

REVIEW ARTICLE

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Challenges and opportunities in next-generation LED therapeutic devices

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Abstract

Phototherapy offers advantages of non-invasiveness, cost-effectiveness, localized treatment, and potential for home-based care across various medical conditions. However, its adoption is hindered by the large size, limited safety, and professional operation requirements of current phototherapeutic devices. Unlike bulky laser phototherapeutic devices, wearable and implantable LED-based devices overcome these limitations, offering improved safety, portability, and uniform light distribution, making them promising prototypes for next-generation phototherapies. This review explores the home-care potentials of phototherapy from a clinical application perspective and provides a comprehensive overview of its therapeutic mechanisms and diverse applications. By synthesizing the latest advancements and cutting-edge research, we identify key clinical challenges associated with wearable and implantable phototherapy devices and propose fundamental strategies to address these limitations, such as miniaturization, biocompatibility, and energy efficiency. Furthermore, we draw on interdisciplinary cutting-edge research to address the challenges faced by phototherapy devices. We also emphasize the critical value of integrating artificial intelligence (AI) and flexible sensing technologies within phototherapy systems. Specific methods and potential applications are discussed for effectively integrating phototherapy systems with AI algorithms to establish a closed-loop diagnostic and therapeutic system. Grounded in clinical applications, we outline concrete research directions for developing next-generation LED-based phototherapy devices. This review delivers valuable insights for clinicians leveraging phototherapy and offers a roadmap for researchers in material science, flexible electronics, and AI, fostering interdisciplinary innovations to advance future phototherapy applications.

Introduction

The application of phototherapy dates back 3500 years, when ancient Egyptians and other civilizations along the Nile River combined medicinal plants with sunlight to treat vitiligo¹. In the late 19th century, sunlight was found to have therapeutic effects on anthrax and rickets. In the early 20th century, Niels Ryberg Finsen utilized artificial

light sources to treat cutaneous tuberculosis (lupus vulgaris), earning the Nobel Prize in Physiology or Medicine in 1903². In 1960, Dr. Maiman developed the solid-state laser and performed the first retinal tumor surgery using laser technology³. Due to its high brightness, monochromaticity, and directionality, laser therapy has been widely applied in treating pigmented disorders⁴, tumors⁵, scars⁶, infections⁷, vascular malformations⁴, and ophthalmic surgeries⁸. An important development occurred in photomedicine in 1983 when Rox Anderson introduced the concept of selective photothermolysis⁹. Building on its historical foundation, phototherapy has evolved into a diverse and versatile field, leveraging various light wavelengths for specific therapeutic applications.

Each segment of the electromagnetic spectrum offers distinct biological effects and clinical advantages based on

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its unique energy, frequency, and wavelength (Fig. 1a). In the gamma-ray range (< 0.01 nm), high-energy radiation targets tumors in radiotherapy¹⁰, while X-rays ($0.01 \sim 10$ nm) are used for diagnostic imaging¹¹. Ultra-violet (UV) light ($10 \sim 400$ nm) addresses skin conditions and tumors¹². Blue light ($450 \sim 490$ nm) is used for anti-bacterial therapy⁷ and neonatal jaundice treatment¹³, while green light ($495 \sim 570$ nm) aids in retinal therapy¹⁴ and pain relief¹⁵. Yellow light ($570 \sim 590$ nm) enhances immune function and improves mood¹⁶, and red light ($620 \sim 750$ nm) promotes wound healing¹⁷, hair growth¹⁸, and deep-tissue phototherapy¹⁹. Near-infrared lights (NIR, $700 \sim 2500$ nm), particularly 808 and 980 nm, are effective for pain management, and technologies like functional near-infrared spectroscopy are used for tissue imaging²⁰. Mid-infrared lights ($2500 \sim 25,000$ nm) include CO₂ lasers (10,600 nm) for surgical procedures²¹, while far-infrared lights ($> 25,000$ nm) generate thermal effects for conditions like arthritis²² (Fig. 1a).

The phototherapeutic mechanisms primarily rely on several pathways (Fig. 1b). Optogenetics²³ is a technique that allows precise control of neural activity and cellular functions through the activation of specific light-sensitive proteins, including ChR2, enhanced bacteriorhodopsin, natronomonas pharaonis halorhodopsin, and the like²⁴. When exposed to a 473 nm blue light, ChR2 channels open, allowing a significant influx of cations like Na⁺, leading to depolarization and subsequent neuronal excitation²⁵. This mechanism enables precise regulation of neuronal and cellular functions, making optogenetics a powerful tool widely used in neuroscience and biomedical research (Fig. 1b). Photobiomodulation (PBM)²⁶, previously referred to as low-level laser therapy (LLLT), typically employs red and NIR ($600 \sim 980$ nm) to activate the rate-limiting enzyme cytochrome C oxidase (CCO) in the mitochondrial electron transport chain. This activation enhances ATP synthesis and reduces oxidative stress while upregulating signaling molecules such as nitric oxide (NO) and calcium ions (Ca²⁺). Consequently, a cascade of downstream signaling pathways is triggered, resulting in the regulation of cellular physiological functions²⁷ (Fig. 1b). Photodynamic therapy (PDT)^{28,29} uses light of a specific wavelength to activate photosensitizers (PSs), generating reactive oxygen species ($\cdot\text{OH}$, $\cdot\text{O}_2^-$, and $^1\text{O}_2$) to eliminate cancers and pathogens³⁰. Blue light phototherapy, utilizing the wavelength of $400 \sim 470$ nm, facilitates the absorption of light energy by bilirubin molecules in the skin and converts it into water-soluble isomers, such as lumirubin. These isomers can be excreted from the body without requiring hepatic metabolism¹³ (Fig. 1b). These mechanisms underpin the therapeutic efficacy of phototherapy across diverse medical scenarios.

Current phototherapy has been successfully applied to several major human organs, including skin, nervous,

circulatory, urinary, musculoskeletal, and digestive systems (Fig. 1c, Table 1). Due to the limited penetration of light, phototherapy is primarily focused on the body surface, such as hair loss¹⁸, dermatological diseases^{31–33}, wound healing^{17,34}, chronic wound management^{35,36}, ophthalmopathy³⁷, and neonatal jaundice^{13,38} (Fig. 1c, Table 1). Such devices are designed to fit the body surface (e.g., skin, mucous membranes) and deliver light energy to superficial tissues, as well as areas that can be penetrated by external light sources, such as subcutaneous capillaries and the cerebral cortex. The therapeutic targets are typically located in the epidermis, dermis, shallow subcutaneous layers, or areas that can be penetrated by near-infrared light, typically up to 3–5 cm beneath the skin³⁹. Since they deliver light to the target area without requiring surgical intervention, these devices are clinically defined as wearable phototherapy devices. For instance, Sahel et al.³⁷ injected an adeno-associated viral vector encoding ChrimsonR into the eye, to facilitate partial vision restoration in a blind patient through the combined use of optogenetics and phototherapy goggles (Fig. 1c). Additionally, the face-fit surface-lighting micro light-emitting diodes (micro-LED) mask developed by Kim et al.³¹ conforms to complex facial contours, giving rise to significant improvement in facial elasticity, sagging, and wrinkles (Table 1). Analogously, the textile-based blue organic light-emitting diodes (OLEDs) developed by Choi et al.¹³ balance comfort and therapeutic efficacy, enabling at-home treatment for neonatal jaundice (Fig. 1c). Recently, we fabricated a stretchable red and blue LED (r&bLED) patch³⁶, which potentially offers a convenient antibacterial and wound-healing facilitation for managing chronic infectious wounds at home (Fig. 1c). Furthermore, a randomized controlled trial validated the efficacy of LLLT in the treatment of traumatic brain injury. Among 68 randomly assigned patients, 33 patients received NIR light therapy using a custom LED-helmet within 72 h post-injury, while 35 patients received sham treatment as controls. The results demonstrated statistically significant changes in multiple brain diffusion tensor imaging parameters during the subacute phase³⁹.

To date, researchers are devoting enormous efforts to overcoming the challenges of delivering light to deeper tissues⁴⁰, with the ultimate goal of expanding the applicability of phototherapy. Among them, fiber-optic and implantable LED devices are being developed to treat heart diseases^{19,41,42}, diabetes^{43–47}, bladder pain syndrome⁴⁸, encephalopathy^{25,49–51}, spinal cord injuries⁵², and neurological disorders^{53,54} (Fig. 1c, Table 1). These devices require implantation through natural body cavities (e.g., gastrointestinal tract, oral cavity, nasal cavity), minimally invasive procedures, or open surgery, to make direct contact with or be placed near deeper tissues, enabling precise light energy delivery. From a clinical application perspective, these

