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Collagen-Based Nanoparticles as Drug Delivery System in Wound Healing Applications

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Background: Conventional wound dressings often adhere to wounds and can cause secondary injury due to their lack of anti-inflammatory and antibacterial properties. In contrast, collagen-based nanoparticles (NPs) as drug delivery systems exhibit both biocompatibility and biodegradability, presenting a promising avenue for accelerating wound healing processes.

Aims of Study: This review aims to provide a comprehensive overview of the mechanisms involved in wound healing, description of the attributes of ideal wound dressings, understanding of wound healing efficacy of collagen, exploring NPs-mediated drug delivery mechanisms in wound therapy, detailing the synthesis and fabrication techniques of collagen-based NPs, and delineating the applications of various collagen-based NPs infused wound dressings on wound healing.

Methodology: This review synthesizes relevant literature from reputable databases such as Scopus, Science Direct, Google Scholar, and PubMed.

Results: A diverse array of collagen-based NPs, including nanopolymers, metal NPs, nanoemulsions, nanoliposomes, and nanofibers, demonstrate pronounced efficacy in promoting wound closure and tissue regeneration. The incorporation of collagen-based NPs has not only become an agent for the delivery of therapeutics but also actively contributes to the wound healing cascade.

Conclusion: In conclusion, In brief, the use of collagen-based NPs presents a compelling strategy for expediting wound healing processes.

Keywords: wound healing, biodegradability, nanoparticles, fabrication techniques, collagen

Introduction

The skin serves as a crucial barrier to protect the internal tissues from mechanical trauma, microbial pathogens, ultraviolet radiation, and temperature extremes.[1,2] Injuries are dermal disturbances arising from diverse origins such as physical trauma, chemical agents, incisive instruments, and thermal exposure.[3,4] Wound healing is conventionally characterized by sequential phases. The phases cover hemostasis, inflammation, proliferation leading to angiogenesis and re-epithelialization, and remodeling. This intricate process is inherently varied and is temporally protracted.[5–7] The process of wound healing encompasses a multitude of factors, such as angiogenesis, extracellular matrix (ECM) responsiveness, collagen synthesis, granulation tissue development, and re-epithelialization.[8–11] However, the effectiveness of wound healing and wound control is significantly influenced by the dressing technique used.[12,13]

In general, wounds may be treated using various dressing techniques. They come with hydrogel, gauze film, foam, scaffold, and hydrocolloid, all of which are commonly prepared with antimicrobial properties.[14–16] An ideal wound dressing material should demonstrate biocompatibility, adhere to the wound without leaving sticky residues, have optimal water absorption capacity, the adaptable to environmental changes such as pH or moisture levels, and have the ability to sustain a moist environment that is favorable for wound recovery.[17–22] Nevertheless, an ideal wound dressing system

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requires the characteristics of a drug delivery vehicle that possesses antimicrobial activity to protect against wound infections.[23] However, numerous traditional wound healing methods encounter challenges in meeting these standards as they encounter difficulties in reliably dispensing therapeutic agents to the wound site, consequently causing a prolonged wound-healing process.

Therefore, researchers aim to devise an innovative approach capable of addressing the challenges mentioned and expediting the wound-healing process. Nanotechnology is deemed a suitable approach, owing to its minute size, versatile characteristics, and ability to deliver drugs precisely to the wounded area.[23,24] The molecular scale of materials usually ranges from 1 to 1.000 nm, with promising implications for biomedical applications.[25,26] To date, a variety of nanomaterials have been used to expedite the wound-healing process. It is done with particular emphasis on nanoparticles (NPs). They have garnered considerable interest for their effectiveness in promoting wound recovery. In the advancement of wound dressings, NPs have been used either as drug delivery carriers or as bioactive components. Both of these aimed at improving wound healing outcomes.[27,28] Numerous research findings indicate that polymer-based NPs drug delivery systems expedite wound healing by protecting therapeutic agents from degradation in specific wound conditions.[29,30]

Drug delivery systems using NPs derived from natural collagen polymers have garnered considerable attention, particularly in the biomedical field due to their safety and environmental friendliness.[31,32] Collagen NPs have benefits in comparison to other natural polymeric NPs. They are attributed to their favourable biocompatibility, biodegradability, and low antigenicity.[33,34] Collagen NPs exhibit a significant potential for high cationic charge density owing to their abundant amino groups, making them more advantageous compared to other synthetic and natural polymer NPs.[35,36] Collagen NPs play a key role in their integration into tissue engineering systems and in their application in wound dressing systems to provide wound healing.[37,38]

Collagen is an environmentally friendly, safe, and efficient source of nanocarriers comparison to other types of polymer NPs. The high cationic properties and biodegradability of collagen-based NPs wound dressing systems facilitate the local administration of drug to the wound area by enhancing drug absorption, and promoting the natural healing process.[39,40]

Collagen has been the focus in many studies to determine its effectiveness in wound healing. A number of recent studies describe the application of collagen-based NPs for wound therapy, which shows the shift of interest towards collagen-based nanotherapeutics. Despite this positive trend, there is still no comprehensive scholarly work that analyze and synthesize the efficacy of collagen NPs as a drug delivery system in wound healing applications. This review aims to summarize the role of collagen-based nanoparticulate drug delivery systems in wound-healing, serving as a reference for scientists working in this field.

Methodology

This comprehensive review used a systematic examination of literature sourced from esteemed databases including Scopus, Google Scholar, and PubMed. This review processed targeted keywords such as “collagen nanoparticles wound”, “collagen nanoparticles wound drug delivery”, and “collagen nanoparticles”, Relevant articles were meticulously curated. The selected literature, comprising both review and research articles, underwent rigorous categorization, with emphasis placed on the relevance to specific thematic areas of interest. The final selection of articles, meticulously chosen based on their alignment with the outlined criteria, is outlined in Figure 1, illustrating the scope and depth of this review.

The Stages of Wound Healing Process

The wound healing process involves several sequential stages in repairing damaged tissue. The following is a brief description of each stage in the wound healing process, as shown in Figure 2.[41] The hemostasis stage in the wound healing process begins immediately after the injury occurs. The main goal is to stop bleeding.[42] Damaged blood vessels will contract to reduce blood flow, while blood clotting factors work to form blood clots or temporary clots. Platelet cells are the first to respond and form blood clots in the wound area.[43] Damaged blood vessels will narrow and form temporary blood clots to stop bleeding.[44] Endothelial cells in blood vessels also play a role in producing blood clotting factors.[45]

The subsequent stage of the inflammatory response begins once the bleeding has ceased, typically concluding within the initial 24–72 hours post-injury.[47] During the inflammation stage, the wound area becomes red, swollen, and warm due

