Y. Yao, W. Xie, M. Opoku et al., Cryotherapy and thermotherapy in the management of osteoarthritis and rheumatoid arthritis: A comprehensive review, Fundamental Research, https://doi.org/10.1016/j.fmre.2024.07.008

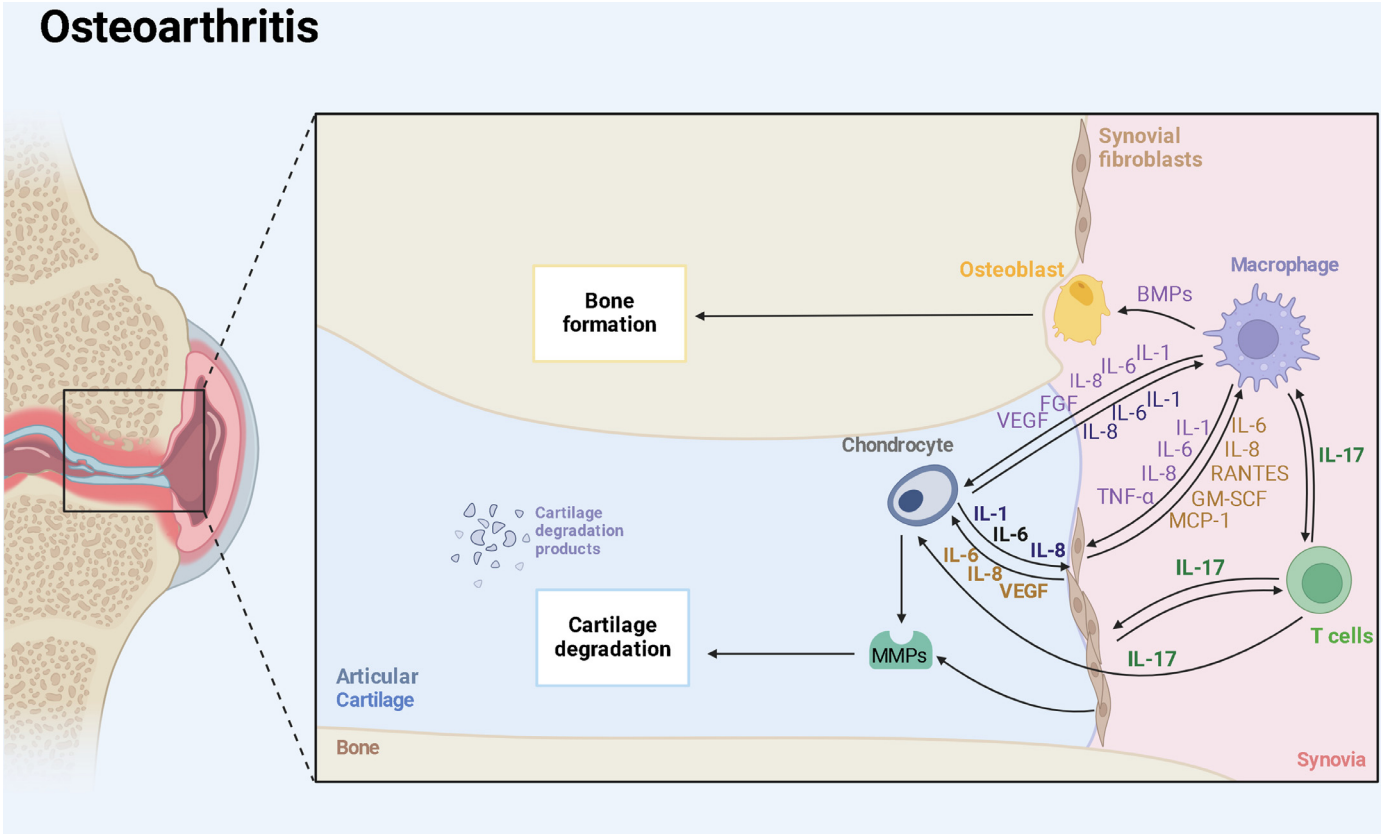

Fig. 1. Mechanism of pathogenesis in rheumatoid arthritis. FGF: Fibroblast Growth Factor; GM-SCF: Granulocyte-Macrophage Colony-Stimulating Factor; IL-1: Interleukin 1; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-17: Interleukin 17; MCP-1: Monocyte Chemoattractant Protein-1; MMPs: Matrix Metalloproteinases; RANTES: Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted; TNF-α: Tumor Necrosis Factor Alpha; VEGF: Vascular Endothelial Growth Factor.

significantly exacerbating joint damage. In an inflammatory environment, synovial cells and macrophages release pro-inflammatory factors such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1, IL-6, IL-8), which worsen cartilage damage and lead to thickening of the synovial membrane and synovitis [12]. Additionally, increased bone formation and T-cell activation indicate that OA affects not only the cartilage, but also the entire joint, including the formation of osteophytes and bone proliferation (Fig. 1). These pathological changes reflect a critical imbalance between tissue repair and destruction in OA, leading to a continual decline in joint function [13]. In contrast, RA typically results from a combination of genetic susceptibility and environmental factors such as specific HLA-DRB1 gene variants and smoking [14]. Its pathogenesis involves the abnormal activation of the immune system, particularly in the joint synovium, resulting in synovial tissue inflammation and thickening. In the inflammatory state, immune cells, including T and B cells, congregate and activate, producing a plethora of inflammatory mediators such as TNF-α, IL-1, IL-6, and IL-17, further promoting inflammation and tissue damage [15,16]. Prolonged chronic inflammation leads to the degradation of joint cartilage, bone erosion, and narrowing of joint spaces, ultimately destroying joint structure and causing loss of function (Fig. 2). Although the specific pathogenic mechanisms of OA and RA differ, both diseases are driven by the activation of immune cells, involvement of multiple cell types, and pro-inflammatory factors, leading to chronic inflammation and continuous damage to joint structures, thereby affecting joint function and patient quality of life [17].

The treatment of arthritis typically employs a comprehensive approach, including pharmacological and non-pharmacological therapies and surgery. The treatment regimen depends on the type and severity of arthritis; however, the general principles are to alleviate pain, control inflammation, protect joint integrity, and enhance the quality of life of the patient [18-20]. Pharmacological treatments include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biologics that effectively reduce inflammation and retard disease progression [21]. Nonpharmacological treatments such as physical therapy, occupational therapy, and tailored exercise programs help enhance joint function, alleviate pain, and improve daily activity capabilities [22]. Additionally, some patients may use alternative therapies such as acupuncture or herbal medicines to complement conventional treatments [23]. In certain cases, particularly when joint damage severely affects quality of life, joint replacement or arthroscopic surgery may be necessary to restore joint function and alleviate symptoms [24,25]. The goal of OA treatment is to limit pain, alleviate symptoms, and improve function [3,21]. Optimal care usually requires a combination of pharmacological and nonpharmacological treatments. Common medications include oral and topical NSAIDs, capsaicin, and duloxetine. Non-pharmacological interventions include education and self-management, exercise, weight loss, specific movements, physical therapy, orthotics, and acupuncture [26,27]. Topical NSAIDs, capsaicin, and other ointments are typically first-line treatments. If these methods do not relieve symptoms, or if the disease presents more systemically, oral NSAIDs should be considered [21]. The overall objective of RA treatment is to achieve long-term remission or a state of low disease activity, maximally control symptoms, prevent joint damage and dysfunction, and improve the quality of life of the patient [28-30]. The treatment regimens include both pharmacological and non-pharmacological therapies. Drug therapy is central to RA treatment and primarily involves NSAIDs, corticosteroids, DMARDs, biologics, and targeted synthetic small molecules. DMARDs are crucial for controlling disease activity and improving long-term prognosis and are typically used as early as possible [31]. Biologics and targeted synthetic

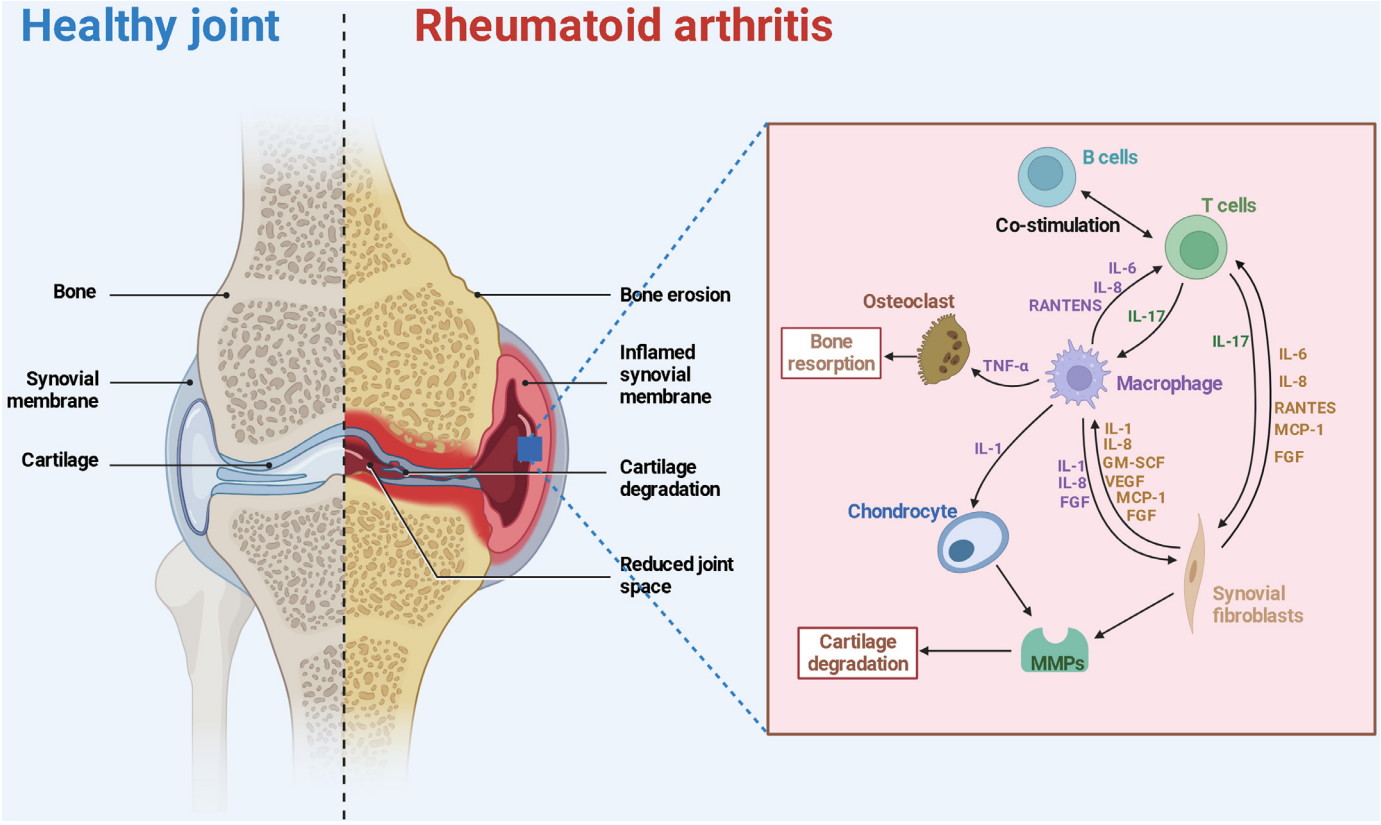

Fig. 2. Mechanism of pathogenesis in osteoarthritis. BMPs: Bone Morphogenetic Proteins; FGF: Fibroblast Growth Factor; GM-SCF: Granulocyte-Macrophage Colony-Stimulating Factor; IL-1: Interleukin 1; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-17: Interleukin 17; MCP-1: Monocyte Chemoattractant Protein-1; MMPs: Matrix Metalloproteinases; RANTES: Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted; TNF-α: Tumor Necrosis Factor Alpha; VEGF: Vascular Endothelial Growth Factor.

small molecules are primarily used for patients who respond poorly to traditional DMARDs [32,33]. Non-drug therapies include physical therapy, occupational therapy, and lifestyle modifications, such as moderate exercise, a balanced diet, and smoking cessation. Physiotherapy aids in increasing joint flexibility and strength, whereas occupational therapy helps patients adopt joint-protective strategies during daily activities to reduce joint stress [34,35].

Pharmacological treatment has always been the primary method for treating OA and RA, whether as a standalone therapy or in combination with physical therapy and dietary adjustments. It plays a crucial role in managing the disease, controlling symptoms, and improving the quality of life of the patient. Although pharmacological treatment is key to managing the symptoms of OA and RA, long-term reliance may lead to a range of side effects. For instance, NSAIDs can effectively alleviate pain and inflammation, but prolonged use may cause gastrointestinal issues, heart disease, and kidney damage [36,37]. Even though cyclooxygenase-2 (COX-2) inhibitors reduce the gastrointestinal side effects, they may increase the risk of cardiovascular events [38]. Further, corticosteroids have potent anti-inflammatory effects, but long-term high-dose use may lead to osteoporosis, hypertension, diabetes, ulcers, and immunosuppression [39,40]. Studies also show that methotrexate may be associated with liver toxicity, cirrhosis, and fibrosis [41]; and biologics like TNF-α inhibitors may increase the risk of malignancies, systemic infections, and tuberculosis [14]. Given the potential side effects of drug treatments, exploring safer alternatives with fewer side effects is critically important. Physical therapy, a significant non-pharmacological treatment option, offers a beneficial alternative for enhancing joint function, alleviating pain, and improving overall activity levels, thereby potentially reducing the need for drug treatment.

In this context, cryotherapy and thermotherapy, which are important physical therapy modalities, are noted for their simplicity, low cost, and minimal side effects. Cryotherapy works by lowering the local temperature, slowing blood flow, reducing metabolism, and alleviating pain and inflammation [42]. Conversely, thermotherapy increases local temperature, enhances blood circulation, eases muscle spasms and joint stiffness, and accelerates tissue repair [43-45]. Both cold and heat therapies have advantages, with the choice depending on the specific type of arthritis and the stage of the condition. In general, cryotherapy is suitable for controlling inflammation in the acute phase, whereas thermotherapy is better suited for pain management and joint function restoration in the chronic phase [46].

Although cryotherapy and thermotherapy are widely used for symptomatic relief in OA and RA, detailed discussions on their mechanisms of action, appropriate conditions, advantages, and limitations relative to traditional treatments remain limited in the academic community. This review aims to systematically organize and describe the current research progress in the treatment of OA and RA with cryotherapy and thermotherapy, discussing their therapeutic principles, implementation methods, and clinical applications to provide comprehensive information to clinicians, assisting them in better understanding and utilizing these non-pharmacological treatments. Moreover, by collating and organizing current knowledge, this study seeks to enhance the comprehensive understanding of the roles of cold and heat therapies in treating OA and RA and to guide future research.

2. The physiological effects and mechanisms of cryotherapy and thermotherapy

Cryotherapy, thermotherapy, and contrast therapy (alternating cold and heat therapy) are the three primary temperature modulation techniques used in physical therapy, each with unique therapeutic principles and a long history of application. Cryotherapy uses the

physical properties of low temperatures to directly affect the human body, regulate physiological responses, alleviate pain, reduce inflammation, and enhance functionality [47]. This method has been used since ancient Egyptian times by physicians using cold environments or objects to treat pain and illnesses [48]. The core principle is that low temperatures cause blood vessels to constrict, reducing blood flow to injured or inflamed areas, thereby alleviating swelling and pain [49,50]. With technological advancements, the application of cryotherapy has evolved from simple cold compresses to more sophisticated cooling techniques, including cold sprays, high-pressure cold CO_2, liquid nitrogen cooling, cold air bags, electronic cooling systems, and whole-body cryotherapy (WBC) using cryotherapy, such as cryochambers and whole-body cold mist showers. These techniques expose the body to extremely low temperatures for short periods, thereby activating defense mechanisms and promoting health. For example, cryochamber treatments typically lower body temperature to a very low level for a short time to stimulate natural recovery processes. This approach is increasingly valued in sports recovery, cardiovascular health enhancement, and chronic pain [51].

Thermotherapy, another traditional physical therapy, uses high temperatures to improve blood circulation and facilitate the elimination and exchange of metabolic waste and nutrients [52,3]. Modern thermotherapy techniques, such as electric heating pads, infrared therapy, shortwave therapy, hydrotherapy, and mud therapy, increase body temperature to activate heat shock proteins, aid in cellular repair, and enhance immune function [54]. Thermotherapy also alleviates chronic pain and muscle tension by affecting the nervous system; a warm environment helps reduce psychological stress and anxiety, promotes physical and mental relaxation, and benefits bodily function recovery [55]. Contrast therapy combines the benefits of both cryo- and thermotherapy, alternating between cold and hot compresses to trigger vasoconstrictive and vasodilative responses, enhance blood circulation, accelerate the removal of inflammatory mediators from tissues, effectively alleviate pain, and promote the recovery of injured areas. This therapy is particularly suitable for post-exercise recovery and chronic pain management and facilitates the recovery of complex musculoskeletal conditions. Research indicates that contrast therapy offers therapeutic effects superior to those of thermotherapy or cryotherapy alone and is particularly effective in managing persistent pain and chronic conditions [56,57].

2.1. Physiological effects and mechanisms of cryotherapy in arthritis treatment

Cryotherapy effectively alleviates arthritic pain, reduces inflammation, and improves joint function through unique physiological effects and mechanisms. Cryotherapy initially induces rapid skin vasoconstriction through hemodynamic effects, followed by reflexive vasodilation (known as the "hunting reaction") mediated by the sympathetic-adrenal system. This physiological response, termed “heat shock,” significantly reduces blood flow in the inflamed area, effectively alleviating inflammation and swelling [58,59]. Second, cryotherapy has neuromuscular effects by reducing the excitability discharge frequency of the cutaneous nerves and nerves associated with the Golgi tendon organs [60]. It alleviates muscle fatigue and stiffness, relieves spasms and pain, and improves muscle function. Finally, cryotherapy directly affects the joints and surrounding connective tissues by lowering the intraarticular temperature to inhibit collagenase activity [61], lengthening tendons, further reducing joint and connective tissue inflammation, increasing the range of motion (ROM) of joints, and enhancing joint flexibility [62]. Despite the significant pain relief and inflammation reduction effects of cryotherapy in the treatment of arthritis, it is noteworthy that in some cases, cold stimulation may exacerbate arthritis symptoms. Particularly for certain types of arthritis, such as diseases associated with Raynaud’s phenomenon or circulatory disorders, cryotherapy may lead to decreased blood flow, worsening pain, and stiffness. Additionally, prolonged cold application may cause cold-related injury of local tissues, affecting the recovery of soft tissues around the joints [63,64].

Studies have shown that the physiological mechanisms of cryotherapy in the treatment of arthritis are closely related to inflammatory factors, intercellular adhesion molecules, and enzymatic pathways. Peyronnel et al. conducted a study using an antigen-induced arthritis (AIA) model. They observed that, after twice daily local cryotherapy, the expression levels of IL-6, IL-1β, and TNF-α significantly decreased in rats [65]. Compared with the placebo group, cryotherapy significantly reduced the white blood cell count and inflammatory cytokine concentration in the synovial fluid. This effect was also observed in rats with KOA induced by anterior cruciate ligament transection [66]. Guillot et al. compared the effects of local ice packs and high-pressure cold CO_2 therapy in patients with non-purulent knee arthritis. They found that local ice packs significantly reduced levels of IL-6, IL-1β, vascular endothelial growth factor (VEGF), nuclear factor κB p65 (NF-κB p65), and prostaglandin E2 (PGE2) in the synovial fluid, particularly in cases of crystal-induced arthritis [67]. Further, a randomized controlled trial (RCT) found that, although there was no change in IL-6 levels after WBC, the level of intercellular adhesion molecule 1 (ICAM-1) showed a downward trend, and a decrease in oxidative stress markers was observed [68]. In vitro experimental results showed that localized cryotherapy in an AIA mouse model exhibited both local and systemic anti-inflammatory effects at the gene and protein levels. This is primarily mediated through the IL-6/IL-17A pathway, independent of TNF-α [69]. Concurrently, some studies have reported that cryotherapy reduces oxidative stress and/or increases antioxidant buffering capacity [70-72].

Moreover, the effectiveness of cryotherapy appears to be closely related to treatment temperature. Studies have indicated that when the temperature is lowered by 10 ˚C, enzyme activity in cellular metabolic pathways decreases by 50% [73]. A systematic review and meta-analysis revealed that moderate cold (11 ˚C-15 ˚C) is more effective in alleviating delayed onset muscle soreness than severe cold (5 ˚C-10 ˚C) [74]. Compared to normal body temperature (37 ˚C), deep hypothermia (17 ˚C) significantly reduces the expression of inflammatory mediators and cytokines [75]. However, in a rat model of knee arthritis, although cryotherapy at 5 ˚C and 10 ˚C significantly reduced pain and swelling, no significant differences were discernable between the two temperatures [76]. A prospective randomized study found that continuous cryotherapy at 10 ˚C significantly relieved postoperative pain in patients undergoing anterior cruciate ligament reconstruction, while treatment at 5 ˚C had no notable effects [77]. These results indicate that there may be an optimal temperature range within which cryotherapy is most effective in relieving pain and inflammation. These findings also suggest that different treatment temperatures may have varying effects on the expression of inflammatory mediators and cytokines, emphasizing the importance of precise temperature control to optimize the effects of cryotherapy.

