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Two-dimensional nanomaterials: A multifunctional approach for robust for diabetic wound repair

Mingming Cui [a], Jin Zhang [b,c], Pengfei Han [d], Ling Shi [b], Xing Li [e], Zhe Zhang [b], Haihua Bao [b], Yubo Ma [b], Ziwei Tao [f], Xianghui Dong [g,***], Li Fu [h,**], Yan Wu [b,*]

[a] Department of Internal Medicine, Harbin Medical University Cancer Hospital, Harbin Medical University, Harbin, Heilongjiang, 150081, China
[b] College of Life Science, Mudanjiang Medical University, Mudanjiang, 157011, China
[c] Clinical Laboratory, Zhejiang Medical & Health Group Quzhou Hospital, Quzhou, 324004, China
[d] Clinical Laboratory, Affiliated Hongqi Hospital of Mudanjiang Medical University, Mudanjiang, 157000, China
[e] Department of Clinical Laboratory, The Quzhou Afiliated Hospital of Wenzhou Medical University (Quzhou People's Hospital), Quzhou, 324000, China
[f] The Key Laboratory for Ultrafine Materials of Ministry of Education, State Key Laboratory of Bioreactor Engineering, Engineering Research Center for Biomedical Materials of Ministry of Education, School of Materials Science and Engineering, East China University of Science and Technology, Shanghai, 200237, China
[g] Department of Pathology, The First Affiliated Hospital of Harbin Medical University, Harbin Medical University, Harbin, Heilongjiang, 150081, China
[h] Department of Oral Implantology, School and Hospital of Stomatology, Jilin University, Changchun, 130021, China

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ABSTRACT

Diabetic wounds pose a clinical challenge due to persistent inflammation, severe bacterial infections, inadequate vascularization, and pronounced oxidative stress. Current therapeutic modalities fail to provide satisfactory outcomes in managing these conditions, resulting in considerable patient distress. Two-dimensional nanomaterials (2DNMs), characterized by their unique nanosheet structures, expansive surface areas, and remarkable physicochemical properties, have garnered considerable attention for their potential in therapeutic applications. Emerging 2DNMs can be loaded with various pharmacological agents, including small molecules, metal ions, and liposomes. Moreover, they can be integrated with various biomaterials such as hydrogels, microneedles, and microspheres, thus demonstrating unprecedented advantages in expediting the healing process of diabetic wounds. Moreover, 2DNMs exhibit exceptional performance characteristics, including high biocompatibility, effective antimicrobial properties, optimal phototherapeutic effects, and enhanced electrostimulation capabilities. These properties enable them to modulate the wound microenvironment, leading to widespread application in tissue repair with remarkable outcomes. This review delineates several emerging 2DNMs, such as graphene and its derivatives, black phosphorus, MXenes, and transition metal dichalcogenides, in the context of diabetic wound repair. Furthermore, it elucidates the translational challenges and future perspectives of 2DNMs in wound healing treatments. Overall, 2DNMs present a highly promising strategy for ameliorating diabetic wounds, thus providing novel avenues for diagnostic and therapeutic strategies in diabetic wound management.

1. Introduction

Diabetic wound repair is a complex process involving coordinated activities of multiple cell types, which restores the function and structure of damaged tissue through continuous metabolic processes. Nevertheless, patients with diabetes inherently lack the regenerative capacity necessary forprompt healing of wounds. Localized inflammatory reactions, microbial invasion, and oxidative stress further extend the duration of recovery. Even upon eventual healing, aberrant deposition of collagen often leads to skin fibrosis. Conventional therapeutic modalities, such as localized antibiotic application, surgical debridement, gauze dressings, and pulse lavage [1], provide some benefits but exhibit significant limitations. For instance, conventional dressings like gauze and bandages may fail to create the moist, optimal environment essential for wound healing, thereby potentially impeding the re-epithelialization of tissues [2]. In instances where the diabetic wound

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: 813318@hrbmu.edu.cn (X. Dong), fuli1127@jlu.edu.cn (L. Fu), wuyan@mdjmu.edu.cn (Y. Wu).

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condition persistently declines and effective therapeutic interventions are unavailable, the drastic measure of amputation may become necessary in severe cases. This circumstance can result in significant physical and emotional suffering for both the patient and their family members. Therefore, it is imperative to develop novel therapeutic strategies to address the challenges associated with managing diabetic wounds.

The ultimate goal of wound repair is skin regeneration, thereby restoring its essential structure and functionality while maintaining systemic homeostasis [3]. Since the 20th century, considerable effort has been devoted to the development of biomaterials for the treatment of diabetic wounds. These biomaterials have continuously undergone innovation and improvement in their formulations and structures to enhance therapeutic efficacy diabetic wounds [4]. Currently, nanomaterials characterized by superior biocompatibility serve as versatile therapeutic modalities in tissue regeneration. These materials efficiently encapsulate medicinal compounds within diverse nanostructures such as liposomes, nanoparticles, nanofibers, and biofilms, thereby accelerating the healing process in diabetic wounds [5,6]. Furthermore, emerging studies underscore the considerable potential of novel nanomaterials in managing diabetic wounds, from metal nanoparticles known for their potent antimicrobial properties [7] to exosomes and vesicles that notably stimulate the rapid proliferation and migration of key cells such as fibroblasts and endothelial cells [8]. These advanced nanomaterials provide unprecedented prospects for healing of patients with diabetic wounds. Notably, two-dimensional nanomaterials (2DNMs) are particularly noteworthy, recognized for their unique properties, such as high electrical and thermal conductivity, and poised to spearhead future advancements in diabetic wound repair.

The isolation of single-layer graphene by Andre Geim and Konstantin Novoselov, achieved through the simple technique of tape exfoliation, marked a significant milestone spurring the growing interest in 2DNMs [9]. Characterized by their ultrathin, sheet-like structure, these materials typically exhibit thicknesses within the nanometer scale, while their lateral dimensions can extend from several tens of nanometers to a few micrometers [10]. Presently, graphene and its derivatives, including black phosphorus (BP), MXene, transition metal dichalcogenides (TMDCs), metal-organic frameworks (MOFs), and hexagonal boron nitride (h-BN), stand at the forefront of clinical research in the field of 2DNMs. The unique planar structure and high surface area of these materials confer upon them exceptional thermal and optical properties and enhanced carrier mobility. These physicochemical properties have facilitated the extensive application of 2DNMs across diverse fields, such as phototherapy, catalysis, sensing, energy storage, and energy transmission [11].

Two-dimensional materials are increasingly integrated into biomedical applications due to their versatile properties. In cancer diagnostics, the exceptional electronic, optical, and chemical properties of two-dimensional materials enable high-sensitivity detection of tumor cells and biomolecules, thereby improving the precision of early-stage cancer diagnostics [12]. Concerning cancer treatment, the remarkable drug-loading capacity [13], exceptional efficiencies in photothermal and photodynamic therapies [14], and optimal characteristics for magnetic resonance imaging [15] position 2DNMs as a formidable force in the realm of personalized oncology therapies. Additionally, materials such as graphene are employed as anti-angiogenic agents to inhibit tumor metastasis. Beyond oncological applications, two-dimensional materials are proving invaluable in orthopedics. Their inherent strength makes 2DNMs ideal scaffolding materials in bone repair, offering excellent environments for cellular adherence and growth, thereby fostering new bone formation [16]. Moreover, these materials can encapsulate bioactive molecules to deliver rapid, targeted therapeutic effects, thus expediting bone regeneration [17]. The integration of 2DNMs into conventional biomaterials also enhances their mechanical strength and stability, offering a beneficial approach to biomaterial enhancement.

Of note, 2DNMs also demonstrate significant potential in the field of diabetic wound repair. Their expansive surface area facilitates the attachment and encapsulation of numerous bioactive components, thereby enabling controlled drug release and targeted therapy at the wound site and enhanced healing outcomes [18]. Given that diabetic wounds are susceptible to frequent infections, the sharp edge structures and photothermal activity of 2DNMs prove beneficial by effectively suppressing pathogenic microbial growth [19]. In addition, the superior electronic and optical properties of 2DNMs have led to their application in the development of biosensors designed to monitor fluctuations in glucose levels among patients with diabetic wounds, thereby facilitating more efficient clinical management [20].

Recent advancements in 2DNM research have been discussed in various reviews, predominantly focusing on their applications in oncology and orthopedics [16,21]. Nonetheless, a systematic summary of the applications of 2DNMs in diabetic wound repair is yet to be developed. This review aimed to address this gap by categorizing and elucidating the emerging types of 2DNMs, with a particular emphasis on their applications in diabetic wound care. It highlights the strengths of 2DNMs in terms of biocompatibility, antimicrobial action, phototherapy, and electrostimulation support (Fig. 1). The review concludes with a discussion on the clinical integration prospects and future potential of 2DNMs to inspire further research and development of advanced 2DNM-based treatments for diabetic wound care.

2. Skin wound healing

Skin injury disrupts the physiological structure and function of the skin, often resulting in localized tissue damage [22]. Skin wound healing is one of the most complex biological reparative processes in the human body, comprising four phases: hemostasis, inflammation, proliferation, and remodeling (Fig. 2). Each phase involves diverse cellular activities and cytokines [23]. Hemostasis, the initial phase, occurs within seconds to minutes following injury. It is crucial for controlling bleeding at the wound site and restricting the systemic dissemination of bacteria and other pathogens. During this phase, damaged blood vessels constrict, activated platelets trigger the coagulation cascade, and, along with fibrin, form a clot that moves swiftly to the wound site. This process creates a provisional hemostatic barrier to prevent further blood loss due to vascular injuries [24]. Simultaneously, the release of cytokines and growth factors from activated platelets mobilizes a significant influx of neutrophils, monocytes, and macrophages to the wound site, thereby initiating the second phase of wound repair: the inflammatory phase. Within minutes of skin damage, neutrophils arrive at the wound as the first line of defense against bacteria and other pathogens. Their numbers peak within 24–48 h post-injury and markedly decline after 3 days. Following this, the release of additional cytokines and chemokines facilitates the activation of monocytes and macrophages derived from them in subsequent healing stages [25]. During the wound healing process, macrophages play a pivotal role by initially removing cellular debris from the wound site and subsequently releasing various cytokines, proteases, and growth factors. These biochemical signals specifically activate keratinocytes, fibroblasts, and endothelial cells, thereby driving wound repair into the third phase: the proliferation phase. Fibroblasts, often the first responders attracted by the fibrin clot, typically arrive first at the wound site and become widely activated. These activated fibroblasts migrate slowly from the wound edges, covering the wound and secreting various extracellular matrix proteins, including fibrinogen, fibronectin, and collagen. They establish a temporary matrix conducive to tissue remodeling and angiogenesis, resulting in the formation of granulation tissue that fills tissue defects [26]. Concurrently, keratinocytes migrate from the wound edges and continuously release transforming growth factor-beta (TGF-β) and epidermal growth factors to expedite the re-epithelialization of the skin and restore its barrier function. Furthermore, endothelial cells in the blood vessel walls breach their basal membranes to form budding vascular structures that develop

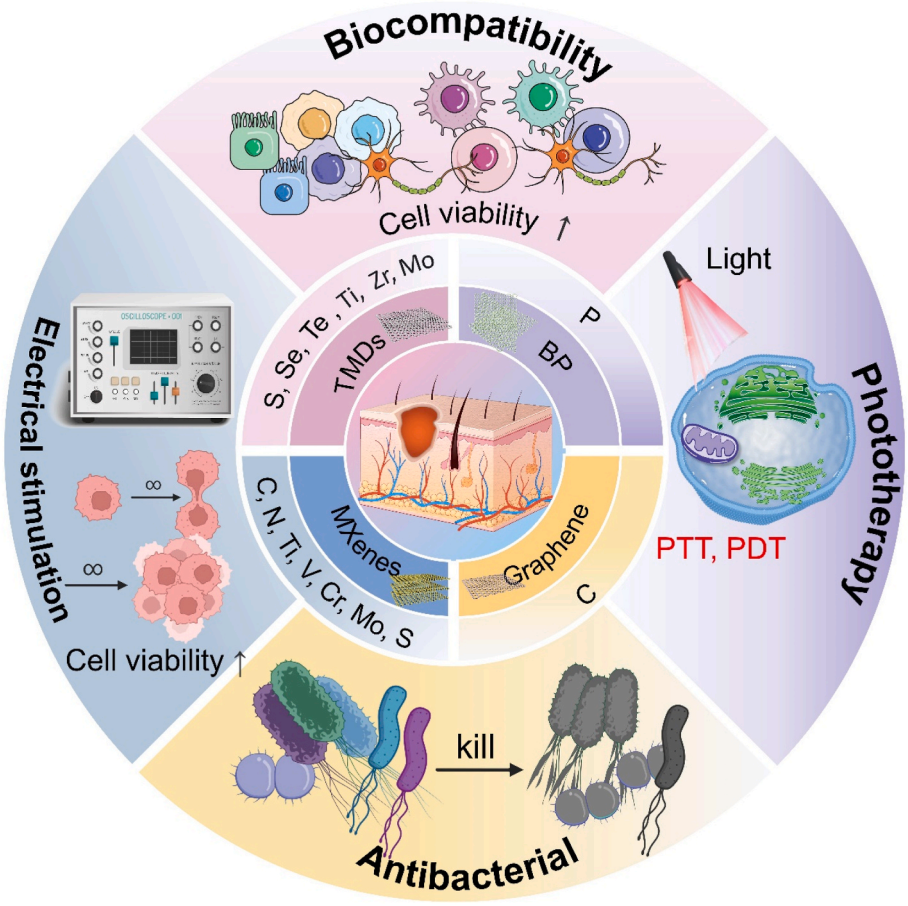

Fig. 1. Potential mechanisms of 2DNMs in skin wound repair primarily include excellent biocompatibility, robust antibacterial properties, optimal phototherapy effects, and supportive electrical stimulation. PTT: photothermal therapy, PDT: Photodynamic therapy.

into microvessels or capillaries, thus enhancing nutrient and oxygen transport to the wound. This process facilitates the recruitment of additional reparative cells, thus fostering wound closure [27,28]. As wound healing progresses to the remodeling phase, inflammatory and proliferative activities cease, new blood vessels regress, and granulation tissue gradually transforms into scar tissue. During this transition, type III collagen is supplanted by type I collagen, thus improving the tensile strength and maturity of the newly formed tissue. Wound healing, as a continuous immune-mediated repair process, is susceptible to disruptions that can alter its course. Factors such as excessive fibrosis can lead to scar formation, while prolonged microbial infections and intensified inflammatory responses can prolong healing durations, potentially resulting in chronic, non-healing wounds such as diabetic ulcers, infectious wounds, and pressure sores [29].

