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MXene-Based Multifunctional Biomaterials for Advanced Wound Healing: From Bench to Bedside

Faisal Ahmad, Atiya Ahmad, and Shamim Ahmad

508 Brentwood Tower, Eros Garden, Charmwood Village, Faridabad, Haryana, India
drsahmad@email.com

ABSTRACT:

Chronic wounds represent healthcare challenge affecting millions of individuals worldwide. Conventional wound-management approaches in vogue often fall short in achieving timely and effective healing, particularly in cases of non-healing or complex chronic wounds. The emergence of nanotechnology has fortunately introduced a novel series of 2D nanomaterials (2D-NMs) with unique properties that hold seemingly enough promise for revolutionizing chronic wound treatment. This review explores the advancements in 2D-NMs and their potential benefits when compared to conventional treatment modalities for chronic wounds. It covers the principles of chronic wound pathophysiology, the limitations of conventional treatments, and how 2D-NMs can address several of these challenges. Various types of 2D-NMs, including graphene, graphene oxide (GO), transition metal dichalcogenides (TMDs), and others are considered along with their applications in wound healing, infection control, drug delivery, and real-time monitoring. Additionally, this review highlights current research, clinical trials, and the regulatory landscape surrounding 2D-NMs in chronic wound care. Finally, it presents few case studies exhibiting the promise for harnessing the potential of 2D-NMs in improving the quality of life for individuals suffering from chronic wounds.

Indexing Terms : Nano biomedicine, 2D-Nanomaterials, Graphene, Graphene Oxides, Transition Metal Dichalcogenides

1. INTRODUCTION

Chronic wounds represent a significant medical and socio-economic burden that affects millions of individuals worldwide and impose substantial costs on healthcare systems globally. Unlike acute wounds that progress through the orderly phases of hemostasis, inflammation, proliferation, and remodeling within a predictable timeframe, chronic wounds fail to follow the normal healing trajectory and persist for extended periods, often lasting months to years. These non-healing wounds impact approximately 2.5% of the total population in developed countries, with prevalence rates reaching up to 8.2 million Medicare beneficiaries in the United States alone. The economic implications are staggering, with annual costs estimated between $28.1 to $96.8 billion in the US Medicare population, while global estimates suggest chronic wound care costs range from $28-31 billion annually [Sen, 2021].

Chronic wounds encompass several distinct categories, each characterized by specific underlying pathophysiological mechanisms. Pressure ulcers (also known as bedsores) result from prolonged mechanical pressure on skin and underlying tissues, predominantly affecting individuals with limited mobility and representing one of the costliest wound types with stage IV ulcers averaging $129,248 per patient. Diabetic foot ulcers constitute another major category, with an annual incidence of 1-4% in diabetic patients and a lifetime occurrence risk of 15-25%. These ulcers are further subdivided into neuropathic (35%), purely ischemic (15%), and neuroischemic (50%) types, with the latter showing the highest prevalence and worst outcomes. Venous leg ulcers, representing 60-80% of all leg ulcerations, affect approximately 0.1-0.3% of the population with a pooled prevalence of 0.32% globally. Arterial ulcers develop secondary to peripheral vascular disease and atherosclerosis, while neuropathic ulcers arise from nerve damage and sensory loss, particularly in advanced diabetes [Khan, et al, 2018].

The pathophysiology of chronic wounds involves complex disruptions in the normal healing cascade, characterized by several key factors that perpetuate the non-healing state. Persistent inflammation represents a hallmark feature, with chronic wounds exhibiting prolonged pro-inflammatory cytokine release and failure to transition to the proliferative phase[Mahmoud, et al, 2022]. Microbial biofilm formation occurs in approximately 60% of chronic wounds compared to only 6% of acute wounds, creating highly resistant bacterial communities that perpetuate infection and inflammation[Ivory, et al, 2025]. Impaired angiogenesis significantly compromises oxygen and nutrient delivery to the wound bed, with defective blood vessel formation being critical for healing progression[Matoori, and Engel, 2025]. Cellular senescence has emerged as an important contributor, with even 15% senescent fibroblasts in the wound microenvironment significantly impeding healing through altered secretory phenotypes and prolonged inflammatory responses[Yang, et al, 2024].Elevated matrix metalloproteinase (MMP) activity leads to excessive extracellular matrix degradation, with chronic wounds showing significantly higher MMP levels that hinder proper tissue remodeling and perpetuate the non-healing state[Lavarti, et al, 2025; Matoori, and Engel, 2025].

Understanding these interconnected pathophysiological mechanisms is essential for developing targeted therapeutic interventions that address the specific molecular and cellular defects underlying chronic wound persistence, ultimately improving patient outcomes and reducing the substantial healthcare burden associated with these challenging conditions.

2. SKIN PHYSIOLOGY

Before moving on to exploring the interventions possible using 2D-NMs in case of chronic wound treatment, it is worth knowing some characteristic features of skin physiology as described in the following.

The skin being the largest organ of the body accounts for approximately 15% of a person's total body weight is essential for performing a wide range of functions, including protection, temperature regulation, and sensory perception. The primary function of the skin is to act as a protective barrier between the body's internal environment and the external world. It serves as a shield against physical trauma, harmful chemicals, pathogens, and harmful UV radiation from the Sun. Skin health can be compromised due to various internal factors, such as local blood flow obstruction, inflammation, or underlying systemic diseases like diabetes affecting wound healing. Skin is also be impaired by external factors, including mechanical injuries like cuts, abrasions, and punctures; chemical corrosion like exposure to corrosive substances; injuries due to electrocution or burns, and thermal injuries including burns from heat or cold. The skin initiates a complex process of wound healing after the damage occurs. This process involves several stages, including haemostasis (blood clotting), inflammation, proliferation (rebuilding tissue), and remodelling (strengthening and refining tissue). Proper skin care and maintenance become essential for preserving its integrity and function. This includes practices such as regular cleansing, moisturizing, sun protection, and avoiding harmful substances or excessive trauma. Impaired skin function or chronic skin conditions can have significant medical and clinical implications. Dermatologists and wound care specialists recommend proper treatment aftercareful diagnosis is necessary for managing the skin disorders and chronic wounds. Effective treatments may include medications, topical therapies, surgical interventions, or specialized wound care products.

In addition to its protective role, the skin can also serve as a diagnostic tool. Changes in skin colour, texture, or the presence of specific lesions can provide valuable insights into an individual's overall health and may help identify underlying medical conditions.Understanding the skin's anatomy, function, and vulnerabilities is crucial for maintaining overall health and well-being. It underscores the importance of proper skincare practices, prompt treatment of skin injuries or conditions, and the need for ongoing medical attention when skin health is compromised due to internal or external factors as reported elsewhere [Jiang, et al, 2022].

There are four phases involved in the natural healing process of the damaged skin. These phases are crucial for restoring the integrity of the skin and ensuring proper wound closure. These phases are haemostasis, proliferation, remodelling, maturity of scar tissues, and final scar formation.Haemostasis is the initial phase that begins immediately after skin damage. Its primary goal is to stop bleeding and prevent excessive blood loss. Platelets rapidly accumulate at the site of injury. When they meet exposed tissue, they become activated and release clotting factors. The activation of platelets leads to the formation of a blood clot or scab, which helps seal the wound and control bleeding. This scab is a temporary protective barrier. The inflammation phase typically begins around 2 to 3 days after the injury. It represents the body's response to clear debris, dead cells, and potential pathogens from the wound. Immune cells, such as macrophages and neutrophils, are recruited to the wound site. They play a crucial role in removing damaged tissue and foreign invaders, like bacteria. Inflammation helps prevent infection by neutralizing pathogens and initiating the healing process.

The proliferation phase follows inflammation and involves the activation of various cell types, including keratinocytes (skin cells), fibroblasts (responsible for collagen production), endothelial cells (forming blood vessels), and more. Keratinocytes migrate to the wound edges, promoting wound closure through re-epithelialization. Fibroblasts contribute to the formation of new collagen and extracellular matrix, which provide strength and structure to the healing tissue. Angiogenesis i.e., formation of new blood vessels, occurs during this phase to improve blood supply to the healing area.The remodelling phase can extend up to 12 months or more after the primary repair is completed. During this time, the processes activated after injury gradually slow down.The regenerated skin tissue matures and becomes more like the surrounding skin. Collagen fibres align, and the healed wound reaches its maximum mechanical strength.Although the scar may appear healed, it often differs in texture and colour from the surrounding skin due to changes in collagen alignment and pigmentation.

Understanding these phases of wound healing is crucial for healthcare providers involved in wound care and for individuals managing their own wound healing. Proper wound care practices, such as keeping the wound clean, protected, and moist, can support these natural healing processes and promote optimal healing outcomes. In some cases, medical interventions may be necessary to facilitate wound closure and minimize scarring as reported in the cited references [Olsson, et al, 2019; Tavakoli, and Klar, 2020; Wilkinson, and Hardman, 2020].

2.1 CONVENTIONAL WOUND TREATMENT

The chronic wounds include pressure ulcers, diabetic foot ulcers, venous ulcers, arterial ulcers, and neuropathic ulcers.Pressure ulcers, also known as bedsores, result from prolonged pressure on the skin and underlying tissues. They commonly occur in individuals with limited mobility, such as those confined to bed or a wheelchair.Diabetic ulcers, on the other hand, develop in individuals with diabetes and often occur on the feet, particularly the soles. Diabetic foot ulcers are a result of nerve damage (neuropathy) and poor blood circulation (peripheral vascular disease).The venous ulcers are typically located on the lower legs and result from chronic venous insufficiency, which causes blood to pool in the lower extremities. This leads to tissue damage and ulceration.The arterial ulcers develop due to insufficient blood supply to the extremities, usually caused by atherosclerosis or other vascular diseases. They often occur on the feet and lower legs.Neuropathic ulcers are associated with nerve damage and loss of sensation, commonly seen in conditions like diabetes. Patients may not feel the injury, and ulcers can develop without their awareness.

The pathophysiology of chronic wounds involves complex interactions among various cellular, molecular, and systemic factors. Chronic wounds deviate from the typical phases of wound healing, which include haemostasis, inflammation, proliferation, and remodelling. In chronic wounds, this process is disrupted, resulting in persistent inflammation and impaired tissue repair. The pathophysiology of chronic wounds include - persistent inflammation, characterized by an excessive release of pro-inflammatory cytokines and an inadequate transition to the proliferative phase. Many

chronic wounds develop microbial biofilms, often exhibit impaired angiogenesis, limiting the delivery of oxygen and nutrients to the wound bed. Cells involved in wound healing, such as fibroblasts and keratinocytes, may undergo senescence, reducing their ability to contribute to tissue repair. Chronic wounds can have elevated levels of MMPs, which degrade the extracellular matrix and hinder proper tissue remodelling.

Better understanding of the pathophysiology of chronic wounds is essential for developing targeted interventions and therapies aimed at promoting healing and addressing the specific challenges associated with these non-healing wounds.

Traditional wound care strategies may involve wound dressing, skin grafting, antibiotics, and tackling the surgical challenges. Traditional wound dressings involving gauze are commonly used but may not be effective for chronic wounds.Skin grafting, and flap transplantation are surgical approaches used to promote wound closure. However, they have limitations, including limited donor sites, donor site damage, and scar formation.Targeted antibiotic therapy is administered when infections are present. However, antibiotic overuse can lead to drug resistance, creating additional challenges.Surgery for chronic wounds can be challenging due to various factors, including limited donor sites, potential donor site damage, scar formation, and the risk of functional and psychosocial complications.

Due to the limitations of traditional methods, there is a pressing need for innovative approaches to treat chronic wounds effectively. These approaches may include advanced wound dressings, regenerative therapies, growth factor-based treatments, and emerging technologies like nanomedicine and tissue engineering.

Refractory chronic wounds, which fail to respond to traditional treatments, require specialized care. This may involve a multidisciplinary team of healthcare providers, including wound care specialists, infectious disease experts, and surgeons, to develop personalized treatment plans.Chronic wounds are a complex medical issue with multiple contributing factors, including diabetes, infections, and chronic inflammation. Treating these wounds is challenging due to their resistance to traditional methods. Addressing chronic wounds effectively requires a combination of innovative approaches, personalized treatment plans, and a multidisciplinary healthcare approach to improve patient outcomes and quality of life as reported in the cited references [Wang, et al, 2018; Olsson, et al, 2019; Mookherjee, et al, 2020; Versey, et al, 2021; Xu, et al, 2021].

2.2 PHYSIOTHERAPY AND WOUND HEALING

Before going to nanobiotechnological interventions in wound healing, it is interesting to examine the beneficial roles played by physiotherapy in managing the wound healing.

Physiotherapy based interventions can play a beneficial role in wound healing, both in terms of accelerating the process and promoting overall health. Salient factors involved in this process are listed below.

Regular exercise has been shown to boost the immune system. A strong immune system is essential for fighting off infections and aiding in the initial stages of wound healing, where the body works to control bleeding and prevent infection. Exercise can help regulate hormonal balance, which is crucial for wound healing. Hormones like cortisol, insulin, and growth factors are involved in various stages of the wound healing process, and exercise can help maintain their proper levels. Exercise is known to reduce stress, and chronic stress can impede the body's ability to heal. By reducing stress, exercise can indirectly support the body's healing processes. Exercise increases blood flow and oxygen delivery to the tissues, which is essential for wound healing. Improved circulation helps transport nutrients and immune cells to the wound site, promoting tissue repair. The formation of new blood vessels (i.e., angiogenesis) is a critical step in wound healing. Exercise can stimulate the production of angiogenic cells, helping to improve vascularization in and around the wound site. Studies have shown that exercise can promote the healing of oral mucosal wounds. This is important for individuals who have undergone oral surgeries or have mouth injuries. Kegel exercises, which target the pelvic floor muscles, can be beneficial for post-partum women in accelerating perineum wound healing and improving muscle tone in the area. Exercise, such as programmed walking and leg exercises, can be effective in accelerating the closure of venous leg ulcers. This is partly due to improved circulation and tissue oxygenation. Exercise can increase the activity of platelets and coagulation factors, which facilitate the clotting process during wound healing.

While exercise can have numerous benefits for wound healing, it should, however, be undertaken with care and under the guidance of healthcare professionals, especially after surgery or in cases of specific medical conditions. The type, intensity, and timing of exercise may vary depending on the individual and the nature of the wound. Exercise can be a valuable complementary intervention to accelerate wound healing by enhancing the immune system, improving circulation, reducing stress, and promoting various physiological processes that aid in tissue repair and regeneration. However, it should be incorporated into a comprehensive healthcare plan and tailored to the specific needs and condition of the patient as discussed elsewhere [Gustirini, et al, 2020; Riyahi, et al, 2021].