By integrating the results of previous research, we have summarized the potential molecular mechanisms involved in cryotherapy for arthritis treatment (Fig. 3) [78]. Cold stimuli first activate cold receptors, with the signal then transmitted via afferent nerves to the central nervous system, subsequently triggering the release of norepinephrine and acetylcholine by sympathetic nerve terminals [79,80]. These neurotransmitters bind to specific receptors on macrophage surfaces, preventing the phosphorylation and degradation of IκB, thus effectively inhibiting the activation of NF-κB. The inhibition of NF-κB activation reduces the release of pro-inflammatory cytokines (such as IL-1β, IL-6, IL-8, and TNF-α) and intercellular adhesion molecules [81], while promoting the production of the anti-inflammatory cytokine IL-10 [82-84]. Additionally, cryotherapy induces vasoconstriction mediated by α-adrenergic receptors and reduces VEGF expression, thereby inhibiting angiogenesis and infiltration of inflammatory cells [85]. At the same time, cryotherapy reduces histamine release in tissues and downregulates the expression of inducible nitric oxide synthase (i-NOS), myeloperoxidase (MPO) [86,87], superoxide dismutase (SOD) [88], and glutathione (GSH) [86], effectively alleviating oxidative stress. Cryotherapy further alleviates inflammatory responses and joint damage by lowering the activities of collagenase [89], MMPs [90] and COX-2.

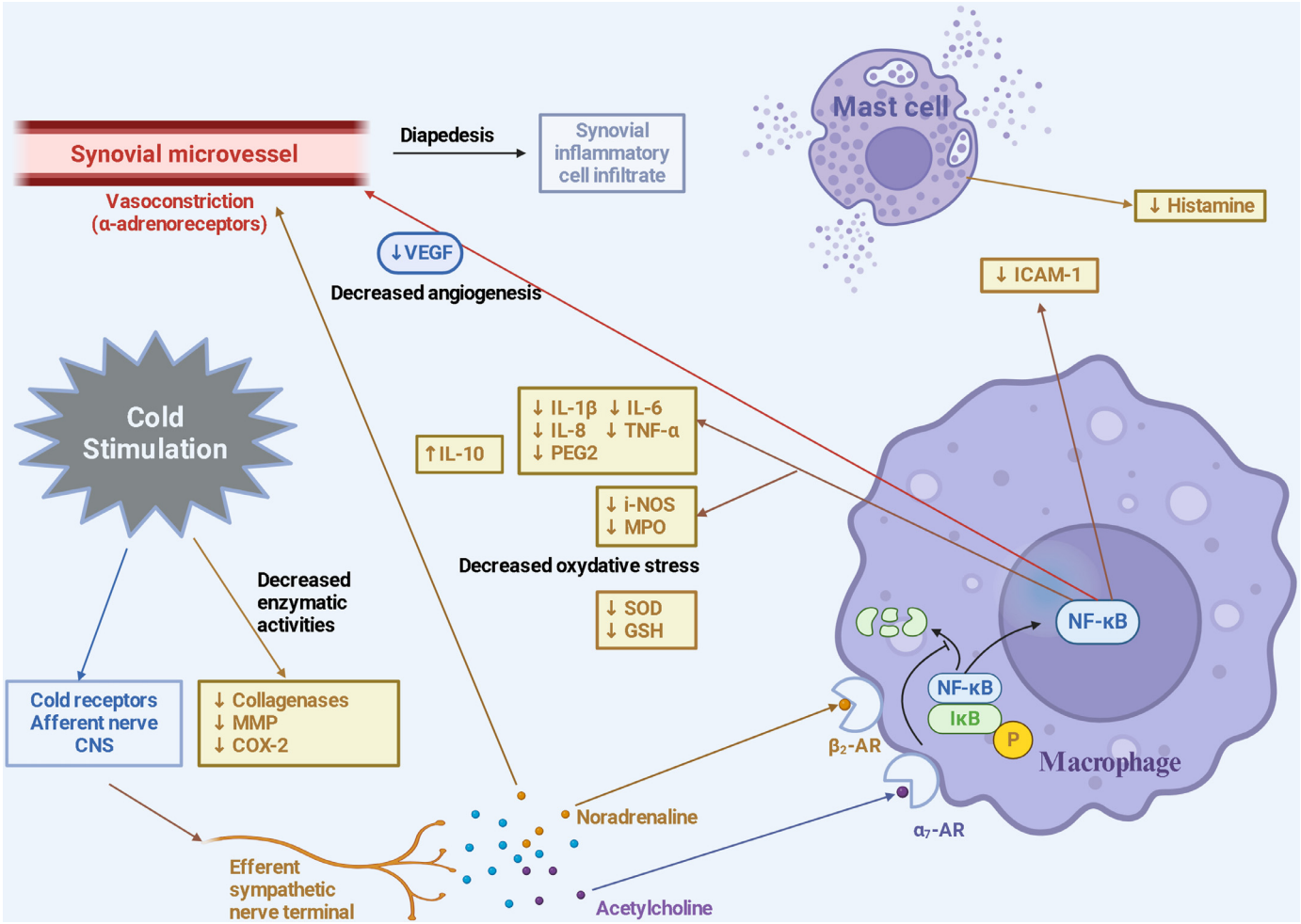

Fig. 3. Molecular pathways involved in cryotherapy for treating arthritis: A proposed model. α7-AR: Alpha-7 Adrenergic Receptor; β2-AR: Beta-2 Adrenergic Receptor; CNS: Central Nervous System; COX-2: Cyclooxygenase-2; GSH: Glutathione; ICAM-1: Intercellular Adhesion Molecule 1; IκB: Inhibitor of kappa B; IL-1β: Interleukin 1 Beta; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-10: Interleukin 10; iNOS: Inducible Nitric Oxide Synthase; MPO: Myeloperoxidase; MMP: Matrix Metalloproteinase; NF-κB: Nuclear Factor Kappa B; P: Phosphorylation; PGE2: Prostaglandin E2; SOD: Superoxide Dismutase; TNF-α: Tumor Necrosis Factor Alpha; VEGF: Vascular Endothelial Growth Factor.

2.2. Physiological effects and mechanisms of thermotherapy in arthritis treatment

Thermotherapy plays a crucial role in arthritis management primarily by increasing local or systemic temperatures to enhance blood circulation, boost tissue oxygen supply, alleviate pain, relieve muscle tension, and improve joint flexibility [91-93]. This therapy improves blood circulation through the application of heat, facilitating the removal of metabolic waste and the delivery of nutrients, thereby accelerating the repair of damaged tissues [94,95]. Further, heat directly acts on pain-sensitive nerve endings, effectively relieving both chronic and acute pain by decreasing the release of inflammatory mediators [55,91]. Certain forms of heat therapy, such as hot spring baths, mud therapy, and paraffin baths, possess unique physiological effects because of their different heat-producing media. Hot spring baths utilize mineral-rich spring water, producing a dual therapeutic effect on patients with arthritis: both the physical effects of heat therapy and the chemical treatment actions of minerals dissolved in the water [96]. The components of hot spring water, such as sulfides, are particularly effective in reducing inflammation, promoting blood circulation, and alleviating muscle pain [97]. When mud application and hydrotherapy are combined, mud therapy acts by deeply penetrating the skin with its unique minerals and thermal retention properties, providing a sustained warming effect [98,99]. This therapy not only promotes blood circulation in deep tissues, but also reduces pain and inflammation, thereby enhancing joint flexibility. Paraffin baths involve immersing the affected areas in melted paraffin to deliver lasting warmth, enhancing blood circulation, and improving skin conditions, and are particularly beneficial for arthritis in the hands and feet, effectively easing joint stiffness and pain [100].

From a molecular perspective, thermotherapy plays a crucial role in the modulation of inflammatory responses. After exposure to 41 °C for 30 min, fibroblast-like synoviocytes isolated from patients with RA showed a significant reduction in IL-1β-induced PGE2 release. The synthesis of pro-inflammatory cytokines and related proteins, including vascular cell adhesion molecule 1 (VCAM-1), ICAM-1, TNF-α, IL-1α, IL-1β, IL-8, and COX-2, was also inhibited [101]. Other research findings also suggest that thermal therapy can lower the serum levels of pro-inflammatory molecules, such as TNF-α, IL-1β, IL-6, PGE2, leukotriene B4 (LTB4), and C-reactive protein (CRP), while promoting the generation of anti-inflammatory molecules like IL-10 and insulin-like growth factor 1 (IGF-1) [102-105]. The NF-κB signaling pathway plays a pivotal role in regulating the inflammatory response. Under unstimulated conditions, NF-κB forms a complex with its inhibitor IκBα in the cytoplasm. When IκBα is phosphorylated and subsequently degraded, NF-κB is released and translocated into the nucleus, initiating the gene expression of various pro-inflammatory factors. Thermotherapy can prevent

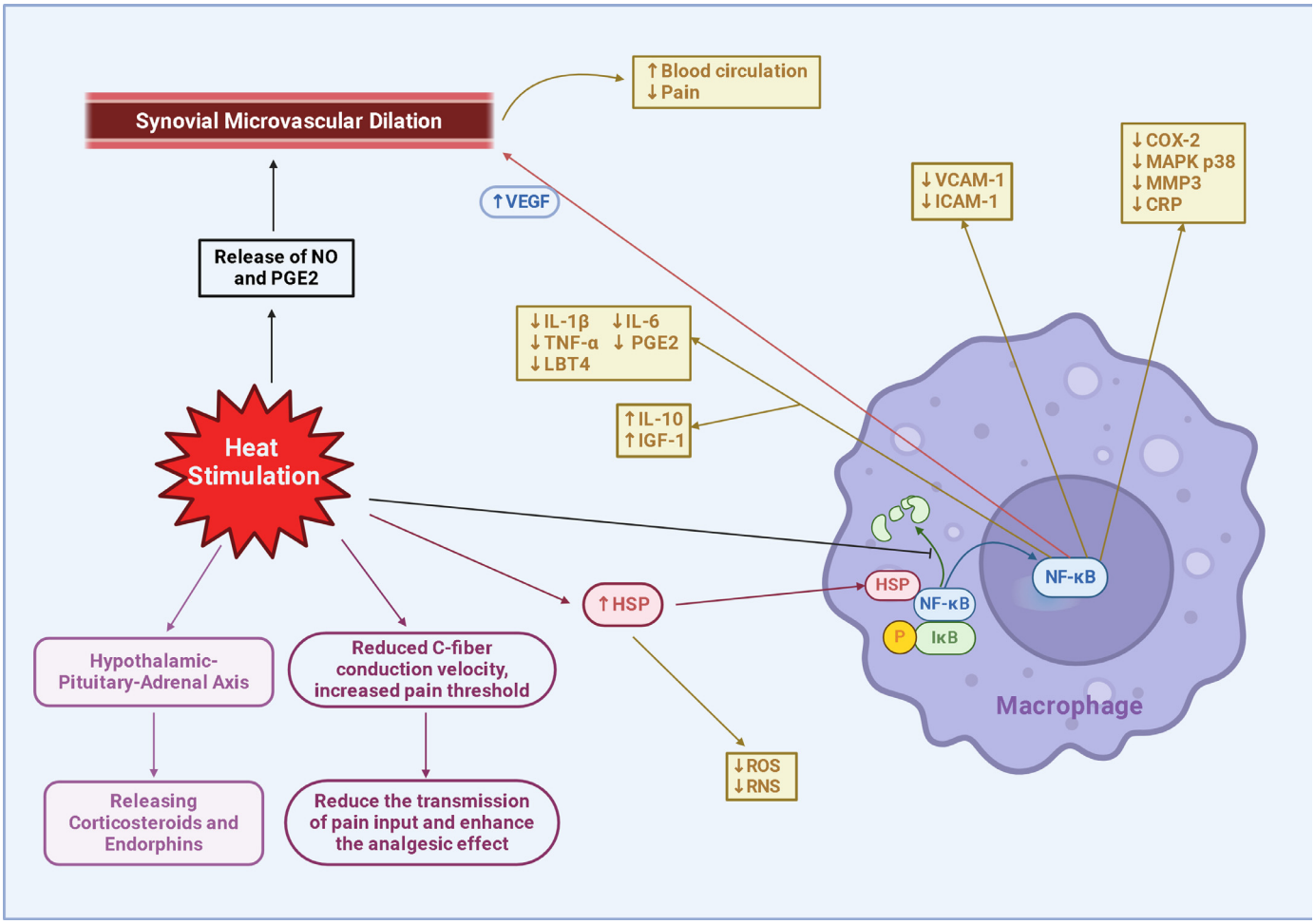

Fig. 4. Molecular pathways involved in thermotherapy for treating arthritis: A proposed model. COX-2: Cyclooxygenase-2; CRP: C-reactive Protein; HSP: Heat Shock Protein; ICAM-1: Intercellular Adhesion Molecule 1; IGF-1: Insulin-like Growth Factor 1; IκB: Inhibitor of kappa B; IL-1β: Interleukin 1 Beta; IL-6: Interleukin 6; IL-10: Interleukin 10; LTB4: Leukotriene B4; MAPK p38: Mitogen-Activated Protein Kinase p38; MMP3: Matrix Metalloproteinase 3; NF-κB: Nuclear Factor Kappa B; NO: Nitric Oxide; PGE2: Prostaglandin E2; P: Phosphorylation; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; TNF-α: Tumor Necrosis Factor Alpha; VCAM-1: Vascular Cell Adhesion Molecule 1; VEGF: Vascular Endothelial Growth Factor.

the phosphorylation and degradation of IκBα, thereby inhibiting the activation of NF-κB and maintaining it in the cytoplasm, reducing inflammation. Moreover, thermal therapy can also promote the production of heat shock protein 70 (HSP70), which binds to members of the NF-κB signaling pathway such as p65, c-Rel, and p50, further impeding the entry of NF-κB complexes into the nucleus, thus alleviating inflammation [54,106,107]. Stuhlmeier et al. discovered that short-term thermal therapy (exposure to 41 °C for 30 min) can block the activation of mitogen-activated protein kinase p38 (MAPK p38), which plays a central role in many pro-inflammatory responses [108]. Additionally, the neuroendocrine response triggered by heat stimulation leads to the release of opioid-like substances such as endorphins and enkephalins, providing significant analgesic effects during and for several weeks after hydrotherapy sessions [109].

Based on the analysis and understanding of earlier studies, we have prepared a list of the key signaling pathways and molecular mechanisms that may be involved in thermotherapy for arthritis treatment (see Fig. 4). First, heat stimulation (or mild thermal therapy) directly inhibits the phosphorylation and degradation of IκBα, preventing the release and activation of NF-κB, thereby suppressing the expression of pro-inflammatory factors [101]. Thermotherapy also promotes the expression of heat shock proteins (such as HSP70 and HSP32) [54,110], which bind to key members of the NF-κB signaling pathway, further stabilizing the NF-κB complex in the cytoplasm [106,107]. These mechanisms work together to effectively inhibit the NF-κB signaling pathway, thereby downregulating the expression of pro-inflammatory factors (such as IL-1β [102,104,105], IL-6 [104,111], TNF-α [102,105,112], PGE2 [102,105], and LTB4 [102,105]) and related proteins (such as COX-2 [113], MAPK p38 [108], MMP3 [114], and CRP [102]), while increasing the production of IL-10 [54] and IGF-1 [102]. Further, inhibition of the NF-κB signaling pathway can decrease the expression of adhesion molecules, such as ICAM-1 and VCAM-1 [101]. Heat stress-induced HSP expression can also directly reduce the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [115], protecting cells from oxidative stress damage. Second, synovial microvessels dilate under the combined action of NO, PGE2, and VEGF, increasing blood circulation that helps alleviate pain and promotes the repair of damaged tissues. An increase in temperature decreases the conduction velocity of C-fiber sensory nerves that transmit pain signals, raises the pain threshold, effectively reduces pain signal transmission, and enhances analgesic effects [55,116]. Thermotherapy triggers a neuroendocrine response, activating the hypothalamic-pituitary-adrenal axis that promotes the release of endorphins and corticosteroids, thereby enhancing anti-inflammatory and analgesic effects [109,117].

In summary, cryotherapy, thermotherapy, and contrast therapy are important non-pharmacological treatments that provide effective support for pain management and functional recovery based on their respective physiological mechanisms. These methods optimize blood

circulation, alleviate muscle tension, and promote wound healing by regulating body temperature, thereby playing a significant role in sports recovery, chronic disease management, and postoperative care. With a growing understanding of the efficacy of these therapies, their value in clinical practice continues to be confirmed, offering patients a broader spectrum of treatment options. These three therapeutic approaches complement each other and offer personalized treatment configurations, such as combining the rapid vasoconstriction effects of cryotherapy with the deep muscle relaxation benefits of thermotherapy or alternating between cold and heat in contrast therapy to adapt to varying symptoms and disease states. Advances in technology and research have led to the development of precise thermo-therapeutic and cryo-therapeutic equipment. These devices not only enhance the safety and efficacy of treatments, but also improve their convenience and acceptability, furthering the scientification and standardization of physical therapy.

3. The application of cryotherapy and thermotherapy in OA and RA

3.1. Cryotherapy

Cryotherapy can be divided into local and whole-body forms; local cryotherapy is typically used for treating inflammation and pain in specific areas, such as joint and muscle injuries, whereas WBC is used to treat conditions affecting multiple parts of the body or the entire system. Each method emphasizes temperature control and application duration. The applications of specific cryotherapy techniques, including treatment protocols and outcomes for various types of arthritis, are summarized in Table 1.

3.1.1. Local cryotherapy

3.1.1.1. Cold compress. As a traditional form of cryotherapy, cold compresses are extensively used in the management of OA and RA and have been clinically validated. An RCT found that patients with KOA who applied reusable gel ice packs to their knees for 20 min, three times a week over a period of 8 weeks while engaging in routine home exercises experienced effective reduction in pain and joint stiffness, with improvements also noted in daily function and balance [118]. Moreover, studies using animal models have supported the clinical application of cold compression therapy. Castro et al. applied a plastic bag filled with crushed ice directly to the affected knee in an AIA mouse model, with each session lasting 20 min and a 2-hour interval. The results indicated that this method increased the expression of Agrin and Atrogin-1 in the muscle environment, aiding in the maintenance of neuromuscular junctions and protection of muscle fibers, while also reducing joint swelling and inflammation [119]. Previous studies have confirmed that clinically analogous cryotherapy significantly increases the footprint area in rat models of knee osteoarthritis, reduces leukocyte counts and inflammatory cytokine concentrations in the synovial fluid, effectively diminishes joint synovitis, and improves locomotive function [66].

Some studies have compared cold compression therapy with other cryotherapies or physical therapies to evaluate its efficacy in patients with nonsuppurative arthritis and OA. Two RCTs compared the effects of local ice packs and high-pressure cold CO_2 (−78 ˚C) treatment on nonsuppurative knee arthritis. The results showed that local ice packs (twice daily for 30 min, at 8-hour intervals, for 1 day) significantly lowered the levels of IL-6, IL-1β, VEGF, NF-kB p65, and PGE2 in synovial fluid, especially in the subgroup with microcrystal-induced arthritis, whereas high-pressure cold CO_2 only reduced VEGF levels [67,120]. Sari et al. compared the effects of cold compresses (15 min daily) and intermittent pneumatic compression therapy (30 min daily) on ROM, muscle strength, knee swelling, pain intensity, and functional status in patients with KOA and found that both methods significantly improved symptoms after 4 weeks and 20 sessions of treatment, particularly intermittent pneumatic compression therapy, which was more effective in reducing knee swelling [121]. A prospective randomized crossover study of patients undergoing TKA investigated the effects of alternating the postoperative placement of cold packs on the palms and knees. The findings revealed no significant differences in outcomes based on the location of the cold application, indicating that both palm and knee cold therapy effectively improved post-TKA patient sensation [122].

Overall, cold compression therapy holds an important position in the management of arthritis as a simple, safe, and non-invasive treatment modality. However, further research is required regarding its specific mechanisms and applicability to different types of arthritis.

3.1.1.2. Cold spray and cold air therapy. Cold spray and cold air therapies are two common cryotherapy methods used to alleviate pain and inflammation in arthritis. Cold spray rapidly reduces the temperature of the affected area through the evaporative cooling effect of the sprayed liquid mist, whereas cold-air therapy uses low-temperature air applied directly to the affected area or the entire body to lessen pain and swelling. Both treatments are noninvasive and widely used in the management of diseases such as RA and OA. To study the effects and mechanisms of cryotherapy in RA treatment, Peyronnel et al. applied cold-spray therapy in an AIA mouse model. From the onset of the disease (day 10 post arthritis induction) to the acute inflammatory phase (day 24 post arthritis induction), each paw was subjected to nine alternating sprays, each lasting 5 s, with a 10-second interval. The results showed that cold spray significantly reduced arthritis scores and structural damage, decreased leukocyte infiltration into the aorta, and improved vascular dilation function. Concurrently, a reduction in the aortic mRNA expression levels of CXCL-1, IL-6, IL-1β, and TNF-α was observed [65].

