FAKULTAS FARMASI
UNIVERSITAS MUHAMMADIYAH PURWOKERTO

PHARMACY: Jurnal Farmasi Indonesia
(*Pharmaceutical Journal of Indonesia*)

Journal homepage: https://jurnalnasional.ump.ac.id/index.php/PHARMACY

Received 07-11-2023 Accepted 06-12-2024 Available online 31-12-2024

A Review: Photodynamic Therapy on Wound Healing

Review: Terapi Fotodinamik untuk Penyembuhan Luka

Hasnita Hasnita[1], Hariyanti Hariyanti[2], Asmiyenti Djaliasrin Djalil[3]*
[1]Magister of Pharmacy, Universitas Muhammadiyah Purwokerto, Banyumas 53182, Jawa Tengah, Indonesia
[2]Department of Pharmaceutical Technology and Pharmaceutics, Universitas Muhammadiyah Purwokerto, Banyumas 53182, Jawa Tengah, Indonesia
[3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Muhammadiyah Purwokerto, Banyumas 53182, Jawa Tengah, Indonesia

A R T I K E L I N F O

Keywords:
Photodynamic therapy, photosensitizer, wound healing

A B S T R A C T

Wound infection poses a significant challenge in wound healing, so overcoming microbial infections and accelerating wounds can be done using PDT (Photodynamic Therapy). PDT is a non-invasive, light-based therapeutic method that can treat several pathological conditions such as wound healing, antimicrobial, antibiotic resistance bacteria, cancer, and skin repair. The review article aims to evaluate the effectiveness of PDT in accelerating wound healing. All articles in this review were taken from the Pubmed and Google Scholar internet databases from 2019 to 2024. Twelve photosensitizers were explored for wound healing using PDT. Some were used in singular form, while others were used in combination. PDT promotes wound healing by killing bacterial cells and stimulating fibroblast proliferation, producing collagen and elastin. The mechanism for faster wound healing was detected by increasing the epithelialization process, decreasing angiogenesis, reducing the number of fibroblast cells, and raising collagen density. Based on research, PDT uses a specific photosensitizer that is activated by light to produce Reactive Oxygen Species (ROS) so that in wound healing, PDT stimulates the wound healing process by improving the quality of tissue formed, fast wound closure, reducing the risk of complications, increasing blood circulation, reduces inflammation and promotes the proliferation of cells involved in tissue regeneration.

Kata Kunci:
Fotosensitizer, penyembuhan luka, terapi fotodinamik

A B S T R A K

Infeksi luka menimbulkan tantangan yang cukup besar dalam bidang penyembuhan luka, sehingga untuk mengatasi infeksi mikroba dan mempercepat luka dapat dilakukan dengan menggunakan Photodynamic Therapy (PDT). PDT adalah metode terapi non-invasif berbasis cahaya yang dapat mengobati beberapa kondisi patologis seperti penyembuhan luka, antimikroba, menghambat bakteri yang resisten terhadap antibiotik, pengobatan kanker, dan perbaikan kulit. Artikel ulasan ini bertujuan untuk mengevaluasi efektivitas terapi fotodinamik dalam mempercepat penyembuhan luka. Semua artikel dalam ulasan ini diambil dari database internet pada Pubmed maupun Google Scholar dari tahun 2019 hingga 2024. Terdapat 12 fotosensitizer yang dieksplorasi untuk penyembuhan luka menggunakan PDT. Beberapa di antaranya digunakan dalam bentuk tunggal, sementara yang lain digunakan dalam bentuk kombinasi. PDT mendorong penyembuhan luka dengan membunuh sel bakteri dan merangsang proliferasi fibroblas, sehingga menghasilkan produksi kolagen dan elastin. Mekanisme penyembuhan luka yang lebih cepat terdeteksi melalui peningkatan proses epitelisasi, penurunan angiogenesis, penurunan jumlah sel fibroblas, dan peningkatan kepadatan kolagen. Berdasarkan penelitian, PDT menggunakan fotosensitizer spesifik yang diaktifkan oleh cahaya untuk menghasilkan Reactive Oxygen Species (ROS), sehingga pada penyembuhan luka, PDT merangsang proses penyembuhn luka dengan meningkatkan kualitas jaringan yang terbentuk, penutupan luka cepat, mengurangi risiko komplikasi, meningkatkan sirkulasi darah, mengurangi peradangan dan mendorong proliferasi sel yang terlibat dalam regenerasi jaringan.

1. Introduction

Wounds are damage that occurs to the skin's protective function or loss of body tissue (Astuti et al., 2023). Wound infections are complex pathologies that can manifest as rapidly developing acute or chronic, protracted conditions. Acute and chronic wound infections are distinguished by their etiology (microbial phenotype), subsequent host immune response, and clinical manifestations (Hurlow & Bowler, 2022). A retrospective analysis of Medicare beneficiaries in 2018 found that 8.2 million people experienced wounds with or without infection. By 2024, from an economic perspective, it is estimated that the annual wound care products market is $15–22 billion (Sen, 2019). Furthermore, the quality of life is affected by chronic wounds for approximately 2.5% of the total population of the United States (Sen, 2023). Meanwhile, between 2014

E-mail address: asmiyentidjaliasrindjalil@ump.ac.id

and 2019, the overall prevalence of chronic wounds among US Medicare beneficiaries by kind of wound, i.e., over 5 years, there are now 10.5 million Medicare patients with wounds, up from 8.2 million previously. The prevalence of wounds rose from 14.5 to 16.4%, a 13% rise. Medicare enrollees <65 had the highest prevalence of chronic wounds (12.5–16.3% for men and 13.4–17.5% for women). Increases in arterial ulcers (0.4% to 0.8%), skin disorders (2.6% to 5.3%), and declines in traumatic wounds (2.7% to 1.6%) were the most notable shifts in the prevalence of wounds (Carter et al., 2023).

Wound infection is one of the main obstacles in wound healing. Inadequate wound healing techniques and indiscriminate antibiotic usage can lead to bacterial development and resistance to treatment. Developing innovative and effective treatment options is crucial for reducing infection-related mortality, patient suffering, and adverse side effects. As a result, there is a significant necessity for alternative treatments for treating infected wounds, one of which is photodynamic therapy (PDT) (T. Yang et al., 2020; Z. J. Zhao et al., 2020; Z. Zhao et al., 2021; Maya et al., 2020; D. Wang et al., 2024).

PDT can treat several pathological problems, including wound healing, antimicrobial resistance, chronic wounds, cancer, skin repair, carbuncle, and free gingival graft (Akbarizare, 2022; Alsaif et al., 2021; P. Chen et al., 2024; Damrongrungruang et al., 2023; de Carvalho et al., 2023; Dey et al., 2022; Djalil et al., 2012; X. Liu, Guo, et al., 2022; Maya et al., 2020; D. Wang et al., 2024; X. Wei et al., 2024; Xiu et al., 2022; Yaghobee et al., 2024; L. Zhang et al., 2020; Z. J. Zhao et al., 2020). PDT requires the application of a Photosensitizer to target cells, followed by irradiation of the wound tissue with a specific wavelength light source. In the presence of oxygen, light triggers Reactive Oxygen Species (ROS) formation and results in cell death (Pucelik & Dąbrowski, 2022). This therapy has effectively cured local and adjuvant treatment infections caused by bacteria (Gholami et al., 2023). Hemostasis, inflammation, proliferation, and remodeling are the four phases of wound healing. Cell signaling and synchronization between cells and chemical transmitters are essential for wound healing because their gradients draw immune cells and stop infections from pathogens (Leśków et al., 2023).

Many research groups have recently expressed interest in PDT's potential for tissue regeneration and wound healing. Several animal models for wounds, such as burns, excisions, and abrasions, were used in in vivo investigations before bringing PDT to human clinical trials (Guo et al., 2024; J. Huang et al., 2021; Pérez et al., 2021;T. Yang et al., 2020; Z. Yang et al., 2021; Z. J. Zhao et al., 2020; D. Wang et al., 2024; X. Liu, Guo, et al., 2022; X. Xu et al., 2020; Abo-Neima et al., 2023; Y. Wang et al., 2022; Abo-Neima et al., 2023; T. Huang et al., 2022; F. Wang et al., 2023; Meng et al., 2023). Bacterial infections can promote inflammation and create virulence factors, leading to tissue damage and delayed recovery (Caldwell, 2020). The evidence supporting the use of PDT in wound healing is compiled in this review.

2. Methods

All articles in this review were obtained from the internet databases "Pubmed" and "Google Scholar" from 2019 to 2024. Article searches were carried out using several keywords, including photodynamic therapy, which obtained 14504 articles, and photodynamic and wound healing, which received 428 articles.

