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Multifunctional Wound Dressings: Nanoparticles loaded Biodegradable Film as a Promising Solution for Wound Management and Infection Control

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Abstract

Chronic wounds, often complicated by bacterial infections, diabetes, and oxidative stress, present a significant healthcare burden globally. Traditional wound care methods frequently fall short in addressing the multifactorial nature of these wounds. Recent advances in nanotechnology have introduced multifunctional nanocomposite wound dressings that offer enhanced therapeutic efficacy. This review focuses on silver-zinc oxide nanoparticles (Ag-ZnONPs) incorporated into gelatin-based polymeric films. Ag-ZnONPs exhibit synergistic wound healing potential, in which, silver nanoparticles (AgNPs) disrupt bacterial membranes and DNA integrity. In contrast, zinc oxide nanoparticles (ZnONPs) promote reactive oxygen species (ROS)-mediated angiogenesis, fibroblast activation, and modulation of inflammation. Gelatin (Gel), a natural, biodegradable polymer, is an ideal carrier for controlled nanoparticle release and mimics the extracellular matrix, enhancing cellular adhesion and proliferation. The review discusses the phases of wound healing, the limitations of conventional dressings, and the role of Ag-ZnONPs loaded Gel film (Ag-ZnONPs@Gel) in overcoming these challenges. Furthermore, it explores current nanoparticle synthesis strategies, especially green synthesis approaches, and their relevance to biomedical safety. Emerging wound assessment technologies, including bioelectrical impedance, imaging, and biomarker analysis, are also addressed. Integrating nanoparticles (NPs) with polymeric matrices represents a promising direction in developing next-generation wound dressings capable of promoting tissue regeneration, controlling infection, and improving patient outcomes in chronic wound care.

Keywords: Silver-zinc oxide nanoparticles, gelatin films, antimicrobial nanocomposites, wound dressings, tissue regeneration, chronic wounds.

Introduction

Skin is our principal barrier for protecting the human body against physical aggressors including mechanical impacts and biological elements. The ability of skin to regenerate depends on two primary elements: the wound's dimensions and the person's overall health condition [1]. Besides shielding the body against outside intruders, the skin operates essential biological processes such as water conservation and body temperature control. The adult body contains skin representing about 15% of total weight while protecting all physical, chemical, and biological agents that come into contact with the body surface. Thermoregulation depends on the skin because it regulates body temperature [2]. The skin features three fundamental structural layers: the epidermis and the dermis, followed by the hypodermis (Figure 1). Any tissue damage from external and internal sources makes up a wound. Medical injuries, along with thermal or chemical exposures, comprise two major wound groups, while chronic ulcerative wounds appear primarily due to existing health problems such as diabetes or pressure ulcers [3]. Society often encounters frequent traumatic events because skin wound regeneration plays a critical role in patient

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treatment. The recent developments in medical science have created various specialized healing procedures that now deliver concentrated treatment solutions for different types of wounds [4].

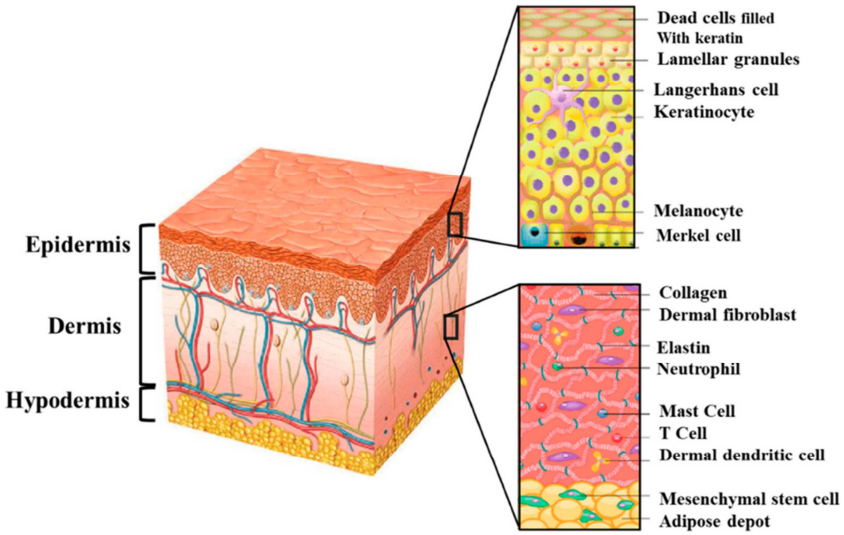

Figure 1: The basic architecture anatomy of normal human skin consists of three primary layers. Each layer plays a specific role in maintaining skin integrity and supporting its various physiological functions [5].

A complex, multi-stage process comprising hemostasis, inflammation, proliferation, and remodeling, wound healing is infections that may seriously hinder healing, resulting in ongoing wounds and lengthening recovery. Various variables, including oxygen availability, hydration, infections, diabetes, inadequate nutrition, obesity, and persistent inflammation, might adversely affect wound healing. Diverse methods, such as topical antimicrobials, antibiotics, and traditional and sophisticated wound dressings, facilitate healing [6,7]. The preparation of nanomaterials based on AgNPs and ZnONPs provides several advantageous roles during wound healing [8,9].

Beyond conventional techniques, advanced wound dressings facilitate healing by integrating bioactive chemicals, nanoparticles (NPs), and intelligent materials. These dressings facilitate expedited wound closure by promoting increased cell proliferation, collagen synthesis, and angiogenesis. They inhibit infection by the application of antimicrobial drugs and the disruption of biofilm. Furthermore, they assist in regulating inflammation, oxidative stress, and moisture levels, facilitating tailored medicine administration for various wound types [10,11]. We focus on the advantage of Ag-ZnONPs loaded Gel film as a wound healing material, owing to its antimicrobial, antioxidant, anti-inflammatory, and regenerative properties, alongside the sustained release of Ag and ZnONPs at the wound site. Ag-ZnONPs loaded Gel film has revolutionized biomedical areas by providing novel options for medication delivery, infection management, wound healing, early illness diagnosis, and tissue engineering. Their extensive surface area, customizable dimensions, and biocompatibility render them ideal for regulated medication delivery and the prevention of bacterial infections by sustained antibacterial action.

Polymeric materials provide regulated release in drug delivery, while NPs such as AgNPs and ZnONPs enhance the antibacterial and photothermal therapy. NPs are essential in oncological therapy and the control of wound infections. Cancer therapies use photothermal and photodynamic treatments administered by NPs and inhibit the wound infections [12,13].

The review explores the potential of silver-zinc oxide NPs loaded gelatin film (Ag-ZnONPs@Gel) as multifunctional wound dressings, emphasizing their biological, antimicrobial, antioxidant, and regenerative properties. It investigated the phases of wound healing, the limitations of conventional dressings, and how Ag-ZnONPs enhance healing by reducing infections and oxidative stress and promoting tissue regeneration. The review highlights the biocompatibility and safety of Ag-ZnONPs@Gel film.

Wound healing process

The body's natural response to tissue damage is wound healing, correcting abnormalities and restoring normal function. Usually, healing results in scar development rather than the complete regeneration of the original tissue. Scar tissue development partly defines the difference between regeneration and wound healing. Wound healing is the study of scar creation and remodeling mechanisms [14]. Wound healing requires immediate closure of the opening and the elimination of pain as well as the creation of scars with optimal cosmetic results [15]. The wound healing process comprises four distinct phases (hemostasis, inflammation, proliferation and remodeling) as illustrated in Figure 2.

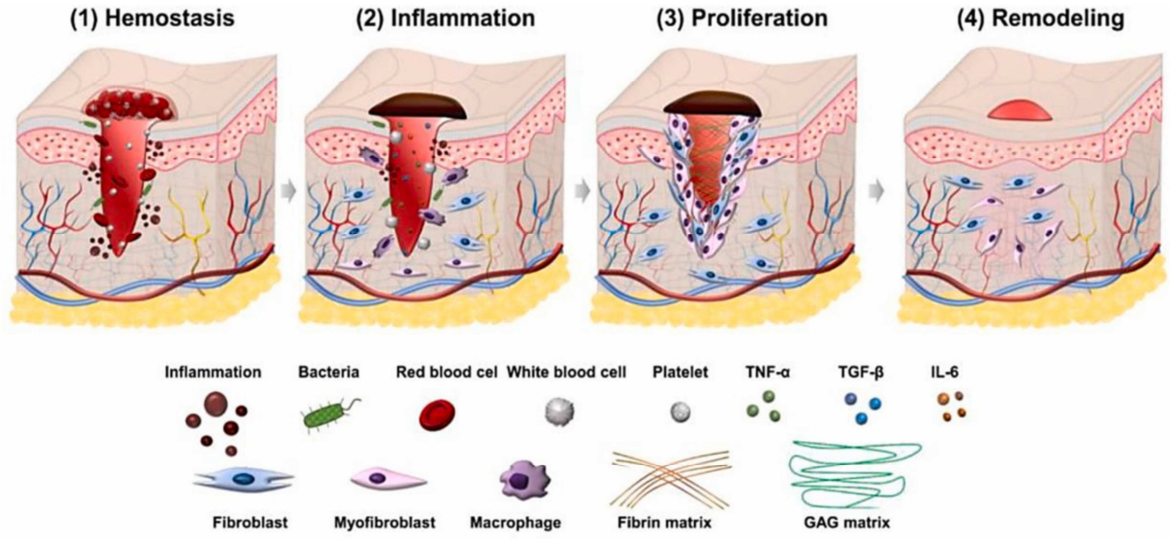

Figure 2: Schematic illustration of four phases in the wound healing process [16]**.**

The healing of wounds commences with hemostasis, in which blood flows out from damaged lymphatic veins to assist in eliminating antigens and bacteria [17]. During this phase, the body activates various clotting cascades, and thrombocytes aggregate around exposed collagen. Simultaneously, platelets induce vasoconstriction to minimize blood loss and form a blood clot that fills the tissue gaps in the injured vessels. This clot, rich in cytokines and growth factors, serves as a temporary matrix and scaffolding for migrating leukocytes, keratinocytes, fibroblasts, and endothelial cells. The clot also acts as a reservoir for growth factors, stabilizing the clot and preventing further bleeding [18].

This mechanism facilitates the activation of coagulation complexes, transforming prothrombin into thrombin. The injured tissue's extracellular matrix (ECM) produces vasoactive chemicals that induce platelet aggregation and fibrin clot formation. This vital stage establishes a framework for migrating and proliferating more cells necessary for healing [19]. Inflammation is the second phase of wound healing; it focuses on debriding the location and preparing it for new tissue formation. Usually lasting 2–5 days after the start of the infection in the wound, neutrophils signal this phase [20]. Essential in phagocytosing bacteria and secreting proteases such as elastase, cathepsin G, and proteinase 3, which help germs be broken down and waste from wounds cleared, are neutrophils. Furthermore, neutrophils produce mediators, including TNF-α, IL-1, and IL-6, to boost the production of VEGF and IL-8, thus facilitating the repair process during wound healing [21] and augmenting the inflammatory response [21].

During the cell proliferation phase of wound healing three vital processes develop namely angiogenesis combined with re-epithelialization along with granulation tissue accumulation. Tissue repair depends significantly on the granulation tissue matrix, including macrophages and fibroblasts. Wound contraction occurs through myofibroblasts' activity, which combines with fibroblast collagen synthesis. This phase breaks into three sections where new blood vessels and connective tissue fill the wound first then the wound edges contract to make the closure tighter before epithelial cells migrate to create wound protection [22]. After injuries, macrophages play roles in controlling inflammation and cell death removal and cell proliferation which results in tissue healing [23].

The fourth phase of wound healing, remodeling, also known as maturation, includes wound contraction, facilitating epithelialization, and scar formation. Fibroblasts infiltrate the wound during the first 3 to 4 days and begin collagen deposition, establishing a matrix essential for tissue integrity [24]. Produced by platelets and macrophages, cytokines and growth factors like PDGF, TGF-β, and FGF boost fibroblast proliferation and migration. TGF-β is crucial for transforming fibroblasts into myofibroblasts, which are needed for wound contraction. Collagen III is gradually supplanted by collagen I, resulting in enhanced the tensile strength and the development of scars [25,26]. This phase primarily includes macrophages, with no involvement from other blood cells or components of the coagulation system [27].

Wound classifications

The structure and function of the skin get disrupted by wounds that develop from physical or chemical or thermal sources of injury. Wounds exist in two distinct healing categories namely acute and chronic wounds. Medical experts report that acute wounds heal fully through 8–12 weeks [28]. The occurrence of such wounds results from mechanical factors like cuts, gunshots, and surgical incisions, along with chemical and burn factors related to radiation exposure and corrosive chemicals, electrical hazards, and thermal exposure. Chronic wounds take longer than 12 weeks to heal since they develop due to repeated tissue damage combined with health conditions such as diabetes or impaired angiogenesis or poor cellular migration. The healing process for chronic wounds could be delayed due to infections and malignancies, poor treatment, and patient-specific causes [29]. Classifying wounds is essential for determining the appropriate course of treatment and managing

complications. Each type of wound, whether acute or chronic, requires a tailored approach, considering the cause, healing time, and tissue involvement [30]. Wounds can be categorized in several ways based on healing progress, cause, nature, and skin integrity.

