Pharmacological Research 208 (2024) 107349

Contents lists available at ScienceDirect

Pharmacological Research

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

Far-infrared radiation and its therapeutic parameters: A superior alternative for future regenerative medicine?

Bo Qin [a,b,1], Shi-jie Fu [a,b,1], Xiong-fei Xu [a,d], Jiu-jie Yang [a], Yuping Wang [a,e], Lin-na Wang [a], Bai-xiong Huang [a], Jing Zhong [a], Wan-yu Wu [a], Heng-ao Lu [a], Betty Yuen Kwan Law [a], Nick Wang [f], Io Nam Wong [c,*], Vincent Kam Wai Wong [a,*]

[a] Dr. Neher's Biophysics Laboratory for Innovative Drug Discovery, State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macao
[b] Department of Orthopedics, The Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, Luzhou, Sichuan 646600, China
[c] Faculty of Medicine, Macau University of Science and Technology, Macau, Macao
[d] Department of Vascular Surgery, The Affiliated Hospital, Southwest Medical University, Luzhou, Sichuan 646600, China
[e] Department of Breast, Thyroid and Vascular Surgery, The Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, Luzhou, Sichuan 646600, China
[f] New Age Technology (Asia) Limited, TML Tower, 3 Hoi Shing Road, Tsuen Wan, Hong Kong

ARTICLE INFO

Keywords:
Far-infrared radiation
Future regenerative medicine
Therapeutic parameters
Molecular mechanisms
Applications

ABSTRACT

In future regenerative medicine, far-infrared radiation (FIR) may be an essential component of optical therapy. Many studies have confirmed or validated the efficacy and safety of FIR in various diseases, benefiting from new insights into FIR mechanisms and the excellent performance of many applications. However, the lack of consensus on the biological effects and therapeutic parameters of FIR limits its practical applications in the clinic. In this review, the definition, characteristics, and underlying principles of the FIR are systematically illustrated. We outline the therapeutic parameters of FIR, including the wavelength range, power density, irradiation time, and distance. In addition, the biological effects, potential molecular mechanisms, and preclinical and clinical applications of FIR are discussed. Furthermore, the future development and applications of FIR are described in this review. By applying optimal therapeutic parameters, FIR can influence various cells, animal models, and patients, eliciting diverse underlying mechanisms and offering therapeutic potential for many diseases. FIR could represent a superior alternative with broad prospects for application in future regenerative medicine.

1. Introduction

Aging and chronic non-communicable diseases are significant global challenges. As the world's population ages, the economic burden of several chronic diseases is increasing, elevating them to the status of major public health threats. Despite remarkable advances in living standards and medical technology, specific societal problems such as drug misuse and tolerance have emerged, affecting clinical outcomes.

Abbreviations: FIR, far-infrared radiation; PLZF, promyelocytic leukemia zinc finger; VEGF, vascular endothelial growth factor; HUVECs, human umbilical vein endothelial cells; NO, nitric oxide; ENOS, endothelial NO synthase; FBI, FIR biological index; BMSCs, bone marrow-derived mesenchymal stem cells; RTECs, renal tubular epithelial cells; RPTCs, renal proximal tubule cells; CM, conditioned medium; PDGF, platelet-derived growth factor; TNF-α, tumor necrosis factor; IL, interleukin; LPS, lipopolysaccharide; ARDS, acute respiratory distress syndrome; HO-1, heme oxygenase-1; CO, carbon monoxide; ECs, endothelial cells; ROS, reactive oxygen species; EPCs, endothelial progenitor cells; VSMCs, vascular smooth muscle cells; AMPK, AMP-activated Protein Kinase; ECFCs, endothelial colony-forming cells; CaM, calmodulin; CaMKII, calmodulin-dependent protein kinase II; BAECs, bovine aortic endothelial cells; SCLU, secretory clusterin; GPCRs, G-protein coupled receptors; SCFA, short-chain fatty acids; TMSCs, tonsil-derived mesenchymal stem cells; TRPV, transient receptors potential vanilloid; CKD, chronic kidney disease; AIA, adjuvant-induced arthritis; HP, haptoglobin; PD, peritoneal dialysis; GDPs, glucose degradation products; MA, methamphetamine; BNP, brain natriuretic peptide; AVF, arteriovenous fistula; ADMA, asymmetric dimethylarginine; DKD, diabetic kidney disease; ABI, ankle-brachial index; PAOD, peripheral artery occlusive disease; HD, hemodialysis; AVG, arteriovenous grafts; RCT, rotator cuff repair; DM, diabetes mellitus.

* Corresponding authors.
E-mail addresses: inwong@must.edu.mo (I.N. Wong), bowaiwong@gmail.com (V.K.W. Wong).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.phrs.2024.107349
Received 3 May 2024; Received in revised form 31 July 2024; Accepted 31 July 2024
Available online 14 August 2024

Regenerative medicine is the "process of replacing, engineering, or regenerating human or animal cells, tissues, or organs to restore or establish normal function" [1]. In future regenerative medicine, technologies, including optics and materials science, are being pursued to develop alternative therapies to stimulate the body's repair mechanisms to achieve functional healing of previously irreparable tissues. Photobiomodulation and far-infrared radiation (FIR) are examples of these therapeutic approaches. Many studies have substantiated the safety and efficacy of FIR in treating various diseases, including inflammatory, cardiovascular, peripheral vascular, and neurological conditions [2–4]. Robust results can be achieved with the use of FIR.

However, there is no standard or consensus recommendation for its therapeutic parameters. The underlying mechanisms remain unclear. Whether FIR can have a satisfactory therapeutic effect, as reported in many studies, remains to be investigated. This review systematically summarizes the progress in using FIR in regenerative medicine, covering cellular mechanisms, small animal models, and clinical trials. This review focuses on elucidating the therapeutic parameters and underlying principles and highlights the characteristics, potential molecular mechanisms, and preclinical and clinical applications of FIR. This comprehensive review will serve as a valuable reference for researchers and clinicians interested in FIR therapy.

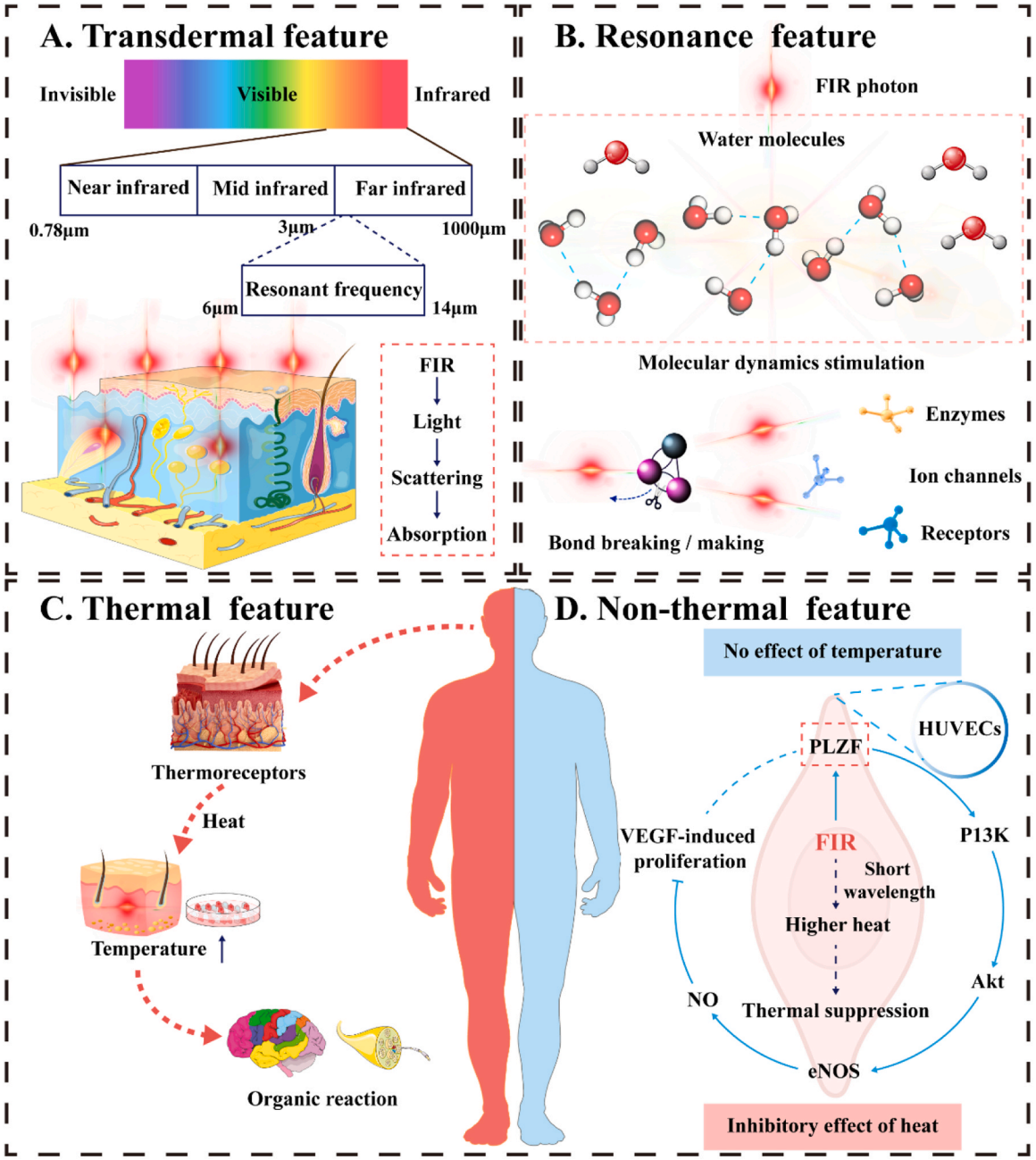

Fig. 1. The four characteristics of the FIR. A. Transdermal feature. FIR energy penetrates subcutaneous tissue and reaches certain depths, influencing atomic and molecular levels. B. Resonance feature. FIR photon energy facilitates interactions between biomolecules and cells, activating water molecules by breaking or forming molecular bonds. C. Thermal feature. FIR, perceived as heat through the skin's thermoreceptors, penetrates subcutaneous tissue, acting on deep tissue to generate and dissipate heat, resulting in an organic reaction. D. Non-thermal feature. The absorption of other FIR components can stimulate biological regulation in HUVECs. Some studies have suggested that FIR itself has no thermal effects on culture media or small animals, while FIR with short wavelengths possesses the property of thermal suppression.

2. Definition and mechanism of FIR

2.1. Definition

The FIR is a particular region within the infrared spectrum of electromagnetic radiation [5]. Distinguished by wavelength, the infrared spectrum comprises the near, mid, and far infrared regions. Most of the literature suggests that the wavelength of FIR is between 3 and 1000 μm. However, there is no agreed-upon wavelength range for the FIR, and different sources may define the range differently [6]. The International Commission on Illumination classifies FIR within the 3–100 μm range, with corresponding photon energies spanning from 3–100 THz. Conversely, an alternative classification in the ISO 20473 standard designates FIR wavelengths between 50 and 1000 μm [6]. Some sources describe the FIR band as ranging from 3–1000 μm or 5.6–1000 μm [6,7].

FIR therapy shares similarities with photobiomodulation therapy, but it falls outside the scope of traditional photobiomodulation. FIR therapy represents living cells' metabolic and cellular response to FIR energy photons. Unlike photobiomodulation therapy, FIR is an invisible light that the eye cannot perceive. In contrast, photobiomodulation typically involves the perception and regulation of visible-spectrum light and invisible-near infrared light. The literature indicates that FIR radiation can have wavelengths up to 9.4 μm when emitted at 35°C. For therapeutic purposes, the wavelengths most beneficial to the human body typically range from 6–14 μm [8,9]. Indeed, FIR exerts various biological effects, leading to therapeutic benefits such as anti-inflammatory effects, immune regulation, and antioxidative stress effects.

2.2. Mechanisms and characteristics

FIR radiation has only one mechanism of action: photons are absorbed by biomolecules, and their energy increases molecular vibrations (mainly stretching and bending) according to infrared spectroscopy principles. The biological molecules that absorb the FIR are primarily water because they are the most abundant, but proteins and lipids can also be involved. According to the literature, there are four main characteristics of FIR in this process: transdermal, resonance, thermal, and non-thermal features (Fig. 1) [6,10]. These characteristics are intricately interconnected, exerting mutual influence.

2.2.1. Transdermal feature

The energy of FIR can penetrate to a certain depth, influencing atomic and molecular levels through energy transfer, leading to thermal and non-thermal biological effects [11]. The effective distance at which FIR energy penetrates subcutaneous tissue is not well established. In biomedical applications, the high water content in human tissues and the strong absorption of FIR radiation typically result in a penetration depth ranging from a few millimeters to a few centimeters. This depth varies depending on the type of tissue and its water content. Literature suggests that FIR energy can be converted into gentle radiant heat by the human body, with the potential to penetrate up to 1.5 in. (approximately 4 cm) beneath the skin [6,12]. Ballistic FIR photons (not absorbed or scattered) penetrate only a short distance (less than 1 mm) into the tissue, as shown by the use of a CO_2 laser (10.6 μm) for tissue ablation/cutting. However, the effects of FIR do penetrate beyond a certain distance into tissue because the vibrational energy undergoes non-radiative energy transfer, probably between adjacent water clusters.

2.2.2. Resonance feature

The water cluster size and temperature significantly affect the FIR absorption spectrum [13]. Biological mechanisms involve subtle changes in the tertiary structure of essential proteins, such as enzymes, ion channels, and receptors, caused by the amplification of vibrational changes inside cells. Resonance induces the activation of water molecules, reinforcing molecular bonds and initiating ion vibrations, ultimately leading to the denaturation of macromolecular substances such as proteins [14–17]. Significantly, some studies have suggested a direct correlation between the biological effects of FIR and changes in Ca^{2+} dynamics [18]. FIR can elevate intracellular Ca^{2+} levels, mediating downstream signaling factors such as calmodulin (CaM), CaM-dependent protein kinase II (CaMKII), and checkpoint kinase 2 [19,20].

2.2.3. Thermal feature

In the infrared spectrum, FIR transfers energy through heat, which is perceptible to the skin's thermoreceptors, penetrating the subcutaneous tissue and acting on the deep tissue to generate heat [6]. Subsequent research confirmed that exposure to FIR for 40 minutes can increase the skin's surface temperature by 4–7 °C [7]. This thermal effect may help improve circulation and regulate changes in the autonomic nervous system.

2.2.4. Non-thermal feature

FIR has been demonstrated to have a non-thermal effect and does not change mice's medium or rectal temperature [10,21,22]. Other studies kept the heating plate at a constant temperature to avoid thermal effects between groups and found that FIR can exert beneficial effects [21]. The implication is that FIR can impact even without heat and that the temperature change during FIR irradiation is insignificant. FIR induces the nuclear translocation of promyelocytic leukemia zinc finger (PLZF), which inhibits vascular endothelial growth factor (VEGF)-induced proliferation in human umbilical vein endothelial cells (HUVECs) by increasing nitric oxide (NO) and endothelial nitric oxide synthase (eNOS) levels [23]. This effect is independent of a thermal mechanism [23] (Fig. 1). Nonetheless, the efficacy of FIR may be impeded by heat exposure. Hsu showed that short-wavelength FIRs (2–5.25 μm) transferred more heat and could increase the temperature of the culture medium, resulting in a decrease in the FIR-induced increase in the FIR biological index (FBI), namely thermal suppression or the inhibitory effect of heat [24].

3. Underlying principle of FIR therapy

Effective treatment with FIR requires an adequate dose of photon energy to penetrate the subcutaneous layer. This penetration allows the energy to act on the targeted tissue, eliciting the desired biological effect. To optimize the biological outcome, selecting the optimal therapeutic parameters is imperative, considering factors such as the appropriate wavelength range, ample power density, suitable irradiation time and distance, sufficient exposure frequency, and other relevant considerations [25].

According to an extensive literature review, The Arndt–Schulz law is typically applied to PBM using visible and NIR light (Fig. 2) [25]. Whether this applies to the FIR has not been confirmed in the literature. However, some studies have suggested that FIR increases mRNA expression in a time- and dose-dependent manner [15]. Theoretically, in cases where the energy produced by the FIR emitter is insufficient, there may not be enough photons to reach deeper tissue. Conversely, an excessive amount of energy has a suppressive effect. As the dose of FIR increases, it reaches its maximum response at a certain value. If the dose surpasses this maximum, the response diminishes, potentially leading to adverse or inhibitory effects.