The inclusion criteria are articles published in 2019-2024, primary literature, articles accessed in full-text form, and articles not from MDPI. The exclusion criteria were that the article was a literature review or systematic literature review, and no complete text was found. The inclusion criteria were narrowed to 121 articles from all articles**.**

3. Results and Discussion

Photodynamic therapy (PDT)

Light, oxygen, and photosensitizers are the three main ingredients of PDT. The PS absorbed by the cells converts into an excited singlet form by light irradiation. The PS excited triplet state is created by intersystem crossing. Type I and type II chemical reactions are the two types that produce ROS. The primary ROS in PDT is singlet oxygen, produced by the type II mechanism, which involves reacting the PS-excited triplet state with molecular oxygen. Through necrosis or apoptosis, the resulting ROS causes cell death. PS is absorbed by cells that multiply rapidly, such as malignant cells and microorganisms.

Mice infected with *A. baumannii* were evaluated for wound healing activity and anti-biophilic efficacy using Antimicrobial photosonodynamic therapy (aPSDT). With no damage to normal human skin fibroblast cell lines, the research showed that curcumin-nisin-based poly (L-lactic acid) nanoparticle (CurNisNp)-aPSDT can efficiently decrease the survival of *A. baumannii* cells through ROS production (Pourhajibagher et al., 2022).

PDT produces ROS which can damage cells which are then used to treat cancer, wound healing, antimicrobial, corneal tissue, inflammatory pseudotumor (IP), malignant tumors, glioma, antiviral (de Souza et al., 2022; T. Huang et al., 2022; Ma et al., 2024; (F. Wang et al., 2023) Y. Wang et al., 2022; Meng et al., 2023; Astuti et al., 2023; W. Huang et al., 2022; Chai et al., 2023; Abo-Neima et al., 2023; J. He et al., 2024; Osaki, T et al., 2023; F. Zhang et al., 2023; X. Liu, Fang, et al., 2022; X. He et al., 2024). PDT can repair tissue and treat uninfected or infected skin wounds due to the potential for inactivation of microorganisms (Abo-Neima et al., 2023) D. Wei et al., 2024). PDT skin wound healing is a complex and dynamic physiological process (Sun et al., 2020). Clinical studies have shown that indocyanine green photodynamic treatment (ICG-PDT) improved cell migration and wound healing in mice by activating the cystic fibrosis transmembrane conductance regulator (CFTR) (Chiu et al., 2019). Mediated *PDT nano-emodin* (n-Emo) shows wound healing (Yaghobee et al., 2024). In vivo, The primary purpose of photodynamic antimicrobial chemotherapy (PACT) has been to promote wound healing, including excisional wounds, burns, and abrasions (Z. J. Zhao et al., 2020).

In two distinct mice models of solid tumors and skin wound infections, Upconversion Dual-Photosensitizer–Bacteria (UDPB) can quickly promote wound healing and elicit a potent antitumor response (M. Chen et al., 2024). Antimicrobial photodynamic therapy (aPDT) can heal wounds in mice infected with bacteria and fungi (Z. J. Zhao et al., 2020; X. Liu, Guo, et al., 2022). PPIX-MED–aPDT treatment combined with antibiotics, in vitro and in vivo, has a promising bactericidal action because it can speed up the healing of infected third-degree burn burns in mice (Z. Zhao et al., 2021).

Photosensitizer

Several photosensitizers have been studied for wound healing in mice (Table 1). The effectiveness of PDT for diabetic wounds in mice is influenced by the type of PS, concentration, and light dose (Zuhayri et al., 2023). 5-aminolevulinic acid (ALA) can promote cutaneous wound healing in mice, lowering *P. aeruginosa* in the lesion and surrounding tissues (T. Yang et al., 2020). The mechanism consists of collagen remodeling, macrophages, and controlling inflammatory factors. ALA-PDT influences cellular responsiveness in chronic wounds to release a neurotransmitter such as NO (Nardini et al., 2024). ALA-PDT treatment is applied to cavities and wound surfaces after incisions and drainage procedures; topical administration of ALA-PDT can accelerate wound healing associated with *Staphylococcus aureus* infections (L. Zhang et al., 2020). Furthermore, using both normal and diabetic cellular wound models, the prior study showed that low-dose photodynamic treatment (LDPDT) could accelerate wound healing in vitro. Normal fibroblast cell viability declines when 5-ALA levels and energy density rise (Khorsandi et al., 2021).

By generating ROS by photoactivation, protoporphyrin IX–ethylenediamine derivative (PPIX-ED) has demonstrated remarkable efficacy in inhibiting the growth of *Pseudomonas aeruginosa*.

Protoporphyrin IX–ethylenediamine derivative–mediated photodynamic antimicrobial chemotherapy (PPIX-ED-PACT) altered the permeability of the bacterial membrane, as shown by acrylidine orange/ethidium bromide staining. Furthermore, PPIX-ED-PACT's antibacterial efficacy was demonstrated in an in vivo model of *Pseudomonas aeruginosa*-infected wounds. The number of P. aeruginosa colony-forming units was reduced by 4.2 log10 by PPIX-ED (100 μM). According to the histological study, PPIX-ED-PACT may successfully stop *P. aeruginosa* growth both in vitro and in vivo. On day 14 following treatment, the wound healing rate was 98%, 10% greater than that of the control group (Z. J. Zhao et al., 2020).

The biodegradable photosensitizer hematoporphyrin monomethyl ether (HMME) has demonstrated the capacity to produce ROS when activated by laser and thus can be used to combat germs. This chemical hydrogel increases angiogenesis, which is important for healing skin disorders, and has enhanced antibacterial activity and good biocompatibility. When the benefits of HMME, Cu_2O nanoparticles, and the gelling properties of carbomer are combined, this hydrogel compound shows promise as a wound dressing material (D. Wang et al., 2024).

The survival rate of *Candida auris* plankton and its biofilms may be considerably decreased by in vitro polylactic acid-hypocrellin a-antimicrobial photodynamic therapy (PLA-HA-aPDT), and the membrane's fungicidal activity remains strong even after four applications. PLA-HA has minimal hemolysis and strong biocompatibility. PLA-HA-aPDT can reduce inflammation and enhance wound healing in *C. auris* infections without clearly harmful side effects, according to in vivo tests. PLA-HA-aPDT may raise endogenous ROS levels, which could cause nuclear fragmentation, cytochrome C release, mitochondrial malfunction, and metacaspase activation, ultimately causing *C. auris* to undergo apoptosis (X. Liu, Guo, et al., 2022).

Two excision wounds on each side of the midline, were made in C57bL/6J mice to test PDT's efficacy and primary mechanism in the mouse model of acute wound healing. The right-sided wound was treated with methyl 5-aminolevulinate hydrochloride (MAL). Red light was applied to the wound incubating it for one to three hours. Red light and MAL were not applied to the left-sided wound. Hematoxylin and eosin (HE) staining on Day 14 revealed a continuous epithelium layer in the untreated lesion. At the base of the wound, the PDT-treated wound had some epithelium missing. The PDT-treated wound had more collagen fibers, inflammatory cells, and a thicker dermis than the untreated wound, according to Masson's Trichrome (MTC) staining. In a mouse wound healing model, immunohistochemical examination revealed considerably more collagen than untreated wounds (Sun et al., 2020).

Compared to either therapy alone, methylene blue (MB) loaded with polyethylene glycol (PEG) (MB-PEG) based hydrogel can enhance and accelerate wound closure in the setting of laser (Hamed et al., 2024). Compared to mupirocin alone or with MB-aPDT, antimicrobial photodynamic therapy based on Methylene Blue (MB-aPDT) produced the best wound healing (Pérez et al., 2021). Compared to MB solution, methylene blue nanoparticles (MPNP) exhibit a significantly more substantial antibacterial impact both in vitro and in vivo. MPNP's reduced aggregation-induced quenching (ACQ) effect increases singlet oxygen production, enhancing the antibacterial action. It was demonstrated that MPNP has a strong antibacterial effect and speeds up wound healing in a mouse skin infection model (X. Xu et al., 2020).

Streptococcus pneumoniae, nontypeable Haemophilus influenzae (NTHi), and planktonic and biofilm-associated Moraxella catarrhalis were all shown to be susceptible to the photosensitizing effects of aPDT with chlorin e6 (Ce6). With a 99.9% loss of viability, the three main otopathogens demonstrated substantial bactericidal action. Specifically, the new dual treatment aPDT technique disinfects effect and prevents bacterial recurrence 24 hours after treatment. Furthermore, a potent and cutting-edge therapeutic approach for successfully treating and curing bacterial otitis media (OM) infections and halting the onset of recurring illness is Ce6-aPDT treatment (Luke-Marshall et al., 2020). Gelatin-Ce6 shows high potential for the efficacy of photodynamic therapy for tumor diseases in vivo clinical application (Son et al., 2019). If the photodynamic mechanism plays a role, Indocyanine green-mediated photodynamic therapy (ICG-PDT) maximally reduces keloid fibroblast migration and cellular activity. This therapy can also prevent collagen formation and induce apoptosis and autophagy.

