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Advancements in employing two-dimensional nanomaterials for enhancing skin wound healing: a review of current practice

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Abstract

The two-dimensional nanomaterials are characterized by their ultra-thin structure, diverse chemical functional groups, and remarkable anisotropic properties. Since its discovery in 2004, graphene has attracted significant scientific interest due to its potential applications in various fields, including electronics, energy systems, and biomedicine. In medicine, graphene is used for designing smart drug delivery systems, especially for antibiotics, and biosensing. Skin trauma is a prevalent dermatological condition that increasingly contributes to morbidities and mortalities, thus representing a significant health burden. During tissue damage, rapid skin repair is crucial to prevent blood loss and infection. Therefore, drugs used for skin trauma must possess antimicrobial and anti-inflammatory properties. Two-dimensional (2D) nanomaterials possess remarkable physical, chemical, optical, and biological characteristics due to their uniform shape, increased surface area, and surface charge. Graphene and its derivatives, transition-metal dichalcogenides (TMDs), black phosphorous (BP), hexagonal boron nitride (h-BN), MXene, and metal-organic frameworks (MOFs) are among the commonly used 2D nanomaterials. Moreover, they exhibit antibacterial and anti-inflammatory properties. This review presents a comprehensive discussion of the clinical approaches employed for wound healing treatment and explores the applications of commonly used 2D nanomaterials to enhance wound healing outcomes.

Keywords Two-dimensional nanomaterials, Wound healing, Nanotechnology, Antibiosis, Anti-inflammatory

Introduction

As the human body's biggest organ, the skin accounts for approximately 16% of an individual's total weight [1]. The skin comprises three layers: epidermis, dermis, and subcutaneous tissue. Each of these layers is densely packed with blood arteries, nerves, and skin appendages. It primarily regulates body water levels and acts as a barrier against the invasion of harmful germs [2]. In living tissue, a "wound" is a disruption in cellular, anatomical, and functional integrity caused by an immune response, chemical reaction, temperature effect, microbial infection, or physical trauma. It can also be defined as a breakdown of epithelial integrity, which is frequently followed

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by structural and functional damage of the underlying normal tissue [3–5].

The speed of wound healing depends on multiple factors, including the patient's health and external factors, making it a complex process [6]. Wound healing occurs in multiple phases, starting with hemostasis. After a skin injury, prompt blood clot formation at the wound site occurs to minimize bleeding. This is followed by the inflammatory phase, during which the bleeding is managed and the injured area undergoes clearance of microbes and damaged cells. Thrombin stimulates platelet activation, prompting the release of different growth factors. This cascade of signals attracts white blood cells, nutrients, and additional growth factors, collectively accelerating wound healing and protecting against infection. The third step, proliferation, involves the remodeling of the wound, initiated by the secretion of proangiogenic substances from both inflammatory cells and platelets. Next, angiogenesis occurs followed by fibroblast proliferation and elastin production. Myofibroblasts, derived from fibroblasts, play an important role in wound closure by contracting and firmly holding the edges of the wound. Maturation is the final phase, where complete wound healing is achieved through the integration of collagen fibers. Apoptosis, also termed programmed cell death, contributes significantly to the wound-healing process. Moreover, collagen cross-linking strengthens the skin of the wounded area [7–10].

Wound healing is an important process that helps in injury recovery, infection prevention, and preserving tissue and organ function [11]. However, prolonged healing due to various factors can result in bacterial infections and other complications, leading to a significant financial burden on governments globally [12]. The global wound care market was valued at $20.8 billion in 2022 and is predicted to rise at a 5% compound annual growth rate (CAGR), reaching $27.2 billion in 2027 [13].

Traditional treatment strategies are associated with certain limitations and often fail to facilitate rapid and effective wound healing. Owing to their uniform shape, increased surface volume ratio, and surface zeta potential, two-dimensional (2D) nanomaterials offer excellent physical, chemical, and biological properties and have become a study focus in recent years [14, 15]. 2D nanomaterials have been employed in biomedicine for antibacterial properties, due to their photothermal characteristics, and for drug delivery, due to their high surface volume ratio. Therefore, the use of 2D nanomaterials in wound healing has a pretty large market [16–18].

To comprehensively understand the research progress on 2D nanomaterials in promoting skin wound healing, '2D nanomaterials' and 'wound healing' were used as keywords, along with relevant subject terms, to search databases such as PubMed, Google Scholar, and Web of Science. The categories of 2D nanomaterials that can be used to promote wound healing were identified. Different categories of 2D nanomaterials and their role in wound healing were then searched in the same databases, with the search period spanning from January 2011 to May 2024. Inclusion criteria included studies (1) Related to 2D nanomaterials; (2) related to the promotion of wound healing by 2D nanomaterials; (3) Journal articles or reviews. Exclusion criteria included (1) Repeated publication; (2) Lower volume of work (3) not related to skin wound healing.

This review provides a detailed description of various types of wound models, current wound healing treatment methods, and the application of common 2D nanomaterials in the field of wound healing. Finally, it discusses new opportunities and challenges associated with the applications of 2D nanomaterials for skin wound healing.

Experimental models and evaluation methods for skin wounds

Experimental models

Experimental models of wound healing have been developed to better understand the tissue repair process and test new therapeutic approaches. Skin wounds are classified based on their depth and tissue loss, categorizing them as either open or closed wounds [3]. Furthermore, acute and chronic wounds are classified by the underlying cause and the presentation of the symptoms. Incisions, burns, and graft wounds are examples classified by the type of injury sustained. Below is a detailed description of the different types of wound models [6, 19, 20].

Incision model

The incision wound model serves for the measurement of wound tensile strength and facilitates research on scar formation. Based on the risk of contamination after trauma and surgery, incisions are often categorized into three types [21–24].

1) Clean incisions, represented by "I", refer to non-traumatic, uninfected wounds resulting from surgical procedures that do not penetrate the respiratory, digestive, genitourinary tract, or oropharyngeal area.
2) A potentially contaminated incision, indicated as "II", refers to a sutured wound susceptible to contamination during surgeries, such as a major gastrectomy.
3) Contaminated incisions, represented by "III", are incisions in the vicinity of infected areas or tissues directly exposed to infected materials. Examples include septic appendicitis surgery, necrotizing intestinal obstruction surgery, and old traumatic wounds containing localized necrotic tissue.

Skin removal model

A partial skin removal model involves preserving the dermis while selectively removing skin to a specific depth using a scalpel or electric knife [25]. The level of damage incurred by this model aligns with that of a knee injury or the damage at the donor's skin excision site. The preservation of the dermis and the presence of developed skin tissues, such as sebaceous glands, hair follicles, and sweat glands, suggest that wound healing initiates from both the base and the edges of the wound. This model can be employed in the development of cytokine-based treatments, local wound preparations, and wound dressings [26, 27].

The epidermis and dermis of the skin are removed, with the depth reaching the subcutaneous fascial layer or fatty layer, using a punch, pair of scissors, implant knife, and other equipment [28]. This model is susceptible to infection due to the release of excess blood and tissue fluid during its development. The characteristics of the model include extensive wound-healing tissue and an epidermal epithelialization process [29]. Specific cytokines, and proteins, the degree of neovascularization, the rate of healing, and the formation of granulation tissue are commonly employed as indicators while investigating the mechanisms of wound healing [30, 31].

Burn model

Burns are skin injuries caused by exposure to heat (from fire, combustion gases, liquids, or solids), often resulting from prolonged skin contact [32]. Further, chemical corrosion, electric energy, and radioactivity cause tissue damage and repair similar to heat burns; hence they are typically categorized as burns. The disruption of the skin barrier is associated with various injuries that may develop in the body following burns. Treating burn wounds without transplanted autografts has been challenging, impacting both the appearance and functionality of the skin barrier [33].

Injuries arising from burns not only degrade blood and lymphocytes but also lead to the skin's degeneration, necrosis, and obstruction of blood and lymphatic vessels. This results in inadequate nutrition within the affected area [34]. Epidermal regeneration is the primary requirement for the treatment of burn injuries [35]. Pharmaceutical and general therapy, exercise, physiotherapy, compression, and skin grafting are some of the main treatment modalities for wounds associated with burns [36–39].

Diabetic chronic wounds model

During the global diabetes epidemic, persistent high blood sugar levels, elevated inflammatory responses, and bacterial infections in chronic wounds pose a significant threat to the health and quality of life of diabetic individual [23, 40]. Wounds in diabetic patients pose a serious risk due to diabetes mellitus (DM). Healing from non-diabetic wounds typically progresses through four stages [41]. However, excessively elevated blood sugar levels interfere with this process, rendering diabetic wound healing unmanageable [42].

Research indicates that products derived from the placenta, along with both local and systemic oxygen treatments, are effective in managing diabetic foot ulcers. Evidence also supports the use of growth factors, bioengineered tissues, stem cell treatment, gene therapy, and peptide therapy in the treatment of diabetic foot ulcers [43]. Nano therapy, employing drugs within the 1–100 nm spectrum, represents an innovative and effective approach to expedite the healing of diabetic wounds. Nanoparticles are tiny and have a high surface area-to-volume ratio, increasing the possibility of biological contact and wound penetration [44]. However, there is no scientific evidence that any single type of wound dressing can effectively address all the limitations associated with diabetic foot [45]. The modeling methods of various skin wound models and their comparisons can be seen in Table 1.

Evaluation methods

Recent research studies have established objective and accurate criteria for evaluating wound healing. When evaluating wound healing, it is crucial to consider factors such as the rate of wound healing, the duration of wound healing, and thorough pathological analysis [47]. Wound healing time, healing rate, histopathological analysis, macrophage quantitation, hydroxyproline content, cell proliferation, interleukin-1, tumor necrosis factor, cell cycle analysis, and transforming growth are among the 13 criteria used for measuring wound healing [48]. Currently, the reliable assessment of wound healing remains elusive, given the limitations associated with each method employed [35].

Currently employed treatment methods of wound healing

Routine dressing replacement stands as the widely used method for wound healing in clinical practice. It remains the first choice due to its advantages including cost-effectiveness and minimal risk profile for patients. However, this method remains inefficient and ineffective. Therefore, methods such as Light therapy, collagen dressing treatment, gene therapy (growth factor treatment), adverse pressure wound treatment, and platelet-rich plasma filling therapy have emerged as promising alternatives [49].

Table 1 Comparisons of different skin wound models and modeling approaches

Skin wound model	Characteristic	Model depth	Model tool	Model method	Ref.
Incision model	varies depending on the surgical incisions wound	varies with the need for surgical incisions	surgical knives, including electric, microwave, ultrasonic, and laser scalpel	a tool is used during the procedure to cut the skin to the desired size	[21, 22]
Skin Removal Model	more mature modeling techniques that are widely used in experiments to promote wound healing	the epidermis and dermis of the skin are removed, with the depth reaching the subcutaneous fascial layer or fatty layer	a punch, pair of scissors, implant knife, and other equipment	full-thickness dorsal skin defect	[29, 46]
Burn model	different degrees of burns can be modeled according to the time the instrument is heated and pressed on the animal.	epidermis and dermis	a metallic instrument with fat active point, heating for 40 s, then press onto the skin of the back for 20 s	third-degree burns	[34]
Diabetic chronic wounds model	common models to promote chronic wound healing	the epidermis and dermis of the skin are removed, with the depth reaching the subcutaneous fascial layer or fatty layer	a punch, pair of scissors, implant knife, and other equipment	after the diabetic model was performed first, a full-layer dorsal skin defect model was performed	[23, 42]

Light therapy

Resistance to infections resulting from trauma has been steadily increasing in recent years due to the overuse and misuse of antibiotics. Light therapy has emerged as a potentially convenient, safe, and effective approach to trauma treatment due to its ability to prevent trauma infection and facilitate wound healing [50].

Experiments conducted over an extended period have demonstrated that photobiological modulation or stimulation can affect certain biological processes. These effects include the stimulation of cellular growth and migration, inflammation reduction, tissue repair stimulation, and acceleration of the wound healing process [51–53]. The multiplication, metabolism, and release of several active components are all involved in how light therapy works. As a result, the application of light therapy in wound treatment has been established [54]. Light therapy uses low-power light to illuminate the injured area without invasion to stimulate the body's healing potential, promising a positive trajectory for clinical applications [55, 56].