Acute and chronic wounds

Frequently leaving very small scars, acute wounds are injuries that heal entirely within 8–12 weeks. These include mechanical injuries like abrasions, rips, punctures, cuts, and burns as well as chemical injuries from caustic substances. Acute wounds are commonly seen in everyday life, resulting from cuts, scrapes, surgeries, or trauma, and they heal through the typical phases of hemostasis, inflammation, proliferation, and remodeling. Acute wounds can progress into chronic wounds if they remain stalled in the inflammatory phase, persisting for extended periods—often months or even years—without advancing toward proper healing [31,32].

In contrast, chronic wounds are characterized by skin defects or lesions that persist for more than 6 weeks or frequently recur. These wounds heal slowly and are often aggravated by repeated trauma, underlying physiological issues, immune deficiencies, or persistent infections. Chronic wounds are commonly associated with conditions like diabetes, obesity, pressure ulcers, and age-related vascular diseases **[33]**. In chronic wounds, the inflammatory phase is abnormally prolonged, characterized by sustained neutrophil activity that leads to continuous degradation of ECM components. This degradation further amplifies the release of pro-inflammatory cytokines, perpetuating a cycle of chronic inflammation. As a consequence, these wounds often exhibit excessive collagen deposition, which may result in fibrotic scar formation. Compared to normal wound healing, chronic wounds are distinguished by reduced cellular proliferation, elevated levels of inflammatory cytokines, and heightened protease activity, factors that collectively impair proper tissue repair. The disturbed healing mechanism produces multiple medical issues, including hernias and wound dehiscence alongside infection and adhesions, hypertrophic scarring, and sepsis. The evaluation process of non-healing wounds requires complete assessments to build successful treatment plans. Wound persistence with chronic conditions results from multiple factors, including tissue ischemia, inadequate protein synthesis and bacterial influence, and the wound's inability to fight germs properly and respond to inflammation **[34,35]**. Figure 3 compares the healing processes of normal and chronic wounds. In normal wounds, the healing process proceeds with efficient keratinocyte migration, fibroblast activity, and angiogenesis, which promote tissue regeneration and wound closure.

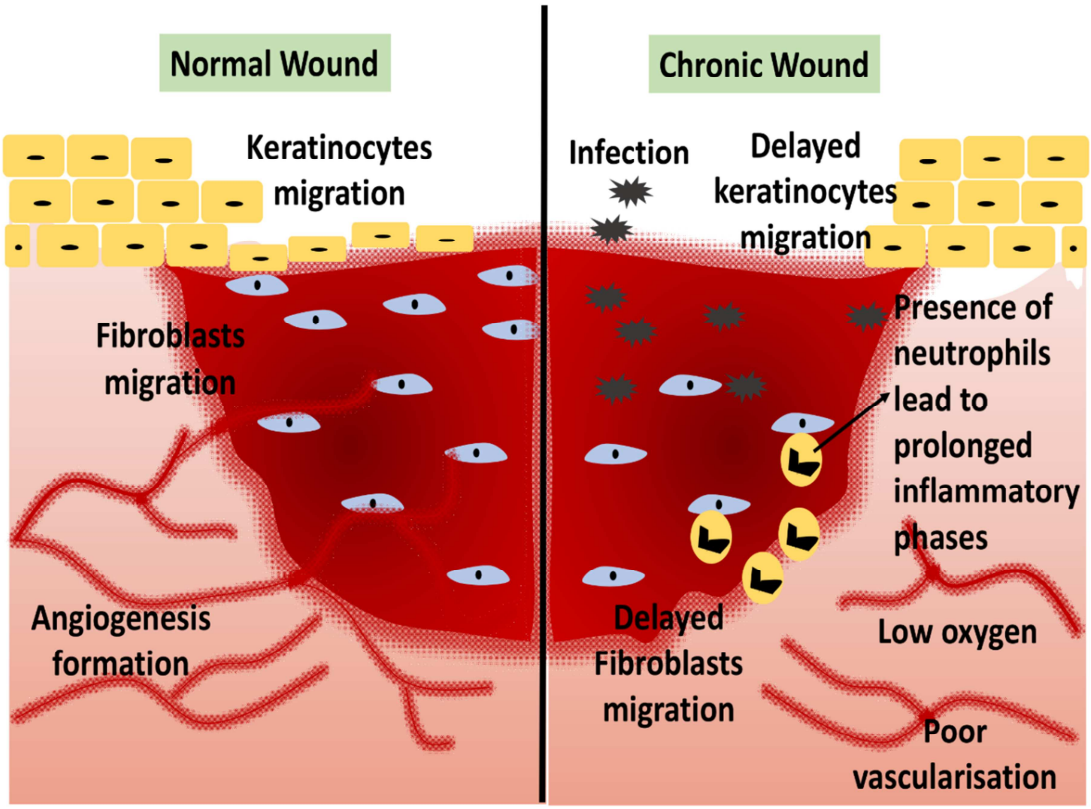

Figure 3: Key differences between normal and chronic wound healing conditions. In a normal wound, the healing process proceeds efficiently, with keratinocytes migrating to cover the wound, fibroblasts contributing to tissue formation, and angiogenesis supporting new blood vessel growth. In contrast, chronic wounds are marked by delayed keratinocyte and fibroblast migration, prolonged inflammation, and the presence of infection [36].

Surgical wounds

Surgical wounds encompass skin lesions resulting from trauma, underlying conditions, or both. These wounds are commonly encountered in acute care settings, with complications such as bleeding and wound dehiscence being frequent concerns. Surgical wounds can be caused intentionally during procedures or occur accidentally [37,38]**.** Disturbance of the skin and subcutaneous tissues sets off the innate immune system, therefore starting the healing process. The nature and degree of the damage determine the method used, sutures, staples, glue, or tape—to seal surgical wounds. Usually, surgical wounds are supposed to heal like acute ones. But infections may hamper healing. Managing surgical wounds requires comprehensive medical care, including pain control, debridement of necrotic tissue, and advanced treatment options like skin grafting and regenerative medicine to promote recovery and tissue restoration. A multidisciplinary approach is essential to accelerate healing and minimize complications [39,40].

Traumatic wounds

Traumatic wounds are injuries caused by external forces or accidents that disrupt the skin's normal structure and underlying tissues [41]. Traumatic wounds can result from a variety of incidents, including falls, motor vehicle accidents, burns, gunshot wounds, or industrial accidents. Traumatic wounds are often classified based on their severity, which may range from superficial abrasions to deep, complex lacerations or puncture wounds. The damage caused by such injuries can extend beyond the skin, affecting muscles, bones, nerves, and internal organs, depending on the nature of the trauma [42].

Effective management of traumatic wounds is essential for preventing complications such as infection, excessive scarring, or impaired function. The treatment of traumatic wounds often includes cleaning the wound, controlling bleeding, and closing the wound through sutures, staples, or other methods. In severe cases, surgical intervention may be necessary to repair deep tissue damage or restore functionality to affected areas. Prompt and appropriate care significantly influences the wound's healing time and the outcome [43].

Diabetic ulcers

More specifically in those with poorly regulated blood sugar levels, diabetic ulcers are a frequent and significant side effect of the condition. Usually affecting the lower extremities, particularly the feet, these ulcers are brought on by a confluence of elements including peripheral neuropathy, inadequate circulation, and compromised immune system. A disease known as peripheral neuropathy, in which nerve damage causes a lack of feeling, raises the likelihood of undetectable injuries, enabling wounds to develop and become worse without quick treatment. Furthermore, impeding the healing process is poor blood circulation resulting from vascular problems in diabetes, which limits the oxygen and nutrition delivery to the afflicted region. Many times, sluggish-to-heal, untreated, or poorly managed diabetic ulcers may cause serious consequences, including infections, gangrene, and, in extreme situations, amputation [44]. A ring-shaped ulcerative lesion was observed on the middle outside region of the right foot bottom (Figure 4). This lesion likely signifies a diabetic foot ulcer, a common consequence of diabetes resulting from compromised circulation and peripheral neuropathy. The ulcer's position and form indicate it may stem from pressure, friction, or an undiscovered injury, which are prevalent in diabetes individuals owing to diminished foot sensitivity. Timely and efficient intervention is crucial to avoid further consequences, including infection or tissue damage.

Regular monitoring and appropriate dressings are essential to prevent infection and promote healing. Advanced wound care techniques, such as debridement, skin grafts, and bioactive agents, may be necessary to accelerate healing in severe cases. Patients with diabetic ulcers often require lifestyle changes, including better glucose management and the use of specialized footwear, to prevent recurrence [45].

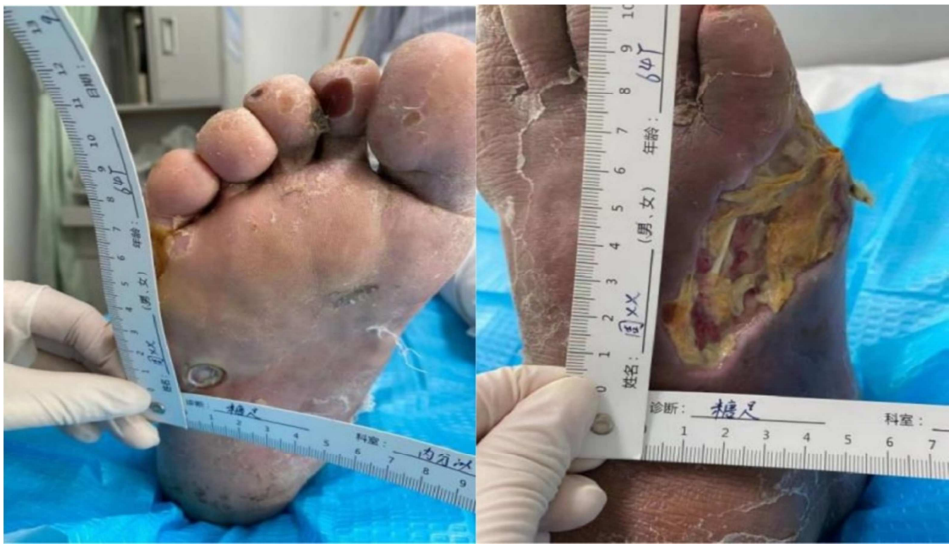

Figure 4: An actual photographic image of a diabetic ulcer (8×6 cm) located on the patient's right foot at the time of admission. The ulcer appears to be a significant wound that likely resulted from underlying diabetic complications such as peripheral neuropathy and poor circulation.

Pressure ulcers

Pressure ulcers, decubitus ulcers, or bedsores, are another challenging type of chronic wound that lacks a universally accepted treatment or prevention standard (Figure 5). These ulcers are a significant concern for patients with limited mobility, often leading to irreversible damage if not properly managed. They develop when sustained pressure restricts blood flow, resulting in tissue damage that can progress from superficial breakdown to deep, necrotic wounds, risking serious complications like infection, osteomyelitis, and even sepsis [46].

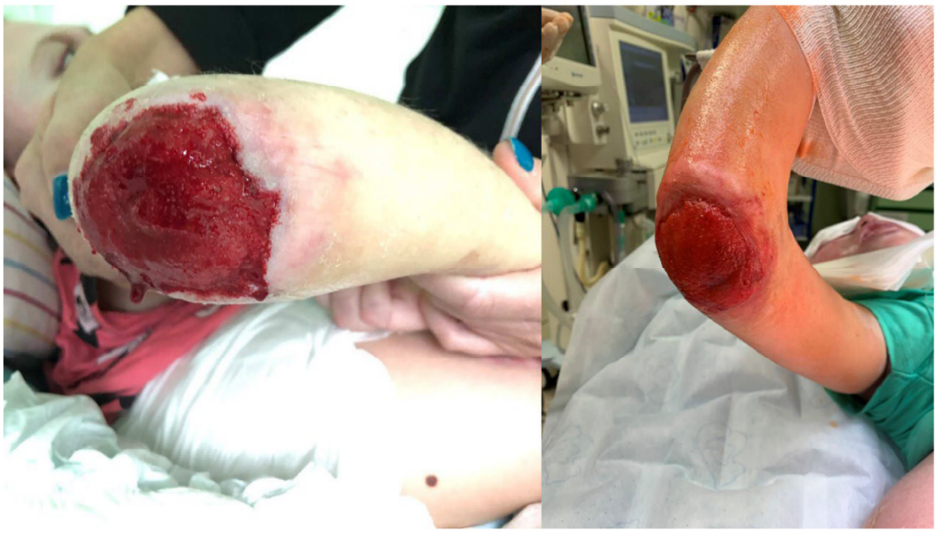

Figure 5: A real photo of the type of pressure ulcers [47].

