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ARTICLE

The Antibacterial Properties of Silver Dressings and Their Application in Wound Healing

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ABSTRACT

Silver-containing dressings have gained popularity in clinical applications due to their exceptional antibacterial properties and ability to enhance wound healing. These dressings primarily exert their antibacterial effects through the utilization of silver ions or nano-silver particles. The antimicrobial property of silver ions is a result of multiple mechanisms, with the most significant being the interaction between Ag or Ag^+ and the bacterial cell wall, as well as the interaction between Ag^+ and bacterial DNA or RNA, which inhibits replication and division. Silver-containing dressings can effectively reduce inflammation in wound tissue and expedite wound healing. The antibacterial and wound-healing promoting effects of these dressings are closely associated with the controlled release rate of silver ions. Consequently, developing novel silver-containing dressings that accurately regulate this release rate has become a prominent area of research interest. With broad prospects for application in wound care, silver-containing dressings are anticipated to offer innovative solutions for addressing numerous challenges encountered in clinical wound management.

1. Introduction

The dressing comprises a backing layer, an adhesive layer, a wound contact layer, and a cover sheet [1]. The backing layer primarily functions to prevent water and prevent the invasion of microorganisms from the outside, which is typically made of materials such as polyurethane; the adhesive layer guarantees that the dressing can be firmly fixed on the skin and prevented from moving; the wound contact layer directly touches the surface of the wound and is of crucial significance for promoting wound healing, and commonly used materials include hydrogel and alginate; the cover sheet protects the dressing before use to prevent contamination. A dressing suitable for early wound treatment should offer a good sterilized healing environment for the wound during treatment and transfer, that is, have good absorption of wound exudate, appropriate humidity, long-lasting and safe antibacterial and anti-inflammatory performance, and promote wound healing function [2-4]. As the wound contact layer directly contacts the wound, the high molecular materials, antibacterial and wound healing agents utilized in the wound contact layer, as well as the design of the dressing structure, play a vital role in the quality of the dressing.

Adding antibacterial agents to wound dressings is an effective approach to reduce wound infections [5-7]. Over the past 60 years, antibiotics have been extensively

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utilized in the treatment of injuries and illnesses due to their distinctive advantages, playing a highly significant role in the management of these conditions. Nevertheless, the prolonged use of antibiotics has also resulted in an increase in bacterial resistance to infection and the emergence of superbugs [6].

As a broad-spectrum antibacterial metal that has been utilized by humans as an antibacterial agent since ancient times, there is a renewed interest in the antibacterial application of silver and its compounds. Silver (Ag), being a non-resistant broad-spectrum antibacterial agent, plays an indispensable role in antibacterial drugs and serves as a necessary supplement to traditional antibiotics. In the past two decades, advancements in nanotechnology have facilitated the synthesis of silver nanoparticles (Ag NPs) at various scales, enabling their utilization in wound management [8]. Ag NPs can interact with proteins on the bacterial cell membrane, enhancing its permeability and leading to bacterial content leakage, ultimately resulting in bacterial death. Silver ions can penetrate into bacteria's interior and bind to key sites on metabolic enzyme proteins (such as sulfhydryl groups and amino groups), causing loss of enzyme protein activity, disrupting energy metabolism, inhibiting growth and reproduction. Silver ions bind to bacteria's DNA or RNA preventing replication, fundamentally impeding bacterial propagation while effectively preventing biofilm formation. Despite possessing potent antibacterial properties, it is crucial not to overlook the cytotoxicity associated with silver nanoparticles which is closely linked to their particle size and concentration. Studies have demonstrated that smaller silver nanoparticles are more likely to enter cells and induce cellular damage; however, methods such as surface modification can significantly reduce cytotoxicity while improving biocompatibility.

Silver-containing dressings possess significant potential for application and development in the field of wound care. By means of meticulous material selection and design, silver-containing dressings not only offer effective antibacterial protection but also facilitate wound healing, providing a more efficient and safe solution for clinical wound management. This article provides an overview of the self-discharge property and antibacterial mechanism of Ag NPs, the cytotoxicity and healing promotion mechanism of Ag NPs, the types and characteristics of silver-containing dressings as well as their role in promoting wound healing, along with their clinical applications.