Exercise has a significant impact on reducing inflammation, both in systemic and local contexts, particularly in obese and aged individuals. One of the primary ways exercises reduces inflammation in obese individuals is by promoting weight loss and decreasing visceral fat mass. Visceral fat is metabolically active and releases pro-inflammatory substances called adipokines. By reducing the amount of visceral fat, exercise can lower the overall burden of these inflammatory molecules. Toll-like receptors (TLRs) are a part of the immune system and play a role in initiating inflammation in response to pathogens. Exercise has been shown to decrease the expression and activation of TLRs. This reduction in TLR activity can lead to reduced inflammation. Exercise can increase the production of anti-inflammatory cytokines. Cytokines like interleukin-10 (IL-10) and IL-1 receptor antagonist (IL-1ra) counteract the pro-inflammatory effects of cytokines like interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha). This shift in the cytokine balance contributes to reduced inflammation. Regular exercise can thus enhance the body's antioxidant defence and repair systems. Oxidative and nitrosative stress, caused by an imbalance between the production of reactive oxygen and nitrogen species and the body's ability to detoxify them, can lead to inflammation and tissue damages. Exercise helps combat these harmful effects by increasing the production of endogenous antioxidants. Exercise can not only improve the overall function of the immune system but also results in a more efficient response to inflammatory challenges, helping to resolve inflammation more effectively. Exercise can reduce the duration of the inflammatory phase, which is particularly important in aging. Chronic inflammation is associated with many age-related diseases, and exercise can help mitigate this risk by shortening the time inflammation persists.

The anti-inflammatory effects of exercise are not limited to obese or aged individuals. Regular physical activity, regardless of age or weight, can contribute to a reduction in chronic inflammation and the associated health benefits. However, it's crucial to engage in exercise in a safe and appropriate

manner, especially for individuals with underlying health conditions. Consulting with a healthcare provider or a fitness professional can help develop a tailored exercise program that meets individual needs and goals while minimizing the risk of injury as reported elsewhere [Irmawati, et al, 2018; Riyahi, et al, 2021].

The evidence from epidemiological studies and animal experiments underscores the beneficial impact of regular exercise on reducing inflammation and improving the inflammatory response following injuries or wounds. Epidemiological studies have consistently demonstrated that regular exercise is associated with lower levels of inflammatory markers in humans. This suggests that individuals who engage in regular physical activity tend to have reduced chronic inflammation, which is linked to various chronic diseases. In aged mice, regular exercise led to lower levels of inflammatory cytokines compared to sedentary mice. This indicates that exercise has the potential to mitigate age-related inflammation, which is a common issue associated with aging.

In the context of wound healing, exercise had a positive impact on the inflammatory phase. After tooth extraction, the exercise regimen resulted in an increased number of polymorphonuclear neutrophils (PMNs) and macrophages in the wound site. These immune cells play crucial roles in the early stages of inflammation and tissue repair. The greatest effect of exercise on wound healing was observed during the first 1 to 5 days post-wounding, with a particular emphasis on the first day. This suggests that exercise can enhance the body's initial response to injury, especially during the early, inflammatory phase of wound healing.

The findings from these studies align with the broader understanding of exercise's role in inflammation and wound healing. Exercise can enhance the body's immune response, improve circulation, and regulate the release of inflammatory mediators. All these factors contribute to a more efficient and effective inflammatory response, which is crucial for the proper healing of injuries and wounds.

Riyahi, et al, 2021, note that while exercise can be beneficial during the inflammatory phase of wound healing, the type and intensity of exercise should be carefully considered to avoid exacerbating the injury or wound. Individualized exercise plans and guidance from healthcare professionals are valuable in these situations to ensure that exercise is used as a supportive and safe intervention for healing.

Regular exercise reduces C-reactive protein (CRP) levels and suppresses systemic low-grade inflammation. In the wound of mice that exercised, inflammatory cytokines levels were low. Contracted skeletal muscle is an endocrine organ and releases myokines that may mediate the beneficial effects of exercise on wound healing. IL-6 is the first cytokine that raises up to 100-fold in circulation during exercise and inhibits the production of TNF-α and IL-1. The increase of IL-6 is dependent on the duration and intensity of exercise and muscle mass that is involved in the training. IL-6 is an anti-inflammatory and immunosuppressive cytokine. IL-15 is an essential mitochondrial signal that helps in wound closure. Its effect is mediated by reducing the growth arrest factor and increasing keratinocyte and fibroblast growth. The positive effect of exercise on wound healing in the elderly is mediated by circulating IL-15. In aged mice, exercise increases circulatory IL-15, which initiates signal transducer and activator of transcription 3 (STAT3) signalling pathway, reduces growth arrest factor, and increases keratinocyte and fibroblasts. Also, 12 weeks of moderate exercise reduced pro-inflammatory cytokines. There is a reverse relationship between the level of physical activity and inflammation. CRP levels of active individuals are less than their sedentary counterparts. The anti-inflammatory effect of exercise depends on the age, the length and intensity of exercise, and the previous subject's fitness level. It seems that the effect of exercise on inflammation depends on its length and intensity, because they are important factors in the regulation of pro-inflammatory molecules concentration [Wong, et al, 2018; Riyahi, et al, 2021].

Experimental observations gathered from animal studies highlight the role of moderate aerobic exercise in reducing oxidative stress and enhancing antioxidant defences, which can have a positive impact on wound healing and overall health. Moderate aerobic exercise has been shown to reduce oxidative stress in the body. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS), often referred to as free radicals, and the body's ability to neutralize them with antioxidants. Chronic oxidative stress can lead to cellular damage and inflammation.Exercise stimulates the production of ROS, which, in controlled amounts, can support processes like vascular growth and tissue vascularization. However, excessive ROS production can lead to inflammation, which, in turn, stimulates angiogenesis. To counteract this, exercise also increases the activity of antioxidant enzymes like catalase, glutathione peroxidase, and superoxide dismutase that help neutralize ROS and prevent oxidative damage.Diabetic and aged individuals often face challenges in wound healing due to overproduction of ROS, which can result in delayed healing. Regular exercise has been demonstrated to be effective in these populations by enhancing antioxidant enzyme activities, thereby reducing oxidative stress, and promoting more efficient wound healing.In rats, one year of training led to increased levels of glutathione peroxidase and superoxide dismutase. This suggests that exercise can have a long-term impact on antioxidant defences.Regular exercise appears to potentiate the body's systemic antioxidative defence mechanisms. This means that exercise can strengthen the body's ability to counteract oxidative stress not only during physical activity but also during periods of rest.

Regular moderate aerobic exercise plays a crucial role in reducing oxidative stress, increasing antioxidant enzyme activities, and enhancing the body's ability to defend against oxidative damage. This is particularly relevant in conditions such as diabetes and aging, where oxidative stress can impede wound healing and contribute to various health issues. Exercise can be viewed as a preventive and therapeutic strategy to promote overall health and accelerate the healing process. However, it's essential for individuals to engage in exercise safely and adapt their routines to their fitness levels and specific health conditions, under the guidance of healthcare professionals if necessary.

It is noted that the role of oxygen supply and blood circulation is crucial in wound healing and how exercise can positively impact these processes is described below. Oxygen is essential for the synthesis of connective tissue and plays a vital role in the wound healing process. Adequate oxygen supply to the wound tissue is necessary to support the metabolic needs of cells involved in tissue repair. Oxygen also contributes to the prevention of wound infection. Oxygen helps in creating an environment that is less favourable for the growth of harmful microorganisms, as many of these pathogens thrive in low-oxygen conditions. In patients with venous leg ulcers, exercise has been shown to accelerate ulcer healing. This is attributed to the role of calf muscles acting as pumps during walking, which improves blood circulation in the lower limbs. Improved circulation enhances oxygen and nutrient delivery to the wound site, promoting healing. Ankle exercise in individuals with diabetes has a positive effect on lower limb wound healing by increasing blood flow. Diabetes can impair circulation, and exercise helps overcome this by enhancing blood supply to the lower extremities.

Exercise, when initiated shortly after injury, can reduce pro-inflammatory chemokines and tumour necrosis factor-alpha (TNF-α) in the wound of aged mice. This reduction in inflammation may be due to increased oxygen partial pressure and improved blood supply to the wound area.

Polymorphonuclear neutrophils (PMNs) and macrophages, key immune cells involved in wound healing, require oxygen to carry out their functions effectively, such as digesting microorganisms and necrotic tissue. Exercise, by improving tissue oxygenation, can enhance the activities of these immune cells.

Regular low-intensity endurance exercise can accelerate wound healing by promoting vascular regeneration and local blood supply in the wound area. This effect is mediated by an increase in endothelial progenitor cells (EPCs) and vasoactive factors in the peripheral blood. EPCs play a role in forming new blood vessels (angiogenesis), which is essential for wound healing.

Physiotherapy plays a crucial role in wound healing by improving oxygen supply, blood circulation, and immune responses at the wound site. These mechanisms collectively enhance tissue regeneration and accelerate the healing process. The effects of exercise on wound healing can vary depending on factors like exercise intensity, duration, and the type of wound, but overall, exercise is recognized as a valuable adjunctive treatment to support the body's natural healing processes as reported elsewhere [Riyahi, et al, 2021].

In an example of tooth extraction moderate exercise after three days was found significantly increasing the VEGF expression. Regular exercise increases adrenaline, which stimulate the expression of VEGF in macrophages. VEGF and nitric oxide (NO) are necessary for angiogenesis. Four weeks of endurance training can increase capillary network. Furthermore, exercise increases NO production that is upstream of VEGF as reported elsewhere [Irmawati, et al, 2018].

The importance of exercise intensity in the context of wound healing and suggests that moderate-intensity training may be more favourable than high-intensity or strenuous-intensity exercise. Several studies have examined the impact of different exercise intensities on wound healing. The consensus from these studies suggests that moderate-intensity training is associated with better wound closure compared to high-intensity and strenuous-intensity exercise. Moderate-intensity exercise appears to be the most effective type of exercise for promoting wound healing in diabetic patients. This underscores the importance of tailoring exercise regimens to specific patient populations and medical conditions. Regular moderate-intensity exercise is associated with the activation of signalling pathways that produce anti-inflammatory and antioxidant responses. These responses can create a favourable environment for wound healing by reducing inflammation and oxidative stress.

Strenuous exercise, on the other hand, can lead to inflammatory reactions due to the overproduction of free radicals. This can result in increased levels of pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in the bloodstream. These cytokines can attract inflammatory cells to the wound bed, potentially delaying the healing process. Polymorphonuclear neutrophils (PMNs) and macrophages are key indicators of wound healing. Studies have shown that aerobic exercises, including moderate-intensity aerobic exercise, can lead to a higher number of PMNs and macrophages in the wound area compared to anaerobic exercises or sedentary behaviour. Both aerobic and anaerobic exercises can speed up wound healing, but aerobic exercise appears to be more beneficial in this context.

Anaerobic exercises may increase the production of reactive oxygen species (ROS) in the wound bed. Excessive ROS production can disrupt the healing process, which could explain why aerobic exercise is more conducive to wound healing compared to anaerobic exercise.

Moderate-intensity exercise is generally associated with better wound closure and a more favourable anti-inflammatory and antioxidant response. Strenuous exercise, on the other hand, can lead to increased inflammation and oxidative stress, potentially hindering the healing process. The choice of exercise intensity should be tailored to individual needs and medical conditions, and it's essential to consult with healthcare professionals for guidance on the most appropriate exercise regimen for specific wound healing goals as reported in the cited literature [Oki, and Amalia, 2020; Amatriain-Fernandez, et al, 2020].

A short-term treadmill exercise (three days before and five days after wounding) had no positive effects on the speed of wound healing in lean rats, but it accelerated wound healing in obese ones. They concluded that the positive effects of exercise depend on the inhibition of the expression of pro-inflammatory cytokines such as IL-1 and TNF-α. Emery et al. showed that three months of moderate-intensity aerobic exercise accelerated wound healing in older adults. However, short-term exercise had no positive effect on wound healing [Riyahi, et al, 2021].Wound healing typically progresses through four phases of haemostasis, inflammation, proliferation, and remodelling. Disruptions in any of these phases can lead to delayed wound healing. Conditions such as aging, obesity, stress, and diabetes can lead to chronic low-level inflammation and increased oxidative stress. This chronic inflammation can extend the duration of the inflammatory phase of wound healing, impairing skin regeneration. Substances like honey and green tea, known for their anti-inflammatory properties, can help reduce inflammation and contribute to the shortening of the wound healing process. Regular moderate-intensity physiotherapy has well-documented anti-inflammatory effects. It enhances the antioxidative system, increases the levels of anti-inflammatory cytokines such as IL-6, inhibits the production of inflammatory cytokines, and reduces resting cortisol levels. These effects collectively contribute to a less inflammatory wound environment. Physiotherapy supplemented treatment promotes angiogenesis and increases local blood flow to the wound site. This is critical for supplying oxygen and nutrients necessary for tissue repair and preventing infection. Improved circulation also supports the synthesis of connective tissue. Physiotherapy potentiates collagen turnover in connective tissue, which can lead to stronger and more resilient scars.

It appears that regular, sustained moderate-intensity physiotherapy is more effective in accelerating the wound healing process compared to short-term or sporadic exercise. Strenuous exercise can lead to an inflammatory reaction that increases the presence of inflammatory cells in the wound bed, potentially delaying healing. It is essential to strike a balance in exercise intensity to optimize wound healing. Moderate-intensity physiotherapy is described as a low-cost intervention that can be beneficial in the treatment of impaired and chronic wounds. It can be recommended as complementary medicine in clinical practice to help accelerate wound healing. Regular moderate-intensity exercise offers a multifaceted approach to wound healing by addressing inflammation, improving blood flow, supporting tissue repair, and enhancing the overall healing process. It can be a valuable adjunctive treatment for individuals with impaired or chronic wounds, but it's important to tailor exercise regimens to individual needs and consider exercise intensity to achieve the best outcomes. Consultation with healthcare professionals is advisable, especially in clinical settings, to incorporate exercise safely and effectively into wound healing protocols.

3. NANOBIOTECHNOLOGICAL INTERVENTIONS

Chronic wound healing is a complex and multifaceted process that can be influenced by various factors, including the use of advanced nanobiotechnological materials like 2D nanomaterials (2D-NMs). 2D-NMs refer to lamellar structures, such as graphene and transition metal dichalcogenides (TMDs) like molybdenum disulphide (MoS2) and tungsten disulphide (WS2). These materials have garnered special interest in the field of wound healing due to their unique properties and potential applications. Characteristic features of 2D-NMs that are pertinent to chronic wound healing include antimicrobial properties, and cell proliferation as well as migration, as discussed below.

The antimicrobial properties of graphene oxide (GO) are found playing a crucial role in managing chronic wounds. Chronic wounds are vulnerable to microbial infections, primarily caused by bacteria (e.g., Staphylococcus aureus) and fungi (e.g., Candida albicans). These infections can prolong inflammation, delay tissue repair, and even lead to more severe complications. GO possesses strong antimicrobial properties, which means it can effectively inhibit the growth and proliferation of these pathogens. This helps create a microbial-free or controlled environment within the wound, supporting the healing process.

Moreover, 2D-NMs can disrupt biofilm formations by physically damaging the biofilm matrix and directly killing the embedded microorganisms. This action can make the infections more susceptible to conventional treatments. One of the advantages of using 2D-NMs as antimicrobial agents is that they may not lead to the development of antibiotic resistance, a growing concern in healthcare. Unlike antibiotics, which bacteria can adapt to over time, the mode of action of 2D-NMs is often less prone to resistance development, making them valuable in combating persistent wound infections. 2D-NMs can be engineered to release antimicrobial agents gradually. This controlled release ensures a sustained antimicrobial effect over an extended period, which is particularly useful in chronic wounds where frequent dressing changes may not be practical or desirable.