Effective pressure ulcer treatment combines regular patient repositioning for pressure relief with support surfaces designed for pressure redistribution and antimicrobial dressings to establish a healing-friendly condition. The field of pressure ulcer management receives a transformative boost from modern research that has developed exciting new therapies, including stem cells and biosensors, as well as improved biomaterials. Innovations help wounds heal faster while minimizing tissue scarring and leading to better medical outcomes for persons with chronic pressure ulcers [48]. Table 1 provides a comparison of the aforementioned wound types.

Table 1: Comparison between different types of wounds

Type of wounds	Description	Ref
	Acute Wound and Chronic Wound	
Acute Wound	• A wound that heals in a predictable and timely manner (usually within 4-6 weeks) without complications. • Heals quickly within weeks. • Caused by trauma, surgery, burns, or sharp objects. • Follows a normal wound healing process (inflammation, proliferation, remodeling). • Surgical wounds, cuts, burns, abrasions, punctures.	[31,49]
Chronic Wound	• A wound that fails to heal within the expected timeframe (usually beyond 6 weeks) due to underlying factors. • Takes longer than 6 weeks and may persist for months or years. • Results from poor circulation, diabetes, infection, or prolonged pressure. • Healing is delayed due to factors like infection, poor blood flow, or underlying diseases. • Diabetic ulcers, pressure sores, venous leg ulcers, non-healing surgical wounds.	[33–35,50]
	surgical wounds, traumatic wounds, burns, diabetic ulcers, and pressure ulcers	
Surgical Wounds	• Intentional incisions during medical procedures. • Clean edges, controlled environment, minimal bleeding. • Risk of infection is low but can occur if not managed properly.	[37,38,51,52]
Traumatic Wounds	• Unintentional injuries (accidents, violence).	[53]

	• Irregular, jagged edges, uncontrolled bleeding. • Higher risk of infection due to non-sterile environment.	
Burns	• Thermal, electrical, chemical, or radiation. • Eschar, blisters, high susceptibility to infection. • Pain management, infection control, and long recovery time.	[54][55][56]
Diabetic Ulcers	• Poor circulation and neuropathy (diabetes). • Chronic, often on feet, poor blood flow, neuropathy.	[45][57]
Pressure Ulcers	• Prolonged healing, impaired blood flow, high risk of infection. • Prolonged pressure on skin (bony prominence). • Localized tissue ischemia, ulcers form over time. • Prevention focuses on relieving pressure, healing can be slow.	[46]

Factors influencing wound healing

A complicated process driven by many internal and external elements is wound healing. Maximizing therapy plans and guaranteeing speedier, more efficient healing depends on an awareness of these elements [58]. Nevertheless, various elements may significantly affect the effectiveness of these stages. The factors most important influencing wound healing are oxygenation, infection, age, sex hormones, stress, diabetes, obesity, medications, alcohol, smoking, and food [59,60].

Oxygenation process and blood supply

Wound healing is an oxygen-dependent process that involves various oxygen-mediated cellular and molecular events, including fibroblast proliferation, collagen synthesis, and angiogenesis. Chronic wounds, such as diabetic ulcers and pressure ulcers, often exist in hypoxic microenvironments due to impaired vascularization. In such cases, oxygen deficiency hinders cell migration and prolongs the inflammatory phase [61]. Comprising many biological and molecular components including fibroblasts, blood cells, cytokines, and ECM elements, the wound healing process is dynamic and complex. Usually, these mechanisms cooperate closely to restore skin integrity in a healing situation. Crucially engaged in both basic physiological processes and cell signaling pathways required for healing, oxygen is also Energy generation, ROS creation, infection control, ECM component synthesis, collagen remodeling, and angiogenesis depend on enough oxygen (Figure 6).

Furthermore, oxygen is especially important in cellular metabolism for synthesizing ATP, which is necessary for almost every step of wound healing [62]. Adequate oxygenation accelerates fibroblast proliferation, supports collagen synthesis, stimulates keratinocyte differentiation, migration, and re-epithelialization, aids in wound contraction, encourages angiogenesis (the creation of new blood vessels), and helps prevent infection [59,60]. Hypoxia, or low oxygen levels, may interfere with these functions and cause partial or delayed recovery. Oxygen flow to the inflammatory and stromal cells inside the wound site is necessary to oxygenate wound tissue. The production of biological energy (ATP), essential for cellular activity, depends on oxygen.

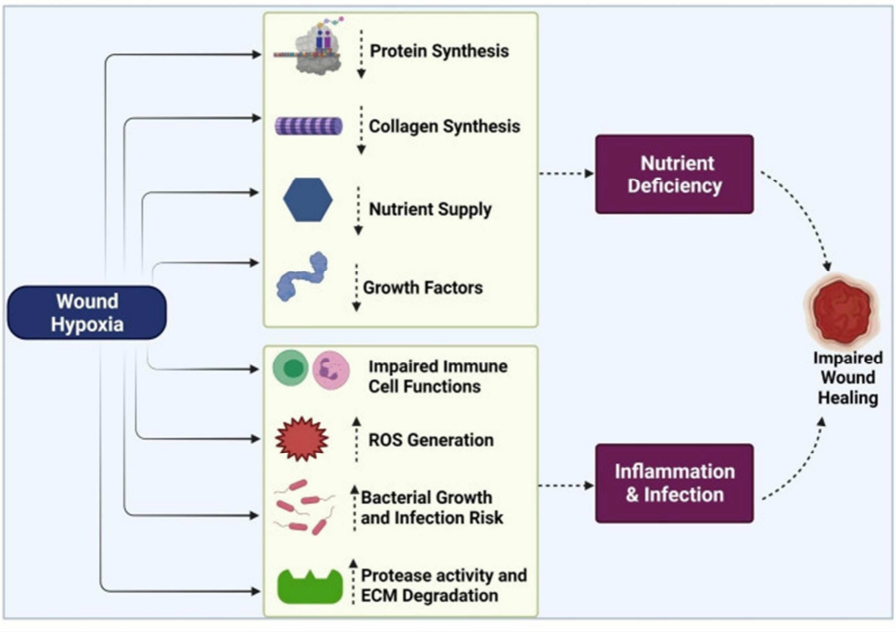

Figure 6: Wound hypoxia, caused by lower oxygen levels, leads to a reduction in protein synthesis, particularly collagen, which is vital for the extracellular matrix. It also impairs nutrient supply, growth factor secretion, and immune cell function while promoting the excessive generation of ROS and the activity of tissue-degrading enzymes [63,64].

Additionally, the respiratory burst in neutrophils, which produces ROS to combat infection, is supported by oxygen during the inflammatory phase [65]. Higher oxygen levels have been shown to improve immune cell bactericidal activity, which lowers wound infection rates. Moreover, oxygen-dependent enzymes such as NADPH-linked oxygenase are very important in wound healing by accelerating the synthesis of ROS, including peroxide anion, hydroxyl ion, and superoxide anion. These ROS are involved in oxidative bacterial killing and regulate critical healing processes like cytokine release, cell proliferation, and angiogenesis [66]. Hypoxia also limits angiogenesis and the formation of new blood vessels, further hindering wound repair and leading to delayed healing [64]. Overall, oxygen's role in promoting wound healing is illustrated in Figure 7.

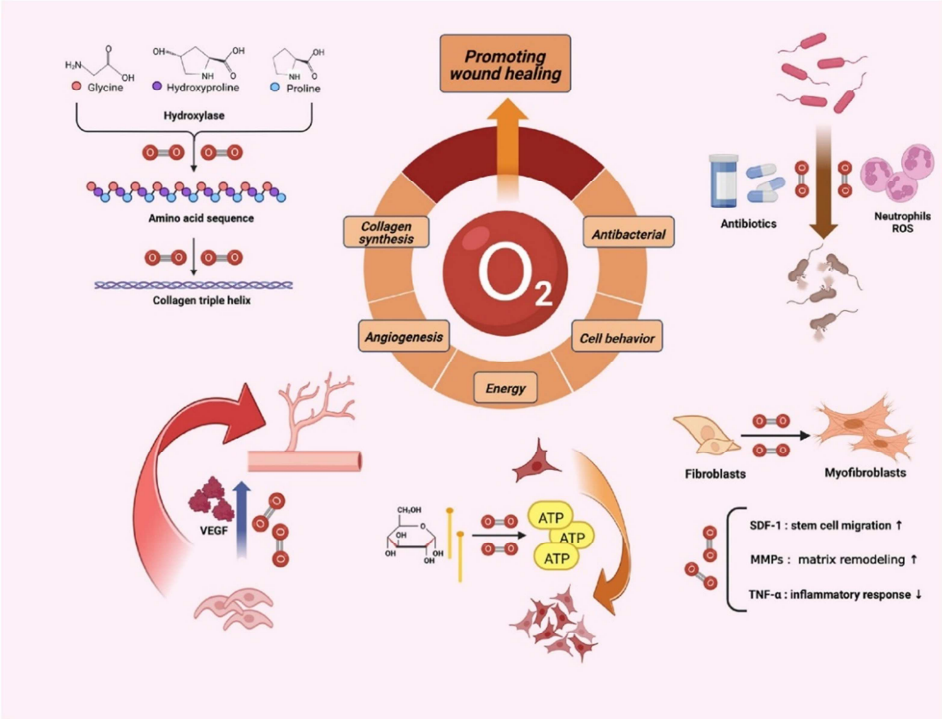

Figure 7: Schematic diagram of oxygen function in promoting wound healing [67].

2. Role of bacterial infection in wounds

Infection is a leading factor in delayed wound healing, particularly in chronic wounds where biofilm formation and multidrug-resistant bacteria are prevalent. The prolonged presence of pathogens sustains the inflammatory phase and disrupts normal tissue regeneration [68]. Moreover, the skin injury creates conditions that allow microbes from surface layers to penetrate deeper tissue regions. Injury treatment requires inflammation as a natural healing response, which helps eliminate dangerous microorganisms. The inflammatory phase becomes longer due to bacteria and endotoxins that raise TNF-α and interleukin-1 (IL-1) pro-inflammatory cytokine levels [69]. Surface skin bacteria commonly found on healthy skin will penetrate deeper tissues during chronic wound injuries thereby preventing proper healing after skin damage (Figure 8). Excessive exudate exists in chronic wounds which create a suitable moist environment where bacteria thrive to colonize and reproduce. Endotoxins and bacteria supply inflammatory signals that cause delayed healing while causing additional harm to the inflammatory process [70]. The initial bacteria presence in chronic wounds belongs to Gram-positive bacteria Staphylococcus aureus before Gram-negative *Pseudomonas aeruginosa* takes over in later infection stages [71]. The virulence factors combined with endotoxins made by bacteria drive pro-inflammatory cytokine production which leads to sustained inflammatory response. Chronic inflammation that develops in wounds induces changes to metabolic activity through elevated MMP expression while causing wounds to heal at reduced rates [72].

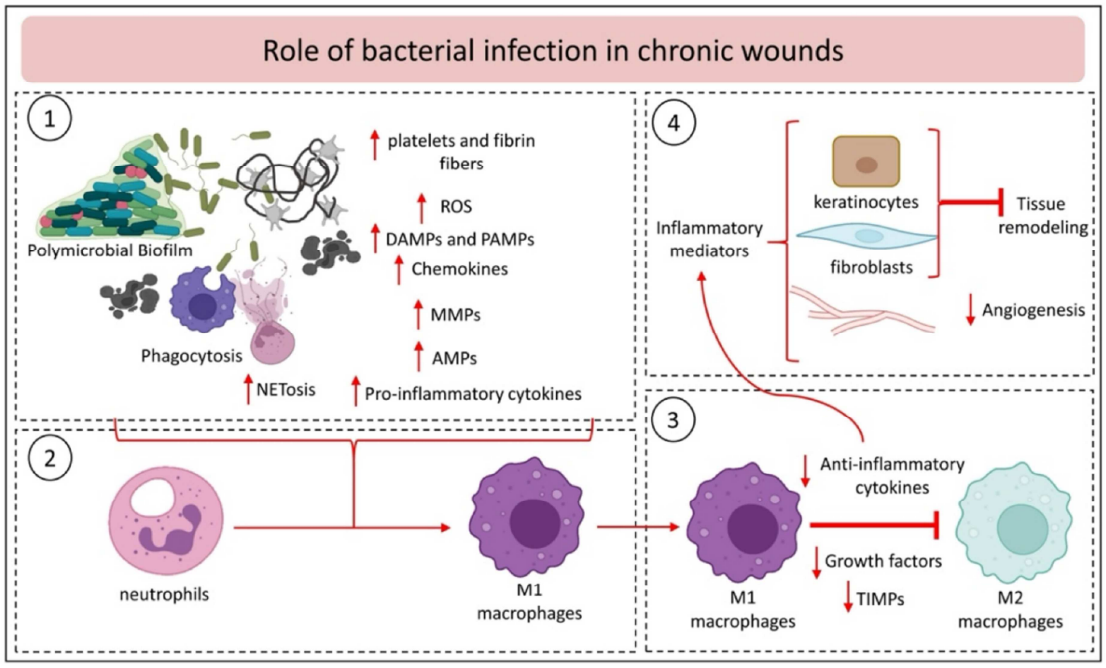

Figure 8: Four stages of wound healing and highlights the impact of bacterial infection on chronic wounds. The chronicity of these wounds and the disruption of the normal healing process are often driven by excessive inflammation. Infected wounds, especially those with biofilm-forming bacteria, experience prolonged inflammation, which impedes the progression of the healing stages and delays tissue repair [73].