3. Diabetic wound healing

The healing of diabetic wounds is notably prolonged due to the specific physiological state of patients with diabetes, thereby presenting substantial challenges in wound management [30]. Diabetic wounds are often characterized by hypoxia, high production ofreactive oxygen species (ROS), sustained inflammatory responses, and frequent pathogen infections, all of which are crucial factors impeding the wound healingprocess [31,32]. Due to the vascular impairment and neuropathy associated with diabetes, the delivery of nutrients and oxygen to wound sites is significantly hindered. Oxygen is essential for the proliferation of fibroblasts and the initiation of angiogenesis, processes critical for wound healing. However, in diabetic patients, the availability of oxygen is severely compromised, and the metabolic demands of the wound for oxygen are high. This discrepancy between supply and demand poses a considerable challenge to the wound healing process [33]. In addition, oxidative stress is a major barrier to effective diabetic wound healing, whereby the excessive accumulation of ROS leads to oxidative damage to cellular components such as lipids, proteins, and nucleic acids. In the inflammatory phase, keratinocytes escalate the production of interleukin 8 (IL-8) due to the heightened generation of ROS within the hyperglycemic milieu. This surge in ROS fosters an increased infiltration of neutrophils, which are chemoattracted by IL-8, thereby exacerbating inflammation and complicating the wound healing process [34]. The overabundance of ROS triggers the release of proinflammatory cytokines, leading to the degradation of the extracellular matrix (ECM) and inflicting oxidative damage [35]. These alterations contribute to the persistence of M1 macrophages, which are proinflammatory, and impede their transition to the anti-inflammatory M2 phenotype [23]. Consequently, this phenomenon obstructs the progression of the inflammatory phase, causing the wound healing process to become arrested at this stage. Moreover, impaired migration of fibroblasts, and endothelial cells results in the inability of the wound to advance to the subsequent proliferation and remodeling phases. Compared to typical wounds, diabetic wounds are also characterized by slower closure rates and increased susceptibility to secretion of exudates, which heightens the risk of bacterial, fungal, and viral infections through the skin into deeper tissues [36,37]. Moreover, impaired migration of fibroblasts, and endothelial cells results in the inability of the wound to advance to the subsequent proliferation and remodeling phases. Compared to typical wounds, diabetic wounds are also characterized by slower closure rates and increased susceptibility to secretion of exudates, which heightens the risk of bacterial, fungal, and viral infections through the skin into

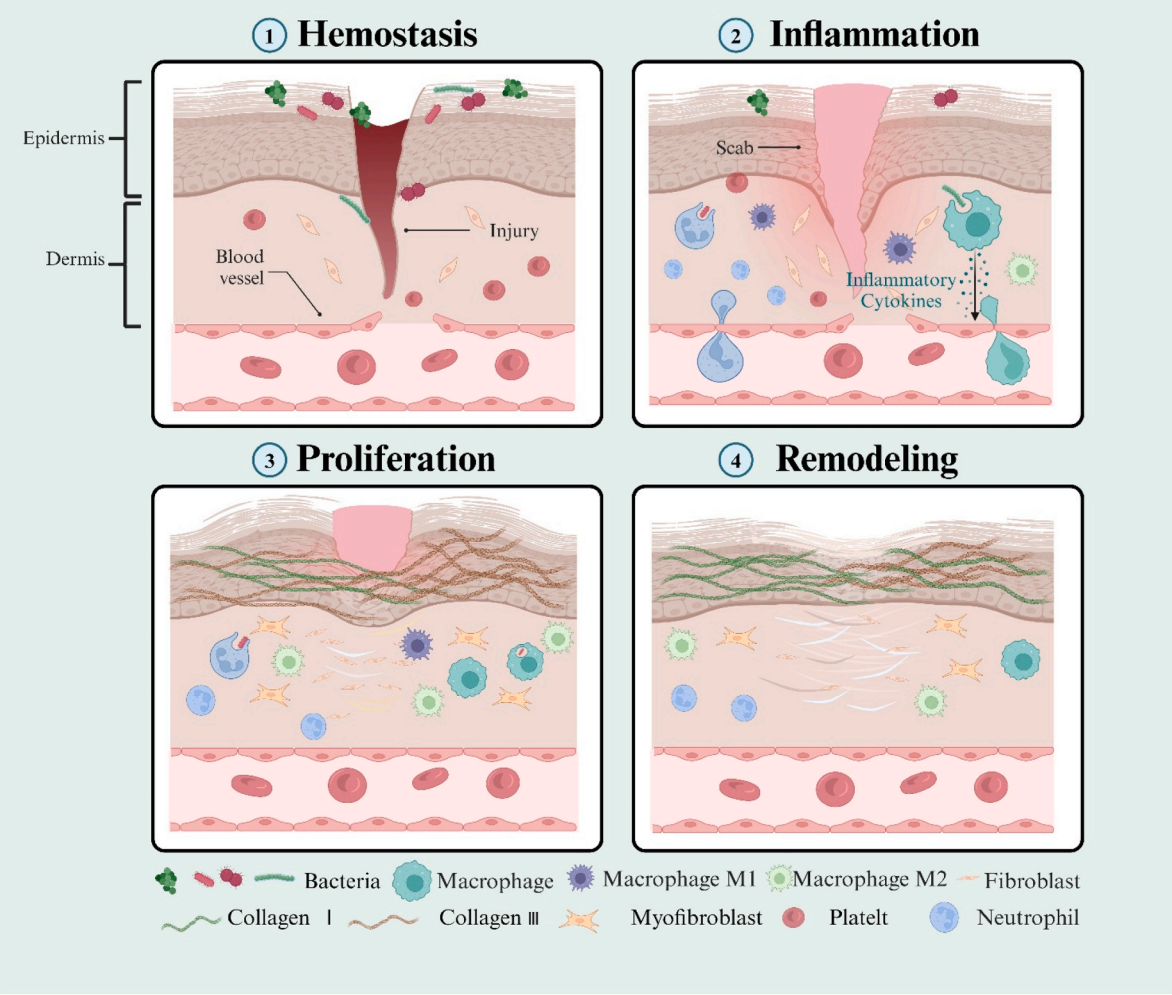

Fig. 2. The process of skin wound healing includes four stages: Hemostasis, Inflammation, Proliferation, and Remodeling (Image created with BioRender.com).

deeper tissues.

In recent decades, researchers have engaged in extensive research on the diverse phases of the wound healing process in diabetic conditions, leading to the development of various biomaterial-based dressings for clinical application. Notably, 2DNMs have emerged as particularly promising entities in wound healing research owing to their function as drug carriers, their applicability in photothermal therapy, and electrostimulation, as well as their broad-spectrum antimicrobial properties.

4. Preparation and characteristics of 2DNMs

4.1. Characteristics of 2DNMs

2DNMs are recognized for their unique array of properties, which are intrinsic to their distinct structural and inter-atomic layer interactions, including robust mechanical stability, expansive surface area, superior electrical conductivity, and optimal photothermal response [38]. The robust inter-particle forces within 2DNMs endow them with the ability to undergo shape alterations, such as bending, in response to certain external forces without succumbing to fracturing, even under extreme stress conditions. More importantly, these particles can rapidly revert to their original state following deformation, rendering 2DNMs highly favored in the manufacturing of sensors and electronic components [39]. The ultrathin structure of 2DNMs confers upon them a substantial specific surface area, which is advantageous for the transport of bioactive molecules. They can adsorb substantial amounts of drugs and transport them to targeted areas. The thinness of 2DNMs exposes a large number of electrons on their surface, facilitating rapid electron transfer across the plane and resulting in excellent electrical conductivity [40]. This property positions them as exceptionally promising candidates for employment in catalysis, sensing, and the production of electronic components. Additionally, when subjected to specific wavelengths of light, 2DNMs absorb photon energy and convert it into thermal energy, thereby inducing a rise in material temperature. Typically, upon entry into the human body and subsequent exposure to near-infrared (NIR) light that can penetrate skin and deep tissues, the nanomaterials absorb the incident light energy and generate heat through plasmon resonance or energy band transitions, thereby providing energy to the affected area [41].

Since the introduction of MXene in 2004, 2DNMs have rapidly gained prominence across numerous applications due to their unique physicochemical properties [42]. The effective utilization of 2DNMs in various applications hinges upon the availability of standardized, reproducible synthesis methods, which are essential to maintain the stability of their physicochemical properties. Researchers have established numerous synthesis techniques for 2DNMs, which are generally categorized into two primary strategies: top-down and bottom-up strategies [43].

4.2. Preparation of 2DNMs

4.2.1. Top-down strategies

In the top-down approach, mechanical exfoliation is one of the most classical and effective methods [44]. Initially elucidated by Andre Geim,

this method capitalizes on the adhesive properties of transparent tape to extract single- or few-layer structures from bulk crystals [45]. Presently, mechanical exfoliation finds extensive application in producing atomically thin layers of various 2DNMs, including molybdenum disulfide (MoS_2) [46], tungsten disulfide (WS_2) [47], tin sulfide (SnS_2) [48], BP [49], and graphitic carbon nitride (g-C_3N_4) [50]. Although mechanical exfoliation is capable of producing two-dimensional nanomaterials (2DNMs) with exceptional purity and crystallinity, its application is largely restricted to small-scale research settings. This is due to the inherent limitations in scaling the process, which makes it impractical for commercial and industrial applications. With the advent of a broader array of 2DNMs, there is a growing need for innovative methodologies to efficiently prepare large volumes of high-quality two-dimensional materials.

Liquid exfoliation is another classic top-down approach for synthesizing 2DNMs, typically accomplished through two steps: intercalation and ultrasonication. Initially, intercalation can be employed to increase the interlayer spacing, thereby reducing the interlayer adhesion. Subsequently, within a specific solvent, ultrasonic treatment can be applied to diminish the van der Waals forces within the nanostructure. Organic solvents such as acetonitrile and N-methyl-2-pyrrolidone (NMP) are commonly used [51]. The efficacy of liquid exfoliation depends critically on the careful selection of solvents, whose surface free energy matches the nanomaterial's surface characteristics. For instance, graphene's exfoliation efficiency markedly elevates when the surface tension of the solvent reaches 40 J/m^2. By using liquid exfoliation method, we can protect the covalent bonds inside the structure from damage, thus achieving the goal of large-scale preparation of 2DNMS. Currently, many 2DNMs have been prepared using this method, such as MoS_2 [52], molybdenum selenide ($MoSe_2$) [53], WS_2 [53], and tantalum diselenide ($TaSe_2$) [54]. While liquid exfoliation addresses the scalability and quality constraints associated with mechanical exfoliation, challenges persist due to the toxicity of organic solvents and the limited efficiency in producing monolayer 2DNMs. Hence, addressing the toxicity of solvents used in liquid exfoliation is imperative to facilitate the sustainable, large-scale manufacturing of 2DNMs using environmentally benign solvents.

The synthesis of 2DNMs has witnessed remarkable innovation with the introduction of electrochemical exfoliation. This method involves the application of voltage or current in an electrolyte to mobilize heterogeneous charged ions and mixtures, resulting in the detachment of films from substrate materials and yielding pure nanoscale, two-dimensional materials [55]. Various two-dimensional nanosheets, such as MX_2 (M = Mo, W, Ta, Ti, or Zr) and graphene oxide (GO) [56–59], have been efficiently synthesized using this method. The process parameters, including electrolyte composition and electrolysis time, can be finely tuned to regulate the exfoliation of 2DNMs. Moreover, this process can be conducted at room temperature without the need for high temperatures or pressures, and the toxicity associated with the utilized electrolytes is relatively low, rendering it suitable for biomedical applications and deemed a safe and reliable method. However, this method remains confined to laboratory settings, and further research is needed to translate it from laboratory-scale to commercialization, including the removal of impurities from the 2DNMs and optimization of the electrolysis conditions.

4.2.2. Bottom-up strategies

In the bottom-up approaches, chemical vapor deposition (CVD) has been extensively used in semiconductor production since 1973 [60] and is currently the most classical method for mass manufacturing high-quality 2DNMs. CVD operates by facilitating chemical reactions of reactive gases on metal substrates under conditions of high temperature and vacuum to successfully produce various ultrathin 2DNMs, including MOS_2 and MOFs [17]. During the process, the substrate is subjected to high-temperature activation to foster the growth of a surface layer that incorporates the precursor element. The selection of precursors and substrates is pivotal, as it directly influences the thickness, size, quality, and overall performance of the synthesized 2DNMs. Although CVD-produced 2DNMs boast excellent electronic characteristics and high uniformity, the process demands strict control over factors, such as high temperatures, high vacuum conditions, and substrate selection. Moreover, it is often hindered by the formation of byproducts.

Solvothermal synthesis, an alternative bottom-up approach, offers a promising avenue for achieving high-yield and cost-effective production. This method uses organic solvents as the reaction medium, wherein solutes are dissolved or reacted at high temperatures and pressures to yield the desired products. The solvothermal process offers a unique physicochemical milieu that facilitates the reaction and crystallization of diverse precursors. It enables chemical reactions, which are challenging or even unfeasible at ambient temperature and pressure, to proceed effectively within high-pressure reactors. Widely adopted in laboratory settings, solvothermal synthesis has facilitated the production of diverse 2DNMs, such as MOS_2 [61] and WS_2 [62]. With issues such as solvent selection and waste disposal addressed, this high-yield, low-cost preparation method holds broad prospects for the future commercial-scale production of 2DNMs.