There are two kinds of optical treatment: Visible Light Therapy and Invisible Light Therapy. Red light therapy and blue light therapy are within the first category [57, 58]. Different forms of light have various therapeutic effects when treating trauma. Light therapy can adjust the human body's immunity, circulation, and nervous system. Light therapy at wavelengths of 500–700 nm has been demonstrated to be effective for treating superficial tissue injuries, whereas wavelengths of 800–1000 nm are effective for treating deep tissue injuries [59, 60].

Electrostimulation therapy

Direct current is known to be present in the wound and persist until the completion of epithelialization. This electric field serves as a guiding force for cells, facilitating their movement across the wound surface and consequently promoting nerve regeneration [61, 62]. The cessation of this activity halts the healing process. Electrostimulation therapy is used to restore the wound electrical field and stimulate vascular endothelial growth factor (VEGF) (endothelial and osteoblast) production [63, 64]. It has also been found that VEGF increases and shortens healing time in patients with chronic ulcers. A research study shows that the group subjected to electrical stimulation had a higher rate of wound closure compared to the control group [65].

Collagen dressings

Using collagen dressing for unresectable wounds has been shown to facilitate tissue growth and migration of cells, such as keratinocytes and fibroblasts. Collagen, serving as a natural substrate or scaffold, plays an important role in the development of new tissue [66]. It can be used at any stage of wound healing, including debridement, vascularization, and epithelialization [67]. Collagen dressings also contain matrix metalloproteinases (MMPs), which allow the body's collagen to participate in wound healing. Such bandages are capable of aiding in the recovery of wounds with both partial and complete thickness, including pressure sores, vein sores, minor

burns, and long-term injuries. Their ability to reduce inflammatory mediators helps initiate the healing cascade [68–70].

Gene therapy

Gene therapy for wound healing involves introducing multiple growth factor genes that promote tissue healing into the cells involved in the repair process. This enables the sustained and localized expression of these genes, addressing limitations of other treatment strategies and ultimately enhancing the quality of wound healing [71]. Growth factors are a group of substances secreted by wound-healing cells that stimulate their growth and proliferation. Consequently, they can accelerate the healing process via cell proliferation. The complex wound-healing process involves various cell types as well as growth factors and cytokines [72, 73].

Growth factor therapy has gained increasing popularity in recent years due to its remarkable effectiveness in treating difficult-to-heal injuries such as pressure sores, venous ulcers, and diabetic feet. Platelet-derived growth factor (PDGF), VEGF, granulocyte-macrophage colony-stimulating factor (GM-CSF), and brain-derived growth factor (BDNF) are the growth factors and cytokines that are most frequently employed for wound healing [74–77].

Negative pressure wound therapy

One of the most cutting-edge approaches to treat wounds is negative pressure wound therapy (NPWT) [78]. Its application extends globally, addressing both acute and chronic wounds, and even extending the longevity of skin grafts. NPWT treats pressure sores, open wounds, sternal injuries, trauma, second-degree burns, skin grafts, etc. [79, 80].

NPWT can help control bleeding and speed up the healing of wounds. The procedure increases blood flow, lessens edema, stops bacterial growth, and lessens post-traumatic immunosuppression [81]. It can administer irrigation solution and antibiotics, treat cut wounds and manage edema using modified types of therapy. Different contact materials can have recognized uses and effects that vary accordingly [82]. To facilitate recovery, NPWT may be employed alongside other wound care products such as dermal scaffolds, and various allogenic or diverse materials [83, 84].

Platelet-rich plasma

The concentration of platelets, leukocytes, and fibrin obtained through the centrifugation of autologous whole blood is known as platelet-rich plasma (PRP) [85]. The primary repair cells, such as endothelium, epidermal, and fibroblasts, are encouraged to proliferate and differentiate once PRP is triggered by several growth factors. White blood cells prevent infection, while fibronectin locally constructs the three-dimensional structures needed for tissue repair. These all help to repair and heal the wound [86].

Recently, PRP has emerged as an effective treatment strategy for acute skin injuries. Both animal and human trials have demonstrated its efficacy in promoting wound healing. Platelets and all kinds of growth factors in PRP can be used to treat chronic tissue damage by providing attachment sites for cell adhesion, speeding up the physical recovery of tissues, alleviating pain, and anti-inflammation [87–89].

However, the above-mentioned methods are associated with the disadvantages of poor patient compliance, high price, and low universality. Therefore, the exploration of new 2D materials and their incorporation into wound care emerges as a primary avenue for advancing adjuvant approaches to promote wound healing.

Effect of different 2D nanomaterials on wound healing

2D nanomaterials are a novel class of materials with thicknesses ranging from a single atomic layer to many atomic layers. They can be elemental allotropes or compounds that are covalently bound transversally and joined by van der Waals forces. Because of the interaction of atoms in and out of their planes, 2D nanomaterials have a high degree of anisotropy, demonstrating remarkable thermal, mechanical, optical, electrical, magnetic, and other physical and chemical properties, attributed to their unique structure [90]. Simultaneously, 2D nanomaterials have substantial benefits for biological applications, such as high drug and gene-carrying capacity, high photothermal conversion efficiency, and good photodynamic characteristics [16]. Since 2004, the discovery of various other 2D nanomaterials has continued to expand this field of study (Fig. 1). Examples include graphene derivatives, transition metal dichalcogenides (TMDs), hexagonal boron nitride (h-BN), MXenes, metal-organic frameworks (MOFs), covalent-organic frameworks (COFs), single elements such as selenium, boron, silicon, black phosphorus, and so on [91, 92]. Novel 2D nanomaterials find diverse applications in many fields including physics, chemistry, and biology. The coupling of 2D nanomaterials with established therapeutic techniques, particularly in biomedicine, has significant promise for drug delivery, disease therapy, and antimicrobial applications [18, 93].

Graphene and its derivatives

The 2D structure of graphene is characterized by a single layer of carbon atoms arranged in a honeycomb configuration. It has been studied in various fields, including energy, environmental, and biomedical sciences, due to its diverse advantages [13]. Graphene is used in

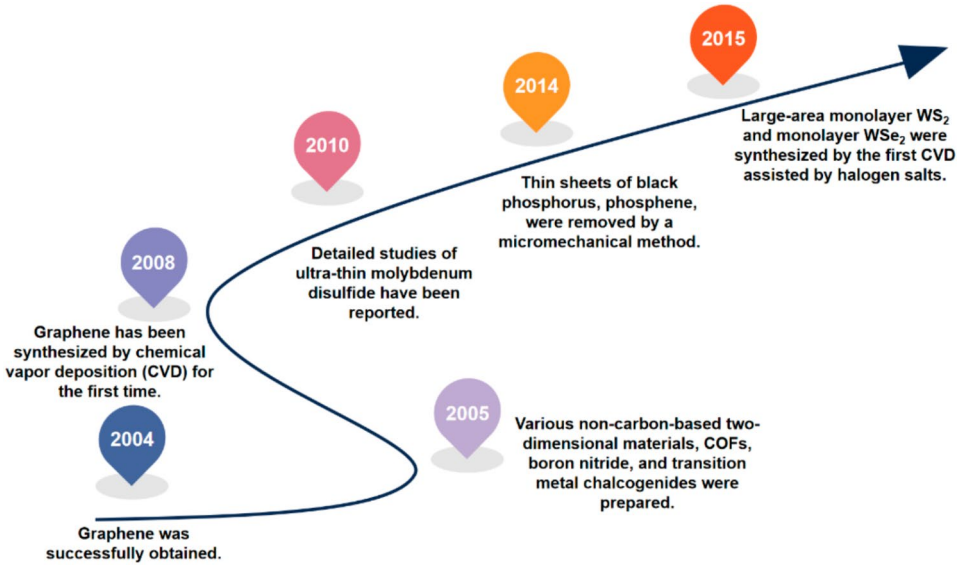

Fig. 1 Important nodes in the process of two-dimensional materials research

several biomedical fields as a biocompatible material for drug delivery, imaging, and biosensor applications [94]. Graphene derivatives such as graphene oxide (GO) and reduced graphene oxide (rGO) have attracted attention in the field of wound healing due to their antimicrobial properties [95]. Their ability to modify the bacterial shape and induce intracellular material leakage has made them a subject of study in the antimicrobial aspects of wound healing [96].

Graphene

Graphene is a 2D substance composed of closely packed sp^2 hybrid linked carbon atoms in a single 2D honeycomb lattice structure. Graphene has remarkable optical, electrical, and mechanical properties, and has promising applications in materials science, energy, healthcare, and other fields, and is expected to revolutionize various industries in the future [97, 98]. Graphene is associated with limitations due to its immature manufacturing methods and high production costs. Moreover, being a single-layer structure, it is too thin and small, prone to fracturing, and inert, making it unable to be easily combined with other substances. Therefore, it is necessary to employ certain methods to improve its surface chemical characteristics to address the issue of instability. It is a highly biocompatible material, and it shows antibacterial action against *E. coli*. To investigate graphene's antibacterial properties at the molecular level, scientists have shown that graphene can slice the bacterial cell membrane, break it down, and eradicate bacteria by extensively pulling phospholipid molecules onto the membrane [99]. Graphene nanomaterials can be used as reinforcement materials to enhance the mechanical strength of their composites [100]. They are effective in neutralizing free radicals, therefore showing a wide range of antioxidant capabilities [101]. Graphene's flat structure facilitates the loading of a wide range of drugs and biomolecules. Graphene nanosheets can interact with biomolecules such as DNA, enzymes, proteins, and peptides, thereby displaying extraordinary tissue regeneration characteristics [102, 103]. All of these studies show graphene's effectiveness in enhancing skin wound healing and tissue regeneration.

Graphene nanomaterials demonstrating antibacterial activity for wound healing

A previous study reported that the production of Chitosan/Gelatin nanofibers (CS/GL NFs) by electrospinning machine, using CS and GL as the main polymeric matrix, and the addition of graphene nanosheets(G NS)as reinforcement can enhance the antimicrobial activity of the electrostatically spun filaments. This enhanced functionality makes it a promising antimicrobial wound dressing, offering protection against wound contamination and reducing the occurrence of wound-related complications. The cell migration of GNS-CS/GL NFs was about 97% within 48 h, which confirmed the rapid wound-healing activity of the material [104].

In another study, experimental results showed that the nanoporous graphene/nitrocellulose (NPGN) membranes had strong antibacterial capabilities. The antibacterial efficacy of the NPGN membrane containing 3 g/L NPG was over 90% for both Gram-negative and Gram-positive bacteria. Further, the high air permeability of the NPGN membranes was attributed to the abundance of nanopores present in the NPG. It was concluded that the NPGN membrane with great antibacterial capabilities

and superior air permeability can significantly increase wound healing ability [105].

Graphene nanomaterials targeting both bacterial infection and hemostasis

Combining graphene with other nanomaterials and applying them to wound healing is another research direction. Priyadarshani Choudhary et al., found that the incorporation of graphene-silver-polycationic peptide (GAP) nanocomposites into chitosan (CS) resulted in a safe and effective hemostatic wound dressing. The improved hemostatic capabilities of the CS-GAP nanobiocomposite were attributed to the electrostatic interactions with blood cells, coupled with graphene's large surface area. CS-GAP also stimulated the production of intracellular reactive oxygen species (ROS), which enhanced the bactericidal efficiency of the nanobiocomposite. The remarkable antibacterial efficacy of the Cs-GAP100 is attributed to the combined antibacterial properties of AgNPs and the enhanced functionality of GAP polycationic peptides. The Cs-GAP100 nanobiocomposite, bearing a positive charge, electrostatically attaches to the negatively charged bacterial cells, causing their physical demise and subsequent death. Combined with its excellent re-epithelialization and blood compatibilities, it has the potential for advancement in trauma management (Fig. 2 A.B) [106].