Forming biofilm, complex clusters of bacteria wrapped in a self-produced extracellular polysaccharide matrix, is common in infected wounds. As biofilms develop into adulthood, they shield bacteria from harm, making them more resistant to common antibiotics. Biofilm, especially those harboring pathogenic microbes, prevent the immune system's phagocytic cells, notably polymorphonuclear neutrophils (PMNs), from eliminating the germs, which is why many chronic ulcers do not heal. Antibiotics are ineffective in treating chronic wounds because of this biofilm's defensive properties [74].

3. Co-morbidities (Diabetes, Obesity)

Co-morbidities such as diabetes and obesity are significant factors that influence the wound healing process. Both conditions impair the body's ability to repair tissue effectively, leading to delayed healing and increased risk of complications [75].

Diabetes

Diabetes mellitus is one of the primary contributors to impaired wound healing, with multiple factors complicating the healing process. Diabetic wounds typically disrupt the skin's natural regenerative abilities, significantly slowing healing [76,77]. A hostile environment, prolonged inflammation, and impaired angiogenesis often characterize these wounds. The complexity of diabetic wound disease means that healing is slow, and medical treatment can be costly. Effective treatment strategies are urgently needed to improve patient's quality of life, reduce pain, and speed up recovery [78,79].

Prolonged uncontrolled diabetes elevates blood sugar levels, making cells dysfunctional, thus delaying wound healing in all its stages. The transition from hemostasis to inflammation becomes delayed because platelet-derived growth factor (PDGF) receptors show decreased expression on endothelial and epithelial cells. The signaling errors in fibroblasts during proliferation may cause insufficient granulation tissue formation together with fibrotic extracellular matrices that slow down keratinocyte migration, thus delaying the re-epithelialization process. Angiogenesis decreases because increased metalloproteinase and ROS cause damage to the ECM. People with peripheral artery disease from diabetes commonly develop peripheral artery disease, which creates tissue injury through blood flow restrictions that result in extended tissue ulcers due to decreased antioxidant enzyme activity [80,81].

The approach to treating diabetic foot ulcers depends on both the overall health status of patients and the severity level of their diabetes. The treatment solutions for this condition consist of surgical revascularization and diabetic foot pressure reduction through braces and cast support combined with oxygen therapy in pressurized chambers. The primary goal of treatment consists of transforming chronic ulcers into actively healing wounds by implementing debridement methods with off-loading techniques and correct moisture control. Debridement combined with moist dressings restores balanced wound conditions for healing alongside off-loading procedures which minimize harmful pressure on the ulcer for successful healing [82].

Obesity

Overweight people generally recover their wounds slower than those with a normal body mass index (BMI). However, the exact mechanisms behind this disparity remain unclear. The most effective wound care therapy for obese individuals is often a multidisciplinary effort [83]. One of the reasons why mending takes longer is because there is less blood

flow. An increase in blood vessels characterizes obesity but not necessarily an increase in adipocytes, the body's fat cells [84,85]. Obese individuals who suffer from wound healing issues have substantial clinical and social consequences. Further, they also face hyperventilation due to restricted diaphragm movement from excess adipose tissue, leading to lower vital capacity and less oxygen in the blood [86].

Venous insufficiency, which may be exacerbated by increased intra-abdominal pressure resulting from abdominal fat accumulation, might cause smaller veins to become blocked by protein-rich fluid entering the interstitial space [87]. This decrease in oxygen tension adversely affects the proliferative and remodeling stages of wound healing, which raises the risk of infection by reducing leukocyte phagocytic activity [88]. Furthermore, obesity is often linked to atherosclerosis and peripheral artery disease (PAD), two severe comorbidities that impair recovery [89]. The inadequate oxygen levels hinder fibroblast function and other oxygen-dependent repair processes in the wound area. Obesity also increases infection risk due to reduced blood circulation to surrounding adipose tissue, making it difficult for immune cells like neutrophils and macrophages to reach and fight off bacteria. Furthermore, skin folds common in obese individuals create a warm, moist environment that fosters bacterial growth, leading to potential ulceration from skin friction [59,90].

3. Antimicrobial wound dressings: Current strategies

Wound dressings are essential in managing and promoting the healing of various types of wounds. Many different types of medical wound dressings are now available for use as stopgap measures. In addition to facilitating wound healing and tissue regeneration, these dressings have shown promise in warding off microbial infections and keeping cells and tissues functioning normally [91]. They play a critical role in facilitating tissue regeneration by maintaining an optimal environment for healing [92]. Selecting an appropriate wound dressing depends on several factors, including the type, depth, location, and severity of the injury, exudate levels, infection presence, and wound adhesion. Traditional dressings like cotton bandages and gauze can excessively absorb moisture, leading to wound dryness, painful removal, and delayed healing. In contrast, advanced polymer-based dressings, such as films, foams, and gels, are designed to maintain optimal moisture balance, promoting tissue regeneration and enhancing healing [93]. An ideal wound dressing promotes healing by maintaining moisture balance, supporting cell migration, and collagen synthesis (Figure 9). It prevents infection by acting as a barrier while allowing the immune system to function. The dressing absorbs exudate without oversaturation, preventing tissue maceration, and is non-adherent to reduce pain during dressing changes [94]. It facilitates gas exchange, ensuring oxygen and moisture vapor reach the wound, and is biocompatible, safe, and flexible to adapt to the wound's shape. Additionally, it controls pain, allows for monitoring of healing progress, and minimizes the need for frequent dressing changes [95].

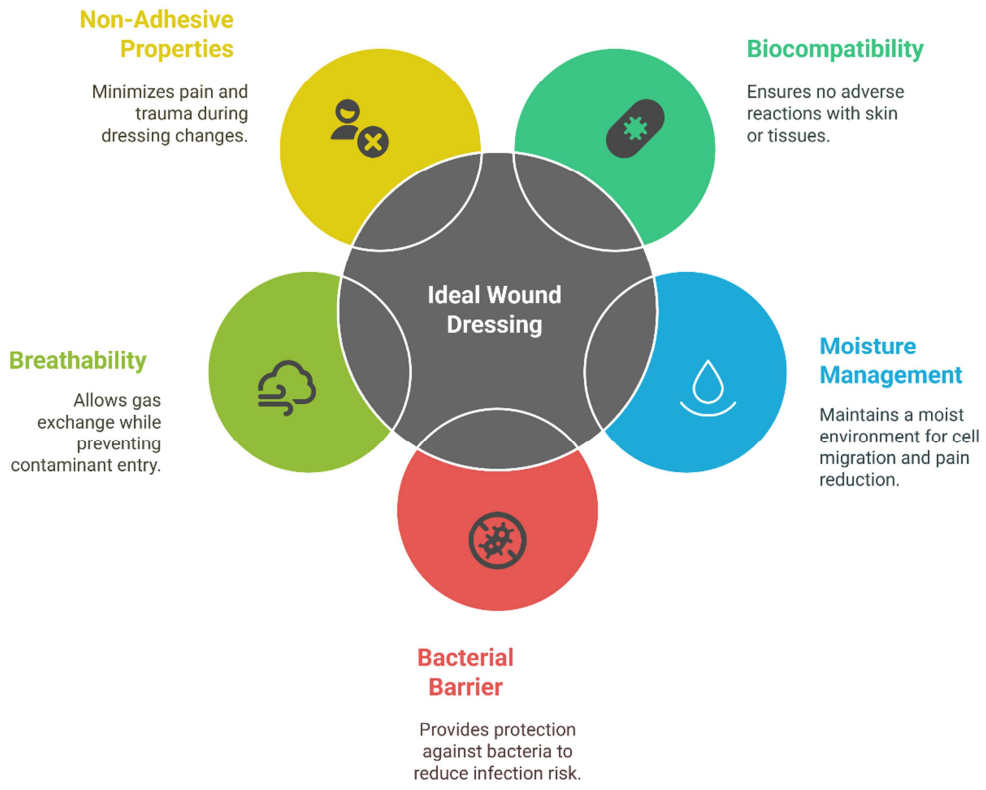

Figure 9: Representation diagram of the optimum wound dressing to comply with the successful enhancement of wound regeneration.

According to the patient's demands and the kind of wound, these dressings usually include many parts that complement each other to provide the best possible healing environment [96]. As shown in Figure 10, these dressings may include growth factor-enhancing capabilities, antibacterial agents, homeostatic elements, analgesics, and temperature control. Biocompatible nanomaterials, stem cells, and keratinocyte growth factor stimulators are common components of multifunctional wound dressings, aiding regeneration and healing processes. These substances influence the immune response, activate growth factors and signaling molecules, and assist build scaffolding for new tissue development [97]. One use of nanotechnology in skin tissue engineering is improving wound treatment by using biomaterials and NPs that promote tissue regeneration, transport growth factors, provide structural support, and regulate immune responses [98].

Wounds provide the perfect conditions for developing microbes since bacteria are inherently good at colonizing both living and nonliving surfaces. Various bacteria may flourish and multiply in an open wound, creating an ideal environment for microbial colonization. Polymicrobial infection is characterized by many pathogens in a wound, including internal bacteria in mucous membranes and external germs on the skin [99]. Wound dressings with antimicrobial properties are essential to modern wound care, particularly in preventing and managing infections that can delay the healing process. The use of antimicrobial dressings helps to create an environment that reduces the risk of bacterial contamination, minimizes the need for systemic antibiotics, and accelerates healing by preventing infections. These dressings are designed to deliver sustained antimicrobial effects, preventing the growth and colonization of pathogens while promoting tissue regeneration [100].

Hydrogels find widespread use in wound care through their three-dimensional structure, which lets them hold significant water levels, thus establishing a moist condition that stimulates tissue healing. Their fundamental weakness in mechanical strength requires additional dressing application for structural stability and mechanism protection [102].

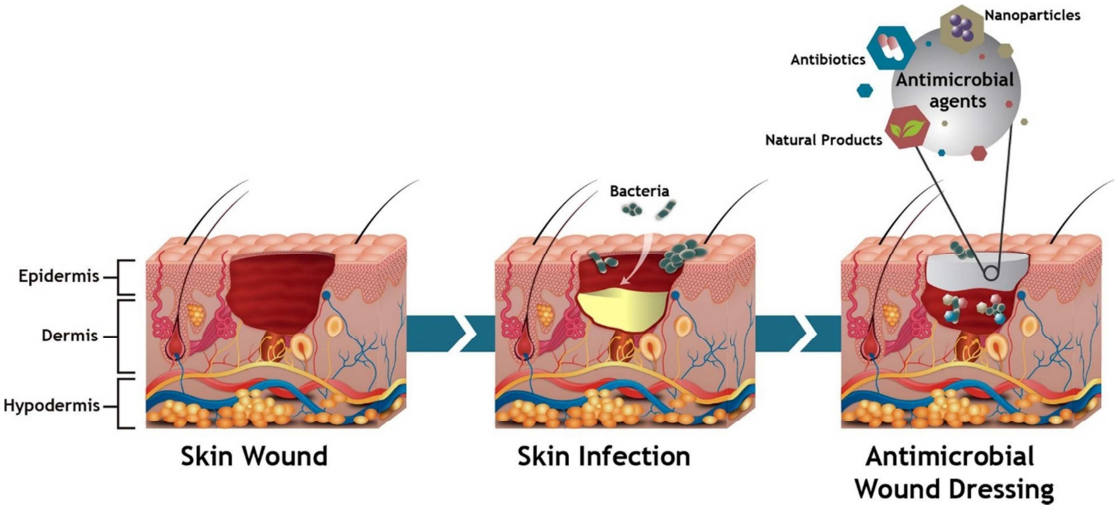

Figure 10: Illustration of antimicrobial wound dressing [101].