4. Therapeutic parameters of FIR

Therapeutic parameters play a critical role in determining the effectiveness of FIR. However, the absence of standardized therapeutic parameters poses a challenge in selecting the most suitable FIR protocols [24]. These parameters, including wavelength, power density, irradiation duration and distance, treatment duration, energy, fluence,

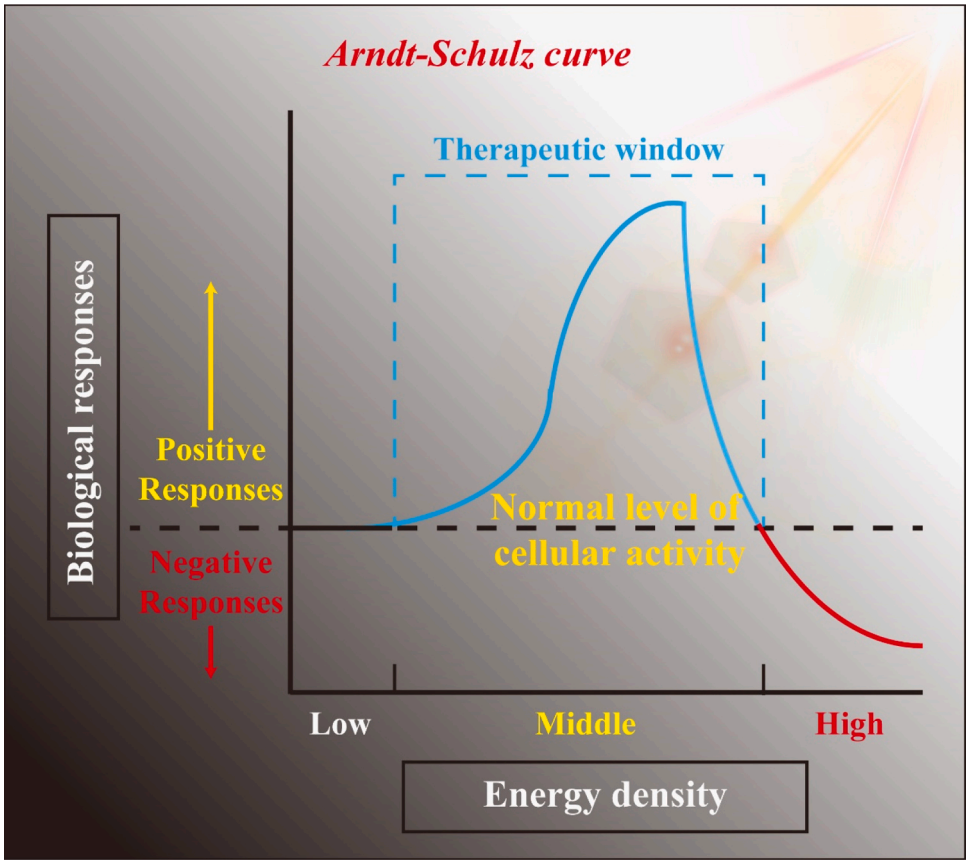

Fig. 2. The Arndt-Schulz curve. The Arndt-Schulz curve, characterized by a biphasic dose-response pattern, delineates the relationship between therapeutic stimulation, low-dose vitiation, and high-dose inhibition. Inadequate parameter selection may result in suboptimal or even adverse treatment outcomes.

irradiance, pulse mode, and repetition, significantly influence biological functions.

4.1. Categories of FIR emitters

Currently, FIR therapy primarily employs three main types of FIR emitters [26,27]. (1) FIR devices, consisting of electrified ceramic plates, provide low FIR energy to increase skin temperature steadily. Examples include the WS TY101 and TY301 FIR emitters (WS Far Infrared Medical Technology, Taipei, Taiwan, China) and the EEFit® Pen (Nick Wang Technology Ltd., Hong Kong, China) [3]. (2) FIR-emitting ceramics and fabrics, such as cFIR pads (Experimental Neuroscience Laboratory, University of Southern Santa Catarina, Brazil) [28], FIR patches (D.FENSTEC s.r.l. Altavilla Vicentina, Italy) [26], and FIR-emitting garments (Marketing of NILIT Fiber Division, © NILIT® Ltd., Italy) [17], are employed for local treatment to maintain the surface temperature below 40°C. These ceramics are typically produced using a blend of oxides, including magnesium, silica, aluminum, tourmaline, and mica. The garments are crafted from traditional textile fibers incorporated with ceramic particles and natural minerals with distinctive electromagnetic absorption and emission properties. These FIR-emitting materials absorb infrared radiation from the human body and re-emit it as radiative energy, reflecting it to the body without releasing any pharmacological substances. (3) FIR dry sauna therapy, often known as "Woan therapy," is also widely used. In this therapy, FIR rays directly heat the body without relying on air as a heat transfer medium.

4.2. FIR wavelengths

The wavelengths of various FIR light sources typically range from 3 to 25 μm, with most falling between 5 and 12 μm and a peak value around 8.2 μm. Cho's study used an FIR wavelength range of 1–20 μm, with a peak value of 4 μm, and achieved satisfactory therapeutic results [20]. Hsu developed a cell detection platform that measures the limits of FIR's biological effects through epithelial cell migration, finding that the most effective irradiation time for FIR is 30 minutes. The most biologically effective wavelength for FIR was found to be 8–10 μm [24]. Using a shorter wavelength (2–5.25 μm) of FIR can impede the therapeutic effects [24]. However, the FIR emitters available on the market apply high temperatures to generate high-intensity FIR, such as Wason therapy and FIR saunas, which may negatively impact the effects of the FIR.

4.3. FIR irradiation duration

Both time and dose play pivotal roles in determining the efficacy of FIR treatment. When the power density remains constant, the energy transmitted increases proportionally to the duration of irradiation [15]. A previous study indicated that FIR sessions typically last 30–60 minutes, most lasting approximately 30 minutes [7]. In a study by Hsu, different exposure times were examined, and a 30-minute exposure was deemed the most efficient for FIR treatment [23,24]. More prolonged exposure did not guarantee optimal FIR performance. Chen's findings suggest that 40 minutes of FIR can significantly increase blood flow in diabetic wound areas, resulting in a 70 % increase on day 8, promoting the healing process [29]. Jeong reported that 50 min of FIR irradiation can enhance the proliferation, survival, and migration of bone marrow-derived mesenchymal stem cells (BMSCs), resulting in a time-dependent increase in cell number [30]. The ideal duration of FIR irradiation varies across studies, and the optimal parameters should be determined based on particular research requirements. Chen proposed that selecting the most appropriate duration of irradiation may be more

effective in accelerating wound healing than controlling diabetes [29].

4.4. FIR irradiation distance

Regarding the irradiation intensity, the effective distance for FIR radiation penetration should be considered, as FIR light sources with different intensities require varying distances to achieve optimal therapeutic effects. Studies have used different irradiation distances, such as 20–40 cm and 3–4 cm, depending on the intensity of the FIR light source. Therefore, discussing the irradiation intensity of FIR light sources used when determining the appropriate irradiation distance is crucial. High-intensity FIR sources may be effective at longer distances (e.g., 20–40 cm), while lower-intensity sources might require shorter distances (e.g., 3–4 cm) to ensure sufficient energy delivery to the target tissue. However, little literature specifically discusses the irradiation intensity of FIR transmission devices. Therefore, this review only summarizes irradiation distances based on different FIR light sources [24].

The literature commonly cites the optimal distance as ranging between 20 and 30 cm, with a preference for the latter. Sharma suggested that under typical experimental conditions, the recommended distance for irradiation is 40 cm, accompanied by a wavelength range of 5–20 μm and strict control over the surface temperature [27]. This approach allows the e biological effect of FIR to be exerted without inducing side effects. Several studies indicate that in comparison to irradiation at a distance of 30 cm (33.5–35.2 °C), achieving a thermotherapeutic impact can be accomplished by reducing the irradiation distance to 20 cm while maintaining the skin temperature at 37.5–38.3 °C [7] or 38–39 °C [31]. In addition, the FIR was found to peak at an adequate intensity ranging from 0.07–0.13 mW/cm^2 at distances ranging from 3–4 cm [24].

At the cellular level, it is advisable to determine the therapeutic parameters of FIR, including effective wavelength, power density, irradiation time, and distance [24]. Hwang proposed the detailed parameters and an experimental design for the cell model (Table 1) [10]. The cells were cultured in a 60 mm dish with 4 mL of culture medium and positioned 30 cm below the FIR emitter. The wavelength range is 3–25 μm, with a peak value of 7.5 μm. According to the experimental specifications, the culture plates were incubated for the appropriate duration following FIR intervention. For animal studies, the animals were subjected to FIR radiation at a distance of 30 cm below the emitter with a wavelength range of 3–25 μm, a peak value of 5–7 μm, and a functional density of 50 mW/cm^2 *in vivo* (Table 2) [32]. Irradiation was administered for 30 minutes thrice daily over an FIR treatment course of 7 weeks. In clinical trials, the affected skin surface was exposed to an FIR radiator at a distance of 30 cm, with a functional density of 10 mW/cm^2, a wavelength range of 5–12 μm, a peak value of 8.2 μm, and an irradiation duration of 40 minutes (Table 3) [33].

Although the therapeutic parameters summarized in Fig. 3 may be suitable for specific treatments, the parameter scheme should be dynamically adjusted based on the particular diseases, treatment requirements, and FIR light sources.

5. *In vitro* mechanisms of FIR

The mechanisms of FIR remain unclear. Its mechanisms rely on the shared characteristics of living cells, such as the presence of mitochondria and the need for energy to operate. Additionally, cells possess specific repair mechanisms governing gene expression, which dynamically regulate their phenotype in response to environmental changes. While the FIR has universal mechanisms in organisms, it executes various pathways, resulting in varied effects due to the heterogeneity of cells, tissues, and organisms (Fig. 4) (Tables 4, 5, 6) [26].

5.1. Biological behaviors of cells

Studies suggest that FIR may influence cellular activity by altering the cell membrane potential, modifying mitochondrial metabolism, or regulating the active functions of crucial dynamic cellular proteins [10, 17,22]. FIR can promote epithelial cell proliferation, migration, and apoptosis [24]. The literature has shown that FIR can enhance the viability and functional characteristics of rabbit renal proximal tubular cells (RPTCs), promote cell proliferation and differentiation, and mitigate cisplatin-induced renal toxicity by reducing cell apoptosis [34]. Under hypertonic injury, cellular apoptotic cell death was induced in HaCaT cells. FIR can suppress apoptosis by acting on the *PI3K/Akt* pathway, and its protective effect may not occur at the transcriptional level [14]. Furthermore, its mechanism is potentially linked to the activation of CXCR4 and ERK to enhance the biological behaviors of cells [30]. Jeong pretreated BMSCs with FIR and found that FIR could activate the *Akt/mTOR* pathway and increase the expression of MITF-BCL2-HIF-1α, which is required for cell survival [35]. In addition, 50 min of FIR preconditioning of conditioned medium (CM)-derived BMSCs increases cellular resilience and adaptation to extreme environmental conditions *in vitro* [35].

Not all studies have demonstrated that FIR preconditioning promotes proliferation. Some findings indicate that FIR inhibits VEGF-induced proliferation in HUVECs and platelet-derived growth factor (PDGF)-stimulated VSMC proliferation [23,36]. Similarly, FIR was found to have an inhibitory effect on the phosphorylation of ERK1/2, peaking after 30 minutes of exposure and gradually decreasing with longer exposure times, consistent with the findings of Hwang. [23]. Exposure to FIR radiation for 60 minutes does not affect the viability of HUVECs; however, it inhibits the proliferation, migration, and angiogenesis of HUVECs in a time-dependent manner [10].

The antiproliferative effects of FIR on cancer cells involve a decrease in cell proliferation and colony formation rather than an increase in cell death. FIR can activate Chk2, inhibiting cancer cell proliferation by increasing nuclear Ca^{2+}/CaM binding, even without DNA damage [20]. Regulation of HSP-70A protein expression has been implicated in the inhibitory effect of FIR on cancer cells [37]. FIR-mediated programmable anticancer gene delivery and photodynamic therapy can increase p53 expression levels for anticancer gene theranostics [38,39]. FIR reduces the viability of MCF-7 cells, achieving maximum cytotoxicity at an exposure of 3.6 μm [40]. At the same time, other studies have shown that FIR does not affect the viability, proliferation, cell cycle, or apoptosis of fibroblast, MCF-7, and MDA-MB-231 cells [41].

5.2. Anti-inflammatory properties

FIR can regulate pro- and anti-inflammatory cytokine levels to exert anti-inflammatory effects. Through the inhibition of tumor necrosis factor (TNF)-α-mediated expression of E-selectin, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and interleukin (IL)-8, FIR therapy may have a potent anti-inflammatory impact on the vascular endothelium [42]. These inflammatory factors are the critical components involved in the induction of inflammatory responses and mediate leukocyte-endothelial interactions. FIR can also alleviate lipopolysaccharide (LPS)-induced acute respiratory distress syndrome (ARDS) in rats, and its functional mechanisms are linked to its ability to mitigate lung inflammation by modulating the Hp protein [43]. In addition, FIR can significantly reduce the inflammatory response induced by hemodialysis (HD) alone by inducing autophagy and inhibiting NLRP3 inflammasome activity [44,45]. For example, single sessions of HD-induced inflammatory responses, including increases in hypersensitive C-reactive protein, soluble ICAM-1, and soluble VCAM-1, are significantly suppressed by FIR therapy [45].

Inflammation is intricately connected to oxidative stress. Based on this thermal effect, FIR can increase the mRNA and protein expression of heme oxygenase-1 (HO-1) in a time-dependent manner. This process is regulated by signaling pathways such as the *p38 MAPK, PI3K/Akt*, and *Nrf2-ARE* [45,46]. The duration of FIR irradiation also affects the expression of HO-1, an inducible enzyme with anti-inflammatory,

Table 1
Therapeutic parameters of FIR *in vitro*.

Ref	Emitter	Country	Source cells	Wavelength range (μm)	Time (min)	Power (mW/cm^2)	Frequency	Incubation	Culture medium	Distance (cm)
Hwang 2014 [10]	Ceramic infrared radiator	Northeim, Germany	HUVECs	3–25 (7.5)	0, 30, 60	0.65, 25.3 kW/m^2	1	0, 24, 48 h	4 mL/ 60 mm	30
Hsu 2019 [24]	PDA−3258 FIR emitter ceramic full-wavelength FIR generator	Taiwan, China	RTECs	1–25	15, 30, 45, 60	0.03–0.13	1	NA	1 mL/24 plate	2, 3, 4, 5, 6
Wang 2019 [22]	WS TM TY301 FIR emitter	Taiwan, China	Neuron-like PC12 cells	5–12 (8.2)	30	3.1	1	1, 3, 5, 7 d	NA	20
Rau 2011 [55]	WS TM TY301 FIR emitter	Taiwan, China	Human microvascular ECs	5–12 (8.2)	0, 15, 30, 60, 120	NA	1	24, 48, 72 h	10 cm	20
Chen 2022 [54]	WS TY101 FIR emitter	Taiwan, China	HUVECs	NA	30	0.13	2/d	30 min	NA	20
Chiang 2017 [34]	WS TY301 FIR emitter	Taiwan, China	RPTCs	3–25	30	NA	1/d	2, 4, 6 8 d	24 plate	30
Chang 2016 [48]	WS TY301 FIR emitter	Taiwan, China	SK-N-SH cell line	3–25 (5−7)	10	NA	3/d	3 d	NA	20
Tsai 2020 [52]	WS TY101 FIR emitter	Taiwan, China	ECFCs	3–25 (5)	40	10	1	24 h	4 mL	30
Ishibashi 2008 [37]	FIR culture incubator	Tokushima, Japan	Human cancer cell lines (A431, HSC3, Sa3, A549, and MCF7)	4–20 (7−12)	60	4, 11.6	1/d	4, 8 d	6 mL/ 10 cm	NA
Park 2013 [19]	S-O.T.M 9 H FIR radiator	Bucheon, Korea	BAECs	6–20	0, 10, 20, 30, 40	NA	1	1 h	60 mm	30
Hwang 2023 [36]	IOT/90–250 ceramic infrared radiator	Northeim, Germany	VSMCs	1–20 (4)	0, 15, 30, 45	65, 2350	1	24 h	3 mL/ 60 mm	20–30
Kim 2019 [18]	IOT/90–250 ceramic infrared radiator	Northeim, Germany	TMSCs	3–25 (7.5)	0, 30, 60	NA	1	18, 24, 48 h, 14 d	4 mL/ 60 mm	30
Chen 2012 [14]	WS TY101 FIR emitter	Taiwan, China	Human keratinocyte cell line HaCaT	3–25 (5−6)	40	16.5	1	20, 22, 24, 26 h	10 cm	25
Wang 2016 [53]	WS TM TY301 FIR emitter	Taiwan, China	ECFCs	5–12 (8.2)	30, 40, 60	NA	1	24 h	NA	30
Jeong 2017 [30]	WS TY101N FIR emitter	Taiwan, China	BMSCs	3–25 (8.2)	0, 10, 20, 30, 40, 50, 60	10, 20	1	3 d	6 plate	30
Kim 2021 [58]	IOT/90–250 ceramic infrared radiator	Northeim, Germany	TMSCs	3–25 (7.5)	30	NA	1	14 d	NA	30
Cho 2021 [20]	IOT/90–250 ceramic infrared radiator	Northeim, Germany	MDA-MB−231 breast cancer cells	1–20 (4)	0, 15, 30	NA	1	24 h, 5 d, 7 d	3 mL/ 60 mm	20–30
Chiu 2017 [89]	WS TM TY301 FIR emitter	Taiwan, China	NIH 3T3 mouse embryonic fibroblasts	3–25	30	0.13	1	6, 12, 24, 48 h	3 mL/ 60 mm	NA
Hsu 2012 [23]	WS TM TY301 FIR emitter	Taiwan, China	HUVECs	3–25 (10)	15, 30, 60, 90	0.13, 0.8, 1.8, 7.2	1	1, 8 h	3 mL/ 60 mm	NA
Lin 2022 [68]	Electrified ceramic plates FIR emitter	Taiwan, China	Human EPCs	3–25	40	4.95–8.26, 11.7–19.5	3/d	5 d	NA	20
Seo 2021 [51]	FIR fabric samples	Seoul, Korea	Rat skeletal muscle L6 cells	5–20	NA	3.45 × 102 W/m^2 μm	1	24, 72 h	NA	1
Lin 2015 [5]	WS TY101 FIR emitter	Taiwan, China	Human EPCs, ECFCs	3–25 (5−6)	30	NA	1	45 min	NA	25
Hsu 2020 [2]	PDA−3258 FIR emitter	Taiwan, China	RIN-m5f cells	8–10	30, 60	0.13	1	24 h	NA	20
Chiu 2016 [44]	WS TY301 FIR emitter	Taiwan, China	THP−1 cells	3–25	10, 20, 30	0.13	1	1, 3, 24 h	3 mL/ 60 mm	NA
Li 2017 [41]	Independently-development	Shanghai, China	Fibroblasts, MCF−7 and MDA-MB231	6–14	60	NA	1/d	7 d	9 cm	30

Note: RTECs: renal tubular epithelial cells

Table 2
Therapeutic parameters of FIR *in vivo*.