While GO has strong antimicrobial properties, its cytotoxicity to mammalian cells can be controlled by optimizing its size, surface functionalization, and concentration. This allows for the selective targeting of pathogens while minimizing harm to healthy host cells. By effectively managing microbial infections, antimicrobial 2D-NMs create a more conducive environment for the natural wound healing processes to occur. This includes reducing inflammation, promoting cell proliferation, and supporting tissue regeneration.It is worth noting that the use of 2D-NMs in wound healing should be approached with caution and carefully evaluated for safety. Dosage, application methods, and potential long-term effects on the wound and surrounding tissues should be thoroughly studied. Additionally, 2D-NMs should ideally be part of a comprehensive wound care plan that considers other factors, such as proper wound cleansing, debridement, and patient-specific factors.

2D-NMs have potential to promote cell proliferation and migration, which are essential processes in wound healing. Fibroblasts are key players in wound healing as they are responsible for producing collagen and other extracellular matrix (ECM) components. Graphene and graphene-based materials have been found to stimulate the activation and proliferation of fibroblasts. This enhanced fibroblast activity can lead to the formation of granulation tissue, which is crucial for wound closure. Keratinocytes are the predominant cell type in the epidermis and play a vital role in re-epithelialization, the process of restoring the protective outer layer of the skin. Some 2D-NMs can facilitate the migration of keratinocytes across the wound bed, allowing for the rapid closure of the wound. This is particularly important in chronic wounds where the normal healing process may be impaired.

Angiogenesis i.e., formation of new blood vessels, is critical for delivering oxygen and nutrients to the wound site. Some 2D-NMs promote angiogenesis by stimulating endothelial cell proliferation and migration. This improved vascularization accelerates the healing process by ensuring an adequate blood supply to the wound area. The interaction of 2D-NMs with ECM components, such as collagen and fibronectin, influences their organization and cross-linking. This can lead to a more favourable ECM microenvironment that supports cell migration and tissue regeneration. Some species can sequester or deliver growth factors involved in wound healing, such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β). By controlling the release of these growth factors, 2D-NMs can regulate cell proliferation and migration in a controlled and targeted manner. 2D-NMs with anti-inflammatory properties can help mitigate this inflammation, creating a more conducive environment for cell proliferation and migration.It's important to note that the effects of 2D-NMs on cell proliferation and migration can vary depending on factors such as the type of nanomaterial, its surface functionalization, and its concentration. Additionally, the safety and biocompatibility of these materials need to be thoroughly assessed before clinical application.

The particular ability of 2D-NMs to enhance cell proliferation and migration makes them promising candidates for developing advanced wound healing therapies and materials, especially in cases of chronic wounds where these processes are often impaired. However, further research and clinical trials are needed to fully understand their potential benefits and risks.

Chronic wounds are often characterized by prolonged and dysregulated inflammation, which can hinder the healing process.2D-NMs can interact with immune cells and cytokines at the wound site. Some species like GO and transition metal dichalcogenides (TMDs), have been shown to modulate the immune response by reducing the release of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines. This rebalancing of the immune response can help resolve chronic inflammation.2D-NMs can interfere with the signalling pathways involved in inflammation. They may inhibit the activation of specific inflammatory mediators, such as nuclear factor-kappa B (NF-κB), which is a key regulator of pro-inflammatory gene expression. Accordingly, 2D-NMs can reduce the production of inflammatory molecules at the wound site.Chronic inflammation can lead to increased oxidative stress in the wound microenvironment, which can further damage tissues and impede healing. Some 2D-NMs possess antioxidant properties and can help mitigate oxidative stress, thereby promoting a more favourable healing environment.

Chronic wounds often cause significant pain and discomfort, partly due to inflammation. By reducing inflammation, 2D-NMs can contribute to pain relief, which can improve the patient's quality of life during the healing process.Excessive and chronic inflammation can lead to fibrosis, the formation of excessive scar tissue. 2D-NMs that have anti-inflammatory effects may help prevent or reduce fibrosis by promoting a more controlled and balanced healing response.A well-regulated inflammatory response is essential for proper tissue remodelling and regeneration. 2D-NMs that modulate inflammation can create an environment conducive to tissue repair and regeneration.2D-NMs can also be combined with other anti-inflammatory agents or wound dressings to achieve synergistic effects in managing inflammation and promoting wound healing.

It's worth noting that while 2D-NMs hold promise for managing chronic wound inflammation, their safety and efficacy should be carefully evaluated through preclinical and clinical studies. The choice of nanomaterial, its concentration, and the method of application should be optimized to achieve the desired anti-inflammatory effects without causing adverse reactions.

2D-NMs have demonstrated the ability to interact with and influence the extracellular matrix (ECM), which is a critical aspect of tissue regeneration and wound healing. Some 2D-NMs, such as graphene and graphene-based materials, possess unique surface properties that allow them to interact with ECM proteins like collagen, fibronectin, and laminin. These interactions can influence the conformation and binding of these proteins, ultimately affecting ECM organization leading to better cross-linking of ECM proteins. Cross-linking strengthens the ECM structure and helps maintain tissue integrity. Enhanced cross-linking can contribute to a more stable wound environment, preventing excessive tissue breakdown.Collagen is a major component of the ECM that plays a crucial role in tissue repair. Some 2D-NMs have been shown to promote collagen production by fibroblasts, the cells responsible for collagen synthesis. Additionally, they can influence the alignment of collagen fibres, which is essential for proper tissue function and tensile strength. 2D-NMs may modulate the activity of enzymes involved in ECM remodelling, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). Proper regulation of these enzymes is essential for maintaining the balance between ECM synthesis and degradation during wound healing. By influencing ECM organization and composition, 2D-NMs can create a microenvironment that supports tissue regeneration. This is particularly important in chronic wounds where ECM remodelling is often impaired. Abnormal ECM remodelling can lead to excessive scar formation. 2D-NMs that promote proper ECM remodelling can help reduce scar tissue and improve the cosmetic and functional outcomes of wound healing.Some 2D-NMs can serve as carriers for growth factors involved in ECM remodelling and tissue regeneration. These nanomaterials can release growth factors in a controlled manner at the wound site, optimizing their effects on ECM dynamics.The impact on ECM remodelling can vary depending on factors such as the type of nanomaterial, its surface properties, and its concentration. Additionally, the safety and biocompatibility of these materials should be thoroughly assessed to ensure they do not induce adverse effects on ECM components or surrounding tissues. 2D-NMs have the potential to play a significant role in promoting proper ECM remodelling, which is critical for tissue regeneration and wound closure. However, more research and clinical studies are needed to fully explore their applications in wound healing and to determine the most effective strategies for utilizing these nanomaterials in clinical settings.

2D nanomaterials have gained attention as potential carriers for drug delivery in wound healing applications. Their unique properties make them suitable for controlled and targeted release of bioactive molecules, which can enhance therapeutic efficacy in managing chronic wounds.2D nanomaterials typically have a large surface area, allowing them to carry a significant payload of bioactive molecules, including growth factors, antimicrobial agents, anti-inflammatory drugs, and more. This high surface area enables efficient loading of therapeutic compounds onto the nanomaterials. 2D nanomaterials can also be functionalized with specific chemical groups to improve their compatibility with various drugs and biomolecules. Functionalization can also control drug release kinetics, enhancing their suitability for wound healing applications.

One of the key advantages of using 2D nanomaterials for drug delivery is their ability to release therapeutic agents in a controlled and sustained manner. This controlled release profile ensures that the drugs are delivered to the wound site over an extended period, maintaining therapeutic concentrations and optimizing their effectiveness.2D nanomaterials can be engineered to target specific cells or tissues within the wound microenvironment. This kind of targeting can minimize systemic exposure to drugs, reducing potential side effects while maximizing their impact on the wound healing process.Some bioactive molecules are sensitive to degradation. 2D nanomaterials can provide a protective shield to these labile compounds, preserving their stability until they reach the wound site.Controlled drug release from 2D nanomaterials can reduce the frequency of drug administration. This is particularly advantageous for patients with chronic wounds who may benefit from fewer dressing changes or injections.

2D nanomaterials can carry multiple therapeutic agents simultaneously, allowing for combination therapy tailored to the specific needs of the wound. For instance, a wound dressing containing 2D nanomaterials may deliver both antimicrobial agents and growth factors to address infection and promote tissue regeneration concurrently.Controlled drug delivery using 2D nanomaterials can help reduce the development of drug resistance in microbes, a concern in chronic wound infections.Targeted drug delivery at the wound site minimizes the exposure of healthy tissues to therapeutic agents, reducing the risk of systemic toxicity.

While 2D nanomaterials hold significant promise in drug delivery for wound healing, it's crucial to thoroughly evaluate their safety, biocompatibility, and long-term effects through preclinical and clinical studies. Additionally, the choice of nanomaterial, its surface modifications, and the specific therapeutic agents used should be carefully considered to optimize their therapeutic potential and minimize potential risks. Enhancing oxygen and nutrient transport to the wound bed is critical for promoting healing, especially in chronic wounds where compromised blood circulation is a common issue. Some 2D nanomaterials have been engineered to address this challenge.

Chronic wounds often suffer from inadequate oxygen supply, which can impede the healing process. Certain 2D-NMs, like GO and graphene-based materials have been designed to carry and release oxygen efficiently. These materials can serve as oxygen reservoirs, gradually releasing oxygen to the wound bed. This helps create an oxygen-rich environment, which is essential for various cellular processes, including collagen production and antimicrobial activity. Some 2D nanomaterials can improve blood flow to the wound area by dilating blood vessels. Improved vasodilation can increase the delivery of oxygen and nutrients to the wound bed, supporting tissue repair and regeneration. This is particularly valuable in chronic wounds associated with reduced blood circulation. In addition to oxygen, 2D nanomaterials can also improve the availability of essential nutrients, such as glucose and amino acids, at the wound site. This can enhance the energy supply for cells involved in tissue repair and promote the synthesis of ECM components. Chronic wounds are often characterized by areas of hypoxia (oxygen deficiency). 2D nanomaterials that release oxygen can help mitigate hypoxia, reducing the risk of tissue damage and promoting cell viability in the wound bed. 2D nanomaterials can be incorporated into wound dressings or scaffolds designed for chronic wounds. These dressings can act as oxygen and nutrient carriers, continuously delivering essential substances to the wound bed over time.

The controlled release capabilities of 2D nanomaterials allow for a sustained and prolonged delivery of oxygen and nutrients. This is particularly advantageous in chronic wounds, where the healing process may be protracted. 2D-NMs can be customized and engineered to release oxygen and nutrients at a rate that matches the specific needs of the wound, providing a personalized approach to wound care.While the concept of using 2D nanomaterials for oxygen and nutrient delivery in wound healing is promising, more detailed investigations are needed to fully understand their safety,

efficacy, and optimal application methods. Additionally, the choice of nanomaterial, its surface modifications, and the engineering of specific oxygen and nutrient release mechanisms should be carefully tailored to the unique requirements of each wound case.

3.1 NANO DRESSING AND SCAFFOLDS

Biomimetic nano dressings are engineered to mimic the extracellular matrix (ECM), enhancing cell adhesion, proliferation, and tissue repair. Techniques such as electrospinning, self-assembly, lyophilization, polymerization, and crosslinking are commonly used. For example, electrospinning efficiently produces nanofibers resembling ECM, and recent innovations like coaxial electrospinning enable the fabrication of multifunctional, core-shell structured nanofibers. This allows sequential drug release: for diabetic wound dressings, chitosan in the shell provides antimicrobial properties first, followed by copper ions from the core that promote blood vessel formation and healing.

Emerging modalities include microadhesion-guided spinning, inspired by silkworm spinning, which allows rapid and customizable nanofiber fabrication. Self-assembly strategies now enable the generation of ultra-short peptide matrices, closely resembling biological fibers.

Hydrogel matrices, produced via freeze-drying, offer macroporous structures that preserve bioactive molecules and simulate ECM more closely. The use of dynamic crosslinking—such as curcumin-Fe(III) nanomedicine—provides high self-healing efficiency, crucial for dressings subjected to movement and mechanical stress [Wang, et al, 2025].

3D printing is becoming a powerful tool for customized nano dressings, facilitating patient-specific solutions. Commercial successes like Integra®, Matriderm®, and StrataGraft®—engineered to mimic native skin structures—demonstrate the clinical efficacy of such approaches. Further, new patents have been filed for hydrogel dressings that integrate marine-derived UV protectants and recombinant collagen, designed to shield wounds from harmful rays while providing ECM-mimetic support. Advanced “hygromorphic” dressings, inspired by natural pinecone mechanics, conform adaptively to irregular wound contours, enhancing comfort and minimizing trauma during changes [Wang, et al, 2025].

Nano-scaffolds are 3D structures composed of polymeric or inorganic nanofibers. Their main advantage is the close emulation of the natural ECM, providing a conducive environment for cellular attachment and growth. These structures are biodegradable and bioabsorbable, which means they are gradually replaced by newly formed tissue—ideal for tissue regeneration and wound healing [Kola, et al, 2025].

The latest fabrication advances offer the following features.

Selective Laser Sintering (SLS)fuses polymers or ceramics into intricate scaffold structures.

Electrospinning produces nanofibrous frameworks closely matching the ECM in both shape and scale.

Bioprintingutilizes bioinks containing living cells and biomaterials, allowing precise construction of tissue architectures.

Hybrid Techniques are integration of methods like electrospinning and 3D printing further enhances scaffold performance and specialization [Kola, et al, 2025].

Key materials explored include collagen, gelatin, chitosan, alginate, and polylactic acid (PLA), each processed using tailored methods such as freeze-drying, solvent casting, and ionic gelation, to build scaffolds with optimal properties for specific medical uses like bone, cartilage, or skin regeneration [Kola, et al, 2025].

Recently, magneto-responsive hydrogel scaffolds have been devised using hyaluronic acid and carbonyl iron microparticles. These allow functions like externally controlled drug release or tissue stimulation and show high biocompatibility and porosity—which is vital for nutrient exchange and cell proliferation. The magnetic sensitivity enables remote actuation, adding a sophisticated dimension of control over tissue repair processes [Gorgol, et al, 2024].

Multifunctionality and Future Directions

Modern nano dressings and scaffolds integrate not just structural support, but also deliver drugs, growth factors, and can intelligently respond to environmental cues (such as pH or infection). New-age smart dressings monitor wound biomarkers and deliver medication on demand. Developments in 3D printing and “bioinks” now enable the integration of living cells and bioactive substances directly into the scaffolds—paving the way for tailored regenerative implants.

Clinical translation is accelerating, with products addressing chronic wounds, burns, and even facilitating targeted tissue restoration. New patents suggest that wearables, sprays, and UV-protective dressings will soon broaden practical applications, benefiting from the rapid customization possible with 3D printing and advanced material science

The field of nano dressings and scaffolds has moved from basic research into tangible therapies and commercial medical devices, integrating advanced fabrication, material, and smart-response technologies for personalized medicine and rapid wound healing[Gorgol, et al, 2024].