On the other hand, film dressings provide exceptional bacterial-blocking properties alongside unobstructed viewing of wounds and easy removal without pain while offering observation advantages. Application of these dressings can be complex while they firmly stick to wounds and may lead to excess exudate. New generation membrane-based dressings made using electrospinning techniques duplicate the properties of extracellular matrix by providing an open network design with broad surface contact area. Cellular growth and overall exchange capabilities and moisture regulation are supported by these characteristics. The production process that incorporates particular polymers and organic solvents brings challenges for biocompatibility because of the limitations they introduce [103]. Many researchers have introduced active agents as a method to improve antimicrobial properties of wound dressing materials. Antimicrobial ingredients used in treatment comprise both conventional antibiotics from the tetracycline, ciprofloxacin, gentamicin, and Ag sulfadiazine categories and metal-based NPs such as AgNPs and natural antimicrobials that include honey, essential oils, and chitosan [101]. The schematic illustration in Figure 11 shows a polymeric antimicrobial dressing that operates as both microbial protection against invasion and an enabling environment for fibroblast cell movement and differentiation which are essential for wound healing success.

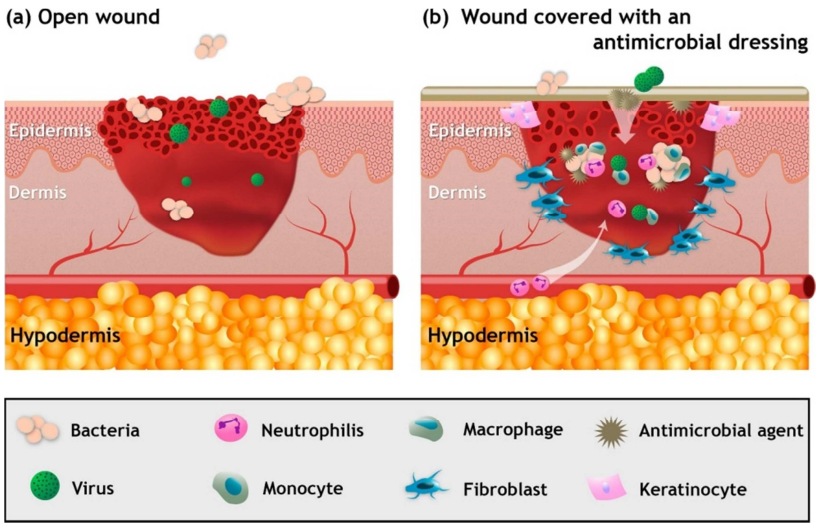

Figure 11: Illustration of the healing process in an open wound (a) and a wound covered with an antimicrobial dressing (b): In an open wound, there is a higher risk of bacterial contamination, which prolongs the inflammatory phase and enhances the activity of metalloproteinases [104].

Biopolymeric Films Based on Gelatin: Properties and Biomedical Applications

The functionality of biodegradable membranes depends heavily on proteins as well as polysaccharides. Throughout their structure, proteins containing twenty basic units demonstrate powerful molecular binding characteristics, which leads to better mechanical strength and barrier functions [105]. Natural polymer materials prepared from plants or animals or microbes bring important benefits such as renewal ability combined with destroying ability and bio-compatibility, which enables their broad use in biomedical fields, including implantable medical devices and drug delivery systems and tissue engineering and wound healing approaches [106]. Albeit their natural origin these polymers show excellent biocompatibility that makes them stand out as better alternatives than synthetic materials because they reduce immune system activation and inflammation responses [107].

Gel's amino acid profile aligns completely with collagen's chemical structure, making it an essential natural polymer. Hydrolyzing or thermally denaturing collagen from skin, bones, and connective tissue yields gelatin as an applicable polymeric compound [108]. This protein offers nineteen amino acids, three amino acids, namely glycine and proline, and hydroxyproline, the largest amount, ranging from 20–24% [105]. Gel's unique group of amino acids functions as a key factor in establishing its characteristics during film and coating production. The packaging performance of mammalian Gel is the most beneficial of all gelatin types since poultry and marine versions vary due to their different molecular compositions [109]. The production method for Gel starts with collagen hydrolysis, which separates large collagen structures into various shorter peptides (Figure 12). The peptide structure of gelatin develops into type A or type B through acid or alkaline hydrolysis treatment applied to animal bone and skin and muscle raw materials respectively [110].

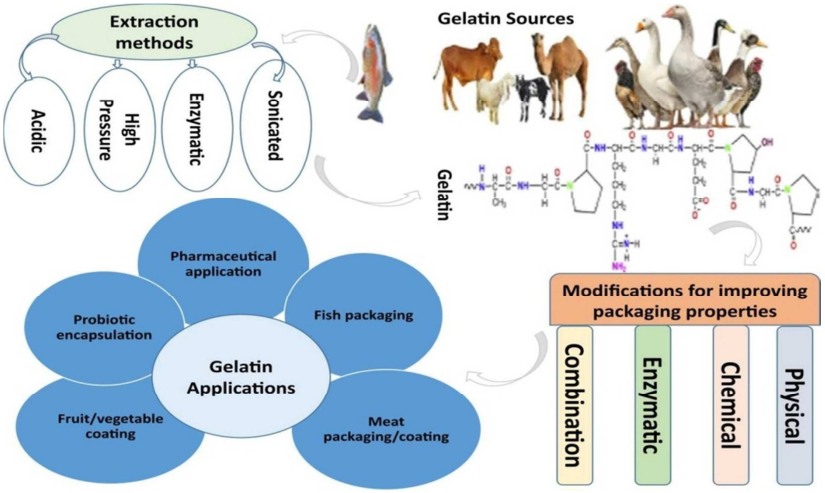

Figure 12: The process of Gel extraction and its applications [111].

Gel, a soluble protein obtained from the partial hydrolysis of collagen, has attracted considerable interest for the production of biodegradable films owing to its availability, biodegradability, and superior film-forming characteristics [112]. Due to its biocompatibility and versatility, gelatin is extensively used as a biomaterial in several medical applications. Functioning as an effective tissue engineering scaffold, it facilitates cellular growth and aids in tissue regeneration. Gel-based wound dressings promote healing by enhancing moisture retention and protecting the site from external contaminants. Gel is further used as a hemostatic agent in surgical procedures to minimize bleeding and facilitate clot formation, while also allowing for the regulated delivery of medications and the progressive release of therapeutic compounds over time [113].

Gel demonstrates exceptional value within biodegradable films production through its ability to form films and its transparency as well as its easy accessibility [114]. Gel adopts a triple-helix arrangement because an increased helix content strengthens its physical characteristics which benefits gelatin-based film structures. The physical gelling capacity of Gel derives from its protein chain orientation changes when the collagen triple helix breaks down into single strands [115]. Highly flexible wound coverings appropriate for many kinds of wounds, including skin grafts, surgical wounds, and superficial burns are nanofilms [116]. Excellent substitutes for injured skin are these soft, flexible, water-resistant film-like coverings [117]. For instance, casting and continuous gelation techniques help manufacture alginate membranes integrated with silica and AgNPs, hence improving their hydration characteristics. These movies also help the Ag ions to be continuously released, preventing biofilm and microbiological growth (Figure 13). In particular, cytotoxicity investigations have shown no adverse effects when human skin keratinocytes and fibroblasts were treated with these films [118].

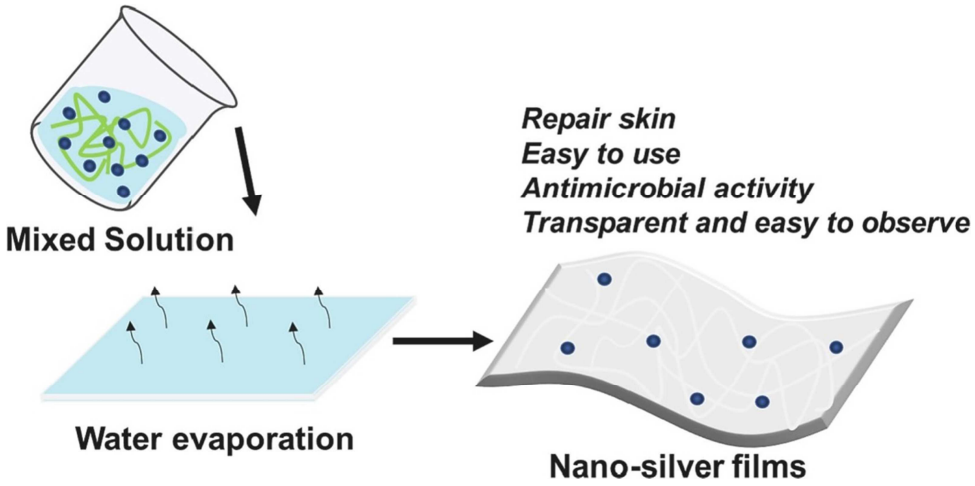

Figure 13: Fabrication of AgNPs-incorporated films [118].

Structural and mechanical properties of gelatin films

Gel films' structural and mechanical properties are significantly influenced by their molecular composition, production methods, and the incorporation of additives. These films exhibit viscoelastic properties, primarily governed by the arrangement and composition of amino acid sequences inside the gelatin molecules. Tensile strength and flexibility are critical mechanical properties, enhanced by the presence of amino acids such as proline and hydroxyproline, which augment stability and stiffness [119]. Increased concentrations of these amino acids promote the creation of the triple helix structure, hence augmenting mechanical strength and resistance to deformation. Additionally, external factors such as plasticizers, cross-linking agents, and other polymers affect the mechanical performance of Gel films by enhancing flexibility and reducing brittleness [120].

Gel's mechanical qualities are greatly influenced by its molecular weight and crystalline structure. Films with elevated molecular weight often exhibit superior structural integrity, creating a denser network that enhances mechanical strength and resistance to deterioration [121]. The inclusion of hydrophobic compounds, such as natural extracts or essential oils, might compromise gelatin films by altering protein-protein interactions, resulting in diminished tensile strength and heightened vulnerability to failure. The use of hydrophilic elements fortifies the films by facilitating hydrogen bond formation among gelatin molecules, hence improving their longevity and mechanical stability [122,123].

Biodegradability of Gelatin-Based Wound Dressings

Gel is a popular biopolymer used in wound dressings and various biomedical and pharmaceutical applications due to its ability to mimic human tissues' ECM [124]. Its key properties, including excellent biocompatibility, biodegradability, cell interaction capabilities, non-immunogenicity, and cost-effectiveness, make it highly valuable in tissue engineering. Additionally, its low antigenicity supports its widespread use in many biological applications [125,126]. The biodegradation of Gel films is particularly advantageous in wound healing applications, as they break down over time, eliminating the need for removal and reducing the risk of infection [127]. Water and moisture in the wound environment accelerate the biodegradation process, ensuring the gradual release of bioactive molecules to promote tissue regeneration [128]. However,

controlling the degradation rate is crucial to ensure the wound dressing remains effective for the necessary healing duration without prematurely breaking down. As such, the biodegradability of gelatin-based wound dressings can be optimized for specific clinical needs by adjusting their formulation and processing conditions [129].

The molecular weight of Gel-based films primarily determines their biodegradability rate. The polymer chains must be broken down into sufficiently tiny molecular weight pieces if microbial metabolism is to take place [133]. Microbes may absorb the carbon content into biomolecules or convert it into carbon dioxide.

Mammalian Gel films have a greater deterioration rate because of their higher hydroxyproline content; single bovine gelatin films usually disintegrate at 18–25% over three days [130]. By contrast, bovine Gel composite films, which include additives such as dialdehyde starch, sodium montmorillonite, carboxymethyl cellulose (CMC), and sorbitol, show lowered biodegradation rates (below 20%). Their denser structure, greater molecular weight, and covalent cross-linking between the gelatin matrix and additives. Higher hydrophilic content composite films, notably those made from Gel/CMC/chitosan mixes, break down more quickly because of greater microbial sensitivity and hydrolysis [131]. On the other hand, since fish gelatin has a low molecular weight, composite films made from fish gelatin/chitosan/tapioca flour show a reduced biodegrading rate. Molecular weight, moisture content, and the presence of additives changing the structural characteristics of the film affect the biodegradation rate of Gel-based films generally [132].

Functionalization strategies for Gelatin-based films

Gel-based films are popular because of their price, accessibility, and functionality. Gel encapsulates bioactive compounds, forms films, and functions as a barrier. These films' mechanical and barrier properties depend on Gel's amino acid content, molecular weight distribution, and extraction conditions. Gel films absorb moisture and expand in high-humidity situations due to their hygroscopic qualities [133,134]. Incorporating NPs into Gel films further improves their mechanical strength, barrier performance, and optical clarity. While pure gelatin films typically lack antimicrobial and antioxidant activity, embedding NPs like ZnONPs and AgNPs within the gelatin matrix not only reinforces the film structure but also imparts strong antimicrobial properties by effectively entrapping the NPs within the polymer network [135]. The effects of NPs on the mechanical and optical properties of Gel films are summarized below.