2. Antibacterial mechanism of Ag NPs and Ag+

In the moist wound environment at pH 5.7, Ag NPs release Ag^+ and one electron. In the aerobic wound environment at pH 5.7, Ag NPs initially oxidize to form Ag_2O and subsequently release silver ions [10]. The reaction mechanism of Ag in batteries has been a subject of debate in academia. For instance, some scholars propose that in an aerobic environment, silver and water results in the formation of Ag+ hydroxide [9]. Lok et al. discovered that it was Ag_2O-NPs, instead of Ag NPs, that demonstrated antibacterial activity against *E. coli* [11]. Marambio Jones and Hoek suggested that within cell mitochondria, silver ions are released through their reaction with peroxides [12]. In diverse physiological environments, whether Ag-NPs release Ag^+ directly or Ag-NPs form Ag_2O-NPs and subsequently release Ag^+, the ultimate outcome of the discharge reaction in various media is the generation of Ag^+[9].

$$Ag \rightleftharpoons Ag^+ + e^- \qquad 0.80V$$

$$2Ag + 2OH^- \rightleftharpoons Ag_2O + H_2O + 2e^- \qquad 0.34V$$

$$Ag + Cl^- \rightleftharpoons AgCl + e^- \qquad 0.22V$$

$$Ag_2 \rightleftharpoons Ag + Ag^+ + e^- \qquad -0.10V$$

$$Ag_3 \rightleftharpoons Ag_2 + Ag^+ + e^- \qquad -0.95V$$

$$Ag\ (atom) \rightleftharpoons Ag^+ + e^- \qquad -1.80\ V$$

Fig.1. The element Ag can undergo various battery reactions in diverse environments.

The antibacterial performance of silver ions stems from multiple mechanisms operating concurrently, with the most significant ones being the actions of Ag and Ag^+ on the cell wall and the actions of Ag^+ on proteins and genes [13-15]. In the moist, pH=5.7 wound environment, the discharge reaction liberates Ag^+, which initially binds to proteins on the cell membrane, resulting in the disruption of the cell membrane and the collapse of the membrane potential [10]. Trace quantities of Ag^+ can impede the transport of electrons in the respiratory chain, inhibit the activity of respiratory chain enzymes, and disrupt the permeability of the membrane to protons and phosphates [16-17]. When the concentration rises to a certain level, Ag^+ will interact with cellular components and nucleic acids, etc. [18]. Ag-NPs or Ag^+ have a strong affinity for the cysteine (-SH) of the main respiratory enzyme proteins (succinate dehydrogenase, NADH2 dehydrogenase, cytochrome oxidase, etc.) within the bacterial body, causing the enzymes to lose their activity, and the Ag^+ bound to the

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enzymes cannot be released again to continue acting on the bacterial body [19]. Additionally, Ag NPs can also form complexes with peptides containing primary amine or carboxyl groups such as arginine, tyrosine, aspartic acid, glutamic acid, etc., leading to the inactivation of the genes containing these molecules and the death of the bacteria [9].

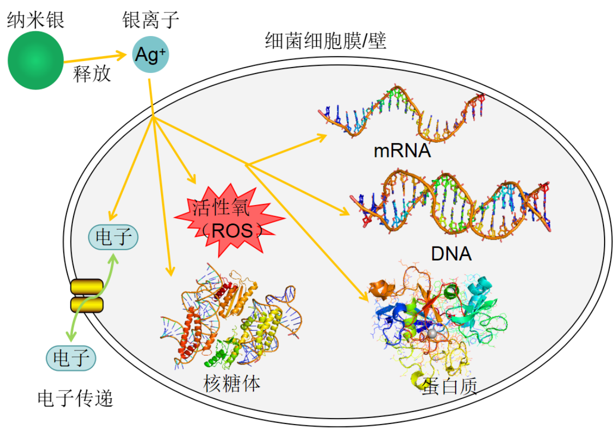

Fig. 2. Antibacterial mechanism of Ag NPs and Ag^+.

The antibacterial ability of Ag NPs shows a scale effect, becoming stronger as the particle size reduces, and the minimum concentration necessary to exert antibacterial effects varies depending on the scale [20]. Smaller Ag NPs are more toxic than free Ag^+. Researches have demonstrated that Ag NPs with a diameter of 500 nm or above do not possess antibacterial properties [21]. Ag NPs with a diameter of 100 nm are effective against Staphylococcus aureus at a concentration of 0.4 μmol/L, while that of silver nitrate is 6 μmol/L [20]. Ag NPs with a diameter of 50 nm can exhibit antibacterial properties against Staphylococcus aureus at a super-low concentration of less than 2 μg/mL. Studies on Ag NPs particle composite films (with a surface particle size of approximately 15 nm) have discovered that the surface can rapidly release ions, free radicals, and atomic clusters, with the discharge rate being dependent on factors such as particle size, oxides in the system, and lattice defects [22]. This Ag NPs particle composite film has superior antibacterial properties to local antibacterial agents (such as silver nitrate solutions and aminosalicylic acid silver) available in the market.