Ref	Emitter	Country	Animal model	Wavelength range (μm)	Time (min)	Power (mW/cm^2)	Frequency	Course of treatment	Distance (cm)
Luo 2021 [43]	Junfeng BFS treatment & healthcare device JF−802	Beijing, China	LPS-induced ARDS rat	NA	30	NA	1/d	7 d	NA
Liu 2019 [32]	WS TY301 FIR emitter	Taiwan, China	Spinocerebellar ataxia type 3 mice	3–25 (5−7)	30	50	3/d	7 m	30
Khan 2020 [57]	EEFit® Pen	Hong Kong, China	Normal mice (Gut microbiota)	4–20	2	NA	5/d	25 d	2
Kimura 2018 [80]	Carbon massager	Kyoto, Japan	Oral mucosal injury rat	5–20	3	NA	1/d	1, 3, 7 d	0
Hsu 2020 [2]	WS TY101 FIR emitter	Taiwan, China	STZ/NA-induced diabetic mice	8–10	30	0.13	1/d	1, 2 w	20
Chen 2022 [3]	EEFit® Pen	Hong Kong, China	AIA rat	4–20	3, 30	NA	1/d	27 d	2
Tu 2013 [46]	WS TY101 FIR emitter	Taiwan, China	Ischemia/reperfusion injury in rat testis	5–12 (8.2)	30	NA	1/d	1 d	25
Li 2022 [4]	JF−802 FIR light emitter	Guangdong, China	Alzheimer's disease-like mice	3–25	60	0.13	1/d	1.5 m	NA
Chui 2016 [44]	WS TY301 FIR emitter	Taiwan, China	Deep second-degree burn rat	3–25	30	0.13	1/d	10 d	NA
Toyokawa 2003 [77]	Ceramic-coated sheet FIR source	Kobe, Japan	Full-thickness skin wound rat	5.6–25 (8−12)	NA	NA	1/d	4, 7, 12, 14 d	40
Hsu 2017 [76]	WS TY101 FIR emitter	Taiwan, China	Full-thickness skin wound rat	3–25 (10)	30	0.13	1/d	8 d	NA
Mai 2018 [64]	i-ONE FILM FIR panel	Gyeonggi-Do, Korea	PKCδ mediates MA-induced recognition memory impairment in mice	5–20	20, 40	NA	1/d	14 d	40
Mai 2018 [50]	i-ONE FILM FIR panel	Gyeonggi-Do, Korea	MA-induced behavioral sensitization and neurochemical changes in mice	5–20	20	NA	1/d	20 d	40
Chen 2021 [29]	WS TY301 FIR emitter	Taiwan, China	Full-thickness wound rat	5–12 (8.2)	20, 40	0.13	3/w	4 w	20
Mai 2018 [63]	i-ONE FILM FIR panel	Gyeonggi-Do, Korea	MA-induced impairment mice	5–20	40	NA	1/d	14 d	40
Tran 2016 [65]	i-ONE FILM FIR panel	Gyeonggi-Do, Korea	Acute restraint stress mice	5–20	20	NA	2/d	5 d	40
Chen 2017 [87]	WS TY101 FIR emitter	Taiwan, China	STZ-induced diabetic mice	3–25 (10)	30	0.13	1/d	1, 2 w	NA
Chen 2022 [54]	WS TY101 FIR emitter	Taiwan, China	Cisplatin-induced vascular injury and endothelial cytotoxicity/dysfunction mice	3–25 (10)	30	0.13	1/d	1,2, 3 d	20

antioxidant, and neuroprotective properties. Moreover, the upregulation of HO-1 expression stimulates fibroblasts and endothelial cells (ECs) to scavenge pro-oxidative iron and produce CO products, exerting anti-apoptotic effects. Therefore, HO-1 plays a pivotal role in the protective mechanisms of FIR postconditioning in living organisms [46].

5.3. Antioxidative stress

Endothelial damage, a precursor to numerous chronic diseases, is intimately linked to oxidative stress. Several studies have shown that FIR effectively regulates HO-1, NO, and eNOS levels to enhance antioxidative activity [27,47]. FIR induces antioxidative stress through the following pathways: (1) FIR upregulates HO-1 to cleave heme into bilirubin and carbon monoxide. Both potent antioxidants improve redox reactions and reduce oxidative stress [46]. (2) FIR upregulates eNOS expression to promote NO production and increase NO bioavailability, thereby improving endothelial function [27].

Current investigations commonly involve cell cultures exposed to a high-glucose environment to induce oxidative stress. This leads to heightened reactive oxygen species (ROS), diminished NO bioavailability, and reduced phosphorylated eNOS levels. FIR has emerged as a countermeasure against this oxidative stress state induced by high glucose [21]. In this context, FIR triggers the eNOS and Akt pathways, elevates eNOS phosphorylation, and promotes NO production. Accordingly, FIR can reduce cellular aging, improve cellular function, and promote cell proliferation. FIR facilitates the homing of endothelial progenitor cells (EPCs), contributing to improved blood flow status and encouraging new blood vessel formation [21]. Furthermore, FIR inhibits VEGF-induced proliferation through eNOS-mediated NO generation, VEGF-induced ROS generation, and VEGF-induced ERK1/2 phosphorylation [23]. FIR exposure induces the nuclear translocation of PLZF, which is correlated with increased PI3K expression. This increase in PI3K activates Akt, leading to eNOS phosphorylation and NO generation in HUVECs [23]. In addition, FIR therapy can induce HO-1 mRNA expression by activating the NF-E2-related factor 2/antioxidant responsive element complex [45]. Elevated antioxidant and HO-1 expression efficiently neutralizes ROS, detoxifies toxic chemicals, and reduces ROS-mediated activation of the *NF-κB* pathway. This, in turn, attenuates the activation of type I protein arginine methyltransferases by increasing shear stress.

5.4. Mitochondrial function

Mitochondria, pivotal for FIR-induced effects, are crucial in metabolism and energy production [24]. FIR regulates diverse cellular processes, including proliferation, migration, apoptosis, calcium signaling,

Table 3
Therapeutic parameters of FIR *in clinical trials*.

Ref	Emitter	Country	Disease	Wavelength range (μm)	Time (min)	Power (mW/cm^2)	Frequency	Course of treatment	Distance (cm)
Lin 2015 [33]	WS TY101N FIR emitter	Taiwan, China	Healthy subjects	5–12 (8.2)	40	10	1/d	0	40
Li 2018 [90]	Independently-development	Shanghai, China	Chronic extremity lymphedema	6–14	2 h	NA	1/d	20 d	75
Li 2017 [8]	Independently-development	Shanghai, China	Lymphedema in stage II and III	6–14	2 h	NA	1/d	20 d	75
Huang 2019 [86]	Firapy WS™ Far infrared Therapy unit	Taiwan, China	Perineal wound pain and sexual function in primiparous women	NA	40	160 W	2/d	3 d	30
Chen 2016 [74]	WS TY101 FIR emitter	Taiwan, China	Patients on HD with PAOD	5–12 (8.2)	40	NA	3/w	6 m	25
Lai 2013 [16]	WS TY101N FIR emitter	Taiwan, China	Percutaneous transluminal angioplasty patients	5–12 (8.2)	40	10, 20	3/w	NA	20, 30
Cheng 2020 [73]	Electrothermal heating far-infrared pad	Taiwan, China	Diabetics	NA	30	NA	3/w	3 m	0
Yoon 2020 [82]	Aladdin-H® FIR radiator	Seongnam, Korea	Arthroscopic RCT	2–25	30	NA	2/d	4 w	30–35
Peng 2020 [7]	WS TY101F FIR emitter	Taiwan, China	Healthy adults over 50 years of age	3–25	40	20	1/d	0	20
Chang 2022 [60]	WS TY301 FIR emitter	Taiwan, China	PD patients	3–25 (8)	40	NA	1/d	6 m	25
Chang 2021 [61]	WS TY101 FIR emitter	Taiwan, China	Diabetic patients with PD	3–25	40	20	2/d	6 m	20
Chen 2022 [42]	WS TY101N FIR emitter	Taiwan, China	Patients with advanced DKD	3–25 (5−6)	40	10	3/w	12 m	25
Li 2017 [41]	Independently-development	Shanghai, China	Breast cancer-related lymphedema	6–14	60	NA	1/d	20 d	75
Choi 2016 [84]	WS TY101N FIR emitter	Taiwan, China	HD patients	3–25 (5−6)	40	10, 20	3/w	12 m	20, 30
Lin 2013 [71]	WS TY101N FIR emitter	Taiwan, China	AVF maturation patients	3–25 (5−6)	40	10, 20	3/w	12 m	20, 30

and the enhancement of mitochondrial function and autophagy status [24,44,48]. For instance, in a cellular model of spinocerebellar ataxia, FIR showed its protective effect by preventing polyQ protein accumulation and facilitating the recovery of mitochondrial function and autophagy induction, ultimately preserving cell viability [48]. Mitochondrial function, a pivotal determinant, influences cell migration [49]. FIR is associated with mitochondrial-mediated cell migration, as evidenced by the upregulation of the protein expression of Drp1 (a mitochondrial fission-related protein) 60 minutes after FIR irradiation and the subsequent downregulation of the expression of Mfn2 (a mitochondrial fusion-related protein) 2 hours after irradiation [24]. Remarkably, FIR significantly amplified the ratio of the enhanced migrating area to the control migrating area. In addition, mitochondrial complex I activity and the NAD^+/NADH ratio were also increased by FIR irradiation. FIR can positively regulate the activity of mitochondrial GPx-1, SOD-2, and mitochondrial complex I. Additionally, FIR elevates mitochondrial transmembrane potential and intramitochondrial Ca^{2+} levels, collectively enhancing mitochondrial function [50]. In the skeletal muscle cells of rats, FIR contributes to mitochondrial biogenesis and promotes GLUT3 expression under low glucose conditions, with a notable increase in Pgc-1a expression after 72 hours of treatment with 30 % of FIR containing bioactive material-coated fabric, particularly in the presence of GLUT3 [51].

Seo's findings suggested that FIR enhanced skeletal muscle oxidative respiration efficiency by activating PINK1-mediated mitochondrial quality control and biogenesis. This finding highlights the significant role of FIR in addressing glucose-deficient metabolic conditions, which are particularly relevant to disorders such as type 2 diabetes and mitochondrial dysfunction [51]. FIR has emerged as a potential regulator of pancreatic islet function in diabetes, with mechanisms rooted in inhibiting apoptosis and promoting insulin secretion. Furthermore, FIR can upregulate beta-cell mitochondrial function and mediate the Sirt1 pathway, thereby reducing pancreatic islet damage and promoting insulin secretion. The upregulation of PLZF by FIR further contributes to its antiapoptotic effects [2].

5.5. Angiogenesis

FIR contributes to the vascular repair and regeneration [29,52,53]. FIR can ameliorate angiogenesis and apoptosis by regulating the *PLZF/PI3K/Akt/HIF-1α/VEGF* pathway. It further promotes the induction of HIF-α and the expression of VEGF in cisplatin-treated HUVECs [54]. FIR can stimulate angiogenesis *in vitro* by activating *MEK/ERK* without affecting the viability of HUVECs [55]. FIR can reduce both basal and PDGF-stimulated vascular smooth muscle cell (VSMC) proliferation by inhibiting the AMP-activated protein kinase (AMPK)-mediated *mTOR/p70S6K* pathway [36]. Furthermore, FIR can improve the function of endothelial colony-forming cells (ECFCs) and augment angiogenic activity *in vitro* by downregulating the expression of miR-548aq-3p and miR-134 and upregulating the expression of NRIP1.

FIR promotes angiogenesis by up-regulating the expression of NO and eNOS [47]. Both NO and eNOS mediate vasodilation, enhancing blood flow and oxygenation. FIR induces an acute increase in NO production by elevating Ca^{2+} mobilization and facilitating

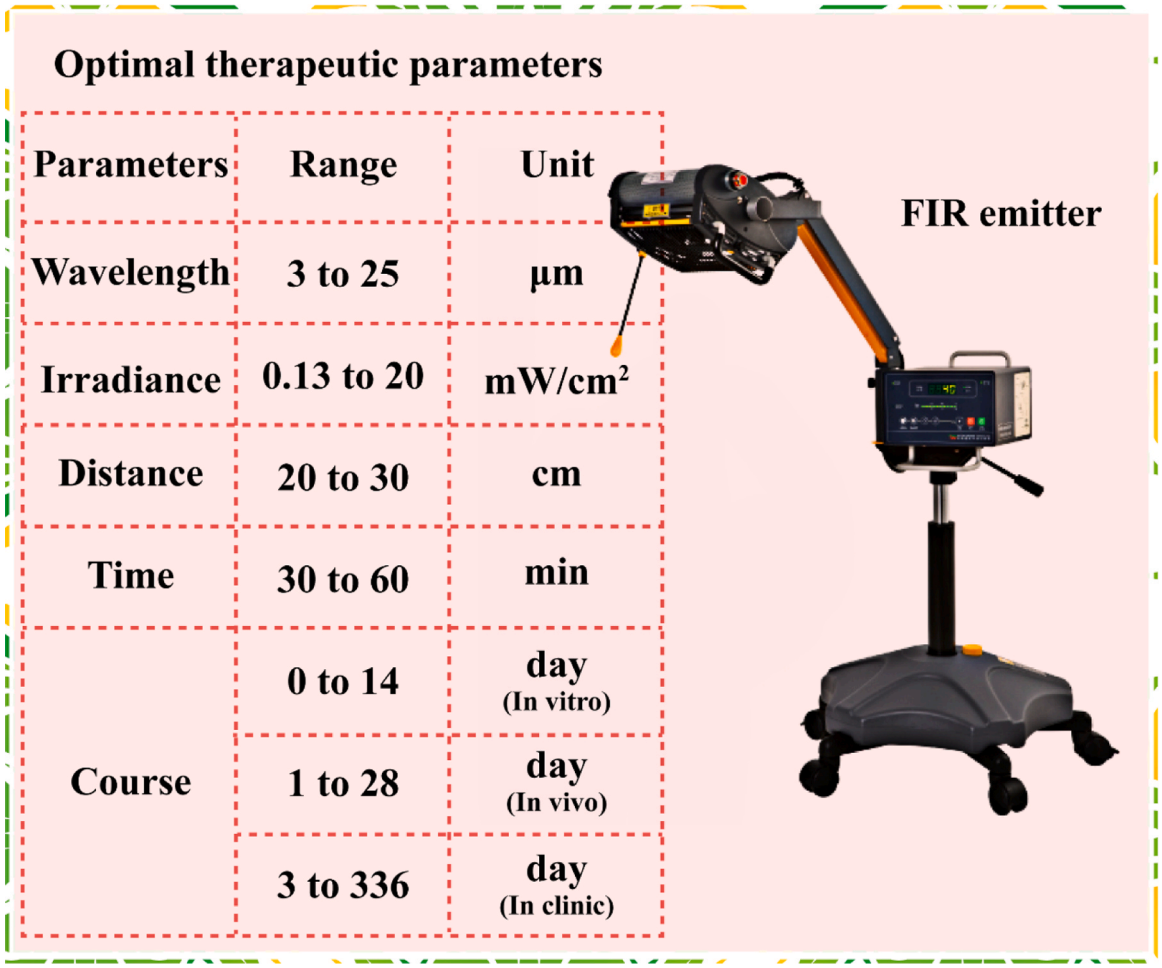

Fig. 3. The therapeutic parameters in cellular, animal, and clinical studies vary. Several parameters must be specified for each disease process, including wavelength, power density, exposure time, and distance.

Ca^{2+}/CaM-dependent protein kinase II (CaMKII)-mediated phosphorylation of eNOS at serine 1179 in bovine aortic endothelial cells (BAECs) [19]. In addition, FIR can improve endothelial function and prevent stenosis of damaged vessels, which is associated with eNOS induction [56].

However, other studies have shown that FIR radiation can stimulate the expression of p53 and reduce the expression of secretory clusterin (sCLU), thereby inhibiting angiogenesis in HUVECs [10]. This inhibition is not attributed to the thermal effect of FIR [10]. These findings suggest that sCLU may mediate the inhibitory effects of FIR on EC angiogenesis under both physiological and pathological conditions.

5.6. Other mechanisms

FIR can activate G-protein coupled receptors (GPCRs) and facilitate changes in the gut microbiota. The intestines of FIR-irradiated mice predominantly express short-chain fatty acids (SCFAs), and the expression of SCFA-sensing GPCRs is up-regulated in the intestinal mucosa of these mice [57]. FIR plays a pivotal role in cellular differentiation processes. Kim reported that FIR inhibited adipogenic differentiation and promoted osteogenic differentiation in tonsil-derived mesenchymal stem cells (TMSCs). The inhibitory effect on adipogenic differentiation is caused by the non-thermal impact, which is mediated, at least in part, by the Ca^{2+}-dependent activation of PP2B [18]. Kim also reported that FIR can activate the transient receptor potential vanilloid (TRPV)2 channel, increasing intracellular Ca^{2+} levels. This activation inhibits adipogenic differentiation, while osteogenic differentiation remains unaffected by the TRPV2 channel [58].