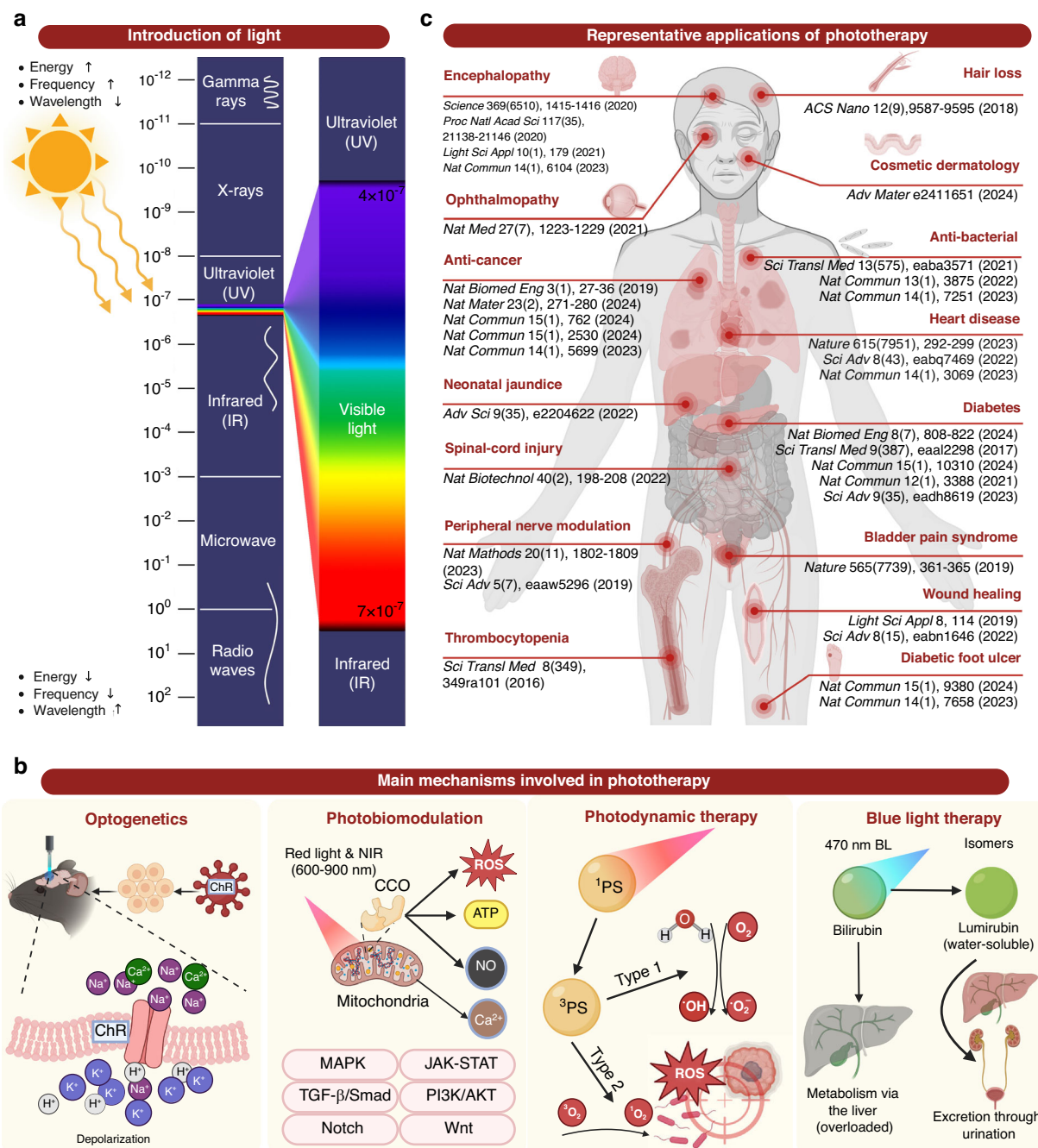


Fig. 1 Phototherapy and the underlying mechanisms. **a** Introduction of light. The electromagnetic spectrum illustrates the distribution of electromagnetic waves across various wavelengths. The enlarged section corresponds to the ultraviolet, visible, and infrared regions, which are the primary wavelengths used in phototherapy applications. **b** Schematic representation of the main mechanisms involved in phototherapy, including optogenetics²⁴, photobiomodulation²⁷, photodynamic therapy³⁰, and blue light therapy¹³. Optogenetics activates light-sensitive proteins, such as channelrhodopsin-2 (ChR2), allowing significant cation influx, particularly Na⁺, through ion channels, leading to depolarization and neuronal excitation. Photobiomodulation employs red and near infrared (NIR) light to activate cytochrome C oxidase (CCO) in the mitochondrial electron transport chain, enhancing ATP synthesis and reducing oxidative stress while upregulating signaling molecules such as nitric oxide (NO) and calcium ions (Ca²⁺). ATP, adenosine triphosphate. Photodynamic therapy uses light of specific wavelengths to activate photosensitizers (PSs), generating reactive oxygen species ([•]OH, [•]O₂⁻, and ¹O₂) to eliminate cancers and pathogens. Blue light phototherapy enhances bilirubin absorption in the skin, converting it into water-soluble lumirubin, which is excreted from the body without hepatic metabolism. **c** Representative applications of diseases treated with phototherapy and their corresponding research references: encephalopathy^{25,49-51}, ophthalmopathy³⁷, anti-cancer^{58,150,165-167}, neonatal jaundice¹³, spinal-cord injury⁵², peripheral nerve modulation^{53,54}, hair loss¹⁸, cosmetic dermatology³¹, anti-bacterial^{7,169,170}, heart disease^{19,41,42}, diabetes⁴³⁻⁴⁷, bladder pain syndrome⁴⁸, wound healing^{17,34}, and diabetic foot ulcer^{35,36}. Figure 1, created with BioRender.com, released under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International license

Table 1 Summary of Recent Advances in Flexible Phototherapy Devices

Phototherapy mechanism	Clinical application	Light emitting material	Light parameters		Substrate	Device type	Highlights	Refs
			Wavelength	Power				
Optogenetics	Nerve stimulation	OLED	400 ~ 580 nm	0.5 mW mm ⁻²	Parylene C	Implantable	Ultra-flexible film OLEDs provide precise light stimulation to the brain and can conform to various anatomical structures.	25
	Vision loss	OLED	600 nm	0.1 mW mm ⁻²	Silicon	Wearable	High-brightness, highly directional OLEDs have been incorporated into wearable prosthetics to facilitate optogenetic therapy for retinal cells.	156
	Control of cardiac rhythms	Micro-LED	591 nm	0.1 mW mm ⁻²		Wearable	The 591 nm micro-LED was integrated into a wearable textile vest, enabling non-invasive optogenetic control of heart rate in mice through the chest wall.	41
	Diabetes	LED	545 nm	0.15 mW cm ⁻²		Wearable	An innovative approach combining smartwatches with green light control provides new possibilities for the precise regulation of transdermal therapeutic gene delivery.	47
	Bladder pain syndrome	Micro-inorganic LED	530 nm	3.3 or 10 mW mm ⁻²	Silicone	Implantable	An innovative wireless closed-loop system has been developed for the optogenetic modulation of peripheral nerves.	48
	Cardiac pacing	Micro-LED array	Blue light	Pulse width of 10 ms, 101 mW mm ⁻²	PI	Implantable	A customized soft, thin-film micro-LED array enables high spatiotemporal precision in optogenetic stimulation delivery, while a closed-loop system allows for rapid pacing or defibrillation upon detection of arrhythmias.	42
	Spinal cord injury	Micro-LED	470 nm 535 nm	Pulse width of 10 ms, 50 mW mm ⁻²	PI	Implantable	Optogenetic stimulation is applied to the entire spinal cord region without the use of wires, while the closed-loop system enables real-time monitoring of physiological responses in mice and automatic adjustment of light stimulation based on feedback.	52
	Diabetes	LED	660 nm	20 mW cm ⁻²		Wearable	An optogenetic switch responsive to red and far-red light has been developed, offering high controllability for precise regulation of target genes.	44
	Diabetes	LED	730 nm	1 mW cm ⁻²		Implantable	Remote control of optogenetic cells is enabled via a smartphone, enhancing operational flexibility and improving patient autonomy in diabetes management.	45
	Wound healing	OLED	629 nm 534 nm 466 nm	5 mW cm ⁻²	Cylindrical-shaped materials, textiles and paper	Wearable	Sandwich-structured transferable OLEDs can be applied to various flexible substrates, such as textiles, enabling them to conform to the complex surfaces of human skin.	34
PBM	Ischemic stroke	LED array	630 nm	17 mW cm ⁻²	PI	Implantable	An implantable multi-LED array achieves stable contact with the target cortical region and the skull for PBM. Optimal results indicate that 630 nm is most effective in reducing infarct volume and neuronal damage following ischemic stroke.	55

Table 1 continued

Phototherapy mechanism	Clinical application	Light emitting material	Light parameters		Substrate	Device type	Highlights	Refs
			Wavelength	Power				
	Skin anti-aging	Micro-LED	627 nm	19.78 $\mu\text{W cm}^{-2}$	GaAs	Wearable	The face-fit surface-lighting μLED mask conforms to complex facial contours (elevations and curves), enhancing the effectiveness of PBM and resulting in significant improvements in facial elasticity, sagging, and wrinkles.	31
	Diabetic retinopathy	LED	630 ~ 1000 nm	120 μW	PET	Wearable	Intelligent wireless near-infrared emitting contact lenses can non-invasively stimulate retinal repair and regeneration, integrated with a smart control system.	157
	Hair-growth	Micro-LED	650 nm	~30 mW mm^{-2}	GaAs	Wearable	Monolithic flexible red vertical LEDs offer excellent light uniformity and are suitable for wearable applications aimed at stimulating hair growth.	18
	Melanogenesis inhibition	Micro-LED	630 nm	0.4 mW cm^{-2}	Plastic substrate	Wearable	The wearable design allows users to incorporate the device more easily into their daily lives.	62
	Wound healing	LED array	630 nm	~13.37 mW cm^{-2}	PI	Wearable	The adhesive nanofiber membrane wound dressing is combined with LED phototherapy.	17
	Hair-growth	OLED	640 nm	10 mW cm^{-2}		Wearable	Red OLEDs have been utilized for the first time in a mouse model to validate the stimulation of hair growth and assess their effects on hair follicle cells.	158
	Diabetes	OLED	600 ~ 700 nm	1.33 mW cm^{-2}	Parylene C	Implantable	Utilizing OLED catheters, uniform PBM within the duodenum has been achieved, with potential implications for the regulation of glucose and insulin metabolism.	43
		QLED	620 nm	~8 mW cm^{-2}	Glass	Wearable	The narrow emission band and wavelength tunability of QLEDs made it possible to fit the emission spectrum into the absorption window of cytochrome C (for PBM).	113
	Hair growth	QD-LED	630, 700 and 730 nm	>23.28 mW cm^{-2}	PET	Wearable	Wearable QD-OLED patch is developed for real-time wavelength controllable high-power NIR photomedicine. NIR QD-OLED demonstrated that it could increase the proliferation of HFDP cells by up to 131% through NIR wavelength control.	114
	Wound healing	QD-LED	NIR	2.5 mW cm^{-2}		Wearable	A red/NIR light source that matches 81.7% of the absorption spectrum of CCO enzyme was produced. Exposure of the produced light source to the wound area accelerated wound healing.	115

Table 1 continued

Phototherapy mechanism	Clinical application	Light emitting material	Light parameters		Substrate	Device type	Highlights	Refs
			Wavelength	Power				
PDT	Anticancer	OLED	Color-tunable	>100 mW/cm ²		Wearable	The parallel stacked OLED structure enhances light output intensity and therapeutic effectiveness while also possessing color adjustment capabilities.	159
	Wound management & antibacterial	OLED	669 ~ 737 nm	>9 mW/cm ²	PET	Wearable	Using flexible OLED as the light source enables uniform illumination for PDT. When combined with methylene blue as a photosensitizer, this approach effectively eliminates over 99% of <i>S. aureus</i> .	160
	Long-term autonomous cancer therapy	Miniature LED	470 nm		PET	Implantable	An implantable system that integrates human motion with PDT has been developed, creating a self-powered treatment solution that reduces reliance on external power sources.	127
	Anti-cancer	LED	630, 530 and 460 nm	<100 μW/cm ²	PDMS	Implantable	An implantable, wirelessly powered PDT system utilizes tissue-adhesive optoelectronics that securely adhere to the internal tissue surface without the need for surgical sutures.	58
Blue light therapy	Oral cancer treatment or diabetic wound repairs	QLED	620 nm		PEN	Wearable	The first in vitro study demonstrates that QLED-based photodynamic therapy effectively eradicates methicillin-resistant <i>Staphylococcus aureus</i> . High-efficiency QLED featuring narrow emission spectra and specific peak wavelengths achieves a luminance exceeding 20,000 cd/m ² under a low driving voltage of 6 V.	112
	Neonatal jaundice	OLED	470 nm	>20 μW/cm ² nm ⁻¹	Textile	Wearable	Textile-based blue OLEDs combine wearable technology with phototherapy, offering a convenient at-home treatment solution for neonatal jaundice.	13
	Dermatological diseases	LED	360 nm	20 ~ 80 mW/cm ²	PI	Wearable	The integration of PLGA microneedles for light conduction enhances the depth of illumination.	32

devices are commonly referred to as implantable phototherapy devices. For example, Ausra et al.⁴² customized a soft, thin-film micro-LED array that enabled high spatio-temporal precision for optogenetic stimulation delivery, facilitating cardiac pacing and defibrillation when implanted in vivo (Fig. 1c). Additionally, the combination of μ LED implants with optogenetically modified neurons expressing channelrhodopsin-2 (ChR2) allows for facile neural modulation within the body^{25,46,48,52,53} (Table 1). Kim et al.⁵⁵ developed an implantable multi-LED array that ensures stable contact with the target cortical region and skull for PBM therapy (Table 1). Their studies demonstrated that 630 nm red light effectively reduced infarct volume and neuronal damage following ischemic stroke. Besides, Kathe et al.⁵² developed a μ LED system capable of conforming to the dura mater of the spinal cord. Using an optogenetic model of spinal cord injury in mice, they integrated a physiological signal sensing module with a phototherapy module to achieve closed-loop control of spinal cord neurons. This innovative approach effectively addressed challenges associated with spinal-cord injuries (Fig. 1c, Table 1).