3. Cytotoxicity and healing promoting mechanism of Ag NPs

For a specific range of Ag NPs, an appropriate concentration effectively inhibits bacterial growth in wounds. However, when the concentration of Ag NPs exceeds a certain threshold, they can penetrate normal tissue cells through the wound and interact with proteins rich in sulfhydryl and carboxyl groups as well as guanine-rich DNA within the cells, resulting in toxicity to the body. The impact of Ag NPs' particle size on cell cytotoxicity is similar to that observed for bacteria. Research has demonstrated that at equivalent concentrations, smaller particle sizes of Ag NPs exhibit increased cytotoxicity [23-24]. The primary mechanism underlying the cytotoxicity of Ag NPs involves inhibition of cellular ATP synthesis and generation of reactive oxygen species [25-27]. Ag NPs particles ranging from 50-80 nm enter cells via endocytosis and accumulate within mitochondria. Reactive oxygen species produced by these particles disrupt mitochondrial bilayer membranes, inhibit ATP synthesis, impede respiratory chain continuity, and induce apoptosis through superoxide free radicals and oxidative stress [28]. Cellular oxidative stress caused by Ag NP particles irreversibly damages DNA structure, arrests cell cycle progression, ultimately leading to apoptosis [29].

Appropriate concentration of silver nanoparticles (Ag NPs) can enhance the process of wound healing. Matrix metalloproteinases (MMPs), which are present in the wound, have the ability to specifically bind with various growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor (TGF), etc., leading to their degradation and inhibition of wound healing [30]. Ag NPs can interact with sulfhydryl, amino, and carboxyl groups in MMPs, thereby inhibiting the function of this metalloprotease and ultimately promoting wound healing [31].

Despite the controversy regarding the release mechanism of Ag NPs, all studies have demonstrated that Ag NPs exert antibacterial activity and cause cell toxicity through the release of silver ions. As a broad-spectrum antibacterial agent, Ag NPs exhibit good inhibitory activity against infectious bacteria on wounds. When the concentration of Ag NPs of a certain scale reaches a specific value, it will generate certain toxicity to normal human cells [1, 15]. The antibacterial activity and cell toxicity are associated with the concentration of Ag NPs, which is related to the scale and crystal face structure. The difficulty in obtaining reproducible and uniform scales of Ag NPs leads to a lack of systematic research and inconsistencies in conclusions; moreover, the limitations of each individual research field and the different experimental conditions set also result in poor relevance and inconsistencies in research conclusions [9].

4. Types of Silver Dressings and Their Function in Wound Healing

The dressing is composed of a backing layer, an adhesive layer, a wound contact layer, and a protective sheet [1]. Traditional dressings primarily utilize sterilized and fat-free cotton, gauze, and bandages, which solely serve as protective barriers without promoting wound healing [32]. They are prone to bacterial growth during usage, while the gauze easily adheres to the wound surface leading to secondary trauma [33]. In addition to providing coverage and protection for damaged skin, medical dressings should also facilitate healing and prevent further damage to the wound [34]. Depending on the type, severity, and location of the wound, different types of dressings should be employed.

In 1962, British scientist Winter found that wounds healed more readily in a moist environment than in a dry one, which gave rise to the development of the wet dressing method as the main theoretical foundation for the design of new medical dressings [4]. In the 1980s, developed countries such as the UK and the US created a series of new medical dressings based on the wet dressing method, including those mineral-based, synthetic polymer-based, biologicall y active, and artificial fibrin dressings. These new dressings possess the advantages of good breathability and flexibility, and some have entered the market. For instance, ConvaTec, a company from the UK, manufactures two products named Versiva and Granuflex, which are composed of agar, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and other high molecular water-based polymers. The gel has a moderate capacity to absorb exudate and can facilitate autolytic debridement, seal the wound bed, protect the wound, prevent water and bacterial infection, and prevent contamination from urine and feces. However, the issue is that the dressing has excessive adhesion, which might cause skin damage and leave residues in the wound bed [36-37]. The Hydrofibertm dressing produced in the UK is made of hydrophilic sodium carboxymethylcellulose fibers and cellulose, and is suitable for treating abrasions, lacerations, minor cuts, minor burns, and minor scalds. It is not appropriate for large-area wounds [38]. The 3M Company based in the US produces a product called Tegagen dressing, which is made of polyurethane materials and low-allergenic medical pressure-sensitive adhesive. It has the benefits of full transparency for easy observation of puncture points, breathability, and firm adhesion, etc. Nevertheless, the safety and effectiveness of the dressing have not been evaluated for children under the age of 18 [35].

