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MINI REVIEW

Silver nanoparticles-loaded electrospun nanofibers for wound healing applications: a mini review

M. Jane Mercy*

Department of Botany, Madras Christian College, Chennai, India

***Correspondence:**
M. Jane Mercy,
janedaws02@gmail.com

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சுருக்கம்:
காயங்கள், தீக்காயங்கள், நீரிழிவு நோய் மற்றும் நாள்பட்ட நோய்களால் ஏற்படும் தோல் புண்கள் தொடர்ந்து ஒரு முக்கியமான மருத்துவப் பிரச்சினையாக உள்ளன, ஏனெனில் அவை தொற்றுநோய்களுக்கு அதிக வாய்ப்புள்ளவையாகவும், அவற்றின் குணமாதல் தாமதமாகவும் இருக்கிறது. உயிரணு புறச்சட்ட அமைப்பை ஒத்த கட்டமைப்பு, மிக அதிக துளையிடும் தன்மை, பரந்த மேற்பரப்பு பரப்பளவு, மற்றும் செல் ஒட்டுதலை ஊக்குவிக்கும் திறன் மற்றும் மருந்து வழங்கலைக் கட்டுப்படுத்தும் திறன் ஆகியவற்றால், மின்-நூற்பு நானோ இழைகள் சமீபகாலமாக தோல் திசு பொறியியலுக்கு ஏற்ற இடைச்சட்டங்களாக அடையாளம் காணப்பட்டுள்ளன. வெவ்வேறு உயிரியல்-செயல்பாட்டு முகவர்களில், வெள்ளி நானோதுகள்கள் அவற்றின் பரந்த-நிறமாலை நுண்ணுயிர் எதிர்ப்புச் செயல்பாடுகள், அழற்சி எதிர்ப்புத் திறன்கள், மற்றும் திசு மறுஉருவாக்கத்தை ஊக்குவிக்கும் தன்மை ஆகியவற்றால் முக்கிய கவனத்தை பெற்றுள்ளன. மின்-நூற்பு நானோ இழைகளின் அமைப்பினுள் AgNPக்களை இணைப்பதன் மூலம், நானோ-இழை இடைச்சட்டங்களின் இயற்பியல் நன்மைகளும், வெள்ளியின் சிகிச்சை பண்புகளும் ஒன்றிணைந்து, தொற்றுநோய்களைத் தடுப்பது மட்டுமல்லாமல் காயம் ஆறுவதையும் ஊக்குவிக்கும் பல்செயல்பாட்டு காய கட்டு பொருட்கள் உருவாகின்றன. இந்த சுருக்கமான கட்டுரை, கலவை மின்-நூற்பு, மேற்பரப்பு நிலைப்படுத்தல், இன்-சிட்டு தொகுப்பு, இணை-அச்சு மின்-நூற்பு, மற்றும் குழம்பு மின்-நூற்பு ஆகிய முறைகள் மூலம் AgNP-ஏற்றப்பட்ட மின்-நூற்பு நானோ இழைகளை உற்பத்தி செய்வது குறித்த புதுப்பிக்கப்பட்ட அறிவை வழங்குகிறது. மேலும், Ag-NPக்களின் இயற்பியல்-வேதியியல் பண்புகள், அவற்றின் நுண்ணுயிர் எதிர்ப்பு செயல்பாடு மற்றும் உடலியல் செயல்பாடுகள், அத்துடன் அவற்றை தீக்காயச் சிகிச்சை, நீரிழிவு புண்கள், நாள்பட்ட காயங்கள், மற்றும் தழும்பு குறைப்பு ஆகியவற்றில் நுண்ணுயிர் எதிர்ப்பு காய கட்டுப் பொருட்களாகப் பயன்படுத்துவது குறித்தும் இது வெளிச்சம் போடுகிறது. மேலும், இந்த மினி-மறுஆய்வு, நச்சுத்தன்மை, திடீர் வெளியேற்றம், நீண்டகால உயிர்ப்பொருந்தல், உற்பத்தி தரப்படுத்தல், மற்றும் மருத்துவ மொழிபெயர்ப்பு உள்ளிட்ட AgNPக்களின் முன்னேற்றத்திற்குத் தடையாக இருக்கும் பிரச்சினைகளையும் சுட்டிக்காட்டுகிறது. அதே நேரத்தில், கட்டுப்படுத்தப்பட்ட-வெளியீட்டு அமைப்புகள், AI-உதவியுடன் கூடிய இடைச்சட்ட வடிவமைப்பு, தனிநபர்மயமாக்கப்பட்ட காய கட்டுகள், மற்றும் பல்செயல்பாட்டு உயிரியல்-செயல்பாட்டு இடைச்சட்டங்கள் ஆகியவற்றின் வரவிருக்கும் சாத்தியக்கூறுகளையும் இது குறிப்பிடுகிறது. சுருக்கமாகக் கூறுவதானால், AgNP-ஏற்றப்பட்ட மின்-நூற்பு நானோ இழைகள் அடுத்த தலைமுறை காயப் பராமரிப்புக்கு ஒரு உற்சாகமூட்டும் சாத்தியக்கூற்றை வழங்குகின்றன, ஆயினும் அன்றாட சுகாதாரப் பராமரிப்பில் இதனை சீராக அறிமுகப்படுத்த மேலும் மருத்துவ ஆதாரங்களும், ஒரே மாதிரியான உற்பத்தி முறைகளும் தேவைப்படுகின்றன.