Over the past five years, the development of wearable and implantable phototherapy devices has accelerated significantly, with their effectiveness in treating various diseases being well demonstrated. Despite significant advancements, wearable and implantable phototherapy devices still face several challenges. Different diseases require specific parameters (wavelength, power density, and exposure duration) yet current devices often lack the precision and monitoring system to meet diverse clinical needs. Long-term comfort, biocompatibility, and energy supply also require optimization. Furthermore, improving therapeutic efficiency, expanding applications, and reducing costs in complex clinical settings remain pressing issues. Addressing these technical bottlenecks and aligning devices with clinical requirements is essential for advancing this field.

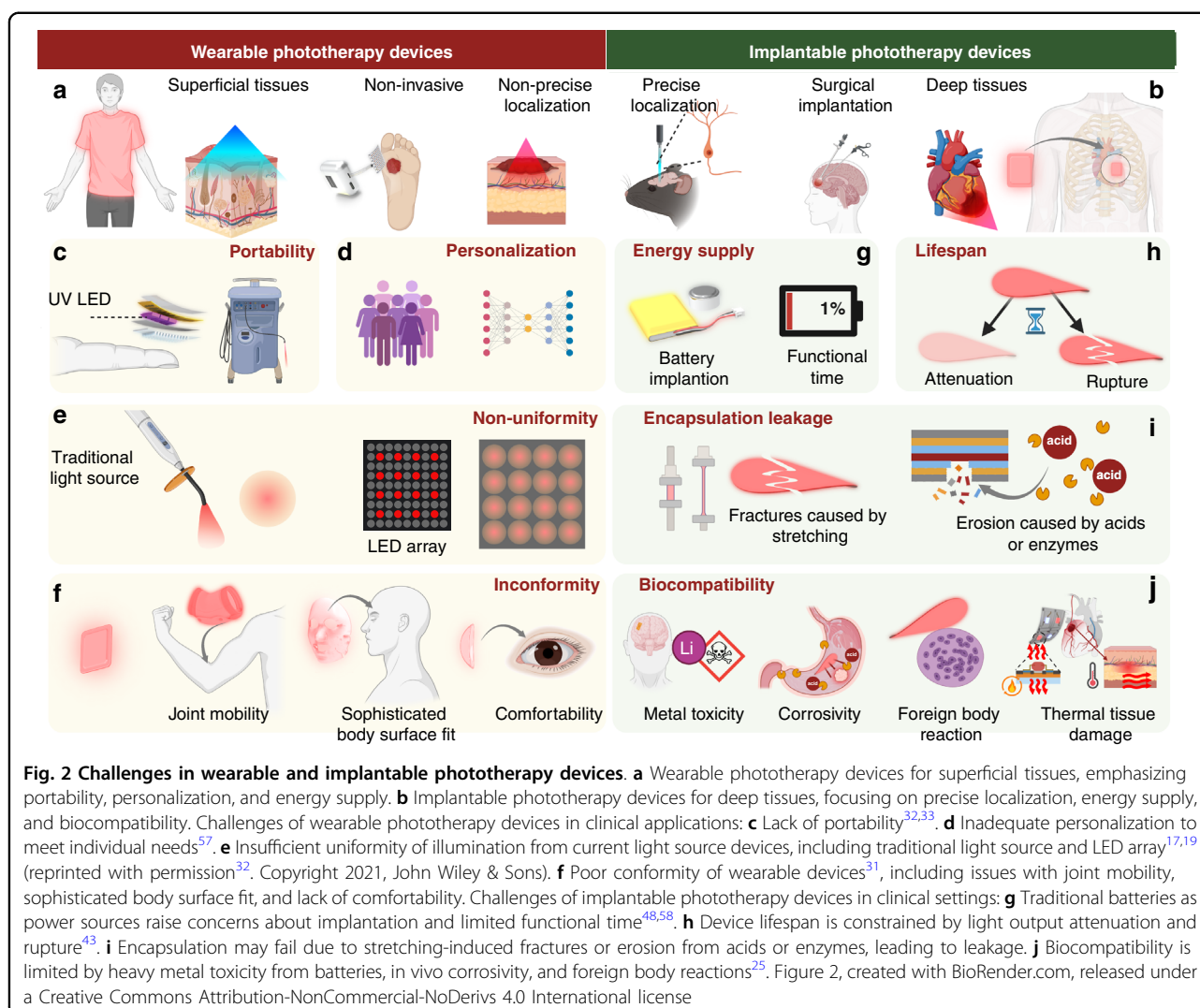
Challenges and unmet clinical needs in phototherapy devices

As previously mentioned, researchers classify LED phototherapy devices into wearable and implantable categories from the perspective of clinical applications. The choice between wearable or implantable phototherapy strategies depends on factors such as the depth of the target tissue⁴⁰, the nature of the disease, and whether anatomical barriers²⁸ (e.g., bone structures, dense fascia) need to be crossed, as well as the need for precise spatial localization⁵⁶ (Fig. 2a, b). Wearable devices do not require surgical intervention, providing higher patient compliance; however, they face limitations in addressing the phototherapy of deeper tissues. Implantable phototherapy devices, on the other hand, help overcome the challenge of delivering light to deeper organs and can enable precise phototherapy (e.g.,

optogenetic control of bladder afferent nerves⁴⁸) (Fig. 2a, b). However, both types face numerous technical and clinical challenges necessitating efforts to improve therapeutic efficacy and user experience. From the perspective of clinical phototherapy applications, wearable devices require excellent portability, personalized phototherapy capabilities, uniform light distribution, and conformity to the contours of the body surface to enhance therapeutic efficacy (left, Fig. 2). In addition to these requirements, implantable phototherapy devices must meet challenges such as energy supply, device longevity, encapsulation leakage, biocompatibility, and so on (right, Fig. 2).

Challenges in wearable phototherapy devices

First, insufficient portability of phototherapeutic devices significantly limits their usage scenarios (Fig. 2c). Phototherapy devices for skin diseases are often large and cumbersome, making them unsuitable for home use by patients³³. In comparison, Zhang et al.³² developed a compact phototherapy device designed for skin treatment. Its enhanced portability enables patients to undergo treatment conveniently at any time, thereby improving therapeutic outcomes. Secondly, current phototherapy devices lack personalized and precise treatment capabilities (Fig. 2d). For instance, managing symptoms in epilepsy patients often relies on preventive medication or optogenetic-based phototherapy⁵⁷. If a system could accurately predict epileptic episodes based on the patient's physiological data and changes in brainwave patterns, timely interventions could significantly improve outcomes. Addressing this challenge is essential for future wearable phototherapy devices to enhance therapeutic efficacy and improve patient compliance. Thirdly, the uniformity of light exposure in phototherapy devices is a critical factor influencing therapeutic outcomes (Fig. 2e). Laser-based point light sources often lead to uneven light intensity, resulting in variable efficacy between central and peripheral regions¹⁹. Researchers have explored LED array configurations to enhance light uniformity; however, insufficient illumination persists in the gaps between LEDs¹⁷. Moreover, irregular surface geometries in the target illumination area further compromise the effectiveness of phototherapy (Fig. 2f). For instance, the high mobility of human joints makes conventional rigid phototherapy devices incompatible with joint movements, preventing effective therapy during motion. Similarly, the complex anatomical structures of the face and periorbital regions, coupled with significant inter-individual variability, pose challenges to achieving uniform light distribution³¹. Apparently, improving phototherapy devices to achieve better illumination uniformity, enhanced portability, and greater adaptability to body surface contours is a critical challenge that must be addressed to enhance therapeutic efficacy (Fig. 2c–f).



Challenges in implantable phototherapy devices

Due to the limited penetration depth of light, its delivery directly to internal tissues remains formidable challenges for wearable devices⁵². On the other hand, implanted phototherapy systems pose unique energy supply challenges, as their batteries not only face implantation difficulties but also present potential biosafety concerns (Fig. 2g). Key considerations include battery size, energy density, and biocompatibility. Mickle et al.⁴⁸ demonstrated wireless power transfer for optogenetic therapy; however, the required coils were bulky and could only power a limited number of LEDs. In contrast, Yamagishi et al.⁵⁸ employed a self-powered approach for high-power PDT, but challenges remain in effectively covering large treatment areas. Apparently, engineering a biocompatible, safe, and optimized energy supply tailored to the specific requirements of implantable phototherapy systems is crucial for advancing their functionality and therapeutic potential. Moreover, implantable phototherapy devices

must contend with the harsh physicochemical environment. Sim et al.⁴³ demonstrated the use of OLED-based phototherapy devices implanted in the small intestine for diabetes treatment. However, the vulnerability of OLED materials to water and oxygen degradation severely limits the duration of effective phototherapy (Fig. 2h). To address this issue, dense and biocompatible encapsulation techniques are required to ensure device longevity. Nevertheless, overly thick encapsulation materials can compromise light intensity and device flexibility, while excessively thin encapsulation increases the risk of harmful material leakage, raising safety concerns (Fig. 2i). Enhancing the durability of light-emitting materials and improving encapsulation quality are critical challenges for advancing implantable phototherapy devices. Most importantly, as implantable devices, phototherapy systems must ensure robust biocompatibility and safety (Fig. 2j). Materials used in batteries, light-emitting components, encapsulation layers, and conductive elements may

contain metals or corrosive materials that can trigger metal toxicity, corrosive reactions, or immune-mediated foreign body responses. Kim et al.²⁵ addressed these challenges by developing a flexible OLED-based phototherapy device using a soft substrate and xylene film encapsulation. This approach minimized mechanical damage to neural tissues while effectively reducing the risk of immune rejection associated with implanted devices. Besides the biocompatibility of materials, heat generated during phototherapy and by the electronic components may cause thermal damage⁵⁹. Therefore, effective heat dissipation design is also crucial (Fig. 2j).

From the perspective of clinical phototherapy applications, future LED phototherapy devices must achieve comprehensive advancements to address the aforementioned challenges. This will require the development of novel conductive materials, light-emitting materials, encapsulation materials, and batteries, as well as advancements in manufacturing processes. Addressing these issues represents a complex interdisciplinary endeavor. In the following sections, we will propose specific strategies and highlight cutting-edge research aimed at overcoming these challenges. Additionally, we will summarize the design principles and fabrication workflows for next-generation LED phototherapy devices.

Strategies to overcome challenges in phototherapeutic prototypes

As phototherapy technologies continue to advance in the medical field, innovations in material science and fabrication technologies have established a robust foundation for addressing technical challenges and achieving substantial improvements in device performance. Incorporating the latest advancements and clinical needs identified by phototherapy specialists, our research team has reviewed and proposed targeted strategies to tackle the current limitations of phototherapy devices. These strategies focus on enhancing light distribution uniformity, advancing device miniaturization, improving implantability, integrating diagnostic and therapeutic functionalities, and enabling the intelligent modulation of phototherapy parameters.

Strategies to improve illumination uniformity

Zhang et al.⁶⁰ demonstrated the use of OLED technology to achieve surface light emission, resulting in improved illumination uniformity and enhanced phototherapy efficacy. QLED materials, which are compatible with the same fabrication processes as OLEDs, were utilized by Bian et al.⁶¹, who employed spin-coating and thermal evaporation deposition techniques to produce QLED devices capable of uniformly emitting high-intensity green light. Similarly, Kim et al.³¹ utilized μ LED technology, achieving comparable uniformity in light distribution with notable

improvements in therapeutic outcomes. Lee et al.⁶² introduced a diffusion layer, such as SiO_2 , and Deng et al.¹⁹ employed fiber optic lenses, enabling phototherapy devices with initially uneven illumination to achieve significantly more uniform light distribution (Fig. 3a). This design significantly reduces the risk of localized burns caused by uneven illumination while enhancing the effectiveness of treatment for large lesions, particularly in anatomically complex areas such as the face⁶², joints⁶³ and curved body surfaces^{36,64}.