In the fabrication of 2DNMs, top-down strategies, such as mechanical exfoliation, liquid phase exfoliation, and electrochemical exfoliation, employ external forces to disrupt van der Waals interactions, thereby facilitating the extraction of 2DNMs from bulk materials [63]. Conversely, bottom-up approaches, such as CVD and solvothermal synthesis, synthesize 2DNMs directly from atomic or molecular precursors through chemical reactions (Fig. 3). The choice of synthesis method markedly influences the properties of the resulting 2DNMs, with no single method universally ideal. Rather, each technique offers distinct advantages tailored to specific needs. For example, despite its limitations in yield and uniformity, mechanical exfoliation remains prevalent in research laboratories due to its simplicity and efficacy for small-scale studies. Future advancements are anticipated to optimize these methodologies, enhancing the efficiency, scalability, and environmental sustainability of 2DNM synthesis.

4.3. Modification of 2DNMs

Further research into 2DNMs has highlighted certain limitations in their inherent properties, necessitating surface modification to overcome these deficiencies. Surface modification of 2DNMs can enhance their stability and biocompatibility, thus broadening their potential applications across various fields. Currently, many surface-modified 2DNMs have been extensively utilized in biomedicine. These modification techniques can generally be categorized into two types: non-covalent bonding through physical adsorption and covalent bonding through chemical links [64]. Physical adsorption involves surface modification of 2DNMs through electrostatic forces, hydrogen bonds, hydrophobic interactions, and van der Waals forces. For example, gold nanoparticles (AuNPs) connected to MXene through electrostatic adsorption enhance drug loading capacity and synergistically improve the photothermal effect, thus appreciably bolstering the antibacterial efficacy of MXene-based nanomaterials [65]. Due to its straightforward and direct methodology, physical adsorption has been widely used in the surface modification of 2DNMs. Conversely, covalent bonding relies on the formation of covalent or coordination bonds, facilitating targeted modifications at the molecular level. For instance, Cheng et al. developed a novel WS_2 nanomaterial coated with polyethylene glycol (PEG), linking WS_2 *via* thiol groups from thioglycolic acid, notably boosting the physiological stability and biocompatibility of the nanomaterials [66]. Overall, the chemical bonding method allows for selective modification of specific functional groups or molecules, emerging as an important method of surface modification of 2DNMs. It enables precise control over the properties and functionalities of the materials, thereby broadening their application spectrum.

The biological efficacy of 2DNMs can be prominently enhanced

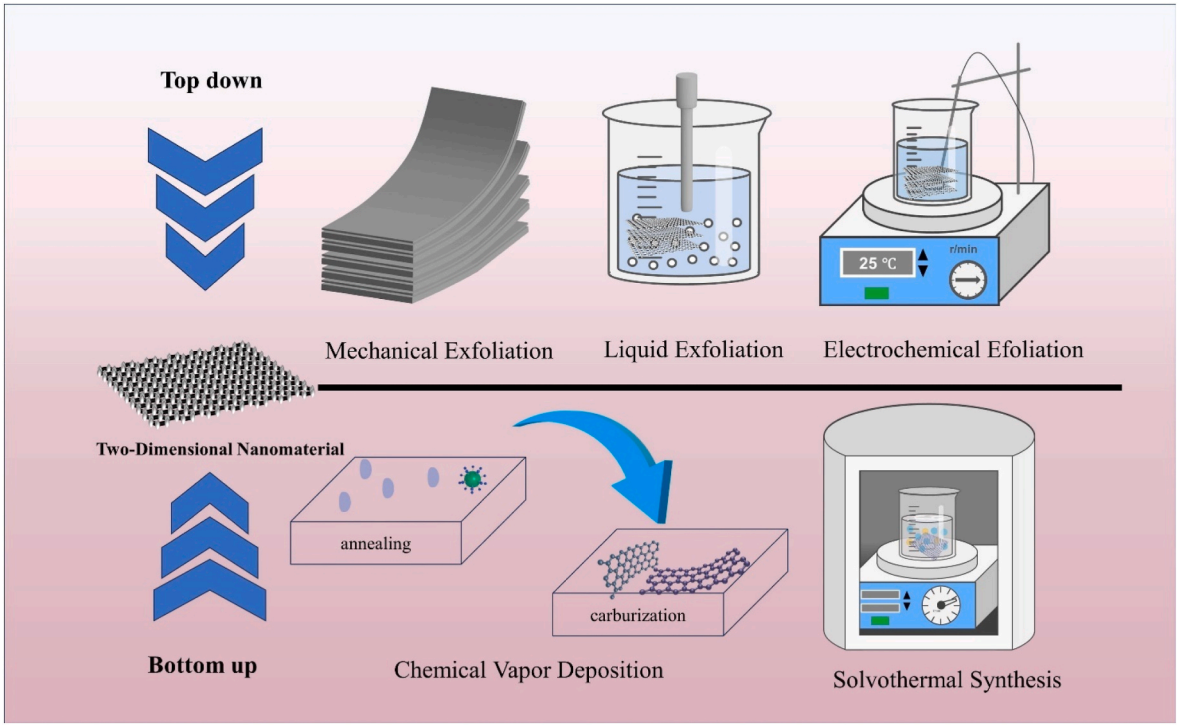

Fig. 3. Schematic illustration of the synthesis method for 2DNM.

through surface modifications. Li et al. developed a novel MXene@polyvinyl alcohol (PVA) hydrogel using a directional-assisted salting-out method, which demonstrated exceptional photothermal effects and broad-spectrum antimicrobial capabilities, while also fostering cell proliferation *in vitro*. This hydrogel has proven effective in promoting wound healing in mouse models [67]. Despite these advancements, the investigation into MXene remains in a preliminary phase, with its stability and cytotoxicity in human physiological conditions yet to be fully elucidated. Certain studies have even highlighted potential toxicity at elevated concentrations [68]. Therefore, it is critical to develop modification techniques that mitigate these biotoxic effects while conferring additional beneficial attributes. For example, Rozmysłowska--Wojciechowska et al. effectively modified the surface charge of MXene using the cationic polymer poly-L-lysine, thereby enhancing its biocompatibility. This modification facilitated the survival of melanoma cells and immortalized keratinocytes even at concentrations of 375 mg/ml, while also significantly augmenting antibacterial efficacy against gram-negative *Escherichia coli* [69]. While these surface modifications of 2DNMs hold promise for expanding their applicability and potential, the development of these techniques is still in its infancy, necessitating ongoing and extensive research efforts.

5. Significant potential of 2DNMs in wound healing

The healing of skin wounds is a complex process involving the coordinated action of multiple cell types to ensure precise regulation of cell proliferation and differentiation, alongside the remodeling of the extracellular matrix [70]. Nanomaterials, recognized for their exemplary capabilities in drug loading and release, have emerged as vital tools in the management of difficult-to-heal wounds in clinical settings [71]. 2DNMs, in particular, are increasingly favored due to their excellent biocompatibility, potent antimicrobial properties, efficient photothermal conversion, and outstanding electrical conductivity. These features enable 2DNMs to confer anti-inflammatory, antibacterial, antioxidative, angiogenic, and epithelialization-promoting effects, rendering them highly valuable in wound repair applications (Fig. 4).

5.1. Biocompatibility

As a new emerging material, 2DNMS is increasingly being used in biomedical applications, and good blood and cell compatibility are prerequisites for its application in tissue repair. In clinical applications, 2DNMS inevitably comes into contact with blood tissue and interacts with various blood components. Traditional 2DNMs possess commendable blood compatibility; however, this attribute is subject to alteration as their concentration fluctuates. For example, the impact of varying concentrations of MXene Ti3C2 on the morphology of red blood cells was notably distinct. At concentrations below 10 μg/ml, red blood cells didn't exhibit significant aggregation or morphological alterations. As the concentration of Ti3C2 escalated, red blood cells manifested protrusions and creases, with particularly pronounced effects observed at concentrations of 30 μg/ml and 60 μg/ml, where the red blood cells' elliptical configuration undergoed a complete transformation [76]. The biocompatibility of 2DNMs is influenced by several factors. It is evident that cell type, material type, and concentration are direct factors influencing the biocompatibility of 2DNMs. For instance, various types of 2DNMs can substantially impact cell viability. For example, MoS_2, WS_2, and tungsten diselenide (WSe_2) exhibit divergent effects on human lung cancer epithelial cells. The effect of MoS_2 and WS_2 on cell viability is very slight. However, WSe_2 showed the opposite resultthe cell viability significantly decreased [77]. Interestingly, the response to 2DNMs can vary across different cell types. Jastrzębska and colleagues examined the effects of MXene on four cell types: MRC-5 (human embryonic lung cells), HaCat (human immortalized keratinocytes), A549 (human non-small cell lung cancer cells), and A375 (human malignant melanoma cells). Compared to normal cell lines (MRC-5 and HaCat), MXene significantly diminished cell viability in cancer cells. The substantial difference in effects observed between normal and cancer cells can be ascribed to the ability of MXene to induce an overproduction of ROS beyond the tolerable threshold for cancer cells, leading to their extensive death [78]. Moreover, material concentration is a critical factor affecting cell viability. Li et al.'s study [72] unveiled that MXene at moderate concentrations (20–80 μg/ml) markedly enhanced the viability of RAW264.7 cells (*versus* control). Conversely, a decrease in

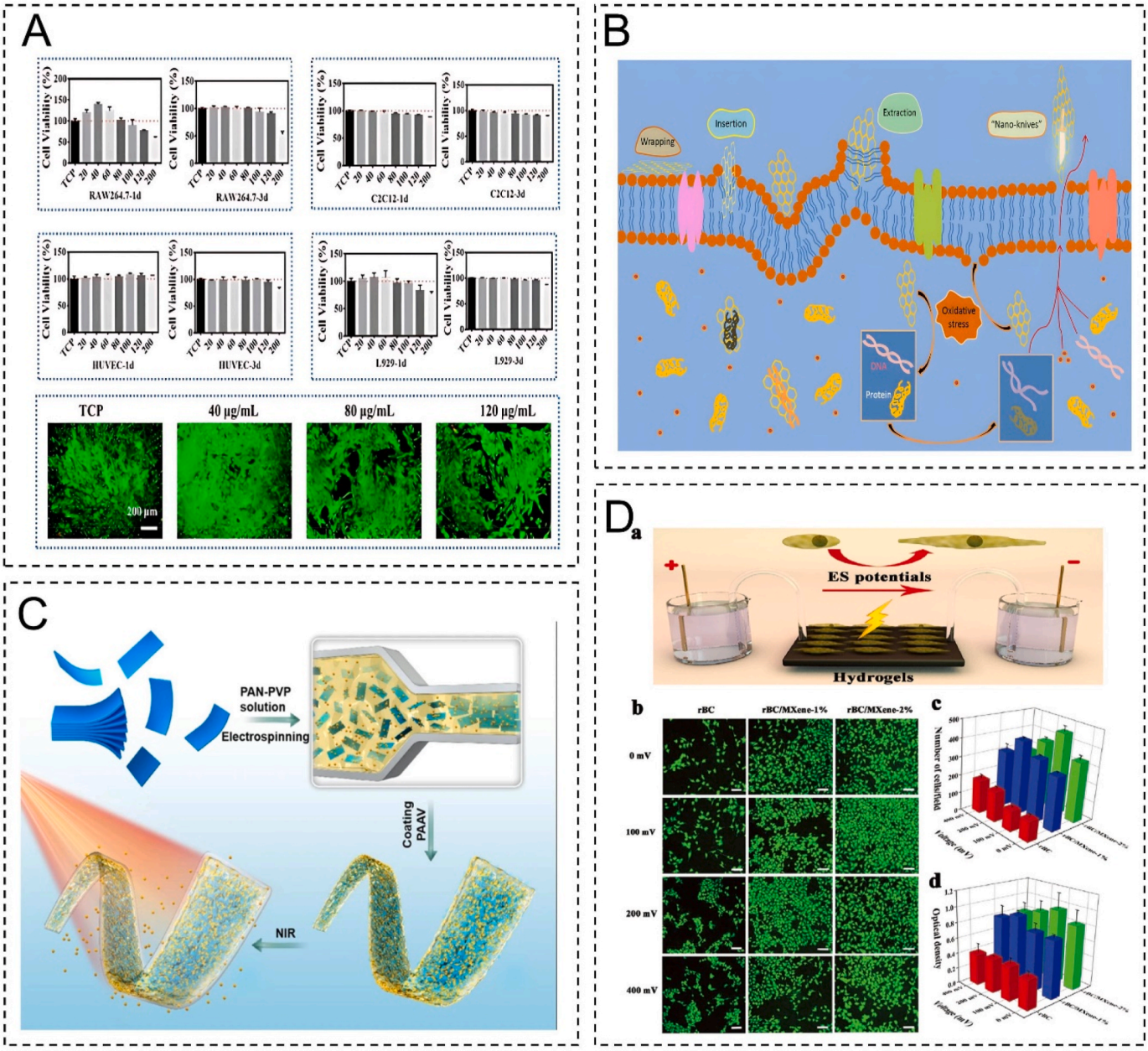

Fig. 4. Advantages of 2DNMs in wound repair processes. (A) Assessment of the cytocompatibility of MXene [72].Copyright 2023, Wiley.(B) Antibacterial activity mechanisms of graphene materials (GMs) [73]. Copyright 2016, American Chemical Society. (C) Fabrication and surface coating schemes of T-rotating magnetic field (RMF) nanoribbons [74]. Copyright 2021, Springer Nature. (D) Electrical stimulation effects of various electrical stimulation (ES) hydrogels on NIH3T3 cells [75]. Copyright 2020, Wiley.

RAW 264.7 cell viability was observed as MXene concentration increased, with most cells dying when the MXene concentration reached 200 μg/ml. MXene might exhibit cytotoxicity at high concentrations, while at lower concentrations, it is non-toxic and may even promote the proliferation of some cell types.

To address these challenges, it is crucial to continuously optimize experimental conditions to broaden the biomedical applications of 2DNMs. Surface modification of 2DNMs can also improve their biocompatibility. PEGylation through covalent bonds is a prevalent technique to increase the biocompatibility of 2DNMs [79]. For instance, research by Liang et al. elucidated that unmodified WS_2 nanomaterials, although soluble in water, tended to aggregate rapidly and significantly reduce cell viability when in direct contact with 4T1 or 293T cells. However, stability and biocompatibility are markedly improved when WS_2 nanosheets are coated with thioctic acid-conjugated PEG *via* W–S bonding, resulting in negligible cytotoxicity [66]. Similarly, in the context of wound healing, Wang et al. addressed the issue of cytotoxicity of MOF nanomaterials by successfully incorporating COOH--PEG–COOH–functionalized zirconium-dibenzene (Zr-Fc) MOF nanosheets into a PEG@Zr-Fc MOF hydrogel. This modification significantly reduces the cytotoxicity of MOF materials and enhances wound healing by alleviating bacterial infections at the wound site [80].