Furthermore, FIR facilitated nerve regeneration in a dose-dependent manner [22]. In NGF-treated neuron-like PC12 cells, FIR promoted neurite outgrowth and nerve regeneration, possibly by activating AKT1 phosphorylation. These findings underscore the diverse impacts of FIR on cellular processes and highlight its potential therapeutic applications in various biological contexts.

6. Preclinical and clinical applications of FIR in regenerative medicine

FIR has shown therapeutic effects in several cellular and animal models and has been applied to treating several types of diseases, including cardiovascular disease, diabetes, and chronic kidney disease (CKD), in clinical trials. Despite these advancements, the precise mechanism of action of FIR has not been fully elucidated. The diverse biological effects of FIR intricately interact and synergistically contribute to therapeutic outcomes across a spectrum of diseases (Fig. 5). FIR exhibits substantial anti-inflammatory properties, rendering them valuable for the treatment of conditions characterized by inflammatory responses, such as peritonitis and rheumatoid arthritis. On the other hand, FIR can promote angiogenesis; therefore, it may also contribute to treating cardiovascular and angiogenesis-related diseases.

6.1. Inflammatory diseases

FIR can exert anti-inflammatory properties and immune regulation

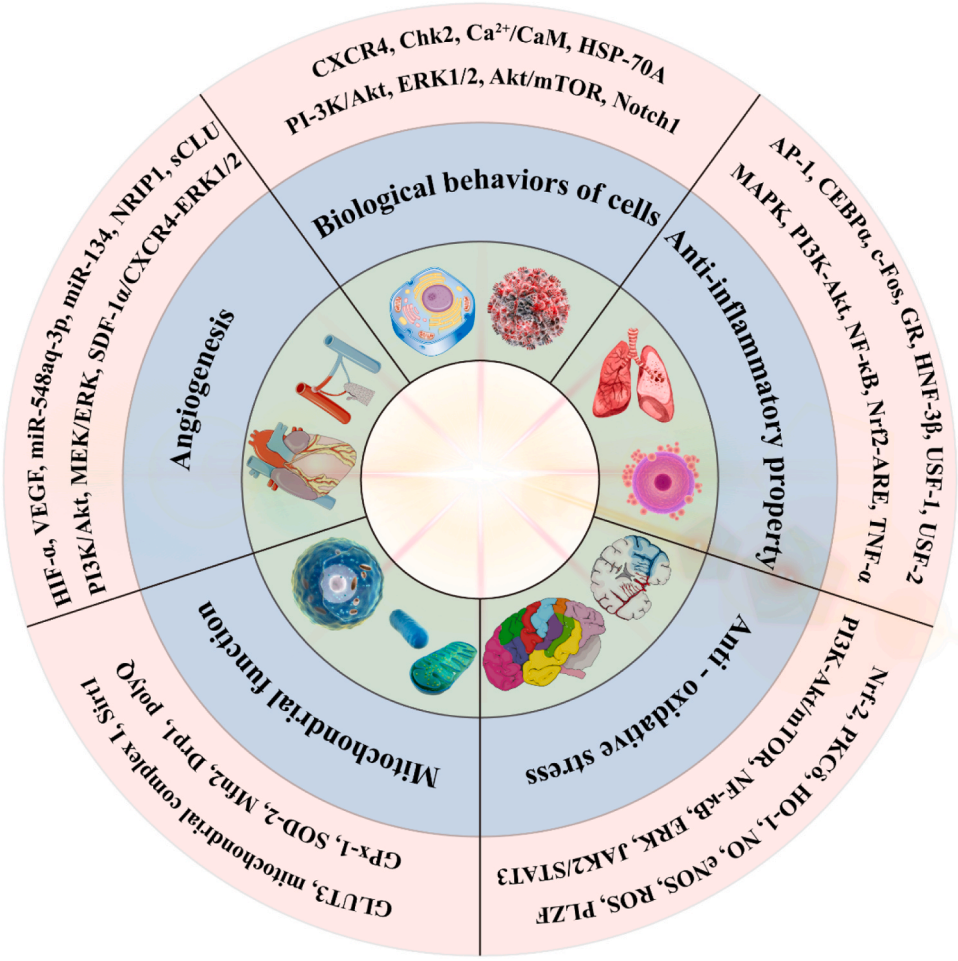

Fig. 4. Schematic illustration of the multiple mechanisms and possible molecular pathways of FIR. FIR involves five significant mechanisms: influencing the biological behaviors of cells, exerting anti-inflammatory effects, mitigating oxidative stress, enhancing mitochondrial function, and promoting angiogenesis.

and significantly improve the inflammatory manifestations of adjuvant-induced arthritis (AIA) rats after 27 days [3]. Mechanistic studies revealed that FIR markedly suppressed the transcription factors AP-1, CEBPα, CEBPβ, c-Fos, GR, HNF-3β, USF-1, and USF-2, inactivating the *MAPK, PI3K-Akt,* and *NF-κB* signaling pathways, and thereby downregulating the expression of inflammatory genes in the synovial tissue of AIA rats. Intriguingly, FIR-treated AIA rats exhibited positive bone-protective effects, suggesting a potential application in bone tissue regeneration. In a model of complete Freund's adjuvant-induced inflammatory hyperalgesia, FIR demonstrated anti-inflammatory and antihyperalgesic effects by inhibiting the release of proinflammatory factors such as TNF-α and IL-1β, along with suppressing the activation of peripheral receptors for opioids, cannabinoids, and adenosine [28]. In addition, studies have indicated that FIR increases the levels of endogenous IL-10, a recognized anti-inflammatory and immunosuppressive factor. Moreover, FIR downregulates the expression of proinflammatory cytokines (IL-1β and IL-6) and haptoglobin (HP) and, therefore, alleviates systemic inflammatory responses characterized by reduced inflammatory cell infiltration and alveolar collapse [43].

FIR also inhibits the inflammatory response in mice with peritonitis by downregulating the expression of inflammatory factors such as IL-6 and TNF-α and upregulating IL-12 expression [59]. For instance, patients with peritoneal dialysis (PD) improved after adjuvant treatment with FIR for six months [60,61]. Furthermore, compared with PD alone, FIR decreased the levels of glucose degradation products (GDPs) and increased the peritoneal Kt/V and eGFR of peritoneal function by improving the peritoneal transport rate and solute removal clearance, resulting in the maintenance of adequate dialysis. These improvements in peritoneal function are attributed to an enhanced peritoneal transport rate and solute removal clearance, ultimately contributing to the maintenance of dialysis adequacy.

6.2. *Nervous system diseases*

Sharma and his team members described the protective mechanisms underlying FIR-mediated antioxidative stress in individuals with psychotic disorders, including but not limited to sleep disorders, depression, anxiety, and parasympathetic activity [11,27,62]. For instance, exposure to FIR ameliorated neuropsychiatric disorders via the induction of anti-inflammatory, antioxidative, antidopaminergic, and cholinergic effects through the modulation of the GPx-1, eNOS, JAK2/STAT3, Nrf-2, PKCδ, dopamine D1 receptor, M1 mAChR, and ERK1/2 pathways. In addition, FIR can also inhibit PKCδ phosphorylation, increase Nrf-2-dependent GSH induction, upregulate ERK-dependent M1 mAChRs, mediate cross-regulation among the M1 mAChRs, Nrf2, and ERK1/2 pathways, and ultimately attenuate methamphetamine (MA)-induced memory dysfunction [63,64]. On the one hand, FIR can enhance the antioxidative effect of MA-induced GPx-1, ameliorate mitochondrial dysfunction, and downregulate dopamine D1 receptor expression and oxidative stress, thereby restoring mitochondrial function and inactivating D1 receptors. This prevents MA-induced M1 mAChR downregulation and associated cognitive dysfunction [50,63]. On the other hand, the memory-enhancing effect mediated by FIR is comparable to the protective potential mediated by the antipsychotic

Table 4
Outcomes of FIR *in vitro*.

Ref	Underlying Diseases	Cell Type	Protective Effect	Molecular Parameters	Outcome
Hwang 2014 [10]	Angiogenesis-related disease	HUVECs	Anti-angiogenesis	sCLU ↓ p53 ↑	**Time-dependent manner.** FIR inhibits HUVEC proliferation, migration, and angiogenesis through suppression of sCLU levels
Hsu 2019 [24]	NA	RTECs	Mitochondrial function	FBI ↑ Drp1 ↑ Mfn2 ↓	FIR promotes epithelial cell migration through the upregulation of mitochondrial function.
Wang 2019 [22]	Nervous system disease	Neuron-like PC12 cells	Neurite outgrowth	AKT1 ↑ NFM, SYN1, SYP ↑	**Dose-dependent manner.** FIR promotes neurite outgrowth through the *AKT1* pathway.
Rau 2011 [55]	Dermal diseases	Human microvascular ECs	Angiogenesis	p38, ERK ↑	FIR promotes angiogenic activity through the *MEK/ERK* pathway.
Chen 2022 [54]	Cisplatin-induced vascular damage and impaired angiogenesis	HUVECs	Angiogenesis Specifically target EC	PI3K, Akt, HIF−1α, VEGF ↑	FIR attenuates cisplatin-induced vascular damage and impaired angiogenesis by activating HIF−1α-dependent processes regulating PLZF and PI3K/Akt.
Chiang 2017 [34]	Cisplatin-induced nephrotoxicity	RPTCs	Biological behaviors of cells	ATPase Na+/K+ subunit alpha 1 and glucose transporter 1 ↑ CDK5R1, GNAS, NPPB, and TEK ↑	FIR promotes cell proliferation and functional properties and protects against the nephrotoxicity induced by cisplatin.
Chang 2016 [48]	Neurodegenerative disease spinocerebellar ataxia type 3	SK-N-SH cell line	Mitochondrial function	OPA1, MFN2 ↑ Drp1 ↓ Beclin−1, LC3-II, ATXN3 ↑ P62 ↓	FIR has rescuing effects in cells expressing mutant pathogenic ataxin−3 by restoring mitochondrial function and autophagy.
Tsai 2020 [52]	Coronary artery disease	ECFCs	Angiogenesis	miR−548aq−3p ↓ ATP11A, BHLHB9, BTBD9, DSTYK, PHF8, and SLC7A2 ↑	FIR improves ECFC function through the down-regulation of miR−548aq−3p.
Ishibashi 2008 [37]	Cancer	Human cancer cell lines (A431, HSC3, Sa3, A549, and MCF7)	Biological behaviors of cells	HSP 70 A ↑	FIR inhibits the proliferation of cancer cells through the regulation of HSP 70 A.
Park 2013 [19]	Coronary heart disease	BAECs	Anti-oxidative stress	Ca^{2+} ↑ CaMKII, eNOS, Ser 1179, NO ↑	**Time-dependent manner.** FIR increases NO production via an increase in CaMKII-mediated eNOS Ser1179 phosphorylation.
Hwang 2023 [36]	Cardiovascular disease	VSMCs	Biological behaviors of cells	p-mTOR, p70S6K, ATP ↓ p-AMPK ↑	FIR decreases PDGF-stimulating VSMC proliferation via the AMPK-mediated inhibition of mTOR/p70S6K.
Kim 2019 [18]	Body fat in obese patients and repairs bone defects	TMSCs	Inhibition of adipogenic differentiation and promotion of osteogenic differentiation	PPARγ, FABP4 ↓ osteocalcin, ALP ↑	**Time-dependent manner.** FIR inhibits adipogenic differentiation by activating Ca^{2+}-dependent PP2B but enhances osteogenic differentiation of TMSCs.
Chen 2012 [14]	Dermal diseases	Human keratinocyte cell line HaCaT	Biological behaviors of cells	p-ERK 1, p-ERK 2, p-Akt ↑ Bax ↓	FIR stimulates the PI−3 K/AKT pathway and reduces BAX expression in cultured keratinocytes stressed by dehydration.
Wang 2016 [53]	DM	ECFCs	Angiogenesis	miR−134 ↓ NRIP1 ↑	Dose-dependent manner. FIR improves the angiogenic activity of HG-dfECFCs and dmECFCs by reducing miR−134 levels and increasing NRIP1 transcript.
Jeong 2017 [30]	Cardiac ischemia	BMSCs	Biological behaviors of cells	Nanog, Sox2, c-Kit, Nkx2.5, CXCR4 ↑	FIR enhances proliferation, cell survival, and migration of rat BMSCs through the *CXCR4-ERK* pathway.
Kim 2021 [58]	Obese and bone defects	TMSCs	Adipogenic differentiation	Ca 2+ ↑ PPARγ, FABP4 ↑	FIR activates the TRPV2 Ca^{2+}-permeable channel, increasing intracellular Ca^{2+} mobilization and inhibiting adipogenic differentiation.
Cho 2021 [20]	Breast cancer	MDA-MB−231 breast cancer cells	Biological behaviors of cells	Ca 2+ ↑ p-Chk2, CaM ↑	FIR inhibited the proliferation of breast cancer cells, independent of DNA damage, by activating the *Ca^{2+}/CaM/Chk2* pathway in the cell nucleus.
Chiu 2017 [89]	Skin photoaging	NIH 3T3 mouse embryonic fibroblasts	Collagen degradation Autophagy	Type I collagen, LC3-II, Beclin 1, TGF-β ↑ MMP−1, MMP−9, Akt, p70S6K ↓	FIR reduced skin thickness in UVB-irradiated mice, inhibited collagen fiber degradation, and induced autophagy by inhibiting the *Akt/mTOR* pathway.
Hsu 2012 [23]	Angiogenesis-related diseases	HUVECs	Biological behaviors of cells Anti-oxidative stress	eNOS, NO, p-Akt, PI3K ↑ p-ERK1/2 ↓	FIR induces nuclear translocation of PLZF, inhibiting VEGF-induced HUVEC proliferation.
Lin 2022 [68]	Chronic rejection-induced vasculopathy	Human EPCs	Angiogenesis	TNF-α, TGF-β1, αSMA, vimentin, p-Smad2, Slug ↓ vWF, VE-cadherin ↑	FIR inhibits OAT vasculopathy through inhibition of the Smad2-Slug axis endothelial mesenchymal transition.

(*continued on next page*)

Table 4 (*continued*)

Ref	Underlying Diseases	Cell Type	Protective Effect	Molecular Parameters	Outcome
Seo 2021 [51]	Metabolic diseases	Rat skeletal muscle L6 cells	Mitochondrial function	GLUT3, ATP ↑	FIR improves mitochondrial biogenesis and GLUT3 expression in skeletal muscle cells in rats under low glucose conditions.
Lin 2015 [5]	Diabetes-related ischemia and metabolic syndrome-associated cardiovascular disorders	Human EPCs, ECFCs	Angiogenesis	RDX, ARHGEF7, VIP, VEGF ↑	FIR up-regulates fibroblast growth factors, MAPK, Janus kinase/signal transducer, and activator of transcription and prostaglandin pathways in HG-EPCs
Hsu 2020 [2]	DM	RIN-m5f cells	Mitochondrial function	PLZF, Sirt1, CaV1.2 ↑	FIR-induced mitochondrial function prevents β-cell apoptosis and increases insulin secretion via the Sirt1 pathway in DM mice.
Chiu 2016 [44]	Burn wound	THP−1 cells	Anti-inflammatory	NLRP3, IL−1β ↓ TRAF6 ↑	FIR induced autophagy in THP−1 macrophages to suppress the NLRP3 inflammasome and induced ASC ubiquitination by increasing TRAF6.
Li 2017 [41]	Breast cancer-related lymphedema	Fibroblasts, MCF−7 and MDA-MB231	Biological behaviors of cells	NA	FIR does not promote breast cancer cell proliferation, attenuate apoptosis, or shorten cell cycles

drug olanzapine and PKC delta gene deletion. This suggests that FIR is a potential therapeutic tool against MA-induced psychotoxicity [27,64]. FIR can increase GPx-1-related antioxidative capacity, inhibit the *JAK2/STAT3* signaling pathway, and positively regulate c-Fos-IR, oxidative stress, and corticosterone levels, attenuating the oxidative damage caused by acute restraint stress [65].

FIR stimulation significantly increased central manifestations and autonomic responses, causing poststimulation physiological responses in healthy subjects [33]. FIR can effectively improve movement and body function in patients and animal models of neurodegenerative disease. FIR improves motor dysfunction and neuropathology in mice with spinocerebellar ataxia type 3, as indicated by enhanced motor coordination, balance, and gait performance *in vivo*. FIR may be involved in the rescue mechanism of SCA3 cells by preventing mutant ataxin-3 protein aggregation and promoting autophagy to protect cell viability *in vitro* [32]. In an Alzheimer's transgenic mouse model, FIR reduced the weight of specific brain regions and increased nerve growth factor and brain-derived neurotrophic factor proteins without significantly improving motor and cognitive function [66]. Some studies have shown that FIR can improve mental and learning deficits in Alzheimer's disease-like mice. Following FIR pretreatment, microglia enhance phagocytosis of Aβ through the P13K/mTOR pathway, resulting in a reduction in neuroinflammatory cytokines and restoration of the expression of the presynaptic protein synaptophysin, which benefits Aβ clearance [66].