The properties of Gel improve via chemical enzymatic and physical processes so that researchers can use it to make eco-friendly biocomposite materials [111]. All its valuable properties including abundance and renewability together with biodegradability and biocompatibility and affordability establish its tremendous suitability for diverse uses. Gelatin includes several functional sections with ionizable groups such as aspartic acid (-COOH), terminal amine (-NH_2) and carboxyl (-COOH) groups and lysine's amine (-NH_2) and imidazolium groups in histidine and the guanidinium group of arginine and phenolic groups [136]. Due to its adaptability, multiple functional groups in gelatin make it possible to modify and conjugate this material at various points.

The structural morphology of Gel can be enhanced through cross-linking and grafting methods that improve its degradability along with its hydrophilicity and functional properties [137–139]. Multiple treatment methods involving chemical cross-linking, phosphorylation, and natural phenolic substance integration enhance protein- and polysaccharide-based films by improving their functional properties. Phosphorylation represents a practical approach in modifying proteins because it adds phosphate groups to hydroxyl sites to boost technological properties [140]. Phosphorylation leads to better emulsification durability by enabling hydrophobic interaction at interfaces similar to what occurs in Gel-based films. The emulsification ability of gelatin improves when it receives phosphate groups through the phosphorylation process, thereby becoming more effective for applications managing stable emulsions [141].

Nanotechnology and wound healing application

Nanomaterials demonstrate unique features because of their small size, creating a large surface area-to-volume ratio that improves their chemical and thermal properties, optical and electronic magnetic properties, and biological properties [142–144]. The enhanced optical catalytic and biological functionalities of bimetallic NPs (BNPs) surpass monometallic NPs (MNPs) due to their significantly increased functionality. A bimetallic NPs contains two dissimilar metal atoms joined together in a unified nano-system. Both single-metal properties combine with new features stemming from the metals' mutual interactions [145]. The combined effects between the two metals yield enhanced capabilities for applications in sensing as well as antimicrobial and biomedical detection. The individual arrangement of metal atoms throughout BNPs is an essential factor that drives their entire physical and chemical performance [146]. The structural arrangements of BNPs configurations consist of core-shell features, heterostructures, multi-shells cluster-in-cluster ensembles, and random alloy structural layouts [147]. Ag/ZnONPs stand out among bimetallic materials due to their antimicrobial wideness, strong potential for biomedical wound healing applications, and extensive photocatalytic use [148].

Silver-doped zinc oxide NPs (Ag-ZnONPs): Synthesis and characterization

ZnONPs catch the attention of researchers because they offer advantages related to low cost and availability. The photocatalytic behavior, piezoelectric and pyroelectric behavior, semiconducting qualities, and 3.37 eV bandgap define ZnONPs [149–151]. ZnONPs are hindered from industrial use due to their inherent oxygen vacancy defects. Research has widely explored using Ag noble metal doping for ZnONPs to improve their properties. ZnO materials become more potent against microbiological threats yet better at photochemical reactions when Ag is added to the mixture making them outperform platinum and gold [152,153]. The bactericidal effects of silver ions show vigorous activity against a wide range of bacterial species. Ag-ZnONPs' antibacterial abilities and optical properties depend on their morphology size and crystal growth patterns. These characteristics change with different synthesis methods to suit various biomedical and industrial uses [154,155]. Table 2 comprehensively compares the most common methods for synthesizing ZnONPs, outlining their advantages and limitations.

Table 2: Comprehensive comparison of different methods used for the synthesis of ZnONPs, highlighting their advantages and limitations

Synthesis Method	Advantages	Limitations	Ref.
Chemical Synthesis	- Enables precise control over particle size, morphology, and crystallinity. - Produces highly pure and stable NPs with uniform dispersion. - Scalable for industrial applications. - Compatible with various doping and surface modification techniques.	- Often involves hazardous and toxic chemicals (e.g., strong acids, reducing agents, organic solvents). - Requires stabilizing or capping agents to prevent agglomeration, some of which may be cytotoxic. - High environmental risk due to chemical waste. - Requires careful handling and post-synthesis purification steps.	[156]
Physical Synthesis	- Produces NPs with excellent crystallinity and phase purity. - Avoids chemical contamination due to the absence of solvents and additives. - Capable of producing uniform NPs in size and shape. - Suitable for dry-state and thin-film applications. - High throughput and fast processing time.	- Requires high-energy equipment (e.g., laser ablation, arc discharge, thermal evaporation), leading to high operational costs. - Limited scalability and material-specific constraints. - Risk of particle instability or uncontrolled agglomeration. - Environmental degradation through energy-intensive processes.	[157]
Green Synthesis (Biogenic)	- Utilizes natural, renewable materials (plants, microbes, enzymes) as reducing and stabilizing agents. - Environmentally benign and non-toxic; aligns with green chemistry principles. - Biocompatible NPs suitable for biomedical and pharmaceutical use. - Requires minimal infrastructure and low energy input. - Produces surface-functionalized NPs with inherent bioactivity.	- Particle size, morphology, and yield can vary significantly based on biological source and reaction conditions. - Reproducibility and consistency remain a challenge. - Lower stability compared to chemically synthesized counterparts. - Limited understanding of precise reaction pathways and active biomolecules.	[158,159]

Methods of Ag-ZnONPs synthesis: chemical, physical, and biological approaches

The synthesis of Ag-ZnONPs has gained significant attention in nanomedicine, especially in wound healing applications due to their excellent antimicrobial and regenerative properties. The choice of synthesis method significantly influences the morphology, size distribution, surface charge, crystallinity, and biological behavior of the NPs [151]. As shown in Figure 14, three primary approaches are used: chemical, physical, and biological methods. Each technique offers distinct advantages and limitations concerning scalability, environmental impact, and control over nanoparticle characteristics.

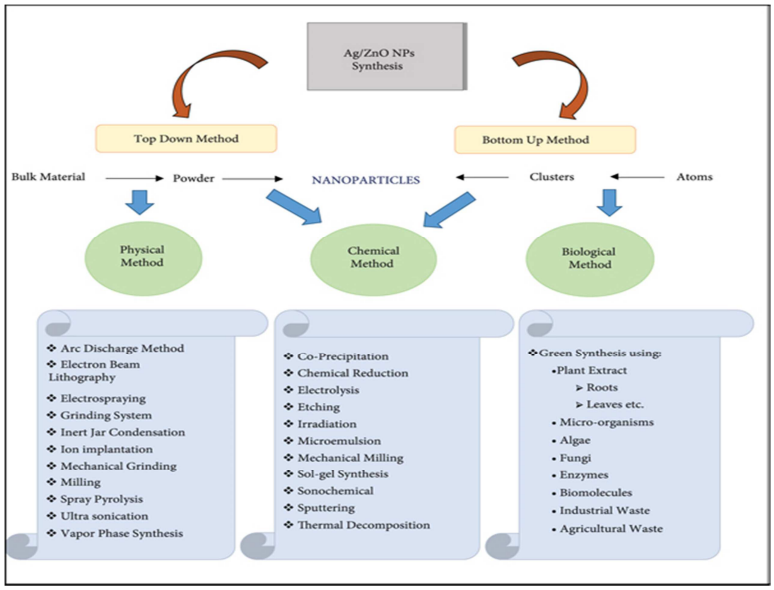

Figure 14: A schematic diagram of diverse approaches for synthesizing the Ag-ZnONPs

Chemical synthesis of Ag-ZnONPs

Chemical synthesis is the most widely employed approach for producing Ag-ZnONPs, owing to its simplicity, scalability, and ability to fine-tune particle morphology, size distribution, and crystallinity. These methods generally rely on reducing metal precursors in the presence of stabilizing agents, under controlled physicochemical conditions. The choice of precursor salts, solvents, reaction time, pH, temperature, and reducing or capping agents play critical roles in determining the quality and function of the resulting nanomaterials [160]. Among the various chemical techniques available, sol-gel, co-precipitation, hydrothermal/solvothermal, and microemulsion methods are the most commonly utilized.

Sol-gel method

The sol-gel synthesis process is highly valued for producing high-purity nanomaterials with controlled porosity and uniform morphology. It is ideal for biomedical applications requiring precise surface and structural properties. The process typically begins with the hydrolysis and subsequent polycondensation of metal alkoxides or inorganic salts, creating a sol. A three-dimensional network forms as the sol-gels, which are then dried and heated to produce crystalline ZnONPs. Further, the sol-gel method involves the hydrolysis and polycondensation of metal precursors, typically silver nitrate ($AgNO_3$) and zinc acetate dihydrate ($Zn(CH_3COO)_2 \cdot 2H_2O$), in a polar solvent such as ethanol or deionized water. During hydrolysis, metal ions react with water to form hydroxide intermediates, which condense into a sol [161]. Upon aging, the sol transforms into a gel network. This gel is dried and subjected to calcination at elevated temperatures (typically 300–600 °C), facilitating the crystallization of the ZnO matrix and the reduction of Ag ions to elemental silver [162].

Co-precipitation method

It is a simple, rapid, and cost-effective approach that involves the simultaneous precipitation of Ag^+ and Zn^{2+} ions by the gradual addition of a base, commonly sodium hydroxide (NaOH) or ammonium hydroxide (NH_4OH), to a mixed aqueous solution of silver and zinc salts [163]. As the pH of the solution increases (typically to 9–12), Zn and Ag hydroxides precipitate, which are later converted into ZnO and metallic Ag upon drying and calcination. This method is advantageous due to its scalability and minimal equipment requirements. Still, careful optimization of pH, temperature, stirring speed, and ion concentration is essential to prevent particle agglomeration and ensure homogeneity [164].

Hydrothermal and solvothermal methods

Hydrothermal synthesis is a solution-based technique in which system pressure is regulated by the reactants' vapor pressure, enabling nanomaterials to be produced across an extensive temperature range. This process is very effective for producing high-purity NPs with slight material degradation or loss, especially when handling volatile precursors [165]. Hydrothermal and solvothermal synthesis are widely employed techniques for producing high-purity, crystalline, and morphologically controlled nanomaterials, including silver-doped zinc oxide NPs (Ag-ZnONPs) [166]. These techniques involve conducting chemical reactions in a closed autoclave under elevated temperatures (typically 120–250 °C) and autogenous pressure. The hydrothermal method utilizes water as the solvent. In contrast, solvothermal synthesis employs organic solvents such as ethanol, ethylene glycol, or dimethylformamide (DMF), which influence the solubility and reactivity of the precursors, thereby affecting the resulting particle size, shape, and crystalline structure [167].

In these processes, metal precursors such as $Zn(CH_3COO)_2 \cdot 2H_2O$ and $AgNO_3$ are dissolved in a suitable solvent, and under controlled thermal conditions, nucleation and growth of NPs occur. The temperature and pressure facilitate the formation of ZnO nanocrystals while concurrently reducing Ag^+ ions into metallic silver or incorporating them into the ZnO lattice as dopants. The morphology of the final Ag-ZnONPs can vary from spherical and rod-like structures to more complex nanoflowers, depending on reaction conditions such as precursor concentration, pH, solvent polarity, and reaction time [168]. Despite these advantages, hydrothermal and solvothermal methods also present some limitations. They typically require specialized equipment (Teflon-lined autoclaves), extended reaction times, and toxic organic solvents may be involved in solvothermal synthesis. However, the ability to tailor nanoparticle properties with high precision makes these methods particularly valuable for developing next-generation antimicrobial wound dressings that combine structural integrity with biological performance [176].

Mechanochemical synthesis

Mechanochemical synthesis is a solvent-free, energy-efficient approach in which mechanical forces initiate chemical reactions rather than thermal or solution-based methods. High-energy ball milling, employing planetary, shaker, or attrition mills, is commonly used to achieve sufficient impact energy to break and reform chemical bonds [169]. These mechanical collisions generate transient high-temperature and high-pressure microenvironments, facilitating the formation of new phases, inducing defects, and promoting the synthesis of nanostructured materials [170]. This approach is particularly effective for fabricating metal oxide NPs such as Ag-ZnONPs, as it allows for fine control over particle size, morphology, and crystallinity without the need for solvents or complex reaction conditions. Mechanochemistry aligns with the principles of green chemistry, offering advantages such as reduced environmental impact, minimal reagent use, and simplified processing steps. Notably, NPs synthesized through mechanochemical routes have demonstrated enhanced antimicrobial activity and high surface reactivity, traits that are especially beneficial in biomedical applications, including antibacterial wound dressings [171].

Modern technological advancements have enabled the development of high-energy ball mills capable of delivering energy densities sufficient to trigger a wide range of chemical reactions. As a result, ball mills have become essential tools in mechanochemical synthesis and are often referred to as “reactive milling” systems [172]. Common types of mills used in this process include planetary, shaker, and attrition mills. Among these, planetary and attrition mills are especially relevant for the industrial-scale production of metal-oxide NPs [169].