The field of chronic wound management has witnessed transformative advances through the integration of two-dimensional (2D) nanomaterials into wound care systems. Recent developments spanning 2024-2025 demonstrate significant progress in harnessing unique properties of these materials for enhanced therapeutic outcomes.

Graphene and Graphene Oxide (GO) Innovations

Graphene-based materials continue to lead the field with remarkable clinical applications. The Graphene Flagship's smart wound dressing technology has progressed toward commercialization, featuring ultra-flexible graphene patches with integrated wireless electronics that enable real-time monitoring of wound parameters. These dressings not only provide non-invasive monitoring but actively stimulate the healing process, as demonstrated in preclinical studies that are transitioning to human trials [PUB-01].

Recent research has shown that slow-sculpting GO/alginate gels loaded with platelet-rich plasma (PRP) exhibit excellent plasticity for irregularly shaped wounds while maintaining platelet activity and promoting collagen synthesis and angiogenesis. The porous structure and optimal water content of these gels create an ideal microenvironment for chronic wound healing, with good biosafety profiles confirmed through comprehensive organ toxicity studies [Chen, et al, 2024].

MXenes have emerged as game-changing materials in wound dressing applications due to their distinctive combination of biocompatibility, electrical conductivity, and antimicrobial properties. Recent developments include: [Luo, et al, 2025].

Conductive wound dressings deliver electrical signals to promote tissue regeneration and accelerate wound closure through external electrical stimulation [Zarepour, et al, 2024].

MXene-chitosan composite dressings demonstrate efficient antibacterial activity against both Gram-positive and Gram-negative bacteria while maintaining excellent biocompatibility with human dermal fibroblasts [Zarepour, et al, 2024].

Smart sensing capabilities detect changes in pH, temperature, and humidity within the wound environment, enabling personalized wound care approaches. [Zarepour, et al, 2024].

Black Phosphorus (BP) nanosheets show exceptional promise in treating infected wounds through synergistic therapeutic approaches.

RECENT INNOVATIONS

Gallium ion-anchored BP nanosheets (BP/Ga^{3+}) demonstrate superior antibacterial efficacy through combined photothermal therapy (PTT), photodynamic therapy (PDT), and a "Trojan horse mechanism" for disrupting bacterial iron metabolism [Li, et al, 2024].

Self-powered BP-based triboelectric nanogenerators (BP-TENG) accelerate skin wound healing in diabetic models through bioelectrical stimulation. Enhanced stability modifications address BP's traditional limitations while maintaining its therapeutic benefits [Ge, et al, 2024; Li, et al, 2024].

Advances in Transition Metal Dichalcogenides (TMDs) based applications include oxygen-bonded amorphous transition metal dichalcogenides with pH-responsive reactive oxygen biocatalysis. These materials demonstrate - Dual function antimicrobial activity in acidic wound environments and antioxidant effects in neutral conditions; Enhanced M2-phenotype polarization of macrophages, crucial for accelerating wound repair processes; Superior biofilm disruption capabilities while promoting angiogenesis and tissue regeneration [Zhao, et al, 2024].

Safety, Efficacy, and Clinical Translation Considerations

Recent studies have addressed critical safety concerns through comprehensive biocompatibility assessments. Key findings include - Minimal cytotoxicity demonstrated across multiple 2D nanomaterial platforms; and Biodegradability optimization to ensure safe degradation within physiological environments. Concentration-dependent studies establish therapeutic windows that maximize benefits while minimizing adverse reactions [Wang, et al, 2025].Advanced formulation approaches now focus on precision dosing of 2D nanomaterials - Multi-metallic nanocomposite systems that reduce required concentrations while enhancing therapeutic efficacy; Controlled release mechanisms that maintain optimal therapeutic levels throughout the healing process; and Surface functionalization techniques that improve bioactivity at lower concentrations[Wang, et al, 2025].

Clinical Application Methods

Innovation in application methodologies includes [Ashwani, et al, 2023] - Electrospinning techniques for creating nanofibrous hydrogel materials with superior wound coverage; Injectable hydrogel systemsto adapt to irregular wound geometries; and Smart responsive dressings to adjust therapeutic release based on wound conditions.

Collaborative Wound Care Management Integration

AI-Powered Treatment Plan based on integration of artificial intelligence with 2D nanomaterial-based wound care represents a paradigm shift toward precision medicine [NOTE-02]. Real-time wound assessment algorithms optimize nanomaterial concentrations based on healing progression. Predictive modeling systems developed anticipate complications and adjust treatment protocols. Personalized therapy selection has been found feasible based on wound characteristics and patient-specific factors [NOTE-02].

Telehealth and Remote Monitoring

Advanced wound care now incorporates comprehensive remote management systems: [Sen, 2025].Smart sensor integration with 2D nanomaterial dressings enables continuous monitoring of wound healing. Virtual consultation platforms help in adjusting nanomaterial-based treatments remotely

Patient education tools are available today for optimizing self-management with nanomaterial wound care products [NOTE-02].

Multidisciplinary Care Approaches are becoming more in demand in contemporary wound management emphasizing holistic patient care through - Integrated treatment protocols combining 2D nanomaterials with regenerative therapies; Standardized assessment frameworks that guide nanomaterial selection and application; Cost-effectiveness optimization through improved healing outcomes and reduced infection rates[Sen,2025].

Future Directions and Clinical Translation

Regulatory Pathway Progress

The pathway toward clinical implementation includes - Enhanced preclinical study designs addressing long-term safety and efficacy endpoints; Standardized manufacturing processes ensuring consistent quality and performance; and Regulatory guidance development specific to 2D nanomaterial wound care applications[Fadilah, et al, 2022].

Emerging Combination Therapies

Future developments focus on synergistic treatment approaches such as - Cold atmospheric plasma integration with 2D nanomaterial dressings for enhanced antimicrobial effects[Raissi-Dehkordi, et al, 2025]; Bioengineered skin substitute combinations incorporating 2D nanomaterials for improved integration; and Gene therapy platforms utilizing 2D nanomaterials as delivery vehicles [Matoori, and Engel, 2025].

Personalized Medicine Integration

The evolution toward precision wound care includes - Biomarker-guided therapy selection using 2D nanomaterial platforms; Patient-specific nanomaterial formulations based on genetic and metabolic profiles; and Predictive healing models that optimize treatment duration and outcomes [Matoori, and Engel, 2025].

The integration of 2D nanomaterials into chronic wound management represents a revolutionary advancement in healthcare technology. Recent developments demonstrate significant progress in addressing traditional challenges through innovative material design, enhanced safety profiles, optimized application methods, and comprehensive care management approaches. The synergy between advanced nanomaterials and digital health technologies promises to transform wound care from reactive treatment to proactive, personalized therapy that significantly improves patient outcomes while reducing healthcare costs.

As these technologies continue to mature through rigorous clinical validation and regulatory approval processes, the future of chronic wound management appears increasingly promising, with 2D nanomaterials positioned as cornerstone technologies in next-generation wound care solutions.

3.2 PRECLINICAL TRIALS

Animal trials are a crucial step in the evaluation of chronic wound healing formulations before they can be tested in human clinical trials. These trials serve several essential purposes as described below.

Animal models, such as mice, rats, and rabbits, are used to assess the efficacy of wound healing formulations. Researchers can evaluate how well the formulation promotes wound closure, tissue regeneration, and overall healing in a controlled environment. Animal trials help identify any potential adverse effects or toxicity associated with the formulation. Investigators monitor the animals for signs of inflammation, infection, or other unwanted side effects. This information is vital for ensuring the safety of the formulation in human trials. Animal studies can provide insights into the underlying mechanisms of how the formulation works. Researchers can investigate cellular and molecular processes involved in wound healing and assess how the formulation affects these processes. Animal trials help determine the optimal dosage and administration route for the formulation. This information is crucial for designing effective treatment regimens for human patients. Researchers often use different animal models to mimic specific aspects of chronic wounds, such as diabetic ulcers or pressure sores. Comparative studies in various animal models can provide a broader understanding of the formulation's effectiveness across different wound types. Chronic wounds can persist for extended periods, and animal trials allow researchers to assess the long-term effects of the formulation on wound healing and tissue remodelling.

The animal trialshelp in assessing the compatibility of the formulation with the host tissue. This includes evaluating whether the formulation induces an immune response or tissue rejection.

It's important to note that the choice of animal model should be carefully considered to reflect the specific characteristics of the chronic wound being studied. Additionally, ethical guidelines and regulations governing animal research must be followed to ensure humane treatment and minimize harm to the animals involved.

3.3 FUTURE PROSPECTS

There has been growing interest in conducting research into the use of 2D nanomaterials for the development of formulations and therapies for chronic wounds. Since then, there may have been further advancements and perspectives in this field. Here are some key perspectives on 2D nanomaterials-based formulations for chronic wounds up to that point.

2D nanomaterials, such as graphene and graphene-based materials, have demonstrated the potential to enhance various aspects of chronic wound healing in terms of offering the antimicrobial properties, promoting the cell proliferation and migration, presenting anti-inflammatory effects, and exhibiting the ability to modulate extracellular matrix (ECM) remodelling. These properties make them promising candidates for developing advanced wound care formulations.Studies have been conducted to explore ways to tailor 2D nanomaterials for specific wound types and patient needs. This includes functionalizing nanomaterials to carry specific drugs or growth factors that address the unique challenges of chronic wounds, such as impaired angiogenesis or persistent inflammation.

The versatility of 2D nanomaterials allows for the creation of combination therapies. They can carry multiple therapeutic agents simultaneously, offering a multifaceted approach to wound healing. For instance, a formulation may combine antimicrobial agents with growth factors to address infection and promote tissue regeneration.One of the key advantages of 2D nanomaterials is their ability to provide sustained and controlled release of therapeutic agents. This is particularly beneficial in chronic wounds, where prolonged treatment is often necessary. 2D nanomaterials -based formulations can release bioactive molecules over time, ensuring a continuous therapeutic effect.Consequent upon these investigations,2D-NMs can be incorporated into wound dressings or scaffolds, creating advanced wound care materials. These dressings not only deliver therapeutic agents but also provide a physical barrier that protects the wound from external contaminants.

Studies are going on to enhance the biocompatibility and safety profiles of 2D nanomaterials. Surface modifications and engineering techniques aim to reduce potential cytotoxicity and immunogenicity concerns. Progress has been made in conducting preclinical studies using animal models to evaluate the efficacy and safety of 2D nanomaterials-based formulations. These studies are essential for translating promising laboratory findings into clinical applications.

4. NANOBIOTECHNOLOGICAL INTERVENTIONS

Nanobiotechnology indeed holds great promise in the field of wound management and chronic wound treatment. It offers a wide range of possibilities for improving the healing process and addressing some of the limitations of traditional wound care approaches. Nanobiotechnology can facilitate the development of advanced wound dressings and scaffolds that promote tissue regeneration. Nano-sized particles can be incorporated into these materials

to enhance their mechanical properties and create surfaces that support cell adhesion and growth. This can lead to faster and more efficient wound healing.NPs can serve as carriers for drugs, growth factors, and genes involved in the wound healing process. Controlled release systems based on nanotechnology can provide a sustained and localized delivery of therapeutic agents to the wound site, improving their efficacy while reducing side effects.Chronic wounds are often susceptible to infections. Nano-sized antimicrobial agents, such as silver nanoparticles, can be incorporated into wound dressings to prevent and treat infections. These nanoparticles can kill or inhibit the growth of bacteria and other pathogens.Nanobiotechnology can enable the development of systems for delivering cells, such as stem cells or specialized wound-healing cells, directly to the wound site. This approach can promote tissue regeneration and accelerate the healing process.Smart materials and hydrogels created using nanobiotechnology can be designed to respond to specific stimuli. These materials can change their properties in response to factors like pH, temperature, or the presence of infection. This allows for dynamic wound monitoring and tailored treatment.Nanoscale biosensors can be used to monitor the status of chronic wounds in real-time. These sensors can detect biomarkers associated with wound healing, infection, or inflammation, providing valuable information for healthcare providers to adjust treatment plans.Nanotechnology can enable minimally invasive techniques for wound assessment and treatment. For example, nanoparticles or nanoscale imaging agents can be used for non-invasive imaging of wounds, helping healthcare professionals assess the healing progress without the need for frequent dressing changes.

While the potential applications of nanobiotechnology in wound management are promising, it's important to note that this field is still evolving, and more research is needed to ensure the safety and efficacy of these advanced technologies. Additionally, regulatory, and ethical considerations will play a significant role in the adoption of nanobiotechnology-based wound treatments in clinical practice. Nonetheless, the convergence of nanotechnology and biology offers exciting possibilities for improving the care of chronic wounds and enhancing the quality of life for individuals with such conditions as discussed in detail in recent publications [Henriques-Antunes, et al, 2019; Ma, et al, 2019; Wang, et al, 2019; Kargozar, et al, 2020; Liu, et al, 2020; Zheng, et al, 2020; Sun, et al, 2021; Wang, et al, 2021; Panesar, et al, 2022]

4.1 NANOPLATFORMS FOR CHRONIC WOUND HEALING

The role of nanoplatforms in chronic wound healing is discussed here to highlights various factors that need to be considered in designing these nanobiotechnology systems. The wound healing process is influenced by various factors, including gene expression, cell functions (migration, proliferation, differentiation), the microenvironment, infection, ischemia-hypoxia, inflammation, and collagen formation. These factors must be considered when designing nanoplatforms for chronic wound repair.Nano-scaffold systems play a crucial role in chronic wound healing. These scaffolds provide a platform for cell adhesion, migration, and proliferation. They also offer the opportunity for multi-functional modification. Nano-scaffold systems are chosen due to their biocompatibility, angiogenic capacity, and biomimetic properties resembling human skin.

Traditional treatment methods for chronic wounds often involve drug administration. Nanobiotechnology has been utilized as an alternative to develop delivery systems for drugs, genes, and exosomes to address limitations such as low solubility and low bioactivity, thus improving the effectiveness of treatment.Infections can hinder the wound healing process. Silver nanoparticles and other nanoplatform-based anti-infection therapies have been explored to combat microbial infections in chronic wounds.Stem cell therapy, particularly for diabetic wound repair, has shown promise in preclinical studies. However, clinical translation faces challenges, such as the need for appropriate methods for cell encapsulation and transplantation. Nanobiotechnology-based cell-carrying systems can enhance the therapeutic effects of cell therapy.

With the advancement of precision medicine, nanobiotechnology is being used to develop therapeutic systems that can monitor wounds and respond to individual stimuli. For example, ferrihydrite NPs can respond to blue light and are effective in antimicrobial and wound healing treatments. This represents a future direction for nanotechnology in wound care.

Nanobiotechnology holds great potential for improving the treatment of chronic wounds. By considering factors like cell scaffolds, drug delivery, infection control, cell therapy, and precision medicine, researchers aim to develop innovative nanoplatforms that enhance the wound healing process and improve patient outcomes as discussed at length in some referred publications [Wang, et al, 2018; Xi, et al, 2018; Ma, et al, 2019; Cha, et al, 2020; Ermini, and Voliani, 2021; Fahimirad, et al, 2021; Li, et al, 2021; Lopes rocha Correa, et al, 2020; Maleki, et al, 2021; Stanescu, et al, 2021; Xue, et al, 2021; Paneysar, et al, 2022].