2DNMs extend their influence beyond merely affecting cell viability and substantially impact various cellular functions. These materials orchestrate the biological behaviors of cells, such as acceleration of cell proliferation and differentiation, enhancement of cell adhesion and migration, reduction of oxidative stress, and promotion of cellular metabolism and autophagy. A novel bismuth sulfide (Bi_2S_3)/titanium carbide (Ti_3C_2Tx) hydrogel, as developed by Li et al., has demonstrated exceptional cytocompatibility and biocompatibility, notably enhancing

collagen fiber formation *in vivo* and expediting skin wound healing. Furthermore, recent advances in graphene foam materials, a novel category of 2DNMs, have facilitated mesenchymal stem cell (MSC) proliferation, moderated the expression of TGF-β1 and alpha-smooth muscle actin (α-SMA), and upregulated basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) levels near wound sites, thereby contributing to facilitated wound healing and minimized scarring [81]. Most 2DNMs are characterized by low cytotoxicity *in vitro* and robust biocompatibility *in vivo*. Potential adverse effects associated with specific 2DNMs can often be alleviated through targeted surface modifications, thus optimizing the tissue repair microenvironment. In summary, the biomedical utility of 2DNMs is substantially influenced by their elemental composition and surface modification. Future research should systematically investigate the unique physicochemical properties of 2DNMs on different cell types to further identify potential risks and ensure their safe application in humans.

5.2. Antimicrobial effects

Bacterial infection remains a critical concern in the field of tissue repair, with antibiotics continuing to serve as the primary treatment modality. However, the increasing prevalence of antibiotic resistance observed in pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) necessitates the exploration of alternative therapeutic modalities [82,83]. The resistance crisis has spurred considerable research efforts aimed at developing novel pharmacological alternatives to combat these resilient bacterial infections.

Nanomaterials, such as silver and copper nanoparticles, are well-recognized for their potent antimicrobial properties and are widely incorporated into medical devices and wound dressings. However, the utility of these nanoparticles is hampered by several drawbacks. Notably, long-term exposure to these nanoparticles can induce resistance in bacteria, and their tendency to aggregate and deposit diminishes their antimicrobial activity [84]. Undoubtedly, 2DNMs are confronted with certain intrinsic challenges. Nonetheless, numerous studies have demonstrated that the majority of 2DNMs that entered the body were eventually excreted through urine or feces after a certain duration. This process effectively addressed the issue of their propensity for aggregation and deposition within the body [85,86]. In this context, 2DNMs, with their unique structures and properties, are emerging as promising antimicrobial materials. Graphene, a prototypical 2DNM composed of a single layer of carbon atoms, is notable for its outstanding electrical and thermal conductivity. Its unique monolayer hexagonal nanosheet structure enables graphene to mechanically disrupt bacterial cells by either inserting its sharp edges into or adhering to the bacterial surface, thereby leading to membrane rupture and subsequent leakage of cellular contents. Furthermore, the small size of graphene relative to human cells renders it virtually harmless to human cells [87]. Additionally, certain bacteria internalize graphene, which continues to exert its antimicrobial function, leading to leakage of bacterial contents and effectively killing the bacteria [73]. A study by Wu et al. highlights the efficacy of Ti_3C_2 MXene, which has demonstrated significant bactericidal effects against a spectrum of 15 bacterial strains. Imaging studies using TEM and SEM have corroborated that Ti_3C_2 disrupts bacterial membranes, culminating in bacterial death [88].

The effectiveness of 2DNMs in combating microbial infections is widely recognized, although the precise mechanisms underlying their antimicrobial action remain a topic of debate. Contrary to the prevailing notion attributing the antimicrobial properties of 2DNMs primarily to their sharp edges, some scholars suggest that electron transfer between the 2DNMs' surfaces and bacterial membranes plays a more crucial role [89]. For example, two-dimensional transition metal sulfides such as MoS_2 and WS_2 can disrupt bacterial cell membranes and walls by either releasing metal ions or inducing the production of ROS, thereby destabilizing bacterial homeostasis and exerting antimicrobial effects [90]. Evidence suggests that surface-modified WS_2, facilitated by photocatalytic activity and glutathione generation, can disrupt the bacterial microenvironment, eliminate bacterial infections at wound sites, and accelerate wound healing [91]. Overall, the dual antibacterial mechanisms of 2DNMs significantly impede bacteria from developing resistance, rendering them materials with vast potential in the realm of skin wound repair. Nevertheless, further research is still needed to fully elucidate the antibacterial mechanisms of 2DNMs.

5.3. Phototherapy

Phototherapy has long been one of the primary methods for the management of various dermatological conditions. Current research on skin wound repair identifies two primary modalities of phototherapy: photothermal therapy and photodynamic therapy. Photothermal therapy leverages the infusion of thermal energy to enhance blood circulation and the supply of oxygen and nutrients, thus supporting cellular regeneration and tissue repair [92]. In photodynamic therapy, light energy directly transfers to nearby oxygen, generating a large quantity of ROS that kill surrounding bacteria and cells, or converting light energy (typically NIR) into thermal energy, thereby elevating local temperature to eliminate cells and bacteria. This therapy improves the microenvironment of damaged tissue and accelerates tissue repair [93]. 2DNMs offer unique advantages in phototherapy due to their monolayer structure and ultrathin thickness, rendering them ideal for light absorption. They can absorb a broad spectrum of light, and most 2DNMs, upon exposure to light, rapidly excite electronic energy levels or lattice vibrations within the material, elevating its energy level and consequently increasing its temperature to efficiently convert it into thermal energy [94]. When applied *in vivo*, 2DNMs demonstrate remarkable efficiency in dispersing this thermal energy into surrounding tissues, thereby enhancing the rate at which these tissues assimilate this energy for healing.

Recent studies on 2DNMs often combine photothermal and photodynamic therapies to accelerate wound healing. Notably, Liu et al. modified chemically exfoliated MoS_2 with thioctic acid-capped PEG, resulting in PEGylated MoS_2. This novel material rapidly heats up under NIR radiation and physically adsorbs the photodynamic agent chlorin e6, thereby substantially fostering the efficiency of photodynamic therapy [95]. Furthermore, the application of MXene in wound care has been demonstrated by Wang et al., who developed a polylactic acid film *via* electrospinning, incorporating titanium carbide and zeolitic imidazolate framework-8. This innovative biomembrane reduces the activation energy, increases electron shuttling rates, and optimizes the laser activation process to accelerate cellular energy absorption. *In vivo* studies have demonstrated that, upon exposure to 808 nm laser irradiation, the polylactic acid film exhibits remarkably high antibacterial efficacy against *Escherichia coli* and *methicillin-resistant Staphylococcus aureus*, with rates reaching 99.9 % and 99.8 %, respectively. This treatment significantly expedites the wound healing process [96]. Similarly, Jin et al. introduced a nanofiber using MXene with controllable release features, responsive to both infrared radiation and temperature. This nanofiber primarily consists of polyacrylonitrile and polyvinylpyrrolidone, loaded with substantial amounts of MXene and vitamin E. Upon exposure to NIR radiation, the high surface area of MXene absorbs considerable light energy, gradually releasing and dissolving surface vitamin E to expedite wound healing [74].

The emergence of novel 2DNMs has propelled photothermal therapy to unprecedented levels in the realm of wound healing. The effectiveness of this therapy is enhanced by its ability to manipulate key variables such as light intensity and frequency. This modality enables clinicians to calibrate treatment temperatures according to specific clinical requirements efficiently and effectively. Despite these advancements, the clinical application of 2DNMs in photothermal therapy remains in its preliminary stages, necessitating careful and judicious use in practice.

5.4. Electrostimulation assistance

Bioelectrical signals are considered an integral part of human life activities, especially in the regulation of cellular behaviors and have long been recognized as a crucial domain in regenerative research owing to their extensive applicability and robust safety profile [97]. The rapid development of conductive biomaterials across various research fields raises speculation regarding the potential synergies when electrostimulation is combined with conductive materials in tissue repair.

Following skin injury, the widespread distribution of sodium and potassium ions generates a direct current electric field and potential difference at the wound site, detectable by various epithelial and inflammatory cells, which then migrate toward the wound [98]. With the refinement of wound repair theories, researchers have observed that the application of direct or alternating current to the wound site considerably enhances the migration and proliferation of epithelial cells, promotes angiogenesis, and improves blood circulation. Consequently, this enhancement facilitates the delivery of oxygen and nutrients [99]. During the inflammatory phase, a substantial influx of inflammatory cells into the wound site undergoes a transition from the M1 to the M2 phenotype upon electrical stimulation. This process results in a significant reduction in pro-inflammatory cytokine expression and a rapid increase in collagen synthesis, thereby facilitating swift re-epithelialization of the wound. However, commonly used conductive materials encounter several unresolved challenges when applied to human tissues. For example, once introduced into the body, these conducive materials become susceptible to the internal biological environment, leading to a noticeable degradation in performance and a rapid decline in lifespan. Moreover, most conductive materials struggle to align with the deformable nature of human tissues, often resulting in mechanical failures post-application [100].

The integration of 2DNMs into electrostimulation strategies for wound regeneration represents a significant advancement, driven by their inherent high safety profiles, simplicity in production, and robust material stability. These properties align well with the prerequisites for conductive materials in wound healing applications, prompting rapid progress in this domain. Recently, Lin et al. developed a composite hydrogel based on regenerated bacterial cellulose and MXene, characterized by excellent mechanical properties, flexibility, and biodegradability. This new hydrogel, under external electrical stimulation, can accelerate cell migration, enhance NIH3T3 cell proliferation, and expedite skin wound healing. Due to the conductive properties of MXene, the hydrogel effectively transmits external electric currents, outperforming commercial Tegaderm films in healing efficacy, offering new insights for wound repair [75]. Additionally, 2DNMs facilitate the transmission of electric currents to wound sites and can also record electrophysiological signals from the wound, allowing for more direct observation of the healing process. Yan et al. utilized polydopamine (PDA) loaded with reduced graphene as a supporting template and combined it with *in situ*-formed two-dimensional planar structures of cellulose crystals to synthesize biodegradable nanosheets. These novel 2DNMs, when subjected to appropriate external electric voltage, enhance the proliferation and adhesion of C2C12 cells, promote differentiation towards myotubes, and stably record electrophysiological signals from wounds [101]. Currently, electrostimulation therapy using 2DNMs for skin wounds has become a common treatment modality. However, the use of conductive materials in wound repair typically involves static electrical stimulation, lacking dynamic control tailored to specific wound conditions. Future advancements should focus on exploiting the dynamic modulation capabilities of 2DNMs to tailor electrostimulation to the specific phases of wound repair, thereby optimizing therapeutic outcomes.

6. Emerging two-dimensional materials and their application in diabetic wound healing

The increasing prevalence of diabetes has positioned diabetic wound management as a critical area in wound healing research. The notable efficacy of 2DNMs in conventional wound care has prompted investigations into their potential utility for managing diabetic wounds. However, the pathophysiology of diabetic wounds significantly differs from that of typical wounds, which commonly result from accidents or surgery. Diabetic wounds, often presenting greater challenges in healing, arise from prolonged hyperglycemia leading to microvascular and neural damage, diminished immune function at the wound site, and extensive bacterial proliferation. Such conditions frequently result in prolonged healing durations, which can progress to severe infections and gangrene, potentially necessitating amputation [102]. Recently, 2DNMs have garnered prominent attention in the field of nanobiomedicine for diabetic wounds owing to their optimal specific surface area, ease of surface modification, and excellent photothermal conversion efficiency. The following section focuses on the impact of various types of 2DNMs on diabetic woundhealing (Table 1).

6.1. Graphene and its derivatives

Graphene is the most renowned member of the two-dimensional material family. It is the first 2DNM to be isolated from graphite by Andre Geim and Konstantin Novoselov in 2004 [103]. Graphene is composed of a monolayer of carbon atoms arranged in a hexagonal lattice, wherein each carbon atom is sp^2 hybridized. This structure endows graphene with several remarkable properties, such as excellent electrical conductivity, thermal conductivity, exceptionally high mechanical strength, and flexibility. Most importantly, the properties and functionalities of graphene can be modified by introducing various functional groups, such as carboxyl, hydroxyl, and epoxy groups, into its existing structure. This functionalization facilitates the binding of various biomolecules and thereby augments the biomedical applications of graphene, concurrently enhancing both its stability and safety [104].

Most common graphene derivatives are synthesized through either covalent or non-covalent methods, including GO, reduced graphene oxide (rGO), graphitic nitrogen oxide (GN), and graphitic chloride (GCl), with GO and rGO being the most extensively studied. These derivatives find extensive application across electronics, sensors, catalysis, energy storage, and particularly in biomedicine due to their versatile properties.

GO consists of a two-dimensional layer of SP^2-bonded carbon atoms adorned with oxygen functional groups. Its ability to promote the proliferation and differentiation of various cell types makes it an excellent adjunct material for enhancing diabetic wound healing. For instance, Chen et al. uncovered that GO could enhance the secretion of extracellular vesicles (EVs) rich in miR-21 from adipose-derived mesenchymal stem cells (AD-MSCs). miR-21-enriched EVs regulated the PVT1/PTEN/IL-17 axis and expedited communication between cells and between cells and other miRNAs, proteins, and growth factors, thus promoting diabetic wound healing [105]. Similarly, Ji et al. demonstrated the effects of GO under hyperglycemic conditions on mitigating apoptosis in AD-MSCs *via* the linc00324/MIR-7977/STK4 signaling pathway, consequently expediting the wound healing process [106].