6.3. Cardiovascular diseases

FIR may exhibit beneficial effects on cardiovascular health [67]. FIR can upregulate the mRNA levels of cardiac-specific and pluripotency-related markers such as NANOG, SOX2, c-KIT, and NKX2.5 in a time-dependent manner. It can also upregulate the expression of Nanog, Sox2, c-Kit, Nkx2.5, and CXCR4 and downregulate the expression of CXCR7 [30]. Studies have shown that this gene-modulating effect may be related to activating the *SDF-1α/CXCR4-ERK1/2* pathways [30]. FIR can upregulate the expression of eNOS mRNA and NO in patients with cardiomyopathy and heart failure and promote the production of eNOS protein. This may be related to an increase in the Ca^{2+}/CaMKII-mediated eNOS phosphorylation pathway. Mediating eNOS activity and upregulation of NO levels can improve vascular endothelial and cardiac function, improve cardiopulmonary exercise tolerance, and inhibit platelet aggregation [68].

However, most studies provide secondary evidence, and more extensive research is required to validate the findings. Takashi selected some patients with chronic heart failure and exposed them to 60 °C sauna therapy as the medium for emitting FIR. The treatment lasted 15 minutes, followed by 30 minutes of rest. The treatment was given once a day for two weeks. The results showed that 85 % (17/20) of patients experienced significant improvements, such as dyspnea, angina, or palpitations. FIR significantly improved endothelial function and reduced the concentration of brain natriuretic peptide (BNP), improving cardiac function in cardiovascular patients. Indeed, the increased microcirculation and enhanced endothelial function may be due to the increase in NO production caused by the upregulation of eNOS [33,67]. Hiromitsu reported a significant improvement in exercise tolerance and clinical symptoms of congestive heart failure after four weeks of treatment with an FIR intervention [69]. Kazuyuki used FIR to intervene in healthy subjects and reported that the thermal effect of FIR radiation increases deep body temperature, reduces afterload, and subsequently causes peripheral vasodilation, suggesting the potential application of FIR in heart failure patients [70].

6.4. Angiogenesis-related diseases

FIR can promote vascular repair, regeneration, and new vessel formation and improve blood flow, potentially useful in angiogenesis-related diseases [21]. For instance, FIR can be an alternative therapy to enhance blood flow and maintain the arteriovenous fistula (AVF) normality. It can reduce the plasma asymmetric dimethylarginine (ADMA) concentration and help improve the blood flow, maturation, and patency of newly formed AVFs in patients with diabetic kidney disease (DKD) [42,71]. On the one hand, it can cause local vasodilation and increase blood flow through thermal effects [71]. This increases shear stress in the vessel wall, stimulates ECs, and increases endothelial NO synthase activity. On the other hand, the endothelial function can be improved by the non-thermal effects of FIR. These include inhibition of intimal hyperplasia, oxidative stress reduction, inflammation inhibition, and endothelial function improvement. In OAT rats, FIR can effectively regulate vascular lesions caused by chronic rejection, such as orthotopic allograft vasculopathy. Its mechanism is correlated with the immunosuppressive effects of FIR [68]. On the one hand, FIR can inhibit humoral immune responses and prevent cytokine-induced dysfunction and EndoMT in EPCs. On the other hand, FIR can reduce collagen damage and pathological accumulation, as well as the proliferation and infiltration of SMCs and fibroblasts in the vessel wall of OAT-treated ACI/NKyo rats. Additionally, FIR can improve intermittent claudication and testicular ischemia-reperfusion injury perfusion [46,72]. It can also improve blood circulation and soft tissue properties in diabetic feet [73].

However, FIR may only be suitable for some. For example, the bilateral ankle-brachial index (ABI) was increased after FIR treatment only in patients with higher uric acid levels or aspirin use in the diagnosis of peripheral artery occlusive disease (PAOD), which is common in HD patients[74]. Similarly, FIR can improve the patency of HD arteries

Table 5
Outcomes of FIR *in vivo*.

Ref	Protective Effect	Diseases	Animal model	Animal	Molecular Parameters	Outcome
Luo 2021 [43]	Anti-inflammatory	ARDS	LPS-induced ARDS rat	Rat	HP ↑	FIR improves pathological hemorrhage and edema in LPS-induced rat ARDS lung tissue and reduces inflammatory cell exudation.
Liu 2019 [32]	Autophagy	Spinocerebellar ataxia type 3	Spinocerebellar ataxia type 3 Mice	Mice	LC3II, Beclin−1 ↑ p62, ataxin−3 ↓	FIR improves spinocerebellar ataxia type 3 mouse motor dysfunction and neuropathology.
Khan 2020 [57]	Compositional and temporal changes in gut microbiota	Intestinal microbiota-related diseases	Normal mice	Mice	GPCR, GPR41, 43, and 109 ↑	FIR induces long-lasting changes in gut microbial composition by modulating GM and host signaling responses such as SCFA-sensing GPCRs.
Kimura 2018 [80]	Regulation of heat shock protein Wound healing	Oral mucosal injury	Oral mucosal injury rat	Rat	Ki67, HSP27, HSP70 ↑	FIR triggers protective and regenerative responses to heat stress and promotes wound healing of oral mucosal injury.
Hsu 2020 [2]	Mitochondrial function	DM	STZ-induced DM mice	Mice	PLZF, Sirt1, CaV1.2 ↑	FIR-induced mitochondrial function prevents β-cell apoptosis and increases insulin secretion via the Sirt1 pathway in DM mice.
Chen 2022 [3]	Anti-inflammatory	Rheumatoid arthritis	AIA rat	Rat	AP−1, CEBPα, CEBPβ, c-Fos, GR, HNF−3β, USF−1, and USF−2 ↓	FIR may exert anti-arthritic effects by inactivating the *MAPK, PI3K-Akt, and NF-κB* pathways.
Tu 2013 [46]	Anti-inflammatory and anti-apoptotic properties of HO−1	Testicular ischemia/ reperfusion (I/R) injury	I/R injury of the testis rat	Rat	HO−1 ↑	FIR attenuated ischemia-reperfusion injury in rat testis by induction of HO−1 expression.
Li 2022 [4]	Mitochondrial function	Alzheimer's disease	Alzheimer's disease-like mice	Mice	Aβ, IL−1β, IL−6 ↓ Synaptophysin, ATP ↑	FIR reduced Aβ levels, alleviated neuroinflammation, restored presynaptic protein synaptophysin expression, and improved learning and memory deficits in AD mice.
Chiu 2016 [44]	Anti-inflammatory Autophagy	Burn wound	Deep second-degree burn rat	Rat	LC3, TRAF6 ↑ Caspase 1, NLRP3, IL−1β ↓	FIR improves burn wound progression and promotes wound healing.
Toyokawa 2003 [77]	Secretion of TGF-β1 or activation of fibroblasts	Wound	Full-thickness skin wound rat	Rat	TGF-β1 ↑	FIR promotes wound healing through stimulation of the secretion of TGF-β1 or the activation of fibroblasts
Hsu 2017 [76]	Biological behaviors of cells	Wound	Full-thickness skin wound rat	Rat	Notch1, Delta1 ↑	FIR accelerates wound healing and reduces scar size by stimulating the Notch1/TWIST1 pathway.
Mai 2018 [64]	Anti-oxidative stress	Recognition memory impairment	MA-induced recognition memory impairment mice	Mice	PKCδ ↓ M1 mAChR, Nrf2, GCLc, GCLm, GSH/GSSG ratio, p-ERK 1/2 ↑	FIR-mediated inhibition of PKCδ phosphorylation activates *ERK1/2* signaling through interactive modulation between M1 mAChR and Nrf2 transcription factor and attenuates MA-induced memory dysfunction.
Mai 2018 [50]	Anti-oxidative stress Mitochondrial function	Drug dependence induced by MA	GPx−1 knockout mice	Mice	GPx−1 ↑ Dopamine D1 receptor, c-Fos, mitochondrial superoxide dismutase, mitochondrial GPx activities, intramitochondrial Ca2+ level, mitochondrial complex-I activity ↓	FIR attenuates MA-induced behavioral sensitization by mitigating mitochondrial dysfunction through up-regulation of GPx−1 and down-regulation of the dopamine D1 receptor.
Chen 2021 [29]	Anti-inflammatory Angiogenesis	Chronic wounds	Dorsal skin defect in an STZ-induced diabetes rodent model	Rat	VEGF, eNOS, EGF, Ki−67 ↑ CD45, 8-OHdG ↓	FIR facilitates diabetic wound healing by inhibiting pro-inflammatory response and promoting neovascularization and tissue regeneration.
Mai 2018 [63]	Anti-oxidative stress	MA-induced memory impairment	MA-induced recognition memory impairment mice	Mice	Nrf2 ↑ PKCδ, ERK 1/2 ↓	FIR protects against MA-induced memory impairment by activating Nrf2-dependent glutathione synthesis and *ERK 1/2* signaling by inhibiting the PKCδ gene.
Tran 2016 [65]	Anti-oxidative stress	Acute restraint stress	Male glutathione peroxidase−1 overexpressing transgenic (GPx−1 TG) mice	Mice	c-Fos-IR, ROS, MDA, protein carbonyl, GSSG, corticosterone level, p-JAK2/STAT3 ↓ GSH, GSH/GSSG ratio, GPx, GPx−1-IR, GPx−1 ↑	FIR protects against ARS-induced increases in c-Fos-IR and oxidative stress by inhibiting JAK2/STAT3 signaling through the induction of GPx−1.
Chen 2017 [87]	Autophagy	DM	STZ-induced diabetic mice	Mice	Bcl−2, Bcl-xL, PI3K p85, PI3K III, p-Akt, LAMP−1 ↑ caspase−3, AGE, iNOS, MCP−1 ↓	**Dose-dependent manner.** FIR-induced PLZF activation in vascular EC protects the vascular endothelium of diabetic mice from AGE-induced damage.

(*continued on next page*)

Table 5 (*continued*)

Ref	Protective Effect	Diseases	Animal model	Animal	Molecular Parameters	Outcome
Chen 2022 [54]	Angiogenesis Biological behaviors of cells	Vascular complications caused by cisplatin	Cisplatin-treated mice	Mice	vWF, cleaved caspase−3 ↓ Bcl−2, VEGF, HIF−1α ↑	FIR improves the blood flow in the abdomen and increases the vWF expression in cisplatin-treated mice.
Lin 2022 [68]	Angiogenesis	Chronic rejection-induced vasculopathy	OAT ACI/NKyo rat	Rat	LDH, HMGB1, SMC, TNF-α, TGF-β1, IFN-γ, IL−12, αSMA, vimentin, Slug, EndoMT ↓ EPC, vWF, VE-cadherin ↑	**Dose-dependent manner.** FIR reduces the severity of vasculopathy by inhibiting smooth muscle cell proliferation, collagen accumulation, and fibroblast infiltration into the vessel wall with higher mobilization and circulating EPC levels.

Table 6
Outcomes of FIR in clinical trials.

Ref	Diseases	Protective Effect	Patient Number	Molecular Parameters	Outcome
Lin 2015 [33]	Heart rate variability and central manifestations in healthy subjects	Autonomic responses and central manifestations	10	nHF ↓ LF/HF, fALFF↑	FIR promotes an increment of central manifestation and autonomic responses, causing the post-stimulation physiological reactions.
Li 2018 [90]	Chronic extremity lymphedema	Anti-fibrosis	64	TGF-β 1, IL−18↓	FIR reduces fibrotic tissue density in the affected limb, increases skin elasticity, and improves clinical symptoms.
Li 2017 [8]	Lymphedema in stage II and III	Dilation of blood vessels	32	IL−6 ↑ Leptin, Extra-M-Hyaluronan, Extra-M-Total protein ↓	FIR improves lymphoedema burden, reduces circumference measurements of lymphoedema-bearing limbs, and reduces thickness of skin and subcutaneous lymphoedema tissue.
Huang 2019 [86]	Perineal wound pain and sexual function in primiparous women undergoing an episiotomy	Dilation of blood vessels	18	VAS, PISQ−12 total score -	FIR has no additional benefit in primiparous women with episiotomy and 2nd-degree perineal lacerations.
Chen 2016 [74]	HD with PAOD	The thermal effect-induced vasodilation and the non-thermal effect of inhibiting intimal hyperplasia	58	ABI ↑	FIR increases bilateral ABI in people with higher uric acid levels or aspirin use.
Lai 2013 [16]	Recurrent obstructive lesions	Improvement of access to blood flow	109	Unassisted patency rates ↑	FIR improves PTA-free HD access patency, especially in the AVG series.
Cheng 2020 [73]	DM	Improvement of blood circulation	10	Skin temperature of the foot, Blood flow, HRV, plantar pressure ↑	FIR improves circulation and changes the soft tissue properties of the diabetic foot.
Yoon 2020 [82]	Arthroscopic RCT	Analgesia	19	pVAS↓ ROM↑	FIR reduces post-operative pain, facilitating rehabilitation and improving ROM in the early postoperative period.
Peng 2020 [7]	Autonomic nervous system	Improvement of blood circulation	22	Skin temperature, HRV↑ FSST ↓	FIR increases the FSST from 4°C to 7°C after 40 minutes of exposure, improving lower extremity circulation and regulating ANS activity.
Chang 2022 [60]	Recurrent peritonitis in PD patients	Anti-inflammatory	32	BUN, creatinine, and peritoneal weekly CCr, IL−6, and TNF-α ↓ Peritoneal Kt/V and eGFR of peritoneal function, IL−12p70 ↑	FIR improves the effectiveness of PD and peritoneal permeability and inflammatory response
Chang 2021 [61]	Diabetic patients with PD	Decreased GDPs	31	Methylglyoxal, furfural, 5-hydroxymethylfurfural, potassium levels ↓ D/D0 glucose ratio, peritoneal Kt/V ↑	FIR can reduce dialysate GDP in PD patients by improving peritoneal transport rate and solute removal clearance while maintaining dialysate adequacy.
Chen 2022 [42]	Advanced DKD with AVF	Improvement of blood circulation	50	AVF blood flow, AVF patency rate, AVF maturation rate ↑ AVF failure rate, ADMA↓	FIR improves AVF prognosis in patients with advanced DKD by regulating incremental changes in plasma ADMA concentration.
Li 2017 [41]	Breast cancer-related lymphedema	Decreased recurrence rate	32	CA125, CA153 -	FIR does not promote breast cancer recurrence or metastasis with no side effects.
Choi 2016 [84]	HD with AVF	Improvement of access to blood flow and analgesia	25	Needling pain score ↓ Qa ↑	FIR improves needling pain and Qa levels.
Lin 2013 [71]	CKD stage 4 or 5	Improvement of blood circulation	60	Qa, physiologic maturation, AVF cumulative unassisted patency, and clinical maturation ↑ AVF malfunction ↓	FIR improves the flow, maturation, and patency of newly created AVFs in CKD stages 4 and 5 patients.

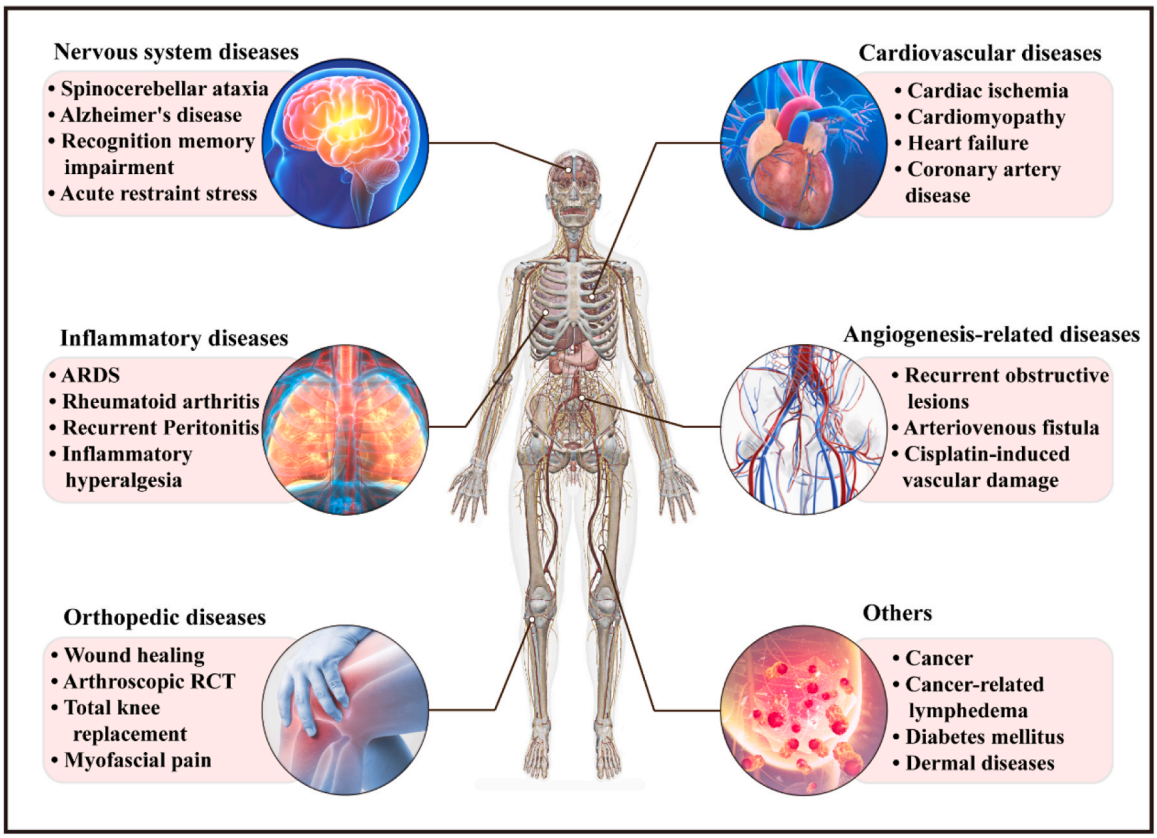

Fig. 5. Schematic overview of FIR for systematic diseases. FIR has beneficial complementary effects on various chronic diseases, including nervous system, cardiovascular, inflammatory, orthopedic, and angiogenesis-related diseases.

without PTA. This is mainly observed in the arteriovenous graft (AVG) series [16].