Table 1. Photosensitizer used in PDT wound healing

No.	Photosensitizer	Use	Study phase	Reference
	5-aminolevulinic acid	Antimicrobial and wound healing	In vitro and in vivo	(Guo et al., 2024)
	5-aminolevulinic acid	Wound healing	In vivo	(Nardini et al., 2024)
	5-aminolevulinic acid combined with human umbilical cord mesenchymal stem cells	Antimicrobial and wound healing	In vitro and in vivo	(Jianhua Huang et al., 2021)
	5-aminolevulinic acid	Antimicrobial and wound healing	In vitro and in vivo	(T. Yang et al., 2020)
	5-aminolevulinic acid	wound healing	In vitro and in vivo	(Z. Yang et al., 2021)
2.	Protoporphyrin IX–ethylenediamine derivative	Wound healing in mice infected with Pseudomonas aeruginosa bacteria	In vitro and in vivo	(Z. J. Zhao et al., 2020)
3.	Cu_2O and hematoporphyrin monomethyl ether	Healing of infected wounds	In vitro and in vivo	(D. Wang et al., 2024)
4.	Polylactic acid-hypocrellin *a*	Wound healing in mice infected with the fungus candida auris (c. Auris)	In vitro and in vivo	(X. Liu, Guo, et al., 2022)
5.	Methyl 5-aminolevulinate hydrochloride	Cutaneous wound healing in mice	In vivo	(Sun et al., 2020)
	Methylene blue or mupirocin or both	Antibacterial and wound healing	In vitro and in vivo	(Pérez et al., 2021)
	Methylene blue nanoparticles	Antibacterial and wound healing	In vitro and in vivo	(X. Xu et al., 2020)
	Methylene blue	Antibacterial and wound healing	In vitro and in vivo	(Abo-Neima et al., 2023; Y. Wang et al., 2022)
	Methylene blue	Antibacterial, anti-corona virus and wound healing	In vitro and in vivo	(Abo-Neima et al., 2023)
7.	Chlorin e6	Antibacterial and wound healing	In vitro and in vivo	(T. Huang et al., 2022)
	Indocyanine green	Wound healing	In vivo	(Ma et al., 2024)
	Indocyanine green	Wound healing	In vitro and in vivo	(Chiu et al., 2019)
9.	Oeo-TPE-MEM (OTM)	Antibacterial and wound healing	In vitro and in vivo	(F. Wang et al., 2023)
10.	Photosensitizer with a porphyrin bearing four ornithine	Antimicrobial and wound healing	In vitro and in vivo	(Meng et al., 2023)
11.	Curcumin	Wound healing	In vivo	(Astuti et al., 2023)
12.	Upconversion dual-photosensitizer–expressing bacteria	Antitumor and wound healing	In vitro and in vivo	(M. Chen et al., 2024)

The in vivo treatment regimen is optimized by the ICG-PDT mechanism, indicating the substantial therapeutic potential of ICG-PDT in clinical keloid treatment (Shao et al., 2024). ICG was employed in another study to create photothermal and photodynamic effects. It was discovered that the hydrogel with ICG-loaded platelets has outstanding wound repair qualities, accelerating wound healing and reducing inflammation under NIR (Ma et al., 2024).

Gram-positive bacteria can be effectively bound and killed by OEO-TPE-MEM (OTM). However, a more significant OTM concentration is required to kill Gram-negative bacteria since its affinity for them is lower than that of Gram-positive bacteria. OTM has excellent biocompatibility with both normal mammalian cells and those exposed to light and darkness. Because OTM can accelerate the healing of bacterial wounds in a mouse model without compromising the organs or blood parameters, it is a great option for clinical use (F. Wang et al., 2023).

A novel cationic photosensitizer against multidrug-resistant Proteus mirabilis (MRPM) was prepared by conjugating aminophenyl porphyrin with amino acid L-ornithine. The effects of laser energy, absorption, MIC and MBC, dose-dependent photoinactivation effect, membrane integrity, and fluorescence imaging were examined, as well as the in vitro photoinactivation efficiency against MRPM in vivo. To evaluate photodynamic antimicrobial chemotherapy (PACT) in vivo, MRPM was used in a mouse wound infection model. In addition to having a strong photoinactivation efficiency against MRPM at 7.81 μM when exposed to light, the photosensitizer with porphyrin containing four ornithine groups can accelerate wound healing through bactericidal action. This combination of ornithine and porphyrin can be a photosensitizer for PACT in treating MRPM infection (Meng et al., 2023).

Curcumin-silica nanoparticles have shown a noteworthy cytotoxic impact against typical human fibroblast and potential wound-recuperating properties, as confirmed by in vitro scratch measures (Mirzahosseinipour et al., 2020). On the other hand, ozone therapy, red laser therapy (650 nm, 3.5 J/cm^2) with ozone, blue laser therapy (405 nm, 3.5 J/cm^2) with ozone, and blue laser therapy (405 nm, 3.5 J/cm2) with ozone and curcumin were used to test the efficacy of wound healing. Before laser and ozone treatment, the wound area was treated with a photosensitizer (10 mg/mL of curcumin). When paired with ozone and curcumin, the red and blue laser efficiently speeds up the healing of MRSA-infected incision wounds (Astuti et al., 2023), inspiring further research and potential for discoveries in wound healing.

Research on the photosensitizer UDPB has shown promising results when used with monochromatic near-infrared irradiation. UDPB showed a potent anticancer response and promoted quick wound healing in two mouse models with solid tumors and skin wound infections (M. Chen et al., 2024).

Mechanism of photodynamic therapy in wound healing

PDT uses light, oxygen, and photosensitizers (PS) to create ROS, which can cause necrosis or apoptosis in cells (F. Wang et al., 2023; Buzzá et al., 2022). PDT mechanism is PS absorbs light, which causes type I and type II reactions to produce singlet oxygen and other ROS (Digby et al., 2021; Pucelik & Dąbrowski, 2022; Taninaka et al., 2023). By rupturing cell membranes, changing the shape of microsomes, and blocking specific processes such as oxidative damage to nucleic acids, ROS and singlet oxygen produced during photodynamic reactions can kill bacteria (Alsaif et al., 2021; Alves et al., 2013; Amos-Tautua et al., 2019; Awad et al., 2016; P. Xiao et al., 2022).

It is fascinating to note that many different microorganisms with unique characteristics can colonize and contaminate exposed subcutaneous tissue. If the host immune response is compromised and the tissue devitalized (ischemic, hypoxic, or necrotic), the conditions favor microbial development. The three primary sources of wound contaminants are the environment (exogenous microorganisms in the air or those caused by traumatic injury), the surrounding skin (which contains normal skin microflora such as *Staphylococcus epidermidis, micrococci, skin diphtheroid,* and *propionibacteria*), and endogenous sources involving mucous membranes (primarily the gastrointestinal, oropharyngeal, and genitourinary mucosae). (Bowler et al., 2001; Duerden, 1994; Negut et al., 2018).

Complex interactions involving several cells, including keratinocytes, vascular endothelial cells, fibroblasts, recruited immune cells, and the extracellular matrix, are necessary for wound healing following skin injury. The effects of PDT showed significant neovascularization, differentiation into myofibroblasts, and proliferation of keratinocytes and fibroblasts. Additionally, PDT was shown to enhance angiogenic responses and accelerate re-endothelialization after damage (Adili et al., 2002; Corsi et al., 2016; Sahu et al., 2015; F. Xiao et al., 2019; Xin et al., 2024).

The process of wound healing by PDT involves four phases: hemostasis, inflammation, proliferation, and remodeling shown in Figure 1 (Leśków et al., 2023; Mack et al., 2024; Ning et al., 2022; D. Wang et al., 2024; D. Wei et al., 2024; Oyama et al., 2020; Ning et al., 2022). Apart from its superior sterilizing properties, PDT can reinforce acute inflammation, encourage the proliferation, migration, and secretion of cytokines by skin-resident cells, and accelerate blood vessel proliferation and deposition of extracellular matrix (elastin and collagen), all of which contribute to skin regeneration (Ning et al., 2022; Xin et al., 2024; Jimi et al., 2020).