Furthermore, rGO is obtained throughfurther reduction of GO, wherein reducing agents transfer electrons to GO and strip away its oxygen atoms. Ponrasu*et al.* developed a novel nanocomposite scaffold using rGO and isabgol. This scaffold stimulates the synthesis of reactive oxygen and nitrogen species in cells, thereby accelerating neovascularization within wounds. Isabgol can absorb a large amount of wound exudate, thereby preventing bacterial contamination and stimulating the release of excess cytokines and matrix metalloproteinases (MMPs) [107], which synergistically expedite diabetic wound healing. In addition, the anti-inflammatory and antioxidant capabilities of rGO

Table 1
Application of various two-dimensional materials in diabetic wound repair.

S. NO	2D nanomaterial	Sizes (lateral dimension)	Modification	Target Cell	Wound model	Animal model	biological function	Ref
1	reduced Graphene Oxide (rGO)	4.53 ± 2.31 nm thickness, 0.79 ± 0.37 μmlateraldimension	biocompatible acellular dermalmatrix (ADM), MSCs	BMSCs, ADSCs, and HSFs	Excision	Male ICR mice, 5 weeks old, about 23 g	robust vascularization, collagen deposition, rapid re-epithelialization	[139]
2	Graphene Oxide (GO)	0.5–5 μm lateral size		Ad-MSC	Excision	Female BALB/C nude mice , 22–24 g, 4–6weeks old	alleviating Ad-MSC apoptosis, accelerating wound healing	[106]
3	rGO		curcumin, carboxymethyl guargum	3T3-L1	Excision	Rabbits of either sex, weighing 2–2.5 kg	accelerate 3T3-L1 cell migration, accelerate granulation tissue, accelerate collagen fibrils	[140]
4	Thermally Reduced Graphene Oxide (TRGO)		dopamine hydrochloride, 2,5-thio-phenediylbisboronic acid,	human embryonic kidney 293 cells (HEK293)	Excision, and infected group infected by the bacterial suspension of ampicillinresistant *E. coli*	Male Wistar albino normal and diabetic rats	antiparasitic property , against nematodes property, accelerating wound healing, antibacterial activity,	[112]
5	rGO	531 nmaverage particle size	isabgol nanocomposite scaffolds	NIH 3T3 L1	Excision	male Wistar rats weighing about 180–200 g	collagen synthesis, collagen crosslinking, wound contraction, the wound re-epithelialization, vascularization antibacterial, activityantioxidant activity, angiogenesis, accelerated wound healing,	[107]
6	GO		PEPhydrogels	HUVECs	Excision	C57BL/6 male mice, 8-week old	accelerate cell proliferation, accelerate cell migration, vascularization, the PVT1/PTEN/IL-17 axis decreased, increase the area of wound healing	[105]
7	rGO		gelatin-alginate hydrogel(GelAlg), platelet-derived extracellular vesicles (pEVs)	L929, RAW264.7	Excision	Wistar rats (200–240 g)	macrophage polarization, reactive oxygen species (ROS)-scavenging, regulated immune response, promoted angiogenesis, enhanced diabetic wound healing	[108]
8	Black Phosphorus (BP)	500 nmlateral dimension, 2.881 nm thickness	CeO_2 and GOx	Human normal liver cells (L-O_2)	Excision and infected group infected by the *S. aureus*	KM mice, female, ≈38 g, 8 weeks old	improving *in vitro* and vivo bacterial inhibition rate, reducted of infiltration inflammatory cells, accelerating wound healing	[19]
9	Black Phosphorus	1.3 μm average size	4-octyl itaconate (4OI) , multifunctional gelatin methacrylamide hydrogel	HUVECs	Excision	five-week-old Sprague-Durer male rats	antibacterial propertiesantioxidant properties promotingneovascularization, accelerating tissue healing	[118]
10	Black Phosphorus	3∼6 nm thicknesses, 342.89 ± 120.76 nm lateral size,	chitosan methacryloyl (CS) fibroblast growth factor hyaluronic acid methacryloyl	HUVECs andNIH/3T3	Excision	Female Sprague-Dawley (SD) rats	promote cell proliferation, cell migration, angiogenesis, macrophage polarization; inhibiting the inflammatory response, promoting angiogenesis and tissues remodeling	[121]
11	Black Phosphorus Quantum Dots (BPQDs)	3nmparticle sizes	EGCG (Epigallocatechin gallate)	HUVECs andHuman skin keratinocytes cells (HaCat)	Excision	MaleSprague Dawleyrats, weighing 190 ± 20 g	promoting the proliferation of vascular endothelial cells and skin epidermal cells, excite PI3K/AKT and ERK1/2 signal pathways, ROS-scavenging, sterilization, and promoting wound healing	[115]
12	Black Phosphorus	4nmparticle sizes	3aminophenylboronic acid modified oxidized chondroitin sulfate (APBA-g-OCS) , polyvinyl alcohol (PVA) , black phosphorus/bismuth oxide/ ε-polylysine (BP/Bi2O3/ε-PL)	NIH3T3 cells ,	Excision	Male SD rats, about 200 g	chemo-photothermal antibacterial, anti-biofilm formation ability, possess antioxidation, inflammatory, accelerating collagen deposition, promoting granulation tissue formation and angiogenesis	[116]
13	Black Phosphorus		Hemoglobin , poly-L-lactide (PLLA) nanofibers , quaternized chitosan , hyaluronic acid	HUVECs and mouse fibroblasts (L929)	Excision	Male BALB/c mice, weighing approximately 25 g,	NIR-assisted oxygen delivery, hemostasis, antibacterial, anti-inflammatory properties, promote cell proliferation, migration, angiogenesis	[119]

(*continued on next page*)

Table 1 (*continued*)

S. NO	2D nanomaterial	Sizes (lateral dimension)	Modification	Target Cell	Wound model	Animal model	biological function	Ref
14	BP QDs		polyvinyl acetate (PVA) , gelatin methacryloyl (GelMA) , Hemoglobin	NIH 3T3 cells	Excision	200–220 g male Sprague-Dawley (SD) rats	inflammatory properties, angiogenesis oxygen carrying and controllable oxygen delivering ability , accelerating wound healing	[120]
15	Ti_2C_3MXenes	2 nm heights	poly-γ-glutamic acid (γ-PGA) hydrogel asiaticoside	Fibroblasts, HUVECs	Excision	diabetic (db/db) mice(10-day-old)	facilitate cell proliferation, angiogenesis, accelerating wound healing	[18]
16	Ti_2C_3MXenes	1.84 nm Thickness, 200 nm average size	Cu_2O		Excision and infected group infected by the *S. aureus*	BKS Cg–Dock7^{m} +/+ Leprdb/J (db/db) male mice (5–6 weeks old, weighing 35–45 g)	antibacterial, accelerating wound healing	[128]
17	Ti_2C_3 MXenes	1.6 nm thickness	sponge-like macro-porous hydrogel (SM-hydrogel)	endothelial cell	Excision		antibacterial, ROS scavenging capacities, accelerating wound healing	[127]
18	Ti_2C_3 MXenes		hyaluronic acid-graft-dopamine (HA-DA), polydopamine, oxyhemoglobin	HUVEC, macrophage	Excision and infected group infected by the *S. aureus*		promotes human umbilical vein endothelial cell, proliferation and migration, scavenging ROS, eradicating bacteria, and promoting angiogenesis and M2 macrophage-polarized anti-inflammation., accelerating wound healing	[130]
19	Ti_2C_3MXenes		microneedle (MN) patchesassembledwith Ti2C3 MXenes polyurethane (PU)		Excision		inflammatory properties, accelerating wound healing	[133]
20	Ti_2C_3MXenes		thermosensitivity Antibacterial Injective Hydrogels, M2 macrophage exosome (Exo), F127	macrophage, NIH/3T3, HUVEC	Excision		antibacterial activity, promoting the proliferation, migration of fibroblasts, angiogenic ability of endothelial cells, inhibiting inflammation, promoting angiogenesis through VEGF secretion, and improving proper collagen deposition	[125]
21	Ti_2C_3 MXenes		Fe_2O_3, glucose oxidase (GOx)	RAW264.7 , L929 and HaCaT cells	Excision and infected group infected by the *S. aureus*	Sprague–Dawley (SD) rats	antibacterial activity, angiogenesis, accelerating wound healing	[129]
22	MoS_2		CeO_2	L929	Excision	SD rats	accelerate re-epithelization, enhance collagen deposition, and bolster angiogenesis, scavenging ROS, eradicating bacteria, accelerating wound healing	[135]
23	MoS_2		bovine serum albumin-modified gold nanoparticle	HUVEC	Excision	Female rats, 250–300 g	consuming glucose, eradicating bacteria, scavenging ROS, providing O_2, and facilitating epithelialization, collagen deposition, and angiogenesis	[136]
24	MoS_2		sodium alginate (SA)	human dermal fibroblasts cells (HDFs), HUVECs and human hair dermal papilla cells (HhDPCs)	Excision	5–7 weeks old female Balb/c nude mice	promoting angiogenesis and hair follicle regeneration, suppressed skin cancer, accelerating wound healing	[138]
25	MoS_2		graphite-phase carbon nitride (g-C_3N_4), glucose oxidase (GOx)	L929 cells	Excision and infected group infected by the *S. aureus*	4–6weeks Balb/c mice aged, 17–25 g	antibacterial activity, accelerating wound healing	[137]

further contribute to tissue repair, as evidenced by Hao et al., who engineered a gelatin-alginate (GelAlg) hydrogel encapsulating human platelet derivatives and rGO, which notably promotes macrophage polarization and ROS scavenging capabilities, thereby facilitating the expedited healing of diabetic wounds [108]. Moreover, the excellent electrical conductivity and biocompatibility of rGO enhance cell attachment and proliferation, thereby bolstering its application in scaffold-based approaches in regenerative medicine. Fu et al. developed a novel rGO-modified acrylamide mannose thioglycolate (ADM) composite scaffold characterized by exceptional conductivity, mechanical properties, and biocompatibility. Notably, the ample surface area of 2DNMs allows for extensive cell attachment and reduces apoptosis when co-cultured with MSCs, thereby effectively facilitating MSC delivery. In diabetic mouse wound models, this innovative composite scaffold also accelerates vascular formation and collagen deposition, thus playing a pivotal role in the wound healing process [109].

Graphene not only enhances cell adhesion and proliferation in tissue regeneration processes but can also inactivate bacteria and viruses through electrostatic interactions to prevent their proliferation. The antimicrobial properties of graphene, however, depend largely on the type and quantity of functional groups attached to it. In many cases, common functional groups such as carboxyl, hydroxyl, and amino groups only increase the hydrophilicity and chemical reactivity of graphene without significantly augmenting its antibacterial properties [110]. Conversely, graphene functionalized with boronic acid groups exhibits enhanced antimicrobial effectiveness by forming covalent bonds with *cis*-diols on bacterial membranes rich in phospholipids and lipopolysaccharides, thereby disrupting bacterial structures [111]. Furthermore, boronic acid-enriched materials contribute to wound healing by increasing the release of essential biomolecules such as proteoglycans, collagen, and glycoproteins, enhancing lymphocyte proliferation, and facilitating extracellular matrix synthesis. According to studies by Beyranvand*et al.*, boronated graphene demonstrates robust antimicrobial activity against both gram-positive and gram-negative bacteria to rapidly encapsulate and eliminate bacteria, particularly effective against nematodes with a reduction in parasite viability to 30 %. In diabetic mouse models, the application of boronated graphene accelerated the process of collagen renewal and the development of new vascular and follicular structures to improve wound healing outcomes. This evidence underscores the potential of boronated graphene as a highly potential material in future biomedical applications [112].

Multifunctional, two-dimensional graphene nanocomposites have emerged as promising candidates in the field of diabetic wound healing (Fig. 5). Despite the optimistic outlook suggested by current research, the clinical application of these materials remains unexplored, with evaluations predominantly confined to animal studies. This gap underscores a critical need for comprehensive research directed towards the biocompatibility aspects of these nanocomposites. Key issues such as biodegradability, elimination pathways, and the long-term toxicity associated with these two-dimensional materials necessitate comprehensive investigation to ensure their safety and efficacy in human medical applications.

6.2. BP

Phosphorus, one of the most abundant elements on Earth, exists in various allotropes, such as BP, white phosphorus, purple phosphorus, and red phosphorus. Among them, BP is the most stable form under ambient conditions and garners substantial interest in scientific research. Extensive research has demonstrated that BP can be mechanically exfoliated into various two-dimensional configurations, such as BP nanosheets (BPNSs), BP nanoparticles (BPNPs), and BP quantum dots (BPQDs) [113]. BP has a layered structure where each phosphorus atom forms covalent bonds with three adjacent phosphorus atoms, resulting in an arrangement akin to a honeycomb lattice. The layers are held together by weak van der Waals forces, rendering them readily exfoliable. The thickness of BP can be modulated through varying degrees of exfoliation, which in turn allows for tunable electronic properties. This tunability enables BP to exhibit different photoelectric properties under various wavelengths of light, thereby suggesting potential applications in optoelectronic devices such as photodetectors and photodiodes [114]. Additionally, BP exhibits excellent electronic transport properties and high carrier mobility, making it a promising material for applications in nanoelectronics.

BP is increasingly recognized for its superiority over graphene in diabetic wound management owing to its stable degradability and two-dimensional ultrathin structure, making it an ideal nanocarrier for transporting therapeutic agents and biomolecules to treat diabetic wounds. Xu and his team developed a novel material termed BPQDs, which were utilized as nanocarriers for the loading of catechins to treat diabetic wounds. This material facilitates bactericidal action through the ROS response and enhances the proliferation of vascular endothelial and epithelial cells by activating the PI3K/AKT and ERK1/2 signaling pathways, thereby accelerating the healing of MRSA-infected deep burn wounds [115]. Further modifications of BP can enhance its performance. For instance, Zhang et al. enhanced the stability of BP under hydrolytic and oxidative conditions by doping it with bismuth oxide (Bi_2O_3). They developed BP-Bi_2O_3/E-PL (ε-PL) nanoparticles, which were coated on a synthetic hydrogel composed of 3-aminophenylboronic acid-modified oxidized chondroitin sulfate (APBA-g-OCS) and PVA. This multifunctional hydrogel exhibits excellent antioxidative and anti-inflammatory properties, improves the wound microenvironment, promotes granulation tissue formation and angiogenesis, and accelerates the healing of infected wounds in diabetic rats [116].