Abstract:
Injuries to the skin from trauma, burns, diabetes, and chronic diseases continue to represent an important medical problem because they are highly prone to infections and their healing is delayed. Electrospun nanofibers have recently been identified as ideal scaffolds for skin tissue engineering because of their extracellular matrix (ECM)-like structures, very high porosities, large surface areas, and outstanding ability to facilitate cell adhesion and also to control drug delivery. Out of different bioactive agents, silver nanoparticles (AgNPs) have been in the limelight due to their broad spectrum of antimicrobial activities, anti-inflammatory capabilities, and facilitation of tissue regeneration. Incorporating AgNPs into the structure of electrospun nanofibers marries the physical benefits of nanofibrous scaffolds with the therapeutic properties of silver, this way giving rise to multifunctional wound dressings that not only prevent infections but also encourage the healing of wounds. This brief article presents up-to-date knowledge on the production of AgNP-loaded electrospun nanofibers by blend electrospinning, surface immobilization, in situ synthesis, coaxial electrospinning, and emulsion electrospinning. It also sheds light on the physicochemical properties of AgNPs, their antimicrobial action, and physiological functions, as well as

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their use as antibacterial wound dressing materials in burn treatment, diabetic ulcers, chronic wounds, and scar reduction. Also, this mini-review points out the issues that act as barriers to the advancement of AgNPs including their toxicity, burst release, long-term biocompatibility, fabrication standardization, and clinical translation. At the same time, it mentions the upcoming possibilities of controlled-release systems, artificial intelligence (AI)-assisted scaffold design, personalized wound dressings, and multifunctional bioactive scaffolds. In a nutshell, AgNP-loaded electrospun nanofibers offer an exciting possibility for next-generation wound care, yet more clinical evidence and uniform production methods are needed for a smooth transition into routine healthcare.

Keywords: electrospinning, silver nanoparticles, nanofibers, skin tissue regeneration, wound healing, antimicrobial biomaterials

Introduction

Skin, the largest organ in the human body, plays an important role of providing mechanical and immune defense against environmental insults, including microorganisms, trauma, and environmental stress (1). Disruption of skin integrity resulting from trauma, burns, surgical procedures, diabetes, or vascular disease could cause tissue damage, either acute or chronic (2). Acute wounds normally complete the reconstruction process and restore tissue integrity in a matter of time, whereas chronic wounds, (e.g., Diabetic foot ulcers, venous leg ulcers, and pressure sores) show reduced or abnormal healing with intense inflammation, infection, deficient angiogenesis, and abnormalities of basic metabolic regulation (3). These conditions generally result in prolonged treatment, higher cost of healthcare, worsened quality of life, and more chances for complications, which is why there is a necessity for new and effective ways of treatment. Skin regeneration is a very complicated and organized biological sequence during which four phases—hemostasis, inflammation, proliferation, and remodeling—take place overlapping each other (4). At the hemostasis stage blood clotting hinders further bleeding as well as functioning. They act as a temporary scaffold for cell, migration, then at the inflammation stage immune cells are recruited to the wound to kill bacteria and clear dead cells (5). The proliferation phase is characterized by the multiplication of fibroblasts and the production of the interstitial matrix [extracellular matrix (ECM)]; also, new capillaries are formed, and the epithelium is using epidermal cells to cover the surface. In the final phase of tissue remodeling, the newly formed tissue is getting stronger and stronger via collagen maturing and the reorganization of tissue (6). Fibroblast communication and cytokine signaling, controlled inflammation, proper blood supply, and ECM turnover should always work in harmony in the wound microenvironment for the tissue to regenerate successfully (7). From this point of view, scaffold-assisted regenerative therapies have become a good alternative to traditional wound dressings because, apart from physically supporting the wound healing process, they are also able to help cell growth and act as a vehicle for therapeutic agent delivery.