Graphene oxide (GO)

Graphene oxide (GO) is a 2D material composed of carbon atoms with oxygen-containing functional groups (=O, -OH, -O-, -carboxy). GO flakes are produced by the chemical oxidation and exfoliation of graphite powder. GO comprises single atomic layers that can extend to tens of microns in lateral size. It can be regarded as an unconventional form of soft material with properties of polymers, colloidals, films, and amphoteric molecules. GO is emerging as a popular choice among 2D materials, yet its interaction with liquid water remains an open question. GO, has chemical characteristics extremely comparable to graphene and is used in a range of applications [108]. It can covalently bind to biological components

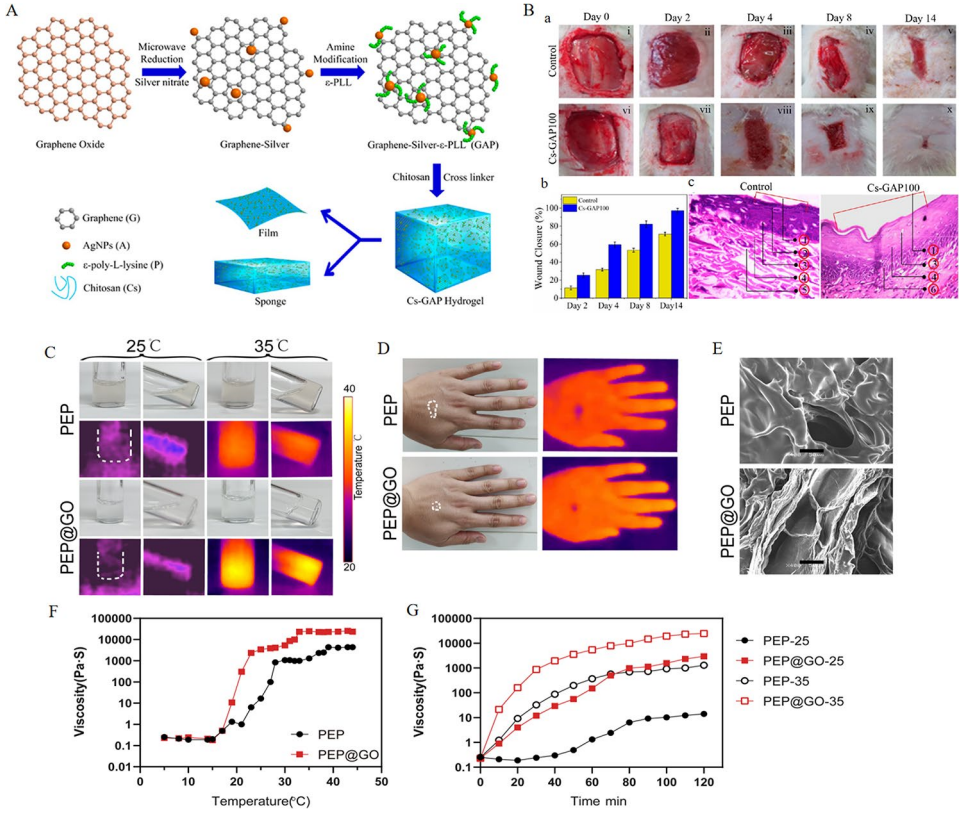

Fig. 2 Application of graphene and its derivatives in wound healing. (**A**) Schematic representation of Cs-GAP nanobiocomposite film and sponge preparation. (**B**) (**a**) In vivo wound-healing images of cotton gauge (i – v), and Cs-GAP100 (vi – x) nanobiocomposite film. (**b**) Wound closure graph in a Wistar rat model. (**c**) Histological images of the skin tissue on the 14th day after treatment with control and Cs-GAP100 nanobiocomposite film on the Wistar rat model (scale bar 50 μm) (1, epidermal Layer; 2, lymphocyte cells; 3, epithelial cells; 4, fibroblast cells; 5, low-density tissue regeneration; 6, high-density tissue regeneration) [106]. (**C**) Digital and infrared thermal images of liquid-gel phase transition during heating and cooling (25–35 ℃). (**D**) Digital and infrared thermal pictures on the back of the hand of human skin at RT. (**E**) High-resolution images(scale bar 50 μm) and (**F**) viscosity curves at different temperatures and (**G**) over time [107]

like proteins, allowing for faster cell development and differentiation due to its surface functional groups. The surface of GO is easily modifiable and can be combined with several biomaterials to improve its properties [109]. The presence of GO has the potential to damage bacterial cell membranes, leading to the expulsion of internal substances and subsequent elimination of the bacteria [99].

The mechanism by which GO promotes wound healing is also related to antibacterial activity. A three-component nanocomposite material was successfully developed as a wound dressing by incorporating curcumin-supported graphene oxide (GO/Cur) into a chitosan matrix. The integration of GO/Cur nanocomposites into chitosan significantly increased PBS absorption, enhancing their potential as a promising option for wound dressings due to their robust antibacterial properties [110]. GO can also be combined with other chemical components to prepare functionalized GO. Another study reported chitosan (CS) composite hydrogels (CS-CGO) with graphene oxide (CGO) grafted by CS. The mechanical properties of CS-CGO composite hydrogels were superior to those of CS hydrogels and GO-filled CS composite hydrogels (CS-GO). It was further confirmed that the CS-CGO composite hydrogel had good biocompatibility and wound-healing properties, making it a viable biological wound dressing [111].

Silver nanoparticles (AgNPs) are a type of antibacterial agent with good performance, although they are frequently employed in combination with other materials due to their instability and strong reactivity to cells. The addition of GO can help stabilize the AgNPs, thereby further enhancing their antibacterial properties. The double-layer scaffold, comprising a collagen sponge as the base material and an outer layer of hydrogel formulated from a gelatin-cellulose composite loaded with GO and AgNPs, displayed higher biocompatibility and antibacterial properties. This composite was concluded to be a potential material for skin wound healing applications [112]. Experiments have shown that the combination of GO with a biocompatible polymer can also promote diabetic wound healing (Fig. 2 C-G) [107].

The integration of GO particles into polyurethane fibers has been reported as wound dressings with improved physicochemical and biological characteristics. In addition to increasing the wound dressing's stiffness, GO also aided the fiber's hydrophilicity, hence, improving their swelling capabilities. Furthermore, studies have shown that the inclusion of GO significantly enhanced the antimicrobial efficacy of wound dressings. The cell viability study revealed that the average cell viability values of all the samples exceeded 80%, indicating their improved biocompatibility. Hence, the electrospinning composite consisting of polyurethane and GO demonstrated considerable potential as a dressing material for skin wound management [113].

Reduced graphene oxide(rGO)

Various chemical techniques are employed to eliminate the oxidation groups bonded to GO, stabilizing its structure. This ensures that the resulting products are not excessively reactive and remain undamaged by chemical treatments. Reduced graphene oxide (rGO) has been found to enhance cell adhesion and promote their proliferation. The rGO is also known to possess various antibacterial properties [114]. It is important to note that rGO not only stimulates wound healing but also significantly enhances wound contraction and reduces scar formation [109]. The current disadvantages of rGO include its higher cost and difficulty in obtaining.

Reduced graphene oxide nanomaterials demonstrating antibacterial activity for wound healing

Non-animal fungal carboxymethyl chitosan (FCMCS) is a modified CS suitable for use in cosmetic formulations. The fabrication of an adhesive hydrogel with enhanced cell/tissue adhesion, and antimicrobial and hemostatic qualities has been reported for wound healing. This was achieved by combining rGO, the favorable biocompatibility of FCMCS, and the adhesive properties of polydopamine (PDA). The FC-rGO-PDA hydrogel demonstrated higher hydrophilicity, thereby stimulating the proliferation and adhesion of dermal fibroblasts and keratin-forming cells while also providing better antibacterial potential against *E. coli* and *S. aureus*. The mechanism may involve the direct interaction of rGO within the FCMCS polymer with the bacterial membrane. The rGO exerts substantial pressure on the bacterial membrane, which in turn leads to physical damage. These multifunctional properties enable the application of hydrogel not only in wound dressing but also in drug delivery and other tissue engineering applications [115].

Reduced graphene oxide nanomaterials targeting both bacterial infection and inflammation

The limited spread and reduction during conventional rGO synthesis restrict the electrical conductivity of graphene hydrogels. This in turn hinders the development of highly sensitive and flexible sensors. Therefore, preparing conductive hydrogels that are highly sensitive, possess antibacterial properties, and have antioxidant abilities continues to be difficult. Yiyong Dou and colleagues refined and reduced GO by employing heparin-polydopamine (Hep-PDA) mixtures. This process produced evenly distributed and consistently reduced Hep-PDA-based GO nanosheets, facilitating the effective development of a Hep-PDA-rGO hydrogel. The hydrogel was observed to contribute to the promotion of wound

healing in chronic diabetes. Its strong antibacterial and antioxidant properties maintained a suitable inflammatory environment, while its intrinsic electrical conductivity promoted angiogenesis. The developed hydrogel demonstrated the potential to serve as a promising dressing option for persistent wound care, alongside its possible application as an epidermal sensor [116].

Transition metal dichalcogenides(TMDs)

In the past few years, with the rise of 2D layered nanomaterials such as graphene, a new category of 2D layered structures, transition-metal chalcogenides (TMDs), has attracted considerable attention from researchers in various fields including physics, chemistry, and electronics. TMDs have a structural formula MX_2 (M=Mo, W, Ti, Zr, etc., X=S, Se, Te), which is similar to that of graphite. They have important characteristics of large surface area, high electrical conductance, and variable oxidation states, which can also be applied to biomedical applications [117]. However, TMDs have a limited band gap, but their application is limited by their low carrier mobility [118].

MoS_2

Molybdenum disulfide (MoS_2) is a common transition metal dihalide with a structure similar to graphene. MoS_2 possesses distinctive electronic, optical, mechanical, and chemical characteristics that make it a promising candidate for biomedical applications [119]. It demonstrates excellent absorption of near-infrared radiation and efficient transformation into photothermal energy, aiding in the release of payloads in photothermal and photodynamic treatments [120]. As a new type of material, MoS_2 is widely used, but it remains in the research stage, and the preparation processes of MoS_2 and its composite materials require further refinement. Transitioning from laboratory research and development to industrial production to maximize the application of MoS_2 and its composite materials is also an urgent problem to be addressed. Researchers are investigating the potential of combining common hydrogel matrices with MoS_2 to develop highly effective antimicrobial agents for wound healing applications, as MoS_2 can eliminate bacteria.

MoS_2 targeting both bacterial infection and inflammation

Yang Li et al., developed a multi-purpose hydrogel based on MoS_2@TA/Fe NSs for healing infected wounds. The MoS_2@TA/Fe NSs hydrogel demonstrated remarkable efficacy in preventing *E. coli* and *S. aureus* infections. It also showed outstanding antioxidant properties that help maintain balance in the antioxidant system, thereby reducing inflammation. Furthermore, the hydrogel was able to stimulate cell growth in a laboratory setting by eliminating bacteria, decreasing inflammation, supplying oxygen, controlling free radical concentrations, and stimulating blood vessel development. These combined effects significantly contributed to the healing of infected wounds [121].

MoS_2 demonstrating antibacterial activity for wound healing

The applications of nano-agents in near-infrared (NIR) laser-triggered photothermal therapy (PTT) have become a highly effective antimicrobial approach. The researchers have reported the development of MoS_2-α-CDBNN6 nanosheets, serving as an innovative 808 nm laser-mediated nanocarrier that releases NO. Adopting this method resulted in treatments that were effective and economical for both Gram-negative and Gram-positive bacteria. When exposed to 808 nm light, hyperthermia induced by MoS_2-BNN6 can precisely control the delivery and on-demand release of NO, accelerating the oxidation of glutathione (GSH), and disrupting the balance of antioxidants in bacteria. NO released by MoS_2-BNN6 interacts with bacteria to induce oxidative/necrosis-stress-oriented DNA damage. Experiments showed that MoS_2-BNN6+NIR effectively inactivated bacteria in less than 10 min (>97.2%) under the condition of PTT/NO synergism compared with PTT alone. The findings from the wound healing experiments showed that this combined antimicrobial technique can be successfully employed to sterilize infected wounds and assist in the healing of injured tissues [122].

Lihui Yuwen et al., used PDA to modify MoS_2 nanosheets (MoS_2 NSs) followed by depositing AgNPs on their surface. The prepared MoS_2@PDA-Ag nanosheets (MPA NSs) acted as a multimodal antimicrobial nanopreparation, demonstrating effectiveness in treating wounds infected by *S. aureus*. The in vitro experiments demonstrated that MPA NSs, when exposed to NIR, successfully eliminated the developed *S. aureus* biofilm (representing 99.99% of the bacteria), exhibiting significantly enhanced effectiveness in comparison to the MPA group and the NIR laser irradiation group. The in vivo experiments showed that almost all of the bacteria in the wound had been eliminated, which aided in the healing of the infected wound [123].