4.2 SCAFFOLDS

Scaffold systems play a crucial role in tissue engineering and wound healing applications, providing a structural framework for cells to attach, proliferate, and differentiate. In the context of chronic wound healing, they need to possess specific features to be more effective. Here are some considerations for the design of scaffold systems in chronic wound treatment.

Scaffold materials must be biocompatible and safe for implantation. They should not trigger significant immune responses or inflammation in the body during their use. This is crucial for ensuring that the scaffold does not worsen the wound or cause adverse reactions.The scaffold's physical properties, such as size, dimensions, and mechanical strength, should be suitable for the specific wound type and location. They should provide the necessary support and maintain their integrity under the mechanical stresses experienced in the wound site.An ideal scaffold should have a well-connected porous structure with an appropriate pore size. This allows for the even distribution of cells, drugs, and bioactive molecules throughout the scaffold, facilitating tissue regeneration and wound healing.Scaffold materials should support and enhance the biological activities of cells involved in wound healing, such as fibroblasts, keratinocytes, and endothelial cells. They should promote cell proliferation and migration, which are essential for tissue repair.The scaffold system should create an appropriate wound healing environment. It should be able to absorb excess wound exudate while preventing wound dehydration. This helps to maintain a moist wound environment, which is conducive to healing and reduces the risk of surface necrosis.

Scaffold systems can be classified based on the source and function of the materials used as described below.

Natural Biomaterials based scaffolds are derived from natural sources such as collagen, fibrin, hyaluronic acid, or chitosan. Natural biomaterials often closely mimic the native extracellular matrix and can promote cell attachment and tissue regeneration.Synthetic scaffolds are otherwise engineered materials created in the laboratory. Examples include polymers like poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG). Synthetic

scaffolds offer greater control over material properties and degradation rates.These scaffolds combine natural and synthetic materials to leverage the advantages of both. Composite scaffolds can be tailored to provide specific mechanical, chemical, and biological properties.Decellularized tissues are created by removing cellular components from natural tissues while preserving the extracellular matrix. These scaffolds provide a biologically relevant environment for cell growth and tissue regeneration.

In addition, the smart or responsive scaffolds can change their properties in response to environmental cues. For example, they can release drugs or growth factors in a controlled manner based on the wound's needs.Scaffolds that are designed to degrade over time as the tissue regenerates. This avoids the need for surgical removal of the scaffold once the tissue has healed.The choice of scaffold type depends on factors like the specific wound type, location, patient characteristics, and the desired therapeutic outcome. Researchers continue to explore and develop innovative scaffold systems to address the complex challenges of chronic wound healing effectively as discussed elsewhere as well [Wang, et al, 2019; Li, et al, 2020; Tian, et al, 2021].

4.3 SOURCES OF MATERIALS

When designing scaffold systems for chronic wound healing, selecting the appropriate matrix source is a critical consideration. Here are some sources of nanocomposites commonly used in wound dressing, with a focus on natural and synthetic materials including collagen, fibrin, hyaluronic acid, chitosan, and alginate; besides polyethylene glycol, polymeric nano fibre, silicone-based materials, and nanoparticles.

Collagen is a widely used natural biomaterial in wound dressings. It is a major component of the extracellular matrix (ECM) and provides a biocompatible scaffold for cell attachment and tissue regeneration. Collagen-based dressings can promote wound healing.Fibrin is a natural protein involved in the blood clotting process. Fibrin-based scaffolds can be derived from the patient's own blood or from other sources. These scaffolds are biocompatible and support cell proliferation.Hyaluronic acid is a natural polymer found in the ECM. It has excellent moisture-retaining properties and can be used to create hydrogel-based wound dressings that maintain a moist wound environment.Chitosan is derived from chitin, a natural polymer found in the exoskeleton of crustaceans. Chitosan-based dressings have antimicrobial properties and can promote wound healing.Alginate is extracted from brown seaweed. It forms a gel-like structure when in contact with wound exudate and can be used to create wound dressings that absorb excess fluid while maintaining a moist environment.

PEG-based nano-scaffolds offer stability and tunability in terms of their structural properties. They can be chemically modified to enhance their suitability for wound healing applications. However, the safety of synthetic materials like PEG needs thorough examination to ensure biocompatibility.Synthetic polymers, such as poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), can be electro spun into nanofibrous scaffolds. These scaffolds have a high surface area and can be loaded with bioactive agents for controlled release.Silicone-based dressings can provide a protective barrier over wounds. They are often used for hypertrophic scars and keloids.Synthetic nanoparticles, including silver nanoparticles, zinc oxide nanoparticles, and other metal nanoparticles, can be incorporated into dressings to impart antimicrobial properties and promote wound healing.

It's important to note that both natural and synthetic materials have their advantages and limitations. Natural materials may vary in quality and cannot always be standardized, while synthetic materials offer greater control over properties but require rigorous safety testing. The choice of matrix source should consider factors such as wound type, desired properties of the scaffold, and patient-specific considerations. Additionally, ongoing research is aimed at developing hybrid materials that combine the benefits of both natural and synthetic components to optimize wound healing outcomes.

4.4 FUNCTIONAL MATERIALS

The field of tissue engineering offers a diverse range of materials and scaffolds tailored to specific tissue types and functions. In the context of skin tissue engineering, a variety of scaffold types and materials have been explored to address the unique challenges of wound healing and tissue regeneration. Here's a closer look at some of the scaffold types and materials used in skin tissue engineering:

Natural Polymerslike chitosan, hyaluronic acid, and collagen are often used in skin tissue engineering. They offer good biocompatibility and can support cell attachment and proliferation. These materials closely resemble the native extracellular matrix (ECM) of the skin, making them suitable for promoting wound healing.

Nanocomposite Scaffolds incorporate nanoparticles or nanomaterials into their structure. Examples include nano-bioactive glass and metal nanoparticles (NPs). These materials can enhance the mechanical properties and bioactivity of the scaffolds, potentially speeding up wound healing.

Conducting Polymers such as polyaniline, polypyrrole, and polythiophene have unique electrical conductivity properties. They can be used to create conductive hydrogels that are capable of electrical stimulation. These hydrogels have been explored for promoting wound healing and tissue regeneration, especially in cases of infected chronic wounds.

Acellular Materials such as acellular human amniotic membrane (HAM), provide a natural ECM-like scaffold for cell cultivation. These materials can be used to create skin substitutes by seeding them with cells, such as adipose-derived stromal cells (ASCs), to facilitate tissue regeneration.

Hydrogels are three-dimensional networks of hydrophilic polymers that can retain a large amount of water. They are suitable for maintaining a moist wound environment and can be loaded with bioactive agents for controlled release.

Composite Materials used in scaffolds combine different materials to harness their unique properties. For example, composite scaffolds may incorporate natural polymers with synthetic materials to achieve a balance of biodegradability, mechanical strength, and controlled degradation.

Porous Scaffoldsoffer a high surface area and can promote cell infiltration and nutrient exchange. They are often used in skin tissue engineering to support cell growth and tissue regeneration.Fibrous Scaffolds, typically created using techniques like electrospinning, mimic the fibrous structure of native skin. They provide a scaffold for cell attachment and can be used to create skin-like structures.Microsphere-Based Scaffolds, often made of biodegradable polymers, can be incorporated into scaffolds to provide controlled drug release. They are useful for delivering bioactive agents to the wound site.

Composite Materials for Bone and Corneal Tissue Engineering, in addition to skin tissue engineering, like hydroxyapatite, β-tricalcium phosphate, and whitlockite are being researched for bone tissue engineering. Amniotic membranes are explored for corneal tissue engineering.

The composite scaffolds combining different materials are gaining popularity in tissue engineering. These composite scaffolds can be customized to achieve specific functions and properties, making them versatile tools for accelerating wound healing and tissue regeneration. Researchers continue to innovate in this field to develop multifunctional scaffolds that address the complex needs of tissue repair and regeneration [Palchesko, et al, 2018; Taghiabadi, et al, 2019; Talikowska, et al, 2019; Cui, et al, 2020; Dodero, et al, 2020].

4.5 TARGETED DELIVERY SYSTEMS

Delivery systems in the field of biomedical research and medicine play a crucial role in ensuring the effective and targeted delivery of various therapeutic agents to specific areas within the body. Here's an overview of different delivery systems and their applications:

Drug delivery systems aim to transport pharmaceutical compounds to their intended sites of action while minimizing systemic side effects. These systems can take various forms, includingNanoparticles (NPs) can encapsulate drugs, allowing for controlled release and targeted delivery. This approach is particularly valuable in cancer therapy, where NPs can accumulate in tumours due to the enhanced permeability and retention (EPR) effect.Liposomes are lipid-based vesicles that can encapsulate both hydrophilic and hydrophobic drugs. They offer versatility and can improve drug solubility and stability.Microparticles are larger than nanoparticles but smaller than macroscopic drug carriers. They are used for sustained and localized drug release.Implantable drug delivery devices, such as drug-eluting stents and biodegradable implants, can provide long-term drug release at a specific site.Transdermal patches allow for the controlled release of drugs through the skin, providing a convenient and consistent delivery method.

Cell delivery systems involve the transplantation or injection of cells into the body to replace or repair damaged tissues. These systems are essential in regenerative medicine and cell-based therapies.In cell therapy, cells are cultured and expanded in vitro before being transplanted into patients to restore tissue function. Common examples include hematopoietic stem cell transplantation and islet cell transplantation for diabetes.Stem cells, including embryonic stem cells and induced pluripotent stem cells, can be delivered to treat a wide range of diseases and injuries.Gene delivery involves introducing genetic material (DNA or RNA) into target cells to correct genetic disorders, modulate gene expression, or deliver therapeutic genes.

Modified viruses are used as vectors to deliver therapeutic genes into target cells. Adeno-associated viruses (AAV) and lentiviruses are commonly used viral vectors.

Non-viral gene delivery methods include lipoplexes, polyplexes, and electroporation, which offer safer and more controllable gene transfer.Exosomes, small extracellular vesicles secreted by cells, have gained attention as natural carriers for bioactive molecules, including miRNAs and small molecules. Exosomes can be engineered to enhance their cargo-loading capacity and target-specific cells or tissues.Nanoparticles can be utilized to deliver bioactive molecules like growth factors, proteins, peptides, and miRNAs. Their nanoscale size allows for efficient cellular uptake and controlled release. Nanoparticles can serve as both diagnostic and therapeutic agents. For example, they can carry contrast agents for imaging while simultaneously delivering drugs for therapy.Targeted drug delivery systems utilize ligands or antibodies on the surface of nanoparticles to specifically target and bind to cells or tissues of interest, reducing off-target effects.Research in these areas continues to evolve, with a focus on improving delivery system efficiency, safety, and specificity. These advancements hold promise for more effective treatments and therapies across various medical conditions, including cancer, genetic disorders, and regenerative medicine [Jain, 2020; Wan, et al, 2020].

4.6 DRUG DELIVERY

Drug delivery systems play a critical role in optimizing the therapeutic efficacy of drugs and ensuring their controlled release at specific sites, including wound sites. In the context of wound healing, various drug delivery systems have been developed to address the challenges associated with conventional drug administration methods. Here's a closer look at the use of nanoparticles (NPs) and microcarriers in wound healing drug delivery as described below.

Nano-scaffolds with varying porous structures can be used to load drugs or bioactive molecules. These porous structures provide a breathable environment for wounds and allow for controlled drug release. The slow degradation of nano-scaffolds ensures long-term drug release, maintaining an optimal drug concentration at the wound site.NPs can carry poorly soluble drugs, enhancing their solubility and bioavailability. This is particularly important for drugs that may have limited effectiveness due to poor solubility.By encapsulating drugs within NPs, their half-life can be extended, ensuring a sustained and controlled release of the drug over time.

Nano-scaffolds and NPs can improve drug efficacy by delivering therapeutic agents directly to the wound site. This targeted delivery minimizes systemic exposure and reduces side effects.In one example, polyvinyl alcohol (PVA)/chitosan/gelatine hydrogels were developed to overcome the short half-life of basic fibroblast growth factor (bFGF). These hydrogels supported the continuous delivery of bFGF, significantly accelerating wound healing.

Microcarriers are small, solid or semi-solid carriers that can be loaded with drugs or bioactive molecules. They offer versatility in drug delivery applications.Microcarriers can be engineered to provide controlled and sustained drug release. This is beneficial for maintaining an optimal drug concentration at the wound site over an extended period.Microcarriers are often biocompatible and can be designed to minimize any adverse reactions or inflammation at the wound site.

Some metal ion-based biomaterials, such as copper ions, exhibit promising antimicrobial properties. These materials are well-suited for the management of diabetic wounds, which are prone to infection.Cuprous ions, with their reducing properties, can provide a therapeutic option for diabetic wounds. They not only have antimicrobial effects but also promote angiogenesis, which is essential for wound healing.Cu2S NPs are utilized as photothermal agents due to their infrared absorption and heat generation abilities. They can be incorporated into wound dressings or scaffolds to harness their photothermal effect and angiogenic properties, thereby promoting diabetic wound healing.These materials, which combine the advantages of various components, demonstrate the effectiveness of novel drug delivery systems for the treatment of biological conditions. In the case mentioned, Cu2S NPs and cuprous ions were used to create a bifunctional biomaterial that not only promoted wound healing but also inhibited the growth of skin tumours.

Nanotechnology-based drug delivery systems, including nanoparticles and microcarriers, have the potential to significantly improve wound healing outcomes by enhancing drug solubility, extending drug half-life, and providing controlled and targeted drug release. Additionally, metal ion-based biomaterials, such as copper ions and Cu2S NPs, offer antimicrobial and angiogenic properties that are beneficial for wound management, especially in diabetic wounds. These innovative drug delivery approaches can improve treatment compliance and overall patient outcomes in chronic wound care as discussed in more detail in cited publications [Kim, et al, 2019; Qiao, et al, 2019; Son, et al, 2019; Dong, et al, 2020; Jain, 2020; Zandi, et al, 2021].

4.7 GENE DELIVERY

Gene therapy for diabetic wound management involves introducing specific genes or gene-related molecules into cells to regulate RNA and protein expression, targeting pathways crucial for wound healing, inflammation, and tissue repair. However, a major challenge lies in the rapid degradation and poor pharmacokinetics of gene-related therapeutics like siRNAs, miRNAs, circRNAs, and lncRNAs, which require repeated administration and can cause adverse effects.

NP-based delivery systems have emerged as key facilitators for gene therapy by protecting these molecules from degradation and enhancing targeted delivery to wound sites. Various NPs—lipid-based, polymeric (e.g., chitosan, PEG), hyperbranched cationic polysaccharides, and silicon-based nanoparticles—offer unique mechanisms to improve cellular uptake and transfection efficiency. A critical obstacle addressed by NPs is enhancing endosomal escape, ensuring therapeutic molecules reach their intracellular targets; for example, poly L-arginine coated NPs promote pore formation in endosomal membranes.

Targeted gene silencing using NP delivery, such as siRNAs against MMP9, has shown promise in promoting diabetic wound closure by inhibiting genes that impede healing. Recently, epigenetic targets like the Wilms tumor 1-associated protein (WTAP)-DNA methyltransferase 1 (DNMT1) axis have been identified as pivotal in diabetic wound pathology. Targeting this axis via gene silencing strategies restores endothelial function, enhances angiogenesis, and accelerates healing, providing a promising new therapeutic avenue.