It is noteworthy that BP nanomaterials can also facilitate tissue repair through photothermal therapy. When exposed to light, the atoms or molecules on the surface of BP absorb photon energy. This energy is absorbed by electrons, which are excited to higher energy states. Following the absorption of photon energy, the electrons in BP undergo thermalization and interact with the lattice, transferring energy to the lattice atoms. After electron thermalization, heat conduction initiates between the electrons and the lattice in BP, thereby gradually spreading the energy to the surrounding molecules and atoms [117]. Wen et al. developed a novel multifunctional glucose oxidase (GOx)-cerium oxide (CeO_2)@BP/aptamer (Apt) nanosheet, wherein the photothermal properties of the BP nanosheets prominently amplify the cascading nanozyme effect of GOx and CeO_2. The synergy of these components not only enhances the antibacterial capabilities of the nanosheet but also mitigates inflammatory cell infiltration, thereby expediting the healing process in diabetic wounds [19].

BP nanosheets, recognized for their photosensitive properties, offer versatile applications in therapeutic delivery by functioning as photoreactive switches. A study by Ding et al. highlighted the innovative utilization of BP nanosheets incorporated into a photosensitive gelatin-methacrylamide hydrogel, modified with 4-octyl itaconate (4OI). In the absence of laser irradiation, BP acts as a carrier to control the release of 4OI and synergistically enhances its antioxidant activity, thereby mitigating excessive ROS damage to endothelial cells and promoting angiogenesis. Conversely, under laser irradiation, this hydrogel transforms into a gelled film that simultaneously produces ROS to combat bacterial infections, thus amplifying the therapeutic efficacy of photothermal and photodynamic therapies [118]. Furthermore, the challenging hypoxic microenvironment of diabetic wounds can be addressed by combining BP with hemoglobin (Hb), which collectively improves oxygenation at the wound site. BP converts NIR radiation into heat to induce on-site oxygen release from Hb. When nanofiber membranes or microneedles loaded with Hb and BP are applied to diabetic wounds, the photothermal effect of BPQDs and the reversible oxygen-binding capability of Hb lead to localized temperature elevations under NIR exposure [119,120], thereby facilitating controlled oxygen delivery. This approach alleviates hypoxia in diabetic wounds and accelerates cellular adhesion and proliferation to foster wound healing. The role of BP

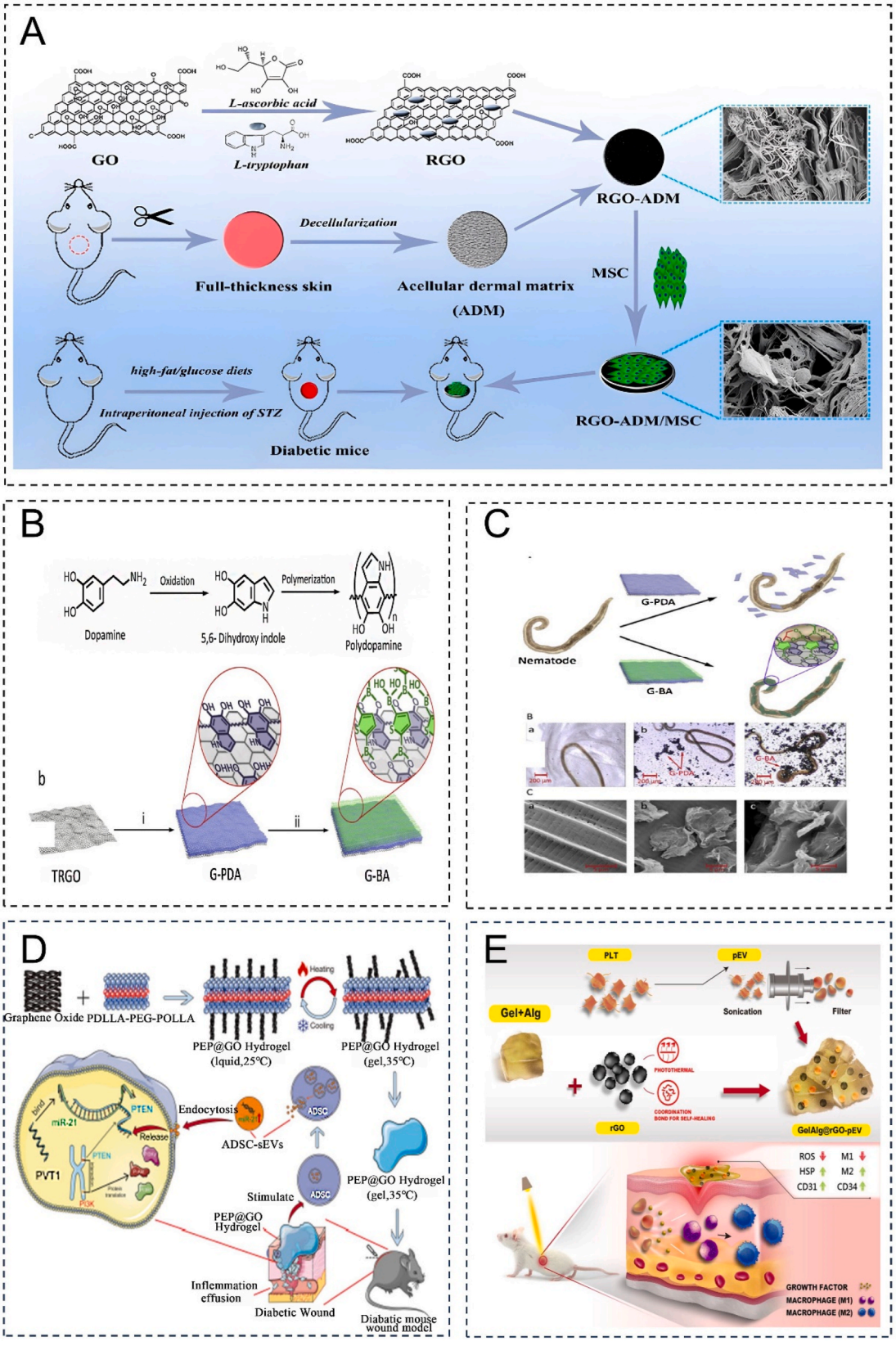

Fig. 5. Therapeutic applications of graphene and its derivatives in diabetic wound management. (A) Schematic representation of the incorporation of MSCs and rGO into an ADM for diabetic wound healing in mice [109]. Copyright 2016, American Chemical Society. (B) Synthesis of PDA, graphene-based PDA (G-PDA), and graphene-based aerogel (G-BA). (C) Schematic depiction of the interaction between nematodes and G-PDA and G-BA, along with optical and scanning electron microscopic images [112]. Copyright 2020,Elsevier.(D) Schematic illustrating the structure of thermosensitive PEP@GO and its capacity to upregulate miR-21 in adipose-derived mesenchymal stem cells (ADSCs) to promote diabetic wound healing [105]. Copyright 2022,BioMed Central. (E) Schematic depiction of a GelAlg hydrogel carrying human platelet-derived EVs (pEVs) and rGO to accelerate diabetic wound healing [108]. Copyright 2023,BioMed Central.

extends beyond serving as an oxygen release switch; it can also be engineered to regulate the degradation of biomaterials. Luo et al. designed a novel charge-driven self-assembling microsphere hydrogel scaffold (SMHS) based on electrostatic interactions. The photosensitivity of BP significantly influences the degradation and drug release kinetics of SMHS under NIR irradiation. This microsphere hydrogel scaffold demonstrates anti-inflammatory, pro-angiogenic, and tissue remodeling properties, thereby markedly reducing wound healing duration [121].

In summary, two-dimensional BP nanomaterials can be extensively utilized for diabetic wound repair owing to their notable photothermal properties and responsive photosensitivity (Fig. 6). Most importantly, these nanomaterials leverage infrared irradiation to facilitate controlled degradation post-application. This effect ensures their efficacious performance within the wound site and promotes their safe elimination from the body.

6.3. MXenes

The introduction of MXenes in 2011 marked a significant development in the field of two-dimensional metal nanomaterials, including transition metal carbides, nitrides, and carbonitrides [122]. MXenes are typically produced by selectively etching the A layer of layered ternary carbides and nitrides, known as MAX phases. This process yields MXene layers with the chemical formula $M_{n+1}AX_n$ (n = 1–3), where 'M' represents an early transition metal, such as Ti, Hf, Sc, Ta, Mo, Cr, Zr, Nb, and V, while 'X' denotes carbon and/or nitrogen elements. The A layer often consists of surface functional groups, such as hydroxyl, oxygen, or fluorine [123]. Currently, more than 30 MXenes have been synthesized and extensively applied in laboratory research, primarily using wet etching and delamination methods. Wet etching entails the use of hydrogen fluoride (HF) or a mixture of strong acids and fluoride salts at room temperature, where the structure and size of MXenes can be controlled by adjusting the etching duration and HF concentration [124]. Alternatively, the delamination approach involves the removal of external oxide layers from transition metal carbides using strong acids or bases to expose the underlying layered structure, followed by the modification of interlayer spacing to accommodate various ions or molecules for property tuning. The diversity of properties within the MXene family is largely ascribed to variations in MAX phases and the incorporation of different functional groups.

The two-dimensional planar topology of MXenes provides an expansive surface area conducive to the efficient loading of various therapeutic agents, such as chemotherapeutic drugs and biological macromolecules. Wang et al. developed a novel microneedle by integrating poly(γ-glutamic acid) (γ-PGA) hydrogel with asiaticoside (AS)-loaded Ti_3C_2Mxene. This combination enables the microneedles to penetrate the stratum corneum for subcutaneous drug delivery. The Ti_3C_2MXene functions as a drug delivery system, which extends the release duration of AS, diminishes inflammatory responses, and intensifies cell proliferation and angiogenesis. Furthermore, the integration of Ti_3C_2MXene augments the mechanical strength of the γ-PGA microneedles, thereby ensuring complete penetration through the stratum corneum [18]. MXenes can also synergize with biomaterials to exert enhanced effects. Jiang et al. developed a novel hydrogel incorporating a nanohybrid of Ti_3C_2Mxene and M2 macrophage-derived exosomes (FM-Exo). This composite material activates the PI3K/AKT signaling pathway, thereby enhancing the proliferative and migratory capacities of fibroblasts and the angiogenic potential of endothelial cells. Notably, this hydrogel facilitates M2 macrophage polarization to accelerate wound healing in diabetic mice while improving collagen deposition and reducing scar formation [125].

Moreover, the proliferation of bacteria in diabetic wounds is one of the primary impediments to their healing process. MXene can mitigate bacterial infections through the utilization of its sharp edges and photothermal effects, which disrupt bacterial membranes [126]. Oxidized MXene facilitates the transformation of charge carriers, displaying exceptional photocatalytic capabilities. Under similar illumination conditions, it can generate an increased number of free radicals, thereby effectively killing *Escherichia coli* and *Staphylococcus aureus* [127]. Nonetheless, the efficiency of ROS generation by standard MXenes remains suboptimal. To address this issue, Hsu et al.enhanced Ti_3C_2 nanosheets by integrating copper ions, which underwent spontaneous redox reactions with MXene to form copper(I) oxide *in situ*, resulting in the creation of Cu_2O/Ti_3C_2 nanosheets. This modification amplifies the generation of electron-hole pairs and promotes photocatalytic ROS production, thereby surmounting the limitations associated with Ti_3C_2 nanosheets. The novel Cu_2O/Ti_3C_2 nanosheets, when subjected to infrared radiation, eradicate bacteria through localized photothermal therapy, *in situ* ROS production, and direct contact-induced membrane disruption, thus effectively driving the healing of diabetic wounds infected with MRSA [128]. However, addressing the challenge posed by intracellular bacteria remains complex. Dai et al. designed a precise ferroptosis bio-heterojunction (F-bio-HJ) composed of Fe_2O_3, Ti_3C_2 MXene, and GOx, which produces substantial ROS under NIR radiation. The ROS attack bacterial membranes and facilitate the permeation of concurrently generated Fe^{2+}/Fe^{3+} ions into the bacteria, leading to bacterial death through iron depletion, Fe^{2+} overload, and lipid peroxidation. This mechanism is further enhanced by the transport of Fe^{2+} ions into bacterial cells*via*ferroportin, thereby intensifying the intracellular iron concentration and effectively killing the bacteria. This strategy not only addresses surface infections but also targets intracellular pathogens, providing a potent approach to managing recalcitrant infections [129].

Hypoxia in diabetic wounds is typically mitigated through enhanced oxygen delivery to the wound area *via* localized or hyperbaric oxygen therapy. Nonetheless, excessive oxygen-induced ROS overproduction can exacerbate cellular and tissue damage, thereby increasing the risk of inflammation and tissue damage at the wound site [22]. MXene, recognized for its unique photosensitivity, is regarded by researchers as a photo-responsive switch for the controlled release of oxygen. Li et al. developed an injectable hydrogel by catalytically crosslinking hyaluronic acid-dopamine (HA-DA) and PDA-coated Ti_3C_2 MXene nanosheets with an oxygenated hemoglobin/hydrogen peroxide (HbO_2/H_2O_2) system under mild photothermal stimulation. In the absence of light, this system enables HbO_2 to bind oxygen from the atmosphere. Upon NIR irradiation, the hydrogel, acting as an oxygen carrier, is activated by the ensuing heat to release oxygen in a regulated manner. The stable photo-responsiveness of MXene ensures the stable release of oxygen from HbO_2. Moreover, this novel MXene hydrogel substantially augments the proliferation and migration of human umbilical vein endothelial cells (HUVECs) and markedly reduces the healing period of diabetic wounds infected with pathogens [130].

MXenes, characterized by their layered structure abundant in metal and carbon elements, exhibit unique physio-electrochemical properties. The metal elements provide pathways for electron conduction, while the carbon elements ensure the stability of electron transport channels [131]. These attributes render MXenes effective electrode materials, which are extensively used in electrochemical sensing to monitor the healing process of diabetic wounds. Vinod Kumar et al. developed a non-enzymatic glucose sensor (NEGS) based on the synergistic effects of Ti_2C MXene and TiO_2 nanoparticles to enhance the electrochemical responsiveness of the sensor. This enhancement affords the sensor a broader linear range, heightened sensitivity, and faster response times [132]. MXene nanocomposites hold potential as next-generation materials for on-site, large-scale screening of diabetic patients. Beyond simple glucose monitoring, MXene is also under investigation as a novel strain-sensing material to monitor excessive stretching in the wound area, thereby averting further injury. Inspired by shark teeth, Wei et al. designed a microneedle patch incorporating Ti_3C_2 to construct an electrical signal sensor on the surface of the microneedles. This sensor provides a more intuitive observation of wound dynamics by detecting changes in the relative resistance of the dressing [133].