Conversely, another study found that compared to cold spray treatment (twice daily at 9AM and 5PM, for 20–30 min each time, over 14 days), ice packs performed better in improving joint scores and reducing swelling and were more tolerable, whereas cold spray may exacerbate arthritis at the beginning of treatment [69]. Further, a prospective study assessed the effectiveness of ethyl chloride spray during functional exercises for recovery after TKA by comparing its use with not using it. The intervention group applied the spray three times daily during functional exercises, with each session lasting approximately 40 s, whereas the control group did not use the spray postoperatively. The results showed that the intervention group significantly outperformed the control group in terms of postoperative pain scores and range of knee joint motion. Particularly notable were the significant reductions in knee circumference at 21 and 28 days postoperatively, the time taken to achieve a knee flexion of 90˚, and the total consumption of analgesic medication. This suggests that ethane chlorohydrin spray plays a positive role in postoperative recovery [123].

In a study by Zerjavic et al., 30 patients with RA underwent cold air (−30 ˚C) or ice massage therapy, with each therapy session lasting 5 min on the back and palm of each hand. The results indicated that both cold therapy methods significantly reduced pain immediately and at 30- and 60-min post-treatment, although the differences were not significant compared to baseline. Grip strength improved post-treatment but not significantly in statistical terms [124]. Another RCT evaluated the effect of whole-body and localized cryotherapy at different temperatures on total antioxidant capacity in patients with active seropositive RA. Sixty patients were randomly assigned to three groups: −110 ˚C WBC, −60 ˚C WBC, and localized cryotherapy, administered three times daily for seven consecutive days. In addition, the patients underwent conventional rehabilitation treatments. WBC was conducted inside a cryochamber, where patients first stayed for 30 s in a −10 ˚C antechamber, then 30 s in a −60 ˚C second chamber, and finally walked for 3 min in a main chamber at −110 ˚C or −60 ˚C. Localized cryotherapy involved the direct application of cold packs or −30 ˚C cold air to swollen joints, each session lasting 10–30 min. The results showed that the −110 ˚C WBC group exhibited a significant increase in the total radical-trapping antioxidant parameter (TRAP) within 1 h after treatment. However, during the week of treatment, although there were significant differences

Table 1
Summary of cryotherapy techniques and their efficacy in treating osteoarthritis (OA) and rheumatoid arthritis (RA).

Technology	Materials/equipment	Disease	Procedure	Modifications ('+': positive effect;'-': negative effect)	Ref.
PBC					
Cold compress	Gel ice packs	KOA	20 min, 3/wk for 8wk	+Pain, +stiffness, +physical function,+total score	[118]
	Ice packs	KOA[d]	20 min, 2/d(every 4 h) for 5d	+Inflammation, +improve gait pattern	[66]
	Thermogel®, Artsana	RA	30 min, 2/d(every 8 h) for 1d	+Pain, +decrease IL-6, IL-1β, VEGF and PDUS score	[67,120]
	Ice pops, Yéti, Yetigel	RA[a]	10–30 min, 2/d(every 8 h) for 14d	+Decrease arthritis score, +joint swelling, +tolerance	[69]
	Crushed ice pack	KOA[b]	20 min, total 2tm(every 2 h)	+Decrease inflammation, swelling and neutrophil migration, +increased Agrin and Atrogin-1 expression	[119]
	Cold Packs	KOA	15 min/d, 5/wk for 4wk	+ROM, +muscle strength, +pain, +improve functional status	[121]
	Hisamitsu Pharmaceutical Co.	TKA for KOA	1–1.5 ˚C, 10 min, 2d	+Pleasant sensation	[122]
Cold spray	Ice Spray, Ghiaccio Spray®	RA[a]	5 s/tm, every 10 s, total 9tm; 2/d for 15d	+Decrease arthritis score and structural damages	[65]
	Ice Spray, Ghiaccio Spray®	RA[a]	10–30 min, 2/d(every 8 h) for 14d	-Inflammation (briefly)	[69]
	Ethyl chloride spray	TKA for KOA	40 s, 3/d for 4wk	+Pain, +ROM	[123]
Cold Air	Cryo 6, Zimmer	RA	- 30 ˚C, 5 min each, back and palm	+Pain, +improve grip strength	[124]
	NR	RA	- 30 ˚C, 10–30 min, 3/d for 7d	+Increase TRAP	[125]
	Zimmer Cryo 5	RA	3 min, 2/d for 10d	+Decrease TNF-α, ++DAS28,+pain, +ROM, +HAQ, +stiffness	[126]
Liquid nitrogen and carbon dioxide cryotherapy	Cold CO_2; Cryo+®, Cryonic	RA	−78 ˚C, 2 min, 2/d(every 8 h) for 1d	+Pain, +decrease IL-6, IL-1β, VEGF and PDUS score	[67,120]
	Liquid nitrogen gas	RA	−160 ˚C, 3 min, 2/d for 10d	+Decrease TNF-α, ++DAS28,+pain, +ROM, +HAQ, +stiffness	[126]
	Cryogenic liquid CO_2 gas	TKA for DA	−78 ˚C, 6 min, 6/wk for 2wk	+ROM, +pain, +edema, +walking	[127]
Cryocompression	U-sport ultimate recover knee cold compression brace	TKA or UKA for OA	5/d for 6wk	?Pain, function, satisfaction	[128]
	Game Ready™	TKA for OA	5 ˚C, 20 min, 6/d for 2wk	+ROM	[129]
	Game Ready™	TKA for OA	1/h, ≥4/d for 2wk	+Pain, +satisfaction	[130]
	Game Ready System® Hip/Groin-wrap	THA for OA	0 ˚C, 30 min, total 15tm(at least every 4 h)	+Pain, +hospital admission time	[131]
Controlled cooling therapy	Zamar Z-one MG465A	TKA for KOA	5 ˚C, 3 h, 2/d for 5d	+Pain, +ROM, +satisfaction	[133]
	Cooling flow device	TKA for OA	Post-surgery first 2h: 7 ± 2 ˚C, afterwards: 12±3 ˚C, 6d	+Pain, +ROM, +blood loss	[135]
	Icing System CF3000, Sigmax	THA for OA	5 ˚C, 3d	+Joint swelling, +satisfaction	[134]
	Icing System 2000, Sigmax	THA for OA	5 ˚C, 4d	+Pain	[132]
	Cryotherapy pack	TKA for KOA	Apply cold therapy for 20 min, rest 30 min, change every 4 h until discharge	+ROM, +joint swelling	[136]
Other local cryotherapy	Cold water; homemade cryotherapy device	KOA[c]	5 or 10 ˚C, 20 min, 1/d for 7d	+Pain, + joint swelling	[76]
	Cold rub gel, GOLDARU	KOA	2/d for 4wk	+Pain, +joint function	[138]
	Wet mud	RA[a]	21 ˚C, 20 min/tm, total 34tm	+Bone metabolism	[137]
	Ice (massage)	RA	5 min each, back and palm	+Pain, +improve grip strength	[124]
WBC					
Whole-body cryochamber therapy	Cryomed s.r.o., Slowakia	RA	−130 ˚C, 90 s for first, 120 s for second, 180 s for third and thereafter, 1/3d (total 6) for 14d	+Pain, +disease activity, +reduce analgesics	[139]
	Cryogenic nitrogen chamber	Lumbar OA	−130 ˚C, 1.5–3 min, total 10tm, 2wk	+Pain	[140]
	NR	RA,OA	−140 to −160 ˚C, 2–3 min, 1/d for 4wk	+Reduced histamine levels	[141]
	Criostream	RA	−145 ˚C, initially 90 s, afterwards 2.5 min, total 9tm, 5d	+Pain, +disease activity, +functional score	[142]
	Mecotec Cryoair	Hand RA	−60 ˚C for 30 s and −110 ˚C for 3min	+Reduce skin temperature	[143]
	Zimmer Medizinsysteme	RA	−60 ˚C for NR and −110 ˚C for 3 min,2/d for 4wk	+Pain, +disease activity	[144]
	Zimmer, Elektromedizin	RA	−10 ˚C for 30 s, −60 ˚C for 30 s and −60 ˚C or −110 ˚C for 3 min, 3/d for 7d	+Increase TRAP(greater with −110 ˚C)	[125]
	NR	RA	−10 ˚C for NR and −60 ˚C for NR, −110 ˚C for 3 min, 1/d for 2wk	+Pain, +disease activity, +fatigue, +walking	[145]
Whole-body cold mist shower therapy	Amandan® device	RA	2 min, 2/d	+Pain, +sleep quality	[146]

a, adjuvant-induced arthritis rat model; b, antigen-induced arthritis mouse; c, rat knee joint arthritis model; d, rat model of KOA induced by anterior cruciate ligament transection; OA, Osteoarthritis; DA, degenerative arthritis; RA, rheumatoid arthritis; KOA, Knee Osteoarthritis; UKA, Unicompartmental Knee Arthroplasty; TKA, Total Knee Arthroplasty; THA, Total Hip Arthroplasty; wk, week; tm, time; d, day; h, hour; min, minute; s, second; NR, Not Reported; PBC, Partial Body Cryotherapy; WBC, Whole Body Cryotherapy; VEGF, vascular endothelial growth factor; PDUS, power doppler ultrasound; ROM, range of motion; DAS28, disease Activity score 28; HAQ, health assessment questionnaire; TRAP, trapping antioxidant capacity of plasma; Ref, reference.

in TRAP values among the treatment groups in the morning, the TRAP values within each group did not change significantly [125].

In summary, cold spray and cold air therapy, two common forms of cryotherapy, effectively reduced arthritic pain and inflammation and improved functional status. Cold spray is suitable for rapid localized cooling and offers the advantage of easy operation, whereas cold air therapy achieves deeper tissue cooling and systemic therapeutic effects. However, caution is required when using cold sprays containing ethyl chloride because studies have suggested that they may be associated with serious adverse reactions such as periarticular infections, deep vein thrombosis, and acute myocardial infarction [123]. Future research should further investigate these adverse reactions and confirm their causal relationships to ensure the safety of the therapy.

3.1.1.3. Liquid nitrogen and carbon dioxide cryotherapy. Liquid nitrogen and carbon dioxide cryotherapy represents a specific form of cryotherapy involving brief applications of extremely cold liquid nitrogen or carbon dioxide to a targeted area, effectively reducing local tissue temperature and alleviating inflammation and pain. These two therapies are primarily used to treat the symptoms of RA, OA, and other forms of arthritis and have also demonstrated favorable outcomes in postoperative rehabilitation. For instance, Jastrzabek et al. compared the effects of nitrogen cryo-flow therapy (−160 ˚C) and cold air flow therapy (−30 ˚C) on patients with active RA. They observed that after twice-daily treatments of 3 min each over a span of 10 days, both the patients treated with liquid nitrogen and those treated with cold air exhibited significant reductions in TNF-α levels, while IL-6 levels did not show noticeable changes. Further, both treatments significantly improved 28-joint Disease Activity Scores (DAS28), pain perception, morning stiffness duration, self-reported fatigue levels, and scores on the Health Assessment Questionnaire (HAQ). Simultaneously, these treatments increased the range of motion of the knee joints and improved performance in the 50-meter walk test [126].

Another recent RCT examined the effects of cryotherapy on ROM, pain, swelling, and gait in patients who underwent TKA. In the experimental group, the affected knee joints were subjected to a direct spray of liquid carbon dioxide gas at −78 ˚C, six times weekly for two consecutive weeks, with 3 min of application both before and after daily physical rehabilitation; the control group received a sham treatment. The results indicated that the experimental group showed significant improvements in knee joint flexion, pain levels, swelling, and performance on the 10-meter walk test, with notable differences compared with the control group. This suggests that a rehabilitation exercise program incorporating cryotherapy is highly effective in improving ROM, alleviating pain and swelling, and enhancing gait [127].

Both liquid nitrogen and carbon dioxide cryotherapies, which are extremely low-temperature cryotherapy methods, have demonstrated significant benefits in improving pain, inflammation, and function in patients with arthritis. Liquid nitrogen therapy is applicable for deeper tissue cooling, whereas liquid carbon dioxide therapy is more frequently employed in postsurgical rehabilitation. Future research should further clarify the application scope of these two cryotherapy methods, offering patients with arthritis more tailored and precise treatment options.

3.1.1.4. Cryocompression therapy. Cryocompression therapy, which combines cryotherapy with compression therapy, is gaining attention in postoperative rehabilitation. This treatment modality leverages the dual effects of cryotherapy and compression to alleviate pain, facilitate healing, and enhance patient satisfaction. In recent years, several studies have explored the effectiveness of cryocompression therapy in patients after knee replacement surgery and in those with osteoarthritis. For example, a single-center, single-blind RCT was planned to use the U-sport ultimate recovery knee cryocompression brace after knee replacement surgery, which delivers cooling via reusable gel packs and uses a manual pump to adjust the compression exerted by the brace [128].

The Game Ready^{TM} system, another commonly used cryocompression therapy device, provides controlled cryotherapy and intermittent pneumatic compression, showing positive results in post-TKA rehabilitation. After undergoing treatment with this system six times daily for 20 min per session for 2 weeks, 36 patients exhibited significantly better knee joint extension on the first and fourteenth day postoperatively compared to the control group [129]. Su et al. confirmed that patients with unilateral KOA, using GameReady^{TM} for cryocompression therapy at least four times daily over 2 weeks post-TKA, significantly reduced their need for postoperative analgesics and improved their performance in the six-minute walk test. Patient satisfaction with this treatment was significantly higher than with traditional ice application and static compression [130].

Additionally, traditional cryocompression therapy has been shown to have certain effects. In a prospective RCT, patients with end-stage OA received 15 sessions of standard elastic compression bandaging and intermittent cryocompression therapy, each lasting 30 min, following TKA. The results showed that on the first postoperative day, the control group experienced a smaller decrease in hemoglobin levels, whereas on the third postoperative day, there were no significant differences between the two groups. The intervention group exhibited a lower trend in morphine use, shorter hospital stay, and less wound drainage, with one case of deep vein thrombosis in the control group [131]. Overall, cryocompression therapy presents a promising outlook for rehabilitation after knee replacement surgery, achieving significant results in alleviating postoperative pain, promoting functional recovery, and enhancing patient satisfaction. Nevertheless, future large-scale studies are required to validate its long-term efficacy, establish optimal treatment protocols, and identify the most appropriate timing to guide clinical practice more effectively.

3.1.1.5. Controlled cooling therapy. Continuous cold flow (CCF) is a method that provides a constant and uniform distribution of cold and heat to the treatment area by continuously delivering cold fluids, primarily used to alleviate inflammation, swelling, and pain [132]. Coviello et al. assessed the therapeutic efficacy of CCF in 100 patients who underwent TKA. The intervention group began receiving CCF treatment set at 5 ˚C from the day before surgery, continuing post-surgery for three h each morning and evening, and lasting until the fifth day after surgery. In the control group, traditional cold compresses were applied for 15 min within 6 h post-surgery and after each physical therapy session. The results showed that the intervention group experienced significantly reduced pain in the early postoperative period, decreased use of opioid medications, and improved passive ROM [133].

A 2012 single-center retrospective study in Japan investigated the impact of continuous local cryotherapy following total hip arthroplasty. Thirty patients underwent continuous treatment for 72 h using cooling devices set at 5 ˚C. Compared with the control group, the intervention group demonstrated significant reductions in thigh circumference on the fourth day after surgery, along with a notable increase in patient satisfaction [134]. Further, past research has validated the effectiveness of CCF in post-TKA recovery. In this study, patients in the intervention group used CCF immediately post-surgery for 6 days, pausing only during brief walking and knee joint exercises. Skin temperature was maintained at 7 ˚C ± 2 ˚C in the first 2 h post-surgery, later adjusted to 12 ˚C ± 3 ˚C. Patients in the control group did not receive cryotherapy after surgery on the contralateral knee joint. The results indicated that patients who underwent cryotherapy had better outcomes in terms of pain scores, consumption of analgesics, amount of drainage, total postoperative blood loss, and better early range of motion recovery [135].

Programmed cryotherapy is a cold therapy method that controls temperature and application time and is often combined with continuous passive motion (CPM) to facilitate postoperative recovery. In a study of 60 patients undergoing computer-assisted total knee arthroplasty, patients in the intervention group started programmed cryotherapy and CPM within 1 h postoperatively. The CPM ranged from 0˚ extension to

60° flexion, and programmed cryotherapy was administered for 20 min, followed by a 30-min pause, with cryotherapy packs replaced every 4 h, continuing from the first day post-surgery until discharge. The patients in the control group did not receive cryotherapy during the study period. By the fourth postoperative day, patients in the intervention group had significantly better ROM than those in the control group (98° vs. 91°), and the intervention group also had lower average joint swelling than the control group (32.2 cm vs. 33.9 cm) [136]. These data suggested that CCF and programmed cryotherapy play crucial roles in postoperative rehabilitation by significantly enhancing postoperative pain management and recovery outcomes.

3.1.1.6. Other localized cryotherapy. Other commonly used cryotherapy methods, such as cold-water immersion, cold mud baths, and cold gel rubs, have a certain history of application and efficacy in the treatment of arthritis. In 2021, Sasaki et al. compared the effects of cold-water immersion at 5 ˚C and 10 ˚C on pain, swelling, CD68+ cell count, and calcitonin gene-related peptide (CGRP) expression on the spinal cord dorsal horn in rats with acute phase arthritis, finding that both temperatures of cold water treatment significantly reduced pain and swelling, and decreased CD68+ cell count and CGRP expression. These findings suggest that cryotherapy effectively alleviates the inflammatory response and central sensitization in arthritis. However, the difference in effectiveness between the two temperatures was not significant [76].

A study conducted in 2012 evaluated the effects of 21 ˚C cold mud baths, 38 ˚C hot mud baths, and hot sand baths at the same temperatures on the skeletal status of male Wistar rats with subacute arthritis. Treatment was administered 4–5 times per week, with each session lasting 20 min. The results showed that 38 ˚C hot mud baths and hot sand baths resulted in a relative decrease in bone density of the right femur compared to the left. Also, cold mud baths significantly alleviated inflammation and pain caused by arthritis and positively influenced skeletal mobility [137].

In contrast to gel ice packs, cold rubbing gels provide simultaneous massage of the affected knee joint during cryotherapy. In one RCT, patients applied a cold gel containing eucalyptus oil, menthol, and camphor to massage their knee joint every 12 h for 4 weeks. The control group used hot packs heated above 54 ˚C for treatment. Research results indicated that both cold rub gel and local heat therapy effectively improved pain and joint function in patients with KOA with comparable efficacy [138].

Various cryotherapy methods used commonly have unique roles and advantages in the treatment of arthritis. Cold water immersion, cold mud baths, and cold rubbing gels effectively alleviate inflammatory responses, reduce pain, and improve joint function. Future research and clinical practice should delve deeper into the scope and best practices of different cryotherapy methods, thereby offering patients with arthritis more personalized and effective treatment solutions.

3.1.2. Whole-body cryotherapy

3.1.2.1. Whole-body cryochamber therapy. WBC therapy alleviates pain and inflammation by exposing the body to extremely low temperatures. This therapy is usually conducted using specially designed cryochambers, which can be categorized into single-, double-, and triple-chamber types, depending on the design. Single-chamber cryochambers offer a basic cryotherapy experience, whereas double and triple chambers provide phased cooling to enhance patient adaptability and comfort, thereby optimizing therapeutic outcomes.

Klemm et al. evaluated the efficacy of single-chamber WBC for treating RA by conducting an RCT. During this study, patients with active-phase RA were treated in a cryochamber at −130 ˚C, dressed solely in swimwear or underwear along with warm socks, and their fingers were placed under their armpits for added comfort throughout a 16-day comprehensive treatment for rheumatism. The initial treatment duration was 90 s, increased to 120 s for the second time, and subsequently increased to 180 s from the third time point, with sessions held every three days. The results of the study indicated that this WBC regimen significantly reduced pain and disease activity in patients with RA and decreased reliance on analgesics, which may be associated with changes in cytokine levels [139]. Additionally, 30 patients with lumbar OA underwent 10 sessions of WBC treatment in a low-temperature nitrogen chamber at −130 ˚C, with each session lasting 1.5–3 min, followed by 45 min of rehabilitation training. The results revealed a significant reduction in lumbar pain intensity after WBC, although there was a slight increase in blood levels of β-endorphin and adrenalin that did not reach statistical significance, while cortisol levels were elevated significantly [140].

A 2010 study compared the effects of WBC regimen and traditional physical therapy on biochemical blood parameters of patients with RA and OA. Twenty patients with RA and 17 patients with OA underwent WBC daily for 4 weeks, with each session lasting 2 to 3 min, conducted in an environment ranging from −140 ˚C to −160 ˚C. Patients in the control group received traditional physical therapy for 4 weeks. The results of the study indicated that WBC significantly decreased blood histamine levels in patients with RA, with effects lasting for at least 3 months, whereas no significant changes were observed in patients with OA [141]. Lange et al. evaluated the effects of WBC on pain relief, disease activity, and pro-inflammatory cytokine levels. Ten arthritis patients underwent nine treatments using the Criostream device, with durations gradually increasing from 90 s to 2.5 min, and the treatment temperature was set at −145 ˚C. These findings suggested that WBC significantly alleviated pain and disease activity, reduced levels of TNF-α and IL-1 and enhanced functional scores. Although two patients reported adverse reactions of headache and cold sensation after the first treatment, the overall patient acceptance of the therapy was high, indicating that WBC is an effective and generally safe method for treating arthritis [142].