Current gene delivery efforts primarily focus on siRNAs, but ongoing advances aim to include delivery of miRNAs, lncRNAs, and DNA for broader therapeutic scope. Innovations in lipid nanoparticle platforms have enhanced RNA-based therapeutic delivery to the wound microenvironment, improving specificity and reducing off-target effects.

Overall, gene therapy, supported by engineered nanoparticle delivery systems, holds great promise for overcoming the complex molecular challenges in diabetic wound healing, improving treatment efficacy, and reducing chronic wound burden.

Key sources for these advances include studies identifying novel small molecule drugs and gene targets impacting diabetic wound healing [Sarthi, et al, **2024**; Al Madhoun, **2025**; Cui, et al, 2025; Feng, et al, **2025**; Wassif, et al, **2025**].

4.8 EXOSOME DELIVERY

Exosomes are small vesicles secreted by various cell types and have gained significant attention in the field of wound healing and regenerative medicine as discussed in brief.

Exosomes can be derived from various cell types, including adipose stem cells (ADSCs), bone marrow stem cells (BMSCs), and mesenchymal stem cells (MSCs). Each type of cell secretes exosomes with specific markers and functions, making them suitable for different therapeutic purposes.

Despite their different cellular origins, exosomes share common characteristics, including their size (30 to 150 nm) and similar composition. This commonality allows for potential therapeutic applications, but it also means that once exosomes are isolated, their cellular source cannot be determined.Exosomes have shown promise in wound treatment, including diabetic wound healing. Researchers have explored embedding exosomes into scaffolds to achieve sustained release, combining the advantages of both exosomes and the scaffold material. This approach can enhance the therapeutic effects by providing a controlled and localized release of exosomes.

Exosomes can also be modified and engineered for specific therapeutic purposes. These engineered exosomes can serve as nanocarriers for drug delivery and targeted therapy. This approach allows for the customization of exosomes to carry specific payloads, such as growth factors or therapeutic molecules, to further enhance their wound-healing properties.To improve the delivery and stability of exosomes, researchers have developed innovative delivery systems, such as nano dressings based on polysaccharides. These systems offer additional benefits, including UV shielding, self-healing properties, anti-infection capabilities, and thermo-sensitivity, which can be particularly advantageous in the context of chronic wound management.Exosomes have demonstrated their potential to accelerate diabetic wound healing both in preclinical studies and in vitro experiments. The combination of exosomes with advanced delivery systems and scaffolds enhances their therapeutic effectiveness, making them valuable tools in managing chronic wounds.

Exosomes hold great promise for diabetic wound management due to their regenerative properties and their ability to modulate various cellular processes involved in wound healing. The combination of exosomes with nanocarriers, porous nanoparticles, and innovative delivery systems represents a multifaceted approach to improving the treatment of chronic wounds in diabetic patients.

The latest developments in exosome delivery for wound healing applications point to significant progress in the use of exosomes as a regenerative therapy with multiple advantages such as - Exosomes being nanoscale extracellular vesicles (~30-150 nm) carry bioactive molecules (miRNAs, proteins, lipids) to facilitate intercellular communication and multilevel tissue repair. They regulate inflammation, promote angiogenesis, and help extracellular matrix remodeling, critical for wound healing, especially in diabetic wounds.Engineered exosomes are emerging as a more effective strategy. By genetically modifying exosomes or their parent cells, their therapeutic efficacy, targeting capability, and cargo can be optimized. This includes loading with specific drugs or therapeutic molecules, such as miR146a for anti-inflammatory effects or VH298 to activate pathways like HIF-1α that promote angiogenesis.Combining engineered exosomes with biomaterials improves delivery and healing outcomes. Natural biomaterials (chitosan, hyaluronic acid) and synthetic ones form hydrogels or scaffolds that protect exosomes, allow slow release, extend retention time at wound sites, and mimic the extracellular matrix to enhance cell interactions.

Recent innovations include exosome-hydrogel composites with pH-responsive release, cryogel-based dressings releasing oxygen alongside exosomes, and sprayable hydrogels with exosomes and oxygen microspheres that promote rapid full-thickness wound healing.Clinical and preclinical data show mesenchymal stem cell-derived exosomes improve healing rates by 30-50% in diabetic wounds, reduce inflammation, scarring, and accelerate reepithelialization. Advanced dressings that combine exosomes with biomaterials and oxygen-releasing components have shown to stimulate macrophage polarization towards anti-inflammatory phenotypes and enhance vascularization.Researches also highlight personalized therapeutic approaches by screening exosome subgroups with patient-specific miRNA or protein profiles and gene editing to reduce immune rejection risks.

Overall, these advances mark exosome delivery as a revolutionary approach in wound care, translating rapidly from bench research to clinical applications, with engineered exosomes and biomaterial delivery systems driving enhanced precision, efficacy, and healing outcomes. Integration with emerging technologies like optogenetics and AI for clinical decision support is also underway, promising future innovations in this field.

5. ANTIMICROBIAL SYSTEMS

Monitoring and managing infection in the wound healing process are critical to prevent complications and promote successful recovery. Traditional methods of infection prevention and treatment often involve the use of antibiotics, but as you mentioned, these approaches can have limitations, including the risk of antibiotic resistance. Infections in wounds, especially chronic wounds, can significantly impede the healing process and lead to complications such as sepsis. Monitoring and controlling infection are vital aspects of wound care.Prolonged or improper use of antibiotics can contribute to the development of antibiotic-resistant bacteria. This poses a significant public health concern, emphasizing the need for alternative antimicrobial strategies.

Antimicrobial nanobiotechnology offers innovative solutions to combat infection in wound healing. Nano-formulations are designed to have antimicrobial properties that can effectively target and eliminate bacteria, fungi, or other pathogens in the wound environment.Antimicrobial nanobiotechnology includes various formulations, such as nanoparticles, nanocomposites, and nano-coatings. These systems can release antimicrobial agents in a controlled manner, ensuring sustained activity at the wound site.

Silver nanoparticles have been extensively studied for their antimicrobial properties. They exhibit a broad spectrum of antimicrobial activity and can be incorporated into wound dressings, scaffolds, or hydrogels to prevent or treat infections.Antimicrobial nanobiotechnology systems can function through multiple mechanisms, including disrupting bacterial cell membranes, interfering with metabolic processes, or releasing antimicrobial agents directly into the wound environment.

These nanobiotechnology-based systems can serve both preventive and therapeutic roles. They can be used in wound dressings to prevent infection in acute wounds and incorporated into advanced wound care products for the treatment of chronic and infected wounds.

One advantage of antimicrobial nanobiotechnology is the ability to provide localized and targeted delivery of antimicrobial agents to the wound site, minimizing systemic exposure and potential side effects.

Ongoing research is focused on optimizing the effectiveness of antimicrobial nanobiotechnology systems, improving their biocompatibility, and exploring novel antimicrobial agents. Additionally, the development of smart wound dressings with infection-sensing capabilities is an exciting area of research.

Antimicrobial nanobiotechnology-based systems offer promising solutions for infection management in wound healing. These innovative approaches aim to address the challenges of traditional antibiotic therapies and provide effective and controlled antimicrobial activity to support the healing process while minimizing the risk of antibiotic resistance [Simoes, et al, 2018].

5.1 INORGANIC NANO ANTIMICROBIAL MATERIALS

Metal NPs such as silver (Ag-NPs), gold (Au-NPs), and copper (Cu-NPs) are gaining prominence as potent antimicrobial agents and promising alternatives to traditional antibiotics. Their antimicrobial action arises from releasing metal ions or generating reactive oxygen species (ROS) that disrupt microbial cells, effectively killing bacteria and viruses. Unlike conventional antibiotics, metal NPs rarely induce antimicrobial resistance, making them highly valuable in combating drug-resistant infections.

Ag-NPs are widely used in wound care, incorporated into hydrogels, dressings, and microneedle patches to continuously release silver ions, inhibiting a broad spectrum of pathogens including MRSA and Pseudomonas aeruginosa. Innovations include chitosan-silver nanocomposites for burn and chronic wounds, and organic framework-based transdermal patches combining Ag-NPs for diabetic wound infection control. Numerous commercial products—Acticoat™, Allevyn® Ag, Aquacel® Ag Surgical, among others—leverage Ag-NPs for enhanced antimicrobial efficacy and wound healing.

Au-NPs demonstrated bactericidal and bacteriostatic effects via binding bacterial DNA and exhibit photothermal properties that can eradicate pathogens and accelerate wound closure. Recent studies highlight Au nanocomposites' effectiveness against MRSA and other resistant strains.

Cu-NPs, valued for their cost-effectiveness and abundance, are integrated into hydrogels and wound dressings, showing strong antibacterial activity against gram-positive and gram-negative bacteria. Their photothermal capabilities enable localized heating to promote healing and pathogen destruction.

Carbon nanomaterials, including carbon nanofibers and nanotubes, are emerging as versatile platforms for wound repair, often combined with Cu-NPs or Zn-NPs to enhance antibacterial effects and prevent infections.

Together, metal NPs and carbon nanomaterials form the basis of advanced, multifunctional wound care technologies with broad antimicrobial spectra, reduced resistance risk, and potential for affordable, scalable clinical use[Haidari et al., **2021**; Ermimi and Voliani, **2021**].

5.2 ORGANIC NANO ANTIMICROBIAL MATERIALS

Nanotechnology-enhanced natural organic biomaterials, especially chitosan and its derivatives, are making significant advances in wound management by addressing infection and promoting healing.Chitosan, a natural, biocompatible polymer derived from chitin, is widely used to create electrospun nanofibers that can be loaded with antimicrobial agents like curcumin or antibiotics. These nanofibers exhibit strong antibacterial effects against

pathogens such as E. coli and MRSA, inhibit biofilm formation, and promote re-epithelialization, thereby accelerating wound closure and tissue regeneration.

Recent innovations include multifunctional chitosan-based nanofibers incorporating natural compounds (e.g., carvacrol, thymol) and nanomaterials like silver-coated carbon quantum dots, which enhance antimicrobial efficacy, moisture retention, and mechanical stability. Advanced fabrication methods such as layer-by-layer assembly and crosslinking optimize drug release and scaffold properties for tailored wound care [Tripathi, et al, 2025].

Beyond chitosan, metal-organic frameworks (MOFs) and natural antibacterial macromolecules are being integrated into nanocomposites, providing potent antimicrobial activity while avoiding metal-related toxicity concerns.

Chitosan-based hydrogels and polyelectrolyte complexes (PECs) serve as effective drug delivery platforms, enabling controlled release of bioactive agents and supporting cell proliferation, angiogenesis, and immune modulation. Stimuli-responsive versions further improve healing by releasing therapeutics in response to wound environment cues [Shah, et al, 2025].

Challenges remain in standardizing chitosan's molecular characteristics to ensure consistent performance and scaling up production cost-effectively for clinical use. Nonetheless, ongoing research and clinical studies are rapidly advancing chitosan-based nanomaterials from the lab toward practical, multifunctional wound dressings that combine antimicrobial, regenerative, and drug delivery functions—offering promising solutions for managing chronic and complex wounds [Tripathi, et al, 2025].

The chitosan-based organic nanomaterials, enhanced with nanotechnology and natural antimicrobials, provide a versatile, effective, and biocompatible platform for next-generation wound dressings that address infection control, tissue regeneration, and sustained drug delivery with improved clinical potential.

5.3 ANTIBIOFILMS

Biofilms are complex communities of microorganisms that adhere to surfaces, and they are recognized as a major contributing factor to chronic wound infections. Biofilms are commonly associated with chronic wounds, such as diabetic foot ulcers and pressure ulcers. These biofilms are composed of various bacteria, fungi, and other microorganisms that exist within a self-produced extracellular matrix. This matrix protects the microorganisms from the host immune system and antimicrobial agents, making biofilm-related infections challenging to treat.

Biofilms exhibit increased resistance to antibiotics and host defenses compared to planktonic (free-floating) bacteria. This resistance is attributed to the protective matrix, altered gene expression, and reduced metabolic activity of biofilm-associated microorganisms.The clinical management of biofilms in chronic wounds typically involves a combination of strategies. This includes wound cleansing, debridement (removal of necrotic tissue), reshaping wound edges, and the application of appropriate wound dressings. In some cases, topical or systemic antibiotics may be used.The diagnosis and treatment of biofilm-related chronic wounds can be challenging. Biofilms are often hidden beneath the wound's surface, making them difficult to detect through traditional clinical examination. Effective treatment requires strategies that can penetrate the biofilm matrix and target the microorganisms within.

Nanomaterials have shown promise in addressing biofilm-related challenges. Nanoparticles, nanofibers, and nanocarriers can be engineered to deliver antimicrobial agents, enzymes, or other biofilm-disrupting substances directly to the biofilm-embedded microorganisms.Nanomaterials used in biofilm therapy can disrupt biofilm structures, enhance the penetration of antimicrobial agents, and inhibit biofilm formation. Additionally, some nanomaterials possess inherent antimicrobial properties that can target biofilm-associated microorganisms.Researchers continue to explore and develop novel nanomaterial-based therapies for biofilm-related chronic wounds. These therapies aim to improve the effectiveness of wound management and reduce the recurrence of infections.Biofilms are a significant concern in chronic wound management due to their resistance to treatment. The field of nanobiotechnology offers innovative approaches to address biofilm-related challenges, with the potential to improve the diagnosis and treatment of chronic wounds associated with biofilm infections [Haalboom, 2018; Percival, et al, 2019].

Nanomaterials based on metals and metal oxides have shown significant potential in combating wound biofilms and managing infectious wounds. These nanomaterials possess unique properties that enable them to effectively disrupt biofilms and inhibit bacterial growth. Here are key points regarding the use of metal and metal oxide nanoparticles (NPs) in wound care.

Various metals and metal oxides have been explored for their antimicrobial properties in wound management. These materials include silver, copper, gold, titanium, zinc oxide, magnesium oxide, copper oxide, and iron oxide. Each of these materials has demonstrated varying degrees of effectiveness against microbial biofilms.Metal and metal oxide NPs exert their antimicrobial effects through multiple mechanisms. Their small size allows them to penetrate bacterial membranes, leading to membrane disruption and bacterial cell lysis. Additionally, these NPs can interfere with bacterial enzyme activity and disrupt the respiratory chain, further compromising bacterial viability.Among the metal-based NPs, silver NPs and silver oxide NPs have been particularly effective against microbial biofilms. Silver NPs have demonstrated strong antimicrobial properties, making them a popular choice for wound dressings and topical treatments.Researchers have explored various strategies to enhance the antimicrobial activity of metal NPs. Functionalization, such as coating silver NPs with lactoferrin, can improve their efficacy against biofilms. This approach enhances the dual-antimicrobial action of silver, making it more effective in managing infectious wounds.