6.5. Orthopedic diseases

In addition to promoting muscular, wound, and other tissue repair and regeneration, FIR can help to alleviate pain. FIR can penetrate the body of rats and stimulate PDGF-mediated cell migration through the extracellular matrix integrin pathway, which stimulates the expression of miRNA in a dose-dependent manner. FIR irradiation for 48 hours can promote wound healing [15]. It further increases the number of fibroblasts or keratinocytes, enhances collagen aggregation, promotes TGF-β1 secretion, and mediates the *Notch1/TWIST1* pathways during FIR-mediated wound healing [75–77]. By suppressing the NLRP3 inflammasome by enhancing autophagy, FIR may promote the healing of burn wounds [44]. In chronic wounds, such as diabetic wounds, FIR also has significant healing effects. Following FIR intervention, leukocyte infiltration is inhibited, CD45+ and 8-OHdG expression is downregulated, oxidative stress is reduced, the inflammatory response is suppressed, Ki-67+ cell proliferation is promoted, and angiogenic factors such as eNOS, VEGF, and EGF are upregulated, which in turn induces epithelial oxidation and promotes wound healing [29]. FIR can accelerate the repair of damaged muscles, relieve approximately 55–60 % of muscle soreness, restore muscle strength and proprioception to baseline levels, and accelerate recovery by 1–3 days [78,79]. In addition, FIR can increase the production of HSP70 to promote a regenerative response to oral mucosal injury [80].

FIR can act on pain sensors. This reduces the pain signals sent to the brain and reduces local pain. Under conditions such as total knee replacement, rotator cuff repair (RCT), osteoarthritis (OA), and myofascial pain, FIR has been shown to increase the pain threshold and significantly reduce pain [81–84]. Patients who underwent surgery for minor to moderate rotator cuff tears after arthroscopic RCT with FIR for ten weeks demonstrated a significant reduction in pain within three months. Postoperative range of motion, functional scores, and healing rate were not adversely affected, contributing to improving early functional exercise to prevent stiffness [82,85]. Lai et al. used an FIR neck brace and a conventional neck brace to treat patients with chronic myofascial neck pain. He found that both devices could improve pain, but the difference was not statistically significant. However, patients in the FIR group significantly reduced neck muscle stiffness after one week of treatment [83]. In addition, some studies have shown that the FIR has no pain-relieving effects on primiparous women undergoing episiotomy or 2nd-degree perineal lacerations [86].

Interestingly, the Italian scientist Valentina observed the beneficial effect of wearing far-infrared emitting clothing in healthy subjects [17]. Exercise performance is improved, and anaerobic metabolism is delayed when wearing FIR clothing. This type of clothing works through non-thermal effects. The mechanism may be to mediate muscle vasodilation, thereby increasing peripheral oxygen delivery.

6.6. Others

FIR has shown sound therapeutic effects in other diseases with widespread promotion and clinical application. For example, FIR is used to treat patients with diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), skin photoaging, and lymphoedema [2,21,73,87–90]. FIR can effectively improve the burden of lymphoedema, reduce limb circumference, skin, and subcutaneous lymphoedema tissue thickness, improve patients' quality of life, and thereby lower the recurrence rate [8,91]. For patients with breast cancer-related lymphedema five years after mastectomy, FIR should be considered feasible and safe [41].

However, despite the large number of cell and animal experiments

that have demonstrated the efficacy of FIR in treating tumors, its clinical application for treating tumor-related complications is relatively limited [41].

7. Advantages and limitations of FIR in regenerative medicine

7.1. Advantages

Numerous experiments, encompassing both cellular and animal models, along with selected clinical trials, have unequivocally demonstrated the effectiveness of FIR. (Fig. 6). The distinctive advantages of FIR therapy are outlined as follows: **(1) Specific spatiotemporal selectivity.** FIR therapy exhibits precise spatiotemporal selectivity, allowing for meticulous control of the energy dosage and duration delivered to the treatment area. This characteristic optimizes efficacy and distinguishes FIR therapy from conventional drug-based approaches. **(2) Increased safety.** FIR therapy has notable safety benefits, characterized by its non-invasiveness, contact-free application, low systemic toxicity, and operational simplicity. In contrast to pharmaceutical interventions, FIR light leaves no residues in the body, ensuring

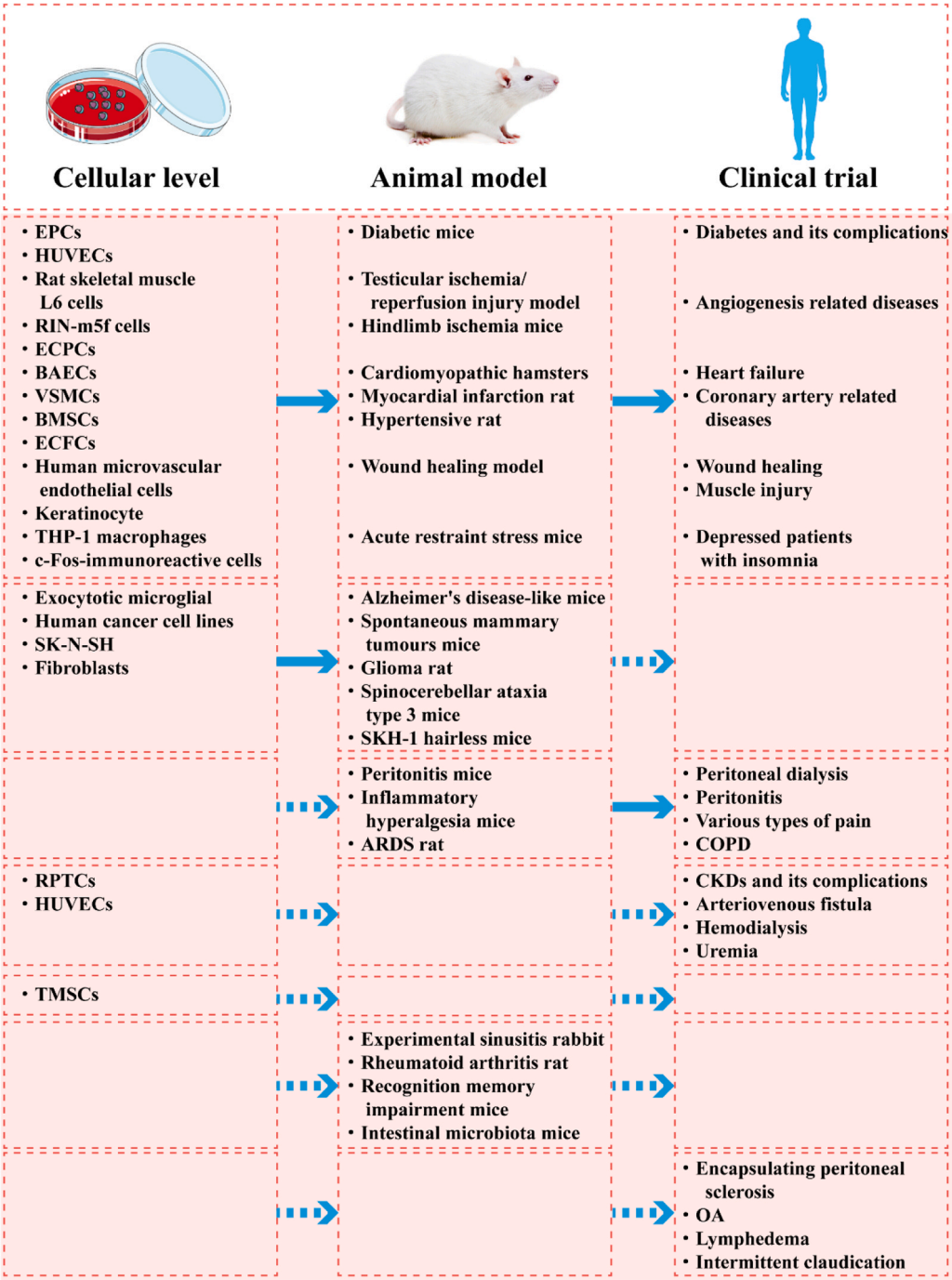

Fig. 6. Comprehensive assessment of the FIR across cellular, animal, and clinical studies. This figure provides a comprehensive overview of FIR in the context of cellular, animal, and clinical studies, particularly emphasizing its widespread application in regenerative medicine. The effectiveness of FIR has been rigorously validated at the cellular level, in animal models, and in clinical trials for various diseases. It is worth noting, however, that for certain conditions, a thorough examination of FIR effects is still pending. Examples include investigations limited to cells, animals, and clinical trials individually or in combinations, such as cells + animals, animals + clinical trials, and cells + clinical trials, highlighting the need for further comprehensive research in these areas.

a lack of residual effects and minimizing the likelihood of side effects. While FIR therapy generally has a high safety profile, it is imperative for future research to evaluate its potential side effects and long-term safety thoroughly. **(3) Clear therapeutic benefits.** FIR therapy transcends the realm of alternative medicine, with some studies suggesting therapeutic effects comparable to those of traditional drugs [64]. FIR can target specific cells without compromising the anticancer activity of substances such as cisplatin. It mitigates cisplatin-induced vascular damage, stenosis, endothelial toxicity, and angiogenesis in murine models and HUVECs [54]. The findings of Jiang further affirmed the ability of FIR to counteract the toxicity induced by anticancer drugs, emphasizing its potential for integration with conventional treatments such as chemotherapy, acupuncture, or surgery to enhance overall efficacy [11,34].

7.2. Limitations

Some limitations or precautions must be taken to promote better application of the FIR. **(1) The underlying mechanism of FIR remains unclear.** Further exploration of this mechanism through extensive cellular investigations, animal experiments, and many clinical trials is essential for providing a more profound theoretical foundation for its application (Fig. 6). **(2) Standardized therapeutic parameters are lacking.** To establish effective treatment ranges and optimal parameter characteristics, multiparameter and multi-radiation experiments focusing on FIR parameters, such as effective wavelength, irradiation time and distance, and irradiation density, need to be conducted. We strive to establish standardized treatment parameters to ensure consistent and effective implementation of this technology in clinical practice. **(3) Systematic clinical trials still need to be improved.** More high-quality clinical trials with large sample sizes, long-term follow-up, and multicenter studies are needed to confirm whether FIR can achieve effects comparable to those of therapeutic drugs, that is, whether it can be considered a single therapy. While current evidence suggests that FIR is primarily utilized as adjunctive physiotherapy, more comprehensive studies are required to validate its efficacy in diverse clinical settings.

8. Forecasting the future development and applications of FIR

(1) **Development of an adjustable FIR emitter.** FIR is promising in biosensing, bioimaging, and anti-cancer therapy [92,93]. Recent studies have revealed distinctive absorption patterns in the FIR spectrum for proteins with non-biological activities and DNA components characterized by unique vibrational modes [94,95]. In cellular models, the inhibitory potential of FIR on the proliferation of various cancer cell types differs significantly with exposure to specific wavelengths. The growth inhibition rates of HSC3, Sa3, and A549 cells were 45.75 %, 74.63 %, and 65.79 %, respectively [37]. In contrast, A431 and MCF7 cells remained unaffected [37]. Intriguingly, sex-dependent difference in oxygenation status is observed during FIR exposure [96]. These findings underscore the cell-type-specific absorption variations in the far-infrared spectrum. Conversely, the literature suggests that different wavelengths and intensities of FIR uniformly influence cellular biological responses [24]. This implies the existence of specialized FIR decoders within biological organisms capable of recognizing and translating information based on distinct cell types and corresponding FIR frequencies. Extensive research is needed to facilitate the selection of FIR wavelengths and intensities tailored to specific cell types associated with different diseases, thereby achieving the desired therapeutic outcomes.

(2) **FIR photochemical and photosensitizing device.** FIR imaging and therapeutic technologies show real-time rapid imaging and noninvasive intelligent therapeutic effects. The amalgamation of FIR imaging and therapy constitutes a groundbreaking diagnostic and therapeutic modality for future regenerative medicine. The literature highlights the potential advantages of the FIR in biometric applications, such as facial recognition and traffic monitoring [97,98]. Moreover, diverse therapeutic outcomes are observed when treating different cell types with FIR. For instance, it enhanced the proliferation and activity of RPTCs, BMSCs, and HaCaT cells [14,34,99], while it also exhibited inhibitory effects on cancer cells and HUVECs [10,37]. This implies that various cell populations display heterogeneity in their biological responses to FIR. In future studies, developing an FIR photochemical instrument coupled with photosensitizers may facilitate the emission of FIR light to identify and label diverse cell types [92,100,101]. This innovation might enable targeted action on specific cell populations within the organism, selectively treating pathological tissues in particular regions and achieving precise diagnostic and therapeutic effects.

9. Conclusions

FIR has excellent potential for application in future regenerative medicine based on promising results in cytology, animal models, and clinical trials. Standardizing therapeutic parameters may improve FIR efficacy and safety. Subsequent research endeavors will focus on elucidating critical factors, including the specific mechanism and optimal therapeutic parameters of FIR. Additionally, the strategic integration of medicine and engineering, coupled with interdisciplinary research incorporating the latest advancements from diverse fields, is envisioned to furnish comprehensive guidance for clinical practices and foster the widespread adoption and dissemination of the FIR.

CRediT authorship contribution statement

Nick Wang: Writing – review & editing, Supervision, Conceptualization. **Bo Qin:** Writing – original draft, Software, Investigation, Conceptualization. **Betty Yuen Kwan Law:** Supervision, Conceptualization. **Heng-ao Lu:** Software. **Wan-yu Wu:** Software. **Jing Zhong:** Writing – review & editing. **Bai-xiong Huang:** Writing – review & editing. **Lin-na Wang:** Software. **Yuping Wang:** Software. **Jiu-jie Yang:** Writing – review & editing, Conceptualization. **Vincent Kam Wai Wong:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Xiong-fei Xu:** Writing – review & editing, Conceptualization. **Io Nam Wong:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Shi-jie Fu:** Writing – original draft, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing interests.

Data availability

No data was used for the research described in the article.

Acknowledgments

This work was supported by a FDCT grant from the Macao Science and Technology Development Fund (Project code: 0124/2022/A; 002/2023/ALC; 0069/2021/AFJ).

References

[1] C. Mason, P. Dunnill, A brief definition of regenerative medicine, Regen. Med 3 (1) (2008) 1–5, https://doi.org/10.2217/17460751.3.1.1.

[2] Y.H. Hsu, Y.C. Chen, Y.W. Chen, T.H. Chiu, Y.T. Kuo, C.H. Chen, Far-infrared radiation prevents decline in β-cell mass and function in diabetic mice via the mitochondria-mediated Sirtuin1 pathway, Metabolism 104 (2020) 154143, https://doi.org/10.1016/j.metabol.2020.154143.