In an RCT investigating dual-chamber WBC for hand RA, patients were acclimatized to low temperatures for 30 s in a pre-cooling chamber at −60 ˚C, followed by exposure for 3 min in the main treatment chamber at −110 ˚C. Twenty-five healthy young individuals participated in this RCT and were divided into two groups: one group wore gloves throughout the procedure, and the other group had partial hand exposure. Thermal imaging was employed to monitor the skin temperature of the joints to assess the pain threshold. The results indicated that the strategy of hand exposure to cold treatment significantly decreased skin temperature, and this may contribute to the management of hand RA [143]. Another prospective study conducted by Braun et al. assessed the effects of WBC on biochemical blood parameters, pain, and inflammation in patients with inflammatory rheumatic diseases. This study included 60 patients, 48 with RA and 12 with ankylosing spondylitis. Treatment was administered using a dual-chamber WBC system, with temperatures set at −60 ˚C in the pre-chamber and −110 ˚C in the treatment chamber, twice daily for 3 min per session, for 4 weeks. The results revealed a significant reduction in DAS28 and visual analog scale (VAS) scores in patients with RA and a notable decrease in the disease activity index in patients with ankylosing spondylitis, suggesting effective improvement in pain and inflammation activity [144].

Gizinska et al. compared the impact of three-chamber WBC and conventional rehabilitation on clinical parameters and levels of IL-6 and TNF-α in postmenopausal women with RA. This study included 44 patients who received a comprehensive treatment regimen that included pharmacotherapy, functional mobility therapy, and physical therapy. Of these, 25 patients received WBC, that included pre-cooling in antechambers at −10 ˚C and −60 ˚C, followed by 3 min of exposure in the main chamber at −110 ˚C, once daily for 2 weeks. Nineteen patients in the traditional rehabilitation group underwent personalized rehabilitation, including both magnetotherapy and electrotherapy. The study found that both treatments significantly improved pain, disease activity, fatigue, and performance in the 50-meter walk test. The conventional rehabilitation group performed better on the HAQ, and both treatments

effectively reduced the levels of IL-6 and TNF-α, indicating a positive effect on inflammatory markers in patients with RA [145].

3.1.2.2. Whole-body cold mist shower. Unlike traditional WBC conducted in cryochambers, whole-body cold-mist showers use cold water mist directly applied to the skin to provide a gentler cooling experience for patients. In a 2017 RCT, Hinkka et al. assessed the effects of this method on pain and sleep quality in patients with chronic inflammatory arthritis as well as its impact on body temperature, blood pressure, and heart rate. During the study, the intervention group used the Amandan® device for the whole-body cold mist shower, with each session lasting 2 min, conducted twice daily, in the morning and evening. During the control period, the same patients did not undergo any cold mist shower treatment and acted as their own controls. The results of the study indicated significant pain relief during the treatment period, with improvements in sleep quality. Therefore, whole-body cold mist showers are considered a potentially safe option for the home self-treatment of pain [146].

As a noninvasive treatment method, WBC offers a relatively safe pain management option that is particularly appealing to patients seeking alternatives to conventional drug treatments. WBC is not merely a simple freezing process; it regulates levels of cytokines such as TNF-α and IL-1, activating the natural defense mechanisms of the body to effectively promote pain relief and inflammation control. Although WBC has shown benefits in alleviating pain and inflammation in RA and OA, its widespread application and efficacy still requires large-scale studies for validation. Future studies should focus on optimizing the treatment parameters to address the needs of various patients and explore the combined use of WBC and other rehabilitation measures.

3.2. Thermotherapy

Thermotherapy is a viable approach for arthritis treatment that employs thermal effects to mitigate pain, promote blood flow, and hasten the repair of damaged tissues. Given the diversity of techniques and methods used in thermotherapy, we have categorized and summarized them in Table 2 to facilitate their clinical adoption and usage. The specific applications of these techniques for different types of arthritis are described and discussed in detail in the following sections.

3.2.1. Paraffin bath

The paraffin bath, a frequently employed thermotherapy method, significantly alleviates hand pain and stiffness and enhances joint functionality, especially in patients with OA. By immersing the hands in heated paraffin, which closely envelops them, a deep thermal effect is produced that promotes blood circulation and relaxes the muscles. In a 2-week prospective single-blind RCT, researchers examined the effects of home-based exercises combined with heated paraffin treatment on hand OA. Patients in the intervention group underwent ten paraffin baths, each involving a 20-minute soak of the hands in 52 ˚C paraffin, followed by wrapping with nylon and a towel. The results indicated that at 2- and 6-weeks post-treatment, all assessment metrics for the intervention group significantly surpassed those for the control group [147]. Another RCT had participants immerse their hands in paraffin heated to 50 ˚C, allow the paraffin to solidify, and then re-immerse, repeating this process ten times. After each treatment, the hands were wrapped in plastic bags and covered with towels for 15 min. Compared with the control group, the paraffin embedded group showed significant improvements in pain during rest and daily activities, ROM in the right hand, and pain and stiffness scores on the Australian and Canadian Hand Osteoarthritis Index [100].

A recent systematic review and meta-analysis confirmed the effectiveness of paraffin bath therapy in alleviating hand pain and improving function, significantly enhancing the quality of life of the patients [148]. These studies suggest that whether combined with basic exercises or used alone, heated paraffin baths significantly improve hand pain and mobility and enhance quality of life. Nonetheless, there are concerns regarding heated paraffin baths, including imprecise temperature control and the risk of infection. Future research should aim to delineate the most effective treatment protocols for paraffin baths and offer patient-tailored and efficacious strategies for treating patients with hand OA.

3.2.2. Infrared therapy

Infrared therapy uses the thermal energy of infrared radiation to promote blood circulation, relieve muscle pain, reduce inflammation, and accelerate the natural healing of body tissues. It penetrates deep into the muscles and joints and raises the local temperature, thereby exerting its therapeutic effects. Chen et al. assessed the therapeutic effects of far-infrared radiation (FIR) on RA in a rat model of AIA. They divided 42 rats randomly into six groups: normal control, AIA control, standard treatment (methotrexate), and three FIR treatment (for varying durations) groups. The results showed that FIR treatment significantly improved arthritis symptoms, with mechanisms involving the regulation of transcription factors associated with multiple signaling pathways, including MAPK, PI3K-Akt, and NF-κB, thus suppressing the expression of inflammatory and autoimmune genes [149].

In another prospective randomized single-blind study involving 34 patients with RA and ankylosing spondylitis, patients received eight infrared sauna therapy sessions over 4 weeks, each 30 min long at 55 ˚C, with wavelengths ranging from 5000 to 1,000,000 nanometers. The results indicated that the treatment significantly reduced pain, stiffness, and fatigue in patients with no reported adverse reactions or increased disease activity [150]. A 2004 study compared the effects of three local thermotherapy methods— infrared, paraffin, and mud therapy—on skin microcirculation in patients with RA and healthy individuals. Participants received 15 min of infrared therapy, 20 min of 52 ˚C paraffin therapy, and 20 min of 60 ˚C mud therapy on the lumbar area, with at least 3 days between each thermotherapy session. The findings demonstrated that all thermotherapy methods significantly enhanced skin microcirculation, skin temperature, and core body temperature. Notably, there were no significant differences in the responses to these therapies between patients with RA and healthy individuals [151].

In summary, infrared therapy has shown notable efficacy in promoting blood circulation, alleviating pain, reducing inflammation, and improving microcirculation. In both animal models and clinical trials, infrared therapy substantially alleviated pain, stiffness, and fatigue in patients with arthritis. However, current infrared therapy lacks standardization in terms of wavelength and temperature control, and there is a potential risk of skin burns. Therefore, future studies should optimize the treatment parameters, establish clearer clinical guidelines, and explore the combined use of infrared therapy with other treatment modalities to provide more personalized and safer treatment options for patients with arthritis.

3.2.3. Local deep heat therapy

Local deep heat therapy employs techniques such as radiofrequency, ultrasonography, or shortwave radiation to deliver heat deep into the joint and muscle tissues to reduce pain, improve function, and promote tissue repair. This therapy has shown significant efficacy in the treatment of KOA and other chronic joint diseases. Jang et al. conducted a comparison between radiofrequency thermotherapy and therapeutic ultrasonography in alleviating pain and restoring function in patients with KOA and found that both treatments significantly improved stride length and speed; however, only the radiofrequency thermotherapy group showed significant improvement in cadence compared to pre-treatment [94]. A 2021 RCT investigated the efficacy of a deep thermal therapy system (DTT-RCA) for KOA. The system was equipped with a high-frequency amplifier, a resonant cavity applicator, and an adjustable arm device, with power settings ranging from 20 to 40 W and frequency ranging between 420 and 470 MHz. The control group underwent conventional exercise therapy. Both groups received treatment

Table 2
Summary of thermotherapy techniques and their efficacy in treating osteoarthritis (OA) and rheumatoid arthritis (RA).

Technology	Equipment/materials	Disease	Procedure	Modifications ('+': positive effect;'-': negative effect)	Ref.
Paraffin bath	Paraffin	Hand OA	52 ˚C, 20 min, 5/2wk for 2wk	+Pain, +hand function, +strength, +quality of life	[147]
	Paraffin	Hand OA	50 ˚C, 15 min, 15tm, 3wk	+Pain, +ROM, +stiffness, +inflammation	[100]
	ParathermDN, Carle	RA	52 ˚C, 20 min/tm	+Increase skin microcirculation, skin and core temperature	[151]
Infrared Therapy	FIR spectrum emission device, EFFIT LITE®	RA[b]		+Improve symptoms of arthritis	[149]
	Health Company Infrared Cabin	RA	55 ˚C, 30 min, total 8tm, 4wk	+Pain, +stiffness, +fatigue	[150]
	Philips lamps, Model Super	RA	15 min/tm	+Increase skin microcirculation, skin and core temperature	[151]
Local Deep Heat Therapy	HIPER-500 diathermy apparatus	KOA	15 min, 3/wk for 4wk(total 10tm)	+Pain, +function, +improve cadence	[94]
	Ultrasonic SUS-2N	KOA	15 min, 3/wk for 4wk(total 10tm)	+Pain, +function	[94]
	DTT-RCA	KOA	20 min, 1/2wk for 6m	+Pain, +joint inflammation	[152]
	Thermal gun, Hong Kong Productivity Council	KOA	43 ˚C, 30 min, 2/wk for 4wk	+Pain, +stiffness, +functional impairment, +quadriceps strength	[161]
	SIEMENS Ultraterm 642 E	KOA	15 min, 3/wk for 3wk, total 10tm	+Pain, +satisfaction (inferior to Spa therapy)	[153]
Spa therapy	Tap water and peloid (from Tuzla Spa Resort)	KOA	mudpacks:43 ˚C, 20 min, baths:38 ˚C; 20 min, 1/2wk for 20wk	+Pain, +functional capacity	[154]
	Mud packs and sulfate-calcium-magnesium-fluorides water	Hand OA	20 min, 12tm	+Function, +HAQ, +improve symptoms of arthritis	[155]
	Thermal bath and mud (from (Abano-Montegrotto Terme)	OA	Mudpacks: 40 ˚C, 20 min, baths: 37–38 ˚C, 10–12 min; 1/d, total 12tm	+Increase IGF-1, +decrease TNF-α	[105]
	Thermal mineral water and mud-packs	KOA	mudpacks: 42 ˚C, 20 min, baths: 37 ˚C, 15 min; total 12tm, 2wk	+Decrease microRNA expression, adiponectin and resistin levels	[156,157]
	Mud packs and bicarbonate-sulfate mineral bath water (from Rapolano Terme)	KOA	mudpacks:45 ˚C, 20 min, baths:38 ˚C; 20 min, total 12tm, 2wk	+Pain, +functional capacity	[202]
	Mud packs and arsenical ferruginous mineral bath water(from Levico Terme)	KOA	mudpacks: 45 ˚C, 20 min, baths: 38 ˚C, 15 min; 1/d for 3wk,total 15tm	+Pain, +satisfaction, +decrease use of symptomatic drugs	[153]
Mud application	Peloid, fortified with sodium chloride-rich mineral waters	RA	41–42 ˚C, 20 min, 5/wk for 2wk	+Disease activity, +pain, +HAQ	[158]
	Brazilian black mud	RA[a]	40 ˚C, 30 min, 1/d, throughout arthritis	+Protective effect	[159]
	Mineral-rich mud	KOA	30–35 ˚C, 20 min, 5/wk for 3wk, total 15tm	+Pain, +Lequesne index	[160]
	Turbatherm, Torfwerk Einfeld	RA	60 ˚C, 20 min/tm	+Increase skin microcirculation,skin and core temperature	[151]
	Medicinal peat (Heiltorf)	RA, OA	20 min, total 9tm, 21d	+Disease activity, +pain, +functional health	[103]
Heat Wraps and Compresses	Heat pack	KOA	43 ˚C, 30 min, 2/wk for 4wk	+ROM, +pain	[161]
	Heat- and steam-generating sheets, Kao Corporation	KOA	40 ˚C, 6 h/d for 12wk	+Clinical symptoms, +walking ability	[162]
	TheraTherm Digital Moist Heating Pads	KOA	40–46 ˚C, 20 min, total 15tm, 4wk(once every other day)	+Pain, +disability, +quality of life	[163]
Balneotherapy	Szigetvár mineral water and tap water	OA	34 ˚C, 30 min, 5/wk for 5wk	+ROM, +WOMAC, +pain, +quality of life	[164]
	Thermal mineral water	RA	36–37 ˚C, 20 min/d, 6/wk for 2wk	+Antioxidant effect	[165]
	Saltwater hot spring	OA	38 ˚C, 20 min/d for 15d	+Pain, +physical function, +walking speed	[166]
	Cserkeszölö thermal water	KOA	36 ˚C, 30 min, 1/d for 15d	+Pain, +ROM	[167]
Combined Radon and Thermal Therapies	LDRnHT, therapeutic Radon cave(from Bad Gastein-Böckstein)	RA, OA	37.5–41.5 ˚C, 60 min, 12tm, 3wk	+Osteoprotective effect	[168]
	NR	RA	Radon baths(37 ˚C)and wax bath(50 ˚C): 20 min, 1/d; faradic hand baths(37 ˚C): 15 min/hand, 1/d	+Improve hand function status	[169]
Dry heat treatment	Fluido^{TM} DHT	RA	46.1–48.9 ˚C, 20 min, 1/d for 15d	-Improve hand function	[170]

a, chronic experimental arthritis simulating RA; b, adjuvant-induced arthritis (AIA) rat models; RA, rheumatoid arthritis; OA, osteoarthritis; KOA, knee osteoarthritis; wk, week; tm, time; d, day; h, hour; min, minute; NR, not reported; Ref, reference; LDRnHT, low dose radon and hyperthermia therapy; DTT-RCA, deep-tissue thermal therapy system with a resonant cavity applicator; ROM, range of motion; HAQ, health assessment questionnaire; IGF-1, insulin-like growth factor 1; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

every 2 weeks, each lasting 20 min, over a period of 6 months. The study findings showed significant improvements in the intervention group in the VAS scores, Japanese Orthopedic Association knee scores, measures of Japanese KOA, and knee injury and OA outcome scores. However, the magnetic resonance imaging T2 mapping results showed no significant changes, suggesting that the system may be effective in the conservative treatment of KOA, although no significant improvement in cartilage degeneration was observed [152].

In a randomized single-blind controlled trial in Italy, 30 patients with chronic KOA underwent spa therapy combining local mud application and arsenic-iron mineral water once daily for 15 sessions over 3 weeks. Shortwave therapy was administered to 24 patients using the SIEMENS Ultraterm 642 E on both knees, with each session lasting 15 min, thrice weekly over 3 weeks. The control group received conventional outpatient treatment. This study revealed that both spa therapy and shortwave therapy effectively ameliorated KOA symptoms, with spa therapy showing sustained effects after treatment [153].

Local deep heat therapy is a noninvasive method that significantly relieves pain and enhances joint function in patients with KOA. Regardless of whether radiofrequency thermotherapy, therapeutic ultrasonography, deep heat therapy systems, or shortwave therapy are used, all of these deep heat treatments have shown effective improvement. However, local deep heat therapy still faces challenges such as standardization of treatment parameters, long-term efficacy evaluation, and development of individualized treatment plans for patients. Future research should optimize the treatment parameters, clarify applicable scenarios, and explore combinations with other treatment modalities to provide more personalized and effective treatment strategies for patients with KOA.

3.2.4. Spa therapy

Terms such as spa therapy, balneotherapy, and hydrotherapy have been used interchangeably in some studies to refer to “spa treatment” or “hydrotherapy.” For the purposes of this review, we have defined spa therapy as a treatment method that begins with mud therapy (mud application) followed by hydrotherapy, whereas balneotherapy involves baths using mineral or tap water. In a study by Adigüzel et al. on patients with chronic KOA undergoing spa therapy, 64 patients were randomly divided into experimental and control groups. All participants were first soaked in 38 ˚C water for 20 min, followed by a 20-minute application of 43 ˚C mud on both knees, repeated ten times, once every 2 weeks. In the experimental group, the mud was applied directly to the skin, whereas in the control group, it was applied through a waterproof film. The results showed that, although both groups experienced significant improvements in pain scores, there was no statistically significant difference between them. Additionally, despite only minor side effects, such as localized temporary skin irritation, the experimental group showed significant functional improvements during all assessment periods, suggesting that mud therapy involving direct skin contact may have additional therapeutic effects [154].

In another prospective randomized single-blind trial for hand OA, the intervention group received daily spa treatments, including a 20-minmud pack at 43 ˚C and a 15-minbath in 38 ˚C calcium magnesium fluoride mineral water, for 2 weeks totaling 12 sessions, alongside ongoing conventional treatment (including exercise, NSAIDs, and/or analgesics). Patients in the control group received conventional treatment alone. The results demonstrated that spa therapy significantly ameliorated symptoms and improved functional outcomes within 6 months after treatment. This suggests that spa treatment is not only effective in the short term but also provides lasting improvement in pain and functional status in patients with hand OA, proving to be a viable long-term treatment option [155]. Bellometti and colleagues found that daily treatment with a 20-minmud pack at 40 ˚C followed by a 10–12 min bath at 37–38 ˚C, for a total of 12 sessions, significantly increased serum IGF-1 levels and decreased TNF-α levels, revealing the non-thermal effects of mud therapy on the biochemical processes of OA [105]. Two other studies also discovered that, compared to conventional exercise and pharmacotherapy, daily local mud application at 42 ˚C for 20 min followed by a 15-min mineral water bath at 37 ˚C, repeated over 2 weeks for a total of 12 sessions, altered the expression of several miRNAs associated with OA and significantly reduced serum levels of adiponectin and resistin [156,157].

The aforementioned results indicate that spa therapy combined with mud and hydrotherapy significantly improves clinical symptoms and biochemical markers in patients with OA. These findings emphasize the effects of nonpharmacological treatments on the long-term management of OA, further confirming the significance of spa therapy in integrated OA management strategies. However, further exploration is needed to standardize treatment parameters, individualize the selection of mud and mineral water components, and assess the long-term efficacy of spa therapy.

3.2.5. Mud application

Mud therapy, a conventional thermotherapy method, is extensively used to relieve arthritis-related pain and inflammation and promote tissue repair. By applying heated mud directly to the affected area, mud therapy effectively increases the local temperature and enhances blood circulation, thereby exerting anti-inflammatory and analgesic effects. In an RCT targeting patients with chronic rheumatoid arthritis, researchers applied mud packs at 41–42 ˚C twice daily to the painful or active joints, wrapped in film for 20 min per session, for a total of 10 sessions over 2 weeks. Although nearly one-third of the patients in the intervention group reached a state of low disease activity after 3 months, with no statistically significant difference compared to the control group, there were significant improvements in HAQ scores, VAS pain scores, global assessments by patients and physicians, and DAS28 indices. No significant adverse events or side effects occurred during the treatment process, with only one patient experiencing local skin irritation symptoms post-treatment that disappeared after the third treatment session, whereas other patients demonstrated good tolerance to the therapy [158]. Further, previous animal studies have evaluated the effectiveness of Brazilian black mud in reducing inflammatory cell migration and protecting against cartilage damage. Daily application of Brazilian black mud at 40 ˚C for 30 min to rats with chronic experimental arthritis significantly reduced leukocyte migration to the synovial membrane and joint cavity. Additionally, an increase in collagen levels and chondrocyte numbers, as well as better preservation of tissue structure, were observed in cartilage protection [159].

In another prospective double-blind controlled study, 40 patients with chronic KOA were treated with natural mud packs enriched with minerals at 30 ˚C-35 ˚C, five times a week, 20 min each time, for a total of 15 sessions over 3 weeks. Compared with the control group, which received demineralized mud packs, patients in the natural mud pack group showed significant reductions in knee pain in all assessments, with improvements in the Lequesne index both at the end of treatment and 1 month later [160]. These findings demonstrate that mud therapy, as a non-pharmacological treatment, has significant potential benefits in relieving pain and improving functionality in patients with RA and KOA. Both natural and heated black mud positively affect inflammation and disease progression in arthritis. However, issues with temperature control, standardization of mineral content, and long-term efficacy assessment in mud therapy remain. Future research should concentrate on optimizing the treatment parameters for mud therapy and developing personalized protocols, thereby enhancing its significant role in the comprehensive management of arthritis.