Strategies for miniaturization of phototherapy devices

Miniaturization technologies are key to realizing wearable and implantable phototherapy devices (Fig. 3b). Through efficient integrated circuit designs and modular structures, the size and weight of devices have been substantially reduced. In this regard, Li et al.³⁶ designed a phototherapy patch comprising a phototherapy module, sensing module, power supply module, and Bluetooth/Wi-Fi module, significantly enhancing the portability and usability (Fig. 3b). The use of soft materials further enables the device to closely conform to the human body, ensuring effective illumination in complex curved areas such as joints, thereby enhancing both comfort and therapeutic results⁶⁵. Additionally, soft materials allow for further miniaturization of the device⁶⁶, making it more suitable for wearable or implantable phototherapy applications.

Strategies to enhance implantability of phototherapy devices

For implantability⁵⁵, optimizing material selection and encapsulation technologies are crucial to ensuring both performance and biosafety. Additionally, the mechanical properties of the implantable phototherapy device and their compatibility with the target organ^{41,67}, along with the choice of energy supply method⁴¹, are equally crucial to the design of implantable phototherapy devices (Fig. 3c). The use of biocompatible materials, such as hydrogels, flexible polymers, and biocompatible metals, significantly reduces the risks of inflammation and immune rejection⁶⁸. Multilayer encapsulation technologies (including both inorganic and organic layers) preserve device stability under extreme in vivo conditions, such as high humidity, acidity, and oxygen levels, while preventing leakage of harmful substances⁶⁹. Furthermore, by adjusting the Young's modulus and tensile strength of device materials to align with the mechanical properties of human tissues, potential biosafety issues post-implantation can be minimized. Ideally, the device's overall Young's modulus should be lower than that of the target tissue, while its tensile strength should exceed that of the tissue⁷⁰. Additionally, depending on the device's expected in vivo residence time, solutions such as soft batteries⁷⁰, micro-batteries⁷¹, wireless power⁴⁸, or energy

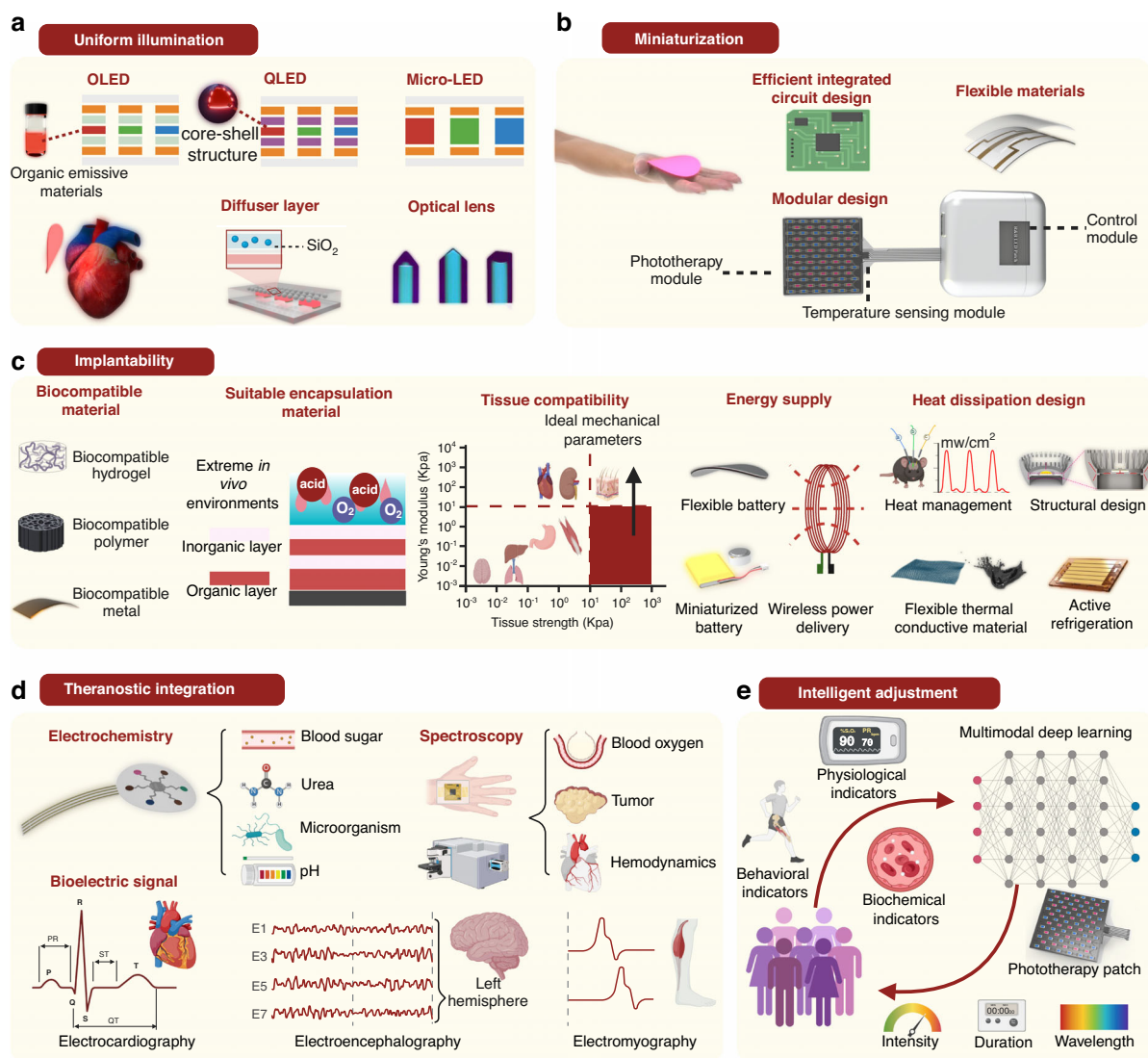


Fig. 3 Advanced strategies to address challenges in clinical applications of phototherapy. **a** Enhance the uniform illumination of phototherapy via OLED⁶⁰, micro-LED³¹, diffuser layer⁶², and optical lens¹⁹ technologies. **b** Achieving miniaturization of the overall device through effective integrated circuits⁵², flexible materials³⁴, and modular design. **c** By selecting biocompatible materials, employing appropriate encapsulation strategies, ensuring the mechanical compatibility of flexible phototherapy devices with tissues, and optimizing energy supply solutions, the implantability of phototherapy devices can be enhanced (the image for structural design is reprinted with permission⁷⁵. Copyright 2023, Nonferrous Metals Society of China. The image for active refrigeration is reprinted with permission⁷⁶ under Creative Common CC BY license. Copyright 2022, John Wiley & Sons). **d** Realizing theranostic integration by monitoring relevant electrochemical⁷⁹, spectroscopic^{67,140,163}, and bioelectric signals⁸⁰. **e** Employing AI to intelligently integrate detection information and output suitable phototherapy parameters⁵⁷. Figure 3, created with BioRender.com, released under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International license

harvesting methods⁵⁸ can be employed to address energy supply challenges (Fig. 3c). Thermal management is critical for implantable phototherapy devices. For low level light power therapies, such as PBM⁴³ or optogenetics⁵², passive heat transfer *via* body tissues suffices to maintain safe temperatures. However, high level light power applications like PDT require effective thermal management. Pulsed light therapy^{72,73} can control heat generation while maintaining efficacy. Flexible thermal

conductive materials⁷⁴, optimized heat dissipation structures^{75,76}, and micro cooling plates⁷⁷ enable passive and active cooling, ensuring the device stays within safe temperature ranges, thus enhancing performance and biosafety (Fig. 3c).

Strategies for integrating monitoring, AI and phototherapy

The integration of therapeutic and diagnostic capabilities represents a critical advancement in phototherapy devices

(Fig. 3d). By incorporating electrochemical sensors⁷⁸ and spectroscopic analysis modules⁷⁹, these devices can monitor biochemical indicators such as glucose, urea, and pH levels, alongside hemodynamic parameters like blood oxygen saturation and tumor markers. Additionally, integrating bioelectric signal monitoring⁸⁰, including electrocardiograms (ECG), electroencephalograms (EEG), and electromyograms (EMG), provides comprehensive physiological data to support personalized diagnosis and treatment (Fig. 3d). Leveraging intelligent adjustment technologies, phototherapy devices can now dynamically optimize treatment parameters based on patients' real-time conditions (Fig. 3e). Using multimodal deep learning algorithms⁵⁷, these devices analyze physiological indicators, biochemical markers, and behavioral data to intelligently adjust parameters such as wavelength, light intensity, and exposure duration. This closed-loop system enhances phototherapy efficiency, reduces reliance on medical professionals, and facilitates home-based applications, paving the way for improved therapeutic outcomes and broader usability.

Based on cutting-edge research, we propose the aforementioned strategies from a clinical perspective to address these challenges in phototherapy. In the following sections, we will elaborate on the implementation of these strategies through advancements in multidisciplinary research and discuss their specific impact on enhancing the phototherapy application.

Cutting-edge technologies and future processes

1. Advances in the development of LED phototherapy devices

To address the challenges of performance and applicability in LED phototherapy devices, researchers have introduced a variety of innovative strategies through material selection and process optimization. Significant progress has been made in areas such as soft substrates, soft active materials, soft emissive layers, soft encapsulations, and power supplies.

Soft substrate

The soft substrate is critical for determining the mechanical properties of phototherapy devices and ensuring compatibility with target tissues (Fig. 4a). An ideal substrate, as summarized in the table shown in Fig. 4a, should have a lower Young's modulus than the target tissue while providing sufficient tensile strength, high-temperature resistance, chemical stability, and stretchability. Polyimide (PI) is well-suited for wearable and implantable devices due to its thermal and mechanical properties¹⁷, while softer, biocompatible materials like Polydimethylsiloxane (PDMS)³², Thermoplastic Polyurethane (TPU)³⁶, Styrene-Ethylene-Butylene-Styrene⁸¹ (SEBS), and Ecoflex⁸² are preferable for dynamic areas.

Tailoring substrate selection to specific applications enables optimal adaptation to target regions. For example, wrapping the spinal cord for optogenetic therapies in paralysis treatment⁵², conforming to the body surface for blue-light therapy in jaundice management¹³, or adhering to the intestinal lining for red-light therapy applications⁴³ (Fig. 4a).

Soft active materials

In the fabrication of wearable or implantable phototherapy devices, soft active materials (Fig. 4b) should exhibit essential characteristics such as high electrical conductivity, stretchability, low cost, compatibility with diverse fabrication processes, biocompatibility, and durability. These requirements are designed to ensure that phototherapy devices maintain efficient optical power output to meet therapeutic needs while preserving stretchability.