Following injury, skin resident cells identify pathogen-associated and damage-associated molecular patterns and several signaling and chemokine-secreted molecules, which cause further inflammation and draw in additional immune cells (Bdeir et al., 2017; Kirchner et al., 2020; Jin et al., 2024). According to recent research, PDT changed the local immunological state (Grandi et al., 2018), causing an acute inflammatory response early in the healing process and later lowering chronic inflammation (T. Yang et al., 2020). More specifically, PDT drew immune cells to the wound site, such as mast cells, neutrophils, monocytes, or macrophages, which facilitated the removal of damaged tissue and the production of pro-inflammatory cytokines. Early bleeding occurs after an injury, and then a clot of blood and fibrin fills the wound space and dries. In the inflammatory phase that follows, macrophages will surface and remove debris similarly to primary union. In order to completely re-coat the gap and produce epithelial changes that resemble primary healing, epidermal cells from both sides of the wound proliferate and move into the wound as epithelial spurs until they converge in the center. Therefore, until the wound space begins to fill with granulation tissue from the base, the surface is not completely covered by the growing epithelial cells. Granulation tissue is then created as a result of fibroblast proliferation and neovascularization of the surrounding living components. Due to increased collagen and decreased vascularity, the newly formed granulation tissue is granular, dark red, and extremely fine. The maturing scar eventually turns pale and white, and unique skin structures like sweat glands and hair follicles cannot be restored in the absence of any living remnants that can regenerate. The activity of myofibroblasts in the granulation tissue will thereafter cause the wound to shrink to a third or a quarter of its initial size (Brunda et al., 2023; Y. Yang et al., 2024)

Tissue regeneration

PDT is capable the handling of cancer, acne, bacterial eradication, dermatological conditions, antifungal, antiviral, dental dentin, analgesic, anti-inflammatory, antitumor effects, chronic wound healing, antimicrobial, etc (Dey et al., 2022; Gonçalves et al., 2021; Ji et al., 2020; Digby et al., 2021; Rodrigues et al., 2024; Li Pomi et al., 2024; Dudzik et al., 2024; Cho & Ha, 2020; Y. Hu et al., 2019; Svyatchenko et al., 2020; K. Cheng et al., 2022; Strazzi Sahyon et al., 2019; Luo et al., 2021; M. Liu et al., 2022; Bu et al., 2024; Nardini et al., 2024; Mirzahosseinipour et al., 2020). PDT can hasten wound closure by increasing the proliferation, differentiation, and migration of epidermal stem cells (EpSC), thereby promoting re-epithelialization and angiogenesis (Z. Yang et al., 2021).

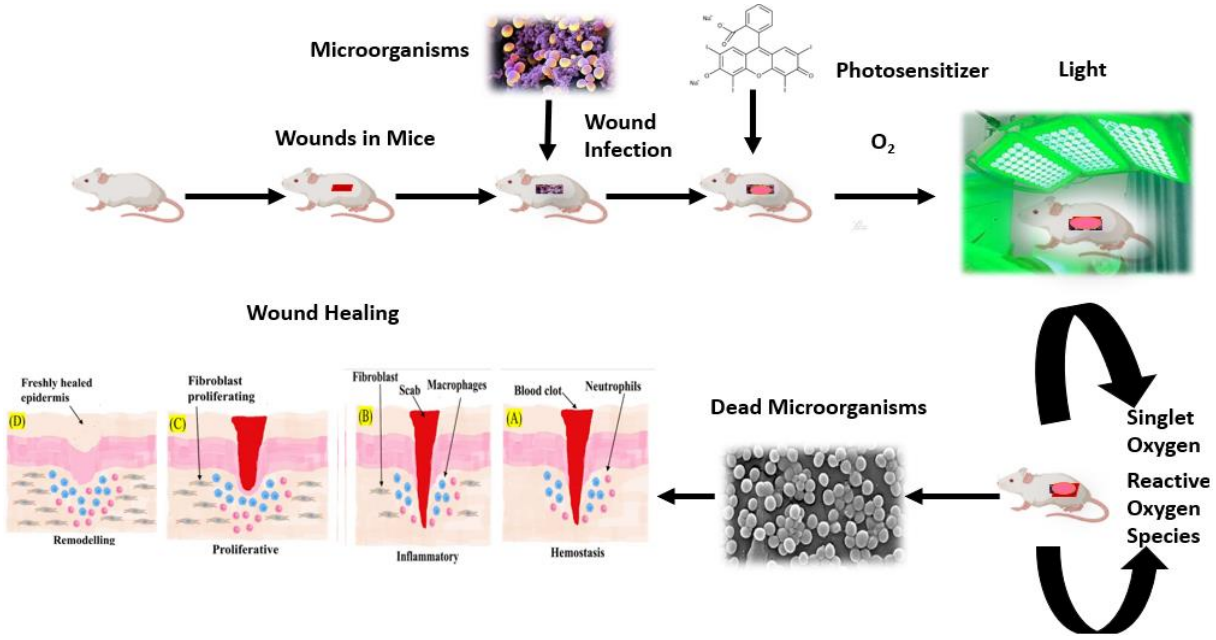

Figure 1. Schematic illustration of photosensitizer-based therapies in mice wound model.

In the PDT-assisted wound healing process, tissue regeneration refers to the action of ROS, which initiates a series of reactions causing cell death (Sztandera et al., 2020; B. Wang et al., 2022) Activatable PS sensitive to specific stimuli has the potential to target various disease biomarkers (Zhai et al., 2019). Proper control of ROS production has positive effects on fibroblasts towards wound healing because photodynamic reactions that produce ROS enable the translocation of phosphorylated Grb2-associated binder-1, which activates extracellular signal-regulated kinase 1/2 and c-Jun N-terminal kinase signaling (Minagawa et al., 2023). Antimicrobial Photodynamic Therapy (aPDT) promotes tissue regeneration by eliminating bacteria (Dantas et al., 2023). PDT based on nanoparticles (NP) greatly enhances wound healing (G. Cheng & Li, 2020).

Hemostasis, inflammation, growth, re-epithelialization, and remodeling are the stages of wound healing, during which granulation tissue replaces the wound to create new connective tissue (M. Rodrigues et al., 2019; Minagawa et al., 2023). The process by which cells or tissues return to their normal structure and function following damage is known as tissue repair and regeneration. To prevent blood loss following an injury, collagen, and blood platelets combine to create a blood clot. Then, neutrophils are the main inflammatory cells. They are activated by chemical signals, which cause the release of enzymes like collagenase, protease, and elastase, which aid in the removing damaged tissue from the wound site. Growth factors like interleukin-1 (IL-1), transforming growth factor (TGF-b1), platelet-derived growth factor (PDGF), and epithelial growth factor (EGF) are produced during inflammation. Following neutrophils and macrophages, monocyte chemotactic proteins, specifically TGF-b1, attract mast cells to the wound site, resulting in the release of histamine, proteoglycans, proteases, and platelet-activating factors. TGFb1 and IL-4 are released by inflammatory cells to inhibit them and reduce inflammation. Fibroblast and endothelial cell proliferation is triggered and regulated by macrophages' secretion of TNF-a and IL-1. Collagen and other glycosaminoglycans are released by stimulated fibroblasts to create an extracellular matrix, which makes up the majority of granulation tissue. Thus, basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), produced by endothelial cells, keratinocytes, and macrophages, initiate angiogenesis, which is necessary for further granulation tissue growth. PDGF, which is released by degranulating platelets, is the cause of the increased structural integrity of blood vessels. During remodeling, granulation tissue is gradually replaced by connective tissue (Brunda et al., 2023; Arshad et al., 2020). Based on the research of Y. Zhang et al., (2023) regarding Ag nanocomposite hydrogel with immune and regenerative microenvironment regulation promoting scar-free healing of infected wounds, it is mentioned that inflammatory cells that accumulate under the epidermis can cause scar tissue formation at the wound site. The regenerated dermis tissue with sebaceous glands and hair follicles as appendages. Collagen is a cell growth promoter that can promote tissue cell differentiation and proliferation. HP-Ag/bFGF composite hydrogel can promote scar-free healing of wounds and accelerate wound regeneration. To assess the hydrogel's anti-inflammatory properties in vivo, TNF-α, a common pro-inflammatory cytokine, was used. To provide enough oxygen, nutrients, and growth factors for tissue regeneration, long-term release of bFGF and Ag encourages the development of mature blood vessels and the regression of immature blood vessels. Growth factor transformation Because the development of scar tissue in tissues is intimately linked to the differentiation of fibroblasts into myofibroblasts, HP-Ag/bFGF composite hydrogel can promote scar-free wound healing by lowering TGF-β expression (Y. Zhang et al., 2023; Hong et al., 2024).

Challenges of photodynamic therapy

PDT faces challenges related to limited light penetration depth, biofilm diffusion, and absorption of photosensitizer bacteria (Digby et al., 2021). Significant improvement in lesions and efficient diagnosis and treatment have always been challenges in PDT (Li Pomi et al., 2024; Xiao et al., 2023). Furthermore, there is currently a dearth of data on how photodynamic therapy affects the immune system, thus it is vital to investigate the effects of different photosensitizers on the immunological response (Soares et al., 2024). PDT can be used in conjunction with other treatments like immunotherapy, chemotherapy, and photothermal therapy to boost treatment effectiveness and provide a synergistic effect of several biological tumor treatment mechanisms (Gong et al., 2022). The combination of photodynamic therapy (PDT) and photothermal therapy (PTT) is required as a cancer treatment because the acidic environment decreases the catalytic activity of nanomaterials in the tumor microenvironment, and hypoxia and inadequate H_2O_2 supply in tumors severely limit the effectiveness of PDT (Jianfeng Huang et al., 2023). PDT is simple to employ in conjunction with other therapy, has minimal side effects, and is effective

(Z. Wang et al., 2021; Death et al., 2023; Du et al., 2021; Qin et al., 2021; Y. Huang et al., 2021; Bassan et al., 2021; G. He et al., 2022).