3.2.6. Heat wraps and compresses

Heat wraps and compresses serve as a therapeutic approach by continuously delivering localized heat to ease arthritic pain, reduce inflammation, and enhance joint functionality. Thermotherapy is commonly used to provide superficial heat, promote blood circulation, and relieve muscle tension during the management of KOA. A research team led by

Ho et al. compared the effects of using heat guns at specific acupoints for local heat therapy to those of traditional heat therapy in the management of KOA. The heat gun group received 43 ˚C heat gun treatment at specific acupoints, heating each point for 5 min with a total treatment time of 30 min, while the control group used heat packs at the same temperature, with each treatment lasting 30 min, twice a week for 4 weeks. Results showed that the heat gun group exhibited significant improvements in functional recovery, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, Short-Form 12 Item Version 2 quality of life scores, and quadriceps strength, whereas the control group outperformed the heat gun group in terms of knee flexion range and average VAS scores. These results imply that localized heat therapy at specific acupoints may be an effective conservative treatment for KOA, and that the combined use of local pressure and heat therapy has synergistic benefits [161].

Additionally, a single-blind randomized controlled clinical trial investigated the therapeutic effects of heat- and steam-generating patches on KOA. Patients in the intervention group used the patch for localized thermotherapy, which continuously generated heat and steam by reacting with oxygen in the air, maintaining a skin temperature of 40 ˚C for up to 8 h, with daily treatments lasting 6 h over 12 weeks. The control group engaged in muscle strength training twice daily for 12 weeks, with 20 repetitions each time. This study noted significant amelioration of clinical symptoms and walking ability in the intervention group, suggesting that this method may have a positive impact on cartilage metabolism [162]. Another 2010 study evaluated the effects of a digital moist heating pad on patients with KOA. The heating pad was set to 105–115˚F, with each treatment lasting 20 min, performed every other day for a total of 10 treatments over 4 weeks. The control group received conventional pharmacological treatment. The findings indicated that the intervention group experienced significant improvements in pain, amelioration of functional impairment, and overall health perception scores, verifying that alternate-day heat treatments effectively alleviated pain and disability in patients with KOA and improved their quality of life [163].

Heat wraps and compresses, as non-invasive treatments, are significantly effective in alleviating pain, improving joint function, and enhancing the quality of life of patients with KOA. Local acupoint heat therapy, steam heat patches, and digital moist heating pads have unique clinical advantages and meet the needs of different patients. Future research should continue to explore the optimization of treatment parameters such as temperature, frequency, and duration to provide more precise personalized treatment strategies and further assess their long-term efficacy in different populations and types of arthritis, thus fully leveraging the role of heat wraps and compresses in the comprehensive management of arthritis.

3.2.7. Balneotherapy

Balneotherapy involves the use of mineral-rich thermal spring-derived or mineral waters to treat arthritis symptoms through soaking, jet massages, and other methods. Through the absorption of minerals and thermal effects, it promotes blood circulation, alleviates pain, improves joint function, and has been used to treat joint diseases, such as OA and RA. In 2018, Hanzel et al. conducted a randomized double-blind controlled study to assess the health effects of Szigetvár mineral water on patients with hip and knee OA. In this study, the intervention group received underwater jet massage treatments in 34 ˚C Szigetvár mineral water for 15 min per session, 5 days a week, for a total of 15 sessions, while the control group received tap water treatments at the same frequency and temperature. The results indicated that the intervention group significantly outperformed the control group in terms of ROM values, WOMAC scores, and the 36-Item Short Form Survey quality of life scores [164]. Additionally, 25 patients with RA underwent saline baths in a 36–37 ˚C mineral water pool for 20 min per day, six times per week, for two weeks, totaling 12 sessions. Compared to patients receiving only medication, balneotherapy showed significant improvements in non-enzymatic superoxide dismutase activity, global assessments by patients and physicians, Health Assessment Questionnaire Disability Index, DAS28, and swollen joint counts [165].

Sahin-Onat et al. conducted a single-blind, randomized controlled clinical trial that combined saline balneotherapy with physical therapy to treat patients with KOA. In addition to daily 45-min physical therapy sessions (including heat packs, transcutaneous electrical nerve stimulation, and ultrasonography therapy), patients underwent 20 min saline balneotherapy daily, 5 days per week for 3 weeks. Compared with the control group that received only physical therapy, the saline balneotherapy group showed significant alleviation of disease activity, pain levels, and improvements in joint function and walking speed [166]. A 2002 study in Hungary reported significant therapeutic effects of thermal water from Cserkeszölö in Hungary for treating patients with KOA. Cserkeszölö thermal water originates from a depth of 1159 m and is rich in minerals such as bicarbonate, silicate, and fluoride. Patients immersed themselves in the 36 ˚C thermal water for 30 min daily for 15 days consecutively. Patients treated with spa water demonstrated significant improvements in various evaluation parameters compared to the control group, whose members used similarly colored and scented tap water as a placebo [167].

The above studies indicate that balneotherapy, as a traditional and effective treatment method, has shown significant efficacy in relieving pain, improving joint function, and enhancing the quality of life in patients with OA and RA. However, the efficacy of balneotherapy currently varies owing to factors such as the composition and temperature of mineral water. Future studies should focus on further exploring the therapeutic mechanisms of different mineral water compositions, clarifying the optimal treatment parameters, and determining the appropriate conditions for various patient types, thereby fully realizing the potential value of balneotherapy for the comprehensive management of arthritis.

3.2.8. Combined Radon and thermal therapies

Radon is a colorless, odorless, and radioactive inert gas that naturally occurs in hot springs, mineral springs, and some mines. Owing to its anti-inflammatory and immunomodulatory properties, Radon has been used to treat chronic inflammatory diseases such as RA and OA. Combined Radon and thermal therapies integrate low-dose Radon exposure with thermotherapy, utilizing the anti-inflammatory effects of Radon and improving blood circulation in thermotherapy to provide a comprehensive treatment for patients. Lange et al. investigated the effects of continuous low-dose Radon and hyperthermia treatment (LDRnHT) on key serum biomarkers of bone metabolism in patients with RA and OA. The study involved 25 patients with RA and 24 non-inflammatory control patients with OA who underwent 12 sessions of LDRnHT, each lasting 60 min, under conditions of 37.5–41.5 ˚C, 70–100% humidity, and approximately 44 kBq/m^3 radon concentration. Following treatment, TNF-α and receptor activator of nuclear factor κB ligand (RANKL) levels significantly decreased in patients with RA and OA, while osteoprotegerin (OPG) levels increased significantly in patients with RA, the RANKL/OPG ratio significantly decreased, and levels of anti-citrullinated protein antibodies (ACPA) also significantly decreased. These findings suggest that LDRnHT counteracts inflammatory diseases by inhibiting osteoclast activity and promoting bone formation. Although a reduction in ACPA levels may contribute to bone protection, the specific physiological significance of this observation remains unclear and requires more research [168].

In an early prospective, randomized, single-blind study, Buljina et al. assessed the short-term effects of physical and exercise therapies on hand function in patients with RA. The study included 100 patients randomly divided into two groups, with 50 in-patients receiving a comprehensive regimen of physical and exercise therapies, including Radon baths, Faradaic hand baths, heated paraffin baths, and ice massages. During the study period, the control group did not receive any physical or exercise therapy. The results showed that the treatment group experienced significant improvements in most assessment metrics compared

to the baseline, whereas the control group showed a slight deterioration. This underscores the importance and effectiveness of physical and exercise therapies in the short-term improvement of hand function in patients with RA [169]. Overall, the combined Radon and thermal therapies have demonstrated significant clinical efficacy in reducing pain, lowering inflammation, and improving functionality in patients with RA and OA. By modulating the serum levels of key inflammatory and bone metabolic factors, and enhancing hand functionality, this therapy provides a unique and effective treatment strategy for managing chronic inflammatory diseases.

3.2.9. Dry heat therapy

Dry heat therapy, involving the provision of a consistent dry heat environment through a heating device, is employed for the treatment of chronic inflammatory diseases such as RA. In 2019, Gündüz et al. assessed the effects of this therapy on hand function in patients with RA. In the study, 47 patients in the intervention group received dry heat therapy using the Fluido^{TM} DHT device, with each session lasting 15 min, once per day, five days per week, for 3 weeks, with the treatment temperature set between 46.1 ˚C and 48.9 ˚C. The 46 patients in the control group participated in the same joint protection and exercise program but did not receive dry heat therapy. The study results showed that by week-12, only the control group showed a significant improvement in the Duruoz Hand Index scores, while the dry heat therapy did not improve hand function in patients with RA [170].

Although some studies suggest that dry heat therapy has potential value in pain management and improving joint function, the aforementioned study showed that dry heat therapy is not significantly superior to traditional joint protection and exercise programs for improving hand function in patients with RA. Therefore, future research should explore the optimal temperatures and treatment parameters for dry heat therapy, and develop more effective integrated treatment strategies in conjunction with other therapies to provide more personalized management plans for patients with RA.

3.3. Contrast therapy

Contrast Therapy, also referred to as cold-hot alternate therapy, is a physical therapy method that alternates between applying cold and hot stimuli to the treatment area to promote local blood circulation, alleviate muscle pain, and enhance the pain threshold. By altering the local temperature, this therapy aims to optimize the recovery process after inflammation and is commonly used for post-exercise recovery or chronic pain management [56,57].

In a recently published RCT, Kim et al. examined the effects of contrast therapy combining infrared (IR) with cold therapy (CR) compared with traditional contrast bath therapy (CBT) on blood flow, muscle tension, and pain threshold in a healthy population. The study included 20 healthy volunteers, and each participant received two different contrast therapies at 1-week intervals. CBT involves immersing participants in hot water at 38–40 ˚C for 4 min, then immediately switching to cold water at 12–14 ˚C for 1 min, alternating this process four times, with a total duration of 20 min. IR and CR contrast therapies were performed at the same temperature, time, and frequency as traditional CBT. The results showed that both therapies significantly improved blood flow, increased muscle elasticity, and reduced stiffness; in particular, IR and CR demonstrated more significant effects in enhancing blood flow and increasing the pain threshold [171]. A study in 2020 utilized hot towels (41–43 ˚C) and cold-water immersion (10–18 ˚C) for CBT, applying 3 min of heat and 1 min of cold to the knee joint, alternating daily for 20 min, over 7 consecutive days. This study found that pressurized CBT was effective in relieving knee joint pain in elderly individuals [172]. Another study found that compared to simple cold application, contrast therapy with alternating heat for 1–5 min twice a day with cold application for 20 min was more effective in controlling pain, improving function, and enhancing the quality of life, suggesting its incorporation into early management strategies for KOA [173].

Priya et al. introduced a smartphone-controlled knee pain relief pad that combined vibration and alternating hot and cold treatments, allowing users to adjust treatment settings based on their pain intensity and location. This alternating hot and cold treatment method is regarded as an appropriate choice for treating musculoskeletal diseases because it can effectively reduce muscle spasms and pain, accelerate nerve conduction velocity, and improve ROM [174]. In addition, a study on patients with unilateral knee OA divided them into a CBT group and a knee pad device (KPD) group. Patients in the CBT group underwent 20 min of cold-hot alternate immersion (4 min of hot water at 38–40 ˚C followed by 1 min of cold water at 1214 ˚C), while the KPD group first applied heat for 4 min and then cold compress for 1 min, totaling 20 min. Both groups of patients showed significant improvement after treatment, but the KPD group exhibited more notable enhancements in pain relief, ROM, WOMAC scores, and the two-minute walk test, indicating that combining KPD with intensified balance training is more effective in reducing pain and improving the quality of life of patients with early KOA [175].

Additionally, some studies have used water circulation devices to implement contrast therapy and explore its effects on pain relief and functional improvement. These treatments typically consist of three rounds of 4-min thermotherapy and 2-min cryotherapy, concluding with thermotherapy. The results indicated that, although cryotherapy, thermotherapy, and contrast therapy all effectively improved pain and functional status, patients exhibited a more positive response to their preferred treatment method. Most patients preferred to use water circulation devices for treatment rather than electric heating pads [176].

Although contrast therapy shows significant effects in promoting blood circulation, relieving muscle tension, and reducing pain, its efficacy varies depending on the treatment method, temperature, and duration. Recent studies have shown that, compared to traditional CBT, contrast therapy combining IR and cryotherapy is more effective in improving blood flow and increasing the pain threshold. Further, the introduction of smart devices has enhanced the potential of contrast therapy for personalized pain management. Future studies should continue to refine the treatment parameters, investigate the long-term effects of contrast therapy in arthritis management, and develop smart devices that offer patients more effective personalized treatment options.

3.4. Guidelines on the use of hot and cold therapy for the treatment of RA and OA

Several clinical guidelines recommend the use of thermotherapy and cryotherapy for treating OA and RA (Table 3). In 2012, the American College of Rheumatology released recommendations for the use of non-pharmacological and pharmacological therapies for hand, hip, and knee OA, including conditional recommendations for the use of heat agents for treatment [177]. By 2019, the association collaborated with the Arthritis Foundation to update these management guidelines, once again conditionally recommending the use of local heating or cooling interventions for patients with knee, hip, and hand OA. Although there are various heat intervention methods such as moist heat, transdermal (electric heating), ultrasonography, and hot and cold compresses, some studies have suggested that research using transdermal therapy or ultrasonography may have placebo issues. The heterogeneity of intervention methods and short duration of benefits are the main reasons for issuing conditional recommendations [178].

The 2023 edition of the "Chinese Knee Osteoarthritis Rehabilitation Treatment Guidelines," led by the Physical Medicine and Rehabilitation Branch of the Chinese Medical Association and West China Hospital at Sichuan University recommends not incorporating thermotherapy, neuromuscular electrical stimulation, high-frequency electromagnetic therapy, and infrared therapy as routine or adjunctive rehabilitation interventions for patients with KOA, after considering factors such as ev-

Table 3
Current guidelines on cold and heat therapy for osteoarthritis (OA) and rheumatoid arthritis (RA).

Institution	Year	Disease	Recommendation Strength	Guideline recommendations
SGRA-TCMR [185]	2020	RA	High	The working group strongly recommends the use of cryotherapy and thermotherapy for the rehabilitation of RA, where cryotherapy is mainly used during the acute phase and thermotherapy during the subacute and chronic phases.
Ottawa Panel [184]	2004	RA	Cryotherapy: low; thermotherapy: high	Compared to the control group that did not receive any interventions, using ice packs as a form of cryotherapy did not show significant effects on joint swelling, pain, medication intake, range of motion, grip strength, or hand function. However, the guidelines indicate that combining paraffin baths with therapeutic exercises demonstrated positive effects on pain, range of motion, and stiffness in non-resistive movements compared to the control group, although the impact on grip strength and pinching ability was not significant.
NICE [182]	2008	OA	Moderate	Consider other therapies such as local heat or cold applications.
CSPMR [179]	2024	KOA	Low or very low	After evaluating the quality of evidence, patient preferences, accessibility, and costs, this guideline advises against using hydrotherapy, neuromuscular electrical stimulation, high-frequency electromagnetic therapy, and infrared therapy as standard or supplementary treatments for knee osteoarthritis.
ACR and AF [178]	2020	OA	Low	The panel conditionally recommends that patients with osteoarthritis of the knee, hip, and/or hand consider thermotherapy, involving the application of local heat or cold.
OARSI [181]	2014	OA	Low	The recommendation is to use balneotherapy or spa therapy, particularly for patients with multi-joint osteoarthritis and comorbidities. This is due to the absence of specific treatment protocols that broadly cover different OA subtypes.
ACR [177]	2012	OA	Low	The panel conditionally recommends that patients with hip and knee OA use thermosensitive agent therapy under professional guidance. For hand OA patients, the use of thermotherapy methods is advised.
EULAR [180]	2018	OA	Very low	The task force considers topical application of heat a self-management strategy that patients can utilize at home, although the evidence supporting its beneficial effects is weak and inconsistent. In instances of inflammation during an OA flare-up, cold packs may provide symptomatic relief. However, no studies have been conducted on hand OA regarding this, and a single study on knee OA that compared hot and cold applications with usual care found no significant differences between the groups.
APTA [183]	2021	RA	NA	Due to limited scientific evidence supporting non-exercise therapeutic interventions for RA and other conditions, and the preference of the physical therapy field for active treatments, the panel strongly advises against using low-power laser therapy, electrostimulation (including TENS), ultrasonography therapy, massage, thermotherapy, medical taping, and dry needling.
ACR[203]	2021	RA	NA	The ACR expert panel did not provide a clear opinion on whether cryotherapy and thermotherapy was recommended for treating RA.
EULAR [204]	2020	RA	NA	In the updated 2019 guidelines, EULAR did not mention whether cold therapy is recommended for RA rehabilitation.
NICE [205]	2018	RA	NA	The guidelines does not explicitly state whether cryotherapy and thermotherapy wasis recommended for treating RA.

APTA, American Physical Therapy Association; ACR, American College of Rheumatology; AF, Arthritis Foundation; SGRA-TCMR, Working Group on Setting up Standardization Guidelines of Rheumatoid Arthritis in Traditional Chinese Medicine Rehabilitation; CSPMR, Chinese Society of Physical Medicine and Rehabilitation; EULAR, European League Against Rheumatism; NICE, National Institute for Health and Clinical Excellence; OARSI:Osteoarthritis Research Society International; OA, osteoarthritis; RA, rheumatoid arthritis; NA, not available.

idence quality, patient preferences, accessibility, and cost [179]. Further, the European League Against Rheumatism noted in its 2018 updated hand OA management recommendations that although local heat application is considered a self-management strategy that can be implemented at home, evidence supporting its benefits is weak and controversial. During an OA flare-up, cold compresses may also provide symptomatic relief if inflammation is present. However, research validating the use of hot and cold therapy to treat hand OA is still pending. Notably, a study comparing cold and hot compresses with standard care in a single center KOA patient cohort found no significant differences between groups [180]. The Osteoarthritis Research Society International recommended the use of balneotherapy/hydrotherapy in its 2014 nonsurgical treatment guidelines for KOA, especially in patients with multijoint OA and associated comorbidities [181]. The National Institute for Health and Care Excellence also mentioned in its 2008 guidelines for the management and care of adult OA that other therapies, such as local heat or cold applications, could be considered [182].

The American Physical Therapy Association, in its 2021 RA Physical Therapy Clinical Practice Guidelines, noted that, based on a systematic literature review, various nonactive interventions, including heat therapy, are not recommended because of a lack of supportive evidence. However, an expert panel believes that the short-term use of passive movements can supplement exercise therapy and is suitable for patients without active inflammation to help increase their range of joint motion [183]. The Ottawa Group, in its evidence-based clinical practice guidelines for the management of adult RA involving electrotherapy and heat therapy interventions, mentioned that using ice packs as a form of cryotherapy did not show significant effects compared to a control group that received no intervention in terms of joint swelling, pain, medication use, ROM, grip strength, or hand function. Nevertheless, the combination of heated paraffin baths with therapeutic exercises showed positive effects in reducing pain, improving ROM, and alleviating stiffness in non-resistant movements, although it had no significant impact on grip strength or pinching ability [184]. The traditional Chinese medicine rehabilitation clinical practice guidelines strongly recommend the use of conductive heat therapies (including paraffin therapy and herbal fumigation) and cryotherapy for RA rehabilitation. However, there is currently a lack of clear evidence to guide the specific application of herbal fumigation therapy, including appropriate temperature ranges, fumigation durations, and treatment courses. Clinically effective prescriptions rely primarily on guidance from traditional theories and personal experience, and lack support from data derived from large-scale studies [185].