Metal thin films are commonly used in device circuits due to their high conductivity and cost-effectiveness. They have been applied in optogenetic modulation for epilepsy⁵⁷, phototherapeutic repair of cerebral infarction⁵⁵, antimicrobial treatments for implant infections⁸³, and red-light therapy for hair loss¹⁸. Structural optimization ensures their flexibility and mechanical stability. Current research mainly focuses on techniques such as serpentine patterns⁵⁷, island-bridge structures⁸⁴, or metal cracks⁸⁵ to enhance their tensile strength. However, these approaches often significantly increase the device's volume, which hinders miniaturization. Therefore, intrinsically stretchable materials such as liquid metals and polymers are better suited for future phototherapy devices. For instance, liquid metal materials, celebrated for their self-healing properties and exceptional ductility, are especially well-suited for dynamic applications⁸⁶, such as treating arthritis, adapting to the beating surface of the heart^{19,41}, and addressing urinary dysfunction through optogenetic modulation in response to bladder pressure changes⁴⁸. Encapsulating liquid metals in elastomers can further improve their stretchability^{87,88}. Furthermore, the liquid metal's inherent chemical stability and the hermetic sealing design effectively address the challenges of oxidation, ensuring long-term performance and reliability in stretchable systems⁸⁶. Conductive polymers, which offer good stretchability and low cost, are another promising option. Although they are susceptible to water and oxygen degradation, surface molecular modifications can significantly enhance their durability⁸⁹, while maintaining good electrical conductivity (Fig. 4b). Many novel soft active materials can meet these requirements but are limited by their thermal tolerance, making them unsuitable for high-temperature processing. Consequently, the development of low-temperature fabrication techniques offers a pathway to expand the applications of these

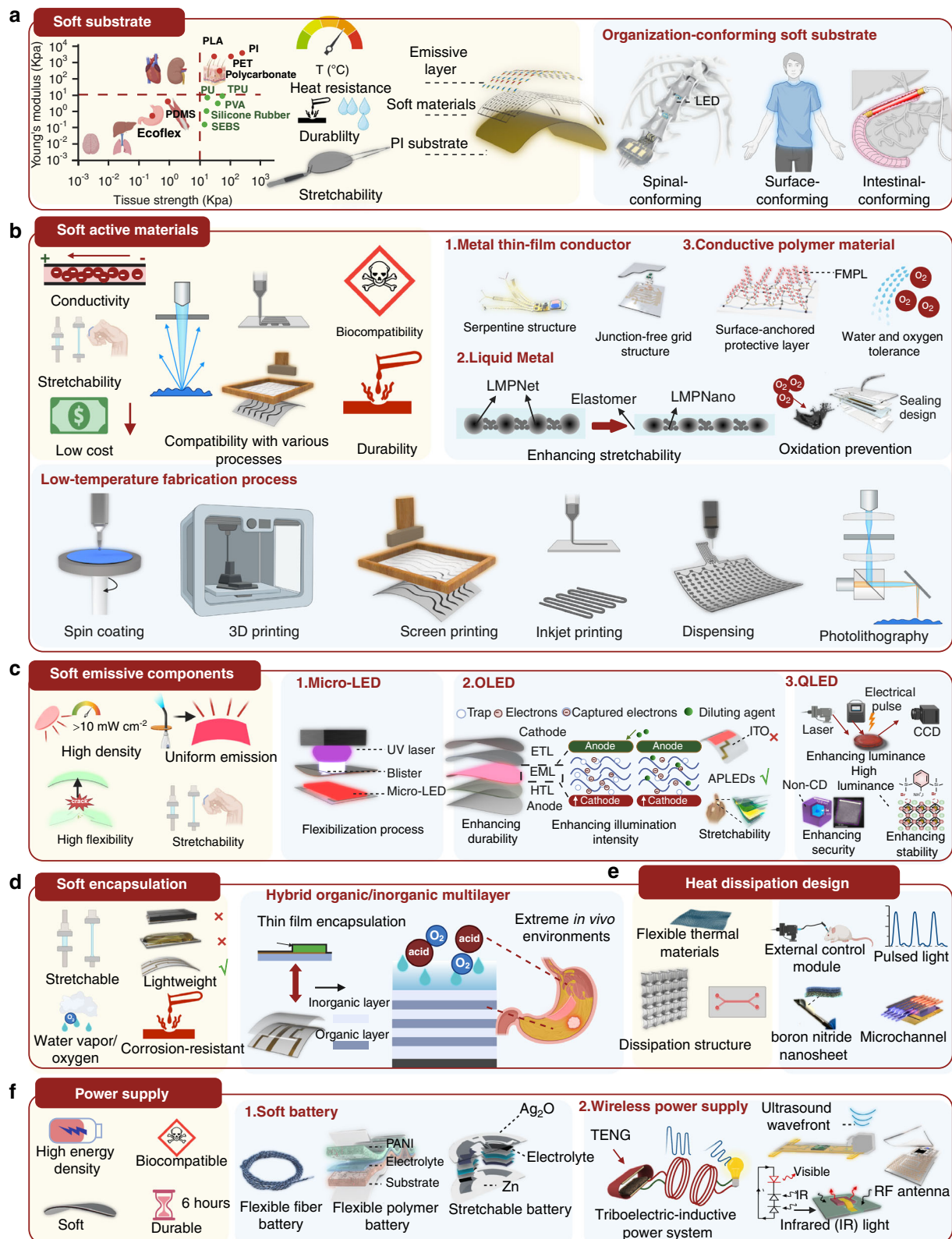


Fig. 4 (See legend on next page.)

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Fig. 4 Key progresses and innovations in processes and materials. **a** The ideal properties required for soft substrates and representative applications in nervous system (reprinted with permission⁵². Copyright 2022, Springer Nature)⁵², body surface¹³, and gastrointestinal tract (reprinted with permission⁴³ under Creative Common CC BY license. Copyright 2023, American Association for the Advancement of Science)⁴³. **b** Soft active materials, including metal thin films (the left image is reprinted with permission⁵⁷. Copyright 2023, Springer Nature. The right image is reprinted with permission⁸⁵. Copyright 2021, John Wiley & Sons)^{57,85}, liquid metals (reprinted with permission⁸⁶. Copyright 2023, American Association for the Advancement of Science)^{86,87,171}, and conductive polymer materials (reprinted with permission⁸⁹. Copyright 2023, Springer Nature)⁸⁹, along with their associated fabrication processes such as spin coating, 3D printing, screen printing, inkjet printing, dispensing, and photolithography. **c** Soft emissive component including Micro-LED³¹ and OLED (reprinted with permission⁶⁰. Copyright 2022, Springer Nature)⁶⁰ (reprinted with permission¹⁰⁵. Copyright 2020, Springer Nature). **d** Soft encapsulation: hybrid organic/inorganic multilayer⁶⁹. **e** Heat dissipation design: flexible thermal materials, external control module^{72,73}, boron nitride nanoseed structure⁷⁴, and microchannels⁷⁷ for enhanced heat management. (reprinted with permission⁷⁴ under Creative Common CC BY license. Copyright 2020, Springer Nature) **f** Power supply including soft battery (the middle image is reprinted with permission¹²² under Creative Common CC BY license. Copyright 2024, Springer Nature. The right image is reprinted with permission¹⁴⁸. Copyright 2022, Springer Nature)^{120–122} wireless power supply^{123–126} (the image for RF antenna is reprinted with permission⁷⁷. Copyright 2020, Springer Nature. The image for Infrared light is reprinted with permission¹²⁵. Copyright 2018, National Academy of Sciences). Figure 4, created with BioRender.com, released under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International license

advanced materials. Cutting-edge processing methods currently include spin coating⁹⁰, 3D printing⁹¹, screen printing⁹², inkjet printing⁹³, dispensing printing, and photolithography⁹⁴ (Fig. 4b).

Soft emissive components

The light sources used in flexible LED-based phototherapy devices can be classified into three main types: μ LEDs, OLED, and QLEDs. μ LEDs^{31,52,95} offer high light intensity ($\sim 1,000,000$ nits), long lifespan ($\sim 100,000$ h), and a narrow FWHM (15–20 nm), but have limitations in heat dissipation, flexibility, and light uniformity compared to OLED^{13,25,43} and QLED^{61,96,97}. OLED-based devices require further enhancement in brightness and resistance to oxygen and moisture^{98,99}, while QLEDs need to improve stability, ensuring no heavy metal incorporation^{61,100} (Table 2). To address these challenges, researchers have proposed various strategies.

In the field of soft emission components, μ LEDs/Micro-LED have become a focal point due to their high brightness, dense emission, and exceptional precision, making them the ideal selection for phototherapy device¹⁰¹ (Fig. 4c, Table 2). The challenge of transferring μ LEDs onto flexible substrates¹⁰² has been effectively resolved with advanced laser transfer technologies³¹. With decreasing costs, flexible μ LEDs show great promise as phototherapy light sources, particularly for complex surfaces like the face^{18,31,34}, intestines⁴³, brain^{52,55}, heart¹⁹, and lungs¹⁰³.

At the same time, OLED materials, conferring flexibility, low-temperature fabrication, and uniform light emission (Table 2), are already being applied in areas such as diabetic management⁴³, hyperbilirubinemia treatment^{13,38}, hemodynamic monitoring⁶⁰, and neuroregulation²⁵. However, their limited lifespan under high-intensity illumination constrains their broader use in phototherapy devices. While photobiomodulation and metronomic photodynamic therapy (PDT) can achieve therapeutic effects at lower light intensities, simultaneous improvements in

brightness and durability are essential to extend OLED applications to a wider range of therapies, including photodynamic and photothermal treatments. Encouragingly, advances in thin-film packaging technologies are now effectively addressing these issues¹⁰⁴. In parallel, new OLED optimization strategies, such as incorporating special solvents to dilute and reduce defects in the regions where electrons are captured within the OLED structure, along with the use of the double-sided polariton-enhanced Purcell effect to improve OLED stability, are further enhancing the light emission efficiency and lifespan of OLEDs^{60,98,99,105–108} (Fig. 4c). As detailed in Table 2, Red/Green (Phosphorescent) OLEDs exhibit lifespans exceeding $\sim 100,000$ h, while Blue OLEDs, especially the phosphorescent type, are showing ongoing improvements^{108,109}. Remarkably, researchers have also achieved major breakthroughs in the fabrication of intrinsically stretchable OLEDs^{60,105,110}, which currently represent the most stretchable light-emitting components developed to date.

QLEDs offer excellent flexibility, uniform surface emission, high light intensity ($> 300,000$ nits), and narrow FWHM (20–30 nm)^{111,112} (Table 2). Current research focuses on developing biocompatible, heavy-metal-free (e.g., Cd-free) flexible QLEDs^{61,100}. However, their limited stability and short lifespan remain significant challenges for phototherapy, with only a few studies addressing these issues^{112–115}. New methods, such as electrically excited transient absorption (EETA)⁶¹, can effectively quantify the issues present in heavy-metal-free QLEDs. By optimizing the core-shell structure¹⁰⁰ and surface passivation strategies¹¹⁶, it is possible to further enhance the luminous efficiency and stability, ensuring the biological safety of QLEDs (Fig. 4c).

Soft encapsulation

Encapsulation technologies also play a vital role in ensuring device stability. The ideal encapsulation should maintain the device's stretchability, lightweight nature,

Table 2 Characteristics and Comparison of LED-based Light Sources for Phototherapy Applications

	μ-LED	OLED	QLED (heavy-metal-free)	Refs
Light intensity	High (~ 1,000,000 nits)	Moderate (~ 10,000 nits achievable; EQE remains at 40% under 0–15,000 cd m ⁻²)	High (> 300,000 nits)	43,61,101,106,107
Emission area	Point light source	Uniform surface-emitting light source	Uniform surface-emitting light source	25,83,116
FWHM	Narrow (15–20 nm)	Relatively broad (> 30 nm)	Narrow (20–30 nm)	13,97
Flexibility	None per se (relies on flexible substrate and chip transfer technology)	Soft and flexible	Soft and flexible	31,60,96
Life span	Long (> 100,000 h)	Red/Green (Phosphorescent): Long (LT ₅₀ > ~100,000 hours); Blue (Fluorescent): Medium (LT ₅₀ ~ 10,000 hours); Blue (Phosphorescent): Limited but under improvement	Medium	13,95,98,100,106,108,109
Stability	High, oxygen- and humidity-resistant	Moderate, oxidation- and moisture-sensitive (requires excellent encapsulation)	Limited	36,99,104,116,161
Heat dissipation	Poor (spot high heat flow)	Excellent (uniform low heat flow)	Medium (faceted medium heat flow)	13,31,97

and durability (Fig. 4d). Hybrid organic/inorganic multi-layer encapsulation^{104,117} combines the gas-barrier properties of inorganic layers with the flexibility of organic layers, providing stability for phototherapy devices in extreme environments such as fluid-filled cavities like the abdominal and thoracic cavities, intracranial regions, and even the gastrointestinal tract, while minimizing the risk of toxic substance leakage—an essential consideration for implantable devices (Fig. 4d).