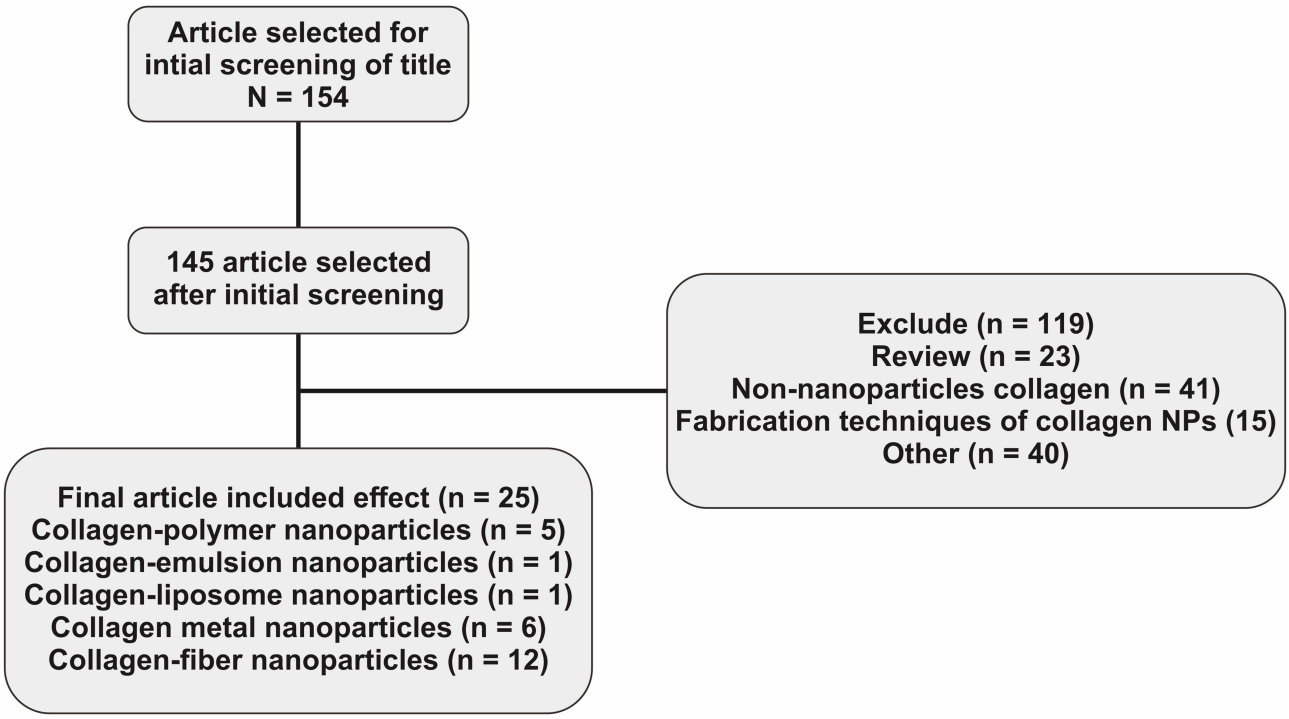

Figure 1 Flowchart illustrating the methodology employed in this review.

to the body's response to the injury.[48] White blood cells, including neutrophils and macrophages, migrate to the wound area to clear debris, eliminate bacteria, and initiate the healing process.[49] Growth factors such as fibroblast growth factor and proinflammatory cytokines are also produced to facilitate tissue regeneration.[50]

The proliferation phase begins with the fibrin matrix being replaced by a new matrix consisting of proteoglycans, collagen fibers, keratinocytes, and anti-inflammatory macrophages, thereby restoring tissue structure and function.[51] Additional significant occurrences during this phase of healing involve the development of granulation tissue and epithelialization.[52] Fibroblasts play a pivotal role in the proliferative phase of healing, as they generate and deposit collagen, proteoglycans, elastin, and other constituents forming the granulation tissue.[53] Type III collagen is produced in large quantities in this stage, including other proteins in the ECM.[54] This phase also covers blood clot formation, temporary ECM formation and various growth factors and proteins, including type I collagen, which are upregulated during this stage.[55]

The final stage of remodeling is done through the repair and strengthening of scar tissue formed during the proliferation stage. In this phase, the number of fibroblast cells decreases. Furthermore, the scar tissue becomes more organized to resemble the surrounding tissue.[56] Collagen, produced during the proliferation stage, undergoes reorganization and repair to increase tissue strength.[57] Type I collagen plays a key role in enhancing the tensile strength of scars. The important aspect of this stage is completed with the regeneration of elastic fibers within the ECM to maintain skin elasticity.[58] Elastin, a protein present in the dermis layer, has various functions in mechanical and cellular interactions. This remodeling process can extend for months to years after the initial injury.[59] A diagram illustrating the primary stages of the wound healing process can be seen in Figure 2.

Advantages and Disadvantages of Clinically Used Materials and the Ideal, Properties of Wound Dressing Excipients

Current Types and Characteristics of Wound Dressings

Various types of wound dressings are available in the clinic for various applications depending on the status and severity of the wound, with the ultimate aim of promoting wound healing (Figure 3). Over time, advancements in science and

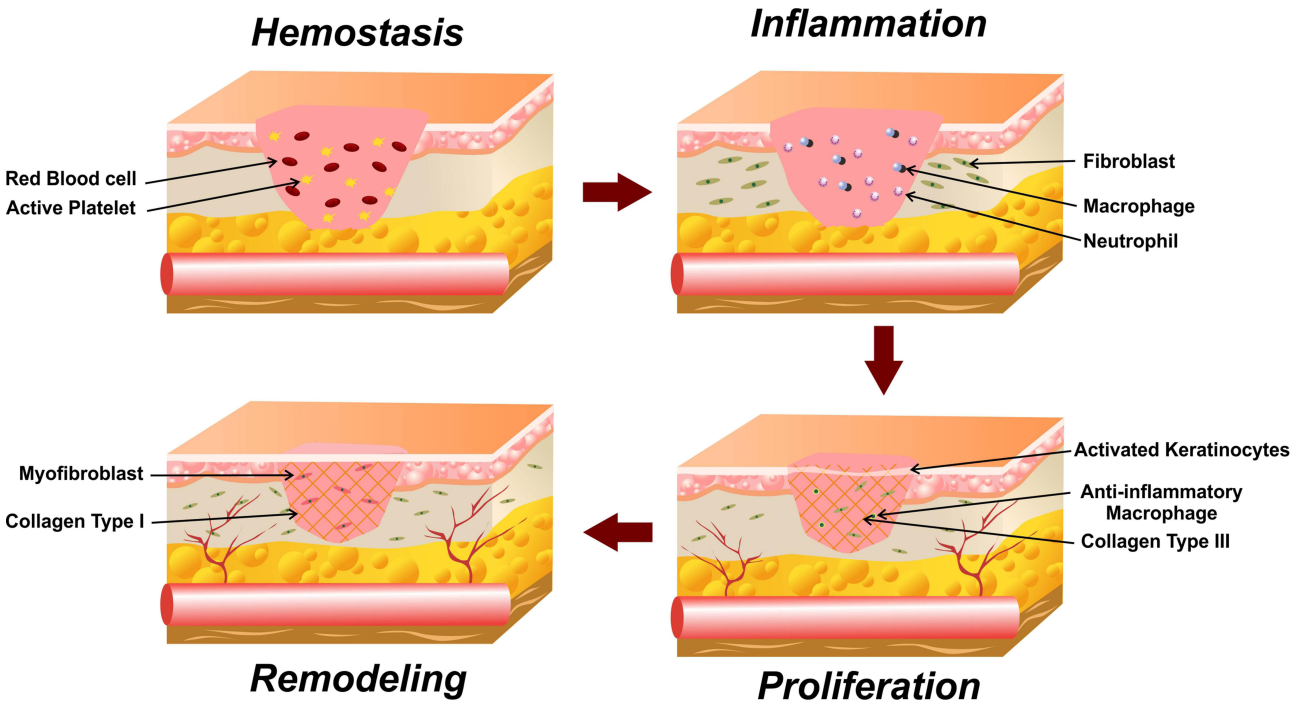

Figure 2 A diagram illustrating the primary stages of the wound healing process.
Notes: Reprinted from *Pharmacol Res*, volume 174, Yazarlu O, Iranshahi M, Kashani HRK et al. Perspective on the application of medicinal plants and natural products in wound healing: A mechanistic review. Copyright 2021, with permission from Elsevier.[46]