Although most current guidelines only provide weak recommendations for hot and cold therapies or do not explicitly recommend them, this does not mean that thermotherapy and cryotherapy are ineffective or are not being used in actual treatment; the lack of strong recommendations is probably due to the limitations of current evidence-based medical findings. In actual clinical practice, physicians may cautiously select and use hot and cold therapies based on individual patient con-

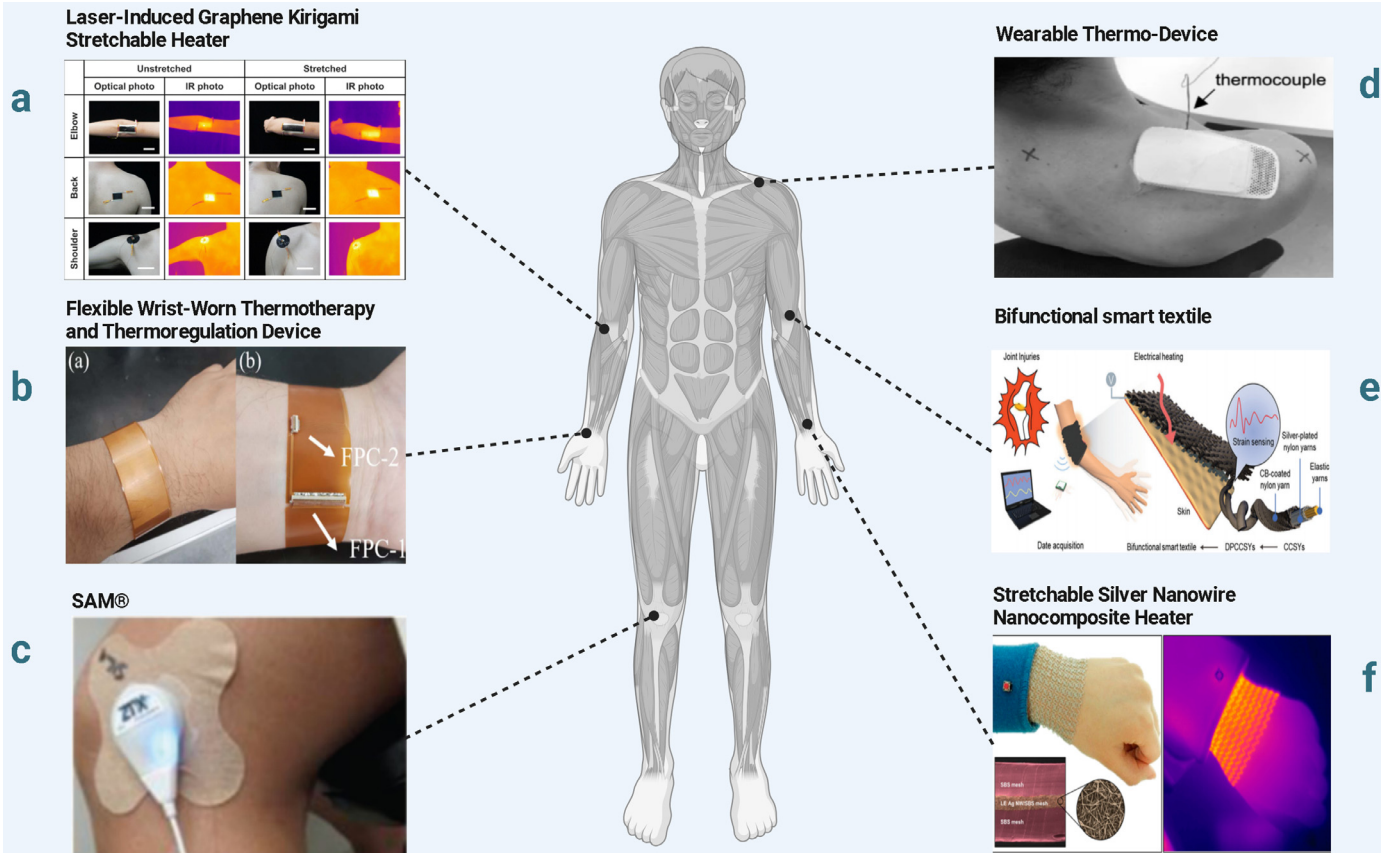

Fig. 5. New devices for treating arthritis. a: The laser-induced graphene Kirigami stretchable heater utilizes a single-step laser manufacturing technique to provide personalized and efficient thermotherapy solutions. Reproduced with permission [186]. Copyright 2024, The Royal Society of Chemistry. b: The flexible wrist-worn thermotherapy and thermoregulation device is an innovative wrist-worn unit that integrates temperature sensing and heating functions to achieve precise local temperature control and thermotherapy. Reproduced with permission [188]. Copyright 2019, IEEE. c: SAM® (Sustained Acoustic Medicine) is a wearable medical device that utilizes low-intensity continuous ultrasound technology to increase tissue temperature and blood flow, accelerating the healing of soft tissue injuries and relieving chronic pain. Reproduced with permission [189]. Copyright 2017, AIP Publishing. d: The wearable thermo-device includes a small temperature sensor and a comfortable, wearable component. Reproduced with permission [190]. Copyright 2022, The Author(s). e: The bifunctional smart textile integrates advanced electronic components for real-time motion monitoring and thermotherapy management, and a flexible, comfortable fabric designed to support and treat injured joints. Reproduced with permission [187]. Copyright 2023, The Authors. Advanced Science published by Wiley-VCH GmbH. f: The stretchable silver nanowire nanocomposite heater is a flexible device made from silver nanowires and a thermoplastic elastomer. The silver nanowires are uniformly distributed through a ligand exchange reaction, creating a highly conductive material that ensures effective heat transfer and sustained thermotherapy during joint movement. Reproduced with permission [195]. Copyright 2015, American Chemical Society.

ditions, preferences, and treatment responses. Future research should provide high-quality evidence to better guide clinical practice and ensure the rational and effective use of thermotherapy and cryotherapy.

4. Novel cold and heat therapy devices and materials

In addition to traditional cold and hot therapies, the development of novel cold and heat therapy devices and materials is also gradually increasing (Fig. 5). By utilizing a laser-induced graphene Kirigami stretchable heater via a single-step laser manufacturing process, resistive heating elements were manufactured directly on a polyimide substrate. The heater utilizes a Kirigami (Japanese paper-cutting art) design, enhances the stretchability and adaptability, and maintains excellent electrical conductivity and heating performance under various mechanical strain conditions. The design was concise, cost-effective, and conducive to large-scale production. Experimental validation demonstrated that this heater can rapidly and uniformly heat and is suitable for treating various symptoms such as muscle spasms, joint injuries, and arthritis, providing an innovative solution for thermotherapy [186]. Researchers have designed and developed a novel bifunctional smart textile that provides immediate and convenient heat therapy to injured joints, while simultaneously monitoring the condition and recovery of the joints. This smart textile integrates thermal therapy with real-time motion monitoring technology, making it particularly suitable for personalized and long-term treatment of joint injuries. Users can autonomously select treatment parameters through a smartphone application, ensuring personalized and convenient therapy [187].

Wearable wrist thermotherapy and temperature control devices are flexible wrist-worn devices equipped with the capability of precise local temperature measurement and regulation. These devices integrate temperature sensors and heating elements using the principle of resistive heating (Joule heating) to effectively regulate the temperatures of specific areas for thermotherapy. Using a closed-loop temperature control system, these devices can automatically adjust the temperature according to environmental changes or bodily needs, thereby ensuring an appropriate temperature for the hand under various environmental conditions. Further, the device design takes into consideration its application in extreme environments, such as high altitudes, polar exploration, and even temperature regulation requirements for space missions. The flexible structure and simple user interface make these devices ideal for daily wear while also supporting continuous thermotherapy during the recovery period from illness [188]. SAM® (Sustained Acoustic Medicine)

is a wearable medical device that uses low-intensity, continuous ultrasound technology to treat soft tissue injuries and alleviate chronic pain. Its mechanism involves increasing tissue temperature and blood flow through ultrasound, accelerating the natural healing process, enhancing cellular metabolism, and stimulating the delivery of more nutrients and oxygen to damaged tissues. SAM® devices are particularly effective in managing chronic pain like OA, providing long-lasting therapeutic effects that help patients manage pain without medication. Moreover, its non-invasive and low-risk characteristics make it an increasingly popular alternative to traditional drug therapies [189]. Wearable Thermo-Device (WTD) is a portable device utilizing Peltier elements to achieve alternate heating and cooling, and is primarily used for treating shoulder stiffness. The device can be controlled through a smartphone application that allows users to customize the duration and intervals of heating and cooling. WTD shows significant effectiveness in relieving muscle stiffness and fatigue. In particular, its alternate hot and cold treatment mode is more effective in reducing muscle stiffness and improving user experience. The portability and non-invasiveness of this device make it an ideal choice for relieving muscle stiffness, particularly in office workers who use computers for long periods [190].

Novel nanotechnologies have been developed, including gold nanoparticles, ferrite nanoparticles, nanocarriers for controlled drug release [191], biomimetic nanomaterials[192], and other nanomaterials with photothermal conversion capabilities [33]. Gold nanoparticles have garnered significant attention owing to their excellent photothermal conversion efficiency and biocompatibility and have been extensively researched for photothermal therapy in arthritis. By adjusting the size, shape, and surface modification of gold nanoparticles, their aggregation and photothermal effects at the sites of arthritic lesions can be optimized, thereby enhancing their therapeutic effects [193]. Iron oxide nanoparticles are also important thermal therapeutic materials that can be directed to inflamed joints under the action of an external magnetic field, enhancing the local drug concentration and reducing systemic side effects. These nanoparticles can release drugs in acidic or specific enzymatic environments, offering a novel approach for treating RA [194]. Moreover, a nanoplatform for the treatment of triple-negative breast cancer, responsive to photothermal and temperature changes, utilizes gold nanorods coated with mesoporous silica to effectively deliver chemotherapeutic drugs, such as paclitaxel prodrugs and camptothecin, demonstrating outstanding photothermal reactions and redox-responsive drug release capabilities, providing an effective method for combined therapy [191].

Silver nanowires are extensively utilized in biomedical and energy technologies because of their high conductivity and large surface area. They exhibit outstanding performance in the fabrication of flexible electronic devices and biosensors. A novel stretchable heater specially designed for joint thermotherapy was developed by a research team led by Suji Choi using a nanocomposite material of silver nanowires. These silver nanowires were uniformly distributed in the thermoplastic elastomers through ligand-exchange reactions, thus forming composites with high conductivity. The heater adopts a serpentine mesh structure that can closely conform to and effectively deliver heat during joint movements, ensuring flexibility and comfort during use. Moreover, this heater can be integrated into customized electronic bands equipped with batteries and microcontrollers, allowing users to continue thermotherapy while moving. The overall design considers ergonomics and long-term wear comfort and offers an innovative treatment solution for joint problems caused by aging, obesity, or occupational overuse [195]. Other innovative nanomaterials, such as molybdenum disulfide nanosheets, can effectively generate heat under near-infrared light irradiation and can be used for local treatment of arthritis [196].

Although these devices and materials are not specifically designed for the treatment of OA and RA, they have the potential to treat these diseases through cold and heat therapies. The design and application of new cold and hot devices and materials provide patients with arthritis with diverse treatment options, possessing significant clinical value and development prospects.

5. Points to note

Extreme caution should be exercised when using cold, heat, or contrast therapies to treat OA and RA. In patients with impaired skin sensation, extreme temperatures can easily cause skin damage because of their diminished perception of temperature changes [197]. Due to possible vascular and neurological impairments, patients with diabetes may exhibit abnormal responses to cold and heat, thus requiring additional caution when applying these therapies [116,198]. In addition, cold therapy may induce vasoconstriction, thereby affecting blood flow, whereas heat therapy may result in vasodilation. These changes may pose risks to patients with vascular disorders, necessitating close monitoring during treatment [199].

The application of cold or heat therapy to areas with open wounds may increase the risk of infection and delay wound healing. Therefore, a thorough assessment of these areas should be conducted before initiating treatment, with avoidance if necessary [200]. Moreover, when using low-temperature mud therapy, attention should be paid to its potential impact on the blood circulation of the patient and cardiovascular system, particularly in patients with cardiovascular diseases or venous lymphatic insufficiency. Seasonal factors may also influence treatment efficacy. For example, heat therapy in winter may be more effective for relieving pain and discomfort, whereas cold therapy in summer may be more effective. Consideration should also be given to the characteristics of heat-sensitive acupoints when using heat therapy as they may influence efficacy and patient response [201]. Finally, when using automated cold, compression, and heat therapy devices, their cost and accessibility should be considered to ensure the widespread availability and affordability of treatment [198].

When applying cryotherapy, in addition to the contraindications mentioned above, it is necessary to consider whether the patient has conditions, such as sensory neuropathy, low body weight [131], cold allergy or urticaria, cryoglobulinemia, paroxysmal nocturnal hemoglobinuria, sickle cell anemia, chronic obstructive arterial disease, and bladder and kidney diseases. Additionally, cryotherapy may lead to adverse reactions, including frostbite [135], headache [142], dizziness, increased pain, shortness of breath, and circulatory failure. For patients undergoing thermotherapy, conditions such as acute infections, fever, edema, hemorrhagic disorders, other serious systemic diseases, and varicose veins must also be ruled out [158]. Heat therapy can also cause adverse reactions, including local skin irritation [154,158], burns and skin damage, exacerbated inflammation, changes in blood pressure, circulatory issues, and rashes or contact dermatitis.

Overall, both cryotherapy and thermotherapy must be carefully administered during treatment to ensure that patients do not have any contraindications that might exacerbate their condition or cause new problems. Any potential adverse reactions must be closely monitored to ensure the safety and efficacy of the treatment.

6. Future outlook

Despite the revelation of the potential benefits of cryotherapy and thermotherapy in treating OA and RA, research in this field is marked by some significant limitations, including limited sample sizes, inconsistent study designs, and lack of assessment of long-term effects. These limitations hinder a comprehensive understanding of the overall effectiveness of these therapies. Future research should adopt more rigorous methodologies, such as conducting large-scale RCTs and long-term follow-up studies, to enhance the reliability of the research findings and confirm the long-term effectiveness and safety of the treatments. Further, more objective assessment metrics such as biochemical markers and imaging techniques should be introduced in future research to comprehensively evaluate treatment outcomes.

Future developments in cryotherapy and thermotherapy research should involve detailed studies on their specific impacts on the microenvironment of arthritis and establish optimal application models for these therapies among patients with various types and stages of arthritis. Additionally, research should consider integrating traditional therapies with modern technologies such as artificial intelligence (AI) and the Internet of Things. The aim of integration is to explore innovative strategies to enhance treatment outcomes. Specifically, smart devices to be developed should automatically adjust temperature settings based on real-time feedback from wearable sensors and utilize AI algorithms to analyze data. This dynamic adjustment of treatment plans can not only increase therapeutic effectiveness, but also reduce treatment risks. Further, by standardizing the treatment parameters (such as temperature, duration, and frequency) and systematically evaluating the efficacy and safety of these methods, future research will provide a solid scientific basis for the clinical application of cryotherapy and thermotherapy, promoting the wider application of these non-pharmacological treatment methods in the treatment of arthritis.

7. Conclusion

Cryotherapy and thermotherapy have significant benefits for the treatment of OA and RA. This review demonstrates that cryotherapy is particularly effective for controlling symptoms during the acute inflammatory phase, whereas thermotherapy is advantageous for managing chronic pain and promoting joint function recovery. These therapeutic approaches are widely favored in clinical practice because of their ease of use, low cost, and fewer side effects. By summarizing the existing literature, this review article underscores the practical value of cryotherapy and thermotherapy as non-pharmacological interventions for alleviating the symptoms of arthritis, and provides scientific evidence to support their broader application. Future research should continue to elucidate the mechanisms of action of these therapeutic interventions in order to optimize treatment strategies and enhance their efficacy.

Abbreviation

AIA, antigen-induced arthritis; CBT, contrast bath therapy; CCF, continuous cold flow; COX-2, cyclooxygenase-2; CPM, continuous passive motion; CR, cold therapy; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Scores; DMARDs, disease-modifying antirheumatic drugs; FIR, far-infrared radiation; HAQ, Health Assessment Questionnaire; HSP, heat shock protein; ICAM-1, intercellular adhesion molecule 1; IGF-1, insulin-like growth factor 1; IL, interleukins; IR, infrared; KOA, knee osteoarthritis; KPD, knee pad device; LTB4, leukotriene B4; MAPK p38, mitogen-activated protein kinase p38; MMPs, matrix metalloproteinases; NF-κB, nuclear factor κB; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PGE2, prostaglandin E2; RA, rheumatoid arthritis; RCT, randomized controlled trial; ROM, range of motion; TKA, total knee arthroplasty; TNF-α, tumor necrosis factor-alpha; VAS, visual analog scale; VEGF, vascular endothelial growth factor; VCAM-1, vascular cell adhesion molecule-1; WBC, whole-body cryotherapy; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

Acknowledgments

This work was supported by the National Key R&D Program of China (2021YFC2502100, 2023YFC3603404, 2019YFA0111900), National Natural Science Foundation of China (82072506, 82272611, 92268115), Hunan Provincial Science Fund for Distinguished Young Scholars (2024JJ2089), Hunan Young Talents of Science and Technology (2021RC3025), Provincial Clinical Medical Technology Innovation Project of Hunan (2023SK2024, 2020SK53709), Provincial Natural Science Foundation of Hunan (2020JJ3060), National Natural Science Foundation of Hunan Province (2023JJ30949), National Clinical Research Center for Geriatric Disorders, Xiangya Hospital (2021KFJJ02, 2021LNJJ05), the Hunan Provincial Innovation Foundation for Postgraduate (CX20230308, CX20230312), the Independent Exploration and Innovation Project for Postgraduate Students of Central South University (2024ZZTS0163). The Figs. 1–4 for this review were generated through the biorender website, and permission to publish has been obtained (https://app.biorender.com/).

References

[1] L. Ma, A. Cranney, J.M. Holroyd-Leduc, Acute monoarthritis: what is the cause of my patient's painful swollen joint? CMAJ. 180 (1) (2009) 59–65.
[2] S. Glyn-Jones, A.J.R. Palmer, R. Agricola, et al., Osteoarthritis, Lancet 386 (9991) (2015) 376–387.
[3] L. Yue, J. Berman, What is osteoarthritis? JAMa 327 (13) (2022) 1300.
[4] D.J. Hunter, S. Bierma-Zeinstra. Osteoarthritis. Lancet. 393 (10182) 1745–1759.
[5] Q. Yao, X. Wu, C. Tao, et al., Osteoarthritis: pathogenic signaling pathways and therapeutic targets, Signal. Transduct. Target. Ther. 8 (1) (2023) 56.
[6] G.D.a.I. Collaborators, Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet 396 (10258) (2020) 1204–1222.
[7] D. Aletaha, J.S. Smolen, Diagnosis and management of rheumatoid arthritis: a review, JAMa 320 (13) (2018) 1360–1372.
[8] A. Finckh, B. Gilbert, B. Hodkinson, et al., Global epidemiology of rheumatoid arthritis, Nat. Rev. Rheumatol. 18 (10) (2022) 591–602.
[9] I.C. Scott, R. Whittle, J. Bailey, et al., Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis epidemiology in England from 2004 to 2020: an observational study using primary care electronic health record data, Lancet Reg. Health Eur. 23 (2022) 100519.
[10] K.D. Brandt, E.L. Radin, P.A. Dieppe, et al., Yet more evidence that osteoarthritis is not a cartilage disease, Ann. Rheum. Dis. 65 (10) (2006) 1261–1264.
[11] J. Martel-Pelletier, A.J. Barr, F.M. Cicuttini, et al., Osteoarthritis, Nat. Rev. Dis. Primers. 2 (2016) 16072.
[12] W.H. Robinson, C.M. Lepus, Q. Wang, et al., Low-grade inflammation as a key mediator of the pathogenesis of osteoa rthritis, Nat. Rev. Rheumatol. 12 (10) (2016) 580–592.
[13] K. Fu, S.R. Robbins, J.J. Mcdougall, Osteoarthritis: the genesis of pain, Rheumatology. (Oxford) 57 (suppl_4) (2018) iv43–iv50.
[14] J.S. Smolen, D. Aletaha, I.B. Mcinnes, Rheumatoid arthritis, Lancet 388 (10055) (2016) 2023–2038.
[15] F.M. Brennan, I.B. Mcinnes, Evidence that cytokines play a role in rheumatoid arthritis, J. Clin. Invest. 118 (11) (2008) 3537–3545.
[16] A. Alunno, F. Carubbi, R. Giacomelli, et al., Cytokines in the pathogenesis of rheumatoid arthritis: new players and therapeutic targets, BMC. Rheumatol. 1 (2017) 3.
[17] C.-H. Tang, Research of pathogenesis and novel therapeutics in arthritis 2.0, Int. J. Mol. Sci. 21 (21) (2020) 8125.
[18] B.L. Kidd, R.M. Langford, T. Wodehouse, Arthritis and pain. Current approaches in the treatment of arthritic pain, Arthritis Res. Ther. 9 (3) (2007) 214.
[19] K. Shaw, J. Zochling, T. Winzenberg, Nonpharmacological interventions for rheumatoid arthritis, Aust. Fam. Physician 36 (10) (2007) 840–841.
[20] F. Wellborne, New directions in the standard of care for inflammatory arthritis, Postgrad Med. Spec No (2006) 24–31.
[21] S. Senthelal, J. Li, S. Ardeshirzadeh, et al., Arthritis, StatPearls, StatPearls Publishing, 2023.
[22] A.B.M. Jiménez, S.C.H. Sarango, C.M.N. Cabrera, et al., Tratamiento de dolor en artritis, Recimundo 7 (3) (2023) 41–49.
[23] M.Y. Khan, I. Aziz, I. Ahmad, et al., A Natural cure to arthritis by phytomedicines-a review, Asian J. Res. Pharmaceut. Sci. 5 (4) (2015) 216–220.
[24] H. Higashi, J.J. Barendregt, Cost-effectiveness of total hip and knee replacements for the Australian population with osteoarthritis: discrete-event simulation model, PLoS. One 6 (9) (2011) e25403.
[25] S. Reichenbach, A.W. Rutjes, E. Nüesch, et al., Joint lavage for osteoarthritis of the knee, Cochrane Database Syst. Rev. (5) (2010) CD007320.
[26] A.E. Nelson, K.D. Allen, Y.M. Golightly, et al., A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. bone and joint initiative, Semin. Arthritis Rheum. 43 (6) (2014) 701–712.
[27] J.A. Block, Osteoarthritis: OA guidelines: improving care or merely codifying prac tice? Nat. Rev. Rheumatol. 10 (6) (2014) 324–326.
[28] R.F. Van Vollenhoven, Treatment of rheumatoid arthritis: state of the art 2009, Nat. Rev. Rheumatol. 5 (10) (2009) 531–541.
[29] B. Bresnihan, Rheumatoid arthritis: principles of early treatment, J. Rheumatol. Suppl. 66 (2002) 9–12.
[30] A. Gibofsky, Y. Yazici, Treatment of rheumatoid arthritis: strategies for achieving optimal ou tcomes, Ann. Rheum. Dis. 69 (6) (2010) 941–942.