Metal and metal oxide NPs are often incorporated into wound dressings and hydrogels to create antimicrobial wound care products. These dressings provide sustained release of NPs at the wound site, ensuring continuous antimicrobial activity and biofilm disruption.Dressings containing metal or metal oxide NPs can offer dual antimicrobial action, effectively targeting both planktonic bacteria and biofilms. This dual approach is crucial for managing infectious wounds and preventing biofilm formation.Metal and metal oxide NPs have emerged as promising tools in the fight against wound biofilms and infections. Their ability to disrupt biofilm structures, inhibit bacterial growth, and offer dual antimicrobial action makes them valuable components of advanced wound care strategies. Researchers continue to explore and optimize these nanomaterials for the development of effective wound dressings and treatments [Suleman Ismail Abdalla, et al, 2021]

Nanotechnology has revolutionized wound care by introducing innovative strategies to combat biofilms and treat infectious chronic wounds. Natural antimicrobials like chitosan, enhanced as nanoparticles, adhere effectively to microbial membranes, disrupting biofilms and improving antimicrobial action. Bacterial cellulose combined with chitosan nanoparticles forms hydrogels exhibiting strong anti-biofilm effects.

Photodynamic therapy (PDT) integrated with nanoparticles, such as curcumin-loaded silica NPs, uses light to generate reactive oxygen species that damage biofilms and inhibit bacterial growth, providing a powerful method for disrupting infections. Nanoparticles excel due to their small size and large surface area, enabling them to penetrate bacterial membranes and deliver targeted antimicrobial effects.

Nanotechnology also enhances antibiotic delivery by improving solubility, prolonging drug half-life, and lowering doses, thereby reducing antibiotic resistance risks. Smart nanomaterials can respond to wound environment changes (e.g., pH, temperature) for controlled drug release tailored to infection status.

Recent advances include stimuli-responsive nanofiber scaffolds and hydrogels that combine antimicrobial, anti-inflammatory, and regenerative functions, accelerating healing and minimizing complications. Integrated sensors now enable real-time monitoring of wound conditions, allowing dynamic treatment adjustments.

Overall, nanotechnology offers a versatile, effective toolkit to overcome infection and biofilm challenges, optimizing chronic wound management with personalized, adaptive therapies that promote faster, safer healing [Khan, et al, 2025].

5.4 CELL CARRYING SYSTEM

Cell-based therapy has emerged as a promising approach for the treatment of chronic wounds, leveraging various types of stem cells derived from sources like bone marrow, umbilical cord, adipose tissue, and cutaneous tissue. These stem cells have the potential to differentiate into multiple tissue types and play crucial roles in promoting wound healing. Nanotechnology, particularly the use of nanofibers and nanoparticles, has significantly advanced cell-based therapy for chronic wound treatment.

Nanofibers produced through techniques like electrostatic spinning are widely used as scaffolds for cell-based therapy. For example, polycaprolactone nanofibrous scaffolds combined with bioactive glass nanoparticles (CPB nanofibrous scaffold) have been employed as a cell-carrying system. These scaffolds can carry epithelial progenitor cells (EPCs) and promote wound healing by enhancing various aspects of the healing process, including cell proliferation, granulation tissue formation, re-epithelialization, and cell adhesion. Nanofibers made of materials like chitosan and poly(vinyl alcohol) have been used to carry curcumin and pad-derived mesenchymal stem cells. These nanofibers can release curcumin and improving cell adhesion and proliferation. This combination suggests their potential use in wound dressings to enhance the therapeutic effects of cell-based therapy.

Injectable silk nanofiber hydrogels embedded with bone marrow-derived mesenchymal stem cells (BMSCs) have been developed for wound healing applications. These nanofiber hydrogels can maintain the stemness of BMSCs and effectively deliver them to the target site. They promote wound healing by increasing angiogenesis (blood vessel formation) and collagen deposition, key processes in tissue repair.

Nanocomposites, including nanoparticles and nanofibers, offer advantages such as pro-differentiation, stemness preservation, and immunoregulation. These properties make them valuable carriers for stem cells used in chronic wound therapy.

With the continued development of nanotechnology, researchers are exploring new nanoscale materials and carriers to enhance cell therapy for chronic wounds. These innovations hold the potential to further improve treatment outcomes and tissue regeneration.

While traditional cell therapy often uses carriers at the microscale level, nanotechnology has enabled the development of nanoscale carriers. The nanoscale carriers offer unique advantages, particularly in terms of their interactions with cells and the wound microenvironment.

Nanotechnology has revolutionized cell-based therapy for chronic wound treatment by providing advanced carriers and materials that enhance the therapeutic effects of stem cells. The development of nanofibers, nanoparticles, and nanocomposites continues to expand the possibilities for improving wound healing outcomes in patients with chronic wounds.

Cell-based therapy, especially using stem cells like mesenchymal stem cells (MSCs) from bone marrow, adipose tissue, and umbilical cord, has become a leading approach for chronic wound healing. These cells help regenerate tissue, modulate immune responses, and promote angiogenesis and collagen deposition, all crucial for wound repair [Tong, et al, 2025].

Nanotechnology is driving this field forward. Nanofibrous scaffolds—such as polycaprolactone combined with bioactive glass nanoparticles—efficiently deliver stem cells and support healing by improving proliferation, re-epithelialization, and granulation. Injectable hydrogels with silk nanofibers and bone marrow stem cells enhance angiogenesis and maintain stem cell viability, while chitosan or polyvinyl alcohol nanofibers can carry both curcumin and stem cells for added therapeutic effect [Li, et al, 2022].

New developments include personalized hydrogels and modular carriers that optimize cell therapy outcomes, with improved cell signaling, drug delivery, and immunoregulation. These innovations boost tissue regeneration and reduce chronic wound complications in clinical use [Tong, et al, 2025].

Advanced cell-based therapies—supported by smart nanofiber and hydrogel technologies—now offer better healing, stemness preservation, and tissue repair for patients with persistent wounds [Li, et al, 2022].

5.5 COLLAGEN MONITORING SYSTEM

Collagen is a critical component of the extracellular matrix and plays a vital role in wound healing and tissue regeneration. Nanobiotechnology-based platforms have been utilized to modulate collagen function and promote effective wound healing as highlighted below.

Researchers have loaded N-acetyl cysteine onto GO nanoparticles to facilitate scarless wound healing. GO nanoparticles have been shown to influence collagen metabolism, leading to an improved balance between collagen formation and degradation. This modulation of collagen dynamics contributes to more efficient wound healing, reducing the likelihood of scarring.

Multi-layered scaffolds composed of polyamide nanofibers have been developed to promote wound healing. These scaffolds encourage the uniform arrangement of collagen, which is crucial for maintaining tissue structure and function during the healing process. Proper collagen alignment supports tissue regeneration and minimizes scarring.

Researchers have synthesized a three-dimensional biomatrix incorporating nanosized praseodymium, a rare-earth metal nanoparticle. This biomatrix has demonstrated the ability to promote collagen function by stabilizing native collagen molecules. This modulation of collagen behaviour enhances its

role in tissue repair and regeneration. Collagen is a key player in wound healing, as it provides structural support, promotes cell adhesion and migration, and contributes to tissue remodelling. Effective collagen modulation can optimize its functions, leading to improved wound closure and reduced scarring.

Deploying nanobiotechnology for collagen modulation holds promise for various wound care applications. Scarless wound healing and enhanced tissue regeneration are among the potential benefits of these innovative approaches.

While these nanotechnology-based strategies show promise in preclinical studies, further research is needed to assess their safety and efficacy in clinical settings. The translation of these technologies into practical wound care solutions may offer new possibilities for patients with chronic wounds.

Nanobiotechnology has opened exciting avenues for collagen modulation in wound healing. These approaches aim to optimize collagen's role in tissue repair and regeneration, ultimately improving the outcomes of wound care and reducing the impact of scarring.

Recent innovations in collagen monitoring systems have revolutionized wound healing assessment by enabling noninvasive, real-time tracking of collagen regeneration and tissue oxygenation. The latest approach utilizes spatially averaged phosphorescence lifetime imaging with dual-function Re(I)-diimine probes. These probes selectively bind to collagen fibers while also measuring oxygenation via their unique phosphorescence lifetime shifts. Using advanced imaging techniques like PLIM and FD-PLM, clinicians can simultaneously and quantitatively monitor both cutaneous collagen deposition and tissue oxygenation, offering precise insights into healing progression—especially in chronic or diabetic wounds [Wang, et al, 2025].

This method provides a comprehensive, label-free solution that overcomes limitations of older methods, which required multiple instruments and disturbed the wound during application and removal. The Re(I)-probe system is biocompatible, penetrates deep tissue, and enables repeated, in situ measurements—thus supporting more accurate wound diagnosis and guiding patient-specific treatment strategies [Wang, et al, 2025].

Alongside this, AI-assisted multimodal sensors are also emerging, integrating the detection of collagen and other key wound biomarkers for continuous, ultra-low-power monitoring in real-world clinical practice [Liu, et al, 2025].

The next-generation collagen monitoring now combines phosphorescent lifetime probes and AI-based biosensing for noninvasive, quantitative wound assessment—heralding faster, safer, and more personalized wound management.

5.6 STIMULI RESPONSIVE SYSTEM

Smart wound-healing systems using stimuli-responsive nanobiotechnology represent a major advance in regenerative medicine. Nanoparticles (NPs) and hydrogels are now engineered to respond to wound-specific cues—like changes in pH, glucose, temperature, or enzymes—mimicking natural skin and enhancing tissue repair.

Recent Innovations

- Glucose-responsive systems, such as poly (acrylic acid)-coated Fe_3O_4 NPs with graphene oxide and metal-organic hydrogels loaded with glucose oxidase (GOx), that produce hydrogen peroxide (H_2O_2) locally, offering targeted antimicrobial action and boosting healing for diabetic wounds [Zhang, et al, 2022].
- Photoactive nanofibers made of cellulose acetate, silk fibroin, and other materials, which generate reactive oxygen species (ROS) under light irradiation, efficiently destroy biofilms and accelerate wound closure.
- Injectable or adhesive hydrogels with MnO_2 nanosheets, gold nanoclusters, and quaternary carboxymethyl chitosan enable real-time wound monitoring and responsive drug release—thermally or chemically triggered—to promote tissue regeneration and fight infection [Yang, et al, 2024].

These smart systems replicate key biological and chemical properties of healthy tissue, offering site-specific, adaptive therapies that address chronic and complex wounds. While clinical translation is ongoing, continued research is rapidly moving these technologies towards practical clinical use.

In summary, stimuli-responsive nano-based wound dressings now provide targeted, real-time therapy tailored to the wound microenvironment, representing a transformative leap in wound care [Gao, et al, 2025].

5.7 WOUND MONITORING SYSTEM

Recent innovations in clinical wound care have focused on smart dressings and sensors that enable continuous, real-time monitoring and personalized treatment for chronic and complex wounds.

Artificial intelligence (AI) and sensor-embedded “smart” dressings now provide real-time data on key wound parameters such as temperature, pH, moisture, and exudate production. These dressings feed data to AI systems, which analyse wound healing progress, predict complications, and recommend treatment adjustments, reducing the need for frequent clinic visits—especially important for patients with mobility issues or those in remote areas[Gefen, **2025**].

Nanofiber membranes made from materials like chitosan and collagen continue to play a critical role, promoting cell growth and tissue regeneration. Adding silver nanoparticles increases antimicrobial activity and sensor sensitivity, enabling early detection of infection and biomarker fluctuations.

An exciting innovation is the use of shape-memory polymers and fluorescent gold nanoclusters in wound dressings. These smart materials change structure or emit signals (like fluorescence) in response to environmental cues, indicating when a dressing needs to be changed and helping to monitor infections, including those caused by multidrug-resistant bacteria [Alberts, et al, **2025**].

The latest smart dressings can deliver drugs or antimicrobial agents when triggered by changes such as pH increase—a hallmark of infection. This ensures drug release is both targeted and timely, optimizing wound healing responses and reducing unnecessary dressing changes [Pang, et al, **2023**].

Interdisciplinary collaboration among clinicians, researchers, and industry is driving development, accuracy, and reliability of these technologies. Ongoing clinical validation is crucial for practical and widespread adoption.

In short, cutting-edge smart dressings now combine nanotechnology, biosensors, and AI to dramatically improve wound assessment, patient comfort, and healing outcomes, signaling a new era in wound care management [Gefen, **2025**].

5.7 CLINICAL TRIALS

Clinical trials have increasingly explored diverse nanoplatforms for wound care, including nanocrystalline silver and nano-fat combined with platelet-rich fibrin, particularly for challenging chronic wounds such as diabetic foot ulcers. These studies aim to establish not only safety and biocompatibility but also cost-effectiveness compared to traditional treatments, emphasizing improved wound closure rates and reduced healthcare resource use. The integration of nanomaterials like silver nanoparticles (Ag-NPs) in dressings continues to demonstrate strong antimicrobial effects crucial for infection control, a common obstacle in chronic wounds [Kolimi, et al, 2022]

Recent clinical research highlights an expanded repertoire of nanotherapeutic agents, such as polymeric nanoparticles, liposomes, nanogels, and nanoemulsions, designed for controlled and targeted delivery of drugs, growth factors, and gene modulators directly to the wound site. These approaches optimally manage microbial infection, modulate inflammation, and accelerate tissue regeneration while minimizing systemic toxicity. Trials have successfully incorporated novel nanocarriers loaded with antibiotics, antimicrobial peptides, and bioactive proteins, showing enhanced penetration and sustained release at the wound site, enabling improved healing outcomes [Khan, et al, 2025].

The translational journey of nanobiotechnology wound treatments faces several challenges. Ensuring robust evaluation in clinical trials that meet strict regulatory standards, including ethical approvals and patient consent, is critical. Importantly, trials increasingly emphasize patient-centered outcomes such as pain reduction, quality of life improvements, and lowered complication rates to evaluate real-world impacts comprehensively [Kolimi, et al, 2022]

Collaborative engagement between researchers, clinicians, and healthcare professionals in clinical trial design and execution remains essential to bridge the gap between experimental nanotherapies and practical clinical use. However, participation of medical practitioners in nanotechnology research is often limited, highlighting the need for interdisciplinary cooperation to align therapeutic innovations with clinical needs.

Several recent innovations in burn wound care highlight the transformative potential of nanotechnology beyond chronic wounds. For instance, nanotechnology-enabled drug delivery systems such as polymeric nanoparticles and stimuli-responsive nanomaterials improve therapeutic precision, reduce side effects, and combine diagnosis with treatment capabilities in theranostic platforms. Products like Acticoat®, anAg-NP-infused dressing, have already transitioned from lab to bedside, illustrating real-world application and impact.

Moreover, advanced scaffolds made of nanofibers that mimic natural extracellular matrices and exosome-based therapies derived from stem cells are under clinical investigation for their regenerative capacity. These therapies demonstrate accelerated healing, better vascularization, and reduced infection in acute and chronic wounds [Khan, et al, 2025].

Regulatory compliance and safety monitoring remain cornerstones for advancing nanobiotechnology in wound care. Clinical trials are increasingly tasked with demonstrating long-term safety to address concerns related to nanomaterial accumulation and unforeseen adverse effects. Manufacturing scalability and cost-effectiveness are also critical considerations for the broader adoption of these sophisticated therapies.