In adults, PDT can be used in acne treatment with good aesthetic results and few side effects, but in children, its use is still not standardized (Li Pomi et al., 2024). The use of tumor microenvironment-responsive nanodrugs is still limited and remains a major challenge in the field of nanotheranostics (D. Liu et al., 2021). There is currently little utilization of nanoparticles as therapeutic carriers, despite their promise potential to go past PDT barriers in tumor tissue (Lee et al., 2022). However, using nanoparticles as a possible delivery system for PS improves its cytotoxic and cellular absorption in vitro and in vivo (Sztandera et al., 2020). The administration of photosensitizers (PS) to eradicate biofilm-related infections is still limited so antimicrobial photodynamic therapy (aPDT) remains a challenge (Y. Xu et al., 2023).

Bacterial infections in wounds are a challenge in wound repair so they can delay wound healing. For that, a photosensitizer that can generate reactive oxygen species through suitable excitation source irradiation is required. Pathogenic microbes and treatments that can enhance extracellular matrix deposition and promote skin resident cell migration, proliferation, and differentiation. Furthermore, they promote reepithelialization, angiogenesis, and tissue remodeling (Ning et al., 2022)

4. Conclusion

PDT uses a specific photosensitizer activated by light to produce ROS. In wound healing, PDT stimulates the process by improving the quality of tissue formed, fast wound closure, reducing the risk of complications, increasing blood circulation, reducing inflammation, and promoting the proliferation of cells involved in tissue regeneration.

5. Funding

This project was supported by LPPM UMP with Grand number A.11-III/543-S.Pj./LPPM/XII/2021.

6. Reference

Abo-Neima SE, El-Sheekh MM, Al-Zaban MI, EL-Sayed AIM. 2023. Antibacterial and anti-corona virus (229E) activity of Nigella sativa oil combined with photodynamic therapy based on methylene blue in wound infection: In vitro and in vivo study, *BMC Microbiology*, *23*(1), 1–18.

Adili F, Scholz T, Hille M, Heckenkamp J, Barth S, Engert A, Schmitz-Rixen T. 2002. Photodynamic therapy mediated induction of accelerated re-endothelialisation following injury to the arterial wall: implications for the prevention of postinterventional restenosis *European Journal of Vascular and Endovascular Surgery*, *24*(2), 166–175.

Akbarizare M. 2022. Photodynamic inactivation property of saffron (Crocus sativus) as a natural photosensitizer in combination with blue light in microbial strains, *Iranian Journal of Medical Microbiology*, *16*(6), 587–593.

Alsaif A, Tahmassebi JF, Wood SR. 2021. Treatment of dental plaque biofilms using photodynamic therapy: A randomised controlled study, *European Archives of Paediatric Dentistry*, *22*(5), 791–800.

Alves E, Faustino MAF, Tomé JPC, Neves MGPMS, Tomé AC, Cavaleiro JAS, Cunha A, Gomes NCM, Almeida A. 2013. Nucleic acid changes during photodynamic inactivation of bacteria by cationic porphyrins, *Bioorganic & Medicinal Chemistry*, *21*(14), 4311–4318.

Amos-Tautua BM, Songca SP, Oluwafemi OS. 2019. Application of porphyrins in antibacterial photodynamic therapy *Molecules (Basel, Switzerland)*, *24*(13).

Arshad T, Mansur F, Palek R, Manzoor S, Liska V. 2020. A double-edged sword role of Interleukin-22 in wound healing and tissue regeneration, *Frontiers in Immunology*, *11*, 1–17.

Astuti SD, Pertiwi WI, Wahyuningsih SPA, Permatasari PAD, Nurdin DZI, Syahrom A. 2023. Effectiveness of ozone-laser photodynamic combination therapy for healing wounds infected with methicillin-resistant Staphylococcus aureus in mice, *Veterinary World*, *16*(5), 1176–1184.

Awad MM, Tovmasyan A, Craik JD, Batinic-Haberle I, Benov LT. 2016. Important cellular targets for antimicrobial photodynamic therapy, *Applied Microbiology and Biotechnology*, *100*(17), 7679–7688.

Bassan E, Gualandi A, Cozzi PG, Ceroni P. 2021. Design of BODIPY dyes as triplet photosensitizers: Electronic properties tailored for solar energy conversion, photoredox catalysis and photodynamic therapy, *Chemical Science*, *12*(19), 6607–6628.

Bdeir K, Gollomp K, Stasiak M, Mei J, Papiewska-Pajak I, Zhao G, Worthen GS, Cines DB, Poncz M, Kowalska MA. 2017. Platelet-specific chemokines contribute to the pathogenesis of acute lung injury, *American Journal of Respiratory Cell and Molecular Biology*, *56*(2), 261–270.

Bowler PG, Duerden B., Armstrong DG. 2001. Wound microbiology and associated approaches to wound management. *Clinical Microbiology Reviews*, *14*(2), 244–269.

Brunda K, Kavitha Rani B, Ravikumar P, Shashidhar B, Ravi R, Akash J, Meghana S, Author C, Shankar B, Manjunatha S, Jayaramu G, Shridhar N, Lakshmishree K, Anupama P, Santhoshkumar C, Niranjan Murthy C. 2023. Tissue repair and regeneration, *Pharma Innovation Journal, 12*(10), 32–46.

Bu F, Kang X, Tang D, Liu F, Chen L, Zhang P, Feng W, Yu Y, Li G, Xiao H, Wang X. 2024. Enhancing near-infrared II photodynamic therapy with nitric oxide for eradicating multidrug-resistant biofilms in deep tissues, *Bioactive Materials*, *33*, 341–354.

Buzzá HH, Alves F, Tomé AJB, Chen J, Kassab G, Bu J, Bagnato VS, Zheng G, Kurachi C. 2022. Porphyrin nanoemulsion for antimicrobial photodynamic therapy: Effective delivery to inactivate biofilm-related infections, *Proceedings of the National Academy of Sciences of the United States of America*, *119*(46), 1–9.

Caldwell MD. 2020. Bacteria and antibiotics in wound healing, *The Surgical Clinics of North America*, *100*(4), 757–776.

Carter MJ, DaVanzo J, Haught R, Nusgart M, Cartwright D, Fife CE. 2023) Chronic wound prevalence and the associated cost of treatment in Medicare beneficiaries: Changes between 2014 and 2019. *Journal of Medical Economics*, *26*(1), 894–901.

Chai N, Stachon T, Berger T, Li Z, Seitz B, Langenbucher A, Szentmáry N. 2023. Human corneal epithelial cell and fibroblast migration and growth factor secretion after rose bengal photodynamic therapy (RB-PDT) and the effect of conditioned medium, *PLoS ONE*, *18*, 1–19.

Chen M, Han Q, Zhang M, Liu Y, Wang L, Yang F, Li Q, Cao Z, Fan C, Liu J. 2024. Upconversion dual-photosensitizer–expressing bacteria for near-infrared monochromatically excitable synergistic phototherapy, *Science Advances*, *10*(10), 1–16.

Chen P, Zou Y, Liu Y, Han W, Zhang M, Wu Y, Yin R. 2024. Low-level photodynamic therapy in chronic wounds, *Photodiagnosis and Photodynamic Therapy*, *46*, 104085.

Cheng G, Li B. 2020. Nanoparticle-based photodynamic therapy: New trends in wound healing applications, *Materials Today Advances*, *6*.

Cheng K, Guo Q, Shen Z, Yang W, Wang Y, Sun Z, Wu H. 2022. Bibliometric analysis of global research on cancer photodynamic therapy: Focus on nano-related research, *Frontiers in Pharmacology*, *13*, 1–19.

Chiu W, Tran TV, Pan S, Huang H, Chen Y, Wong T. 2019. Cystic fibrosis transmembrane conductance regulator: A possible new target for photodynamic therapy enhances wound healing, *Advances in wound care (New Rochelle), 8*(10), 476–486.

Cho GL, Ha JW. 2020. Erythrosine B (red dye no. 3): A potential photosensitizer for the photodynamic inactivation of foodborne

pathogens in tomato juice, *Journal of Food Safety*, *40*(4).

Corsi A, Lecci PP, Bacci S, Cappugi P, Pimpinelli N. 2016. Early activation of fibroblasts during PDT treatment in leg ulcers, *Giornale Italiano Di Dermatologia e Venereologia: Organo Ufficiale, Societa Italiana Di Dermatologia e Sifilografia*, *151*(3), 223–229.

Damrongrungruang T, Puasiri S, Vongtavatchai V, Saeng-on C, Petcharapiruch T, Teerakapong A, Sangpanya A. 2023. Anticandidal efficacy of erythrosine with nano-TiO2 and blue LED-mediated photodynamic therapy against Candida albicans biofilms on acrylic resin: A preliminary study, *European Journal of Dentistry*, *18*(1), 273-280.