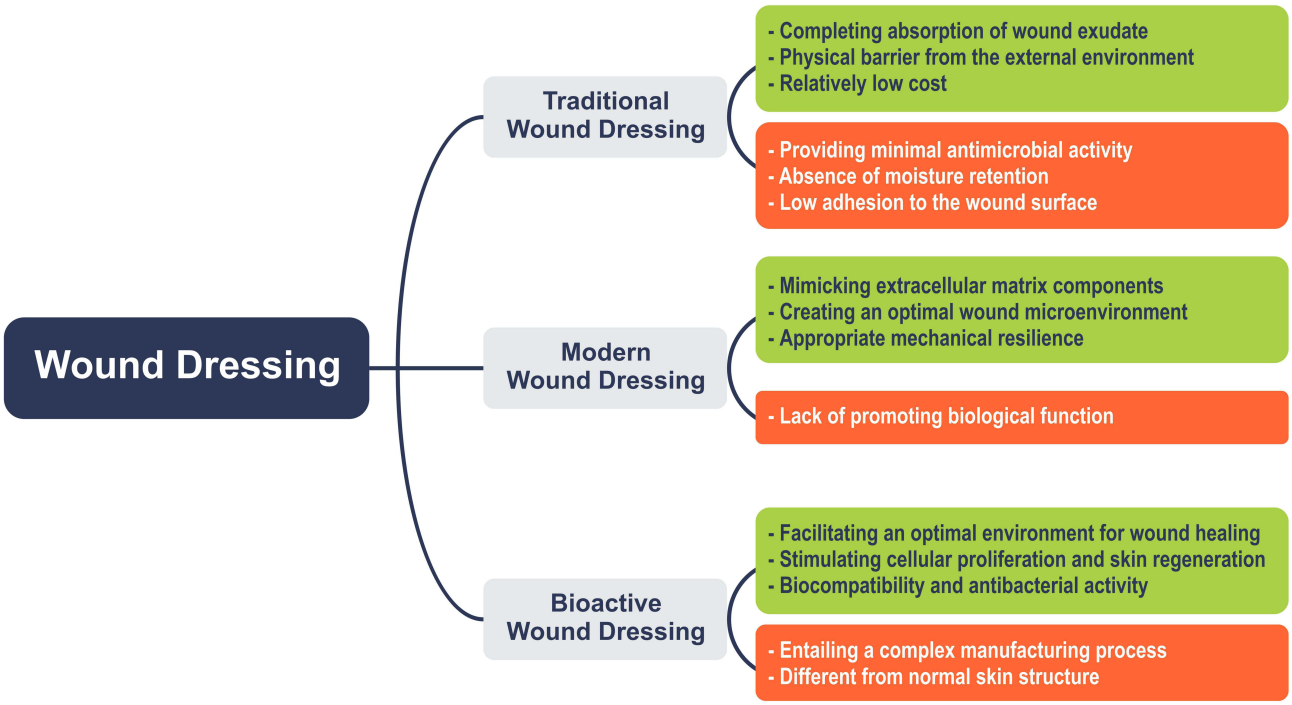

Figure 3 Development and characteristics of wound dressings. The advantages and disadvantages of various dressings are outlined in green and orange squares, respectively.

technology with a deeper comprehension of wound healing mechanisms, have led to continuous evolution and enhancement of wound dressing functionalities.[60,61] Traditional wound dressings are primarily made of materials like cotton, polyester fiber, and gauze.[62] This wound dressing material is easy to prepare, readily available, and effective in absorbing wound exudate to aid drainage of the wound.[63] However, their drawbacks include limited protective and healing effects due to the lack of moisture and excessive water absorption, causing the wound to absorb and drain more quickly.[64] Once the dressing dries, it adheres to the wound and has the potential to cause secondary injury during dressing changes. Moreover, their large pore structure fails to provide adequate isolation from environmental bacteria. In addition, as they lack anti-inflammatory and antibacterial properties, it is hence challenging to create an optimal sterile environment for wound healing.[65,66] Consequently, modern wound dressings are increasingly being used in place of traditional ones due to their superior benefits.

The manufacture of modern wound dressings uses base layer materials that have superior characteristics. This wound dressing system reflects the structure of the natural extracellular matrix to some extent, thereby stimulating cell growth and facilitating wound healing.[67] The materials used as the matrix for the dressing have also certain wound-healing properties.[68] For example, collagen polymers have a role in controlling bleeding, retaining moisture, and facilitating gas exchange.[59] Furthermore, by employing different types of materials as the matrix for the wound dressing preparation, different properties and functions can be imparted, thereby creating an improved wound microenvironment.[22] The incorporation of bioactive substances has been shown to enhance the differentiation of biological functions, wound dressing properties, antibacterial and anti-inflammatory effects, and cellular proliferation.[69,70] These dressings, which are known as bioactive dressings, can promote cell growth and wound healing by delivering bioactive substances to the wound surface.[71]

Properties of Ideal Excipients for Wound Dressings

Currently, available wound dressings can repair wounds to a certain extent and speed up healing. However, the availability of technology and materials is limited, so there is no perfect wound dressing product for use in clinical care.[72] Traditional dressings, such as bandages, gauze, and cotton, have evolved into smart dressings, and modern tissue-engineered dressings, with improved the properties and functionalities.[73] Traditional dressings mainly provide a physical barrier and drainage function for the wound but often adhere to the wound and can cause secondary injury due to their lack of anti-inflammatory and antibacterial properties.[62]

Modern dressings, which are made from natural materials like chitosan and collagen, as well as synthetic ones such as polyvinyl alcohol, have been devised to address these limitations.[35] By using natural or synthetic ingredients to create hydrogel, hydrocolloid, and other forms, the dressings can enhance moisture retention and absorption properties. They can ensure wound conformity and a moisture-rich environment conducive to healing.[74] Nevertheless, individual biological matrix materials have limited properties and cannot fully address wound inflammation, hemostasis, growth promotion, and bacterial infection.[75] To enhance the efficacy of wound dressings, bioactive substances are incorporated into functional matrix materials such as chitosan and collagen.[76] Incorporating silver ions into the matrix can enhance the dressing's antibacterial properties, bolster the immune response, and accelerate wound healing.[77] Similarly, the introduction of nerve growth factor (NGF) into the matrix triggers the release of endothelial cells, and keratinocytes, facilitating the migration and proliferation of fibroblasts, thereby promoting wound healing.[78]

Therefore, an ideal and good wound dressing system for skin wounds must have the following characteristics: (1) the ability to moisturize the skin well, (2) an optimal water absorption capacity, (3) sufficient air circulation, (4) an appropriate mechanical strength, (5) the ability to adhere to the wound without leaving a sticky residue, (6) antimicrobial properties, (7) good biocompatibility, (8) the ability to sustain a moist environment that is favorable for wound recovery, (9) affordable cost, and (10) the ability to support the growth and regeneration of skin cells in the skin tissue structure.[79,80]

Wound Healing Properties of Collagen

The structure of the collagen molecule consists of a triple helix arrangement formed from by three intertwined polypeptide chains. These chains are stabilized through hydrogen bonds in the CO and NH groups, along with electrostatic interactions (Figure 4). An important advantage of integrating collagen into wound dressings is its capacity to expedite the healing process, especially in challenging wound scenarios. Collagen promotes the migration of macrophages and fibroblasts to the wound