The combination of MoS_2 with other nanomaterials to enhance wound healing represents a commonly adopted approach in research and development. For example, TiO_2NTs@MoS_2 can generate a large amount of OH under visible light irradiation. The loading of MoS_2 extends the photoresponse of titanium dioxide to the visible range and enhances the photocatalytic activity. The combination of MoS_2 with TiO_2NTs significantly increased its enzyme-like activity. Experiments using *E. coli* and MRSA as models revealed that the prepared TiO_2NTs@MoS_2 had excellent broad-spectrum antimicrobial ability. Its anti-infective ability was well illustrated

in a rat model of wound infection. It was concluded that TiO_2NTs@ MoS_2 displayed improved and practical antimicrobial and wound-healing effects in vitro when exposed to visible light-induced nano-enzymatic activity [124].

Using MoS_2 nanoparticles, a versatile nanoplatform (MQCP@ZIF-8) responsive to both pH and near-infrared light (NIR) was developed, yielding a combined effect of photothermal and photodynamic antibacterial properties. The photothermal conversion efficiency of the nano platform was 56%. The treatment effectively reduced the viability of MDR *E. coli* and MDR *S. aureus* by over 95%, enhancing wound recovery in mice infected with MDR *S. aureus* (Fig. 3) [125].

$MoSe_2$

Molybdenum(IV) selenide ($MoSe_2$) based nanosheets have been reported for their outstanding peroxidase activity. Similarly, $MoSe_2$ films have also demonstrated rapid and efficient wound disinfection and healing properties by using minimal quantities of hydrogen peroxide in vivo. This helps avoid the adverse effects associated with excessive hydrogen peroxide in conventional pharmaceutical treatments. The fabrication of an economical and efficient thin layer of $MoSe_2$ nanosheets in an aqueous medium, employing carboxyl-modified silk fibroin, has been reported. The obtained $MoSe_2$ nanosheets had an exceptional concentration, excellent solution stability, and biocompatibility. Furthermore, the nanosheets improved superior peroxidase activity, effectively combating bacterial infections and promoting wound healing. These findings offer a novel approach for the practical implementation of two-dimensional TMD nanosheets in a clinical setting [126].

WS_2

Recently, there has been a significant increase in the use of 2D transition metal dichalcogenides (TMDs) in biomedical applications, particularly in the area of photocatalytic antimicrobial therapy. WS_2, a typical TMD, has a unique structure and outstanding performance, making it suitable for use in antibacterial and anti-tumor treatments. Further, it has a high drug-loading capacity without any adverse effects [127, 128].

Na Yang et al. reported that the composite hydrogel, prepared by incorporating WS_2 nanosheets as a synergistic combination of PTT agent and antibiotic, displayed enhanced bactericidal efficiency compared to the use of antibacterial agents alone. Further, the gel possessed excellent antioxidant properties that mitigated inflammation caused by bacterial infection and PTT treatment, thereby facilitating wound healing [129].

Single element

Selenium

Selenium is a vital trace element for the human body. Elemental selenium nanoparticles have attracted greater scientific interest in recent years due to their excellent bioactivity and low toxicity [130]. Similarly, the exceptional stability of elemental selenium nanoparticles (SeNPs) in liquid has identified them as promising therapeutic materials. SeNPs have been shown antioxidant, anticancer, and biofilm-inhibitory effects. The active core of many antioxidant enzymes and functional proteins contains selenium, which plays an important role in lowering oxidative stress in the body. SeNPs have attracted significant attention due to their antibacterial, antiviral, and anticancer effects, as well as substantial antioxidant and anti-inflammatory characteristics and wound healing properties [131]. However, in the complex physiological

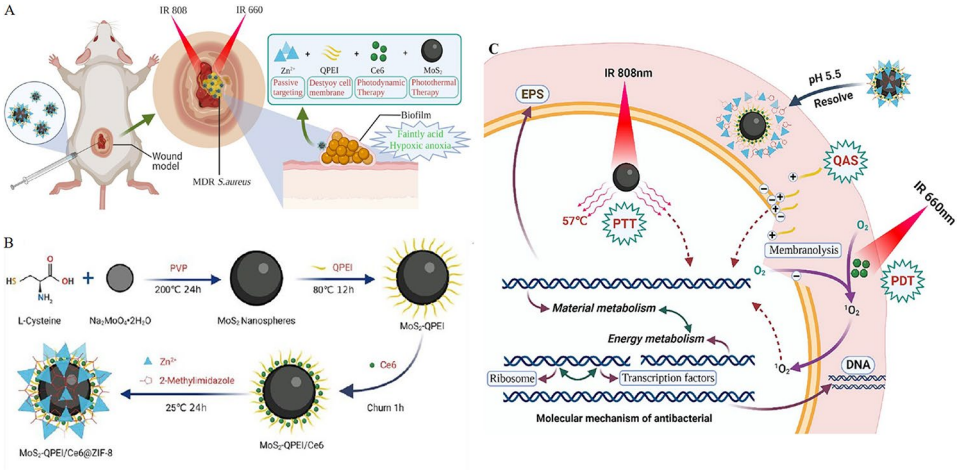

Fig. 3 (**A**) Schematic diagram of wound infection treatment using a combination of PTT/PDT/antibacterial active ingredients. (**B**) Schematic diagram of the synthesis of MQC@ZIF-8. (**C**) Schematic diagram of the molecular mechanism of the MQC@ZIF-8 nanobacterial platform against drug-resistant bacteria [125]

and pathological environment of the human body, the potential toxicity of nano-selenium, its ability to participate in the activation of immune, nerve, and endocrine cells, and the mechanisms by which it exerts its effects require further study.

Selenium nanosheets demonstrating antibacterial activity for wound healing

The synthesis of SeNPs that can be effectively stimulated by a yellow light source (YL) for improving their antibacterial activity has been reported. The nanoparticles were encapsulated with polyethylenimine (PEI) and modified with indocyanine green (ICG), which combined photoacoustic therapy to promote the healing of the wound infected by drug-resistant bacteria. The composite displayed an antibacterial efficacy of over 99% against methicillin-resistant *S. aureus* (MRSA) and *E. coli* in both in vitro and in vivo experiments within 10 min. It also effectively eliminated resistant bacteria, facilitating wound healing with higher safety [132].

Selenium nanosheets demonstrating antioxidant activity for wound healing

The incorporation of SeNPs and VE can significantly affect the size, permeability, mechanical characteristics, and hydrophilicity of nanofibers, and can lead to a continuous release of VE and SeNPs. Histopathological studies and oxidative stress tests confirmed that the composite stent significantly improved the healing process of skin wounds by decreasing edema, inflammation, and oxidative stress in the affected area [133]. The anti-biofilm and anti-oxidant activity of SeNPs was found to increase proportionally with the increase in concentration, decreasing to 75% at 3.2 μg. The wound healing activity of SeNPs showed that 5% selenium cream cured Wistar rats with an 85% wound healing rate within 18 days compared to standard ointment [134].

Selenium nanosheets demonstrating inflammation activity for wound healing

Promoting wound contraction and collagen deposition is also one of the reasons selenium nanosheets are used to promote wound healing. Multifunctional nanocomposite hydrogels composed of bacterial cellulose (BC), gelatin (Gel), and nano-selenium (SeNPs) have been reported for their wound healing potential. The BC/Gel/SeNPs hydrogel exhibited excellent performance in promoting skin wound healing in a rat full-layer defect model. This was demonstrated by its significant reduction in inflammatory response, promotion of wound closure, formation of granulation tissue, and deposition of collagen [135].

SeNPs can also be combined with common drugs to enhance their therapeutic effects. Chitosan transdermal patches prepared with SeNPs and doxorubicin have been found to show a better effect on wound healing [136]. The preparation of selenium-chitosan-Mupirocin (M-SeNPs-CCH) complexes has also been reported. Experimental results showed that the nanohybrid system reduced the minimum inhibitory concentration (MIC) of Mupirocin by 3 times, had synergistic antibacterial activity, and played an important role in wound shrinkage, angiogenesis, collagen deposition, hair follicle proliferation, and epidermal growth [137]. The manufacturing of elemental selenium nanoparticles using chitosan as a modifier has been reported to significantly increase the planar and histological indexes of full-layer wound healing, thereby realizing the potential of wound healing [131].

Silicon

Porous silicon (PSi) is a promising inorganic material due to its large surface area, variable pore size, and modifiable surface chemistry. It has been extensively investigated in biological fields such as drug delivery, tissue engineering, and immunotherapy [138–140]. The results demonstrate that nano-silicon has high therapeutic properties and biosafety, however, accurately modulating key structural parameters remains challenging, and the therapeutic mechanism remains unclear [141].

Porous silicon demonstrating antibacterial activity for Wound Healing

PSi, as a carrier, can be combined with other drugs to improve its antibacterial effect. Altering the surface of PSi using PDA results in the development of a unique CUPDA-coated PSi microcarrier (CuPPSi), while maintaining the mesopore configuration. This enables the conventional drug carrier to possess a substantial photothermal effect, thus enhancing the antibacterial treatment efficacy. Cu PSi can produce the release of loaded curcumin (Cur) and antimicrobial Cu^{2+} in response to various stimuli, including pH, reactive oxygen species, and NIR laser emission. At a moderate PTT temperature of 45 ℃, the composite displayed a bactericidal activity of more than 98% against both *S. aureus* and *E. coli*. The results reveal that CuPPSi can enhance fibroblast migration without any significant cytotoxicity. Effective bacterial ablation and wound healing were also demonstrated in a mouse model of bacterial infection [142].

The development of a double-collaborative antibacterial platform based on a composite of Ag NPs and antimicrobial peptides (AMPs) within PSi, with on-demand release capabilities, has been reported. PSi acts as a carrier for the effective loading of AgNP and AMP under mild conditions, enabling the on-demand and synergistic release of platforms. In *S. aureus* infection rat wound models, wound dressings containing AgNPs-AMP@PSiMPs showed significant in vivo bactericidal activity, accelerated wound healing, and low biotoxicity. PSi MPS

could, thus, be a potential platform for loading antibiotic-free fungicides that can be distributed in a synergistic and demand-driven manner to treat wound infections and promote wound healing [143].

PSi accelerates wound healing by promoting angiogenesis

In addition to its antibacterial effect, PSi can also accelerate wound healing by promoting angiogenesis. Qingyan Zeng et al., developed self-luminous porous silicon (LPSi) particles with higher biocompatibility and degradability, and adhesion strength. Furthermore, in a mouse skin incision model, this adhesive composite closed the wound rapidly, improved angiogenesis and epidermal regeneration, and aided in wound healing. More importantly, the self-luminescence strength of LPSi particles at the wound site enabled the evaluation of wound healing rates [144].

Boron

Boron nanosheets (BNSs) are unique 2D materials that, when compared to other materials, offer a high potential for photothermal treatment (PTT) [145, 146]. Boron is one of the most essential trace elements required for the proper functioning of living beings. It regulates metabolic processes and has anti-inflammatory properties. This phenomenon could be exploited in drug-delivery systems to treat inflammatory diseases [147].

Liquid-phase stripping and electrostatic adsorption techniques have been employed to engineer a multifunctional nanoplatform termed B-QCS-BNN6. This innovative platform was based on quaternized chitosan (QCS) coated with boron nanosheets (BNS) and served as a nitric oxide (NO) donor. The B-QCS-BNN6 nanoplatforms demonstrated rapid and potent efficacy in combating both standard Gram-negative and Gram-positive bacteria. These platforms not only demonstrated the effects of PTT but also enabled precise regulation of the 808 nm laser-stimulated NO release following 808 nm laser stimulation. The PTT/NO antimicrobial efficacy was greater than 99.9% within 5 min. This synergistic antimicrobial technique can be simply employed to disinfect methicillin-resistant *S. aureus* infected wounds, allowing for the regeneration of damaged tissue and the treatment of MRSA-infected wounds [148].