Dantas JBDL, Fortuna T, Cella HR Della, Da Silva FLMDS, Santana RC, Martins GB. 2023. Evaluation of the effect of Matricaria recutita monotherapy or in combination with photodynamic therapy on tissue repair in the dorsum of the tongue of rats, *Journal of Applied Oral Science*, *31*, 1–14.

de Carvalho BMDF, Garcia BA, Gomes AKP, Alcantara DD, de Freitas Pontes KM. 2023. Antimicrobial photodynamic therapy as a technique for decontamination of acrylic resin devices provided by different dental laboratories, *Journal of Lasers in Medical Sciences*, *14*.

de Souza MVF, Shinobu-Mesquita CS, Meirelles LEF, Mari NL, César GB, Gonçalves RS, Caetano W, Damke E, Silva VRS, Damke GMZF, Consolaro MEL. 2022. Effects of hypericin encapsulated on pluronic F127 photodynamic therapy against triple-negative breast cancer, *Asian Pacific Journal of Cancer Prevention*, *23*(5), 1741–1751.

Dey A, Singhvi G, Puri A, Kesharwani P, Dubey SK. 2022. An insight into photodynamic therapy towards treating major dermatological conditions, *Journal of Drug Delivery Science and Technology*, *76*, 1–39.

Digby EM, Tung MT, Kagalwala HN, Ryan LS, Lippert AR, Beharry AA. 2021. Dark dynamic therapy: Photosensitization without light excitation using chemiluminescence resonance energy transfer in a dioxetane-erythrosin B conjugate, *ACS Chemical Biology*, *17*(5), 1082–1091.

Djalil AD, Nurulita NA, Limantara LW, Ibrahim S, Tjahjono DH. 2012. Biological evaluations of protoporphyrin IX, pheophorbide a, and its 1-hydroxyethyl derivatives for application in photodynamic therapy, *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(SUPPL.3), 741–746.

Du J, Wan Z, Wang C, Lu F, Wei M, Wang D, Hao Q. 2021. Designer exosomes for targeted and efficient ferroptosis induction in cancer via chemo-photodynamic therapy, *Theranostics*, *11*(17), 8185–8196.

Dudzik T, Domański I, Makuch S. 2024. The impact of photodynamic therapy on immune system in cancer – an update, *Frontiers in Immunology*, *15*, 1–10.

Duerden BI. 1994. Virulence factors in anaerobes, *Clinical Infectious Diseases: An Official Publication of the Infectious DiseasesSociety of America*, *18(Suppl 4)*, S253-S259.

Gholami L, Shahabi S, Jazaeri M, Hadilou M, Fekrazad R. 2023. Clinical applications of antimicrobial photodynamic therapy in dentistry, *Frontiers in Microbiology*, *13,* 1020995.

Gonçalves MLL, Santos EM, Renno ACM, Horliana ACRT, Cruz Mde A, Parisi JR, Prates RA, Leal-Rossi A, Fernandes KPS, Mesquita-Ferrari RA, Bussadori SK. 2021. Erythrosine as a photosensitizer for antimicrobial photodynamic therapy with blue light-emitting diodes – An in vitro study, *Photodiagnosis and Photodynamic Therapy*, *35*.

Gong G, Pan J, He Y, Shang J, Wang X, Zhang Y, Zhang G, Wang F, Zhao G, Guo J. 2022. Self-assembly of nanomicelles with rationally designed multifunctional building blocks for synergistic chemo-photodynamic therapy, *Theranostics*, *12*(5), 2028–2040.

Grandi V, Bacci S, Corsi A, Sessa M, Puliti E, Murciano N, Scavone F, Cappugi P, Pimpinelli N. 2018. ALA-PDT exerts beneficial effects on chronic venous ulcers by inducing changes in inflammatory microenvironment, especially through increased TGF-beta release: A pilot clinical and translational study, *Photodiagnosis and Photodynamic Therapy*, *21*, 252–256.

Guo N, Chen J, Kong F, Gao Y, Bian J, Liu T, Hong G, Zhao Z. 2024. 5-Aminolevulinic acid photodynamic therapy for chronic wound infection in rats with diabetes, *Biomedicine and Pharmacotherapy*, *178*, 117132.

Hamed E, Al Balah OFA, Refaat M, Badr AM, Afifi A. 2024. Photodynamic therapy mediated by methylene blue-loaded PEG accelerates skin mouse wound healing: An immune response, *Lasers in Medical Science*, *39*(1).

He G, Li Y, Younis MR, Fu LH, He T, Lei S, Lin J, Huang P. 2022. Synthetic biology-instructed transdermal microneedle patch for traceable photodynamic therapy, *Nature Communications*, *13*(1), 1–18.

He J, Weng T, Ba W, Liang X, Yang Y, Li C. 2024. Photodynamic therapy for cutaneous inflammatory pseudotumor: A case report, *Photodiagnosis and Photodynamic Therapy*, *45*, 103962.

He X, Luo Y, Li Y, Pan Y, Kwok RTK, He L, Duan X, Zhang P, Wu A, Tang BZ, Li J. 2024. D-type neuropeptide decorated AIEgen/RENP hybrid nanoprobes with light-driven ROS generation ability for NIR-II fluorescence imaging-guided through-skull photodynamic therapy of gliomas, *Aggregate*, *5*(1), 1–11.

Hong J, Zhu J, Cao X, Pang B, Xian J, Yin X, Deng Q, Chen M, Qin Z, Liu C, Nath Varma S, Xiao Y, Xiao L, Li M. 2024. Photo-triggered multifunctional gold-based hybrid nanoflowers promote infectious skin regeneration, *Chemical Engineering Journal*, *482*, 148937.

Hu Y, Qi X, Sun H, Lu Y, Hu Y, Chen X, Liu K, Yang Y, Mao Z, Wu Z, Zhou X. 2019. Photodynamic therapy combined with antifungal drugs against chromoblastomycosis and the effect of ALA-PDT on Fonsecaea in vitro, *PLoS Neglected Tropical Diseases*, *13*(10), 1–14.

Huang CJ, Pu CM, Su SY, Lo SL, Lee CH, Yen YH. 2023. Improvement of wound healing by capsaicin through suppression of the inflammatory response and amelioration of the repair process, *Molecular Medicine Reports*, *28*(2), 1–13.

Li Z, Guo L, Lin L, Wang T, Jiang Y, Song J, Feng J, Huang J, Li H, Bai Z, Liu W, Zhang J. 2023. Porous SiO2-based reactor with self-supply of O_2 and H_2O_2 for synergistic photo-thermal/photodynamic therapy, *International Journal of Nanomedicine, 18*, 3623–3639.

Huang J, Wu S, Wu M, Zeng Q, Wang X, Wang H. 2021. Efficacy of the therapy of 5-aminolevulinic acid photodynamic therapy combined with human umbilical cord mesenchymal stem cells on methicillin-resistant Staphylococcus aureus-infected wound in a diabetic mouse model, *Photodiagnosis and Photodynamic Therapy*, *36*, 102480.

Huang T, Zhou Z, Li Q, Tang X, Chen X, Ge Y, Ling J. 2022. Light-triggered adhesive silk-based film for effective photodynamic antibacterial therapy and rapid hemostasis, *Frontiers in Bioengineering and Biotechnology*, *9*, 1–9.

Huang W, Yuan H, Yang H, Tong L, Gao R, Kou X, Wang, J., Ma X, Huang S, Zhu F, Chen G, Ouyang G. 2022. Photodynamic hydrogen-bonded biohybrid framework: a photobiocatalytic cascade nanoreactor for accelerating diabetic wound therapy, *JACS Au*, *2*(9), 2048–2058.

Huang Y, Guan Z, Dai X, Shen Y, Wei Q, Ren L, Jiang J, Xiao Z, Jiang Y, Liu D, Huang Z, Xu X, Luo Y, Zhao C. 2021. Engineered macrophages as near-infrared light activated drug vectors for chemo-photodynamic therapy of primary and bone metastatic breast cancer, *Nature Communications*, *12*(1), 1–22.

Hurlow J, Bowler PG. 2022. Acute and chronic wound infections: Microbiological, immunological, clinical and therapeutic distinctions, *Journal of Wound Care*, *31*(5), 436–445.

Ji J, Zhang R, Li H, Zhu J, Pan Y, Guo Q. 2020. Analgesic and anti-inflammatory effects and mechanism of action of borneol on photodynamic therapy of acne, *Environmental Toxicology and Pharmacology*, *75*.

Jimi S, Jaguparo, A, Nurkesh A, Sultankulov B, Saparov A. 2020. Sequential delivery of cryogel released growth factors and cytokines accelerates wound healing and improves tissue regeneration, *Frontiers in Bioengineering and Biotechnology*, *8*, 1–14.

Jin Y, Lu Y, Jiang X, Wang M, Yuan Y, Zeng Y, Guo L, Li W. 2024. Accelerated infected wound healing by probiotic-based living microneedles with long-acting antibacterial effect, *Bioactive Materials*, *38*, 292–304.

Khorsandi K, Fekrazad R, Hamblin MR. 2021. Low-dose photodynamic therapy effect on closure of scratch wounds of normal and diabetic fibroblast cells: An in vitro study, *Journal of Biophotonics*, *14*(7), e202100005.

Kirchner S, Lei V, MacLeod AS. 2020. The cutaneous wound innate immunological microenvironment, *International Journal of Molecular Sciences*, *21*(22).