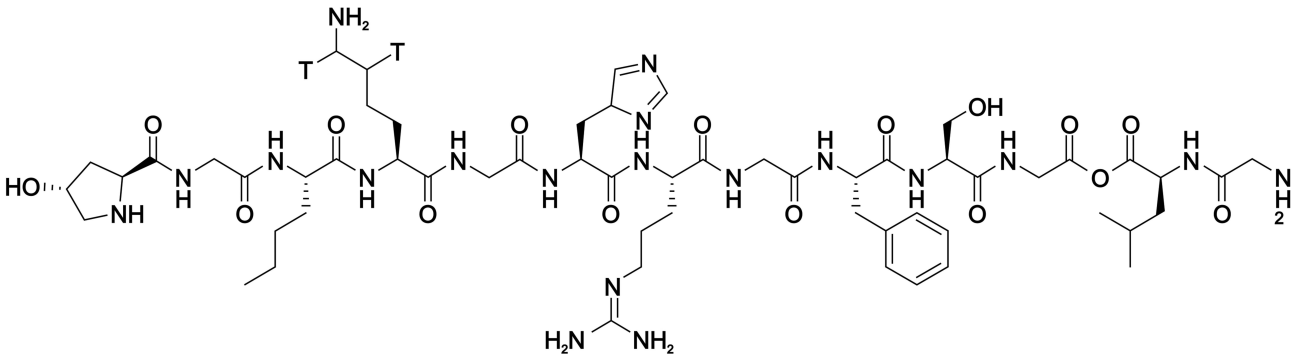

Figure 4 Molecular structure of collagen type I.
Notes: Reprinted from *Life Sci*, volume 290, Sharma S, Rai VK, Narang RK, Markandeywar TS. Collagen-based formulations for wound healing: A literature review. 290. Copyright 2022, with permission from Elsevier.[84]

area, facilitating the development of a new collagen framework.[81] Additionally, collagen's high hydrophilicity makes it suitable for wound dressings as it can absorb wound fluids containing diverse matrix metalloproteinase (MMPs) and growth factors, further aiding the healing process.[82,83]

Collagen displays its wound healing efficacy through various well-researched mechanisms, including enhancing hemostasis, exhibiting antimicrobial properties, promoting proliferation, encouraging migration, and modulating the inflammatory response (Figure 5). The physicochemical characteristics of collagen, which characterized by the high cationic charge of its amino groups, enable it to enhance hemostasis at the wound site through several identified mechanisms.[59,85] Collagen with its positive charge, can cluster negatively charged erythrocytes, platelets, and plasma

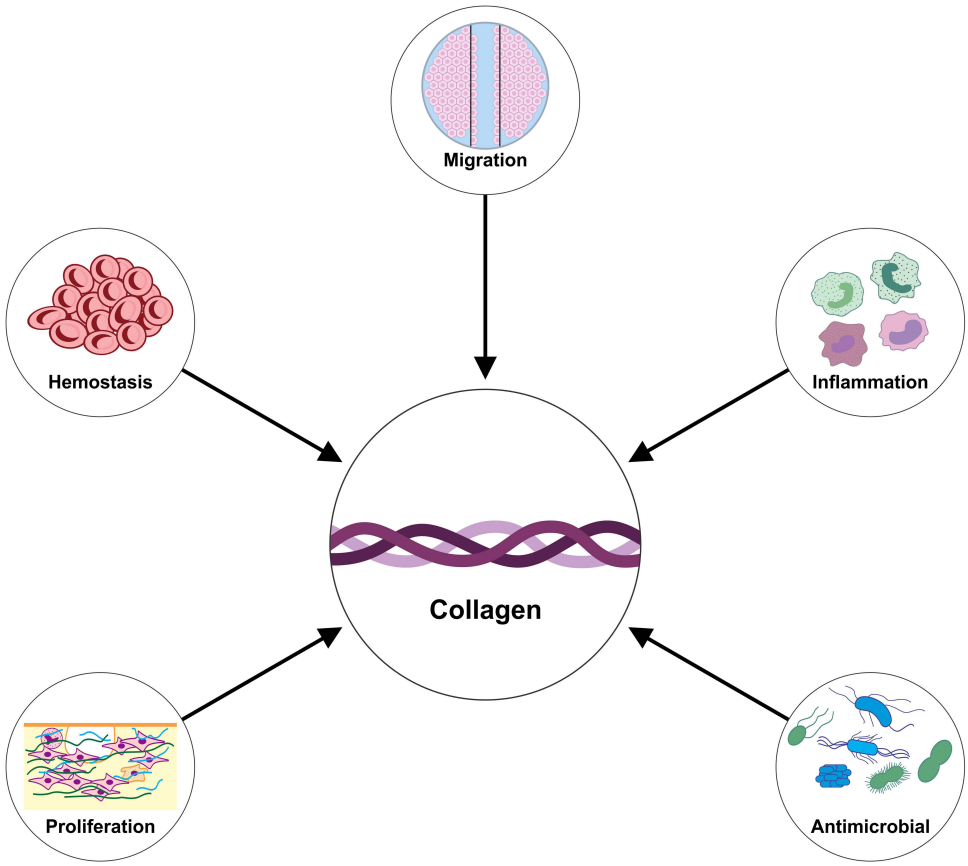

Figure 5 Summary of the healing attributes facilitated by collagen.

proteins such as fibrinogen. These interactions contribute to hemostasis and blood clot formation.[59] The wound-healing properties of collagen also include its ability to promote cell proliferation, stimulating the growth and development of new cells in the wound area.[86] By facilitating cell proliferation, collagen helps accelerate tissue regeneration and the formation of new scar tissue in the wound area.[87]

Collagen promotes migration in the wound-healing process, facilitating new tissue growth and faster wound closure. Additionally, collagen aids in the formation of the extracellular matrix, which is essential for effective wound healing.[88] Collagen contributes to preventing infections at wound sites by exerting antimicrobial effects through interactions between its positively charged amino groups and the negatively charged components of bacterial cell membranes.[89] Additionally, its capability to bind trace amounts of ions on the surface membrane of bacterial cells also adds to its antimicrobial properties, although to a lesser degree.[90] Prolonged inflammation beyond the normal duration can lead to chronic wounds and interfere with the natural wound-healing process.[91] Collagen, possessing immunostimulatory properties, can regulate both pro-inflammatory and anti-inflammatory cytokines.[92] This modulation plays a crucial role in controlling the inflammatory response at the wound site, which is essential for effective wound healing.[93]

Several strategies are hence crucial to enhance the efficacy of collagen in wound healing while also serving as a drug delivery vehicle.[31] One effective technique in material development for wound healing involves converting collagen into NPs. These collagen-based NPs can effectively deliver drugs to wound areas, thereby enhancing drug absorption by the target tissue and expediting the wound-healing process.[39,94]

The Application of NPs as a Drug Delivery System in Wound Healing

NPs have become a significant asset in various realms of pharmaceutical and medical exploration due to their minute sizes, adaptable attributes, and capability to accomplish precise and controlled drug delivery.[95] The vast potential of NPs stems from their ability to be tailored and precisely released.[96] NPs are garnering growing interest for their use in wound dressing materials, serving both as carriers for drug delivery systems and as active agents, ultimately enhancing wound healing process,[79,97] as shown in Figure 6.