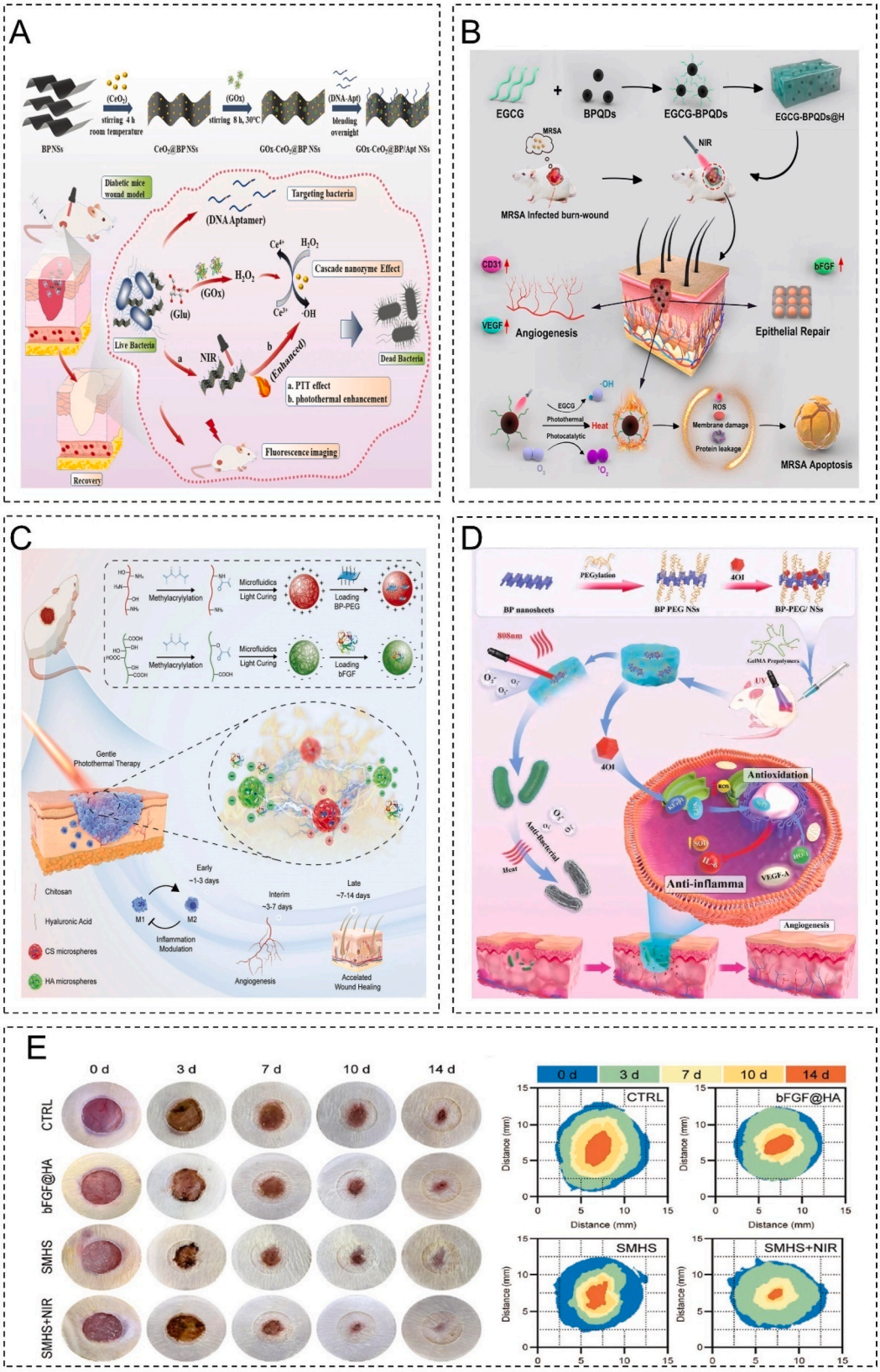

Fig. 6. BP treatment approaches for diabetic wounds. (A) Schematic depiction of the fabrication and application of GOx-CeO_2@BP/Apt in diabetic infected wounds [19].Copyright 2023, Wiley. (B)Schematic illustration of the synthesis of the epigallocatechin gallate (EGCG)-BPQDs@H nanocomposite and its acceleration of healing diabetic infected wounds [115]. Copyright 2021,BioMedCentral. (C) Design and fabrication schematic of charge-driven self-assembling microsphere scaffolds developed for the treatment of diabetic wounds [121]. Copyright 2023,Wiley. (D) Synthesis of the multifunctional 4OI-BP@Gel hydrogel and its application in diabetic wound healing [118].Copyright 2022, Wiley. (E) Representative images of the wound healingprocess in diabetic rats [121]. Copyright 2023,Wiley.

Currently, MXene has been engineered for multifaceted applications, including drug delivery, antimicrobial treatments, and biosensing. Particularly, the excellent conductivity and photothermal effects of MXene render it highly amenable for clinical use (Fig. 7). Innovative methods for surface functionalization tailored to its properties have paved a promising pathway for expanding its applications in biomedicine.

6.4. TMDCs

TMDCs are compounds primarily composed of transition metal elements and chalcogens. The transition metals typically implicated in these compounds range from groups 4 to 12 of the periodic table and include elements such as molybdenum (Mo), tungsten (W), iron (Fe), and copper (Cu), while the chalcogens are generally sulfur (S). These compounds are chemically represented as "MX_2," where "M" denotes the transition metal and "X" represents a chalcogen. The specific composition of a TMDC can vary based on the specific transition metal and chalcogen used [64]. Based on their composition, TMDCs may function as semiconductors, metals, semimetals, or superconductors. Unlike graphene, which is composed of a single layer of carbon atoms, TMDCs are structured in a sandwich-like formation where a central transition

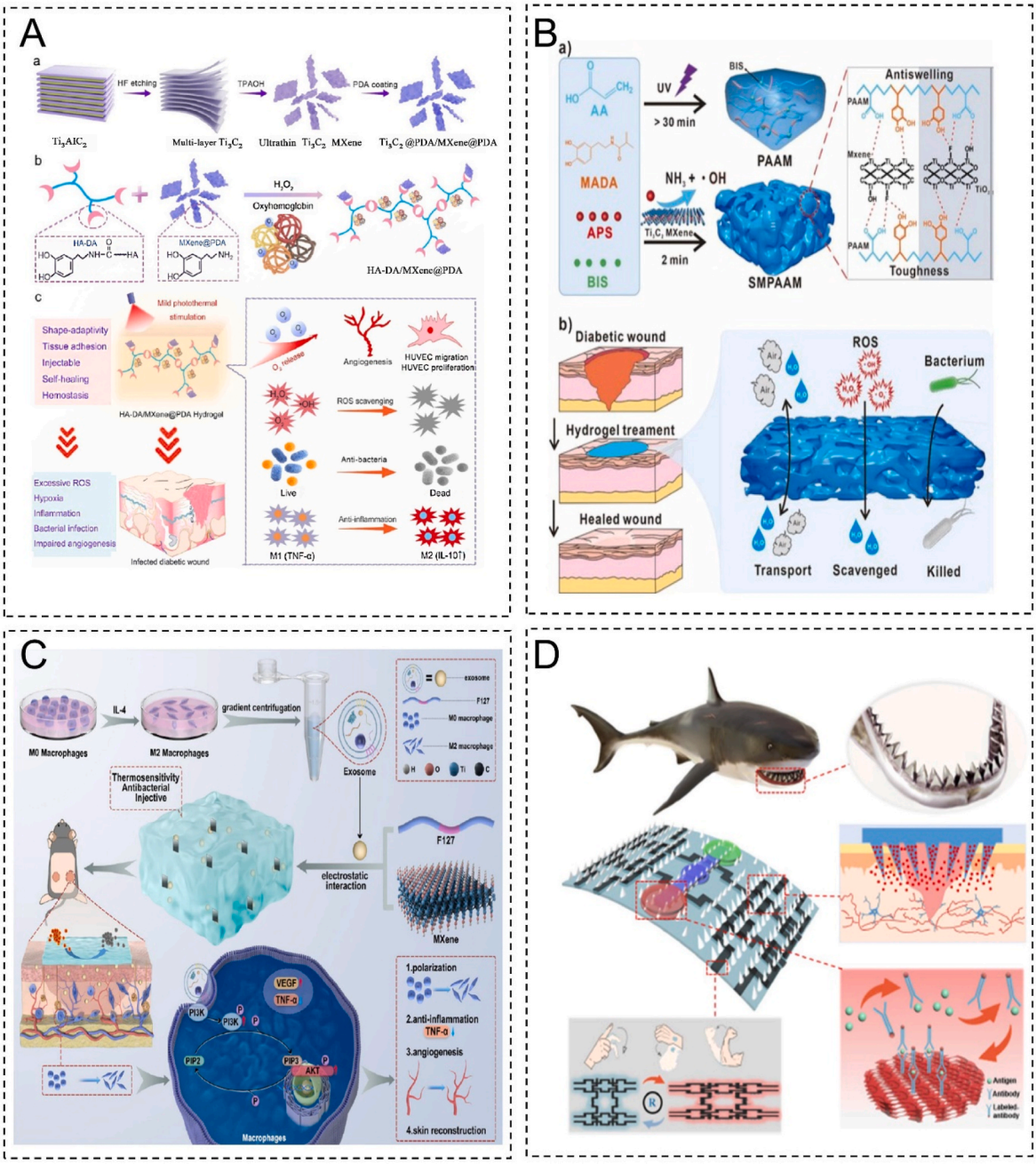

Fig. 7. MXenes in diabetic wound treatment. (A) Synthesis diagram of MXene@PDA nanosheets and HA-DA/MXene@PDA hydrogel mechanisms for oxygen supply, ROS clearance, bacterial eradication, and inflammation suppression to promote diabetic wound healing [130]. Copyright 2022, American Chemical Society.(B) Design strategy for a spongy macroporous hydrogel system [127]. Copyright 2023, Wiley.(C) Schematic representation demonstrating the multifunctional FM-Exo hydrogel's role in promoting diabetic wound healing and skin reconstruction [125]. Copyright 2024, American Chemical Society.(D) Schematic depiction of microneedle dressings designed for smart wound care, including motion sensing, biochemical analysis, and healing [133].Copyright 2021, American Chemical Society.

metal layer (e.g., Mo, W, Nb) is flanked by two layers of chalcogens (e.g., S, Se, Te). This arrangement, coupled with the van der Waals forces between layers, facilitates the mechanical exfoliation of TMDCs into two-dimensional forms [134].

TMDCs, characterized by their two-dimensional layered structure, exhibit extensive surface areas suitable for loading a wide array of biomolecular drugs. Ma et al. developed a cerium dioxide-loaded MoS_2 nanocomposite modified with PEG, which demonstrated efficient photothermal antibacterial activity and prominently curbed the growth of both gram-positive and gram-negative bacteria. This effect, combined with the outstanding antioxidant capabilities of cerium dioxide and its promotion of cell proliferation and migration, synergistically enhanced

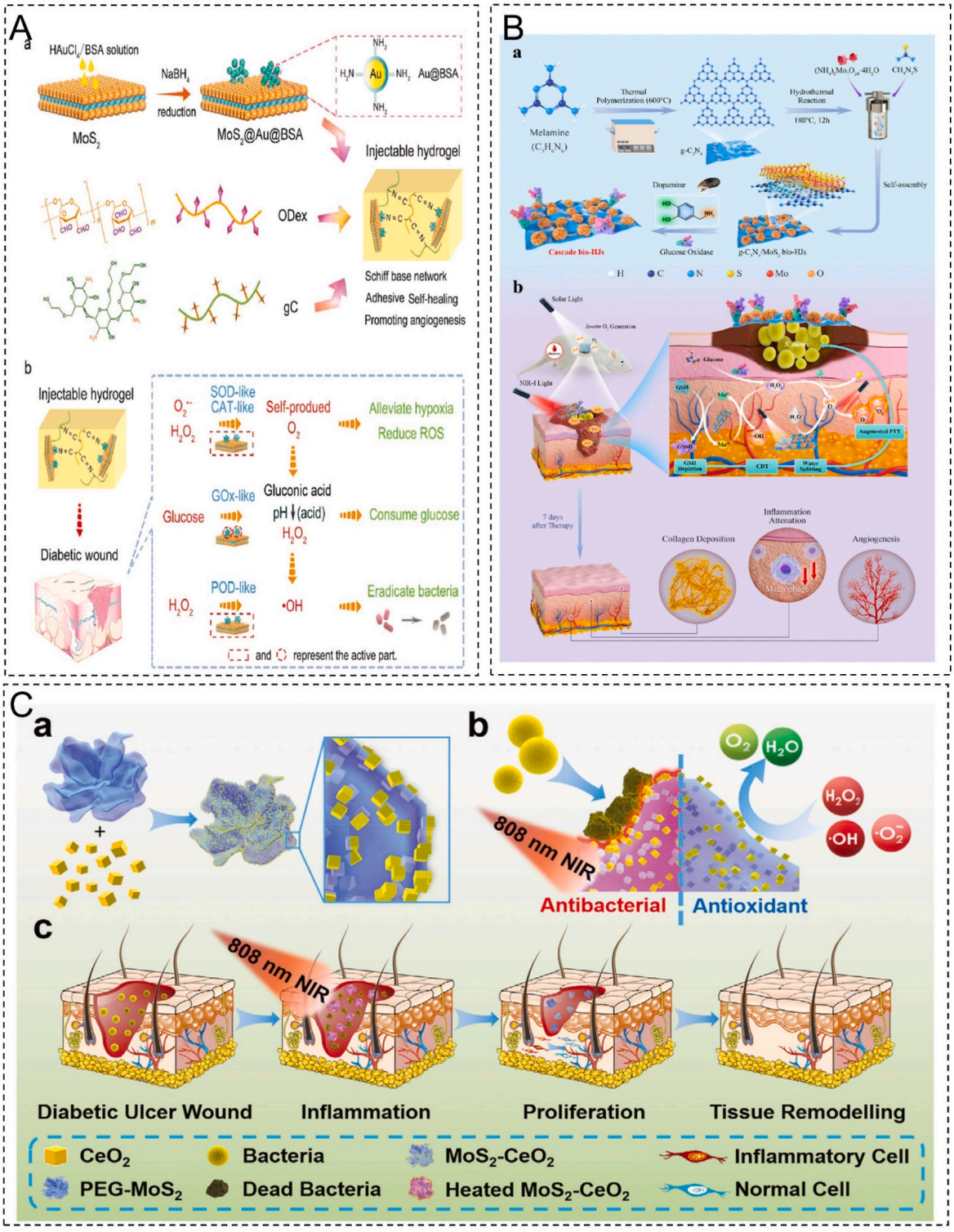

Fig. 8. Two-dimensional TMDCs in diabetic wound treatment. (A) Synthesis of MoS_2@Au@bovine serum albumin (BSA) nanosheets and preparation of injectable hydrogel [136]. Copyright 2022, Wiley. (B) Synthesis of g-C_3N_4/MoS_2-based C-bio-HJs and their loading with GOx for the treatment of infected diabetic wounds [137]. Copyright 2023, KeAi Communications. (C) Schematic representation of MoS_2–CeO_2 nanocomposite for diabetic wound treatment [135]. Copyright 2021, Wiley.