Lee D, Kwon S, Jang S, Park E, Lee Y, Koo H. 2022. Overcoming the obstacles of current photodynamic therapy in tumors using nanoparticles, *Bioactive Materials*, *8*, 20–34.

Leśków N, Karp Z, Banaszewski M, Popielska K, Grześkowiak M, Mikołajski J, Mozdziak PE, Kranc W. 2023. Characteristics and cellular mechanism of the wound healing process in the oral mucosa, *Medical Journal of Cell Biology*, *11*(1), 1–12.

Liang Y, Wang P, Liu Z, Sun H, Wang Q, Sun G, Zhang X, Li Y, Xie, S. 2023. Dual stimuli-responsive micelles for imaging-guided mitochondrion-targeted photothermal/photodynamic/ chemo combination. *International Journal of Nanomedicine*, 18, 4381–4402.

Li Pomi F, Vaccaro M, Peterle L, Borgia F. 2024. Photodynamic therapy for severe acne. *Photodiagnosis and Photodynamic Therapy*, *45*, 103893.

Liu D, Liu L, Liu F, Zhang M, Wei P, Yi T. 2021. HOCl-activated aggregation of gold nanoparticles for multimodality therapy of tumors, *Advanced Science*, *8*(17), 1–9.

Liu M, Chen Y, Guo Y, Yuan H, Cui T, Yao S, Jin S, Fan H, Wang C, Xie R, He W, Guo Z. 2022. Golgi apparatus-targeted aggregation-induced emission luminogens for effective cancer photodynamic therapy *Nature Communications*, *13*(1).

Liu X, Fang R, Feng R, Li Q, Su M, Hou C, Zhuang K, Dai Y, Lei N, Jiang Y, Liu Y, Ran Y. 2022. Cage-modified hypocretin against multidrug-resistant Candida spp. with unprecedented activity in light-triggered combinational photodynamic therapy, *Drug Resistance Updates*, *65*, 100887.

Liu X, Guo C, Zhuang K, Chen W, Zhang M, Dai Y, Tan L, Ran Y. 2022. A recyclable and light-triggered nanofibrous membrane against the emerging fungal pathogen Candida auris, *PLoS Pathogens*, *18*(5), 1–23.

Luke-Marshall NR, Hansen LA, Shafirstein G, Campagnari AA. 2020. Antimicrobial photodynamic therapy with chlorin e6 is bactericidal against biofilms of the primary human otopathogens, *MSphere*, *5*(4), 1–11.

Luo T, Nash GT, Xu Z, Jiang X, Liu J, Lin W. 2021. Nanoscale metal-organic framework confines zinc-phthalocyanine photosensitizers for enhanced photodynamic therapy, *Journal of the American Chemical Society*, *143*(34), 13519–13524.

Ma TQ, Chen NN, Xiao RC, Li QR, Zhan MY, Gou CL, Hu J, Leng F, Li LG, Han N, Li HT, Peng XC, Chen SY, Li XY, Li TF. 2024. Indocyanine green-loaded platelet activated by photodynamic and photothermal effects for selective control of wound repair, *Photodiagnosis and Photodynamic Therapy*, *45*, 103945.

Mack KL, Talbott HE, Griffin MF, Parker JBL, Guardino NJ, Spielman AF, Davitt MF, Mascharak S, Downer M, Morgan A, Valencia C, Akras D, Berger MJ, Wan DC, Fraser HB, Longaker MT. 2024. Allele-specific expression reveals genetic drivers of tissue regeneration in mice, *Stem Cell. 30*(10), 1368–1381.

Maya R, Costa Ladeira LL, Maya JEP, Gonçalves LM, Bussadori SK, Paschoal MAB. 2020. The combination of antimicrobial photodynamic therapy and photobiomodulation therapy for the treatment of palatal ulcers: A case report, *Journal of Lasers in Medical Sciences*, *11*(2), 228–233.

Meng S, Xu Z, Wang X, Liu Y, Li B, Zhang J. Zhang X, Liu T. 2023. Synthesis and photodynamic antimicrobial chemotherapy against multi-drug-resistant Proteus mirabilis of ornithine-porphyrin conjugates in vitro and in vivo, *Frontiers in Microbiology*, *14*.

Minagawa E, Yamauchi N, Taguchi Y, Umeda M. 2023. Photodynamic reactions using high-intensity red LED promotes gingival wound healing by ROS induction, *Scientific Reports*, *13*(1), 1–11.

Mirzahosseinipour M, Khorsandi K, Hosseinzadeh R, Ghazaeian M. Shahidi FK. 2020. Antimicrobial photodynamic and wound healing activity of curcumin encapsulated in silica nanoparticles, *Photodiagnosis and Photodynamic Therapy*, *29*, 101639.

Nardini P, Notari L, Magazzini M, Mariani B, Rossi F, Rossi S, Van Aardt E, Marszalek K, Grandi V, Corsi A, Pimpinelli N, Bacci S. 2024. Neuroimmunomodulatory effect of nitric oxide on chronic wound healing after photodynamic therapy, *Photodiagnosis and Photodynamic Therapy*, *47*, 104078.

Negut I, Grumezescu V, Grumezescu AM. 2018. Treatment strategies for infected wounds, *Molecules*, *23*(9), 1–23.

Ning X, He G, Zeng W, Xia Y. 2022. The photosensitizer-based therapies enhance the repairing of skin wounds, *Frontiers in Medicine*, *9*.

Osaki T, Hibino S, Murahata Y, Amaha T, Yokoe I, Yamashita M, Nomoto A, Yano S, Tanaka M, Kataoka H, Okamoto, Y. 2023. Vascular-targeted photodynamic therapy with glucose-conjugated chlorin e6 for dogs with spontaneously occurring tumours, *Veterinary Medicine and Science,* 9(6), 2534-2541

Oyama J, Fernandes Herculano Ramos-Milaré ÁC, Lopes Lera-Nonose DSS, Nesi-Reis V, Galhardo Demarchi I, Alessi Aristides SM, Juarez Vieira Teixeira J, Gomes Verzignassi Silveira T, Campana Lonardoni MV. 2020. Photodynamic therapy in wound healing in vivo: A systematic review, *Photodiagnosis and Photodynamic Therapy*, *30*, 101682.

Pérez M, Robres P, Moreno B, Bolea R, Verde MT, Pérez-Laguna V, Aspiroz C, Gilaberte Y, Rezusta A. 2021. Comparison of antibacterial activity and wound healing in a superficial abrasion mouse model of Staphylococcus aureus skin infection using photodynamic therapy based on methylene blue or mupirocin or both, *Frontiers in Medicine*, *8*, 673408.

Pourhajibagher M, Pourakbari B, Bahador A. 2022. Contribution of antimicrobial photo-sonodynamic therapy in wound healing: An in vivo effect of curcumin-nisin-based poly (L-lactic acid) nanoparticle on Acinetobacter baumannii biofilms, *BMC Microbiology*, *22*(1), 1–16.

Pucelik B, Dąbrowski JM. 2022. Photodynamic inactivation (PDI) as a promising alternative to current pharmaceuticals for the treatment of resistant microorganisms, *Advances in Inorganic Chemistry*, *79*, 65–103.

Qin X, Wu C, Niu D, Qin L, Wang X, Wang Q, Li Y. 2021. Peroxisome-inspired hybrid enzyme nanogels for chemodynamic and photodynamic therapy *Nature Communications*, *12*(1), 1–15.

Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. 2019. Wound healing: A cellular perspective, *Physiological Reviews*, *99*(1), 665–706.

Rodrigues VC, dos Santos AR, Bona E, Freitas CF, de Silva JVO, Malacarne LC, Machinski Junior M, de Abreu Filho BA, Mikcha JMG. 2024. Optimization of the erythrosine-mediated photodynamic therapy against Escherichia coli using response surface methodology, *Photodiagnosis and Photodynamic Therapy*, *45*.

Sahu K, Sharma M, Dube A, Gupta PK. 2015. Topical antimicrobial photodynamic therapy improves angiogenesis in wounds of diabetic mice, *Lasers in Medical Science*, *30*(7), 1923–1929.

Sen CK. 2019. Human wounds and its burden: An updated compendium of estimates, *Advances in Wound Care*, *8*(2), 39–48.

Sen CK. 2023. Human wound and its burden: Updated 2022 compendium of estimates, *Advances in Wound Care*, *12*(12), 657–670.

Shao J, Hu M, Wang W, Pan Z, Zhao D, Liu J, Lv M, Zhang Y, Li Z. 2024.

Indocyanine green based photodynamic therapy for keloids: Fundamental investigation and clinical improvement, *Photodiagnosis and Photodynamic Therapy*, *45*, 103903.

Soares N, Ferreira-strixino J, Pacheco-soares C. 2024. Editorial: Photodynamic therapy: Challenges and innovations for treating cancer, *Frontiers in Oncology, 9*, 1–2.