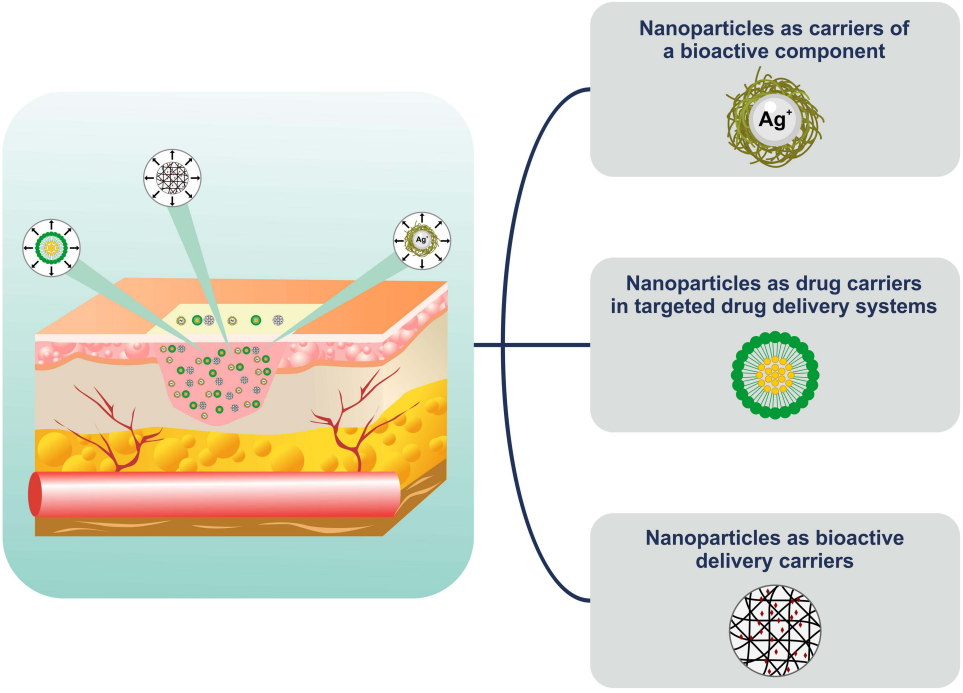

Figure 6 Overview of the application of NPs for wound healing.
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NPs serve as excellent carriers for transporting active compounds to enhance wound healing outcomes as drug delivery vehicles.[2] Likewise, NPs play an important role in protecting and extending the half-lives of short-lived therapeutic agents, such as growth factors and nitric oxide, which are susceptible to degradation by proteolytic enzymes and are transient.[99] Furthermore, NPs have been instrumental in achieving precise and controlled delivery of antimicrobial agents and natural products for treating wounds, besides being used in gene therapy aimed at modifying the wound microenvironment by delivering specific genetic material to the site of injury.[100] Interestingly, bioactive polymers like collagen offer an intriguing reservoir of important elements for NP systems, showcasing notable benefits in promoting wound healing.[35,101,102] Overview of the application of NPs for wound healing can be seen in Figure 6.

Discussion - Techniques for Producing Collagen-Based NPs

Collagen NPs can be produced via three techniques: self-assembly, chemical, and physical. Chemical methods can be carried out by emulsification whilst, physical methods include electro spraying and electro spinning methods.[103] In addition to these methods desolvation and milling will also be discussed to provide insight into the diverse production methods available for collagen-based NPs.[31]

Self Assembly

Proteins that undergo hydrophobic modification and are introduced into water-based solutions can autonomously assemble with the hydrophobic cores serving as pathways for active molecules.[104] Self-assembly methods also involve dissolving individual protein chains in a solution that exceeds a critical micelle concentration, at a specific solution temperature suitable to the formation of nanoscale aggregates.[105] Research has demonstrated that self-assembled wound dressings containing collagen stimulate fibroblast production and accelerate wound healing. By manipulating the self-assembly conditions of collagen constructs, the controlled release of biomolecules in these bioactive wound dressings can be achieved.[106]

Solvent Extraction/Emulsification

Polymers and drugs precipitate into droplets, and NPs will be formed by solvent extraction via evaporation. The double emulsion method for nanoparticle synthesis is both rapid and cost-effective.[107] This technique involves using a surfactant to stabilize the emulsion during dispersion. Subsequently, the organic solvent is removed to preserve the NPs in an aqueous buffer. A stabilizing agent and surfactant are necessary to maintain the stability of the emulsion, which is typically thermodynamically unstable These components influence the interactions between the drug and the matrix, as well as the rate of drug release.[108]

Electrospraying

High voltage is employed to dispense a protein-containing, resulting in the ejection of a liquid jet stream from the nozzle and the formation of aerosolized droplets that comprise protein NPs of colloidal size.[109] This process facilitates the incorporation of drugs into these NPs. Parameters such as applied voltage, distance of operation, gauge diameter of the needle, and flow rate may vary depending on the type of drug delivery system. A higher voltage is applied to ensure that the polymer solution exits the syringe as NPs. Electrospraying is an economical and easily implemented method with high encapsulation efficiency. It enables the production of stable NPs without concerns regarding biocompatibility and reduced encapsulation efficiency.[110]

Desolvation

Simple coacervation or desolvation is a self-assembly technique in the production of protein NPs, whereby a collagen solution containing a drug is mixed with a desolvation agent, such as alcohol or a natural salt.[111] This agent induces changes in the collagen structure, reducing its solubility. Once a critical level of desolvation is reached, a crosslinking agent like glutaraldehyde is introduced to the collagen mixture, leading to the formation of NPs. Factors such as pH, protein concentration, desolvation rate, and temperature influence the size of the NPs produced through desolvation. Lower protein concentration and higher pH result in smaller NPs, achieved by decreasing protein solubility with the addition of the desolvation agent.[112]

Milling

Nanoscale collagen can be synthesized using a milling procedure. In this method, mechanical energy is applied to break down the polymer material into finer NPs.[113] Grinding balls are utilized to generate high-energy mechanical impacts effectively disintegrating of the polymer. Cooling the grinding vessel is crucial to prevent material degradation or overheating. As collagen is temperature-sensitive, mechanical grinding with liquid nitrogen is employed to maintain a temperature below approximately −150°C preventing heat-induced denaturation.[114]

Electrospinning

One commonly employed method for fabricating collagen-based nanofibers is electrospinning. In electrospinning, a polymer solution, such as collagen, is ejected through a needle subjected to a high electrical charge. The electrically induced force attracts the polymer solution, resulting in the formation of exceedingly thin fibers that are drawn towards the surface of a collector.[115] These fibers are then accumulated to create an extremely fine fiber matrix. This process produces nanometer-scale fibers with diameters typically ranging from hundreds of nanometers to several micrometers. In the production of collagen-based nanofibers, the collagen solution is initially prepared by dissolving it in an appropriate organic solvent. This solution is then fed into a pump and dispensed through the electrospinning needle. After fiber formation, chemical or physical treatments may be applied to enhance their mechanical properties and biocompatibility.[116]

Collagen-Based NPs as Drug Delivery Systems in Wound Healing

The literature documents various collagen formulations for wound healing, including sponges, hydrogels, and films, all of which utilize collagen as the primary ingredient. However, these larger structures cannot be compared to collagen-based NPs, which offer distinct advantages due to their significantly smaller particle size.[117] The NPs nano-scale dimensions facilitate enhanced penetration through skin tissue, potentially reaching the wound area more effectively and leading to improved wound healing outcomes.[118] In addition, collagen-based NPs possess a high cationic charge, stemming from the abundance of amino groups in their structure, thereby enabling various functions owing to their distinctive properties.[32]

This strong cationic charge result in good stability as electrostatic repulsion forces between similar charges prevent aggregation.[40] It also allows effective interaction between the NPs and the cells involved in the wound healing process, including bacterial cells and mucosal tissue, which further promotes the wound-healing process.[35,102] The development of collagen-based NPs is increasingly offering avenues to improve wound healing outcomes by enabling controlled release, precise delivery of therapeutic substances, and prolonging the activity of the encapsulated therapeutic agents.[101] Compounds with therapeutic properties, when administered through collagen-based NPs, demonstrate the additional benefit of improved skin deposition and penetration.[101] This indicates that the safety profile of therapeutic compounds may also be enhanced by utilizing formulations involving collagen-based NPs.[119] There are six types of collagen-based NPs that are reported in the literature. These include collagen nanofibers, collagen nanopolymers, collagen nanoemulsions, nanocollagen films, collagen nanoliposomes, and collagen metal NPs (Figure 7).

Studies on Collagen-Based NPs as Drug Delivery Systems in Wound Healing Applications

Table 1 summarizes the previously reported studies of collagen-based NPs in wound healing applications.