Scaffold fabrication methods are concerned; the electrospinning technique stands out as an amazing method to produce extremely thin fibers that are similar in size to the fibrous elements of the native ECM (8). Besides having the properties of ECM in a physical sense, electrospun nanofibers are made of interconnected porous structures, have a high surface-area-to-volume ratio, their mechanical properties can be adjusted, and they have excellent oxygen permeability and supply of nutrients making them one of the best materials for skin tissue engineering (9). Their morphology, which mimics the ECM, greatly increases the performance of fibroblasts through their enhanced attachment, keratinocyte migration, collagen production, and the formation of new vessels (10). Besides that, these nanofibers keep the wound in a moist environment, which is one of the main factors that contributes to a rapid healing of such wounds. And electrospun nanofibers are a handy tool to deliver different bioactive components, including antimicrobial agents, different growth factors, anti-inflammatory agents, and various nanoparticles, which allow multifunctional wound dressings with regulated therapeutic release.

In the field of wound care, many types of nanomaterials have been used, but among all of them silver nanoparticles (AgNPs) stand out the most. Silver is known to have an excellent antimicrobial effect not only against common Gram-positive and Gram-negative bacteria but also against fungi and various strains resistant to antibiotics, which are the ones that lead to wound infections (11). AgNPs' effectiveness against microbes consists of destruction of the microbial cell wall with massive leakage of cell constituents, production of reactive oxygen species (ROS), hindermost of the microbial enzymes, inhibition of DNA replication, and blockage of biofilm formation (12). Apart from their antimicrobial effects, AgNPs also possess anti-inflammatory, antioxidant, pro-healing properties that, in all, make the process of wound healing faster (13). AgNPs assist in wound healing by altering inflammatory mediators, boosting skin cell growth and migration, causing new blood vessel formation, and increasing collagen accumulation. Yet, deciding on the best concentration of silver and the way it is released are two important issues that should be addressed so that not only the therapeutic effect is maximized but also the toxicity to human cells is also minimized.

Integrating AgNPs into electrospun nanofibrous scaffolds is a very effective way to make wound dressings that not only provide structural support but also have sustained antimicrobial and cell-regenerative properties. These composites offer targeted silver release, decrease the chances of bacterial infection, improve the interaction of cells with the biomaterial, and help the skin to heal more rapidly. This mini review highlights the progress made in electrospun nanofibers incorporating AgNPs for skin tissue regeneration.

Electrospun nanofibers as skin tissue engineering scaffolds

Electrospinning is an easy and highly adaptable method to make nanofibrous scaffolds that have a similar structure to the natural ECM of skin cells (14). It involves the use of a very high voltage on a polymer solution or melted polymer material and throwing this fine jet of polymer particles in the air. With the evaporation of solvent, they get hard and continuous nanofibers. Finally, the fibers are collected in the form of a porous, nonwoven mat with modifiable morphology and mechanical properties. By changing different processing parameters like polymer concentration, voltage applied, flow rate, and distance between the collector and the needle, the electrospun scaffolds can be designed to completely fulfill targeted skin tissue engineering needs (15).

Electrospun nanofibers have a number of benefits over traditional wound dressings like gauze and hydrocolloids, which help skin regeneration. Firstly, the fibrous structure almost resembles the natural ECM, providing an ideal platform for cell activities like attachment, growth, and movement. Secondly, through their high porosity and interconnected pore structure, the exchange of nutrients and removal of wastes as well as the vascularization process are enhanced, whereas the high surface-area-to-volume ratio is conducive to the adsorption of proteins and subsequent cell-material interactions (16). Also, electrospun nanofibers are highly permeable to oxygen and retain moisture very well, which keeps the wound environment at an optimal level to support re-epithelialization and lower the risk for infection (17). Due to their very high capacity for drug loading, substances like antimicrobial agents, growth factors, nanoparticles, and other bioactive molecules can be incorporated for sustained and localized therapeutic release to promote wound healing.

The polymer type can greatly impact the biological and the mechanical properties of electrospun scaffolds. Natural polysaccharides, proteins, and other biopolymers like chitosan, gelatin, collagen, silk fibroin, and alginate are the first choices of researchers for making such scaffolds due to their excellent biocompatibility, biodegradability, and the ability of cells to adhere, survive, and multiply on them (18). Besides, chitosan contains antimicrobial and hemostatic agents, collagen, and gelatin are best to mimic ECM for cell attachment; silk fibroin is a very strong material and elicits little immune response; and alginate can hold a lot of water and forms gels, making it suitable for highly exuding wound situations.

Synthetic polymers are added to natural ones for improving the mechanical properties and stability of the scaffold (19). Polycaprolactone (PCL) stays one of the most popular polymers, being highly flexible, biocompatible, biodegradable, and having a slow degradation rate (20). Polyvinyl alcohol (PVA), without a doubt, stands very high in electrospinnability and hydrophilicity, and poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) are capable of providing mechanical support and controlled biodegradation (21–23). Another polymer, polyurethane (PU), is well-known for its elasticity and durability. PU-based wound dressings can be stretched and bent repeatedly without changing their structures (24).