In the wild, wounds are typically contaminated, increasing the likelihood of bacterial infection [6]. Due to limited medical conditions, comprehensive and thorough wound treatment cannot be provided. Therefore, a dressing that can maintain the cleanliness of the wound, possess long-lasting antibacterial activity, and address deep wound problems is necessary. Dressings without antibacterial agents or with only one type of antibacterial agent often have less potent antibacterial and healing promotion effects compared to combination dressings [39]. Adding another antibacterial and healing promoting material to the dressing in addition to Ag NPs, or using high molecular weight fiber materials with antibacterial and healing promotion functions to composite with Ag NPs, will yield better antibacterial and healing promotion effects. The Ag NPs/alginate composite dressing can significantly reduce bacterial infection on wound surfaces and facilitate wound healing [40]. The silver/graphene polyacrylic acid hydrogel has a high swelling rate, good biocompatibility, and antibacterial activity, and can enhance the wound healing rate [41]. The nonwoven fabric impregnated with Ag NPs solution exhibits good antibacterial performance against Staphylococcus aureus and Escherichia coli [42]. Stephan et al. coated Ag NPs with polyacrylic acid, added the appropriate amount of diluent, and precipitated the antibacterial particles on silk and nylon, significantly enhancing their antibacterial performance [43]. Madhumathi and Ong utilized Ag NPs in combination with chitosan to create a dressing for treating burns and scalds, which can resist Staphylococcus aureus, Escherichia coli, and other bacteria and show excellent hemostasis effects [44-55]. The Ag NPs dressing has stronger antibacterial effects than vaseline poultice and can accelerate wound healing more rapidly [46]. Demling et al. indicated that the Ag NPs dressing has a better promotion effect on epithelialization after burn skin grafting [47].

5. Clinical Application of Silver Dressings

The silver dressings that have been put into practice include Algisite, a non-woven, alginate calcium dressing produced by Smith & Nephew of the UK. It is impregnated with silver nitrate, sterilized, and possesses functions such as moisture absorption, antibacterial activity, hemostasis, and wound healing. However, it is not suitable for dry wounds or those with continuous heavy bleeding [48]. Another Ag NPs ion dressing (ActicoatTM) produced by Smith & Nephew consists of three layers of polyethylene meshes embedded with Ag NPs particles (diameter < 20 nm) and two layers of artificial polyester, which releases Ag NPs to exert antibacterial effects on wounds [49]. Econolac Silver, manufactured by ConvaTec Limited of the UK, is composed of carboxymethylcellulose sodium and 1.2% silver ions. It can absorb wound exudate by binding to cations in the wound exudate and releasing silver ions to kill various pathogens [50]. The alginate silver ion dressing produced by Molnlycke of Sweden is composed of high G (gulonic acid) alginate calcium, carboxymethylcellulose (CMC),

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and a silver ion compound (silver hydroxide zirconium phosphate). It is suitable for covering superficial and full-thickness wounds with moderate to severe exudate, but the silver ions are prone to oxidation and degradation [51]. A silver dressing named Silverlon is abundantly stocked by the US military, and its manufacturing technology mainly involves coating silver particles on the surface of nylon fibers (polyamide 66) through impregnation, with the silver content reaching up to 546mg/100cm^2 [52]. At this concentration, the silver in the silver dressing can electrolyze and release silver ions on the wound surface. It not only has a stronger antibacterial effect, reduces wound exudate, and promotes wound healing, but also is low-cost, easy to store, and transport. The drawback of silver nylon is that its antibacterial ability is still inferior to that of other related products with lower silver content [52]. The American KCI Comfeel Silver Antimicrobial Dressing is a synthetic polyacrylate polymer containing silver chloride and can be used for the care of shallow and deep wounds [53]. The antibacterial silver collagen wound dressing (ColActiveAg) developed by Covalon Technologies, a Canadian company, is a collagen antibacterial dressing containing silver and is suitable for the treatment of all types of wounds, including partial wounds [49]. Silver nitrate and sulfadiazine silver are prone to generating oxidized silver when exposed to light or heat, which can result in a too-high local silver ion concentration and cause significant cell toxicity.