Black phosphorus

2D materials, including black phosphorus, have recently attracted scientific attention in the biomedical field. Because of its crumpled rhombic crystal shape, BP has a larger surface volume ratio, thus increasing its drug loading capacity [149]. BP has a negative charge on its surface due to the presence of phosphoric acid. This feature facilitates the incorporation of positively charged pharmaceuticals or nanoparticles via electrostatic interactions in the interlayer area [150, 151]. BP has been found useful in various fields including bone therapy, cancer treatment, and the management of neurodegenerative diseases [152–154]. The main bactericidal mechanisms of BP involve reactive oxygen species-dependent oxidative stress and membrane damage. Its application as an effective photothermal agent and oxygen carrier contributes significantly to wound healing [155]. Despite its broad application prospects, BP is extremely unstable in the air, and prone to oxidation and degradation, which severely limits its application [118].

Black phosphorus demonstrating antibacterial activity for wound healing

Jiang Ouyang et al., have reported the efficacy of in situ spray, NIR-reactive, pain-relieving BP-based gels in treating diabetic ulcers (DU). The results of in vitro and in vivo experiments suggest that this BP-based gel can simultaneously and effectively address individual characteristics of various wound healing environments, such as chronic wounds, impaired cellular regeneration, persistent pain, bacterial infections, and increased inflammation. This suggests a significant potential for improvement in the treatment of patients with DU [156]. The development of a 2D antibacterial nanoplatform based on the antibacterial ability of 808 nm laser irradiation combined with PTT and PDT has been reported. A combination of BP and tellurium-doped carbon quantum dots (CQDs) was used to construct the nanoplatform. The findings indicated that BP@CQDs had enhanced antibacterial effects, with inhibition rates of up to 92.7% and 98.4% against *S. aureus* and *E. coli*, respectively. BP@CQDs were also found to be biocompatible during treatment in vitro and in vivo studies [157].

Our research group has also reported that BP can be used to promote wound healing. A heat-sensitive BP hydrogel for wound healing was successfully prepared by incorporating silver sulfadiazine (SSD) and chitosan within the thermosensitive hydrogel. This characteristic allowed for a continuous release of SSD when exposed to near-infrared radiation, thus allowing for a joint photothermal and antibacterial treatment. In a rat skin wound model, it promoted collagen deposition, and neovascularization and inhibited inflammatory indicators (Fig. 4 A.B) [158].

Black phosphorus nanosheets promote angiogenesis

Xueshan Bai et al., investigated the effects of BP nanosheets on angiogenesis and reducing inflammation. The in vivo study using a comprehensive, full-layer excised rat wound splint model revealed that BP nanosheets have beneficial biological effects on wound healing. These effects include enhanced anti-inflammatory properties, angiogenesis, collagen accumulation,

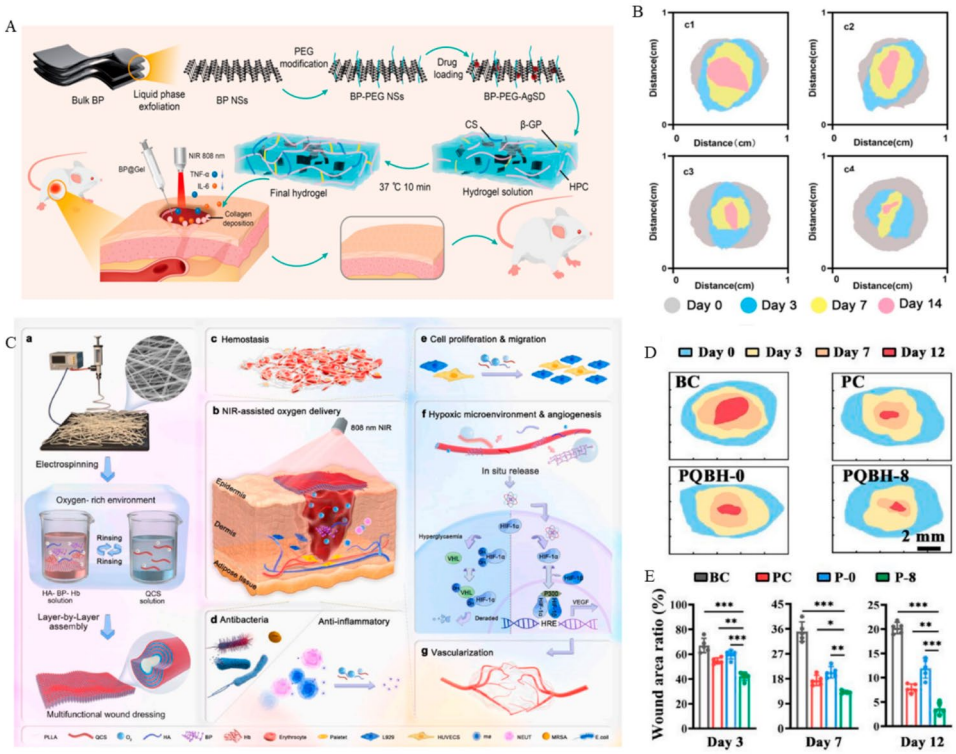

Fig. 4 (**A**) Schematic diagram of the mechanism of BP@Gel to promote skin wound healing. (**B**) Schematic diagram of wound healing simulated by image software in Control group (**c1**), NIR group (**c2**), BP@Gel group (**c3**) and BP@Gel + NIR group (c4). [158] (**C**) Schematic illustration of the preparation and application of photothermal PQBH-n nanofibers. (**a**) electrospinning PLLA/QCS composite nanofibers were LBL self-assembled with positively charged QCS solution and negatively charged HA/BP/Hb solution. (**b–g**) The produced PQBH-n nanofibers are multifunctional and remodel the harsh HME owing to the all-in-one bioactive properties, such as NIR-assisted oxygen delivery, hemostasis, and antibacterial and anti-inflammatory properties, thereby promoting cell proliferation, migration, and vascularization. (**D**) Contour map of the wound healing process(scale bar 2 mm). (**E**) Wound area ratio at different time points ($n = 5$) [161]

and skin re-epithelialization. At the molecular level, BP nanosheets triggered the JAK-STAT-OAS signaling route, and enhanced endothelial cell activity and mitochondrial energy metabolism, thereby aiding in wound healing [159].

Black phosphorus can enhance antioxidant function

Besides its antibacterial properties, BP is capable of enhancing antioxidant functions. A novel PTT and photodynamic therapy (PDT) system was developed by integrating 4-octinitaconic acid (4OI) modified BP nanosheets into a photosensitive multifunctional gelatin methacrylamide hydrogel. When exposed to laser light, the hydrogel coated with 4OI-BP rapidly formed a protective layer on the wound, thus eliminating the risk of bacterial contamination. Without laser radiation, BP functioned as a carrier, regulating the release of 4OI and working together to boost antioxidant activity. This lowered the excessive damage that ROS caused to endothelial cells, thus improving neovascularization and accelerating the closure of diabetic wounds. The results suggest that multifunctional hydrogels encapsulated in 4OI-BP offer a step-by-step countermeasure with antioxidant and antibacterial qualities to aid in the healing of diabetic wounds [160].

As a photothermal agent, BP also plays a vital role in promoting wound healing. Hemoglobin (Hb) and layered black phosphorus BP nanosheets were found to self-assemble onto electrospinning Poly(L-lactic acid) (PLLA) nanofibers in the presence of charged quaternary ammonium chitosan (QCS) and hyaluronic acid (HA). NIR radiation can be converted into heat by BP, which can also cause Hb to release oxygen on the spot. The development of a series of composite wound dressings with different layers (designated PQBH-n) has also been reported. Their therapeutic potentials for diabetic wounds were investigated in vivo, revealing them as suitable dressings for wound healing (Fig. 4 C-E) [161].

Photothermal black phosphorus nanosheets (BPNSs) were incorporated into bioabsorbable gelatin-PCL (GP) matric to fabricate a nanofiber scaffold. Utilizing Doxorubicin (DOX) infused BPNSs enhanced the effects of both PTT and heat-induced DOX treatments. As a portion of the loaded DOX was released into the wound tissue, resulting in a microenvironment that resulted in tumor growth inhibition, the isolated DOX molecules

concurrently penetrated the wound tissue, further impeding melanoma progression. This dual action achieved anti-melanoma effects and promoted wound healing [162]. Fibroin protein (SF) can be used as a stripping agent to produce long-term stable thin-layer BP nanosheets. The integration of SF impedes the rapid oxidation and degradation of the produced BP nanosheets, enhancing their physiological efficiency. BP wound dressing, serving as a potent photothermal agent, effectively prevents bacterial infections and facilitates wound healing [163].

Hexagonal boron nitride

Boron nitride (BN), a crystalline substance, is made up of nitrogen (N) and boron (B) atoms in stoichiometrically equivalent proportions, with hexagonal boron nitrides (h-BNs) being one of its structural varieties. h-BNs are a 2D layered structure, also known as white graphene due to their structural resemblance to conventional graphene. This structural similarity also influences the mechanical, optical, and electronic properties of h-BNs [164]. In biomedicine, h-BNs are known to accelerate wound healing due to their antioxidant properties and facilitation of cell movement. However, h-BN applications are limited by their insulation properties and poor absorption in the visible light region [118].

Boron derivatives produced by h-BNs, generated from boric acid (BA), have been found to help in wound healing. Treatment with h-BNs significantly enhanced the proliferation and migration of human umbilical vein endothelial cells (HUVECs) and human dermal fibroblasts (HDFs) during the wound healing phase, whereas there was minimal improvement in cells treated with BA. Furthermore, the angiogenesis ability of HUVECs treated with h-BNs was shown to be beneficial, and h-BNs may also aid wound healing through its antioxidant capacity to lower ROS. The researchers have also found that h-BNs could protect cells from apoptosis, whereas BA had minimal influence on cell death pathways. The experimental findings demonstrated that BA and h-BNs both sped up wound healing. However, the gradual deterioration of h-BNs can compensate for this short half-life of BA by serving as a source of regulated release of BA. h-BNs, ultimately, appear to be a promising treatment choice for wound healing therapy [165].

Being mussel adhesion, the development of a combination involving h-BNs nanoparticles, AgNPs, and PDA has been reported. hBN@PDA and hBN@PDA-AgNPs, coated with PDA and modified with AgNPs, respectively, were developed. The cellular uptake capability and compatibility of hBN@PDA and hBN@PDA-AgNPs within living organisms were initially investigated in a laboratory setting. Both composites were evaluated for their ROS levels in damaged cells, and their impact on cell migration, intracellular tube formation, and myosin organization was observed through light and confocal microscopy, respectively. The results indicated that hBN@PDA-AgNPs substantially decreased ROS production and facilitated wound healing [166].

MXene

Transition metal carbides/nitrides/carbonitrides (MXenes) have attracted the attention of researchers in recent years as a novel class of 2D materials [167]. MXenes are currently recognized as the largest group of 2D materials, with approximately 30 types documented and numerous others analyzed statistically [168]. The basic equation they use is $M_{n+1}X_nT_x$, with M symbolizing an early transition metal element (like Ti, Zr, V, Nb, and Mo), n ranging from 1 to 3, X denoting C and N, and Tx indicating surface termination points (such as OH, O, F, and Cl). MXenes find their use across multiple domains, such as energy storage, catalytic processes, and pharmaceuticals, owing to their improved conductivity, modifiable surface end, and adjustable thickness [169, 170]. They have also shown excellent light absorption. Under NIR laser stimulation, the light absorption properties of MXenes promote their application as a photothermal material in deep tissue PTT and PDT. The antibacterial mechanism of MXenes mainly includes physical trapping theory, infrared thermal effect, ROS generation theory, intercellular molecular leakage theory, etc. Therefore, MXenes are expected to become safer, more effective, and broad-spectrum antibacterial materials. More importantly, various surface modifications can be made to improve some of the defects of MXenes in vivo, including poor water dispersion, slow degradation slightly toxic, etc., without affecting their inherent properties. Therefore, the biological applications of MXenes have become the subject of research interest [171].

MXene targeting both bacterial infection and inflammation

Yang Li et al., reported the development of an innovative injectable hydrogel utilizing a combined oxygen-hemoglobin/hydrogen (HbO_2/H_2O_2) system and gentle photothermal stimulation. The system aimed to improve the treatment of diabetic wounds with hyaluronic acid that involves dopamine (HA-DA) and Ti_3C_2 MXene nanosheets coated with PDA (Fig. 5A) [172]. Zongjia Li et al., developed a MXene@PDA-CPT antibacterial nano-system with good ROS and nitrogen scavenging capabilities which effectively inactivated drug-resistant bacteria and biofilms, improving wound healing. With a higher anti-bacterial and anti-inflammatory effect, the inclusion of cryptotanshinone further enhanced the benefits of this system [173].