Silver nanoparticles in skin tissue regeneration

Ag NPs are becoming increasingly popular for skin tissue engineering due to their special physicochemical properties and versatile biological activities. Their nanoscale size, large surface-area-to-volume ratio, and high surface reactivity are proven to enable Ag NPs to have a greater interaction with microbial cells and biological tissues than bulk silver (25). Features like particle size, shape, surface charge, and surface functionalization affect the physicochemical properties of AgNPs, which in turn determine their performance with stability, antimicrobial effect, cellular uptake, and biocompatibility (26). Smaller particles generally offer higher antimicrobial activity because they expose a larger reactive surface area, but a suitable surface modification may also improve dispersion, prevent aggregation, and enable the controlled release of silver ions. These characteristics of AgNPs make them very attractive materials for the production of wound healing dressings and tissue engineering scaffolds.

Besides being antimicrobial, which effectively kills the most variety of bacteria, fungi, and even those pathogenic drug-resistant microbes (27). AgNPs have multiple wound-healing factors, which include killing micro-organisms in various ways at once, which practically stops micro-organisms from developing resistance. First, they adsorb to and penetrate the microbial cell membrane, thereby causing higher membrane permeability and cellular content leakage through the membrane. Following entering the cells, AgNPs generate ROS, which through oxidative stress, leads to the destruction of important cell parts like the DNA. It bind to the DNA of the microbe, hindering DNA replication and division of cells; simultaneously, it will attach to the microorganism's proteins and enzymes, resulting in protein denaturation or breakdown of the enzymes and the prevention of vital metabolic pathways (28). AgNPs are also very strong inhibitors of the formation and maturation of microbial biofilms, which are the major cause of chronic infections and the wound healing delay. Using AgNPs to hinder biofilm development will result in better infection control and create a more appropriate environment for tissue regeneration.

Apart from their antimicrobial effects, AgNPs also participate in various biological functions that are vital for tissue repair and regeneration (29). For instance, by reducing excessive inflammatory reactions and limiting the release of pro-chemicals from the cell surface, anti-inflammatory functions prevent tissue degradation in a non-healing wound (30). This mild inflammatory situation helps the change from the inflammatory to the proliferative phase of wound healing. Also, it was discovered that AgNPs can improve angiogenesis through the development of new blood vessels, a process that is vital for supplying fresh oxygen and nourishment to the regenerating tissues (31). This enhancement in vascularization allows the wound bed to be covered by granulated tissue more quickly and nourish the skin cells living at the site.

AgNPs also have a positive effect on increasing the migration and proliferation of fibroblasts, cells that regulate different processes on ECM and tissue contraction (29). This increase in activity of fibroblasts results indirectly in formation of more collagen, a vital component providing structural integrity and tensile strength to the newly formed tissue (**Figure 1**). In addition, AgNPs assist epidermal cells or keratinocytes, to migrate and multiply, a key process for the healing of epithelium or re-establishment of an epidermal barrier layer (32). All these properties of AgNPs have brought about faster healing and a decrease in the rate of infection, besides tissue architecture restoration and, finally, functional recovery.

Fabrication of silver nanoparticle-loaded electrospun nanofibers

Fabricating nanofiber wound dressings with antibacterial properties and healing-promoting qualities for a long time can be effectively achieved with the electrospun AgNP nanofibrous approach (33). Through different routes, these AgNP-containing wound dressings have been designed to ensure nanoparticles are uniformly scattered, silver is discharged in a gradual manner, and the dressings have biocompatible characteristics. Blending electrospinning technique is the simplest and most widespread among those routes: AgNPs prepared earlier were directly added to the polymeric solvent, which is then used for electrospinning. The procedure proved to be effective for even distribution of the nanoparticles within nanofibers and very easy to carry out (34). Though, improper optimization of the dispersion could result in agglomeration of nanoparticles and a large burst release of silver ions during the initial stages.

Surface immobilization is a different method often used where AgNPs are fixed to the surface of the electrospun nanofibers that have been made earlier via physical adsorption or chemical bonding. Since the nanoparticles stay on the fiber surface, this is a way of giving microbes more direct access to them, which can cause better antimicrobial effectiveness in some cases. Then again, if the surface interactions are weak, the nanoparticles may come off during use for a longer period of time. In situ synthesis is an alternative method that is becoming more popular where silver ions are first added to the electrospun scaffold, and then they are changed into AgNPs either inside or on the fibers (35). This approach usually results in nanoparticles that are very well spread out and strongly bonded to the polymer matrix, which stabilizes the nanoparticles and also reduces aggregation.