Heat dissipation design

LED phototherapy devices must address the potential side effects of heat generation during use. The skin’s outer layers, including the epidermis, dermis, and sub-cutaneous tissue, have low thermal conductivity ($\kappa \approx 0.3 \text{ W m}^{-1} \text{ K}^{-1}$)¹¹⁸, posing challenges for heat management. An ideal design integrates flexible thermal materials, efficient heat dissipation structures, and effective heat transfer mechanisms (Fig. 4e). In phototherapy, an effective strategy for preventing thermal damage is to transmit the LED light source *via* optical fibers while keeping the heat-generating control units external¹¹⁹. Metronomic PDT^{72,73}, using low-dose, extended-duration, high-frequency light, reduces local thermal load accumulation and provides an effective heat management solution. This approach offers a viable strategy for addressing heat dissipation in PBM, optogenetics, and blue light therapy. However, further studies are needed to assess its applicability across other phototherapy strategies. Additionally, advanced thermal management designs, such as polymer/boron nitride

nanosheets⁷⁴ and miniaturized microchannel heat sinks⁷⁷, offer potential solutions for enhancing heat dissipation in LED phototherapy devices (Fig. 4e).

Power supply

The power supply for phototherapy devices (Fig. 4f) plays a pivotal role in determining their functionality and application potential. An ideal power source should combine high energy density, soft, biocompatibility, and durability to meet the diverse demands of wearable and implantable phototherapy systems. Recent innovations in power systems have been driven by soft batteries and wireless power transfer technologies, enabling both device miniaturization and extended operational lifespans. Soft batteries have progressed significantly, making it possible to integrate them into textiles for wearable phototherapy devices, such as LED therapy patches designed to treat skin conditions like acne, wounds, and psoriasis¹²⁰. Alternatively, they can be incorporated as miniaturized droplet¹²¹ or thin-film batteries¹²² in micro-sized phototherapy devices, allowing precise energy delivery for localized treatments. For implantable phototherapy devices, the choice of power source is dictated by the application. Solid-state batteries, with their ability to prevent toxic substance leakage, are better suited for long-term implantable systems. Wireless power transfer technologies, such as magnetic induction and triboelectric nanogenerators¹²³ (TENGs), can harness kinetic energy from the human body to power implantable devices. These technologies expand the usability of phototherapy systems in scenarios requiring portability and frequent use.

Additional methods, such as ultrasonic power¹²⁴, infrared functionality¹²⁵, and far-field communication (RF)¹²⁶, present promising wireless energy options for implantable applications. These approaches are particularly advantageous for treatments requiring minimal device maintenance and long-term functionality. Despite these advances, phototherapy devices often demand substantial power for high-intensity light output, particularly in applications such as deep tissue treatment⁵⁸ or PDT¹²⁷. In these cases, wireless power solutions alone are insufficient to sustain real-time energy needs and they must be paired with integrated batteries to provide reliable energy storage. The careful selection and integration of power systems, tailored to the specific clinical context, ensures that phototherapy devices achieve optimal performance across a wide range of medical applications.

2. Future manufacturing processes for LED phototherapy devices

In response to the challenges currently faced by LED-based phototherapy devices in clinical applications, as well as recent advancements in the field, we present a universal fabrication process for future wearable/implantable LED phototherapy devices.

Selection of soft substrates

Selecting the appropriate soft substrate based on the intended application is a key step toward achieving device flexibility and stretchability (Fig. 5a). Textile-based substrates, with their breathability and softness, are particularly suitable for large-area treatment scenarios¹³, such as phototherapy garments for jaundice treatment, phototherapy knee braces for arthritis management, and phototherapy caps for promoting hair growth. Hydrogel substrates, known for their high biocompatibility and transparency, are preferred for devices in direct contact with the skin or organs⁷⁰. Polymer substrates, which balance mechanical strength and flexibility, are better suited for highly deformable regions and implantable phototherapy devices. Current soft substrates face significant challenges in conforming to complex biological surfaces (e.g., brain gyri or joint folds). As shown in Fig. 4a (left), the elastic modulus of brain and lung tissues is an order of magnitude lower than that of common polymer substrates (PI, PET, PDMS, SEBS), and the grooves in regions like the brain and skin hinder full adhesion of flexible phototherapy devices, affecting treatment uniformity¹²⁸. Flexibility is influenced by device thickness, Young's modulus, and width⁶⁶, with studies showing that a thickness of 10–100 μm ensures effective brain tissue adaptation¹²⁹. Ultra-flexible nanoelectronics (<10 μm feature size, 1 μm thickness) can further reduce chronic inflammation¹³⁰. Currently, phototherapy devices are often fabricated on polymer substrates, and researchers

have employed various methods to optimize the interface compatibility with tissues. OLED and QLED devices have achieved thicknesses around 10 μm ^{25,43,100}, offering excellent flexibility, while micro-LEDs can enhance tissue and organ compatibility and phototherapy efficacy through substrate design (octopus' structure)⁹⁵.

Fabrication processes for electrodes

To address the temperature tolerance of new materials, low-temperature fabrication techniques are better suited for future LED phototherapy devices¹³¹ (Fig. 5b). Methods like inkjet and 3D printing enable precise fabrication of complex structures⁹³ while optimizing conductive ink properties for multilayer flexible circuits. Spin-coating¹³² further improves the uniformity and optical performance of emissive layers with precise film thickness control (Fig. 5b).

Preparation of soft emissive components

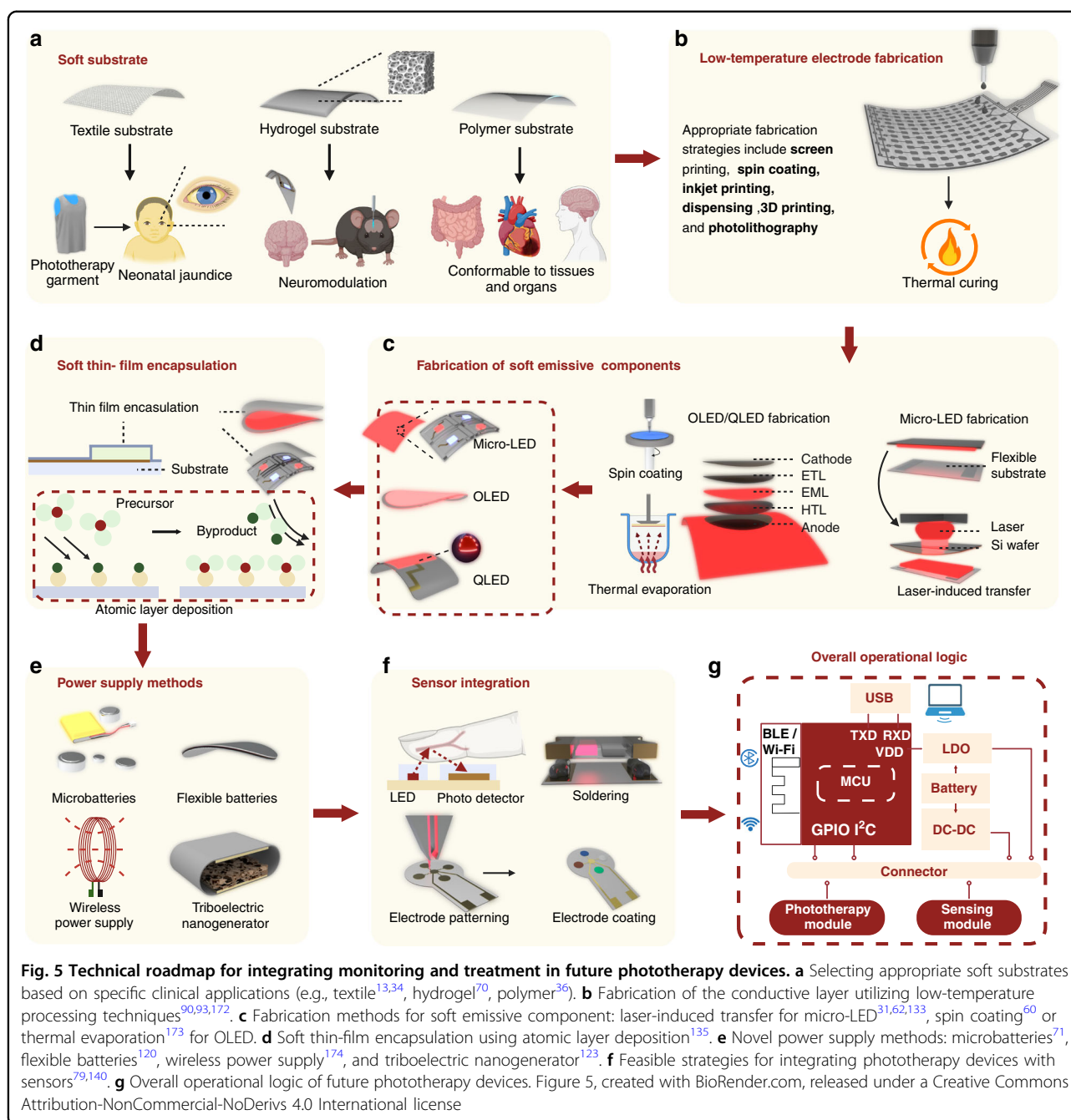
The manufacturing processes for soft emission components are continuously optimized to improve efficiency and reduce costs (Fig. 5c). Laser-induced transfer technology enables high-precision and large-scale production of μLEDs ¹³³, making them one of the most promising solutions for future phototherapy applications. Meanwhile, thermal evaporation¹³² techniques and advanced spin-coating⁹⁰ methods significantly enhance the luminous efficiency and lifespan of OLED and QLED devices by improving the fabrication of the emissive layer. When combined with elastomers, OLED⁶⁰ and QLED¹³⁴ devices exhibit enhanced stretchability and flexibility. Both of these light-emitting components can achieve ultra-uniform surface emission and meet the optical power requirements of phototherapy. Additionally, Surface-Mount Device LEDs can be directly integrated into phototherapy devices through soldering³⁶ (Fig. 5c).

Soft thin-film encapsulation

To preserve the softness and thinness of future LED phototherapy devices, atomic layer deposition¹³⁵ (ALD) (Fig. 5d) can sequentially deposit organic and inorganic layers, providing effective water and oxygen barriers. ALD's self-limiting growth mechanism ensures smooth atomic surfaces and uniform nanoscale films, making it a promising approach for thin-film encapsulation⁶⁹.