[3] X. Chen, H. Zhang, W. Zeng, N. Wang, H.H. Lo, C.K. Ip, L.J. Yang, W.L.W. Hsiao, W.M. Sin, C. Xia, B.Y.K. Law, V.K.W. Wong, 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, https://doi.org/10.1016/j.jare.2021.08.015.
[4] Q. Li, J. Peng, Y. Luo, J. Zhou, T. Li, L. Cao, S. Peng, Z. Zuo, Z. Wang, Far infrared light irradiation enhances Aβ clearance via increased exocytotic microglial ATP and ameliorates cognitive deficit in Alzheimer's disease-like mice, J. Neuroinflamm. 19 (1) (2022) 145, https://doi.org/10.1186/s12974-022-02521-y.
[5] T.C. Lin, C.S. Lin, T.N. Tsai, S.M. Cheng, W.S. Lin, C.C. Cheng, C.H. Wu, C.H. Hsu, Stimulatory influences of far infrared therapy on the transcriptome and genetic networks of endothelial progenitor cells receiving high glucose treatment, Acta Cardiol. Sin. 31 (5) (2015) 414–428, https://doi.org/10.6515/acs20141201c.
[6] F. Vatansever, M.R. Hamblin, Far infrared radiation (FIR): its biological effects and medical applications, Photonics Lasers Med (4) (2012) 255–266, https://doi.org/10.1515/plm-2012-0034.
[7] T.C. Peng, S.P. Chang, L.M. Chi, L.M. Lin, The effectiveness of far-infrared irradiation on foot skin surface temperature and heart rate variability in healthy adults over 50 years of age: a randomized study, Med. (Baltim.) 99 (50) (2020) e23366, https://doi.org/10.1097/md.0000000000023366.
[8] K. Li, Z. Zhang, N.F. Liu, S.Q. Feng, Y. Tong, J.F. Zhang, J. Constantinides, D. Lazzeri, L. Grassetti, F. Nicoli, Y.X. Zhang, Efficacy and safety of far infrared radiation in lymphedema treatment: clinical evaluation and laboratory analysis, Lasers Med Sci. 32 (3) (2017) 485–494, https://doi.org/10.1007/s10103-016-2135-0.
[9] A. Dominguez-Vidal, N. Kaun, M.J. Ayora-Cañada, B. Lendl, Probing intermolecular interactions in water/ionic liquid mixtures by far-infrared spectroscopy, J. Phys. Chem. B 111 (17) (2007) 4446–4452, https://doi.org/10.1021/jp068777n.
[10] S. Hwang, D.H. Lee, I.K. Lee, Y.M. Park, I. Jo, Far-infrared radiation inhibits proliferation, migration, and angiogenesis of human umbilical vein endothelial cells by suppressing secretory clusterin levels, Cancer Lett. 346 (1) (2014) 74–83, https://doi.org/10.1016/j.canlet.2013.12.011.
[11] C.C. Yang, G.M. Lin, J.H. Wang, H.C. Chu, H.T. Wu, J.J. Chen, C.K. Sun, Effects of combined far-infrared radiation and acupuncture at st36 on peripheral blood perfusion and autonomic activities, Evid. Based Complement Altern. Med 2017 (2017) 1947315, https://doi.org/10.1155/2017/1947315.
[12] Y. Ozaki, Infrared spectroscopy-mid-infrared, near-infrared, and far-infrared/terahertz spectroscopy, Anal. Sci. 37 (9) (2021) 1193–1212, https://doi.org/10.2116/analsci.20R008.
[13] M.S. Lee, F. Baletto, D.G. Kanhere, S. Scandolo, Far-infrared absorption of water clusters by first-principles molecular dynamics, J. Chem. Phys. 128 (21) (2008) 214506, https://doi.org/10.1063/1.2933248.
[14] Y.C. Chen, L.C. Lai, Y.P. Tu, S.D. Wu, C.F. Chen, B. Li, Far infrared ray irradiation attenuates apoptosis and cell death of cultured keratinocytes stressed by dehydration, J. Photochem. Photobio. B 106 (2012) 61–68, https://doi.org/10.1016/j.jphotobiol.2011.10.006.
[15] D. Lee, Y. Seo, Y.W. Kim, S. Kim, H. Bae, J. Choi, I. Lim, H. Bang, J.H. Kim, J. H. Ko, Far-infrared radiation stimulates platelet-derived growth factor mediated skeletal muscle cell migration through extracellular matrix-integrin signaling, Korean J. Physiol. Pharm. 23 (2) (2019) 141–150, https://doi.org/10.4196/kjpp.2019.23.2.141.
[16] C.C. Lai, H.C. Fang, G.Y. Mar, J.C. Liou, C.J. Tseng, C.P. Liu, Post-angioplasty far infrared radiation therapy improves 1-year angioplasty-free hemodialysis access patency of recurrent obstructive lesions, Eur. J. Vasc. Endovasc. Surg. 46 (6) (2013) 726–732, https://doi.org/10.1016/j.ejvs.2013.09.018.
[17] V. Mantegazza, M. Contini, M. Botti, A. Ferri, F. Dotti, P. Berardi, P. Agostoni, Improvement in exercise capacity and delayed anaerobic metabolism induced by far-infrared-emitting garments in active healthy subjects: a pilot study, Eur. J. Prev. Cardiol. 25 (16) (2018) 1744–1751, https://doi.org/10.1177/2047487318768598.
[18] H.Y. Kim, Y. Yu, S.Y. Oh, K.K. Wang, Y.R. Kim, S.C. Jung, H.S. Kim, I. Jo, Far-infrared irradiation inhibits adipogenic differentiation and stimulates osteogenic differentiation of human tonsil-derived mesenchymal stem cells: role of protein phosphatase 2B, Cell Physiol. Biochem 52 (2) (2019) 240–253, https://doi.org/10.33594/000000018.
[19] J.H. Park, S. Lee, D.H. Cho, Y.M. Park, D.H. Kang, I. Jo, Far-infrared radiation acutely increases nitric oxide production by increasing Ca(2+) mobilization and Ca(2+)/calmodulin-dependent protein kinase II-mediated phosphorylation of endothelial nitric oxide synthase at serine 1179, Biochem Biophys. Res Commun. 436 (4) (2013) 601–606, https://doi.org/10.1016/j.bbrc.2013.06.003.
[20] D.H. Cho, H.J. Lee, J.Y. Lee, J.H. Park, I. Jo, Far-infrared irradiation inhibits breast cancer cell proliferation independently of DNA damage through increased nuclear Ca(2+)/calmodulin binding modulated-activation of checkpoint kinase 2, J. Photochem. Photobio. B 219 (2021) 112188, https://doi.org/10.1016/j.jphotobiol.2021.112188.
[21] P.H. Huang, J.W. Chen, C.P. Lin, Y.H. Chen, C.H. Wang, H.B. Leu, S.J. Lin, Far infra-red therapy promotes ischemia-induced angiogenesis in diabetic mice and restores high glucose-suppressed endothelial progenitor cell functions, Cardiovasc Diabetol. 11 (2012) 99, https://doi.org/10.1186/1475-2840-11-99.
[22] J.L. Wang, Y.C. Lin, T.H. Young, M.H. Chen, Far-infrared ray radiation promotes neurite outgrowth of neuron-like PC12 cells through AKT1 signaling, J. Formos. Med Assoc. 118 (2) (2019) 600–610, https://doi.org/10.1016/j.jfma.2018.08.015.
[23] Y.H. Hsu, Y.C. Chen, T.H. Chen, Y.M. Sue, T.H. Cheng, J.R. Chen, C.H. Chen, Far-infrared therapy induces the nuclear translocation of PLZF which inhibits VEGF-induced proliferation in human umbilical vein endothelial cells, PLoS One 7 (1) (2012) e30674, https://doi.org/10.1371/journal.pone.0030674.
[24] Y.H. Hsu, Y.W. Chen, C.Y. Cheng, S.L. Lee, T.H. Chiu, C.H. Chen, Detecting the limits of the biological effects of far-infrared radiation on epithelial cells, Sci. Rep. 9 (1) (2019) 11586, https://doi.org/10.1038/s41598-019-48187-0.
[25] R. Zein, W. Selting, M.R. Hamblin, Review of light parameters and photobiomodulation efficacy: dive into complexity, J. Biomed. Opt. 23 (12) (2018) 1–17, https://doi.org/10.1117/1.Jbo.23.12.120901.
[26] D. Pastore, F. Pacifici, G. Ciao, V. Bedin, G. Pasquantonio, D. Della-Morte, Far infrared technology (FIT) therapy patches, protects from inflammation, oxidative stress and promotes cellular vitality, Curr. Pharm. Des. 26 (34) (2020) 4323–4329, https://doi.org/10.2174/1381612826666200427112023.
[27] N. Sharma, E.J. Shin, N.H. Kim, E.H. Cho, B.T. Nguyen, J.H. Jeong, C.G. Jang, S. Y. Nah, H.C. Kim, Far-infrared ray-mediated antioxidant potentials are important for attenuating psychotoxic disorders, Curr. Neuropharmacol. 17 (10) (2019) 990–1002, https://doi.org/10.2174/1570159x17666190228114318.
[28] R.F. Rosas, A.A. Emer, A.P. Batisti, D.D. Ludtke, B.L. Turnes, F. Bobinski, F. J. Cidral-Filho, D.F. Martins, Far infrared-emitting ceramics decrease Freund's adjuvant-induced inflammatory hyperalgesia in mice through cytokine modulation and activation of peripheral inhibitory neuroreceptors, J. Integr. Med 16 (6) (2018) 396–403, https://doi.org/10.1016/j.joim.2018.08.002.
[29] R.F. Chen, K.F. Liu, S.S. Lee, S.H. Huang, Y.C. Wu, Y.N. Lin, C.T. Wang, Y.R. Kuo, Far-infrared therapy accelerates diabetic wound healing via recruitment of tissue angiogenesis in a full-thickness wound healing model in rats, Biomedicines 9 (12) (2021), https://doi.org/10.3390/biomedicines9121922.
[30] Y.M. Jeong, X.W. Cheng, S. Lee, K.H. Lee, H. Cho, J.H. Kang, W. Kim, Preconditioning with far-infrared irradiation enhances proliferation, cell survival, and migration of rat bone marrow-derived stem cells via CXCR4-ERK pathways, Sci. Rep. 7 (1) (2017) 13718, https://doi.org/10.1038/s41598-017-14219-w.
[31] S.Y. Yu, J.H. Chiu, S.D. Yang, Y.C. Hsu, W.Y. Lui, C.W. Wu, Biological effect of far-infrared therapy on increasing skin microcirculation in rats, Photo Photo Photo 22 (2) (2006) 78–86, https://doi.org/10.1111/j.1600-0781.2006.00208.x.
[32] S.W. Liu, J.C. Chang, S.F. Chuang, K.H. Liu, W.L. Cheng, H.J. Chang, H.S. Chang, T.T. Lin, C.L. Hsieh, W.Y. Lin, M. Hsieh, S.J. Kuo, C.S. Liu, Far-infrared radiation improves motor dysfunction and neuropathology in spinocerebellar ataxia type 3 mice, Cerebellum 18 (1) (2019) 22–32, https://doi.org/10.1007/s12311-018-0936-3.
[33] Y.J. Lin, Y.Y. Kung, W.J. Kuo, D.M. Niddam, C.M. Cheng, C.C. Chou, T.C. Yeh, J. C. Hsieh, J.H. Chiu, Effects of far-infrared radiation on heart rate variability and central manifestations in healthy subjects: a resting-fMRI study, Lasers Med Sci. 30 (1) (2015) 295–301, https://doi.org/10.1007/s10103-014-1662-9.
[34] I.N. Chiang, Y.S. Pu, C.Y. Huang, T.H. Young, Far infrared radiation promotes rabbit renal proximal tubule cell proliferation and functional characteristics, and protects against cisplatin-induced nephrotoxicity, PLoS One 12 (7) (2017) e0180872, https://doi.org/10.1371/journal.pone.0180872.
[35] Y.M. Jeong, W. Kim, FIR-preconditioning promotes Akt-mTOR-exosome manufacture in cooperation with MITF to boost resilience of rat bone marrow-derived stem cells, Heliyon 9 (4) (2023) e15003, https://doi.org/10.1016/j.heliyon.2023.e15003.
[36] Y.J. Hwang, J.H. Park, D.H. Cho, Far-infrared irradiation decreases proliferation in basal and PDGF-stimulated VSMCs through AMPK-mediated inhibition of mTOR/p70S6K signaling axis, J. Korean Med Sci. 38 (41) (2023) e335, https://doi.org/10.3346/jkms.2023.38.e335.
[37] J. Ishibashi, K. Yamashita, T. Ishikawa, H. Hosokawa, K. Sumida, M. Nagayama, S. Kitamura, The effects inhibiting the proliferation of cancer cells by far-infrared radiation (FIR) are controlled by the basal expression level of heat shock protein (HSP) 70A, Med Oncol. 25 (2) (2008) 229–237, https://doi.org/10.1007/s12032-007-9020-4.
[38] J. Wang, H. He, X. Xu, X. Wang, Y. Chen, L. Yin, Far-red light-mediated programmable anti-cancer gene delivery in cooperation with photodynamic therapy, Biomaterials 171 (2018) 72–82, https://doi.org/10.1016/j.biomaterials.2018.04.020.
[39] D. Wang, M.M.S. Lee, G. Shan, R.T.K. Kwok, J.W.Y. Lam, H. Su, Y. Cai, B.Z. Tang, Highly efficient photosensitizers with far-red/near-infrared aggregation-induced emission for in vitro and in vivo cancer theranostics, Adv. Mater. 30 (39) (2018) e1802105, https://doi.org/10.1002/adma.201802105.
[40] P. Peidaee, N. Almansour, R. Shukla, E. Pirogova, The cytotoxic effects of low intensity visible and infrared light on human breast cancer (MCF7) cells, Comput. Struct. Biotechnol. J. 6 (2013) e201303015, https://doi.org/10.5936/csbj.201303015.
[41] K. Li, L. Xia, N.F. Liu, F. Nicoli, J. Constantinides, C. D'Ambrosia, D. Lazzeri, M. Tremp, J.F. Zhang, Y.X. Zhang, Far infrared ray (FIR) therapy: an effective and oncological safe treatment modality for breast cancer related lymphedema, J. Photochem. Photobio. B 172 (2017) 95–101, https://doi.org/10.1016/j.jphotobiol.2017.05.011.
[42] C.F. Chen, C.Y. Lee, F.A. Chen, C.Y. Yang, T.H. Chen, S.M. Ou, K.H. Lee, C.P. Li, C. H. Chan, P.C. Lee, Y.T. Chen, T.L. Lee, Y. Ho, F.Y. Chen, H.W. Ma, J.Y. Chen, A. C. Tan, S.Y. Li, C.C. Lin, Far-infrared therapy improves arteriovenous fistula patency and decreases plasma asymmetric dimethylarginine in patients with advanced diabetic kidney disease: a prospective randomized controlled trial, J. Clin. Med 11 (14) (2022), https://doi.org/10.3390/jcm11144168.
[43] C. Luo, Y. Li, X. Liang, Y. Chen, Q. Zou, Y. Kong, Z. Guo, W. Sun, X. Wang, Special electromagnetic field-treated water and far-infrared radiation alleviates lipopolysaccharide-induced acute respiratory distress syndrome in rats by regulating haptoglobin, Bioengineered 12 (1) (2021) 6808–6820, https://doi.org/10.1080/21655979.2021.1969201.
[44] H.W. Chiu, C.H. Chen, J.N. Chang, C.H. Chen, Y.H. Hsu, Far-infrared promotes burn wound healing by suppressing NLRP3 inflammasome caused by enhanced