[31] J.S. Smolen, R.B.M. Landewé, J.W.J. Bijlsma, et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 u pdate, Ann. Rheum. Dis. 79 (6) (2020) 685–699.
[32] E. Molinelli, A. Campanati, G. Ganzetti, et al., Biologic therapy in immune mediated inflammatory disease: basic science and clinical concepts, Curr. Drug Saf. 11 (1) (2016) 35–43.
[33] H. Shang, H. Gu, N. Zhang, From traditional to novel treatment of arthritis: a review of recent advances in nanotechnology-based thermal therapy, Nanomedicine (Lond) 16 (23) (2021) 2117–2132.
[34] G.J. Mccoll, Treatment of rheumatoid arthritis in the elderly, J. Pharm. Pract. 35 (2) (2005) 151–154.
[35] M. Doumen, R. Westhovens, S. Pazmino, et al., The ideal mHealth-application for rheumatoid arthritis: qualitative fi ndings from stakeholder focus groups, BMC. Musculoskelet. Disord. 22 (1) (2021) 746.
[36] J.W.J. Bijlsma, F. Berenbaum, F.P.J.G. Lafeber, Osteoarthritis: an update with relevance for clinical practice, Lancet 377 (9783) (2011) 2115–2126.
[37] P. Mcgettigan, D. Henry, Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2, JAMa 296 (13) (2006) 1633–1644.
[38] C. Bombardier, L. Laine, A. Reicin, et al., Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group, N. Engl. J. Med. 343 (21) (2000) 1520–1528.
[39] J.R. Curtis, N. Patkar, A. Xie, et al., Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists, Arthritis Rheum. 56 (4) (2007) 1125–1133.
[40] A. Kavanaugh, A.F. Wells, Benefits and risks of low-dose glucocorticoid treatment in the patient with rheumatoid arthritis, Rheumatology. (Oxford) 53 (10) (2014) 1742–1751.
[41] N. Zhang, P.R. Wardwell, R.A. Bader, In vitro efficacy of polysaccharide-based nanoparticles containing disease-modifying antirheumatic drugs, Pharm. Res. 31 (9) (2014) 2326–2334.
[42] M. Dehghan, F. Farahbod, The efficacy of thermotherapy and cryotherapy on pain relief in patients with acute low back pain, a clinical trial study, J. Clin. Diagn. Res. 8 (9) (2014) LC01–LC04.
[43] L. Brosseau, S. Milne, V. Robinson, et al., Efficacy of the transcutaneous electrical nerve stimulation for the treatment of chronic low back pain: a meta-analysis, Spine (Phila Pa 1976) 27 (6) (2002) 596–603.
[44] S. Masiero, F. Vittadini, C. Ferroni, et al., The role of thermal balneotherapy in the treatment of obese patient with knee osteoarthritis, Int. J. Biometeorol. 62 (2) (2018) 243–252.
[45] R. Rutkowski, A. Straburzyńska-Lupa, P. Korman, et al., Thermal effectiveness of different IR radiators employed in rheumatoid hand therapy as assessed by thermovisual examination, Photochem. Photobiol. 87 (6) (2011) 1442–1446.
[46] S.D. French, M. Cameron, B.F. Walker, et al., Superficial heat or cold for low back pain, Cochrane Database Syst. Rev. 2006 (1) (2006) CD004750.
[47] A. Lubkowska, Cryotherapy: physiological considerations and applications to physical therapy, in: Physical Therapy Perspectives in the 21st Century—Challenges and Possibilities, 2012, pp. 155–176.
[48] A. Freiman, N. Bouganim, History of cryotherapy, Dermatol. Online J. 11 (2) (2005) 9.
[49] D. Tomchuk, M.D. Rubley, W.R. Holcomb, et al., The magnitude of tissue cooling during cryotherapy with varied types o f compression, J. Athl. Train. 45 (3) (2010) 230–237.
[50] N.G. Versey, S.L. Halson, B.T. Dawson, Water immersion recovery for athletes: effect on exercise performance and practical recommendations, Sports Med. 43 (11) (2013) 1101–1130.
[51] B. Dugue, W. Douzi, P. Carette, et al., What everybody should know about whole–body cryotherapy/cryostimulation: an up-dated mini review, in: 39th Informatory Note on Refrigeration Technologies/39e Note d'Information sur les technologies du froid, 2019, 2019, pp. 2868–2871.
[52] I.M. Wilcock, J.B. Cronin, W.A. Hing, Physiological response to water immersion: a method for sport recovery ? Sports Med. 36 (9) (2006) 747–765.
[53] P.S. Tepperman, M. Devlin, The therapeutic use of local heat and cold, Can. Fam. Physician 32 (1986) 1110–1114.
[54] C.-T. Lee, K.M. Kokolus, N.D. Leigh, et al., Defining immunological impact and therapeutic benefit of mild heating in a murine model of arthritis, PLoS. One 10 (3) (2015) e0120327.
[55] S.F. Nadler, K. Weingand, R.J. Kruse, The physiologic basis and clinical applications of cryotherapy and the rmotherapy for the pain practitioner, Pain. Physician 7 (3) (2004) 395–399.
[56] C.R.J. Denegar. Therapeutic modalities for athletic injuries. (2000)
[57] R.M.I.M. Weerasekara, S.U.B. Tennakoon, H.J. Suraweera, Contrast therapy and heat therapy in subacute stage of grade I and II lateral ankle sprains, Foot Ankle Spec. 9 (4) (2016) 307–323.
[58] L. Mourot, C. Cluzeau, J. Regnard, Hyperbaric gaseous cryotherapy: effects on skin temperature and system ic vasoconstriction, Arch. Phys. Med. Rehabil. 88 (10) (2007) 1339–1343.
[59] D.I. Abramson, L.S. Chu, S. Tuck Jr., et al., Effect of tissue temperatures and blood flow on motor nerve conduction velocity, JAMa 198 (10) (1966) 1082–1088.
[60] A.A. Algafly, K.P. George, The effect of cryotherapy on nerve conduction velocity, pain threshold and pain tolerance, Br. J. Sports Med. 41 (6) (2007) 365–369.
[61] A. Stålman, L. Berglund, E. Dungnerc, et al., Temperature-sensitive release of prostaglandin E_2 and diminished energ y requirements in synovial tissue with postoperative cryotherapy: a pr ospective randomized study after knee arthroscopy, J. Bone Joint Surg. Am. 93 (21) (2011) 1961–1968.
[62] M.H. Cameron, Physical Agents in rehabilitation: from Research to Practice, Elsevier Health Sciences, 2012.
[63] D.C. Mac Auley, Ice therapy: how good is the evidence? Int. J. Sports Med. 22 (5) (2001) 379–384.
[64] T.J. Hubbard, C.R. Denegar, Does Cryotherapy Improve Outcomes With Soft Tissue Injury? J. Athl. Train. 39 (3) (2004) 278–279.
[65] C. Peyronnel, P. Totoson, V. Petitcolin, et al., Effects of local cryotherapy on systemic endothelial activation, dysfunction, and vascular inflammation in adjuvant-induced arthritis (AIA) rats, Arthritis Res. Ther. 24 (1) (2022) 97.
[66] G.M. Barbosa, J.E. Cunha, T.M. Cunha, et al., Clinical-like cryotherapy improves footprint patterns and reduces synovial inflammation in a rat model of post-traumatic knee osteoarthritis, Sci. Rep. 9 (1) (2019) 14518.
[67] X. Guillot, N. Tordi, C. Laheurte, et al., Local ice cryotherapy decreases synovial interleukin 6, interleukin 1β, vascular endothelial growth factor, prostaglandin-E2, and nuclear factor kappa B p65 in human knee arthritis: a controlled study, Arthritis Res. Ther. 21 (1) (2019) 180.
[68] A. Stanek, A. Cholewka, T. Wielkoszyński, et al., Whole-body cryotherapy decreases the levels of inflammatory, oxidative stress, and atherosclerosis plaque markers in male patients with active-phase ankylosing spondylitis in the absence of classical cardiovascular risk factors, Mediators. Inflamm. 2018 (2018) 1–11.
[69] X. Guillot, H. Martin, S. Seguin-Py, et al., Local cryotherapy improves adjuvant-induced arthritis through down-regulation of IL-6 /IL-17 pathway but independently of TNFα, PLoS. One 12 (7) (2017) e0178668.
[70] A. Lubkowska, W. Dudzińska, I. Bryczkowska, et al., Body composition, lipid profile, adipokine concentration, and antioxid ant capacity changes during interventions to treat overweight with exe rcise programme and whole-body cryostimulation, Oxid. Med. Cell Longev. 2015 (2015) 803197.
[71] A. Lubkowska, Z. Szygula, A.J. Klimek, et al., Do sessions of cryostimulation have influence on white blood cell coun t, level of IL6 and total oxidative and antioxidative status in health y men? Eur. J. Appl. Physiol. 109 (1) (2010) 67–72.
[72] B. Dugué, J. Smolander, T. Westerlund, et al., Acute and long-term effects of winter swimming and whole-body cryother apy on plasma antioxidative capacity in healthy women, Scand. J. Clin. Lab. Invest. 65 (5) (2005) 395–402.
[73] C. Swenson, L. Swärd, J. Karlsson, Cryotherapy in sports medicine, Scand. J. Med. Sci. Sports 6 (4) (1996) 193–200.
[74] A.F. Machado, P.H. Ferreira, J.K. Micheletti, et al., Can water temperature and immersion time influence the effect of cold water immersion on muscle soreness? A systematic review and meta-analy sis, Sports Med. 46 (4) (2016) 503–514.
[75] A. Diestel, J. Roessler, F. Berger, et al., Hypothermia downregulates inflammation but enhances IL-6 secretion by stimulated endothelial cells, Cryobiology 57 (3) (2008) 216–222.
[76] R. Sasaki, J. Sakamoto, Y. Kondo, et al., Effects of cryotherapy applied at different temperatures on inflammatory pain during the acute phase of arthritis in rats, Phys. Ther. 101 (2) (2021) pzaa211.
[77] Y. Ohkoshi, M. Ohkoshi, S. Nagasaki, et al., The effect of cryotherapy on intraarticular temperature and postoperat ive care after anterior cruciate ligament reconstruction, Am. J. Sports Med. 27 (3) (1999) 357–362.
[78] X. Guillot, N. Tordi, L. Mourot, et al., Cryotherapy in inflammatory rheumatic diseases: a systematic review, Expert. Rev. Clin. Immunol. 10 (2) (2014) 281–294.
[79] F. Marino, J.M. Sockler, J.M. Fry, Thermoregulatory, metabolic and sympathoadrenal responses to repeated brief exposure to cold, Scand. J. Clin. Lab. Invest. 58 (7) (1998) 537–545.
[80] R. Bugaj, The cooling, analgesic, and rewarming effects of ice massage on localized skin, Phys. Ther. 55 (1) (1975) 11–19.
[81] J. Cao, J. Xu, W. Li, et al., Influence of selective brain cooling on the expression of ICAM-1 mRNA and infiltration of PMNLs and monocytes/macrophages in rats suffering from global brain ischemia/reperfusion injury, Biosci. Trends. 2 (6) (2008) 241–244.
[82] M.A. Yenari, H.S. Han, Influence of hypothermia on post-ischemic inflammation: role of nuclear factor kappa B (NFkappaB), Neurochem. Int. 49 (2) (2006) 164–169.
[83] L. Mourot, C. Cluzeau, J. Regnard, Hyperbaric gaseous cryotherapy: effects on skin temperature and systemic vasoconstriction, Arch. Phys. Med. Rehabil. 88 (10) (2007) 1339–1343.
[84] V.A. Pavlov, K.J. Tracey, The cholinergic anti-inflammatory pathway, Brain Behav. Immun. 19 (6) (2005) 493–499.
[85] J. Leppaluoto, T. Westerlund, P. Huttunen, et al., Effects of long-term whole-body cold exposures on plasma concentrations of ACTH, beta-endorphin, cortisol, catecholamines and cytokines in healthy females, Scand. J. Clin. Lab. Invest. 68 (2) (2008) 145–153.
[86] H. Zhang, J.-J. Zhang, Y.-W. Mei, et al., Effects of immediate and delayed mild hypothermia on endogenous antioxidant enzymes and energy metabolites following global cerebral ischemia, Chin. Med. J. (Engl) 124 (17) (2011) 2764–2766.
[87] H. Zhang, M. Zhou, J. Zhang, et al., Therapeutic effect of post-ischemic hypothermia duration on cerebral ischemic injury, Neurol. Res. 30 (4) (2008) 332–336.
[88] E. Miller, L. Markiewicz, J. Saluk, et al., Effect of short-term cryostimulation on antioxidative status and its clinical applications in humans, Eur. J. Appl. Physiol. 112 (5) (2012) 1645–1652.
[89] E.D. Harris Jr., P.A. Mccroskery, The influence of temperature and fibril stability on degradation of cartilage collagen by rheumatoid synovial collagenase, N. Engl. J. Med. 290 (1) (1974) 1–6.
[90] E. Suehiro, H. Fujisawa, T. Akimura, et al., Increased matrix metalloproteinase-9 in blood in association with acti vation of interleukin-6 after traumatic brain injury: influence of hyp othermic therapy, J. Neurotrauma 21 (12) (2004) 1706–1711.
[91] G.A. Malanga, N. Yan, J. Stark, Mechanisms and efficacy of heat and cold therapies for musculoskeletal injury, Postgrad. Med. 127 (1) (2015) 57–65.

[92] A. Sarsan, N. Akkaya, M. Ozgen, et al., Comparing the efficacy of mature mud pack and hot pack treatments for knee osteoarthritis, J. Back. Musculoskelet. Rehabil. 25 (3) (2012) 193–199.
[93] C.M. Bleakley, J.T. Costello, Do thermal agents affect range of movement and mechanical properties in soft tissues? A systematic review, Arch. Phys. Med. Rehabil. 94 (1) (2013) 149–163.
[94] Y. Jang, L.G. Je, S. Lee, et al., Efficacy of transcutaneous 4.4 MHz radiofrequency diathermy versus therapeutic ultrasound for pain relief and functional recovery in patients with knee osteoarthritis: a randomized controlled study, J. Clin. Med. 12 (18) (2023) 6040.
[95] P. Klemm, I. Aykara, M. Eichelmann, et al., Treatment of back pain in active axial spondyloarthritis with serial locoregional water-filtered infrared A radiation: a randomized controlled trial, J. Back. Musculoskelet. Rehabil. 35 (2) (2022) 271–278.
[96] C. Protano, M. Fontana, A. De Giorgi, et al., Balneotherapy for osteoarthritis: a systematic review, Rheumatol. Int. 43 (9) (2023) 1597–1610.
[97] S. Cheleschi, I. Gallo, S. Tenti, A comprehensive analysis to understand the mechanism of action of balneotherapy: why, how, and where they can be used? Evidence from in vitro studies performed on human and animal samples, Int. J. Biometeorol. 64 (7) (2020) 1247–1261.
[98] E. Odabasi, M. Turan, H. Erdem, et al., Does mud pack treatment have any chemical effect? A randomized controlled clinical study, J. Altern. Complement. Med. 14 (5) (2008) 559–565.
[99] A.M. Beer, H.E. Junginger, J. Lukanov, et al., Evaluation of the permeation of peat substances through human skin in vitro, Int. J. Pharm. 253 (1–2) (2003) 169–175.
[100] B. Dilek, M. Gozum, E. Sahin, et al., Efficacy of paraffin bath therapy in hand osteoarthritis: a single-blinded randomized controlled trial, Arch. Phys. Med. Rehabil. 94 (4) (2013) 642–649.
[101] M. Markovic, K.M. Stuhlmeier, Short-term hyperthermia prevents activation of proinflammatory genes in fibroblast-like synoviocytes by blocking the activation of the transcription factor NF-kappaB, J. Mol. Med. (Berl) 84 (10) (2006) 821–832.
[102] M.C. Maccarone, G. Magro, U. Solimene, et al., From in vitro research to real life studies: an extensive narrative review of the effects of balneotherapy on human immune response, Sport Sci. Health 17 (4) (2021) 817–835.
[103] G. Dischereit, J.E. Goronzy, U. Muller-Ladner, et al., [Effects of serial mud baths on inflammatory rheumatic and degenerative diseases], Z. Rheumatol. 78 (2) (2019) 143–154.
[104] I.H. Tarner, U. Muller-Ladner, C. Uhlemann, et al., The effect of mild whole-body hyperthermia on systemic levels of TNF-alpha, IL-1beta, and IL-6 in patients with ankylosing spondylitis, Clin. Rheumatol. 28 (4) (2009) 397–402.
[105] S. Bellometti, M. Cecchettin, L. Galzigna, Mud pack therapy in osteoarthrosis. Changes in serum levels of chondrocyte markers, Clin. Chim. Acta 268 (1–2) (1997) 101–106.
[106] I.V. Guzhova, Z.A. Darieva, A.R. Melo, et al., Major stress protein Hsp70 interacts with NF-kB regulatory complex in human T-lymphoma cells, Cell Stress. Chaperones. 2 (2) (1997) 132–139.
[107] D.L. Feinstein, E. Galea, D.A. Aquino, et al., Heat shock protein 70 suppresses astroglial-inducible nitric-oxide synthase expression by decreasing NFkappaB activation, J. Biol. Chem. 271 (30) (1996) 17724–17732.
[108] K.M. Stuhlmeier, Short term hyperthermia prevents the activation of mitogen-activated protein kinase p38, Exp. Gerontol. 44 (6–7) (2009) 406–412.
[109] P. Giusti, L. Cima, A. Tinello, et al., Stress hormones liberated by fangotherapy. ACTH and beta-endorphin lev els under heat stress, Fortschr. Med. 108 (32) (1990) 601–603.
[110] J. Yan, X. Ma, D. Liang, et al. An autocatalytic multicomponent DNAzyme nanomachine for tumor-specific photothermal therapy sensitization in pancreatic cancer. 14 (1) (2023) 6905.
[111] M. Sobieska, T. Stratz, W. Samborski, et al., Interleukin-6 (IL-6) after whole body cryotherapy and local hot mud pack treatment, Eur. J. Phys. Med. Rehabil. 3 (5) (1993).
[112] S. Bellometti, L. Galzigna, P. Richelmi, et al., Both serum receptors of tumor necrosis factor are influenced by mud pa ck treatment in osteoarthrotic patients, Int. J. Tissue React. 24 (2) (2002) 57–64.
[113] A. Beer, P. Zagorchev, M. Filipova, et al., Effects of aqueous peat extract on the activity of cyclooxygenase and cyclooxygenase-1 and cyclooxygenase-2 isoforms, Physikalische Medizin, Rehabilitationsmedizin, Kurortmedizin 25 (01) (2015) 51–54.
[114] S. Bellometti, P. Richelmi, T. Tassoni, et al., Production of matrix metalloproteinases and their inhibitors in osteoa rthritic patients undergoing mud bath therapy, Int. J. Clin. Pharmacol. Res. 25 (2) (2005) 77–94.
[115] P.C. Braga, G. Sambataro, M. Dal Sasso, et al., Antioxidant effect of sulphurous thermal water on human neutrophil bur sts: chemiluminescence evaluation, Respiration. 75 (2) (2008) 193–201.
[116] G.A. Malanga, N. Yan, J. Stark, Mechanisms and efficacy of heat and cold therapies for musculoskeletal injury, Postgrad. Med. 127 (1) (2015) 57–65.
[117] A. Fioravanti, M. Karagülle, T. Bender, et al., Balneotherapy in osteoarthritis: facts, fiction and gaps in knowledge, Eur. J. Integr. Med. 9 (2017) 148–150.
[118] H.A. Mohammedsadiq, M.T. Rasool, Effectiveness of home-based conventional exercise and cryotherapy on daily living activities in patients with knee osteoarthritis: a randomized controlled clinical trial, Medicine (Baltimore) 102 (18) (2023) e33678.
[119] P. Castro, D.H. Machanocker, G.F. Luna, et al., Clinical-like cryotherapy in acute knee arthritis protects neuromuscular junctions of quadriceps and reduces joint inflammation in mice, Biomed. Res. Int. 2022 (2022) 7442289.
[120] X. Guillot, N. Tordi, C. Prati, et al., Cryotherapy decreases synovial Doppler activity and pain in knee arthritis: a randomized-controlled trial, Joint. Bone Spine 84 (4) (2017) 477–483.
[121] Z. Sari, O. Aydogdu, I. Demirbuken, et al., A better way to decrease knee swelling in patients with knee osteoarthritis: a single-blind randomised controlled trial, Pain. Res. Manage 2019 (2019) 8514808.
[122] T. Nishigami, S. Nakao, H. Kondo, et al., A pleasant sensation evoked by knee or hand icing influences the effect on pain intensity in patients after total knee arthroplasty: a prospective, randomized, cross-over study, J. Pain. Res. 12 (2019) 3469–3475.
[123] W. Rui, G. Long, G. Li, et al., Effects of ethyl chloride spray on early recovery after total knee arthroplasty: a prospective study, J. Orthop. Sci. 22 (1) (2017) 89–93.
[124] N. Laktašić Žerjavić, E. Hrkić, I. Žagar, et al., Local cryotherapy, comparison of cold air and ice massage on pain and handgrip strength in patients with rheumatoid arthritis, Psychiatr. Danub. 33 (Suppl 4) (2021) 757–761.
[125] H. Hirvonen, H. Kautiainen, E. Moilanen, et al., The effect of cryotherapy on total antioxidative capacity in patients with active seropositive rheumatoid arthritis, Rheumatol. Int. 37 (9) (2017) 1481–1487.
[126] R. Jastrzabek, A. Straburzynska-Lupa, R. Rutkowski, et al., Effects of different local cryotherapies on systemic levels of TNF-alpha, IL-6, and clinical parameters in active rheumatoid arthritis, Rheumatol. Int. 33 (8) (2013) 2053–2060.
[127] B. Lee, D. Yoon, J. Yim, Effects of an early exercise program with cryotherapy on range of motion, pain, swelling, and gait in patients with total knee arthroplasty: a randomized controlled trial, J. Clin. Med. 13 (5) (2024) 1420.
[128] A.J. De Vries, H.K. Aksakal, R.W. Brouwer, Effects of 6 weeks of cryotherapy plus compression therapy after total or unicompartmental knee arthroplasty: protocol for a single-centre, single-blind randomised controlled trial, BMJ Open. 14 (1) (2024) e077614.
[129] M. Marinova, A. Sundaram, K. Holtham, et al., The role of a cryocompression device following total knee arthroplasty to assist in recovery: a randomised controlled trial, Knee Surgery, Sports Traumatol., Arthrosc. 31 (10) (2023) 4422–4429.
[130] E.P. Su, M. Perna, F. Boettner, et al., A prospective, multi-center, randomised trial to evaluate the efficacy of a cryopneumatic device on total knee arthroplasty recovery, J. Bone Joint Surg. Br. 94 (11) (2012) 153–156 Suppl A.
[131] N.C. Leegwater, J.H. Willems, R. Brohet, et al., Cryocompression therapy after elective arthroplasty of the hip, Hip. Int. 22 (5) (2012) 527–533.
[132] N. Saito, H. Horiuchi, S. Kobayashi, et al., Continuous local cooling for pain relief following total hip arthroplasty, J. Arthroplasty. 19 (3) (2004) 334–337.
[133] M. Coviello, A. Abate, F. Ippolito, et al., Continuous cold flow device following total knee arthroplasty: myths and reality, Medicina (Kaunas) 58 (11) (2022) 1537.
[134] K. Iwakiri, A. Kobayashi, Y. Takeuchi, et al., Efficacy of continuous local cryotherapy following total hip arthroplasty, SICOT. J. 5 (2019) 13.
[135] E. Morsi, Continuous-flow cold therapy after total knee arthroplasty, J. Arthroplasty. 17 (6) (2002) 718–722.
[136] M.C. Chen, C.C. Lin, J.Y. Ko, et al., The effects of immediate programmed cryotherapy and continuous passive motion in patients after computer-assisted total knee arthroplasty: a prospective, randomized controlled trial, J. Orthop. Surg. Res. 15 (1) (2020) 379.
[137] H. Zivna, L. Maric, I. Gradosova, et al., The effect of mud-bath therapy on bone status in rats during adjuvant subchronic arthritis, Acta Medica (Hradec. Kralove) 55 (3) (2012) 133–137.
[138] M. Ariana, A. Afrasiabifar, S. Najafi Doulatabad, et al., The effect of local heat therapy versus cold rub gel on pain and joint functions in patients with knee osteoarthritis, Clin. Nurs. Res. 31 (6) (2022) 1014–1022.
[139] P. Klemm, J. Hoffmann, T. Asendorf, et al., Whole-body cryotherapy for the treatment of rheumatoid arthritis: a monocentric, single-blinded, randomised controlled trial, Clin. Exp. Rheumatol. 40 (11) (2022) 2133–2140.
[140] M. Barlowska-Trybulec, K. Zawojska, J. Szklarczyk, et al., Effect of whole body cryotherapy on low back pain and release of endorphins and stress hormones in patients with lumbar spine osteoarthritis, Reumatologia 60 (4) (2022) 247–251.
[141] E. Wojtecka-Lukasik, K. Ksiezopolska-Orlowska, E. Gaszewska, et al., Cryotherapy decreases histamine levels in the blood of patients with rheumatoid arthritis, Inflamm. Res. 59 (S2) (2010) S253–S255 Suppl 2.
[142] U. Lange, C. Uhlemann, U. Muller-Ladner, [Serial whole-body cryotherapy in the criostream for inflammatory rheumatic diseases. A pilot study], Med. Klin. (Munich) 103 (6) (2008) 383–388.
[143] G. Polidori, F. Bogard, F. Legrand, et al., Efficiency of a whole-body cryotherapy protocol at -110°C for hand rheumatoid arthritis: a controlled trial, J. Therm. Anal. Calorim. 147 (20) (2022) 11159–11167.
[144] K.P. Braun, S. Brookman-Amissah, K. Geissler, et al., [Whole-body cryotherapy in patients with inflammatory rheumatic disease. A prospective study], Med. Klin. (Munich) 104 (3) (2009) 192–196.
[145] M. Gizinska, R. Rutkowski, W. Romanowski, et al., Effects of whole-body cryotherapy in comparison with other physical modalities used with kinesitherapy in rheumatoid arthritis, Biomed. Res. Int. 2015 (2015) 409174.
[146] H. Hinkka, S. Vaattanen, S. Ala-Peijari, et al., Effects of cold mist shower on patients with inflammatory arthritis: a crossover controlled clinical trial, Scand. J. Rheumatol. 46 (3) (2017) 206–209.
[147] M. Kasapoglu Aksoy, L. Altan, Short-term efficacy of paraffin therapy and home-based exercise programs in the treatment of symptomatic hand osteoarthritis, Turk. J. Phys. Med. Rehabil. 64 (2) (2018) 108–113.
[148] S.G. Kim, J.W. Kang, J.H. Boo, et al., Effectiveness of paraffin bath therapy for the symptoms and function of hand diseases: a systematic review and meta-analysis of randomized controlled trials, J. Hand. Ther. 36 (3) (2023) 706–712.