Collagen-Based Polymer NPs

Polymeric NPs can be broadly classified as either synthetic or natural-based NPs. Natural-based NPs have attracted great attention for their potential in accelerating wound healing. Collagen is a type of natural polymer that can be prepared by assembling the particles themselves or mixing them with other particles using several reported methods.[31] Natural polymers have a structure that is more similar to normal tissue than synthetic polymers, thus supporting the formation of extracellular matrix in wounds.[131] Most natural polymers consist of polysaccharides or peptides, that have better adhesion and hydrophilic properties, and hence will better support the growth of cells attached to their surfaces.[132] Furthermore, natural polymers also have a special

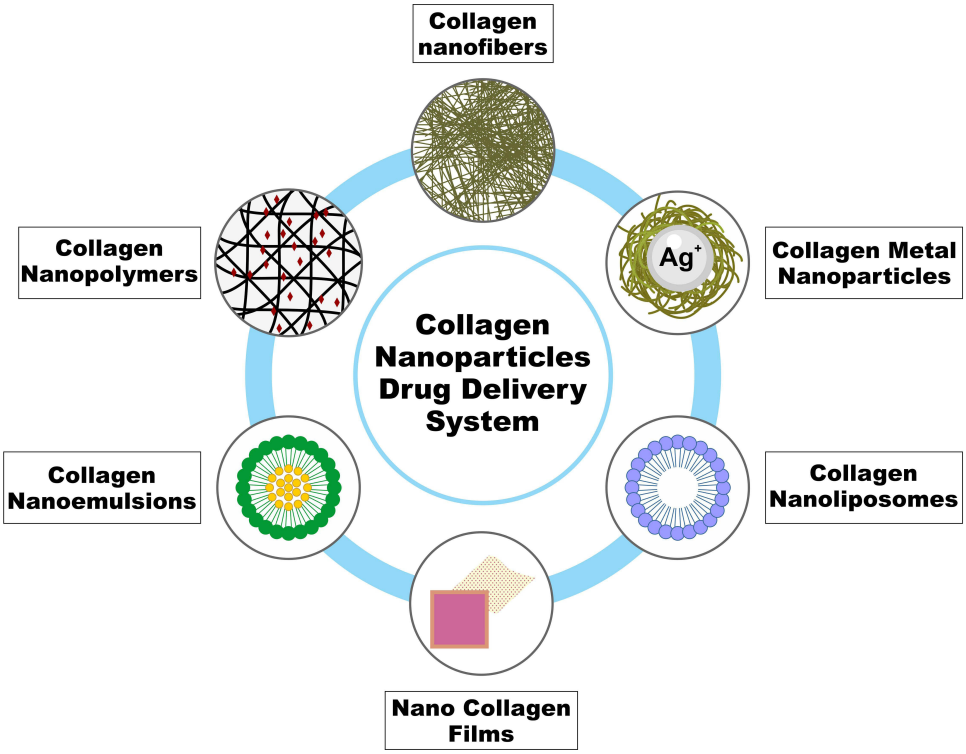

Figure 7 Different collagen-based NPs drug delivery systems in wound healing applications.

role in facilitating the wound-healing process. As an example, collagen is a structural protein that has biodegradable properties, good biocompatibility, effective bioadhesion, and minimal immunogenicity. These properties further support its application in tissue regeneration for wound healing purposes.[133]

Table 1 Studies on Collagen-Based NPs as Drug Delivery Systems and Their Therapeutic Agent Effects

Formulation	Material	Dressing Form	Results	Ref.
Collagen-based polymer NPs	Collagen type I, PVA, curcumin	Composite film	Significant antibacterial activity	[35]
			Good biocompatibility	
			Improves wound healing in excisional skin	
	Collagen type I nanomaterials	Nanoparticles gel	Increase cell proliferation	[39]
			Accelerates the wound-healing process	
	Collagen type I, chitosan, henna extract	Nanocomposite	Significant antimicrobial potential	[119]
			Improves wound healing significantly	
	Collagen type I, macrophage membrane	Nanosuspension	Inhibits the growth of gram-positive bacteria	[102]
			Good biocompatibility	
			Promotes wound healing in infected skin	
	Collagen type I nanosheets	Nanosheets	Good biocompatibility and antibacterial activity	[90]
			Promotes macrophage polarization	
			Promotes wound healing of corneal infections	

(*Continued*)

Table 1 (Continued).

Formulation	Material	Dressing Form	Results	Ref.
Collagen-based emulsion NPs	Collagen type I peptide	Nanoemulsion	Increases collagen deposition	[94]
			Promotes diabetic wound healing	
Collagen-based liposomes NPs	Collagen type I, gelatin alginate, dexamethasone	Hydrogel film	Inhibits the growth of gram-negative bacteria	[120]
			Low cytotoxic properties	
			Promotes corneal wound healing	
Collagen-based metal NPs	Ag NPs, collagen type I	Hydrogel	Promotes antibacterial activity	[101]
			Good biocompatibility	
			Accelerates wound healing in excisional skin	
	Ag NPs, mupirocin, collagen type I	Nanoparticles solution	Increases the migration rate of fibroblast cells	[40]
			Accelerates wound healing in excisional skin	
	Ag NPs, collagen type I, alginates	Biocomposite	Significant antimicrobial activity	[121]
			Low cytotoxic properties	
	ZnO NPs, niosom, collagen type I	Nanocomposite	Increases significant antibacterial activity	[122]
			Promotes wound healing in fibroblast cells	
	ZnO NPs, collagen type I	Nanocomposite	Increases significant antibacterial activity	[123]
			Improves wound healing in excisional skin	
	Ag, collagen type I	Nanocomposite	Good biocompatibility and antibacterial activity	[124]
			Increases the formation rate of fibroblast cells	
			Promotes diabetic wound healing	
Collagen nanofibers	Doxycycline, collagen type I	Nanofibers	Low cytotoxic and Increases collagen deposition	[38]
			Promotes wound healing	
	Sulfated hyaluronic acid, collagen type I	Nanofibers	Significantly cell proliferation	[118]
			Promotes diabetic wound healing	
	Polyhydroxy butyrate, gelatin, ostholamide collagen type I	Nanofibers	Promote cell proliferation	[125]
			Good biocompatibility and antimicrobial activity	
			Improves wound healing in excisional skin	
	Silk fibroin, collagen type I, and Ag NPs	Nanofibers	Significant antimicrobial activity	[126]
			Promotes cell adhesion and tissue regeneration	
			Promotes significant wound healing	

(*Continued*)

Table 1 (Continued).