Hongbin Li et al., developed a MXene@polydopamine (MXene@PDA) decorated chitosan non-woven fabric

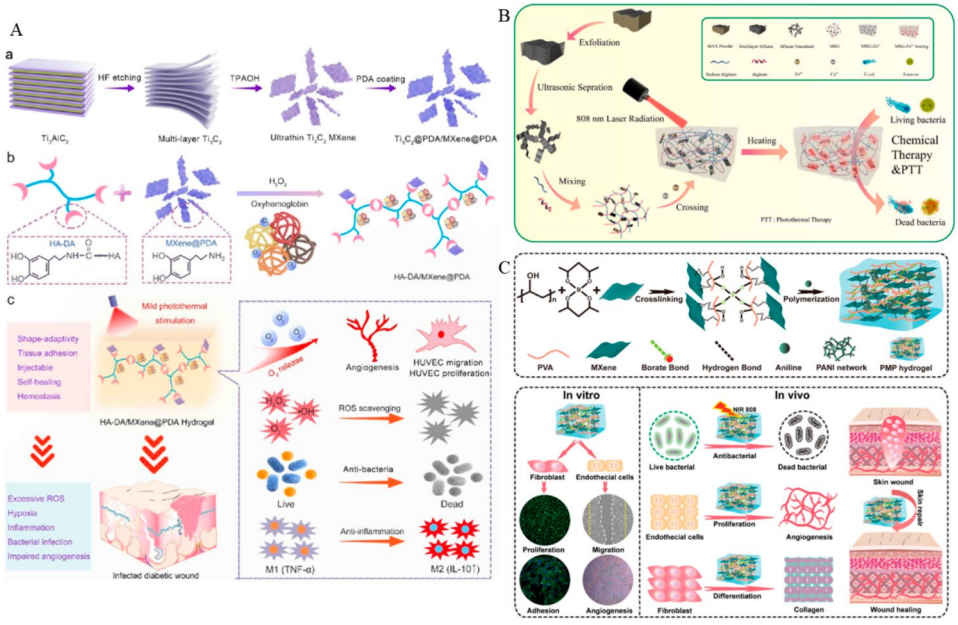

Fig. 5 (**A**) (a) Synthesis Diagram of MXene@PDA Nanosheets. (**b**) Schematic Illustrations of Injectable HA-DA/MXene@PDA Hydrogel Preparation. (**c**) Infected Diabetic Wound Healing Mechanism of HA-DA/MXene@PDA Hydrogel through Supplying O_2, Scavenging ROS, Eradicating Bacteria, and Inhibiting Inflammation [172]. (**B**) The schematic diagram of chemo-photothermal synergetic treatment of localized bacterial infection by the MSG-Zn^{2+} hydrogel [180]. (**C**) Fabrication of PMP hydrogels and their application in skin wound healing [177]

(M-CNF) hemostatic dressing, characterized by high hydrophilicity and suitability for wound healing and regeneration. In full-layer skin defect models, M-CNF with 15 mg/mL MXene@PDA (M-CNF-15) showed superior antibacterial and coagulation properties compared to CNF. Three days post-surgery, COL3A1 expression in the M-CNF-15 group significantly exceeded that in the control and other groups, suggesting a greater fibrinogen production in the M-CNF-15 group compared to the CNF group. MXene@PDA was found to facilitate fibrinogen production and improve scar development and wound repair, indirectly indicating cell growth and diversification. Furthermore, the M-CNF-15 also demonstrated superior wound-healing capabilities [174].

MXene demonstrating antibacterial activity for wound healing

Polyvinyl alcohol (PVA) has emerged as a leading candidate material due to its viscoelasticity, which closely resembles tissue structure. However, its applications are limited due to its lack of mechanical strength. Incorporating MXene along with various other substances enhances the mechanical robustness and properties of PVA hydrogels. A study has reported the development of an antibacterial nanofiber film, MXene-AMX-PVA, fabricated by combining amoxicillin (AMX), MXene, and PVA through an electrospinning technique. PVA substrates in composite nanofiber membranes regulated the controlled release of AMX, effectively combating bacterial infections. Similarly, MXene acted as a converter of near-infrared lasers into heat, inducing localized hyperthermia that promoted the AMX release. The results showed that the film not only serves as an actual boundary for AMX and MXene but has also improved antibacterial and wound-recuperating properties [175].

The MXene@PVA hydrogel, developed via a coordinated freezing salt-out approach, has been reported for excellent mechanical properties when subjected to confined hyperthermia in the contaminated area using a NIR laser (808 nm). Owing to the MXene's strength, the hydrogel effectively inhibited *E. coli* and *S. aureus* by 98.3% and 95.5%, respectively. Moreover, in the mouse wound model, the hydrogel restrained the wound contamination and advanced skin wound recuperation. The results suggest that MXene@PVA hydrogel could be an excellent antibacterial wound healing dressing [176]. Another study has also reported the development of a high-strength and antibacterial PVA hydrogel using $Ti_3C_2T_x$ (MXene) and polyaniline (PANI) to promote skin wound healing. MXene enhanced the hydrogen bonds between PVA molecules and provided antibacterial performance when illuminated by NIR light. At the same time, the hydrogel promoted cell proliferation, cell migration, angiogenesis ES, and collagen deposition through, and significantly accelerated skin wound healing (Fig. 5 C) [177].

So far, the MXene family consists of dozens of 2D transition metal compounds. However, only a few transition elements such as Ti, Nb, and Ta, and their compounds have stable chemical properties suitable for application in

the biomedical field [178]. Li Zhou et al., found that Ti_3C_2 was the most effective material for skin wound healing. They developed a multifunctional scaffold (HPEM) by combining poly (glycerin-ethyleneimine), $Ti_3C_2T_x$ MXene@polydopamine (MXene@PDA) nanosheets, and oxidized hyaluronic acid. The scaffold had remarkable self-healing and antibacterial properties, with an impressive 99.03% antibacterial efficacy against MRSA. The results suggest that the HPEM framework could enhance cellular growth, vessel formation, granulation tissue development, collagen accumulation, vascular endothelial transformation, and angiogenesis, besides speeding up wound recovery in MRSA infections [179]. In another study, a reliable mixed hydrogel (MSG-Zn^{2+}) was developed for rapid and efficient sterilization by combining sodium alginate (SA) and AGAR (AG) with $Ti_3C_2T_x$ MXene and zinc ions (Zn^{2+}). The incorporation of Zn^{2+} improved the viable contact between hydrogel and microorganisms, enhancing its efficacy for photothermal antibacterial and synthetic antibacterial applications (Fig. 5 B) [180].

MXene can also be combined with current clinical methods to promote wound healing. Composite hydrogels with a 2 wt% MXene (rBC/MXene-2%) ratio demonstrated the highest electrical conductivity and the highest biocompatibility. In vitro and in vivo results showed that hydrogels combined with electrical stimulation (ES) substantially increased cellular proliferation and accelerated the injury recuperating process contrasted and non-ES controls [181]. Multilayer nanosheets of 2D MXenes were combined with oxidized alginate and gelatin hydrogels in nanosheet form, forming hybrid conductive hydrogels (CHs) with different concentrations of MXene. In contrast to pure oxidized alginate dialdehyde gelatin (ADA-GEL), the incorporation of MXene, with its abundant surface groups and increased electrical conductivity, significantly improved the mechanical characteristics and electrical conductivity of composite hydrogels [182]. The common characterization of the above inorganic two-dimensional materials and their composites and their role in wound healing can be seen in Table 2.

Metal-organic frameworks (MOFs)

The Metal-organic Frameworks (MOFs) consist of a composite of organic and inorganic elements, including metal ions/clusters and organic crosslinkers. The integration of these elements opens up various applications such as catalytic processes, gas capture/separation, photoluminescence, detection, adsorption, and administering drugs [187]. MOFs have led to the development of composites with improved properties compared to their structural components due to their outstanding structural characteristics including large specific surface area and excellent biocompatibility [188]. MOFs are primarily used as drug delivery vehicles for certain drug molecules for different purposes. MOFs, in addition to possessing a metal core capable of hosting a variety of metal ions, including Zirconium (Zr), zinc (Zn), and copper (Cu), can be tailored to suit a wide range of applications. Studies have demonstrated that the degradation process of MOFs, which releases metal ions from the MOF center, is highly effective in treating wound infections [189–191]. However, their ability to scale up synthesis and molding remains limited, hindering the realization of large-scale commercial applications [192].

Cu-based MOFs

Cu-based MOFs demonstrating antibacterial activity for wound healing

Cu-based MOFs can promote wound healing through antibacterial action. Wang Siyu et al., prepared Cu-MOFs (HKUST-1) based wound dressing by electrospinning mixed chitosan/polyvinyl alcohol fiber (HKUST-1/CS/PVA). The composite fiber material demonstrated good antibacterial activity against *E. coli* and *S. aureus*, achieving an antibacterial efficiency of 99%. Compared with the control group, HKUST-1/CS/PVA was more effective in wound healing with less inflammation [193]. The complete encapsulation of AgNPs in CuTCPP MOFs resulted in Ag-CuTCPP MOFs displacing improved antibacterial efficacy in vitro compared to penicillin. The inhibition ratios of Ag-CuTCPP MOFs for *E. coli*, *B. subtilis*, *S. aureus*, and their mixed strains were 82.18%, 72.8%, 89.1%, and 80.4%, respectively. The Ag-CuTCPP MOFs also revealed good in vivo antibacterial effects and extremely low cytotoxicity, while also demonstrating significant efficacy in promoting wound healing [194].

A combination of 2D nanomaterials can also be used to promote skin wound healing. Nan Zhang et el., reported the fabrication of a Ti_3C_2Tx (MXene) hydrogel, known for its high conductivity and antibacterial properties, using a mixture of chitosan, PVA, and AgCu-H_2PYDC MOF. Within the hydrogel, the MXene layer served as an electrical conductor, with MOF metal ions binding with chitosan molecules, enhancing the crosslinking density among these molecules and boosting the hydrogel's mechanical properties. The PCMM hydrogel exhibited complete antibacterial efficacy against *E. coli* and *S. aureus*. The 1 V electrostimulated PCMM hydrogel enhanced mouse wound healing by accelerating cell migration and the formation of new blood vessels, achieving a healing rate of 97 ± 0.4% by the 14th day [195].