Energy supply methods

The power supply for future LED phototherapy devices should be tailored to specific application requirements (Fig. 5e). For wearable devices, rechargeable micro-batteries are ideal, offering extended use³⁶ for applications such as acne, wounds, and psoriasis. Implantable devices for short-term applications may utilize high-energy-density micro-batteries or soft batteries, particularly for treating heart diseases, cancer, and deep tissue



disorders. Long-term implantable devices require wireless power transfer systems to provide sustained energy supply. While wireless coils are commonly used, their size constraints limit achievable power levels and application scenarios. Alternative methods, including RF communication¹²⁶, ultrasound¹²⁴, infrared¹²⁵, and energy harvesting technologies like piezoelectric nanogenerators¹³⁶ or self-powered systems¹³⁷, show potential but are insufficient for high-power phototherapy applications. However, their real-time power output often falls short of the

demands of high-intensity phototherapy applications, necessitating battery storage to ensure a reliable and continuous energy supply.

Integration of sensing modules

The integration of sensors is pivotal for enhancing the intelligence of phototherapy devices (Fig. 5f). Electrodes for electrochemical and electrophysiological sensors are typically patterned using laser engraving¹³⁸, with functional materials deposited to enable targeted data

collection¹³⁹. Photoelectric detectors, based on spectroscopic principles, are fabricated similarly to LED emissive materials⁶⁸, while pre-packaged detectors can be soldered directly onto flexible circuits¹⁴⁰. As shown in Fig. 5g, the design of future phototherapy devices incorporates micro-processing chips that collect sensor data and use built-in algorithms to dynamically adjust treatment parameters in real time. Sensors monitoring parameters such as tissue oxygen levels, skin temperature, and light absorption enable real-time feedback and optimization of therapy, ensuring maximum efficacy tailored to specific clinical conditions.

Integrating sensors that monitor physiological parameters marks a significant advancement in phototherapy device technology. These sensors enable real-time feedback and dynamic optimization of treatment parameters, ensuring maximum therapeutic efficacy by adapting to specific clinical conditions. Seamless integration of sensors during device fabrication enhances functionality, streamlines design, and creates compact, efficient systems that reduce manual adjustments and improve adaptability across diverse clinical scenarios. Future devices, leveraging advanced Internet of Things technologies, will better meet clinical needs and address the growing demand for professional phototherapy services in home settings, further broadening the scope and impact of phototherapy technology.

Future directions: towards intelligent and integrated phototherapy systems

The rapid development of soft wearable and implantable sensors drives phototherapy devices toward enhanced intelligence and integration. A range of wearable and implantable sensor devices (Fig. 6a), including smart glasses¹⁴¹, smart contact lenses^{142–144}, monitoring headphones⁸⁰, implantable EMG, EEG and ECG devices⁵⁷, smartwatches¹⁴¹, microneedle patches⁷⁹, tendon sensors⁶³, and wound monitoring patches¹³⁸, have been developed to continuously monitor a wide variety of physiological, biochemical, and behavioral indicators (Fig. 6b).

In the treatment of chronically infected wounds (Fig. 6c), phototherapy devices integrated with sensors collect key physiological and biochemical data, such as pH, temperature, lactate, uric acid, and oxygen saturation, providing real-time insights into wound infection and healing progress¹³⁸ (Fig. 6b). These data are wirelessly transmitted to cloud platforms, where deep learning models, trained on large datasets, analyze the wound state, and recommend optimized phototherapy parameters (Fig. 6c). Models are embedded into phototherapy devices, using algorithms like CNNs for image data, LSTMs for time-series data, and Transformers for multimodal spatiotemporal inputs. Reinforcement learning methods,

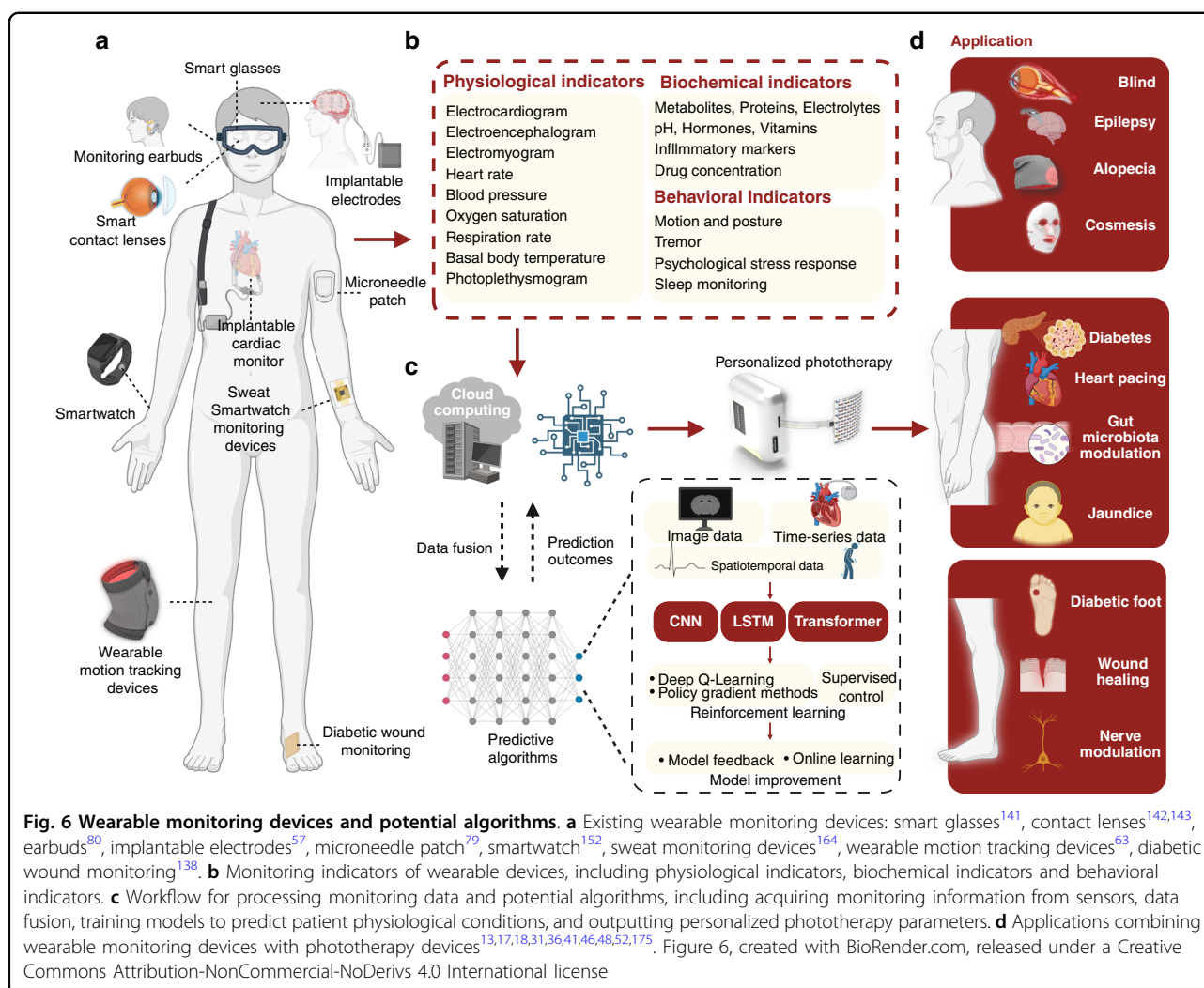
including Deep Q-Learning, Policy Gradient methods, and supervised control, refine the settings by learning from therapeutic outcomes. Model feedback and online learning further enhance adaptability, ensuring continuous optimization based on real-world data. This intelligent system dynamically adjusts phototherapy parameters—such as wavelength, intensity, and duration—creating a closed-loop framework for precise, efficient, and personalized wound management (Fig. 6c).

Based on the integration strategy of phototherapy devices with AI, Table 3 summarizes representative sensors that could be integrated with phototherapy systems in the future. Possible application scenarios are illustrated in Fig. 6d, with their integration approaches described as follows:

For the head, phototherapy devices based on optogenetics have been developed for the treatment of epilepsy⁵⁷, Alzheimer's disease^{145,146}, and depression¹⁴⁷ (Figs. 1a, 6d). These devices can integrate with wearable sensors, such as earbuds⁸⁰ and smart contact lenses^{142,143}, to monitor brainwaves, neural signals, and tissue oxygenation levels (Table 3), enabling personalized optical therapies tailored to the patient's disease progression. Additionally, facial sweat sensors¹⁴⁸ and electrochemical biosensors⁷⁹ (Table 3) have the potential to be combined with phototherapy masks³¹ and soft light-emitting patch¹⁷ for applications in acne treatment¹⁴⁹, pigmentation disorders¹⁵⁰, and facial rejuvenation⁶² (Figs. 1a, 6d).

In the torso region, wearable microneedle sensors⁷⁹, electrochemical sweat sensors¹⁵¹, and smartwatches¹⁵² are capable of monitoring blood glucose levels, blood oxygen saturation, heart rate, pulse, ECG signals, and physical activity acceleration, providing valuable insights into both cardiac and behavioral functions (Table 3). These advancements support applications such as light-based modulation of glucose metabolism⁴³, Parkinson⁴⁹ and optogenetic cardiac pacemakers⁴¹ (Figs. 1a, 6d). Moreover, integrating transcutaneous bilirubin sensors^{153–155} with phototherapy garments¹³ enhances the treatment of hyperbilirubinemia (Table 3), while implantable sensors combined with phototherapy devices hold promise for simultaneously monitoring gastrointestinal microbiota and modulating gut flora⁴³ (Fig. 6d).

For the limbs, sensors that measure deep tissue oxygen concentration⁶⁷ and peripheral metabolites⁷⁹ (Table 3), when integrated with phototherapy devices, enable closed-loop management of chronic infectious wounds, offering new solutions for addressing diabetes-related complications (Fig. 6d). Furthermore, optogenetic peripheral nerve modulation is becoming increasingly sophisticated. For example, integrating implantable pressure sensors with phototherapy devices allows precise regulation of bladder pressure, providing a solution for urinary dysfunction⁴⁸. Lastly, incorporating sensors capable of



detecting visual evoked potentials and electroretinography signals into phototherapy glasses allows real-time monitoring of visual function and supports vision restoration through targeted phototherapy³⁷(Fig. 6d).

The future of intelligent phototherapy systems extends beyond parameter adjustment to deep integration with treatment feedback mechanisms. Through real-time data analysis, these systems can detect subtle changes in disease states and automatically update AI models, further enhancing treatment precision. The high level of integration between phototherapy devices and sensors enables lightweight and non-invasive designs, making them highly suitable for daily use in home settings.

In conclusion, the advancements in soft wearable and implantable sensors, combined with the powerful data processing capabilities of AI algorithms, provide a solid foundation for the widespread application of intelligent phototherapy devices. This direction not only enhances treatment efficiency and safety but also advances the field

of precision medicine, offering personalized solutions for a range of complex diseases.

Conclusions and future perspective

This review adopts the perspective of clinical phototherapy practitioners, addresses specific clinical needs, and summarizes the extensive applications of phototherapy devices in the medical field. It highlights the major challenges encountered during the implementation of wearable and implantable phototherapy devices. Drawing on advancements in photomedicine, materials science, and soft electronics, the review proposes targeted strategies to address these challenges, summarizes interdisciplinary research contributing to the future development of phototherapy devices, and outlines a potential fabrication roadmap for future devices. Furthermore, it explores the integration of emerging AI technologies and soft sensing modules to design closed-loop phototherapy-monitoring systems for enhanced therapeutic outcomes.