autophagy, J. Mol. Med (Berl.) 94 (7) (2016) 809–819, https://doi.org/10.1007/s00109-016-1389-0.
[45] C.C. Lin, X.M. Liu, K. Peyton, H. Wang, W.C. Yang, S.J. Lin, W. Durante, Far infrared therapy inhibits vascular endothelial inflammation via the induction of heme oxygenase-1, Arterioscler. Thromb. Vasc. Biol. 28 (4) (2008) 739–745, https://doi.org/10.1161/atvbaha.107.160085.
[46] Y.P. Tu, S.C. Chen, Y.H. Liu, C.F. Chen, T.C. Hour, Postconditioning with far-infrared irradiation increases heme oxygenase-1 expression and protects against ischemia/reperfusion injury in rat testis, Life Sci. 92 (1) (2013) 35–41, https://doi.org/10.1016/j.lfs.2012.10.019.
[47] Y. Akasaki, M. Miyata, H. Eto, T. Shirasawa, N. Hamada, Y. Ikeda, S. Biro, Y. Otsuji, C. Tei, Repeated thermal therapy up-regulates endothelial nitric oxide synthase and augments angiogenesis in a mouse model of hindlimb ischemia, Circ. J. 70 (4) (2006) 463–470, https://doi.org/10.1253/circj.70.463.
[48] J.C. Chang, S.L. Wu, F. Hoel, Y.S. Cheng, K.H. Liu, M. Hsieh, A. Hoel, K. J. Tronstad, K.C. Yan, C.L. Hsieh, W.Y. Lin, S.J. Kuo, S.L. Su, C.S. Liu, Far-infrared radiation protects viability in a cell model of Spinocerebellar Ataxia by preventing polyQ protein accumulation and improving mitochondrial function, Sci. Rep. 6 (2016) 30436, https://doi.org/10.1038/srep30436.
[49] S. Hamada, A. Sato, M. Hara-Chikuma, H. Satooka, K. Hasegawa, K. Tanimura, K. Tanizawa, M. Inouchi, T. Handa, T. Oga, S. Muro, M. Mishima, K. Chin, Role of mitochondrial hydrogen peroxide induced by intermittent hypoxia in airway epithelial wound repair in vitro, Exp. Cell Res 344 (1) (2016) 143–151, https://doi.org/10.1016/j.yexcr.2016.04.006.
[50] H.N. Mai, N. Sharma, E.J. Shin, B.T. Nguyen, J.H. Jeong, C.G. Jang, E.H. Cho, S. Y. Nah, N.H. Kim, T. Nabeshima, H.C. Kim, Exposure to far infrared ray protects methamphetamine-induced behavioral sensitization in glutathione peroxidase-1 knockout mice via attenuating mitochondrial burdens and dopamine D1 receptor activation, Neurochem Res 43 (5) (2018) 1118–1135, https://doi.org/10.1007/s11064-018-2528-5.
[51] Y. Seo, Y.W. Kim, D. Lee, D. Kim, K. Kim, T. Kim, C. Baek, Y. Lee, J. Lee, H. Lee, G. Jang, W. Jeong, J. Choi, D. Hwang, J.S. Suh, S.W. Kim, H.K. Kim, J. Han, H. Bang, J.H. Kim, T. Zhou, J.H. Ko, Far-infrared rays enhance mitochondrial biogenesis and GLUT3 expression under low glucose conditions in rat skeletal muscle cells, Korean J. Physiol. Pharm. 25 (2) (2021) 167–175, https://doi.org/10.4196/kjpp.2021.25.2.167.
[52] W.C. Tsai, W.H. Chiang, C.H. Wu, Y.C. Li, M. Campbell, P.H. Huang, M.W. Lin, C. H. Lin, S.M. Cheng, P.C. Chang, C.C. Cheng, miR-548aq-3p is a novel target of Far infrared radiation which predicts coronary artery disease endothelial colony forming cell responsiveness, Sci. Rep. 10 (1) (2020) 6805, https://doi.org/10.1038/s41598-020-63311-1.
[53] H.W. Wang, S.H. Su, Y.L. Wang, S.T. Chang, K.H. Liao, H.H. Lo, Y.L. Chiu, T. H. Hsieh, T.S. Huang, C.S. Lin, S.M. Cheng, C.C. Cheng, MicroRNA-134 contributes to glucose-induced endothelial cell dysfunction and this effect can be reversed by far-infrared irradiation, PLoS One 11 (1) (2016) e0147067, https://doi.org/10.1371/journal.pone.0147067.
[54] C.H. Chen, M.C. Chen, Y.H. Hsu, T.C. Chou, Far-infrared radiation alleviates cisplatin-induced vascular damage and impaired circulation via activation of HIF-1α, Cancer Sci. 113 (6) (2022) 2194–2206, https://doi.org/10.1111/cas.15371.
[55] C.S. Rau, J.C. Yang, S.F. Jeng, Y.C. Chen, C.J. Lin, C.J. Wu, T.H. Lu, C.H. Hsieh, Far-infrared radiation promotes angiogenesis in human microvascular endothelial cells via extracellular signal-regulated kinase activation, Photochem. Photobio. 87 (2) (2011) 441–446, https://doi.org/10.1111/j.1751-1097.2010.00853.x.
[56] C.F. Chen, W.C. Yang, C.C. Lin, An update of the effect of far infrared therapy on arteriovenous access in end-stage renal disease patients, J. Vasc. Access 17 (4) (2016) 293–298, https://doi.org/10.5301/jva.5000561.
[57] I. Khan, S. Pathan, X.A. Li, W.K. Leong, W.L. Liao, V. Wong, W.L.W. Hsiao, Far infrared radiation induces changes in gut microbiota and activates GPCRs in mice, J. Adv. Res 22 (2020) 145–152, https://doi.org/10.1016/j.jare.2019.12.003.
[58] H.Y. Kim, S.Y. Oh, Y.M. Choi, J.H. Park, H.S. Kim, I. Jo, Transient receptor potential vanilloid 2 mediates the inhibitory effect of far-infrared irradiation on adipogenic differentiation of tonsil-derived mesenchymal stem cells, Stem Cell Res 53 (2021) 102291, https://doi.org/10.1016/j.scr.2021.102291.
[59] Y. Chang, The effect of far infrared radiation therapy on inflammation regulation in lipopolysaccharide-induced peritonitis in mice, SAGE Open Med 6 (2018) 2050312118798941, https://doi.org/10.1177/2050312118798941.
[60] Y. Chang, J.T. Chang, M.Y. Lee, M.Z. Huang, Y.C.C. Chao, Y.L. Shih, Y.R. Hwang, Does far-infrared therapy improve peritoneal function and reduce recurrent peritonitis in peritoneal dialysis patients, J. Clin. Med 11 (6) (2022), https://doi.org/10.3390/jcm11061624.
[61] C.N. Chang, C.Y. Niu, A.C. Tan, C.H. Chan, C.F. Chen, T.H. Chen, S.Y. Li, Y. T. Chen, F.Y. Chen, W.S. Liu, C.C. Lin, G.J. Wei, The effect of far-infrared therapy on the peritoneal expression of glucose degradation products in diabetic patients on peritoneal dialysis, Int J. Mol. Sci. 22 (7) (2021), https://doi.org/10.3390/ijms22073732.
[62] K. Honda, S. Inoué, Sleep-enhancing effects of far-infrared radiation in rats, Int J. Biometeorol. 32 (2) (1988) 92–94, https://doi.org/10.1007/bf01044900.
[63] H.N. Mai, N. Sharma, E.J. Shin, B.T. Nguyen, P.T. Nguyen, J.H. Jeong, C.G. Jang, E.H. Cho, S.Y. Nah, N.H. Kim, T. Nabeshima, H.C. Kim, Exposure to far-infrared rays attenuates methamphetamine-induced recognition memory impairment via modulation of the muscarinic M1 receptor, Nrf2, and PKC, Neurochem Int 116 (2018) 63–76, https://doi.org/10.1016/j.neuint.2018.03.009.
[64] H.N. Mai, N. Sharma, E.J. Shin, B.T. Nguyen, P.T. Nguyen, J.H. Jeong, E.H. Cho, Y.J. Lee, N.H. Kim, C.G. Jang, T. Nabeshima, H.C. Kim, Exposure to far-infrared ray attenuates methamphetamine-induced impairment in recognition memory through inhibition of protein kinase C δ in male mice: comparison with the antipsychotic clozapine, J. Neurosci. Res 96 (7) (2018) 1294–1310, https://doi.org/10.1002/jnr.24228.
[65] T.H. Tran, H.N. Mai, E.J. Shin, Y. Nam, B.T. Nguyen, Y.J. Lee, J.H. Jeong, H. Y. Tran, E.H. Cho, S.Y. Nah, X.G. Lei, T. Nabeshima, N.H. Kim, H.C. Kim, Repeated exposure to far infrared ray attenuates acute restraint stress in mice via inhibition of JAK2/STAT3 signaling pathway by induction of glutathione peroxidase-1, Neurochem Int 94 (2016) 9–22, https://doi.org/10.1016/j.neuint.2016.02.001.
[66] K. Fukui, S. Kimura, Y. Kato, M. Kohno, Effects of far infrared light on Alzheimer's disease-transgenic mice, PLoS One 16 (6) (2021) e0253320, https://doi.org/10.1371/journal.pone.0253320.
[67] T. Kihara, S. Biro, M. Imamura, S. Yoshifuku, K. Takasaki, Y. Ikeda, Y. Otuji, S. Minagoe, Y. Toyama, C. Tei, Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure, J. Am. Coll. Cardiol. 39 (5) (2002) 754–759, https://doi.org/10.1016/s0735-1097(01)01824-1.
[68] Y.W. Lin, C.S. Tsai, C.Y. Huang, Y.T. Tsai, C.M. Shih, S.J. Lin, C.Y. Li, C.Y. Lin, S. Y. Sung, F.Y. Lin, Far-infrared therapy decreases orthotopic allograft transplantation vasculopathy, Biomedicines 10 (5) (2022), https://doi.org/10.3390/biomedicines10051089.
[69] H. Miyamoto, H. Kai, H. Nakaura, K. Osada, Y. Mizuta, A. Matsumoto, T. Imaizumi, Safety and efficacy of repeated sauna bathing in patients with chronic systolic heart failure: a preliminary report, J. Card. Fail 11 (6) (2005) 432–436, https://doi.org/10.1016/j.cardfail.2005.03.004.
[70] K. Kominami, K. Noda, N. Takahashi, T. Izumi, K. Yonezawa, Cardiovascular reactions for whole-body thermal therapy with a hot pack and Waon therapy, Int J. Hyperth. 37 (1) (2020) 184–191, https://doi.org/10.1080/02656736.2020.1723719.
[71] C.C. Lin, W.C. Yang, M.C. Chen, W.S. Liu, C.Y. Yang, P.C. Lee, Effect of far infrared therapy on arteriovenous fistula maturation: an open-label randomized controlled trial, Am. J. Kidney Dis. 62 (2) (2013) 304–311, https://doi.org/10.1053/j.ajkd.2013.01.015.
[72] F.G. da Silva, G.E.G. Herr, F.J. Cidral-Filho, F. Petronilho, L.G. Danielski, D. Florentino, F. Bobinski, D.D. Ludtke, C. Vieira, D.F. Martins, E.R. Winkelmann, Antioxidant effect of far infrared radiation produced by bioceramics in individuals with intermittent claudication: a randomized, controlled pilot study, Alter. Ther. Health Med 25 (6) (2019) 34–43 (https://doi.org/).
[73] Y.C. Cheng, C.W. Lung, Y.K. Jan, F.C. Kuo, Y.S. Lin, Y.C. Lo, B.Y. Liau, Evaluating the far-infrared radiation bioeffects on micro vascular dysfunction, nervous system, and plantar pressure in diabetes mellitus, Int J. Low. Extrem Wounds 19 (2) (2020) 125–131, https://doi.org/10.1177/1534734619880741.
[74] S.C. Chen, M.Y. Lee, J.C. Huang, I.C. Kuo, H.C. Mai, P.L. Kuo, J.M. Chang, S. J. Hwang, H.C. Chen, Association of far-infrared radiation therapy and ankle-brachial index of patients on hemodialysis with peripheral artery occlusive disease, Int J. Med Sci. 13 (12) (2016) 970–976, https://doi.org/10.7150/ijms.17329.
[75] Y.H. Lin, T.S. Li, The application of far-infrared in the treatment of wound healing: a short evidence-based analysis, J. Evid. Based Complement. Alter. Med 22 (1) (2017) 186–188, https://doi.org/10.1177/2156587215623436.
[76] Y.H. Hsu, Y.F. Lin, C.H. Chen, Y.J. Chiu, H.W. Chiu, Far infrared promotes wound healing through activation of Notch1 signaling, J. Mol. Med. 95 (11) (2017) 1203–1213, https://doi.org/10.1007/s00109-017-1580-y.
[77] H. Toyokawa, Y. Matsui, J. Uhara, H. Tsuchiya, S. Teshima, H. Nakanishi, A. H. Kwon, Y. Azuma, T. Nagaoka, T. Ogawa, Y. Kamiyama, Promotive effects of far-infrared ray on full-thickness skin wound healing in rats, Exp. Biol. Med (Maywood) 228 (6) (2003) 724–729, https://doi.org/10.1177/153537020322800612.
[78] T.C. Chen, Y.C. Huang, T.Y. Chou, S.T. Hsu, M.Y. Chen, K. Nosaka, Effects of far-infrared radiation lamp therapy on recovery from muscle damage induced by eccentric exercise, Eur. J. Sport Sci. 23 (8) (2023) 1638–1646, https://doi.org/10.1080/17461391.2023.2185163.
[79] C.C. Hsieh, K. Nosaka, T.Y. Chou, S.T. Hsu, T.C. Chen, Effects of far-infrared radiation-lamp therapy on recovery from simulated soccer match running activities in elite soccer players, Int J. Sports Physiol. Perform. 17 (9) (2022) 1432–1438, https://doi.org/10.1123/ijspp.2022-0084.
[80] I. Kimura, T. Yamamoto, K. Nakamura, T. Uenishi, T. Asai, M. Kita, N. Kanamura, Effects of far infrared radiation by isotropic high-density carbon on the human oral mucosa, Arch. Oral. Biol. 94 (2018) 62–68, https://doi.org/10.1016/j.archoralbio.2018.06.011.
[81] C.H. Wong, L.C. Lin, H.H. Lee, C.F. Liu, The analgesic effect of thermal therapy after total knee arthroplasty, J. Alter. Complement Med 18 (2) (2012) 175–179, https://doi.org/10.1089/acm.2010.0815.
[82] J.Y. Yoon, J.H. Park, K.J. Lee, H.S. Kim, S.M. Rhee, J.H. Oh, The effect of postoperatively applied far-infrared radiation on pain and tendon-to-bone healing after arthroscopic rotator cuff repair: a clinical prospective randomized comparative study, Korean J. Pain. 33 (4) (2020) 344–351, https://doi.org/10.3344/kjp.2020.33.4.344.
[83] C.H. Lai, T.K. Leung, C.W. Peng, K.H. Chang, M.J. Lai, W.F. Lai, S.C. Chen, Effects of far-infrared irradiation on myofascial neck pain: a randomized, double-blind, placebo-controlled pilot study, J. Alter. Complement Med 20 (2) (2014) 123–129, https://doi.org/10.1089/acm.2013.0122.
[84] S.J. Choi, E.H. Cho, H.M. Jo, C. Min, Y.S. Ji, M.Y. Park, J.K. Kim, S.D. Hwang, Clinical utility of far-infrared therapy for improvement of vascular access blood flow and pain control in hemodialysis patients, Kidney Res Clin. Pr. 35 (1) (2016) 35–41, https://doi.org/10.1016/j.krcp.2015.12.001.

[85] J.H. Park, J.Y. Yoon, M.G. Jeong, H.J. Jeong, J.H. Oh, Far-infrared radiation to improve clinical outcomes after arthroscopic rotator cuff repair: a prospective randomized comparative clinical study, Clin. Orthop. Surg. 15 (5) (2023) 826–833, https://doi.org/10.4055/cios22386.
[86] L.H. Huang, Y.F. Lai, G.D. Chen, M.S. Lee, S.C. Ng, Effect of far-infrared radiation on perineal wound pain and sexual function in primiparous women undergoing an episiotomy, Taiwan J. Obstet. Gynecol. 58 (1) (2019) 68–71, https://doi.org/10.1016/j.tjog.2018.11.013.
[87] C.H. Chen, T.H. Chen, M.Y. Wu, T.C. Chou, J.R. Chen, M.J. Wei, S.L. Lee, L. Y. Hong, C.M. Zheng, I.J. Chiu, Y.F. Lin, C.M. Hsu, Y.H. Hsu, Far-infrared protects vascular endothelial cells from advanced glycation end products-induced injury via PLZF-mediated autophagy in diabetic mice, Sci. Rep. 7 (2017) 40442, https://doi.org/10.1038/srep40442.
[88] M. Umehara, A. Yamaguchi, S. Itakura, M. Suenaga, Y. Sakaki, K. Nakashiki, M. Miyata, C. Tei, Repeated waon therapy improves pulmonary hypertension during exercise in patients with severe chronic obstructive pulmonary disease, J. Cardiol. 51 (2) (2008) 106–113, https://doi.org/10.1016/j.jjcc.2008.01.004.
[89] H.W. Chiu, C.H. Chen, Y.J. Chen, Y.H. Hsu, Far-infrared suppresses skin photoaging in ultraviolet B-exposed fibroblasts and hairless mice, PLoS One 12 (3) (2017) e0174042, https://doi.org/10.1371/journal.pone.0174042.
[90] K. Li, Z. Zhang, N.F. Liu, P. Sadigh, V.J. Evans, H. Zhou, W. Gao, Y.X. Zhang, Far-infrared radiation thermotherapy improves tissue fibrosis in chronic extremity lymphedema, Lymphat Res Biol. 16 (3) (2018) 248–257, https://doi.org/10.1089/lrb.2016.0057.
[91] L. Xia, C. Cui, F. Nicoli, A. Al-Mousawi, C.C. Campisi, D. Lazzeri, N.F. Liu, B. Xie, K. Li, Y. Zhang, Far infrared radiation therapy for gynecological cancer-related lymphedema is an effective and oncologically safe treatment: a randomized-controlled trial, Lymphat Res Biol. 20 (2) (2022) 164–174, https://doi.org/10.1089/lrb.2019.0061.
[92] C. Chen, Y. Hua, Y. Hu, Y. Fang, S. Ji, Z. Yang, C. Ou, D. Kong, D. Ding, Far-red/near-infrared fluorescence light-up probes for specific in vitro and in vivo imaging of a tumour-related protein, Sci. Rep. 6 (2016) 23190, https://doi.org/10.1038/srep23190.
[93] W. Xu, M.M.S. Lee, J.J. Nie, Z. Zhang, R.T.K. Kwok, J.W.Y. Lam, F.J. Xu, D. Wang, B.Z. Tang, Three-pronged attack by homologous far-red/NIR AIEgens to achieve 1 +1+1>3 synergistic enhanced photodynamic therapy, Angew. Chem. Int Ed. Engl. 59 (24) (2020) 9610–9616, https://doi.org/10.1002/anie.202000740.
[94] Y. Han, S. Ling, Z. Qi, Z. Shao, X. Chen, Application of far-infrared spectroscopy to the structural identification of protein materials, Phys. Chem. Chem. Phys. 20 (17) (2018) 11643–11648, https://doi.org/10.1039/c8cp00802g.
[95] B.M. Fischer, M. Walther, P. Uhd Jepsen, Far-infrared vibrational modes of DNA components studied by terahertz time-domain spectroscopy, Phys. Med Biol. 47 (21) (2002) 3807–3814, https://doi.org/10.1088/0031-9155/47/21/319.
[96] W.L. Kao, C.W. Sun, Gender-related effect in oxygenation dynamics by using far-infrared intervention with near-infrared spectroscopy measurement: a gender differences controlled trial, PLoS One 10 (11) (2015) e0135166, https://doi.org/10.1371/journal.pone.0135166.
[97] P. Giménez, A. Linares, C. Sessa, H. Bagán, J.F. García, Capability of Far-Infrared for the selective identification of red and black pigments in paint layers, Spectrochim. Acta A Mol. Biomol. Spectrosc. 266 (2022) 120411, https://doi.org/10.1016/j.saa.2021.120411.
[98] E. Mazandarani, U. Lucke, K. Yoshida, M. Köppen, Comparison of Near and Far Infrared Vision for Biometric Applications, 2015 International Conference on Computer Application Technologies (CCATS 2015), Ieee, Matsue, JAPAN, 2015, pp. 34–37.
[99] J. Tian, W. Chen, Y. Xiong, Q. Li, S. Kong, M. Li, C. Pang, Y. Qiu, Z. Xu, Q. Gong, X. Wei, Small extracellular vesicles derived from hypoxic preconditioned dental pulp stem cells ameliorate inflammatory osteolysis by modulating macrophage polarization and osteoclastogenesis, Bioact. Mater. 22 (2023) 326–342, https://doi.org/10.1016/j.bioactmat.2022.10.001.
[100] S. Jia, E.M. Sletten, Spatiotemporal control of biology: synthetic photochemistry toolbox with far-red and near-infrared light, ACS Chem. Biol. 17 (12) (2022) 3255–3269, https://doi.org/10.1021/acschembio.1c00518.
[101] L. Sansalone, S. Tang, J. Garcia-Amorós, Y. Zhang, S. Nonell, J.D. Baker, B. Captain, F.M. Raymo, A photoactivatable far-red/near-infrared BODIPY to monitor cellular dynamics in vivo, ACS Sens 3 (7) (2018) 1347–1353, https://doi.org/10.1021/acssensors.8b00262.