The last five years have witnessed pivotal clinical trial advances in nanobiotechnology-based wound healing that have expanded the evidence base, improved understanding of safety profiles, and demonstrated therapeutic benefits. Continued multidisciplinary collaboration, patient-focused trial design, and adherence to regulatory frameworks are crucial to overcoming remaining hurdles and accelerating the translation of these innovative wound treatments for the benefit of patients with chronic and complex wounds.

This evolving clinical landscape confirms that nanobiotechnology holds substantial promise for revolutionizing wound care, making therapeutic regimens more effective, personalized, and responsive to the dynamic needs of patients [Moreira, et al, 2021; Kolimi, et al, 2022]

6. EXAMPLE OF SOME RECENT PRODUCTS

Surgical wound care has seen significant advancements in recent decades, with the introduction of various assistive technologies and techniques to optimize wound healing. These innovations aim to facilitate wound closure, reduce complications, and promote efficient tissue repair and regeneration. Some of the components and technologies used in modern surgical wound care are listed below.

Sutures and Absorbable Products

Traditional sutures, both non-absorbable (e.g., silk, nylon) and absorbable (e.g., Vicryl, Monocryl), are still commonly used to approximate wound edges and secure tissue layers. They provide mechanical support during the initial stages of wound healing. Absorbable sutures are designed to break down gradually within the body, eliminating the need for suture removal. This reduces patient discomfort and minimizes the risk of infection during removal.

For example, primary closures of wounds are facilitated by any combination of staples, sutures including numerous absorbable products namely - MONOCRYL™ (poliglecaprone 25) Suture, Ethicon, Inc. and polydiaxone 910 [Vicryl (K183183) (Ethicon)], VICRYL Polyglactin 910 sterile synthetic absorbable surgical suture, PDS II polydioxanone sterile synthetic absorbable surgical suture, PDS Plus antibacterial polydioxanone sterile synthetic absorbable surgical suture [Dermabond (P960052, K152096 from Ethicon, Inc. and Liquiband (K211878) (AMS)], and adhesive strips from 3M - Steri-Strips (K813265). All of these eliminate dead space and minimize tension on the wound, promoting tissue repair and regeneration [Freedman, et al, 2023].

Cyanoacrylate Adhesives

Cyanoacrylate adhesives like Dermabond and Liquiband are tissue adhesives that bond wound edges together. They create a protective barrier over the wound and are often used for small, superficial lacerations and incisions. These adhesives eliminate the need for sutures in some cases, reducing procedure time and improving patient comfort.

Adhesive Strips

Steri-Strips are adhesive strips applied over the wound to help approximate wound edges. They are particularly useful for small cuts, incisions, and lacerations in areas where sutures may be challenging to apply, such as the face or joints. Steri-Strips provide support during the early stages of wound healing.

Staplers

Surgical staplers are mechanical devices used to quickly and precisely close wounds, particularly in procedures involving large incisions or tissue resections. They are commonly used in abdominal, thoracic, and cardiovascular surgeries.

Negative Pressure Wound Therapy (NPWT)

NPWT involves the use of specialized devices that apply controlled negative pressure to a wound. This technique helps remove excess fluid, reduce edema, improve blood flow, and promote the formation of granulation tissue. NPWT is particularly valuable for complex wounds, such as large surgical incisions, diabetic ulcers, and pressure sores.

Advanced Dressings

Bioactive dressings incorporate substances like growth factors, silver, or honey to promote wound healing and prevent infection. Hydrocolloid and Foam Dressings maintain a moist wound environment, absorb excess exudate, and protect the wound from external contaminants. They are often used in chronic wound care.

Tissue Engineering and Regenerative Medicine

Advanced wound care may involve the use of bioengineered skin substitutes that promote tissue regeneration and wound closure. These substitutes are particularly useful for large or deep wounds.

Infection Control

To minimize the risk of infection, various antimicrobial agents, including silver dressings and antibiotic-impregnated materials, are used in wound care.
These advancements in surgical wound care technologies aim to enhance patient outcomes by minimizing complications, reducing the risk of infection, and accelerating the wound healing process. The choice of wound closure technique and technology depends on factors such as the type and location of the wound, patient characteristics, and the surgeon's preference. Healthcare providers continually assess and adopt new technologies to optimize patient care and surgical outcomes.
Pressure injuries, also known as pressure ulcers or bedsores, are a significant concern in healthcare, particularly for institutionalized patients who may be at higher risk due to immobility. To prevent and manage pressure injuries, various advanced technologies, and strategies, including foam dressings and specialized mattresses, have been developed. Overview of how these technologies are used to mitigate the risk of pressure injuries is given below.

Foam Dressings (e.g., Mepilex)

Foam dressings are designed to provide an optimal environment for wound healing while reducing the risk of pressure injuries. They offer cushioning and protection to areas at risk of pressure ulcers, particularly bony prominences like heels, sacrum, and elbows. Foam dressings help distribute pressure evenly, reduce friction, and absorb excess moisture, preventing skin breakdown. Some foam dressings also have antimicrobial properties to prevent infection in wounds. For example, Mepilex (K123892) (Molnlycke)] are available in this context.

Special Clinical Mattresses

Specialized clinical mattresses are designed to alleviate pressure on vulnerable areas of the body, especially for patients who spend extended periods in bed or are immobile. These mattresses come in various types, including foam, water, and autonomously alternating air mattresses.
Foam mattresses, like Ultrafoam, provide consistent support and pressure relief by distributing body weight evenly. Water mattresses conform to the body's shape, reducing pressure points and promoting comfort.
Alternating Air Mattresses (e.g., Protekt Aire, Aura, Clinitron) feature air cells that alternate pressure to different areas of the body and help prevent prolonged pressure on specific body parts and promote circulation.
In addition to specialized mattresses, proper patient positioning and frequent offloading are essential strategies for preventing pressure injuries. Healthcare providers use cushions, pillows, and adjustable beds to relieve pressure on vulnerable areas. Frequent changes in patient position and regular repositioning are crucial to prevent prolonged pressure on any single body part.

Risk Assessment and Monitoring

Healthcare professionals conduct risk assessments to identify patients at higher risk of pressure injuries. Continuous monitoring of at-risk patients is essential to detect early signs of pressure injuries or changes in skin condition.

Education and Training

Healthcare staff receive training in pressure injury prevention and management, including proper patient handling and use of assistive devices.

Nutritional Support

Adequate nutrition plays a vital role in preventing pressure injuries. Malnourished patients are at higher risk, so nutritional support may be necessary.

Comprehensive Care Plans

Individualized care plans are developed for patients at risk of pressure injuries, addressing their unique needs and risk factors.
Preventing pressure injuries is a complex process that involves a multi-disciplinary approach, including nurses, wound care specialists, and healthcare providers. The use of advanced technologies like foam dressings and specialized mattresses is an integral part of this approach, helping to reduce the incidence and severity of pressure injuries and improve the overall quality of care for institutionalized patients [Afzali Borojeny, et al, 2020].
The management of open chronic wounds involves a multi-faceted approach to promote wound healing and prevent complications. The principles of wound management for chronic wounds typically include the following components. Debridement is the process of removing necrotic tissue, foreign material, and non-viable tissue from the wound. This is essential to create a healthy wound bed conducive to healing. Methods of debridement include sharp excision, mechanical debridement, autolytic debridement, enzymatic debridement, and surgical debridement. The choice of method depends on the wound characteristics and healthcare provider's assessment. Sharp excision involves the precise removal of necrotic tissue using sterile instruments, while mechanical debridement may involve irrigation or wet-to-dry dressings to aid in tissue removal. Enzymatic debridement agents like Santyl are topical medications that contain enzymes to break down dead tissue in the wound.

Moisture Balance

Maintaining an optimal moisture balance in the wound bed is crucial for wound healing. Excessive dryness or excessive moisture can impede the healing process. Moist wound dressings, such as hydrogels, hydrocolloids, and foam dressings, help create a moist environment that supports cell migration, angiogenesis, and tissue repair.

Infection Prevention

Preventing and managing wound infections is critical to successful wound healing. Infections can significantly delay the healing process and lead to complications. In cases of gross contamination or infection, antimicrobial agents may be used. These agents can include topical solutions like sodium hypochlorite (e.g., Vashe Wound Solutions and Dakin's Solution) or silver-impregnated materials (e.g., Mepilex Ag, Contreet, Allevyn Ag).

Medical Optimization of Comorbidities

Many patients with chronic wounds have underlying medical conditions that can impede healing, such as peripheral vascular disease, diabetes, or nicotine use. Managing and optimizing these comorbidities is crucial. For example, controlling blood glucose levels in diabetic patients and addressing smoking cessation can improve wound healing outcomes.

Regular Assessment and Monitoring

Wounds should be regularly assessed and monitored for signs of healing progress or complications. Healthcare providers may use wound assessment tools to document wound characteristics, such as size, depth, and appearance.

Patient Education

Patients should receive education on proper wound care, including dressing changes, hygiene, and signs of infection. Compliance with the prescribed treatment plan is essential for successful wound healing.

Advanced Wound Care Products

Advanced wound care products, such as silver-impregnated dressings and foam dressings, can aid in promoting healing and preventing infection in chronic wounds. These products are designed to create a conducive environment for wound healing.
Overall, the management of open chronic wounds is a comprehensive process that involves the expertise of healthcare providers, patient cooperation, and the use of advanced wound care products and techniques. The goal is to create an optimal wound healing environment, prevent complications, and ultimately achieve wound closure and tissue regeneration [Georgiadis, et al, 2019; Gil, et al, 2021].
In highly exudative wounds, excess moisture can cause maceration of the wound bed and surrounding tissues impeding the healing process. For example, products like Alginates [Kaltostat (K904488) ConvaTec] and Tegaderm Alginate (K973036, 3M, hydrocolloids [DuoDerm (K990368) (ConvaTec), Suprasorb H (K183208) (Lohmann and Rauscher)], and hydrofibers (Aquacel (K982116) (ConvaTec)], and hydrogels [Purilon (K971597) (Coloplast) and Hydrosorb (K041105) (Hartmann)] are available for holding varying degrees of fluid. Negative pressure wound therapy (NPWT) [VAC (K062227) (KCI), Avelle (K180205) (ConvaTec), and Avance (K203369) (Monlycke)] can also provide moisture control in addition to enhancing several other mechanisms that can improve healing of dry or wet wounds, including increased capillary perfusion, wound contraction, evacuation of debris, and micromechanical force.
In refractory chronic wounds over sensitive areas, for example, the pericardium, pleura, or bowel; gliding services for example, over tendons, or surgically created wounds, for example, flap donor sites; biologics or dermal regeneration templates namely - Integra Dermal Regeneration Template (P900033), Integra Lifesciences, and Novosorb (K172140) from PolyNovo, and AlloDerm from LifeCell with or without impregnated growth factors like Primatrix (K153690), Integra Lifesciences, and Helisorb from Medira and even cultured epidermal autografts like Epicel (HDE: BH990200.34) from Vericel have been used.
Several other emerging technologies are now entering the market. These include products for the detection of elevated protease activity as a proxy for impaired wounds such as Woundchek (DEN180014) from Systagenix, epidermal harvest and suspension systems like Cellutome (KCI) and Recell (BP170122) from Avita, targeted pulsed electromagnetic therapy like SofPulse (K070541) from Endonovo, topical wound oxygen therapy such as TWO2 from WoundSource, and ultrasound therapy like UltraMIST (K1407828 from WoundSource. In the complex milieu of healing wounds, several growth factors including epidermal growth factor, fibroblast growth factor, transforming growth factor–β, and platelet-derived growth factor (PDGF)

have been described. Ongoing technology development has yielded growth factors like PDGF supplementation such as Regranex (BLA103691) from Smith + Nephew, as adjuncts for tenacious wounds, including diabetic neuropathic ulcers [Lockmann, et al, 2018].

7. CONCLUSIONS AND PROSPECTS

Nanobiotechnology has significantly advanced the management and treatment of chronic wounds, particularly by enhancing scaffold design and fabrication for accelerated wound healing. Biomimetic nano-scaffolds, produced through techniques such as electrospinning, have shown considerable promise in promoting tissue regeneration and wound closure. Ongoing research is currently focussing on improving the quality and biocompatibility of both natural and synthetic nano-biomaterials used in these scaffolds.

Metal nanoparticles (NPs), especially silver nanoparticles (Ag-NPs), are widely employed in chronic wound therapy for their antimicrobial properties. However, concerns about potential DNA and cellular damage due to metal deposition highlight the need for further investigation. Future research should prioritize developing nanomaterials that effectively prevent infection while minimizing toxicity and heavy metal accumulation. To this end, alternative nanocomposite materials offering infection control without the risks associated with heavy metals are a critical area of focus.

Nanotechnology has also enabled controlled and targeted delivery of therapeutic agents, including drugs, growth factors, and gene-related molecules. While much attention has been given to siRNAs, expanding delivery systems to include other gene regulators like miRNAs and lncRNAs could substantially advance wound management strategies. Ensuring the biocompatibility of nanomaterials remains essential to their safe and effective application, with ongoing efforts aimed at designing materials that elicit minimal adverse reactions.

Looking ahead, the future of nanobiotechnology in chronic wound care is promising, offering the potential for more advanced, multifunctional systems. Innovative nano techniques and materials should continue to be explored to address the complex and dynamic nature of chronic wounds. One exciting avenue is the development of smart dressings equipped with real-time monitoring and stimuli-responsive capabilities, which can dynamically respond to changes in the wound environment such as infection, inflammation, pH shifts, or temperature variations.

To create these effective smart dressings and wound-monitoring systems, researchers must investigate a wide range of nanomaterial properties, including photothermal effects, chemo-dynamic activity, fluorescence, and thermo-sensitivity. Such multifunctional smart systems will better meet the demands of varying wound conditions and improve healing outcomes.

Translating nanobiotechnology-based wound care products from the lab to clinical practice faces several challenges. Robust preclinical testing using animal models that closely mimic human skin and wound healing is imperative, given the limitations of rodent models. Cost and scalability remain significant barriers to commercialization, necessitating optimization of production processes to make these technologies broadly accessible and affordable.

Regulatory approval and safety assessments are crucial. Early engagement with regulatory bodies can streamline the path toward clinical trials and market introduction. Long-term safety and efficacy must be evaluated, including monitoring for any adverse effects stemming from prolonged exposure to nanomaterials.

The advancement of nanobiotechnology benefits from multidisciplinary collaboration across materials science, biology, medicine, and engineering. Such interdisciplinary approaches drive innovation and enhance solution effectiveness. Moreover, user-centric design prioritizing patient comfort and convenience is essential for adoption and adherence in clinical settings.

In summary, while nanobiotechnology offers tremendous potential for improving chronic wound care, successful clinical translation requires addressing scientific, technical, regulatory, and economic challenges. Collaborative, patient-centered efforts are vital to overcome these hurdles and deliver nanobiotechnology-based wound care solutions that significantly benefit patients.

The evolution of this field has paved the way for sophisticated nanomaterials and nanoplatforms capable of not only accelerating wound repair but also improving the overall quality of care for chronic wound patients. Smart dressings incorporating nanotechnology for real-time wound monitoring and responsive behavior provide valuable early detection of complications and optimized healing environments. Such innovations promise to enhance treatment compliance by reducing dressing changes and increasing patient comfort.

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