Son J, Yi G, Kwak MH, Yang SM, Park JM, Lee BI, Choi MG, Koo H. 2019. Gelatin-chlorin e6 conjugate for in vivo photodynamic therapy, *Journal of Nanobiotechnology*, *17*(1), 1–12.

Strazzi Sahyon HB, da Silva PP, de Oliveira MS, Cintra LTA, Dezan-Júnior E, Gomes-Filho JE, Jacinto RdeC, dos Santos PH, Sivieri-Araujo G. 2019. Influence of curcumin photosensitizer in photodynamic therapy on the mechanical properties and push-out bond strength of glass-fiber posts to intraradicular dentin, *Photodiagnosis and Photodynamic Therapy*, *25*, 376–381.

Sun Y, Tosa M, Takada H, Ogawa R. 2020. Photodynamic therapy delays cutaneous wound healing in mice, *Journal of Nippon Medical School*, *87*(3), 110–117.

Svyatchenko VA, Nikonov SD, Mayorov AP, Gelfond ML, Loktev VB. 2021. Antiviral photodynamic therapy: Inactivation and inhibition of SARS-CoV-2 in vitro using methylene blue and Radachlorin, *Photodiagnosis and Photodynamic Therapy, 33*, 102112.

Sztandera K, Gorzkiewicz M, Klajnert-Maculewicz B. 2020. Nanocarriers in photodynamic therapy - in vitro and in vivo studies, *WIRE Nanomedicine and Nanobiotechnology*, *12*(3*), e1509*

Taninaka A, Kurokawa H, Kamiyanagi M, Ochiai T, Arashida Y, Takeuchi O, Matsui H, Shigekawa H. 2023. Polphylipoprotein-induced autophagy mechanism with high performance in photodynamic therapy, *Communications Biology*, *6*(1), 1–11.

Wang B, Zhou L, Guo Y, Guo H, Zhong Y, Huang X, Ge Y, Wang Q, Chu X, Jin Y, Lan K, Yang M, Qu J. 2022. Cyanobacteria-based self-oxygenated photodynamic therapy for anaerobic infection treatment and tissue repair, *Bioactive Materials*, *12*, 314–326.

Wang D, Jin J, Zhang C, Ruan C, Qin Y, Li D, Guan M, Lei P. 2024. Carbomer hydrogel composed of cu2o and hematoporphyrin monomethyl ether promotes the healing of infected wounds, ACS *Omega*, *9*(4), 4974–4985.

Wang F, Shi Y, Ho PY, Zhao E, Kam C, Zhang Q, Zhao X, Pan Y, Chen S. 2023. An AIE-active bacterial inhibitor and photosensitizer for selective imaging, killing, and photodynamic inactivation of bacteria over mammalian cells, *Bioengineering and Translational Medicine*, *8*(6), 1–12.

Wang Y, Yao H, Zu Y, Yin W. 2022. Biodegradable MoOx@MB incorporated hydrogel as a light-activated dressing for rapid and safe bacteria eradication and wound healing, *RSC Advances*, *12*(15), 8862–8877.

Wang Z, Peng H, Shi W, Gan L, Zhong L, He J, Xie L, Wu P, Zhao Y, Deng Z, Tang H, Huang Y. 2021. Application of photodynamic therapy in cancer: Challenges and advancements, *Biocell*, *45*(3), 489–500.

Wei D, Hamblin MR, Wang H, Fekrazad R, Wang C, Wen X. 2024. Rose Bengal diacetate-mediated antimicrobial photodynamic inactivation: Potentiation by potassium iodide and acceleration of wound healing in MRSA-infected diabetic mice, *BMC Microbiology*, *24*(1), 1–10.

Wei X, Ni J, Yuan L, Li X. 2024. Hematoporphyrin derivative photodynamic therapy induces apoptosis and suppresses the migration of human esophageal squamous cell carcinoma cells by regulating the PI3K/AKT/mTOR signaling pathway, *Oncology Letters*, *27*(1).

Xiao F, Cao B, Wang C, Guo X, Li M, Xing D, Hu X. 2019. Pathogen-specific polymeric antimicrobials with significant membrane disruption and enhanced photodynamic damage to inhibit highly opportunistic bacteria, *ACS Nano*, *13*(2), 1511–1525.

Xiao P, Shen Z, Wang D, Pan Y, Li Y, Gong J, Wang L, Wang D, Tang BZ. 2022. Precise molecular engineering of type i photosensitizers with near-infrared aggregation-induced emission for image-guided photodynamic killing of multidrug-resistant bacteria, *Advanced Science*, *9*(5), 1–11.

Xiao R, Zheng F, Kang K, Xiao L, Bi A, Chen Y, Zhou Q, Feng X, Chen Z, Yin H, Wang W, Chen Z, Cheng X, Zeng W. 2023. Precise visualization and ROS-dependent photodynamic therapy of colorectal cancer with a novel mitochondrial viscosity photosensitive fluorescent probe, *Biomaterials Research*, *27*(1), 1–12.

Xin J, Yang Z, Zhang S, Sun L, Wang X, Tang Y, Xiao Y, Huang H, Li W. 2024. Fast fabrication of "all-in-one" injectable hydrogels as antibiotic alternatives for enhanced bacterial inhibition and accelerating wound healing, *Journal of Nanobiotechnology*, 22(1). BioMed Central.

Xiu W, Wan L, Yang K, Li X, Yuwen L, Dong H, Mou Y, Yang D, Wang L. 2022. Potentiating hypoxic microenvironment for antibiotic activation by photodynamic therapy to combat bacterial biofilm infections, *Nature Communications*, *13*(1).

Xu X, Hu Y, Zhang LP, Liu B, Yang Y, Tang T, Tian J, Peng K, Liu T. 2020. Lactic-co-glycolic acid-coated methylene blue nanoparticles with enhanced antibacterial activity for efficient wound healing, *RSC Advances*, *10*(21), 12304–12307.

Xu Y, Liu S, Zhao H, Li Y, Cui C, Chou W, Zhao Y, Yang J, Qiu H, Zeng J, Chen D, Wu S, Tan Y, Wang Y, Gu Y. 2023. Ultrasonic irradiation enhanced the efficacy of antimicrobial photodynamic therapy against methicillin-resistant Staphylococcus aureus biofilm, *Ultrasonics Sonochemistry*, *97*,106423

Yaghobee S, Pourhajibagher M, Bahrami R, Isaabadi M. 2024. Nano-emodin mediated photodynamic therapy for wound healing of donor site after free gingival graft: A parallel clinical trial, *Photodiagnosis and Photodynamic Therapy*, *45,* 103958.

Yang T, Tan Y, Zhang W, Yang W, Luo J, Chen L, Liu H, Yang G, Lei X. 2020. Effects of ALA-PDT on the healing of mouse skin wounds infected with Pseudomonas aeruginosa and its related mechanisms, *Frontiers in Cell and Developmental Biology*, *8*, 585132.

Yang Y, Wang J, Huang S, Li M, Chen J, Pei D, Tang Z, Guo B. 2024. Bacteria-responsive programmed self-activating antibacterial hydrogel to remodel regeneration microenvironment for infected wound healing, *National Science Review*, *11*(4).

Zhai, W., Zhang, Y., Liu, M., Zhang, H., Zhang, J., & Li, C. 2019. Universal Scaffold for an Activatable Photosensitizer with Completely Inhibited Photosensitivity. *Angewandte Chemie - International Edition*, *58*(46), 16601–16609.

Zhang F, Wen C, Peng Y, Hu Z, Zheng S, Chen W, Wen L. 2023. Biomimetic lipid nanoparticles for homologous-targeting and enhanced photodynamic therapy against glioma, *European Journal of Pharmaceutical Sciences*, *190*, 106574.

Zhan L, Hao L, Huang Y, Huang H, Hu J, Bi M. 2020. Photodiagnosis and photodynamic therapy satisfactory response of a back carbuncle to 5-aminolevulinic acid (ALA) photodynamic therapy: A case report, *Photodiagnosis and Photodynamic Therapy*, *30*, 101618.

Zhang Y, Kang J, Chen X, Zhang W, Zhang X, Yu W, Yuan WE. 2023. Ag nanocomposite hydrogels with immune and regenerative microenvironment regulation promote scarless healing of infected wounds, *Journal of Nanobiotechnology*, *21*(1), 1–17.

Zhao ZJ, Xu ZP, Ma YY, Ma JD, Hong G. 2020. Photodynamic antimicrobial chemotherapy in mice with Pseudomonas aeruginosa-infected wounds, *PLoS ONE*, *15*, 1–19.

Zhao Z, Ma J, Wang Y, Xu Z, Zhao L, Zhao J, Hong G, Liu T. 2021. Antimicrobial photodynamic therapy combined with antibiotic in the treatment of rats with third-degree burns, *Frontiers in Microbiology*, *12*, 1–14.

Zuhayri H, Samarinova AA, Borisov AV, Guardado DAL, Baalbaki H, Krivova NA, Kistenev YV. 2023. Quantitative assessment of low-dose photodynamic therapy effects on diabetic wound healing using Raman spectroscopy, *Pharmaceutics*, *15*(2).