Table 1. Currently available Ag-containing dressing products.

Name	Manufacturer	Product performance structure and composition	Application
ActicoatTM	Smith&Nephew	Consists of three layers of polyethylene mesh embedded with Ag NPs particles (diameter < 20 nm) and two layers of artificial polyester.	Works by releasing nanosized silver particles onto the wound to fight bacteria.
AQUACELTMAg	ConvaTec Limited	Consists of carboxymethylcellulose and 1.2% silver ions.	Used for the care of both superficial and deep wounds.
ColActiveAg	Covalon Technologies	Silver-containing collagen antibacterial dressing	It is suitable for treating both full and partial injuries.
Silver ion alginate dressing	Advanced Medical Solutions Ltd.	Non-woven antibacterial dressing, consisting of calcium alginate, sodium carboxymethylcellulose (CMC), polyethylene glycol, and silver ion compounds. Single-use.	Suitable for the treatment of moderate to severe exuding wounds, including wounds with cavities, pressure sores, leg ulcers, diabetic ulcers, second-degree burns, skin grafts, donor sites, or trauma wounds.
AcryDerm	AcryMed, Inc.	Consists of a synthetic polymer of polyacrylic acid with silver chloride. It is disposable.	Used to care for shallow and deep wounds, including pressure ulcers, diabetic foot ulcers, leg ulcers, skin tears, 1st and 2nd degree burns, graft donor sites, surgical incision, and skin abrasions.
Askina Calgitrol Ag	Collooney, Co. Sligo, Ireland	A dual-layer sterile dressing consisting of an absorbent polyurethane foam layer and an alginate silver ion matrix.	Used to treat infected or uninfected, superficial or deep wounds, stage I-IV pressure ulcers, venous ulcers, second-degree burns, and donor sites.
Comfeel Purilon Gel	Coloplast Denmark	Composed of carboxymethylcellulose suspended in a petroleum jelly mesh and contains evenly distributed sulfadiazine silver in the petroleum jelly.	Suitable for other severe infections with low to high exudate, acute superficial burns and skin abrasions, donor sites and postoperative wounds, as well as wounds with delayed healing due to severe bacterial infection or suspected infection risk, to promote wound healing.
Silver ion dressing	Changsha Hairun Biotechnology Co., LTD	Made of antibacterial sterile gauze, antibacterial sterile knitted fabric, or antibacterial nonwoven fabric, and medical silver ion particles.	Suitable for patients with I and II degree burns (scalds). It has strong penetration ability and can prevent infection, promote wound healing, and reduce scar formation.
Silver ion antibacterial medical dressing	Changsha Hairun Biotechnology Co., LTD	Mainly composed of silver ion antibacterial layer, and the self-adhesive type also includes adhesive layer (medical pressure-sensitive adhesive tape), absorbent layer (adhesive fiber), isolation layer (release paper), and anti-adhesion layer (PE film).	Suitable for trauma, burns, scalds, surgical incision, and various infectious wounds.

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6. Conclusion

Silver-containing dressings have manifested considerable advantages in clinical wound management because of their high efficacy in antibacterial ability and wound healing facilitation. Research indicates that silver ions or nanosilver particles exert their antibacterial effects through diverse mechanisms. In facilitating wound healing, silver-containing dressings not only effectively control local infections, mitigate inflammatory responses, but also stimulate the formation of granulation tissue and the proliferation of epithelial cells, accelerating wound closure. The release rate and concentration of silver ions are crucial factors influencing their antibacterial effects and wound healing promotion. A rationally designed silver-containing dressing can achieve controlled release of silver ions, guaranteeing sustained and effective antibacterial effects while reducing the potential cell toxicity caused by excessive silver ion release. Future research will center on developing silver-containing dressings with higher biocompatibility, lower toxicity, and superior antibacterial and wound healing promotion effects to meet the treatment requirements of different types of wounds, especially in the treatment of chronic non-healing wounds, where the application prospect of silver-containing dressings is particularly promising. Additionally, exploring the combined use of silver ions with other biologically active substances to enhance their comprehensive therapeutic effects is also an important direction for future research. In conclusion, the application and development potential of silver-containing dressings in wound care is vast, and they are anticipated to provide more efficient and safe solutions for clinical wound management.

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