the healing process of diabetic wounds, suggesting notable potential for broad clinical application [135]. Moreover, two-dimensional TMDCs not only exhibit high drug-loading capacities but also serve as nanozymes, stimulating the biological activities of natural enzymes such as peroxidase (POD), superoxide dismutase (SOD), and catalase (CAT). Li et al. designed a MoS_2 nanosheet hydrogel loaded with AuNPs and modified with bovine serum albumin. This system simulates SOD activity by converting superoxide (O_2^-) into H_2O_2, which is then converted into water by oxidase to mitigate oxidative stress. This mechanism fosters epithelialization, collagen deposition, and angiogenesis to significantly accelerate the regeneration of infected diabetic skin [136]. Furthermore, MoS_2 can carry biomaterials and form nano-heterostructures with other 2DNMs to enhance photocatalytic efficiency. In a study by Deng et al., g-C_3N_4 was combined with MoS_2 to augment its light-harvesting capabilities and promote the separation of photo-generated charges, conferring potent photodynamic antimicrobial effects. Additionally, carbon nitride (CN)/MoS_2 loaded with GOx can metabolize glucose in diabetic wounds and generate excessive H_2O_2 to facilitate a starvation therapy approach, thereby expediting diabetic wound healing [137].

Recent advancements in biomaterials have demonstrated their capability to treat multiple diseases simultaneously. Biomaterials synthesized from two-dimensional TMDCs also offer integrated therapeutic functions, not only accelerating the healing of diabetic wounds but also improving wound healing affected by skin cancer. Bing Ma et al. reported a biomaterial synthesized from MoS_2 nanosheets, denoted as SA-MS hydrogel. This hydrogel features a porous microstructure with a uniform distribution of Mo elements. The release of Mo^{4+} ions from the SA-MS hydrogel significantly enhances the migration and proliferation of human dermal fibroblasts (HDFs), HUVECs, and human hair papilla cells (HhDPCs), markedly expediting the healing process of diabetic wounds. Moreover, under light exposure, the MoS_2 within the SA-MS hydrogel generates substantial heat to kill cancer cells, thereby accelerating the repair of melanoma-affected skin [138]. In the field of tissue regeneration, two-dimensional TMDCs promote diabetic wound healing through antioxidative, antibacterial, and angiogenesis-enhancing mechanisms. Compared to other two-dimensional materials such as graphene and BP, TMDCs offer distinct advantages in biomedical applications. For instance, TMDCs possess greater hydrophilicity, which enhances their dispersibility and stability in physiological settings, rendering them more practical and user-friendly for biomedical applications. The multifunctionality of TMDCs underscores their growing significance in medical research and therapy, heralding a new frontier in the integration of treatment modalities (Fig. 8).

7. Future prospects

In recent years, 2DNMs have found extensive applications across various biomedical fields, including drug delivery, biosensing, bioimaging, and regenerative medicine. Particularly, 2DNMs have

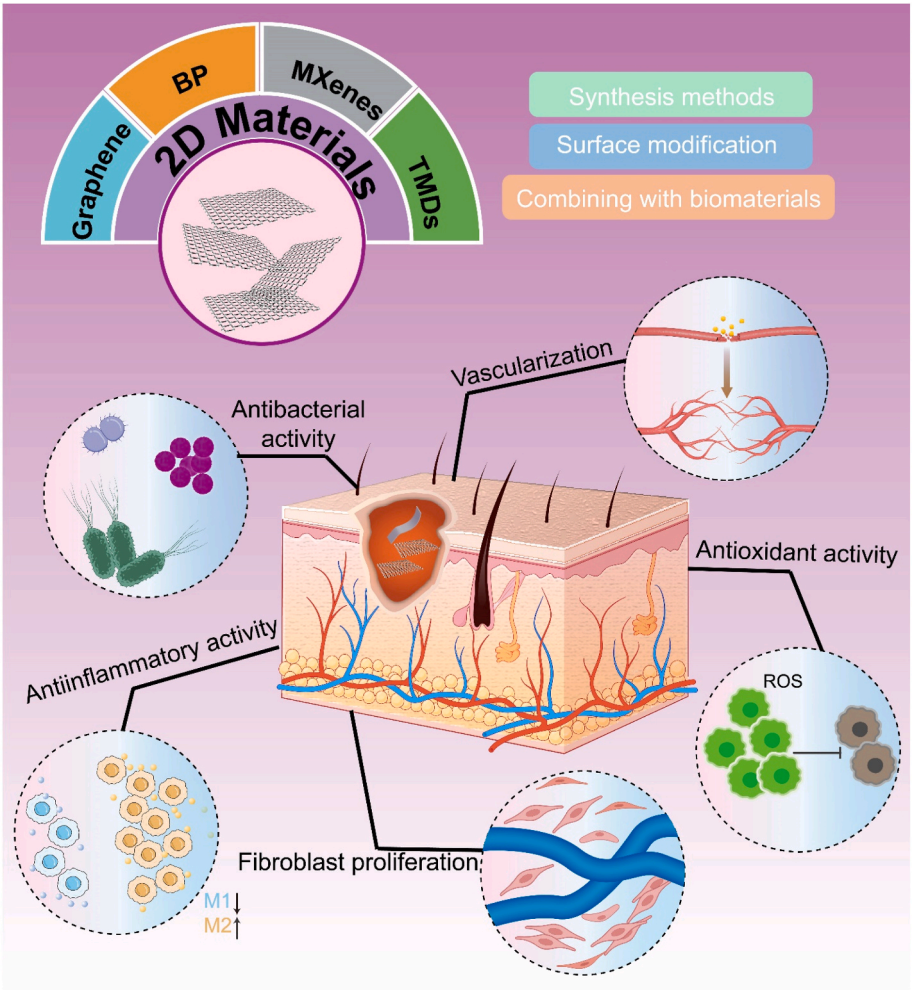

Fig. 9. Integration of 2DNMs or their surface-modified counterparts with biomaterials accelerates the healing of diabetic wounds. This synergistic integration manifests robust antioxidant, anti-infective, and anti-inflammatory properties to facilitate wound healing in diabetic conditions by promoting the proliferation and differentiation of fibroblasts, neovascularization, and collagen deposition.

demonstrated notable potential from diagnosis to treatment in the field of diabetic wound management. The inherent advantages of 2DNMs, such as their expansive surface area, distinctive planar structures, effective photothermal capabilities, and versatile biological functions, continue to attract intensive research focus. This review delineates key members of the 2DNM family, including graphene and its derivatives, BP, MXenes, and TMDCs, and emphasizes their strategic benefits and pioneering contributions to the field of diabetic wound management (Fig. 9).

Despite the considerable interest in 2DNMs, research in this field remains largely in its infancy, with several challenges impeding their clinical application. (1) Synthesis requirements vary widely across different application contexts, necessitating material adaptation to suit specific diseases. Furthermore, it represents the principal concern that warrants consideration upon transitioning to clinical practice in the future. Researchers should integrate clinical observations and patient physiological changes to more comprehensively predict and enhance the impact of 2DNMs, thereby developing personalized materials with tunable sizes and shapes to optimize therapeutic outcomes. (2) The complexity of interactions among various bioactive substances loaded onto 2DNMs is poorly understood, including critical aspects such as drug load ratios, non-specific bindings, aggregation, and potential losses of bioactivity from bench to bedside. Particularly within the clinical realm, a multitude of intricate factors, encompassing both the external environment and the internal microenvironment of the human body, may exert influence on its therapeutic efficacy. Therefore, Balancing functional efficacy with design complexity is crucial, and the design of 2DNMs requires standardized protocols that harmonize various attributes and functionalities to enhance their long-term performance. (3) Securing the safety profile of 2DNMs is a pivotal prerequisite for their translation from bench to bedside.Most 2DNMs tend to accumulate primarily in the liver and spleen, posing potential physiological toxicity risks. There is also concern over their tendency to reaggregate within the body, which could disrupt physiological balance. The incorporation of heavy metals and metal oxides in the fabrication of 2DNMs necessitates careful consideration of metal dosages to prevent accumulation in the liver and other metabolic organs. Another pivotal approach involves enhancing their biodegradability, which facilitates renal excretion to mitigate hepatic toxicity and ensures environmental safety. For instance, 2DNMs such as GO and MoS_2 can be eliminated through oxidative degradation in biological environments. Developing novel chemical modifications to induce degradability in biological environments becomes essential for those lacking intrinsic biodegradability. (4) The synthesis of 2DNMs necessitates intricate methodologies and stringent conditions, which may engender variability between batches and escalate production expenses. This factor also stands as a significant impediment to the transition of 2DNMs from the research environment to clinical applications. Consequently, the development of a streamlined and standardized protocol for 2DNMs, grounded in economic viability, is of paramount importance at present. (5) The integration of genomic analysis, systemic mapping, and high-throughput screening technologies can enhance our understanding of the impact of 2DNMs on genes and proteins post-administration, thereby aiding in better predictions of the interactions between 2D nanomaterials and biological systems. This detailed insight allows for the precise tailoring of 2DNMs to address specific challenges encountered in biomedical applications. Despite many unresolved issues, the development of functionally efficient and biologically safe 2DNMs holds promising prospects for future clinical applications.

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CRediT authorship contribution statement

Mingming Cui: Writing – original draft, Software, Investigation. **Jin Zhang:** Writing – review & editing, Supervision, Conceptualization. **Pengfei Han:** Project administration, Conceptualization. **Ling Shi:** Software, Formal analysis. **Xing Li:** Supervision, Project administration, Conceptualization. **Zhe Zhang:** Supervision, Project administration, Conceptualization. **Haihua Bao:** Resources, Project administration, Conceptualization. **Yubo Ma:** Resources, Project administration. **Ziwei Tao:** Supervision. **Xianghui Dong:** Supervision, Resources. **Li Fu:** Supervision. **Yan Wu:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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Abbreviations

2DNMs	Two-dimensional nanomaterials
BP	phosphorus
TMDCs	transition metal dichalcogenides
MOFs	metal-organic frameworks
h-BN	hexagonal boron nitride
PTT	photothermal therapy
PDT	Photodynamic therapy
TGF-β	transforming growth factor-beta
ROS	reactive oxygen species
WS_2	tungsten disulfide
SnS_2	tin sulfide
g-C_3N_4	graphitic carbon nitride
$MoSe_2$	molybdenum selenide
$TaSe_2$	tantalum diselenide
NMP	N-methyl-2-pyrrolidone
GO	graphene oxide
CVD	chemical vapor deposition
NIR	near-infrared
AuNPs	gold nanoparticles
PEG	polyethylene glycol
PVA	polyvinyl alcohol
GMs	graphene materials
RMF	T-rotating magnetic field
ES	electrical stimulation
WSe_2	tungsten diselenide
MRC-5	human embryonic lung cells
HaCat	human immortalized keratinocytes
A549	human non-small cell lung cancer cells
A375	human malignant melanoma cells
Bi_2S_3	bismuth sulfide
Ti_3C_2Tx	titanium carbide
MSC	mesenchymal stem cell
α-SMA	alpha-smooth muscle actin
bFGF	basic fibroblast growth factor
VEGF	vascular endothelial growth factor
MRSA	methicillin-resistant *Staphylococcus aureus*

VRE	vancomycin-resistant *Enterococci*
rGO	reduced graphene oxide
GN	graphitic nitrogen oxide
GCl	graphitic chloride
EVs	extracellular vesicles
AD-MSCs	adipose-derived mesenchymal stem cells
MMPs	matrix metalloproteinases
GelAlg	gelatin-alginate
ADM	acrylamide mannose thioglycolate
G-PDA	graphene-based PDA
G-BA	graphene-based aerogel
ADSCs	adipose-derived mesenchymal stem cells
pEVs	platelet-derived EVs
BPNSs	BP nanosheets
BPNPs	BP nanoparticles
BPQDs	BP quantum dots
Bi_2O_3	bismuth oxide
APBA-g-OCS	3-aminophenylboronic acid-modified oxidized chondroitin sulfate
GOx	glucose oxidase
CeO_2	cerium oxide
4OI	4-octyl itaconate
Hb	hemoglobin
SMHS	self-assembling microsphere hydrogel scaffold
EGCG	epigallocatechin gallate
HF	hydrogen fluoride
AS	asiaticoside
FM-Exo	M2 macrophage-derived exosomes
HA-DA	hyaluronic acid-dopamine
HUVECs	human umbilical vein endothelial cells
NEGS	non-enzymatic glucose sensor
Mo	molybdenum
W	tungsten
Fe	iron
Cu	copper
POD	peroxidase
SOD	superoxide dismutase
CAT	catalase
O_2^-	superoxide
CN	carbon nitride
HhDPCs	human hair papilla cells
BSA	bovine serum albumin

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