Electrospinning methods that are more sophisticated have made it possible to develop more designs for wound dressings containing AgNPs. With coaxial electrospinning, two nozzles, one inside the other, are used. This way, it is possible to make core-shell nanofibers so that AgNPs can be put only in the core or the shell layer (36, 37). This design keeps the nanoparticles safe and makes it possible to release silver slowly and in a controlled way, which reduces potential cell damage due to rapid ion release. Also, emulsion electrospinning uses polymer solutions that have been emulsified to make fibers that have core-shell-like structures in a single-step procedure. Through this method, it is possible to encapsulate AgNPs and other therapeutic agents simultaneously, which makes it really very useful for the development of multifunctional wound dressings that combine antimicrobial, anti-inflammatory, or regenerative activities.

The work of AgNPs-containing electrospun scaffolds is affected by a number of factors related to fabrication. Fiber size or diameter plays a big role because it affects the surface area, mechanical properties, degradation behavior, and release of silver. Nanofibers that are smaller in diameter tend to have a bigger surface area, which enables better cell attachment and offers more amount of antimicrobial agents (38). Besides that, another very essential parameter is the loading or concentration of AgNPs. A smaller amount may result in not very good performance against microorganisms. Yet, an excessive amount of silver may be toxic to the cells and also prevent the development of new tissues. That means determining the amount of AgNPs is extremely crucial

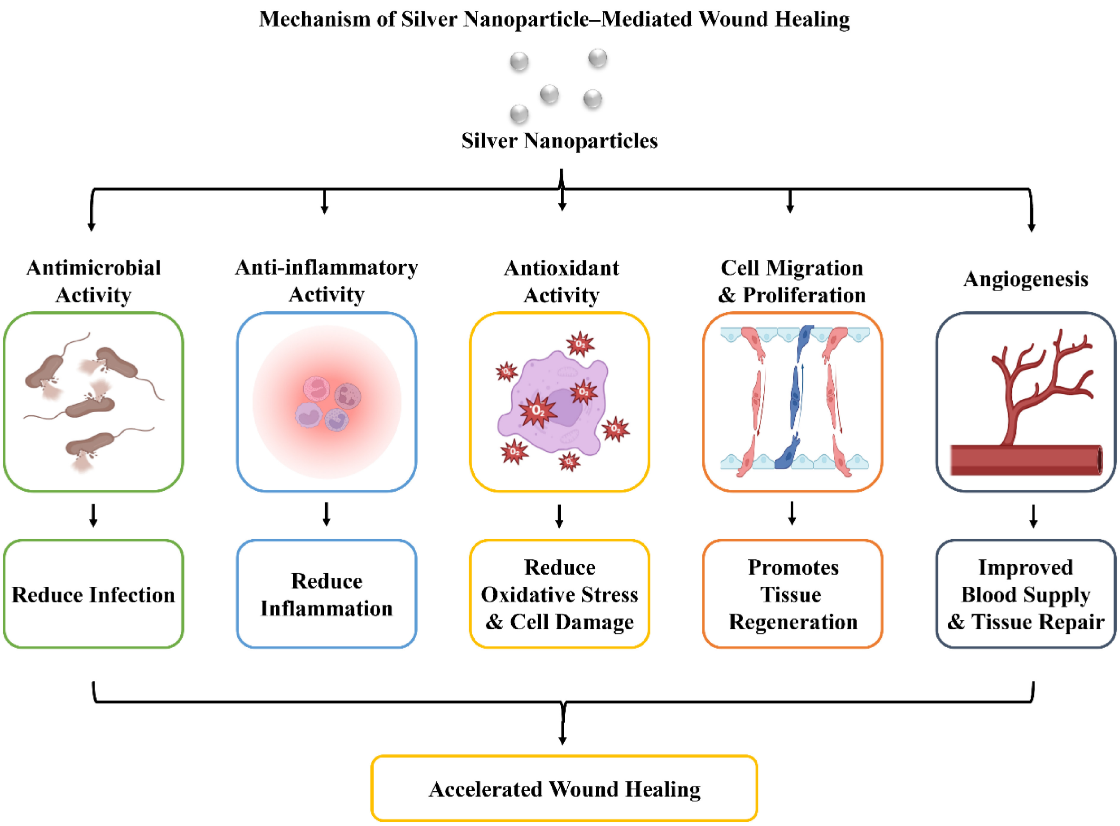

FIGURE 1 | Mechanism of AgNP-mediated wound healing.

to combine the properties of effective antimicrobial and compatibility with the body.

Therapeutic applications in skin tissue regeneration

AgNP-loaded electrospun nanofibers are one of the most effective biomaterials for skin regeneration owing to the combined advantages of both nanofibrous scaffolds and the versatile role of AgNPs as microbial fighters and tissue regrowth. Because of their similarity with natural ECM, they can not only support cell functions that are needed for tissue growth but also, through the silver ion charge, are a source of protection from microbial infections. Their super abilities have led to their deployment in smart wound dressing solutions for skin damage caused by both sudden and long-term conditions.