Mechanochemical reactions occur through the continuous application of mechanical force, which drives atoms out of their stable lattice positions, resulting in changes in bond angles and lengths and, in some cases, electronic excitation. These structural distortions lead to lattice defects, amorphous regions, or metastable intermediates, accumulating energy until

molecular bonds break and new chemical reactions initiate. However, characterizing these transformations remains challenging due to collision events' transient, localized nature. Despite these difficulties, researchers have pursued in situ monitoring, thermodynamic modeling, and kinetic simulations to understand better the mechanistic pathways involved [173,174].

Mechanochemical techniques have been applied to synthesize various materials, including metals, alloys, oxides, chalcogenides, and common salts like phosphates and carbonates. Furthermore, this method has proven effective for producing refractory compounds such as carbides and silicides [175]. Mechanochemistry has also synthesized more complex materials, such as organometallic compounds, metal-organic frameworks (MOFs), and hybrid nanostructures that integrate inorganic cores with organic shells. Its capability to fabricate nanostructured and functionalized materials was recognized early in the development of nanotechnology, reinforcing its importance as a scalable and environmentally conscious synthetic strategy [176].

Green synthesis

Several physical and chemical manufacturing techniques, such as microwave-assisted synthesis, co-precipitation, hydrothermal processing, and sol-gel methods, continue to be widespread for nanoparticle production. Environmental regulations and social preference for sustainable practices have directed the scientific focus toward creating eco-friendly approaches for nanoparticle synthesis [177]. The bond between nanotechnology and biotechnology uses biological systems including plant extracts and microbes together with proteins and lipids as reducing and stabilizing agents [178]. Green nanotechnology, which seeks the ecologically friendly and sustainable synthesis of NPs via biological systems, is one of the most intriguing derivatives of this advancement. Green synthesis methods are very suitable for forming NPs between 1 and 100 nm, offering advantages such as reduced toxicity, environmental friendliness, and simplicity [179]. The NPs synthesized biologically possess beneficial properties involving stable suspension in solutions, measured particle dimensions, and optimal surface chemistry. The main advantages of green methods stem from their simple operational nature, low cost, and minimal infrastructure requirements, making these methods appropriate for research and industrial applications at various scales [180–182]. The overview of procedures uses naturally occurring biological agents as reducing, capping, and stabilizing agents, including plant seed extracts, algae, fungi, and other microbial systems are illustrated in Figure 15.

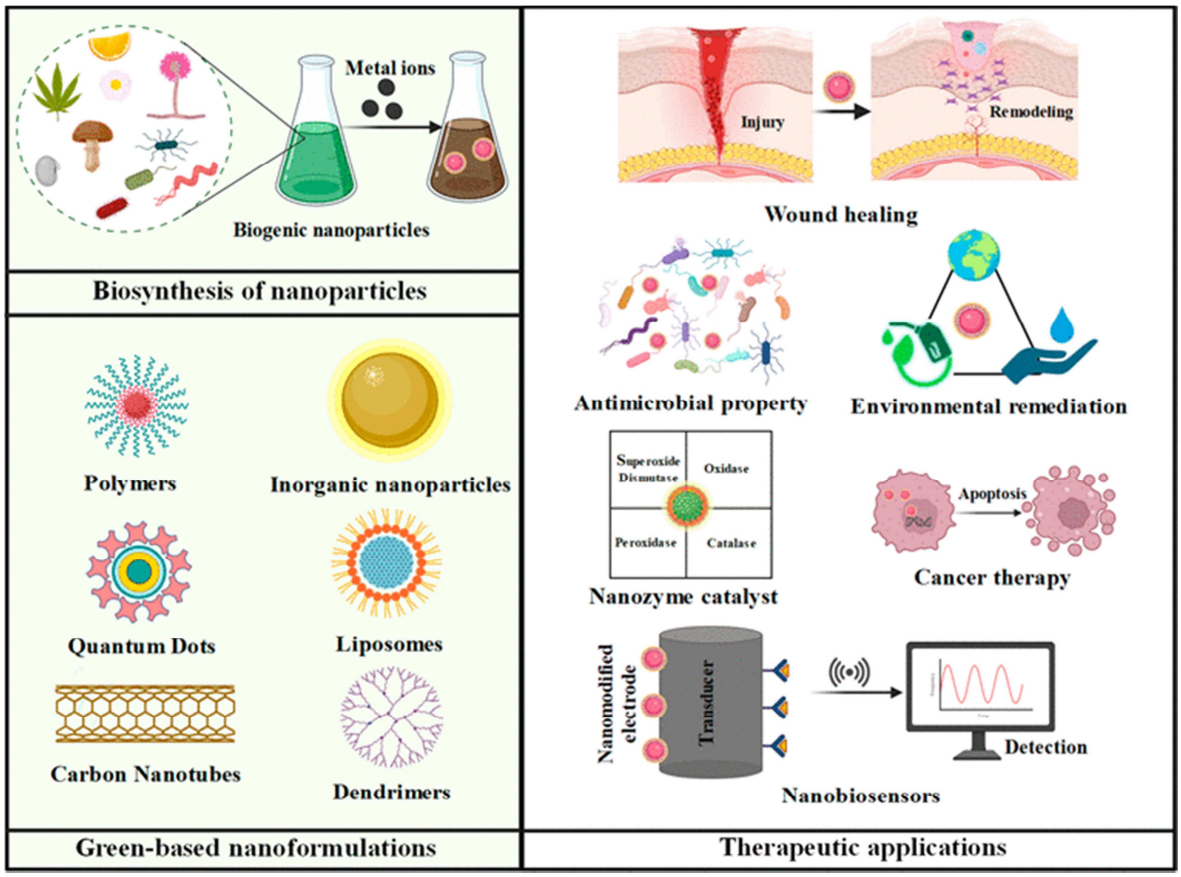

Figure 15: Overview of green-based nanotechnology: Biosynthesis of NPs using biological sources (plants, fungi, bacteria, algae) leads to various green-based nanoformulations such as polymers, inorganic NPs, liposomes, quantum dots, carbon nanotubes, and dendrimers [179].

The formation of biogenic NPs via biological systems is a complex yet highly efficient process involving reducing and stabilizing metal ions by naturally occurring biomolecules. In contrast to conventional chemical or physical synthesis methods, biogenic synthesis utilizes plant extracts, bacteria, fungi, algae, and even viruses as eco-friendly nano-factories. These biological agents contain a wide range of functional biomolecules, such as polyphenols, flavonoids, terpenoids, alkaloids, proteins, enzymes, amino acids, and polysaccharides, which act simultaneously as reducing, capping, and stabilizing agents during nanoparticle formation [183]. The mechanism of biogenic nanoparticle synthesis generally proceeds through the following key stages. Initially, metal ions (Ag^{+}, Zn^{2+}) are introduced to the biological system, where they come into contact with functional groups such as hydroxyl (-OH), carboxyl (-COOH), amino (-NH_2), and sulfhydryl (-SH) present in biomolecules. These groups serve as nucleation centers, chelating the metal ions and preparing them for reduction. Reductive biomolecules (e.g., phenolics in plant extracts or reductase enzymes in microbes) donate electrons to metal ions, reducing them to their zero-valent state (Ag^0 or Zn^0). This reduction is the critical step that leads to nucleation and subsequent growth of NPs. In plant-mediated synthesis, redox reactions often occur rapidly at room temperature, without external energy input. Once reduced, metal atoms cluster together, forming small nuclei. These nuclei act as seeds that grow into NPs via further deposition of metal atoms. The size and shape of the NPs are governed by the kinetics of nucleation versus growth, as well as the availability of stabilizing agents [184]. Various biomolecules adsorb onto the nanoparticle surface to prevent aggregation and maintain nanoscale size, forming a stabilizing shell. This capping layer provides colloidal stability and enhances the biocompatibility and functionality of the NPs for biomedical applications. In microbial systems, proteins and extracellular polymeric substances contribute significantly to this step [185]. As shown in Figure 16, the TEM and SEM images of plant-medicated the synthesis of Ag-doped ZnONPs.

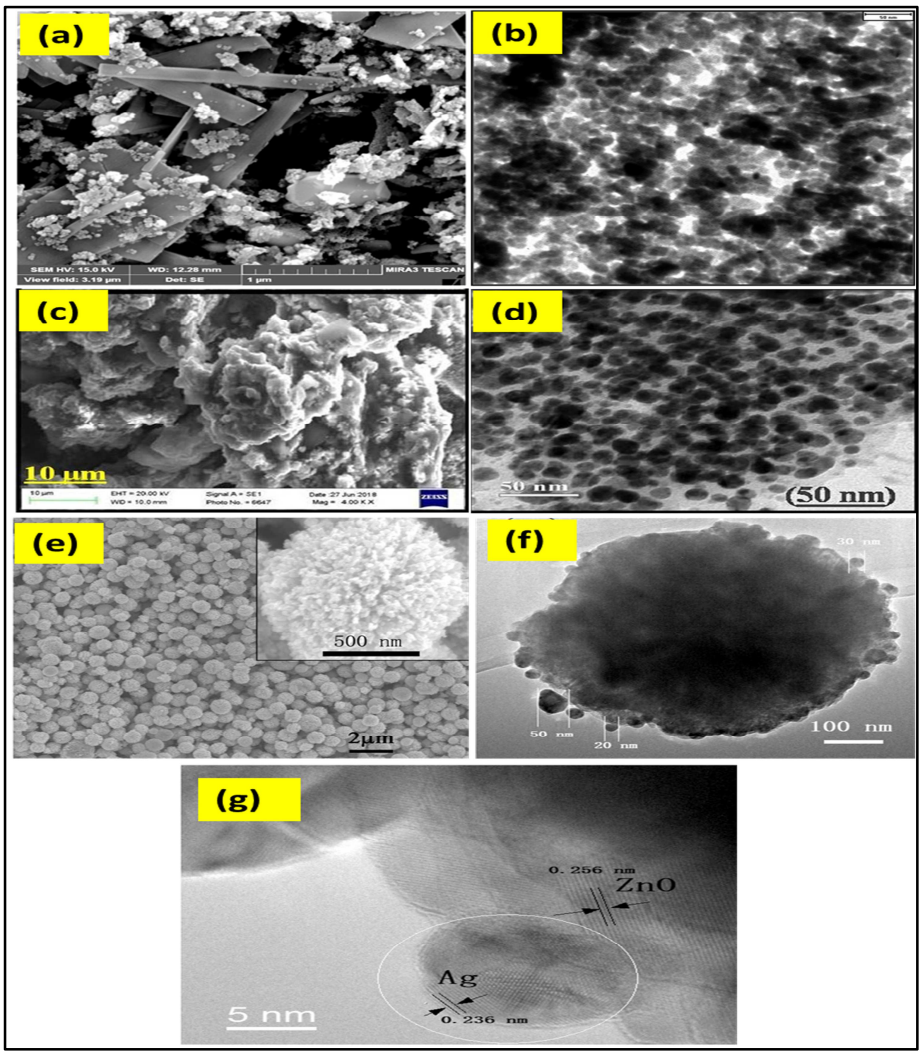

Figure 16: SEM and TEM images of Ag-ZnO nanocomposite: (a, b) synthesized using *Trigonella foenum-graecum* leaf extract [158], (c, d) prepared with *Ocimum tenuiflorum* (Tulsi) seed extract, (e, f) fabricated via a microwave-assisted technique], and (g) HRTEM images with SAED pattern.

Therapeutic application of Ag and ZnONPs

NPs have emerged as potent therapeutic agents owing to their unique physicochemical properties, including high surface area-to-volume ratio, tunable size and shape, and the ability to be functionalized with bioactive molecules. These attributes enable NPs to interact with biological systems at the molecular level, offering significant advantages in targeted drug delivery, antimicrobial therapy, tissue regeneration, and cancer treatment [186]. NPs such as AgNPs and ZnONPs and their nanocomposites are particularly interesting due to their multifunctional roles in therapeutic applications.

Wound healing and tissue regeneration

NPs have garnered increasing attention in recent years as multifunctional agents in wound care, owing to their unique physicochemical properties and ability to interact with biological systems at the cellular and molecular levels. Their dual role in promoting tissue regeneration and combating bacterial infections makes them highly effective in addressing the complex and often chronic nature of wound healing [187]. NPs are vital in accelerating wound healing and promoting tissue regeneration by influencing key cellular and molecular events throughout the healing cascade. Chronic wounds pose a significant global health burden, especially among diabetic patients, affecting millions annually and leading to significant healthcare costs. Their complex and prolonged healing process requires more effective and affordable therapies. In recent years, NPs have emerged as promising agents in chronic wound treatment, functioning as drug carriers and active therapeutic agents. They influence various stages of healing by modulating intracellular signaling pathways [188]. Figure 17 illustrates that nanoparticle-integrated wound dressings are multifunctional in managing chronic or infected wounds. These systems simultaneously address infection control, inflammation modulation, and tissue regeneration by acting at molecular, cellular, and tissue levels. Integrating various NPs into biomaterial-based films or carriers enhances therapeutic outcomes, stability, bioavailability, and target specificity.