Cu-based MOFs used for the reduction of inflammation

Cu-based MOFs also have anti-inflammatory effects and promote angiogenesis. Tianlong Wang et al., reported a novel copper-nicotinic acid (CuNA) doughnut-type MOF

Table 2 Characterization of inorganic two-dimensional materials and their composites and their role in wound healing

2D material	Characterize	Efficiency	Ref.
Graphene	SEM, TEM, Raman spectra, FTIR, UV-vis, XRD, Zeta potential, TGA, XPS	antibacterial, promote cell migration and skin tissue repair, fast hemostasis, efficient sterilization	[104], [105], [106]
Graphene Oxide (GO)	SEM, EDX, FTIR, XRD, TGF, DMA	promote cell migration, antibacterial, promoted angiogenesis and epidermal regeneration	[112], [183]
Reduced Graphene Oxide(rGO)	UV–vis, Strain amplification rheology, SEM, NTA, TEM, FTIR	antibacterial, hemostatic, promote cell growth, promote angiogenesis, promote skin collagen formation and re-epithelialization	[115], [184], [185]
MoS_2	TEM, AFM, Raman spectra, FTIR, UV–vis, NIR, photothermal effect, HAADF-STEM image, XPS, XRD	antibacterial, photothermal antibacterial, anti-inflammatory, promote blood vessel growth	[122], [121], [123]
WS_2	SEM, AFM, TEM, XRD, FT-IR, UV-vis	antibacterial and anti-inflammatory	[127], [129]
Selenium	UV–vis, FT-IR, XRD, EDX, HR-TEM, SEM, Raman spectra, TEM, Zeta potential	significantly promote granulation tissue formation, collagen deposition, angiogenesis, antibacterial, anti-inflammatory, and wound contraction	[134], [135], [137], [186]
Silicon	TEM, SEM, EDS, Elemental mappings, DR-FTIR, XPS, UV – vis, MALDI TOF MS spectra, Thermal images	fast wound closure, promote angiogenesis and epidermal regeneration, antibacterial	[144], [142], [143]
Boron	TEM, HRTEM, AFM, XPS, FTIR, UV–vis, STEM-EDS mapping, Zeta potential	antibacterial	[148]
Black phosphorus	TEM, SEM, elemental mapping, scanning transmission, XPS, Raman spectra, AFM, EDX, HRTEM, FTIR, EDS, Zeta potentials, UV–vis, SAED, ESR signal	antibacterial, hemostatic, promote angiogenesis, antioxidant, promote wound closure, analgesia	[161], [160], [163], [156], [157], [158]
Hexagonal Boron Nitride	SEM, TEM images, FT-IR, Raman spectra, UV-vis	accelerate wound closure, enhance angiogenesis activity and reduce reactive oxygen species levels	[165], [166]
MXene	SEM, TEM, HAADF-STEM, XRD, XPS, EDS, Zeta potential, UV-vis, AFM, Elemental mapping, optical images	clear ROS, antibacterial, anti-inflammatory, promote angiogenesis, promote fibrinogen recombination, promote coagulation	[172], [173], [174], [175], [176]

prepared via solvothermal reaction, followed by its incorporation into a photosensitive composite hydrogel based on GelMA. In the animal skin wound full-thickness defect model, the prepared CuNA-bFGF@GelMA composite hydrogel significantly accelerated wound healing by inhibiting inflammatory response, promoting the formation of new blood vessels, and the deposition of collagen and elastic fibers (Fig. 6 C) [196].

Zinc-based MOFs

Zinc-based MOFs targeting both bacterial infection and inflammation Based on the physicochemical characteristics of MOFs and the potent antibacterial and anti-inflammatory activities of zinc ion (Zn^{2+}), a nanoscale zinc-based MOF called Zn-BTC was reported for the delayed release of Zn^{2+}. The developed Zn-BTC was found to be non-toxic to major organs, showed low toxicity to fibroblasts, increased cell migration and proliferation, and demonstrated good bactericidal activity against a range of drug-resistant bacteria. It also significantly improved skin wound healing in SD rats [197].

Zinc-based MOFs demonstrating antibacterial activity for wound healing Chaofeng Wang et al., reported the development of the environmentally friendly zinc nanohybrid material (Zn DMZ) by combining zinc-doped molybdenum disulfide (Zn-MoS_2) nanosheets and a biodegradable metal-organic framework (MOF, ZIF-8). The developed Zn DMZ had a high antibacterial effect of 99.9% against *S. aureus* under 660 nm light irradiation for 20 min, with minimal cytotoxicity due to photocatalytic effect, photothermal effect, and released zinc ions. The in vivo studies demonstrated that this nano-hybrid material stimulates wound healing due to the zinc ions release [198]. Jiaxin Li et al. successfully developed a flexible hydrogel composed of sodium alginate (SA) matrix embedded with and curcumin (CCM) loaded MOFs, enhancing prolonged drug dispersion and antibacterial effects. The developed hydrogel demonstrated improved bactericidal potential, and controlled drug release [199].

Zinc-based MOFs have antioxidant properties The Zn-MOF encapsulated methacrylate hyaluronic acid (Me HA) microneedles (MNs) arrays have been shown to facilitate the process of wound healing. The zinc ions released from Zn-MOF have oxidative stress damage capabilities, while the low molecular weight hyaluronic acid (HA) resulting from MeHA hydrolysis promotes tissue regeneration. These results suggest that MOFs combined with biodegradable MNs arrays significantly help in promoting wound healing [200].

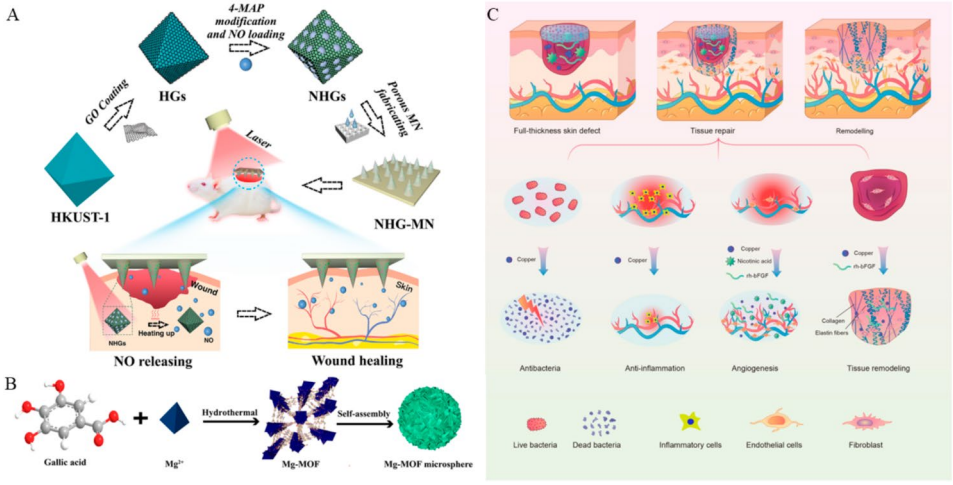

Fig. 6 (**A**) Schematic diagram of the preparation and application of the porous MOF MN array, which was fabricated by PEGDA and encapsulated with NHGs via a template infusion method [206]. (**B**) Schematic illustration of the synthesis of Mg-MOF microsphere [201]. (**C**) Illustration of the multifunctional CuNA-bFGF@GelMA hydrogel for accelerating the process of wound repair [196]

Other metal-based MOFs

Other metal-based MOFs targeting both antibacterial and antioxidant effects

The support layer MN-MOF-GO-Ag, combining multifunctional organic magnesium frameworks (Mg-MOFs) with poly(γ-glutamic acid) (γ-PGA) hydrogel and graphene oxide-silver nanocomposite material (GO-Ag), improves the healing process and offers oxidation resistance (Fig. 6 B) [201]. Hydrogels incorporating alpha-lipoic acid (alpha-La) along with hyaluronic acid (HA) and potassium-gamma-cyclodextrin metal-organic framework (K-gamma-CD-MOFs) have been reported. These hydrogels demonstrated antibacterial activity and antioxidant properties, thus promoting the wound healing process, formation of granulation tissue, and collagen deposition. The hydrogels were found to be an effective treatment strategy for chronic full-layer skin wound healing [202].

Other metal-based MOFs demonstrating antibacterial activity for wound healing

The development of ultra-small gold nanoparticles (UsAuNPs) on ultra-thin 2D MOFs by in-situ reduction has also been reported. The results indicated that the prepared ups/MOFs exhibited favorable antibacterial characteristics against *E. coli* and *S. aureus.* The in vivo experiments showed that the mixed material can effectively promote wound healing and has good biocompatibility [203].

MOF nanoparticles (PCN-224) can be easily attached to titanium employing a straightforward cation exchange process. Enhanced photocatalytic efficiency was observed in the bimetallic PCN-224 (Zr/Ti), which produced reactive oxygen species upon exposure to visible light, demonstrating its effectiveness as an antibacterial material. The combination of PCN-224 (Zr/Ti) NPs with lactic-co-glycolic acid nanofibers in wound dressings showed high biocompatibility, minimal cytotoxicity, and proved effective in vivo for healing persistent MDR bacterial infection wounds due to PDT. Interestingly, the formulation achieved an antibacterial effect without adding other drugs [204]. When the multifunctional microneedle (MN) patch punctured the skin, low-dose antibiotics, and small bioactive molecules encapsulated in PCN-224 MOF nanoparticles (DMOG@PCN-224 NPs) quickly dissolved through the MN tip and efficiently and selectively delivered the payload to the wound. MOF-based NPs can convert O_2 to $^1O_2$ under light irradiation, showing good chemical photodynamic antimicrobial properties. NPs could realize sustained release of growth factors at the wound, stimulating the formation of epithelial tissue and new blood vessels, therefore speeding up chronic wound healing [205].

Other MOFs

A study reported the NO-supported Cu-benz-1, 3, 5-tricarboxylate (HKUST-1) MOF encapsulated with GO, resulting in NO@HKUST-1@GO particles (NHGs) displaying NIR photothermal properties and facilitating the regulated release of NO molecules. The synthesized NHG-MN was used to heal wound models of rats with type I diabetes. Its ability to accelerate vascularization, promote tissue regeneration, and enhance collagen deposition suggests its potential applicability in various treatments, including wound healing (Fig. 6 A) [206].

Ganghua Yang et al., reported the use of a carbonized mushroom aerogel (QMOFs-PCMA) with magnesium/gallic acid bio-MOFs in conjunction with PTT to eliminate biofilms from skin injuries. The purpose of biological MOFs is to control immunity. The developed system

demonstrated the ability to remove ROS and provide antioxidants. It also caused a reduction in inflammatory cytokines and an increase in anti-inflammatory cytokines when tested in animals. Carbonized mushroom aerogels are the primary source of PTT. The QMOFs-PCMA+NIR group improved the clearance of biofilms and inflammatory response, which provided a strong basis for wound healing, leading to a significant increase in granulation tissue formation, re-epithelialization, and angiogenesis [207].

Covalent-organic frameworks (COFs)

Covalent-organic frameworks (COFs) are a novel type of crystalline porous polymer materials with harmonious pore size, long porosity, thermal stability, and low density, thus making them promising candidates for a variety of applications. During their development, various functional groups can be incorporated to tailor specific components, such as antibodies and enzymes [208]. COFs possess exceptional stability, biocompatibility, and functional diversity, making them highly promising candidates for biomedical applications. Further, their long-term antimicrobial properties, coupled with their covalent bonding through a porous mixture of materials, have been extensively investigated to improve the efficacy of wound-healing dressings [209]. However, challenges persist, including poor industrial application, high preparation costs, and inadequate long-term stability.

A study has reported the development of a versatile porphyrin-COF specifically designed for bacteria-targeted and response-enhancing phototherapy/chemotherapy sterilization, as well as wound healing. The prepared Por-COF exhibited higher cytocompatibility and minimal systemic toxicity, as demonstrated by both in vitro and in vivo studies [53]. The synthesis of the inclusion compound involved the combination of electrospinning and electrospinning thermoplastic polyurethane fiber (ENR-FM-COF-TPU), resulting in a β-cyclodextrin COF containing enrofloxacin and flunixin glucoside. A mouse model of a full-layer skin defect was used to investigate the efficacy of the composite fiber in preventing *S. aureus* and *E. coli*, with an inhibitory efficiency of 99% within 50 h. The findings indicate that ENR-FM-COF-TPU can drastically hasten and facilitate the healing of wounds [210].