AgNP-loaded electrospun nanofibers resist a wide spectrum of microbes, which is the cornerstone of their appearance in antibacterial wound dressings. Besides interfering with the bacterial proliferation and biofilm formation, the continuous silver ion release from nanofibers containing AgNPs is capable of reducing the colonization of microbes at the wound location, which in itself is a highly positive point for wound healing (39). The exchange of oxygen and the moisture level maintaining by the fiber's porousness help not only in tissue regeneration but also in putting the patient's life on the least-used dressing track.

AgNP-loaded electrospun materials are an effective weapon against the microbial challenge in burn wounds, which often suffer from losing large amounts of fluids besides the physical injury to the skin barrier. Making the infection control part of the burn procedure, entry of Pseudomonas infection to the damaged tissue, attracting inflammatory cells for hours, and late necrosis of new skin (40). Having AgNPs in the burn dressing can help to not only fight all these aspects of infection but can also be involved in the process of reducing the wound's inflammation level, safeguarding the wound with a moist environment, and supporting fibroblast growth, collagen networking, sprouting of new vessels, etc., all taking the skin above the baseline toward full recovery. **Table 1** summarize the AgNP-loaded nanofibers for wound healing applications.

Among the different fabrication strategies of AgNPs-loaded electrospun nanofibers, green synthesis and in situ chemical reduction methods have been identified as highly effective because they not only allow for uniform distribution of nanoparticles but also reduce the use of harmful reducing agents. Green synthesis is the main principle behind those systems like PCL/PEO, PVA, and PLA/Col1 nanofibers, which have been consistently found to have the highest antibacterial effect, promote fibroblast proliferation, and have excellent cytocompatibility.

TABLE 1 | Comparative summary of AgNP-loaded nanofibers for wound healing applications.

Nanofiber composition	AgNP loading method	Physicochemical characterization	Biological evaluation	Wound healing mechanism	Toxicity/ biocompatibility	Clinical translation potential	Major findings	Limitations	Ref.
CS/Gelatin/PCL	Chemical reduction	XRD, SEM, FTIR, TGA	Antibacterial, cytotoxicity	Antibacterial activity, enhanced fibroblast	Good cytocompatibility	Nil	Improved antibacterial efficacy and cell adhesion	Limited in vitro studies	(41).
PCL/PEO	Green synthesis	SEM, TGA, FTIR	Antibacterial, cytotoxicity	Antibacterial activity, enhanced fibroblast	Good cytocompatibility	Nil	Improved antibacterial efficacy and cell adhesion	Limited in vitro studies	(42).
PVA	Green synthesis	FESEM, EDX, XRD, FTIR	Antibacterial, cell proliferation	Antibacterial activity, enhanced fibroblast	Good cytocompatibility	Nil	Improved antibacterial efficacy and cell proliferation	Limited in vitro studies	(43).
PVDF	-	ATR-FTIR, XRD, AFM, SEM, TEM	Antibacterial, cytotoxicity, cell proliferation, in vivo wound healing	ECM mimicry	Concentration-dependent toxicity	Preclinical	Excellent mechanical strength and wound healing	Limited clinical evidence	(44).
PDMS	-	SEM, FTIR, EDS	Antibacterial, antioxidant	Antibacterial activity	Good cytocompatibility	Nil	Improved antibacterial efficacy	Limited in vitro studies	(45).
CA	-	SEM, FTIR, EDX, TGA	Antibacterial, in vivo wound healing	Antibacterial activity, enhanced fibroblast	Good biocompatibility	Preclinical	Improved antibacterial efficacy and wound healing	Limited clinical evidence	(46).
CS/PLA	-	SEM, EDX	In vivo wound healing	Enhanced fibroblast	Good biocompatibility	Preclinical	Enhance wound healing	Limited clinical evidence	(47).
PLA/Col1	Green synthesis	TEM, XRD, XPS, FTIR	Antibacterial, cytotoxicity, cell proliferation, in vivo wound healing	ECM mimicry	Good cytocompatibility and biocompatibility	Preclinical	Improved antibacterial efficacy and wound healing	Limited clinical evidence	(48).

So, they seem to be the best suited for wound healing (42, 43, 48). Mainly, the PLA/Col1 scaffold prepared by green synthesis combined antibacterial properties with ECM mimics, cell proliferation, and wound healing in vivo, which showed the most biocompatible features (48). On the opposing front, the chemically reduced CS/Gelatin/PCL nanofibers presented quite well for killing bacteria and allowing fibroblasts to stick; yet, only their in vitro test results were presented, and because of this, their therapeutic efficacy for the long run remained uncertain (41). Besides, some studies described AgNPs without giving details of the loading method; still, electrospun PVDF and cellulose acetate (CA) nanofibers showed exceptional wound healing results in animal experiments due to their structural integrity, persistent antibacterial activity, and tissue regeneration (44, 46). Overall, available data indicate that green synthesis coupled with electrospinning offers the optimal compromise between biological properties, nanoparticle stability, and environmental friendliness; yet further detailed comparative studies of various AgNP loading methods all with the same experimental conditions are still needed.