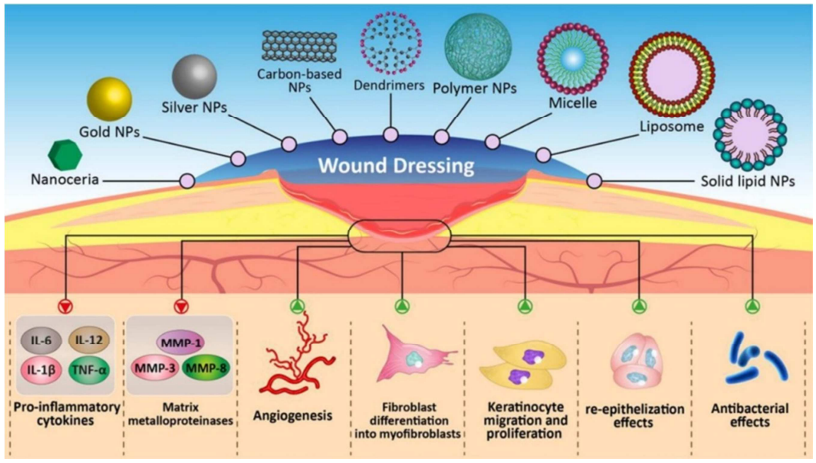

Figure 17: Schematic representation of various nanoparticle-based wound dressings and their therapeutic roles in wound healing. Different classes of NPs, including gold, silver, cerium oxide, carbon-based NPs, dendrimers, polymeric NPs, micelles, liposomes, and solid lipid NPs, are incorporated into wound dressings to exert multiple biological effects. These include reduction of pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α), regulation of matrix metalloproteinases (MMP-1, MMP-3, MMP-8), promotion of angiogenesis, fibroblast differentiation, keratinocyte migration, re-epithelialization, and enhanced antibacterial activity [188].

ZnONPs exhibit multiple therapeutic properties that contribute to wound healing. These include strong antibacterial activity, which helps reduce microbial load and prevent infections that commonly delay wound closure. They are effective against a wide range of bacterial and fungal pathogens. Additionally, ZnONPs generate ROS at the wound site, removing cellular debris and promoting tissue regeneration [189]. Their anti-inflammatory effects further support healing by modulating the inflammatory response, suppressing pro-inflammatory cytokines, and encouraging the resolution of chronic inflammation, an essential step for effective tissue repair. These properties allow ZnONPs to facilitate key processes across various phases of healing, including re-epithelialization and fibroblast activation [190]. Innovative formulations have been developed to harness these properties. The antibacterial wound dressings were prepared by saturating cotton with coffee grounds and incorporating ZnONPs, enhancing the dressings' antimicrobial and regenerative potential. Such approaches highlight the versatility of ZnONPs when combined with natural substrates for advanced wound care [191].

Zinc (Zn) plays a crucial role in diabetic wound healing by promoting neoangiogenesis and exerting potent antioxidant effects, which are essential for accelerating tissue repair and mitigating oxidative stress (Figure 18). The antioxidant features of zinc help neutralize oxidative stress obstructing successful diabetic wound healing. Through its antioxidant mechanism, zinc acts as a protective agent for enzyme sulfhydryl groups and proteins. It disrupts the interaction between copper and iron during Fenton reactions to decrease hydroxyl radicals. DNA repair and transcription become possible through zinc finger protein activation while the production of antioxidant enzymes also receives stimulation. Zinc stabilizes the metallothionein (MT) structure to improve its radical-scavenging ability [192]. Zinc serves as a core element in superoxide

dismutase (SOD) which stands as the crucial antioxidant defense enzyme in cellular biology. Multiple beneficial effects of Zn help diabetic wound healing by reducing oxidative stress while promoting cellular repair systems [193].

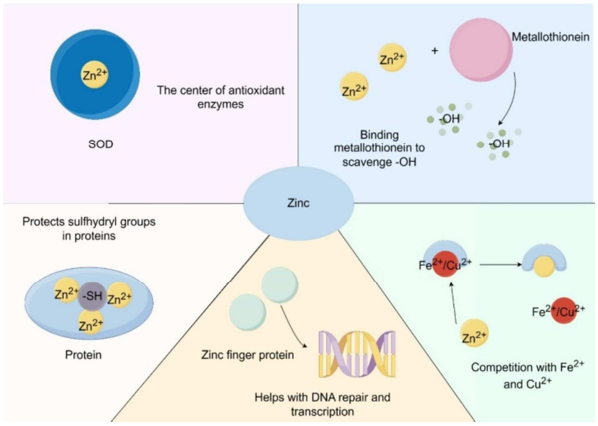

Figure 18: Illustration of zinc's antioxidant mechanisms in diabetic wound healing. Zinc contributes by stabilizing sulfhydryl groups in proteins, acting as a cofactor in superoxide dismutase (SOD), competing with Fe^{2+} and Cu^{2+} to limit hydroxyl radical formation, supporting DNA repair via zinc finger proteins, and enhancing hydroxyl radical scavenging through metallothionein binding [194].

On the other hand, AgNPs also contribute significantly to wound healing by reducing microbial load at the wound site, minimizing inflammation, and creating a conducive environment for tissue regeneration. The topical treatment with AgNPs proves effective for multiple types of wounds, which include incision wounds and excision wounds, as well as burn wounds. The treated wounds did not exhibit any bleeding signs, infections, or pus (Figure 19). The wound healing properties of AgNPs were proven through faster wound closure rates, elevated hydroxyproline content levels and reduced epithelialization time. The repair process benefited from the elevated production of inflammatory cytokines while antioxidant enzymes also helped the recovery. The research demonstrates AgNPs function as dual antimicrobial and tissue-regenerative agents which shows great potential for improving advanced wound care treatment [195]. Importantly, AgNPs have demonstrated effective topical activity in treating various wound types, including incisions, excisions, and burns. Treated wounds showed no signs of bleeding, infection, or pus formation. Their wound-healing efficacy was evidenced by accelerated wound closure, increased hydroxyproline levels, and shortened epithelialization time. Elevated inflammatory cytokines and antioxidant enzyme levels also contributed to enhanced tissue repair. These findings support the therapeutic potential of AgNPs as antimicrobial and regenerative agents for advanced wound care applications [196].

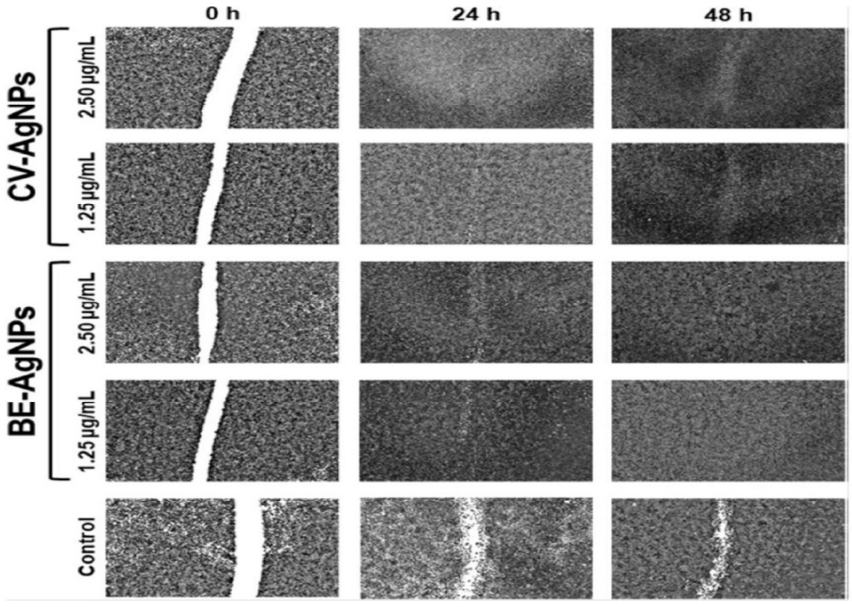

Figure 19: Scratch assay images showing in vitro wound healing activity of CV-AgNPs and BE-AgNPs at 2.50 µg/mL concentrations and 1.25 µg/mL in L929 fibroblast cells over 0, 24, and 48 hours. Both nanoparticle types significantly enhanced cell migration and wound closure compared to the untreated control group [196].

Antibacterial activities of Ag doped ZnONPs

The antimicrobial potential of NPs is one of their most extensively studied therapeutic properties. AgNPs and ZnONPs exhibit broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria and antifungal and antiviral properties. Their mechanisms of action include disrupting bacterial cell walls and membranes, generating ROS, interfering with intracellular components (proteins, DNA, and RNA), and inhibiting enzymatic activity essential for microbial survival [197]. NPs function differently than antibiotics because they provide several bacterial inhibition methods and produce minimal adverse effects. The antimicrobial mechanism involves three pathways: bacterial cell wall interaction, toxic metal ion release, and ROS generation . The positive charge of NPs enables robust electrostatic bonding to Gram-negative bacterial lipopolysaccharides and Gram-positive bacterial peptidoglycan structure together with teichoic acid surface components [198]. Through the development of membrane pores, this interaction causes bacterial cell wall devastation, which results in cell component leakage until death occurs [199]. NPs can easily penetrate bacterial cells effectively while damaging their membranes, interrupting cellular metabolic functions, including ROS production, from which oxidative stress develops. NPs exert their antibacterial effects by disrupting bacterial proton efflux pumps, leading to pH imbalance and alterations in membrane surface charge. Their interaction with bacterial DNA, ribosomes, and lysosomes initiates a cascade of cellular damage, including enzymatic degradation, electrolyte imbalance, enzyme inhibition, and protein denaturation, ultimately resulting in bacterial cell death [200]. Figure 20 displays NPs' main bacterial targets and examples of how NPs treat skin infections.

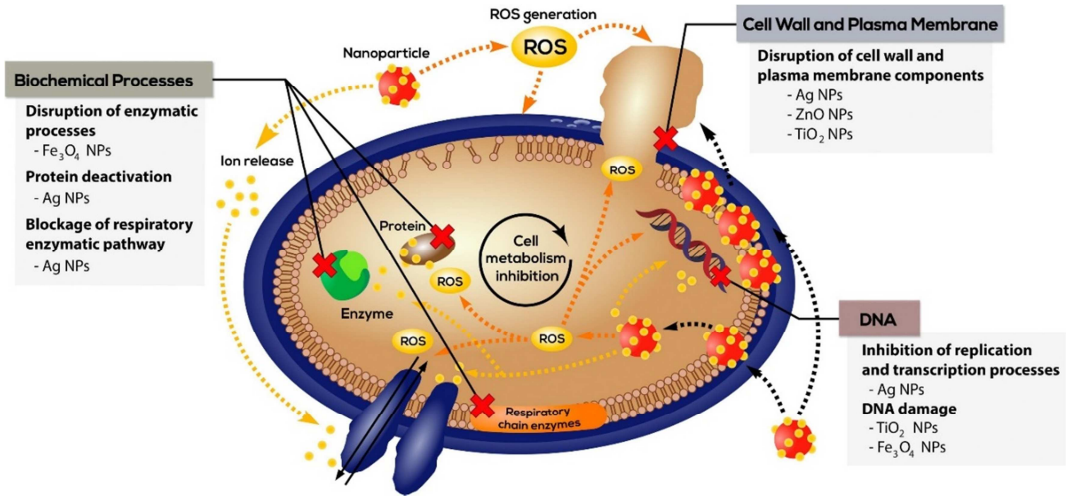

Figure 20: Diagrammatic illustration of the mechanism of antibacterial action of NPs and provides examples of NPs used to treat skin infections [200].

Conclusion

Wound care is evolving through integrating nanotechnology with biopolymeric materials, offering innovative solutions for chronic wound management. This review underscores the promising role of silver-zinc oxide NPs (Ag doped ZnONPs) embedded in gelatin-based films as multifunctional wound dressings. These nanocomposites provide mechanical support and therapeutic functionality, including antimicrobial action, modulation of oxidative stress, and tissue regeneration. AgNPs exert antibacterial effects via membrane disruption and ROS production, while ZnONPs promote angiogenesis and regulate inflammation. Gelatin (Gel) enhances biocompatibility, supports cell proliferation, and ensures sustained nanoparticle release. Green synthesis methods further improve these nanomaterials' environmental and clinical safety profiles. Despite these advantages, challenges remain in nanoparticle reproducibility, long-term safety, and large-scale production. Overall, Ag doped ZnONPs-loaded Gel film represents a next-generation, bio-responsive platform poised to improve outcomes in chronic wound therapy significantly.

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Conflict of Interest

The author declares no conflict of interest.

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