Table 3 Summary of Sensor Modules Compatible with Phototherapy Devices

Application site	Targeted disease	Application method	Detection indicators	Detection mechanism	Highlights	Phototherapy strategy	Refs
Head	Epilepsy	Implantation	Oxygenation in deep tissue	Spectroscopy	Ultra-flexible film OLEDs provide precise light stimulation to the brain and can conform to various anatomical structures.	Use of blue/yellow wavelength light to promote neuroregeneration and seizure prevention, with intensity modulated based on oxygenation and EEG signal feedback.	⁶⁷
	Postoperative free flaps and replanted digits	Noninvasive, on-skin biosensor	Blood oxygen saturation, pulse rate	Photoplethysmography (PPG) signals	Wireless, continuous monitoring with a self-adhesive robust substrate	Use of near-infrared light to improve vascular perfusion and prevent tissue necrosis, with real-time modulation based on blood oxygen saturation and pulse rate data.	¹⁴⁰
Tendon/Connective tissue	Biomechanical strain monitoring	Implantable sensor	Strain in connective tissue	Capacitive strain sensing (wireless)	Stretchable, wireless operation, high sensitivity, biocompatible	Use of near-infrared or targeted wavelength light to promote tissue repair and regeneration, with intensity modulated by strain data feedback	⁶³
Brain	Postoperative monitoring of intracranial pressure and temperature	Implantation	Intracranial pressure, temperature	Pressure and temperature sensors	Fully bioresorbable, eliminating the need for surgical removal; demonstrated efficacy in rat models	Use of targeted wavelength light (e.g., near-infrared) to promote neuroregeneration and reduce inflammation based on detected brain pressure or temperature abnormalities	¹⁶²
Bladder	Bladder dysfunction	Implantation	Bladder volume and voiding events	Soft, stretchable strain gauge to monitor bladder filling and voiding	Fully implantable, wireless system combining real-time monitoring with optogenetic neuromodulation; demonstrated efficacy in normalizing bladder function in rat models	Use of optogenetic stimulation to modulate bladder sensory afferents, thereby controlling bladder function	⁴⁸
Ear	Neurological conditions, metabolic disorders	Non-invasive, in-ear wearable device	Brain activity (EEG, EOG, EDA), lactate levels in sweat	EEG, EOG, EDA, electrochemical sensing	Flexible, integrated sensor array for simultaneous monitoring of electrophysiological signals and sweat biomarkers; potential for real-time health monitoring	Use of targeted blue and near-infrared light to improve neurological function and metabolic regulation, guided by real-time EEG and lactate level monitoring.	⁸⁰

Table 3 continued

Application site	Targeted disease	Application method	Detection indicators	Detection mechanism	Highlights	Phototherapy strategy	Refs
Skin (Wrist)	Metabolic diseases (e.g., diabetes)	Noninvasive, on-skin wearable microneedle array	Glucose, lactate, alcohol levels	Electrochemical sensing	Integrated microneedle array enabling wireless, real-time, continuous monitoring of multiple biomarkers; paired with a smartphone app for data visualization	Use of near-infrared light for metabolic stimulation, with real-time intensity adjustments based on glucose, lactate, and alcohol level feedback.	79
Skin (e.g., forearm)	Metabolic monitoring	Noninvasive, on-skin wearable biosensor	Glucose, pH, sodium ions, sweat rate, skin temperature	Electrochemical detection, impedance analysis	Autonomous operation powered by flexible perovskite solar cell; continuous monitoring under lighting conditions; wireless data transmission	Use of near-infrared and green light to enhance metabolic processes, dynamically modulated by sweat biomarkers and skin temperature data.	78
Neck (carotid artery and jugular vein)	Cardiovascular health monitoring	Noninvasive, on-skin conformal ultrasonic device	Central blood pressure waveforms	Ultrasonic sensing	Ultrathin (240 μm), stretchable (up to 60%) device enabling continuous and accurate monitoring of deep arterial and venous sites; overcomes limitations of traditional bulky ultrasound probes	Use of targeted wavelength light to improve vascular elasticity and function, with intensity modulated by central blood pressure waveform feedback.	163
Skin (e.g., forearm)	Stress response assessment	Noninvasive, on-skin electronic skin	Vital signs: pulse waveform, galvanic skin response, skin temperature; Sweat biomarkers: glucose, lactate, uric acid, sodium ions, potassium ions, ammonium	Electrochemical sensors for sweat biomarkers; Physical sensors for vital signs	Continuous monitoring of physiological and biochemical stress markers; High accuracy in differentiating stressors with machine learning integration	Use of blue and red light to alleviate physiological stress markers, dynamically adjusted by sweat biomarker and vital sign data processed through machine learning.	164
Chest and foot	Vital signs monitoring in neonates	Noninvasive, on-skin epidermal electronic systems	ECG, (PPG), skin temperature	ECG: electrical potential measurement; PPG: optical sensing of blood volume changes; temperature: thermal sensing	Wireless, battery-free operation; ultrathin, soft, skin-like devices; real-time, in-sensor data analytics; time-synchronized, continuous data streaming; gentle adhesive interfaces suitable for fragile neonatal skin; compatibility with medical imaging techniques	Use of blue light for jaundice treatment and oxygenation improvement; integrated with vital sign data from ECG and PPG sensors for optimized therapy delivery.	154

Table 3 continued

Application site	Targeted disease	Application method	Detection indicators	Detection mechanism	Highlights	Phototherapy strategy	Refs
Forehead	Neonatal jaundice	Noninvasive, wearable transcutaneous bilirubinometer	Bilirubin levels, blood oxygen saturation (SpO ₂), heart rate (HR)	Colorimetric analysis for bilirubin; pulse oximetry for SpO ₂ and HR	Continuous, real-time monitoring; simultaneous measurement of bilirubin, SpO ₂ , and HR; effective during phototherapy	Automatic adjustment of blue light intensity for bilirubin breakdown, based on real-time bilirubin, SpO ₂ , and heart rate monitoring.	¹⁵⁵
Skin surface (e.g., arm)	Monitoring of hemodynamic parameters and metabolic biomarkers	Non-invasive, skin-conformal wearable patch	Blood pressure, heart rate, glucose, lactate, caffeine, alcohol levels	Ultrasonic transducers for hemodynamic parameters; electrochemical sensors for metabolic biomarkers	Simultaneous monitoring of multiple parameters; flexible and stretchable design; real-time data acquisition	Use of near-infrared light for hemodynamic improvement; dynamically controlled by blood pressure and metabolic biomarker feedback.	¹⁵¹
Skin surface over chronic wounds	Infected chronic wounds	Stretchable, wireless, wearable, bioelectronic patch	Uric acid, lactate, pH, temperature	Multiplexed multimodal electrochemical biosensor array	Continuous, real-time monitoring; controlled drug delivery; electrical stimulation for tissue regeneration	Use of antimicrobial blue light therapy and tissue-regenerative near-infrared light, with controlled intensity and duration based on pH, uric acid, and temperature feedback.	¹³⁸
Skin surface (e.g., forearm)	Monitoring of sweat biomarkers	Noninvasive, stretchable, on-skin biosensor	pH, sodium ions, glucose, lactate	Electrochemical sensors	Integrated printed battery; real-time data visualization via electrochromic display; fully autonomous operation	Use of light-based therapy for metabolic enhancement, with real-time adjustments guided by sweat biomarker data visualized on electrochromic display.	¹⁴⁸
Skin surface (e.g., chest, abdomen)	Continuous monitoring of vital signs in neonates and pediatric patients	Noninvasive, skin-conformal, wireless biosensor	Heart rate, respiration rate, temperature, blood oxygenation	Soft, flexible sensors with wireless data transmission	Measurement equivalency to clinical standards; additional features like movement tracking and acoustic cardiac monitoring; supports skin-to-skin contact	Use of therapeutic light for respiratory and circulatory support, with intensity modulated by real-time heart rate, respiration rate, and oxygenation data.	¹⁵³

Building on the outlined challenges and strategies for advancing phototherapy devices, it is essential to recognize the transformative role of photomedicine in clinical practice. Photomedicine has emerged as a cornerstone in disease diagnosis and treatment, transitioning from its historical role as an adjunct therapy to serving as a first-line treatment for various conditions. It has demonstrated remarkable efficacy in managing neonatal jaundice, wound healing, pigmentary disorders, and vascular anomalies. This transition underscores its value as a low-cost, highly precise physical therapy. The increasing clinical relevance of photomedicine necessitates its broader adoption, particularly as advancements in technology continue to improve its therapeutic precision and accessibility. Despite its promise, significant challenges remain in the design and engineering of wearable and implantable phototherapy devices. Wearable devices often face issues related to portability, personalization, illumination uniformity, and compatibility with the mechanical and optical properties of target tissues. We highlight the potential of OLED and μ LED technologies, combined with optical lenses and diffusion layers, to improve illumination uniformity and facilitate miniaturization through modular designs. On the other hand, implantable devices, while offering more targeted treatment, encounter limitations such as insufficient energy supply, reduced durability, encapsulation leakage, and biosafety concerns. Novel biomaterials, multilayer thin-film encapsulation, and soft or micro-batteries can be incorporated to enhance durability and biosafety. Additionally, integrating sensors such as electrochemical, spectroscopic, and electrophysiological systems enable closed-loop diagnostic and therapeutic capabilities, further advancing the precision and effectiveness of phototherapy applications.

Advances in light-emitting and conductive materials are also shaping the future of phototherapy devices. μ LEDs and OLEDs are identified as the most suitable light-emitting materials due to their high efficiency, flexibility, and biocompatibility. Similarly, liquid metals and stretchable conductive polymers are emerging as promising candidates for soft active materials, enabling devices to better conform to complex anatomical surfaces. To realize the potential of these technologies, low-temperature fabrication techniques are essential, particularly for new soft active materials that are sensitive to high-temperature environments. Additionally, hybrid organic-inorganic thin-film encapsulation and advanced wearable/implantable power solutions further accelerate the development of future phototherapy devices. To support the development of next-generation phototherapy devices, we outline a comprehensive design framework that incorporates the selection of soft substrates, active material deposition, and device schematics. This framework provides a roadmap for researchers and engineers to create devices that meet the stringent

requirements of medical applications, including safety, durability, and user-friendliness.

Finally, integrating AI with phototherapy devices represents a significant opportunity to advance the field. Leveraging wearable and implantable sensing technologies, AI has the potential to enable closed-loop systems that combine diagnostic and therapeutic capabilities, allowing for real-time adjustments to various clinical applications. Such intelligent systems hold transformative potential, as evidenced by proposed application scenarios that demonstrate their ability to improve outcomes across a range of medical conditions. These advancements highlight the exciting future of photomedicine and its growing role in precision healthcare.

Acknowledgements

We would like to thank all authors for their significant contributions to this review. Chenxi Wang and Qiang Yu conducted the writing, literature search, figure preparation, and summarization of key findings. Ming Li, Haoyi Chen, Huizhen Fan, and Yingying Ma assisted with literature retrieval, reference verification, table preparation, and manuscript proofreading. Zhitao Zhang provided expert guidance on OLED and Micro-LED processes and materials, helping refine the manuscript framework. Mei X. Wu offered professional insights on phototherapy development and clinical applications and reviewed the manuscript. Min Lu conceptualized the overall framework and supervised the writing and revisions. We would like to extend our special thanks to the Wellman Center for Photomedicine and Dermatology Department, Harvard Medical School and Harvard University, for their invaluable support and guidance, which greatly facilitated the successful completion of this review. Their expertise and resources provided critical insights into the development and clinical translation of phototherapy devices.

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Conflict of interest

The authors declare no competing interests.

Received: 18 December 2024 Revised: 10 July 2025 Accepted: 25 July 2025
Published online: 15 September 2025

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