Formulation	Material	Dressing Form	Results	Ref.
	Poli (ε-kaprolakton), collagen type I	Nanofibers	Increases collagen deposition	[127]
			Accelerates wound healing in excisional skin	
	Polivinil alkohol, collagen type I	Nanofibers	Increased cell migration and proliferation	[115]
			Promotes antibacterial activity	
			Accelerates wound healing in incisions skin	
	Polycaprolactone, collagen type I	Nanofibers	Promotes antibacterial activity	[34]
			Good demonstrate biocompatibility	
	Polycaprolactone, collagen type I, propolis	Nanofibers	Significantly cell proliferation and viability	[103]
			Good demonstrate biocompatibility	
	Collagen type I, sodium alginate, polyethylene oxide	Nanofibers, hydrogel	Increases cell proliferation and growth factors	[89]
			Good demonstrate biocompatibility	
	Cellulose acetate, collagen type I	Nanofibers	Low cytotoxic properties	[128]
			Promotes wound healing in fibroblast cells	
	Collagen type I, Poly (l-lactic) acid, *Zataria multiflora*	Nanofibers	Significant antibacterial activity and viability cells	[129]
			Antifungal activity and good biocompatibility	
	Polycaprolactone, collagen type I, MgO NPs	Nanofibers	Inhibits the growth of gram-positive bacteria	[130]
			Promotes wound healing and cell regeneration	

Based on the studies outlined in Table 1, the use of collagen-based polymeric NPs as drug delivery systems for wound healing has shown significant promise. In formulations designed for wound dressings, collagen is often combined with other materials, such as polyvinyl alcohol (PVA) and chitosan to enhance the formation of composite films and nanocomposites.[35,119] For instance, Leng et al [35] developed a formulation to produce curcumin nanoparticles within a PVA/chitosan/collagen composite film, effectively accelerating skin wound healing. The incorporation of collagen-based NPs has been instrumental in promoting the healing process, as evidenced by macroscopic and histological examination, demonstrating their capability to enhance tissue regeneration and expedite wound closure.[39]

Additionally, Li et al[102] introduced a novel strategy involving collagen-based NPs encapsulated within macrophagic membranes for targeted therapy against multidrug-resistant bacterial infections. Their research demonstrated robust antibacterial activity both in vitro and in vivo from collagen-based NPs containing chlorine against *S. aureus*. Another significant study by Huang et al[90] explored collagen nanosheets containing antimicrobial peptides for treating bacterial keratitis, a condition characterized by corneal inflammation and infection. The authors highlighted the beneficial effects of various collagen-based NPs in wound healing applications, particularly in managing bacterial infections associated with corneal wounds. The synergistic action of collagen and antimicrobial peptides not only combats pathogenic bacteria but also creates an environment conducive to tissue regeneration and repair.

Collagen-Based Emulsion NPs

Emulsion NPs modified with natural polymers represent a formulation that combines nanoparticle technology with the benefits of natural polymers to enhance wound healing effectiveness.[134] These emulsion NPs offer several advantageous

characteristics for wound healing. Natural polymers share structural similarities with normal skin tissue, enabling modified emulsion NPs to create a conducive environment for cell growth and tissue regeneration.[135]

Collagen serves as a foundational material for modifying NPs in emulsions. As outlined in Table 1, collagen-based emulsion NPs have attracted attention due to their potential application in wound healing. As an example, Hou et al[94] developed a nanoemulsion containing collagen peptides extracted from purified sturgeon fish skin to explore its potential for treating diabetes and promoting wound-healing in mice. This research demonstrated the therapeutic potential of collagen peptides with varying molecular weights and doses of nanoemulsion in wound-healing.

Collagen-Based Liposome NPs

Liposome NPs modified with natural polymers represent a formulation that integrates liposome technology with the benefits of natural polymers to enhance wound healing efficacy. A key advantage of these modified liposome NPs is their capability to deliver active compounds such as drugs or growth factors directly to the wound site.[14] Acting as carriers, liposomes facilitate enhanced absorption of active compounds into the skin and their diffusion into damaged tissue. In addition, natural polymers incorporated into liposomes contribute to creating an environment conducive to wound healing.[136] For example, collagen can serve as a fundamental material for modifying liposome NPs. Chang et al [120] introduce a novel ophthalmic formulation that combines a nanostructured lipid carrier containing moxifloxacin and dexamethasone with biodegradable collagen, alginate, and gelatin for long-term ophthalmic applications (Table 1). The results highlight the potential of collagen-based liposomal NPs as a promising anti-inflammatory formulation for treating eye diseases. Integrating liposomal NPs with collagen-based materials offers a viable strategy to address challenges in ocular drug delivery, such as rapid drug loss before reaching the cornea and the need for sustained release. Collagen-based liposomal NP drug delivery systems hold significant promise for enhancing therapeutic outcomes in managing corneal infections and promoting ocular wound healing.

Collagen-Based Metal NPs

Metal NPs modified with natural polymers hold significant potential for enhancing wound healing effectiveness. The primary advantage of natural polymers modified with metal NPs lies in their potent antibacterial and anti-inflammatory properties.[137] Metal NPs, such as silver, exhibit robust antimicrobial characteristics, which reduce the risk of infection at the wound site. Moreover, natural polymers modified with metal NPs contribute to the formation of an extracellular matrix that facilitates cell proliferation and tissue regeneration, thereby accelerating the healing process and promoting optimal skin recovery. Furthermore, this technology also enables targeted delivery of drugs or growth factors to the wound site.[138]

Ragothaman et al[101] focused on developing a bio-hybrid hydrogel combining collagen-coated silver and melatonin NPs to accelerate tissue regeneration in damaged skin. Similarly, research by Sankar et al[40] aimed to enhance synergistic wound healing activity by formulating mupirocin-adsorbed collagen-stabilized silver NPs. This approach shows the potential for advancing wound care through an effective drug delivery system using collagen-stabilized silver NPs. Malathi et al[122] investigated the application of collagen mixed with ZnO NPs embedded in niosome nanocomposites for wound healing applications. Their findings show the multifunctional potential of collagen-based metal NPs in wound management. Furthermore, silver nanoparticle-doped collagen-alginate biocomposites have been explored as potential wound dressings with antimicrobial properties. Integration of silver NPs into the collagen-alginate matrix enhances its antibacterial activity, making it an effective barrier against microbial colonization of wounds.[121]

Another research by Sucharita et al[124] explored the use of Ag-collagen nanocomposites, offering a dual function as a biocompatible scaffold for tissue regeneration while exhibiting potent antibacterial and antibiofilm properties through silver NPs. These nanocomposites were evaluated in animal models under hyperglycemic conditions, with a particular focus on resistant pathogens like *Acinetobacter baumannii*. The study highlighted the effectiveness of these nanocomposites in addressing wound healing challenges in a diabetic environment while mitigating potential cytotoxicity. Recent advancements in collagen-based NPs for wound healing have demonstrated promising outcomes by combining collagen's biocompatibility with the antimicrobial and regenerative properties of silver NPs.[40,101,124] However, ongoing challenges include concerns regarding the scalability of production, consistent efficacy across different wound types, and the long-

term safety of metal-based NPs.[139] These issues underscore the need for comprehensive studies to ensure their safe and reliable use in clinical applications.[138]

Collagen-Based Nanofibers

Nanofibers can be considered a nanoparticle-based system due to their nanoscale dimensions and potential in drug delivery applications.[140] These nanofibers are produced using electrospinning techniques to create ultra-fine fibers at the nanoscale. The primary advantage of collagen-based nanofibers lies in their structural similarity to normal skin tissue.[128] As a natural component of the skin, collagen provides an environment conducive to cell growth and tissue regeneration.[126] Furthermore, collagen-based nanofibers possess properties that support wound healing, including the ability to retain skin moisture, promote cell adherence to the wound area, and stimulate the proliferation of skin cells.[115] These nanofibers are engineered to deliver therapeutic agents such as drugs or bioactive molecules directly to wound sites, thereby promoting tissue regeneration and accelerating the healing process.[89]

Serdar et al[38] focused on the development of a three-layer doxycycline-collagen nanofiber wound dressing with promising characteristics for healing acute and chronic wounds. This wounds dressing, composed of core-shell nanofibers containing polycaprolactone, collagen, doxycycline, polyethylene oxide, chitosan, and sodium alginate, exhibited aligned nanofibers with excellent mechanical properties, bioadhesion, and biocompatibility. Similarly, research by Kandhasamy et al[125] described the synthesis and fabrication of collagen-coated ostholamide electrospun nanofiber scaffolds for wound healing. The controlled release of ostholamide from these nanofibrous scaffolds, along with their cytocompatibility and demonstrated wound healing efficacy in vitro and in vivo, positions them as effective biomaterials for tissue engineering and wound repair. In addition, the development of biodegradable nanofiber scaffolds comprising silk fibroin, collagen, and silver-gold NPs showcased a dual therapeutic approach for treating bacterial infections and promoting wound healing. These composite nanofibers exhibited excellent antibacterial activity and enhanced cell proliferation, making them promising candidates for advanced wound healing applications.[130]