[149] X. Chen, H. Zhang, W. Zeng, et al., Far infrared irradiation suppresses experimental arthritis in rats by down-regulation of genes involved inflammatory response and autoimmunity, J. Adv. Res. 38 (2022) 107–118.
[150] F.G. Oosterveld, J.J. Rasker, M. Floors, et al., Infrared sauna in patients with rheumatoid arthritis and ankylosing spondylitis. A pilot study showing good tolerance, short-term improvement of pain and stiffness, and a trend towards long-term beneficial effects, Clin. Rheumatol. 28 (1) (2009) 29–34.
[151] M.N. Berliner, A.I. Maurer, Effect of different methods of thermotherapy on skin microcirculation, Am. J. Phys. Med. Rehabil. 83 (4) (2004) 292–297.
[152] K. Harada, K. Takahashi, F. Ikuta, et al., Efficacy of a Deep Thermal Therapy System for Osteoarthritis of the Knee, J. Nippon. Med. Sch. 88 (4) (2021) 335–341.
[153] L. Cantarini, G. Leo, C. Giannitti, et al., Therapeutic effect of spa therapy and short wave therapy in knee osteoarthritis: a randomized, single blind, controlled trial, Rheumatol. Int. 27 (6) (2007) 523–529.
[154] T. Adiguzel, B. Arslan, H. Gurdal, et al., Evaluation of the therapeutic and the chemical effects of balneological treatment on clinical and laboratory parameters in knee osteoarthritis: a randomized, controlled, single-blinded trial, Int. J. Biometeorol. 66 (6) (2022) 1257–1265.
[155] A. Fioravanti, S. Tenti, C. Giannitti, et al., Short- and long-term effects of mud-bath treatment on hand osteoarthritis: a randomized clinical trial, Int. J. Biometeorol. 58 (1) (2014) 79–86.
[156] A. Fioravanti, C. Giannitti, S. Cheleschi, et al., Circulating levels of adiponectin, resistin, and visfatin after mud-bath therapy in patients with bilateral knee osteoarthritis, Int. J. Biometeorol. 59 (11) (2015) 1691–1700.
[157] C. Giannitti, A. De Palma, N.A. Pascarelli, et al., Can balneotherapy modify microRNA expression levels in osteoarthritis? A comparative study in patients with knee osteoarthritis, Int. J. Biometeorol. 61 (12) (2017) 2153–2158.
[158] F.D. Guneri, F.B.E. Forestier, R.J. Forestier, et al., Peloidotherapy in rheumatoid arthritis: a pilot randomized clinical trial, Int. J. Biometeorol. 65 (12) (2021) 2171–2180.
[159] Z.M. Britschka, W.R. Teodoro, A.P. Velosa, et al., The efficacy of Brazilian black mud treatment in chronic experimental arthritis, Rheumatol. Int. 28 (1) (2007) 39–45.
[160] D. Flusser, M. Abu-Shakra, M. Friger, et al., Therapy with mud compresses for knee osteoarthritis: comparison of natural mud preparations with mineral-depleted mud, J. Clin. Rheumatol. 8 (4) (2002) 197–203.
[161] K.K. Ho, A.W. Kwok, W.W. Chau, et al., A randomized controlled trial on the effect of focal thermal therapy at acupressure points treating osteoarthritis of the knee, J. Orthop. Surg. Res. 16 (1) (2021) 282.
[162] S. Ochiai, A. Watanabe, H. Oda, et al., Effectiveness of thermotherapy using a heat and steam generating sheet for cartilage in knee osteoarthritis, J. Phys. Ther. Sci. 26 (2) (2014) 281–284.
[163] N. Yildirim, M. Filiz Ulusoy, H. Bodur, The effect of heat application on pain, stiffness, physical function and quality of life in patients with knee osteoarthritis, J. Clin. Nurs. 19 (7–8) (2010) 1113–1120.
[164] A. Hanzel, K. Horvat, B. Molics, et al., Clinical improvement of patients with osteoarthritis using thermal mineral water at Szigetvar Spa-results of a randomised double-blind controlled study, Int. J. Biometeorol. 62 (2) (2018) 253–259.
[165] M. Karagulle, S. Kardes, O. Karagulle, et al., Effect of spa therapy with saline balneotherapy on oxidant/antioxidant status in patients with rheumatoid arthritis: a single-blind randomized controlled trial, Int. J. Biometeorol. 61 (1) (2017) 169–180.
[166] Ş.Ş.O.Şahin Onat, Balneotherapy in the treatment of knee osteoarthritis: a controlled study, Arch. Rheumatol. 30 (4) (2015) 292–297.
[167] I. Kovacs, T. Bender, The therapeutic effects of Cserkeszolo thermal water in osteoarthritis of the knee: a double blind, controlled, follow-up study, Rheumatol. Int. 21 (6) (2002) 218–221.
[168] U. Lange, G. Dischereit, I. Tarner, et al., The impact of serial radon and hyperthermia exposure in a therapeutic adit on pivotal cytokines of bone metabolism in rheumatoid arthritis and osteoarthritis, Clin. Rheumatol. 35 (11) (2016) 2783–2788.
[169] A.I. Buljina, M.S. Taljanovic, D.M. Avdic, et al., Physical and exercise therapy for treatment of the rheumatoid hand, Arthritis Rheum. 45 (4) (2001) 392–397.
[170] N.Erdinc Gunduz, D. Erdem, R. Kizil, et al., Is dry heat treatment (fluidotherapy) effective in improving hand function in patients with rheumatoid arthritis? A randomized controlled trial, Clin. Rehabil. 33 (3) (2019) 485–493.
[171] J. Kim, H. Jung, J. Yim, Effects of contrast therapy using infrared and cryotherapy as compared with contrast bath therapy on blood flow, muscle tone, and pain threshold in young healthy adults, Med. Sci. Monit. 26 (2020) e922544.
[172] E. Rusminingsih, N.W. Agustina, D.a.N.J.M. Wulan, The effectiveness of contrast bath to reduce joint pain in the elderly, Medisains 17 (3) (2020) 53.
[173] M.Ibrahem Abd Elfatah, Effect of cold application versus contrast hydrotherapy on patients knee osteoarthritis outcomes, Am. J. Nursing Sci. 8 (4) (2019).
[174] L. Priya, V. Vignesh, V. Krishnan, et al., Design and development of a smart knee pain relief pad based on vibration and alternate heating and cooling treatments, Technol. Health Care 26 (3) (2018) 543–551.
[175] P. Fokmare, P. Phansopkar, The effect of contrast bath therapy and knee pad device on pain, range of motion, and functional disability in patients with osteoarthritis knee: a randomized control trial, Cureus. 15 (10) (2023) e47586.
[176] C.R. Denegar, D.R. Dougherty, J.E. Friedman, et al., Preferences for heat, cold, or contrast in patients with knee osteoarthritis affect treatment response, Clin. Interv. Aging 5 (2010) 199–206.
[177] M.C. Hochberg, R.D. Altman, K.T. April, et al., American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee, Arthritis Care Res. (Hoboken) 64 (4) (2012) 465–474.
[178] S.L. Kolasinski, T. Neogi, M.C. Hochberg, et al., 2019 American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee, Arthritis Care Res. (Hoboken) 72 (2) (2020) 149–162.
[179] S. Zhu, Z. Wang, Q. Liang, et al., Chinese guidelines for the rehabilitation treatment of knee osteoarthritis: an CSPMR evidence-based practice guideline, J. Evid. Based. Med. 16 (3) (2023) 376–393.
[180] M. Kloppenburg, F.P. Kroon, F.J. Blanco, et al., 2018 update of the EULAR recommendations for the management of hand osteoarthritis, Ann. Rheum. Dis. 78 (1) (2019) 16–24.
[181] T.E. Mcalindon, R.R. Bannuru, M.C. Sullivan, et al., OARSI guidelines for the non–surgical management of knee osteoarthritis, OsteoArthritis Cartilage 22 (3) (2014) 363–388.
[182] P.G. Conaghan, J. Dickson, R.L. Grant, et al., Care and management of osteoarthritis in adults: summary of NICE guidance, BMJ 336 (7642) (2008) 502–503.
[183] W.F. Peter, N.M. Swart, G.A. Meerhoff, et al., Clinical practice guideline for physical therapist management of people with rheumatoid arthritis, Phys. Ther. 101 (8) (2021) pzab127.
[184] P. Ottawa. Ottawa panel evidence-based clinical practice guidelines for electroth erapy and thermotherapy interventions in the management of rheumatoid arthritis in adults. Phys. Ther.. 84 (11) 1016–1043.
[185] J. Luo, P. Lan, C.J.R.M. Hongyu, Clinical practice guidelines in traditional Chinese medicine rehabilitation—rheumatoid arthritis, Rehabil. Med. 30 (01) (2020) 16–25.
[186] J. Chen, Y. Shi, B. Ying, et al., Kirigami-enabled stretchable laser-induced graphene heaters for wearable thermotherapy, Mater. Horiz. 11 (8) (2024) 2010–2020.
[187] Y. Liu, D. Xu, C. Ge, et al., Bifunctional smart textiles with simultaneous motion monitoring and thermotherapy for human joint injuries, Adv. Sci. (Weinh) 11 (4) (2024) e2305312.
[188] P. Kassanos, F. Seichepine, M. Keshavarz, et al., Towards a flexible wrist-worn thermotherapy and thermoregulation device, 2019 IEEE 19th International Conference on Bioinformatics and Bioengineering (BIBE), IEEE, 2019.
[189] M.D. Langer, W. Huang, A. Ghanem, et al., Skin temperature increase mediated by wearable, long duration, low-intensity therapeutic ultrasound, in: AIP Conf Proc. 1821, 2017.
[190] T. Sawada, H. Okawara, D. Nakashima, et al., Effects of alternating heat and cold stimulation using a wearable thermo-device on subjective and objective shoulder stiffness, J. Physiol. Anthropol. 41 (1) (2022) 1.
[191] W. Zhou, X. Ma, J. Wang, et al. Co-delivery CPT and PTX prodrug with a photo/thermo-responsive nanoplatform for triple-negative breast cancer therapy. 1 (1) (2022) e20220036.
[192] X. Lin, L. Fan, L. Wang, et al. Fabricating biomimetic materials with ice-templating for biomedical applications. 2 (3) (2023) e20230017.
[193] R.R. Arvizo, S. Bhattacharyya, R.A. Kudgus, et al., Intrinsic therapeutic applications of noble metal nanoparticles: past, present and future, Chem. Soc. Rev. 41 (7) (2012) 2943–2970.
[194] S. Zhang, L. Wu, J. Cao, et al., Effect of magnetic nanoparticles size on rheumatoid arthritis targeting and photothermal therapy, Colloids. Surf. B Biointerfaces. 170 (2018) 224–232.
[195] S. Choi, J. Park, W. Hyun, et al., Stretchable heater using ligand-exchanged silver nanowire nanocomposite for wearable articular thermotherapy, ACS. Nano 9 (6) (2015) 6626–6633.
[196] Y. Zhao, C. Wei, X. Chen, et al., Drug delivery system based on near-infrared light-responsive molybdenum disulfide nanosheets controls the high-efficiency release of dexamethasone to inhibit inflammation and treat osteoarthritis, ACS. Appl. Mater. Interfaces. 11 (12) (2019) 11587–11601.
[197] F.G. Oosterveld, J.J. Rasker, Effects of local heat and cold treatment on surface and articular temperature of arthritic knees, Arthritis Rheum. 37 (11) (1994) 1578–1582.
[198] M. Morcos, A.-a.J.A. Golrokhian-Sani, Technology. Automated cold, compression, and heat gloves for arthritis: a proposal for combination therapy, Aging (Geron) Technol. 1 (1) (2023).
[199] F.G. Oosterveld, J.J. Rasker, *Treating Arthritis With Locally Applied Heat or cold*. in *Semin Arthritis Rheum*, Elsevier, 1994.
[200] K.W. Hayes, Heat and cold in the management of rheumatoid arthritis, Arthritis Care Res. 6 (3) (1993) 156–166.
[201] D.-Y. Xie, Y.-X. Jiang, R.-X. Chen, et al., Study on the thermesthesia features of heat-sensitive acupoints in patients with knee osteoarthritis, J. Acupunct. Tuina Sci. 14 (2) (2016) 110–114.
[202] A. Fioravanti, F. Iacoponi, B. Bellisai, et al., Short- and long-term effects of spa therapy in knee osteoarthritis, Am. J. Phys. Med. Rehabil. 89 (2) (2010) 125–132.
[203] L. Fraenkel, J.M. Bathon, B.R. England, et al., 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis, Arthritis Rheumatol. 73 (7) (2021) 1108–1123.
[204] J.S. Smolen, R.B.M. Landewe, J.W.J. Bijlsma, et al., EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update, Ann. Rheum. Dis. 79 (6) (2020) 685–699.
[205] A. Allen, S. Carville, F. Mckenna, et al., Diagnosis and management of rheumatoid arthritis in adults: summary of updated NICE guidance, BMJ 362 (2018) k3015.

Yuming Yao received his Bachelor of Medicine (M.D. equivalent) degree from Nanchang University in 2024. Then he joined the department of orthopedics, Xiangya hospital, Central South university and became a M.S.candidate. His research interests focus on osteoarthritis and rotator cuff diseases.

Wenqing Xie received his Bachelor's degree from Northwest University for Nationalities in 2020, and Master's Degree from Central South University in 2023. He is currently pursuing a Doctorate in Orthopedics at Xiangya Hospital of Central South University. His research focuses on Orthopedic degenerative diseases and sports injury.

Zhou Li (BRID: 08220.00.08215) received his Bachelor's degree from Wuhan University in 2004, and Doctor's Degree from Peking University in 2010. Zhou Li serves as the Doctoral Supervisor, Deputy Director at the Institute of Nanoenergy and Nanosystems, Chinese Academy of Sciences (CAS), and is a professor at the University of the Chinese Academy of Sciences. Celebrated with the National Natural Science Fund for Distinguished Young Scholars in 2021 and other notable awards such as the Beijing Natural Science Fund for Distinguished Young Scholars. His research focuses on the advancement of bioelectronic and medical devices, namely in the areas of wearable and implantable electronic health monitoring and therapy devices, biosensors, biodegradable electronics, and biomechanical investigations.

Yusheng Li (BRID: 03513.00.36220) received his M.D and Ph.D. degree from Central south university in 2011, specializing in Orthopedics. From 2016–2019, he worked as a postdoctoral fellow at the department of Orthopedic surgery, Johns Hopkins university. He currently is an associate professor and associate chief physician at the department of Orthopedics, Xiangya hospital, Central South university. His research focuses on Orthopedic degenerative diseases and sports injury.