The biological and mechanical characteristics of biocomposite wound dressings are largely dependent on the type of polymer used as the matrix. For example, PVDF not only gives excellent mechanical resistance but also makes antibacterial activity, cell proliferation, and healing acceleration in vivo possible simultaneously, which is why PVDF became one of the most promising wound dressings with the highest mechanical strength (44). Its dosing level, though, has been found to be cytotoxic, dependent on concentration, which calls for the fine-tuning of AgNP dosage (44). A natural-polymer-based composite like PLA with collagen type 1 or CS with gelatin/PCL is expected to have better biological functioning in that they closely match the composition of a native ECM; it allows for improvement of fibroblast adhesion, proliferation, and tissue regeneration without affecting cell compatibility positively (41, 48). CA nanofibers in the same line of argument showed high biocompatibility tied to very significant antimicrobial activity and improved healing of wounds in preclinical evaluations (46). Chitosan/PLA composites, in their turn, contributed to the tissue regeneration due to reality, chitosan is bioactive, and they presented an encouraging result on the wound healing of animals (47). But if PCL/PEO and PVA have the advantage of antibacterial activity and promoting cell proliferation, then the mechanical performance and the long-term behavior after implanting these scaffolds need further investigations (42, 43). Overall, the research results support that the strategy of a dual polymer system in which the artificial polymer gives the mechanical properties while the biological part is provided by the natural polymer for cell interaction is the way to go if one wants a wound dressing based on electrospun fibers loaded with AgNP capable of both structural and biological functions (41, 44, 46–48).

Challenges and future perspectives

One reason why a broad adoption of Ag NP-loaded electrospun nanofibers is being slowed down, besides the promising regenerative effect on skin tissue that they may produce, is the existence of some issues that need to be resolved. One of the main challenges is about the toxic effect of silver. A high dose of silver ions or an uncontrolled release of a very large amount of these ions might lead to oxidative stress, reduction of the viability of various skin cells, and delay in tissue regeneration. So, the nanoparticles' size, concentration, and distribution should be highly adjusted for achieving a suitable equilibrium between the antibacterial potential and the cell compatibility. Besides that, the so-called burst release, the release of silver ions instantly following the scaffold's introduction into the body, could bring a short-lived antimicrobial effect while a bit increasing the risk of damage to cells. Research on nanomaterial-based dressings is focused mainly at present on the fabrication of silver-releasing scaffolds, which, unlike the former, can deliver silver ions in a continuous and safe manner. Though, the long-term biocompatibility of AgNP-containing matrices remains a question. While many lab and animal models have shown successful outcomes of wound healing, only a limited number of detailed, comprehensive investigations with nanoparticle accumulation, degradation behavior, and systemic safety have been published. Also, lack of a standardized way to make the product causes inconsistencies when it comes to getting the fibers' shape, nanoparticles' dispersion, mechanical performance, and the therapeutic results of the samples made from different research groups. Variations in the electrospinning parameters, the type of polymers and the methods of nanoparticles synthesis are commonly the main factors why one sample is not comparable to another with direct comparison and why the results cannot easily be reproduced.

Scaling a technology or method from a laboratory level to commercial manufacturing level often presents additional challenges. The fact is, electrospun nanofibers, which still maintain their quality about uniformity, reproducibility, and cost-efficiency, can even so be manufactured on an industrial scale only if these technical issues are first resolved. But, besides that, consider that before the regulatory authorities allow nanotechnology-based wound dressings to be marketed, the manufacturers are going to need proof of safety through extensive preclinical studies, clinical trials, and compliance with strict manufacturing standards. All this will probably lead into a significant increase of development time as well as development costs. Though it is a rather straightforward operation, at the laboratory level, the large-volume manufacturing of electrospun nanofibers, which also takes into account high-quality polymers, nanoparticle synthesis, sterilization, and quality control, is the cost-efficiency issue that can really put off the use in a clinical setting. New research might take a path of developing highly effective electrospun wound dressings for practical applications. Besides aiding optimization of fiber architecture, polymer composition, and nanoparticle loading using predictive scaffold performance and therapeutic outcomes, artificial intelligence (AI)-assisted scaffold designing may usher in a new era of wound dressings. Everyone knows that diabetic wounds tend to become chronic ones, and a dressing personalized to a patient's unique characteristics and conditions of the wound would be highly effective. Controlled-release nanofibers that have advanced for a long time are expected to work as delivery systems of silver ions that are both sustained and have least toxicity and yet have an antimicrobial effect for a long time.