Overall, these studies underscore the promising role of collagen-based NPs as versatile platforms for drug delivery in wound healing applications.[118] Through innovative fabrication techniques and the incorporation of bioactive compounds, such nanofiber scaffolds offer unique advantages such as controlled drug release, antimicrobial properties, and enhanced tissue regeneration.[103] This positions them as crucial in the development of effective wound dressings and therapeutics in the field of regenerative medicine.[129]

Authors' Perspective

The aim of this review is to explore potential of collagen-based NPs as a drug delivery system and revolutionary platform in wound healing applications. By harnessing the unique properties of collagen, the natural building block of the extracellular matrix, these NPs offer a multifaceted approach to accelerate and enhance the healing process.[98] Existing literature indicates that collagen's natural origin ensures excellent biocompatibility, minimizing the risk of adverse reactions.[141,142] Additionally, its biodegradability eliminates the need for removal after wound healing. Collagen itself serves as a scaffold for cell growth and tissue repair, further accelerating wound closure.[143] These collagen-based NPs can encapsulate therapeutic agents and deliver them directly to the wound site, improving their efficacy and reducing systemic side effects. The design of these NPs allows for sustained and controlled release of drugs over time, optimizing the healing process and minimizing the need for frequent dosing.

Combining the natural polymer collagen with NPs has the potential to revolutionize wound healing. Collagen-based NPs can improve treatment efficacy through targeted drug delivery and increasing bioavailability, while minimizing side effects by reducing systemic exposure to the therapeutic agent. Additionally, optimizes the healing process with controlled drug release and a biocompatible environment for tissue regeneration. The illustration of the application of collagen-based NPs for wound healing can be seen in Figure 8.

Many studies have investigated various types of collagen-based NPs, including nanopolymers, metal NPs, nanoemulsions, nanoliposomes, and nanofibers, demonstrating efficacy in promoting wound closure and tissue regeneration.[144] The incorporation of collagen-based NPs has not only serves an agent for the delivery of therapeutics but also actively contributes to the wound healing cascade. The application of collagen-based NPs paves the way for the development of

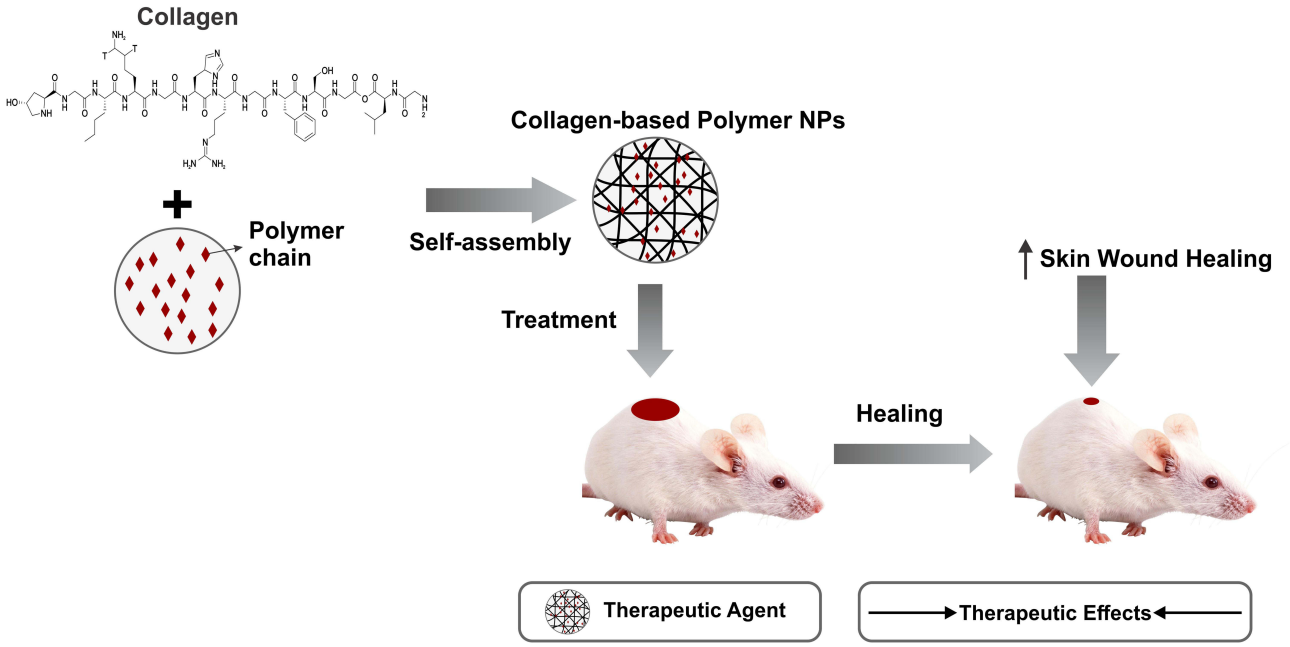

Figure 8 The illustration of the application of collagen-based NPs for wound healing.

new and highly effective therapeutic strategies in wound management. By harnessing the multifaceted properties of collagen-based NPs, a future can be envisioned where wound healing faster, more efficient, and minimal complications. This advancement will significantly improve patient outcomes and enhance the quality of life for individuals suffering from chronic or complex wounds.

Conclusion

Collagen-based polymeric NPs represent a promising approach in wound healing due to their ability to incorporate bioactive compounds that may help to enhance tissue regeneration and accelerate wound closure, thereby improving healing outcomes. These NPs leverage collagen's favourable physicochemical attributes and biocompatibility, making them effective platforms for delivering therapeutic agents.

Emulsion NPs derived from collagen, particularly those sourced from fish skin collagen peptides, have shown promising properties in treating diabetes and promoting wound healing in animal models. These biomaterials highlight the therapeutic potential of collagen-based formulation, demonstrating their ability to address various health challenges effectively.

Collagen-based liposomal NPs offer another promising strategy for ocular drug delivery and wound management. They provide optimal therapeutic concentrations and sustained release profiles, which are crucial for promoting corneal wound healing and managing ocular conditions effectively.

Metal-based NPs incorporating collagen, especially those containing silver and melatonin, show promise in expediting tissue regeneration and addressing infected chronic wounds. These NPs demonstrate bactericidal efficacy against wound pathogens and modulate growth and inflammatory factors essential for wound healing processes. Furthermore, collagen-based nanofibers serve as a versatile platform for drug delivery in wound care applications. They offer a controlled release of therapeutic agents and promote wound healing by enhancing tissue regeneration and maintaining a conducive environment for cellular growth.

In summary, this review summarizes the important role of collagen-based NPs drug delivery systems in promoting tissue regeneration, accelerating wound closure, and addressing challenges in both wound management and ocular drug delivery. These innovative approaches hold promise for advancing therapeutic outcomes in various clinical settings, leveraging collagen's natural properties and integrating them with advanced nanotechnology for enhanced medical

treatments. While collagen-based NPs show significant promise for drug delivery in wound healing, they present several challenges. Key concerns include scalability in manufacturing, maintaining consistent nanoparticle size, and potential cytotoxicity, particularly with metal-based NPs. Additionally, long-term safety, storage stability, and controlled release mechanisms require further investigation. Overcoming these limitations will necessitate optimizing synthesis techniques and conducting comprehensive in vivo and clinical studies to ensure safe therapeutic application.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there are no conflicts of interest in this work.

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