TP-Por CON@BNN6 was demonstrated to be highly effective in eliminating *E. coli* and *S. aureus in vitro*. It was also found to be biocompatible, biodegradable, phototoxic, anti-inflammatory, and capable of healing wounds in mice (Fig. 7 A) [58]. The in-situ interface polymerization and impregnation of a Porphyrin COF-based membrane, encapsulated with ibuprofen (IBU), yielded an IBU@DhaTph membrane. The innovative membrane demonstrated exceptional antibacterial and anti-inflammatory properties. These effects were achieved through the combined action of photoinduced singlet oxygen ($^1O_2$) generation and controlled release of IBU. The results showed the IBU@DhaTph membrane-based dressing to be biocompatible with excellent anti-infection and tissue remodeling activity [211]. A nano-inhibitor targeting thiols was synthesized using the enzyme reaction known as Covalent Organic Framework (COF)(Ag-TA-CON@EBS@PEG). The results indicated that the inhibitor precisely discharged EBS and Ag^+ at

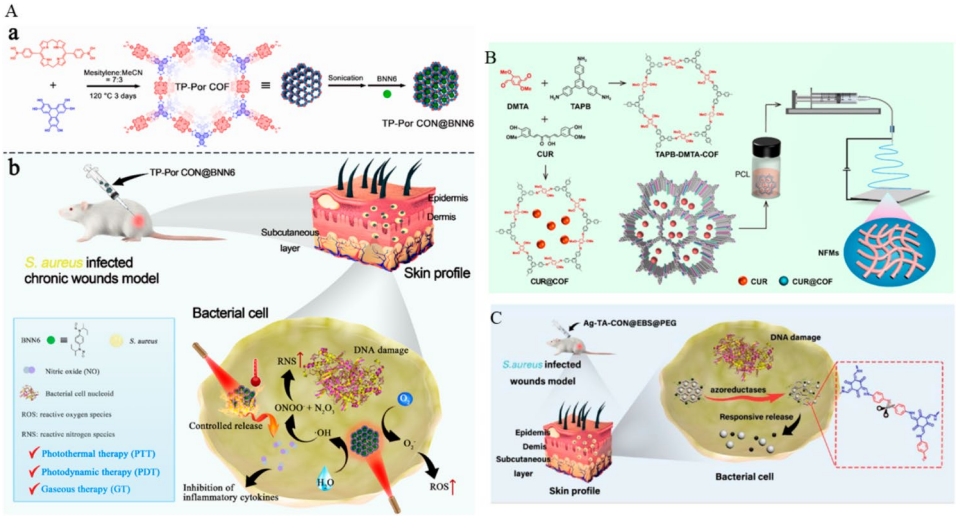

Fig. 7 (**A**) Schematic Representation of the TP-Por CON@BNN6-Integrated Heterojunction Working Principle as an Antibacterial and Anti-infection Therapy. (**a**) TP-Por CON@BNN6 is composed of a porphyrin-based COF loaded with NO donor molecules of BNN6; (**b**) TP-Por CON@BNN6-integrated heterojunction destroyed the bacterial cells by producing ROS, increasing the temperature, and releasing NO, realizing a synergistic effect of PDT, PTT, and GT [58]. (**B**) Schematic Illustration of the Preparation of CUR@COF and PCL Nanofibrous Membranes with the Incorporation of CUR@COF [213]. (**C**) Working Principle of the Ag-TA-CON@EBS@PEG as an Intelligent Drug Release Platform in Infected Wounds [212]

the infection site, killing both Gram-positive and Gram-negative bacteria in vitro, with low toxicity to normal cells. In mice experiments, the material showed higher biocompatibility, anti-inflammatory properties, and rapid wound healing (Fig. 7 C) [212]. The common characterization of organic 2D materials and their role in wound healing can be seen in Table 3.

In another study, curcumin was incorporated into a covalent organic framework (CUR@COF), and electrospinning was used to integrate CUR@COF into a polycaprolactone (PCL) nanofiber membrane, resulting in the development of CUR@COF/PCL NFMs, a pH-triggered drug release platform for wound dressings. The new system promoted wound healing and skin regeneration by decreasing TNF-α expression and enhancing VEGF (Fig. 7 B) [213].

Table 3 Characterization of organic 2D materials and their role in wound healing

2D material	Specific material	Characterize	Efficiency	Ref.
MOFs	Nanoparticles (NPs) of MOFs (PCN-224(Zr/Ti))	SEM, TEM, XRD, Photoluminescence spectra, HR-TEM, elemental mapping, XPS, Dynamic light scattering, UV–vis, FTIR, BET analysis	Promote ROS production to achieve sterilization, inhibit microbial growth, promote epithelial tissue regeneration, collagen deposition and angiogenesis	[204], [205]
	Zinc-based MOFs(ZIF-8)	TEM, EDS elemental mapping, HRTEM image, XPS, UV–vis, EIS spectra, SEM	Antibacterial, accelerate epithelial cell regeneration and neovascularization	[198], [200]
	Cu-MOFs (HKUST-1)	SEM, FT-IR, XRD, Physical properties, EDS analysis, Thermogravimetric analysis	Antibacterial, accelerate wound healing, promote wound vascularization, tissue regeneration and collagen deposition	[193], [206]
COFs	Por-COF	FT-IR, Pawley refinement, N_2 adsorption–desorption isotherms, XPS, CLSM imaging, SEM, TEM, HRTEM, elemental mapping	Antibacterial, promote granulation tissue formation, collagen deposition and angiogenesis, anti-inflammatory	[53], [58]
	PCOF@E-Exo	PXRD profiles, SEM, TEM, EDX mapping image, High-angle annular dark-field scanning transmission electron microscopy, AFM	Inhibition of oxidative stress, immune regulation and antibacterial	[214]

Perspectives and challenges

Wound infections pose significant obstacles in clinical practice. If wound infections are not effectively treated, they can increase patient mortality, cause additional complications, and raise medical expenditures. The emergence of antibiotic resistance in various bacteria has also led to challenges for the topical treatment of wound infections in recent years. Because antibiotic-resistant microbes are currently a severe threat to public health, therefore, researchers are investigating cutting-edge methods such as nanotechnology. These methods can lead to the development of novel treatment approaches in the post-antibiotic age.

Recent studies indicate that nanotechnology may enhance wound healing by suppressing microbial proliferation and modulating immune reactions. Research suggests that nanotechnology can effectively prevent the growth of microorganisms in the burn wound microenvironment, either alone or as a multifunctional targeted and intelligent agent. Nanoscale drug delivery systems can accelerate drug loading rates, improve biodistribution, and enhance sustained-release characteristics, thereby reducing toxicity and increasing effectiveness. The diverse physical and chemical characteristics of 2D materials have attracted significant research interest, particularly for their potential applications in areas such as sensors and drug delivery [215]. Moreover, nanotechnology may be used to develop scaffolds based on stem cells for skin remodeling and reconstruction. Insights from the unique properties of stem cells combined with nanostructured scaffolds could lead to considerable advances in wound healing.

Even though 2D nanomaterials boast advanced physicochemical characteristics and varied biological functions, they remain in the preliminary phases of research, facing significant hurdles in their clinical use [216]. The current results are mainly from animal experiments and lack comprehensive or standardized conclusions. The short-term safety of 2D nanomaterials has been demonstrated by numerous research; nevertheless, a more thorough investigation of their long-term hazardous effects is still necessary. There is a consensus in the scientific literature that 2D nanomaterials display some levels of toxicity, raising concerns about their potential hazards to living organisms. Therefore, various studies have been carried out to understand their toxic effects and strive to mitigate them. Further investigation is necessary to ascertain the clinical safety of these 2D nanomaterials because it is

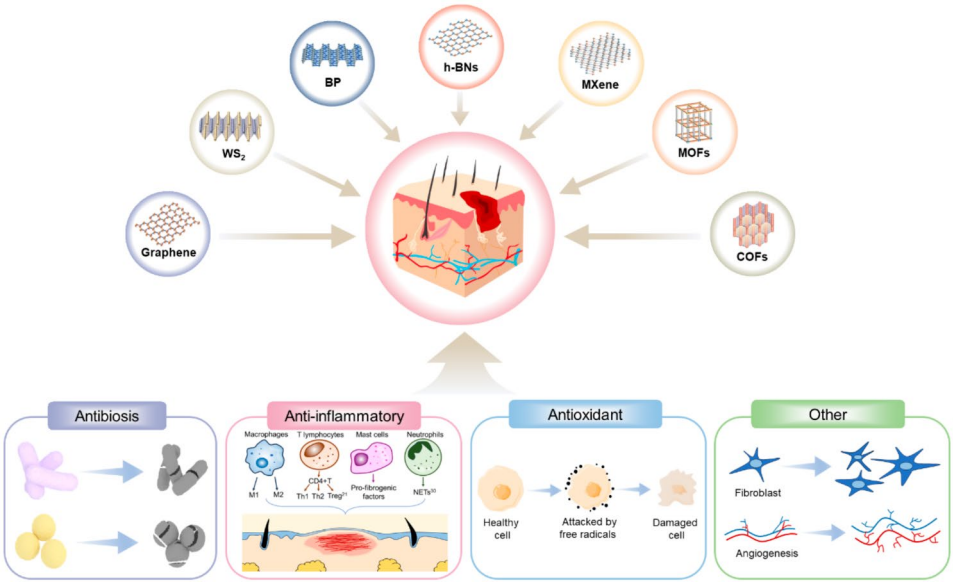

Fig. 8 Two-dimensional nanomaterials for promoting wound healing Summary Figure

unclear how they interact with the immune system and whether they will interfere with the reproductive system. 2D nanomaterials' biodegradation and excretion characteristics are also thought to be important issues that need to be resolved. Studies have shown that changes in the dimensions, shape, and surface properties of 2D materials significantly influence their toxicological characteristics and properties, as well as their fate in physiological environments. However, existing methods of preparation pose challenges in accurately determining the dimensions and shape of 2D materials. The absence of control complicates the systemic assessment of their biological interactions [217]. Furthermore, current formulations of 2D nanomaterial primarily focus on pharmacodynamics to aid in wound recovery, with limited research on associated mechanisms, highlighting their existing limitations.

Similarly, relevant studies remain in their preliminary stages. Future research could explore the integration of nanomaterials with 2D materials to advance wound healing potentials. Compared to conventional skin treatments, nanotechnology might be a technological advancement that could reduce infection in thermal injuries and facilitate the recovery of damaged tissues. The combination of 2D nanomaterials with drugs offers unlimited possibilities for the development of new materials at the nanoscale, revolutionizing conventional approaches to treat wound infections. The current development in the field of nanotechnology shows that research into its potential is expected to increase steadily in the future. Furthermore, nanotechnology offers many advantages in the healthcare industry, and more effective methods to improve wound healing and benefit patients are expected in the near future.

Conclusion

2D nanomaterials, such as graphene, BP, MOFs, MXenes, COFs, etc., have good hemostasis, antibacterial, and anti-inflammatory properties, as well as the ability to induce wound tissue regeneration (Fig. 8). However, many issues such as uncertain long-term toxicity, biodegradation, and clinical safety persist. A significant area of focus for 2D nanomaterials research in the future will be the development of biodegradable 2D nanomaterials as well as modifications necessary for renal clearance and excretion. This review summarized the current advancements in investigating the effects of 2D nanomaterials on wound healing. The findings of reviewed studies demonstrate that 2D nanomaterials can have major therapeutic effects due to their good mechanical, photothermal, biocompatible, and antibacterial properties. Currently, black phosphorus nanosheets, MXene, and MOFs stand as the leading 2D nanomaterials for enhancing wound healing. An increasing number of research studies are investigating their efficacy in wound healing owing to rising scientific interest in these materials, accompanied by advancements in preparation techniques, biosafety assessments, and related aspects. However, the current limitations associated with 2D nanomaterials indicate the need for further improvement.

Abbreviations

2D	Two-dimensional
TMDs	Transition-metal dichalcogenides
BP	Black phosphorous
h-BN	Hexagonal boron nitride
MOFs	Metal-organic frameworks
COFs	Covalent-organic frameworks
VEGF	Vascular endothelial growth factor
MMPs	Matrix metalloproteinases

PDGF	Platelet-derived growth factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
NPWT	Negative pressure wound therapy
PRP	Platelet-rich plasma
GO	Graphene oxide
rGO	Reduced graphene oxide
CS	Chitosan
ROS	Reactive oxygen species
PDA	Polydopamine
NIR	Near-infrared light
PTT	Photothermal therapy
GSH	Glutathione
BC	Bacterial cellulose
Gel	Gelatin
MIC	Minimum inhibitory concentration
ICG	Indocyanine green
MRSA	Methicillin-resistant S. aureus
Psi	Porous silicon
AMPs	Antimicrobial peptides
QCS	Quaternized chitosan
PLLA	Poly(L-lactic acid)
HA	Hyaluronic acid
PDT	Photodynamic therapy
DOX	Doxorubicin
SSD	Silver sulfadiazine
BA	Boric acid
HUVECs	Human umbilical vein endothelial cells
HDFs	Human dermal fibroblasts
AMX	Amoxicillin
PVA	Polyvinyl alcohol
SA	Sodium alginate
ES	Electrical stimulation
MN	Microneedle
IBU	Ibuprofen
PCL	Polycaprolactone

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Author contributions
J.Q.Z.: Conceptualization, Resources, Investigation, Writing – original draft, Visualization, Writing – review & editing, Validation. T.J.L.: Investigation. Y.J.Y.: Resources. X.N.L.: Investigation. Z.J.X.: Validation. H.Z.: Supervision. X.T.: Conceptualization, Supervision.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors gave their consent for the publication of the manuscript.

Competing interests
The authors declare no competing interests.

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