Though preclinical data is promising, there are a few main reasons that the development of AgNP-loaded electrospun nanofibers has not made it to real-life medical applications yet. The major problem is that there is almost no clinical evidence—all research has really been limited to studies in tubes or test animals. Only some of these systems, like PVDF CA CS/PLA and PLA/Col1 nanofibers, got validated through preclinical studies (44, 46–48). Also, another big reason is that releasing too much silver ions can be harmful to cells, mostly for those cases of PVDF where studies show that higher concentrations are actually toxic (44). Besides, many studies have only looked into antibacterial and cytocompatible activities and have ignored biodegradation, pharmacokinetics, systemic silver accumulation, immunological responses, or chronic toxicity (41–48). There are also no uniform electrospinning standards or AgNP loading procedures that would allow consistent release of AgNP and reliable manufacturing. Limited evaluation of stability on a shelf, sterilization ability, compatibility with storage, and cost-effective production methods also hinder the move towards commercialization. Because of this, although AgNP-loaded electrospun nanofibers possess a considerable potential, only clinical translation that includes standardized methods of production, in-depth biosafety evaluations, industrial manufacturing techniques, and carefully planned out clinical trials may result in successful results (44, 46–48).

There are many crucial topics left to explore in the creation of AgNP-loaded electrospun nanofibers for wounds. A large majority of the available research is focused on antibacterial properties and very short time period cytocompatibility with few explanations about the molecular mechanisms for the processes involved in healing such as angiogenesis, collagen inflammation, polarization of macrophages, and growth factors during wound repair (41, 48). Comparative studies of different polymer matrices, AgNPs synthesis methods, and loading techniques under similar experimental conditions that would help to pinpoint the best scaffold design are not performed either. Besides, there haven't been many research efforts to optimize the levels of AgNP that, on one hand, deliver the best treatment effect and, on the other hand, the least cell toxicity because of silver, even though there were some accounts of concentration-dependent toxicity in some setups like PVDF (44). The way these dressings degrade over time and the release of silver at the right rate as well as how they interact with a wound microenvironment and their potential of these dressings in fighting against polymicrobial and antibiotic-resistant infections is an area that needs more attention and study. Most importantly, there is a great lack of translation research through large animal models, GMP-compatible fabrication processes, regulatory evaluations, and randomized clinical trials (44, 46, 48). Bridging the described shortcomings by involving experts across the fields of materials science, nanotechnology, molecular biology, and clinical investigation shall For sure, it will be the key for moving AgNP-loaded electrospun nanofibers from prototypes in labs to clinical wound care products. It will also be necessary to do multidisciplinary investigations if we hope for the latter to become a reality.

Though, there must be a lot of work done in the field of clinical translation of such types of wound dressings involving thorough preclinical studies, large-scale clinical trials, and the establishment of standardized manufacturing protocols to help with the regulatory approval process. In the near term, the new wound dressings may include AgNPs combined with growth factors, stem cells, antimicrobial peptides, anti-inflammatory agents, or natural bioactive compounds to obtain therapeutic synergy, and this way, interaction between the various therapeutic agents will be essential. The appearance of multi-functional bioactive scaffolds that can do what comes next simultaneously, avert infection, resolve inflammation, encourage angiogenesis, and facilitate tissue regeneration will be a promising development in the forthcoming generation of wound care products. Introducing a different point of view that collaborating across disciplinary borders should be a critical element in addressing these problems, alongside working between materials scientists, biomedical engineers, clinicians, and the regulatory agencies. This will make it possible to change AgNP-loaded electrospun nanofibers from being just a research item to becoming a routine clinical practice.

Conclusion

Electrospun nanofibers are set to become the new generation of scaffolds for skin tissue engineering since their architecture, which mimics ECM, generates a suitable microenvironment that can support cell adhesion, proliferation, and tissue regeneration. Adding AgNPs to these scaffolds has increased their efficiency as therapeutic agents by providing them with features like broad-spectrum antimicrobial, anti-inflammatory, and regenerative properties that together speed up wound healing, and at the same time, the risk of infection is minimized. However, the release of silver in a controlled and sustained manner is paramount for enhancing therapeutic effects and, at the same time, maintaining cytocompatibility through the reduction of the likelihood of side effects caused by excessive exposure to silver. Smart and multifunctional electrospun nanofiber systems that are responsive to stimuli and include bioactive scaffolds have recently been introduced, and these can be used for the treatment of chronic and infected wounds effectively. Although the outcomes of pre-clinical studies are very encouraging, there is still a need for additional long-term safety studies, suitably designed clinical trials, methods of fabrication that are standardized, and manufacturing processes that can be scaled up to speed up the translation of these advanced wound dressings into everyday clinical practice. Generally, electrospun nanofibers loaded with AgNPs constitute a very attractive platform for skin tissue regeneration and wound management in the future.

Ethics approval

Not applicable.

Data availability statement

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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